Guy's and St Thomas' NHS
NHS Foundation Trust

SELECTED CUTANEOUS SOFT TISSUE TUMOURS
HOT TOPICS IN DERMATOPATHOLOGY
ROME, ITALY, APRIL 4-5/2025

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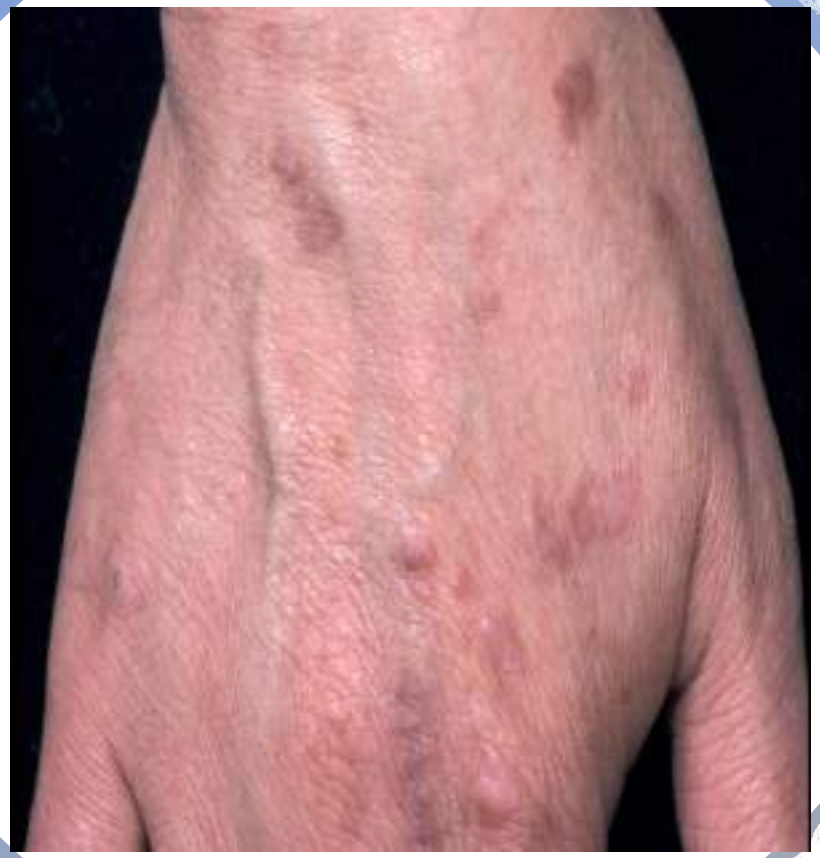
Guy's and St Thomas´s Hospital NHS Foundation Trust
London, United Kingdom

Multinucleate cell angiohistiocytoma

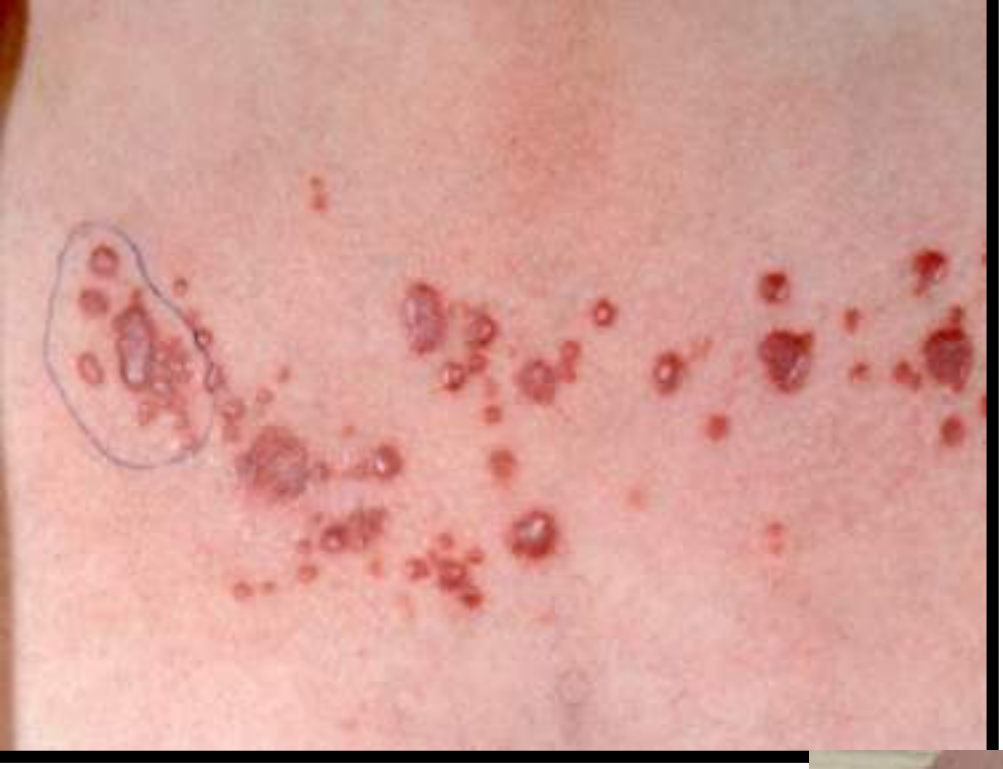


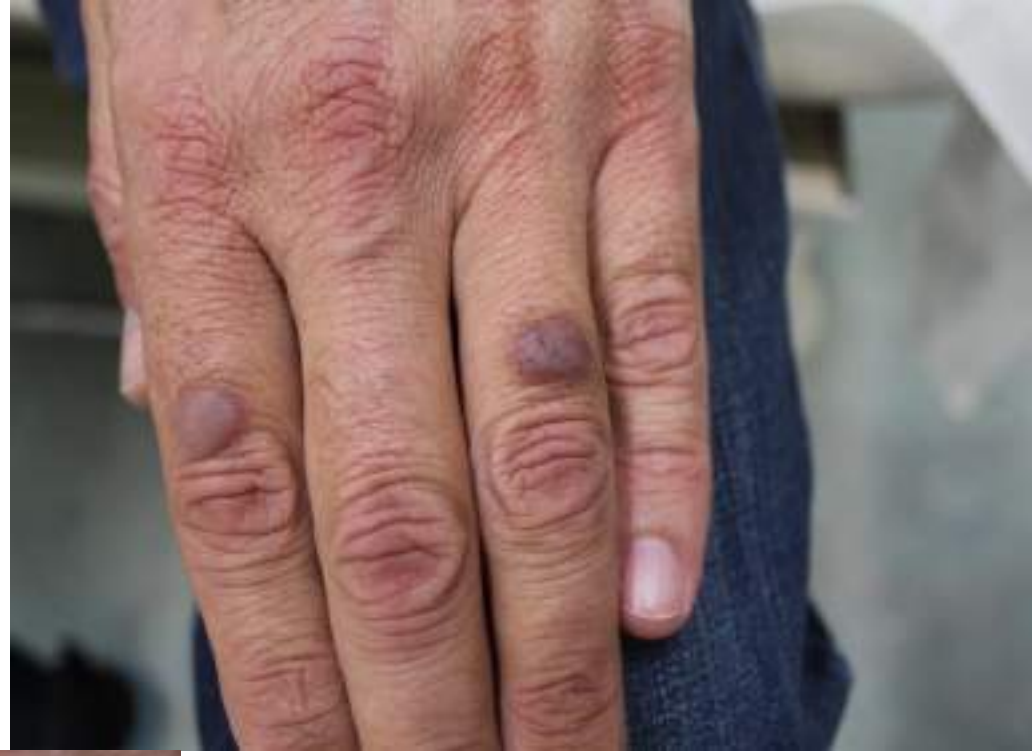
- Benign proliferation composed of thin-walled capillaries and veins with scattered multinucleated cells

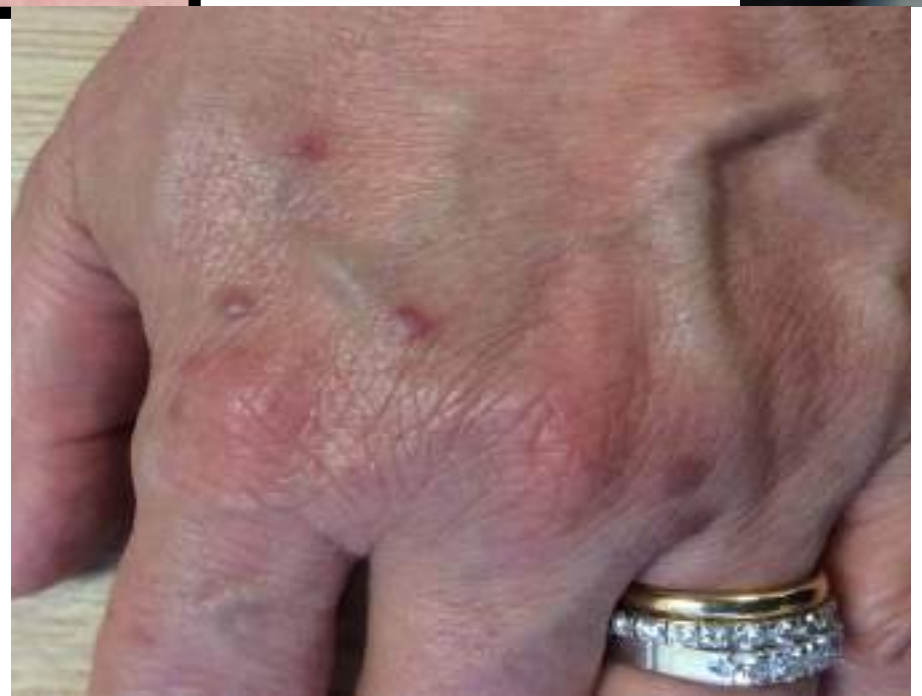
- Female predominance, middle-aged
- Slowly growing single or multiple firm red-brown to violaceous papules
- Over distal extremities, dorsum of the hands, wrists, thights
- Less frequent: face, trunk
- Mucosal site, oral cavity

Clinical variants:

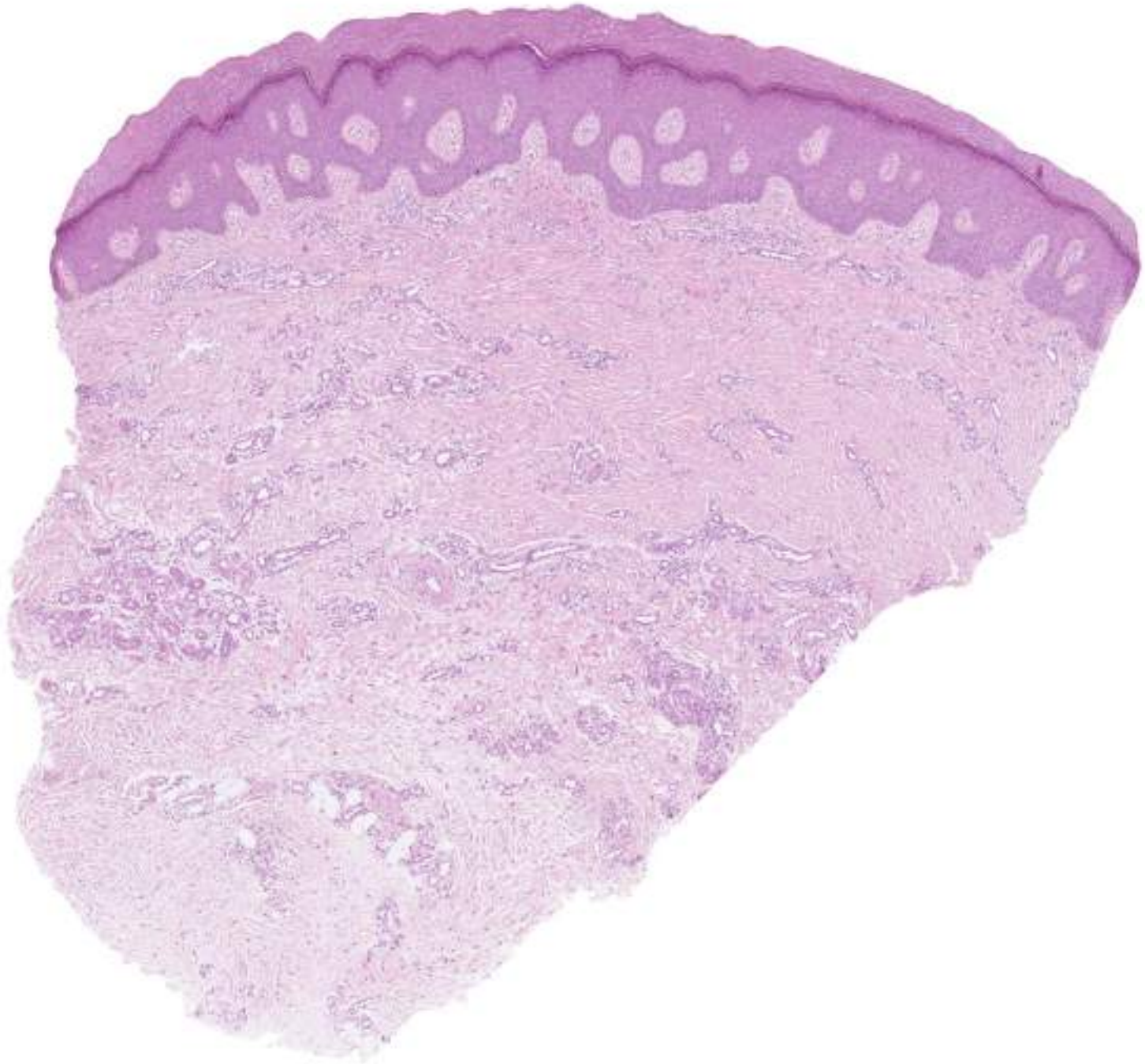
- Linear
- Eruptive
- Plaque-like
- Disseminated/generalized

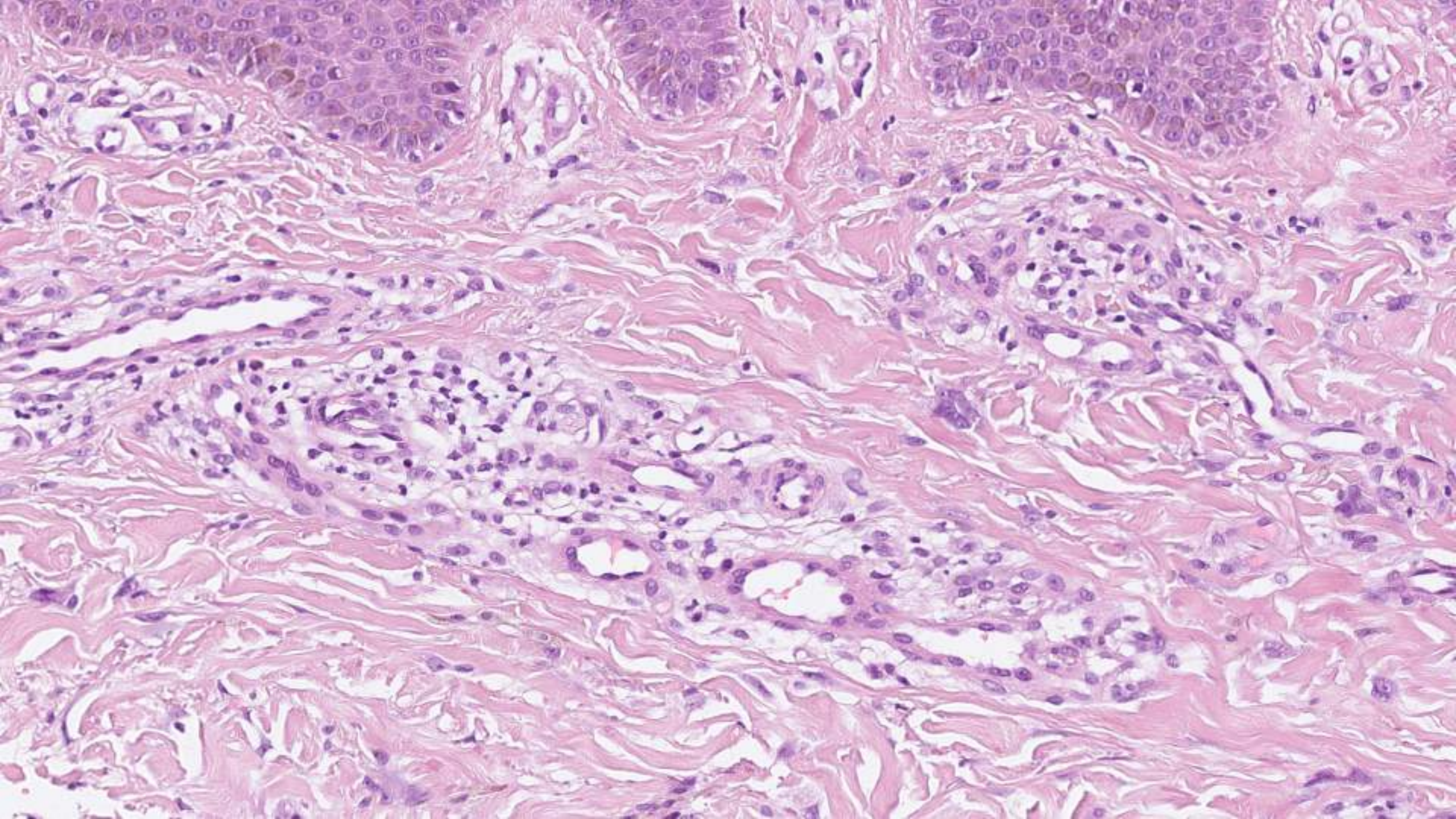


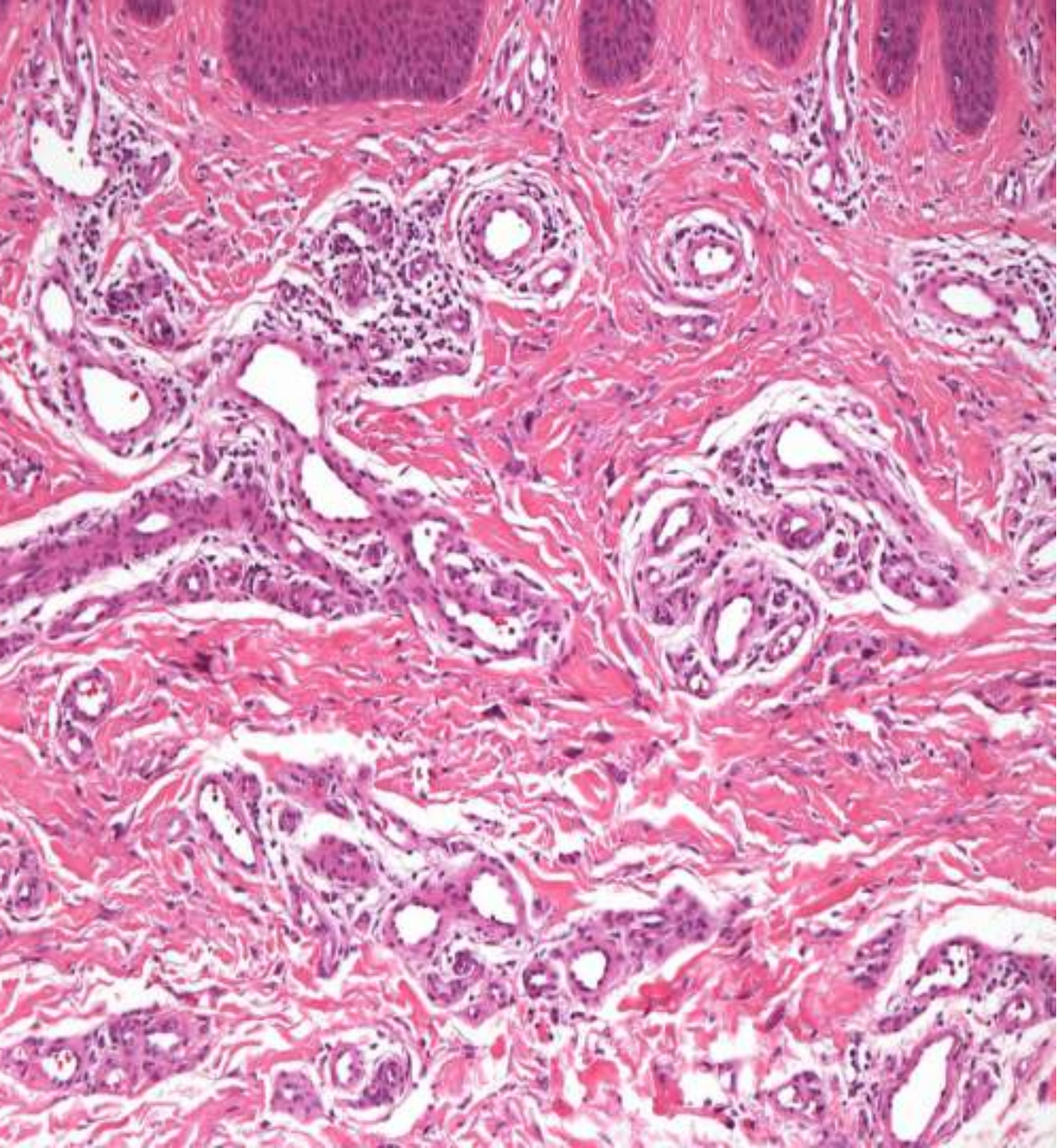
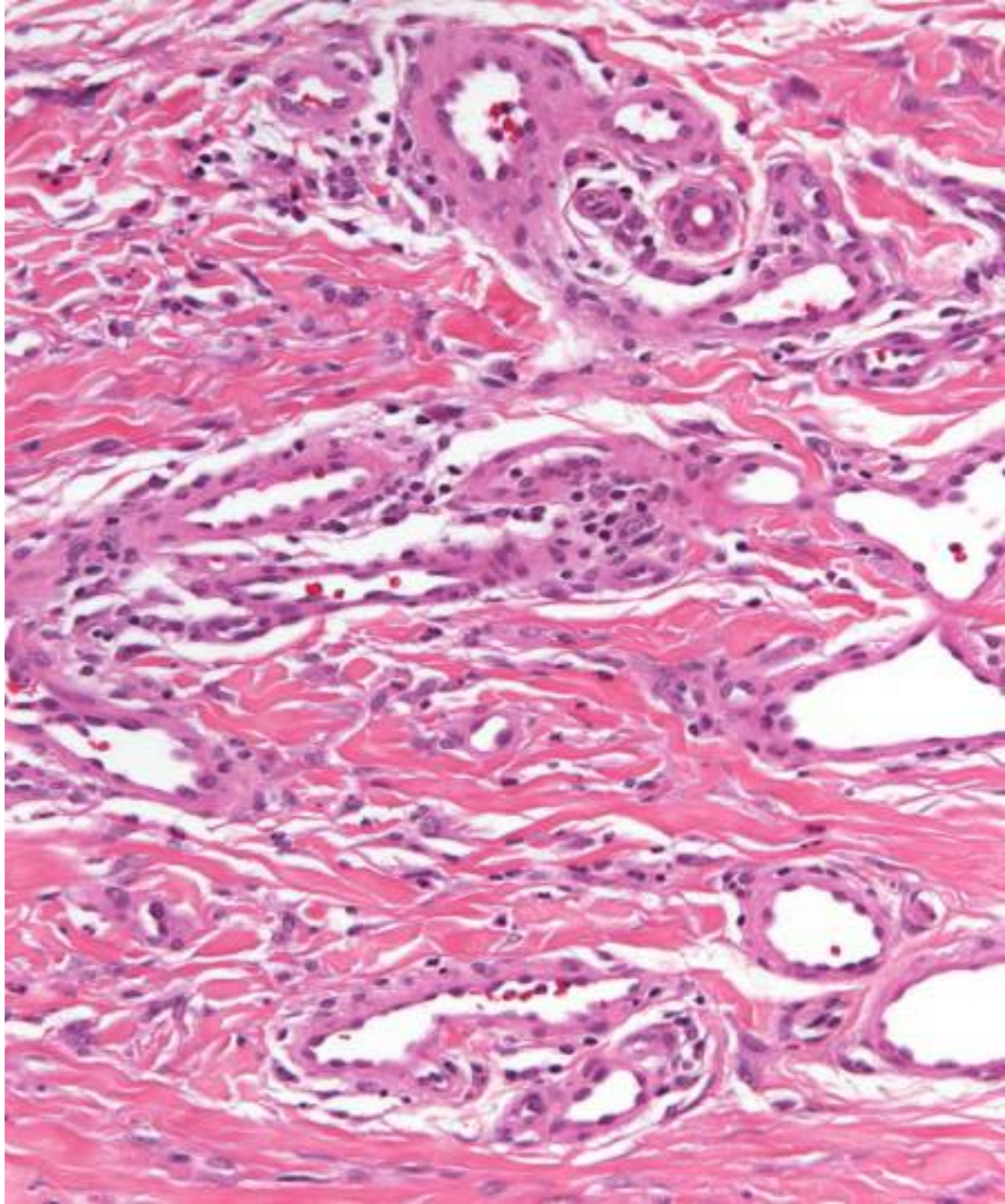




Multinucleated cell angiohistiocytoma histology

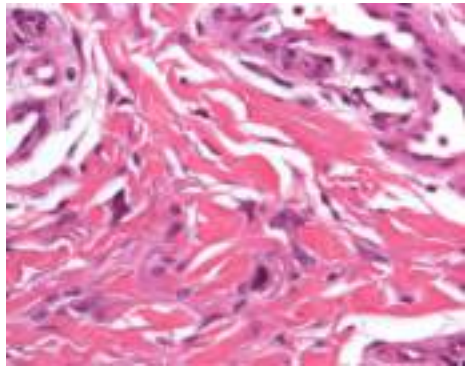


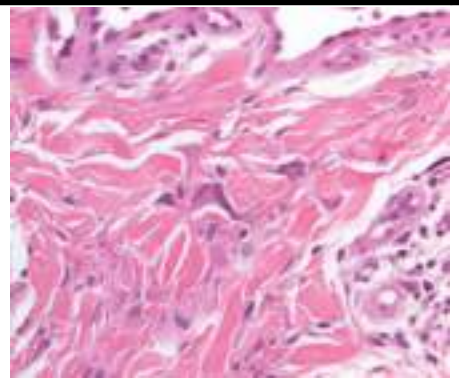


Immunohistochemistry

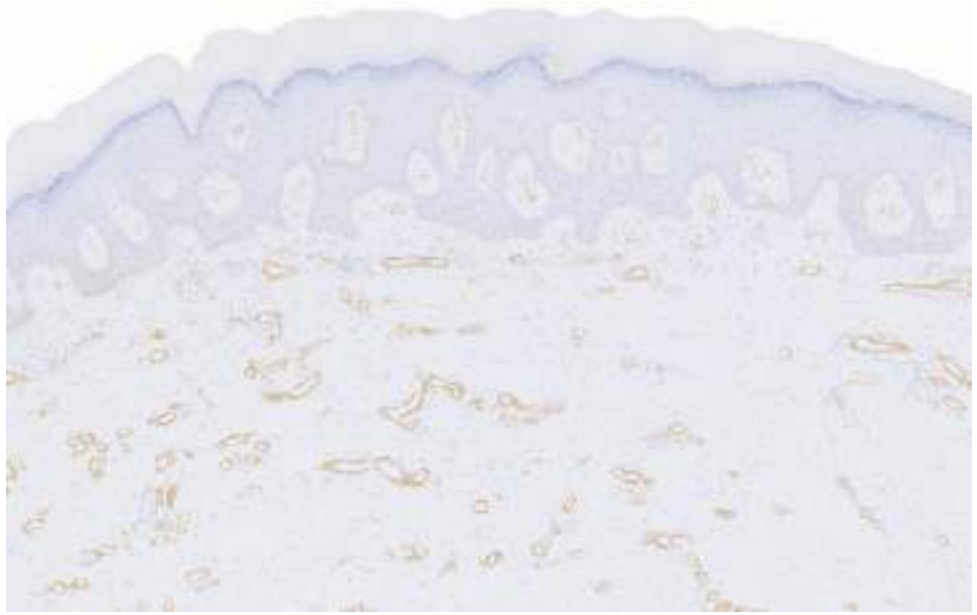
Positive



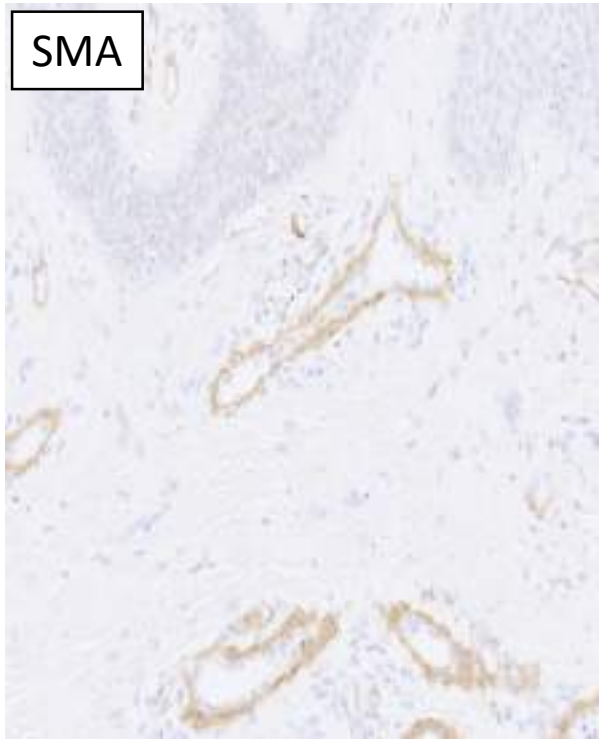


Negative

Multinucleated cells CD68



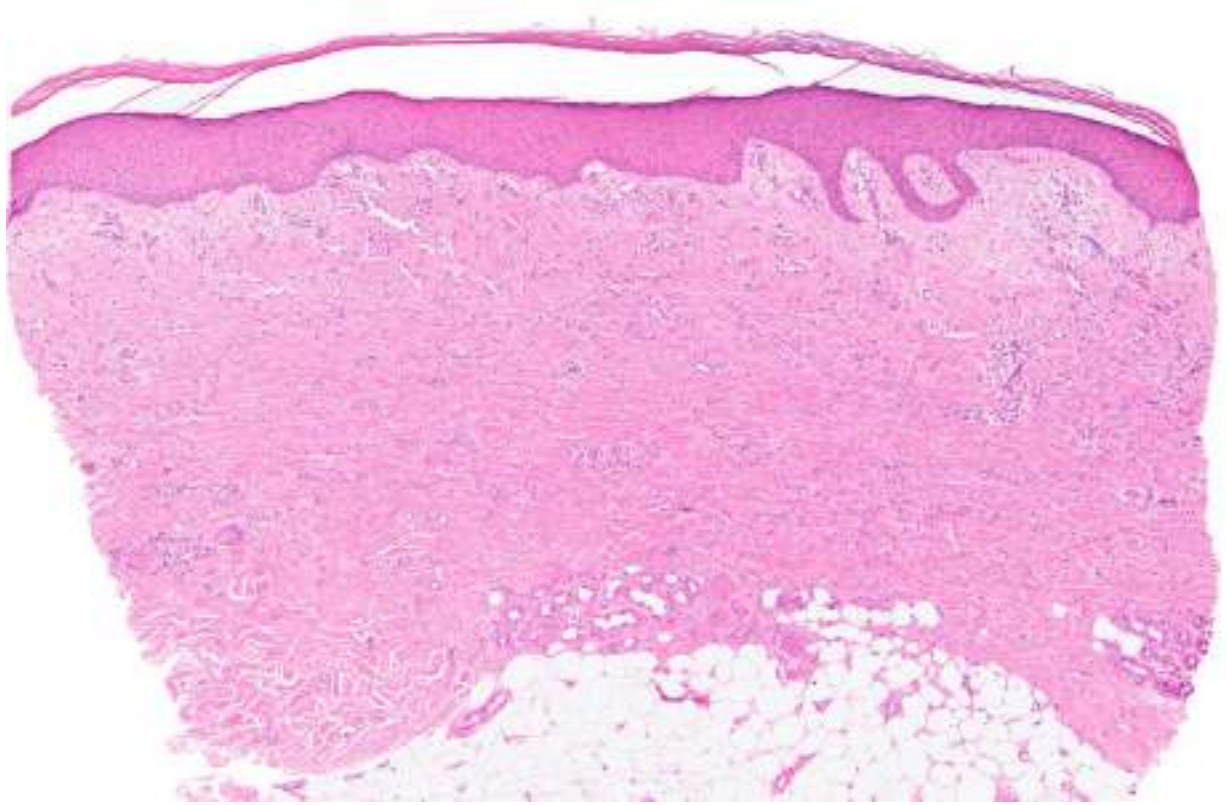
SMA

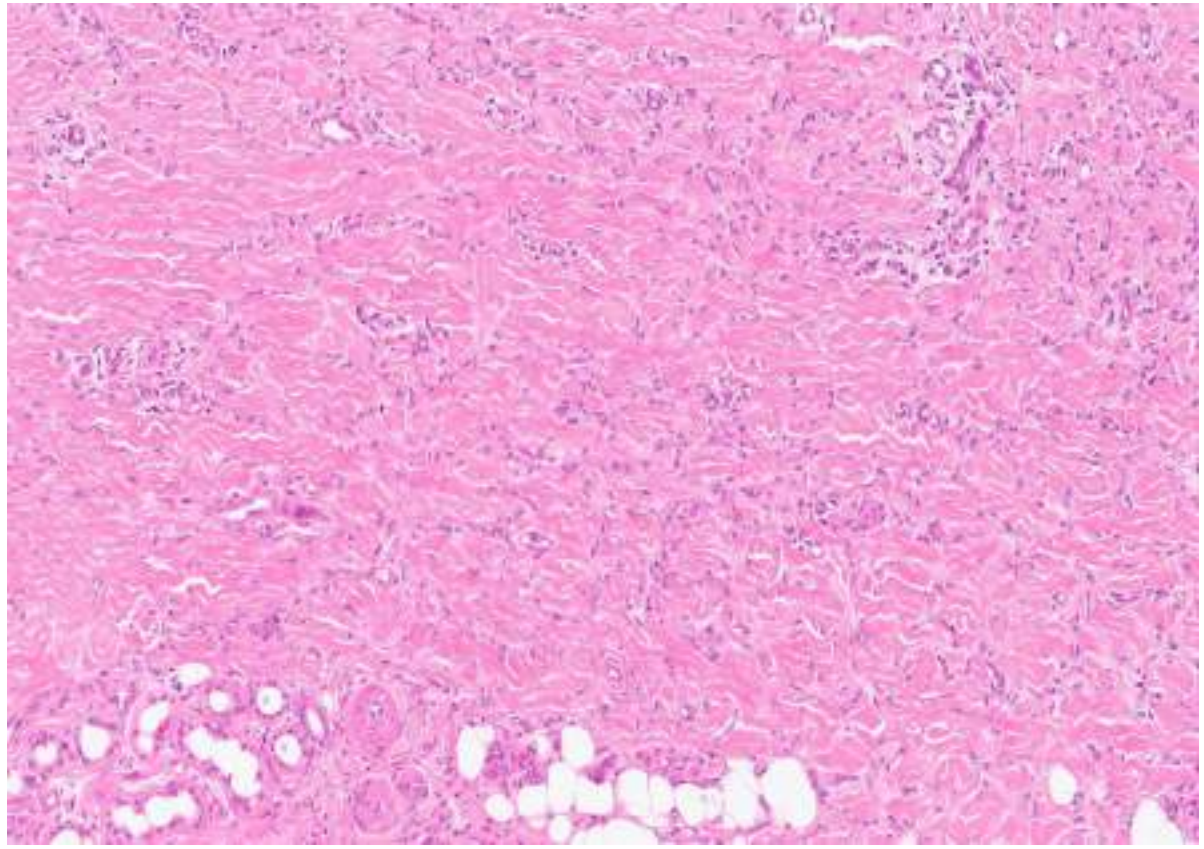


- CK
- EMA
- S100 protein

Differential diagnosis

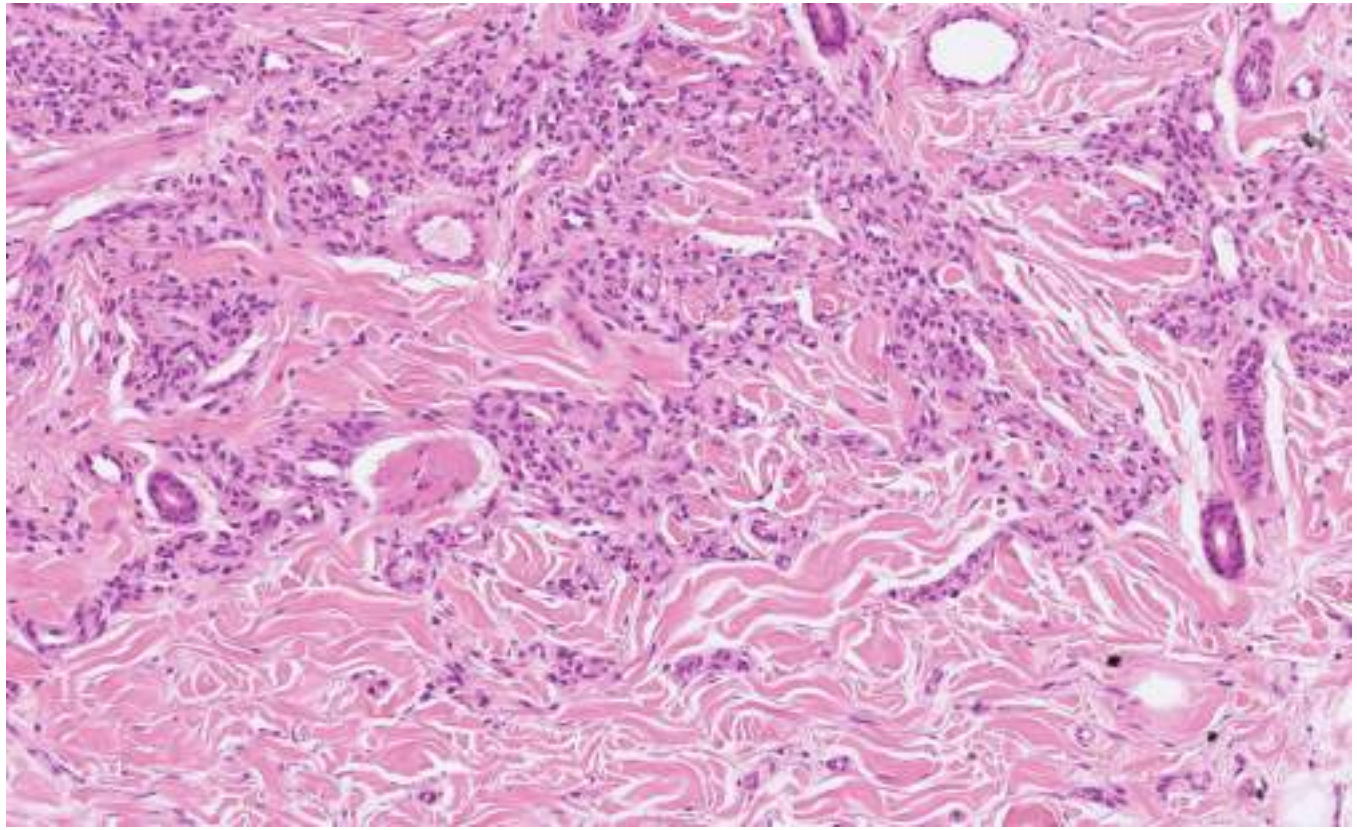
Atrophic dermatofibroma





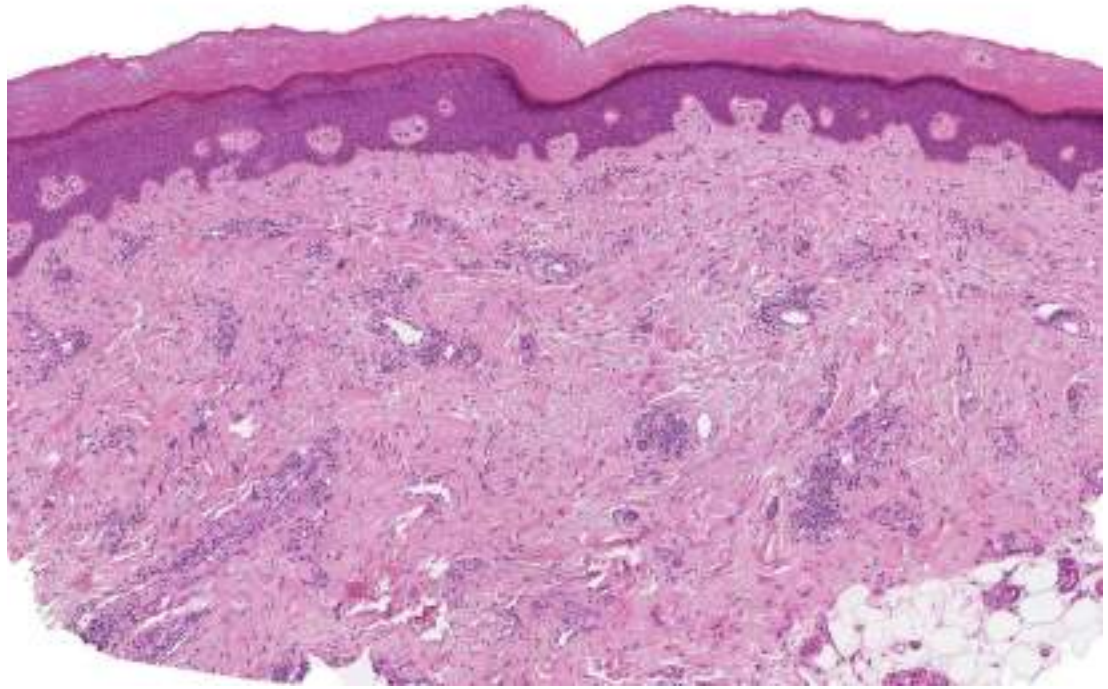
Differential diagnosis

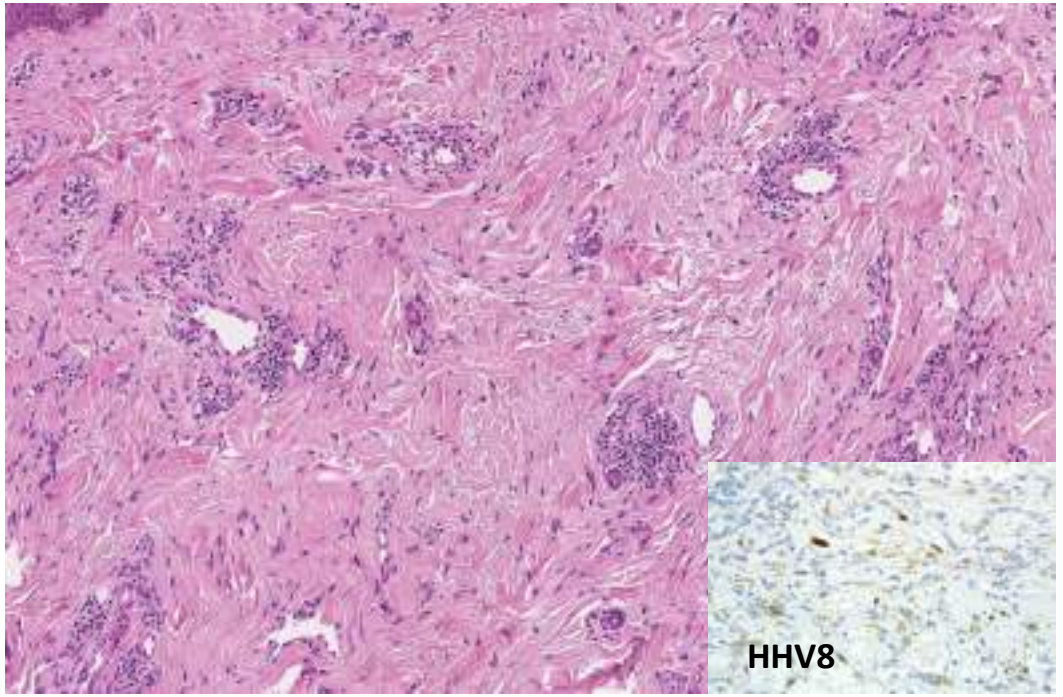
Microvenular hemangioma



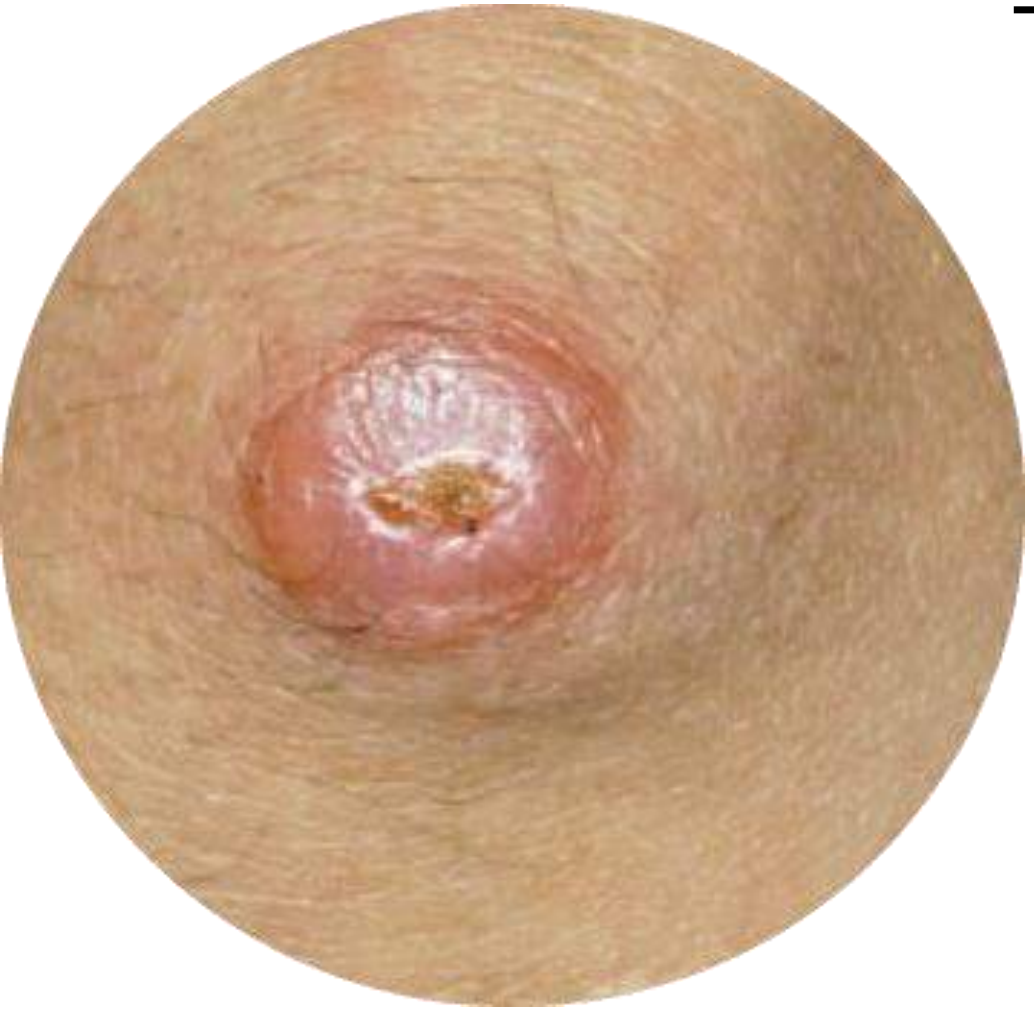
Differential diagnosis

Kaposi sarcoma





Atypical (pseudosarcomatous) fibrous histiocytoma

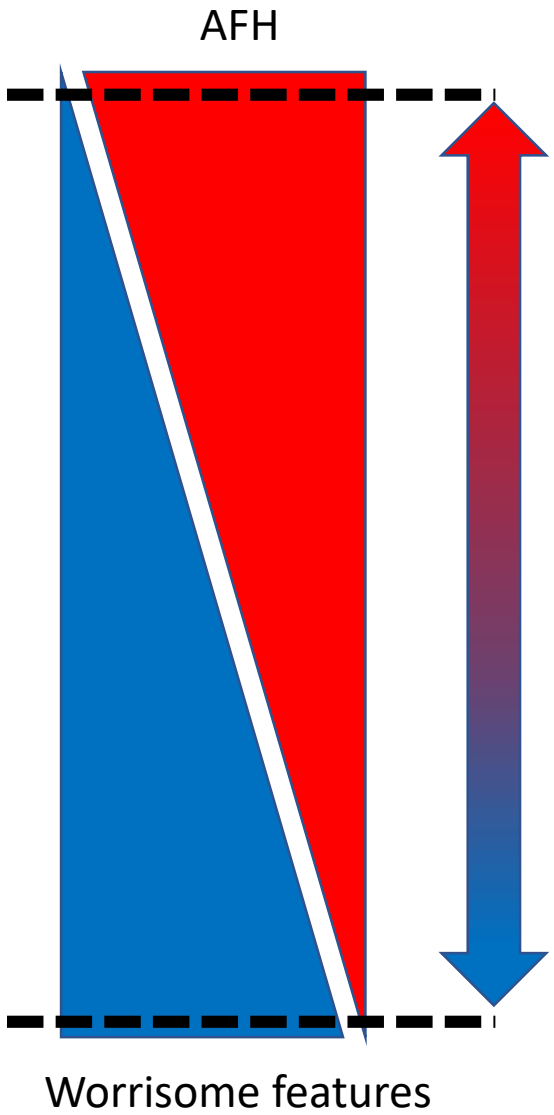


Definition: Composed of variably pleomorphic spindle and epitheloid cells in the background of an ordinary benign fibrous histiocytoma

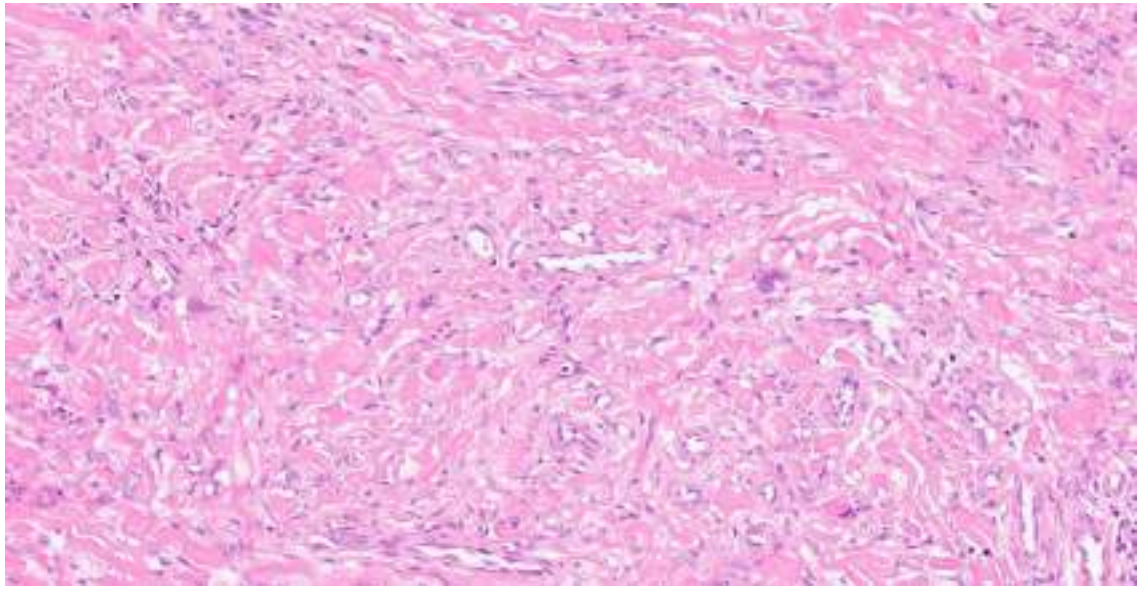
- Young to middle age adults
- Equal gender distribution
- Lower limbs/ limb girdle (44%), upper limbs/ limb girdle (32%), trunk, head and neck, genital region

- Metastatic disease exceptional (lung)
- No histological features have been detected to predict metastatic potential

AFH: atypical fibrous histiocytoma

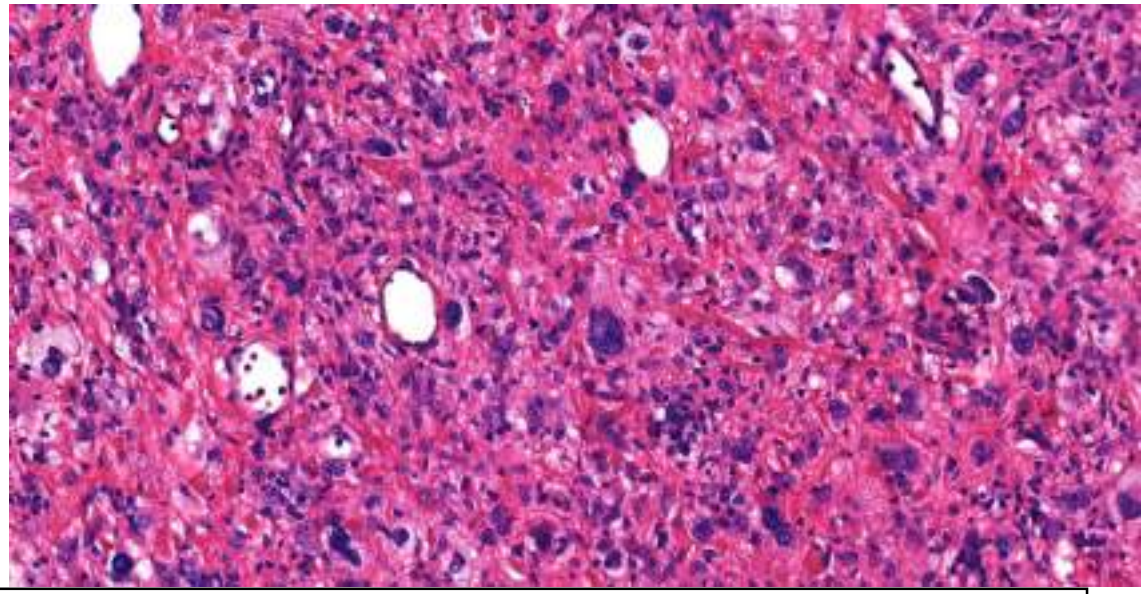


- Only mild or focal pleomorphism
- Small, well circumscribed, and superficially located in the upper dermis
- No difficulties in histologic diagnosis



AFH

- Marked pleomorphism
- Large size (>2 cm in diameter)
- More infiltrative margins,
- Extension to the subcutis,
- Frequent (>5 per 10 HPFs) or atypical mitotic figures
- Necrosis
- May be misinterpreted as pleomorphic sarcoma

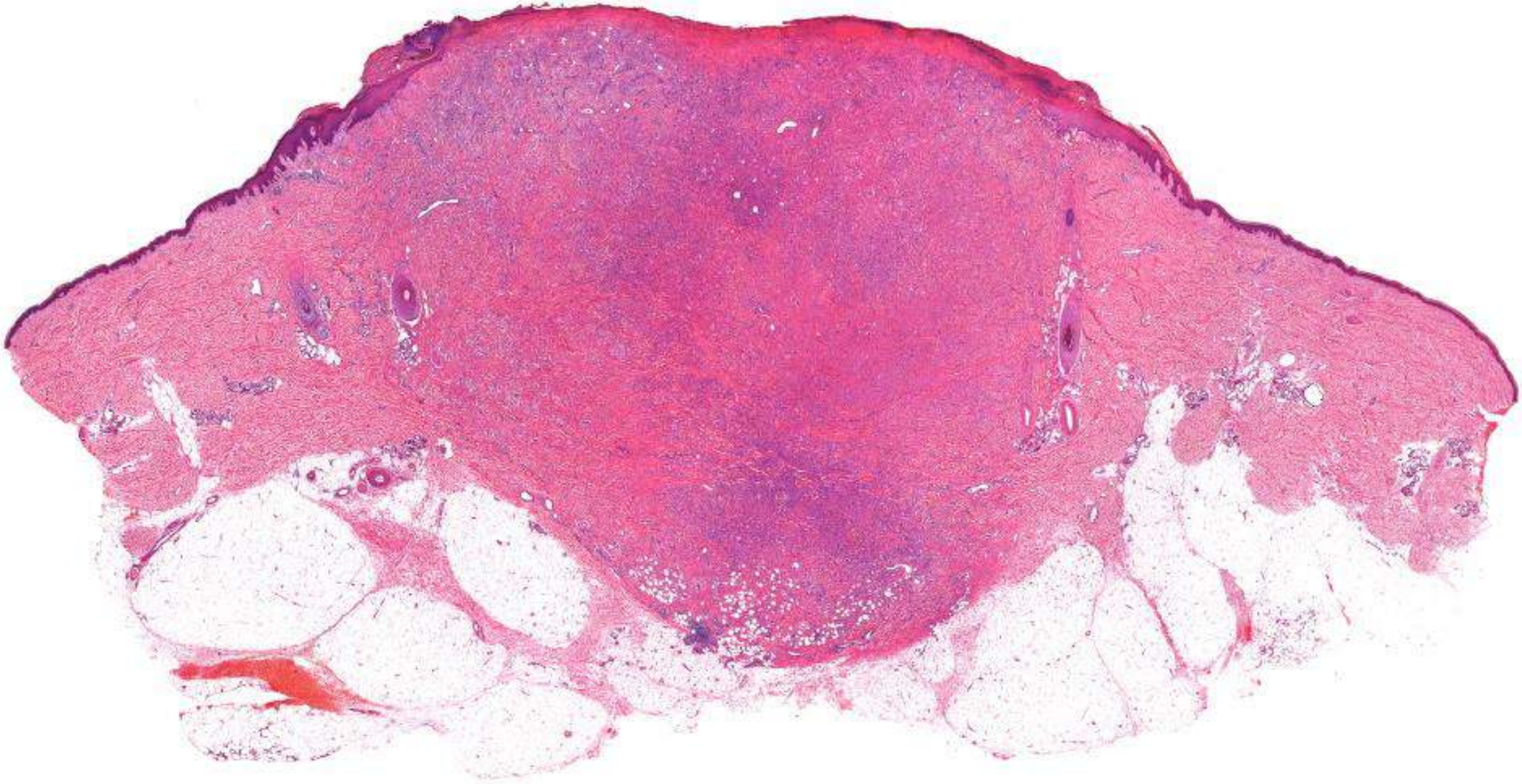


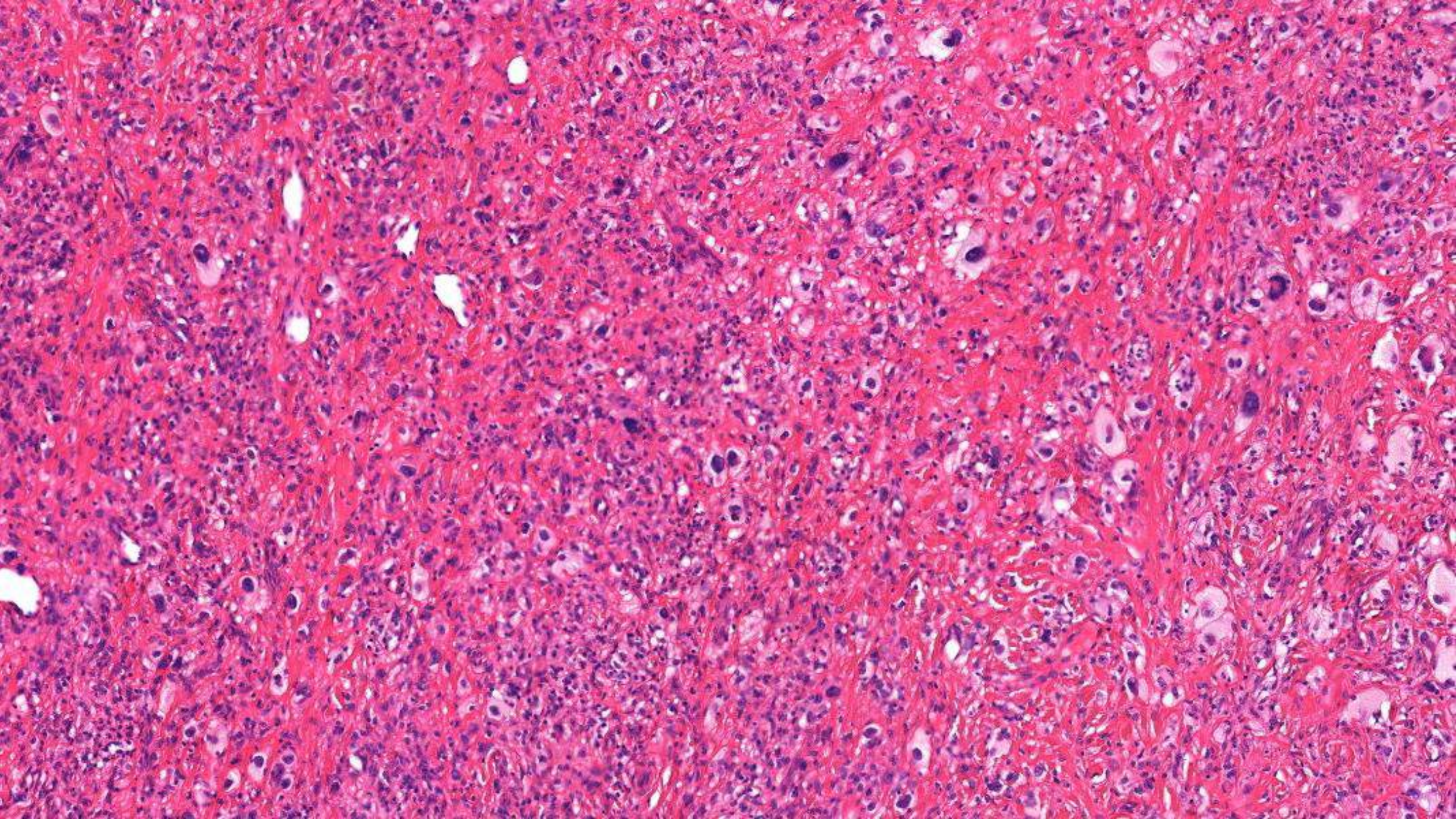
Kaddu S et al. Atypical fibrous histiocytoma of the skin: clinicopathologic analysis of 59 cases with evidence of infrequent metastasis. Am J Surg Pathol. 2002 Jan;26(1):35-46.

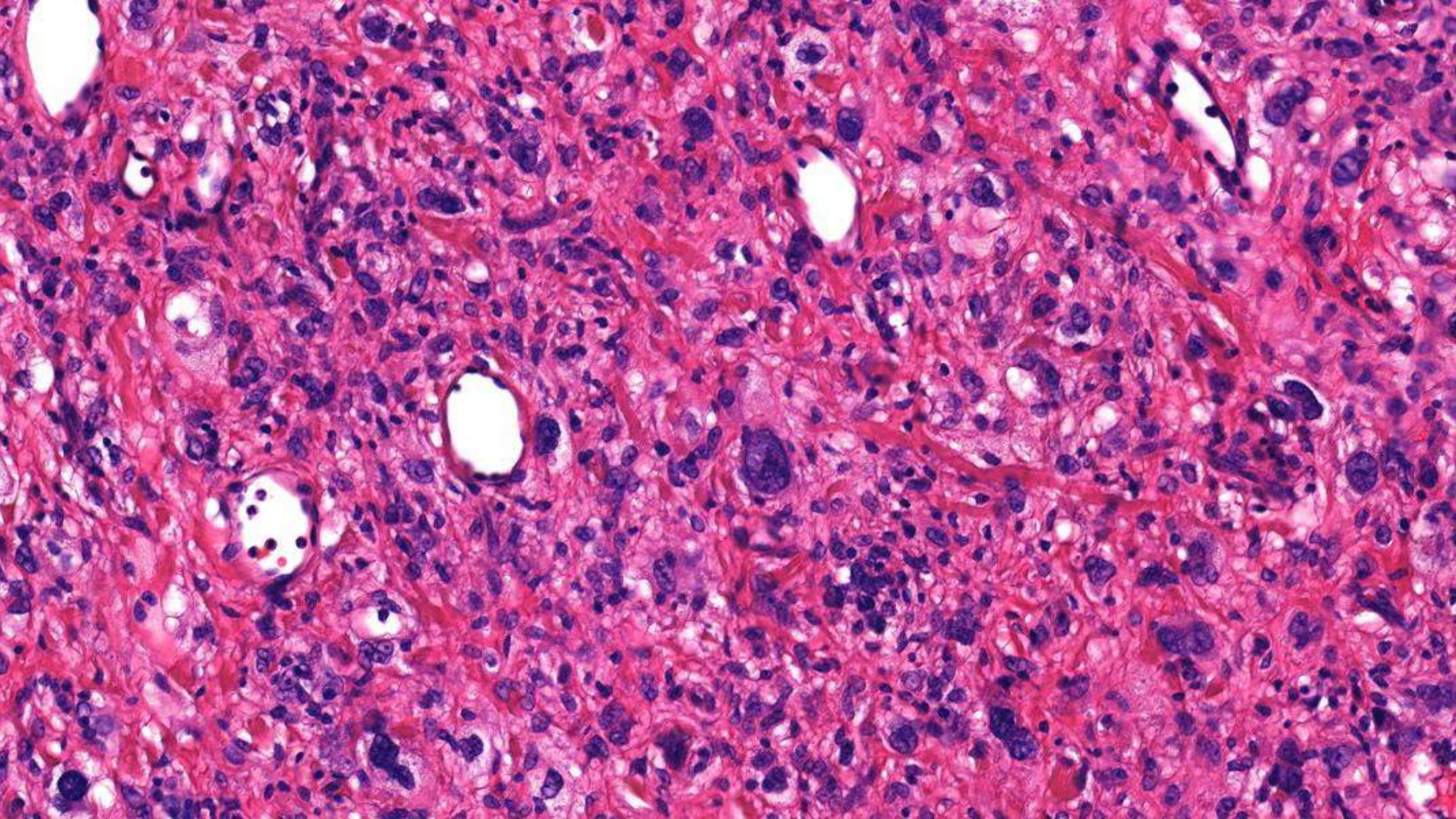
Histological variants of Fibrous histiocytoma (dermatofibroma)

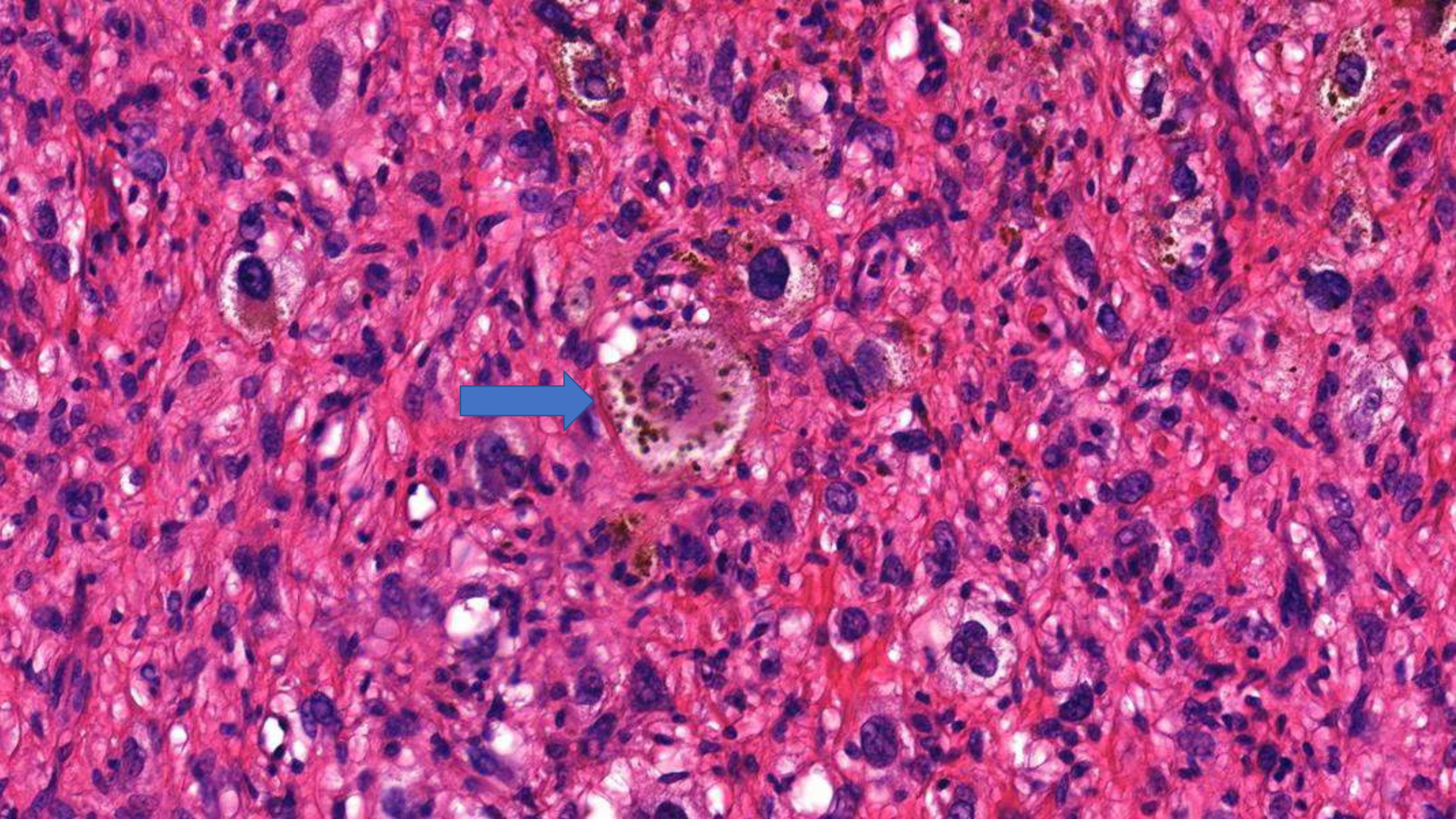
- Cellular
- Aneurysmal
- Atypical (pseudosarcomatous)
- Lipidised (ankle-type)
- Atrophic
- Clear cell
- Granular cell
- Lichenoid
- Palisaded
- Keloidal

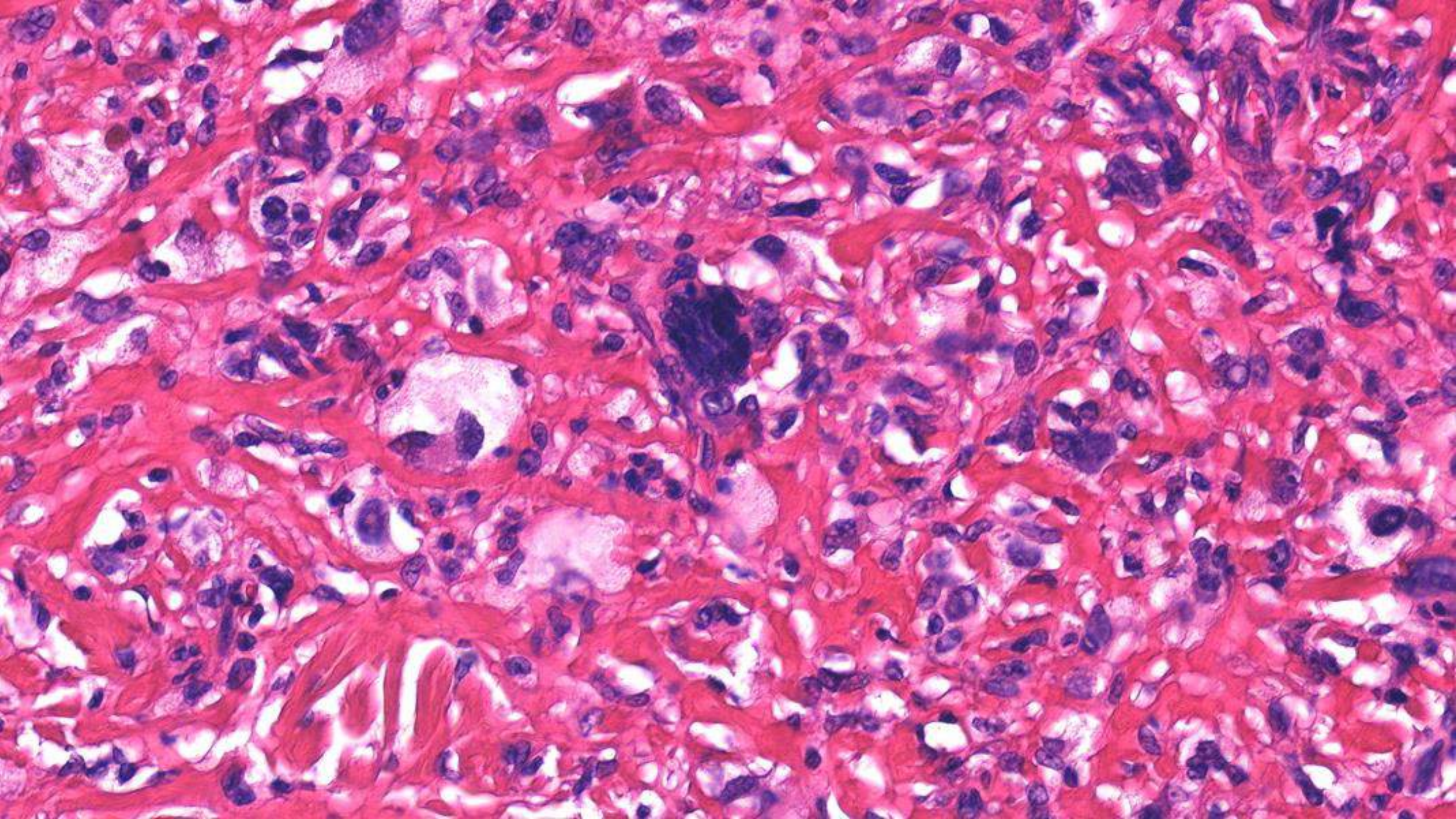
Tendency for local recurrence and exceptional metastatic spread

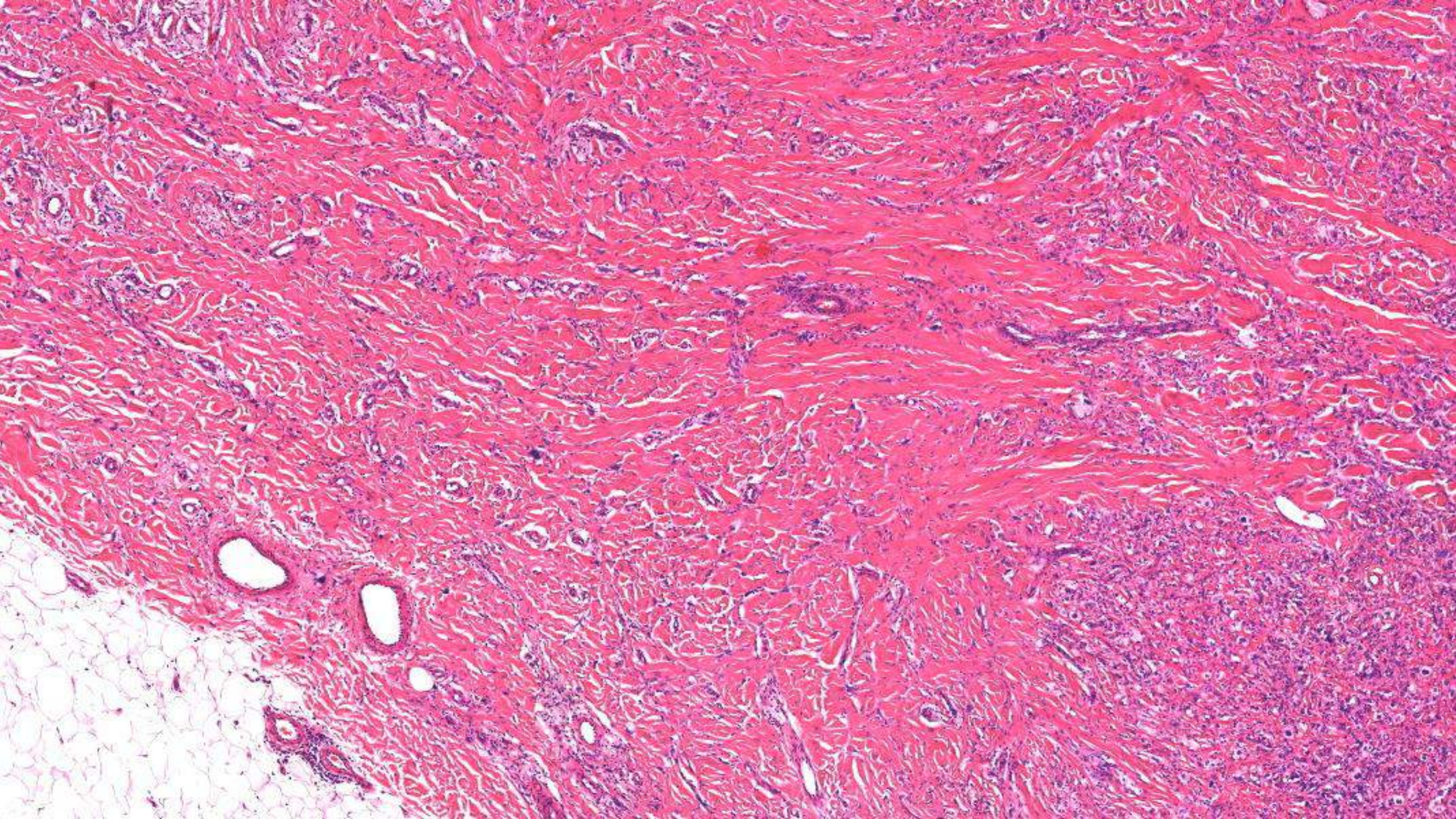


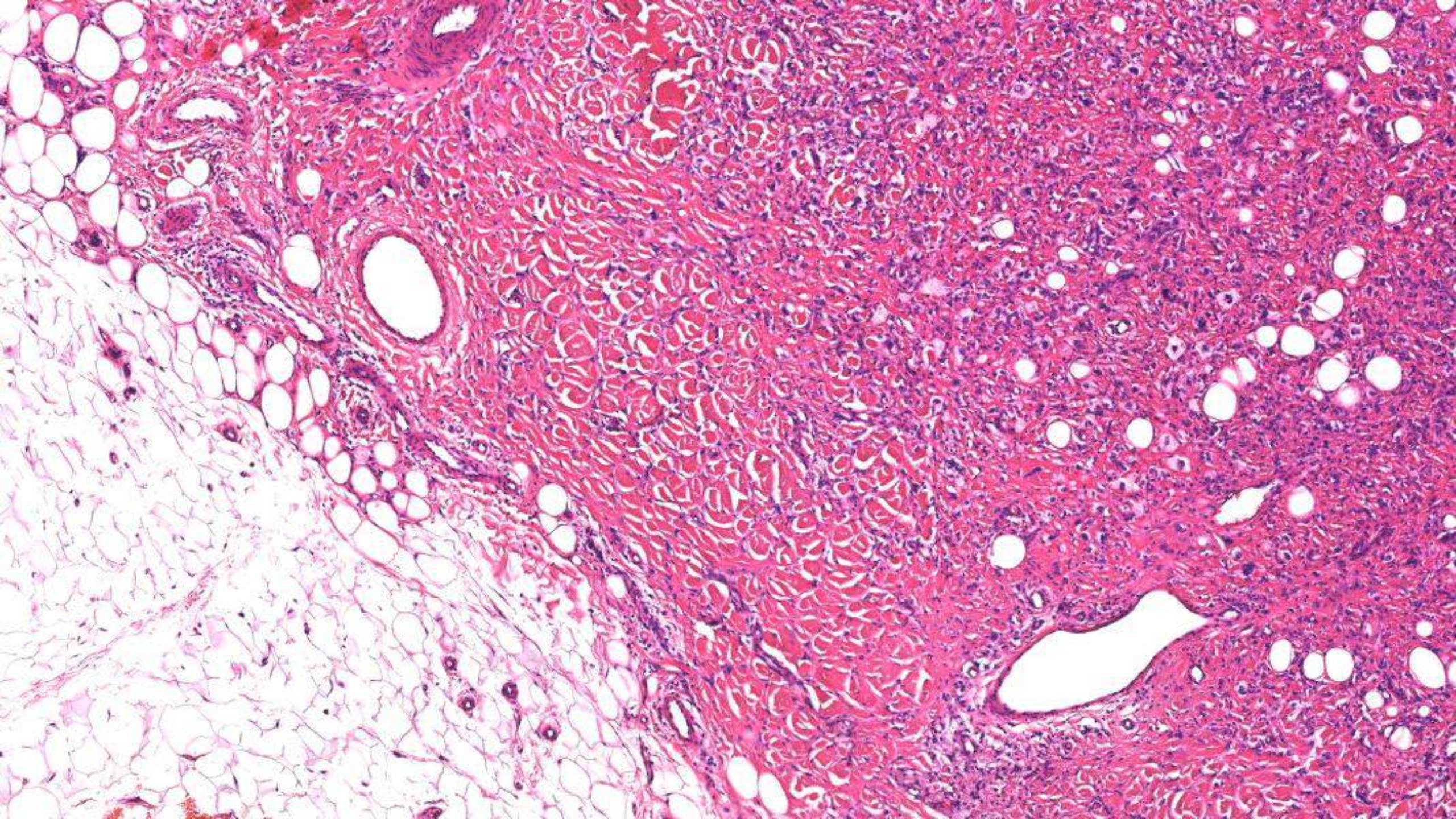


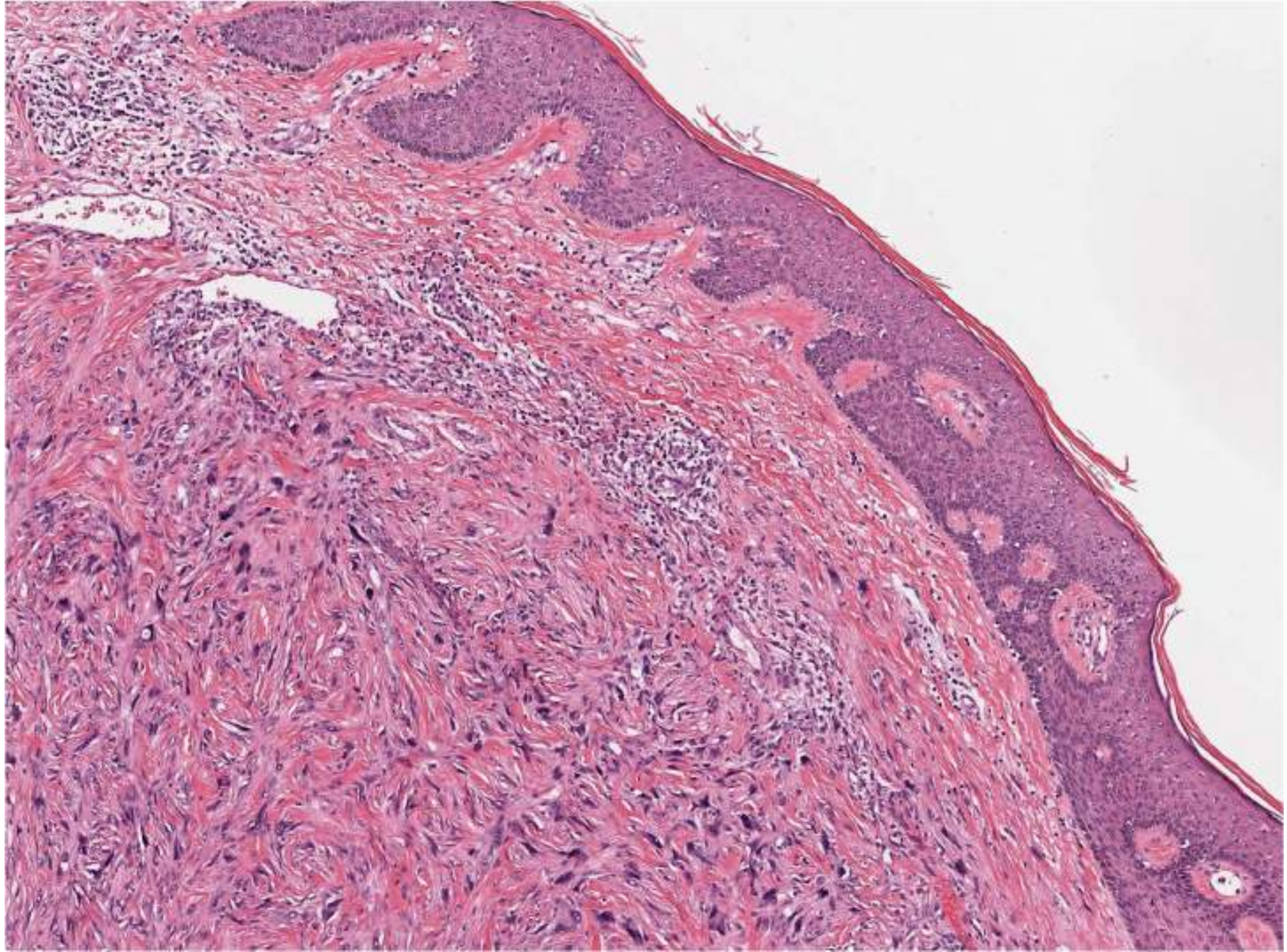


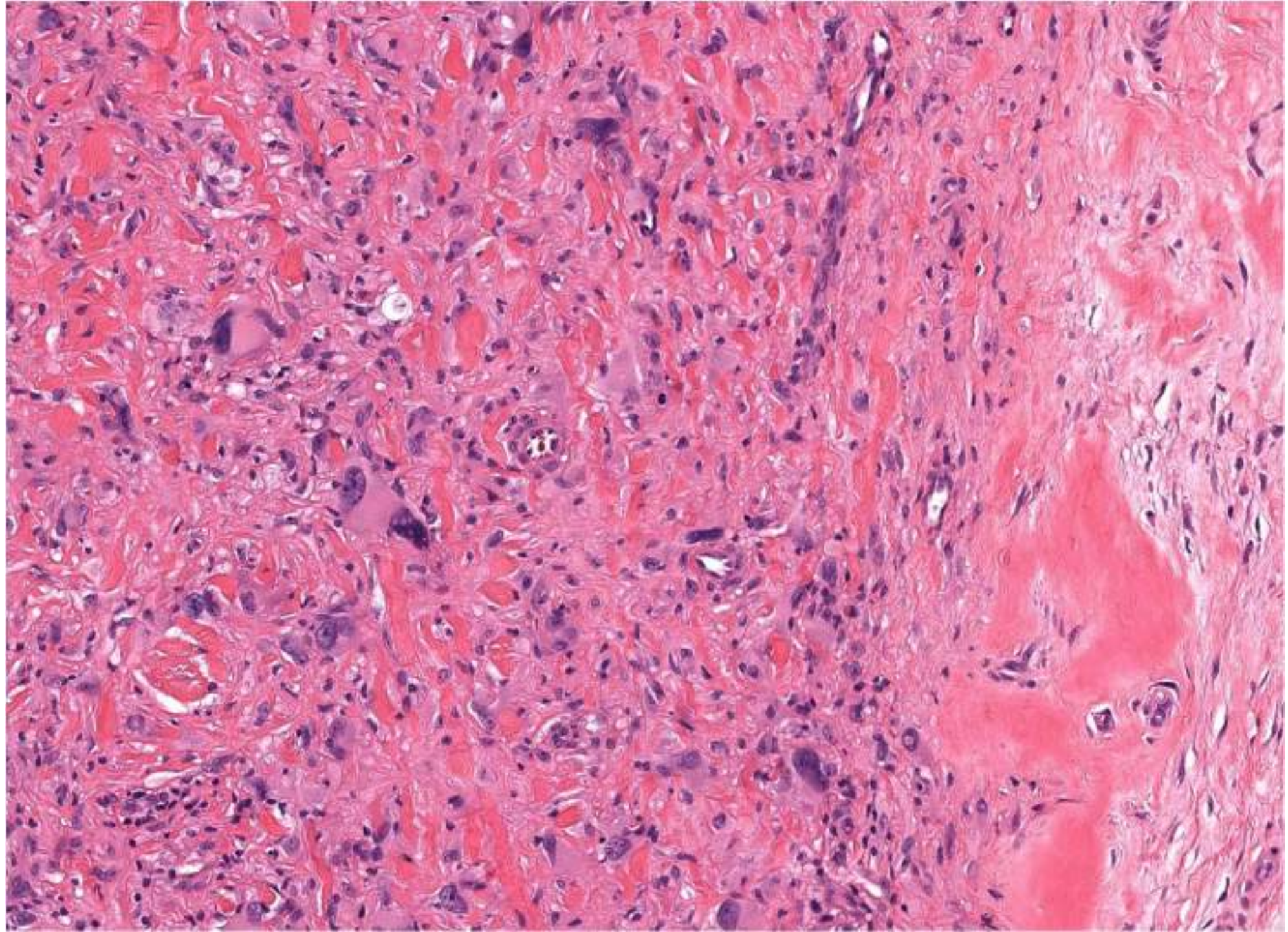


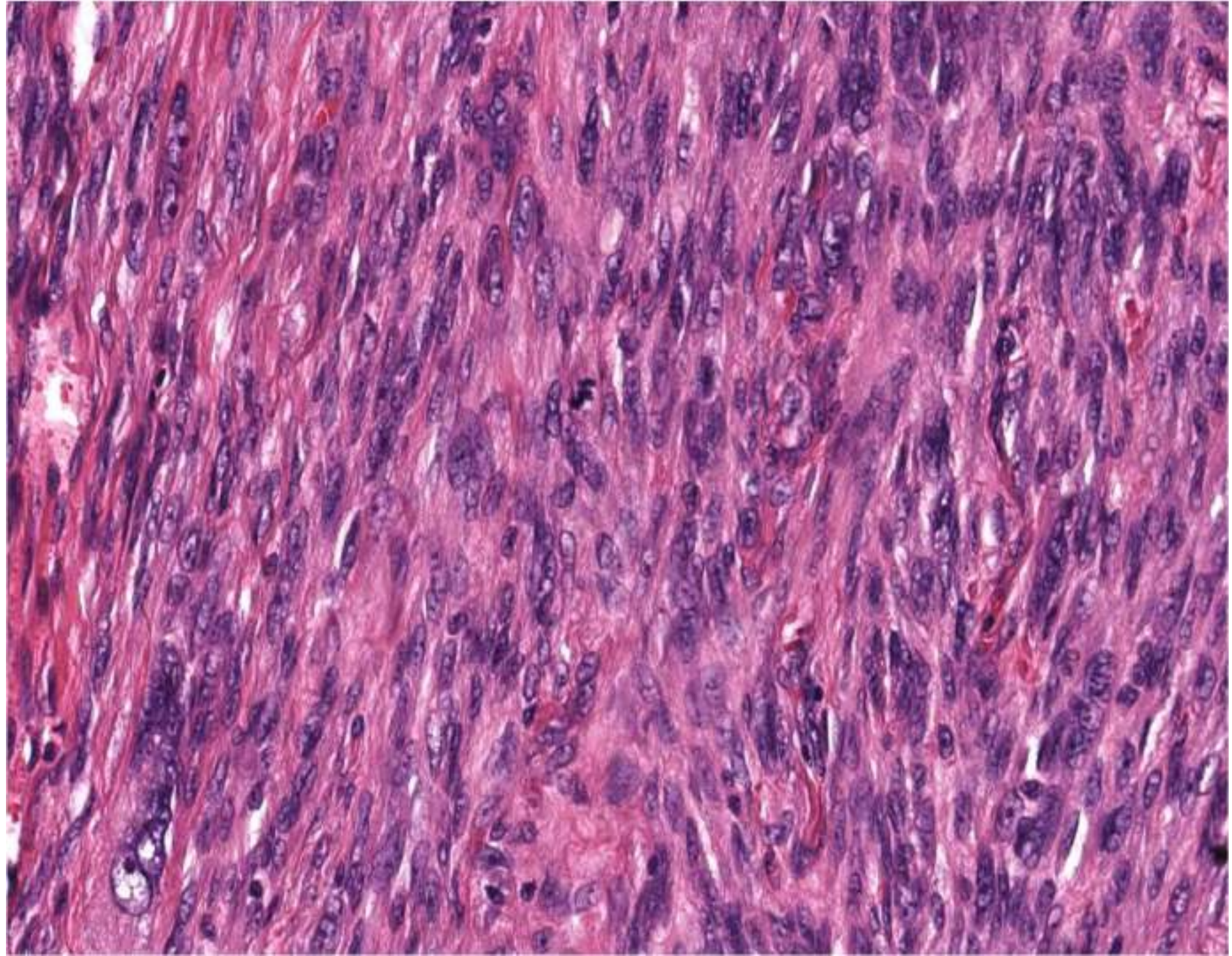












Immunohistochemistry

Positive

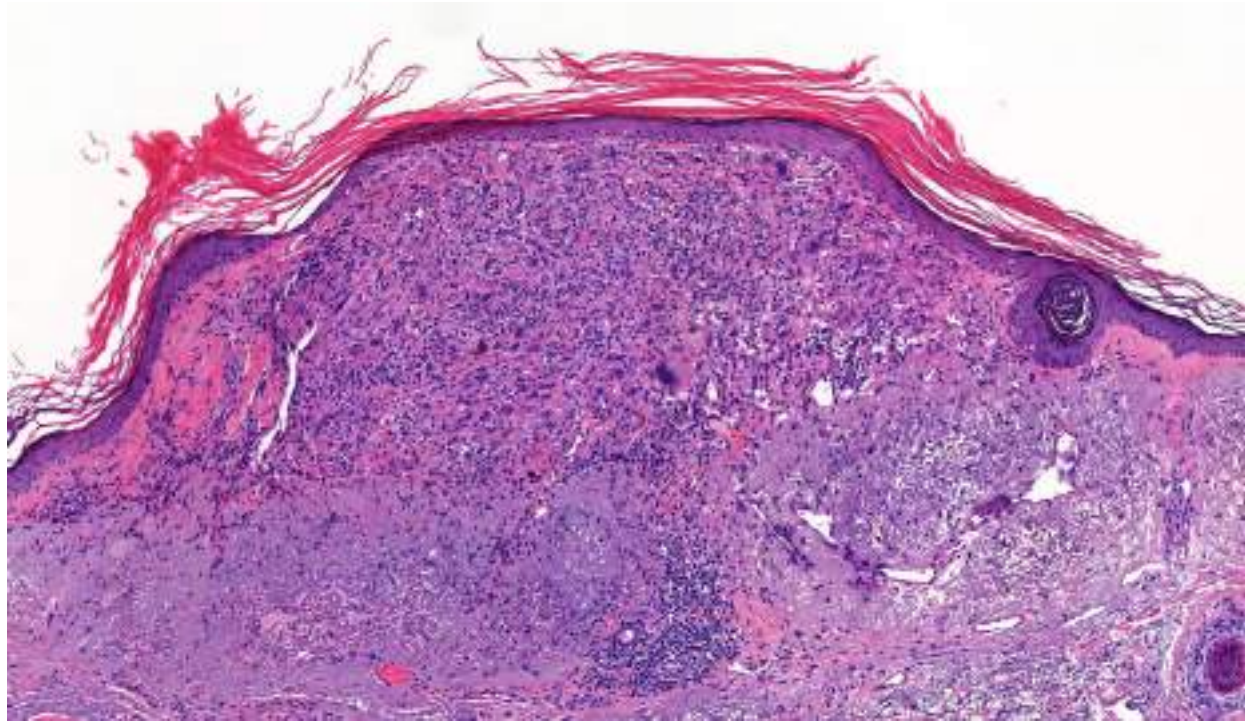
- Focally + for SMA

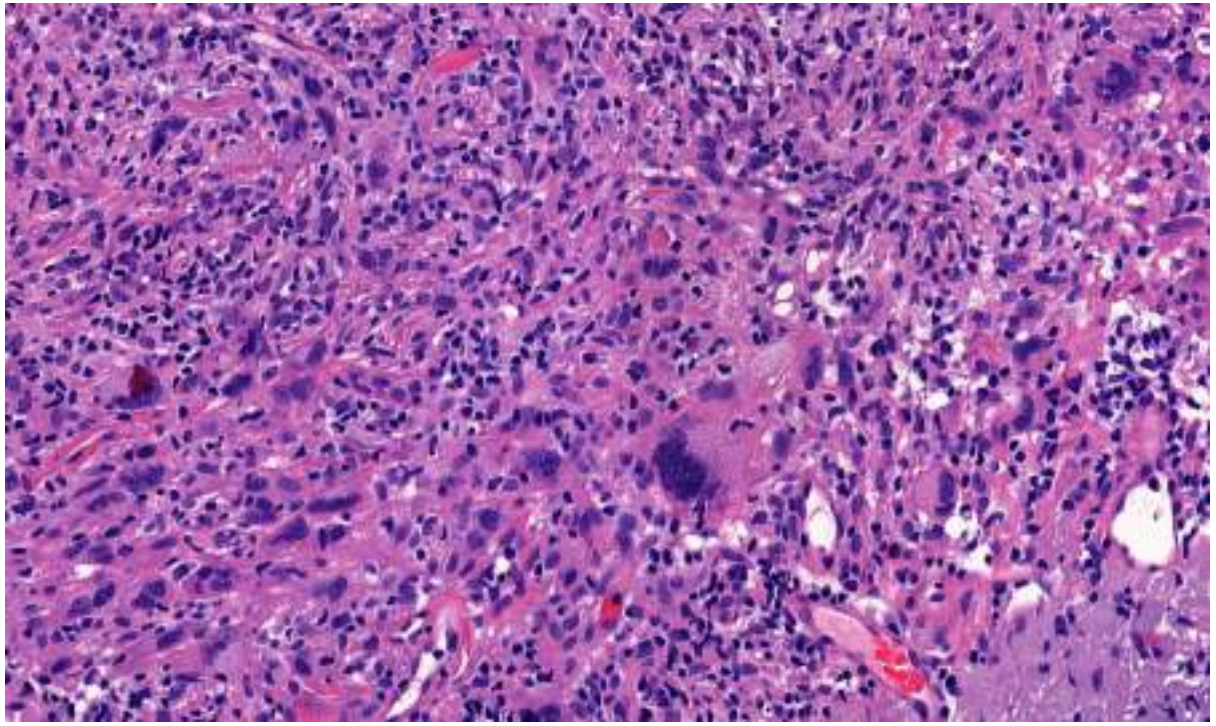
Negative

- Desmin
- CK
- CD31
- CD68
- EMA

Differential diagnosis

Atypical fibroxanthoma (AFX)





Histopathology

Histopathology 2024, 85, 939–949. DOI: 10.1111/his.15282

Clinicopathologic and molecular study of superficial CD34-positive fibroblastic tumours mimicking atypical fibrous histiocytoma (dermatofibroma)

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Date of submission 10 April 2024
Accepted for publication 5 July 2024

Wakefield C B, Mertens F, Fletcher C D M & Anderson W J

(2024) *Histopathology* 85, 939–949. https://doi.org/10.1111/his.15282

Clinicopathologic and molecular study of superficial CD34-positive fibroblastic tumours mimicking atypical fibrous histiocytoma (dermatofibroma)

Aims: Superficial CD34-positive fibroblastic tumour (SCD34FT) is an uncommon but distinctive low-grade neoplasm of the skin and subcutis that shows frequent CADM3 expression by immunohistochemistry (IHC). In this study, prompted by an index case resembling 'atypical fibrous histiocytoma (FH)' that was positive for CADM3 IHC, we systematically examined a cohort of tumours previously diagnosed as 'atypical FH' by applying CADM3 and fluorescence *in situ* hybridization (FISH) for *PRDM10* rearrangement, to investigate the overlap between these tumour types.

Methods and Results: Forty cases of atypical FH were retrieved, including CD34-positive tumours ($n = 20$) and CD34-negative tumours ($n = 20$). All tumours were stained for CADM3. All CADM3-positive tumours were evaluated by FISH to assess for *PRDM10* rearrangement. Eleven CD34-positive tumours (11/20, 55%) coexpressed CADM3 and were reclassified as SCD34FT. None (0/20) of the CD34-negative atypical FH were CADM3-positive. Reclassified SCD34FT (10/11) arose on the lower extremity, with frequent involvement of the thigh ($n = 8$). Features suggestive of atypical FH were observed in many reclassified cases including variable cellularity, spindled morphology, infiltrative tumour margins, collagen entrapment, epidermal hyperpigmentation, and acanthosis. Variably prominent multinucleate giant cells, including Touton-like forms, were also present. An informative FISH result was obtained in 10/11 reclassified tumours, with 60% (6/10) demonstrating *PRDM10* rearrangement.

Conclusion: A significant subset of tumours that histologically resemble atypical FH, and are positive for CD34, coexpress CADM3 and harbour *PRDM10* rearrangement, supporting their reclassification as SCD34FT. Awareness of this morphologic overlap and the application of CADM3 IHC can aid the distinction between SCD34FT and atypical FH.

Keywords: CADM3, fibrous histiocytoma, immunohistochemistry, pleomorphic, PRDM10, sarcoma, soft tissue, superficial CD34-positive fibroblastic tumour

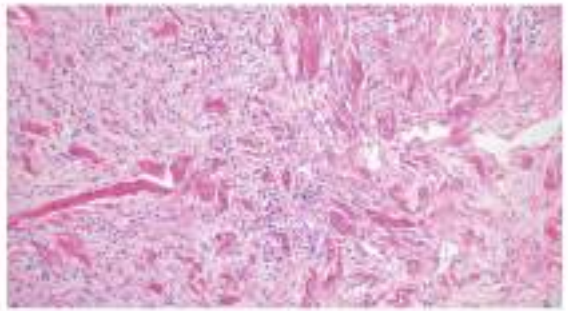


Figure 2. Entrapment of hyalinised collagen bundles was frequently observed at the advancing edge of superficial CD34-positive fibroblastic tumours mimicking atypical FH. This tumour also demonstrated areas of low-grade nuclear atypia.

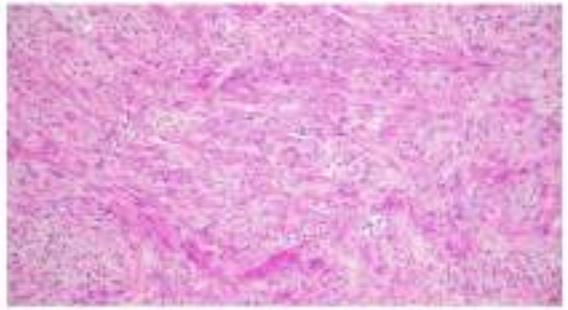


Figure 3. Spindle cell-predominant superficial CD34-positive fibroblastic tumour in which the tumour cells demonstrate uniform low-grade atypia. [Colour figure can be viewed at wileyonlinelibrary.com]

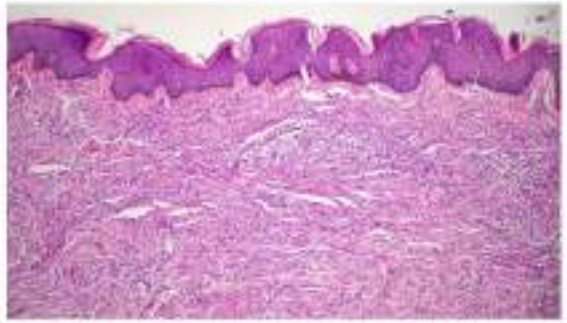


Figure 4. In this superficial CD34-positive fibroblastic tumour, there is extension into the superficial dermis. Many of the superficial dermal tumours elicited reactive epidermal changes. Note the acanthosis and basal hyperpigmentation. [Colour figure can be viewed at wileyonlinelibrary.com]

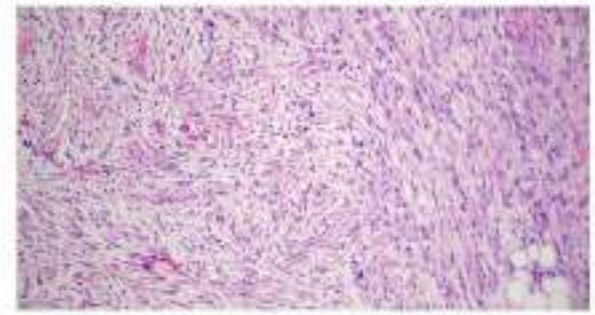


Figure 5. Some of the superficial CD34-positive fibroblastic tumours demonstrated focally myxoid stroma and areas that were less densely cellular. [Colour figure can be viewed at wileyonlinelibrary.com]

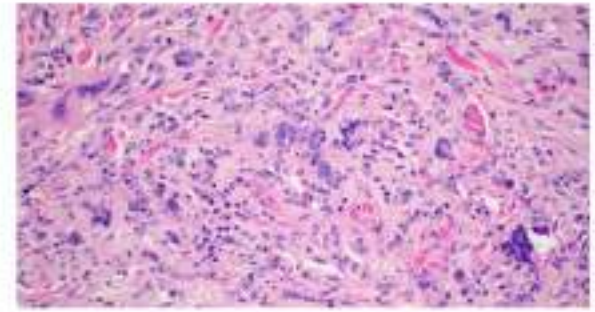
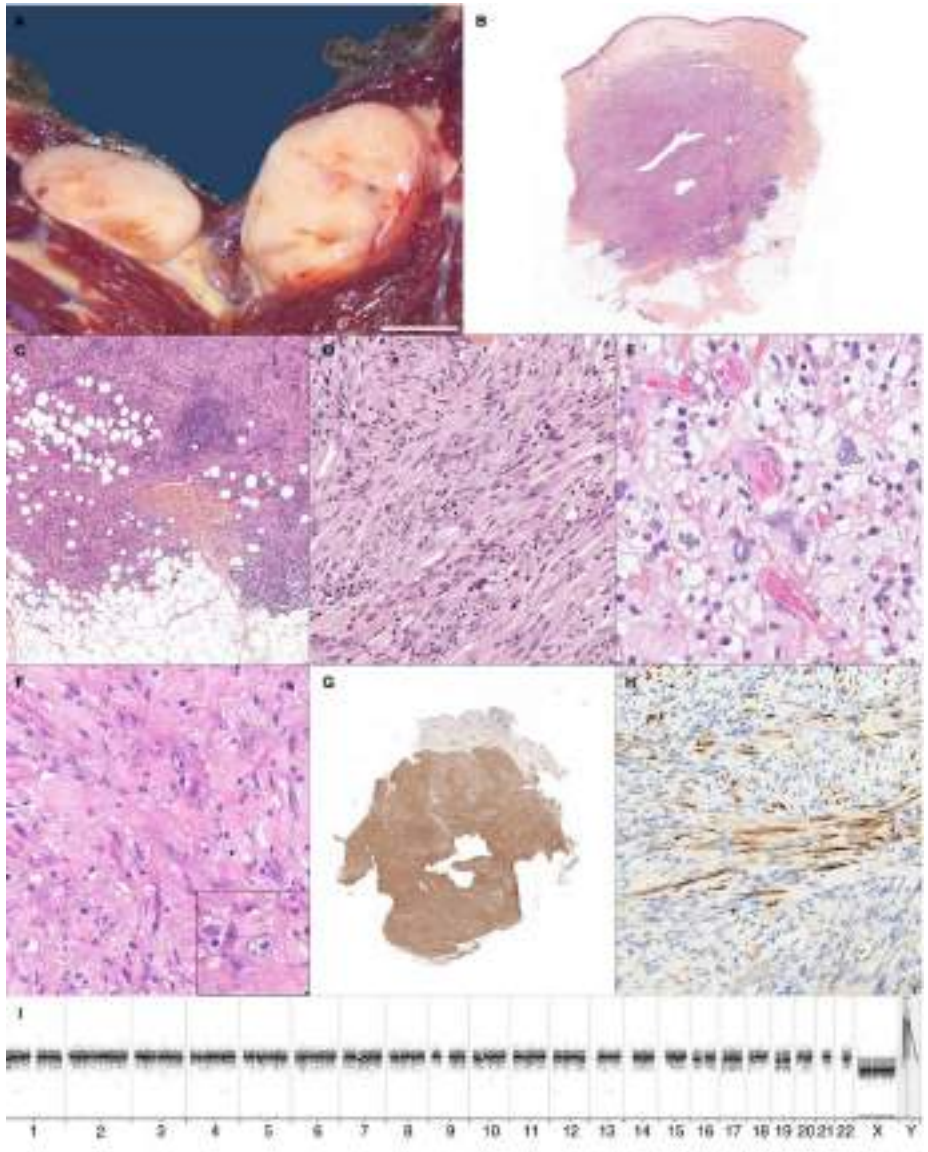


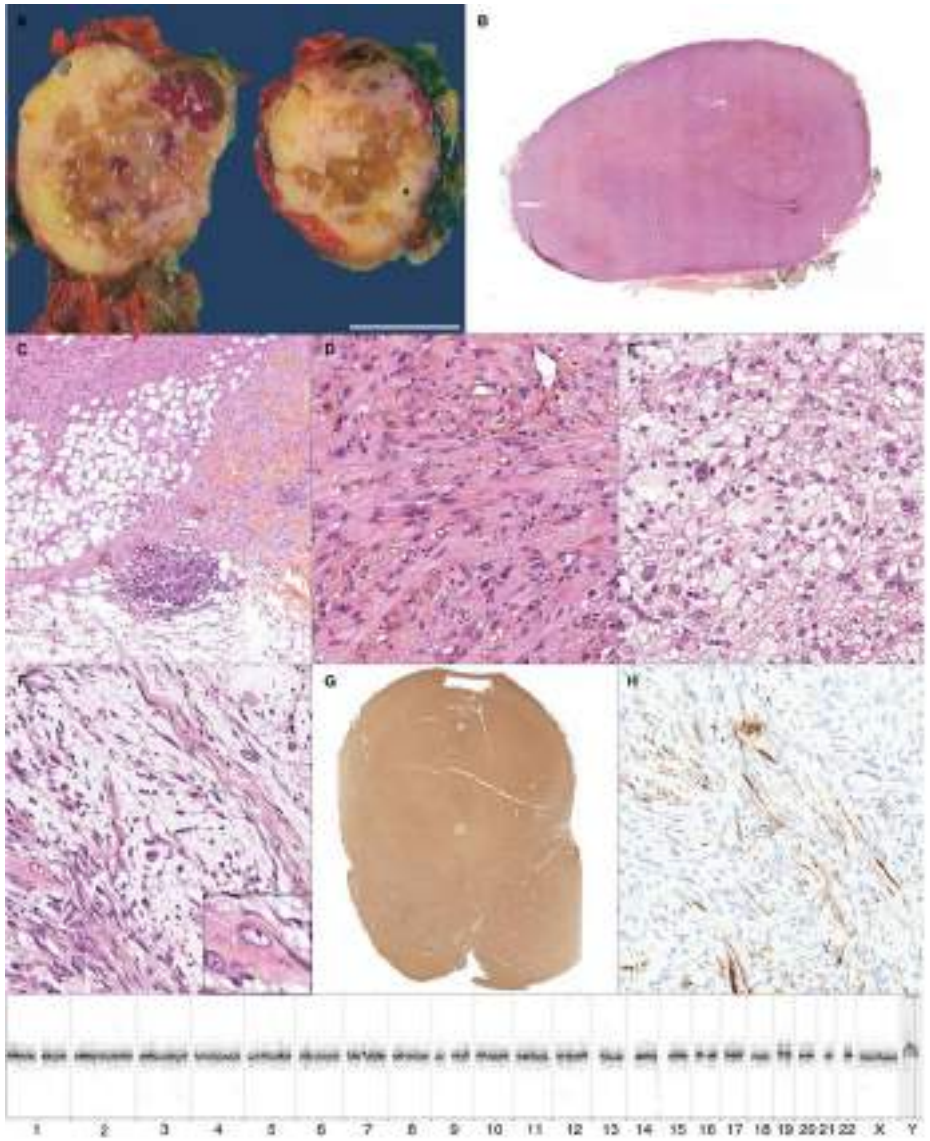
Figure 6. Multinucleate giant cells, including occasional forms with Touton-like morphology, were observed in two superficial CD34-positive fibroblastic tumours. [Colour figure can be viewed at wileyonlinelibrary.com]

Figure 7. CADM1 positivity in the index case (shown) prompted assessment of tumours previously diagnosed as 'atypical FH'. Expression in superficial CD34-positive fibroblastic tumour is often strong and diffuse. [Colour figure can be viewed at wileyonlinelibrary.com]

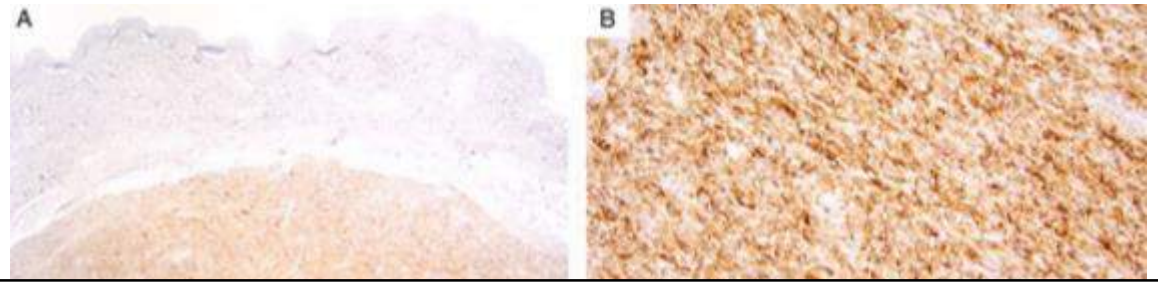
SCD34FT



PRDM10-STT



Perret R et al: Superficial CD34-positive fibroblastic tumor and PRDM10-rearranged soft tissue tumor are overlapping entities: a comprehensive study of 20 cases. Histopathology. 2021 Nov;79(5):810-825.

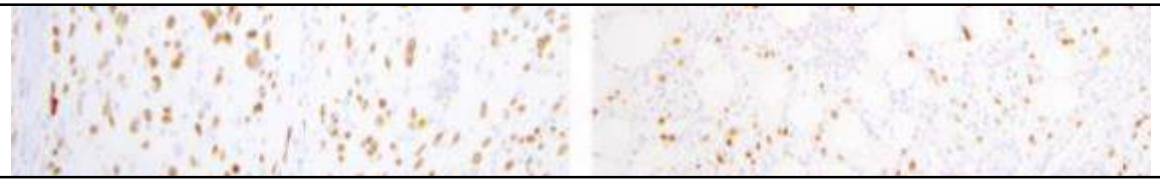


CADM3 in distinguishing SCD34FT from morphologic mimics, while also identifying WT1 as a novel ancillary marker

Finally, like others, we have found no discernable differences between SCD34FT with *PRDM10* rearrangement (that could be regarded as *PRDM10*-STT) and those that lack evidence of this alteration, and therefore concur that these very likely represent a single entity

- SCD34FT was typically diffusely positive and sharply demarcated from the surrounding negatively stained stroma

- WT1 was diffusely positive in 52% of SCD34FT, including all 3 with confirmed *PRDM10* rearrangement



Anderson, William J et al. Superficial CD34-Positive Fibroblastic Tumor: A Clinicopathologic, Immunohistochemical, and Molecular Study of 59 Cases. The American Journal of Surgical Pathology 46(10):p 1329-1339, October 2022.

Superficial CD34-positive fibroblastic tumor: report of 18 cases of a distinctive low-grade mesenchymal neoplasm of intermediate (borderline) malignancy

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Fibroblastic mesenchymal tumors show a spectrum of biological behavior, from benign to fully malignant. We report our experience of two decades with a distinctive, previously undescribed low-grade fibroblastic tumor of the superficial soft tissues. Eighteen cases were identified within our consultation files, previously coded as 'low-grade sarcoma, not further classified' and 'indolent fibrous histiocytoma, low grade'. The tumors occurred in adults

Superficial CD34-positive fibroblastic tumour: a clinicopathological and immunohistochemical study of an additional series.

Author information

Abstract

AIMS: To describe an additional series of superficial CD34-positive fibroblastic tumour, a newly described neoplasm, in order to enhance the recognition of an emerging novel entity.

METHODS AND RESULTS: The clinicopathological features and immunophenotypes of 11 cases of superficial CD34-positive fibroblastic tumour were studied. There were eight males and three females, with a median age of 36 years. Tumours occurred in the thigh (n = 4), buttock (n = 3), shoulder (n = 2), upper arm (n = 1), and waist (n = 1). Histologically, all tumours were characterized by relative circumscription, pleomorphic spindled to polygonal cells with variably enlarged blando-appearing cells, intranuclear cytoplasmic pseudoinclusions, and extremely low mitotic activity. Immunohistochemically, neoplastic cells showed diffuse and strong expression of CD34 and focal staining of cytokeratin. Follow-up thus far has revealed an indolent clinical behaviour.

CONCLUSIONS: Superficial CD34-positive fibroblastic tumour represents a new member of the family of cutaneous CD34-positive spindle-cell tumours. Familiarity with its clinicopathological characteristics is helpful in avoiding confusion with a variety of cutaneous mesenchymal tumours with overlapping features.

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KEYWORDS: CD34; fibroblast; immunohistochemistry; intermediate malignancy; skin

Superficial CD34-positive fibroblastic tumour/PRDM10 rearranged soft tissue tumour

CD34-positive fibroblastic tumour/ PRDM10 rearranged soft tissue tumour

Clinical Features

- Painless, slow-growing nodule on the lower extremities
- Size: 1.5-10 cm
- Adults of either sex
- Some risk for local recurrence, but low risk for metastasis
- Treatment: complete surgical excision with negative margins

CD34-positive fibroblastic tumour/ PRDM10 rearranged soft tissue tumour

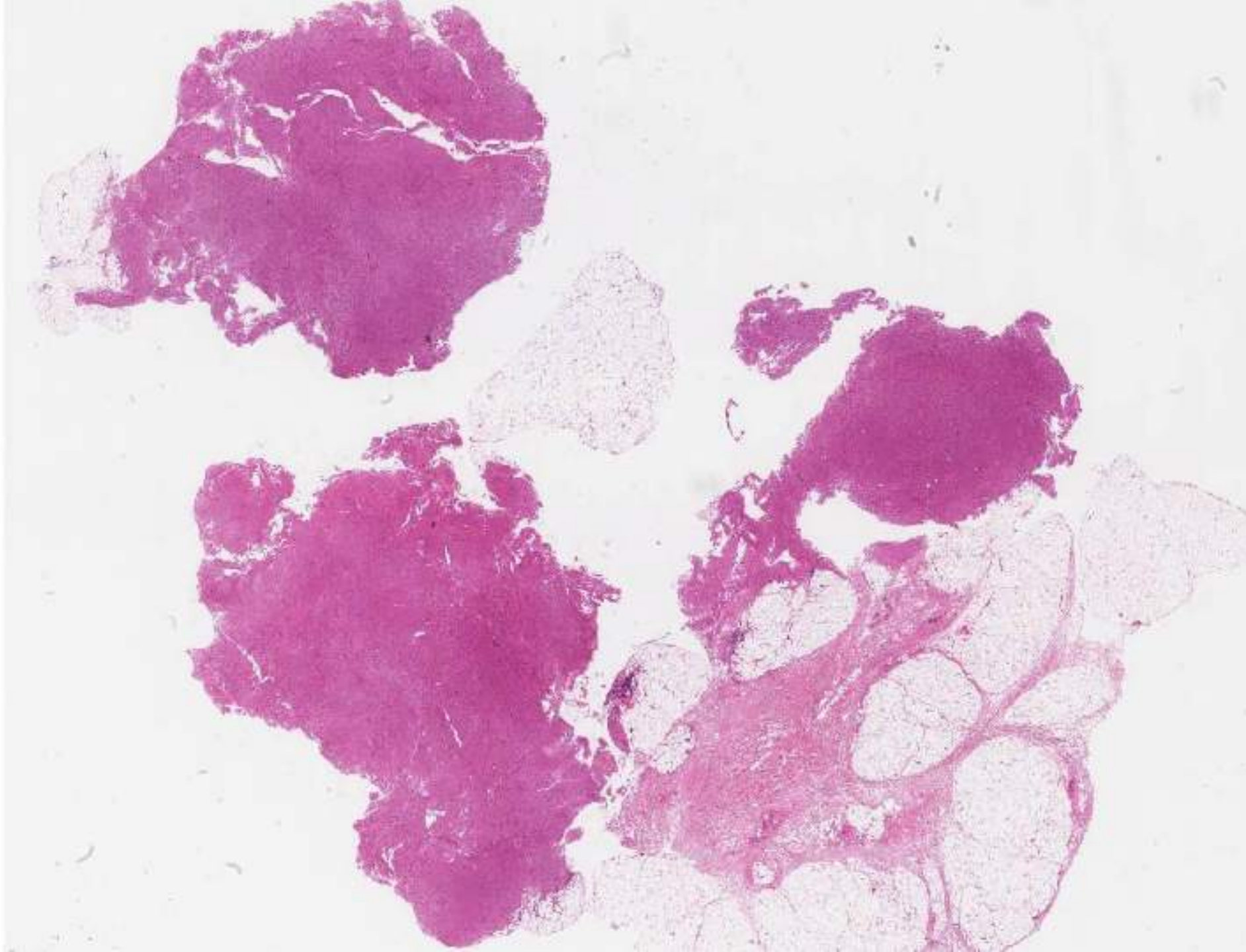
Histological Features

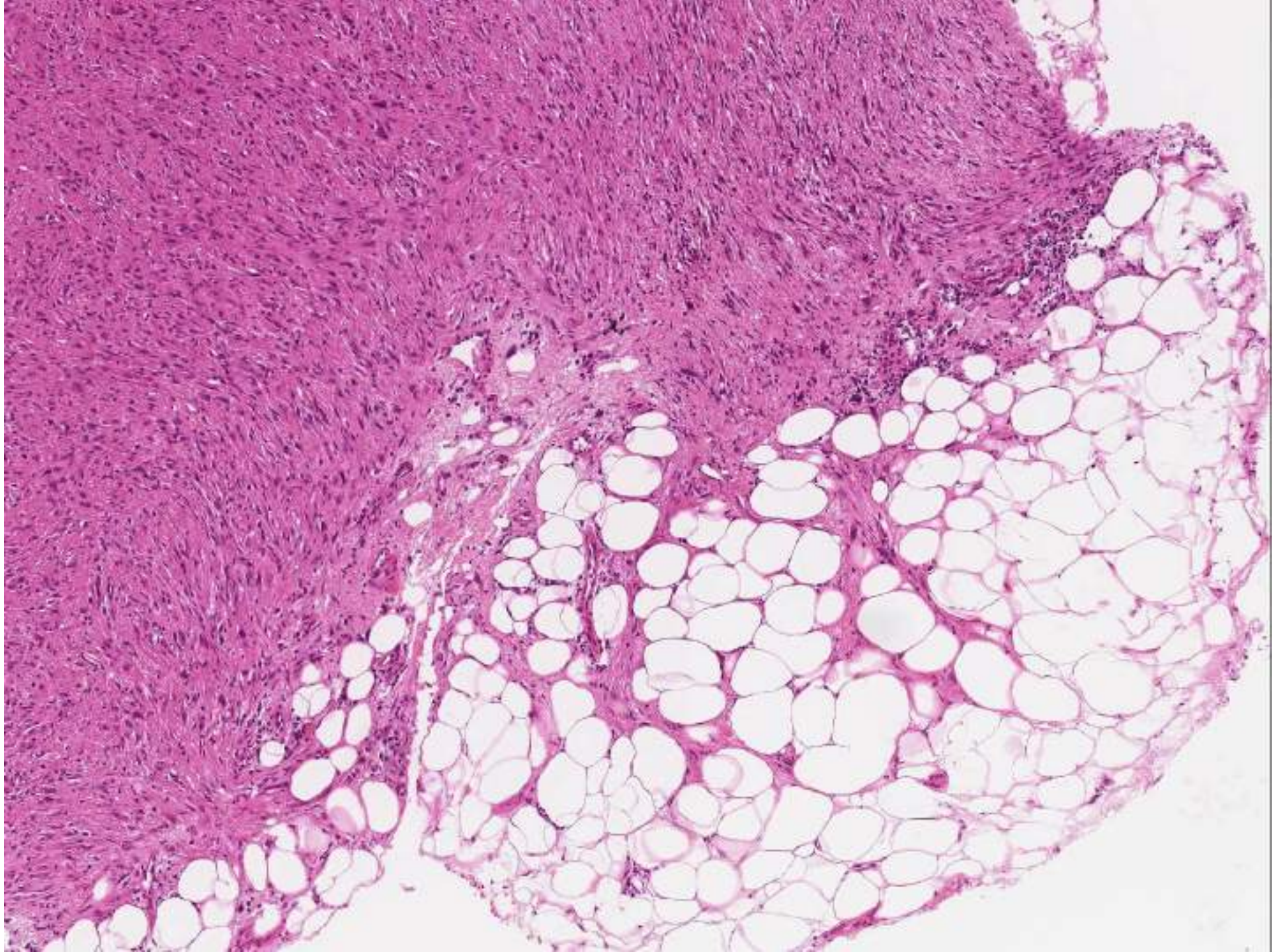
- Deep dermis or superficial subcutis
- Relatively well circumscribed, but infiltration of the subcutis is possible
- Moderately to highly cellular fascicles and sheets of spindled and epithelioid cells
- **Striking pleomorphism**
- Hyperchromatic, bizarre-appearing cells with abundant granular, fibrillary, or glassy cytoplasm; intranuclear cytoplasmic pseudoinclusions
- Arborizing thin-walled capillary-sized vasculature, particularly in areas showing a fascicular growth pattern
- **Very low mitotic activity (<1 per 50 high-power fields)**
- **No necrosis**

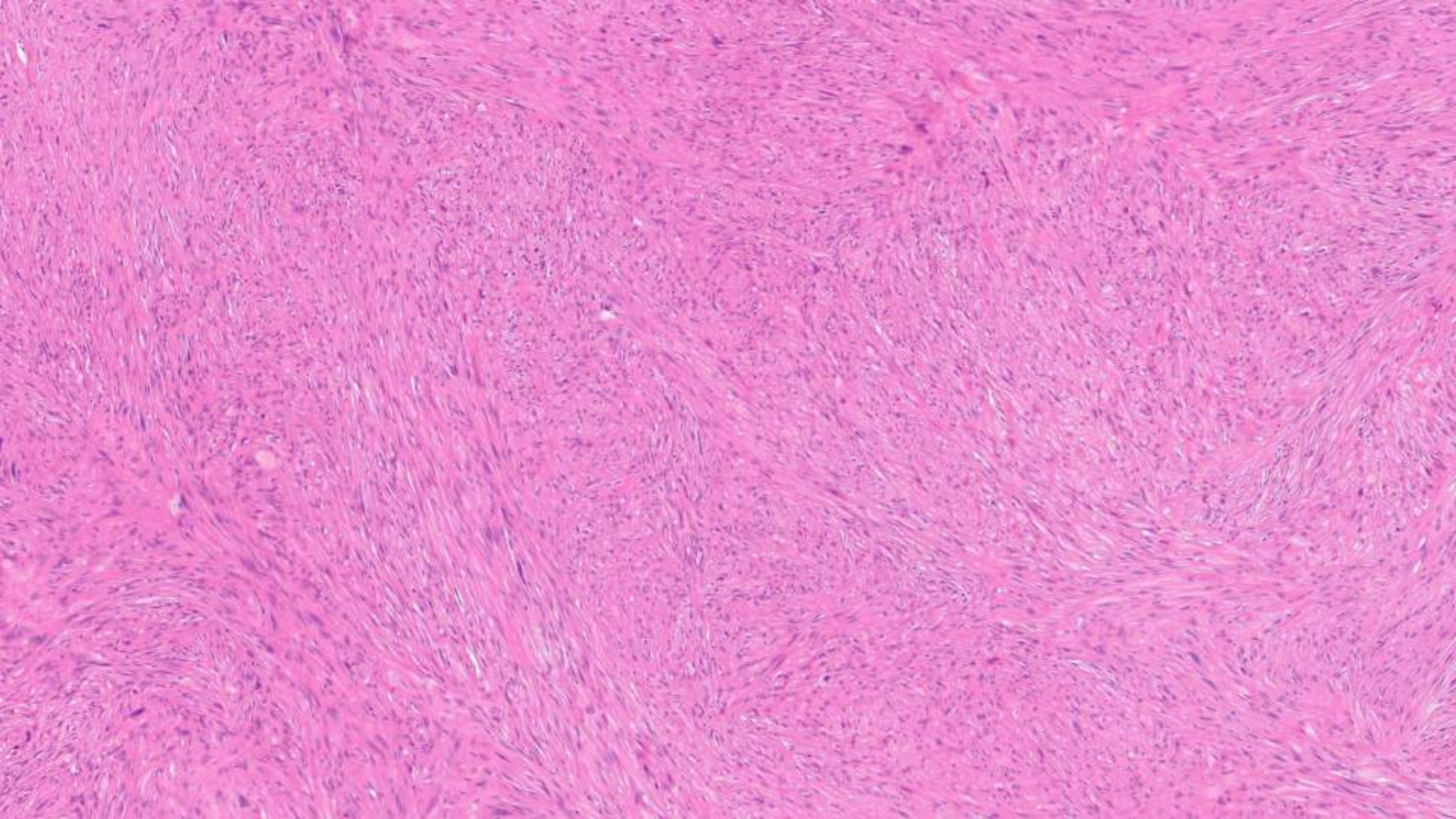
CD34-positive fibroblastic tumour

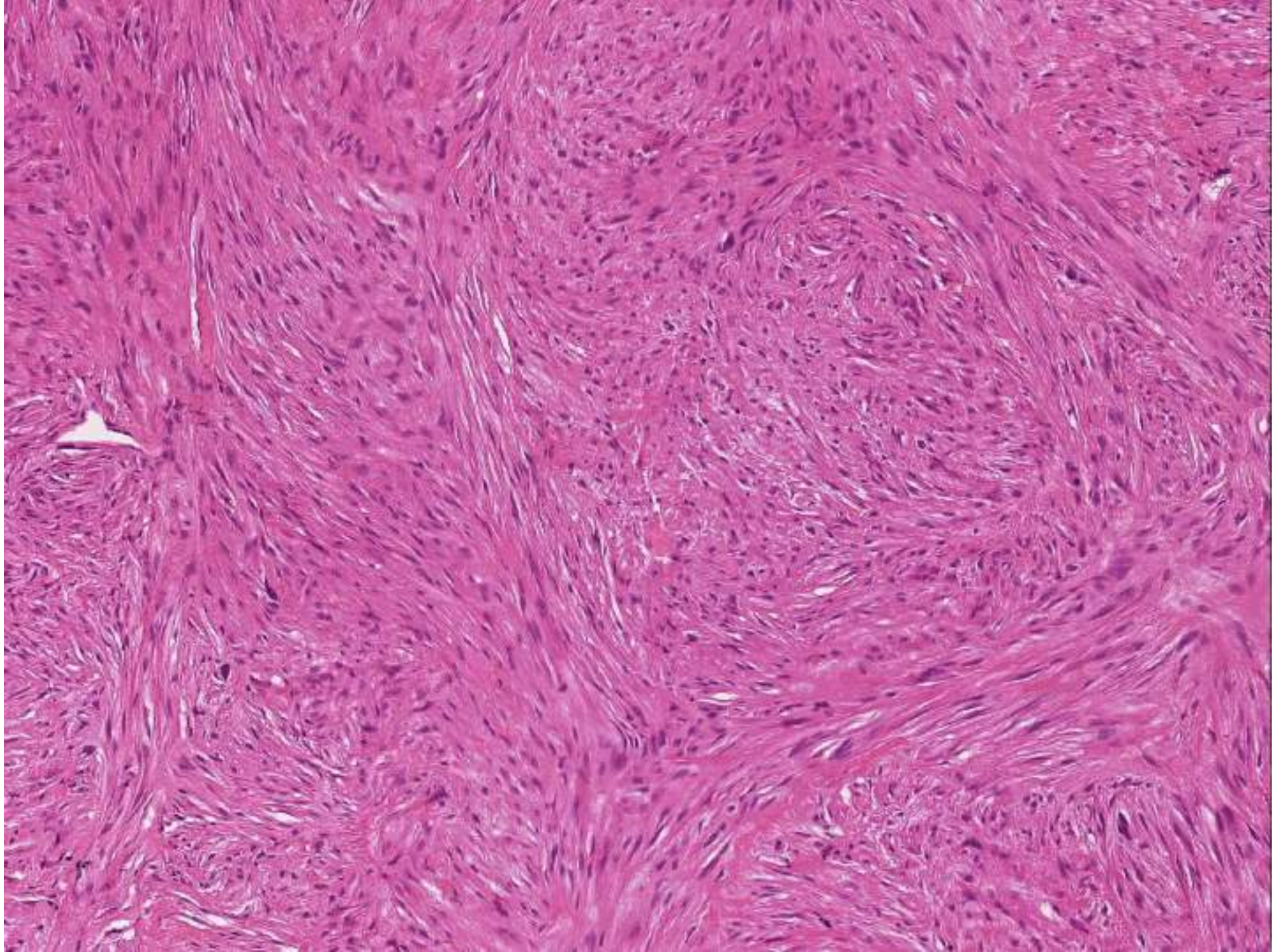
Immunohistochemistry

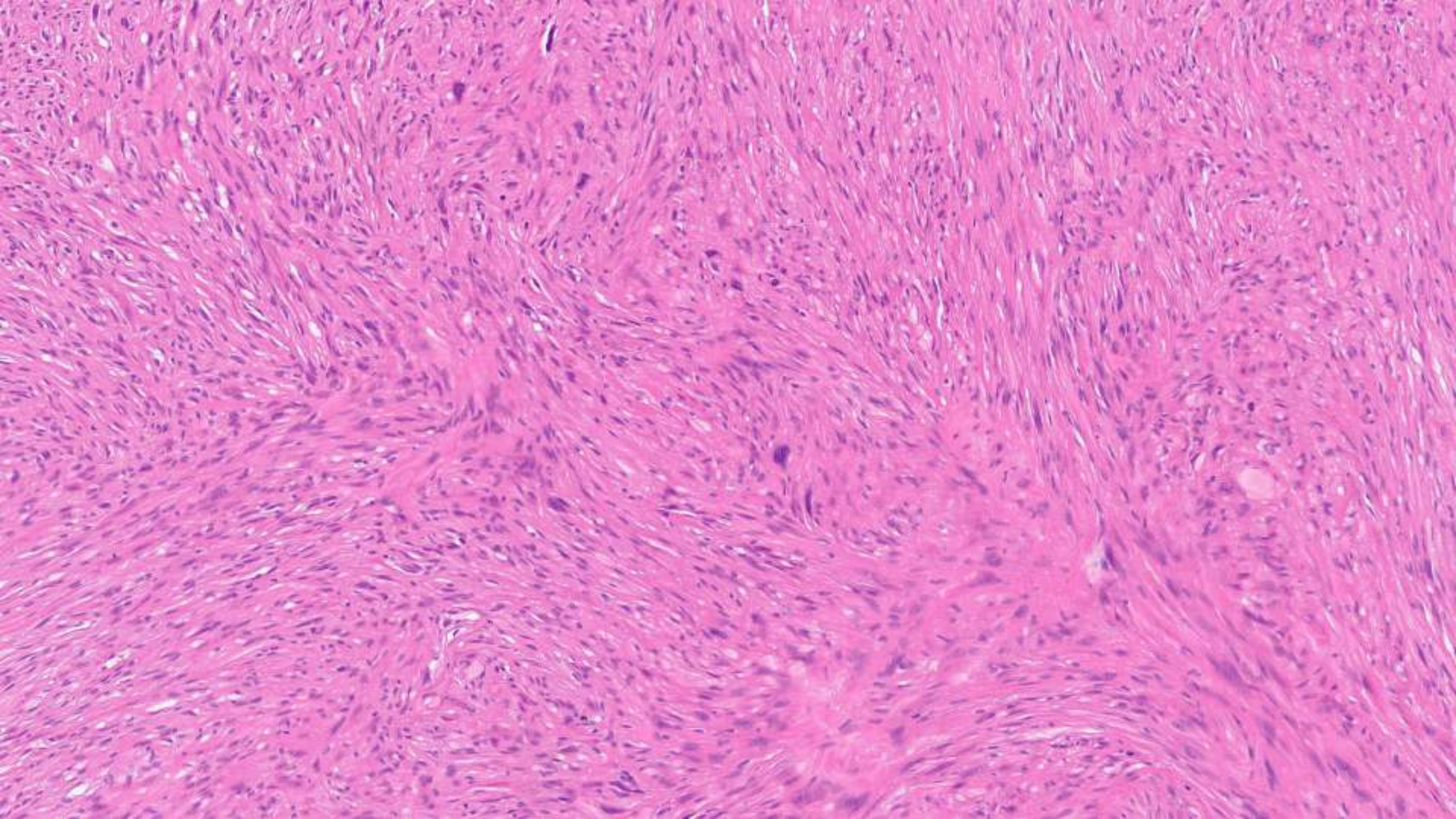
- **Diffuse CD34+**
- Limited expression of cytokeratins (50-69%, AE1/AE3 and CAM5.2)
- Lacked expression of ERG and FLI-1 proteins
- Retained expression of the SMARCB1 tumour suppressor gene product
- S100 protein, desmin, SMA -
- **Ki-67-index is extremely low (1-5% of cells)**

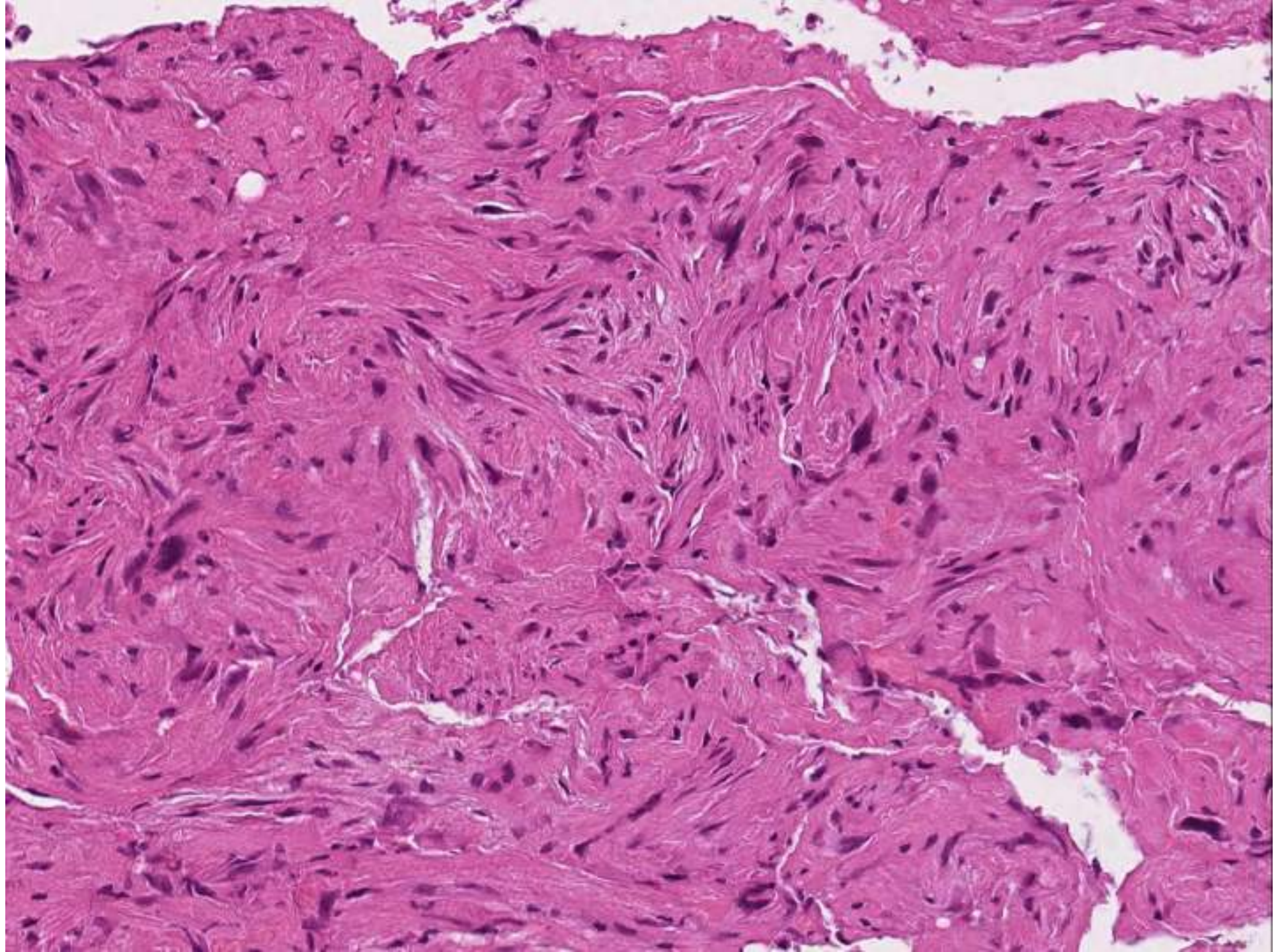


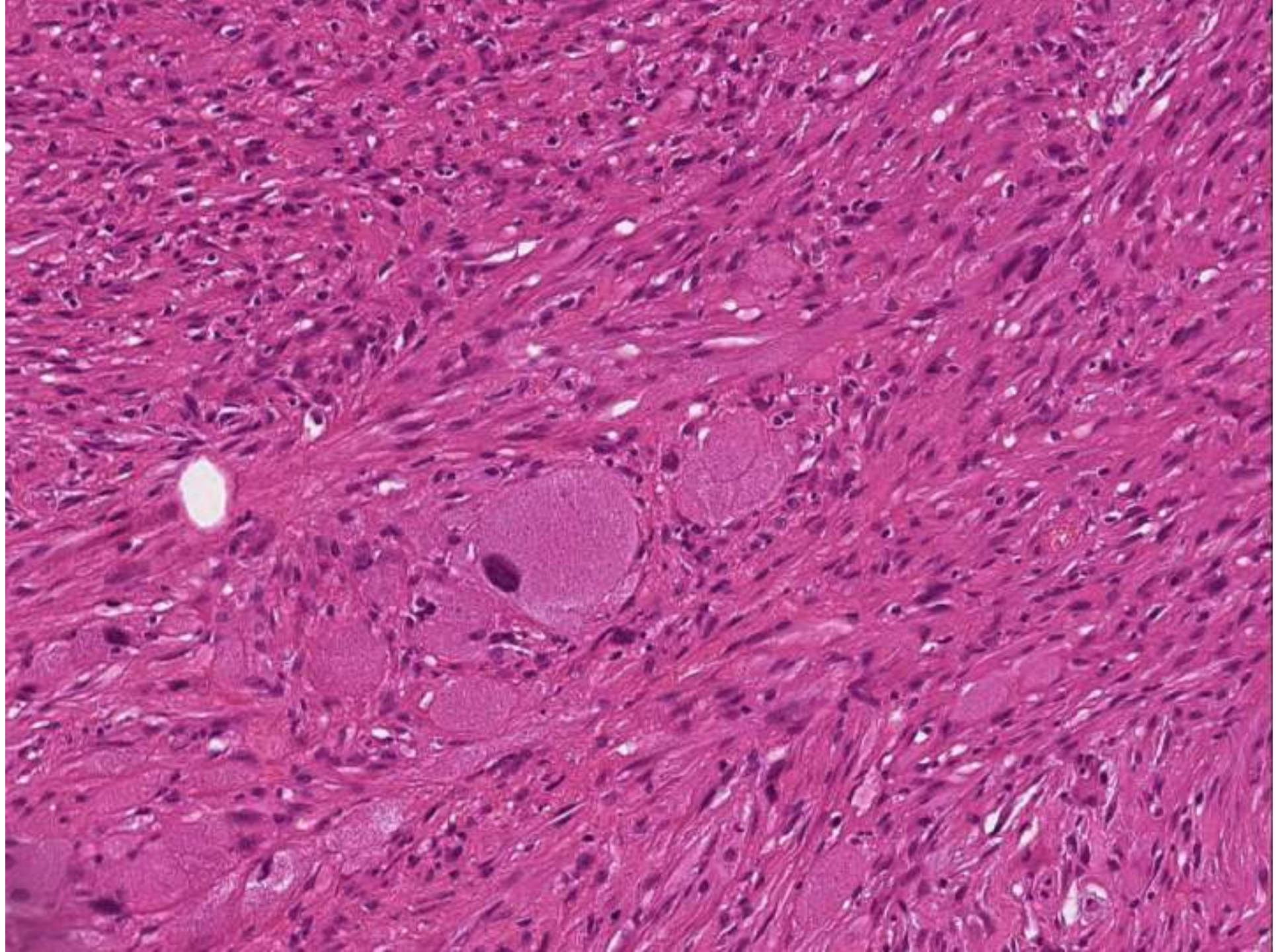


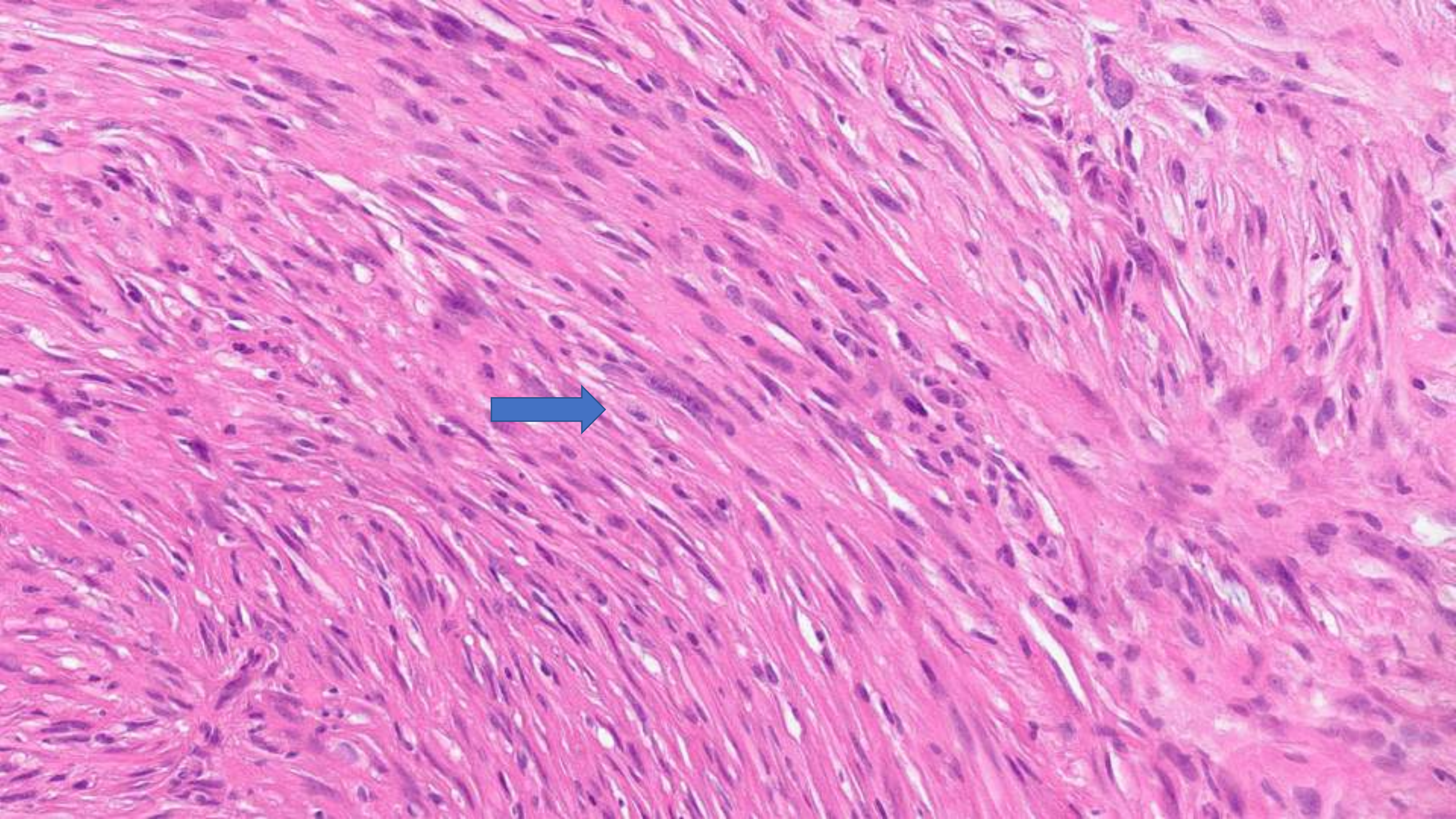


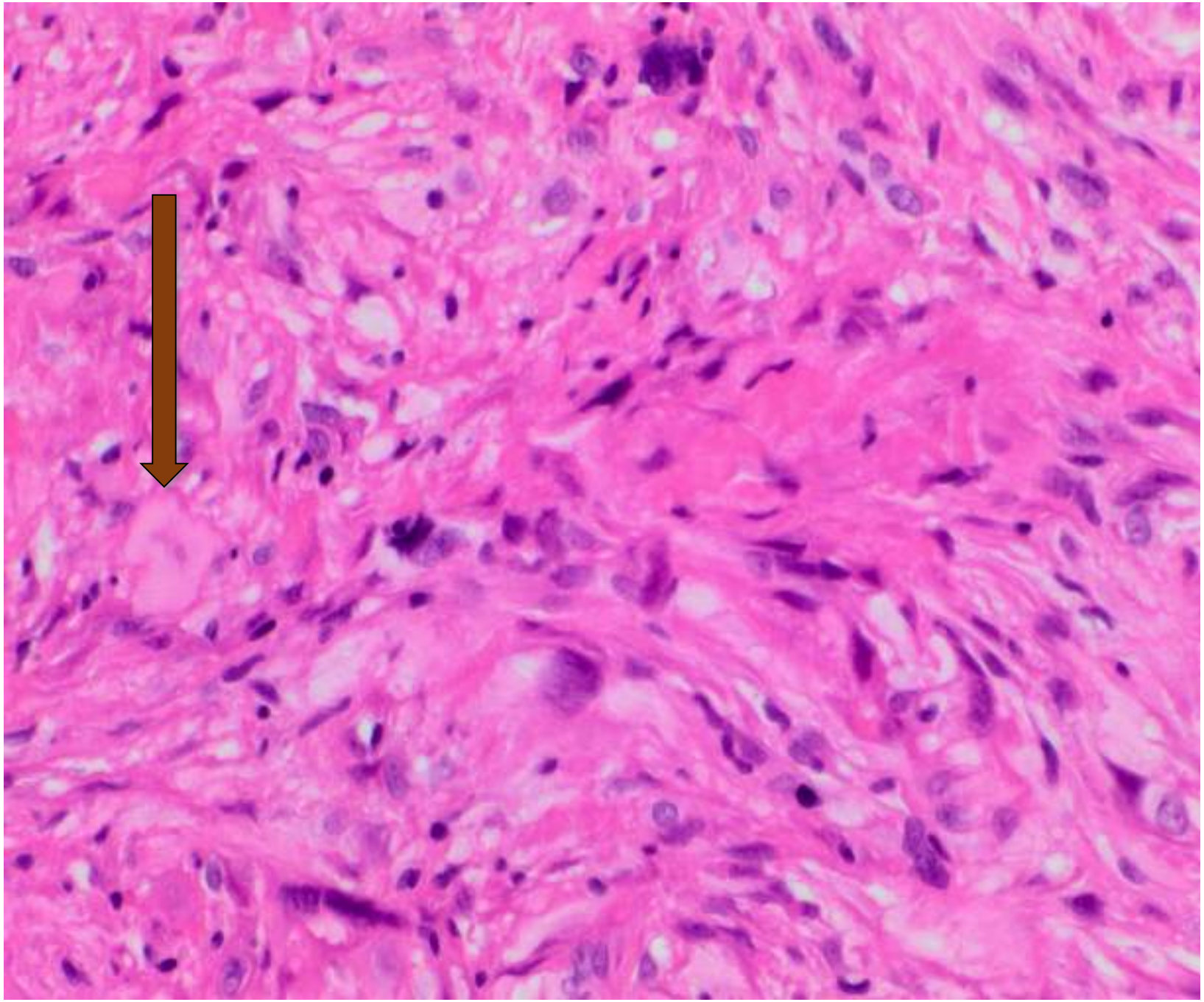


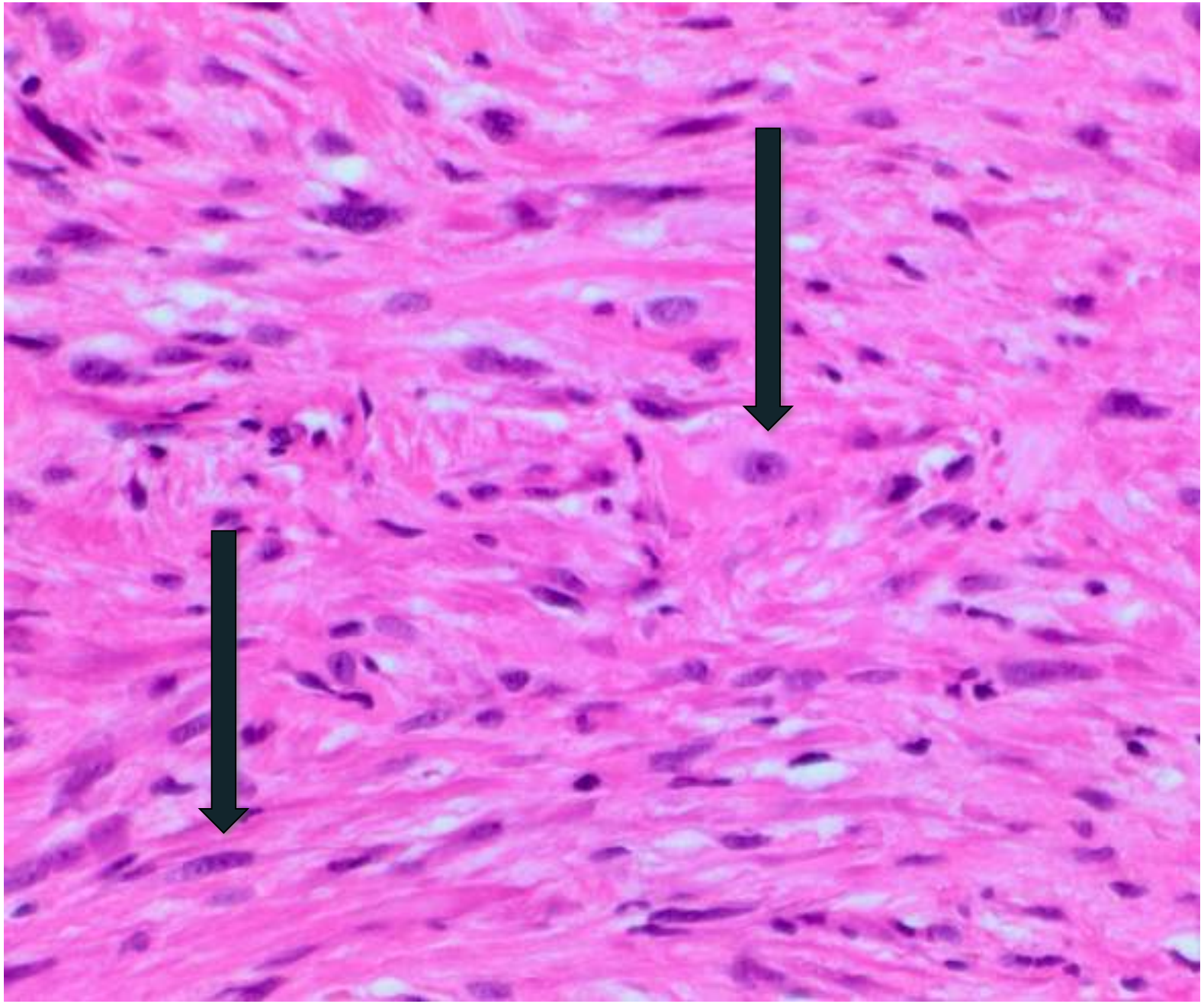


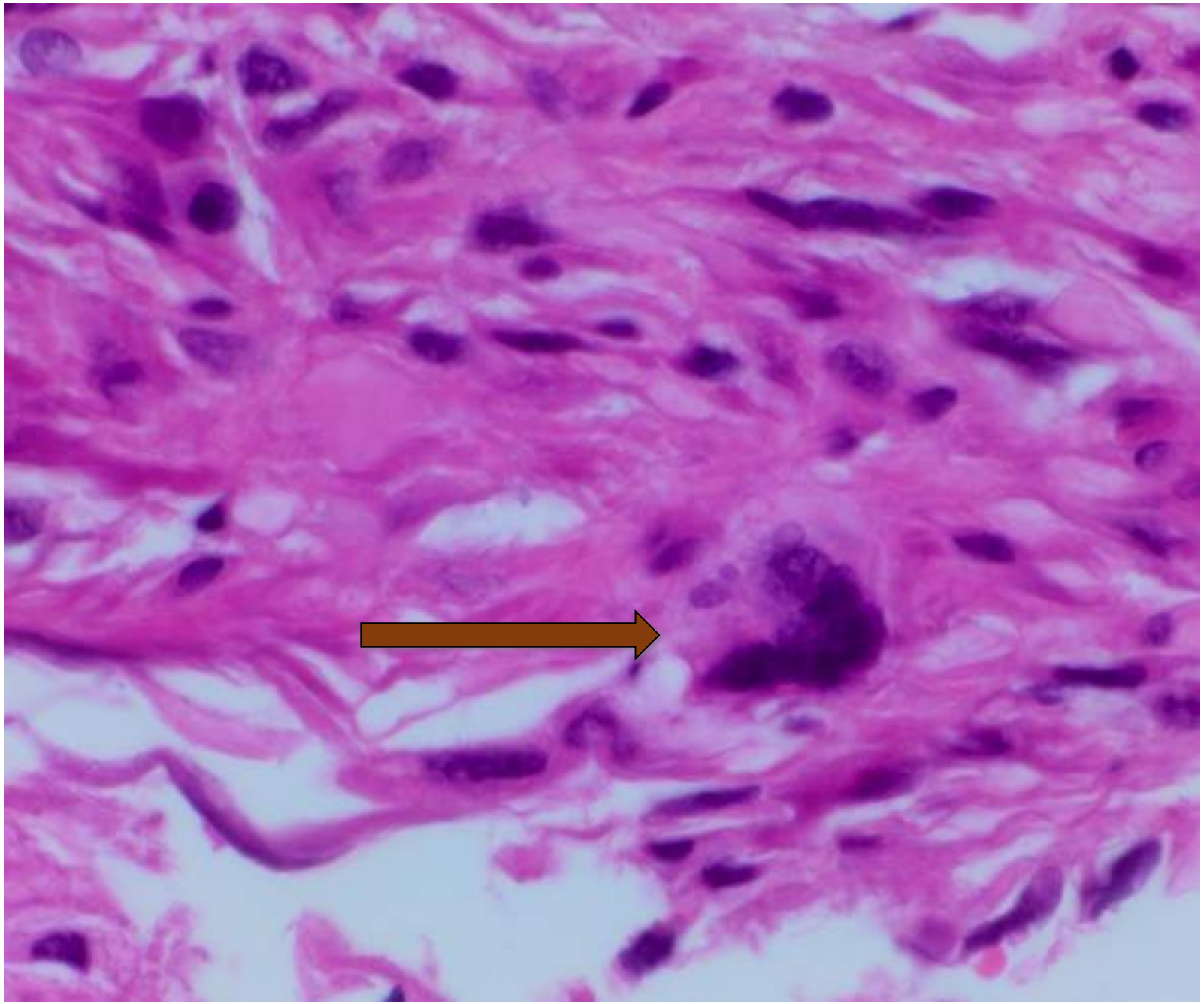


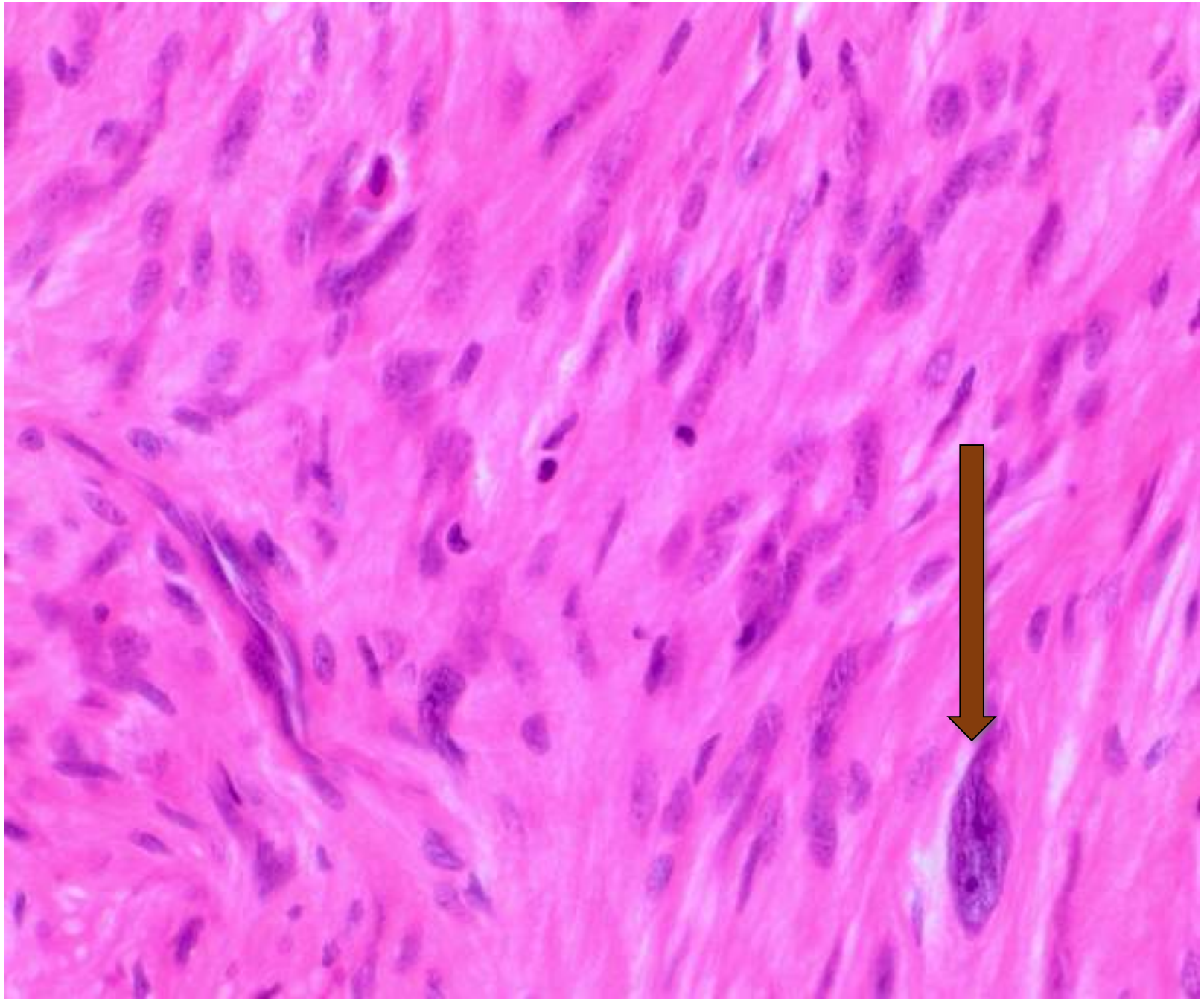


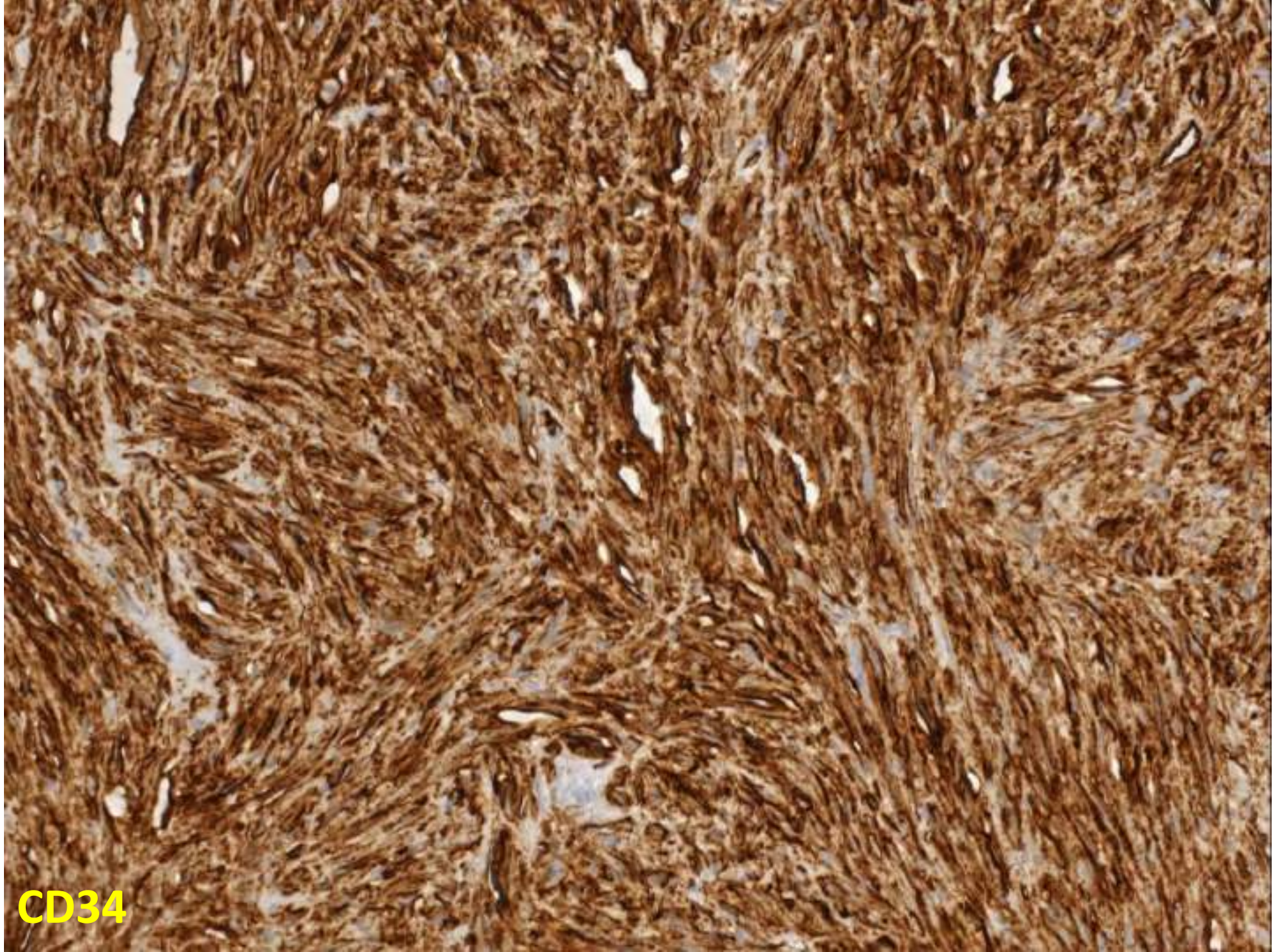


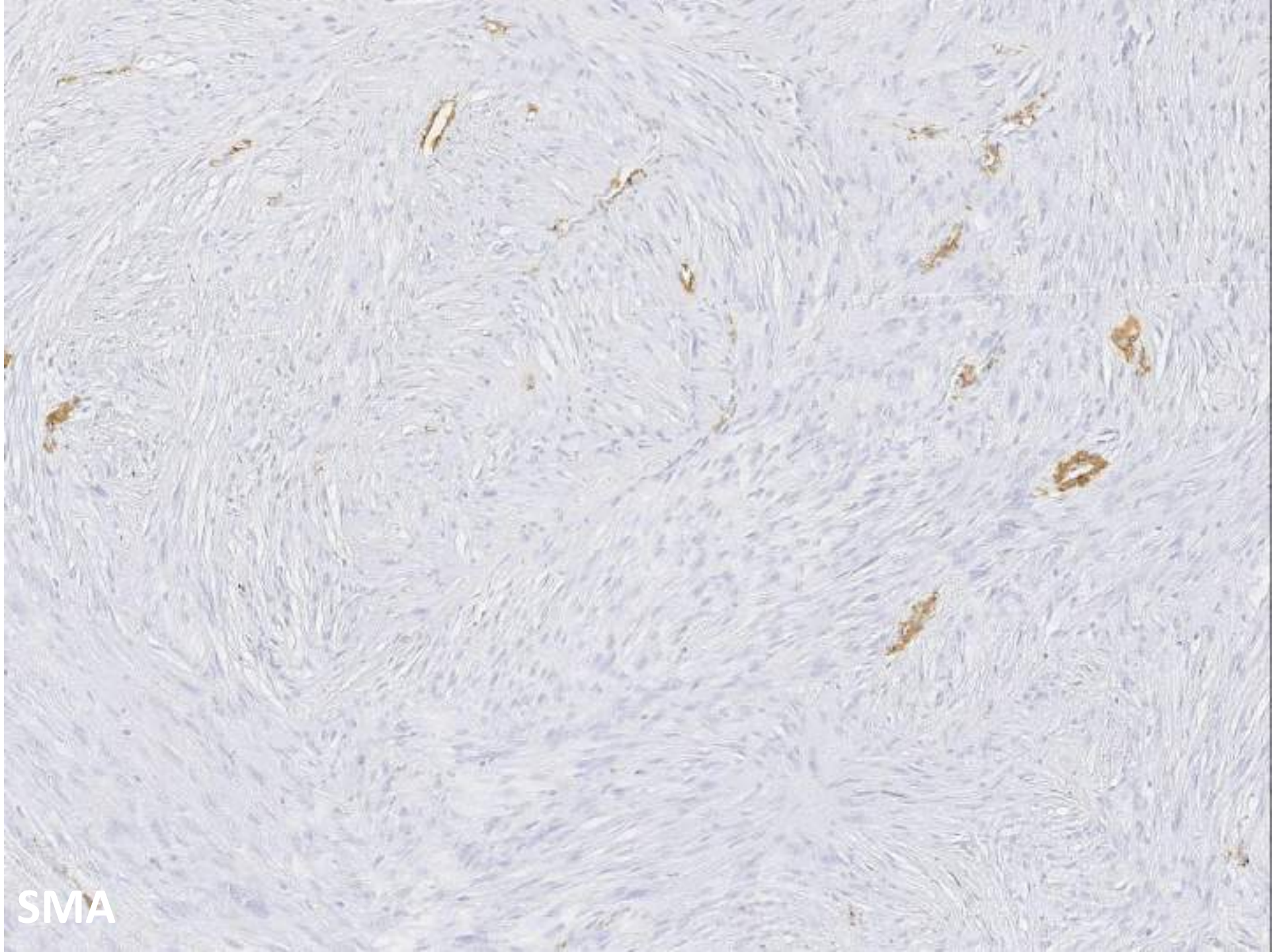


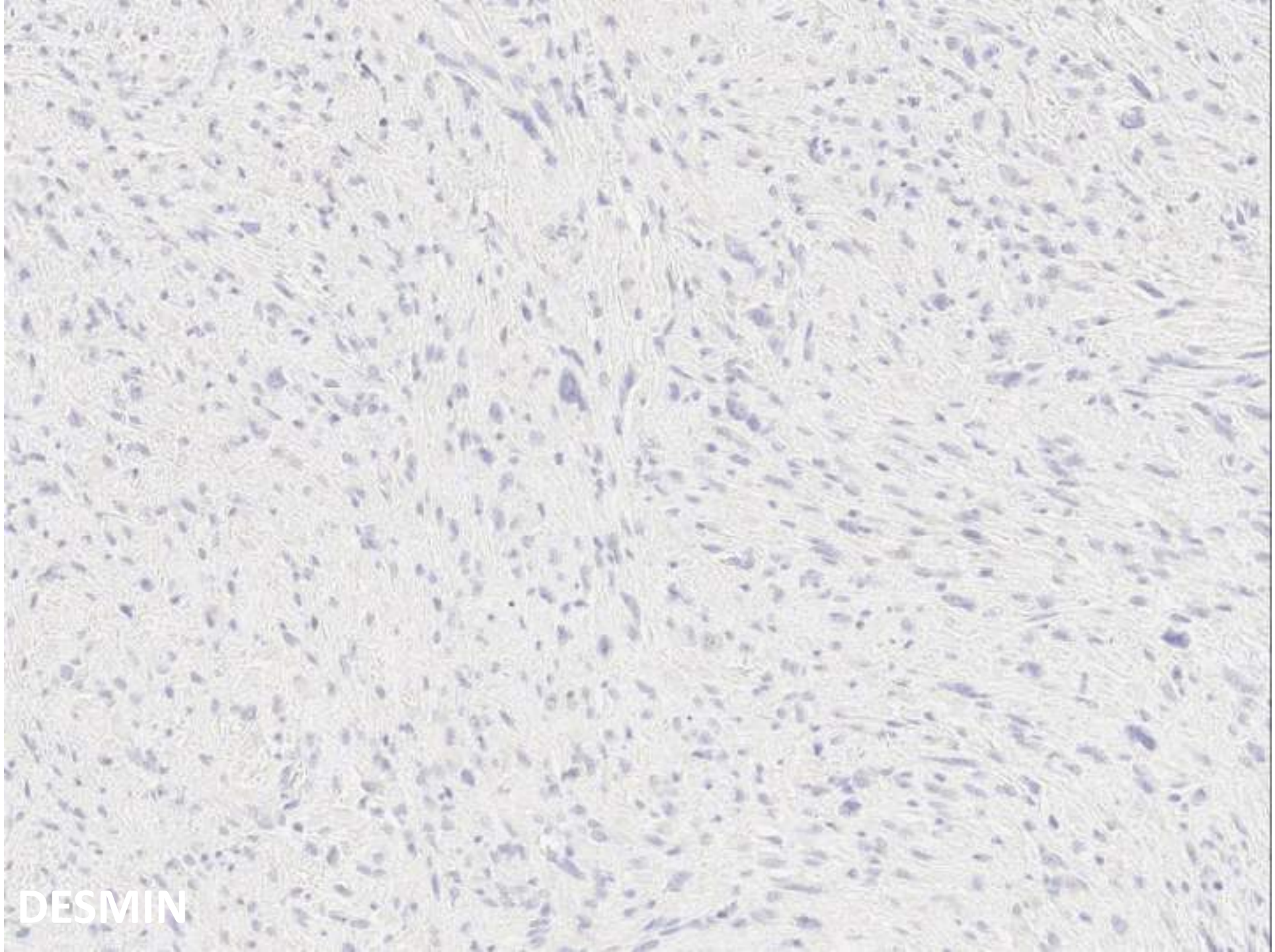







CD34


SMA


DESMIN

Immunohistochemistry

Positive

- Diffuse CD34
- Focally + CK (AE1/AE3)
- CADM3 (synCAM3)
- WT1

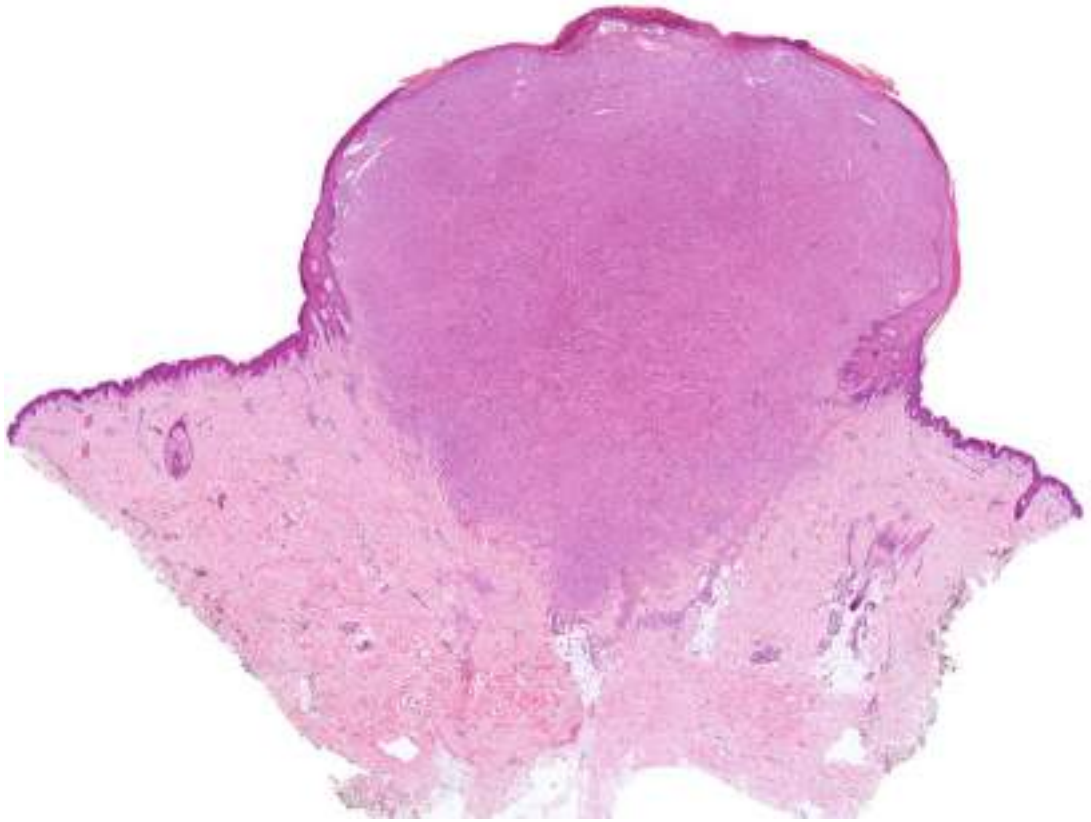
Negative

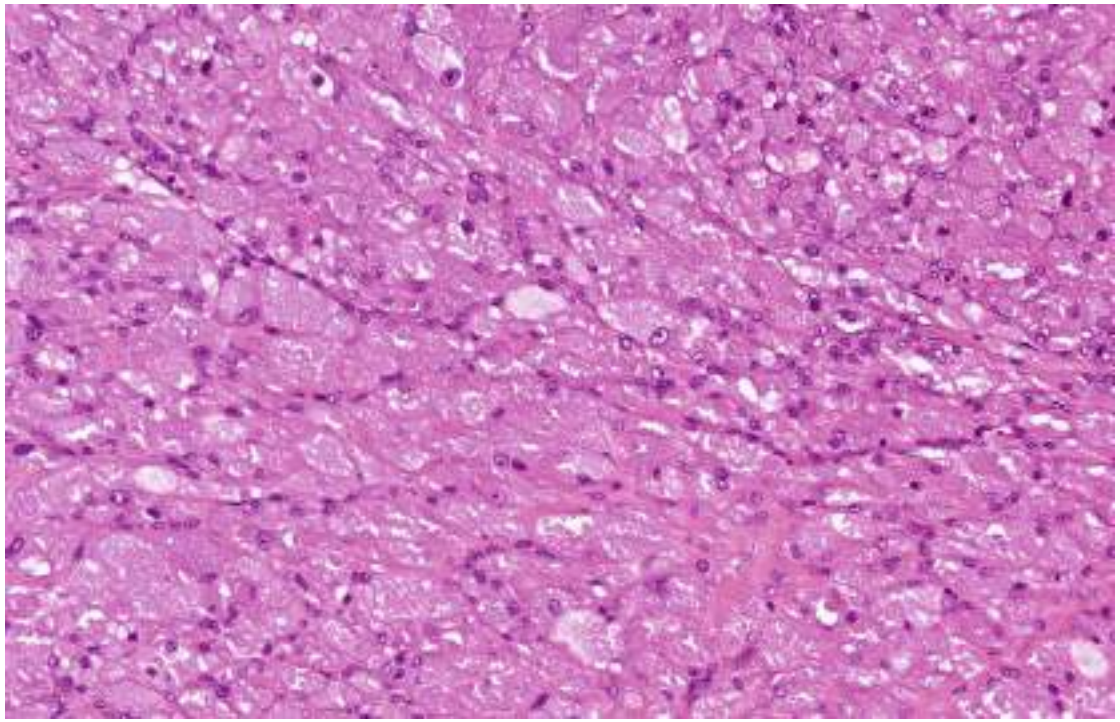
- S-100 protein
- Desmin
- SMA
- CD31
- ERG

Puls F et al: Overlapping morphological, immunohistochemical and genetic features of superficial CD34-positive fibroblastic tumor and PRDM10-rearranged soft tissue tumor. Mod Pathol. 2021 Dec 30.

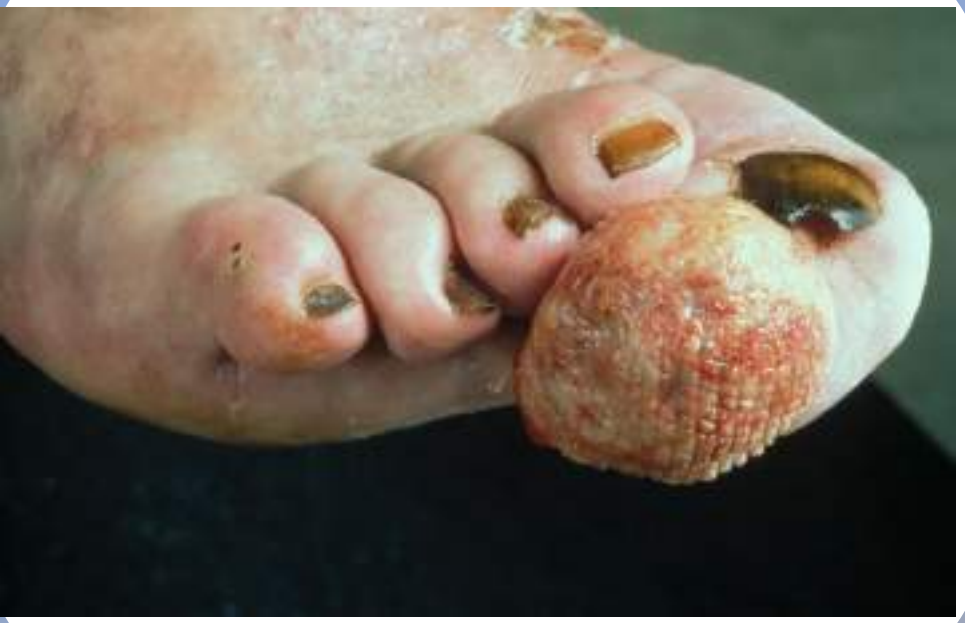
Differential diagnosis

Dermal non-neural granular cell tumour



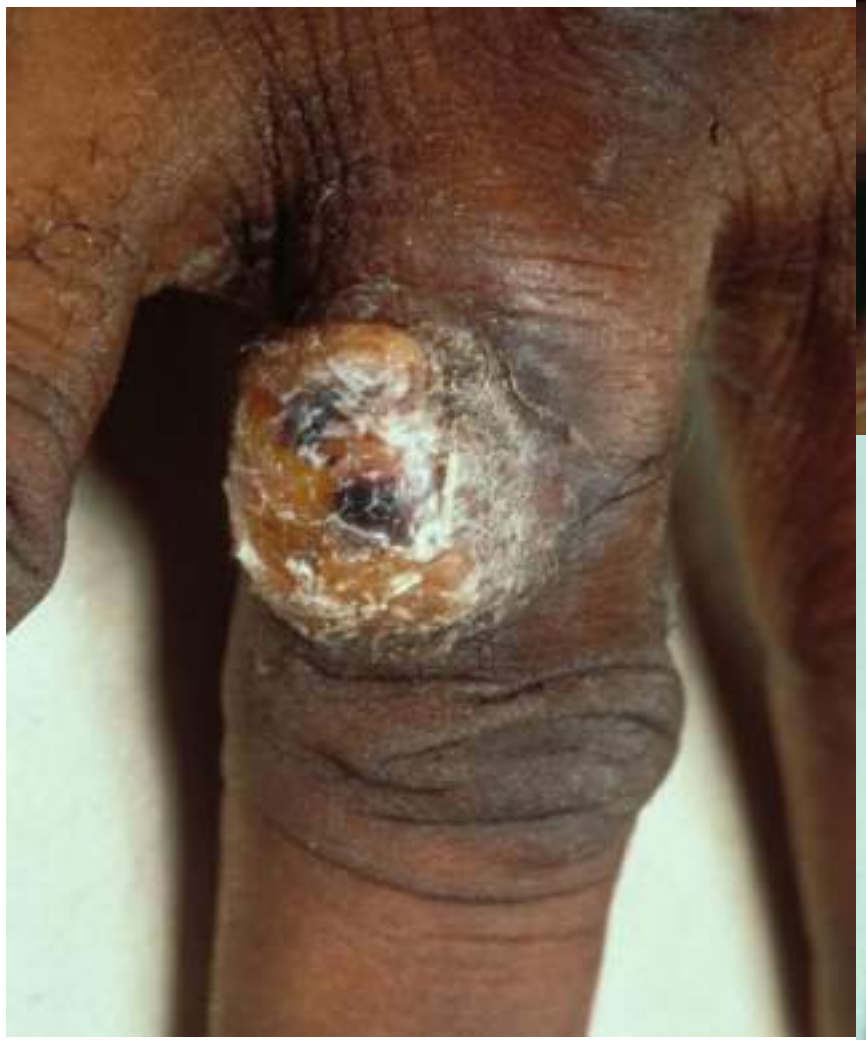


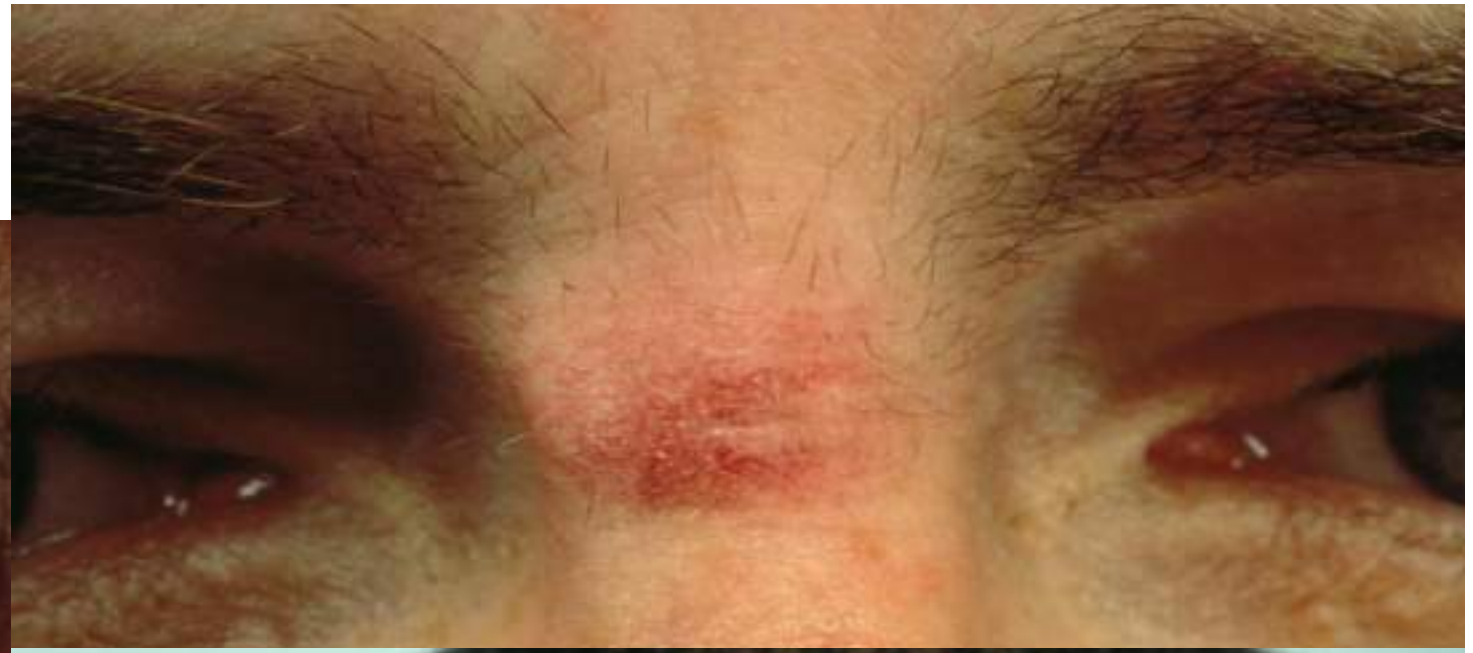
Cellular fibrous histiocytoma

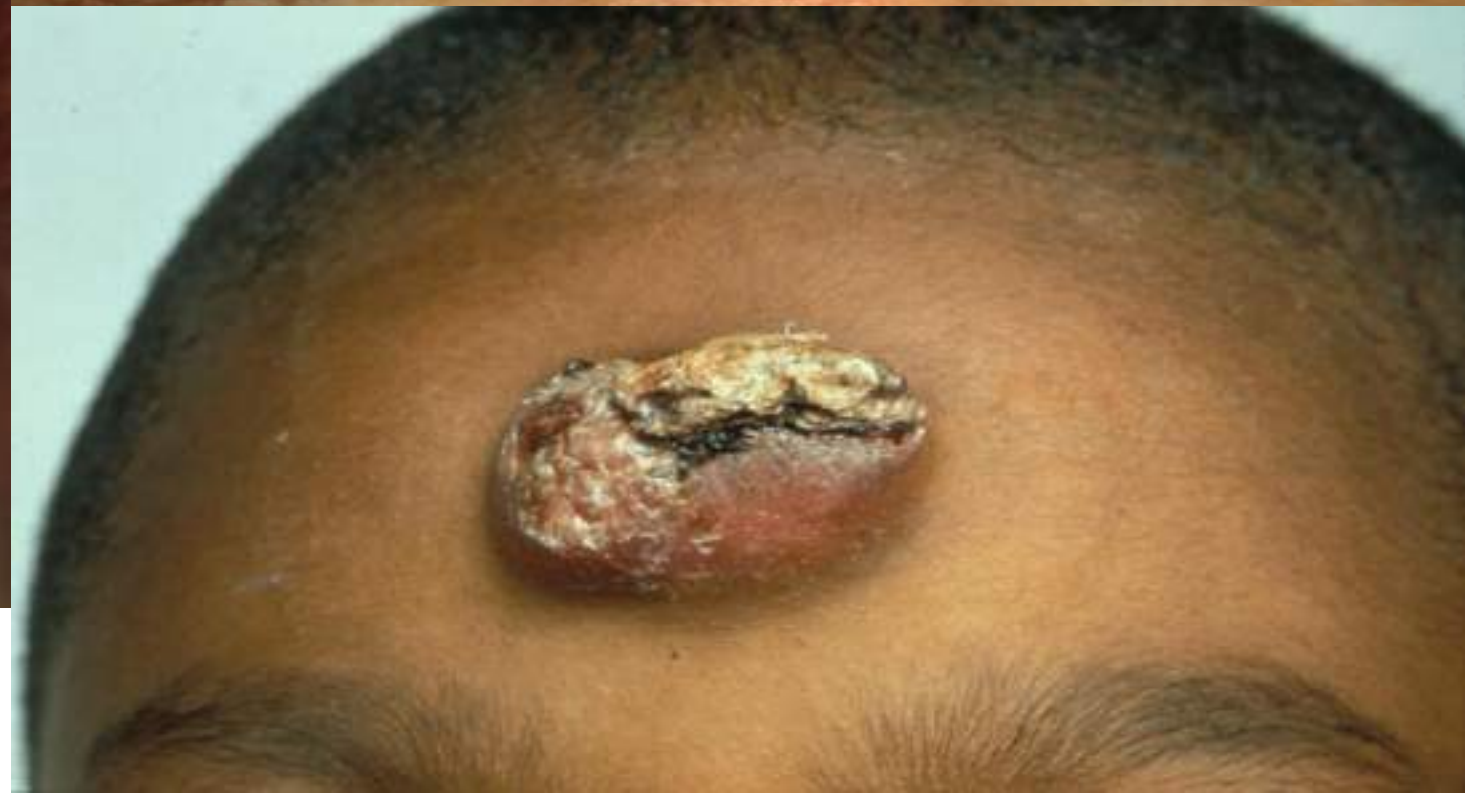


Definition: Highly cellular monomorphous proliferation of spindle cells, growing in a fascicular and very focal storiform pattern

- Wide age range, peak in young to middle age adults
- M>F
- Upper and lower limbs, head and neck, trunk
- Clinical behaviour usually benign with local recurrence (26%) with exceptional locoregional (soft tissues, lymph node) and/or systemic metastasis (lung)

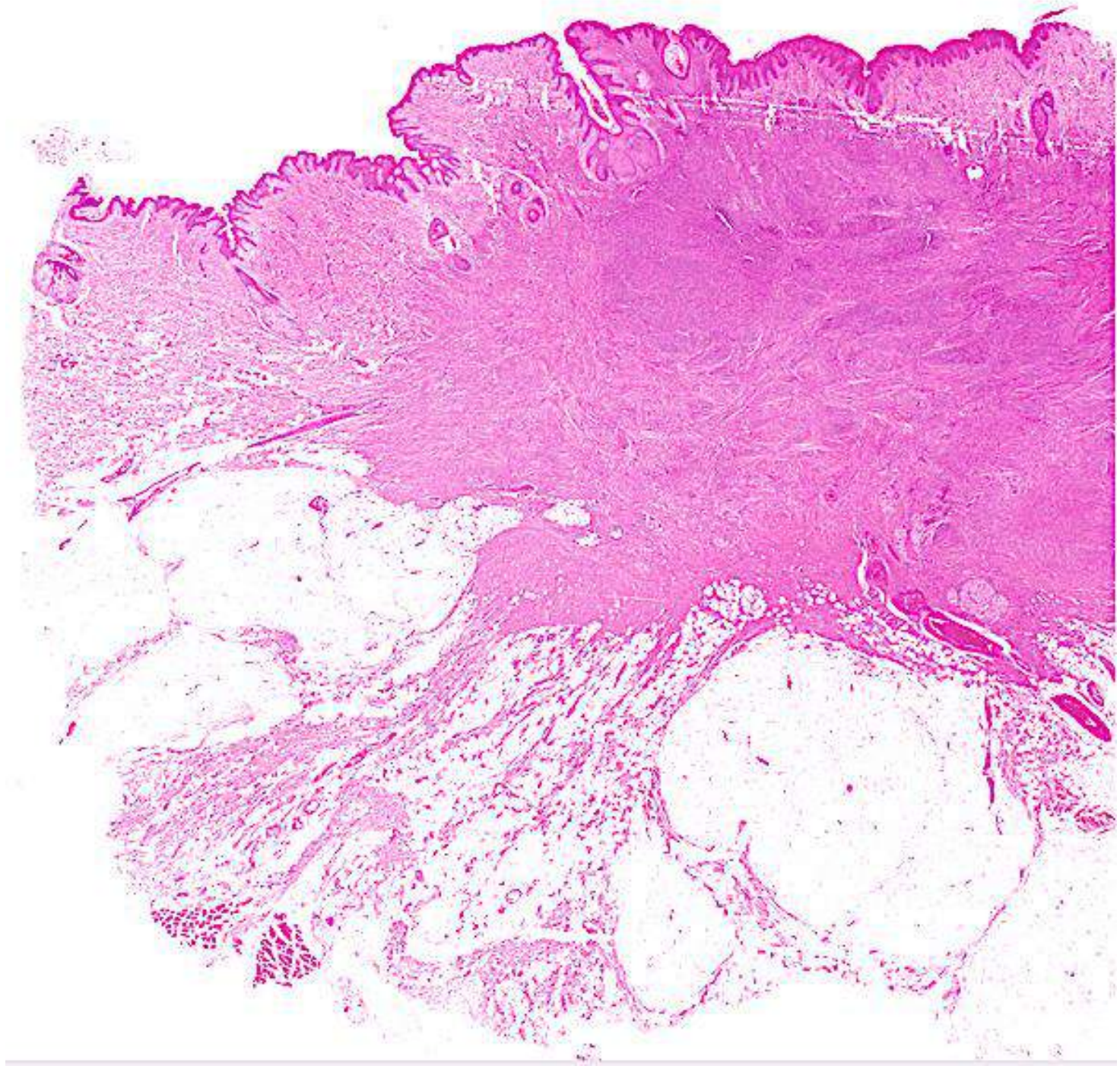


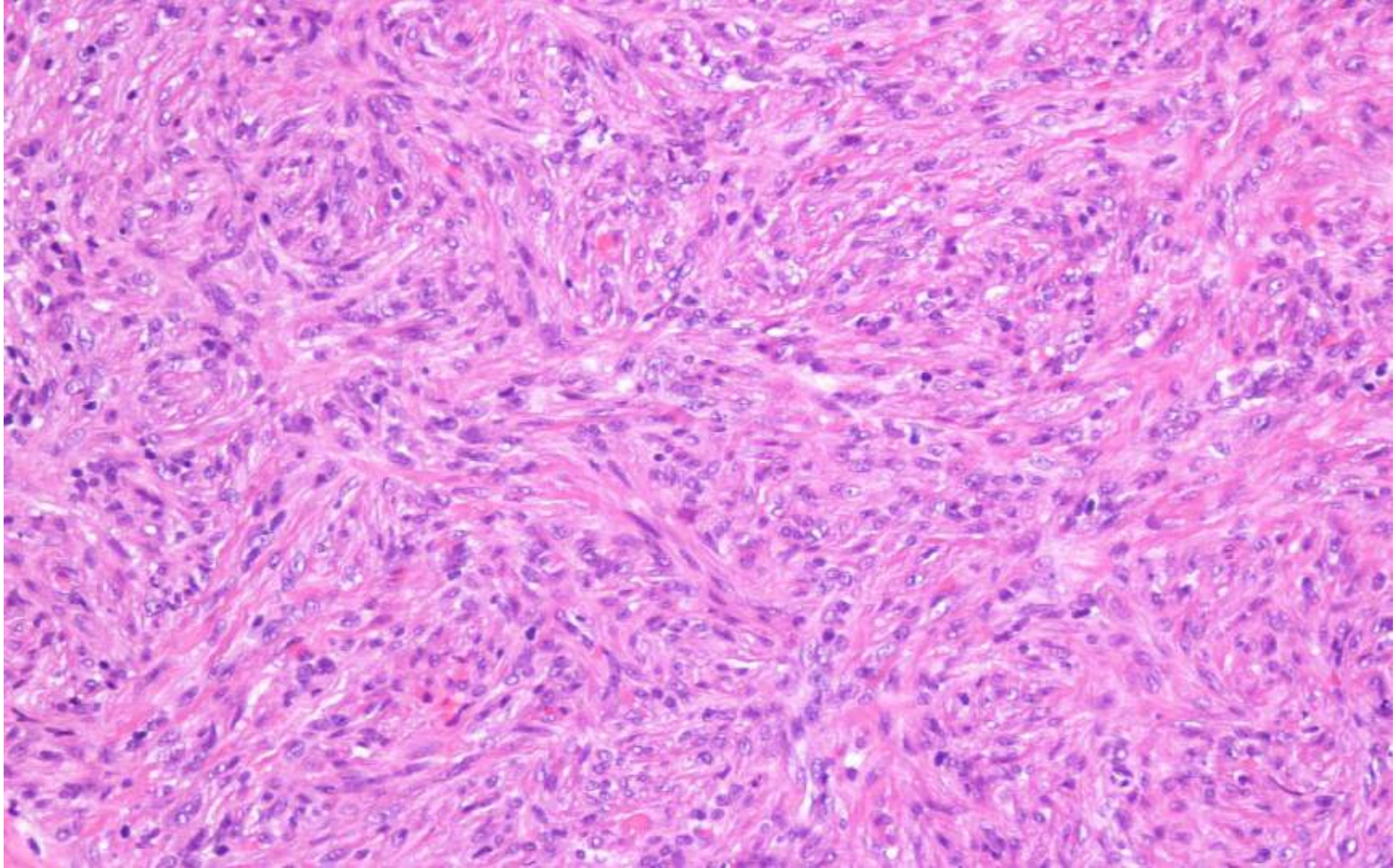


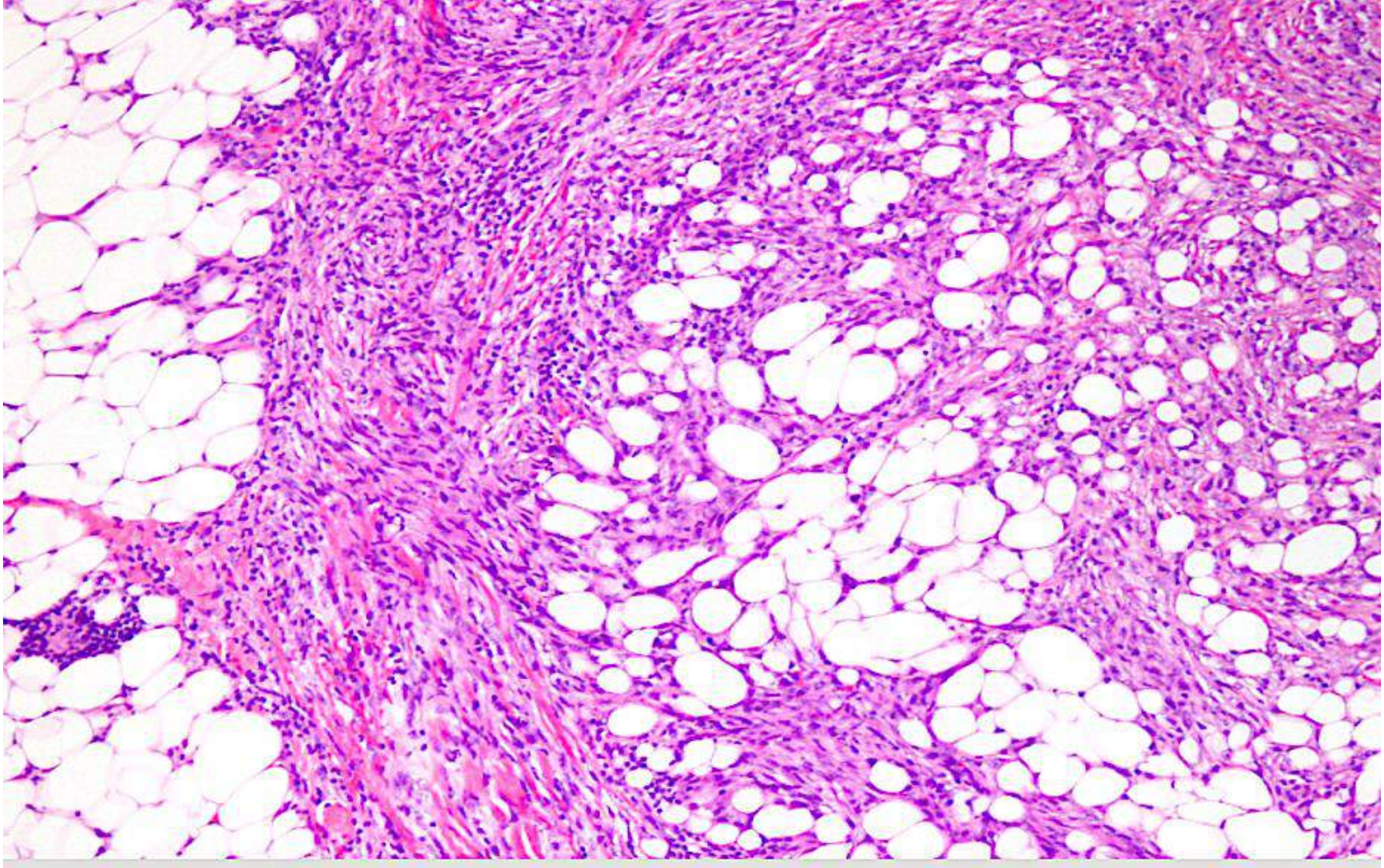


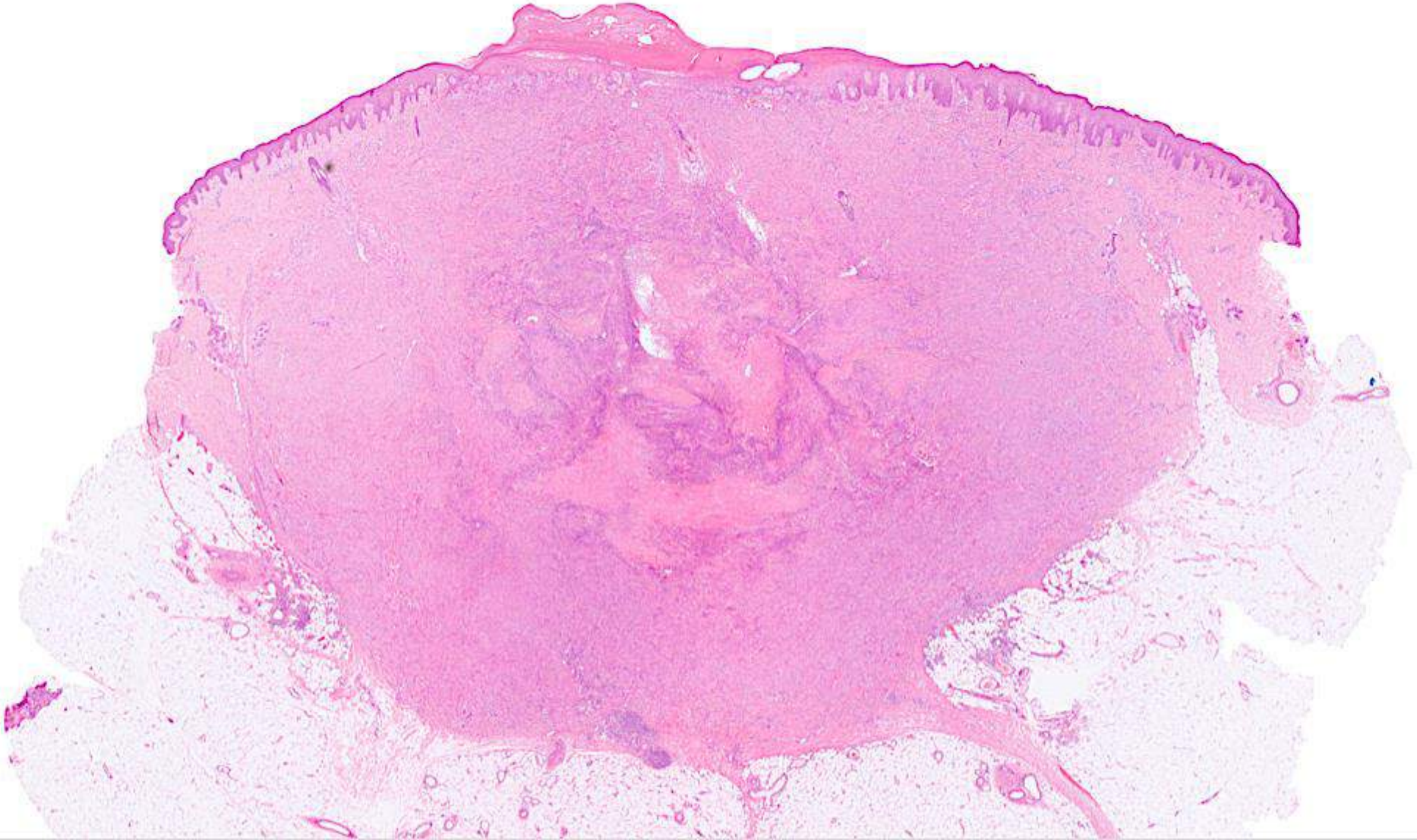
CELLULAR FIBROUS HISTIOCYTOMA HISTOLOGICAL FEATURES

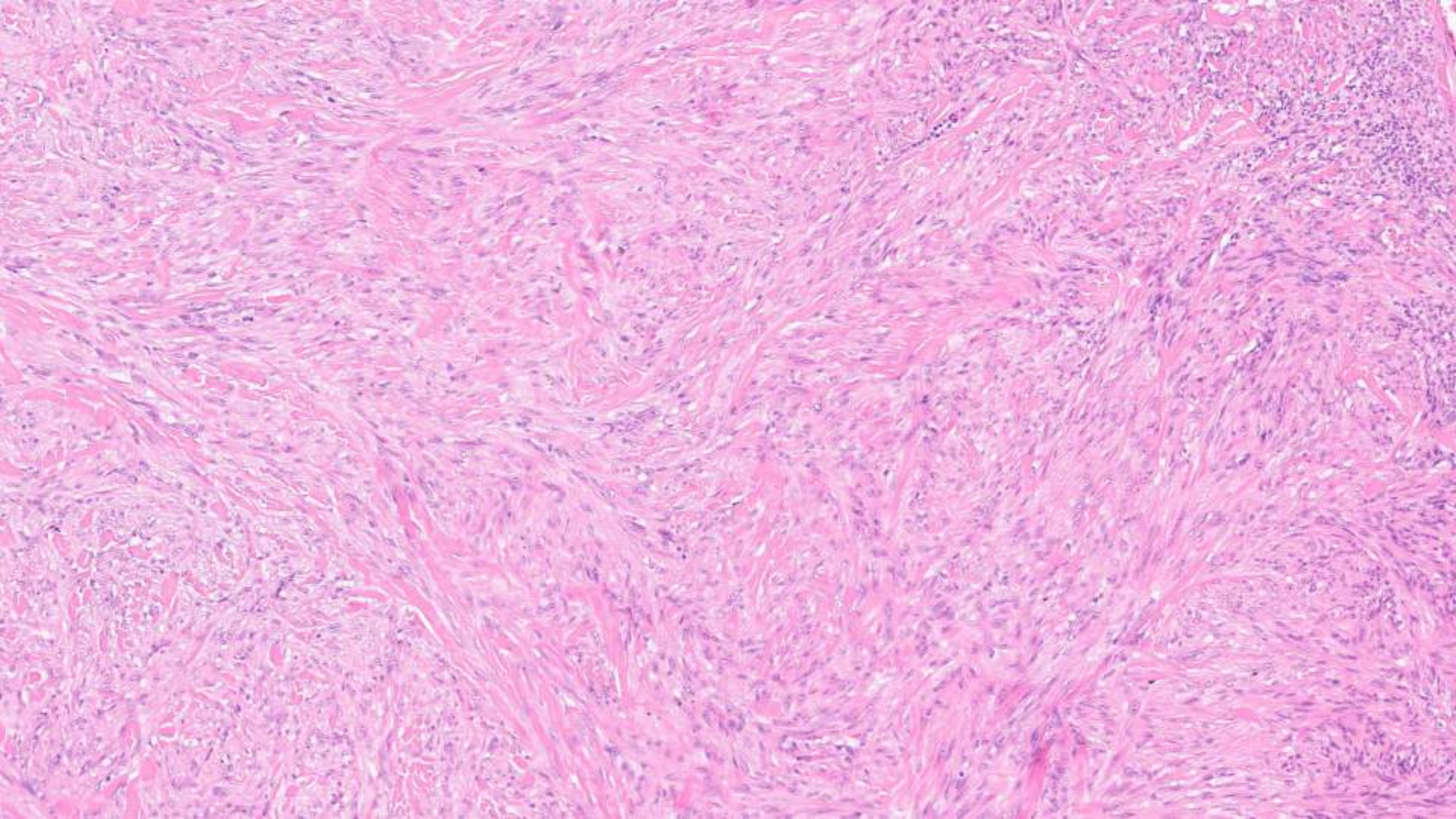
- Epidermal hyperplasia
- Much less polymorphic than ordinary FH
- Bundles of myofibroblast-like cells with a focal storiform pattern
- Variable number of inflammatory cells
- Mitotic rate varies
- Necrosis (12%)
- More frequent involvement of the subcutis (mainly along the septae)

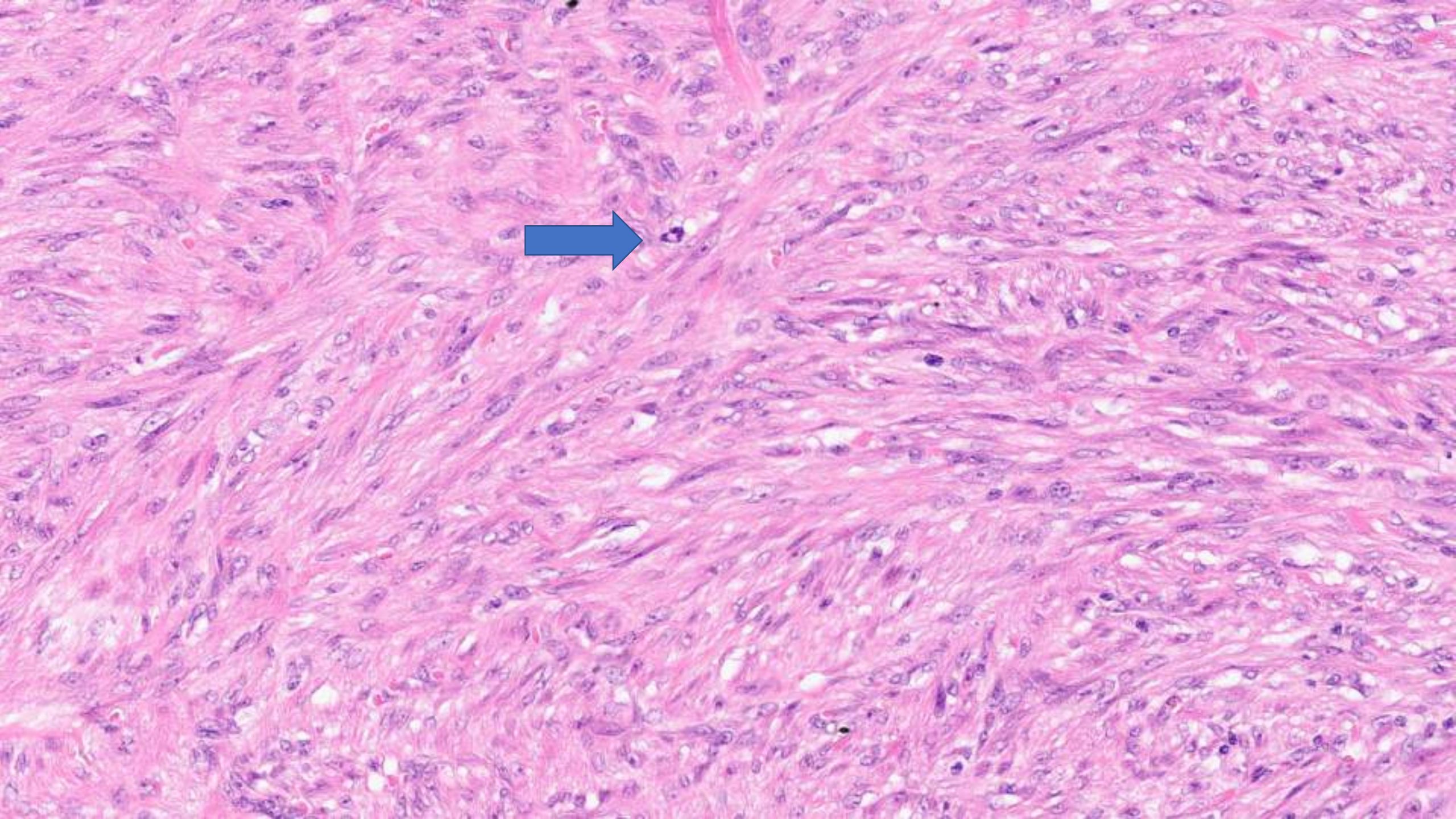


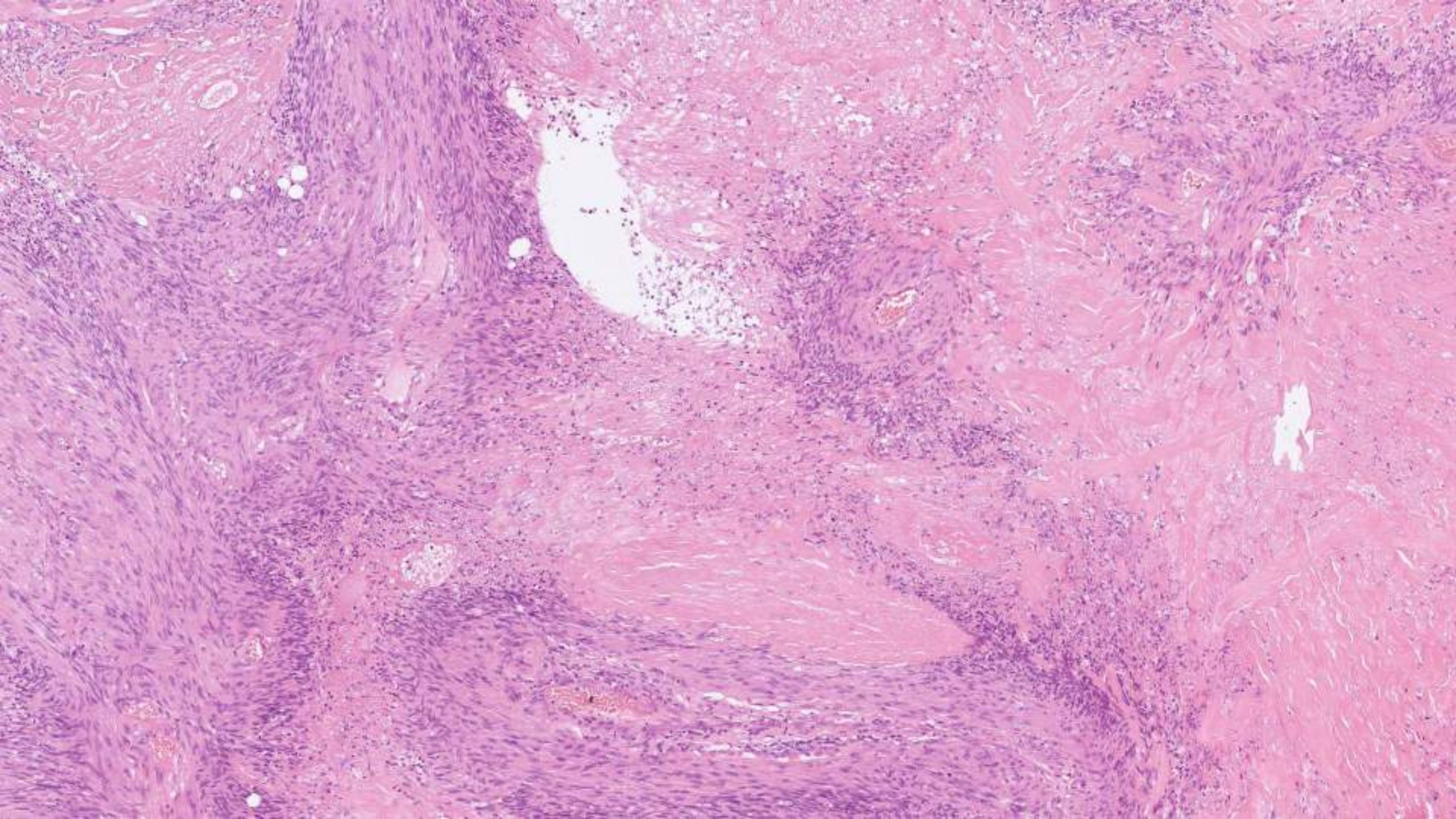


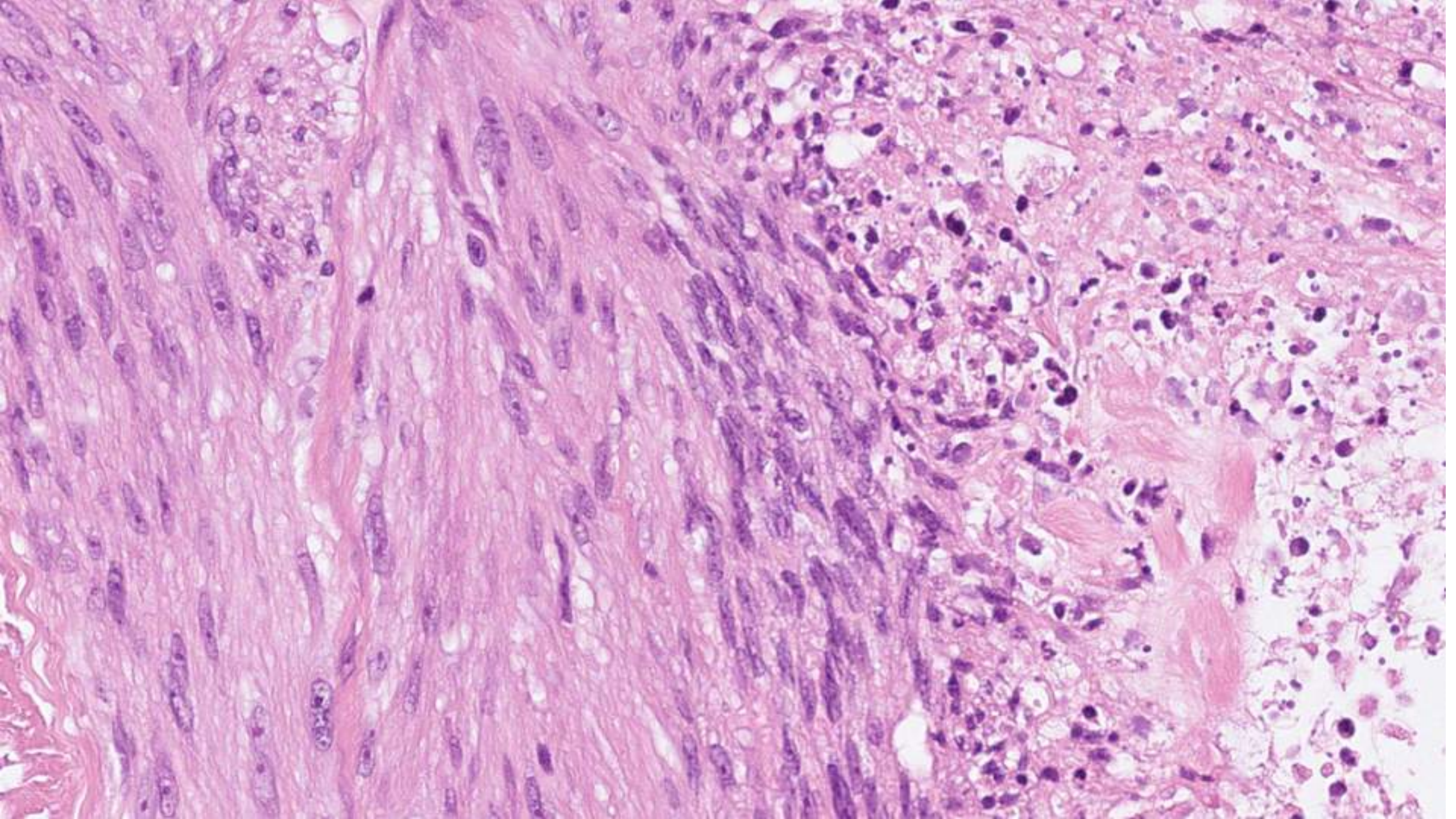








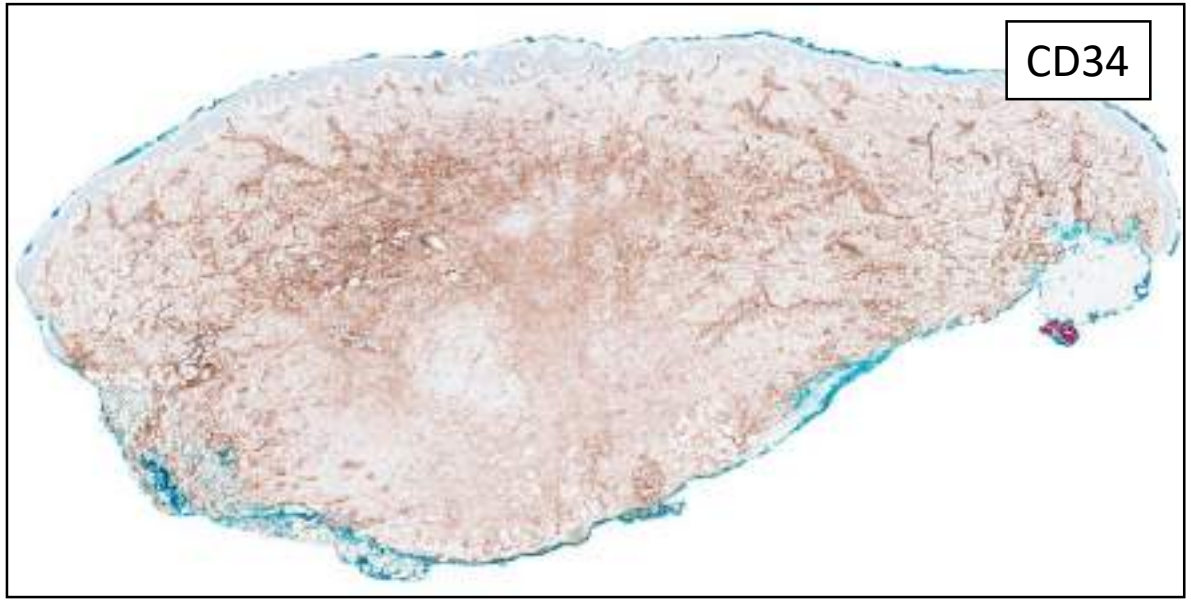




Immunohistochemistry

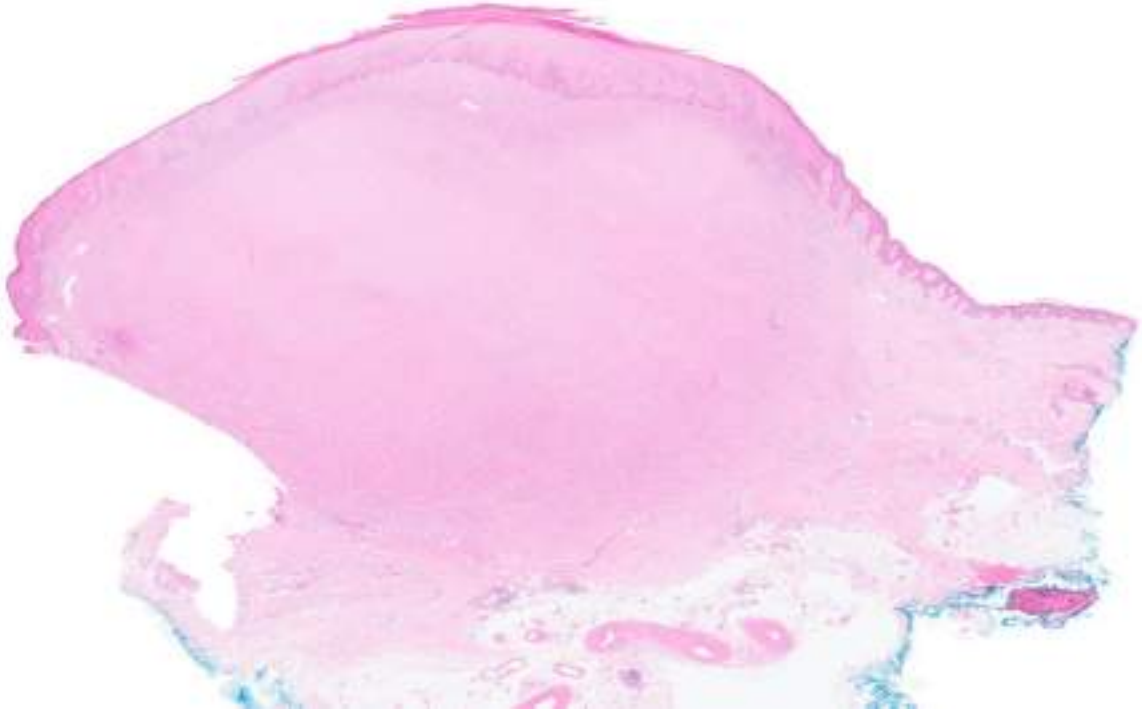
Positive

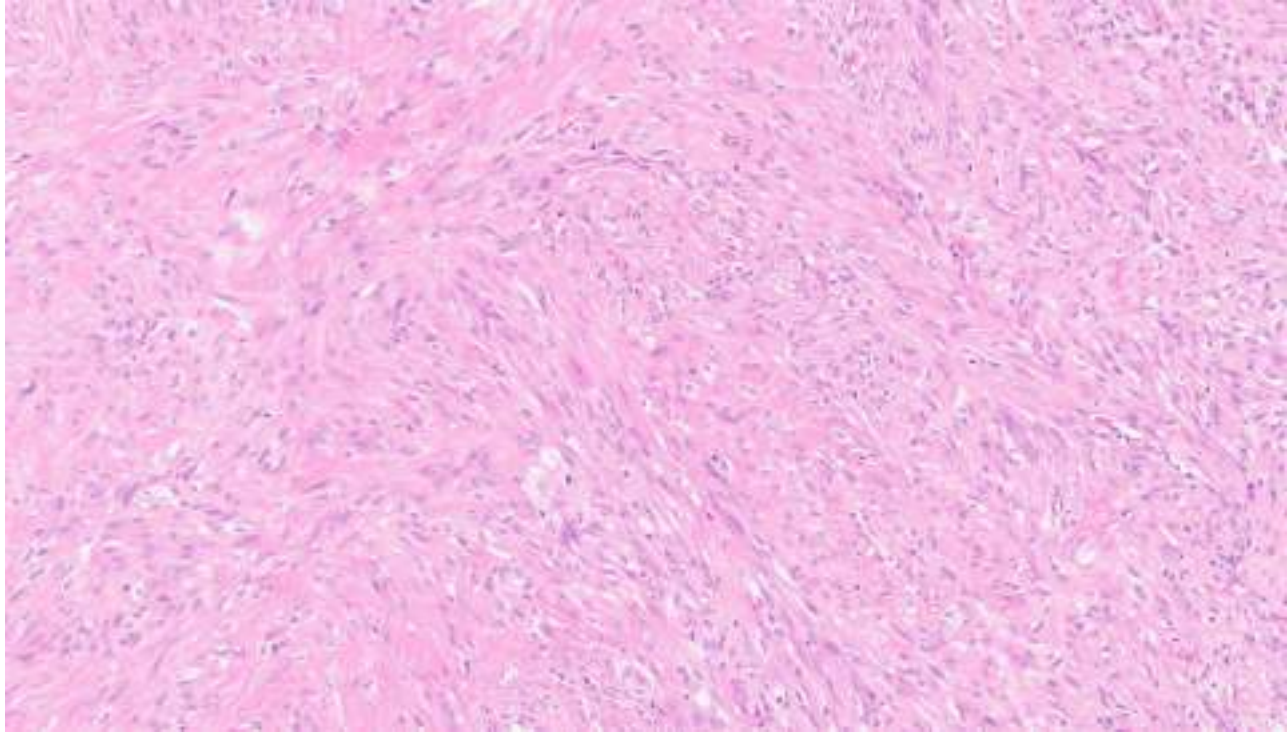
- SMA 90%
- Desmin 32%
- CD34 periphery of the lesion
- Rare H-caldesmon focal positivity
- D2-40 may be focally positive

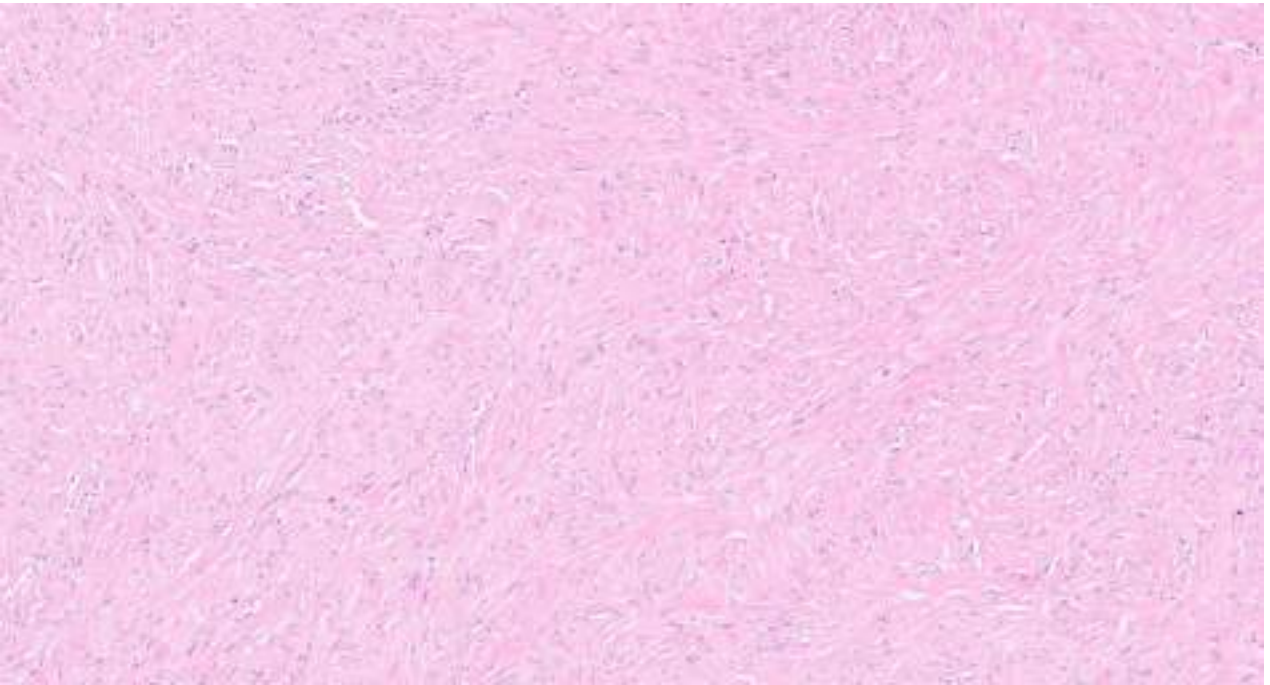


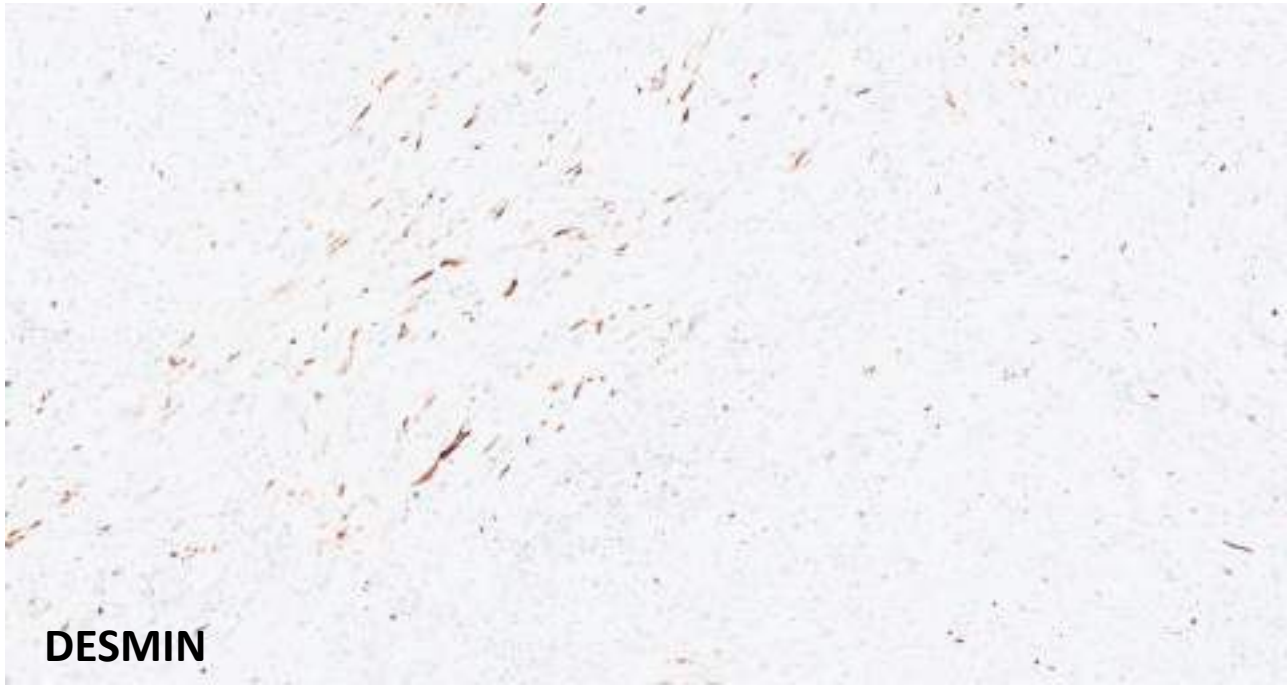
Negative

- CK
- EMA
- S100

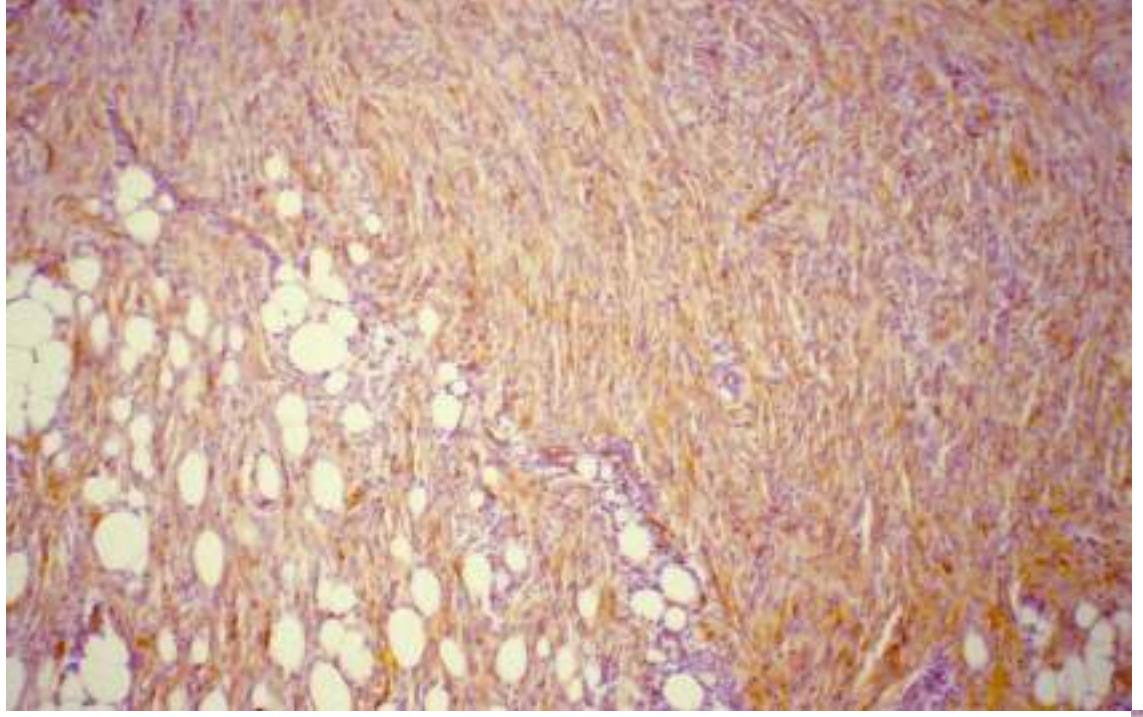


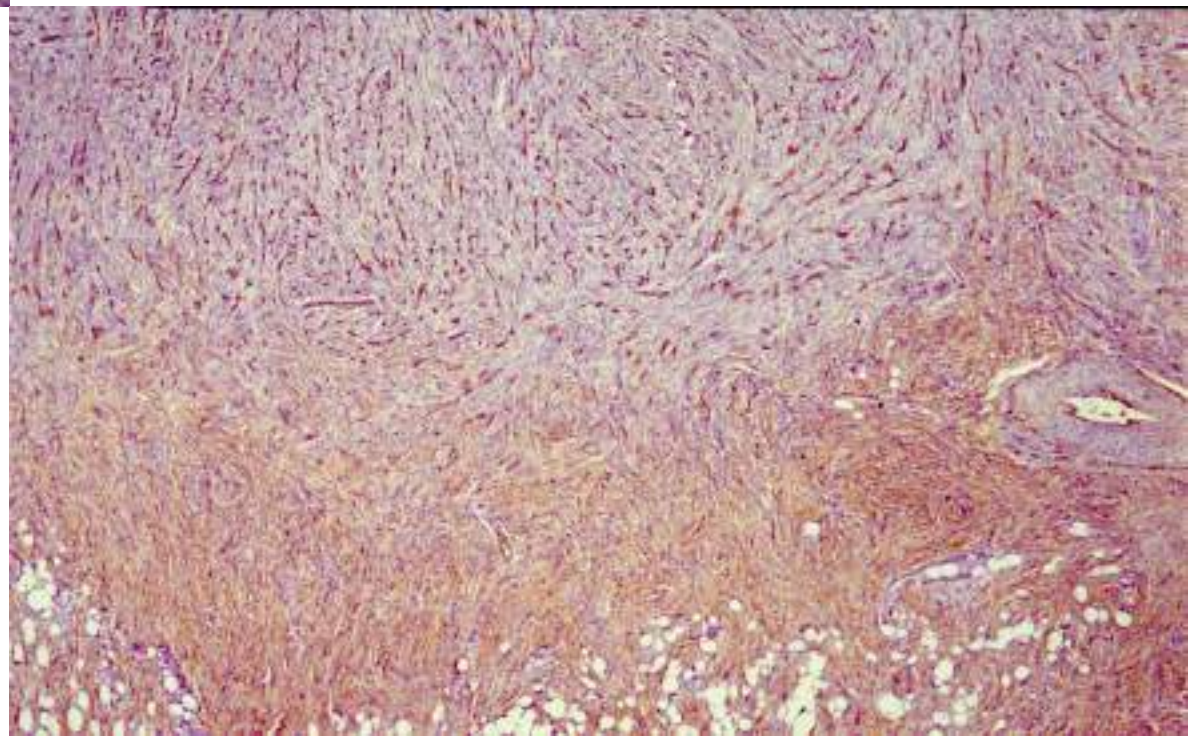






DESMIN

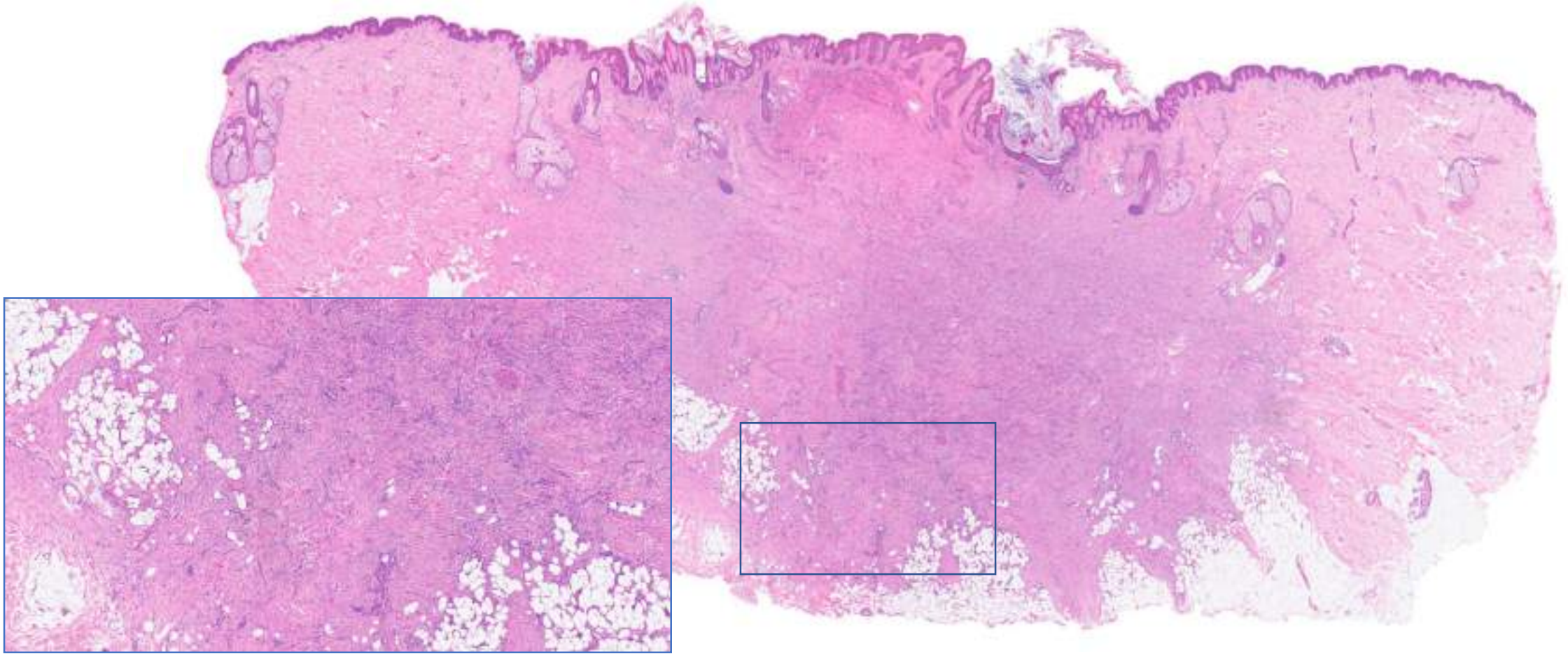


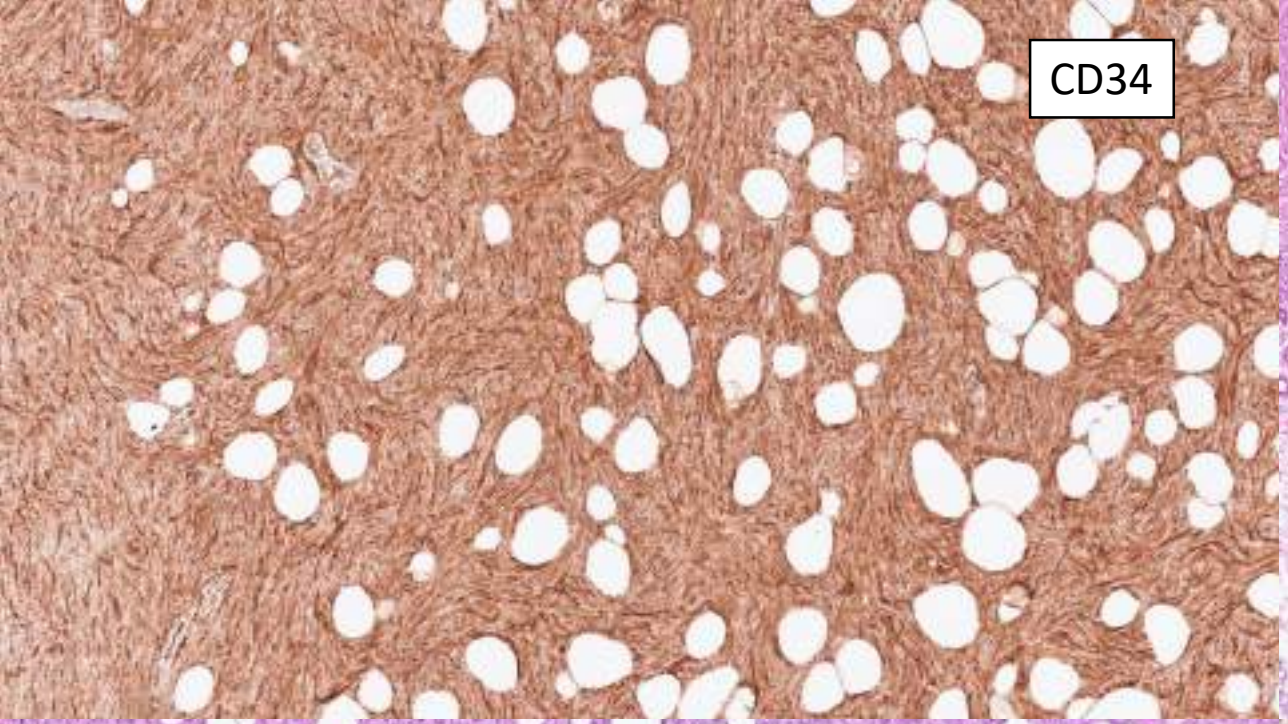


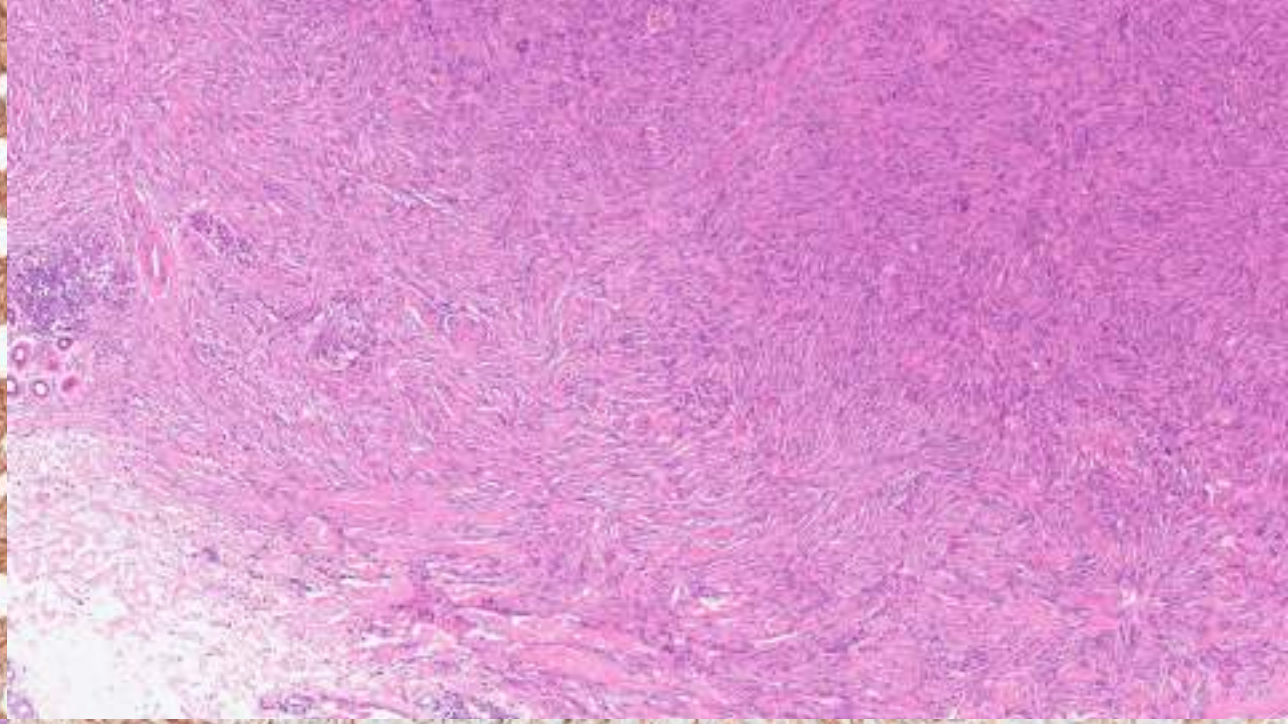
CD34

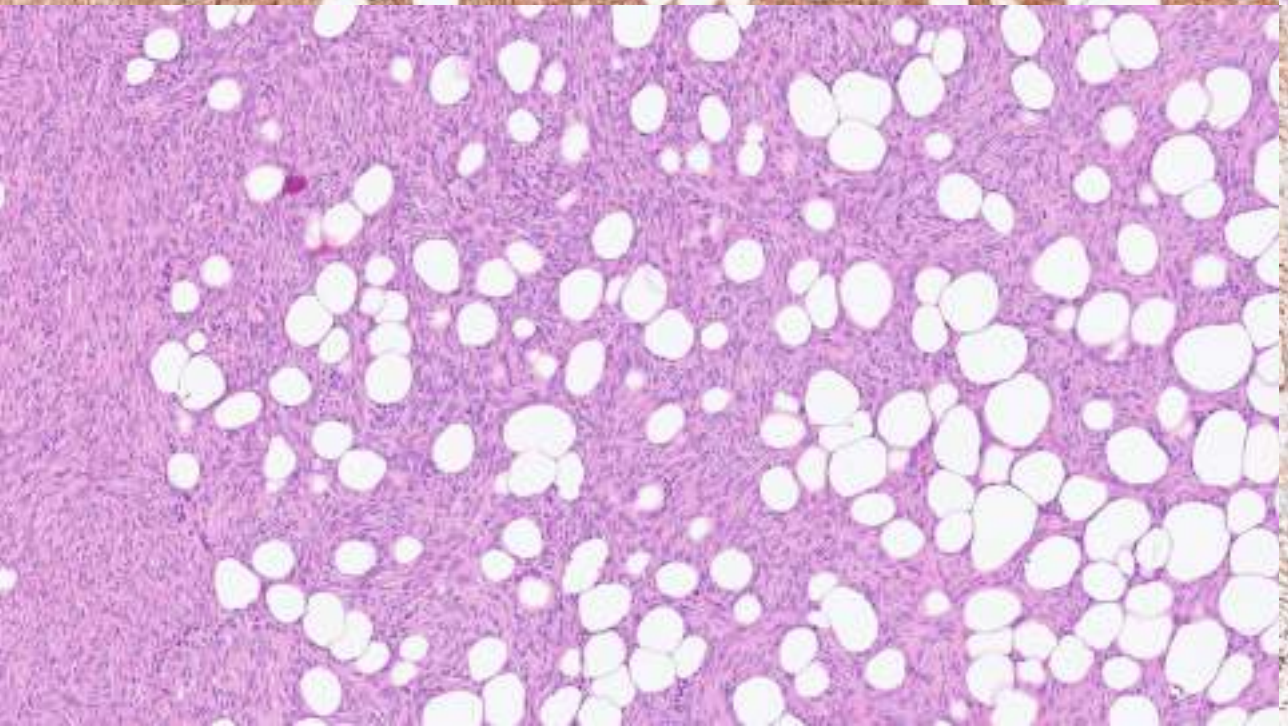
Differential diagnosis

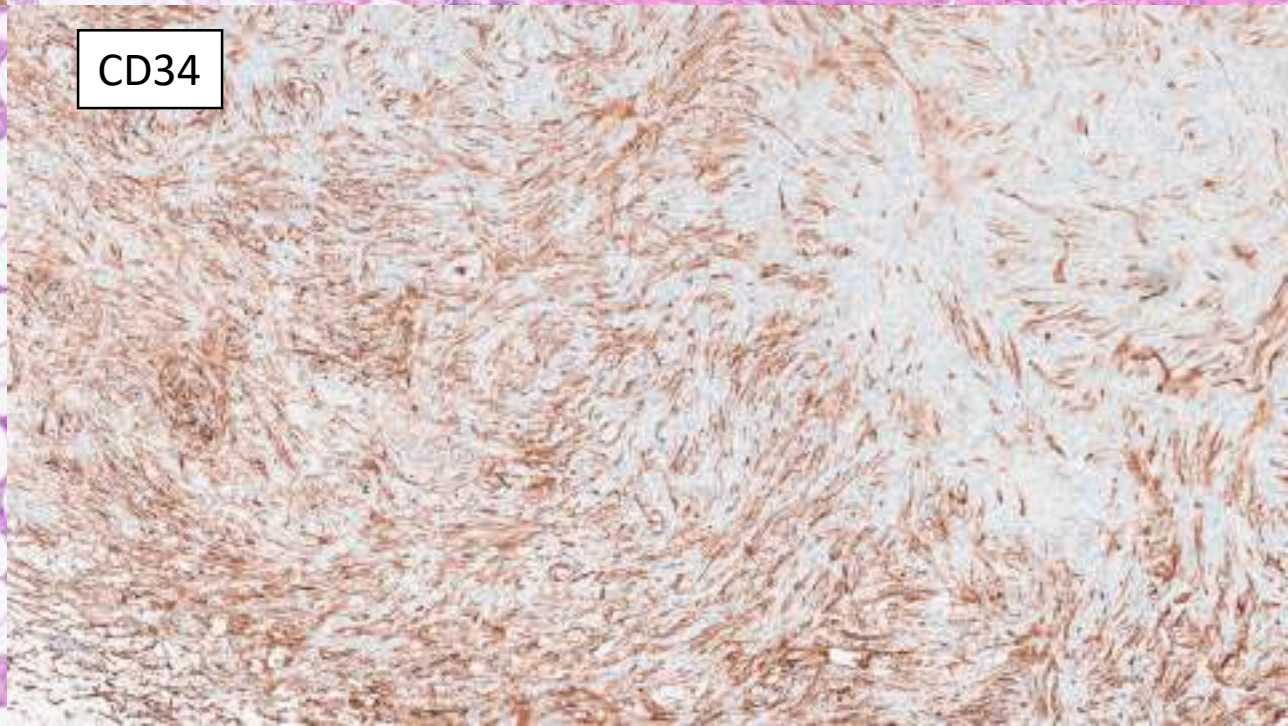
Dermatofibrosarcoma protuberans




CD34






CD34

CELLULAR FH vs DFSP

CELLULAR FH

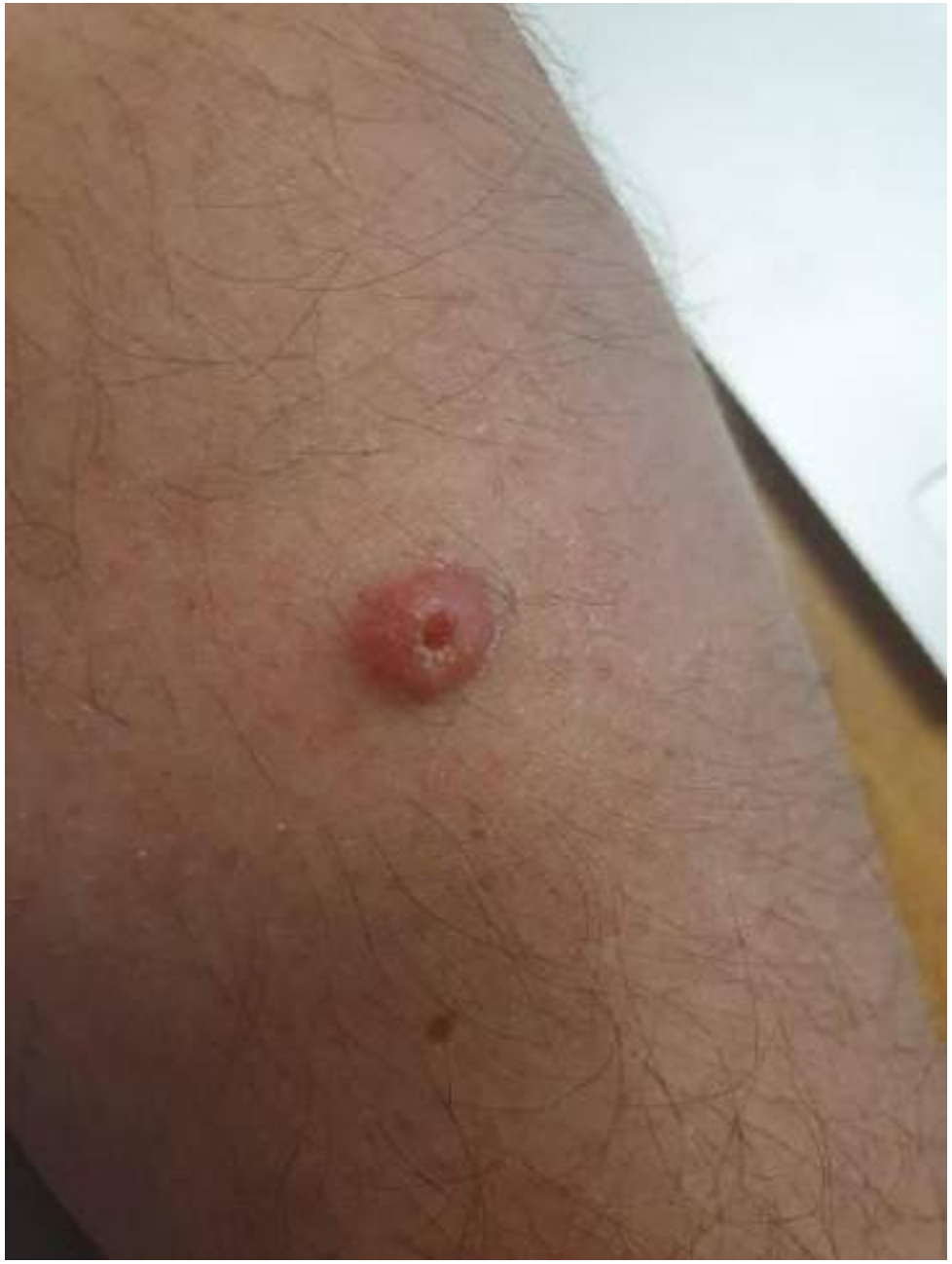
- **Epidermal changes**
- **Mainly fascicular**
- **Mild polymorphism**
- **Cells with vesicular nucleus and eosinophilic cytoplasm**
- **Mitotic activity varies**
- **Focal extension into subcutis, mainly along septa**

DFSP

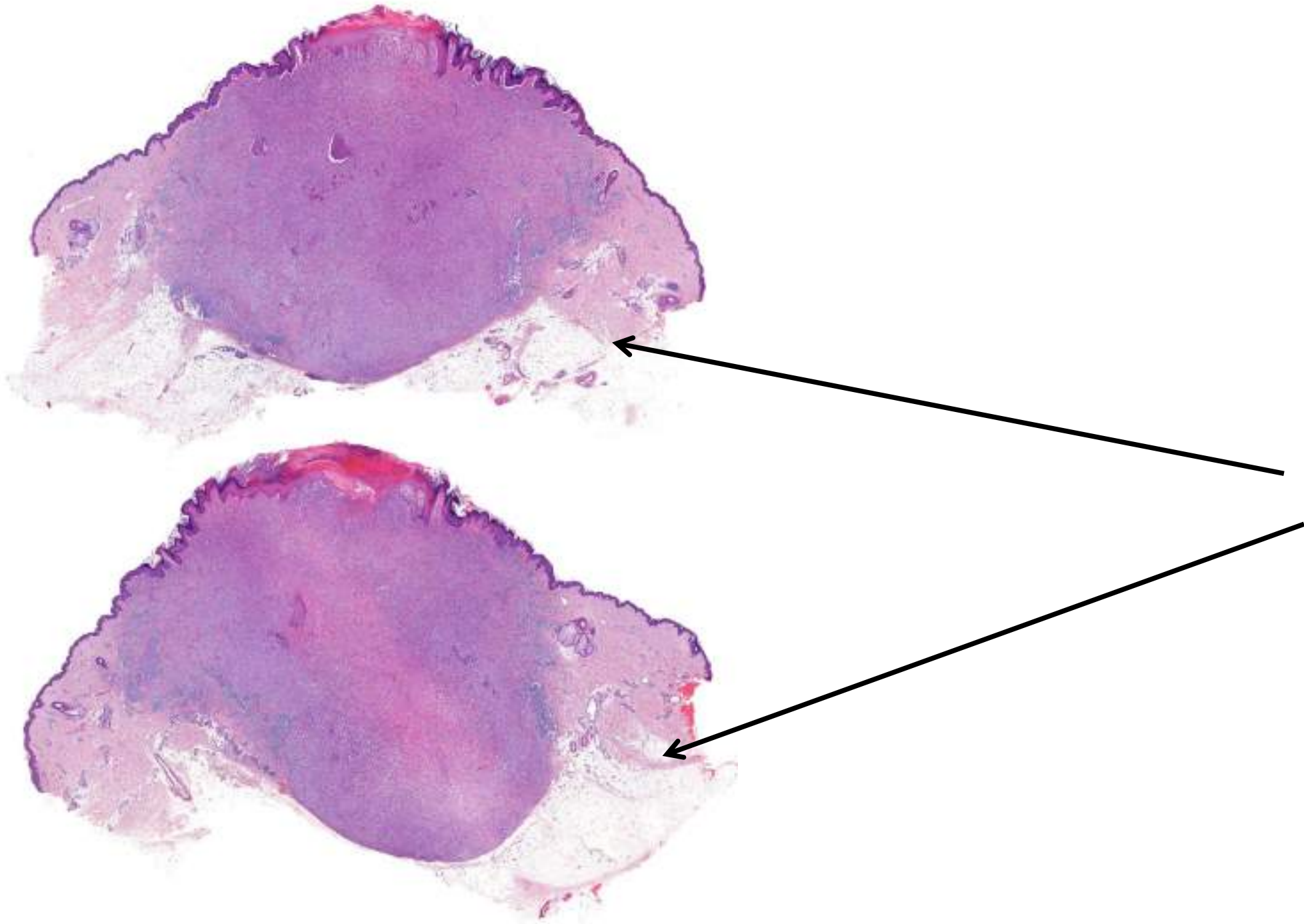
- **No epidermal changes**
- **Mainly storiform**
- **No polymorphism**
- **Cells with thin dark nucleus and scanty cytoplasm**
- **Very low mitotic activity (except DFSP)**
- **Extensive invasion of subcutis**

Case Presentation:

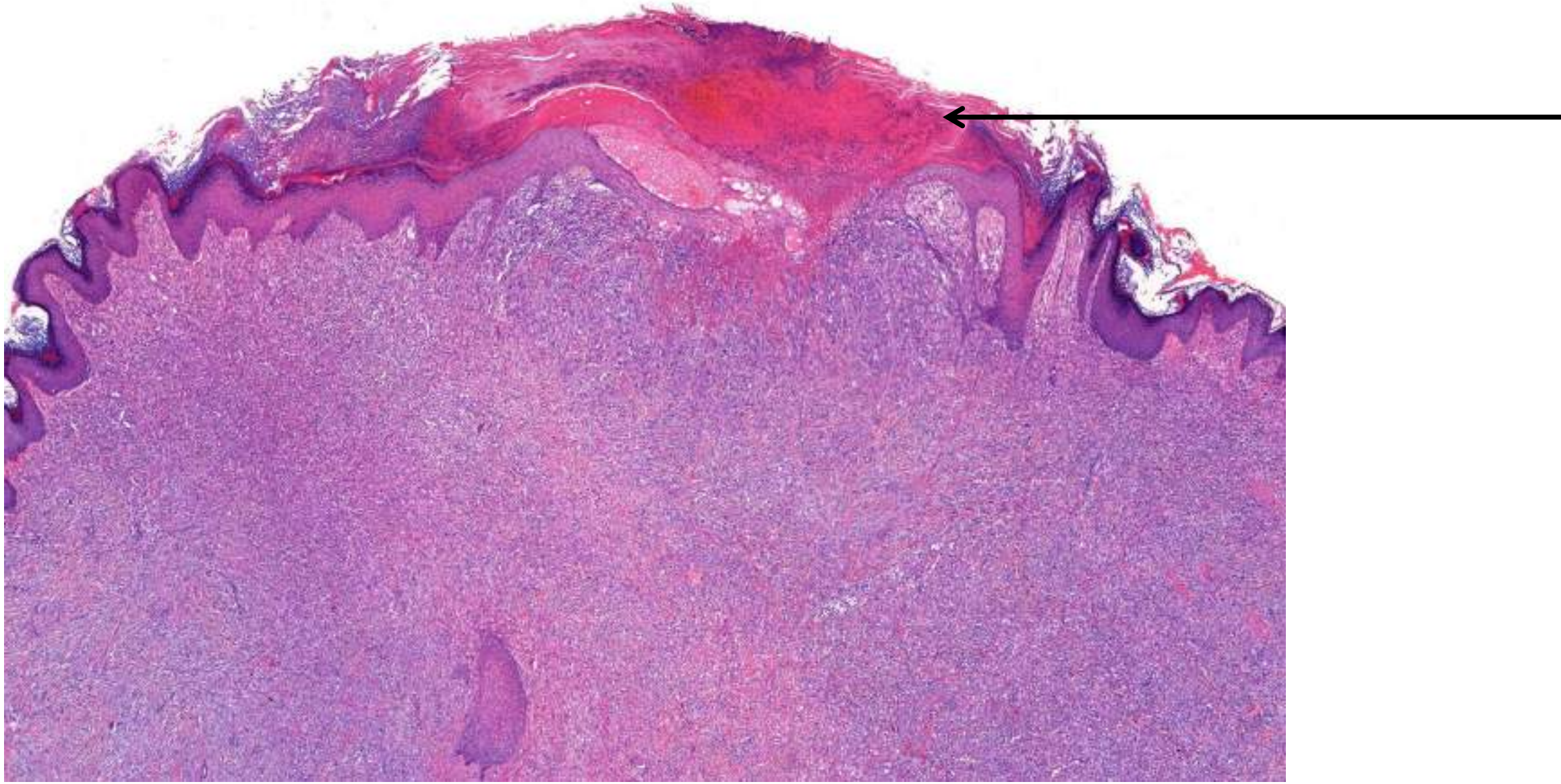
- 27-year-old male
- 3-month history
- 9mm tender, nodule on forearm
- Nil PMH



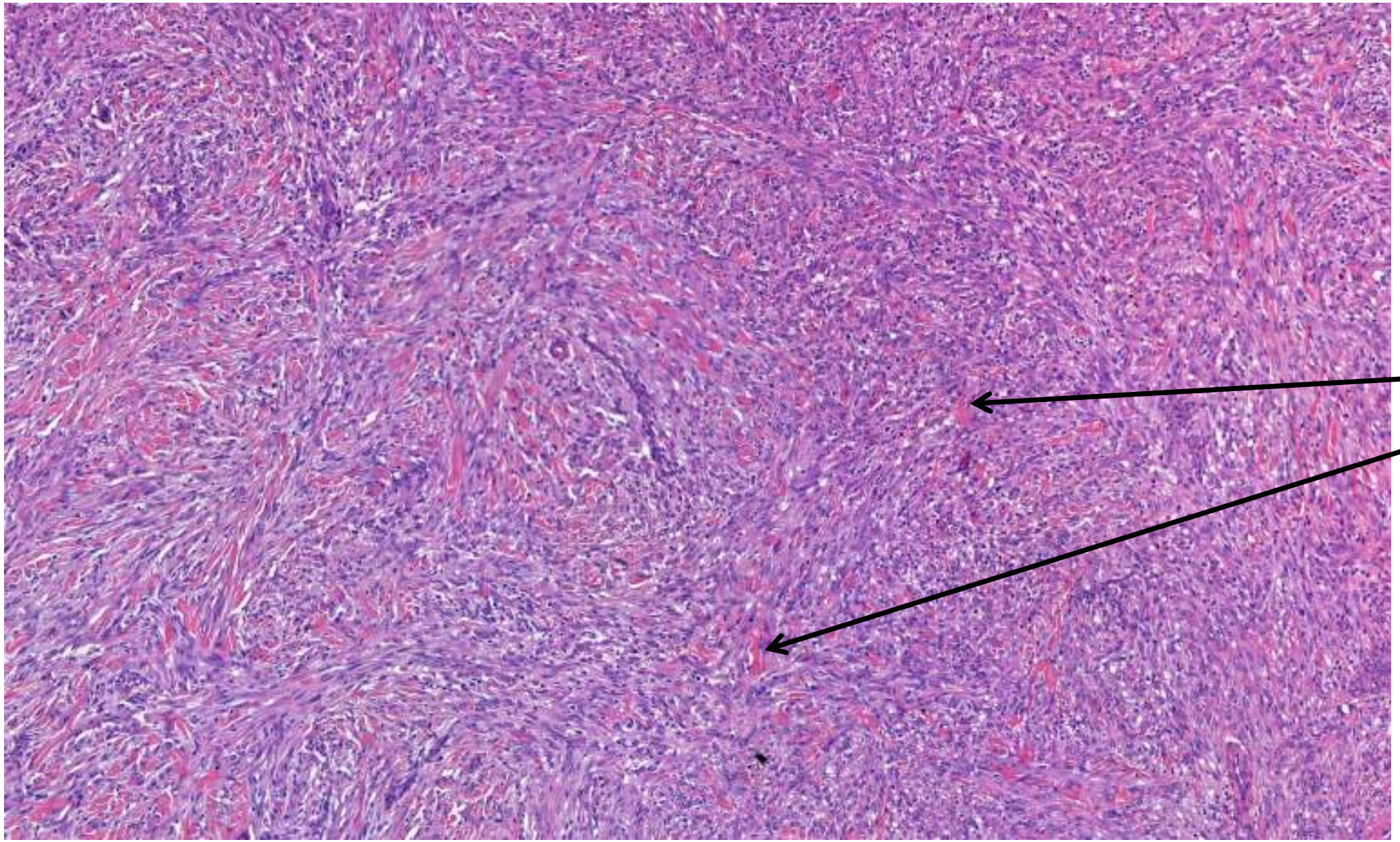
Histology



Histology

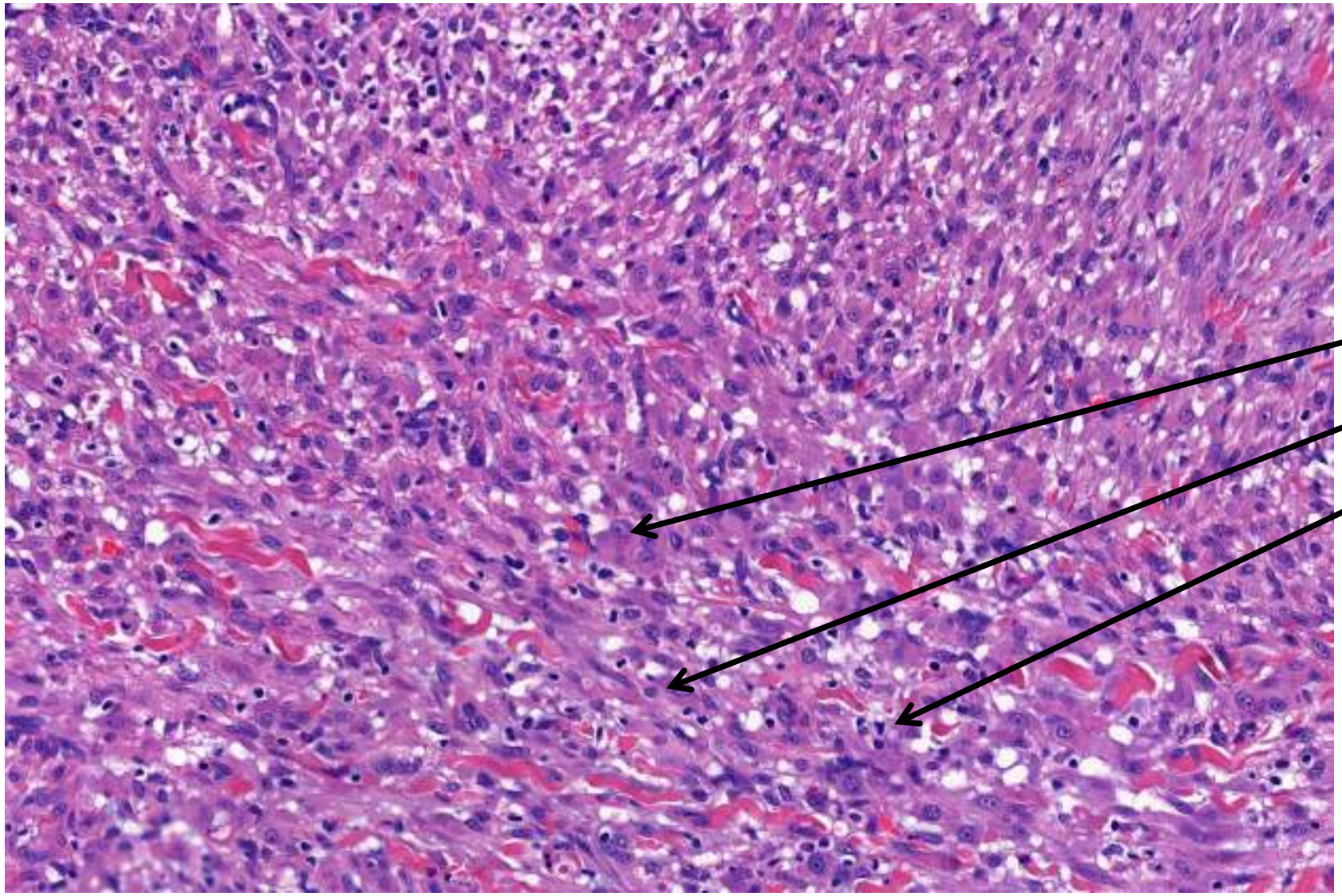


Histology



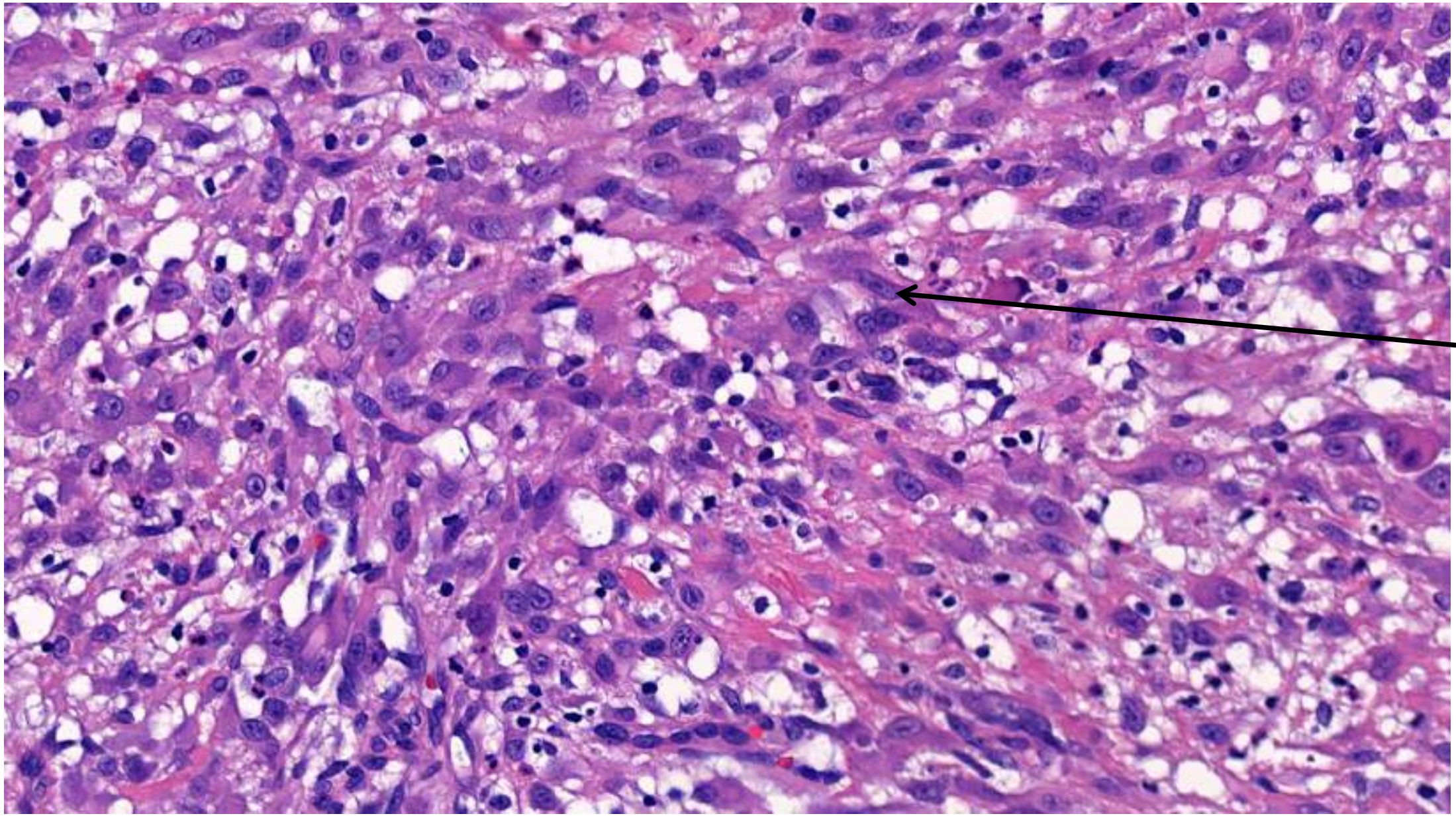
x10 magnification

Histology



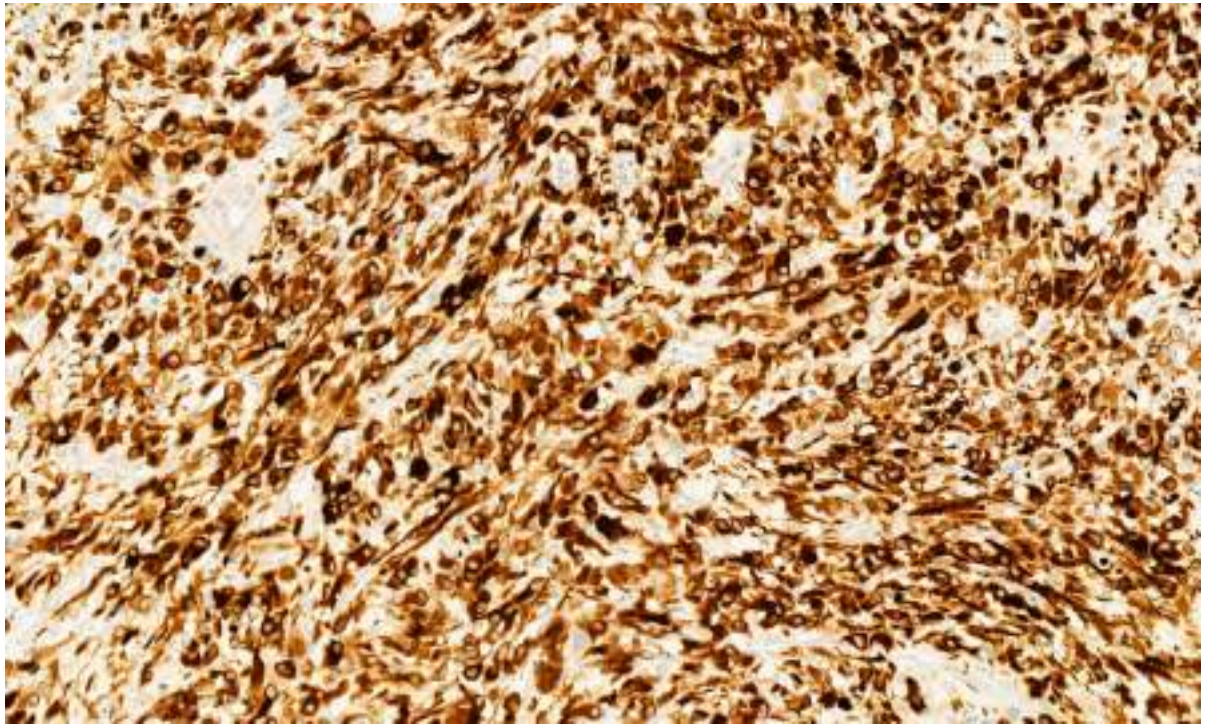
x20 magnification

Histology



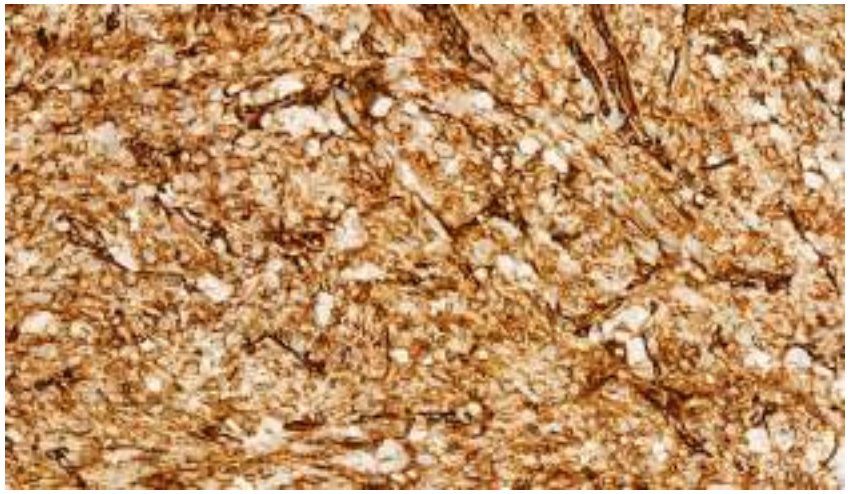
Immunohistochemistry

High power cytokeratin (CK) AE1/AE3 positivity

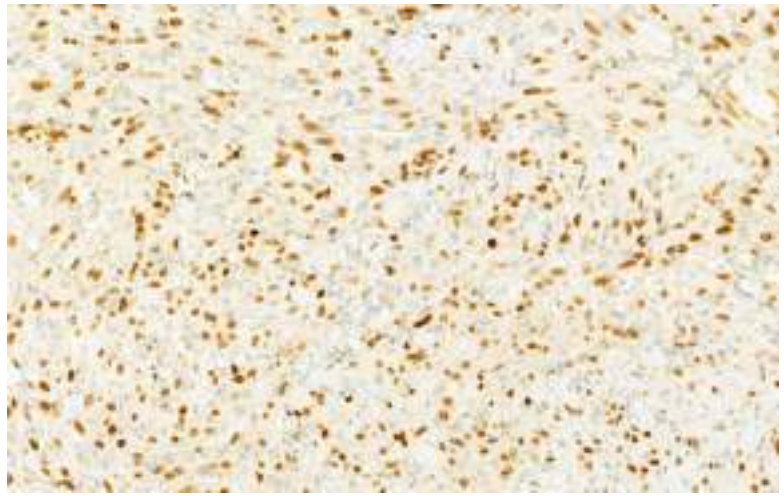


(+) stains include:

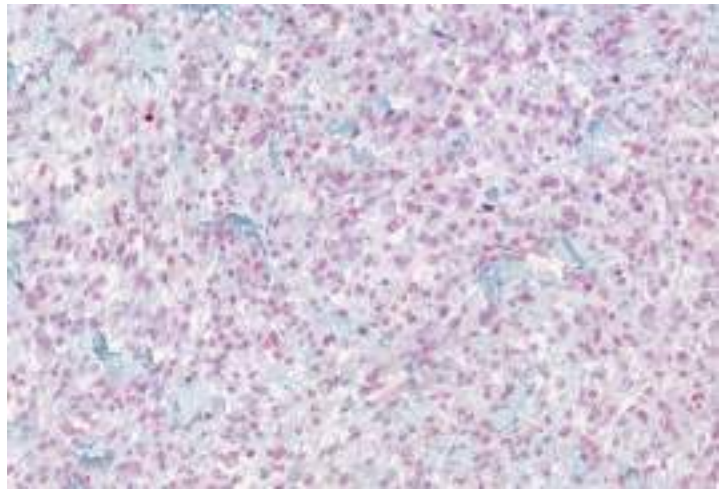
- Vascular markers: CD31 and ETS-related gene (ERG)
- Integrase interactor 1 (INI1) showed retained nuclear expression.
- FOSB



CD31

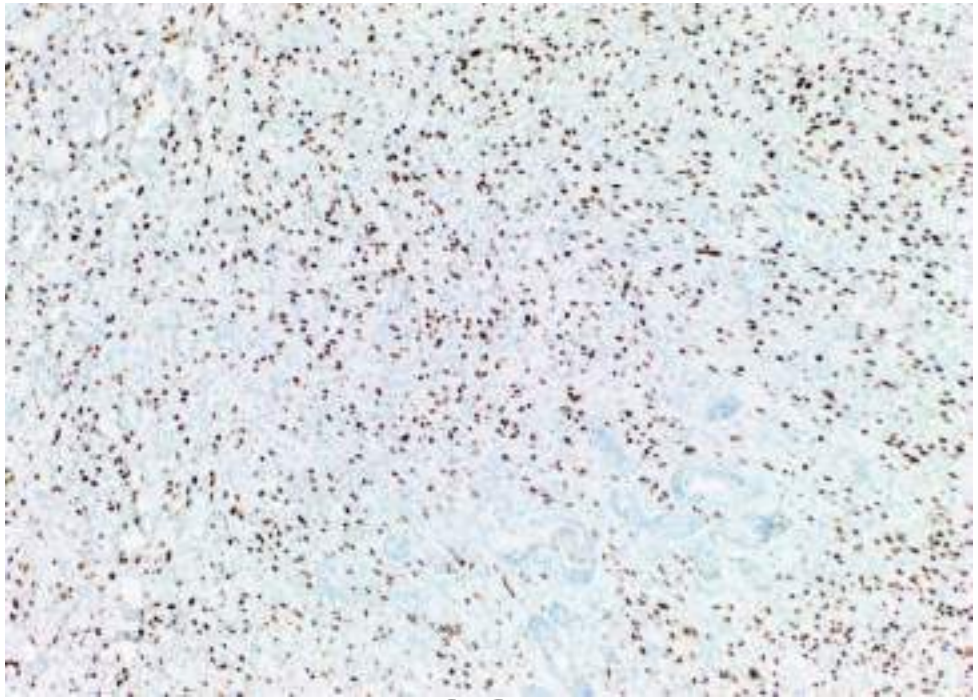


ERG



INI1

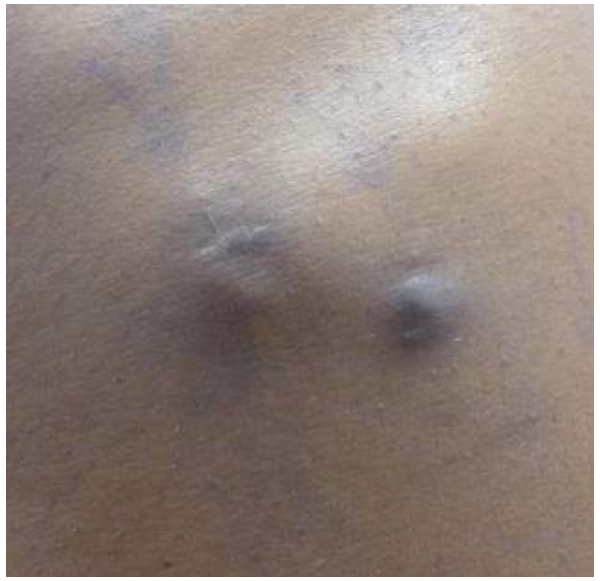
SERPINE1-FOSB gene fusion due to the chromosomal translocation t(7;19)(q22;q13)

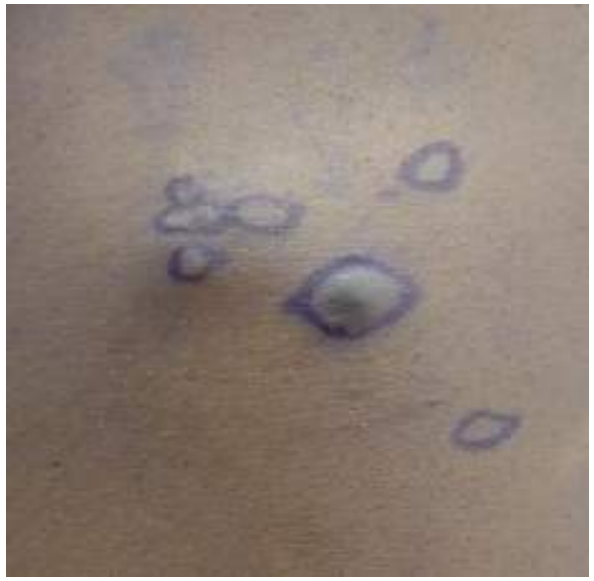


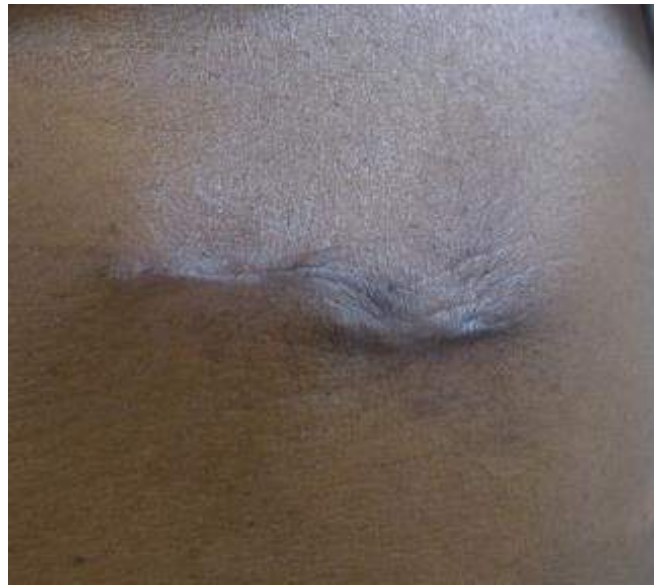
FOSB

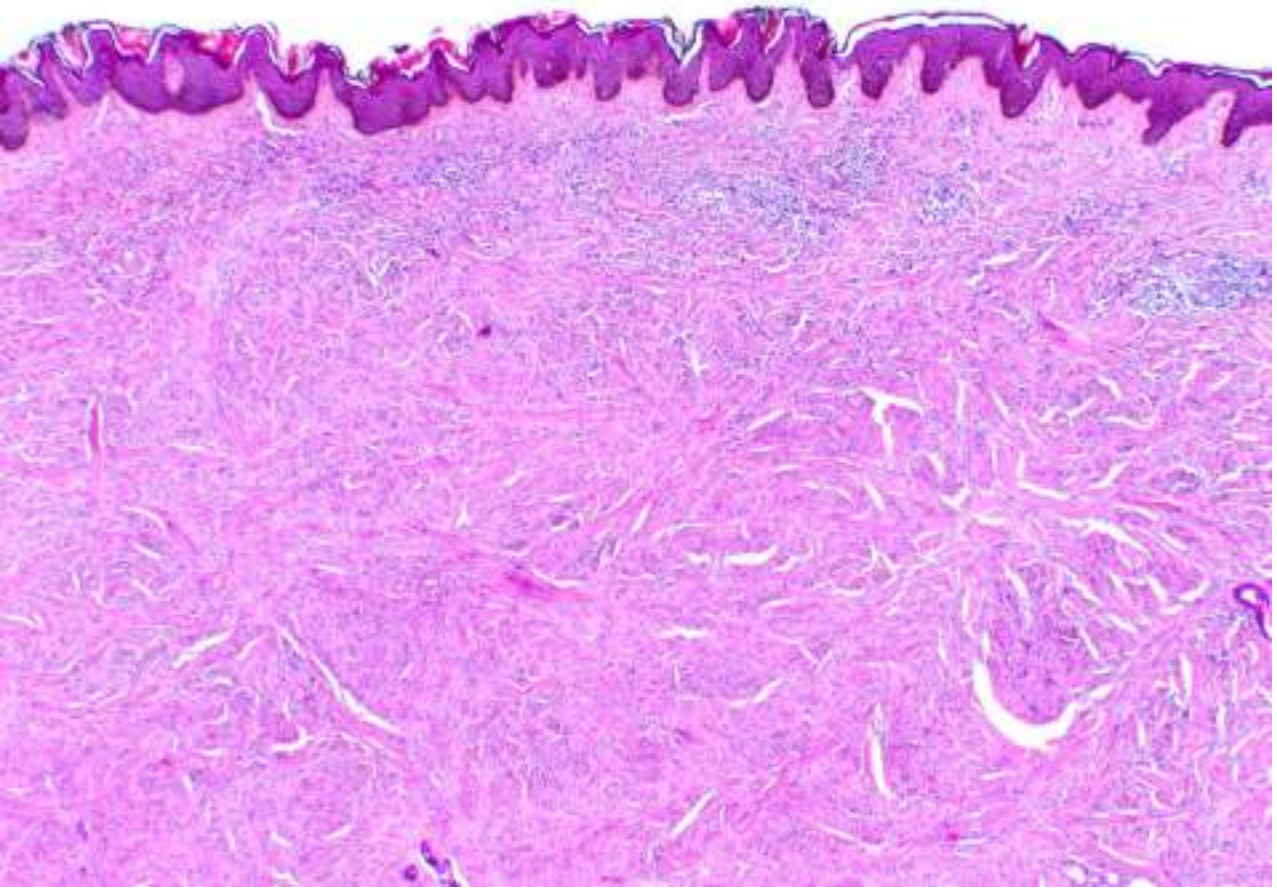
Diagnosis: Pseudomyogenic haemangioendothelioma

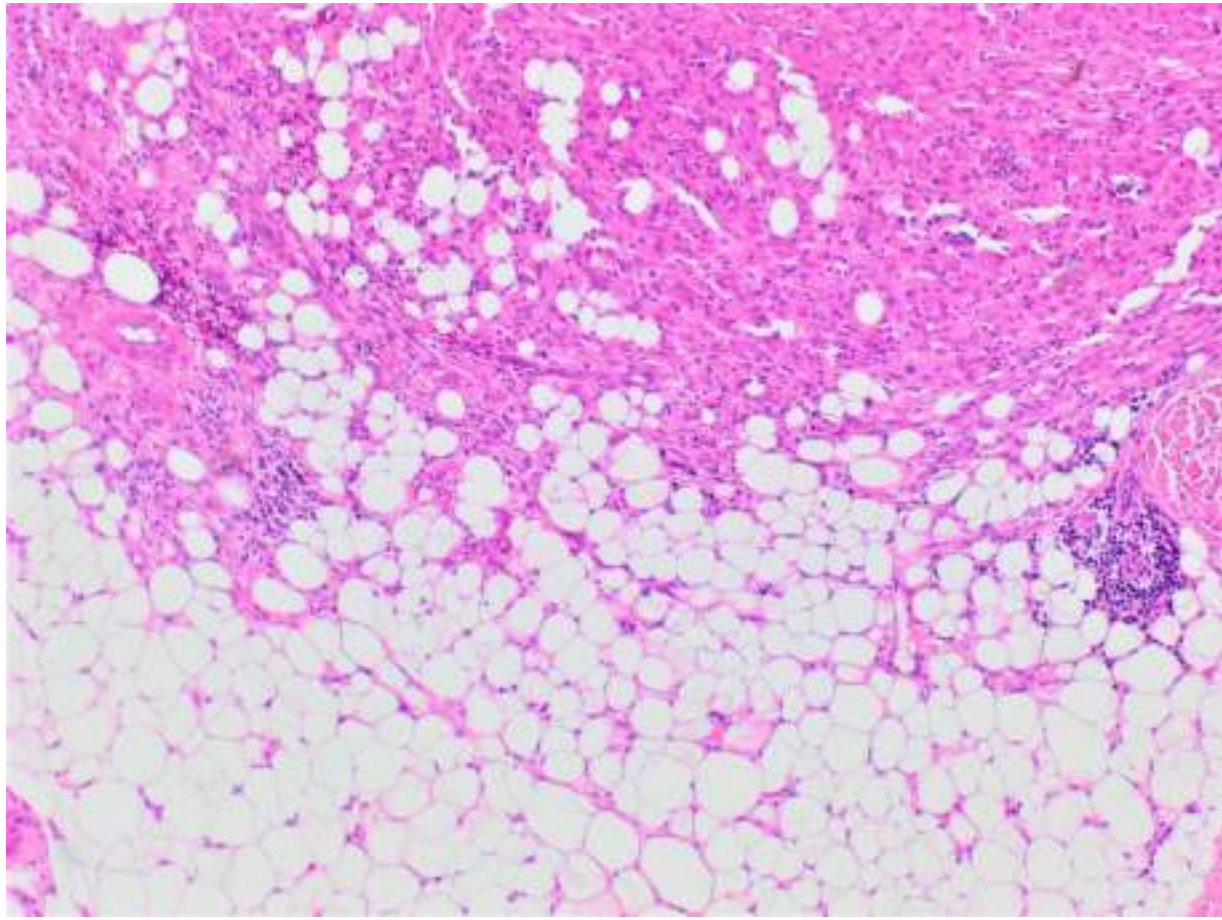
- 47 yo F
- 1 year history of multiple painful lesions on the left side of the abdomen
- PMH Graves disease

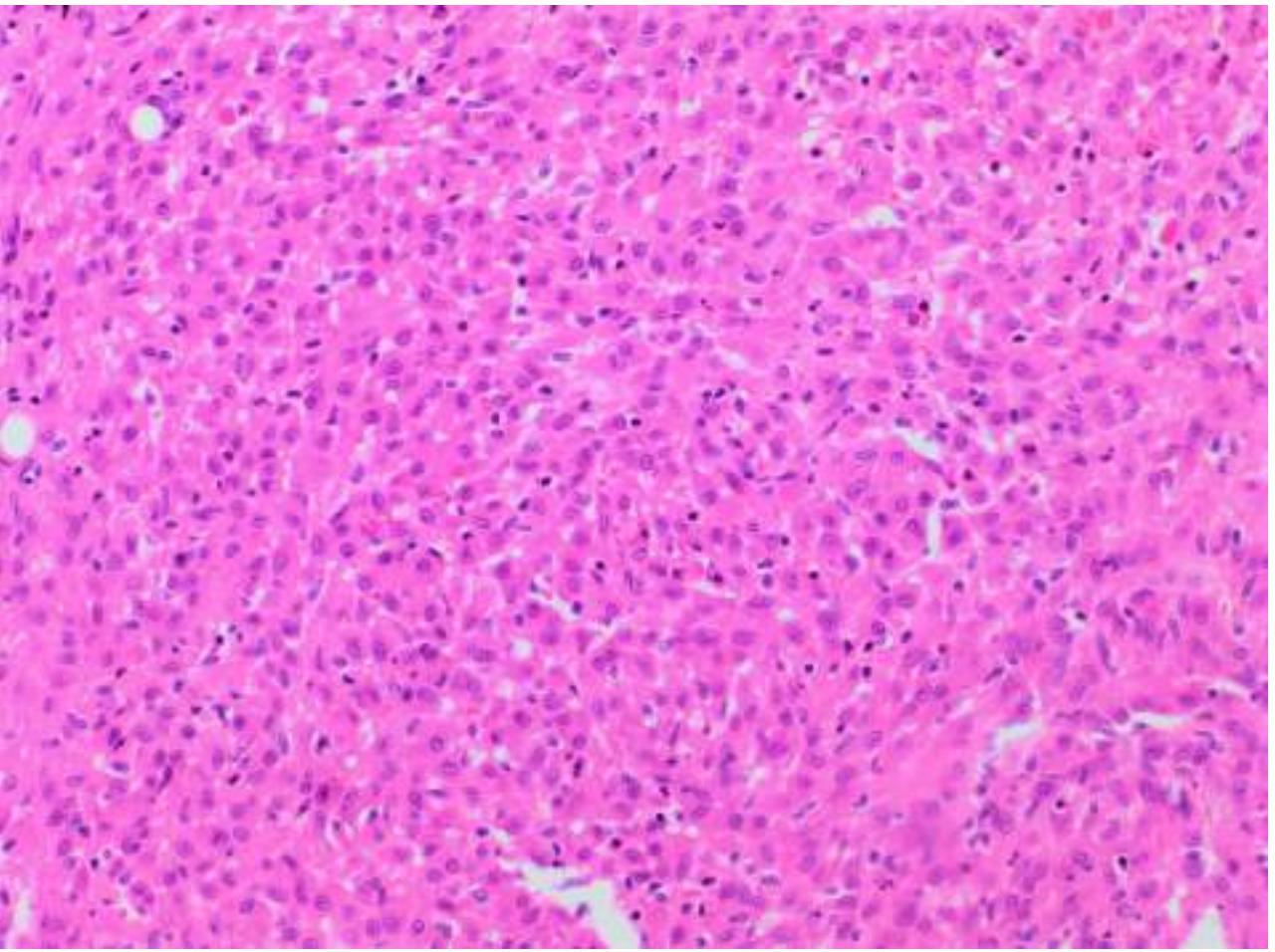


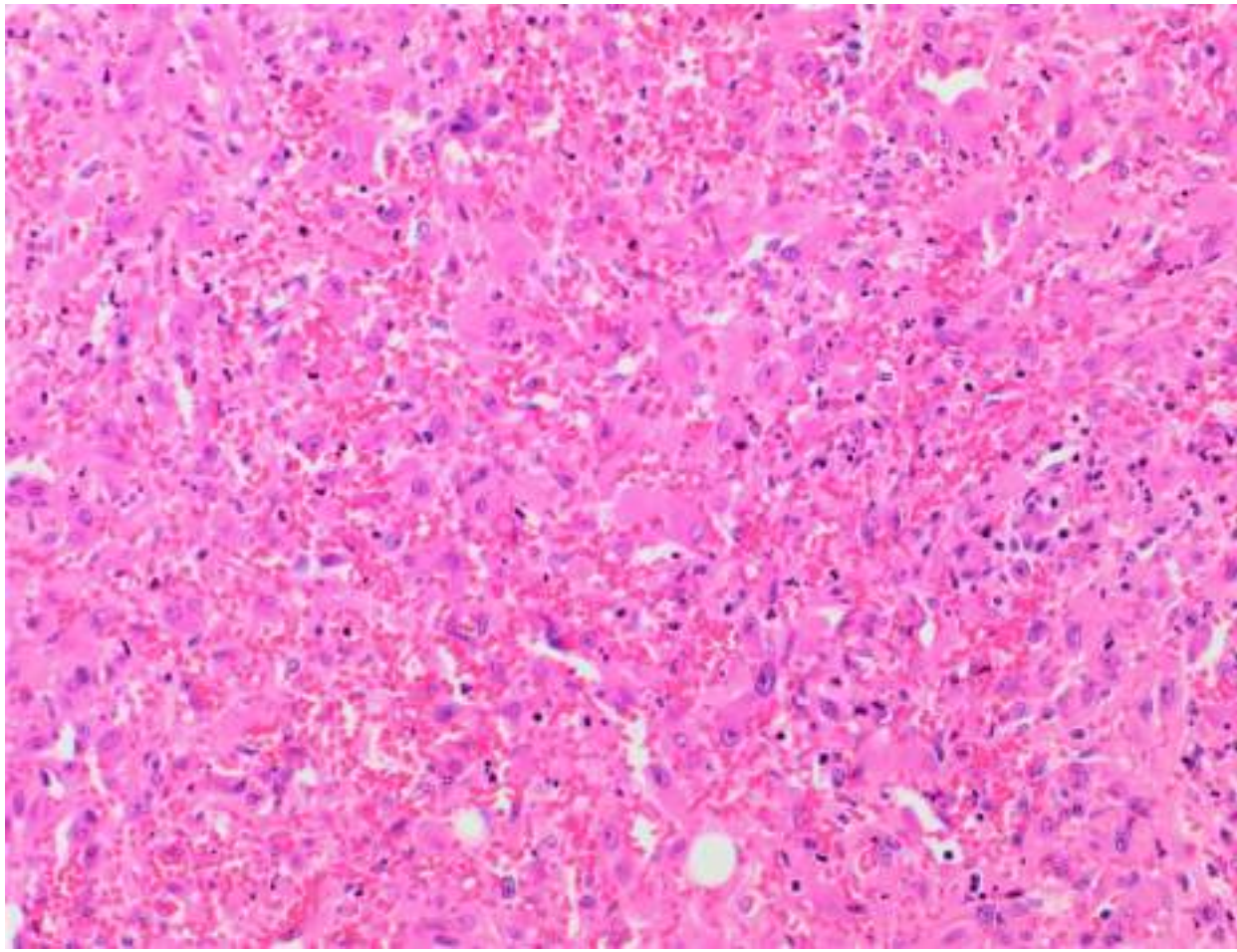


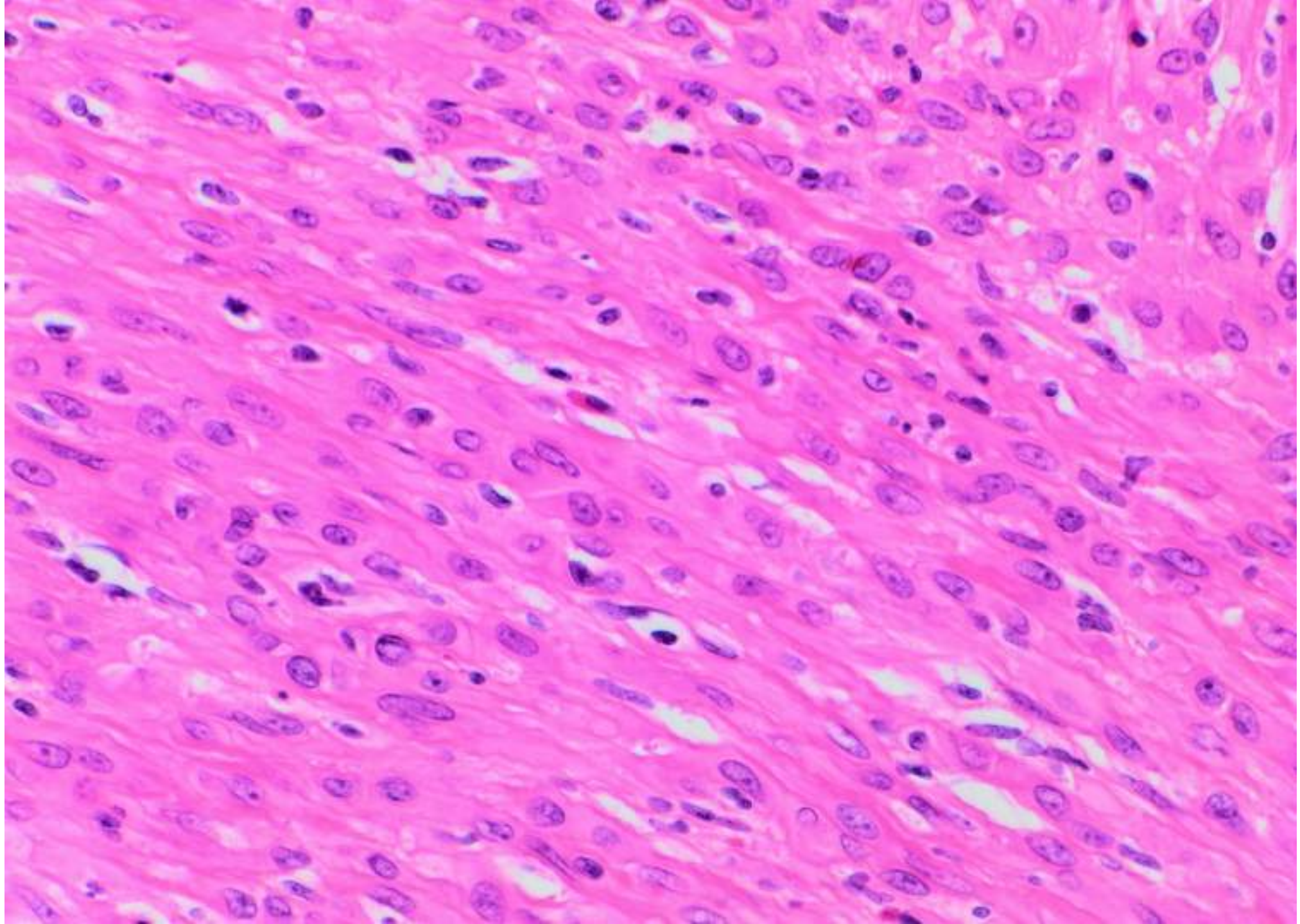


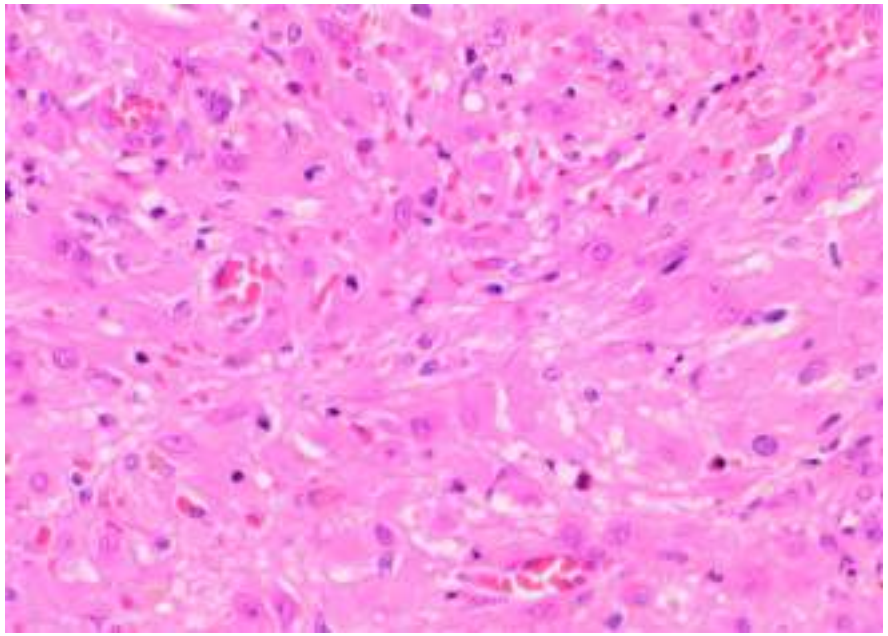


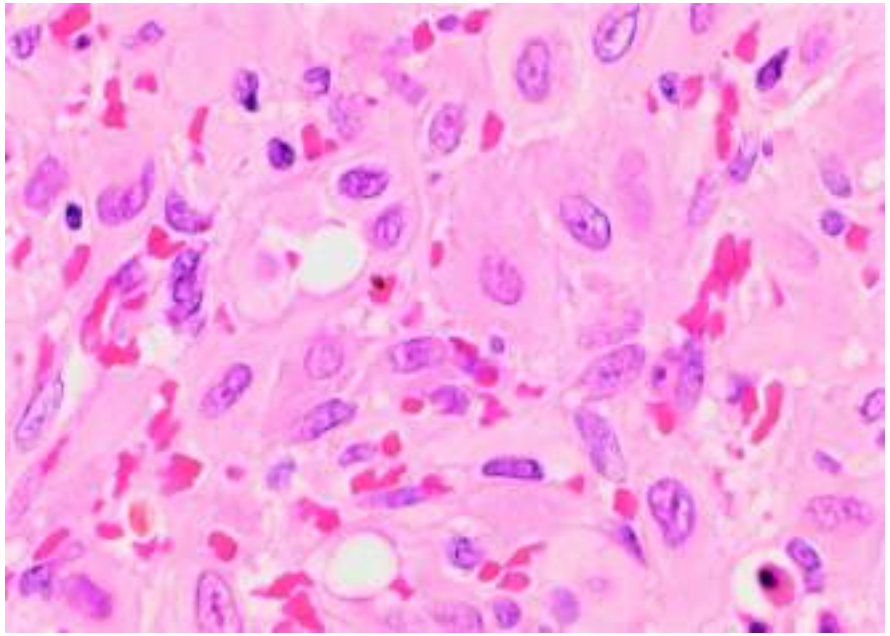


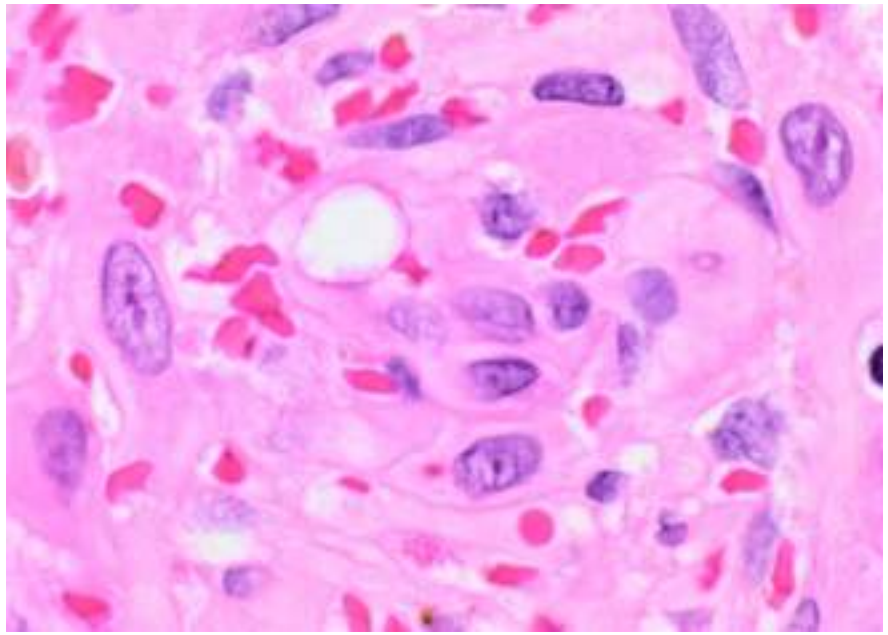


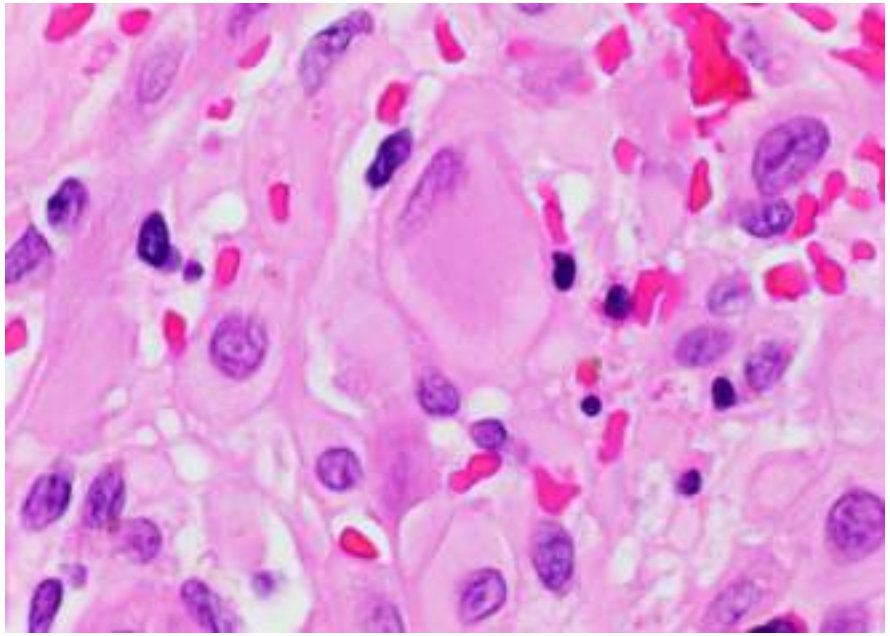




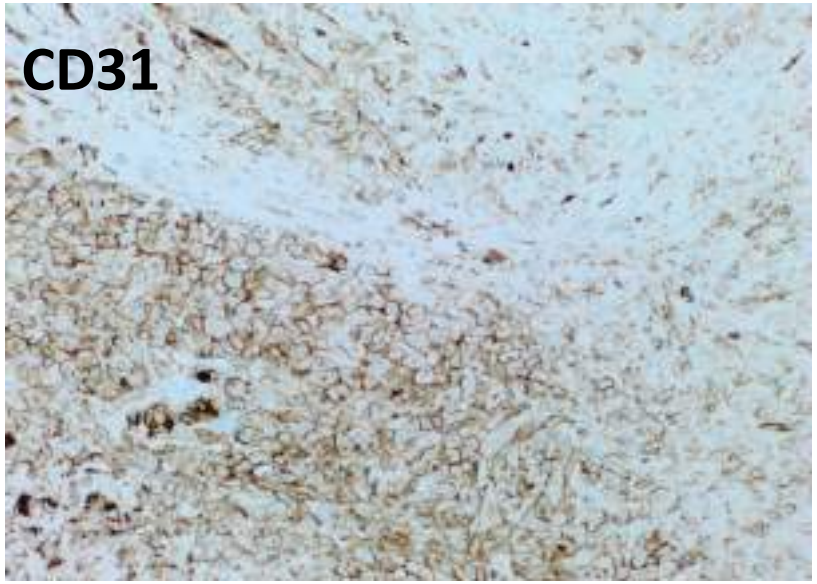


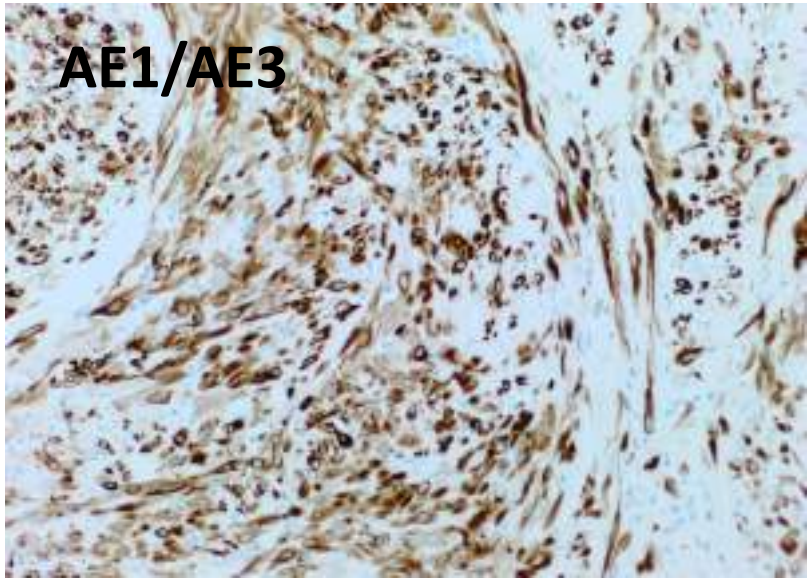


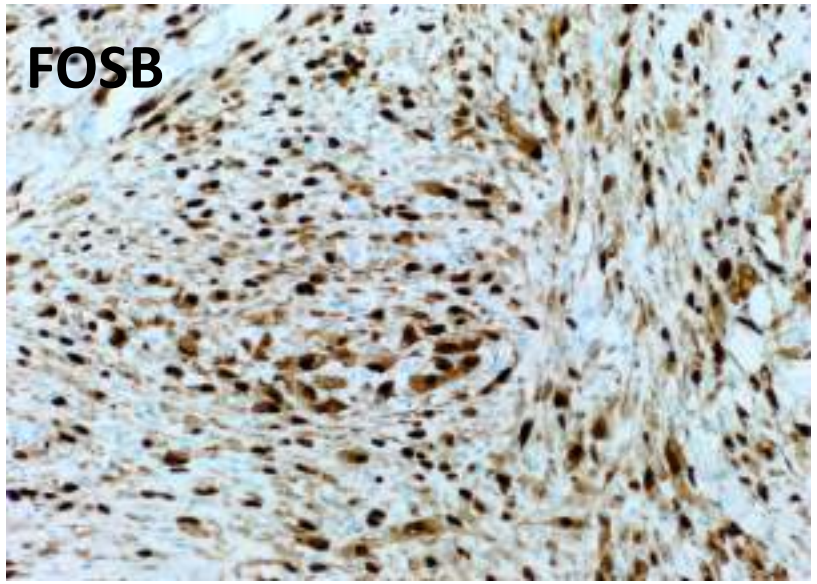




IHC



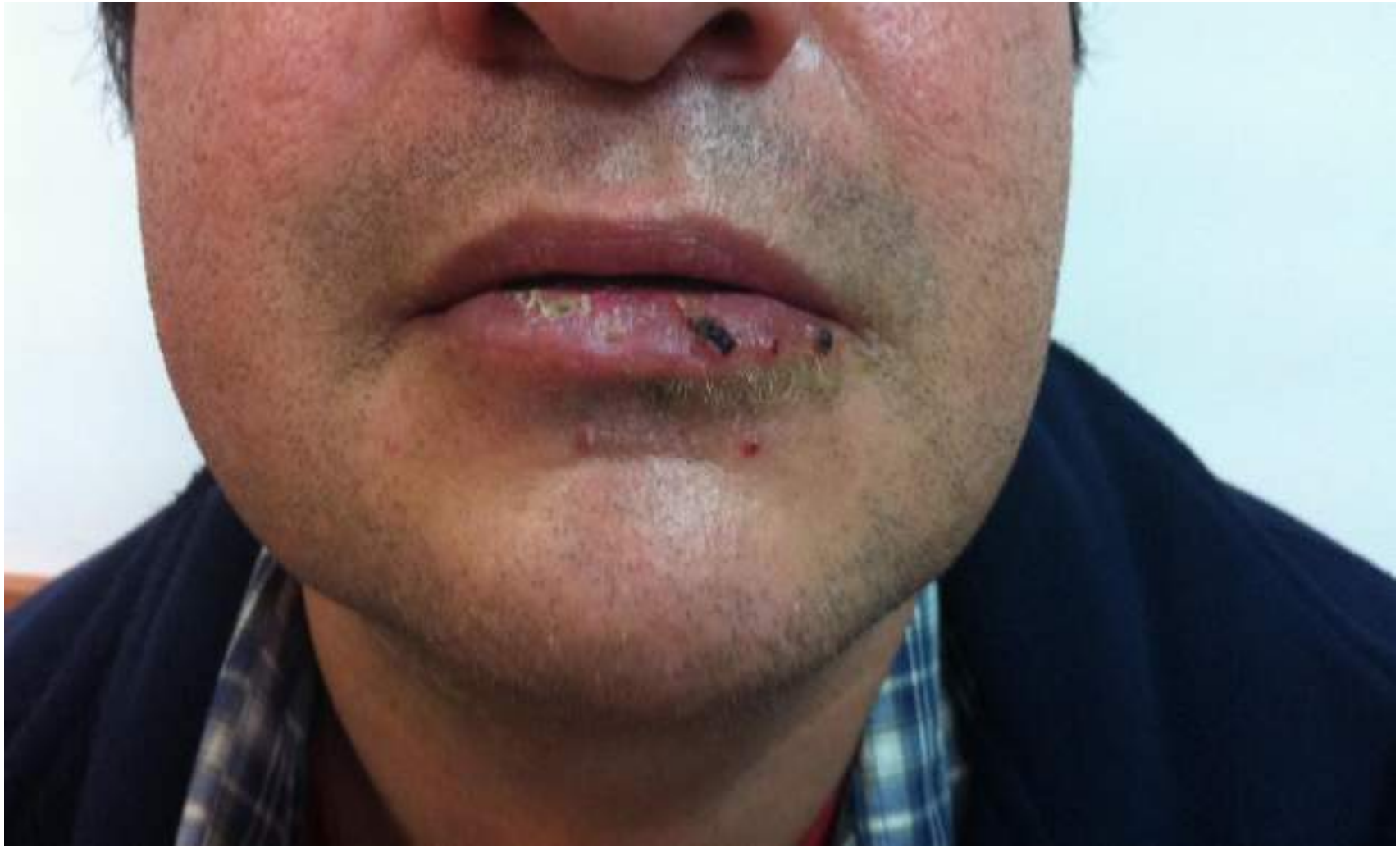




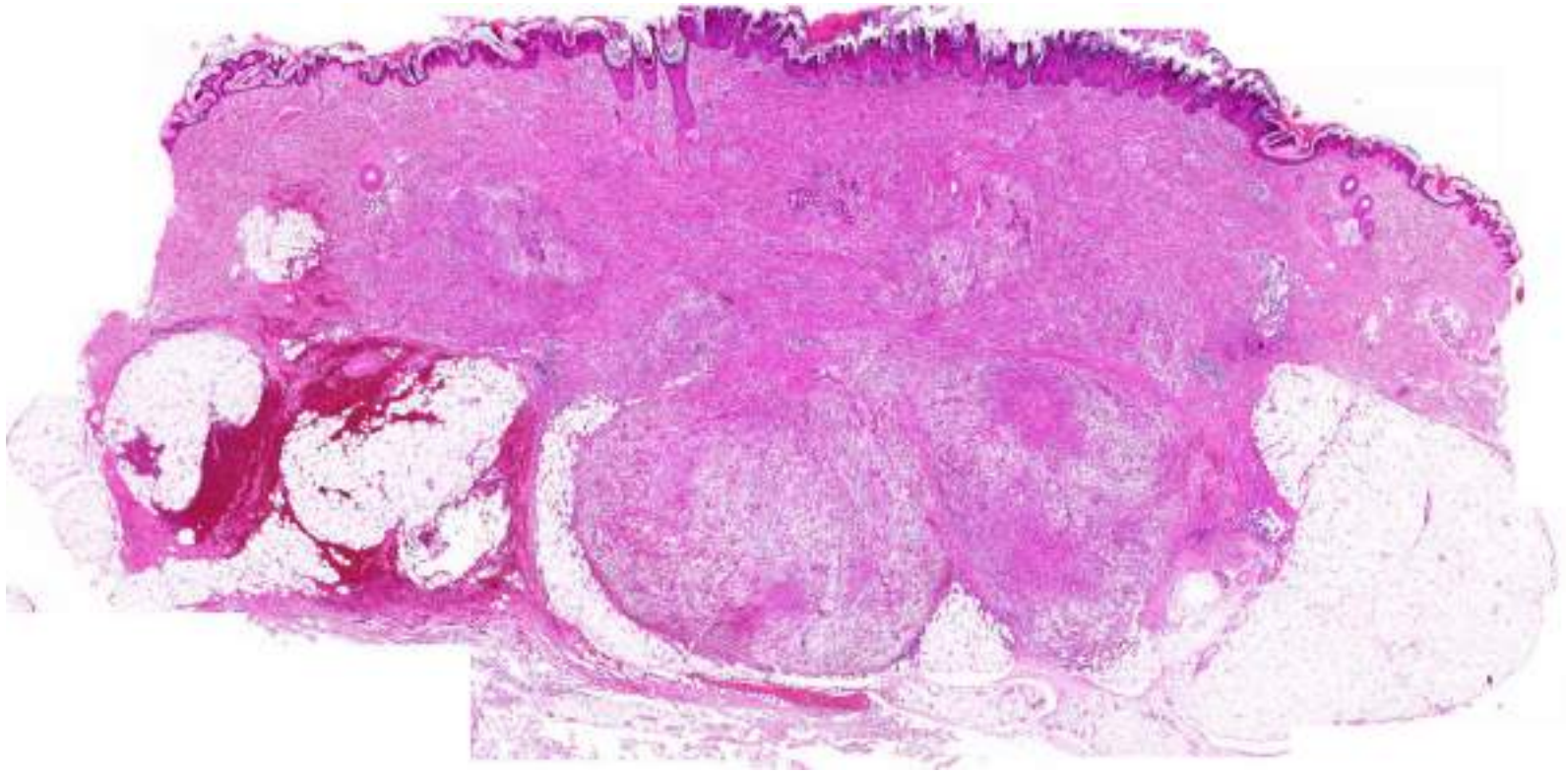
(-) STAINS

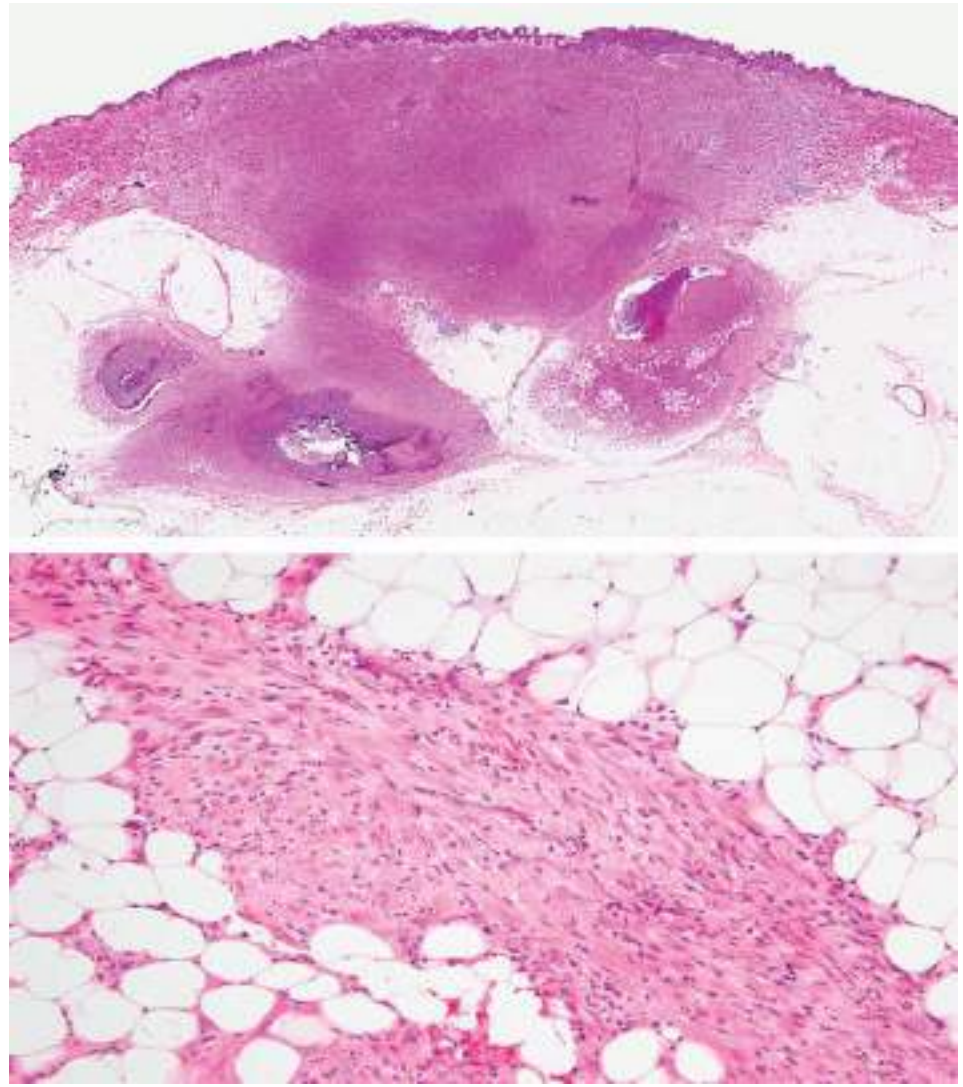
CD34, CAMTA-1, D2-40, HHV-8, S100 p, EMA, MNF116, SMA, desmin, TFE3

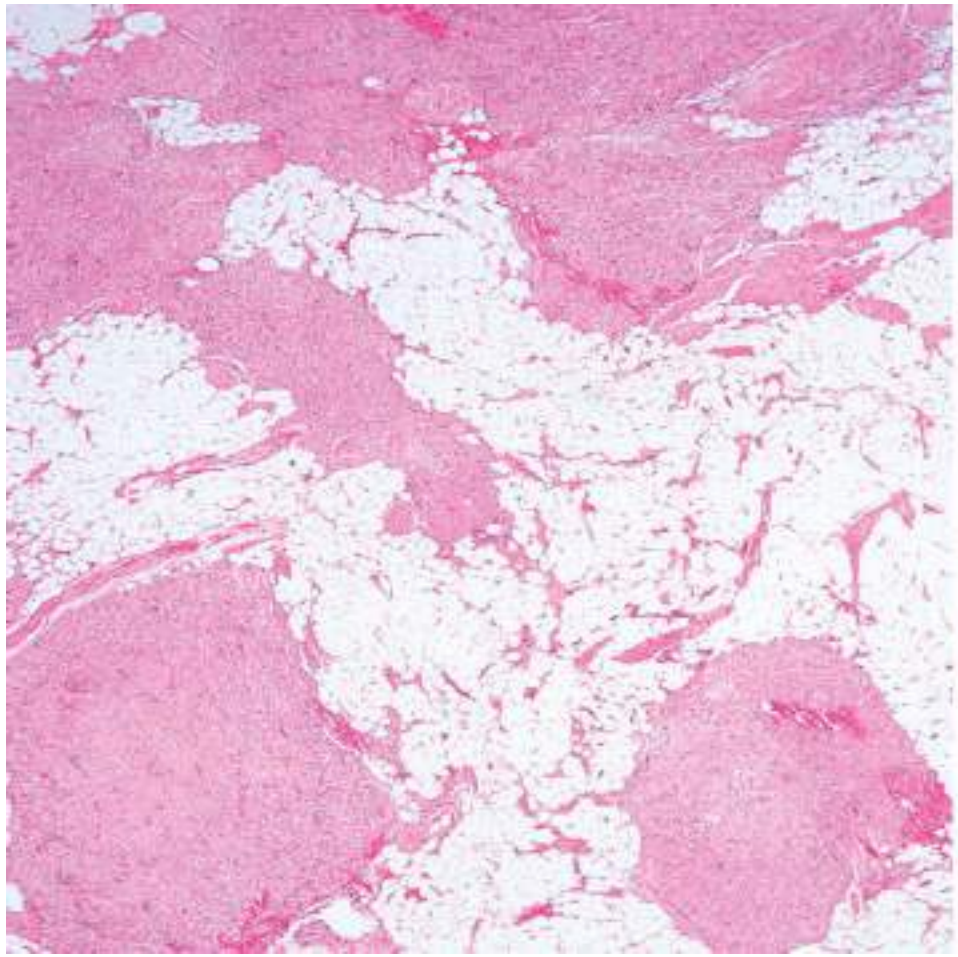
Pseudomyogenic haemangioendothelioma

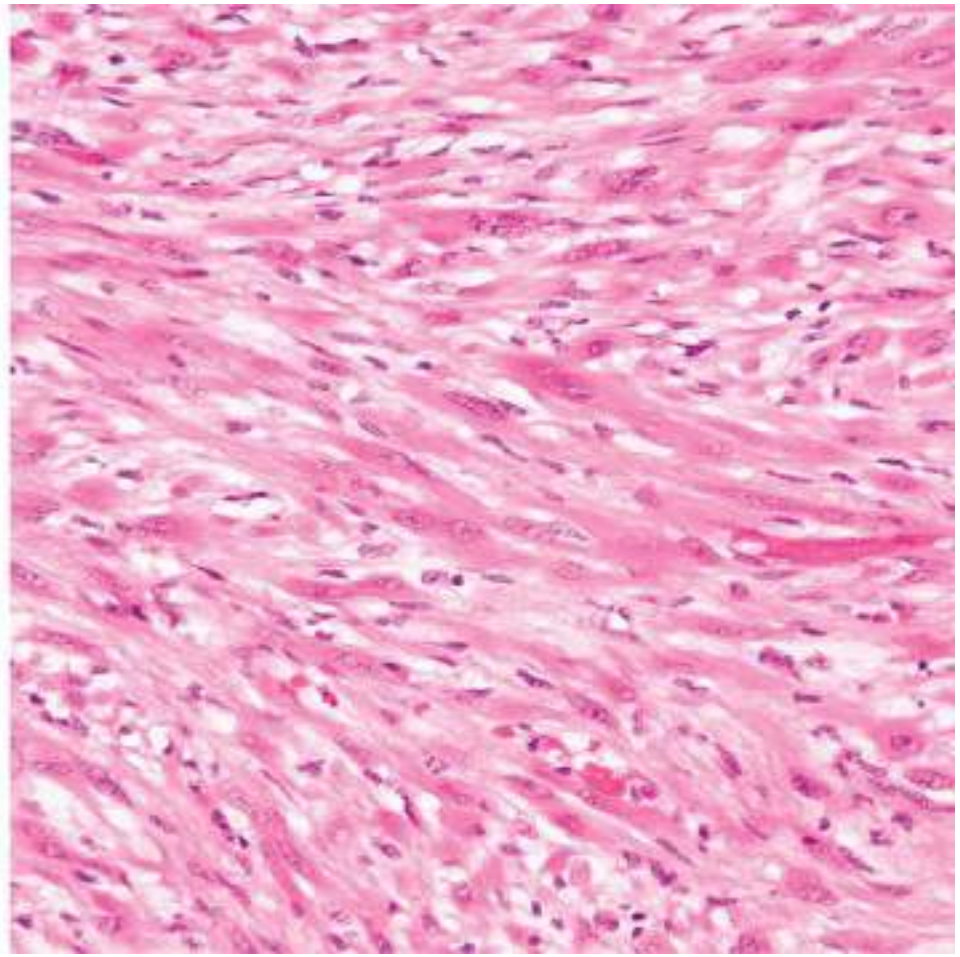


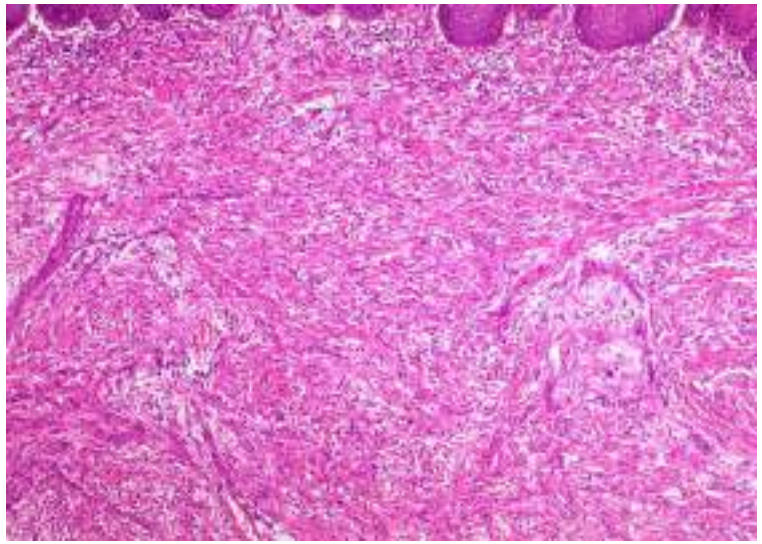
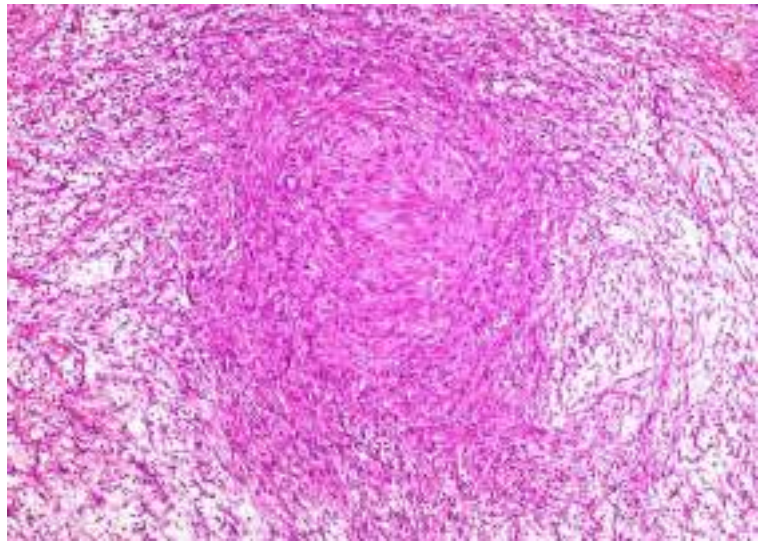
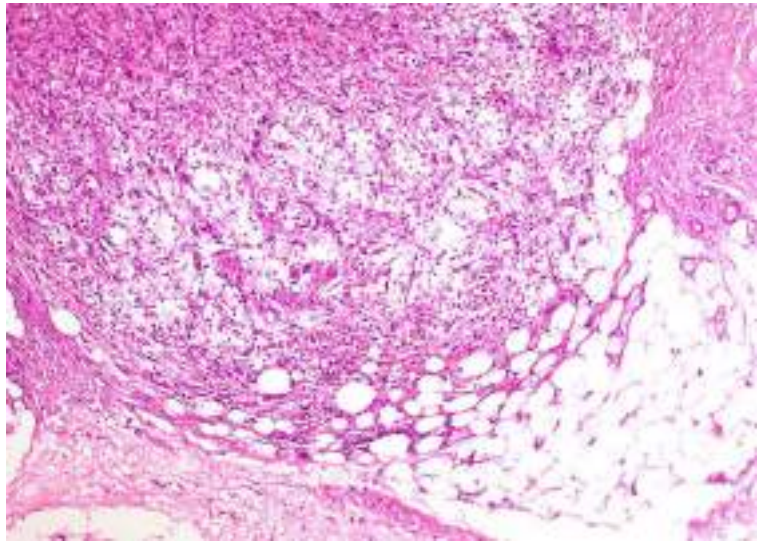
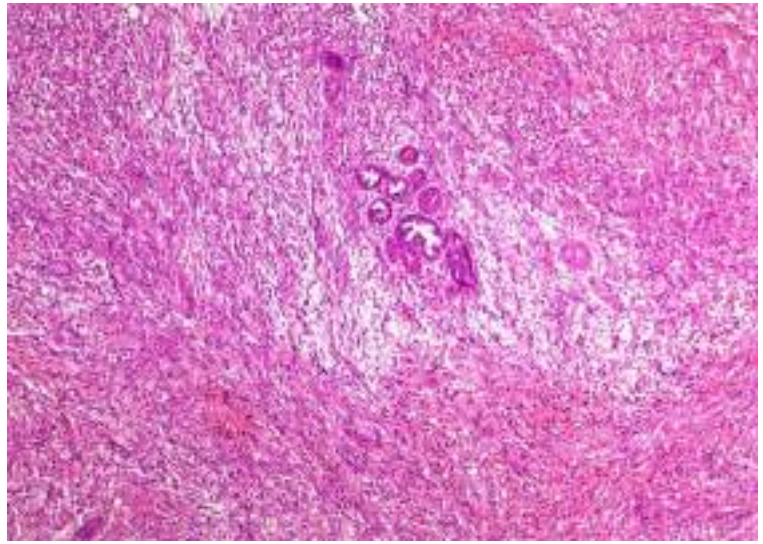
8 year-old male. Multiple painless nodules on the thigh

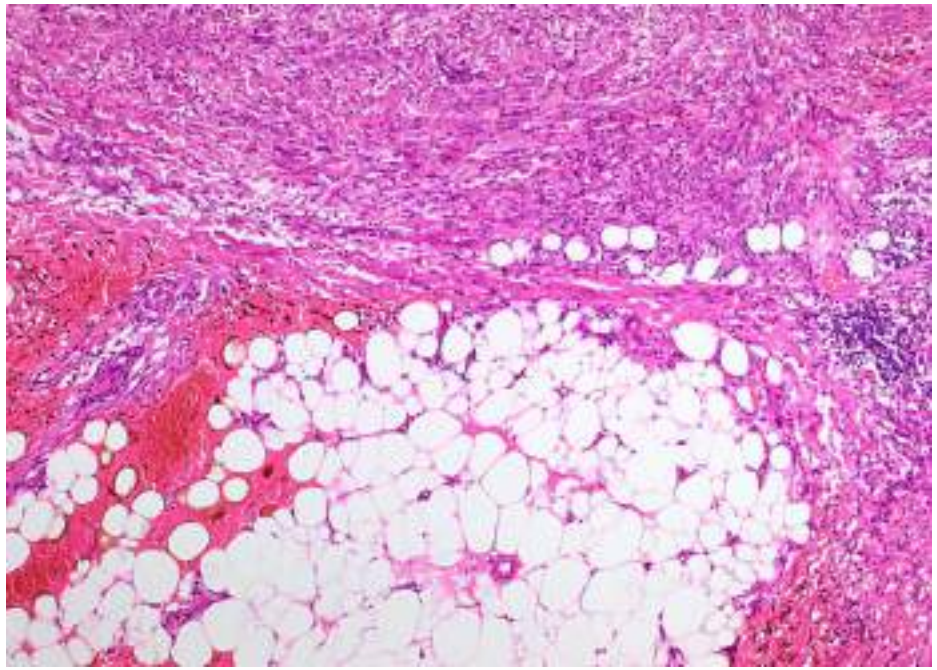


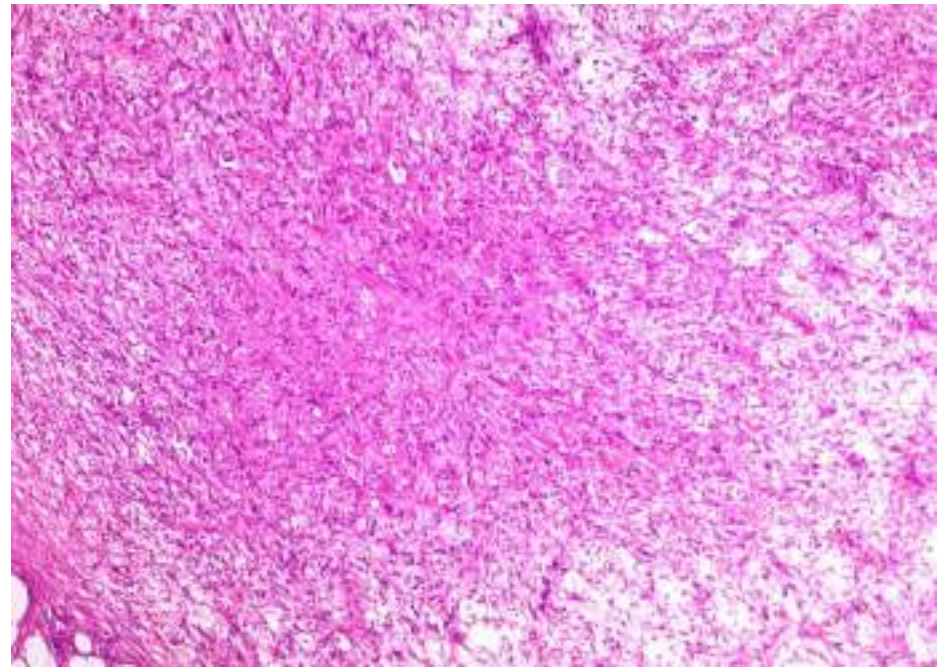






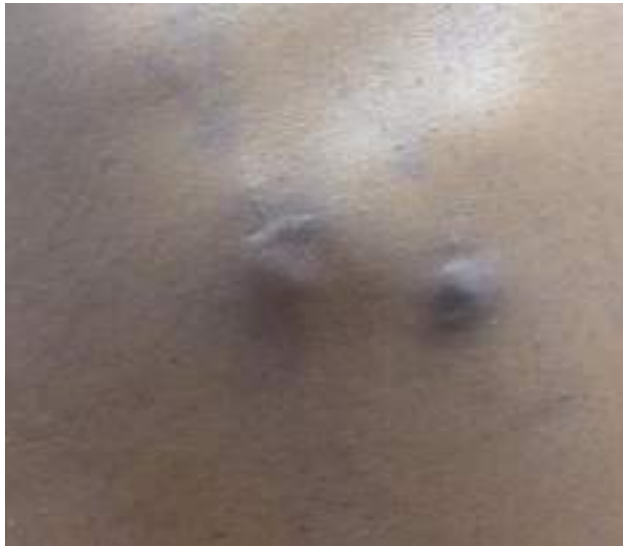









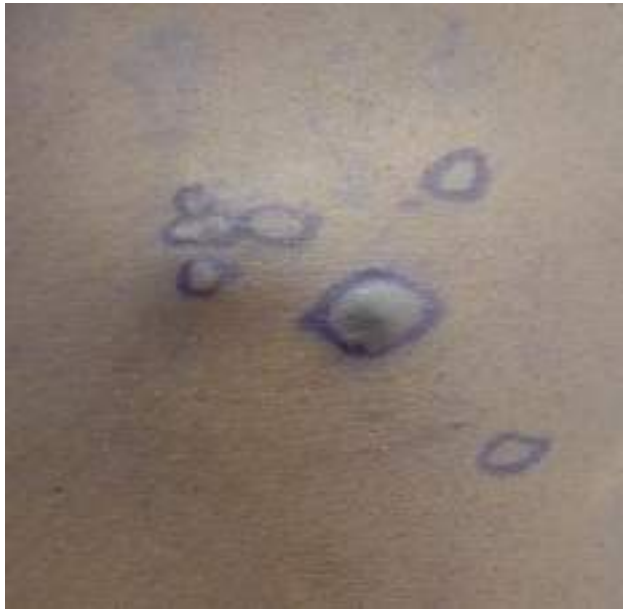
Pseudomyogenic haemangioendothelioma

- ‘fibroma-like’ variant of epithelioid sarcoma or epithelioid sarcoma-like haemangioendothelioma.
- Rare vascular neoplasm



CLINICAL PRESENTATION

- Subcutaneous nodules, frequently painful, mainly located in the extremities, trunk or head and neck
- M>>F, 2^{nd}-5^{th} decade
- Multifocality is common and it may involve bone and soft tissue
- Low grade malignancy with intermediate biological potential



Pseudomyogenic haemangioendothelioma

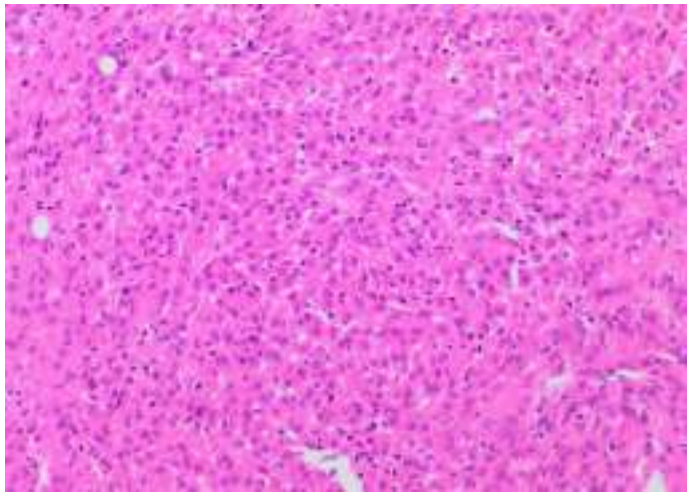
HISTOLOGY

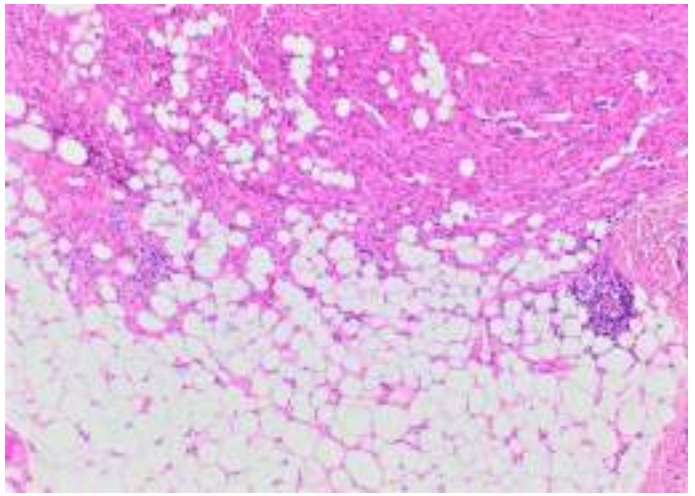
- Dermal and subcuctaneous, poorly circumscribed, infiltrative margins
- Epithelioid, spindled and rhabdoid cells
- Non vasoformative, intracytoplasmic lumina rare
- CD31, ERG, INI1 and AE1/AE3 positive; CAMTA1 and MNF116 negative

MOLECULAR

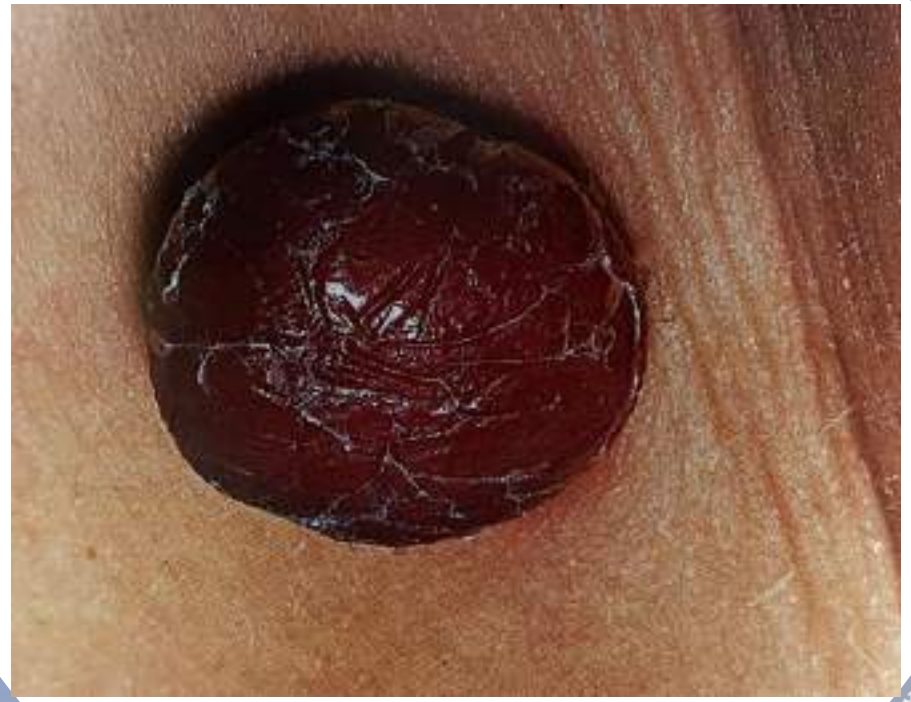
SERPINE1-FOSB gene fusion derived from t(7;19)(q22;q13),

Patognomonic, not been observed in any other vascular or soft tissue tumours, and can be demonstrated by the strong and diffuse nuclear positivity for FOSB immunostain





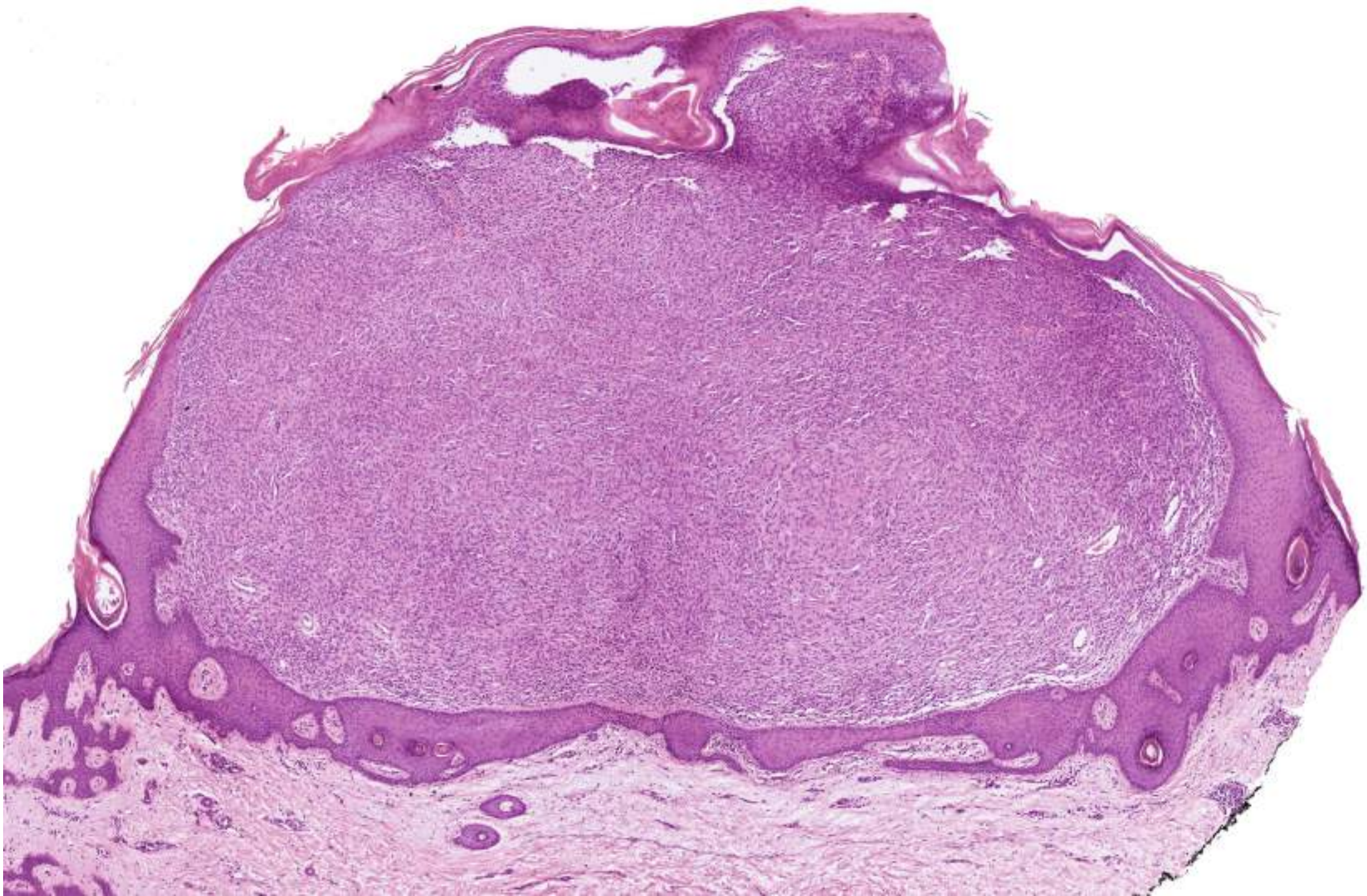
Epithelioid fibrous histiocytoma

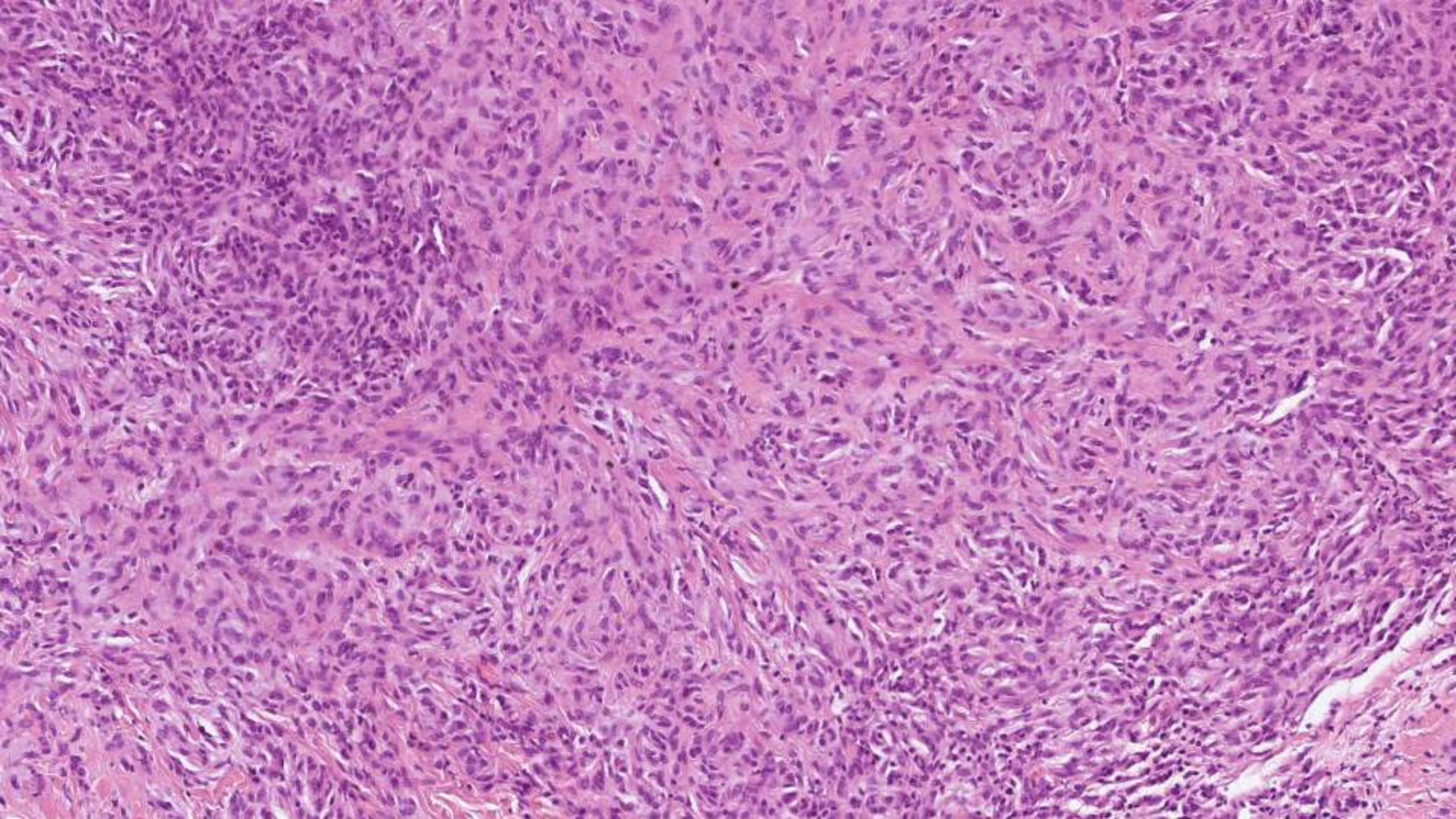


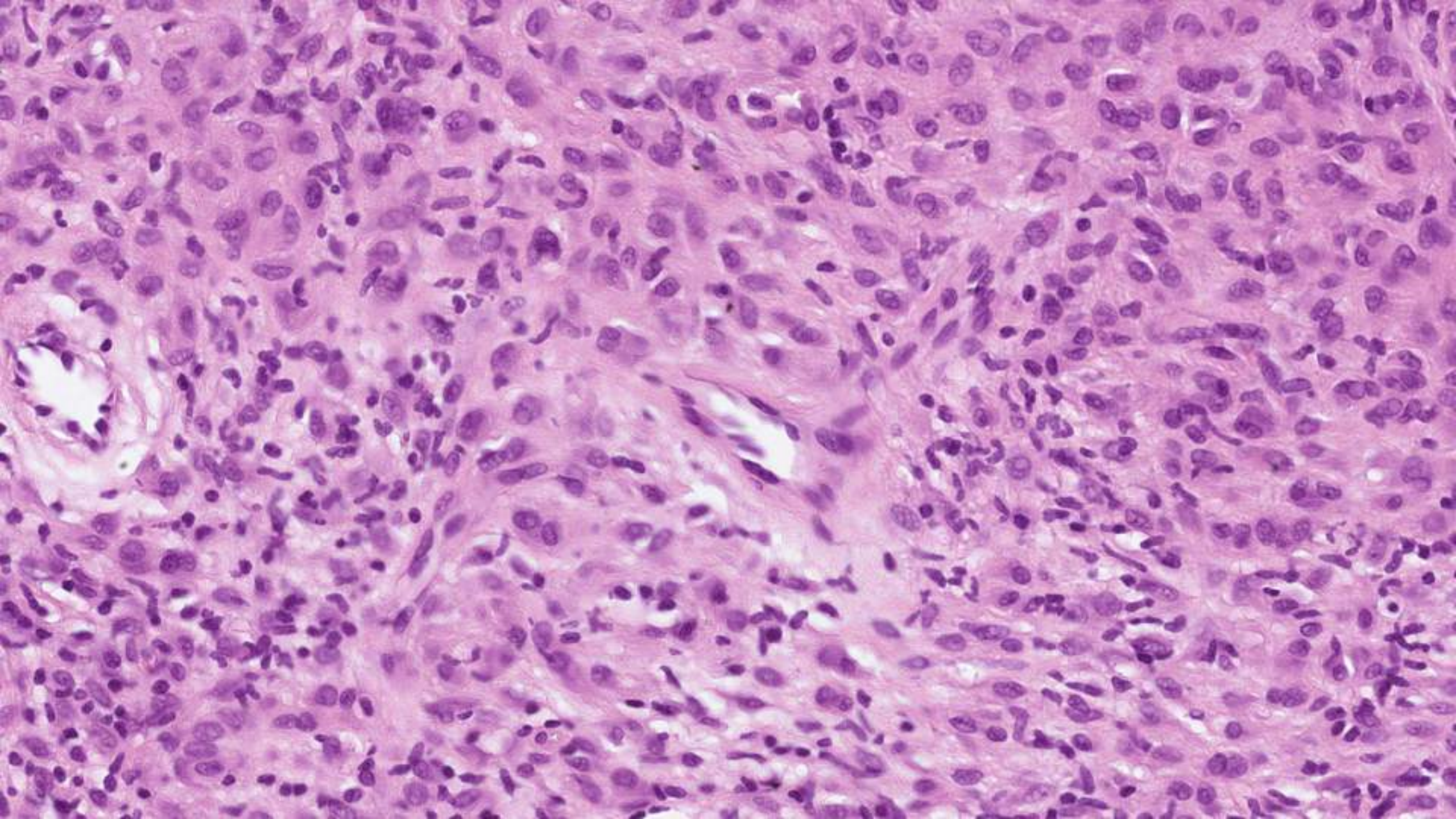
Definition: Distinctive tumour type, proliferation of rounded or epithelioid cells comprising at least 50% of the lesional cell population

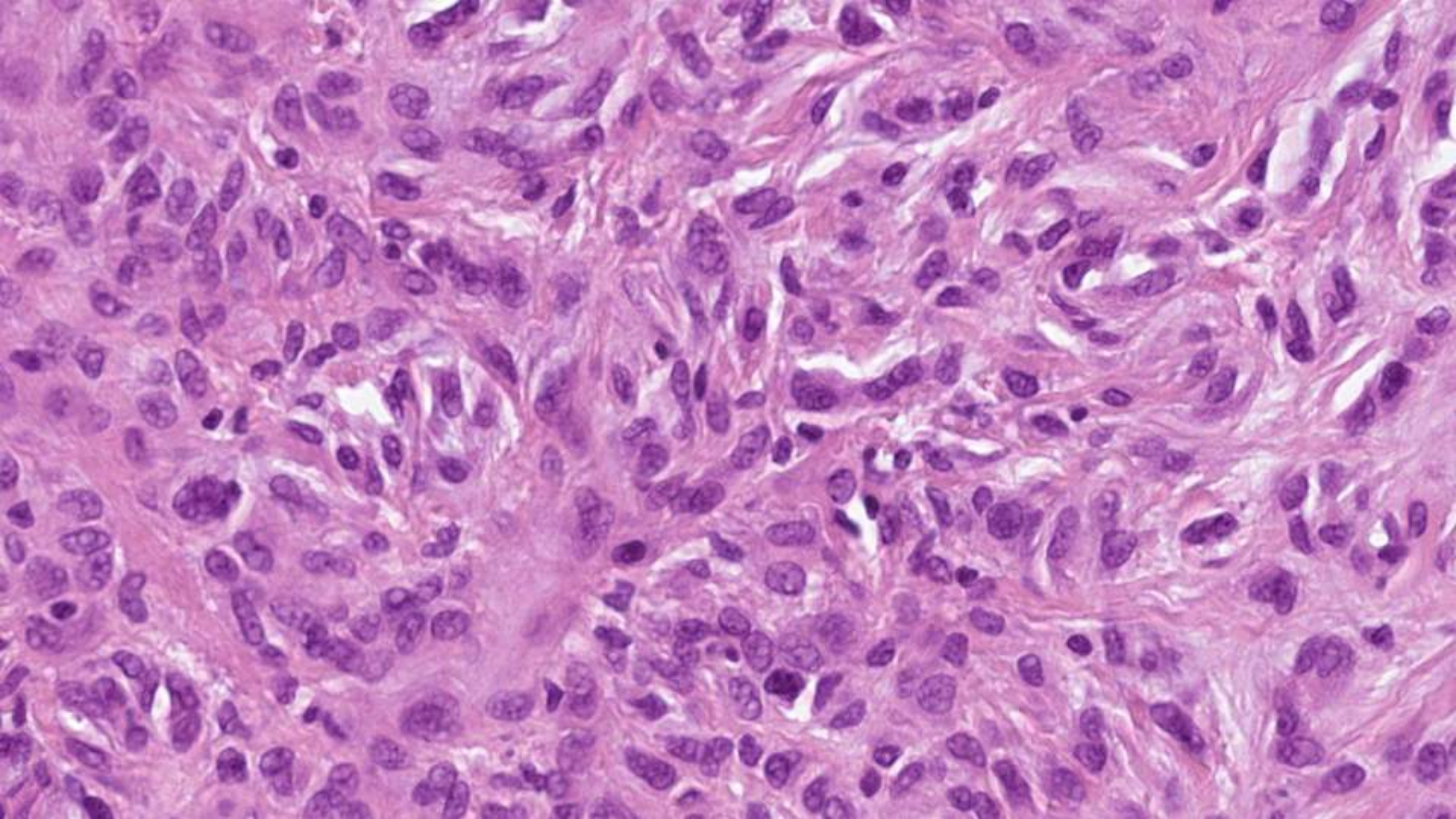
Not a variant of FH/DF

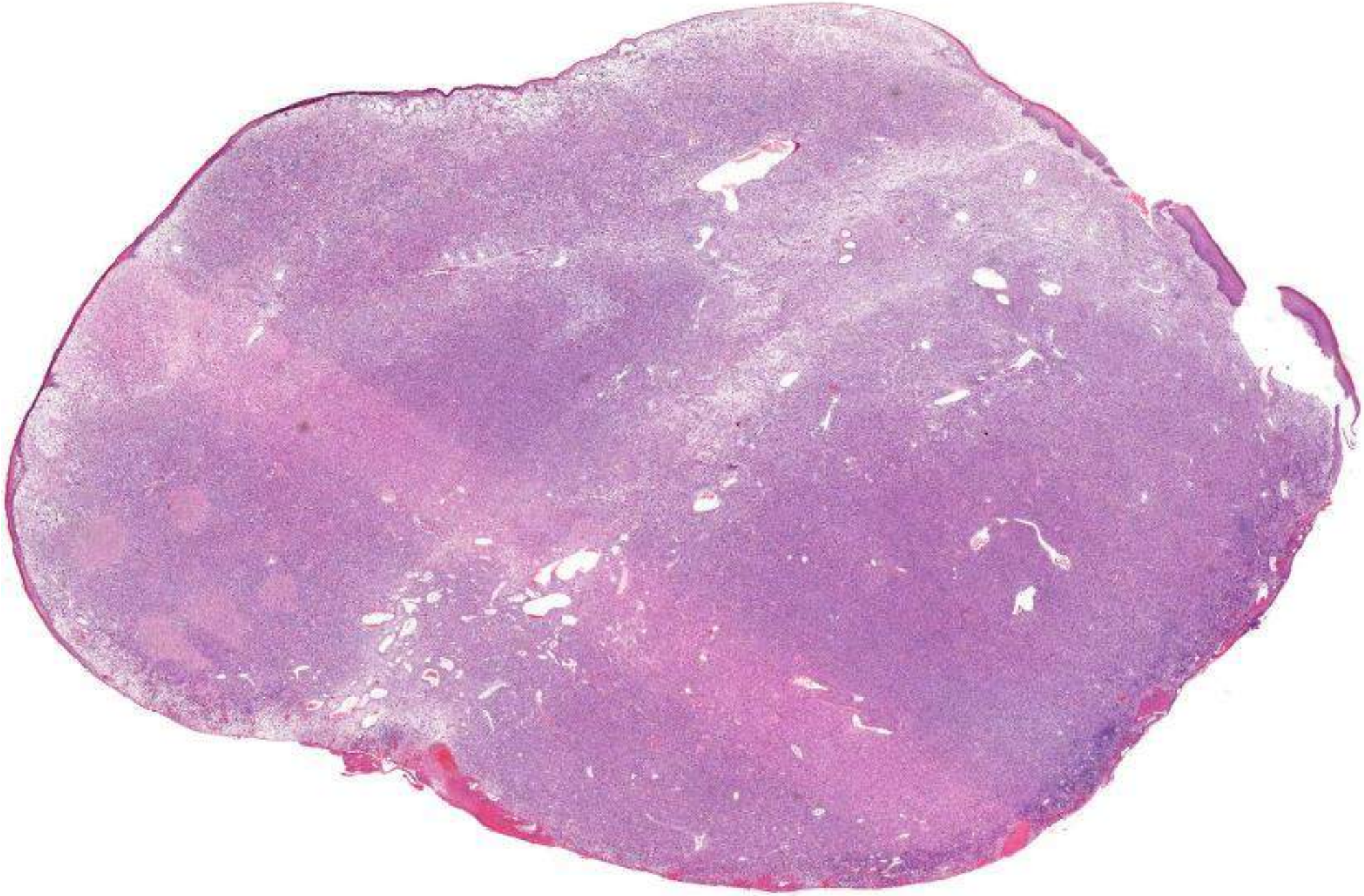
- Fifth decade of life
- Slight male predominance
- Lower extremities, upper extremities, trunk, head and neck
- Polypoid/vascular appearance/usually not ulcerated (like a non-ulcerated pyogenic granuloma)

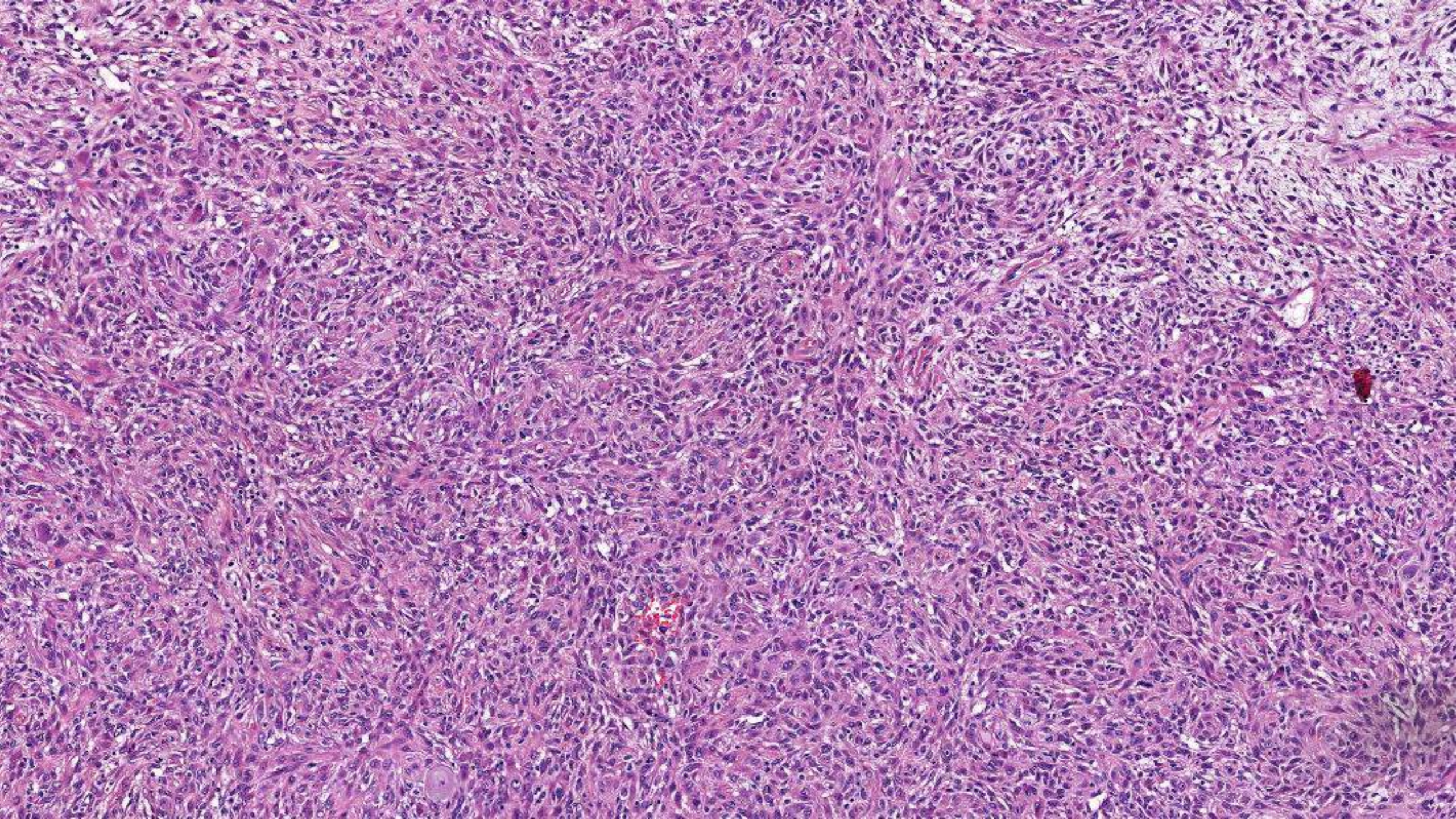


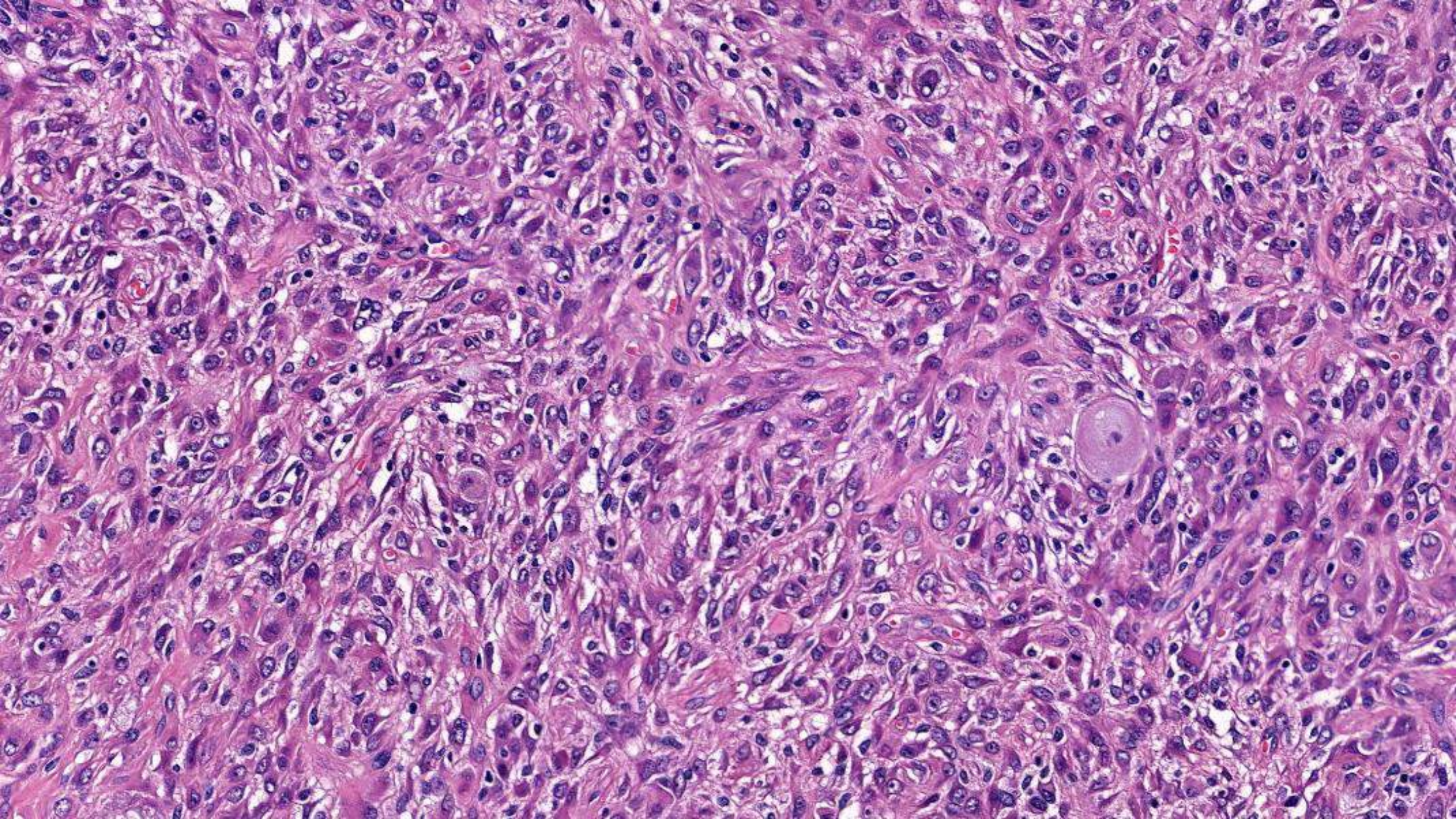




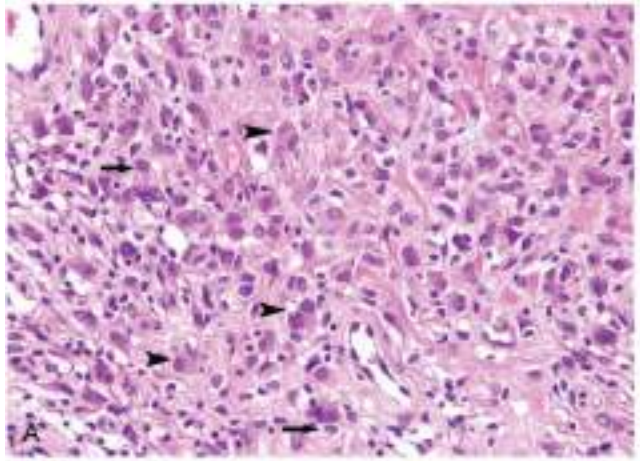


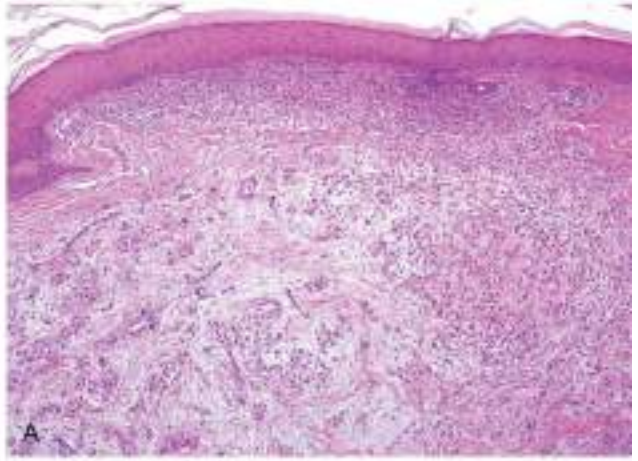






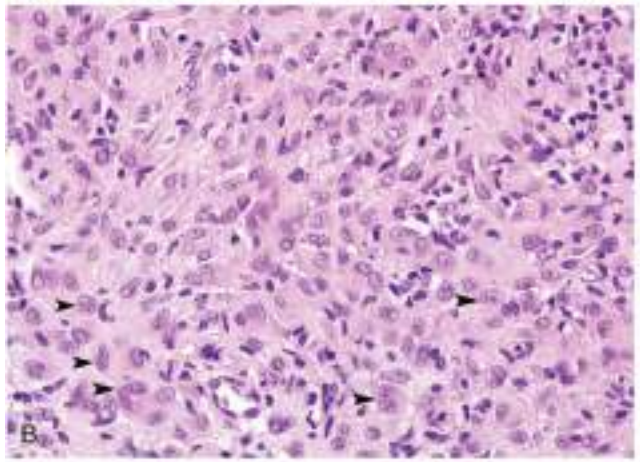
Bi- or tri nucleated cells

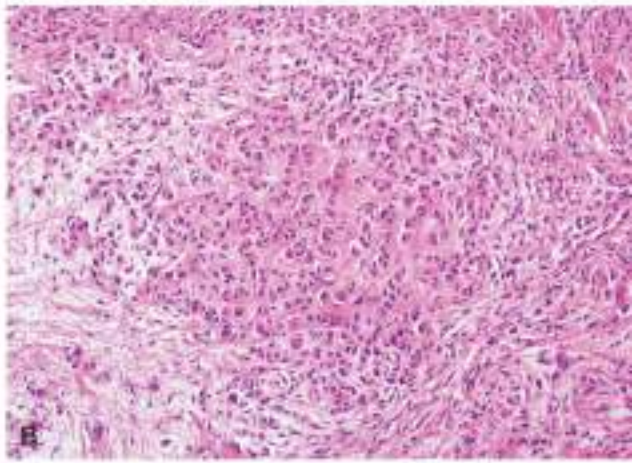




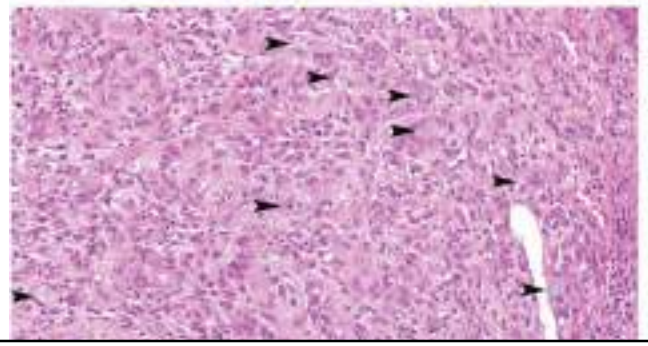
Nested pattern

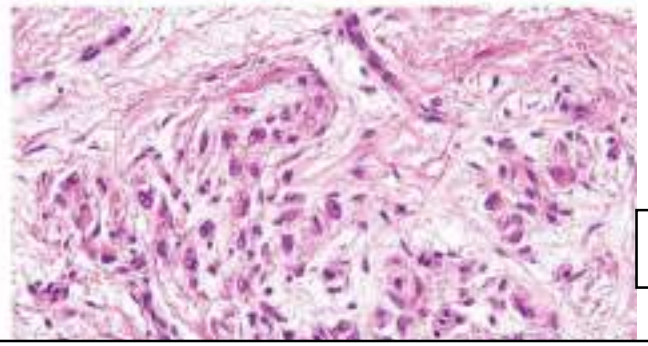
Cells with nuclear grooves





Numerous mucinous cells

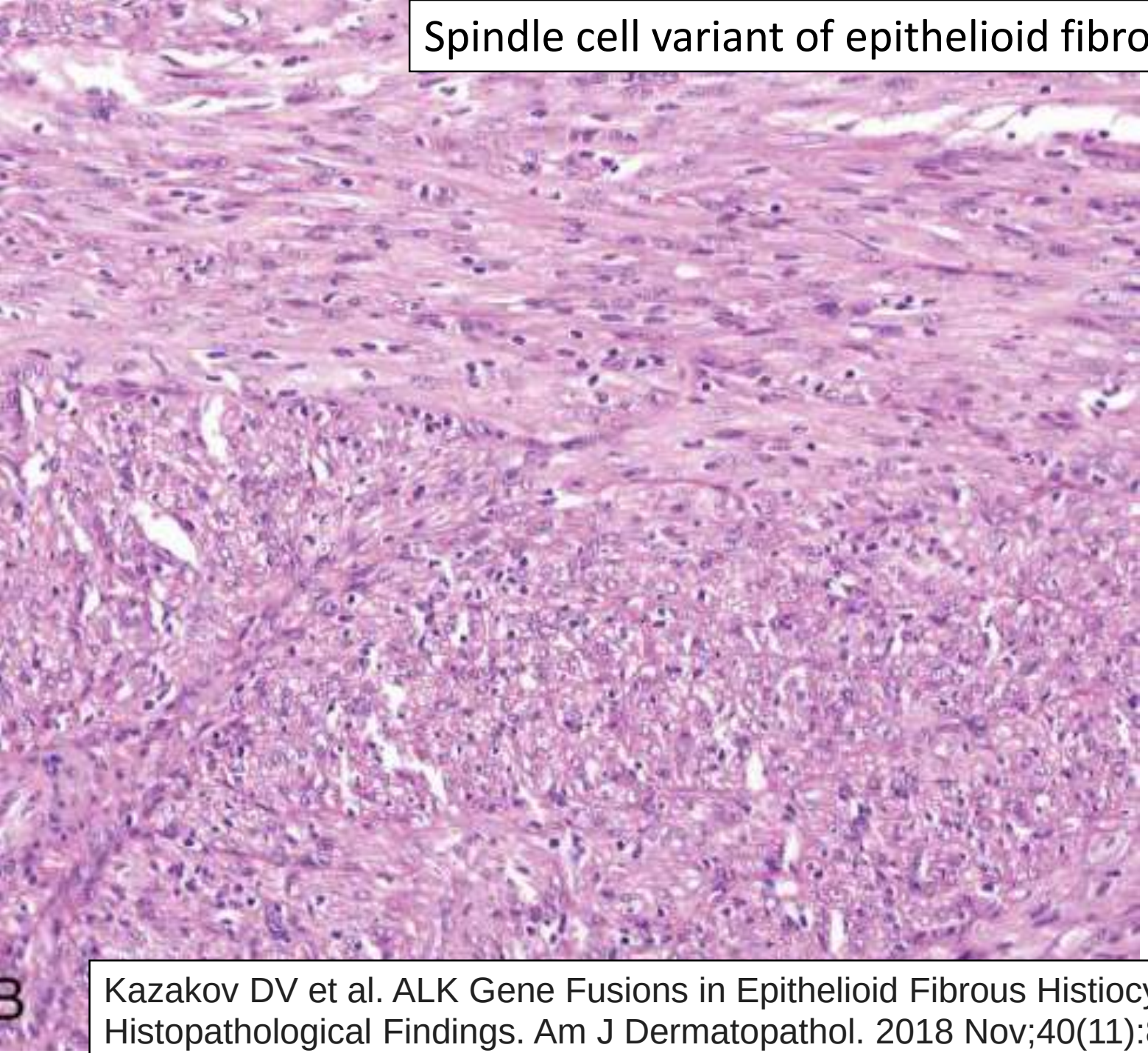


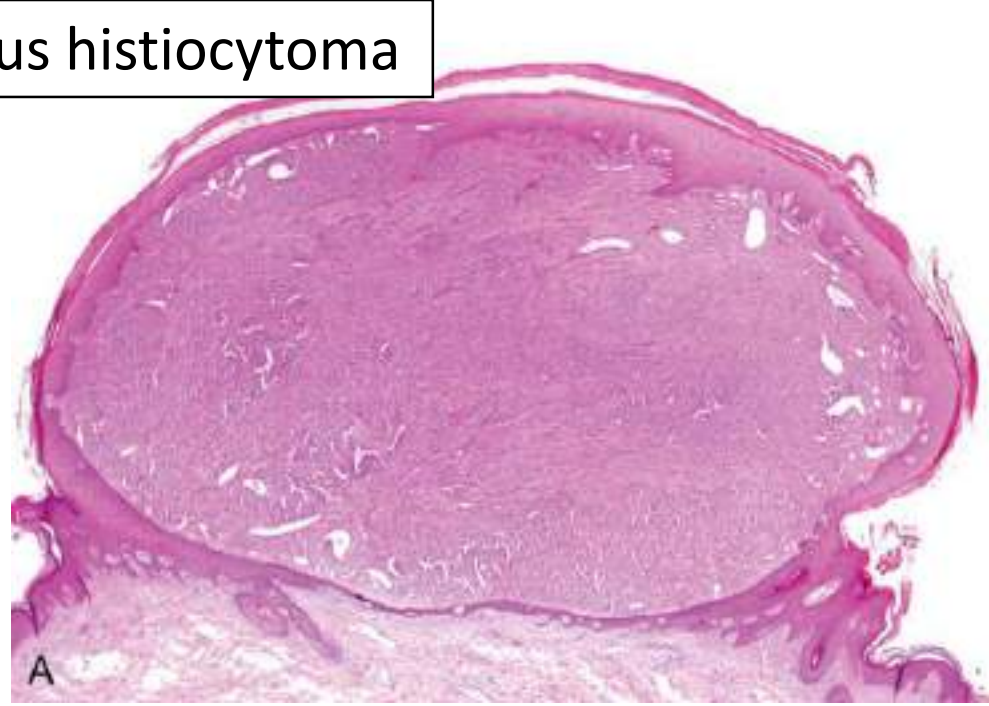


Intranuclear pseudoinclusions

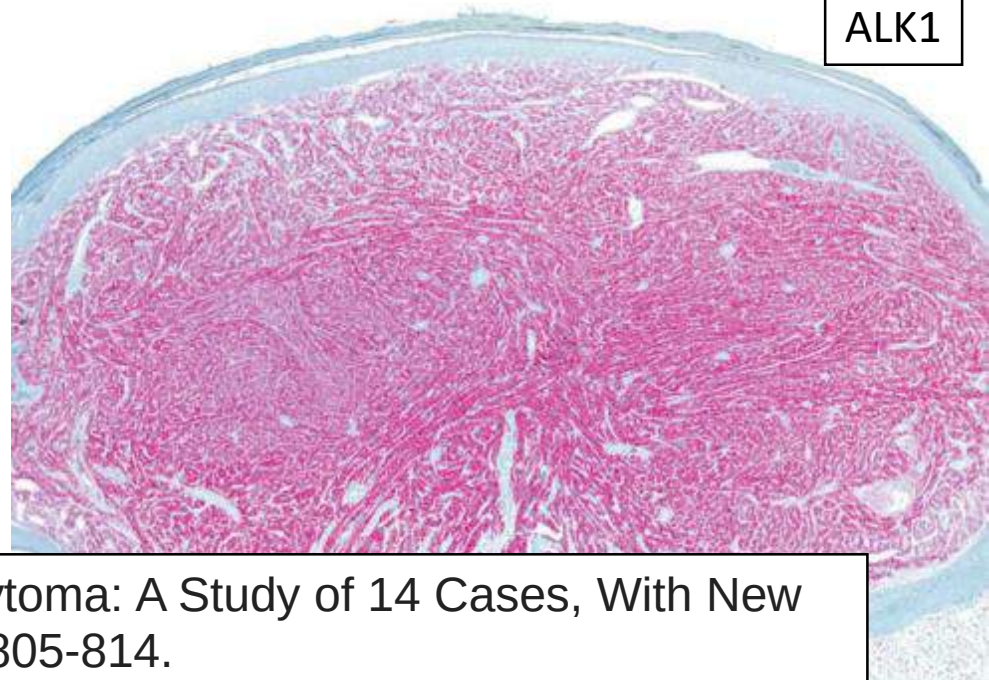
Kazakov DV et al. ALK Gene Fusions in Epithelioid Fibrous Histiocytoma: A Study of 14 Cases, With New Histopathological Findings. Am J Dermatopathol. 2018 Nov;40(11):805-814.

Spindle cell variant of epithelioid fibrous histiocytoma





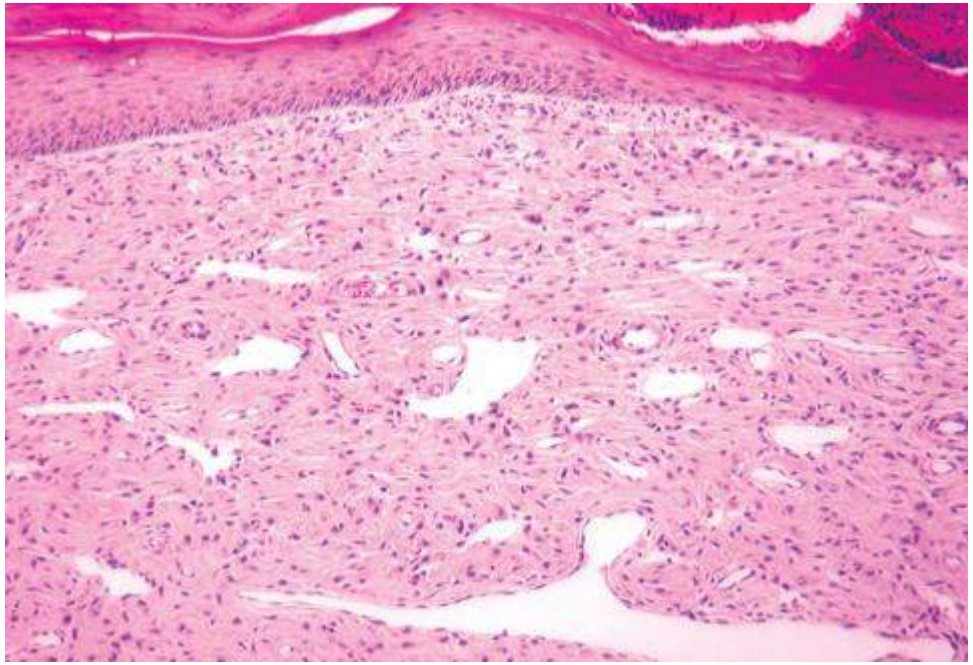
ALK1

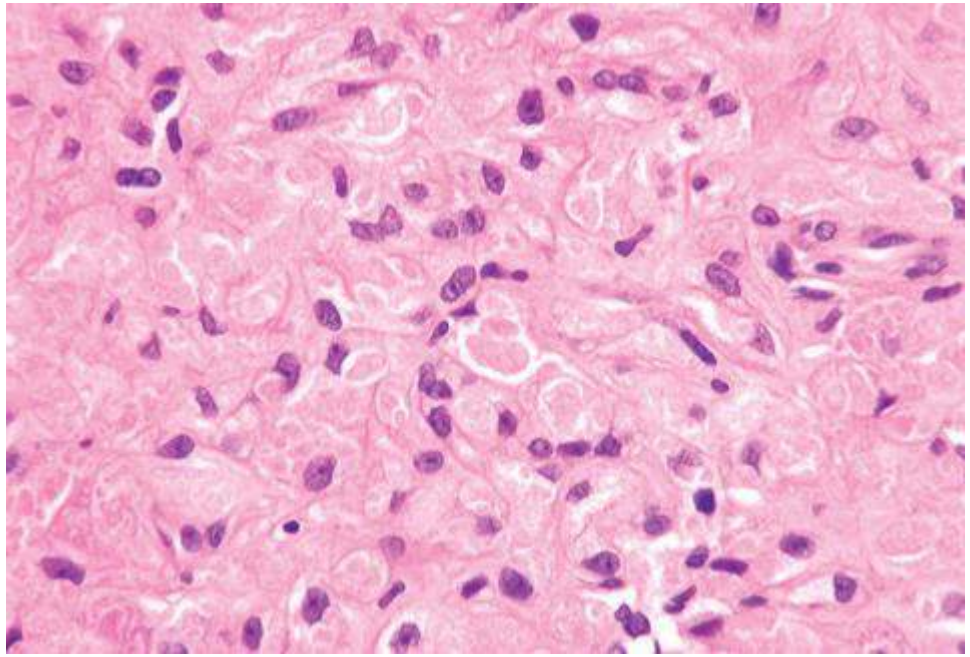


Kazakov DV et al. ALK Gene Fusions in Epithelioid Fibrous Histiocytoma: A Study of 14 Cases, With New Histopathological Findings. Am J Dermatopathol. 2018 Nov;40(11):805-814.

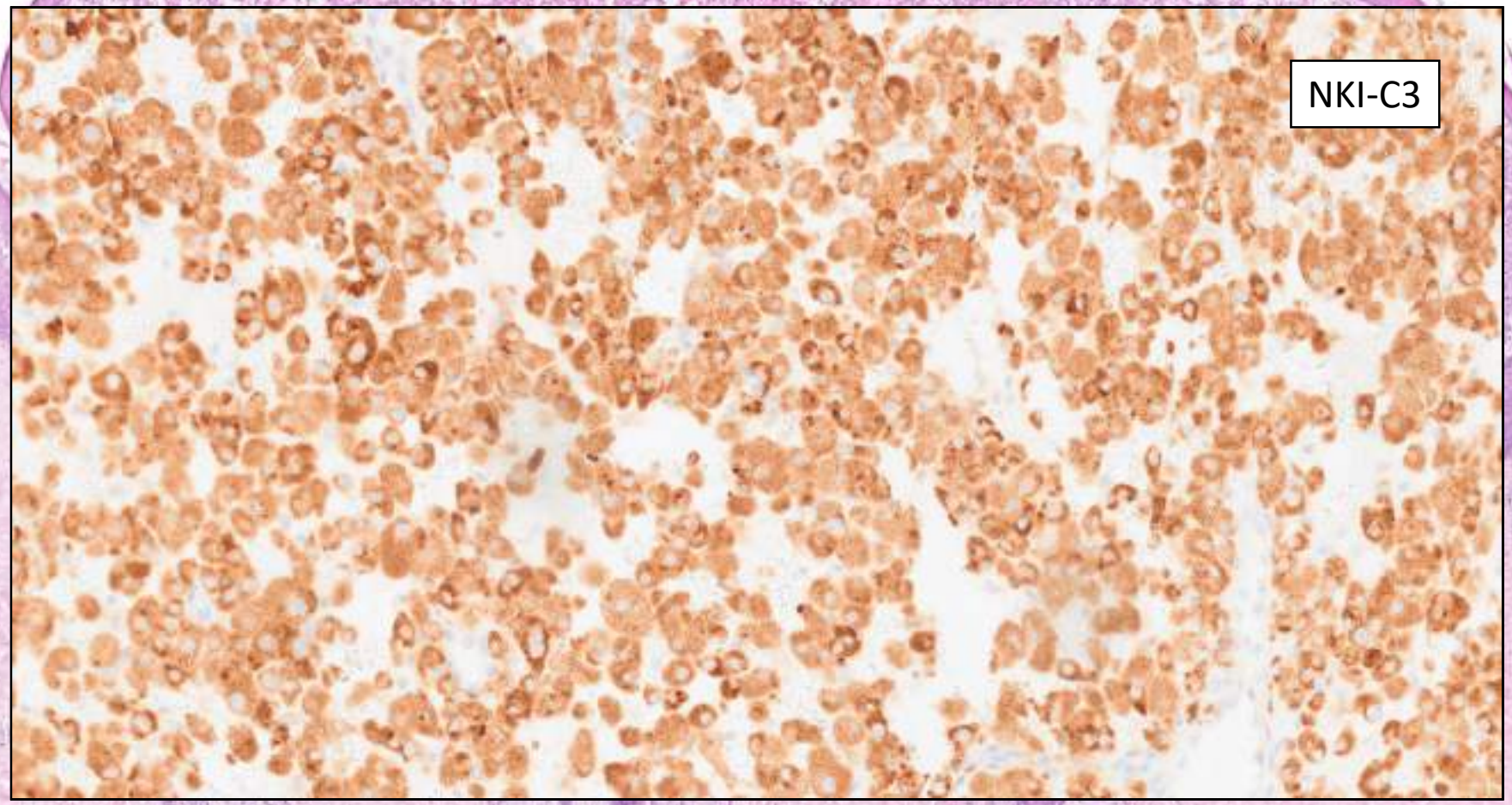
Epithelioid Cell Histiocytoma With Granular Cells (Another Nonneural Granular Cell Neoplasm)

Jessie Lee, MD

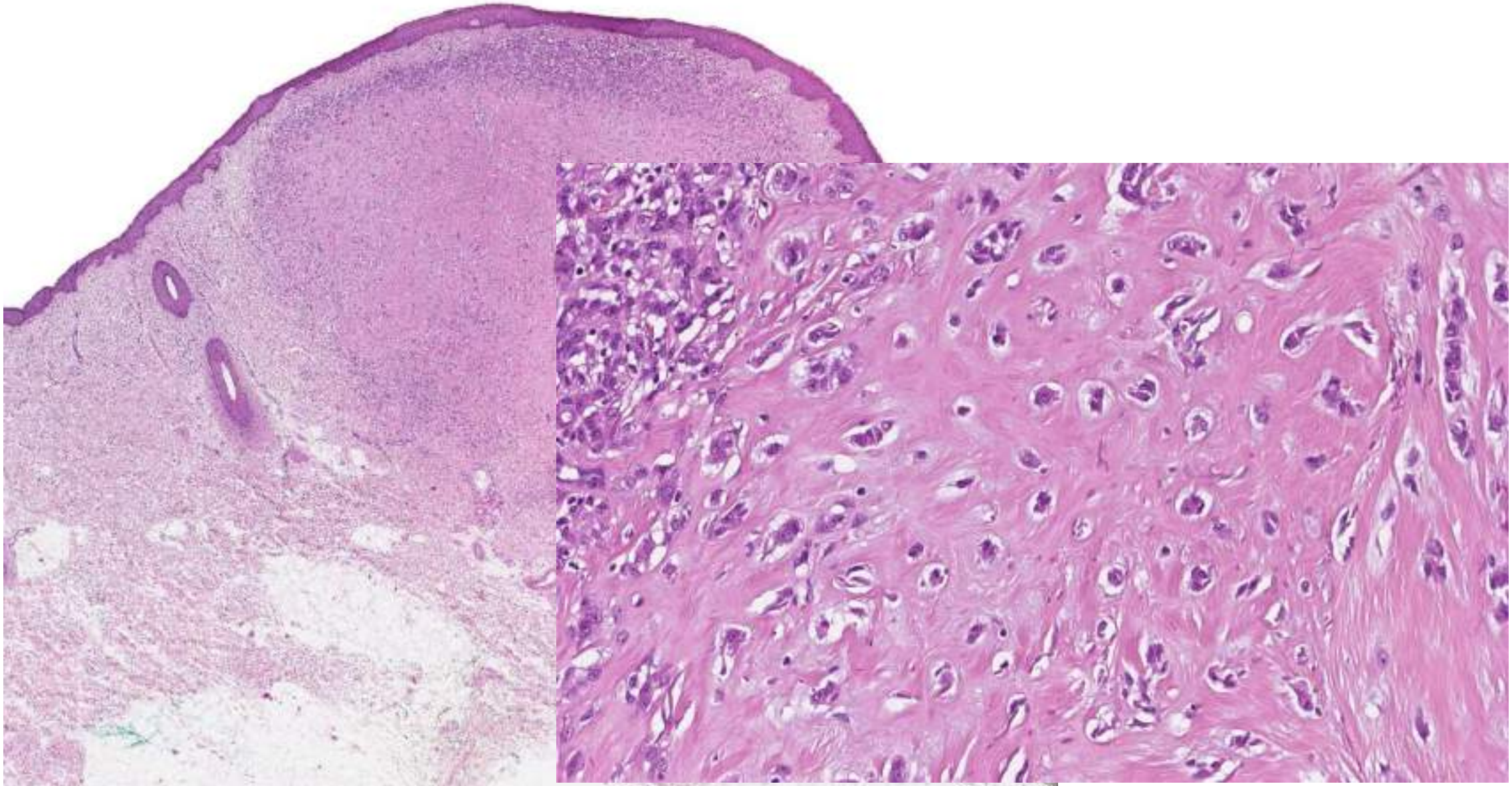




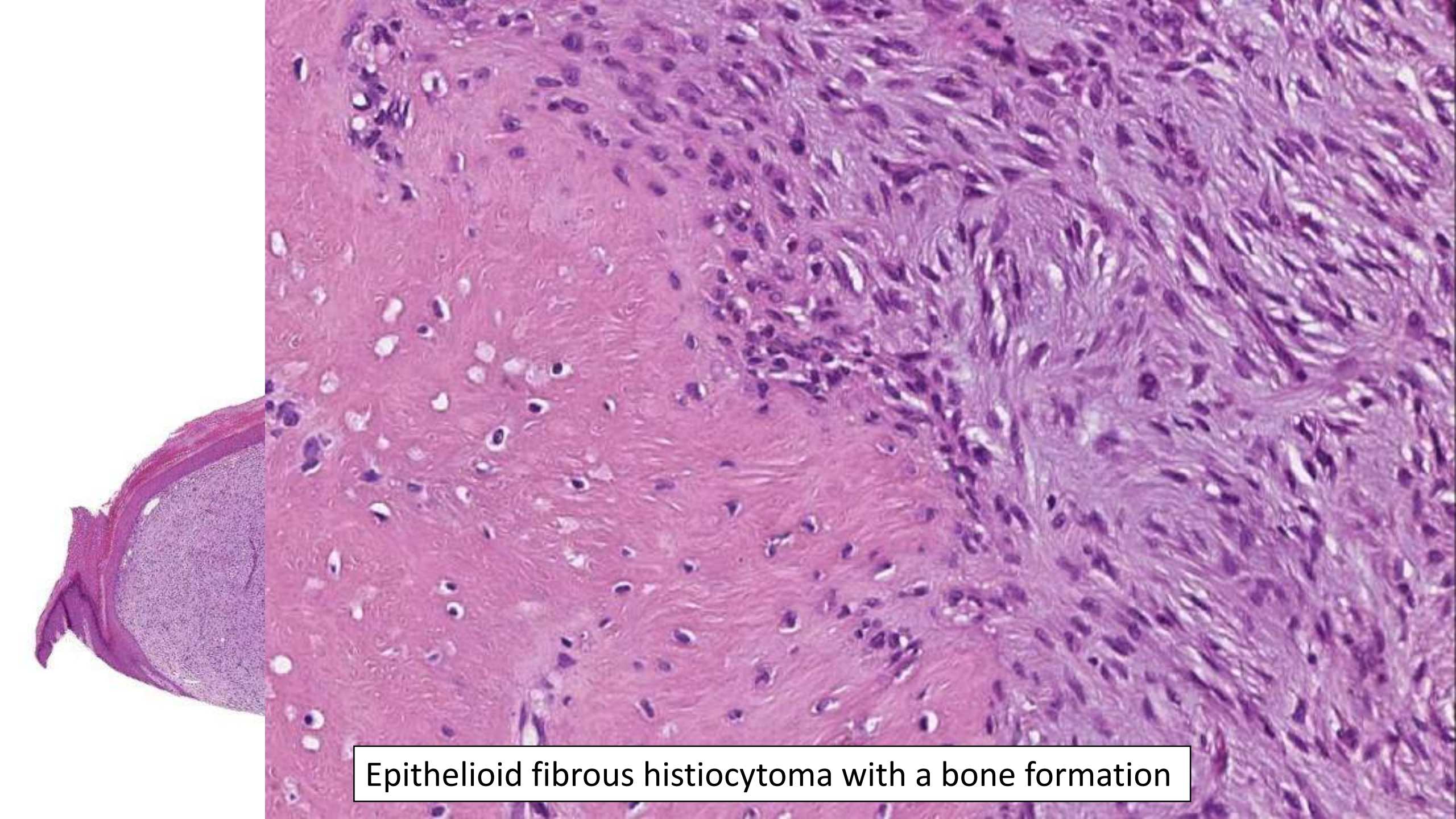
(*Am J Dermatopathol* 2007;29:475–476)



Granular cell variant of epithelioid fibrous histiocytoma



Extensively hyalinized epithelioid fibrous histiocytoma



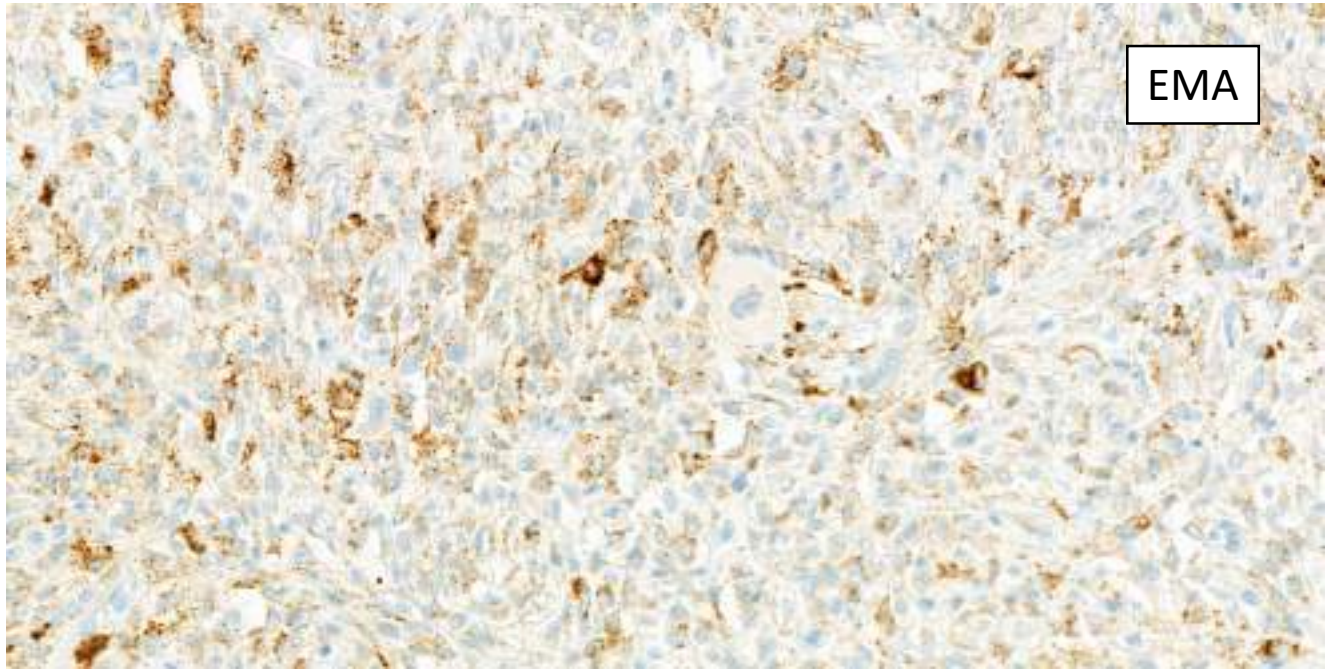
Epithelioid fibrous histiocytoma with a bone formation

Immunohistochemistry

Positive

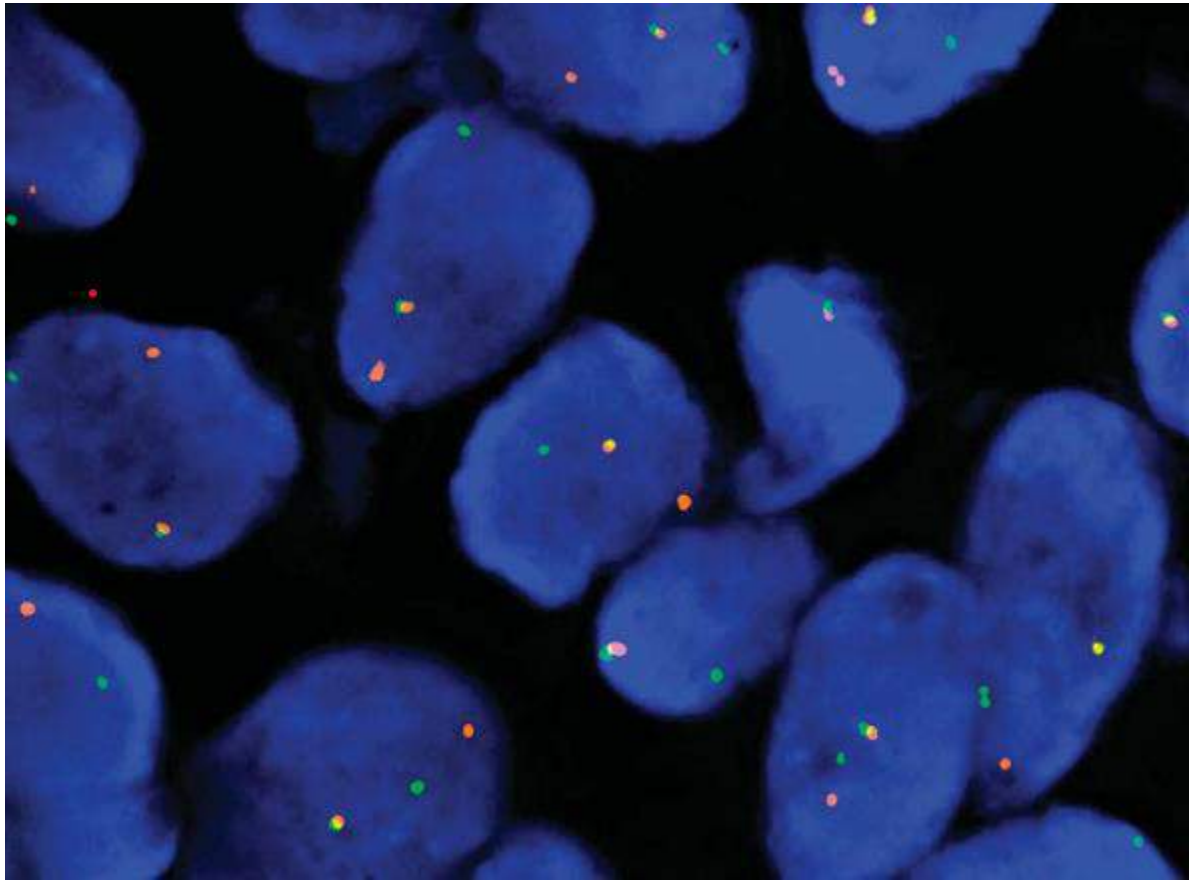
- EMA 2/3 of cases
- D2-40 50%
- ALK1 cytoplasmatic

- TFE3 (11 of 14 cases)



Kazakov DV et al. ALK Gene Fusions in Epithelioid Fibrous Histiocytoma: A Study of 14 Cases, With New Histopathological Findings. Am J Dermatopathol. 2018 Nov;40(11):805-814.

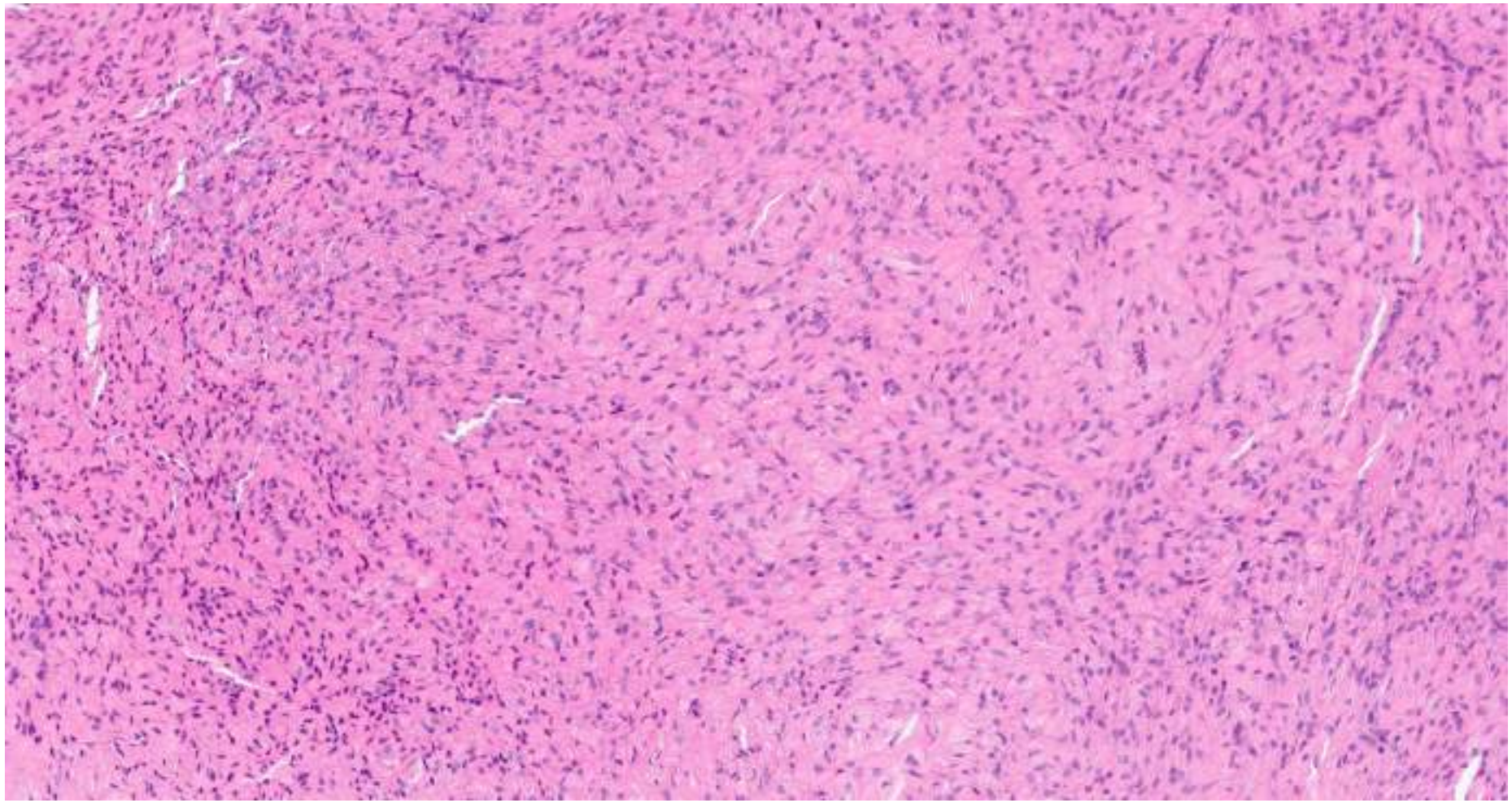
Genetic profile



- ALK gene fusions that involve various protein-coding genes
- *PRKCA*, *PRKCB* and *PRCKD* rearrangements

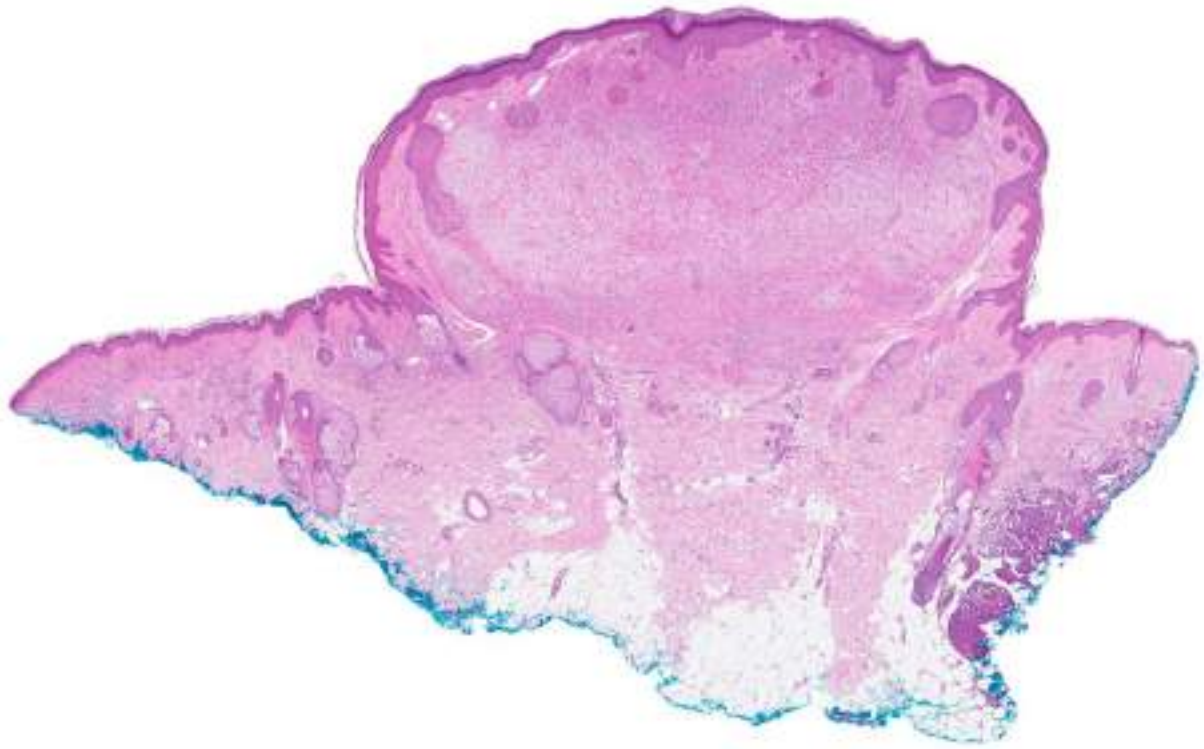
Differential diagnosis

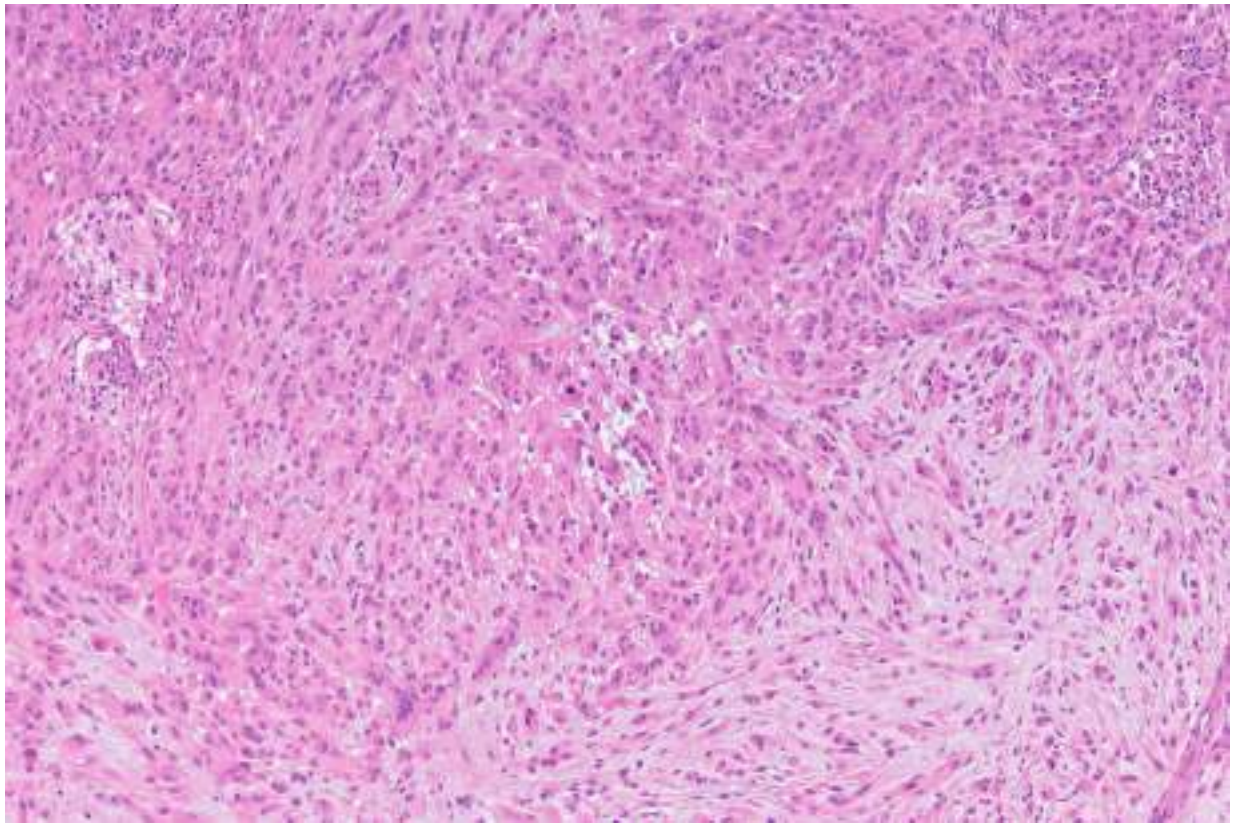
- Perineurioma: EMA, Claudin1 and CD34 (+/-)



Differential diagnosis

- Spitz naevus: junctional component, maturation, S100 protein, Melan A, SOX10 +



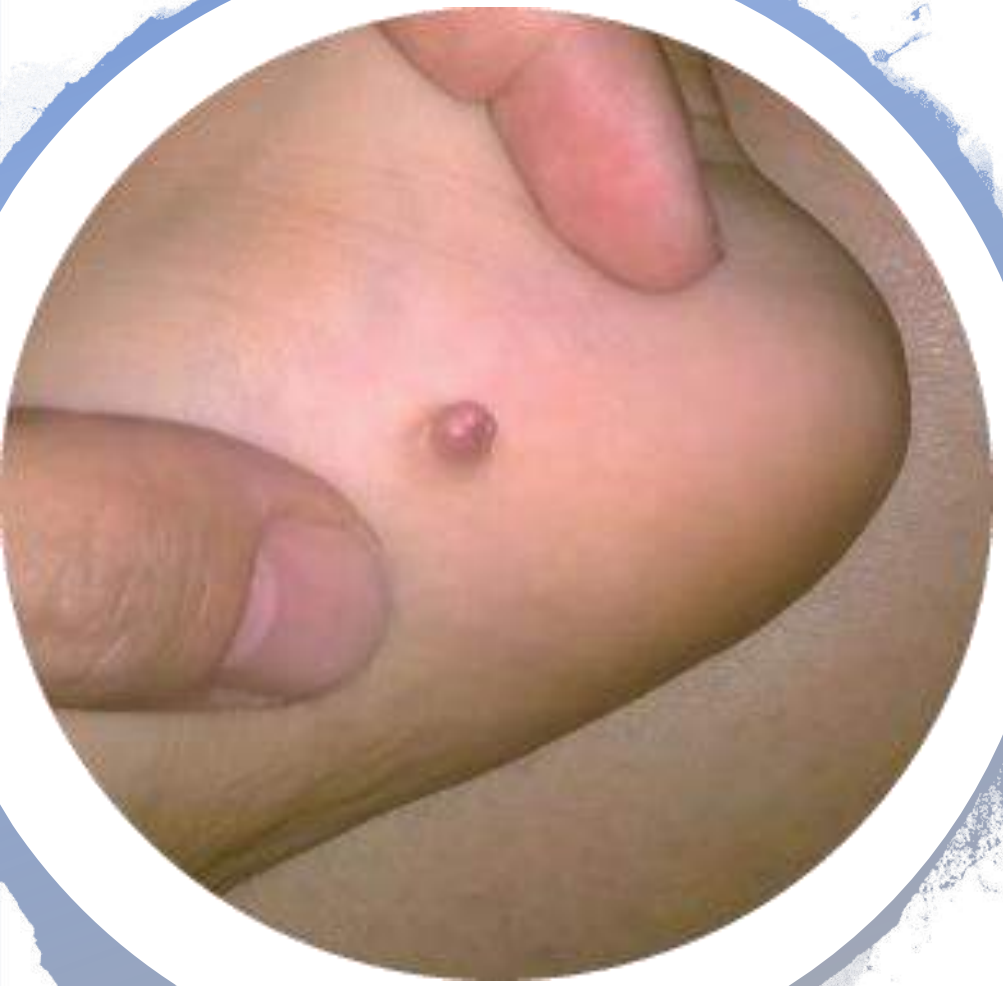


Classification of fibrohistiocytic tumors

Intermediate (rarely metastasizing)

1. Giant cell tumour of soft tissue
2. Plexiform fibrohistiocytic tumour

Plexiform fibrohistiocytic tumor (PFHT)



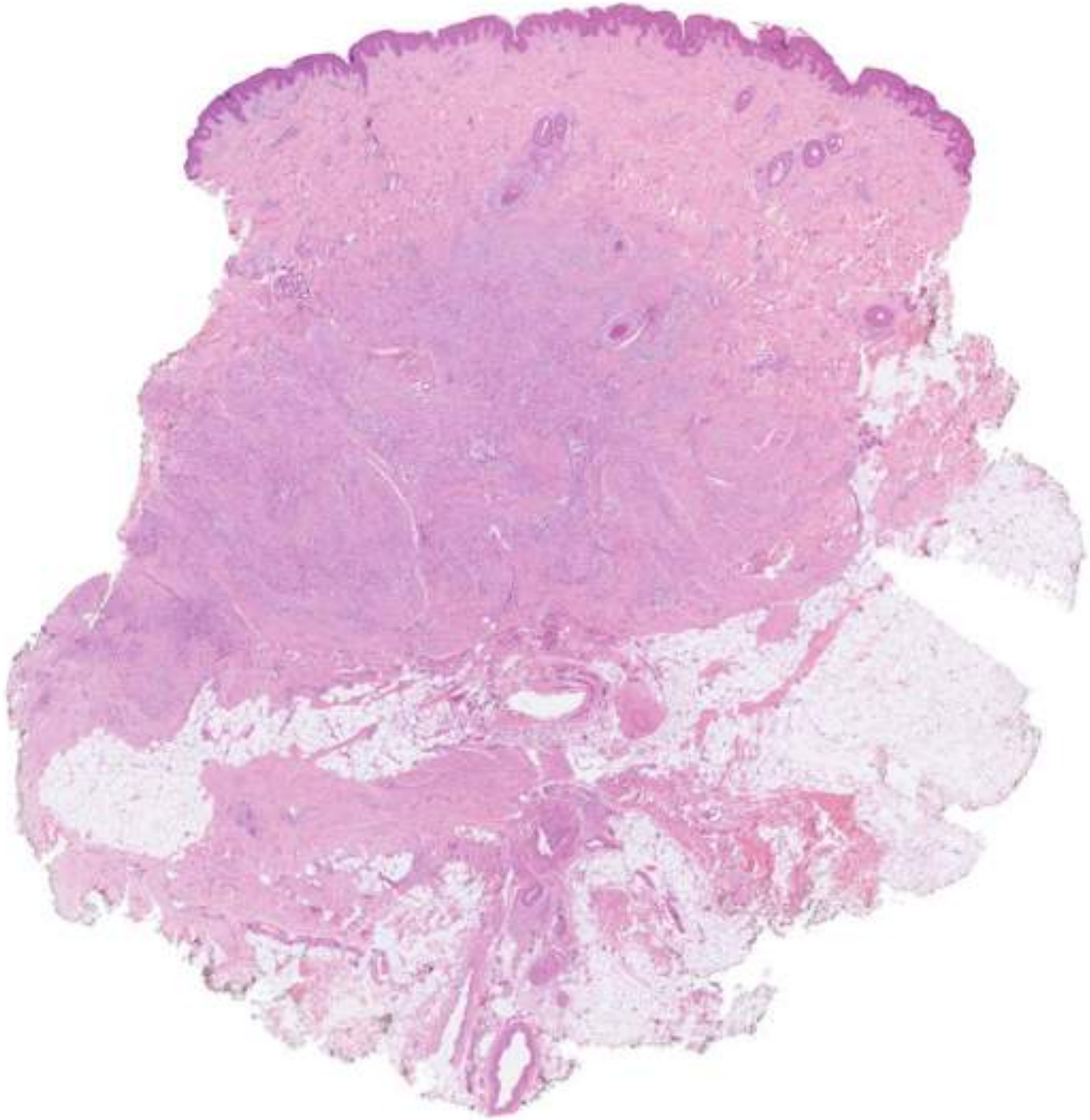
Definition: Low-grade malignant lesion, characterized by nodules of histiocyte –like cells and multinucleated (osteoclast-like) giant cells associated with spindle cells , arranged in plexiform fascicles

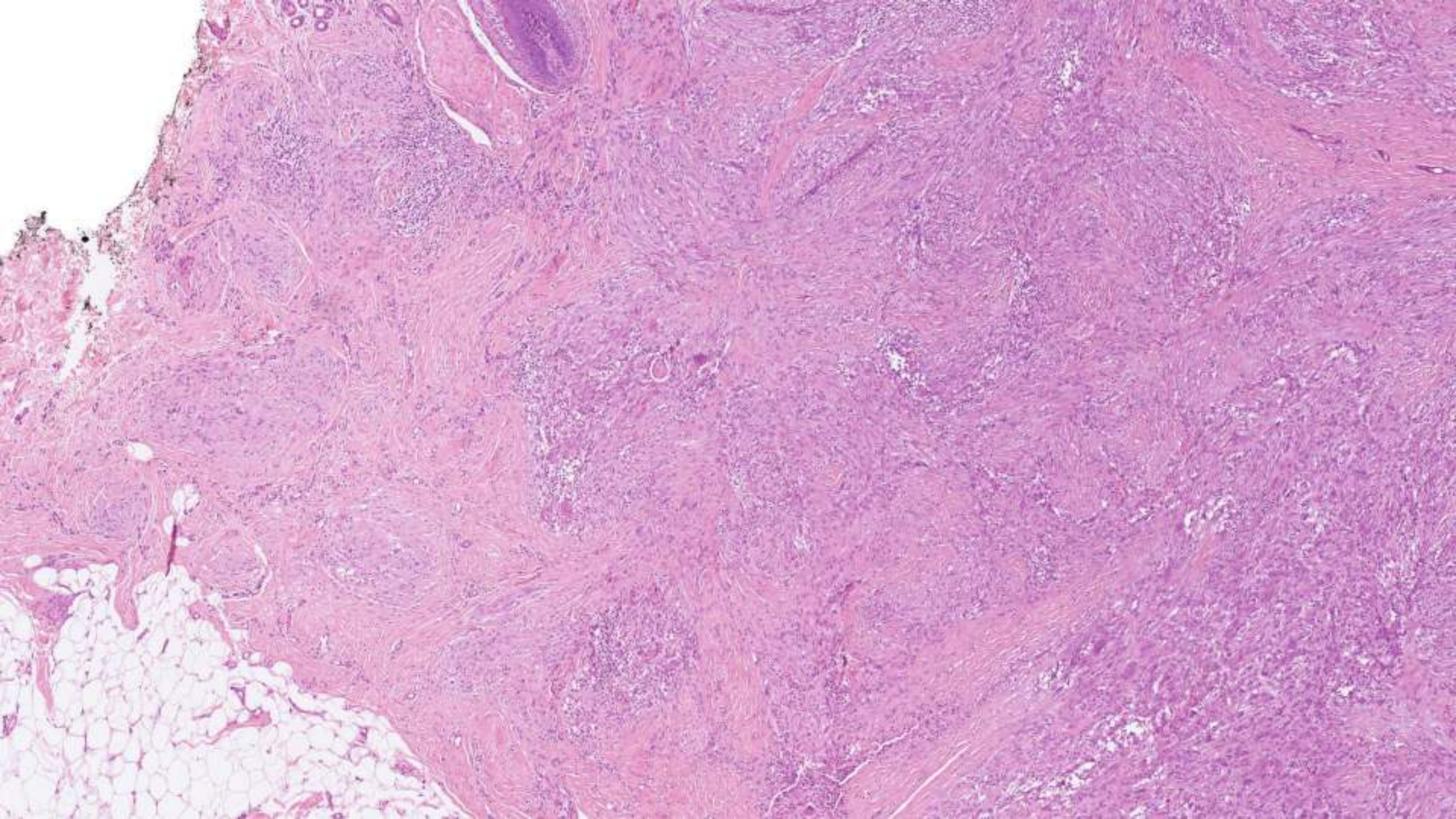
- Children, adolescents, 70% younger than 20 years old
- Congenital cases rare
- F>M

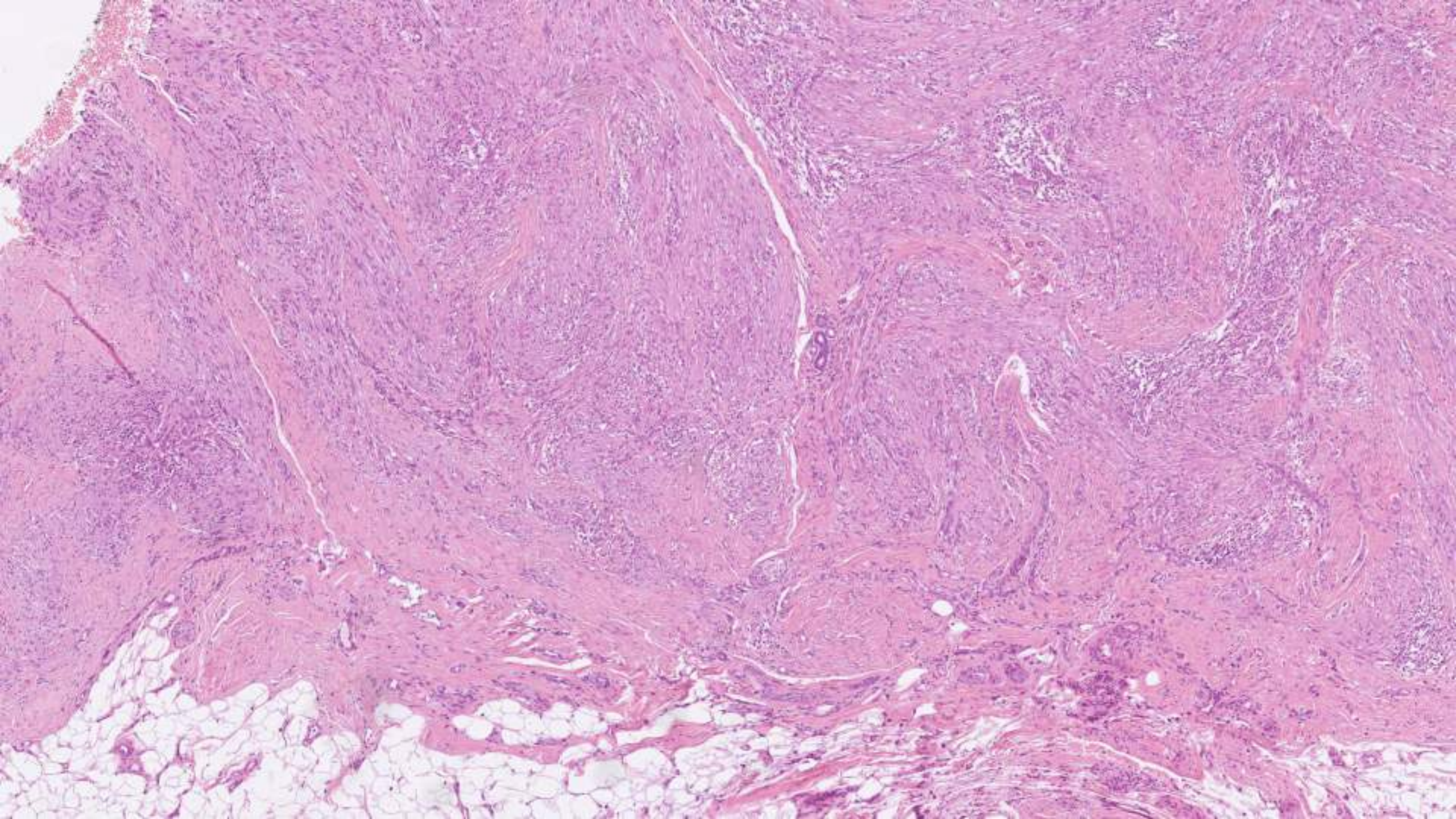
- Slowly growing, nodule, plaque
- Upper extremities, lower extremities, trunk, head and neck area

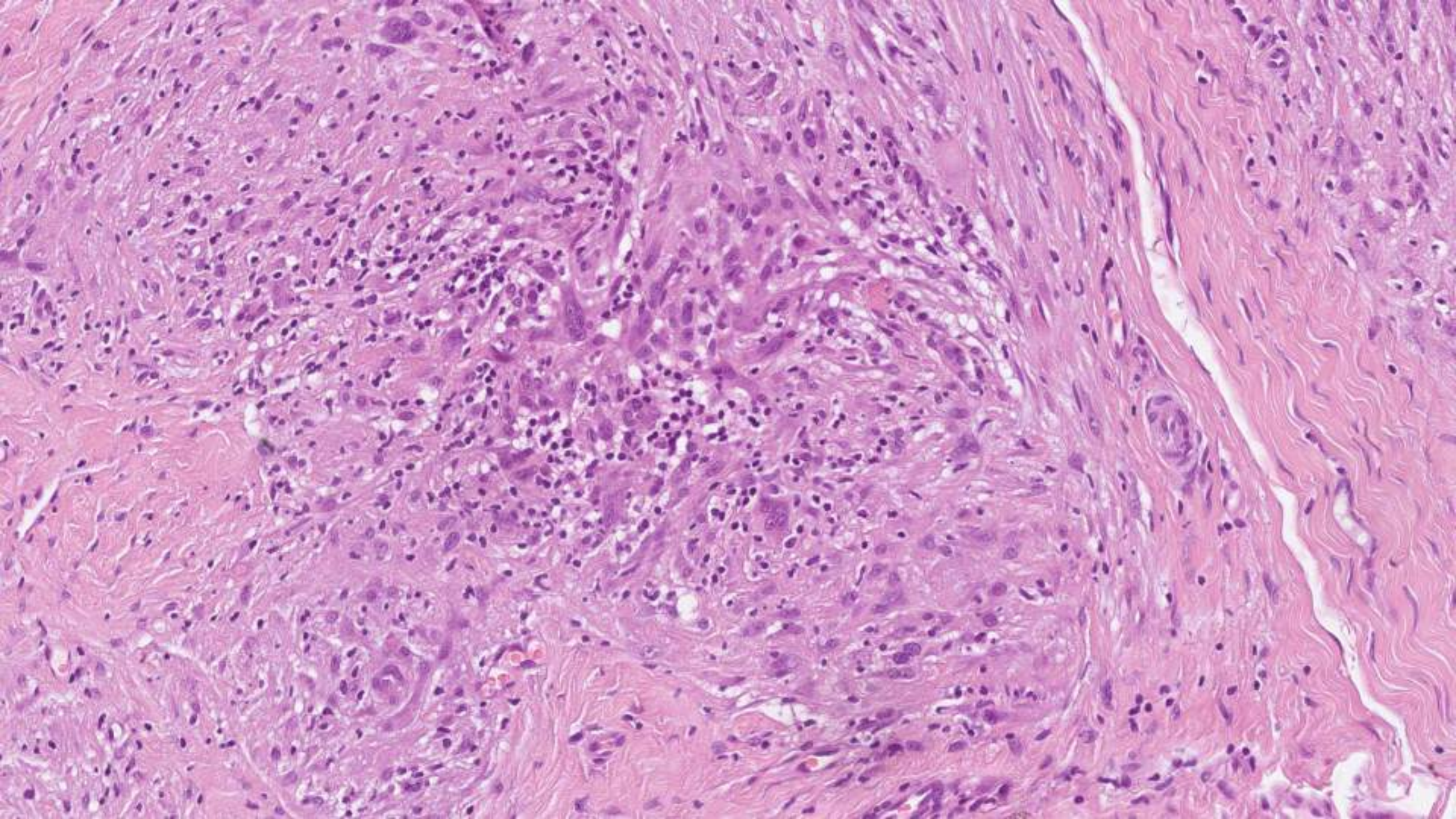
- Local recurrence common
- Spontaneous regression well documented
- Lymph node and distant metastasis
- No specific histological features to suggest aggressive biologic behaviour

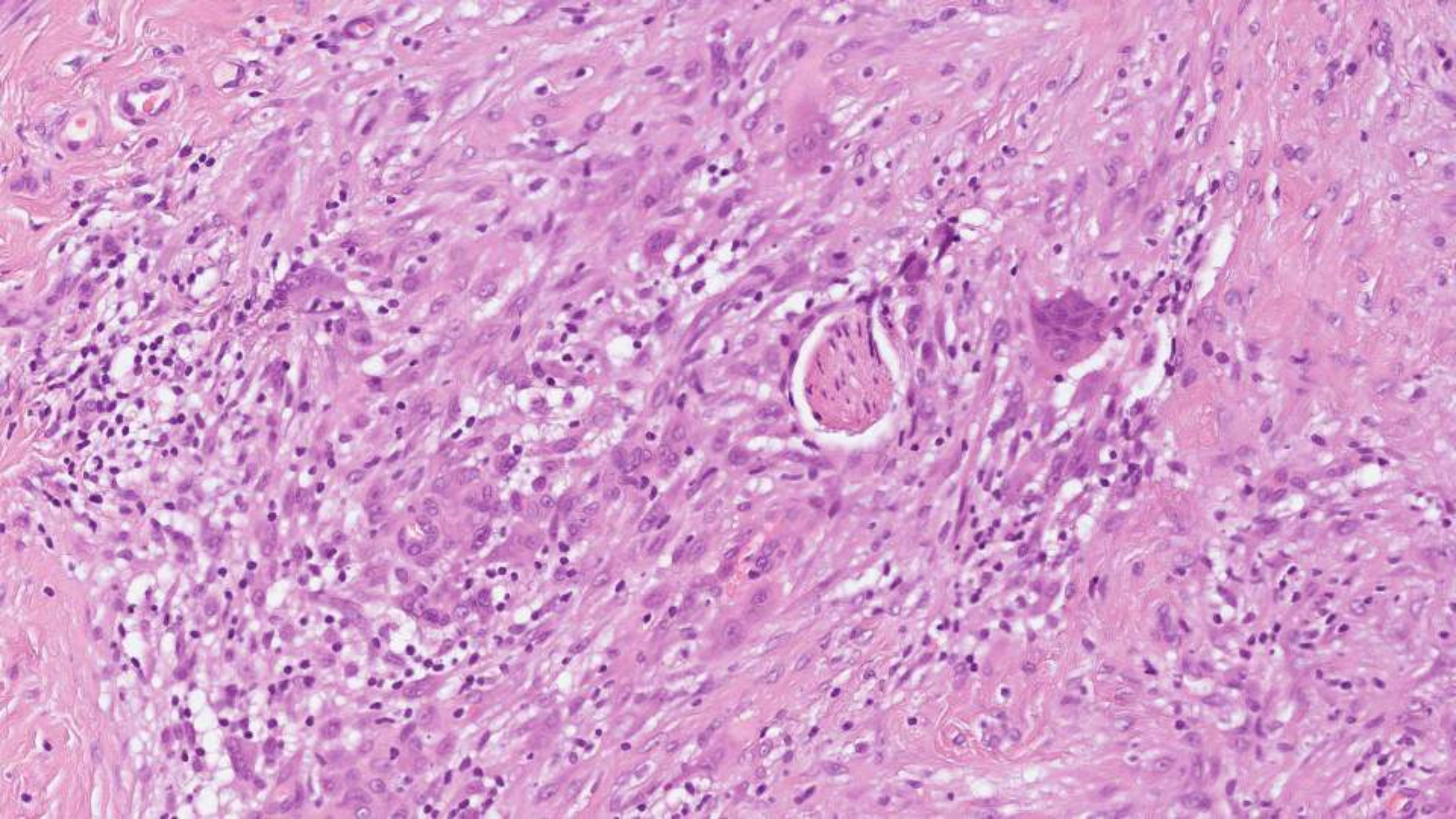
Plexiform fibrohistiocytic tumor histology

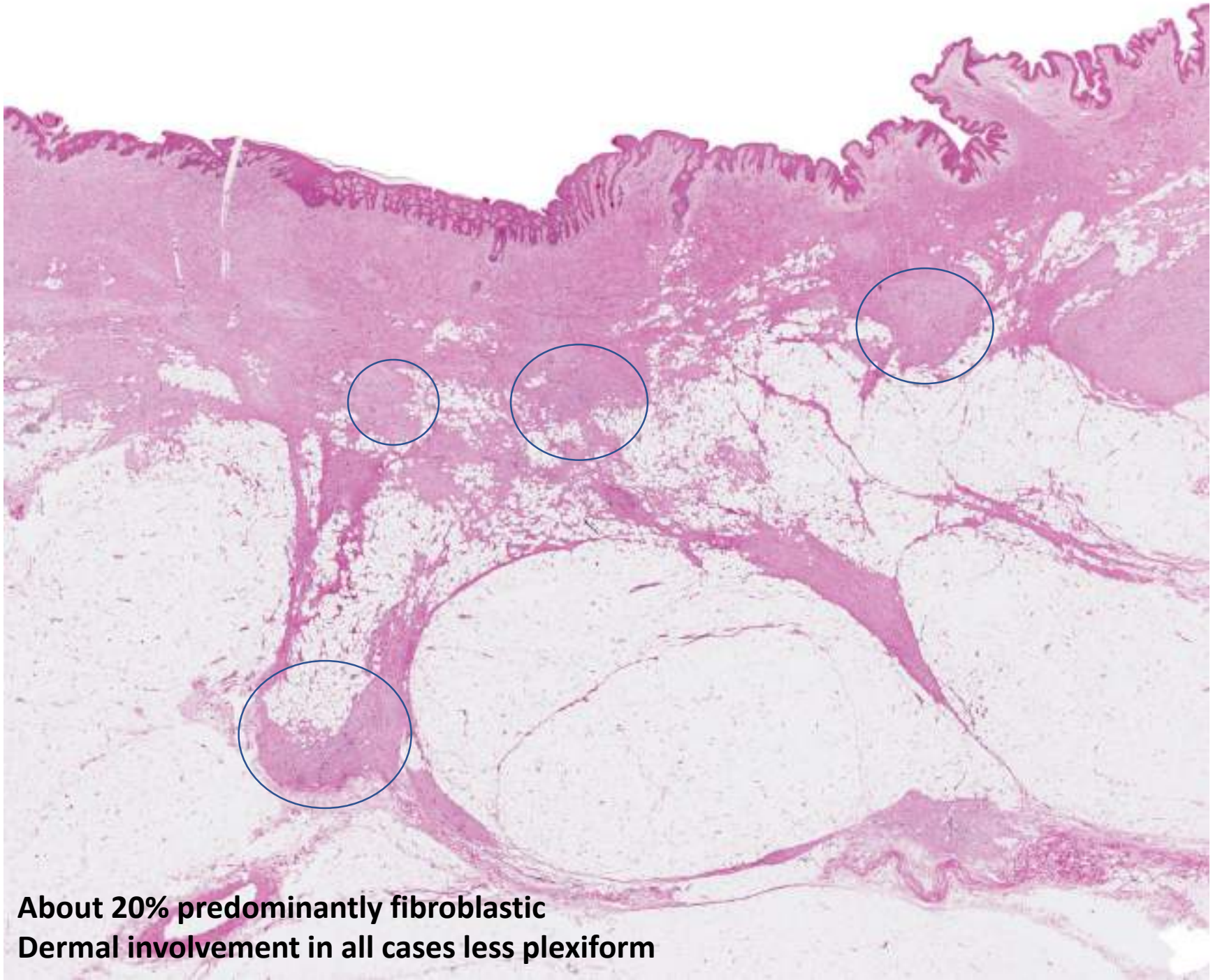




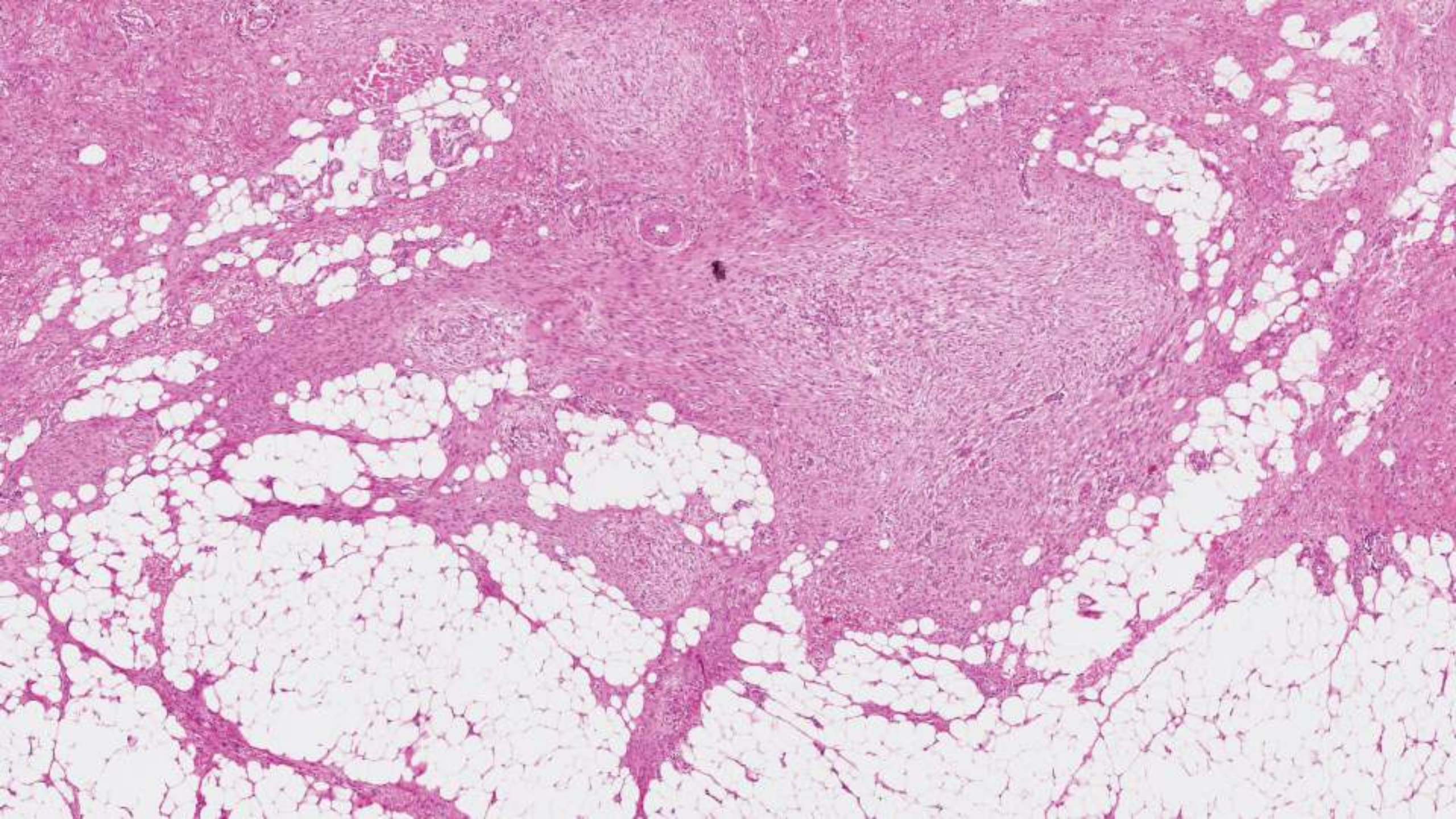


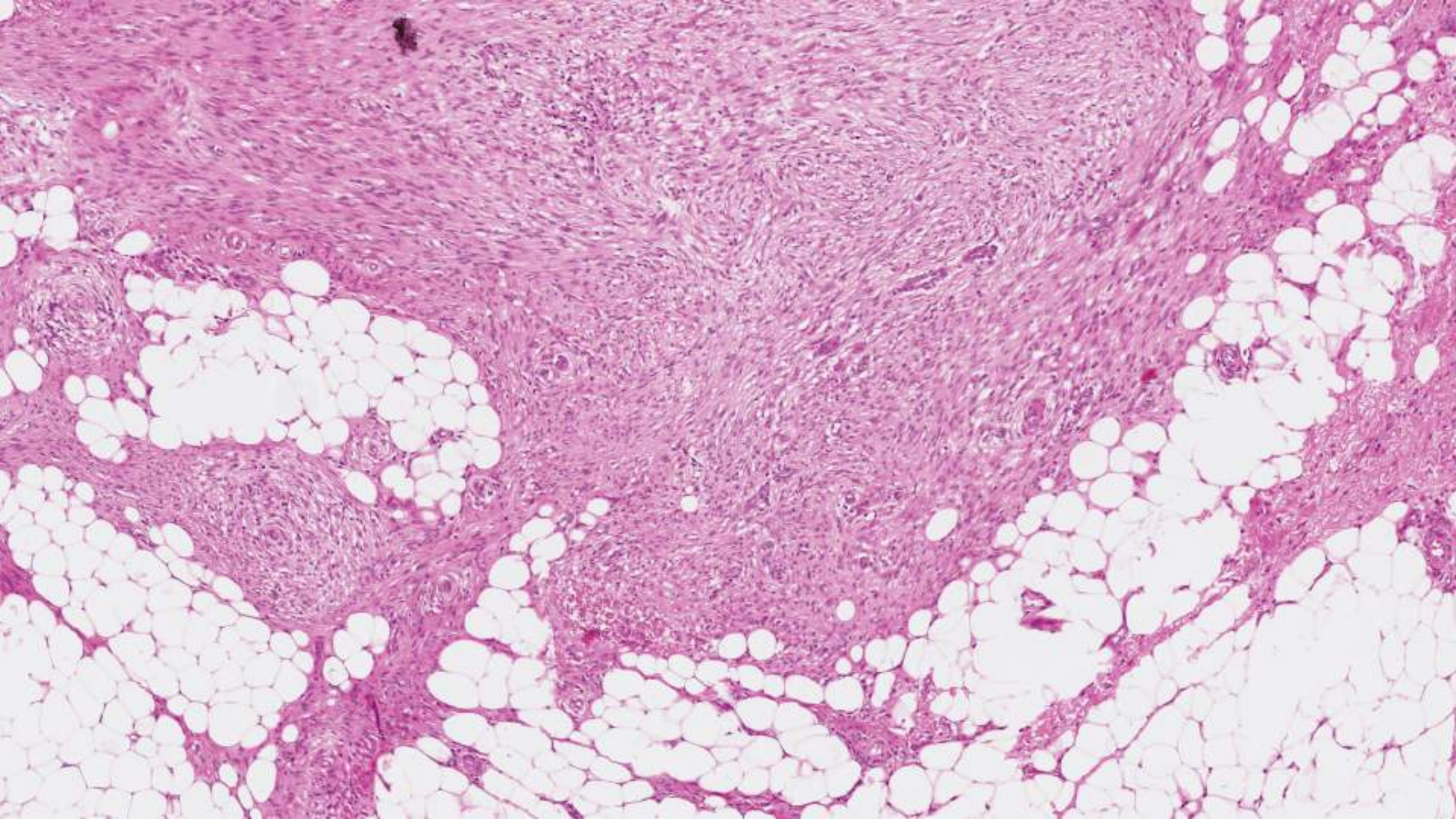


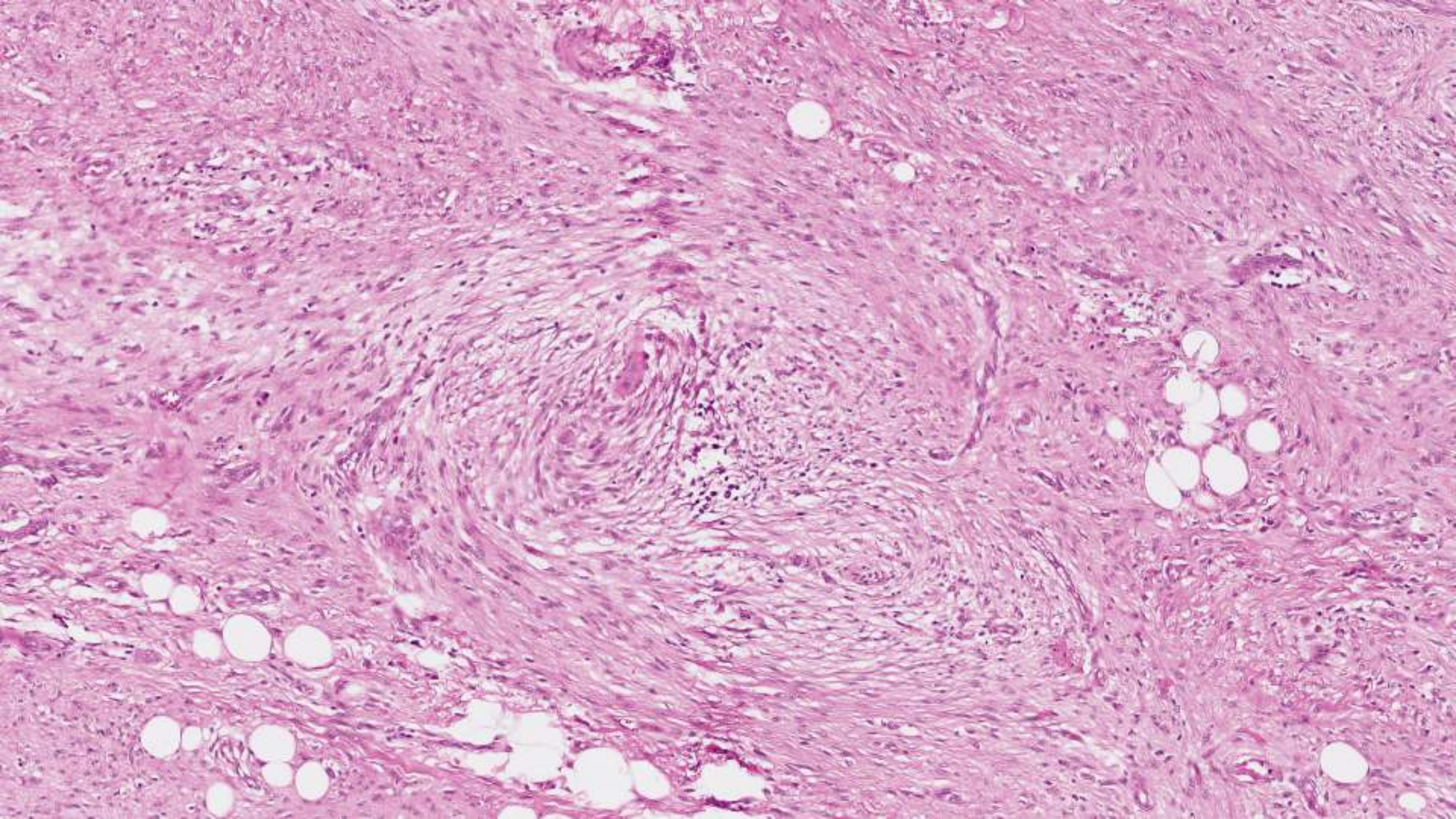


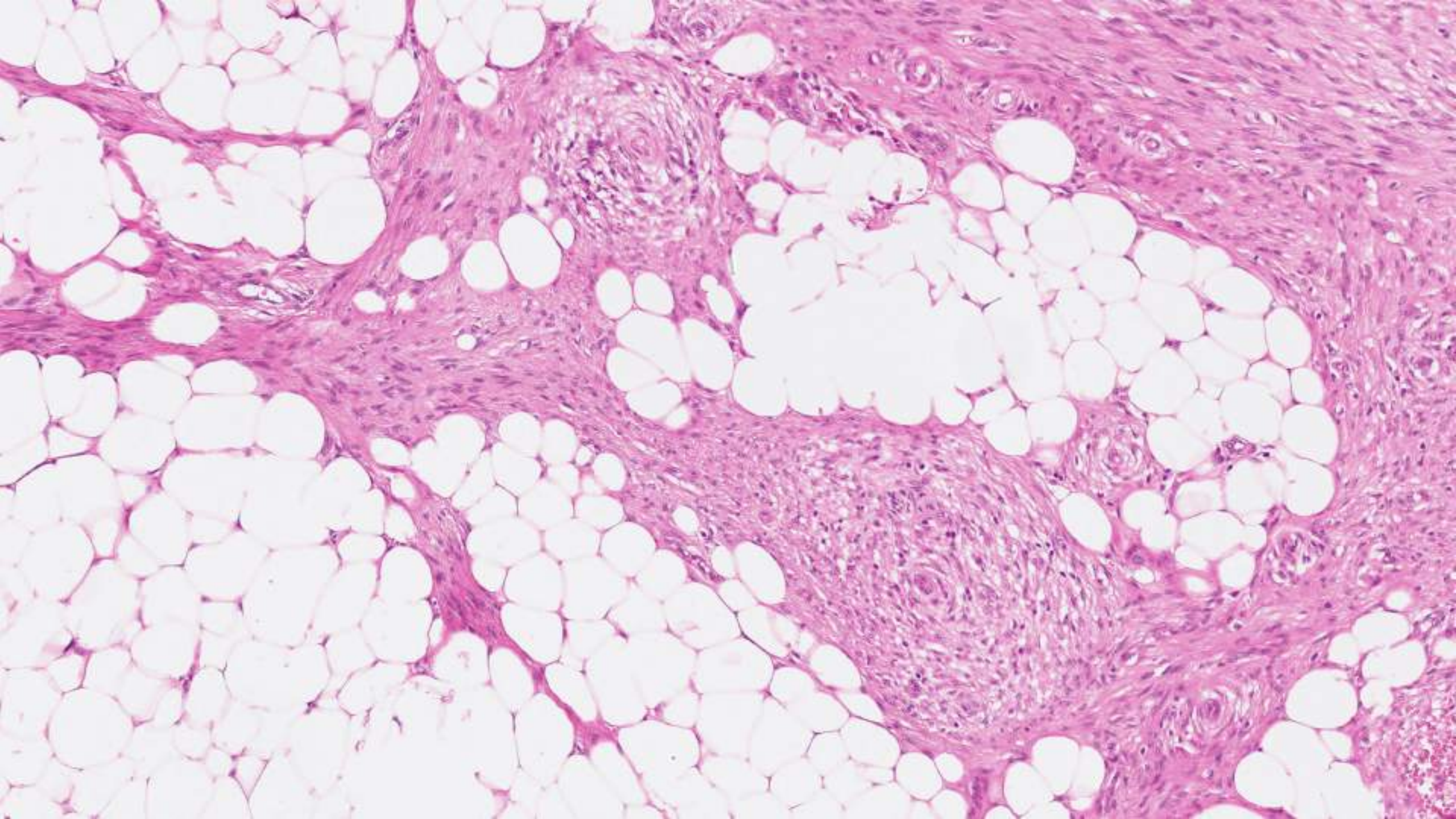


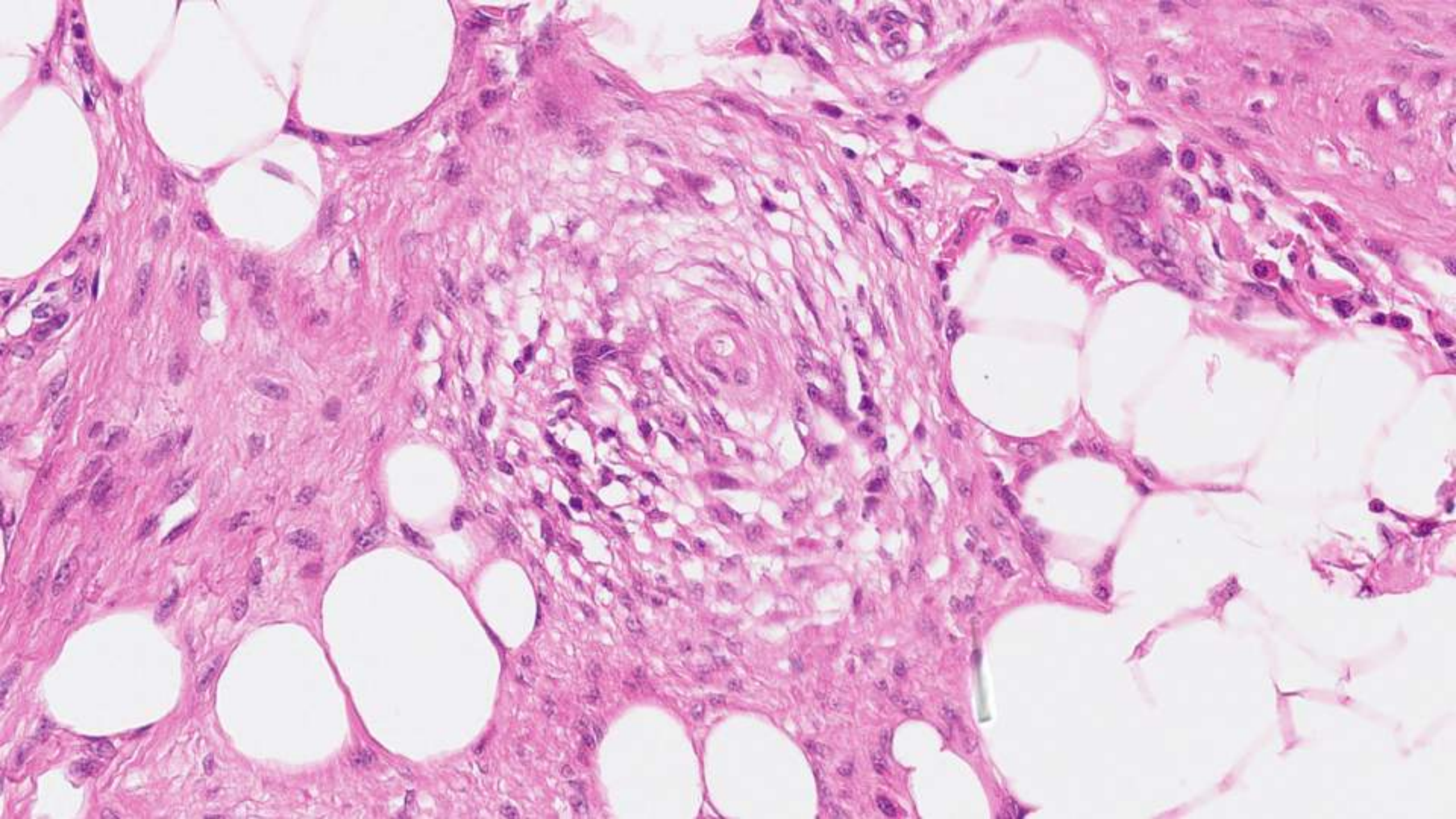
About 20% predominantly fibroblastic
Dermal involvement in all cases less plexiform

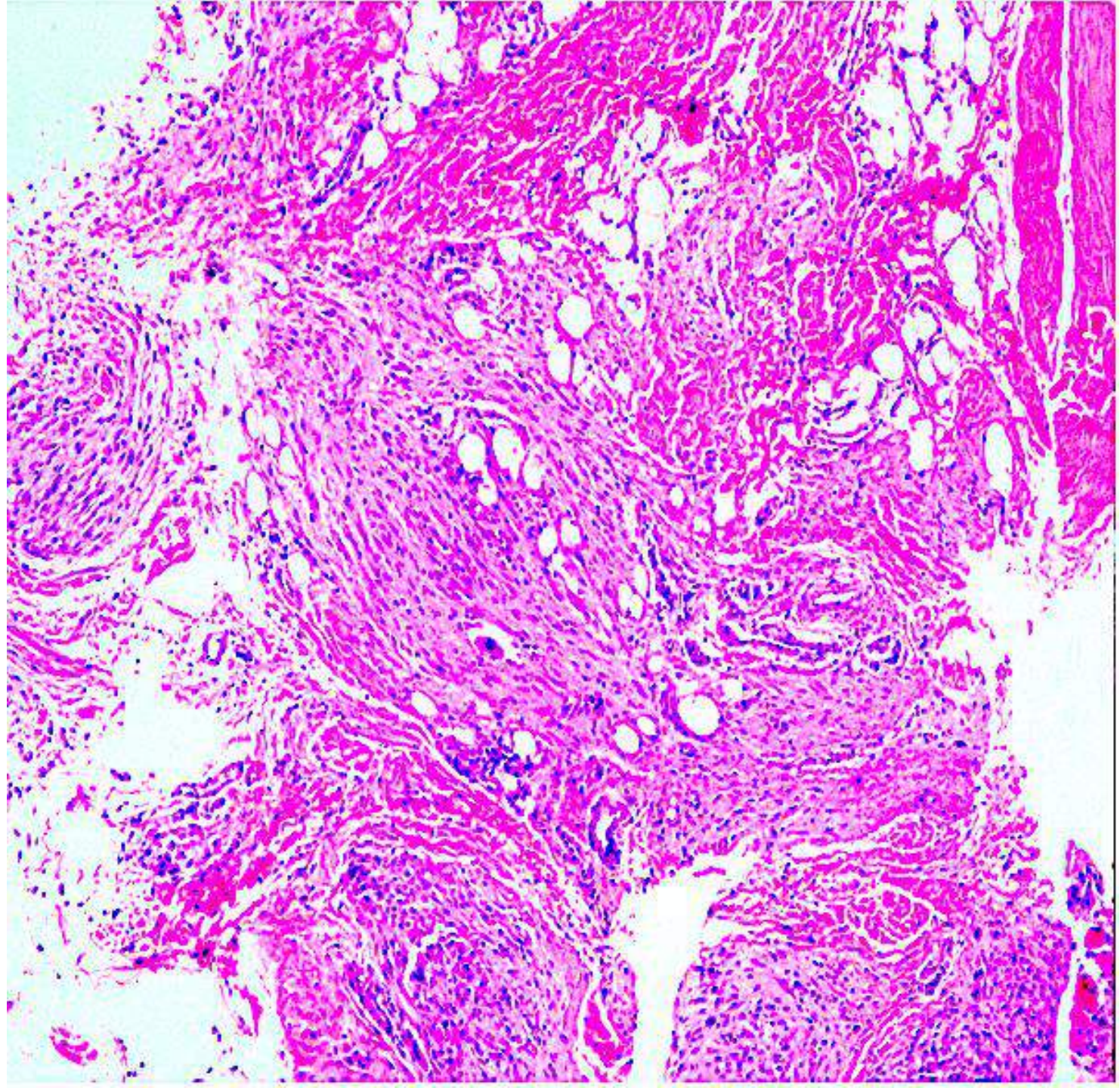


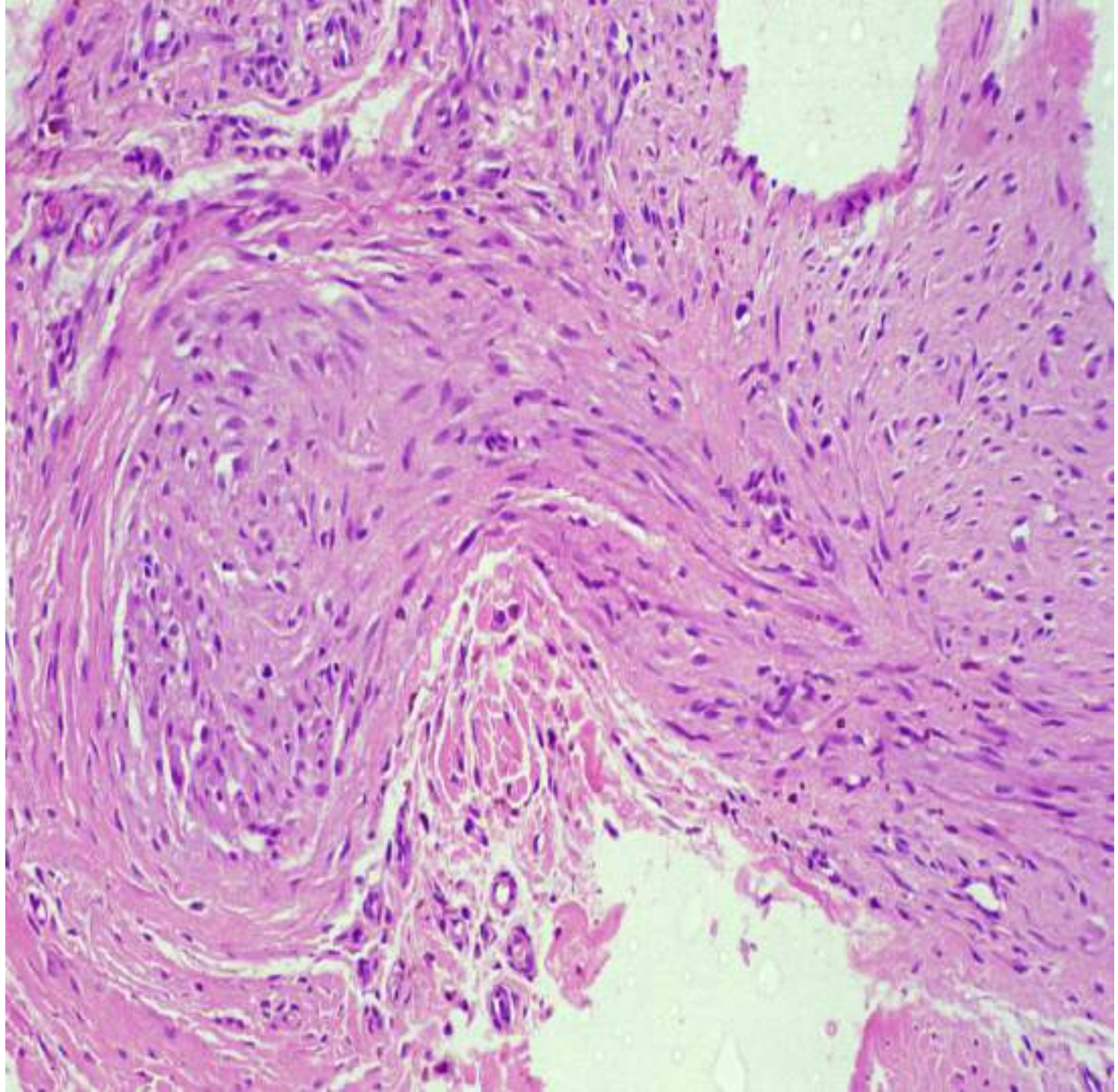


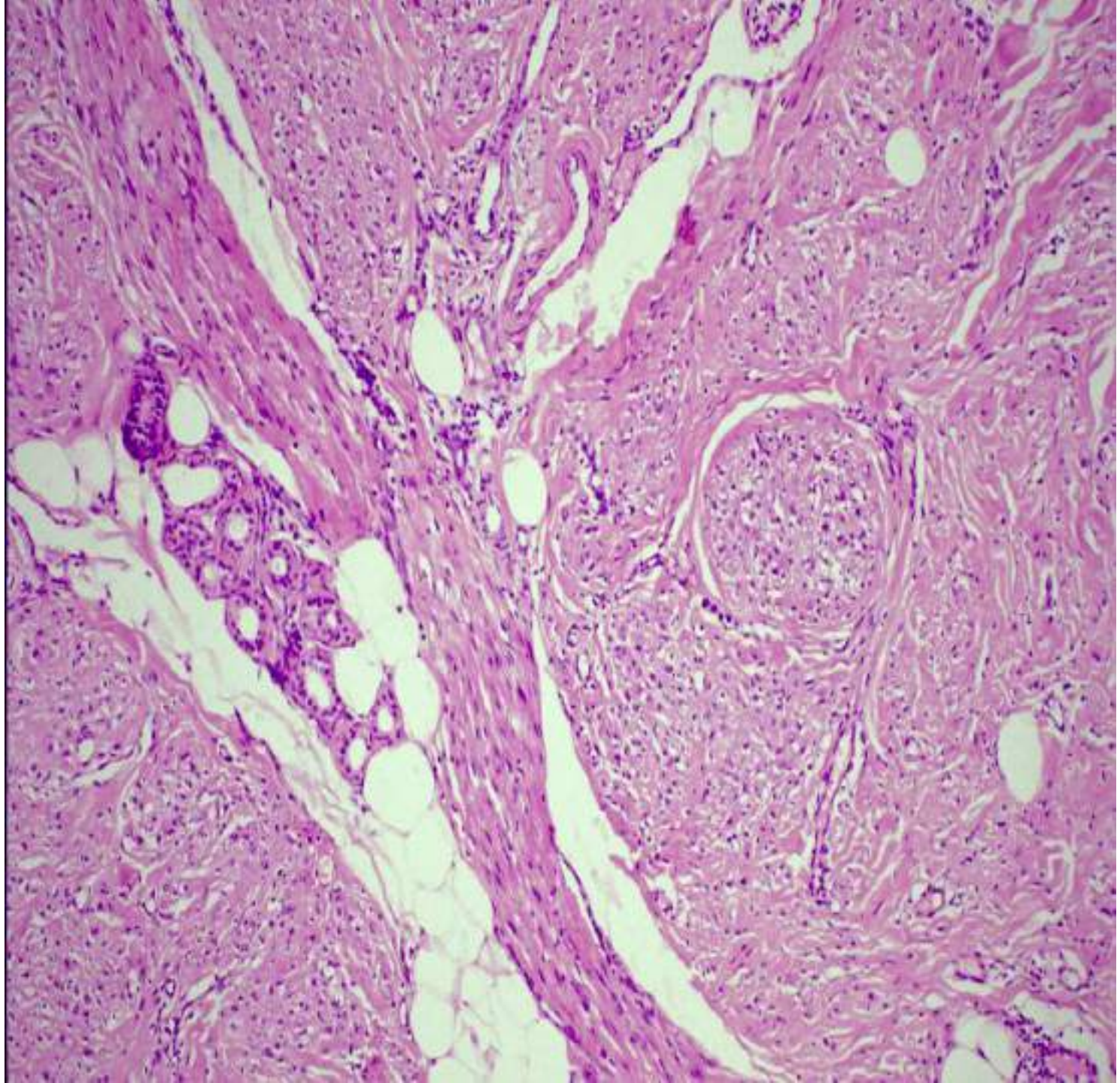


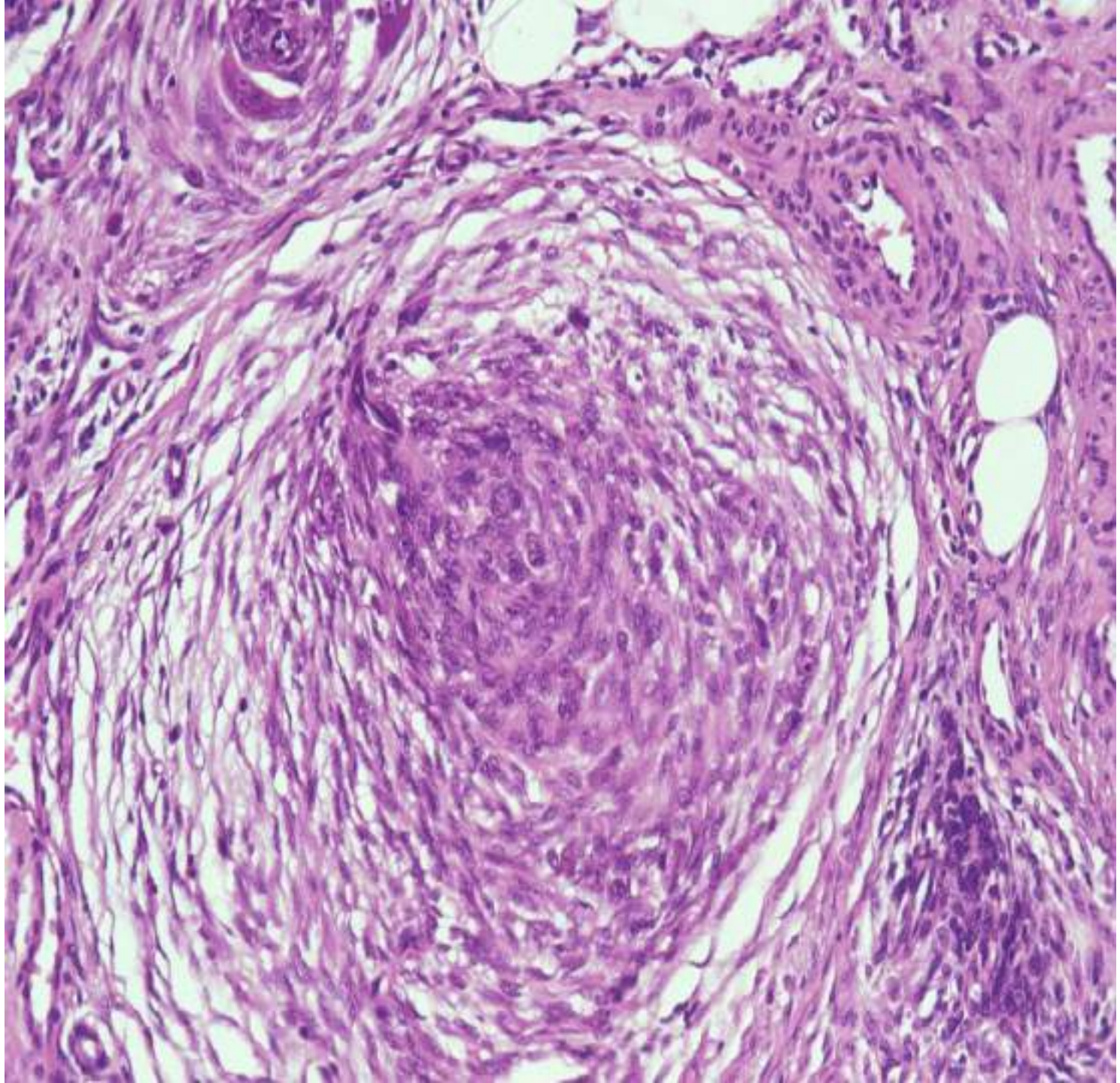


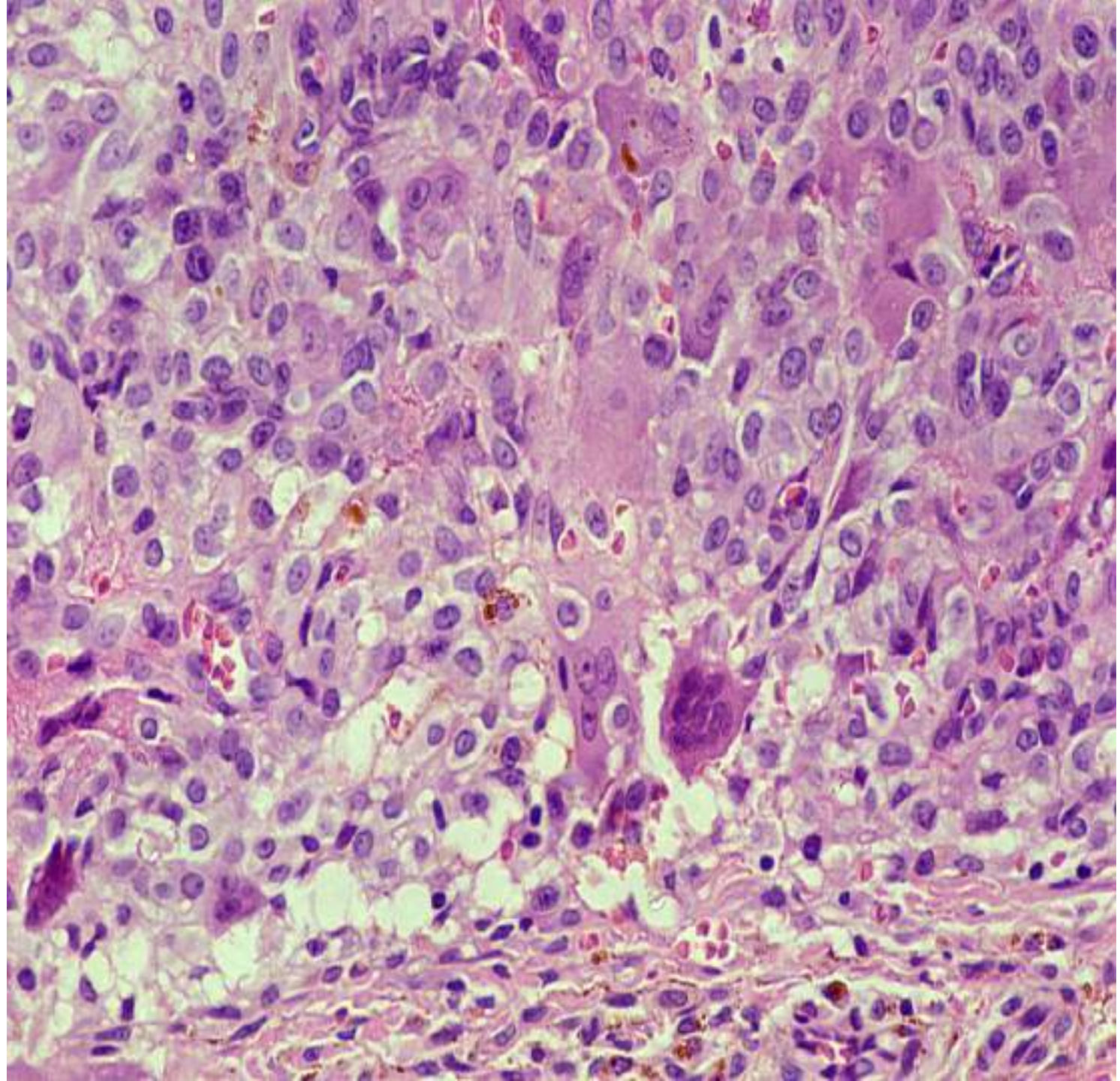


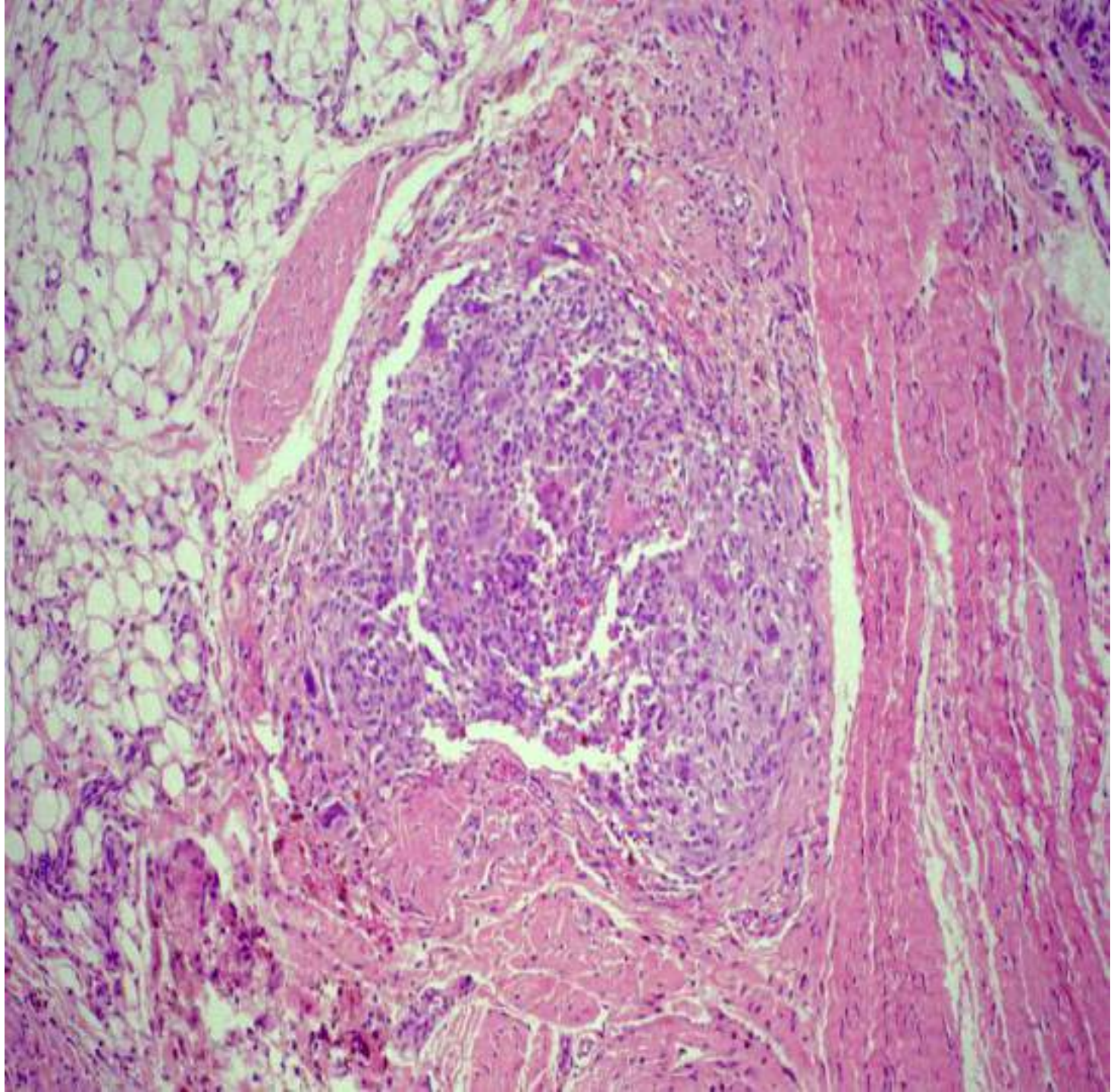








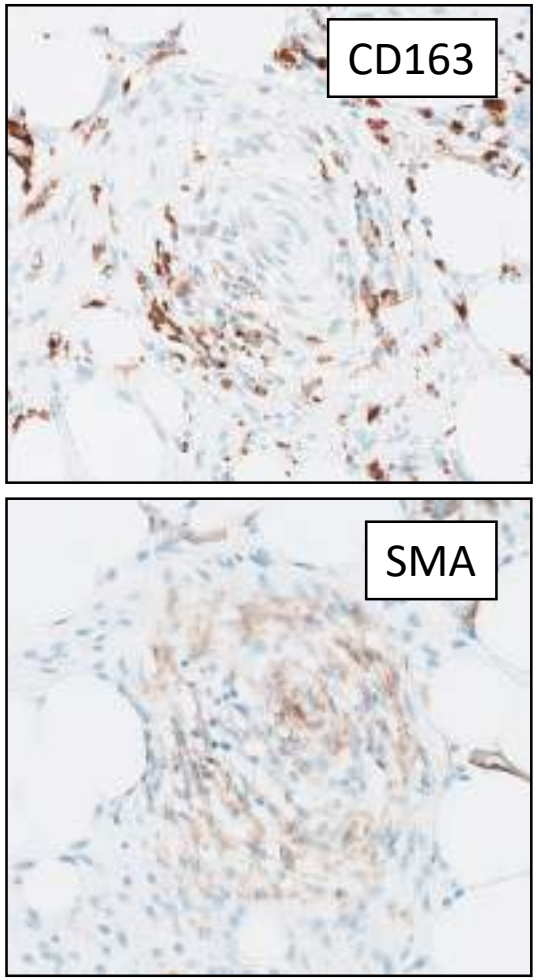




Immunohistochemistry

Positive

- Histiocyte-like osteoclast-like giant cells:
  - CD68, CD163
- Fibroblast-like cells:
  - SMA (focally)
  - NKI-C3 and CD10

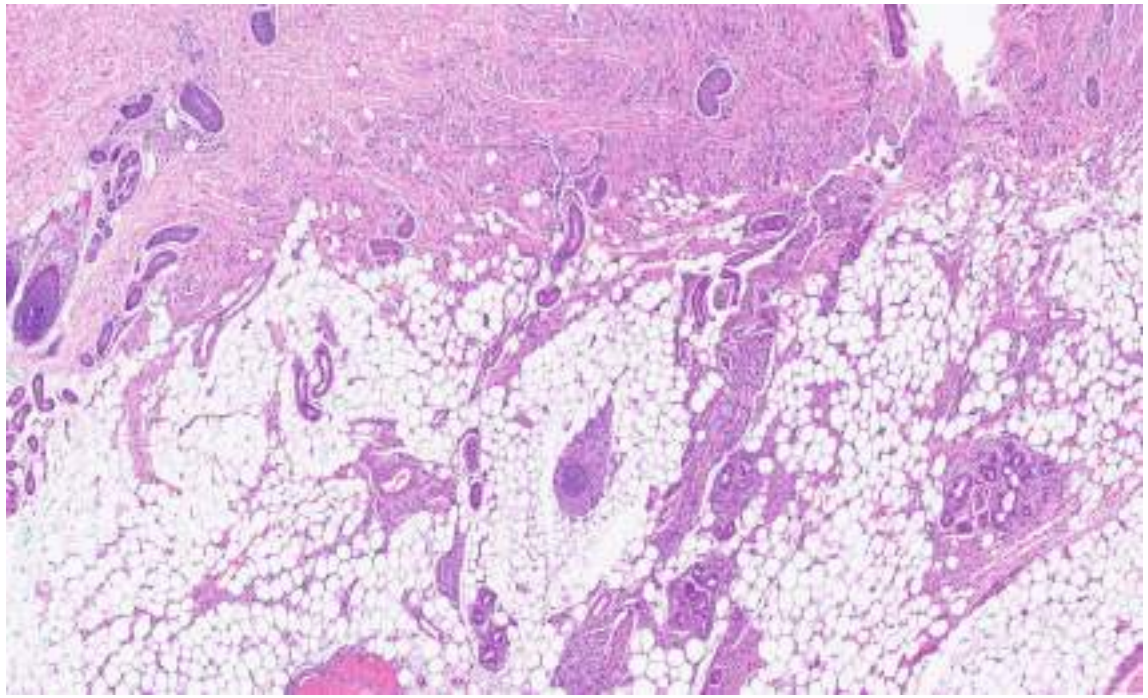


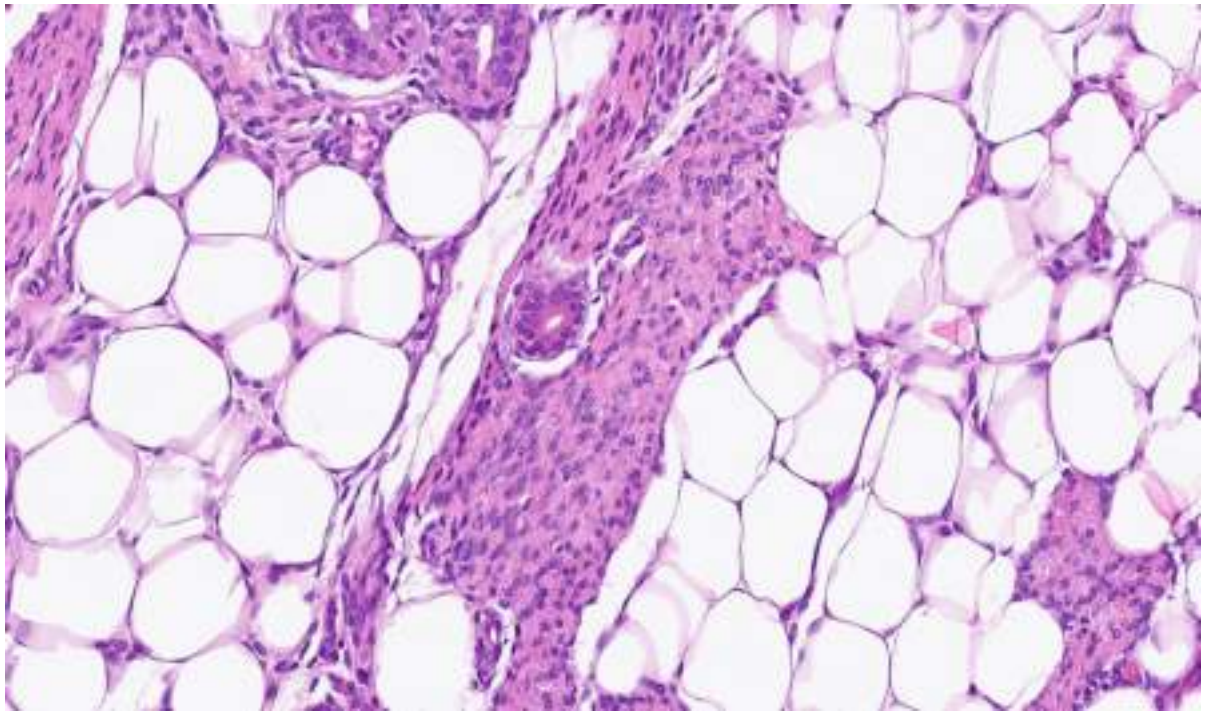
Negative

- CK
- S100 protein
- Desmin
- CD34

Differential diagnosis

Fibrous hamartoma of infancy

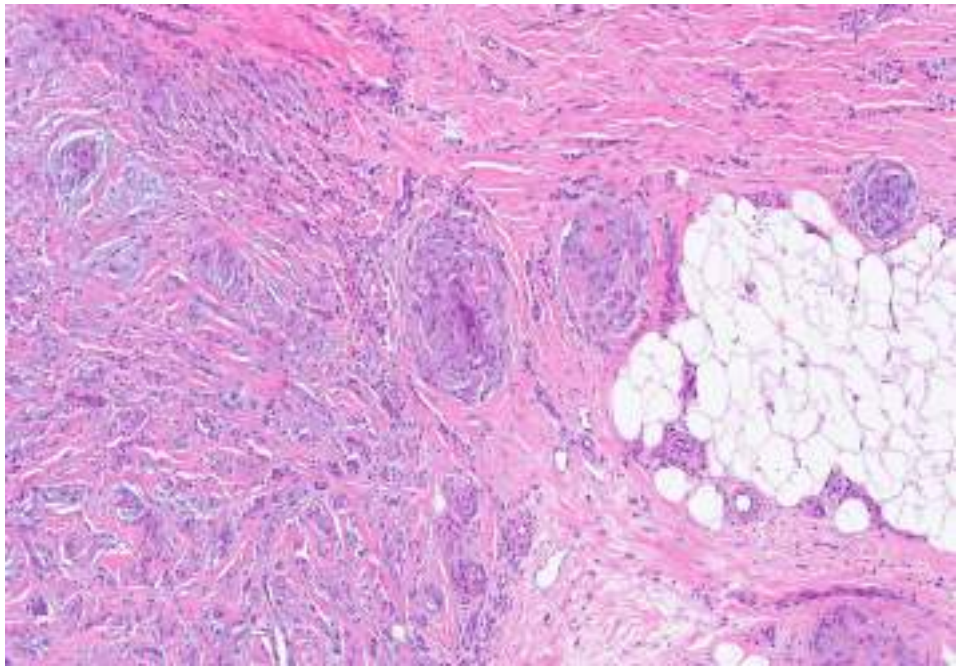




Differential diagnosis

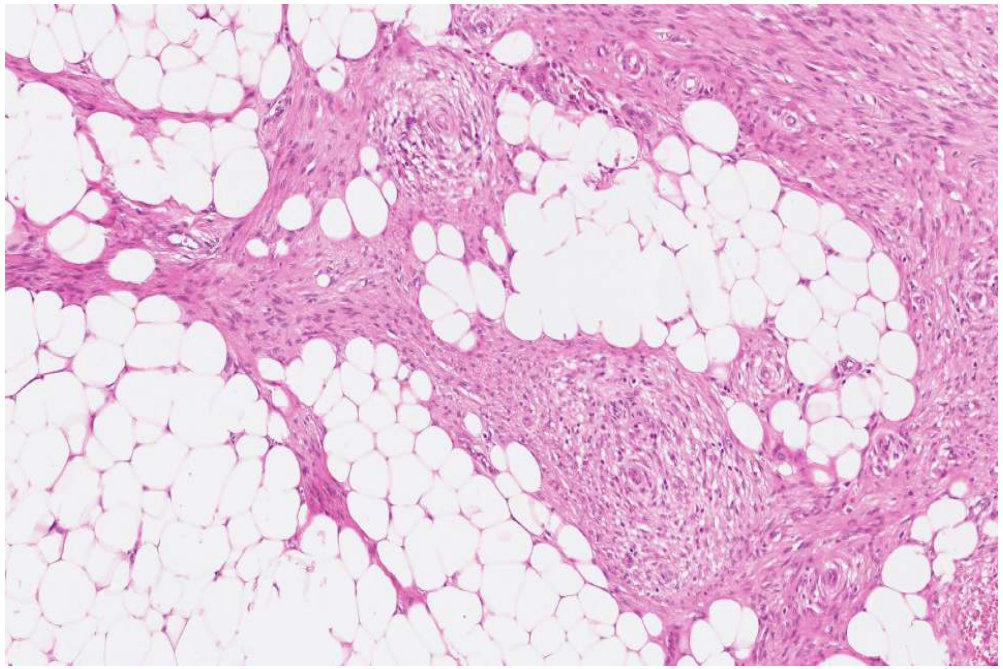
Cellular neurothekeoma (CNTK)

CNTK



- Infiltrative border
- Growth pattern
- Similar cell composition
- Giant cells (PFHT>CNTK)
- No.of nuclei in giant cells
- (PFHT>CNTK)
- Common IHC
- Histogenetic link?

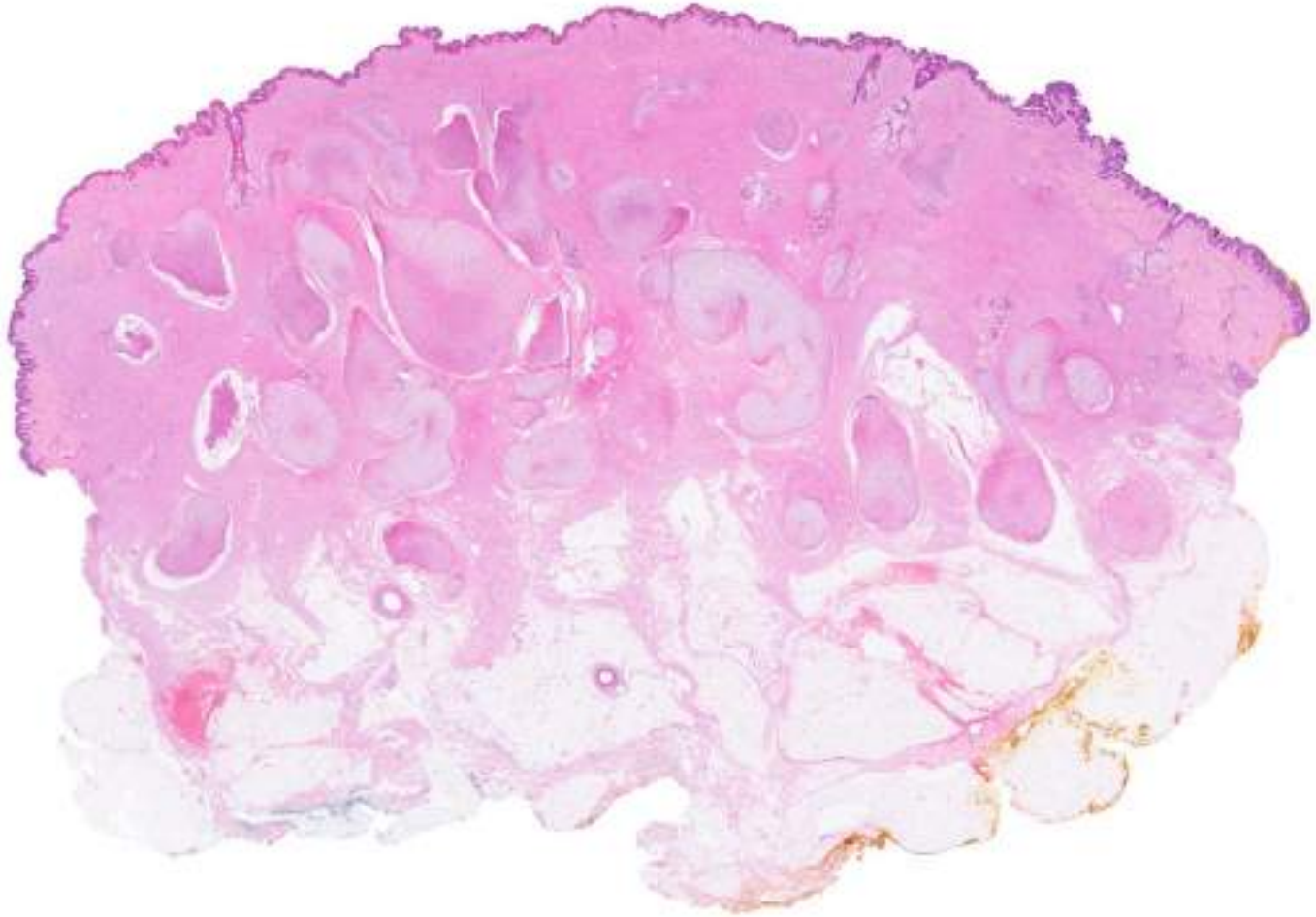
PFHT

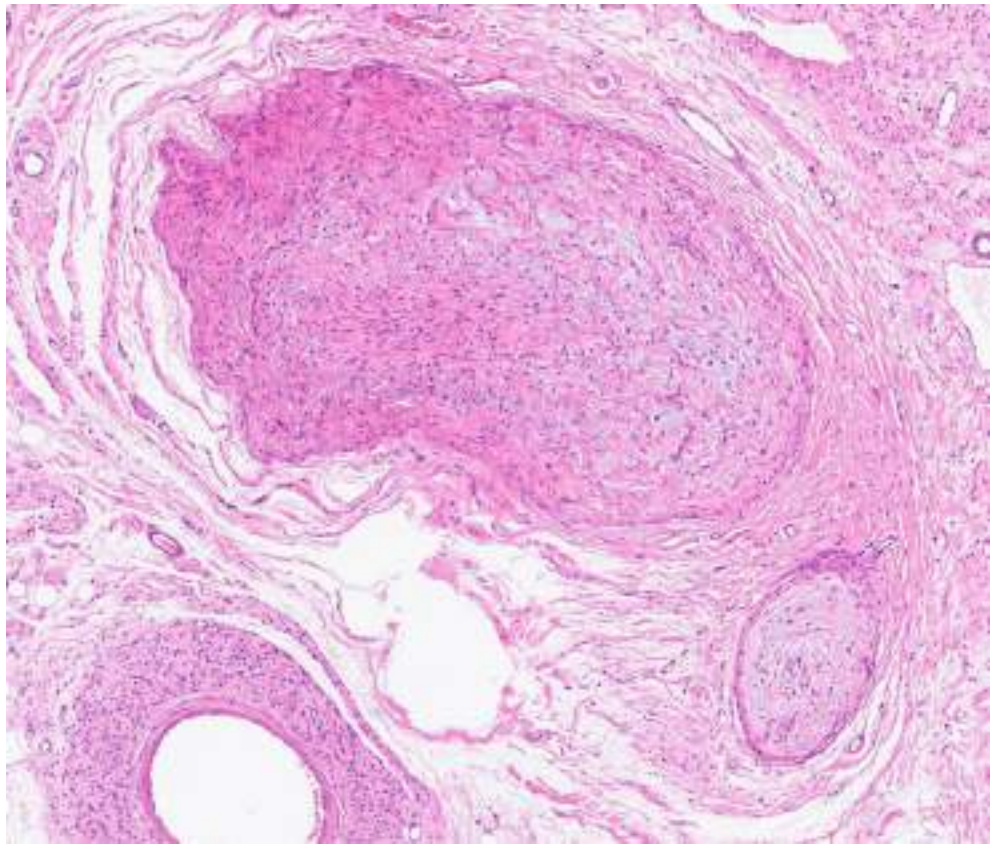


Jaffer S et al. Neurothekeoma and plexiform fibrohistiocytic tumor: mere histologic resemblance or histogenetic relationship? Am J Surg Pathol. 2009 Jun;33(6):905-13.

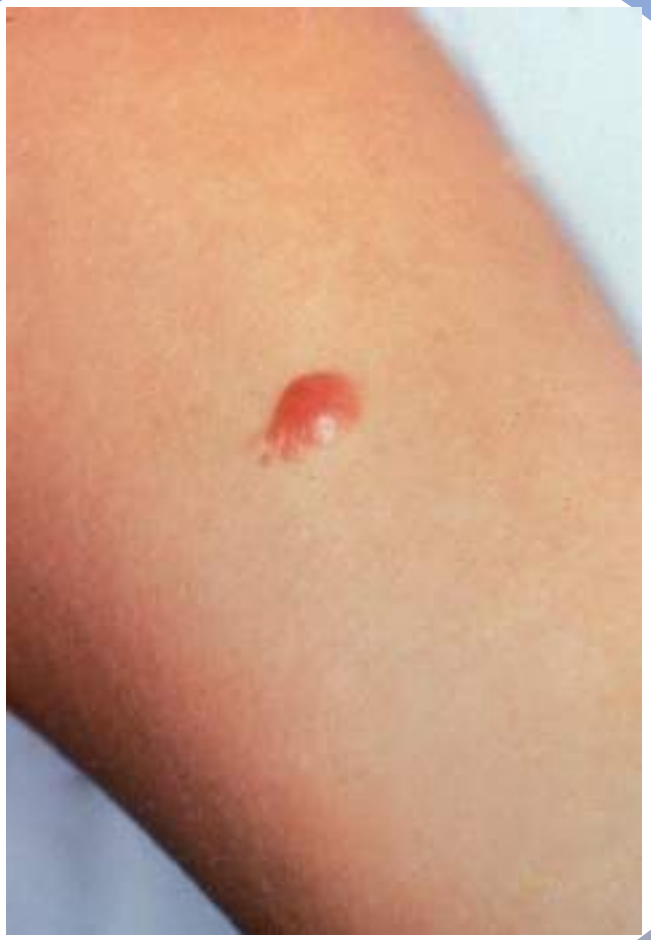
Differential diagnosis

Plexiform neurofibroma





Cellular neurothekeoma



Definition: Lobular or micronodular proliferation of nested epithelioid and spindle cells in a background of variable myxoid and hyalinised stroma

- F>M
- Second and third decade of life

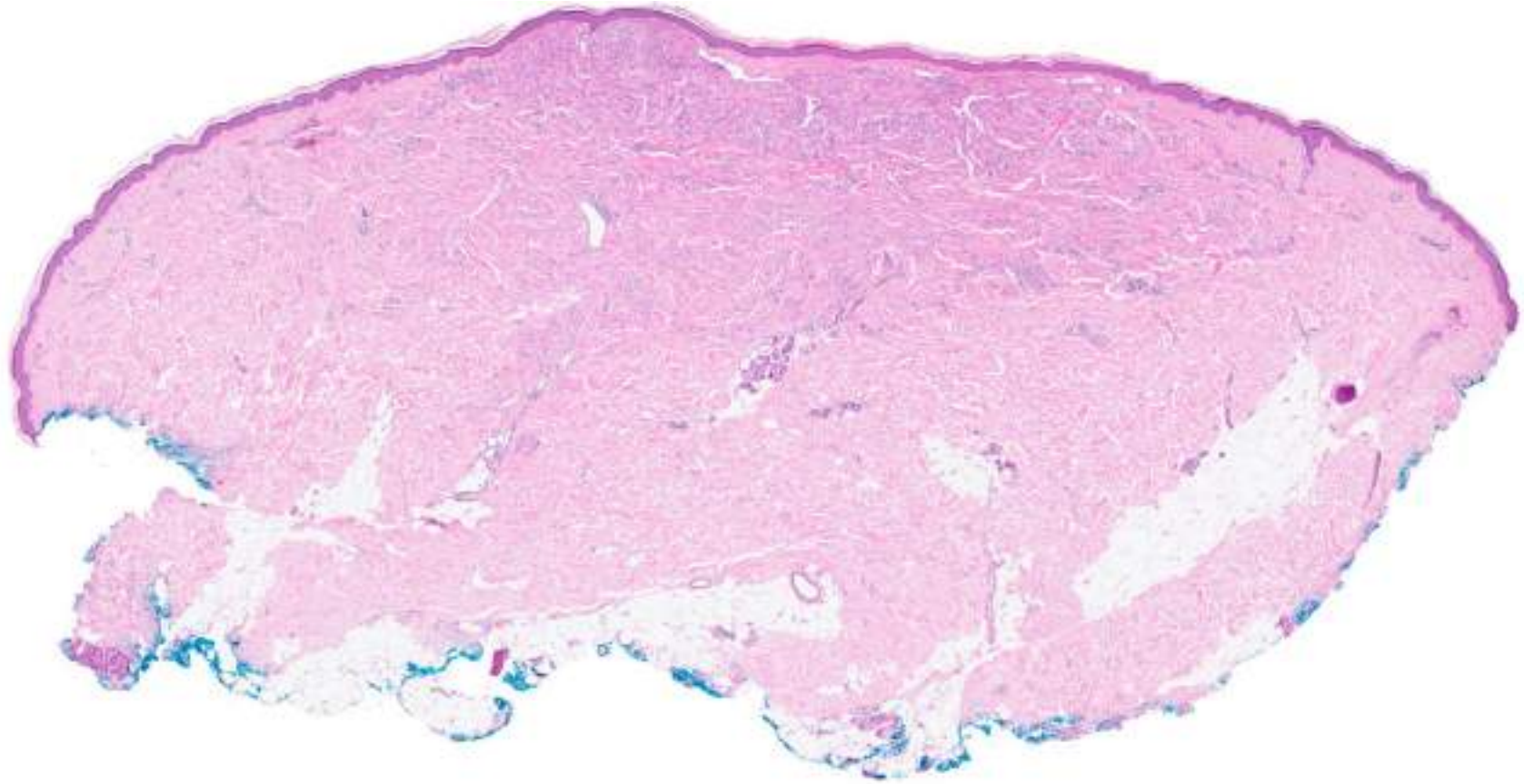
- Slowly growing, dome- shaped nodule, papule
- Multifocal
- Head and neck area, upper extremity
- Unusual locations: oral cavity, paranasal sinusies, maxilla, conjuctiva

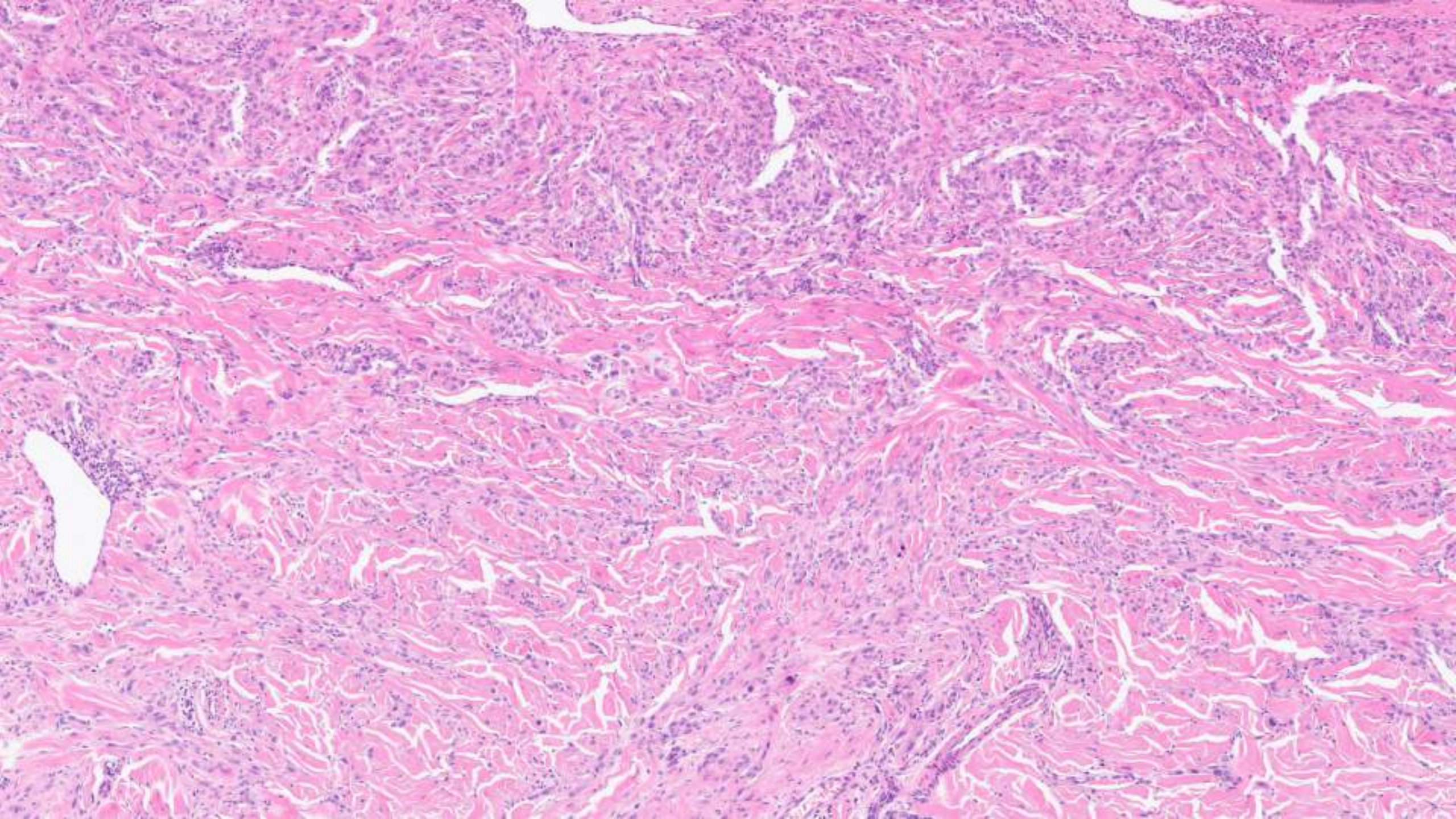
- Uniformly benign clinical course, even atypical neurothekeoma
- Increased recurrences on the face

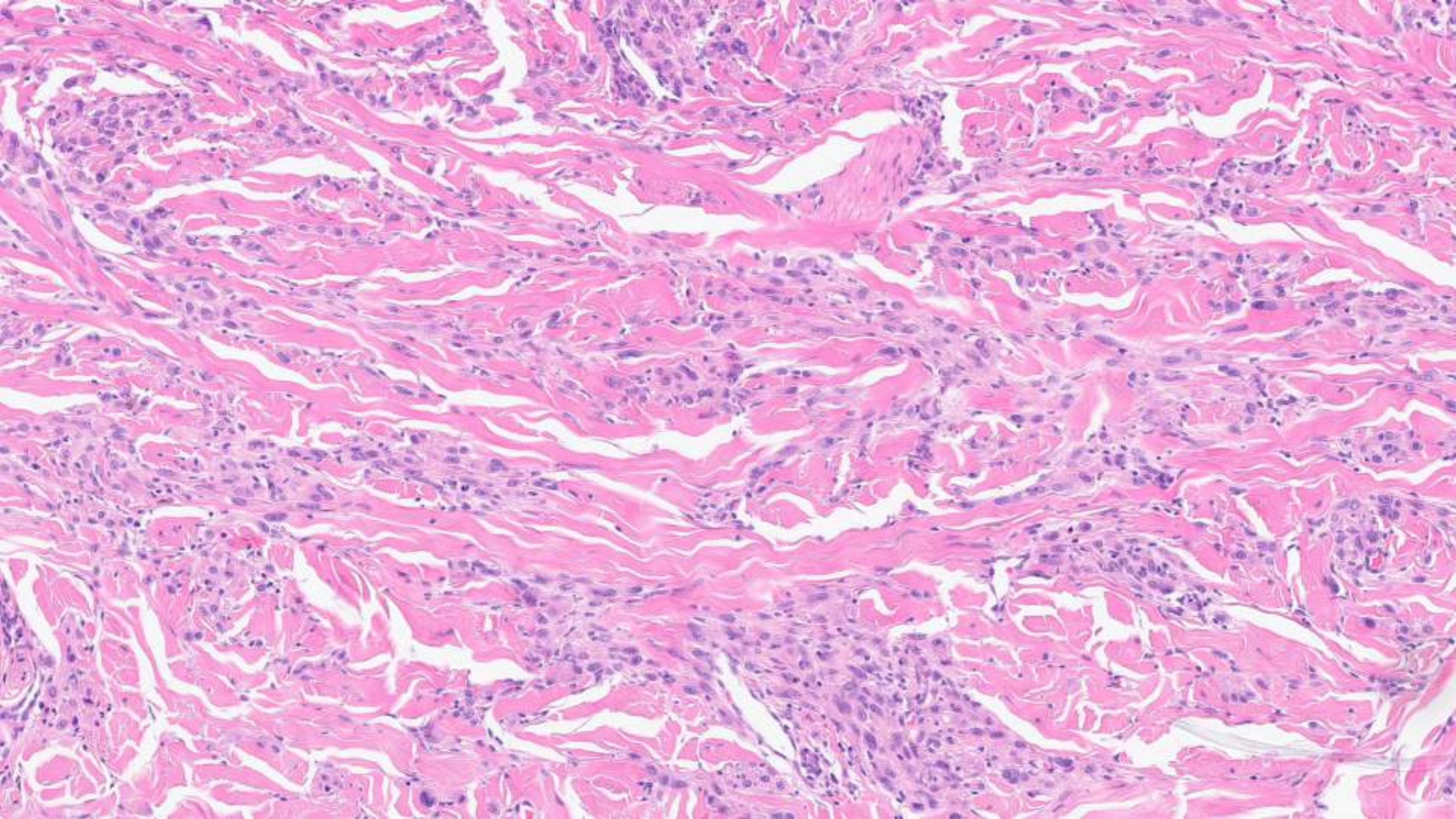
- Anecdotal metastasis (2020)

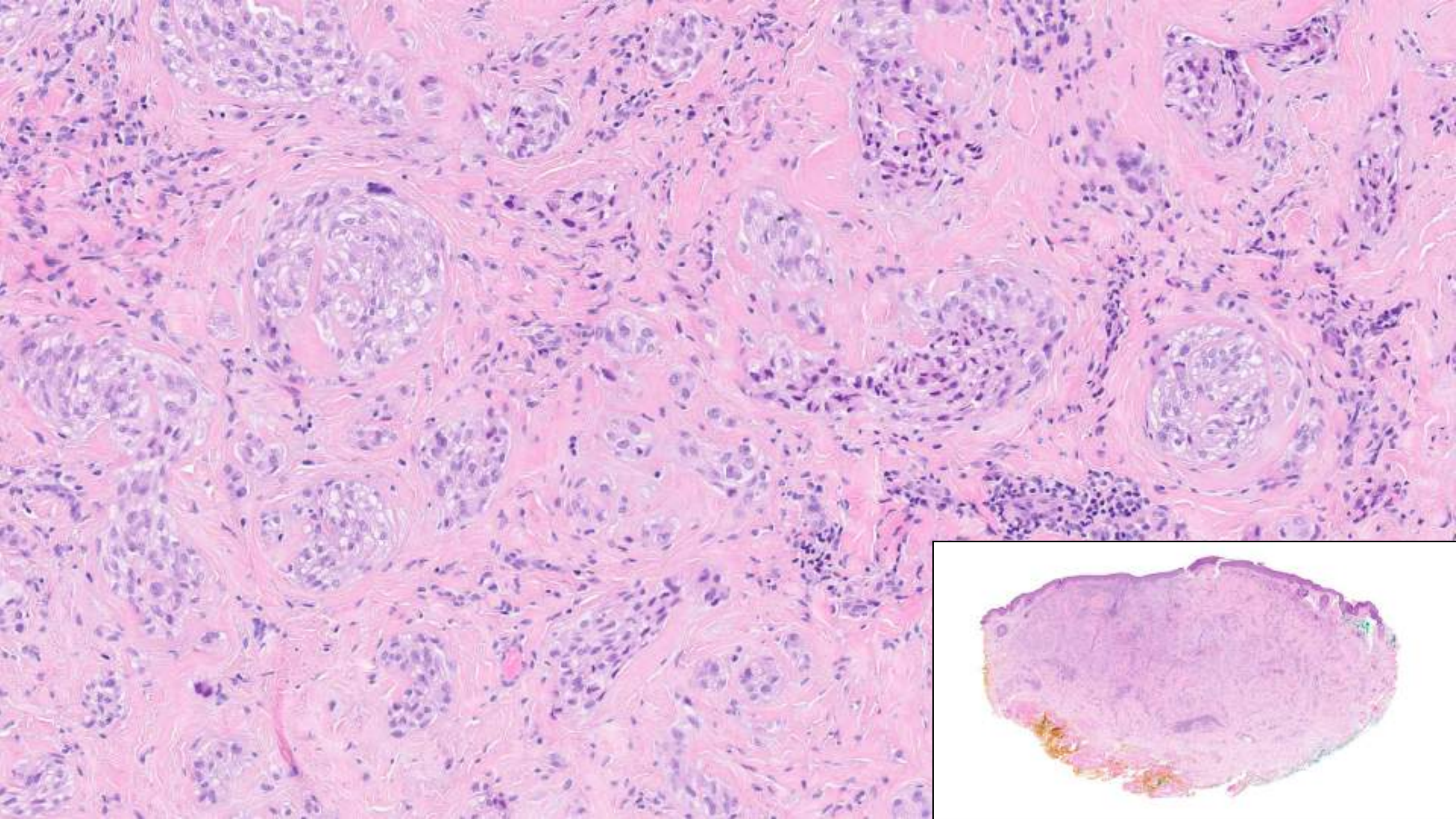
Cellular neurothekeoma histology

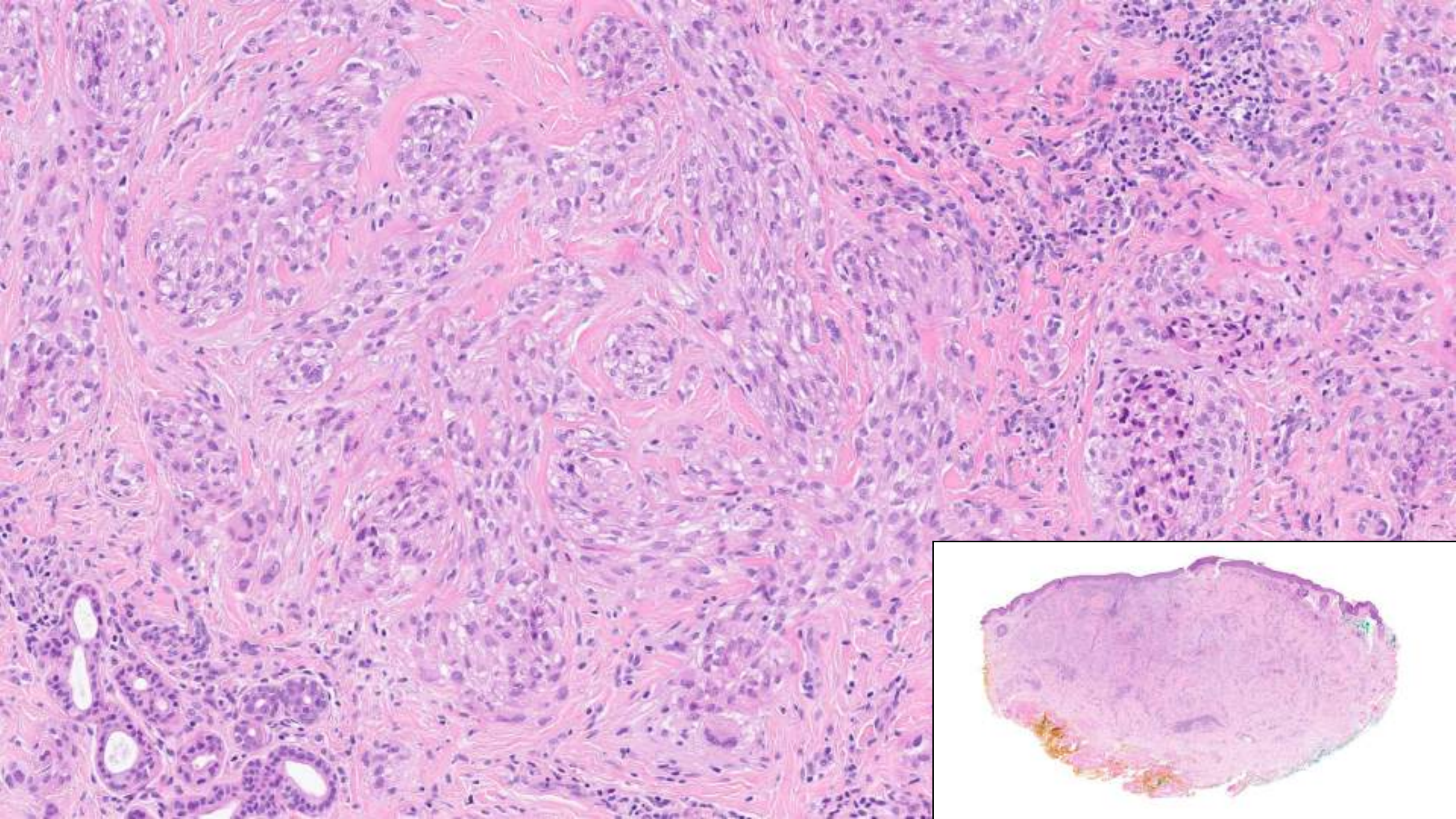
Half limited to the dermis and half also involving the subcutis
Poorly marginated
Micronodular/nested or lobulated
Composed of epithelioid to spindle-shaped cells with abundant palely eosinophilic cytoplasm
At least focally myxoid stroma is seen in around one-third of lesions, and approximately 10% are diffusely myxoid (morphologic overlap with DNSM)

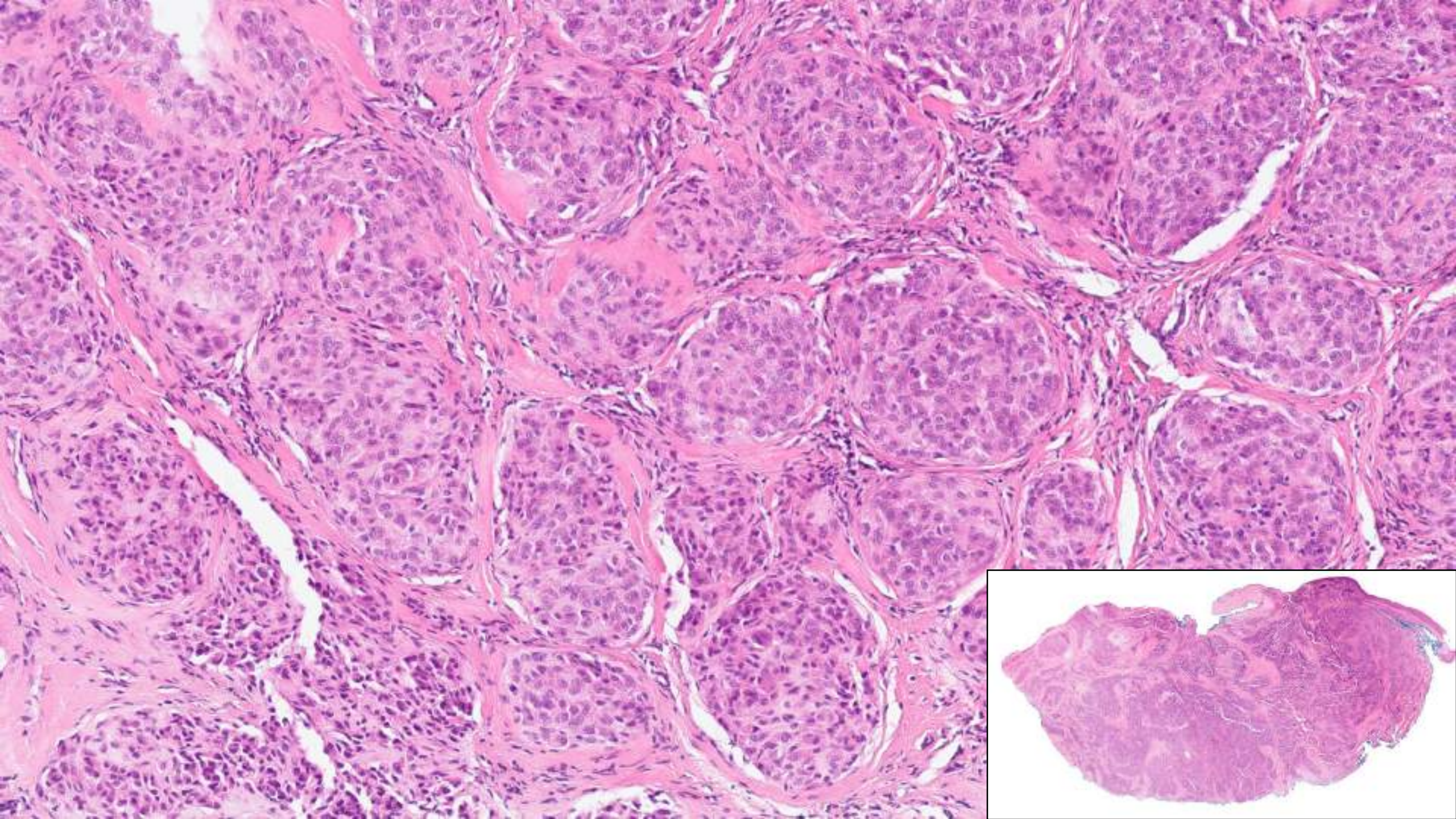


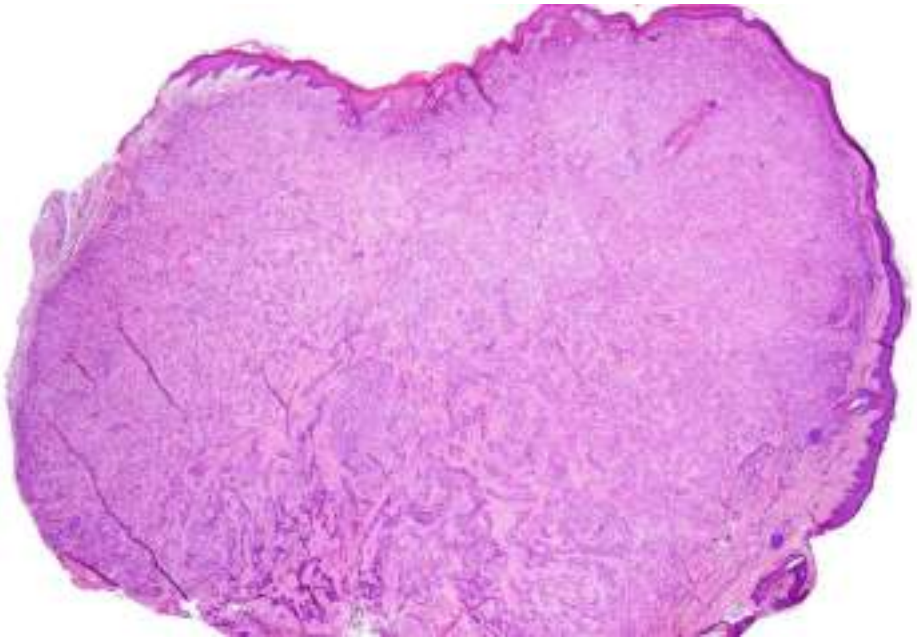


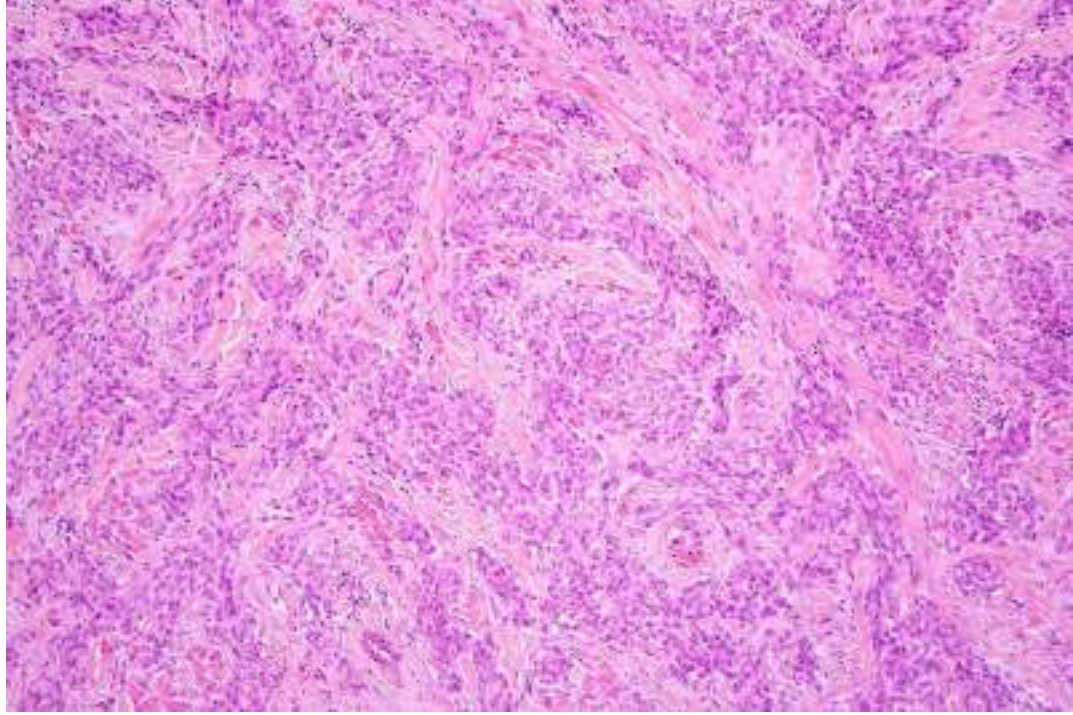


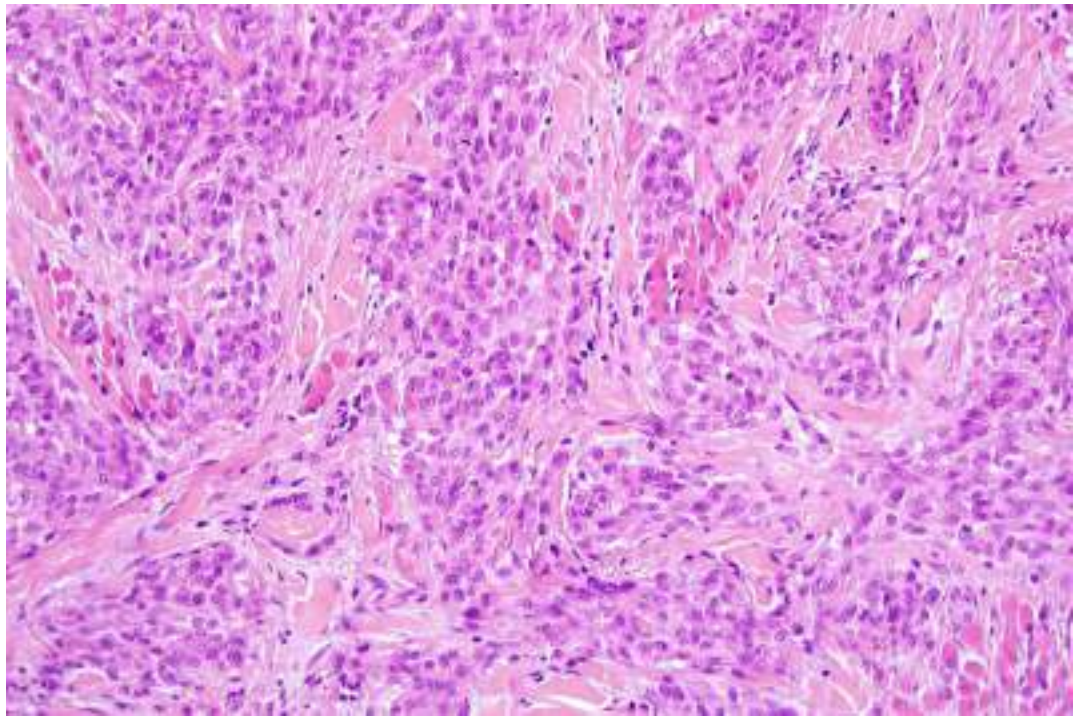


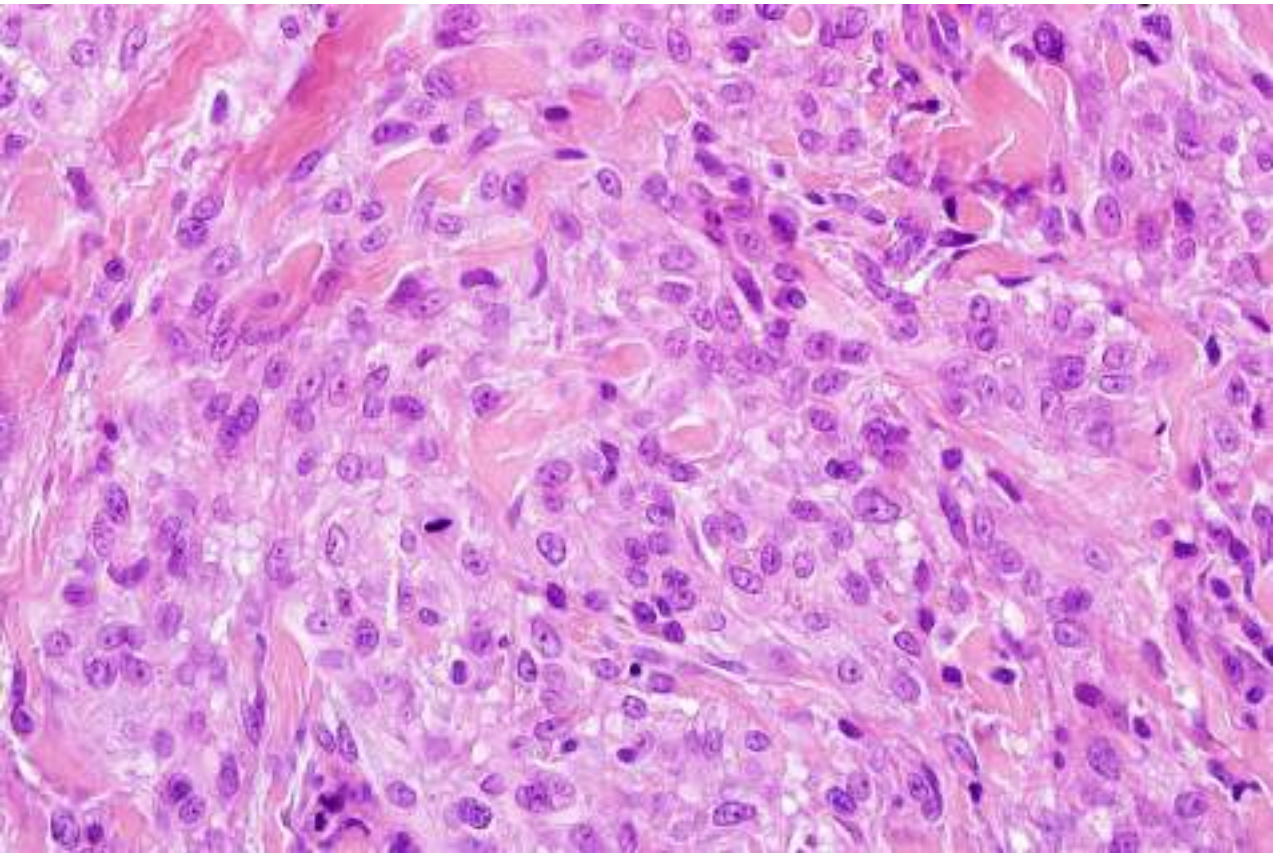


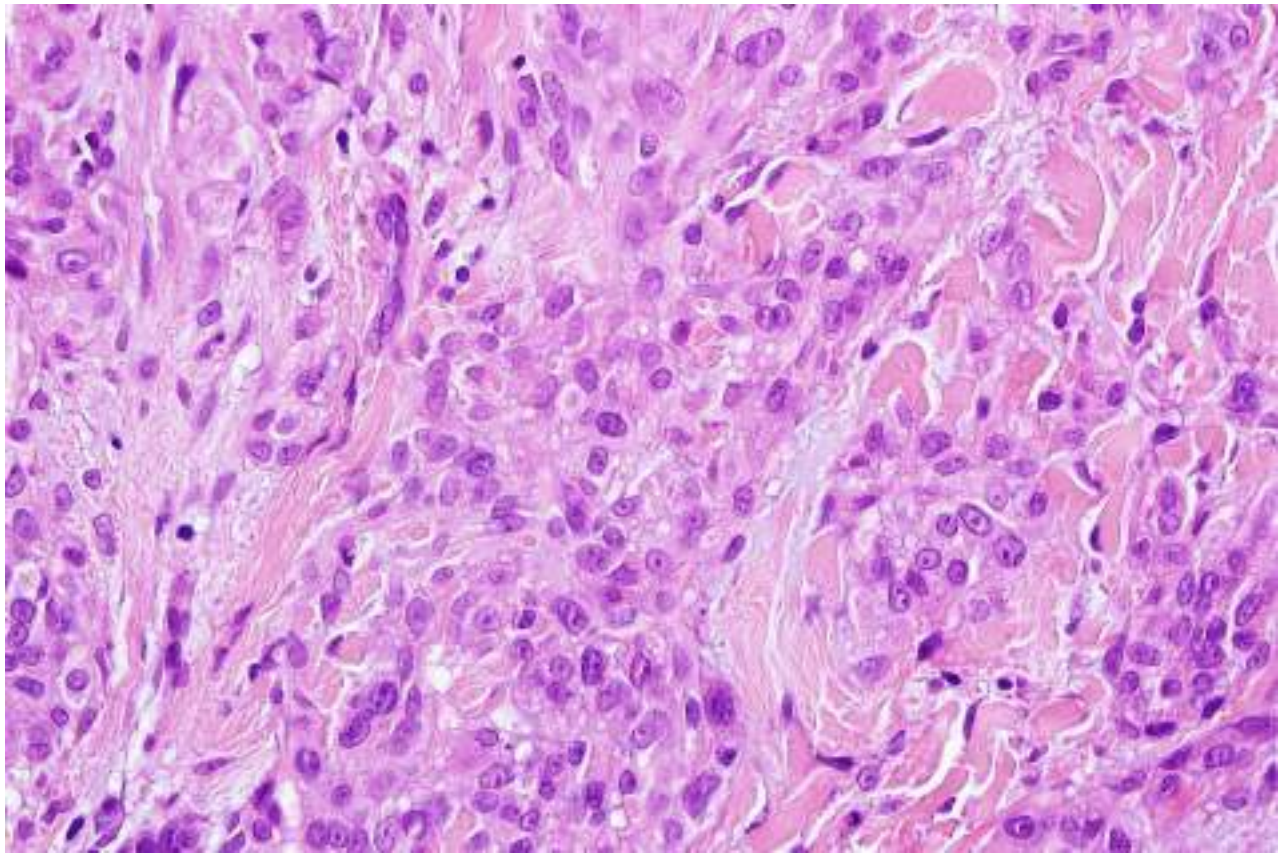


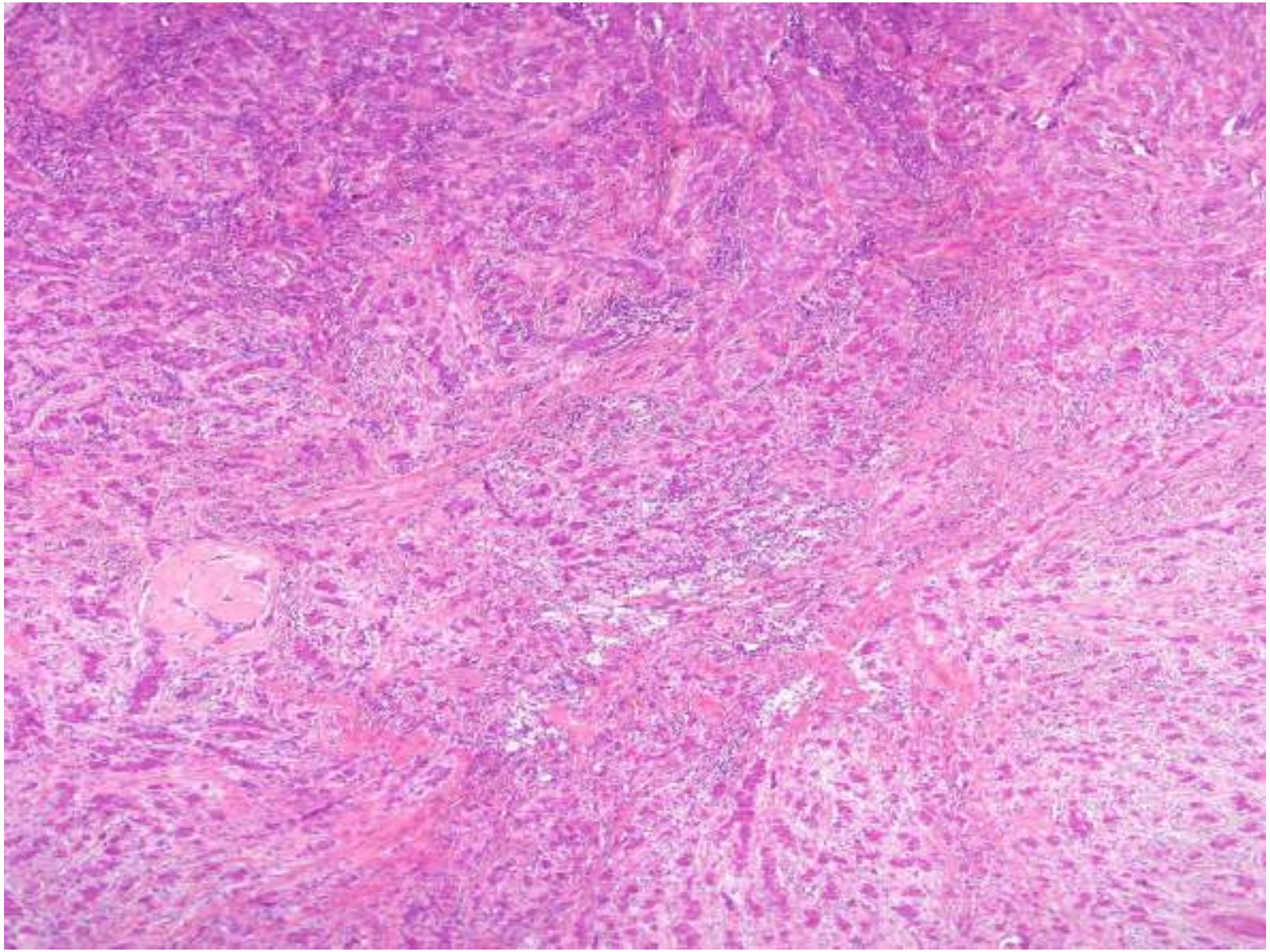


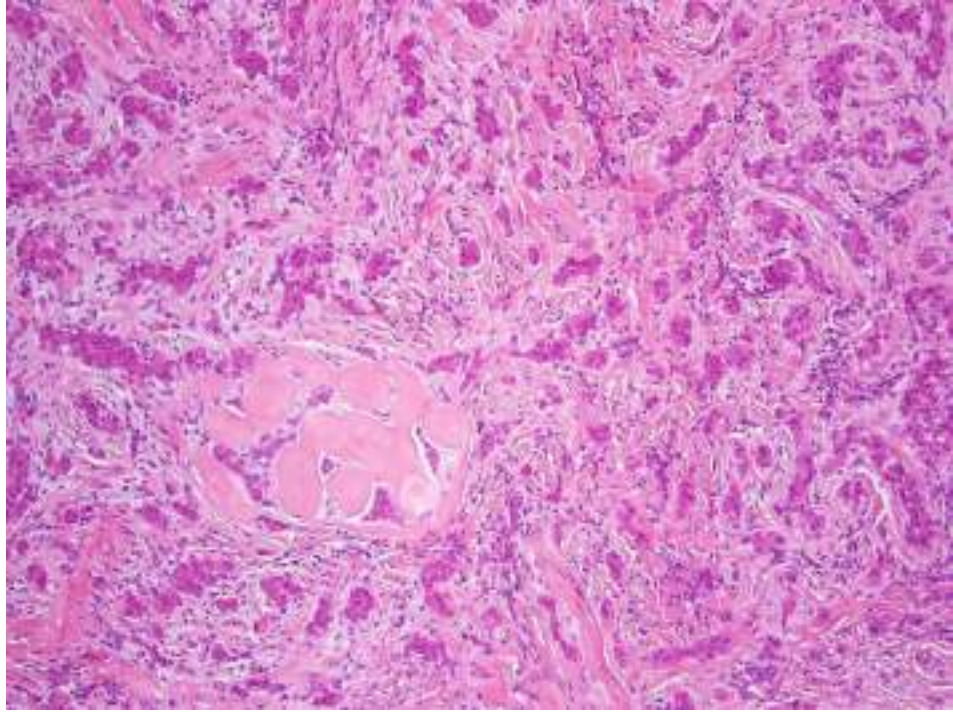


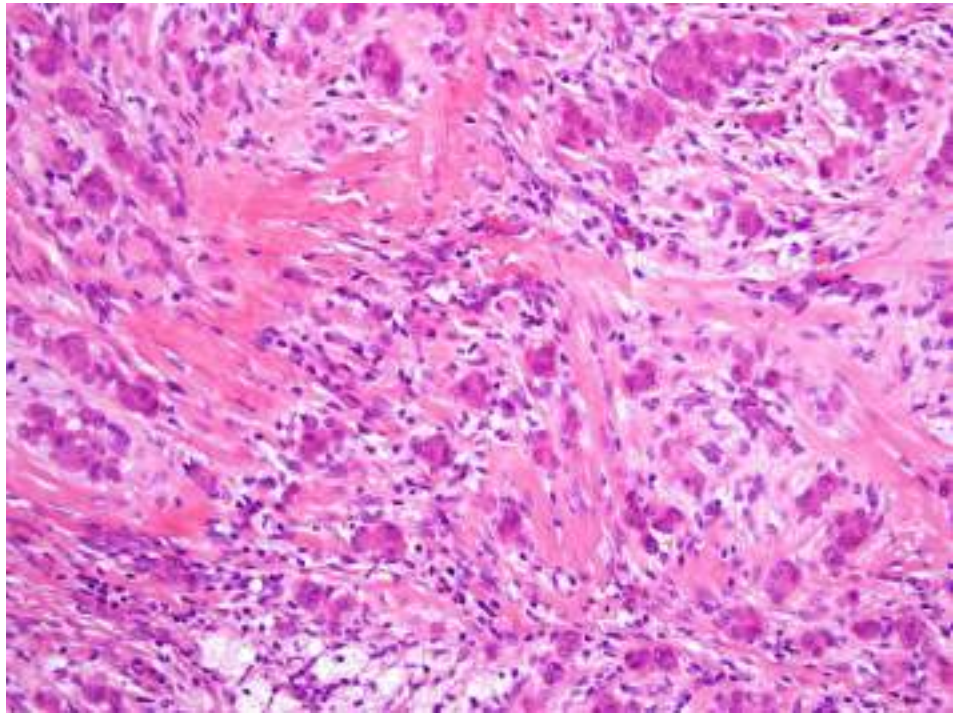


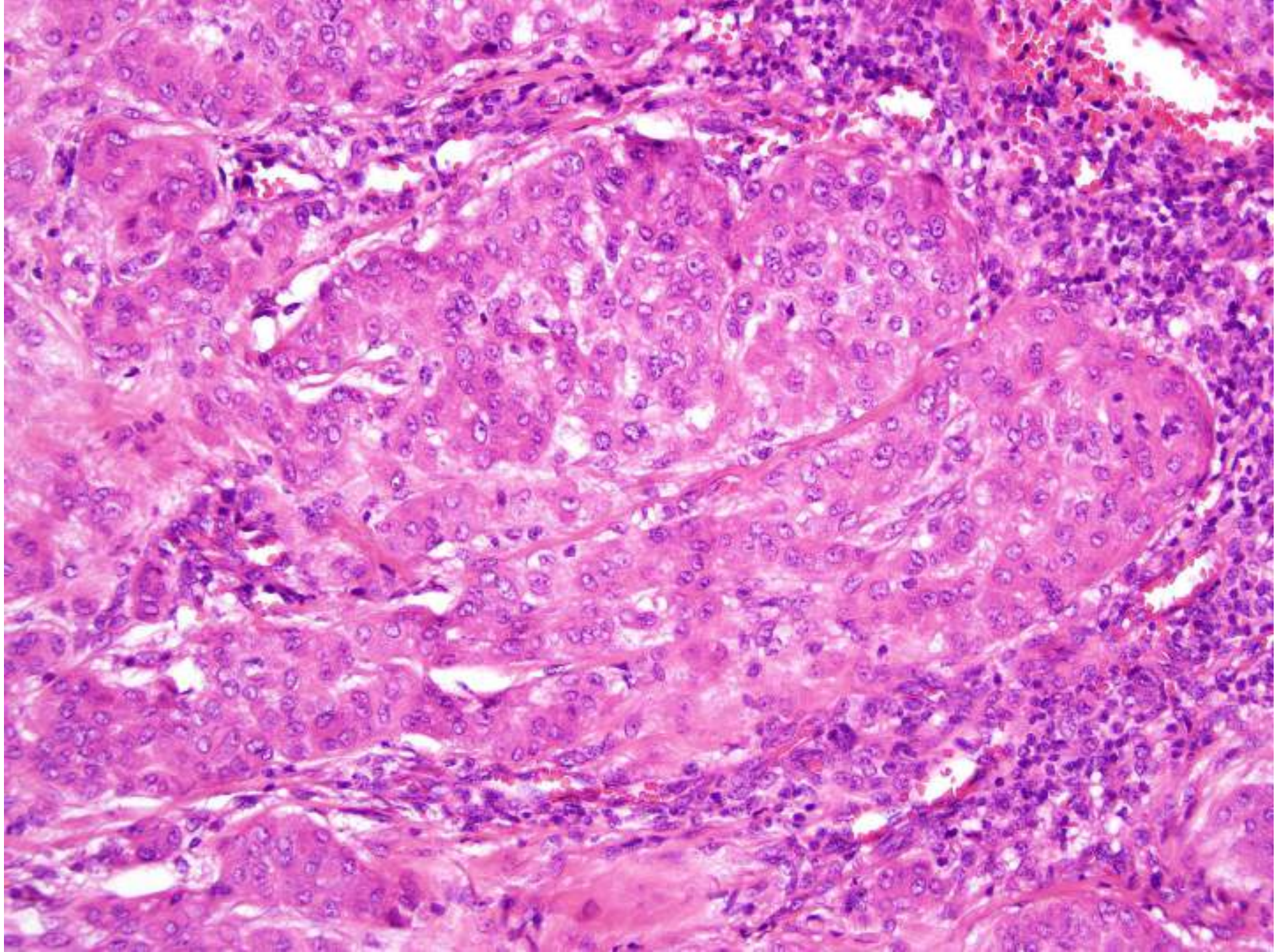


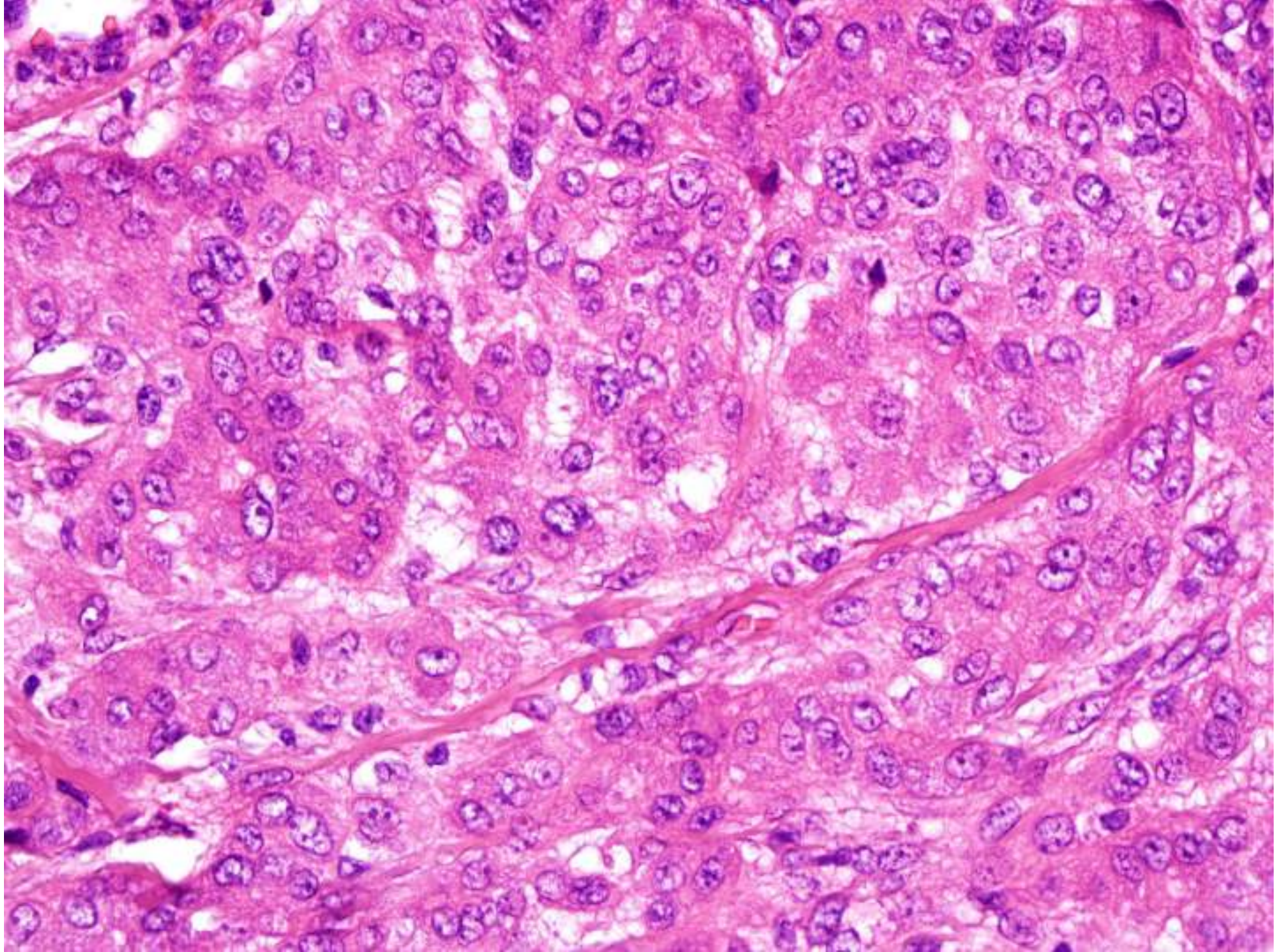


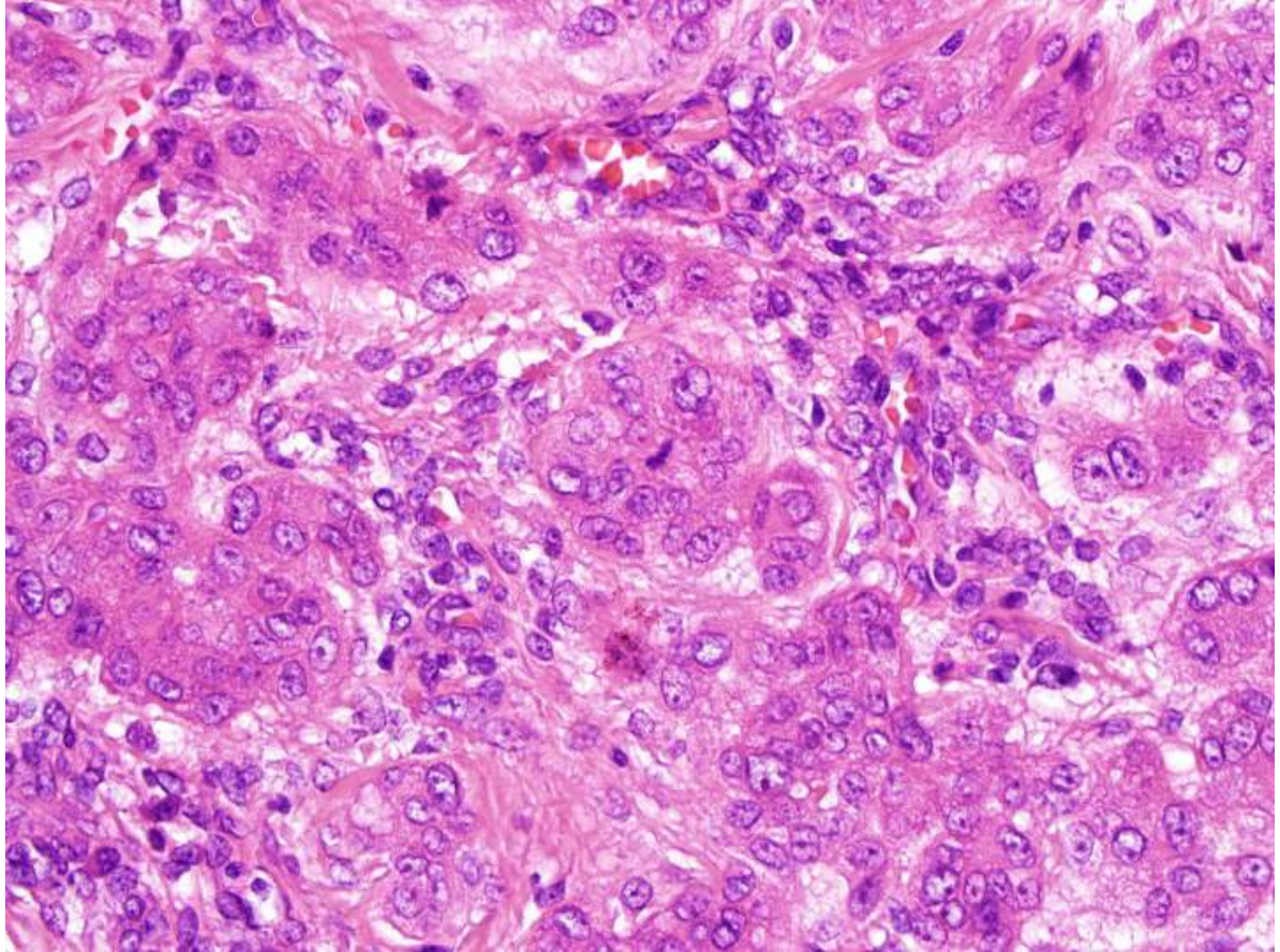


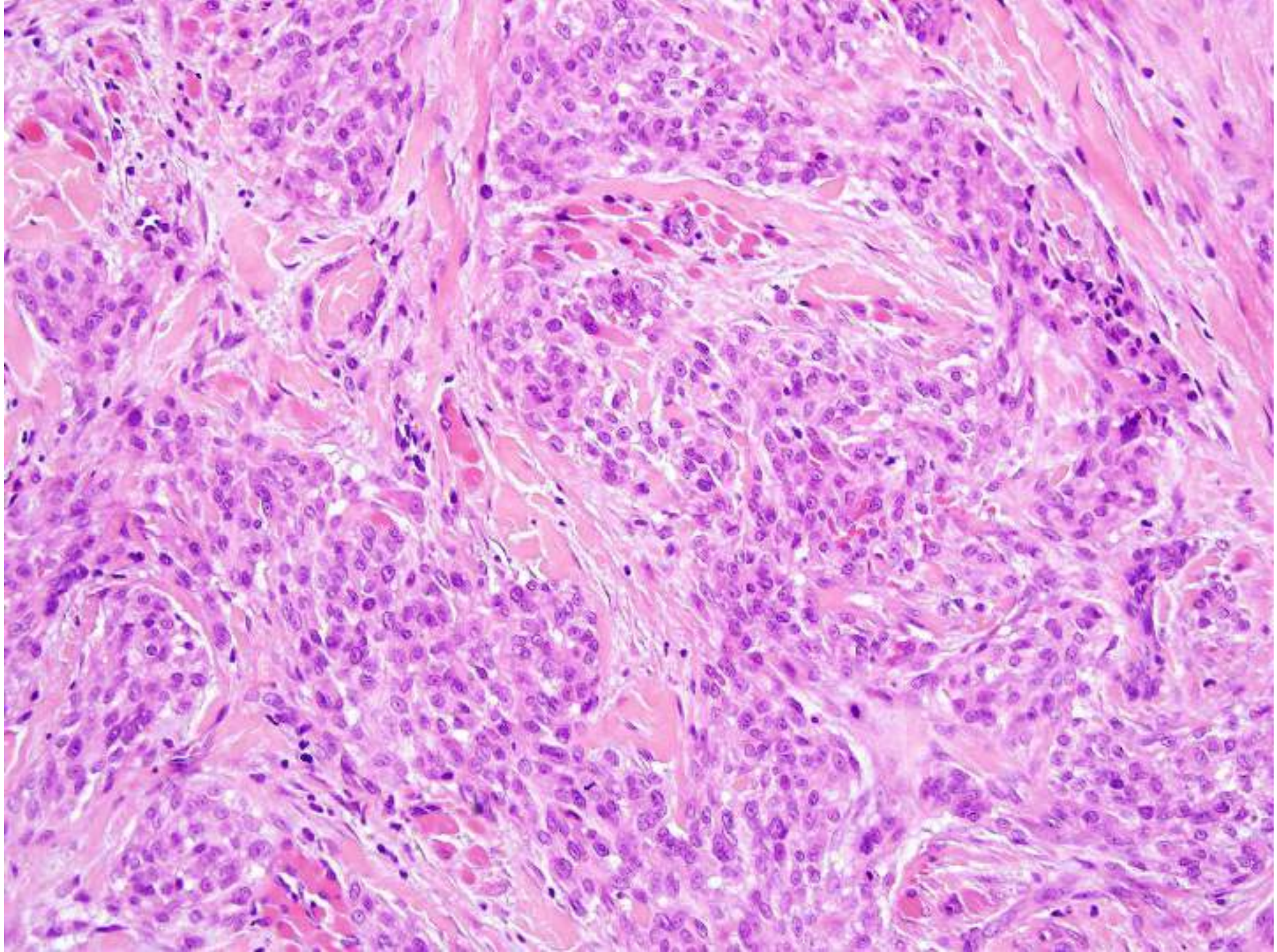


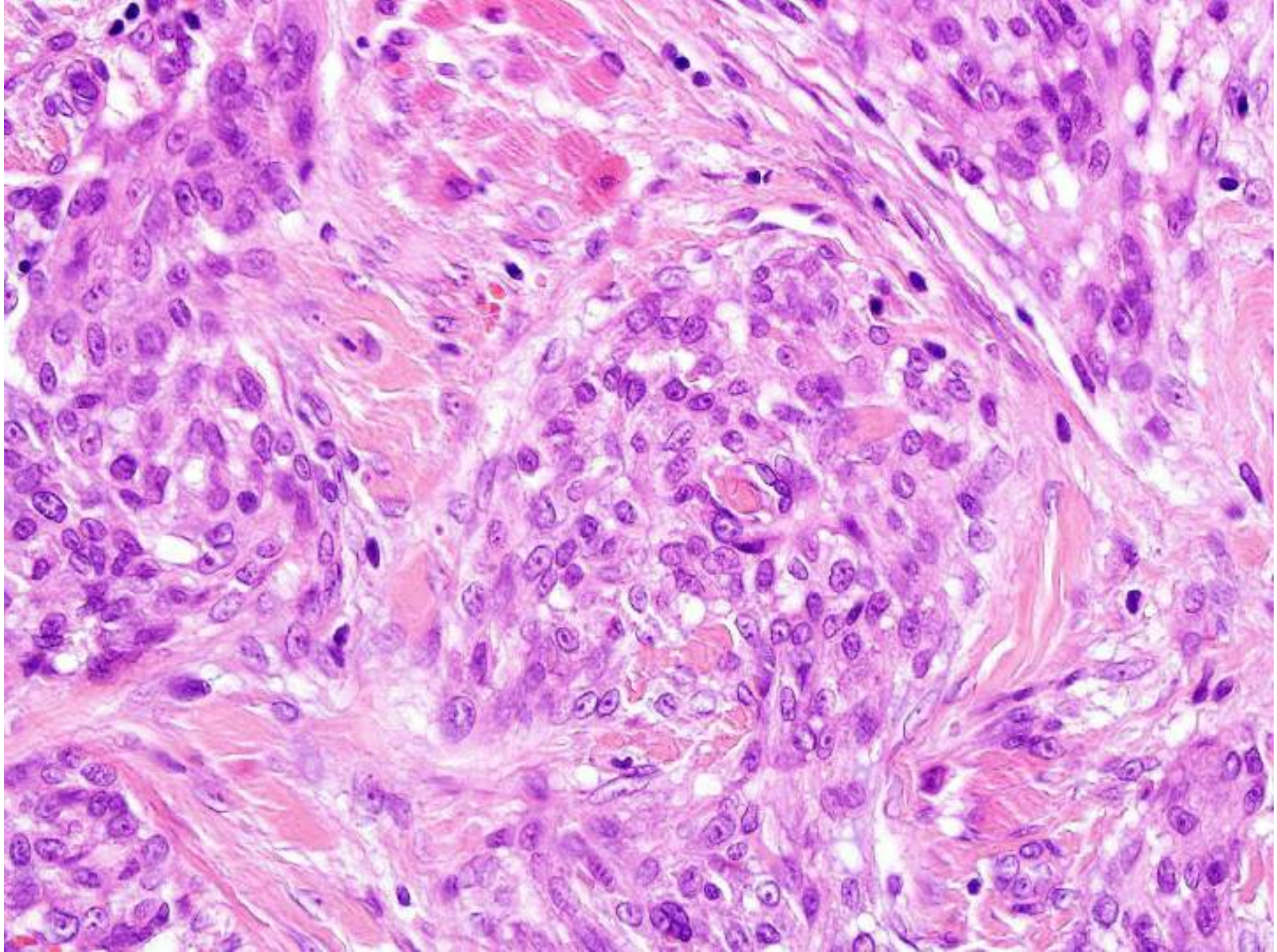


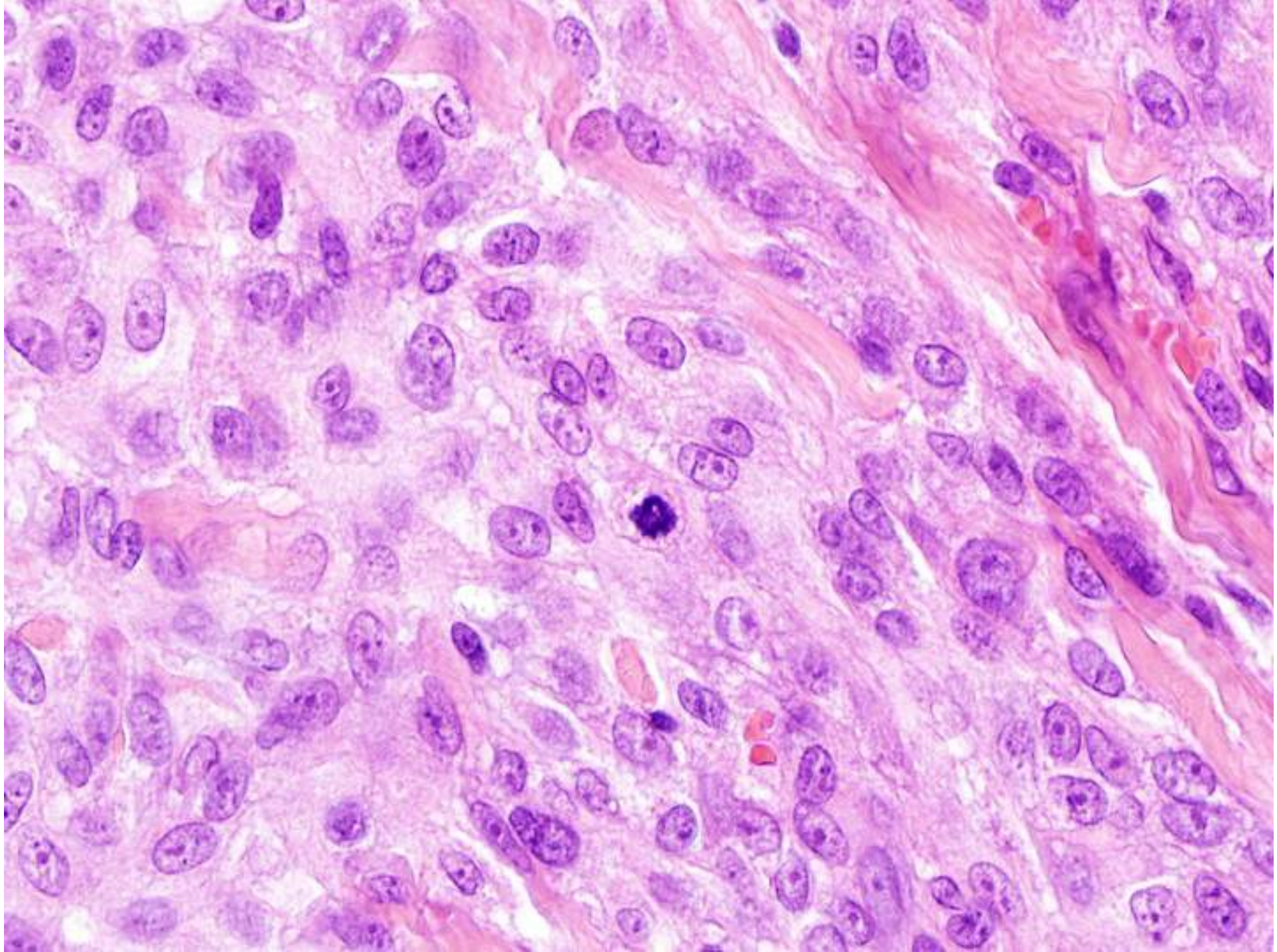








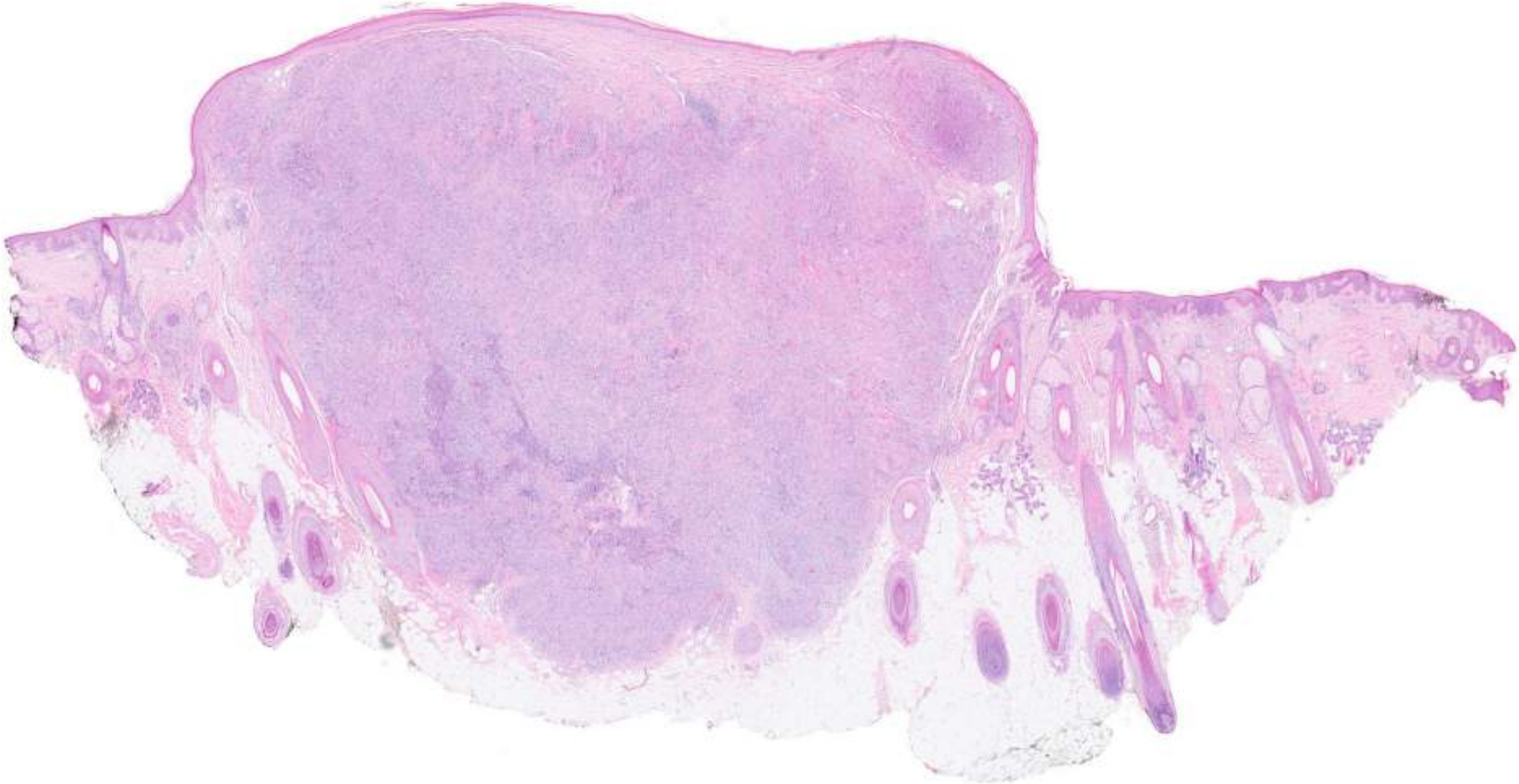


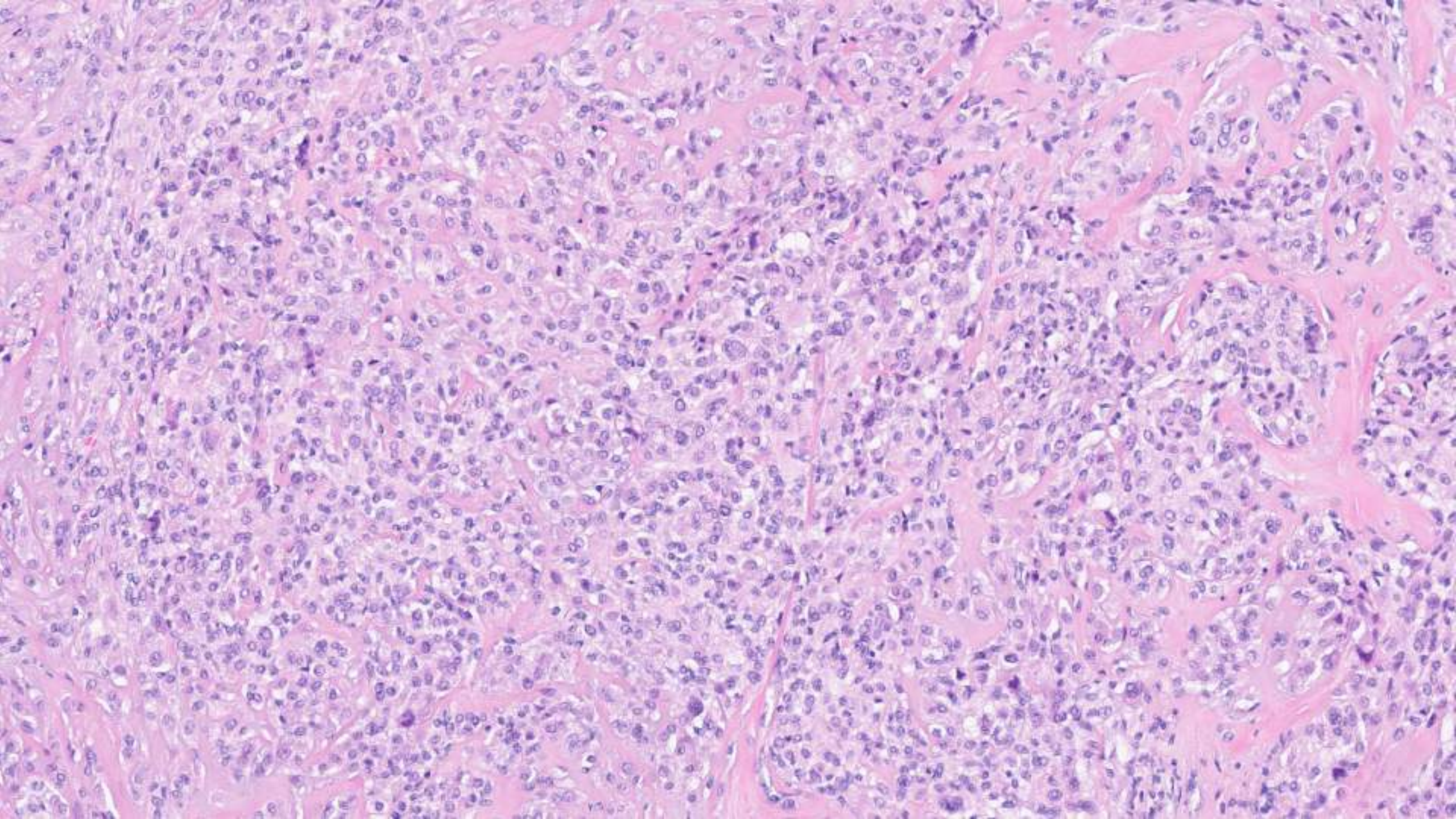


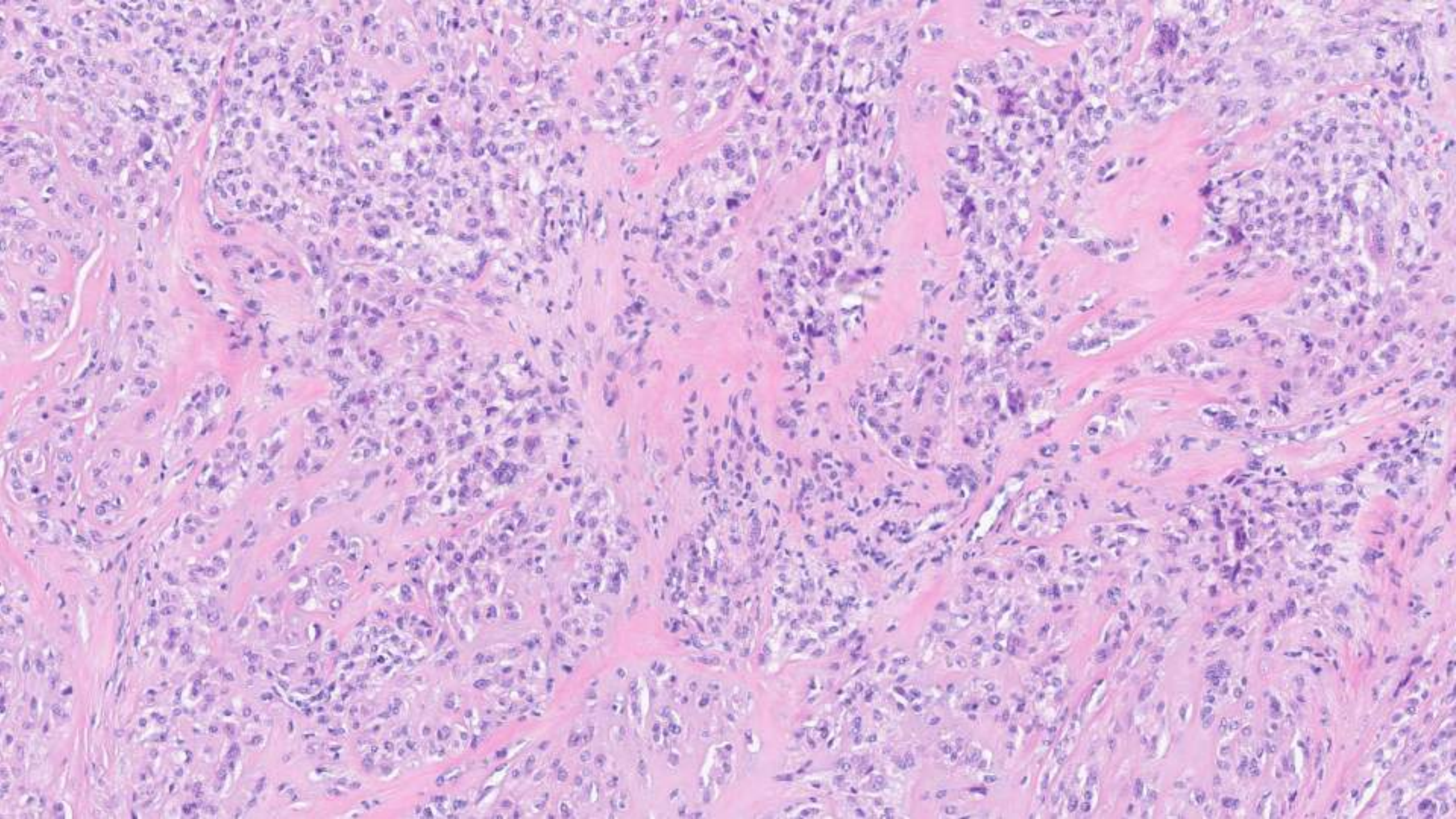
Atypical histological features:

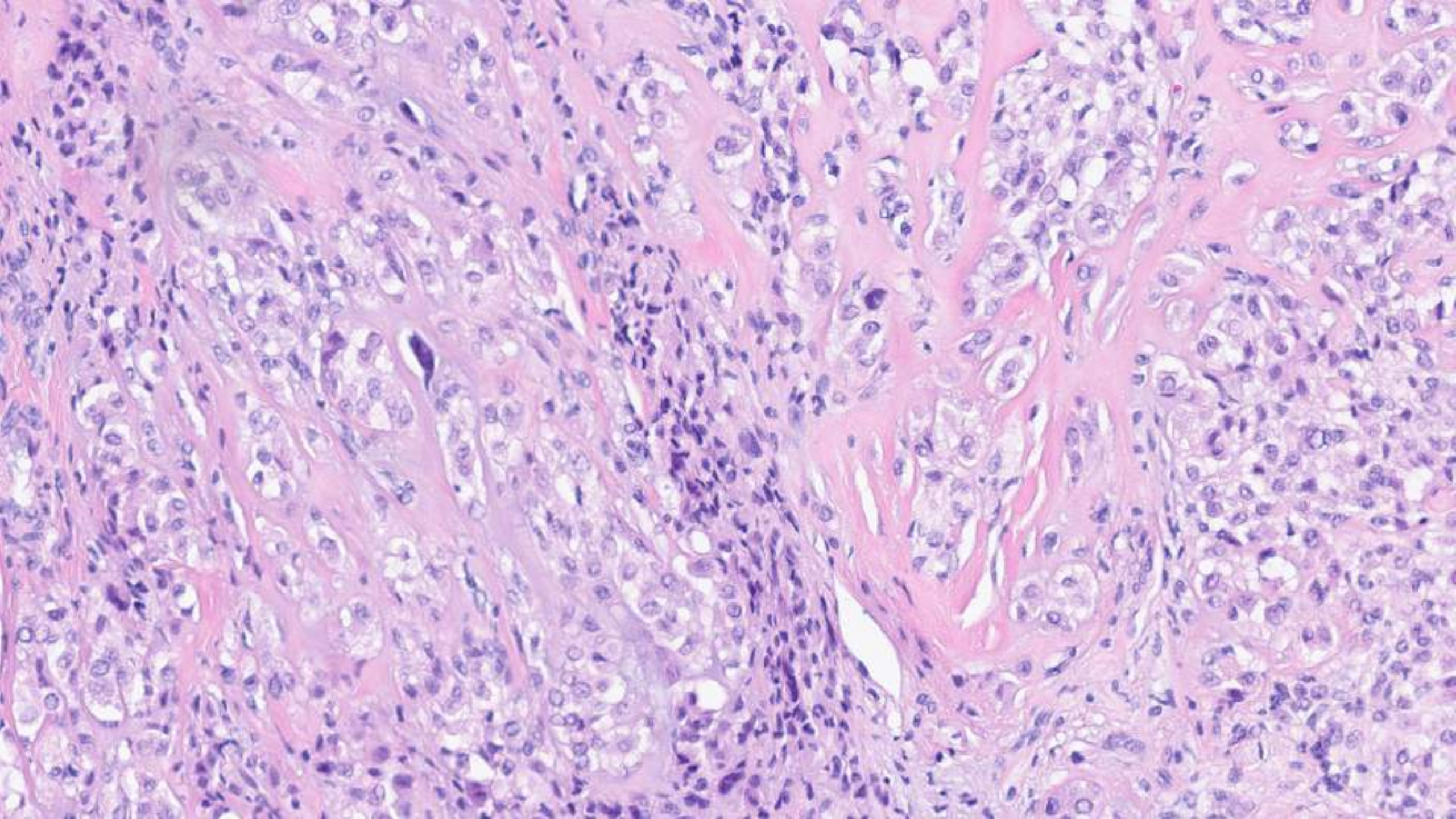
- Size more than 5 cm
- Scattered pleomorphic cells
- Infiltration of fat or skeletal muscle (especially in lesions on the face)
- High mitotic rate, more than 5 mitosis/10 HPF
- Marked cytological atypia
- Vascular and perineural invasion

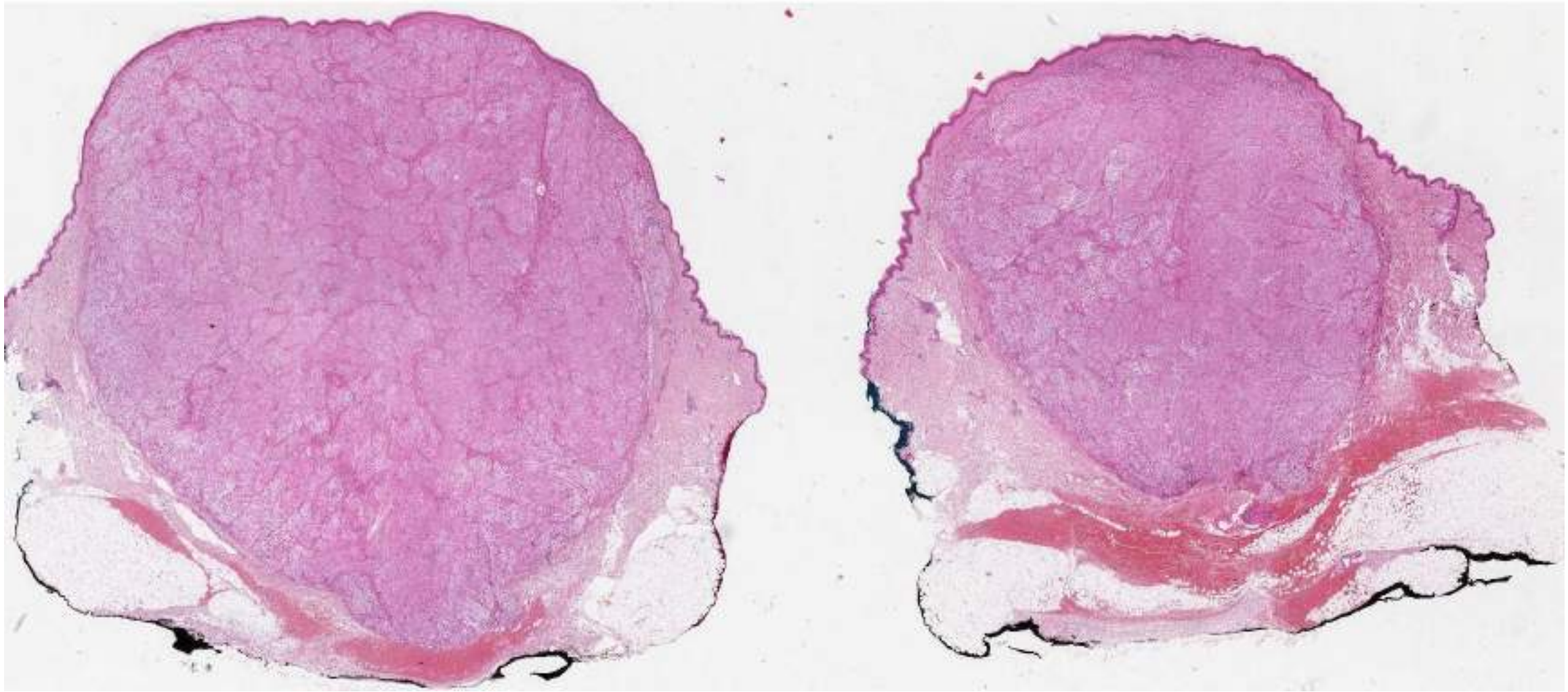
NOT ASSOCIATED WITH BEHAVIOUR OR PROGNOSIS

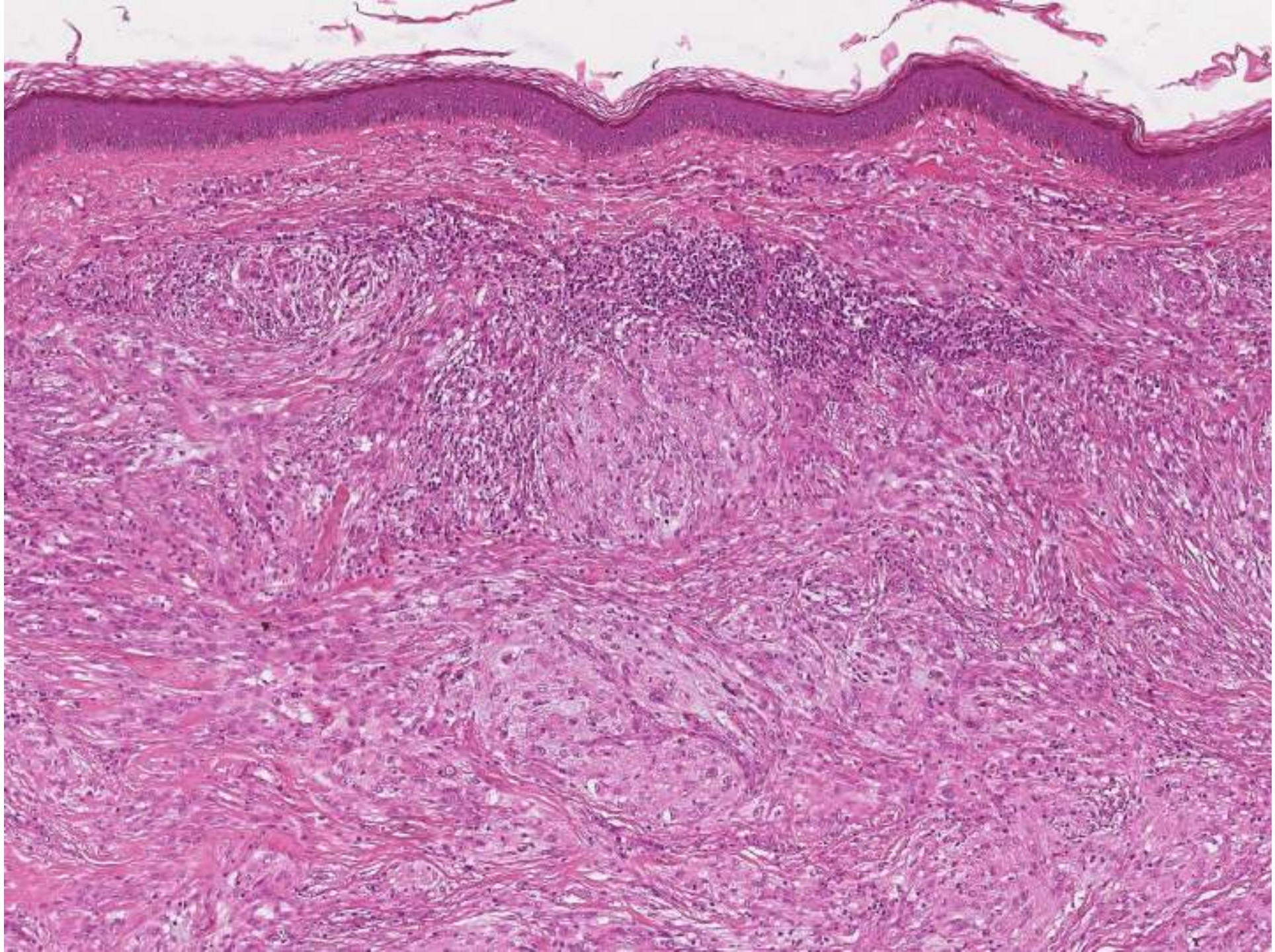


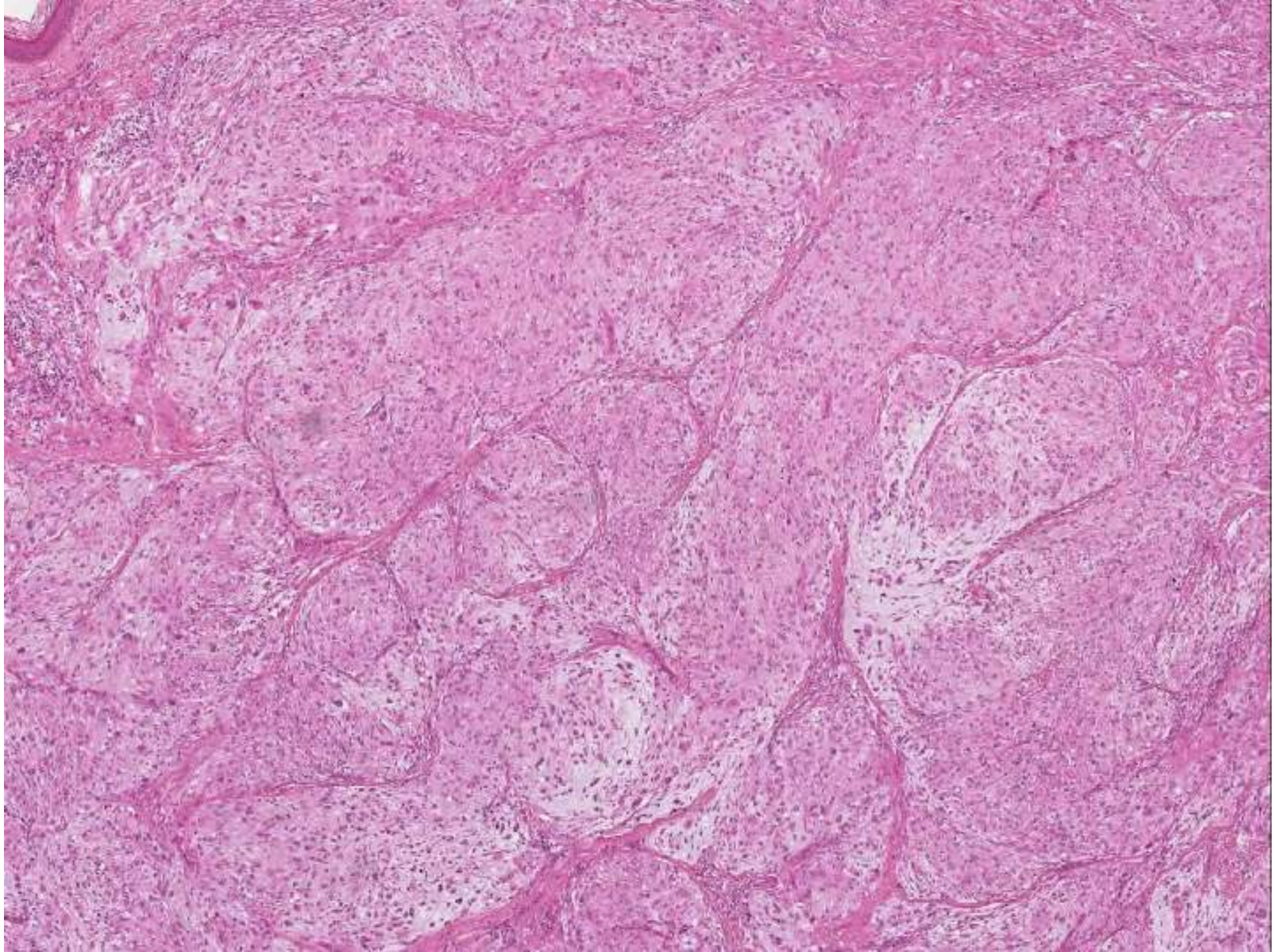


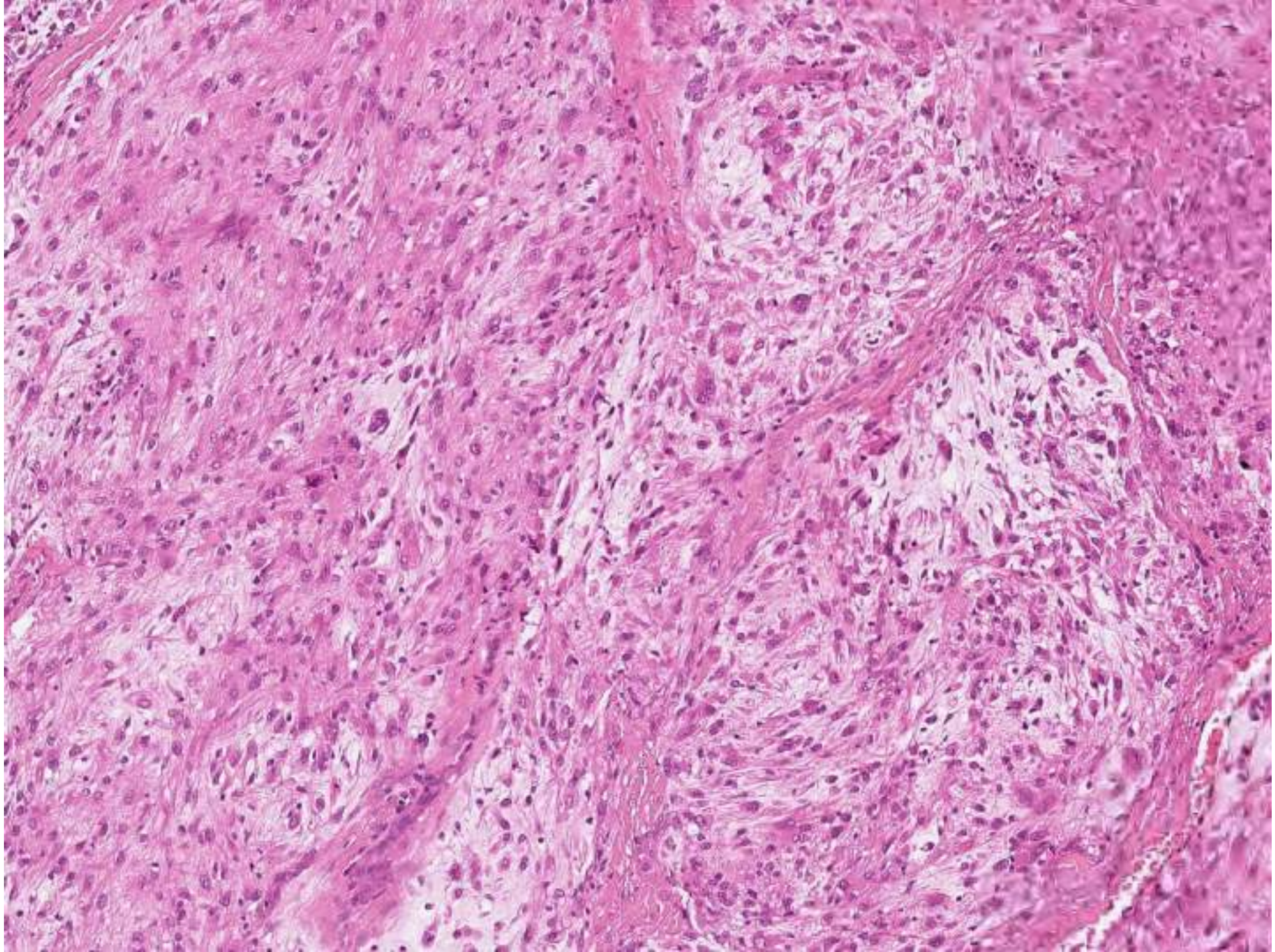


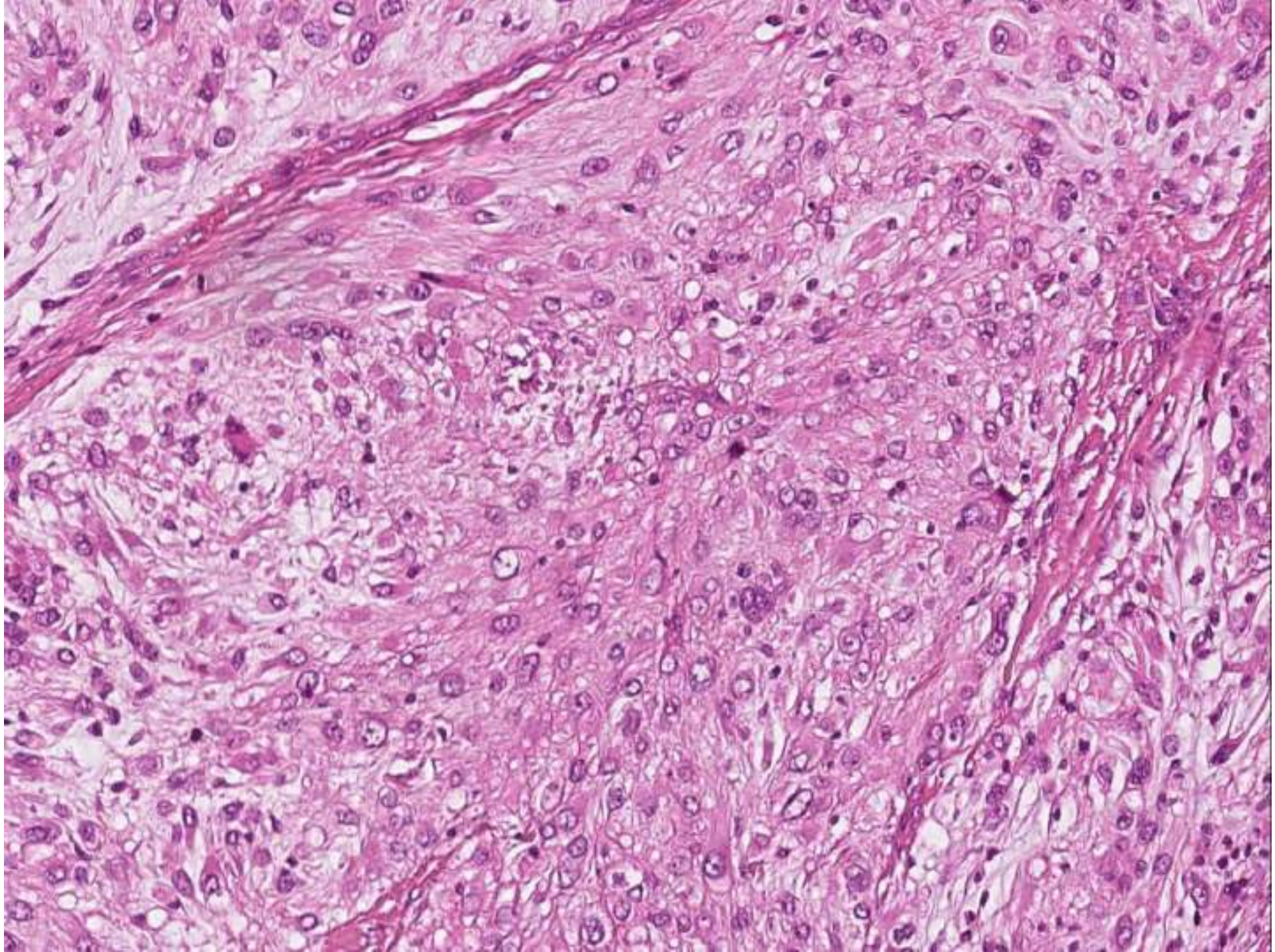


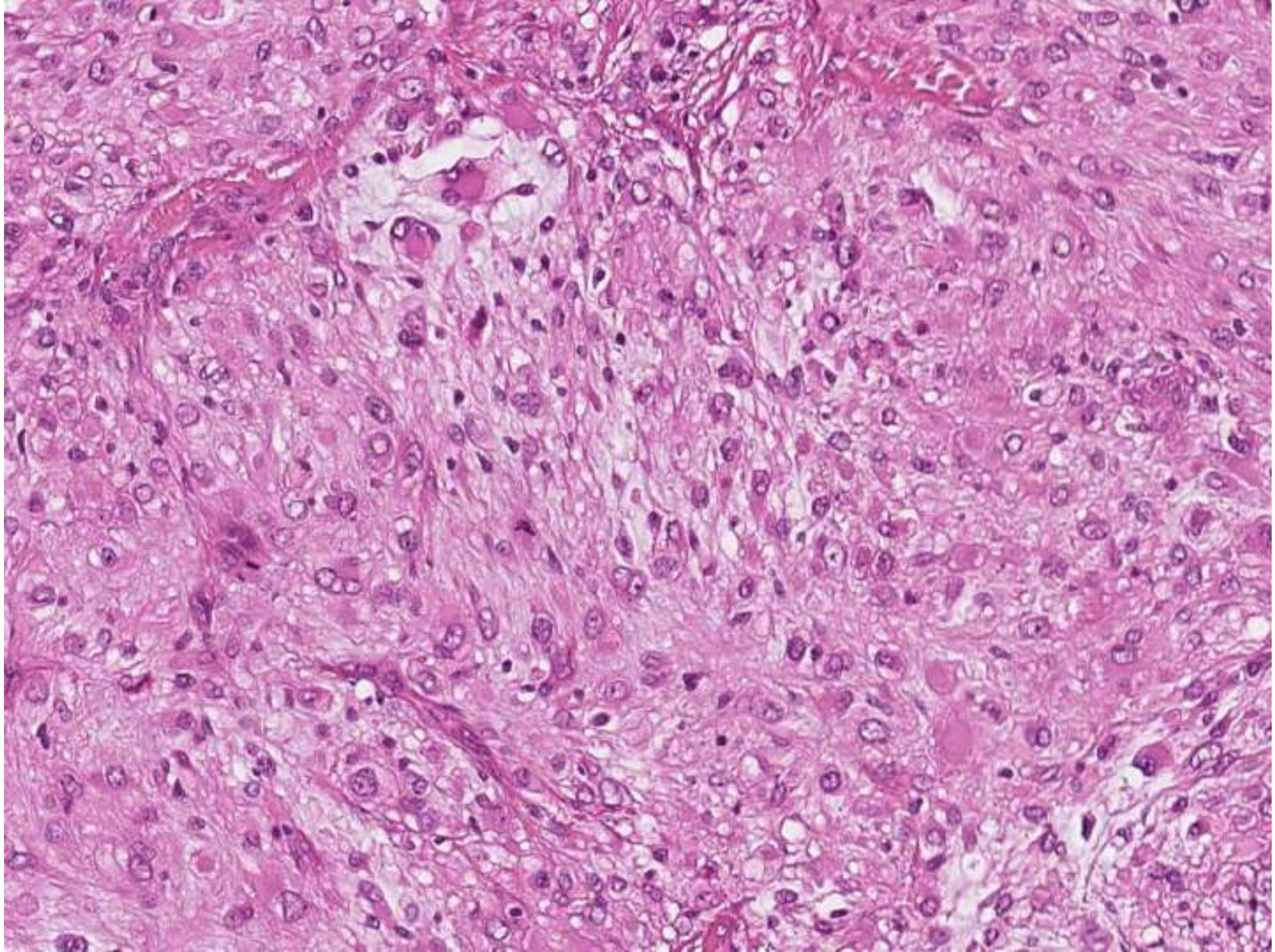












Cutaneous Melanocytoma With *CRTC1-TRIM11* Fusion

Report of 5 Cases Resembling Clear Cell Sarcoma

Lucie Cellier, MD, Emilie Perron, MD, MSc,*†‡ Daniel Pissaloux, PhD,* Marie Karanian, MD,* Veronique Haddad, PharmD,* Laurent Alberti, PhD,* and Arnaud de la Fouchardière, MD, PhD**

Abstract: We report 5 cases of primary intradermal nodular unpigmented tumors with a melanocytic immunophenotype associated with a novel *CRTC1-TRIM11* fusion. Clinically, the cutaneous nodules were slowly growing in 3 women and 2 men (25 to 82 y old, median, 28 y) with no specific topography. Lesion size ranged from 4 to 12 mm (median, 5 mm). The tumors were strictly located in the dermis with a nodular pattern. The cells were arranged in confluent nests and fascicules. Central fibronecrotic areas were present in 2 cases. Cells were medium to large, sometimes multinucleated, and presented a spindled and epithelioid cytology with prominent nucleoli. Cytonuclear atypia was constant, and mitotic activity in hotspot areas ranged from 1 to 5/mm². Immunohistochemistry found a constant positivity with S100, MiTF, and Sox10, and a heterogenous staining by MelanA or HMB45. NTRK1 was strongly positive in 3 cases. In all cases, RNA sequencing found an invariable *CRTC1(e1)-TRIM11(e2)* fusion, confirmed by fluorescent in situ hybridization techniques with a *TRIM11* break-apart probe. In 4/4 cases, nuclear TRIM11 expression was positive by immunohistochemistry. Fluorescent in situ hybridization techniques showed no rearrangement of *NTRK1* or *EWSR1*, and array-comparative genomic hybridization displayed no alteration (1 case) or only a whole chromosome 7 gain (2 cases) when performed. No relapse or metastatic event was observed during follow-up [3 to 72 months (median, 14 mo)]. Cutaneous clear cell sarcoma was the main differential diagnosis. Overlapping morphologic features previously described in primary dermal melanomas and paraganglioma-like melanocytic tumors were present. The *CRTC1-TRIM11* fusion appears to be specific of an unpigmented nodular tumor combining a melanocytic phenotype and low-grade tumor behavior.

Key Words: cutaneous nodule, primary dermal melanocytic tumor, *CRTC1-TRIM11* fusion, low-grade melanoma, melanocytoma

(*Am J Surg Pathol* 2018;42:382–391)

Unpigmented nodular dermal tumors with positive expression of melanocytic markers (S100, MelanA, or HMB45) studied by immunohistochemistry (IHC) are rare. In this setting, the most frequent diagnosis is a cutaneous metastasis of melanoma. In the absence of melanoma history and after an extensive work-up, a primary tumor must be considered. A careful microscopic analysis of the overlying dermis in search of signs of melanoma regression or a nearby scar is advised to rule out a partially regressive or relapsing melanoma without a recognizable junctional component. Among the remaining diagnoses are the exceptional cases of primary dermal melanoma (PDM), paraganglioma-like dermal melanocytic tumors (PDMTs), and cutaneous clear cell sarcoma (CCS). Morphologically, PDMs and PDMTs have been described as dermal deposits of atypical melanocytes, and their molecular profile remains mostly unknown.[1] The cutaneous variants of CCS form an ill-defined unpigmented dermal tumor expressing various melanocytic differentiation markers by IHC. At the molecular level, they are characterized by the presence of *EWSR1-ATF1* or *EWSR1-CREB1* fusions.[2] We report 5 tumors appearing as dense dermal nodules made of large unpigmented atypical cells displaying a melanocytic immunophenotype that harbored a novel *CRTC1-TRIM11* fusion.

MATERIALS AND METHODS

Patients

The cases were derived from the author's (A.d.l.F.) consultation cases reviewed at the Department of Biopathology at the Centre Léon Bérard in Lyon, France (2009 to 2017). Following the simultaneous identification

Cutaneous Melanocytic Tumor With *CRTC1::TRIM11* Translocation

An Emerging Entity Analyzed in a Series of 41 Cases

John Hanna, MD, PhD, Jennifer S. Ko, MD, PhD,† Steven D. Billings, MD,† Felix Boivin, MSc,‡ Olivia Beaudoux, MD,§ Daniel Pissaloux, PhD,‡‖ Franck Tirode, PhD,‡ Alvaro Laga, MD,* Christopher D.M. Fletcher, MD,* and Arnaud de la Fouchardiere, MD, PhD‡‖*

Abstract: Cutaneous melanocytic tumor with *CRTC1::TRIM11* fusion (CMTCT) is a recently described dermally based neoplasm with melanocytic differentiation. It can easily be confused with clear cell sarcoma and metastatic melanoma. Our understanding of this lesion, including its potential for aggressive disease, has been limited by the small number of previously reported cases (13) and the limited clinical follow-up data. Here, we report a series of 41 CMTCT confirmed by molecular studies. We find that the lesion shows highly uniform and reproducible morphologic, immunohistochemical, and genetic features across a wide variety of anatomic locations and age groups. Among 22 cases with follow-up, 1 local recurrence and 1 nodal metastasis were identified. Our data support the classification of CMTCT as a unique nosologic entity and emphasize the importance of distinguishing this entity from its histologic mimics, especially clear cell sarcoma and metastatic melanoma, to guide therapy and establish accurate prognostic expectations.

Key Words: CRTC1, TRIM11, melanocytic, translocation, clear cell sarcoma

(*Am J Surg Pathol* 2022;00:000–000)

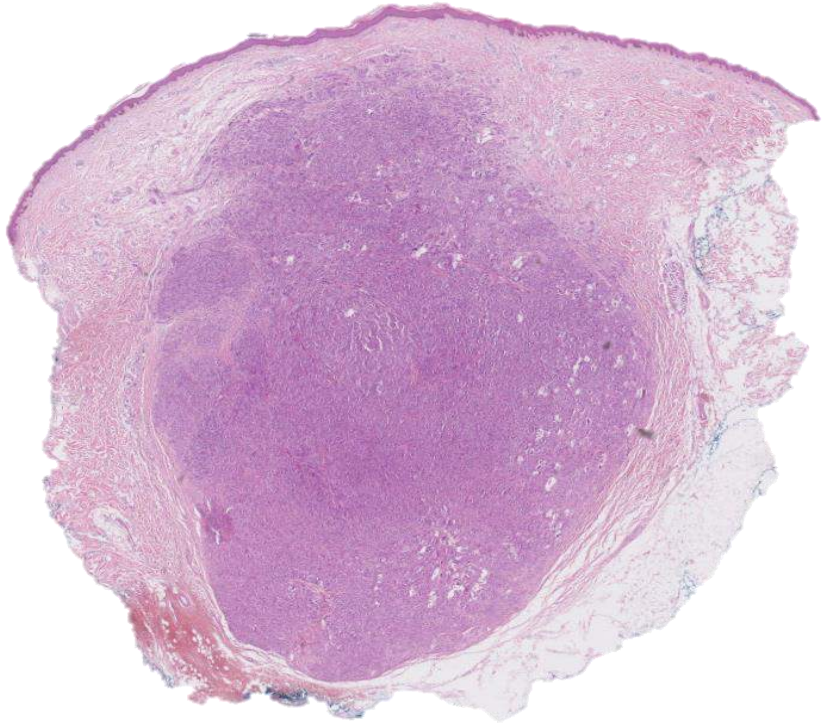
Tumors with melanocytic differentiation represent an important and often difficult area of surgical pathology. While many melanocytic lesions show an intraepidermal origin, there are also tumors with melanocytic differentiation that do not arise from surface epithelium but are rather found in the dermis, subcutis, or deeper soft tissue. Some of these entities, including metastatic melanoma and cellular blue nevus, are still true melanocytic tumors, whereas others appear most likely to be of non-melanocyte origin. The best-characterized example is clear cell sarcoma (CCS), a spindle cell neoplasm that typically occurs in deep soft tissue but which can also arise intradermally.[1] CCS tends to affect younger patients and pursues a slow but aggressive course. Recurrences and metastases, including nodal metastases in about 50% of patients, are common, and the 20-year survival is ~10%.[2,3] CCS is characterized by cytogenetic translocations, either *EWSR1::ATF1* or *EWSR1::CREB1*.[4] ATF1 and CREB1, along with a third protein, CREM, constitute a family of related bZIP transcription factors that stimulate the cAMP-dependent expression of MITF (microphthalmia-associated transcription factor), the master regulator of melanin synthesis.[5] The EWSR1::ATF1 and EWSR1::CREB1 fusion proteins retain the transcriptionally active bZIP domain but lose the protein kinase A–dependent phosphorylation site, resulting in constitutive cAMP-independent transcription of MITF. Hyperactive MITF function not only accounts for melanocytic differentiation in CCS but is required for the growth and survival of the tumor.[6] These fusions are not found in melanoma, and the typical driver mutations of melanoma are not common in CCS. Thus, despite early conceptions of CCS as "melanoma of soft parts," the 2 tumors appear biologically distinct, and CCS is most likely not of true melanocytic origin.

CRTC1::TRIM11 CUTANEOUS TUMOUR (CUTANEOUS MELANOCYTIC TUMOUR WITH *CRTC1::TRIM11* FUSION)
-CLINICAL FEATURES-

- **F>M**
- **Wide age range (11-87)**
- **Extremities>trunk>head and neck**
- **Rare mucosal cases**
- **Papule or nodule**
- **Variable size (median: 1 cm)**

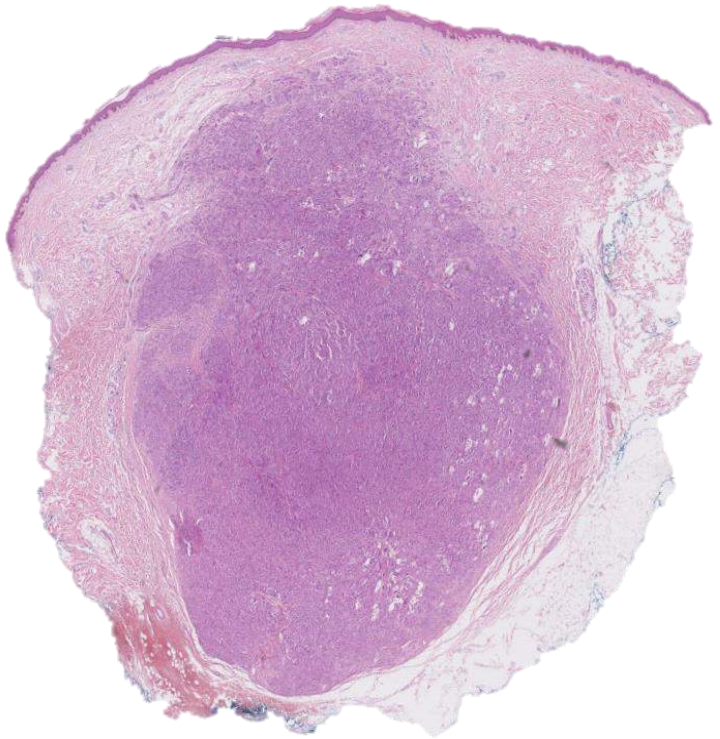
CRTC1::TRIM11 CUTANEOUS TUMOUR (CUTANEOUS MELANOCYTIC TUMOUR WITH *CRTC1::TRIM11* FUSION)
-HISTOLOGICAL FEATURES-

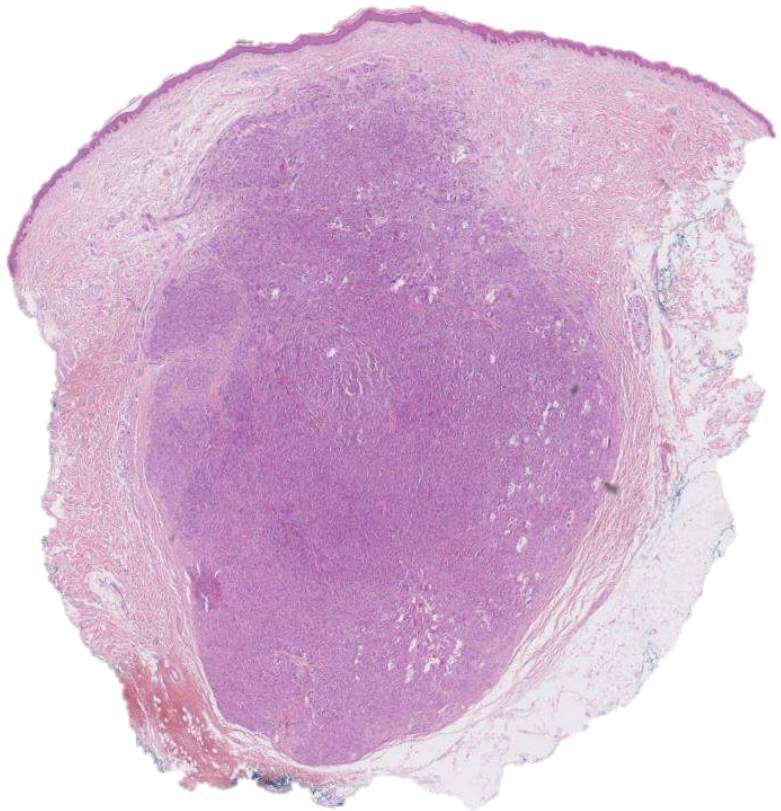
- No epidermal component
- Dermal and/or subcutaneous
- Nodular o multilobular
- May be focally infiltrative
- Sheeets of spindle-shaped or epithelioid cells
- Fascicles or nests of monotonous cells
- Mild or moderate cytological atypia
- A single prominent nucleolus
- Multinucleated tumour cells
- Mitotic activity: 1-12/10 HPFs

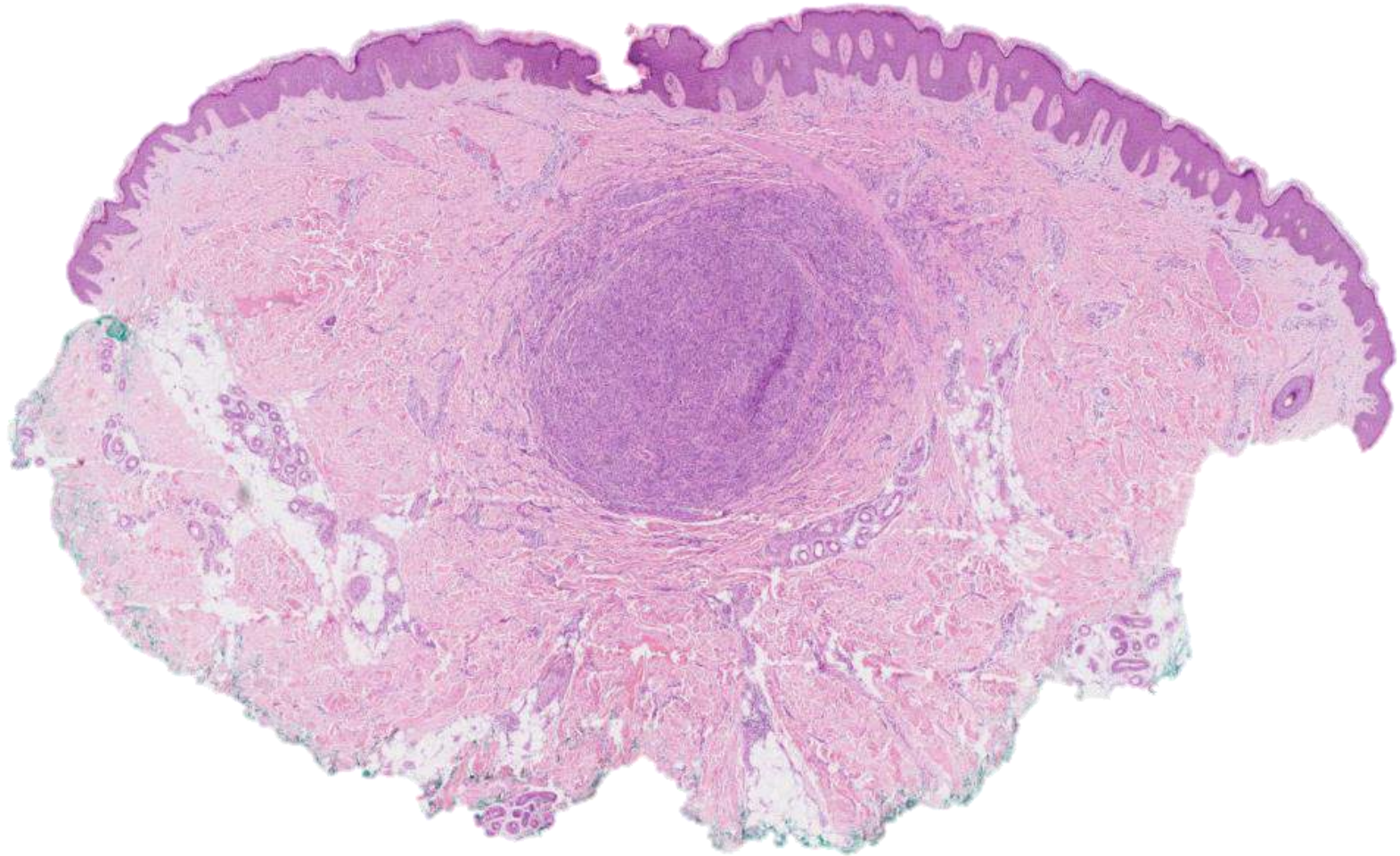


CRTC1::TRIM11 CUTANEOUS TUMOUR (CUTANEOUS MELANOCYTIC TUMOUR WITH *CRTC1::TRIM11* FUSION)
-UNUSUAL HISTOLOGICAL FEATURES-

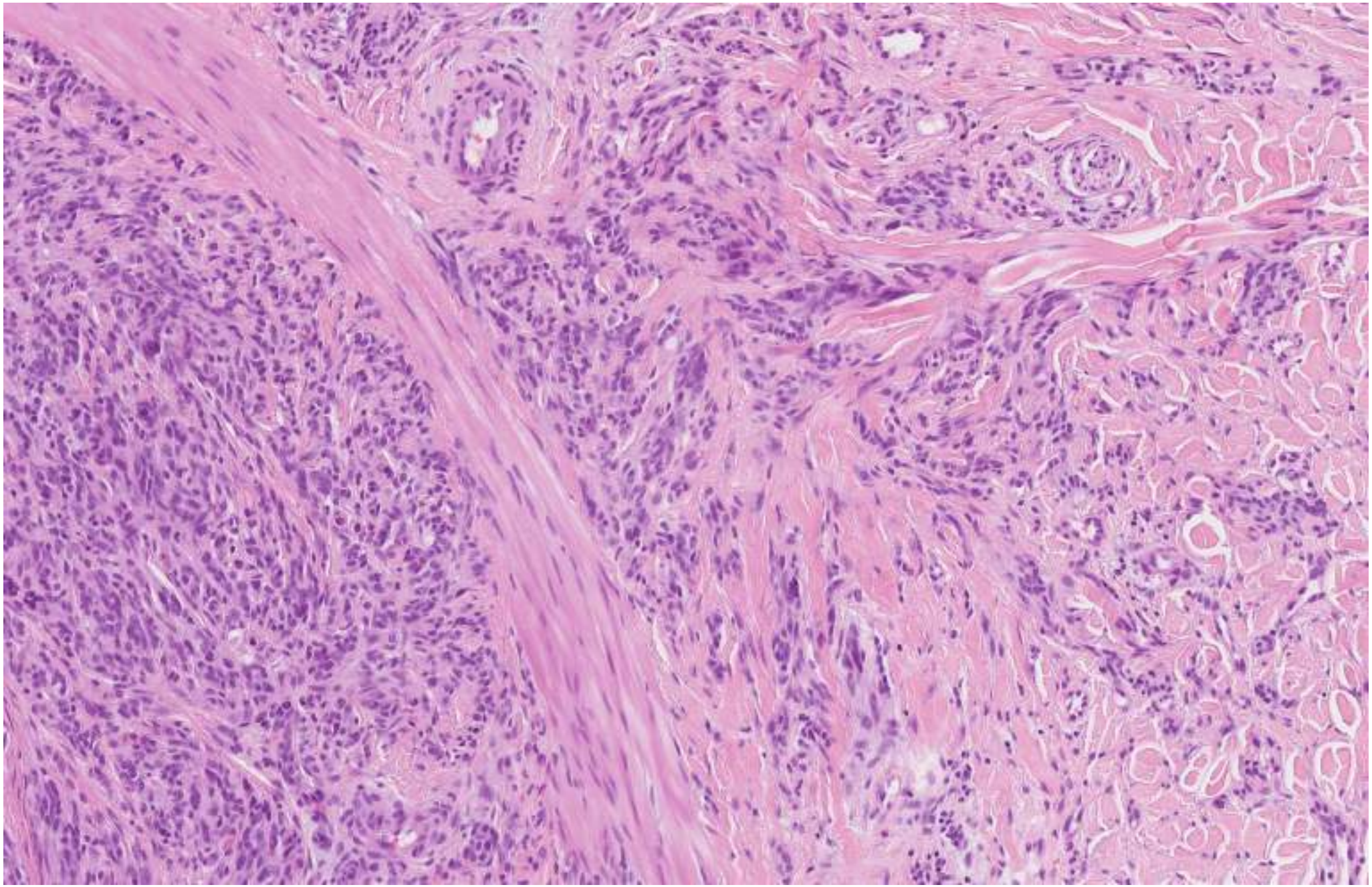
- **Intranuclear cytoplasmic pseudoinclusions**
- **Pigment**
- **Focal necrosis**
- **Mild inflammation**

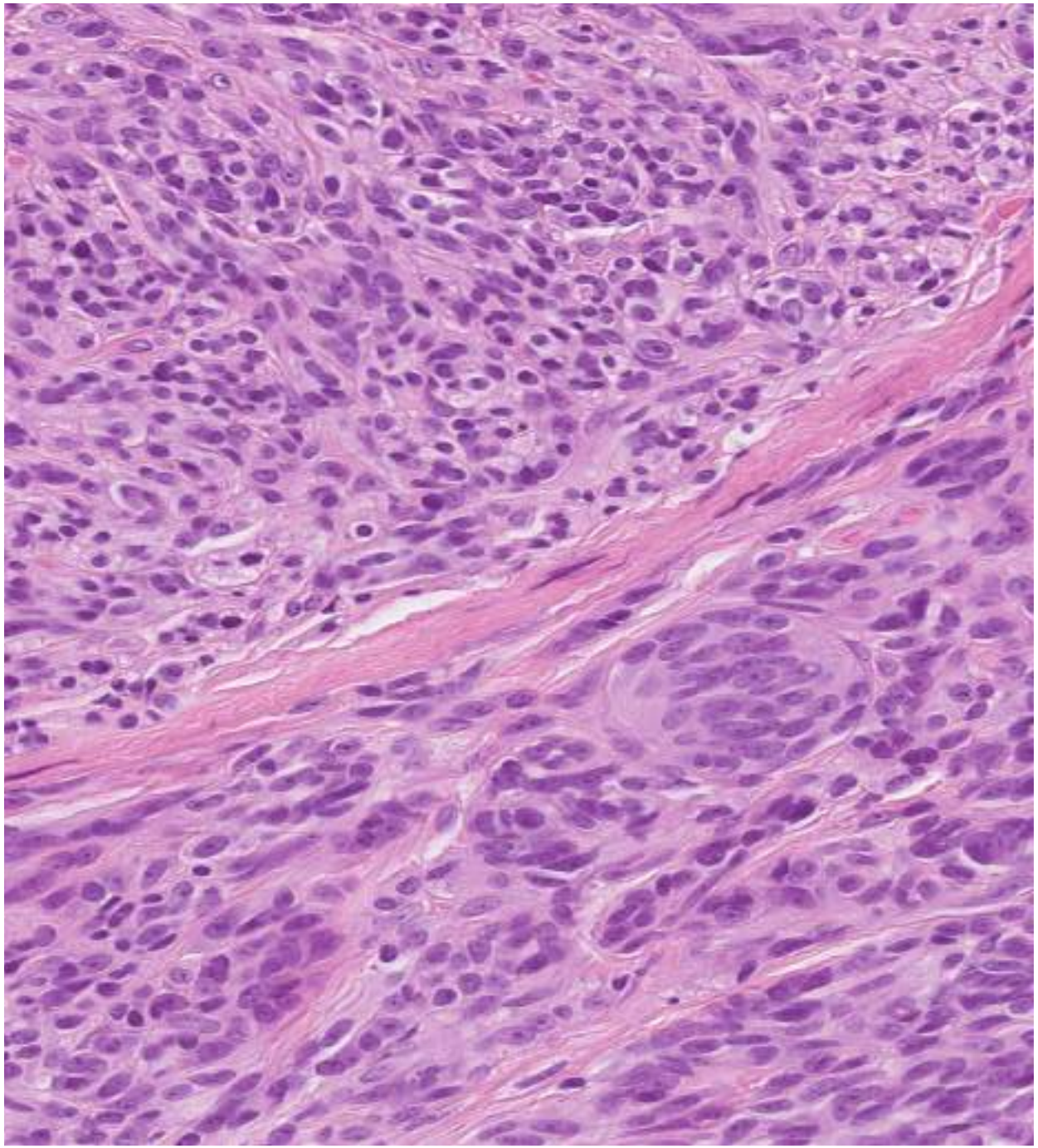


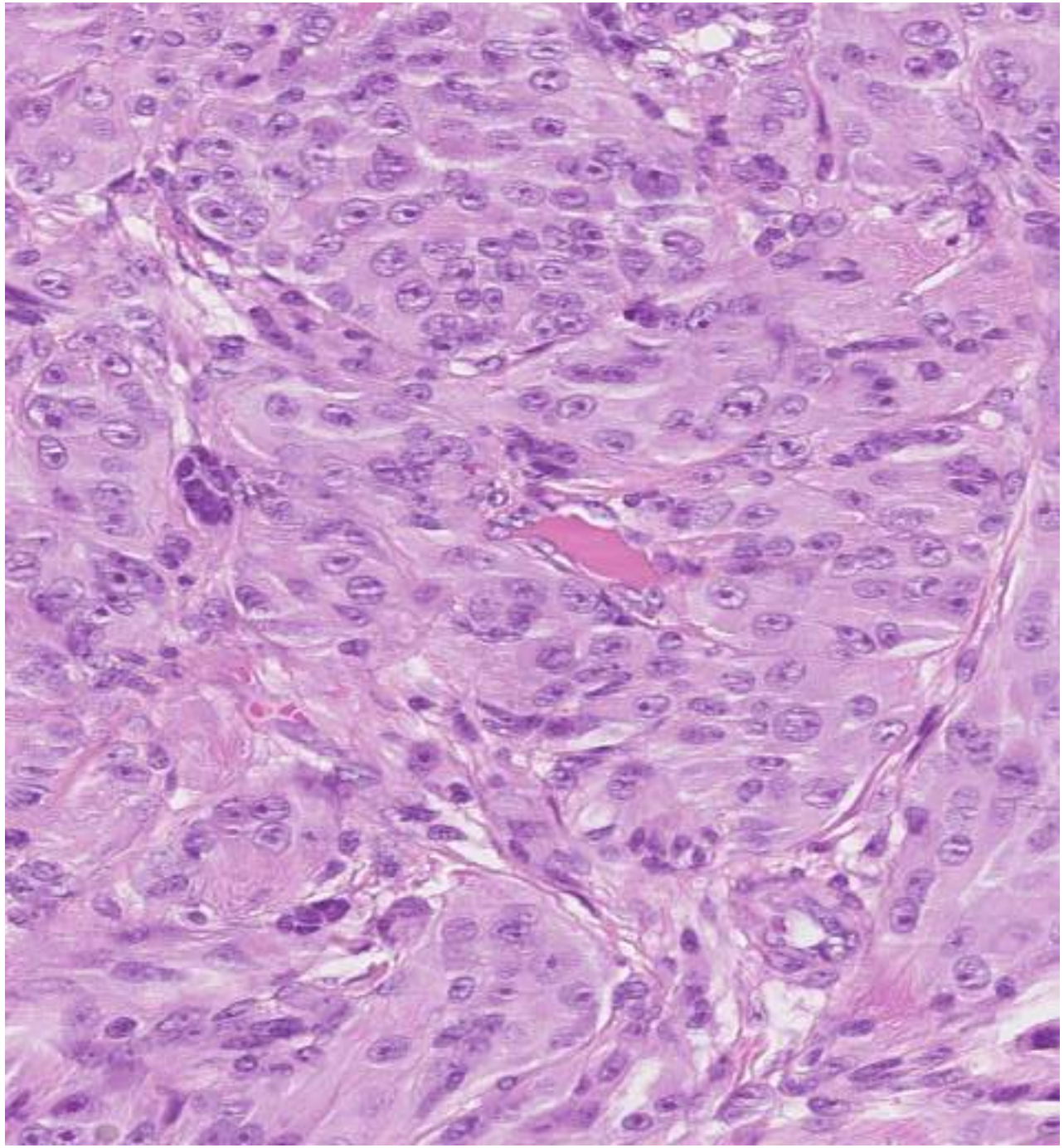


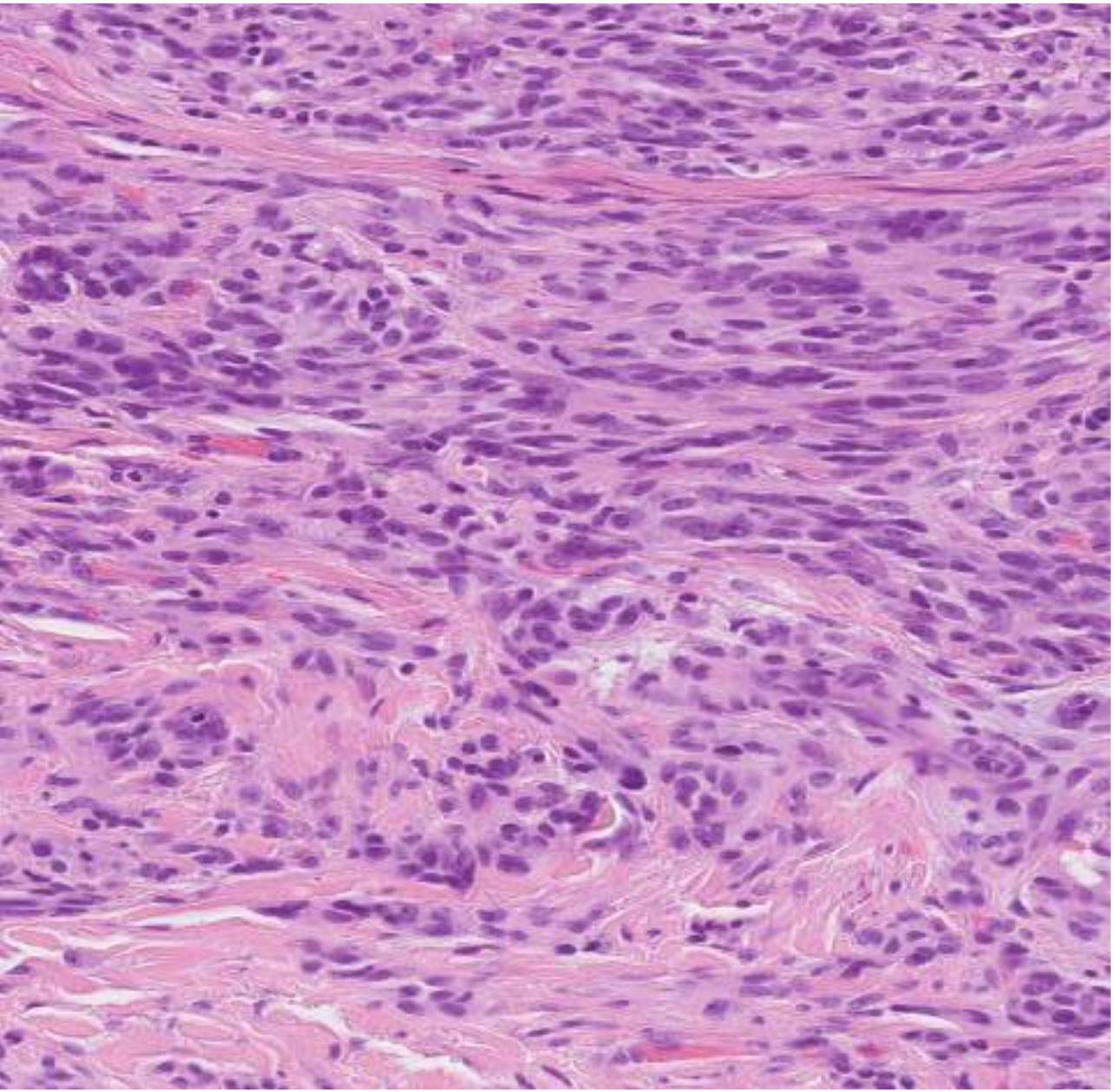


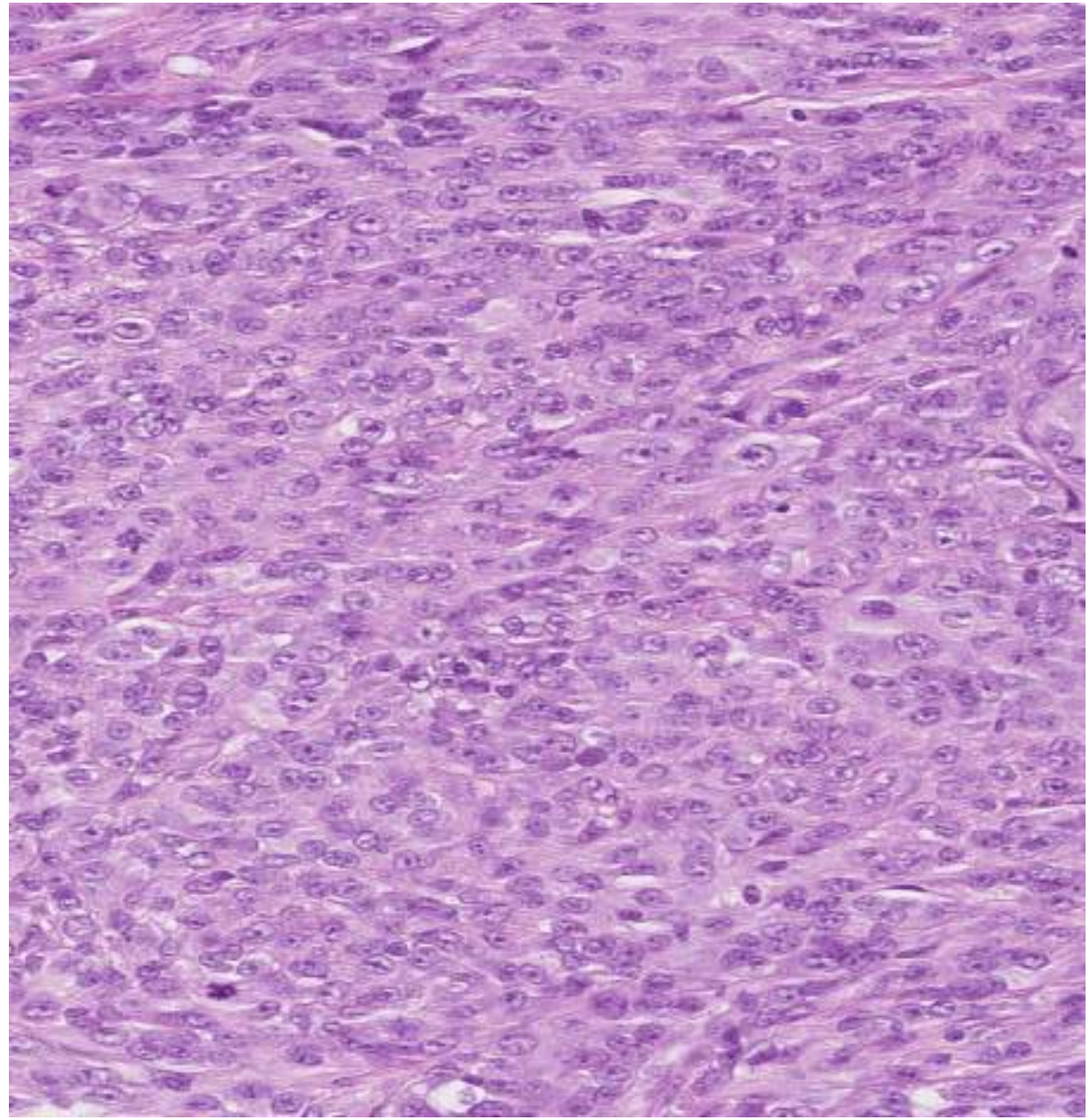
Courtesy Bostan Luzar, Slovenia

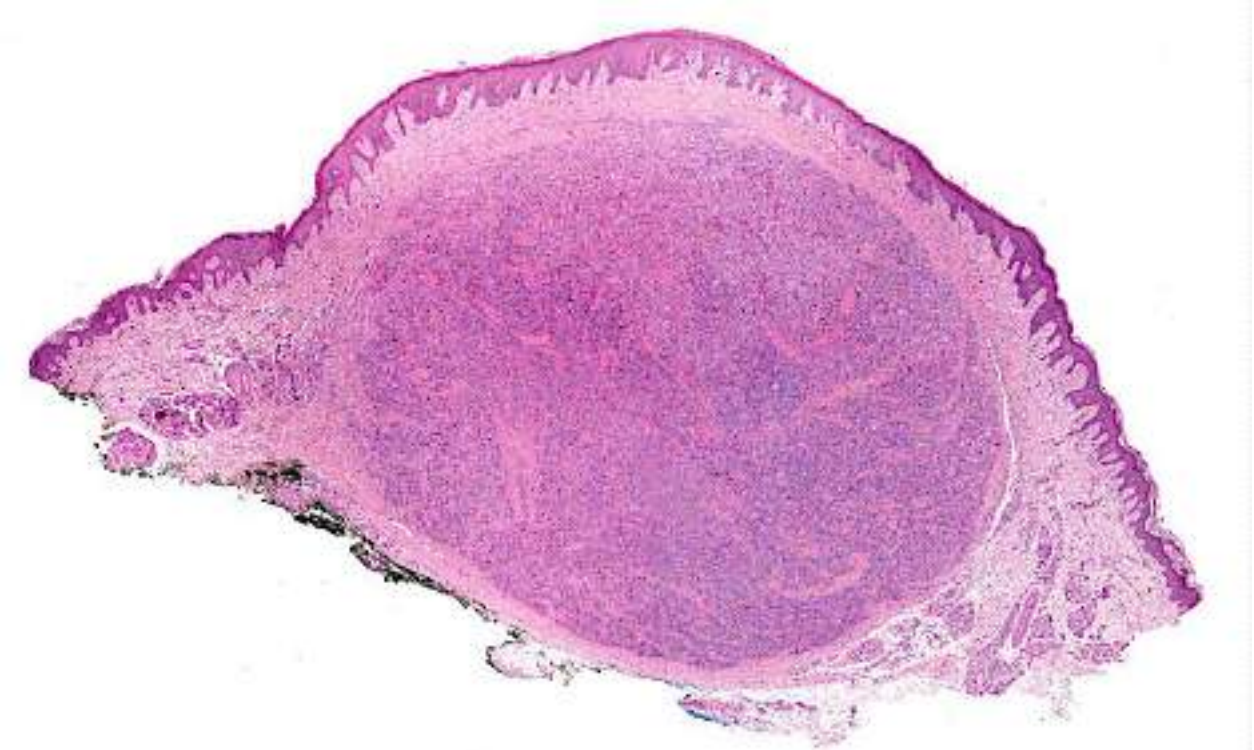


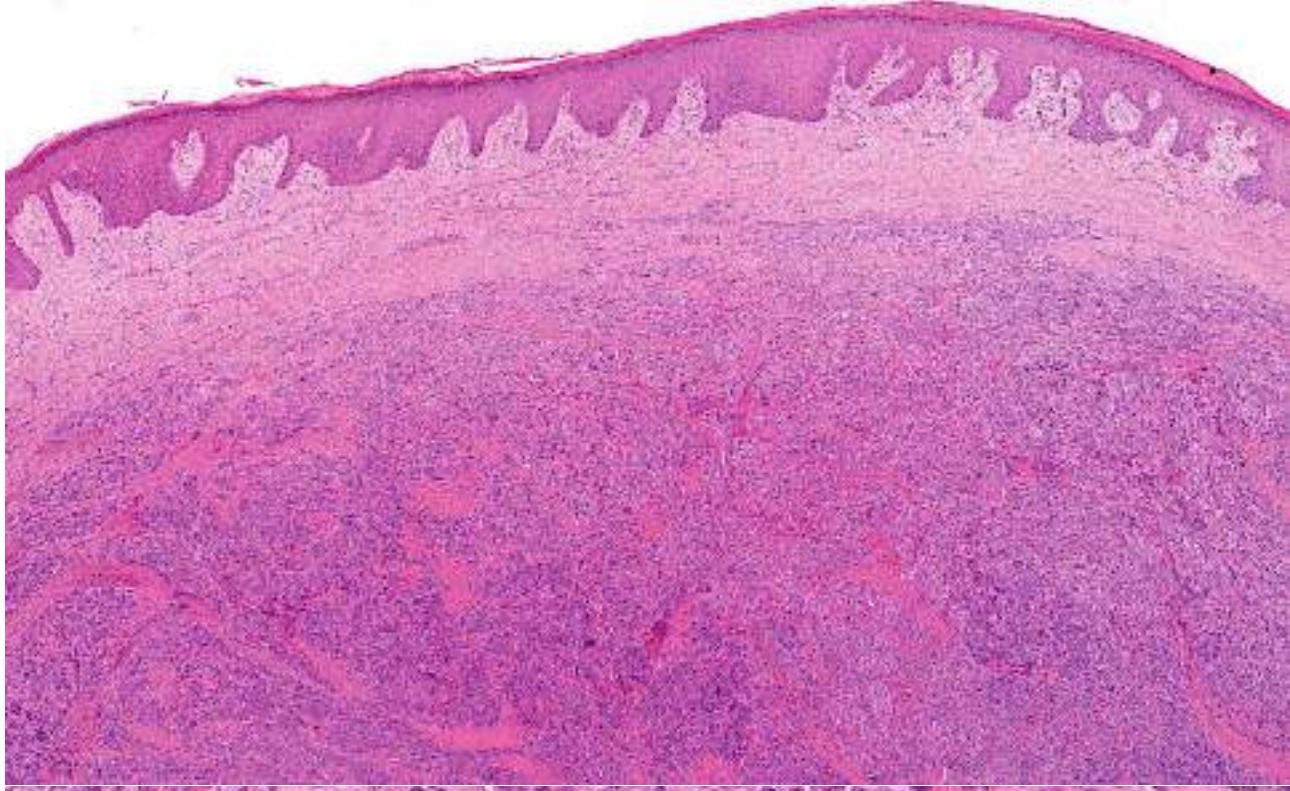


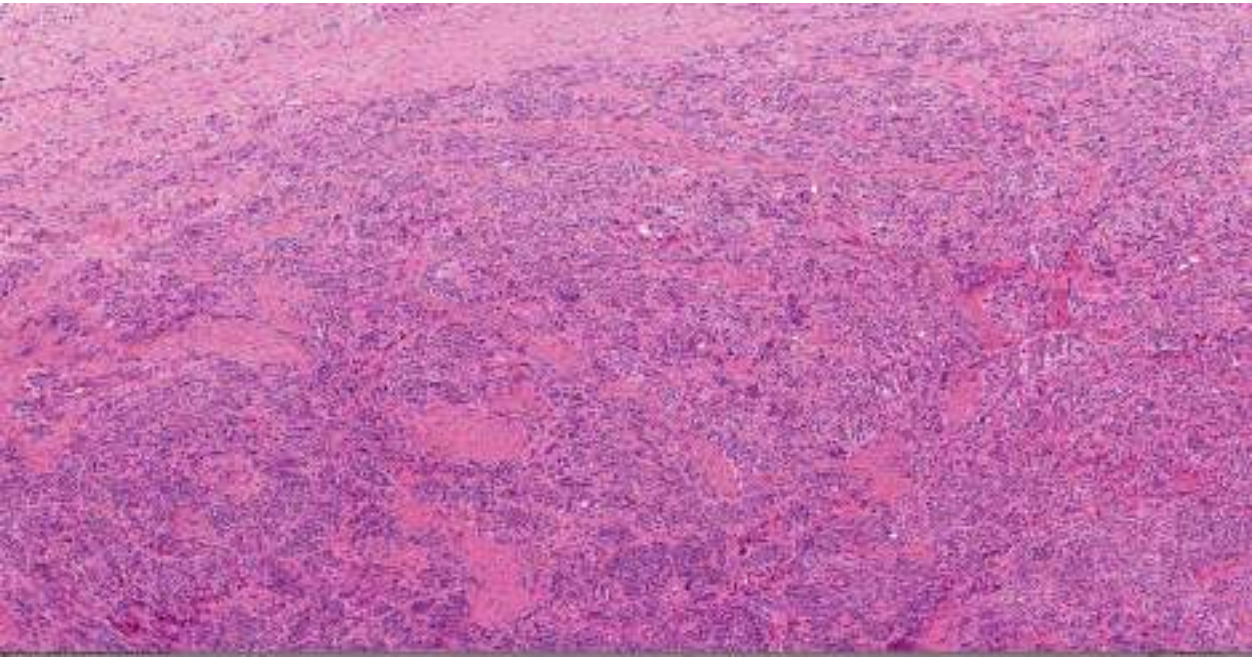


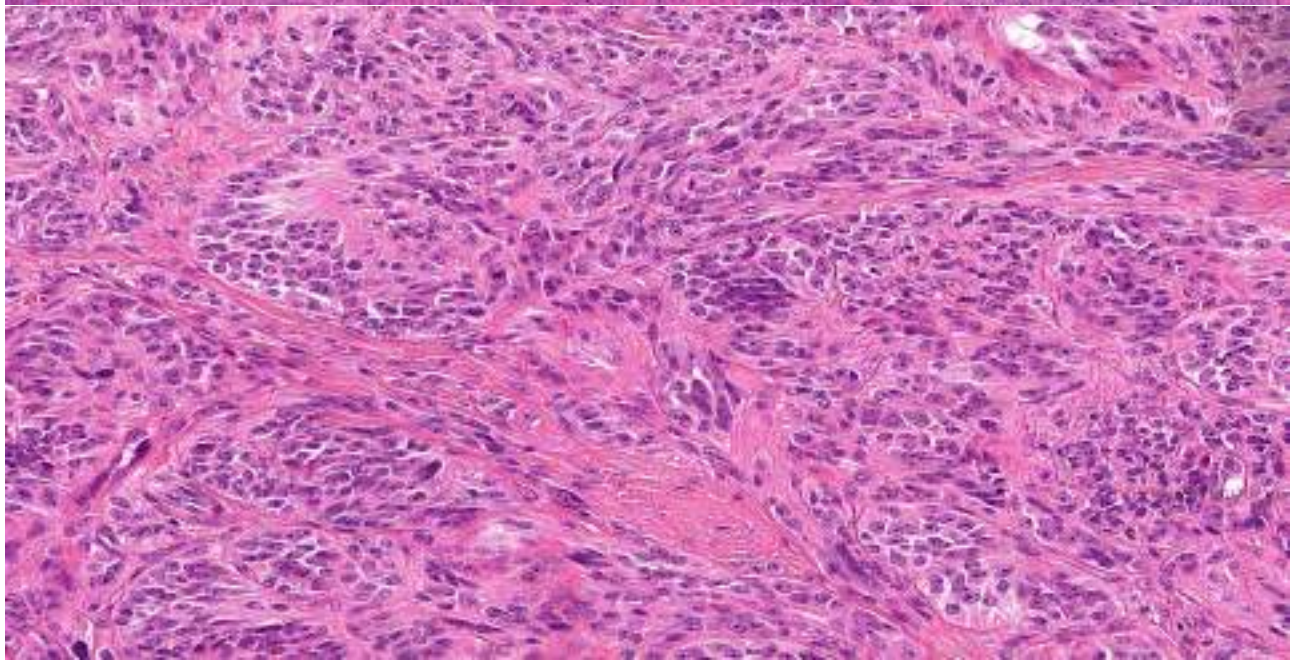


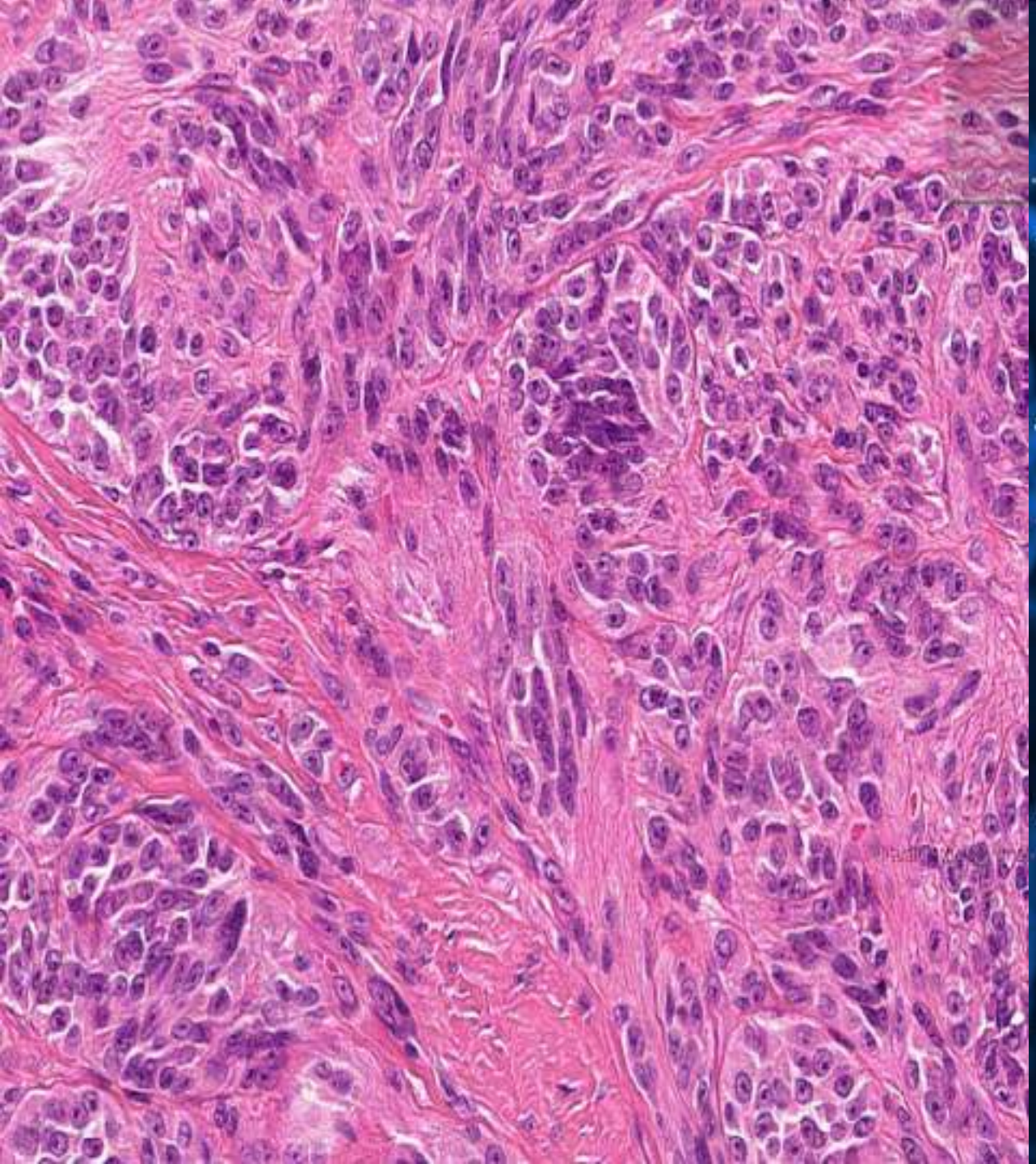


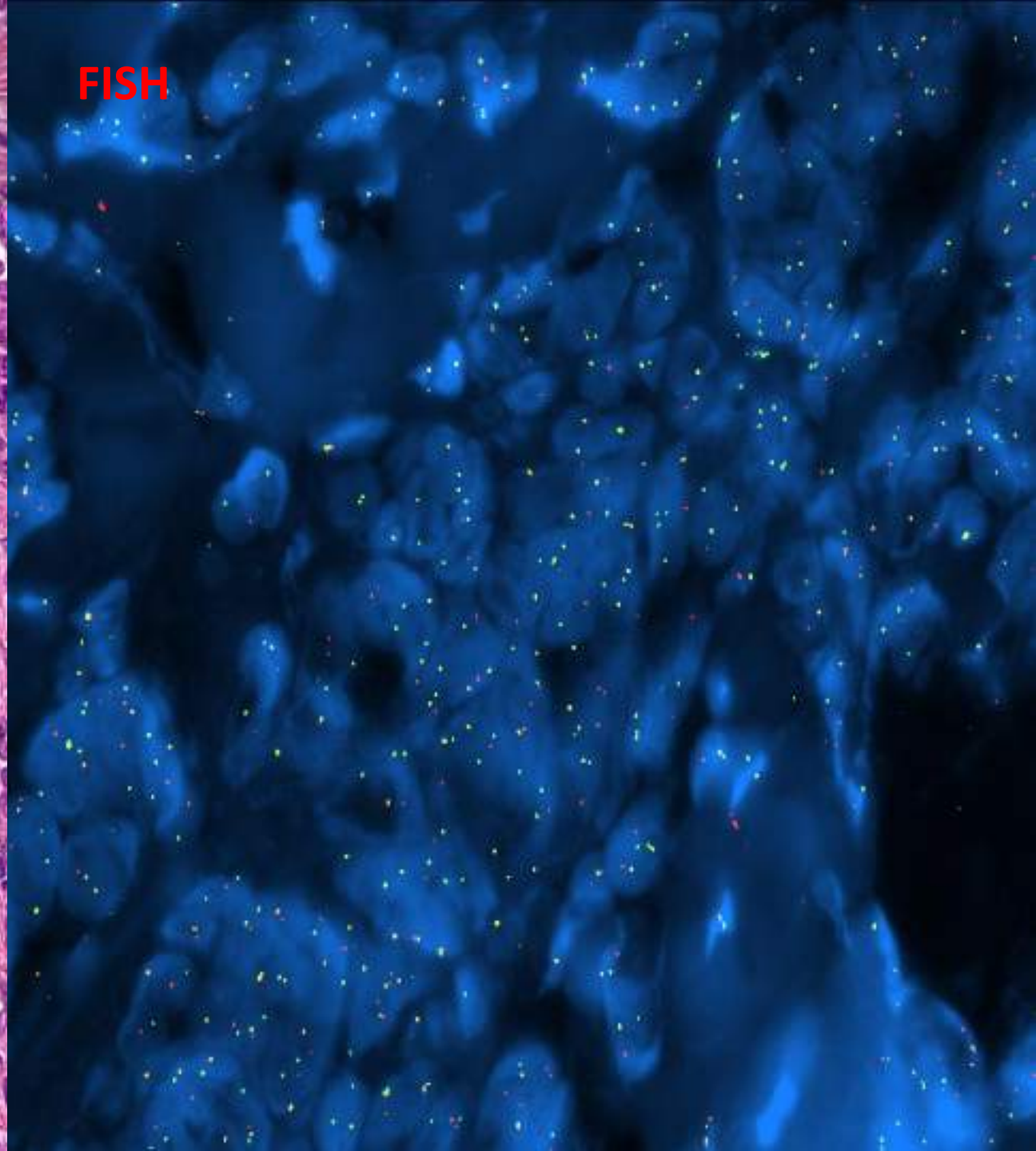






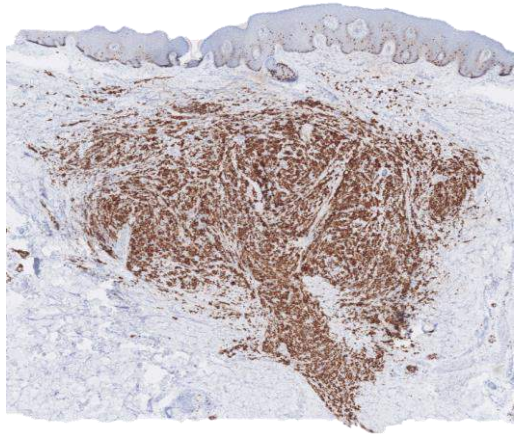




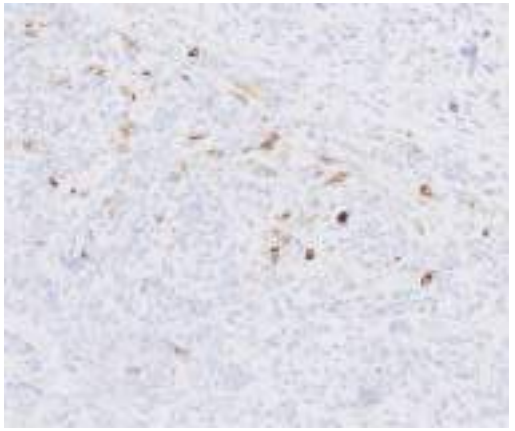

FISH

CUTANEOUS MELANOCYTIC TUMOUR WITH *CRTC1::TRIM11* FUSION - IMMUNOHISTOCHEMICAL FEATURES-

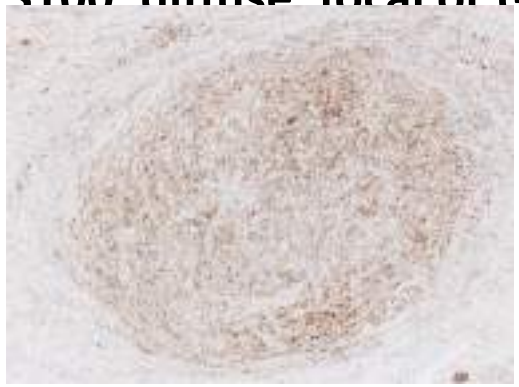
SOX10 & MITF1: diffuse



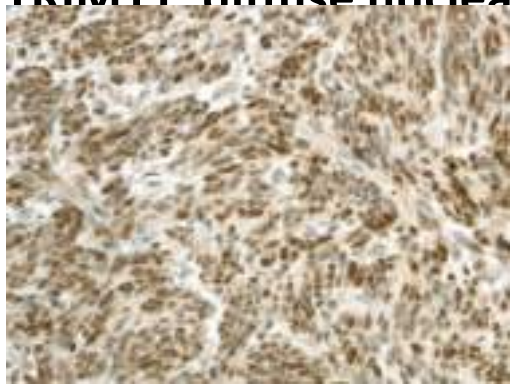
HMB45 & Melan A: focally (+) or (-)



S100: diffuse, focal or (-)

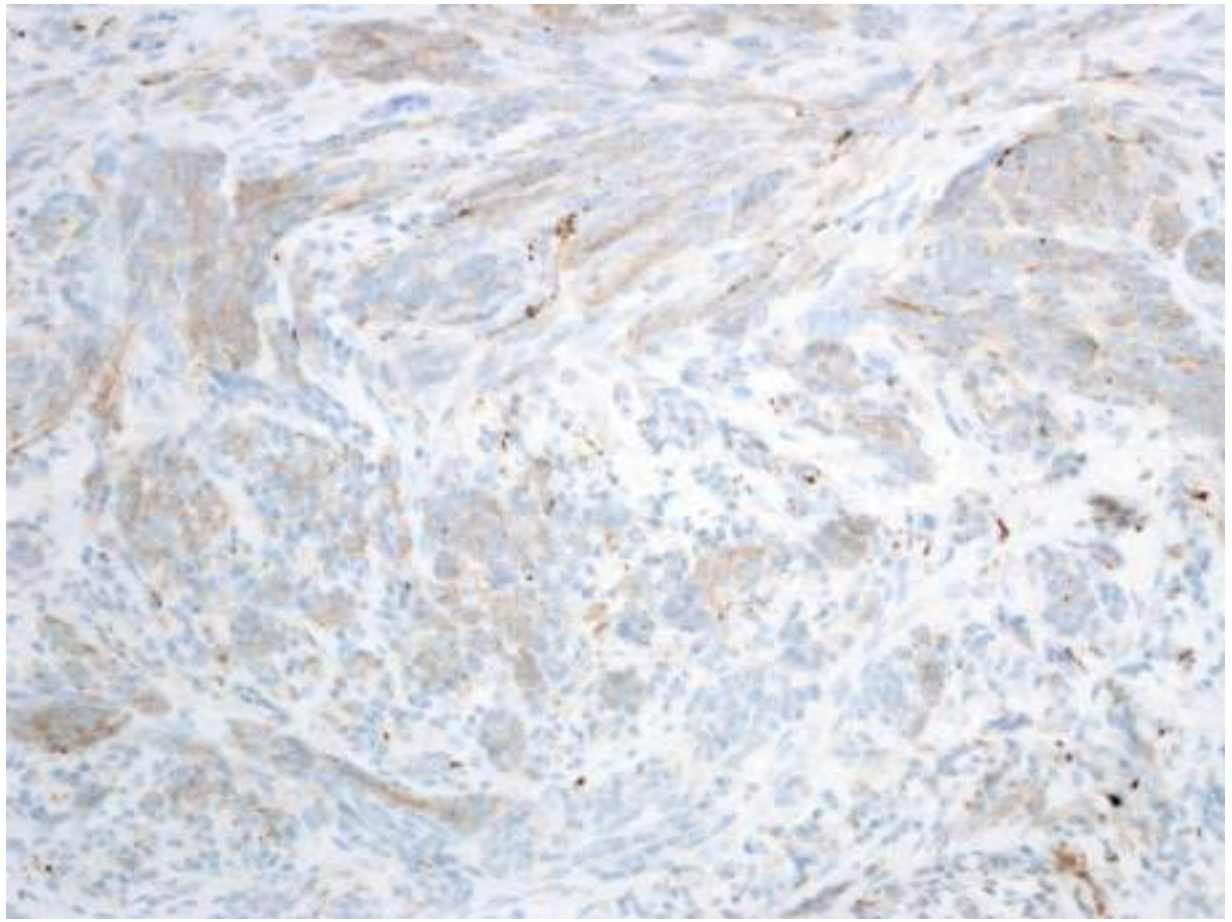


TRIM11: diffuse nuclear (+)



CUTANEOUS MELANOCYTIC TUMOUR WITH *CRTC1::TRIM11* FUSION - IMMUNOHISTOCHEMICAL FEATURES-

- **NTRK +**
- **Aberrant expression**
- **No molecular NTRK aberrations**



CUTANEOUS MELANOCYTIC TUMOUR WITH *CRTC1::TRIM11* FUSION -PROGNOSIS-

- **25 cases with follow-up**
- **Indolent behaviour (88%)**
- **One case local recurrence**
- **One case lymph node metastasis**
- **One case local recurrence after 13 years with axillary and lung metastasis**

CUTANEOUS MELANOCYTIC TUMOUR WITH *CRTC1::TRIM11* FUSION
- DIFFERENTIAL DIAGNOSIS-

CUTANEOUS CLEAR CELL SARCOMA

- *EWSR1::ATF1*
- *EWSR1::CREB1*

PRIMARY/METASTATIC MELANOMA

- CLINICAL WORK-UP
- BRAFV600E OR NRASQ61R IMMUNOPOSITIVITY
- TRIM11 IMMUNOHISTOCHEMISTRY NEGATIVE
- NO *CRTC1::TRIM11*

CLEAR CELL TUMOUR WITH MELANOCYTIC DIFFERENTIATION AND *MITF::CREM* FUSION

- *MITF* REARRANGEMENTS

CLEAR CELL TUMOUR WITH MELANOCYTIC DIFFERENTIATION AND *ACTIN::MITF* FUSION

- *MITF* REARRANGEMENTS

INTRADERMAL SPITZ PROLIFERATIONS

- DIFFERENT GENETIC ABNORMALITIES - ONCOGENIC KINASE DRIVERS

ORIGINAL ARTICLE

Cutaneous Clear Cell Sarcoma: A Clinicopathologic, Immunohistochemical, and Molecular Analysis of 12 Cases Emphasizing its Distinction from Dermal Melanoma

Markus Hantschke, MD, Thomas Mentzel, MD,* Arno Rütten, MD,* Gabriele Palmedo, PhD,* Eduardo Calonje, MD,† Alexander J. Lazar, MD,‡ and Heinz Kutzner, MD**

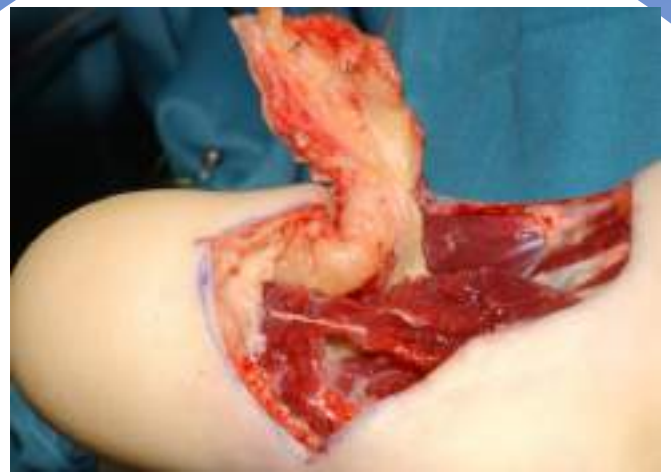
Abstract: Clear cell sarcoma (CCS) of tendons and aponeuroses/malignant melanoma (MM) of soft parts is a rare tumor and in the majority of cases presents a characteristic reciprocal translocation t(12;22)(q13;q12) that results in fusion of the *EWS* and *ATF1* genes. Although the melanocytic differentiation of CCS is indisputable, its precise lineage remains unclear. Typically, the slowly growing tumor affects the extremities of adolescents or young adults, especially around the ankle and foot. CCS is classically regarded as a deep soft tissue tumor associated with tendons or aponeuroses. This traditional view is put into perspective by the description of primary CCS of the cases by fluorescence in situ hybridization. Local recurrences and metastases developed in 2 and 3 patients, respectively, and 1 patient died of the disease.

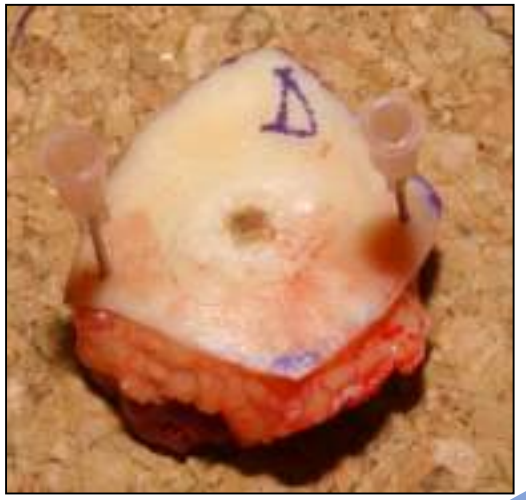
Key Words: clear cell sarcoma, melanoma of soft parts, melanoma

(*Am J Surg Pathol* 2010;34:216–222)

Clear cell sarcoma (CCS) of tendons and aponeuroses/malignant melanoma (MM) of soft parts is a unique

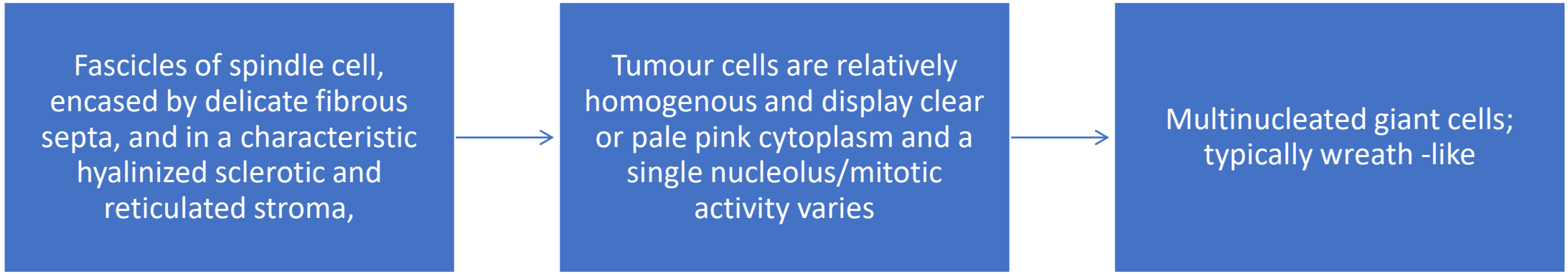
Dermal clear cell sarcoma

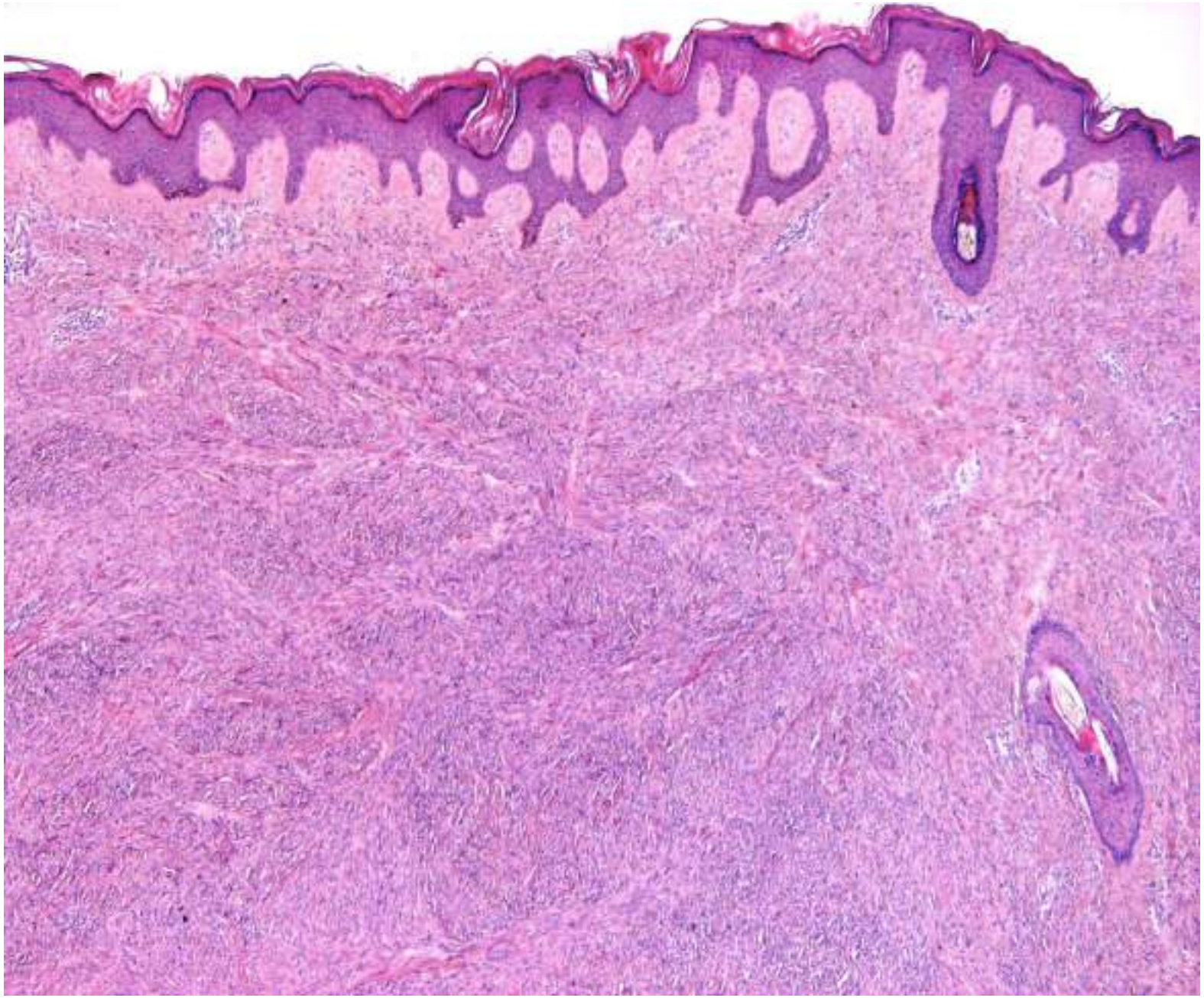


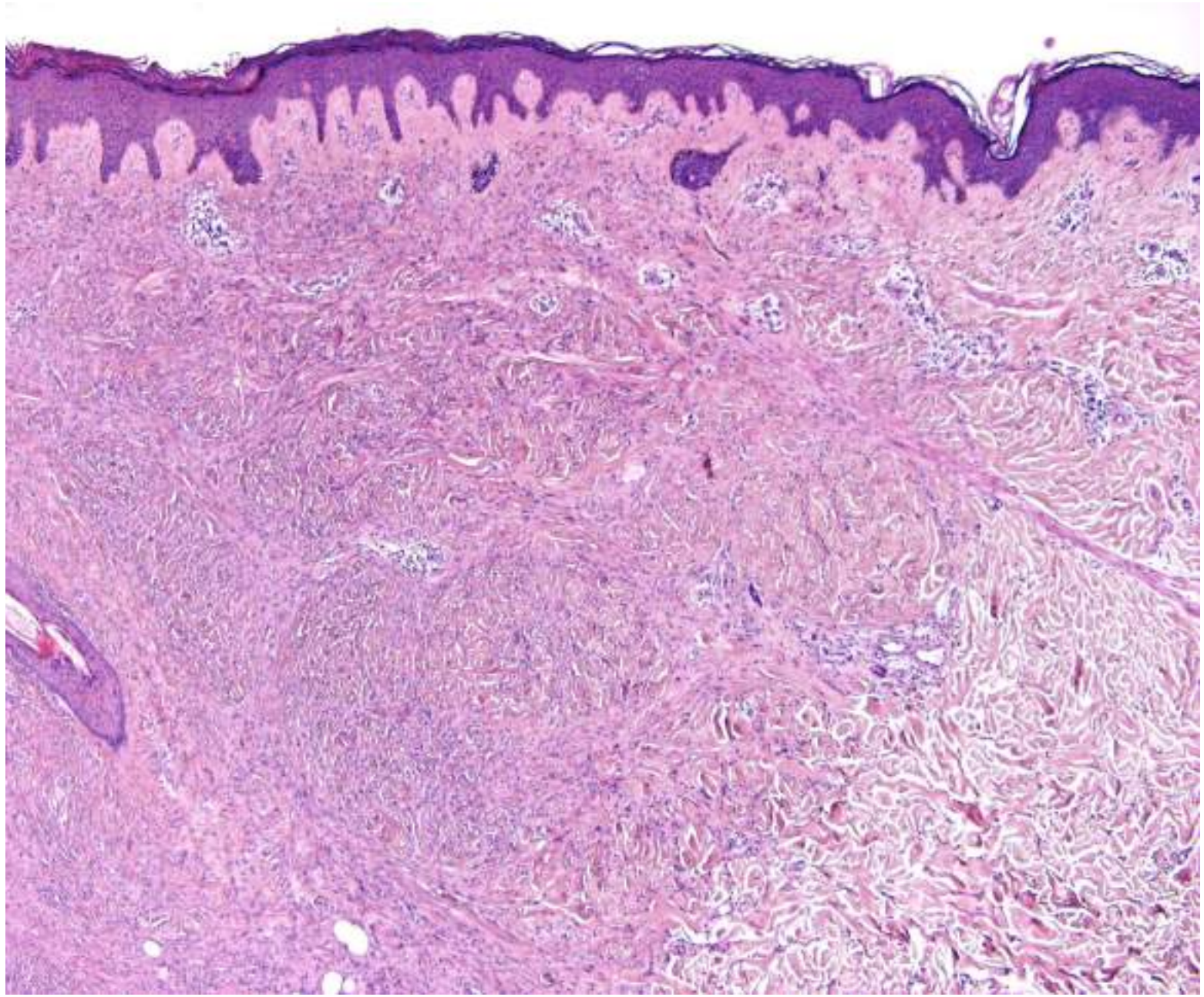


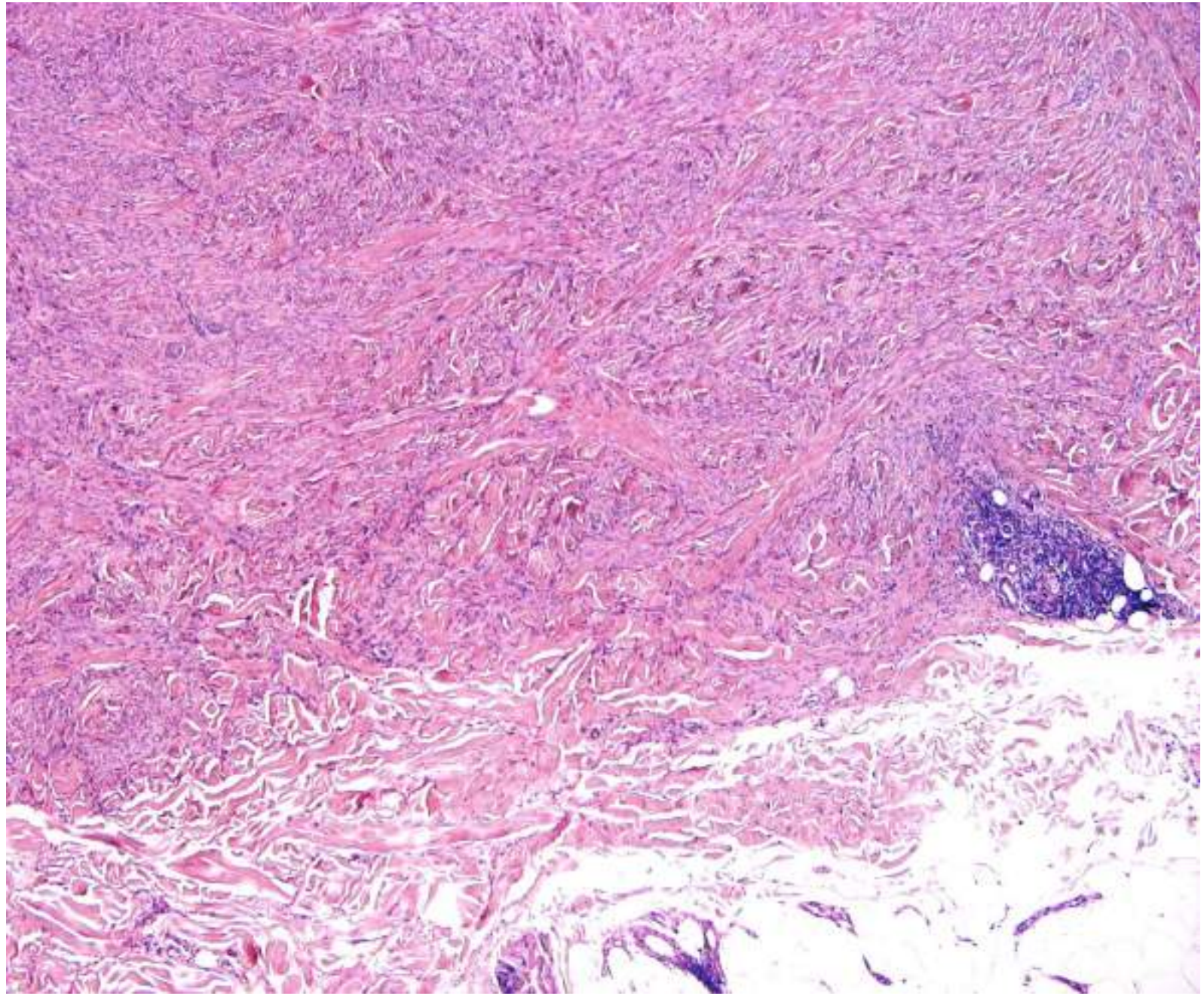
- Rare
- Adolescents and young adults
- Slight female predominance
- Predilection for acral sites
- Slowly growing occasionally painful nodule
- Small
- 5 year survival 60%
- Local recurrences common

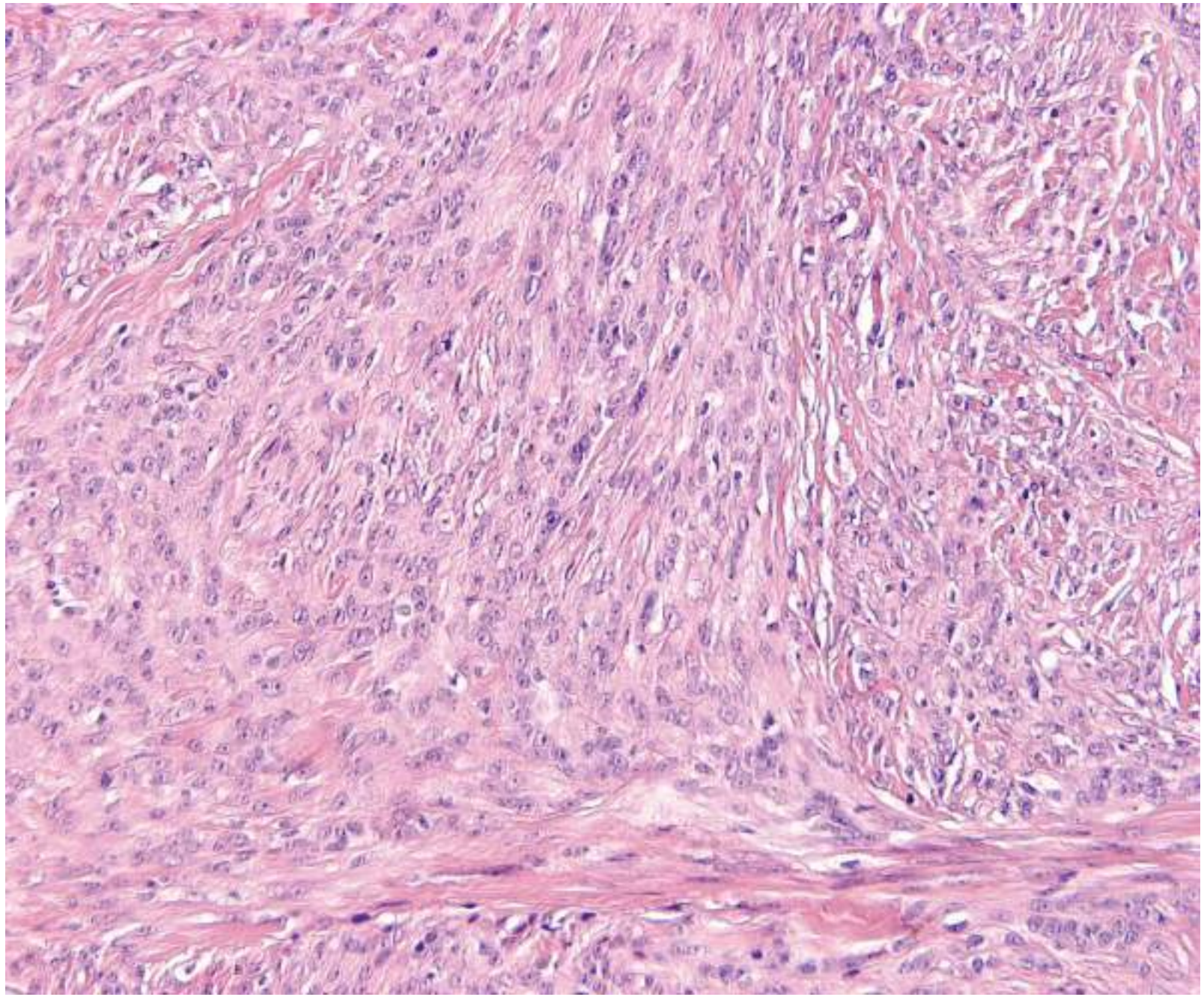
Primary Dermal Clear Cell Sarcoma Histological Features

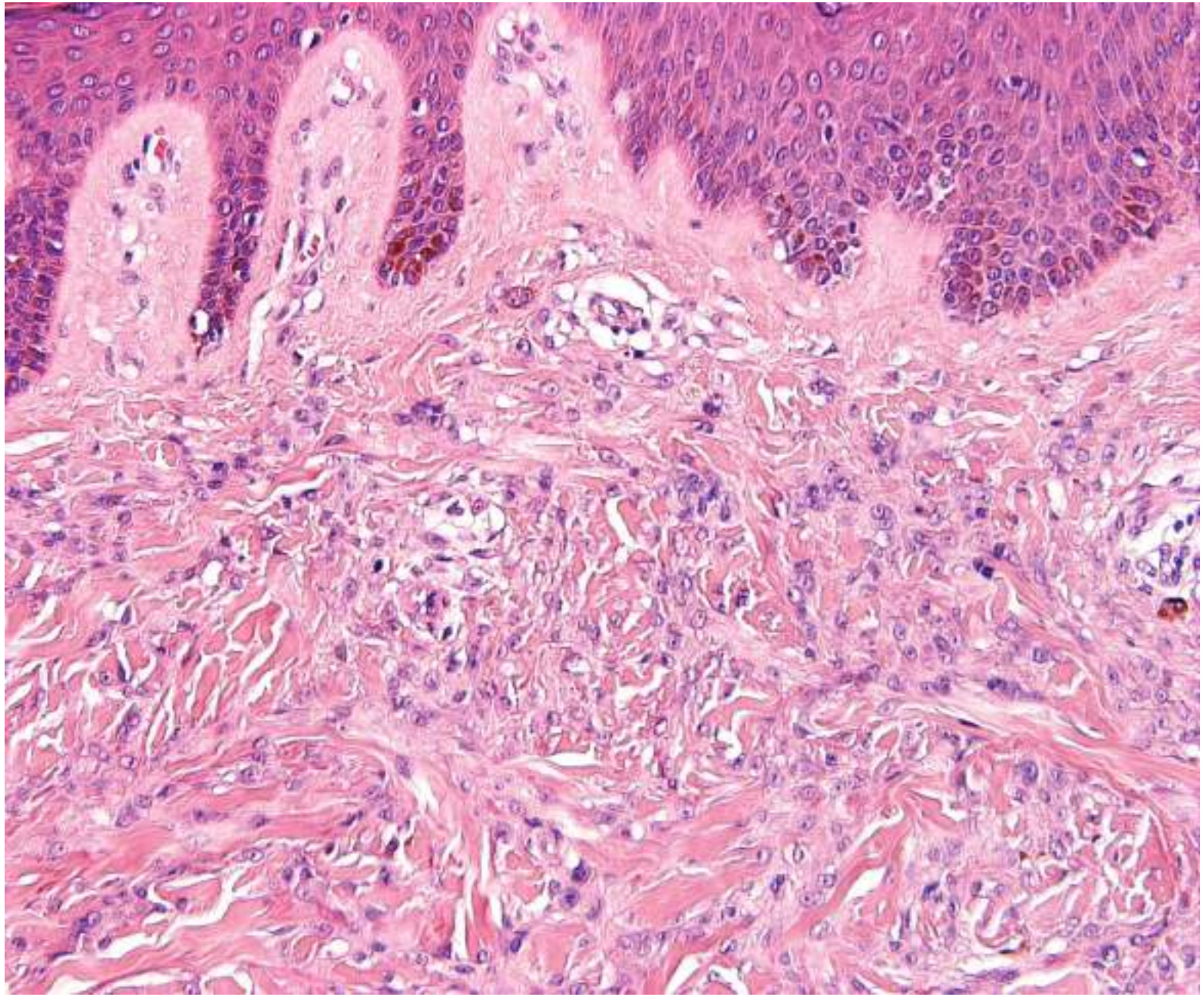


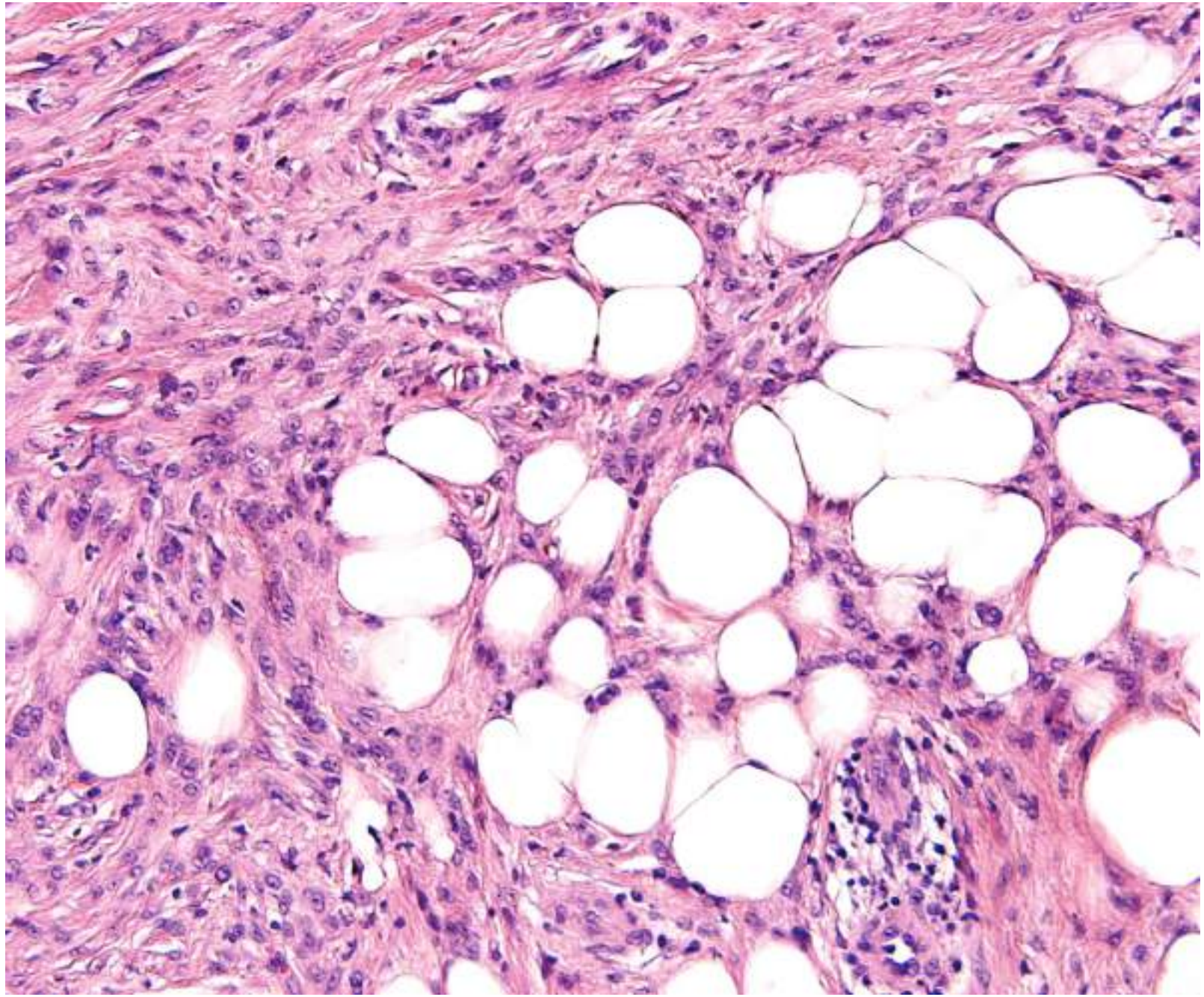


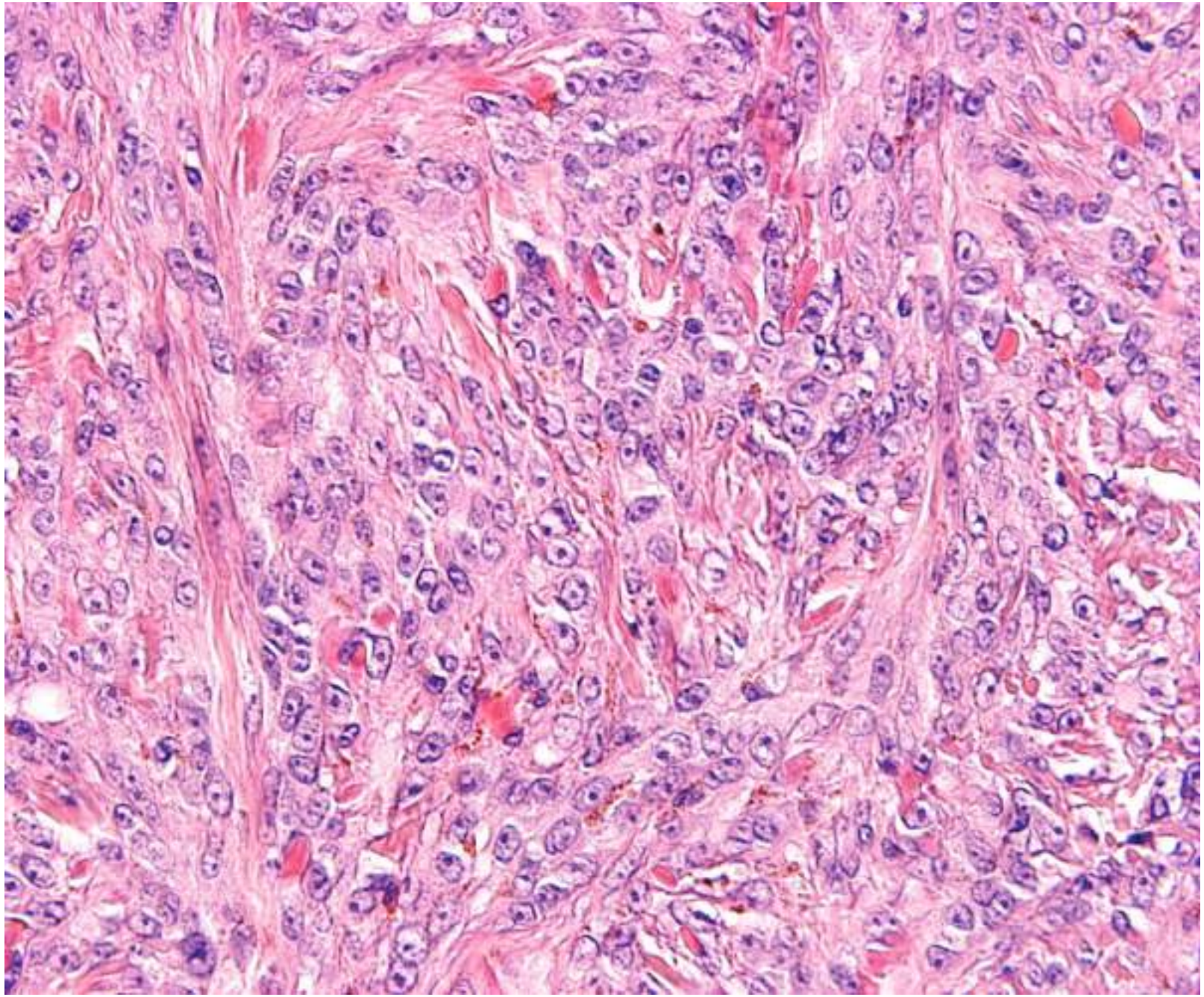


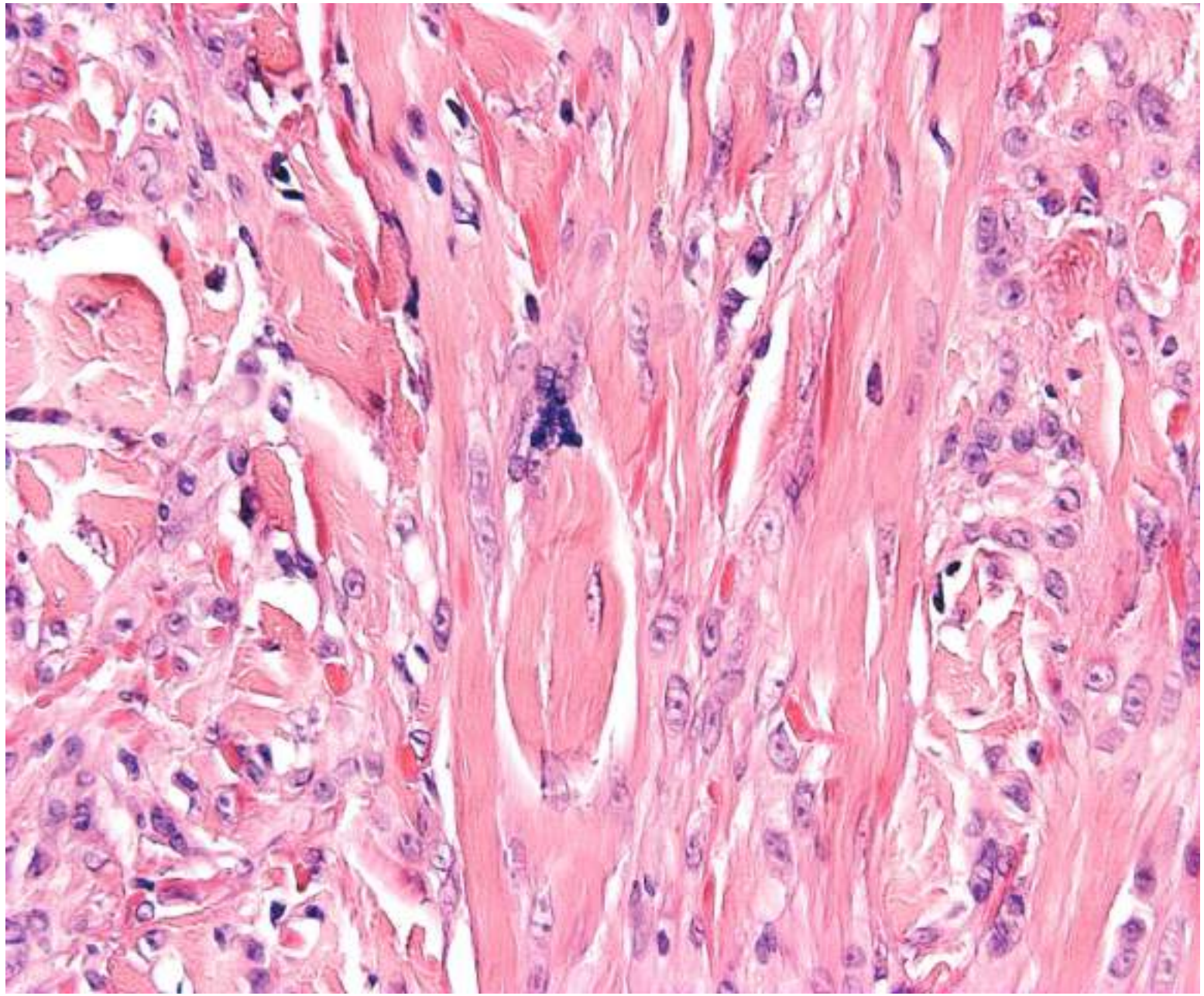


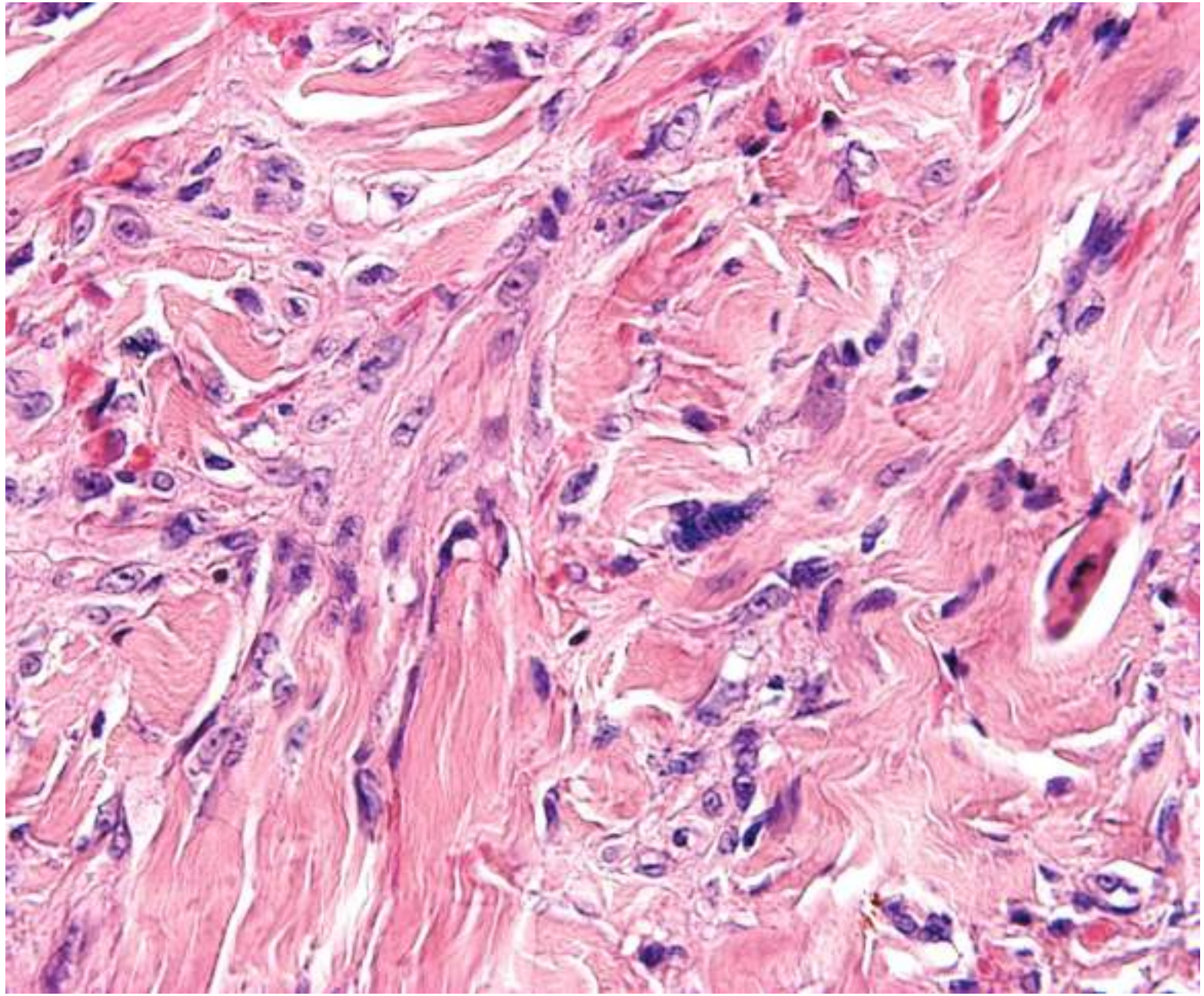


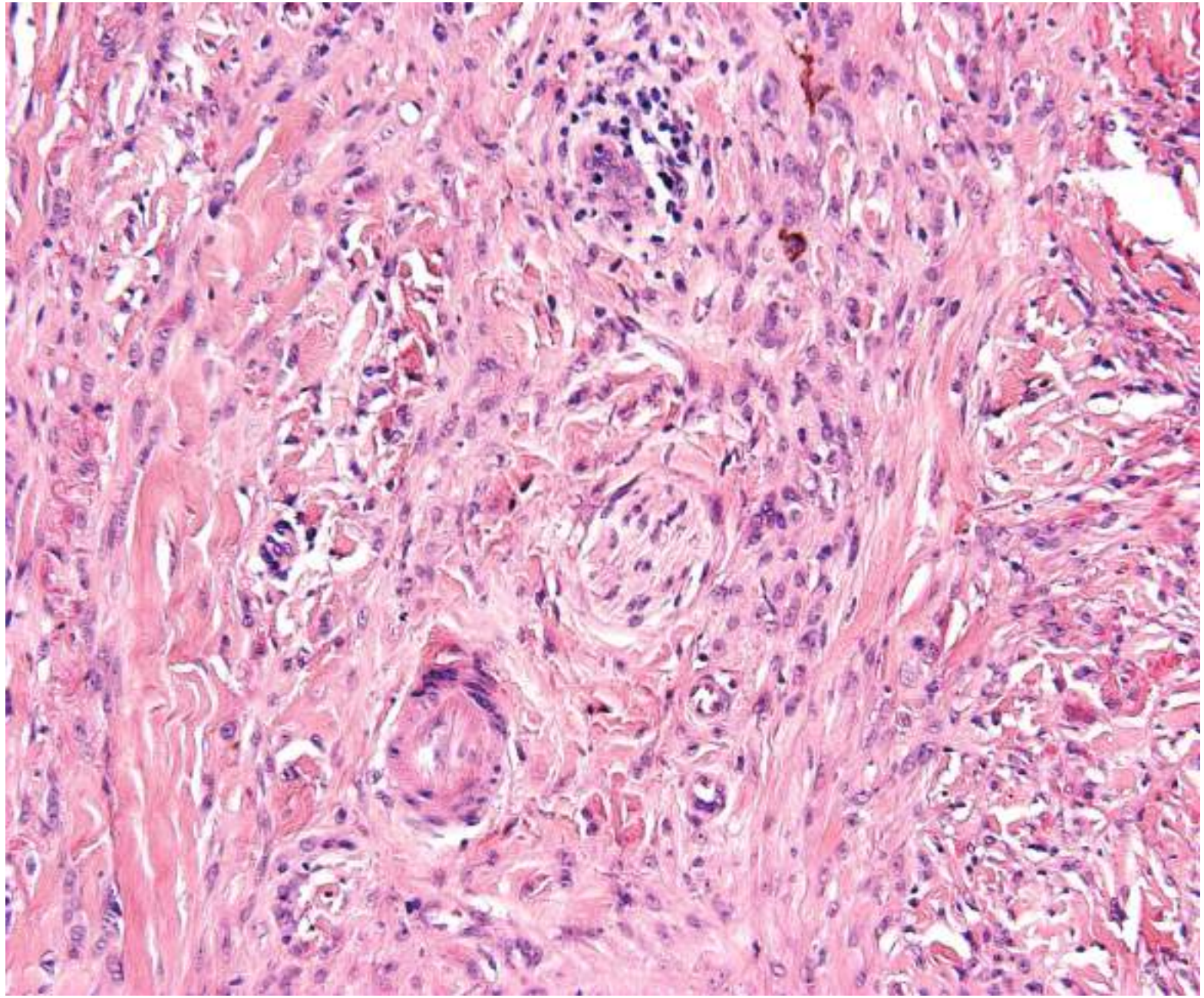


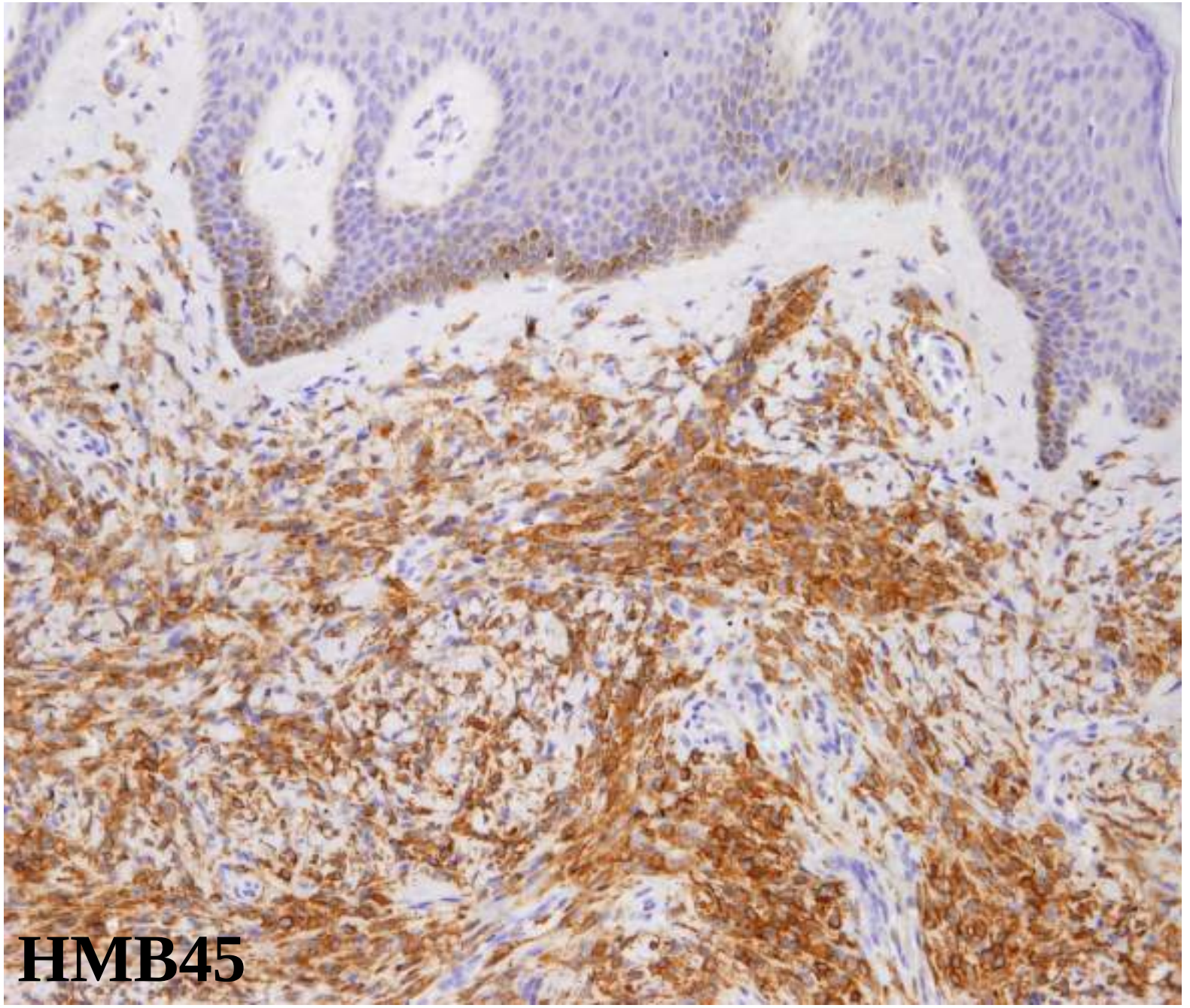








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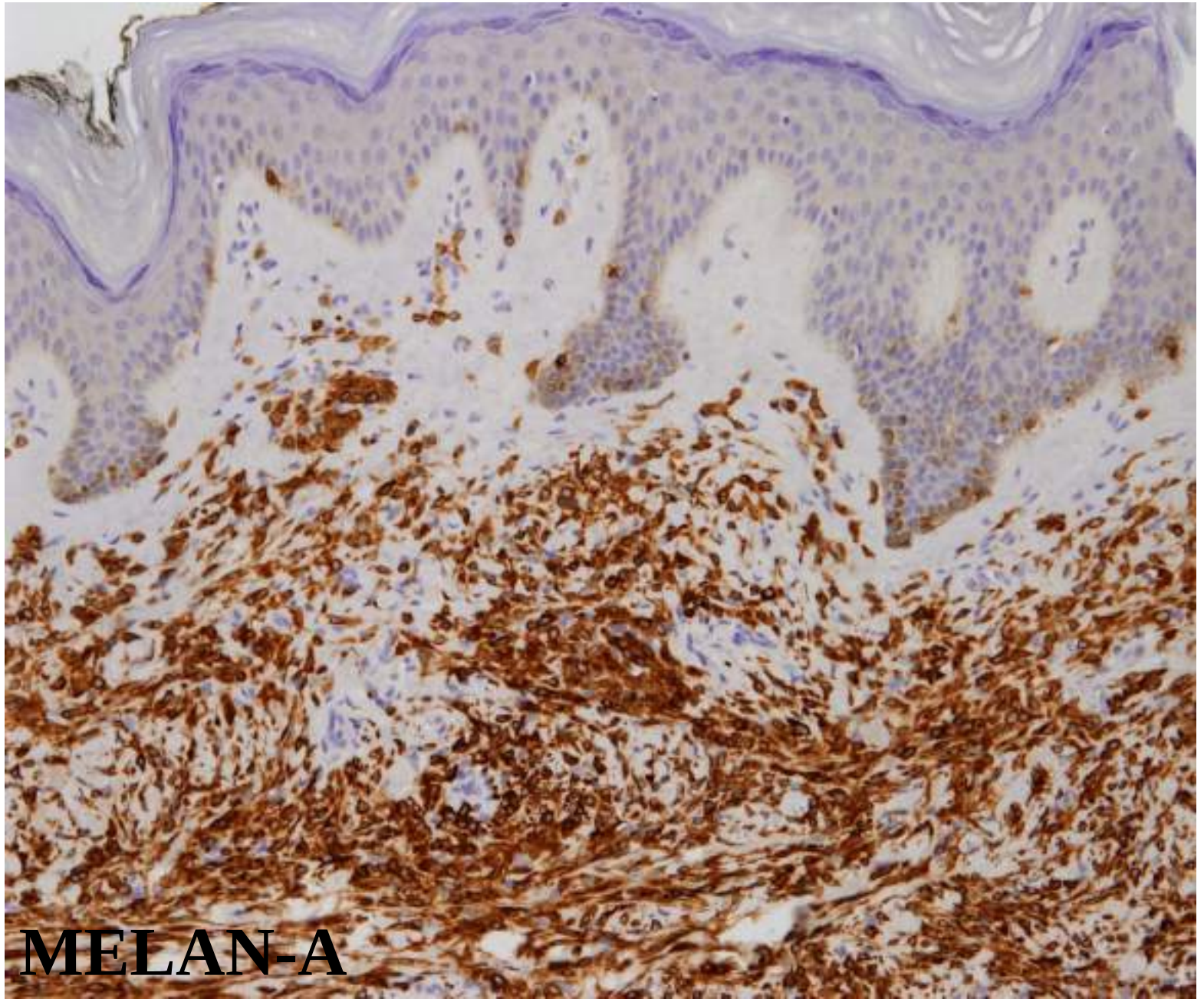
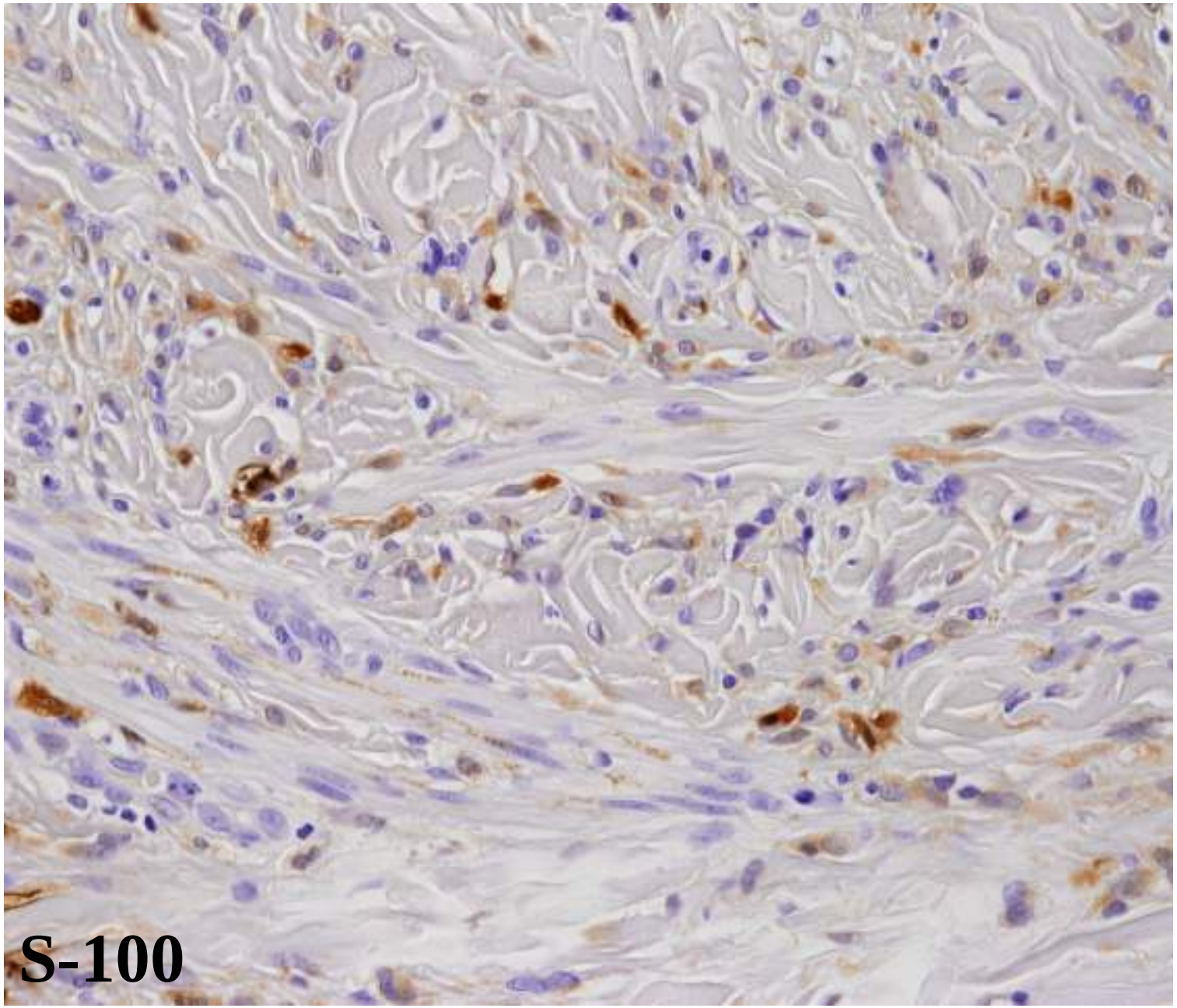
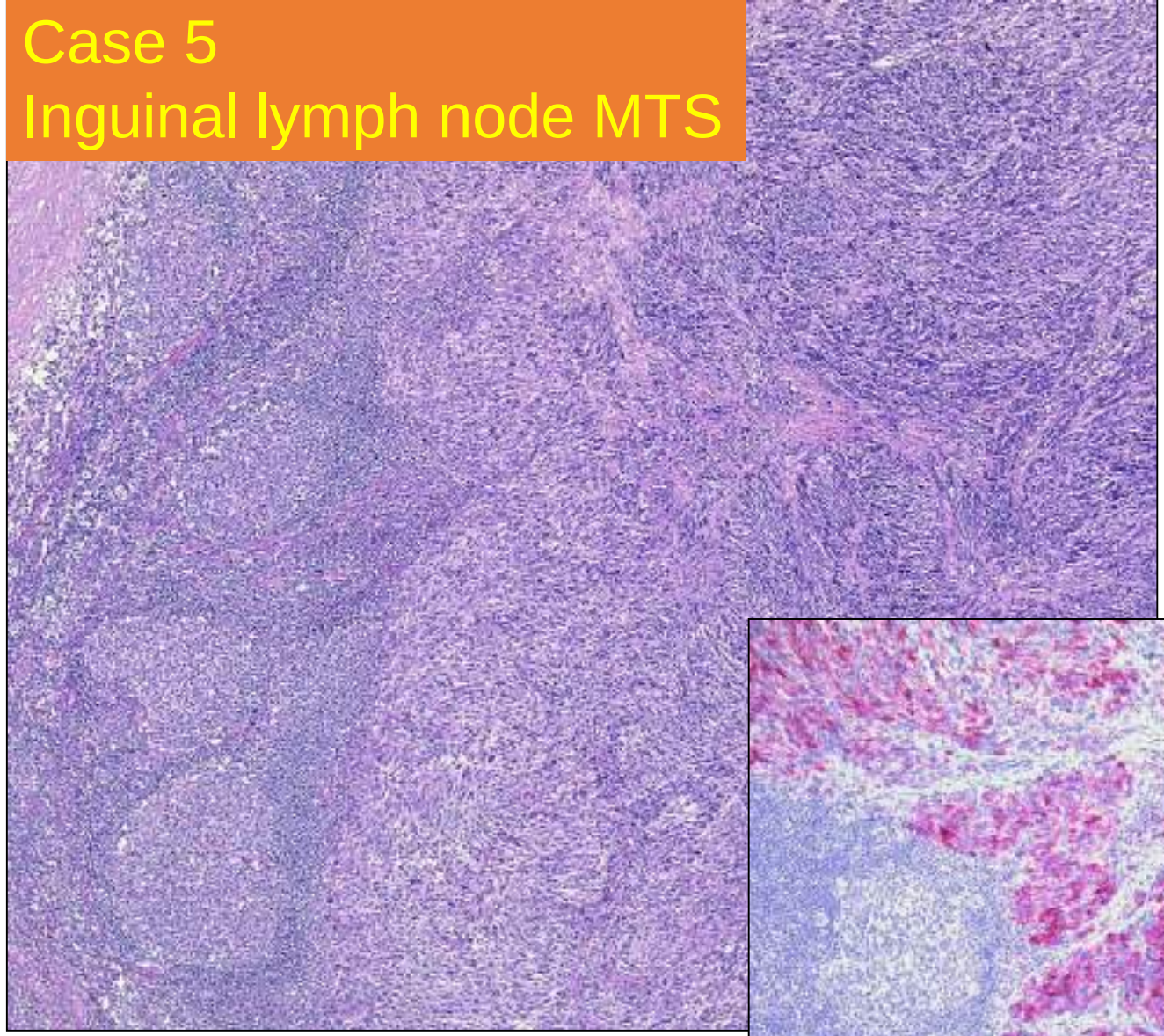
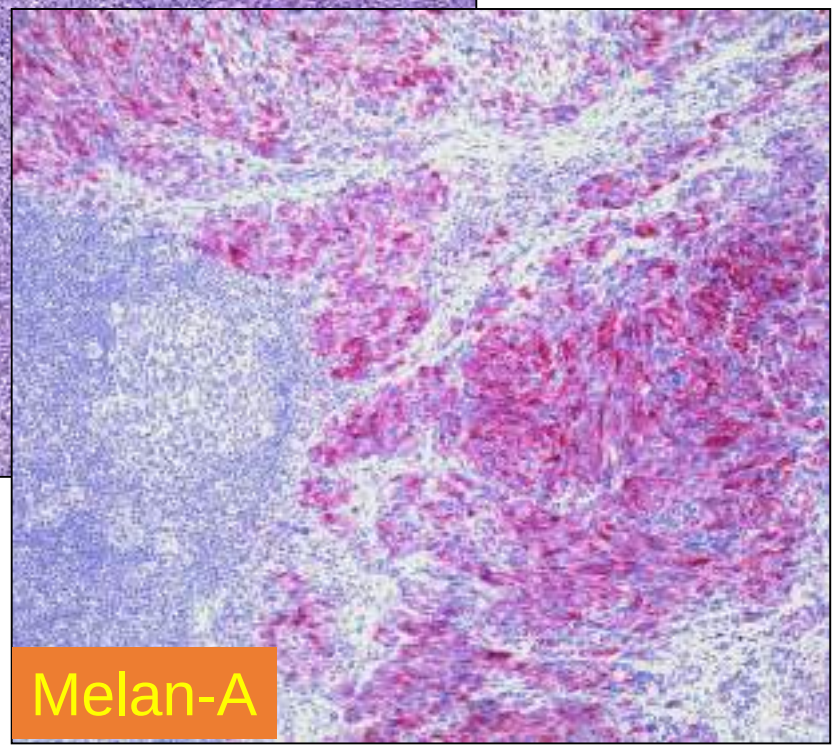

MELAN-A

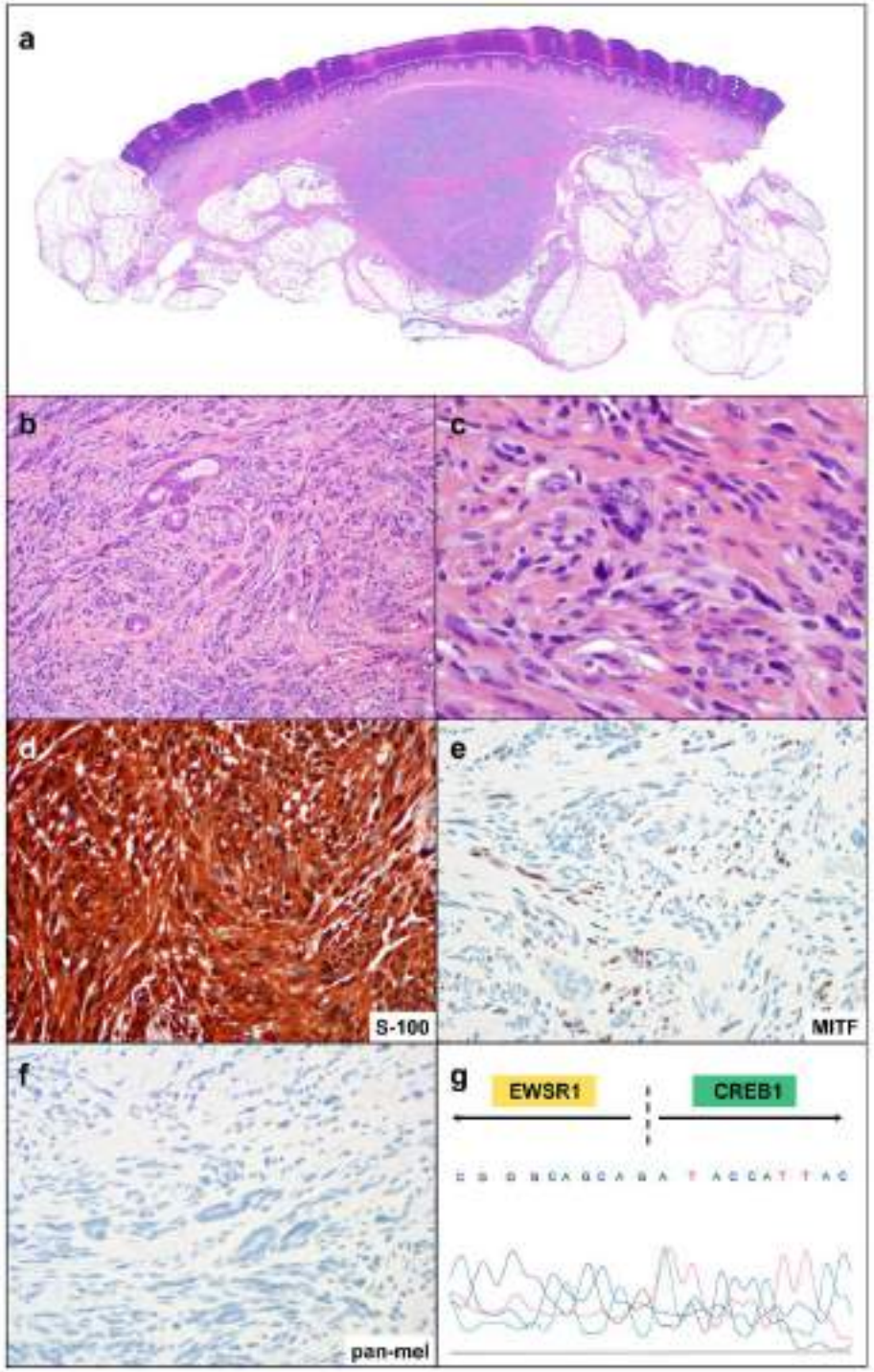

S-100

Case 5
Inguinal lymph node MTS



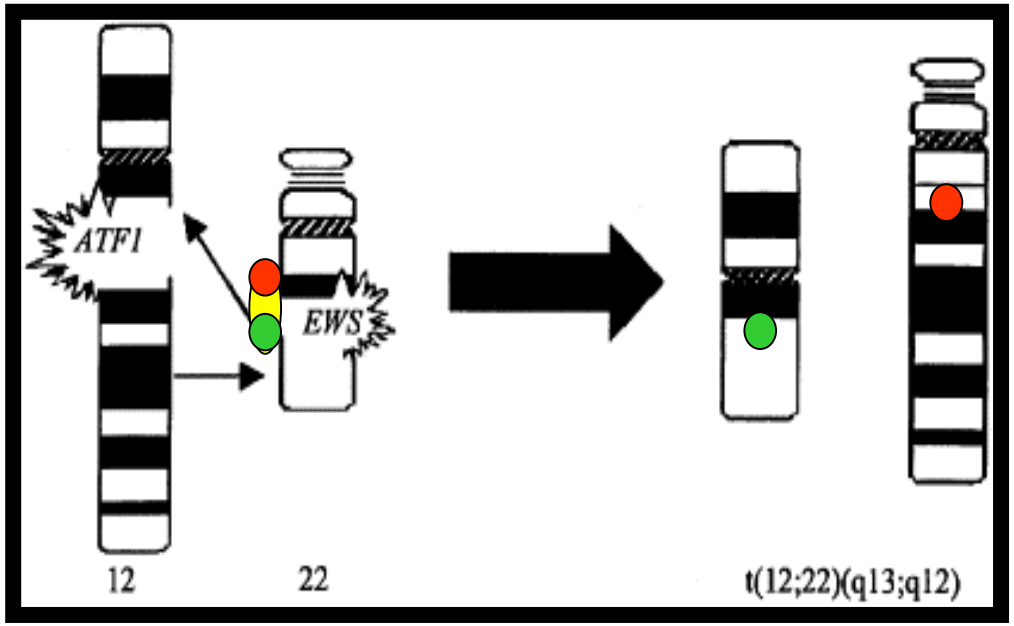


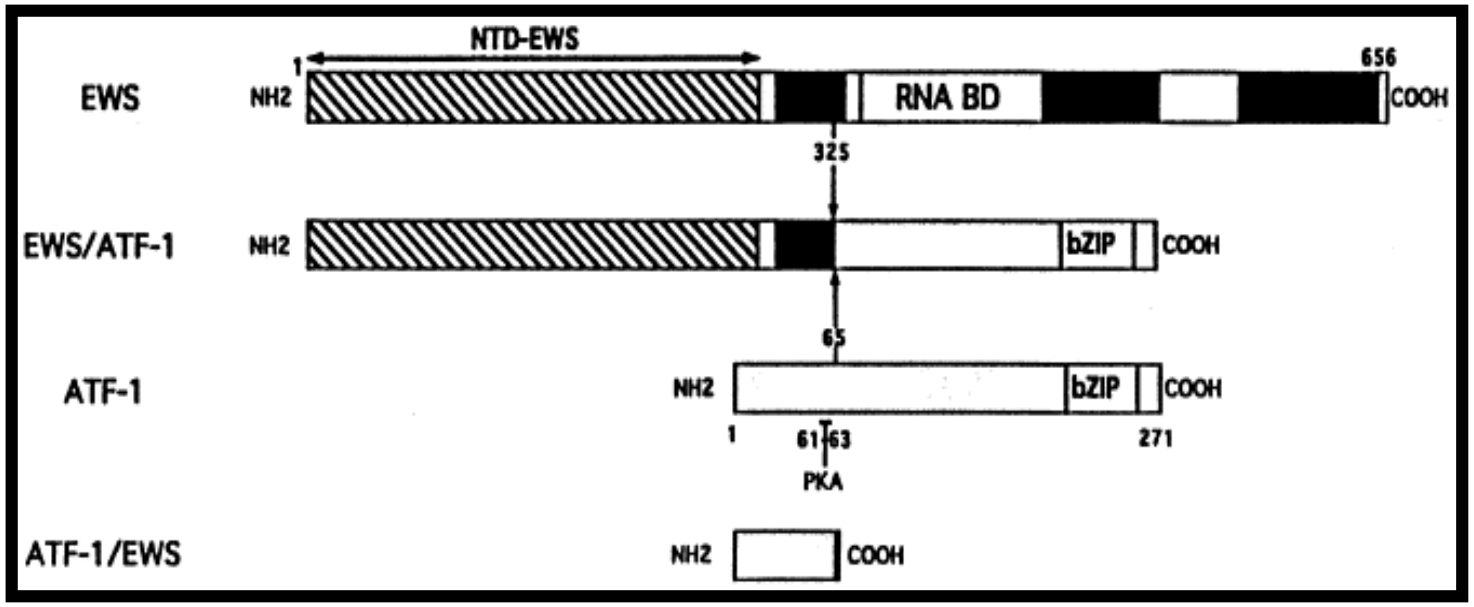
Melan-A



Case 8
F65, left palm

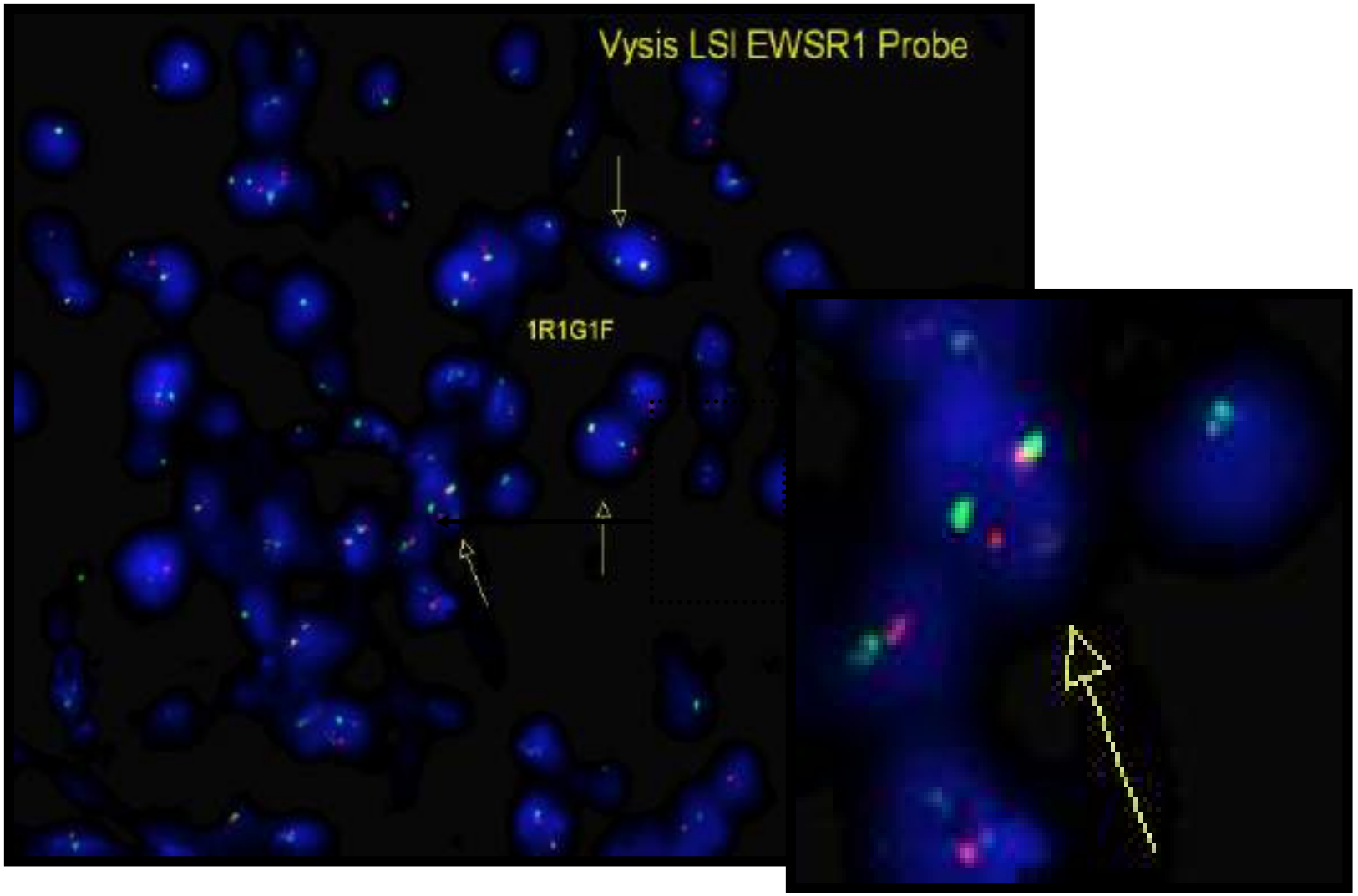
presented with initial lymph-node metastasis





Bridge and Sandberg, Cancer Genet Cytogenet, 2001

Clear Cell Sarcoma
t(12;22) ATF-1/EWS



J Cutan Pathol 2013: 40: 950–954
doi: 10.1111/cup.12197
John Wiley & Sons. Printed in Singapore

Journal of
Cutaneous Pathology

Compound clear cell sarcoma misdiagnosed as a Spitz nevus

Clear cell sarcoma (CCS) typically presents as a tumor in the deep soft tissue of extremities, but when centered in the dermis it may be confused with a melanocytic nevus, primary nodular or metastatic melanoma. Compound variants of CCS, i.e. tumor cells present in both the epidermis and underlying soft tissue have not yet been described. Herein we report such a case, which initially presented as a nodule on the left wrist of a young woman at 19 years of age. The lesion was then interpreted as 'Spitz nevus, compound type'. Twelve years later the patient noticed an enlarged lymph node in the right axilla. The excised lymph node was nearly completely replaced by malignant tumor cells, which were immunoreactive for S100 protein. They resembled the tumor cells of the wrist lesion. Cytogenetic analysis of the metastatic tumor revealed a t(12;22) translocation. Fluorescence *in situ* hybridization confirmed Ewing's sarcoma breakpoint region 1 (EWSR1) rearrangement in 70% of the tumor cells, thereby supporting the diagnosis of metastatic CCS. Our case is of interest because it documents that CCS can involve the epidermis. This observation expands the morphological spectrum associated with this tumor.

Keywords: cutaneous neoplasm, dermatopathology, melanocytic lesions, S100, soft tissue tumors

Kiuru M, Hameed M, Busam KJ. Compound clear cell sarcoma misdiagnosed as a Spitz nevus.
J Cutan Pathol 2013; 40: 950–954.

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Accepted for publication July 20, 2013

ORIGINAL ARTICLE

Compound Clear Cell Sarcoma of the Skin—A Potential Diagnostic Pitfall

Report of a Series of 4 New Cases and a Review of the Literature

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Abstract: The proliferation of cells with melanocytic lineage and a nested pattern has traditionally been regarded as a characteristic feature of a wide range of benign and malignant melanocytic proliferations. Herein, we report a series of 4 clear cell sarcomas, including 3 primary cutaneous and 1 metastatic to the skin, associated with a clear-cut intraepidermal proliferation of tumor cells representing a serious potential diagnostic pitfall. All patients were male individuals, aged from 17 to 71 years (mean: 42 y). The size of the tumors ranged from 8 to 55 mm (mean: 22.2 mm, median: 13 mm). Two tumors arose on a lower extremity and 1 each on the scalp and chest. Cutaneous metastasis developed on the limb proximal to the amputation site. Histologically, all tumors were variably circumscribed nodular or multinodular proliferations within the dermis, focally extending into the subcutis. They were composed of nests and fascicles of pale spindled and epithelioid cells with finely granular or pale cytoplasm, elongated nuclei with a single prominent nucleolus, featuring mild nuclear pleomorphism, and surrounded by delicate fibrous septa. Scattered wreath-like giant cells were present in all cases. Mitotic activity was low (mean and median: 3.5 mitoses/mm^2). The intraepidermal component consisted in all 4 cases of nests of tumor cells localized at the dermal-epidermal junction. Nests were well-defined and composed of spindled or epithelioid cells with irregular hyperchromatic nuclei, prominent nucleoli, and scant to moderately abundant eosinophilic to pale cytoplasm. Lentiginous proliferation of epithelioid tumor cells was coupled with focal upward migration of isolated tumor cells in a single case. By immunohistochemistry, all tumors were S100 protein, melan A, and HMB45 positive. By fluorescence in situ hybridization analysis, 3 tumors displayed rearrangements in the *EWSR1* gene, whereas reverse transcriptase polymerase chain reaction confirmed *EWSR1(e8)/ATF1(e4)* translocation in the remaining case. In conclusion, an epidermal component in primary cutaneous clear cell sarcomas, or cutaneous metastasis of the tumor, is exceptional and represents a potential diagnostic pitfall. Careful attention to the salient morphologic features in the dermal component of the tumor, as well as confirmation of *EWSR1* gene rearrangement by fluorescence in situ hybridization or reverse transcriptase polymerase chain reaction, is necessary for correct recognition of the tumor and to avoid erroneous diagnosis of a benign or malignant melanocytic proliferation.

Key Words: clear cell sarcoma, superficial/cutaneous, metastasis to skin, intraepidermal component, *EWSR1/ATF1*, *EWSR1/CREB1*, fusion

(*Am J Surg Pathol* 2020;44:21–29)

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Conflicts of Interest and Source of Funding: The authors have disclosed that they have no significant relationships with, or financial interest in, any commercial companies pertaining to this article.
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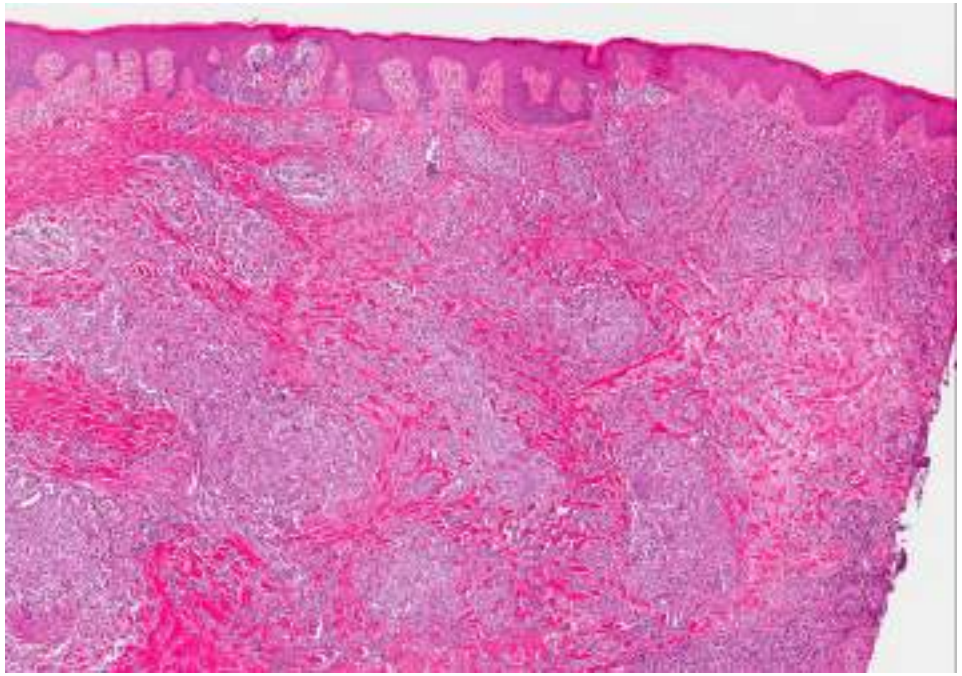
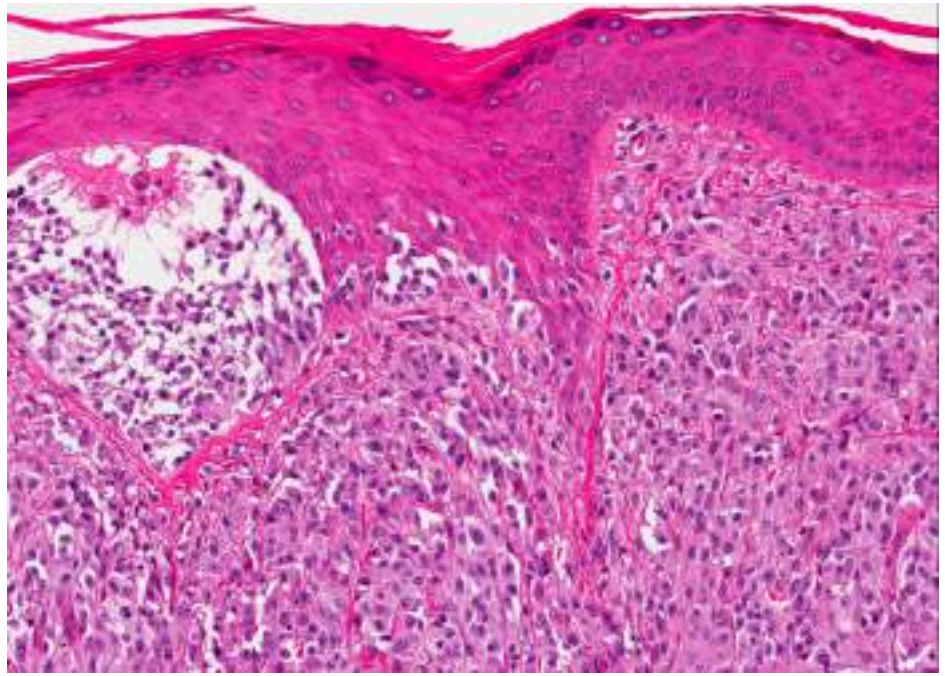
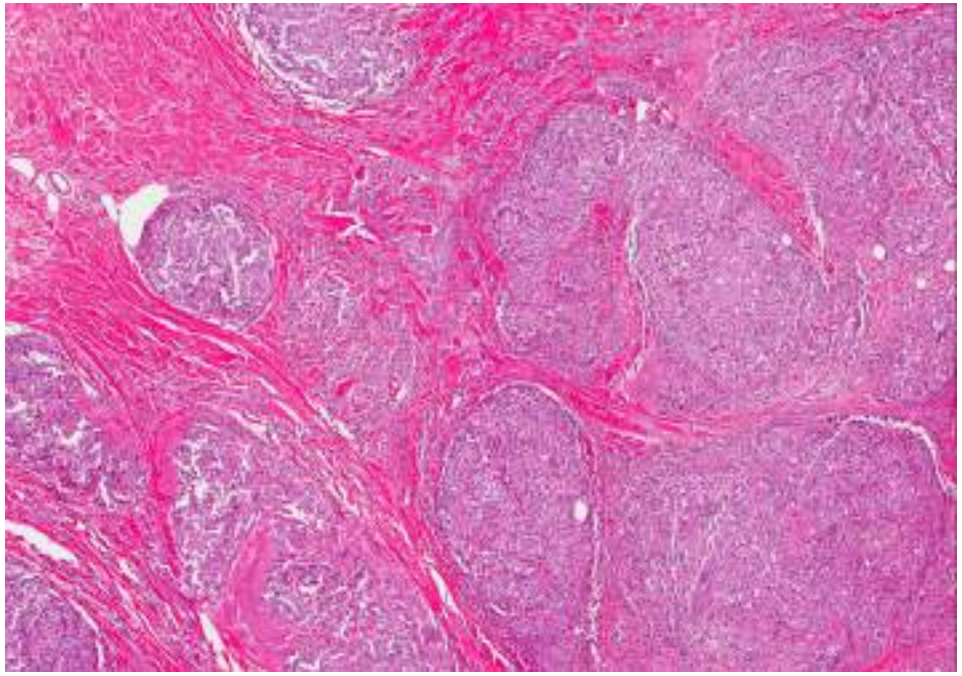
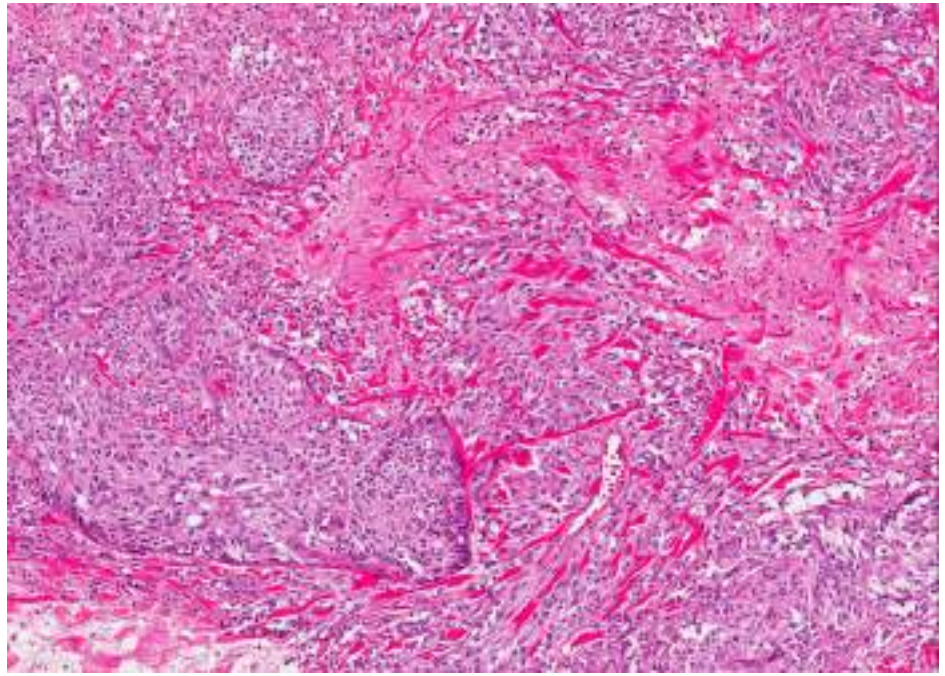
Clear cell sarcoma, also designated melanoma of soft parts, was initially reported by Franz Enzinger in 1965 in a series of 21 cases as a tumor of fascias, tendons, and aponeuroses with a predilection for the extremities of young adults.[1,2] Although initially regarded as a tumor of uncertain histogenesis,[1] a neural crest derivation was subsequently suggested by immunohistochemical (ie, diffuse S100 protein positivity) and ultrastructural studies (ie, the presence of melanosomes).[3,4] Nevertheless, despite sharing melanocytic differentiation and thus having overlapping histologic, immunohistochemical, and ultrastructural features, clear cell sarcoma and conventional melanoma are now clinically and genetically regarded as 2 distinct entities.[5] The distinction between cutaneous clear cell sarcoma and conventional melanoma is crucial due to their differences in biological behavior and treatment options.[6]

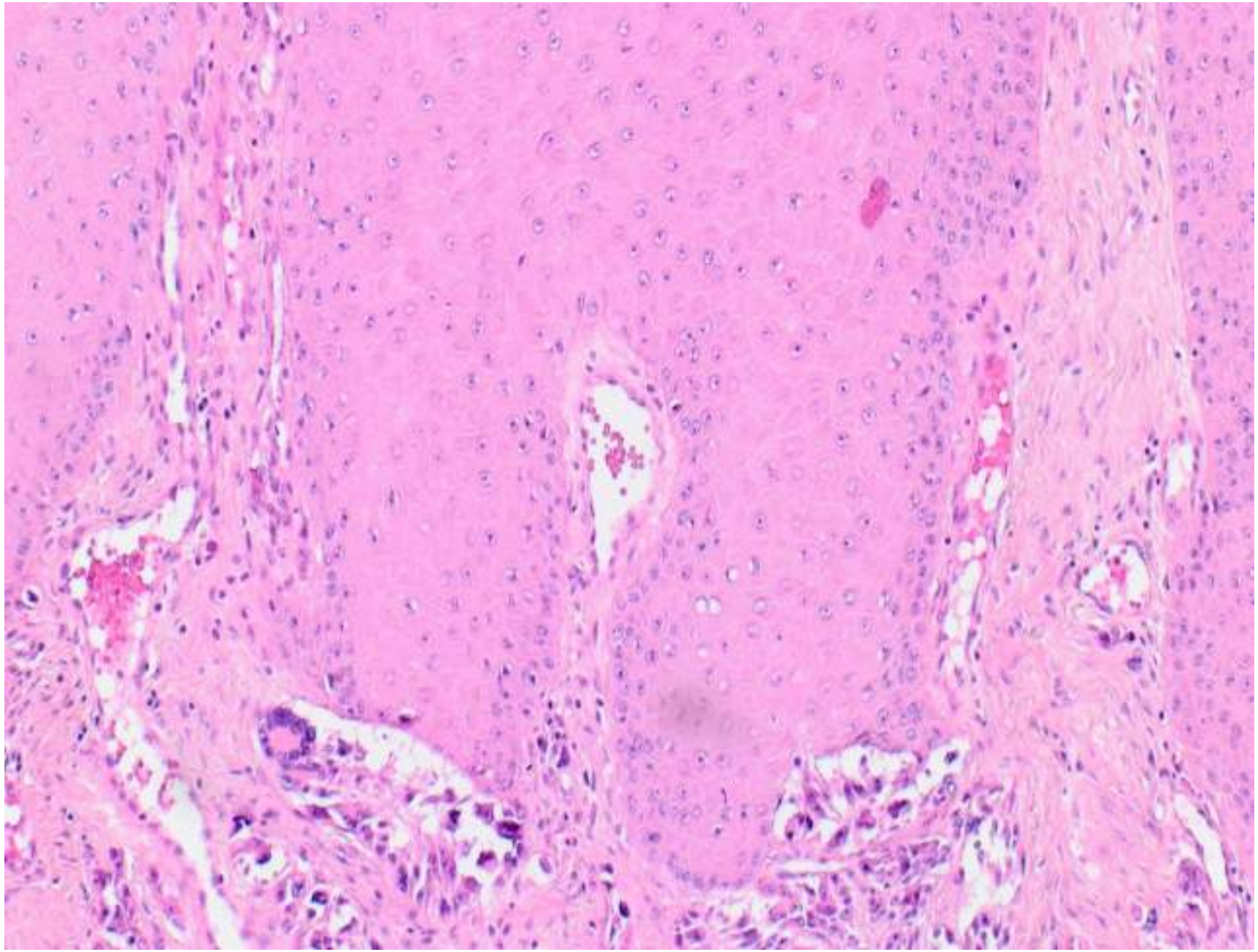
At the molecular genetic level, clear cell sarcoma is typically associated in about 80% of cases with reciprocal translocation t(12;22)(q13;q12) involving the *Ewing sarcoma* (*EWSR1*) gene,[7] resulting in fusion of the *EWS1* gene on 22q12 with the *activating transcription factor-1* (*ATF1*) gene on 12q13, leading to the formation of the *EWSR1/ATF1* fusion gene.[8–10] Importantly, this translocation has not been found in conventional melanoma, enabling distinction between the 2 entities at a cytogenetic level.[8] In addition, an alternative *EWSR1/CREB1* fusion resulting from translocation t(2:22)(q34;q12) has also been detected and represents a genetic hallmark of a malignant

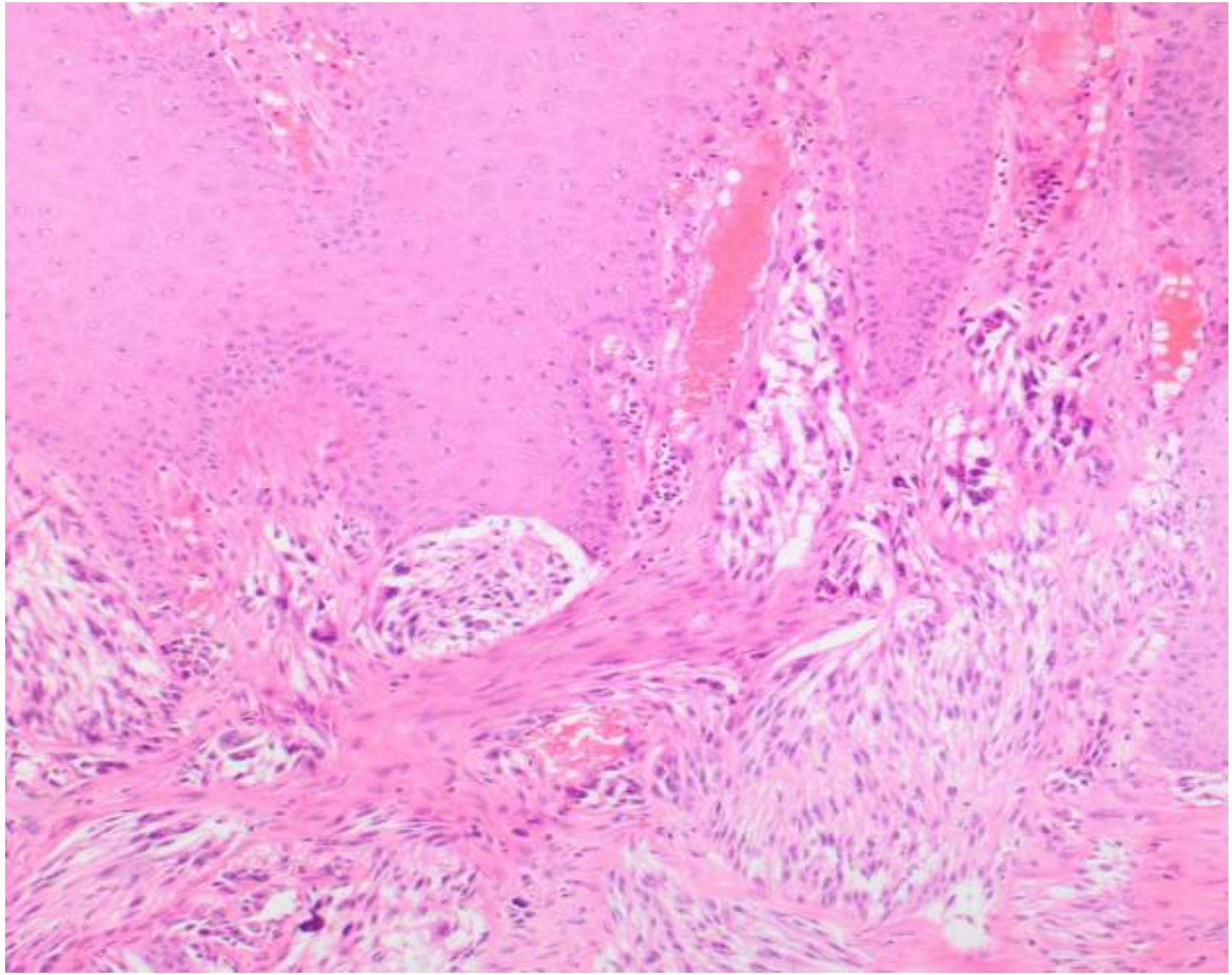






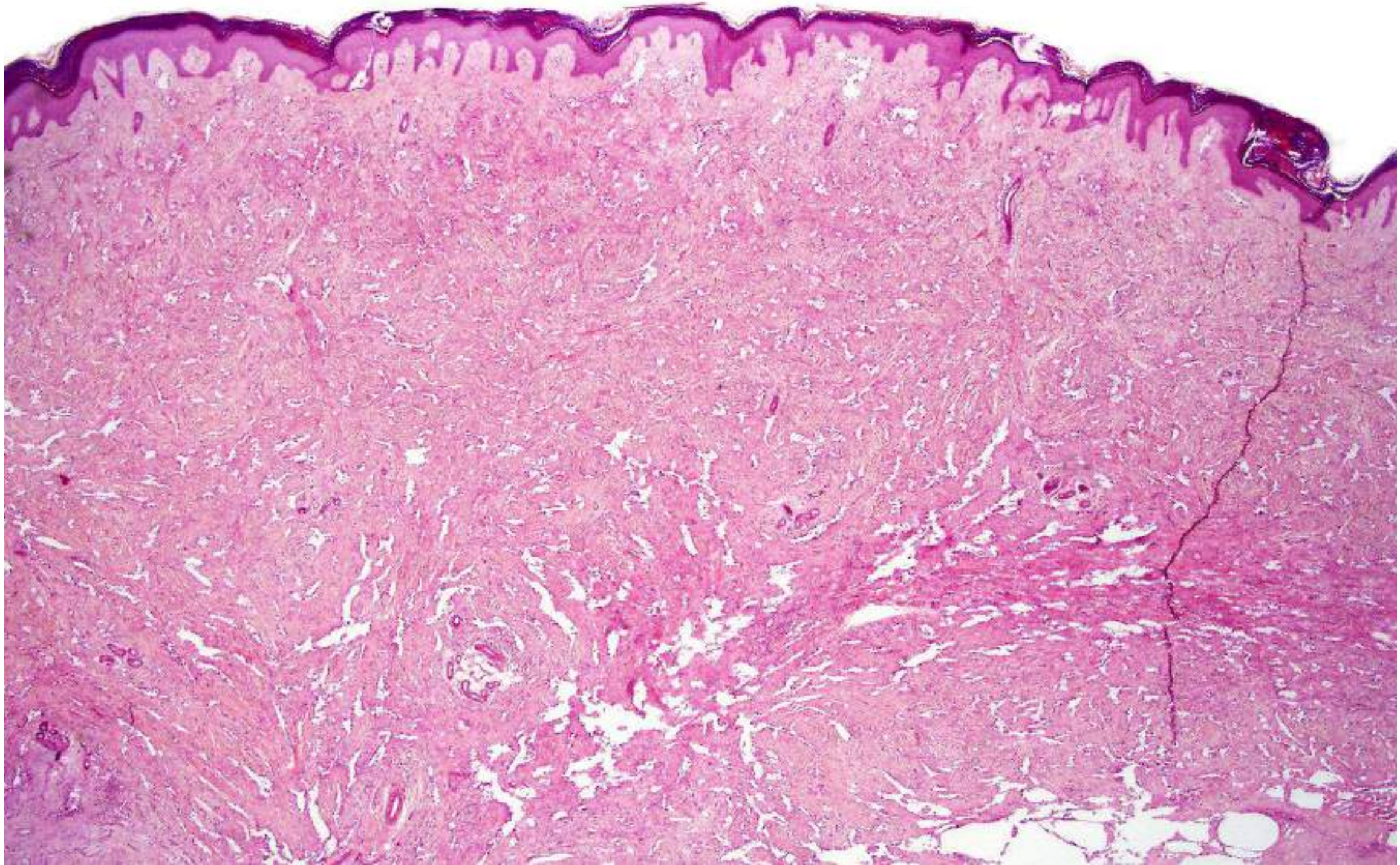


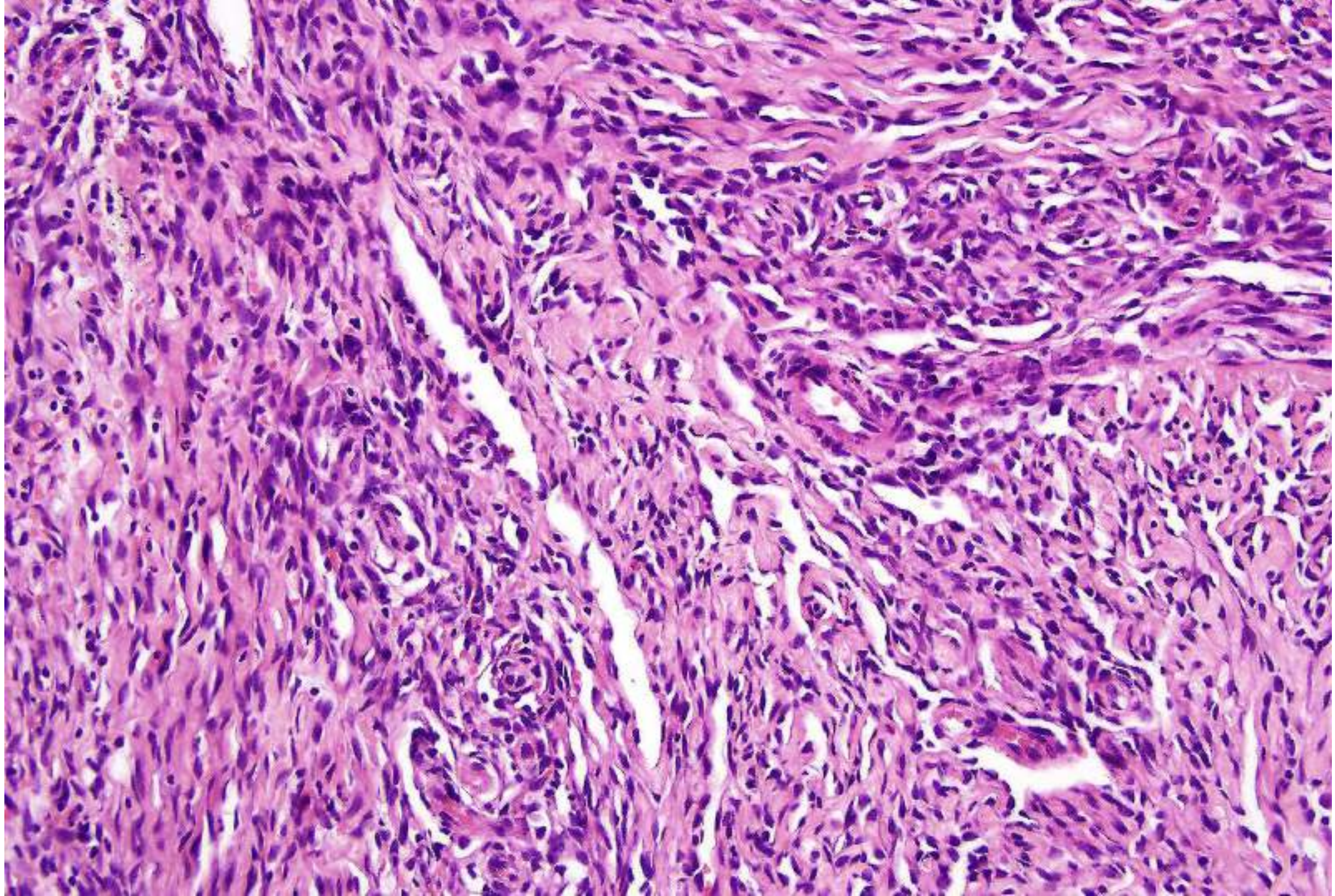


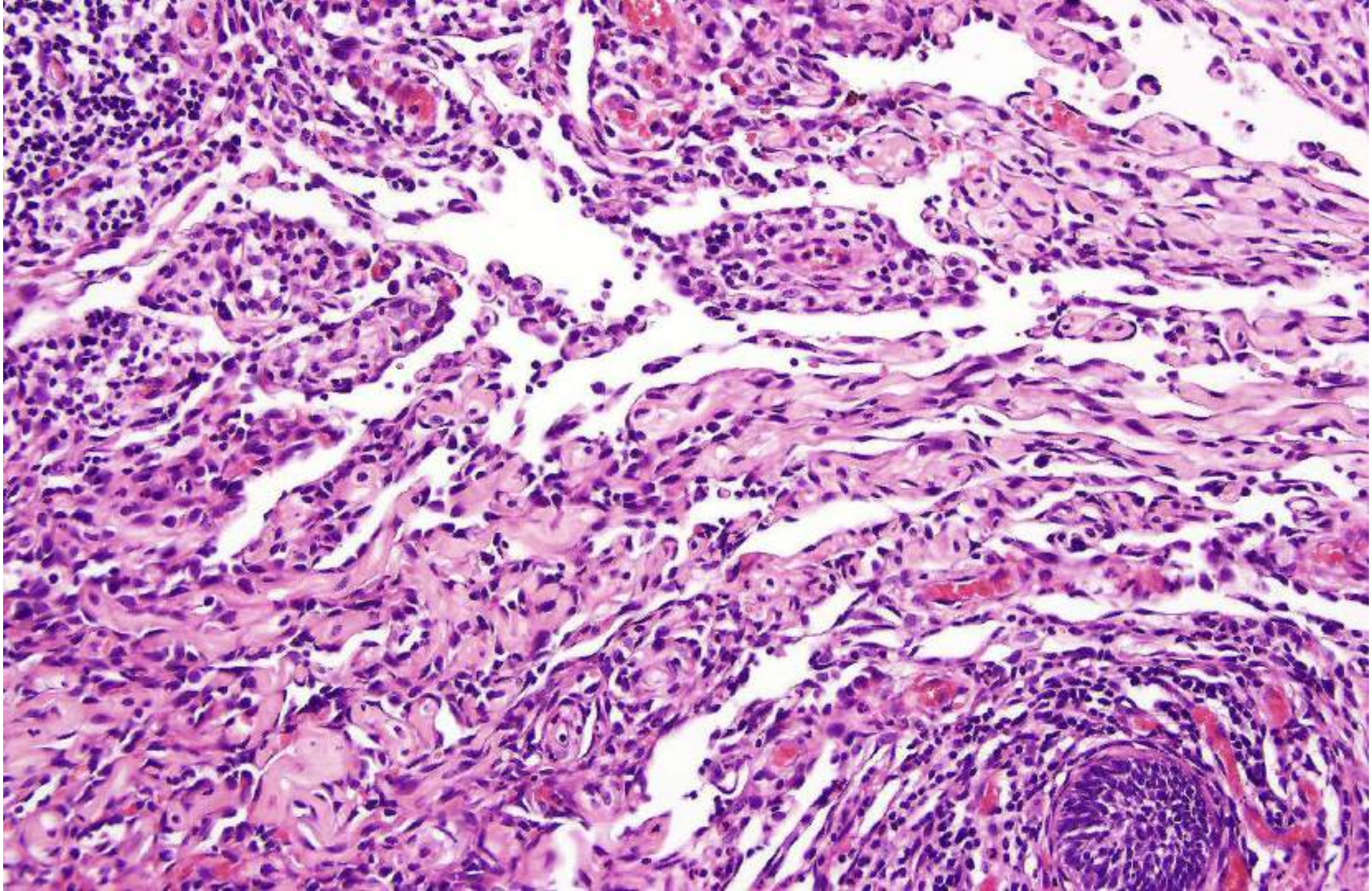


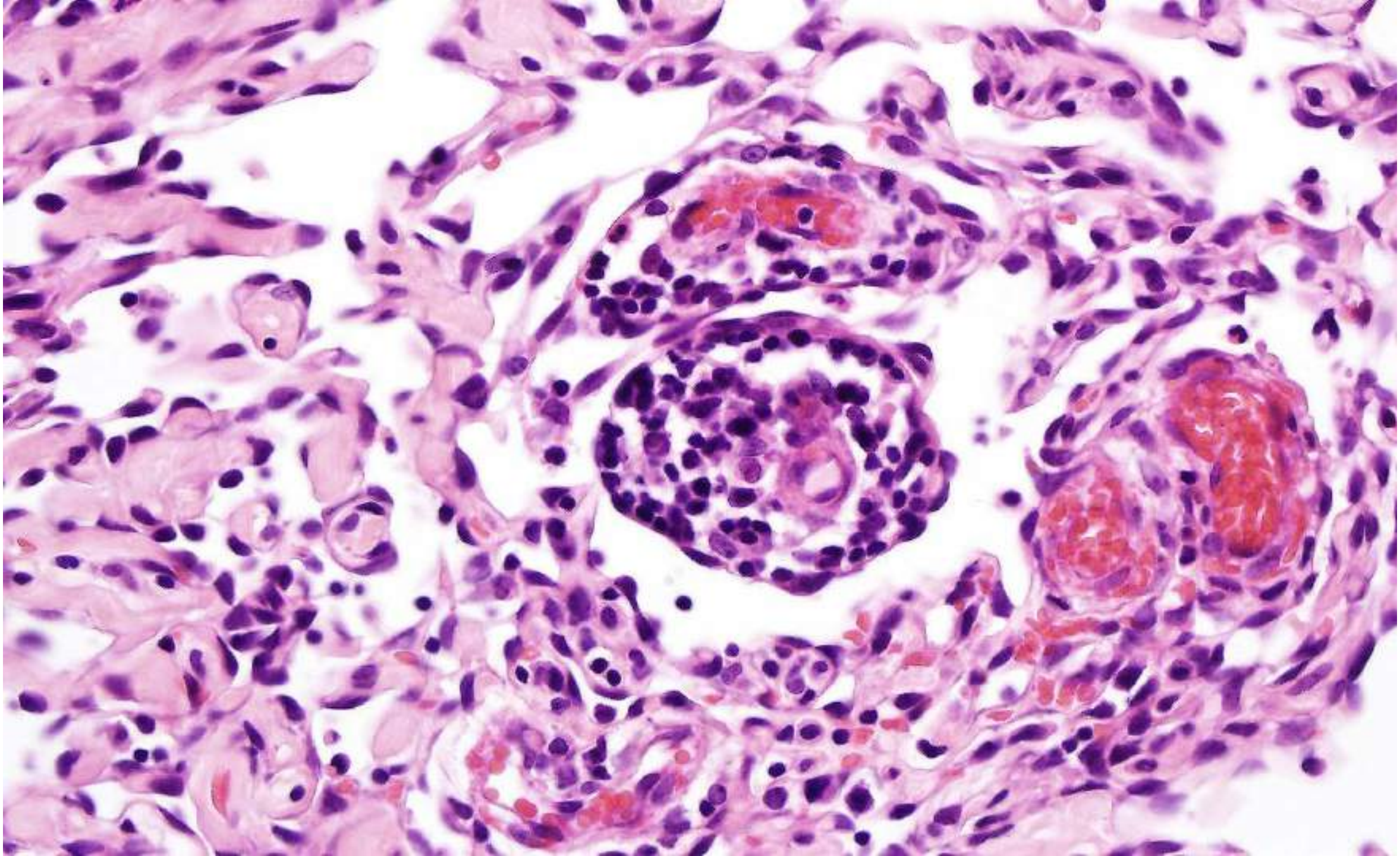
COMPOSITE HAEMANGIOENDOTELIOMA

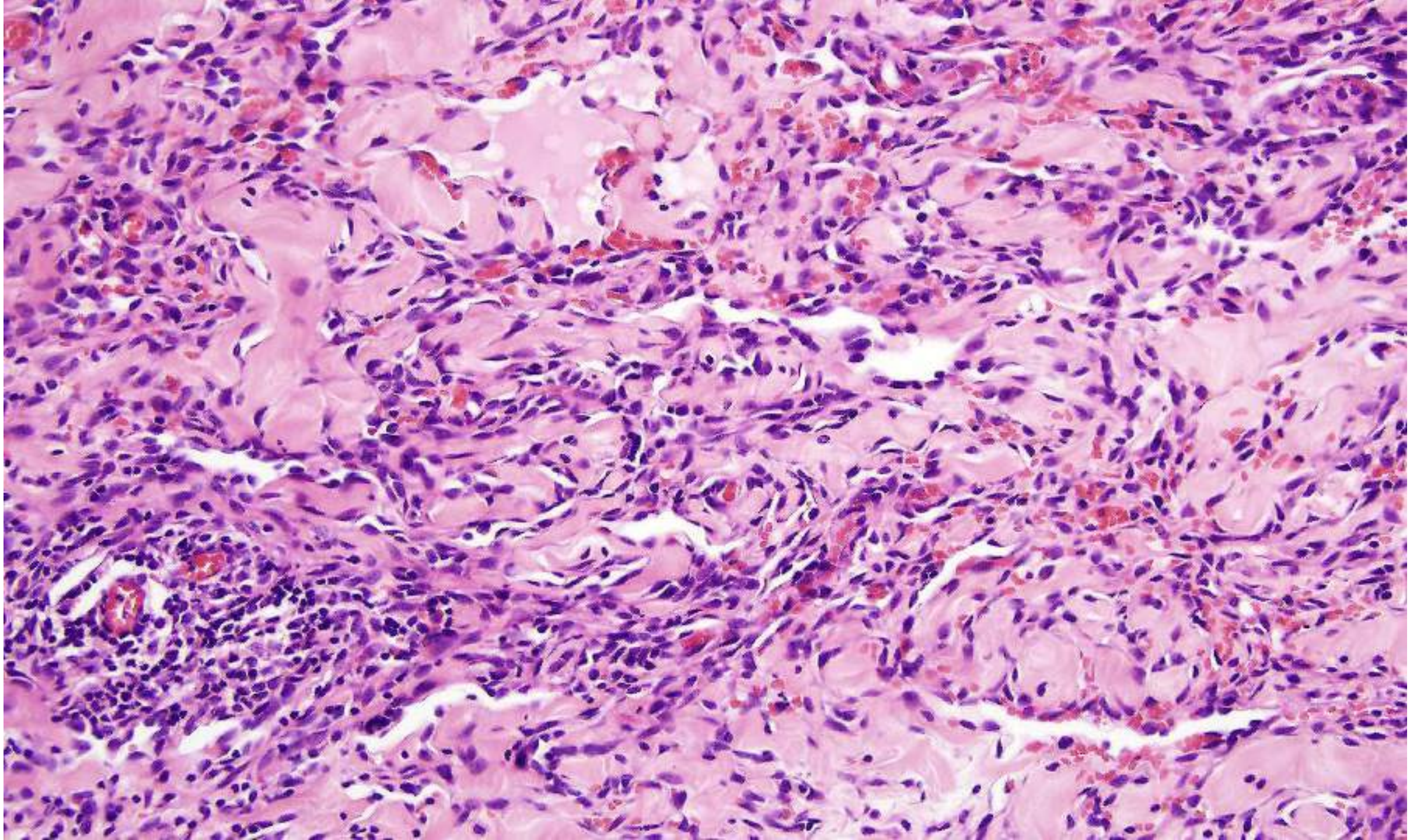
- **Definition: combinacion in a vascular neoplasm of two or more low-grade vascular tumors and one or more benign vascular tumours**
- **If there is a high grade component (angiosarcoma), this component has to be highlighted and determines prognosis**
- **Tendency for local recurrence, low risk of metastatic spread**

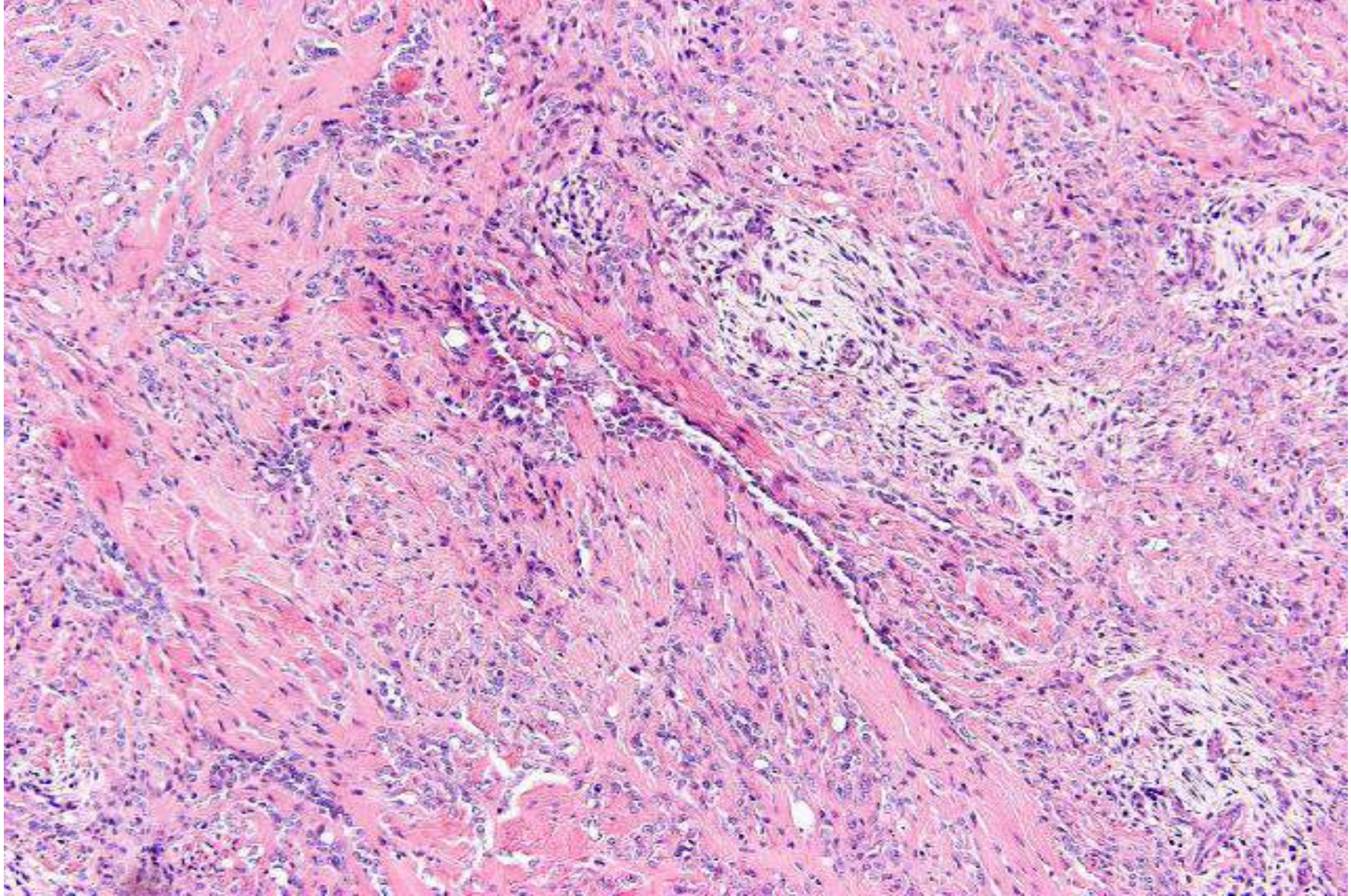


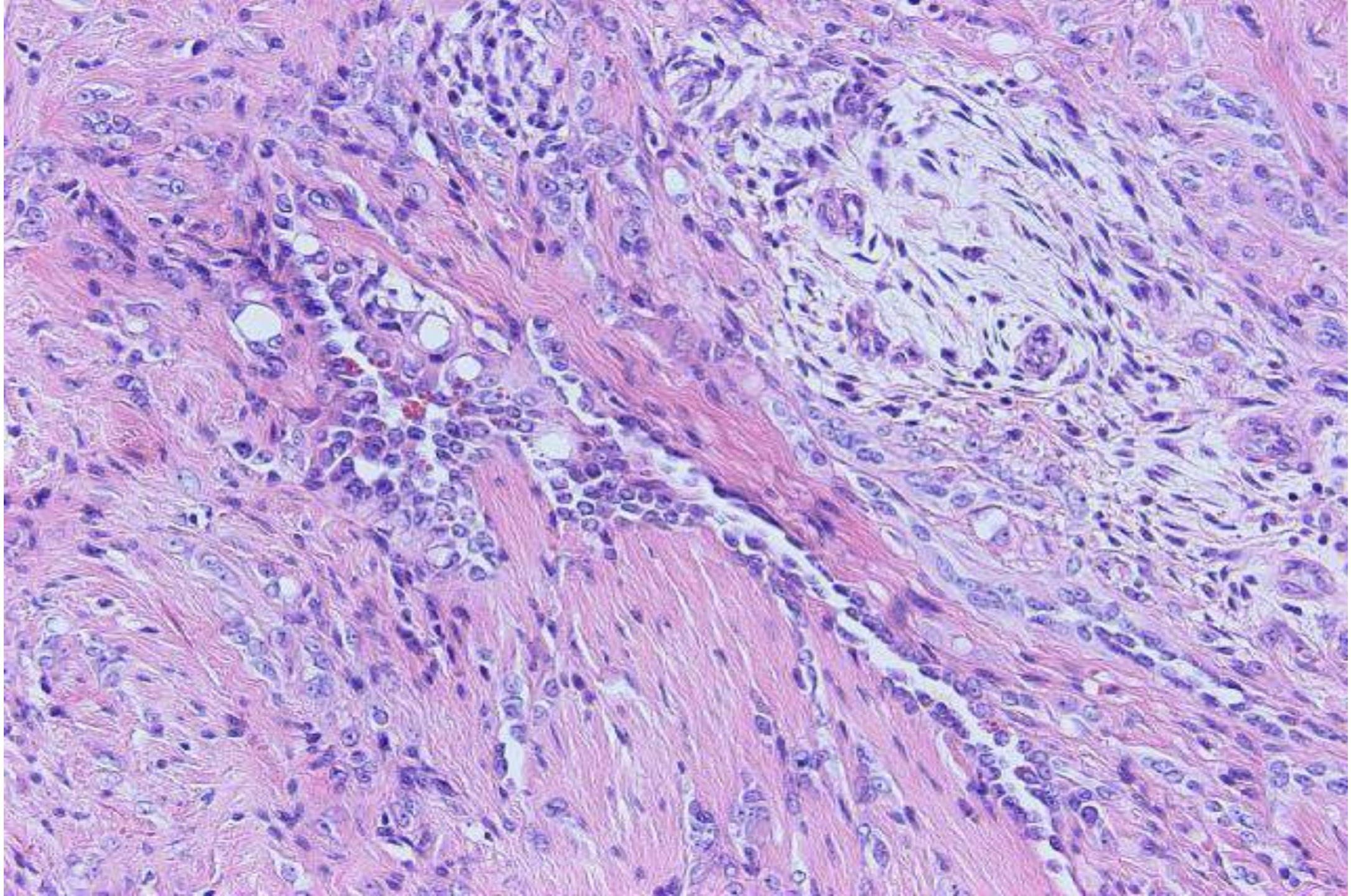


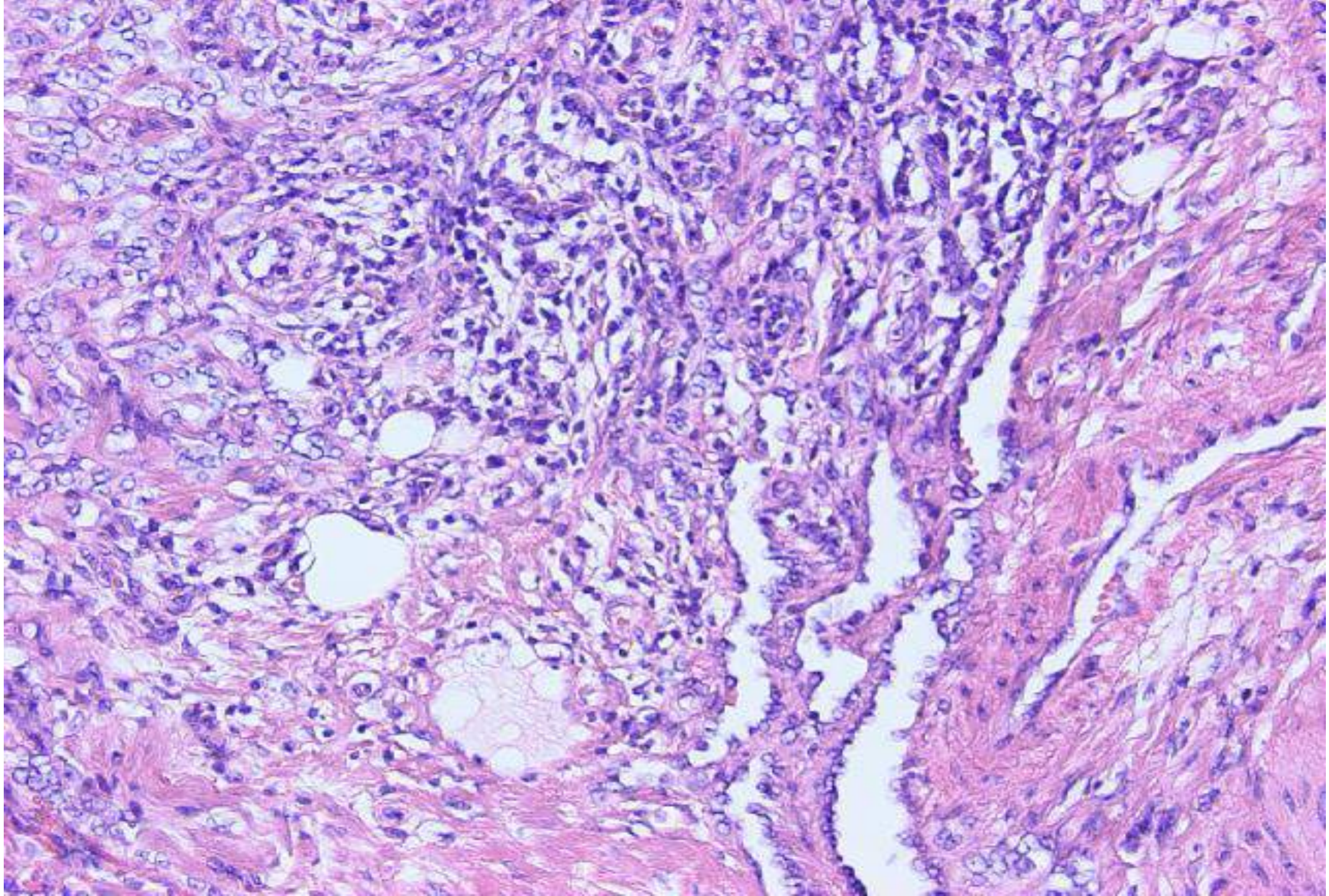












Composite hemangioendothelioma with neuroendocrine marker expression: an aggressive variant

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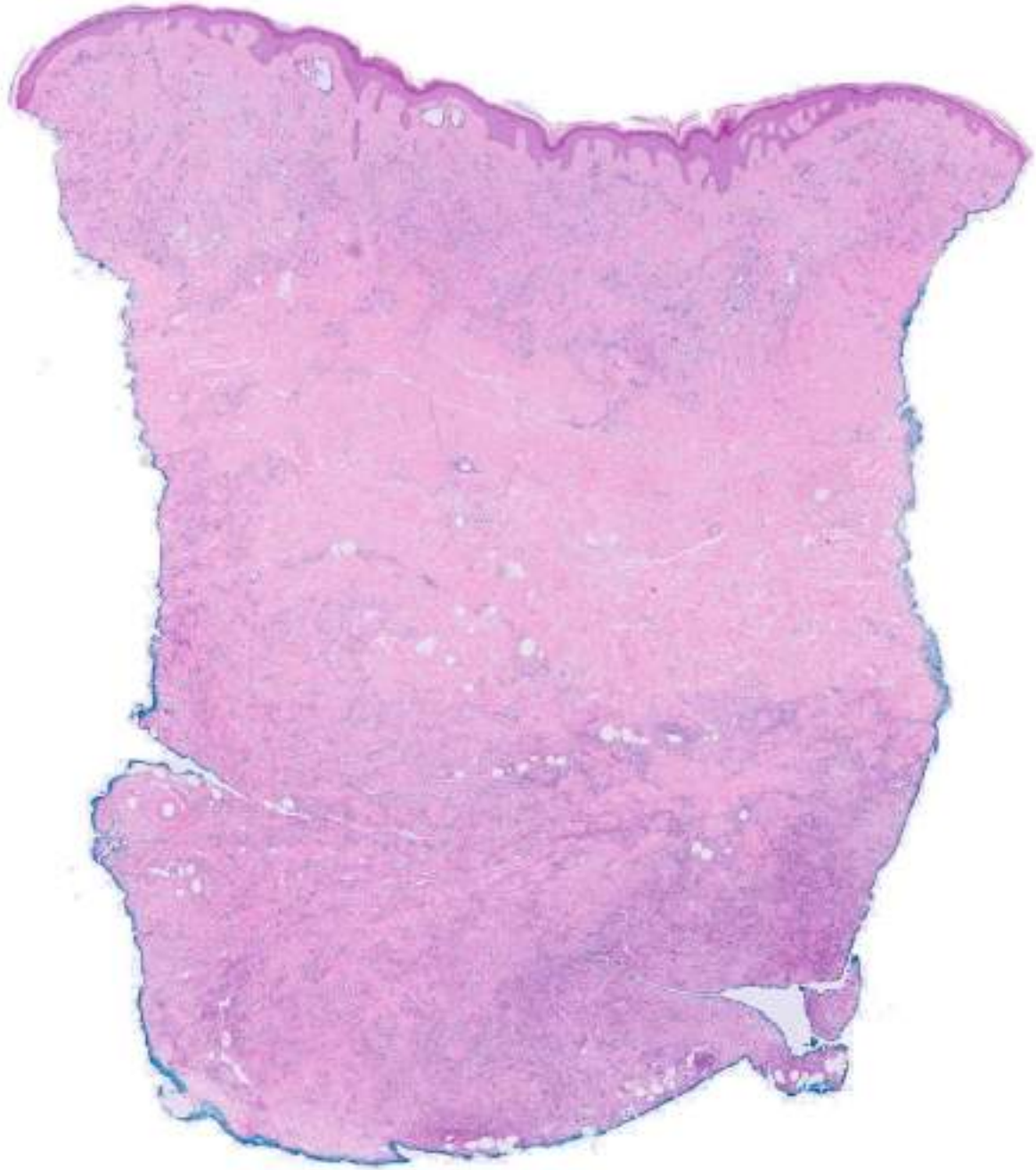
Aberrant expression of neuroendocrine markers is extremely rare in endothelial neoplasms, with only a single report describing three cases. Although originally classified as conventional angiosarcoma, further assessment of these tumors revealed a strikingly composite morphology composed of retiform and epithelioid elements reminiscent of composite hemangioendothelioma, a rare subtype of hemangioendothelioma. To further investigate these findings, available materials from 11 morphologically distinctive endothelial tumors showing neuroendocrine marker expression were retrieved from our archives. Immunohistochemistry for CD31, CD34, FLI-1, synaptophysin, chromogranin, D2-40, ERG, keratin (OSCAR), and CAMTA1 was performed. Total RNA from five cases were extracted and subjected to whole transcriptome sequencing. Clinical follow-up was obtained. These tumors were found to arise in five males and six females in patients from 9 to 55 years in age (median 47 years). They arose both in superficial (wrist, ankle, scalp, hip, and foot) and deep (periaortic tissues, C5 vertebra, pulmonary vein, and liver) locations. All contained elongated, retiform vascular channels lined by hyperchromatic 'hobnail' endothelial cells and a solid growth of uniform epithelioid cells reminiscent of epithelioid hemangioendothelioma. Hemangioma-like foci also lined by hobnail endothelial cells were frequently present. Mitotic activity was typically < 1/10 HPF, and necrosis or areas of conventional angiosarcoma was absent. The results of immunohistochemistry were: CD31 (10/10), FLI-1 (10/10), ERG (9/9), CD34 (5/10), D2-40 (7/10), synaptophysin (11/11), chromogranin A (1/11), CD56 (5/11), keratin (0/11), and CAMTA1 (0/6). Sequencing analysis showed one case with *PTBP1-MAML2* and one case with *EPC1-PHC2* fusion transcripts; fusion transcripts were not identified in the remaining cases. Follow-up (8 cases) revealed local recurrence in one patient and metastatic spread in four individuals (bone, lung, liver, and brain). One person died of disease. Although the morphological features of these tumors are characteristic of composite hemangioendothelioma, this distinctive subset with neuroendocrine differentiation more often involves deep locations and displays more aggressive behavior than typically described in other cases of composite hemangioendothelioma.
Modern Pathology (2017) **30**, 1589–1602; doi:10.1038/modpathol.2017.83; published online 21 July 2017

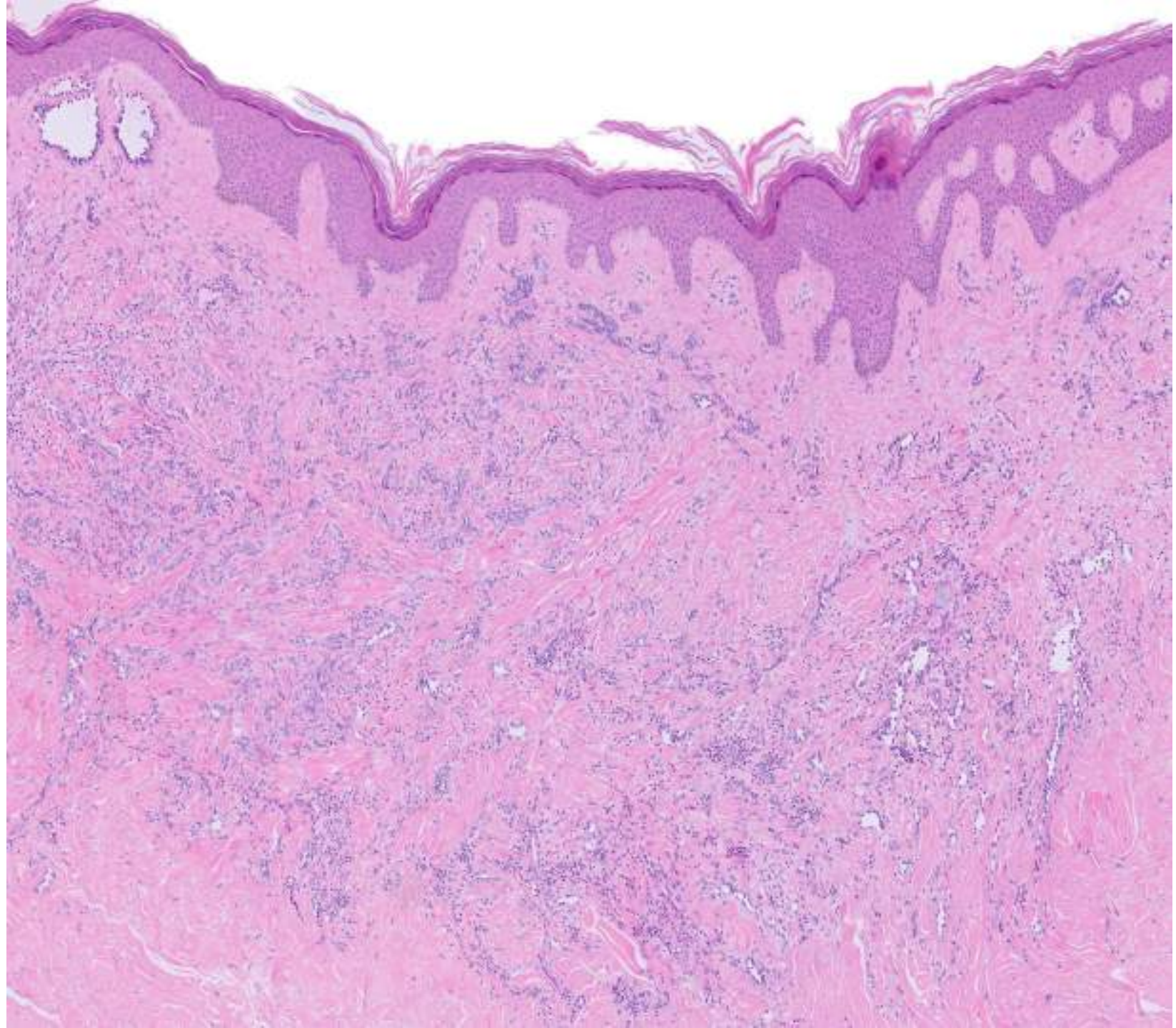
COMPOSITE HAEMANGIOENDOTHELIOMA WITH EXPRESION OF NEUROENDOCRE MARKERS
CLINICAL FEATURES

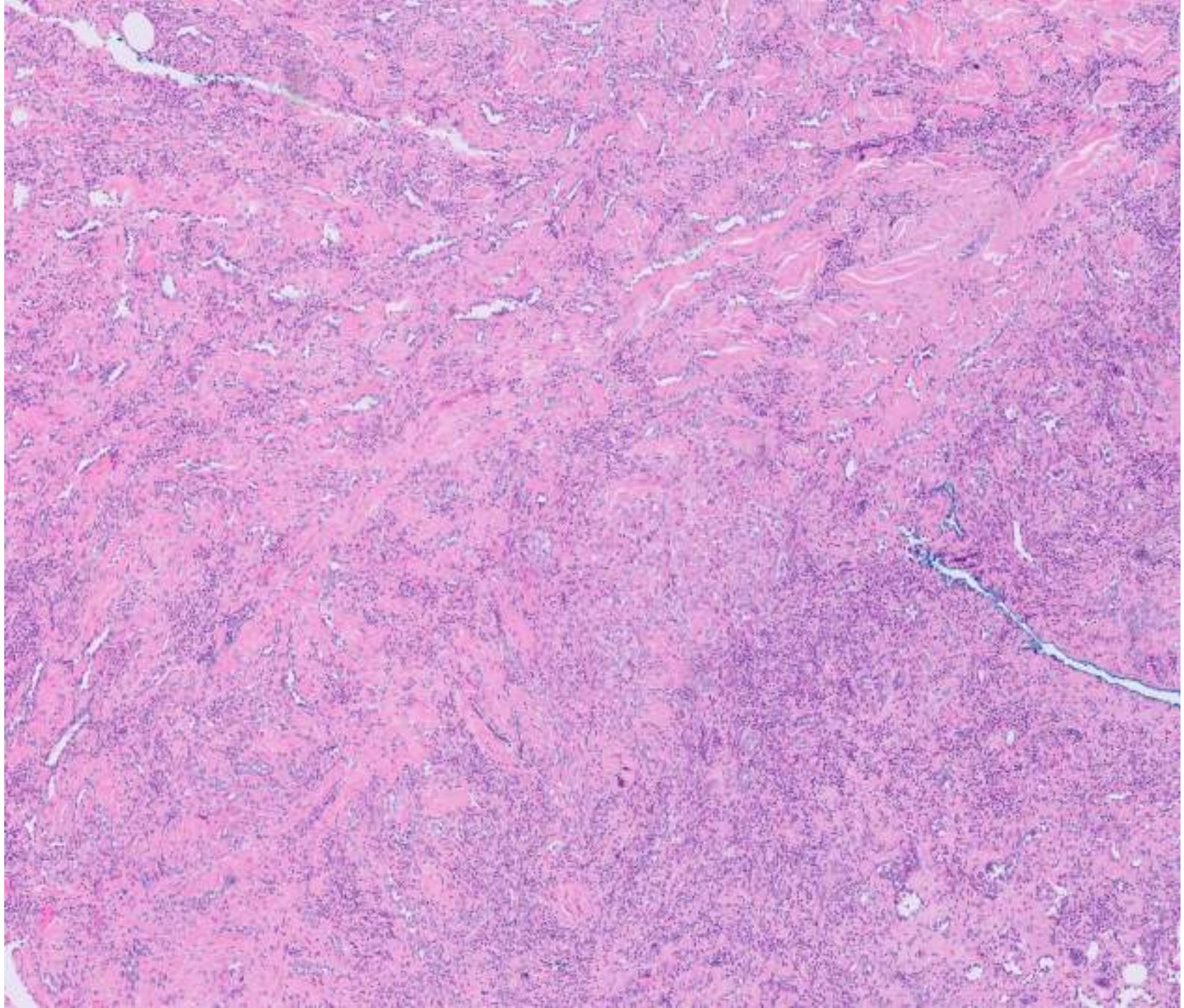
- **11 cases**
- **6M, 5H**
- **Age range: 9-55 (median: 47)**
- **Four cutaneous/soft tissue and seven in internal organs**
- **Follow-up: 8 cases, local recurrence 1, bone, lung, liver and brain metastasis in 4, one died of disease**
- **Four cases in our series: all female, on tongue, right thigh, right arm and back.**

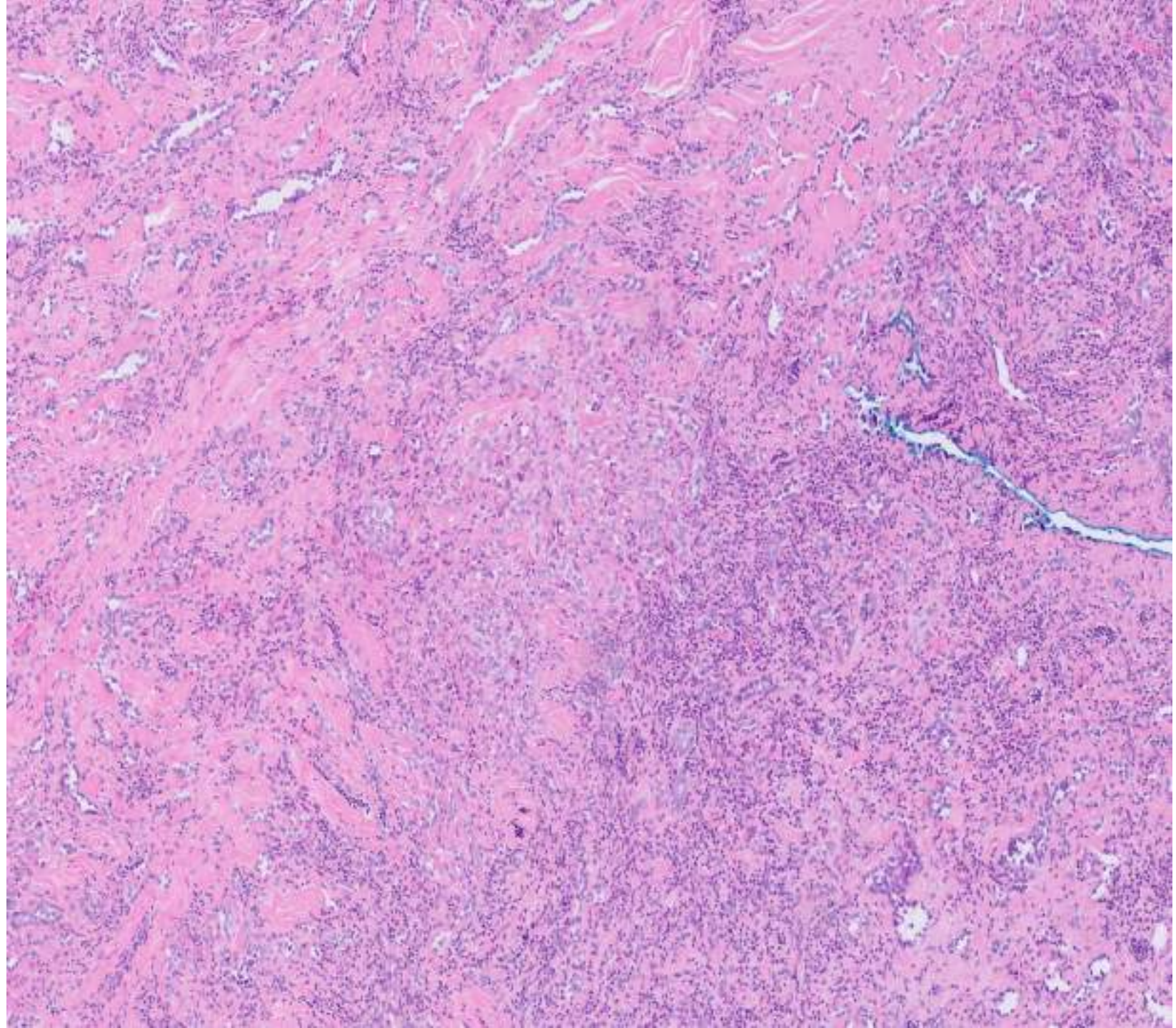
COMPOSITE HAEMANGIOENDOTHELIOMA WITH EXPRESION OF NEUROENDOCRE MARKERS -HISTOLOGICAL FEATURES-

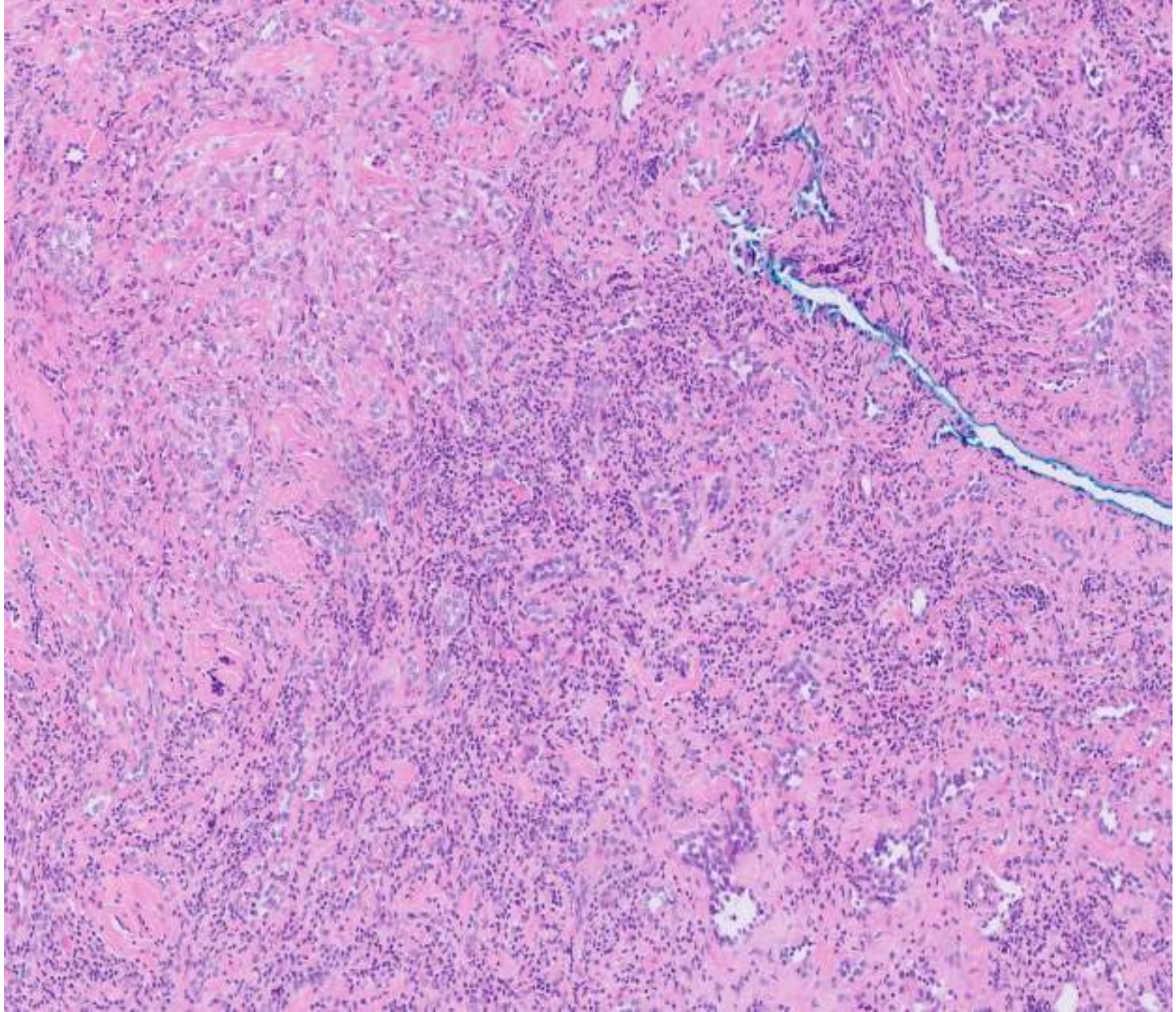
- **Poorly circumscribed**
- **Infiltrative**
- **Dermis and subcutis**
- **Two components: elongated thin-walled vascular channels, lined by a single layer of hobnail endotelial cells (retiform haemangioeendothelioma) and solid aggregates of epithelioid cells with intracytoplasmic lumina**
- **Rare haemangioma-like areas**
- **Low-mitotic activity**
- **Absence of high grade áreas**
- **CD31/ERG/FLI: +. Variable positivity for CD34 and D2-40. Usually positive for synaptophysin, rarely positive for chromogranin**

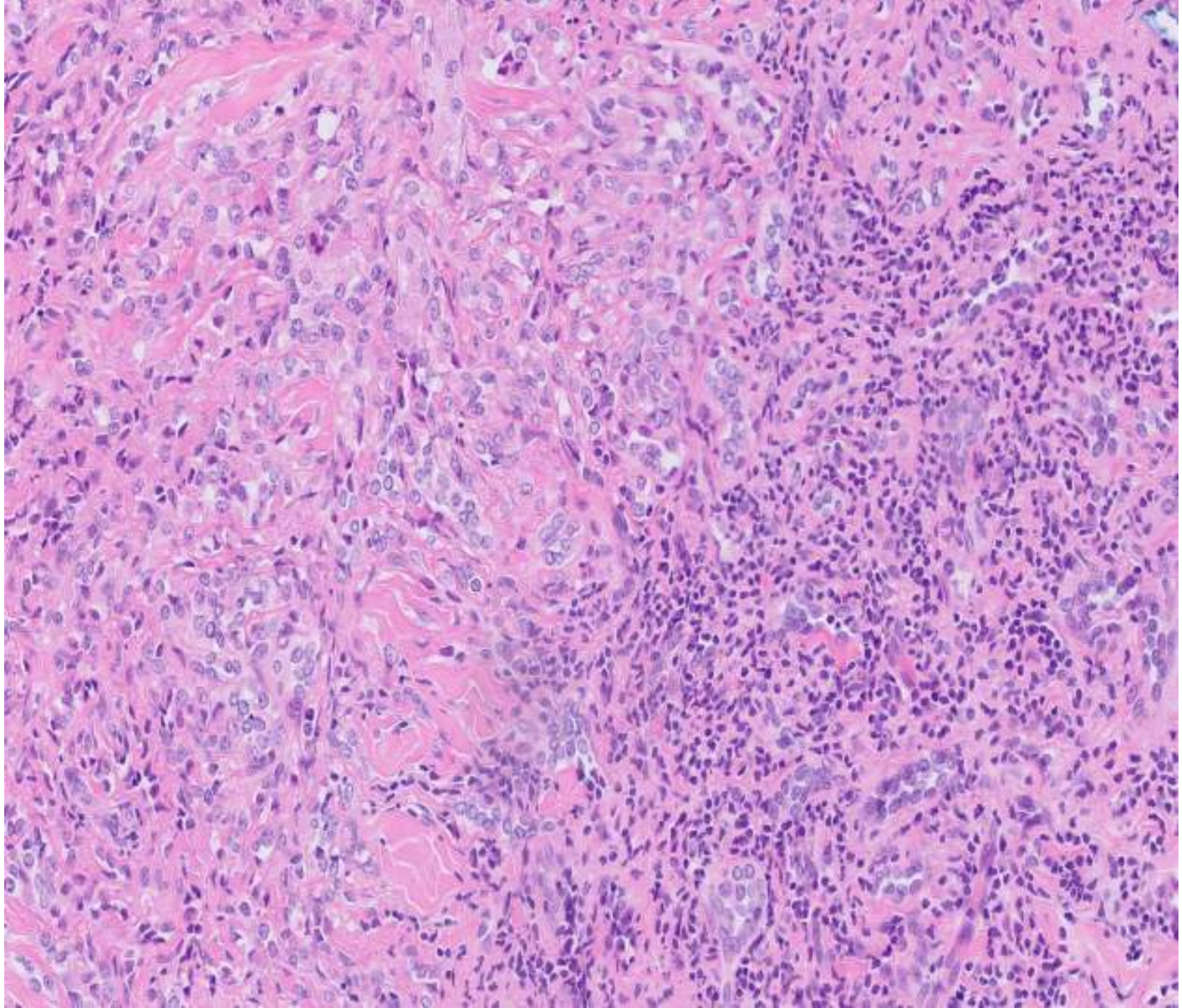




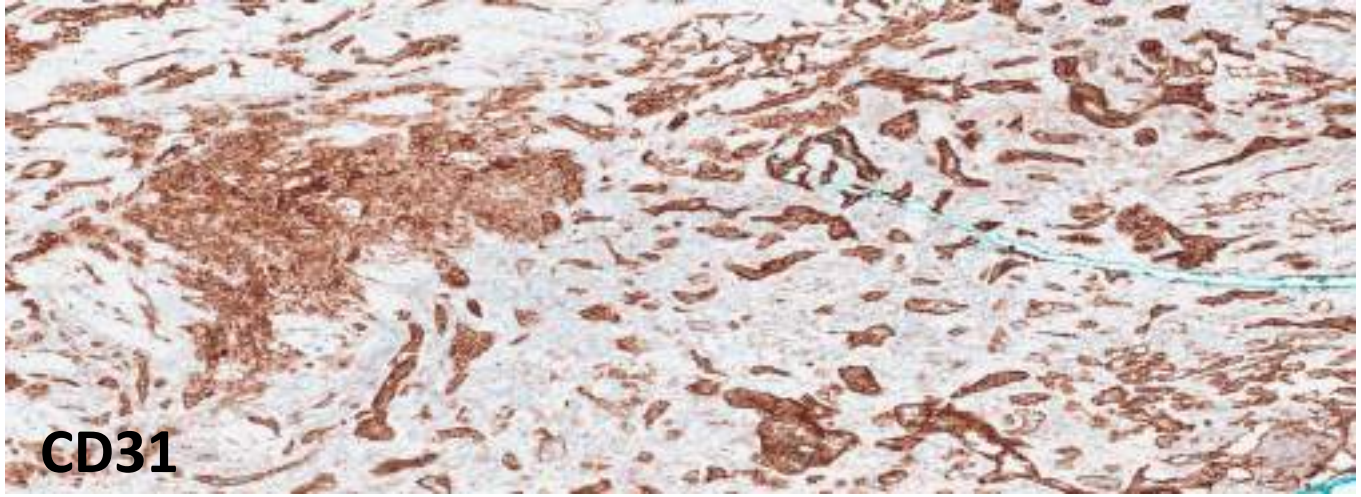









CD31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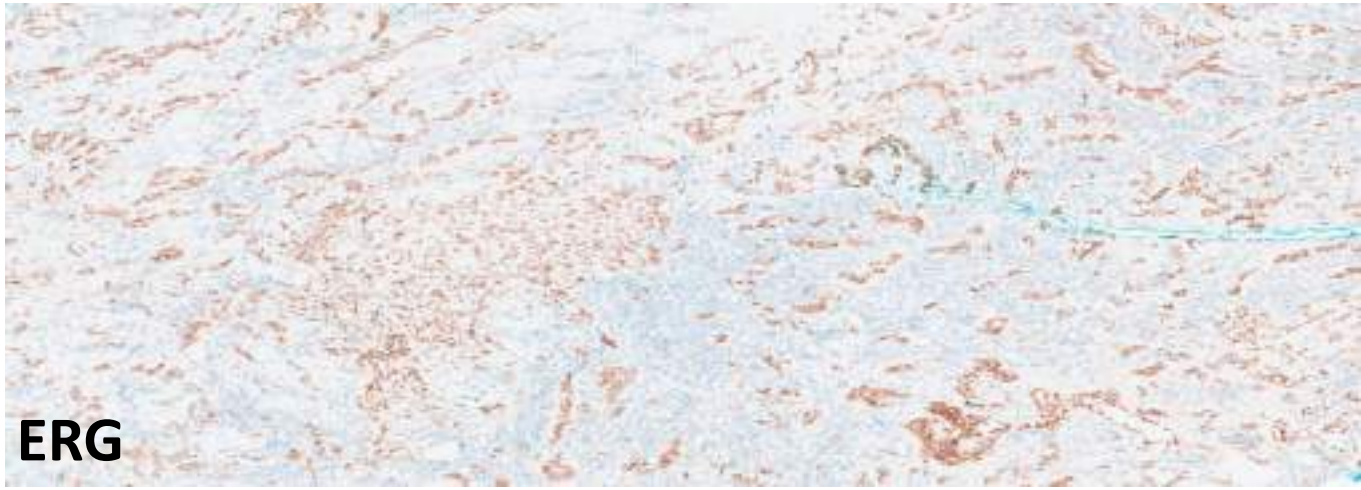
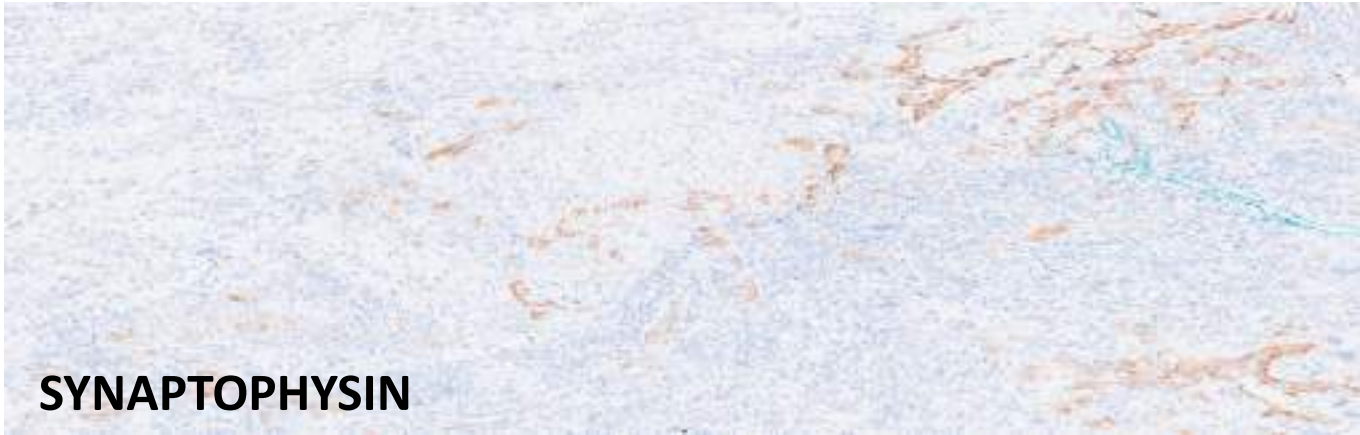
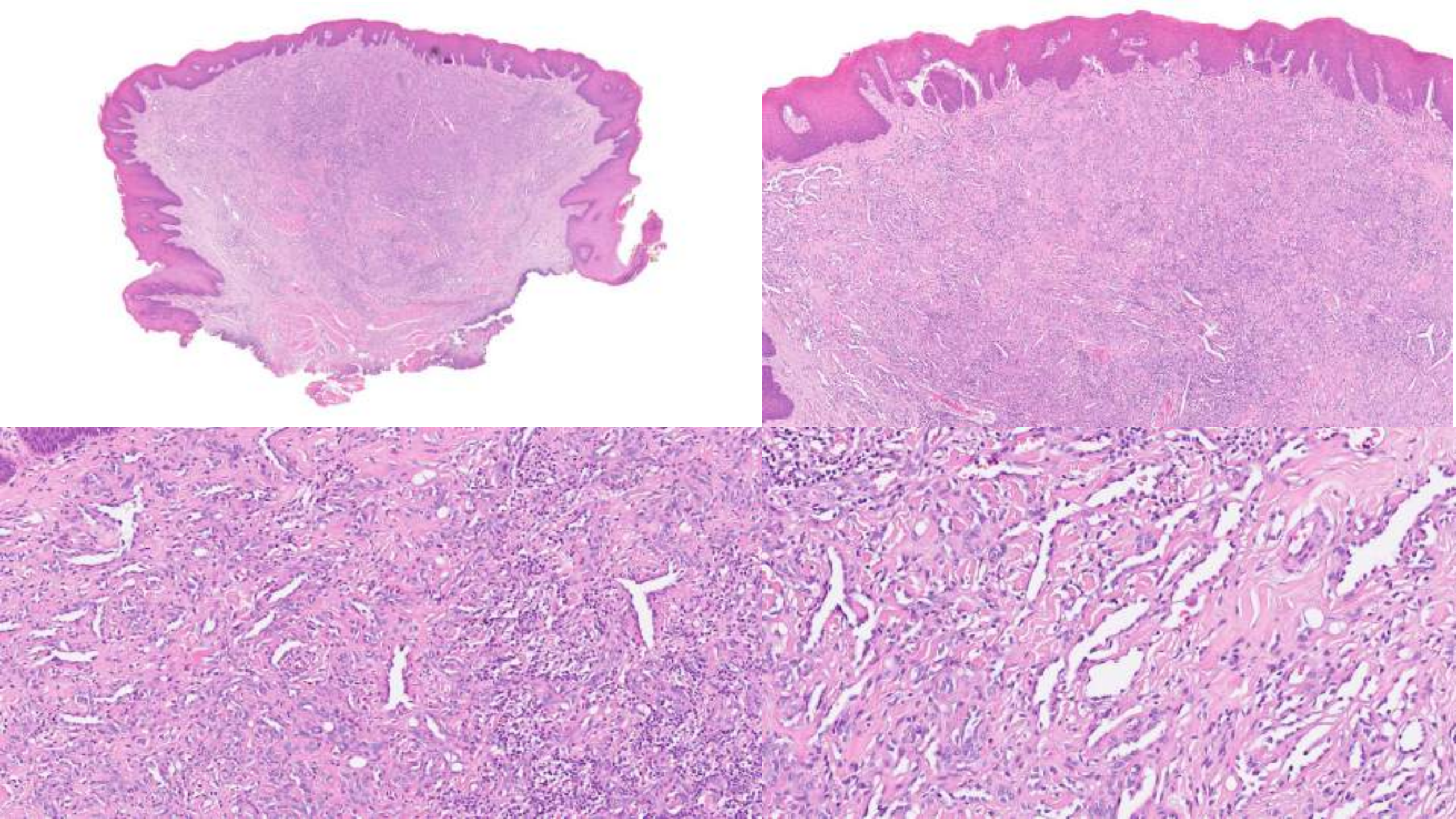
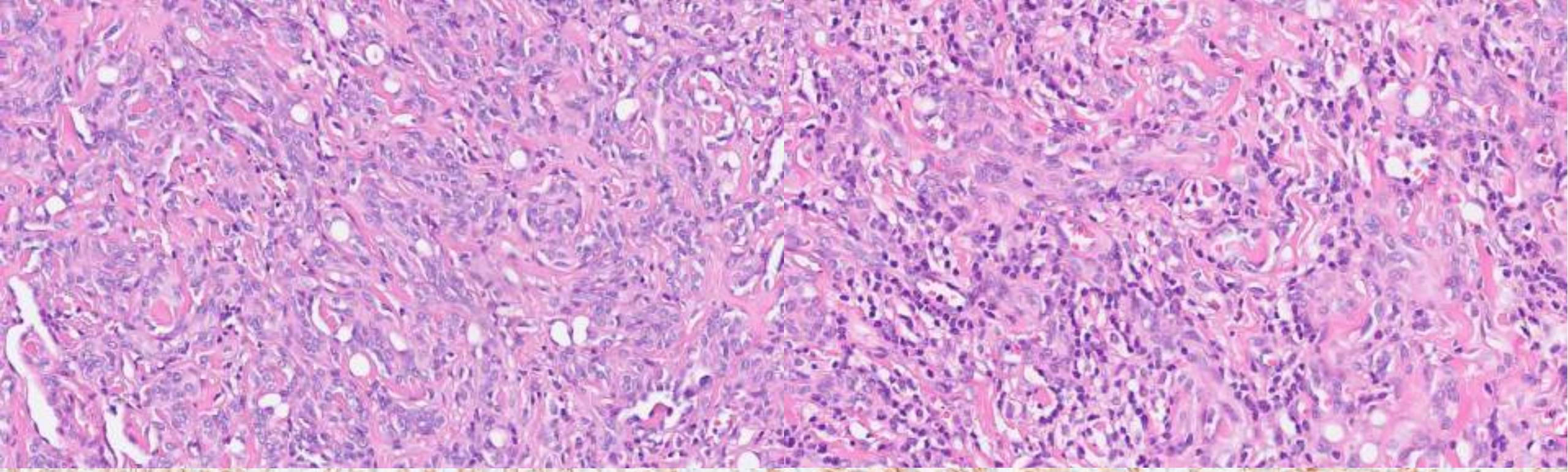
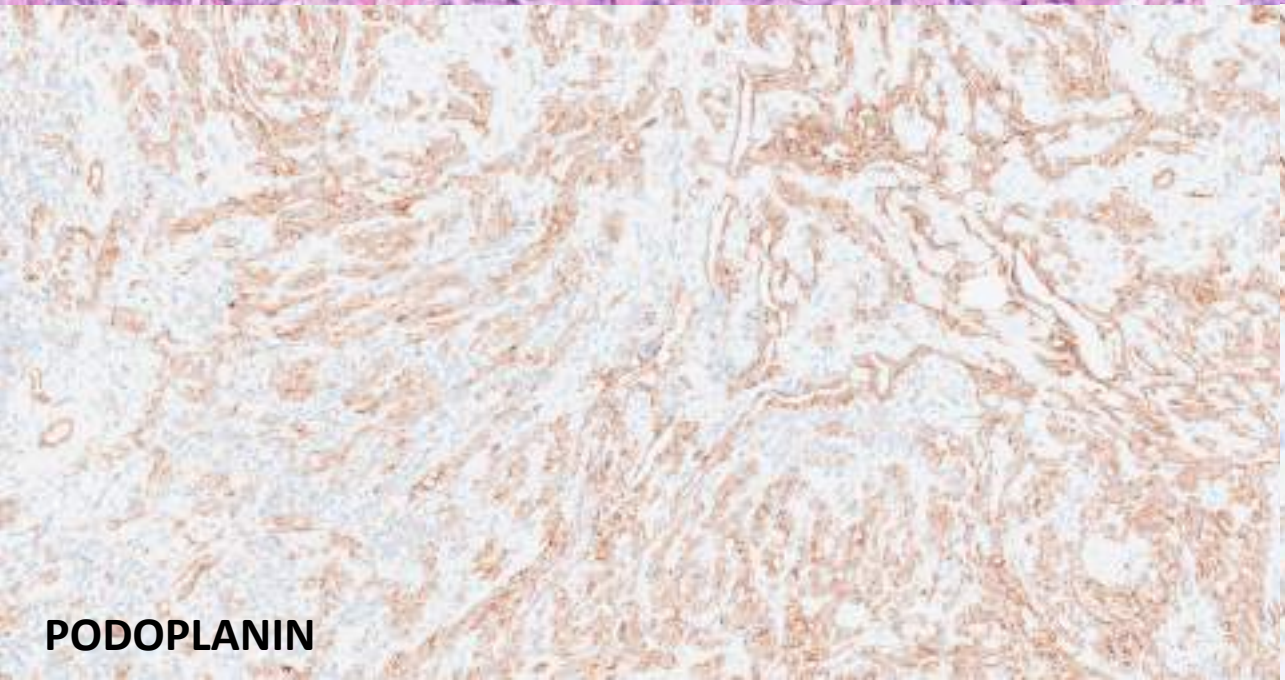

ERG


SYNAPTOPHYSIN



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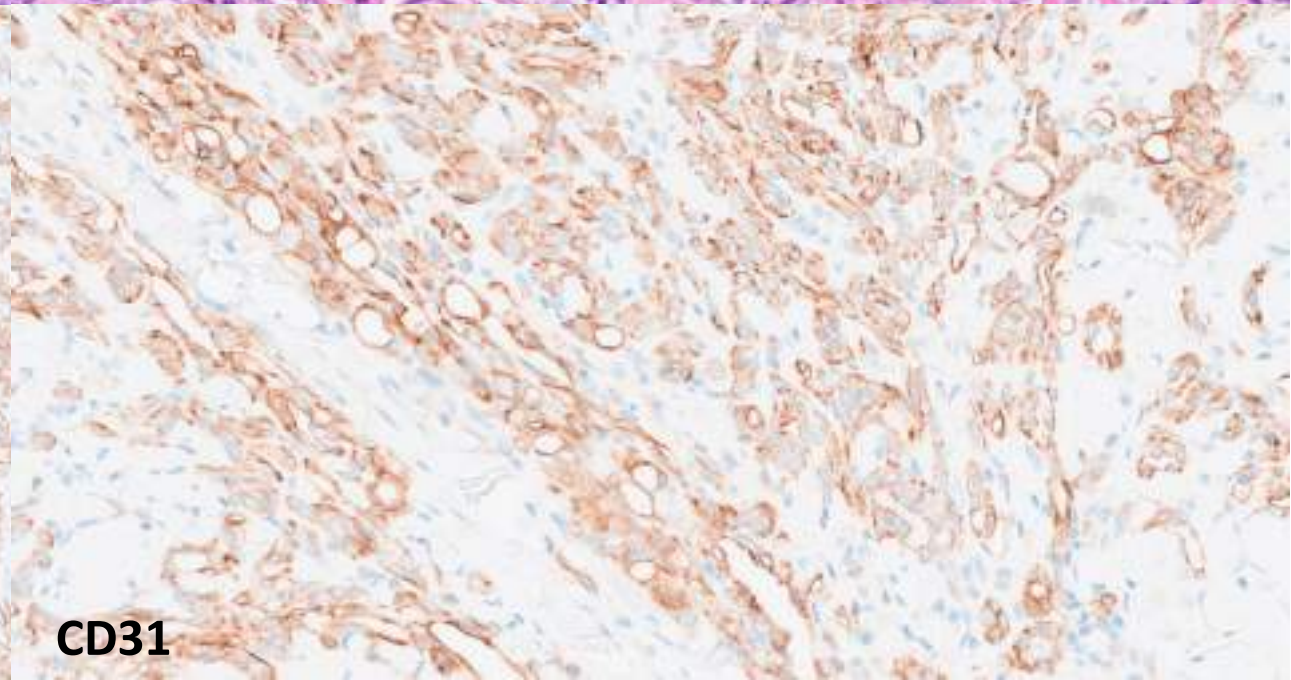
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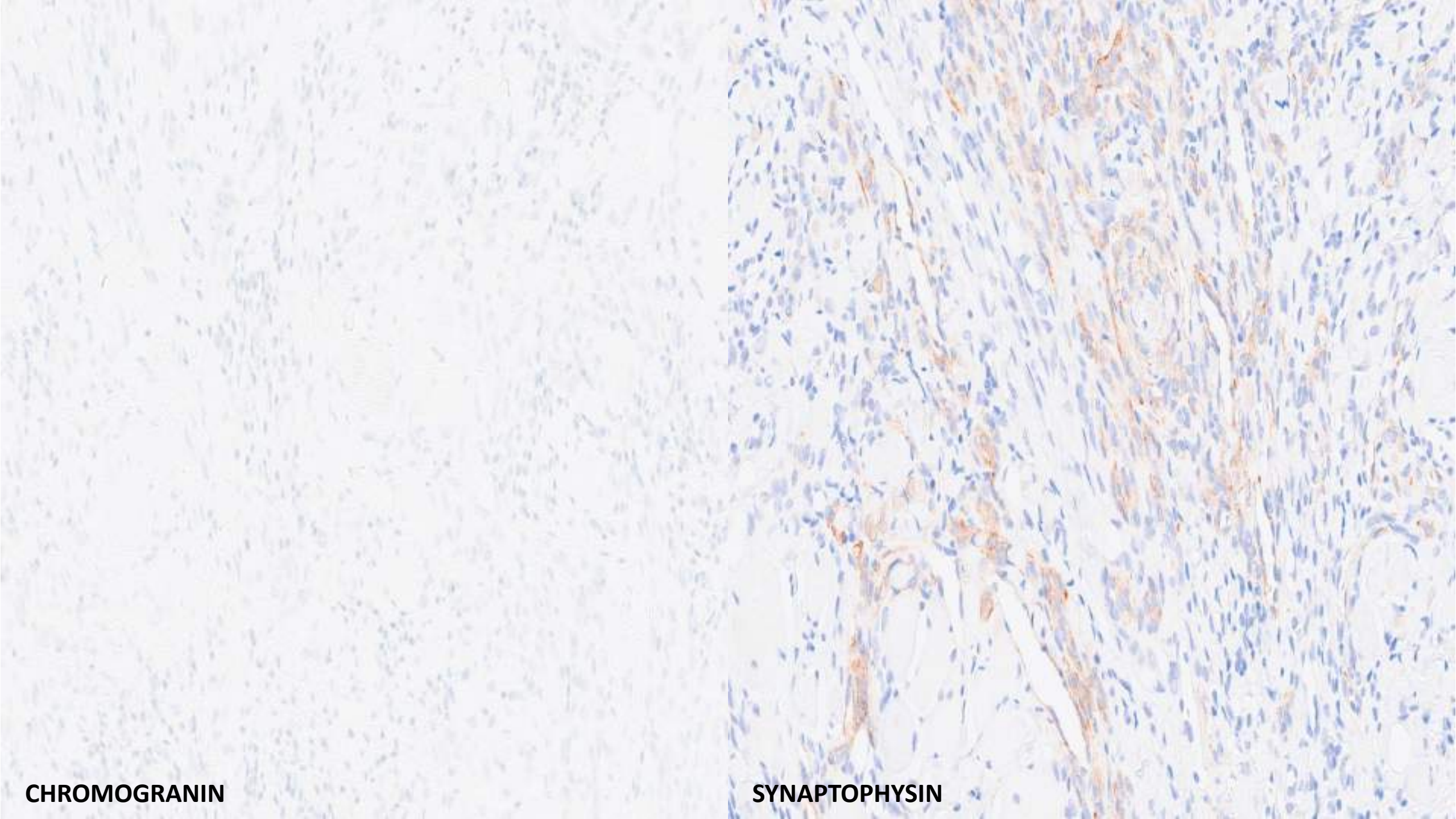
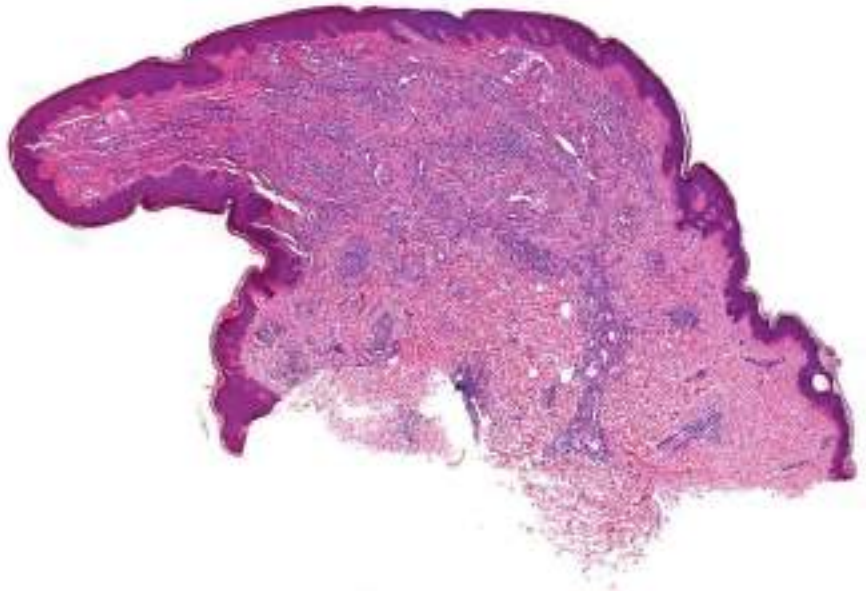
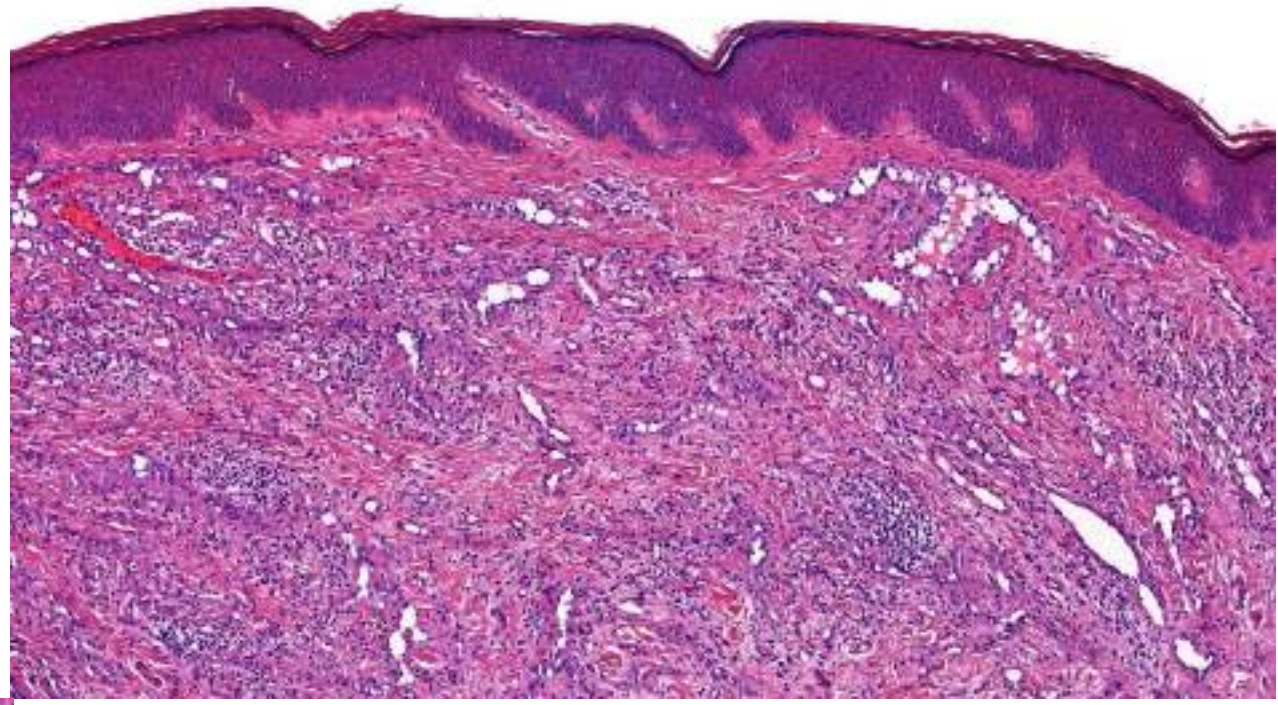
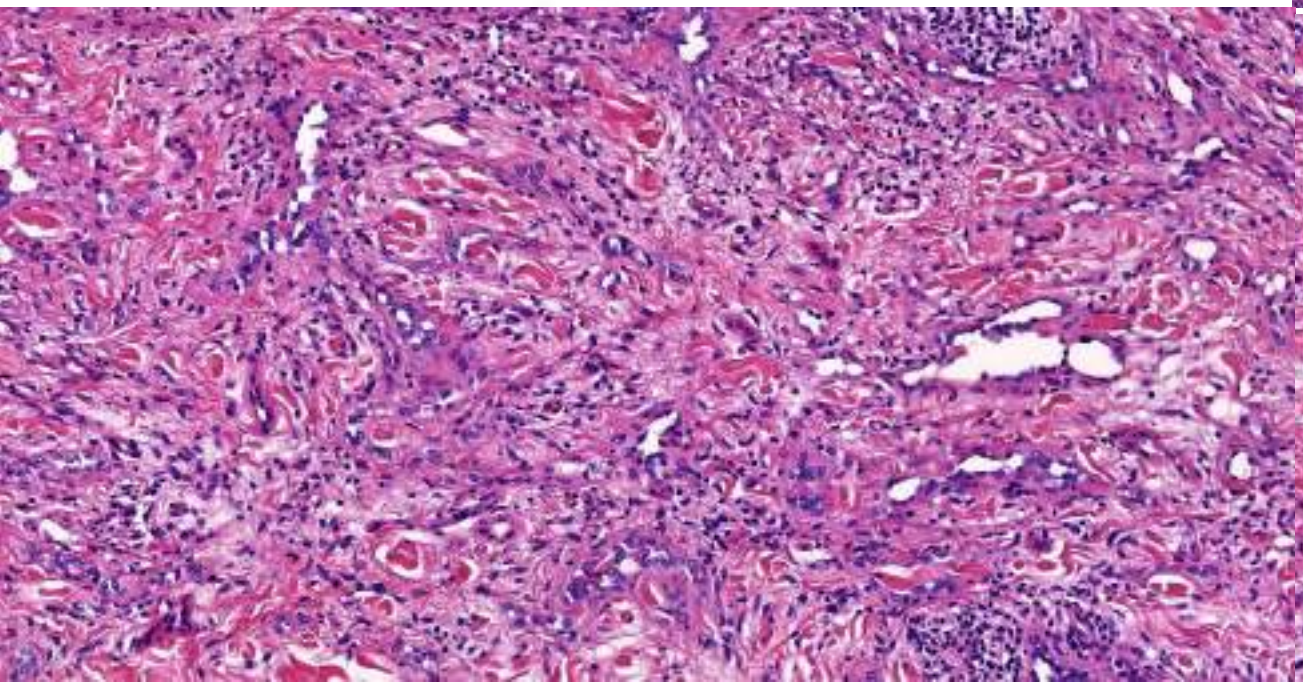


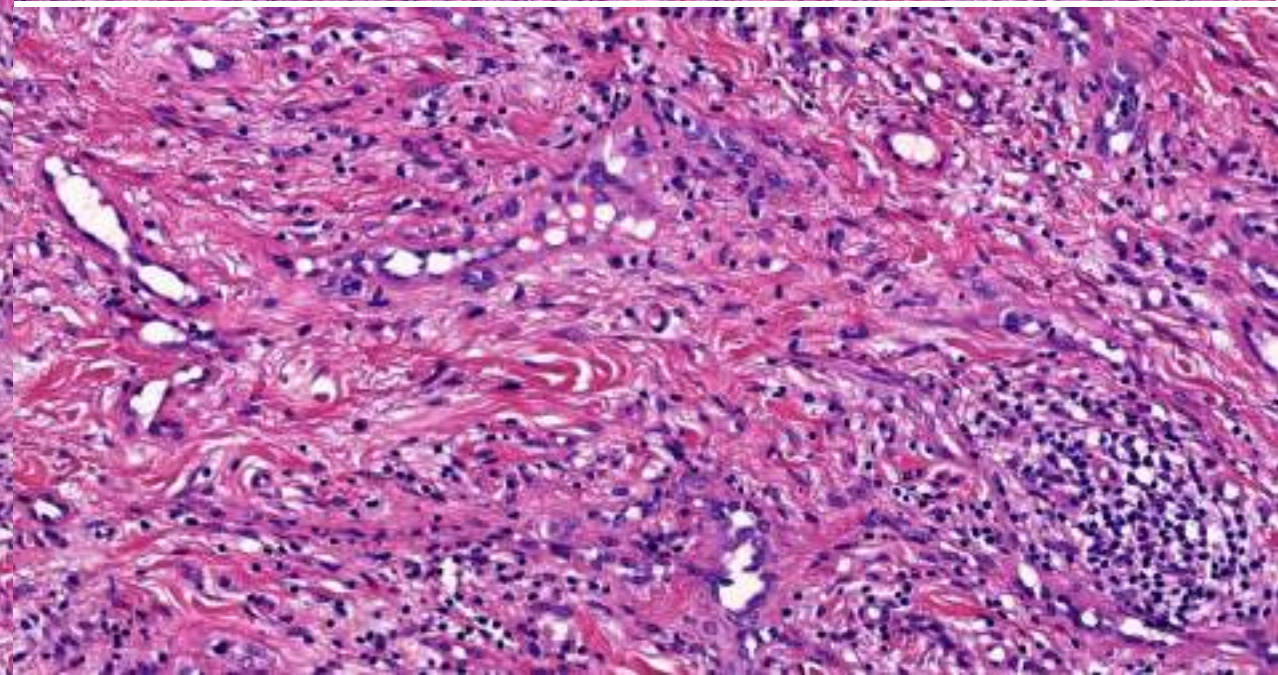
CHROMOGRANIN

SYNAPTOPHYSIN









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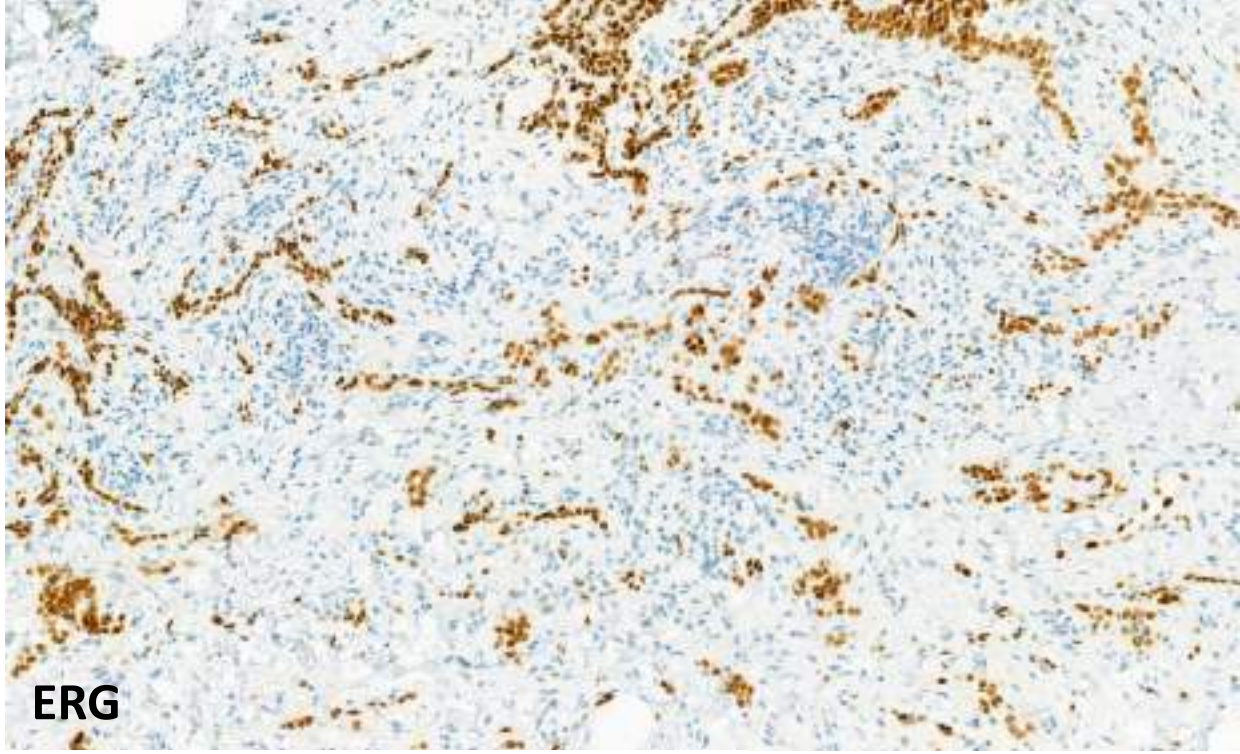

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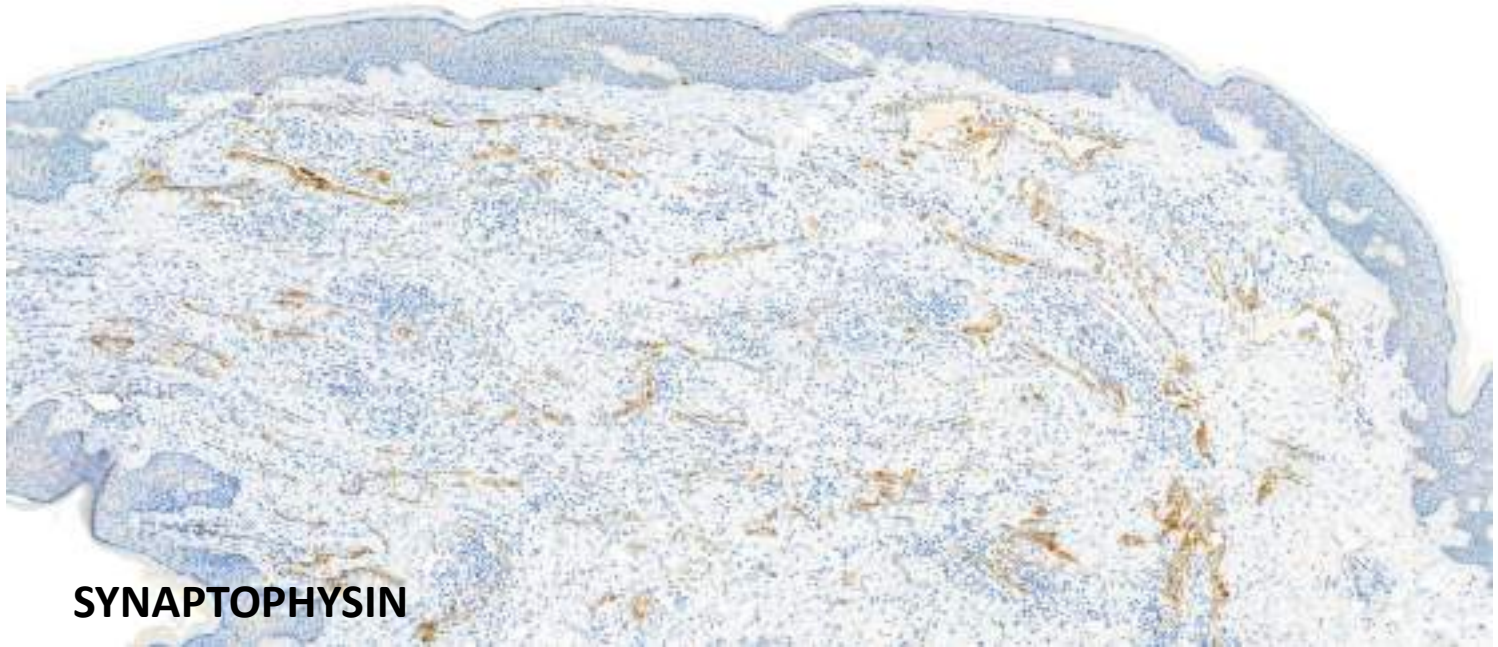

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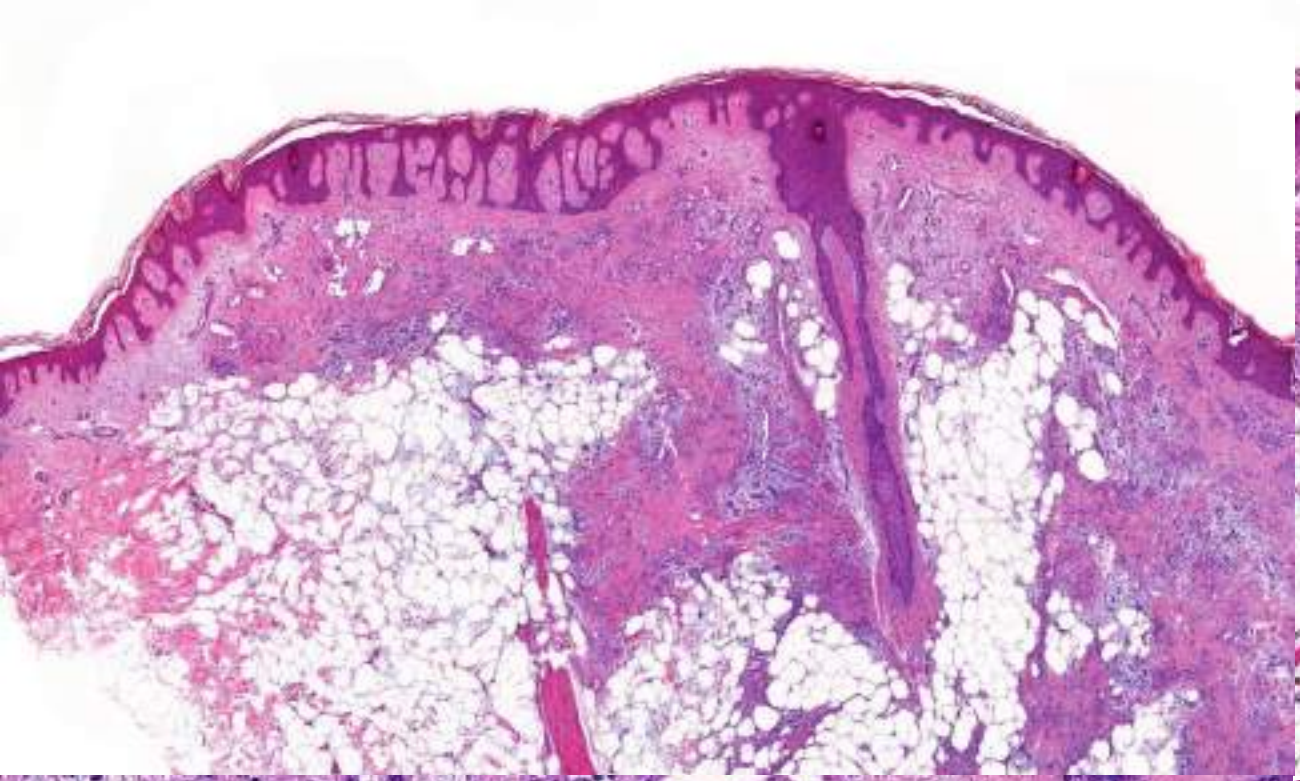
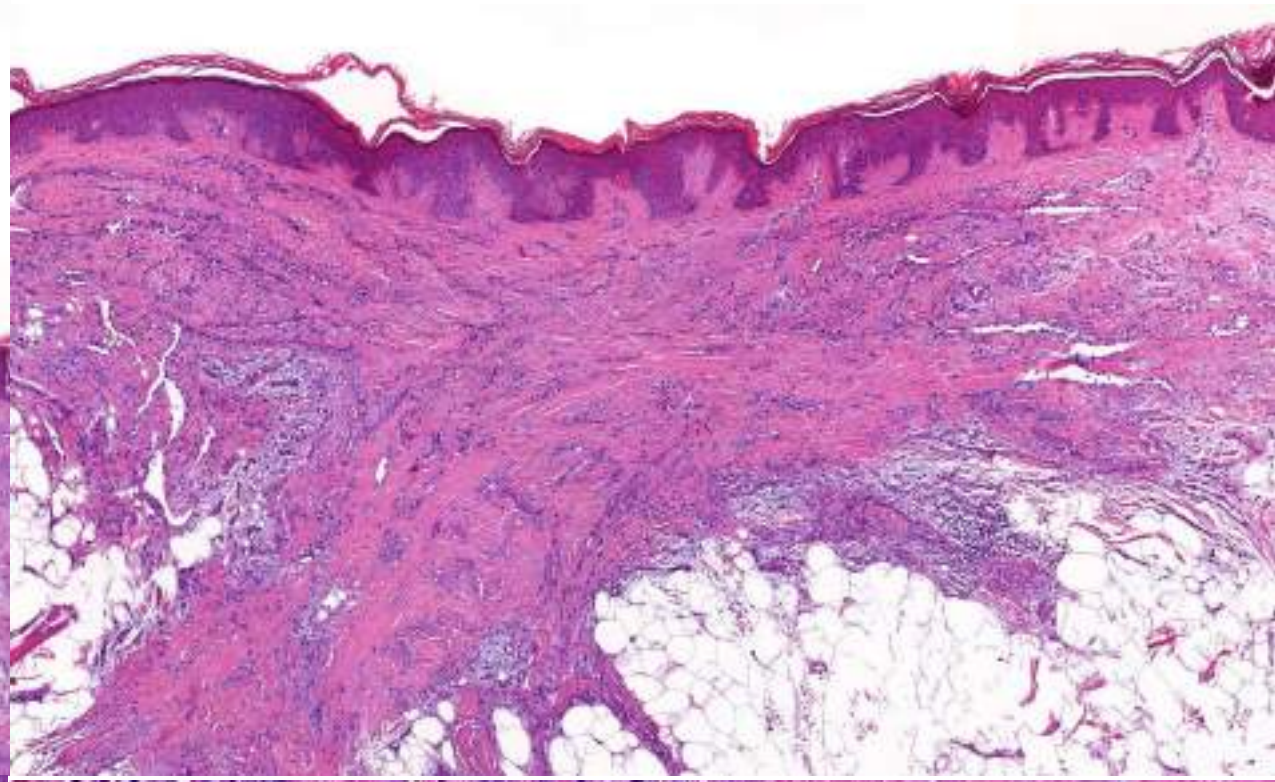
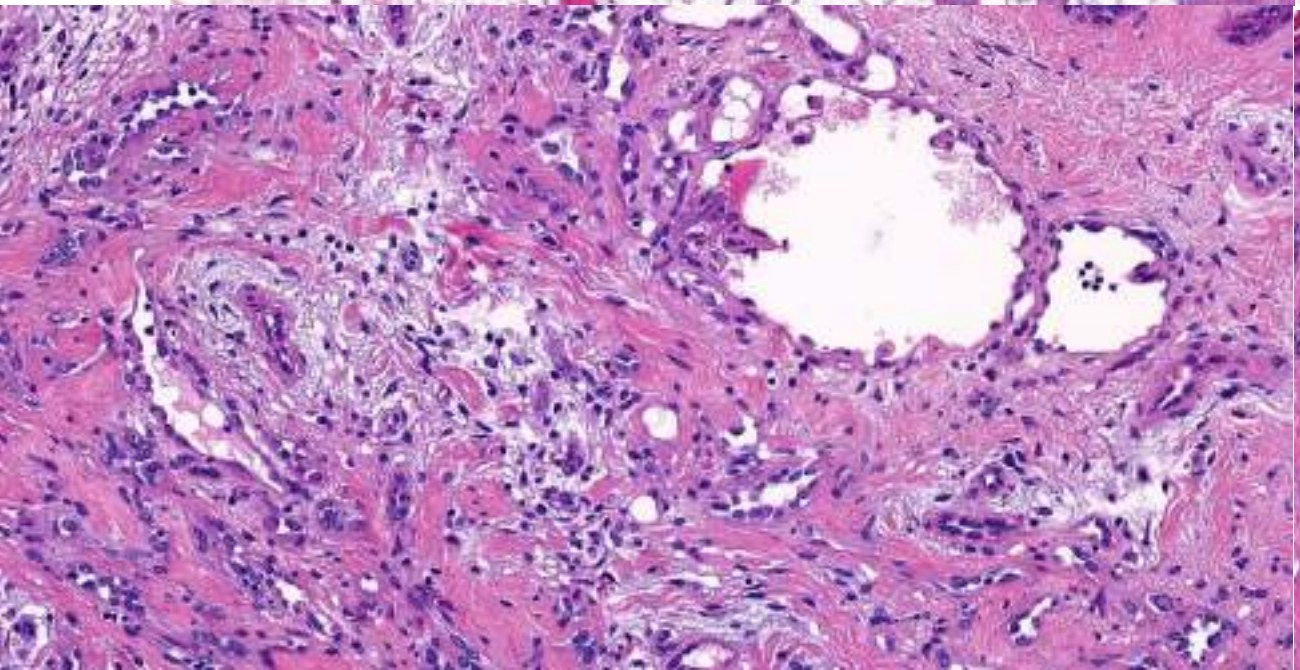
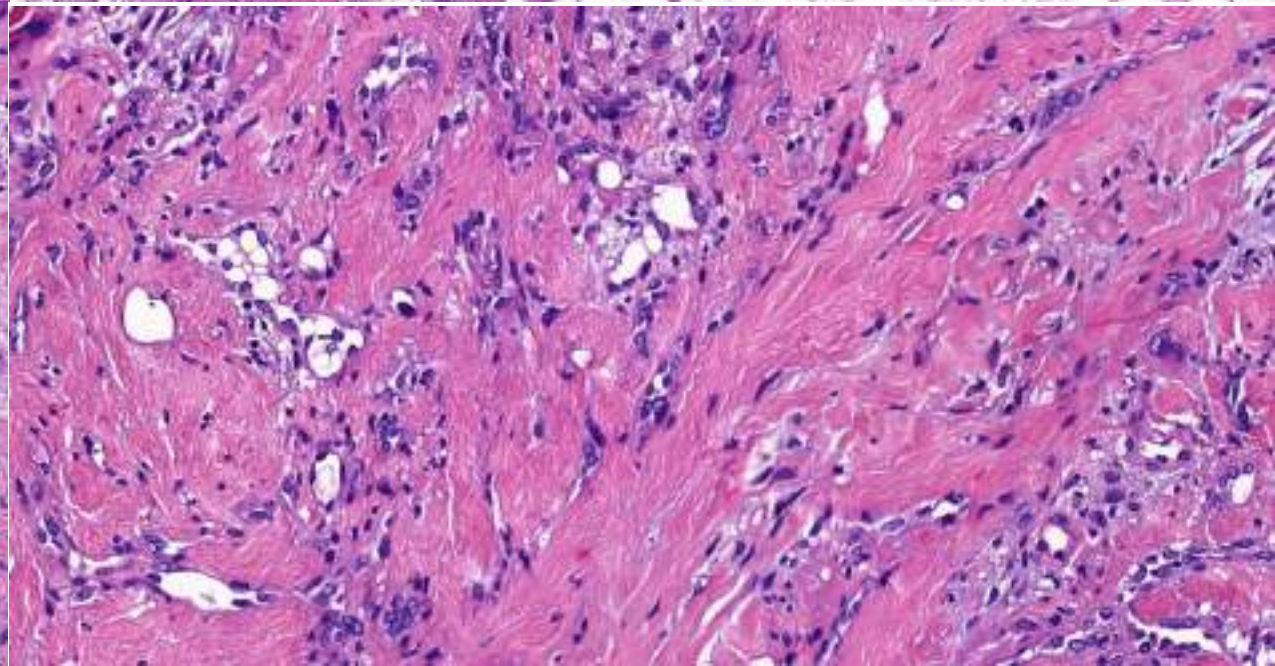

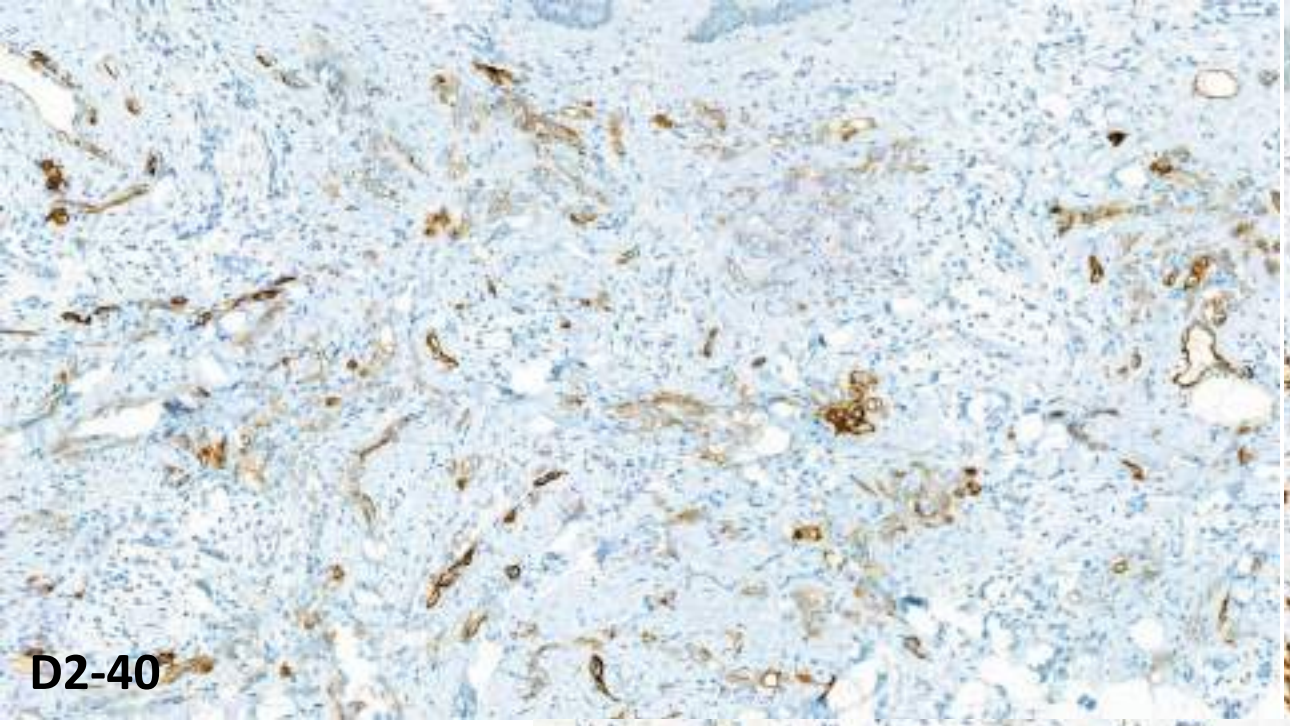
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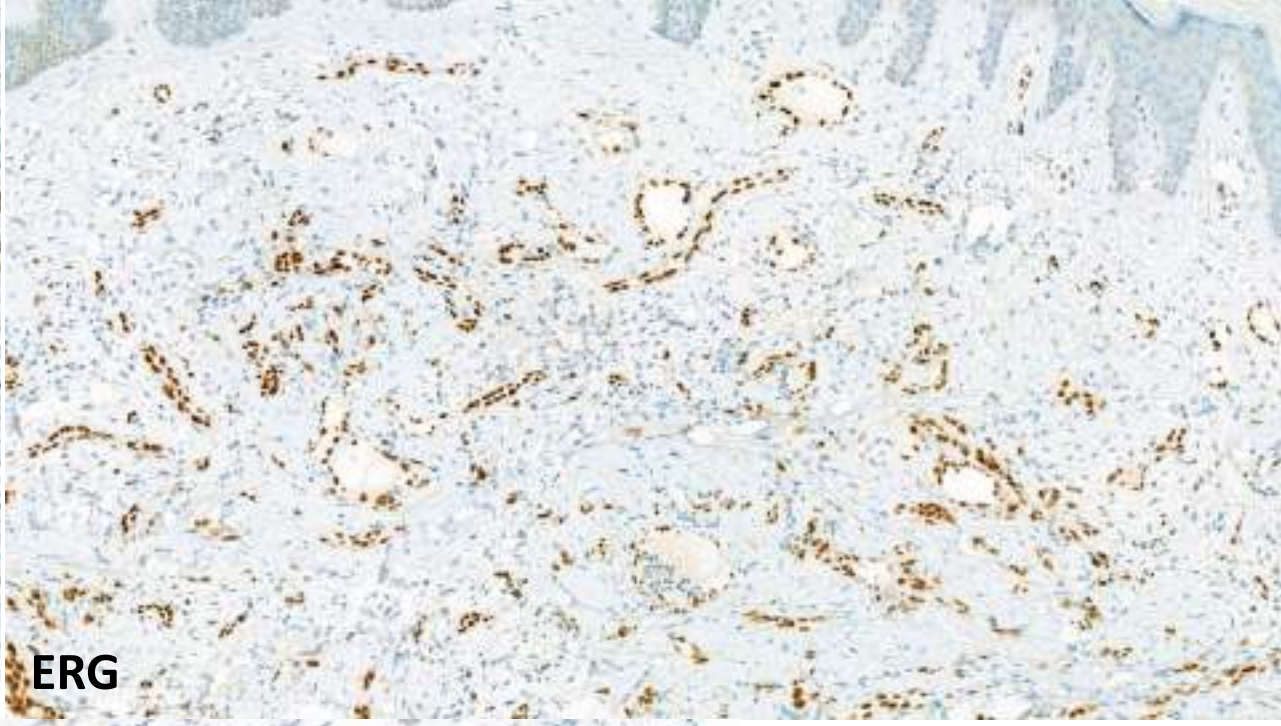
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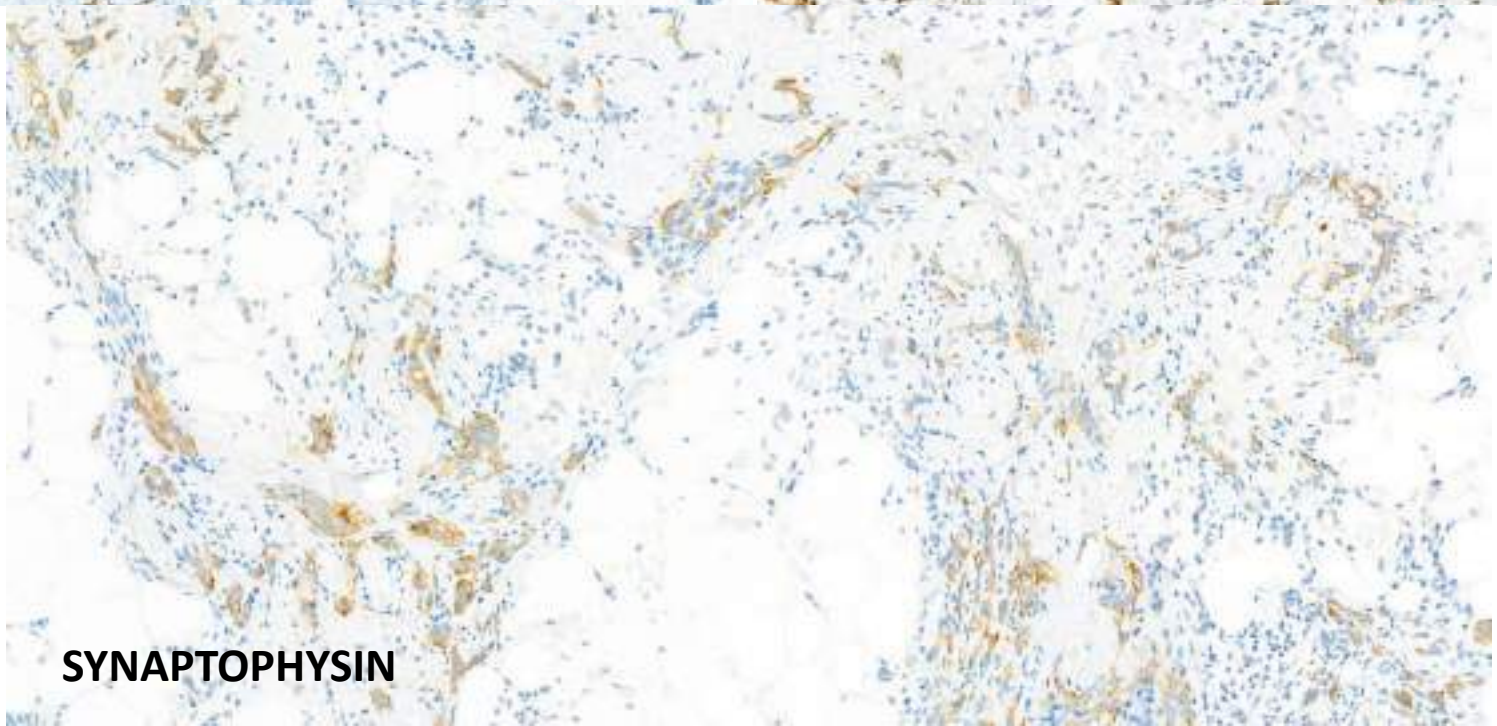

SYNAPTOPHYSIN

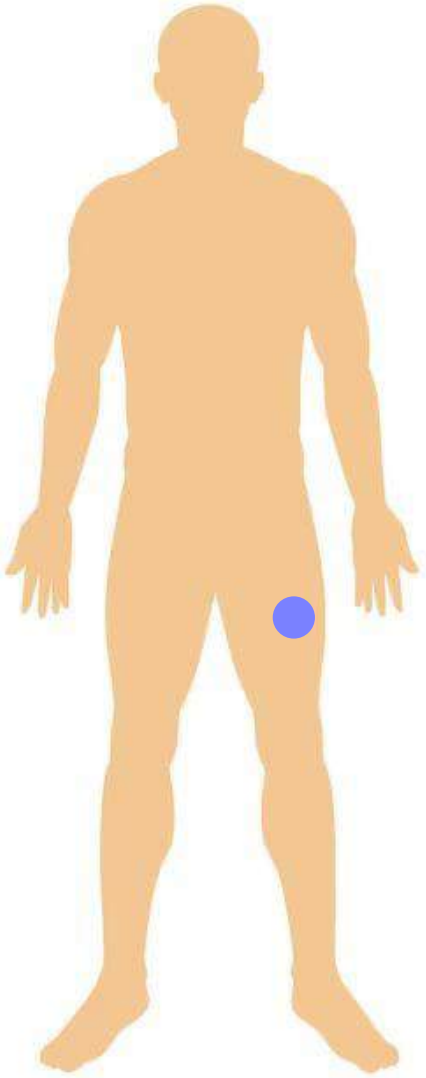
GRF23-90077

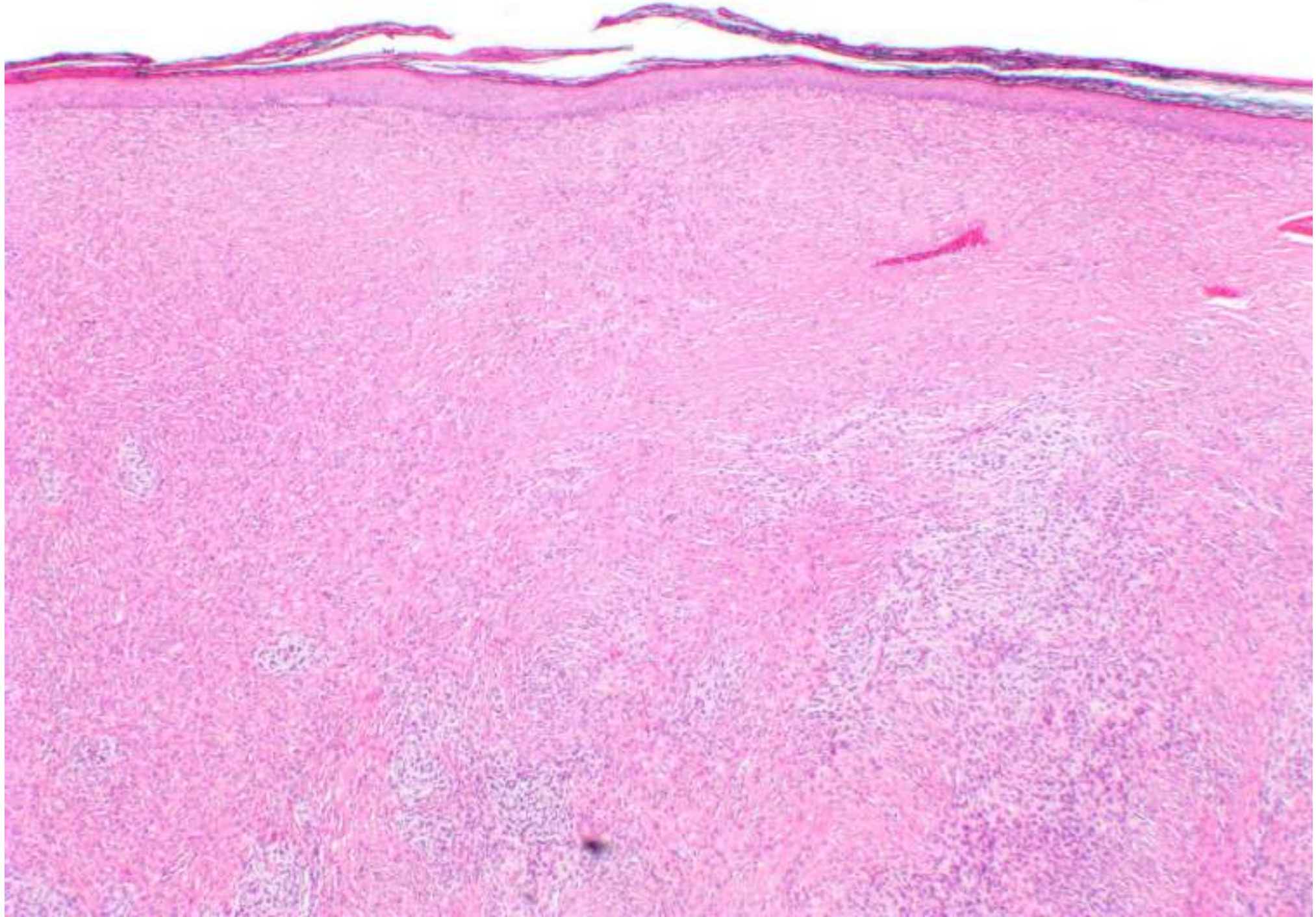
Case presentation

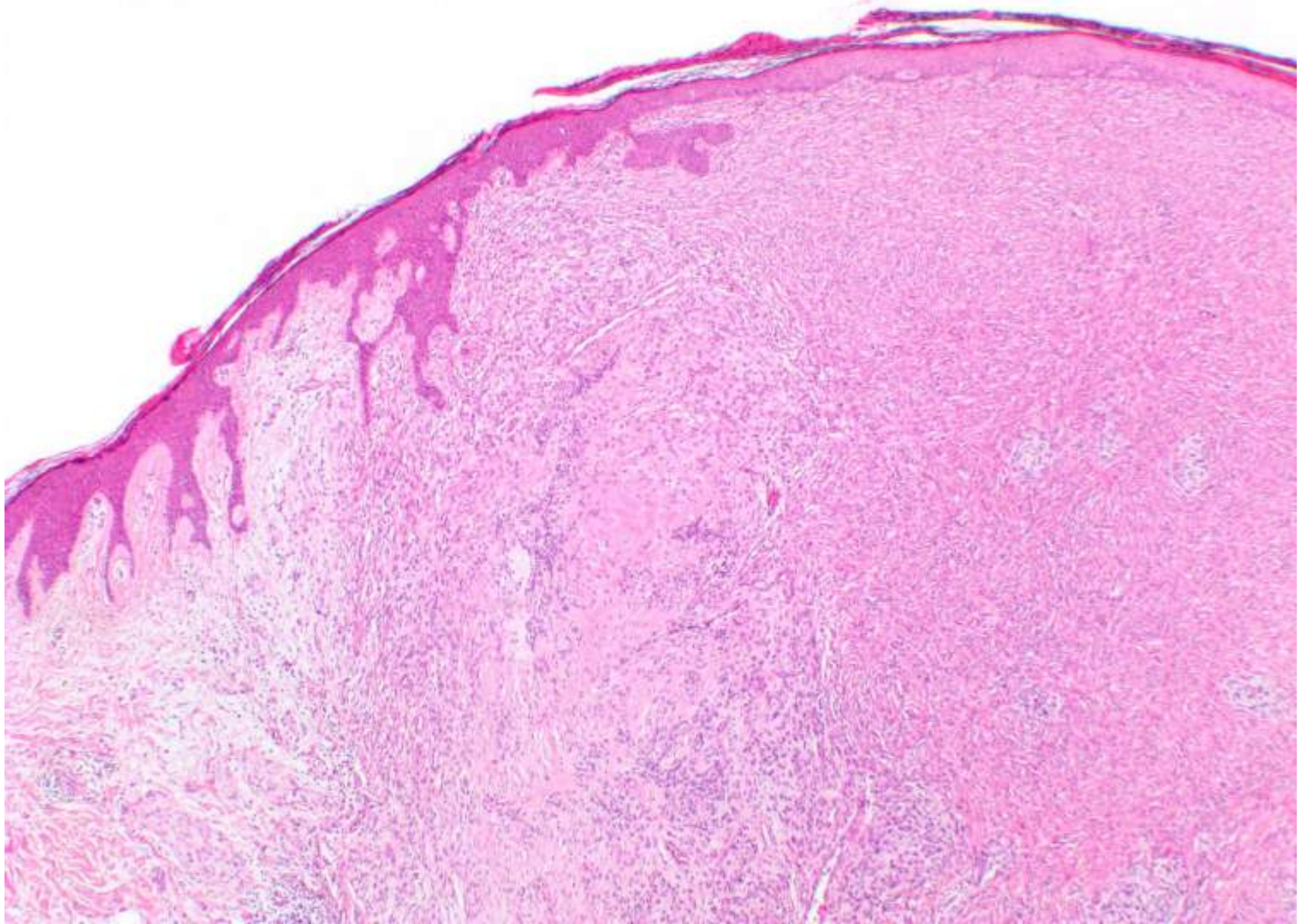
- 81 yo male

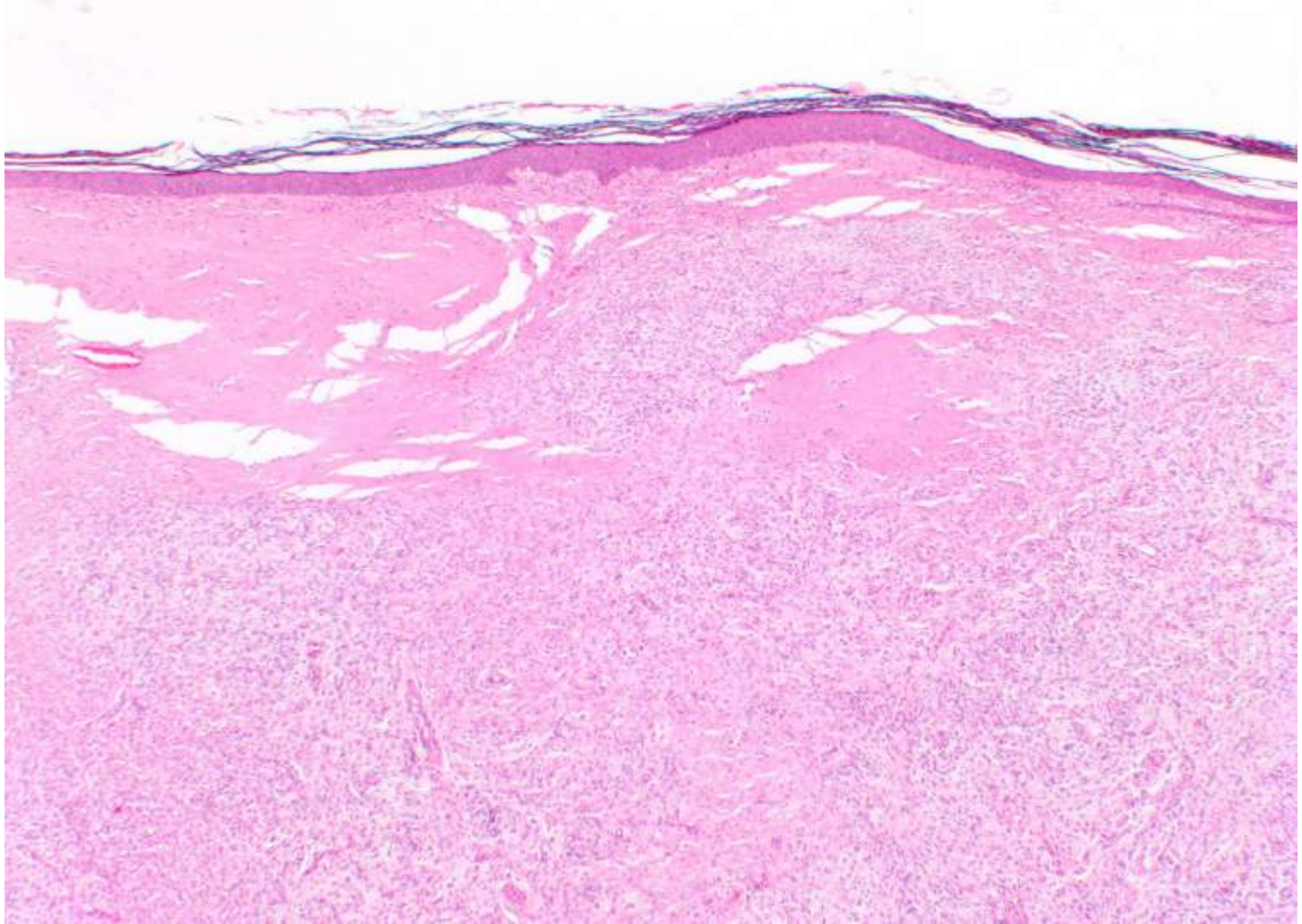
- Past medical history:
  - Lung cancer

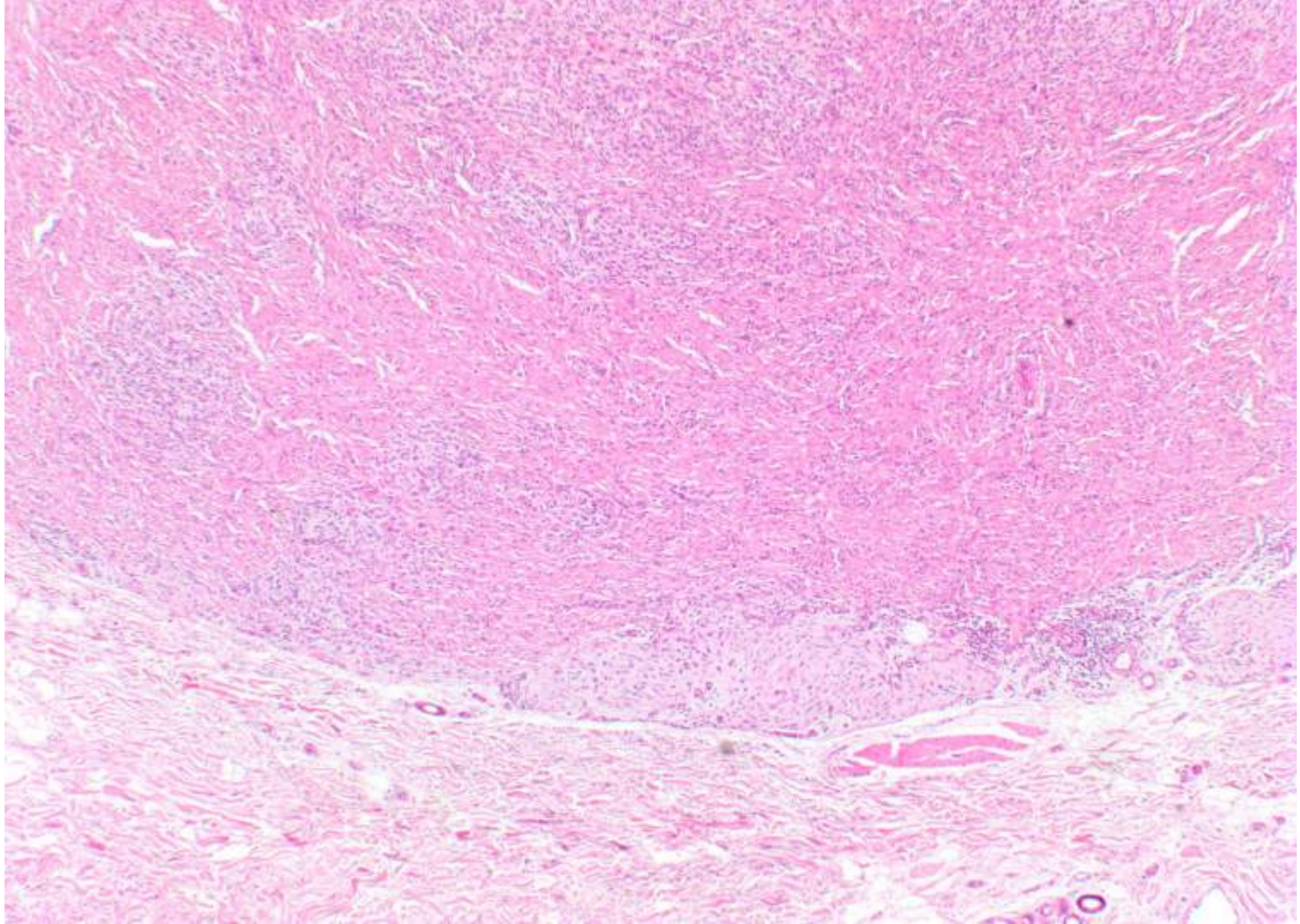
- Current episode:
  - Upper left thigh lesion → Excision
  - ?Amelanotic Malignant Melanoma ?Basal Cell Carcinoma

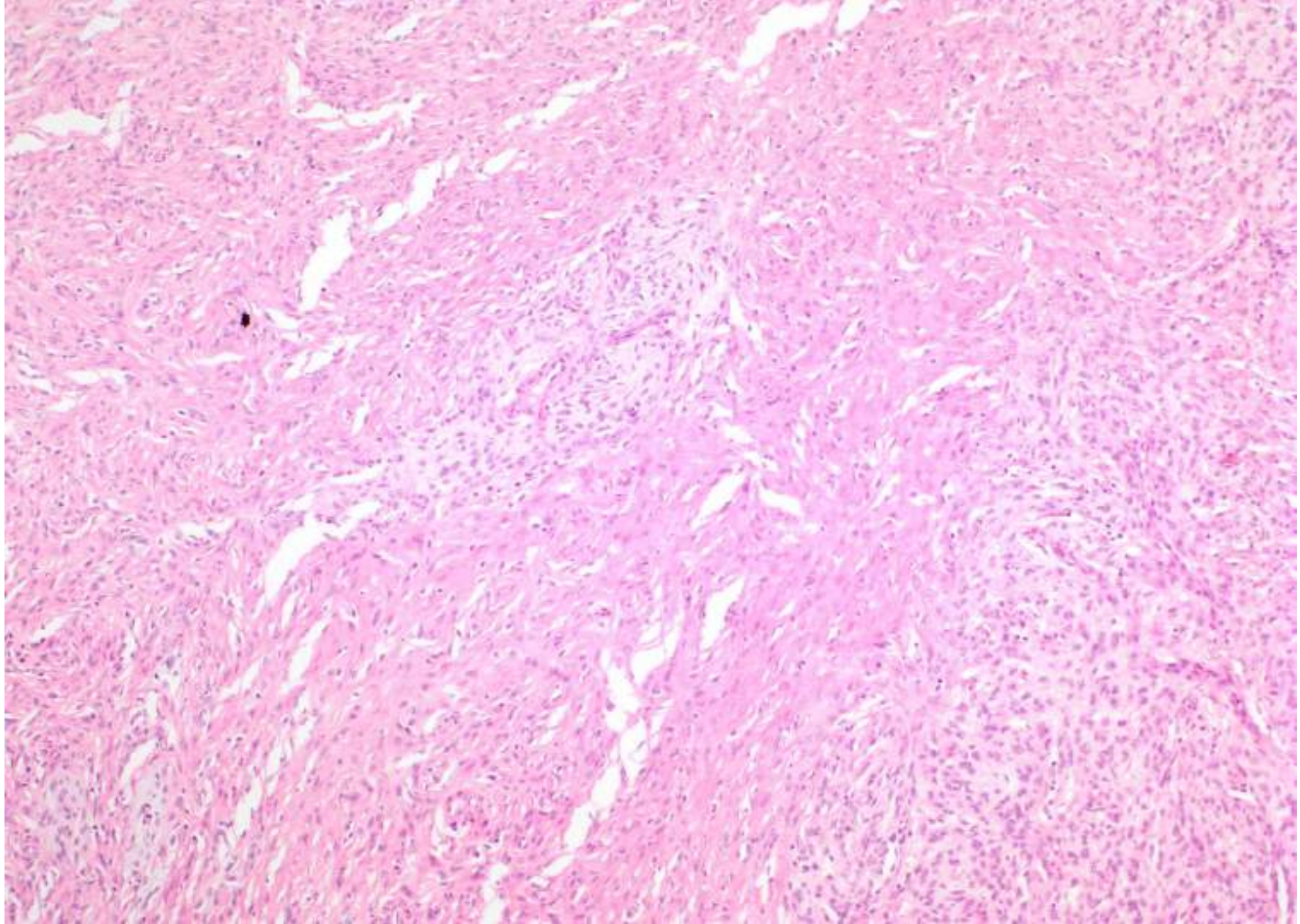


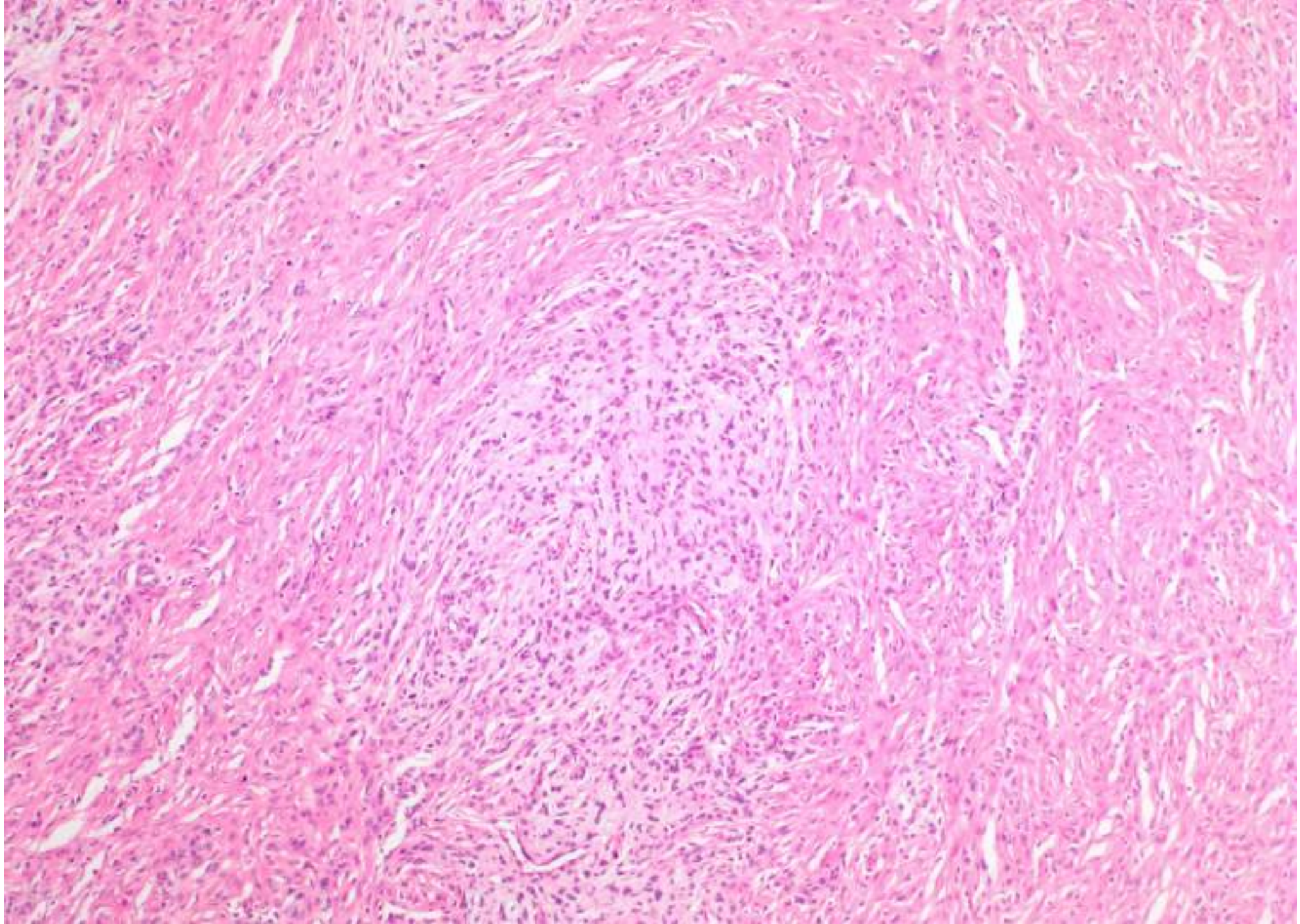


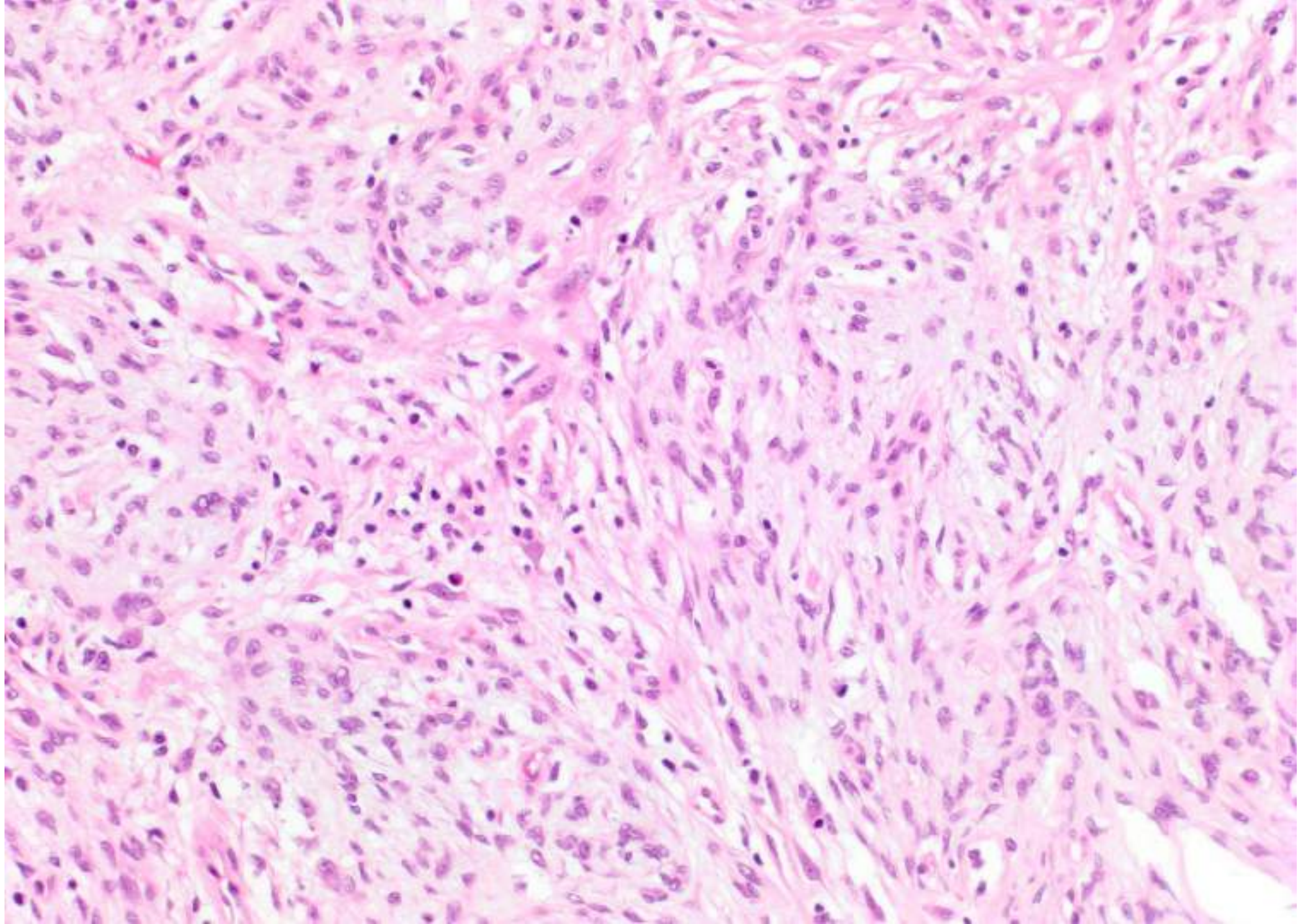


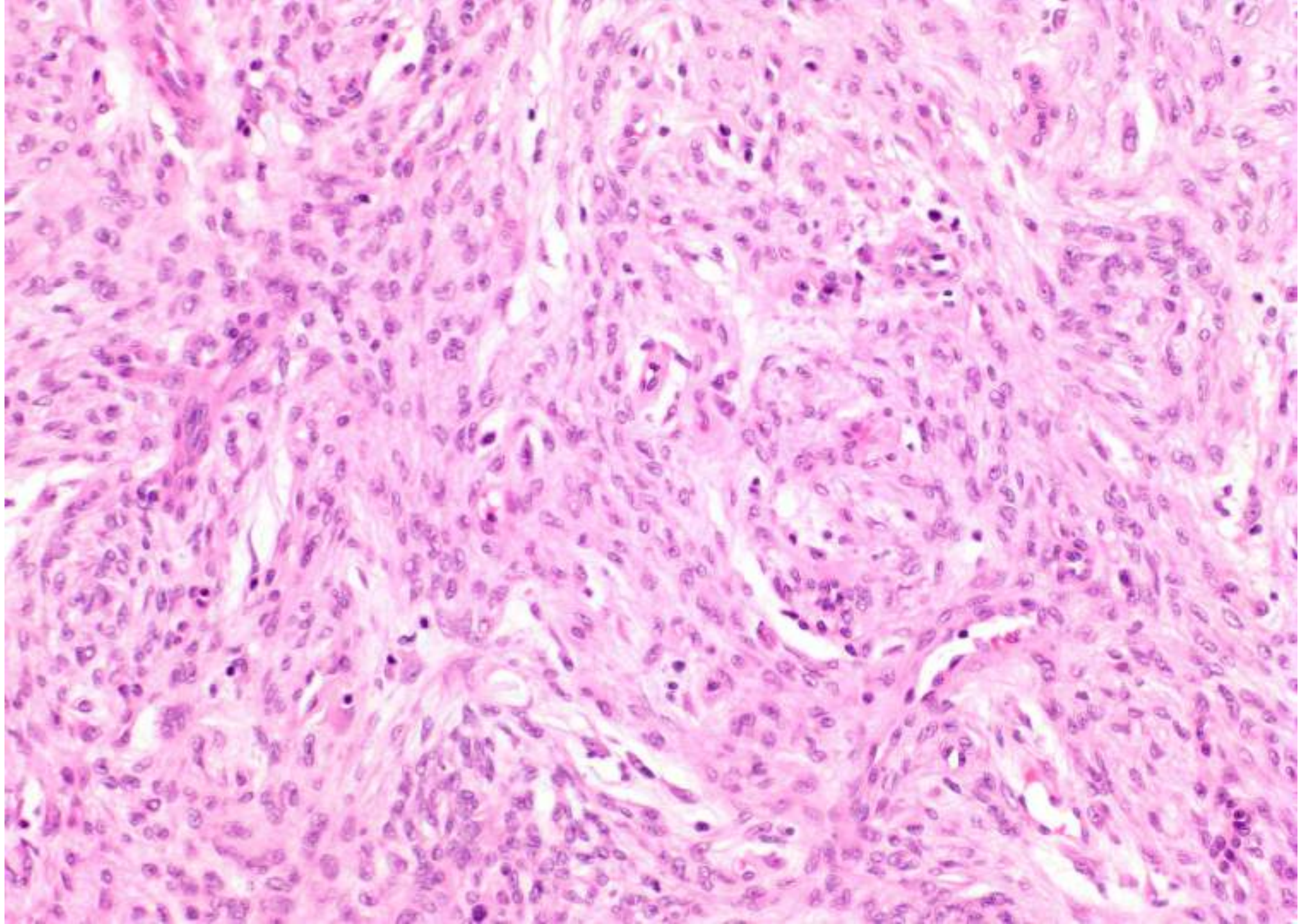


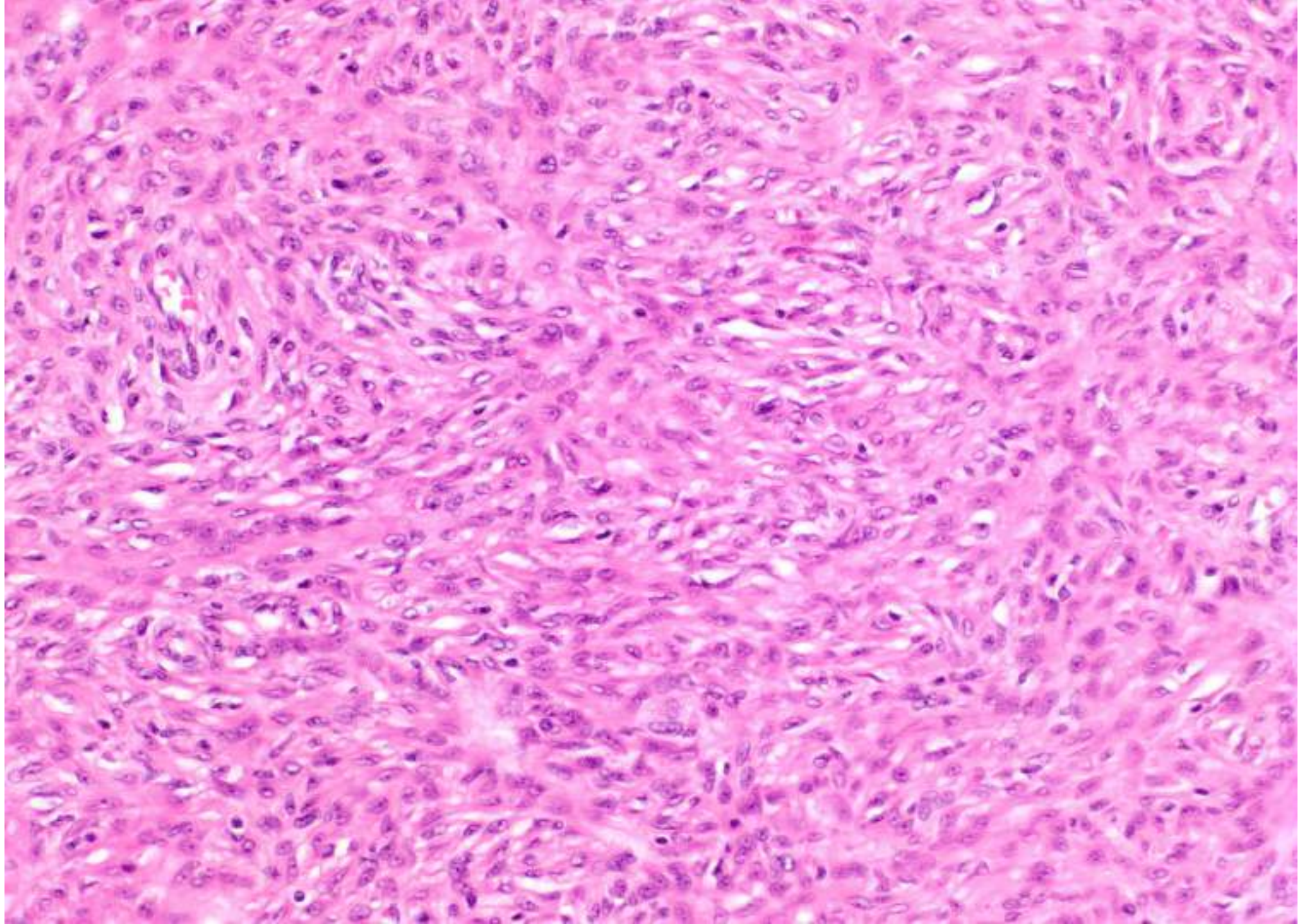


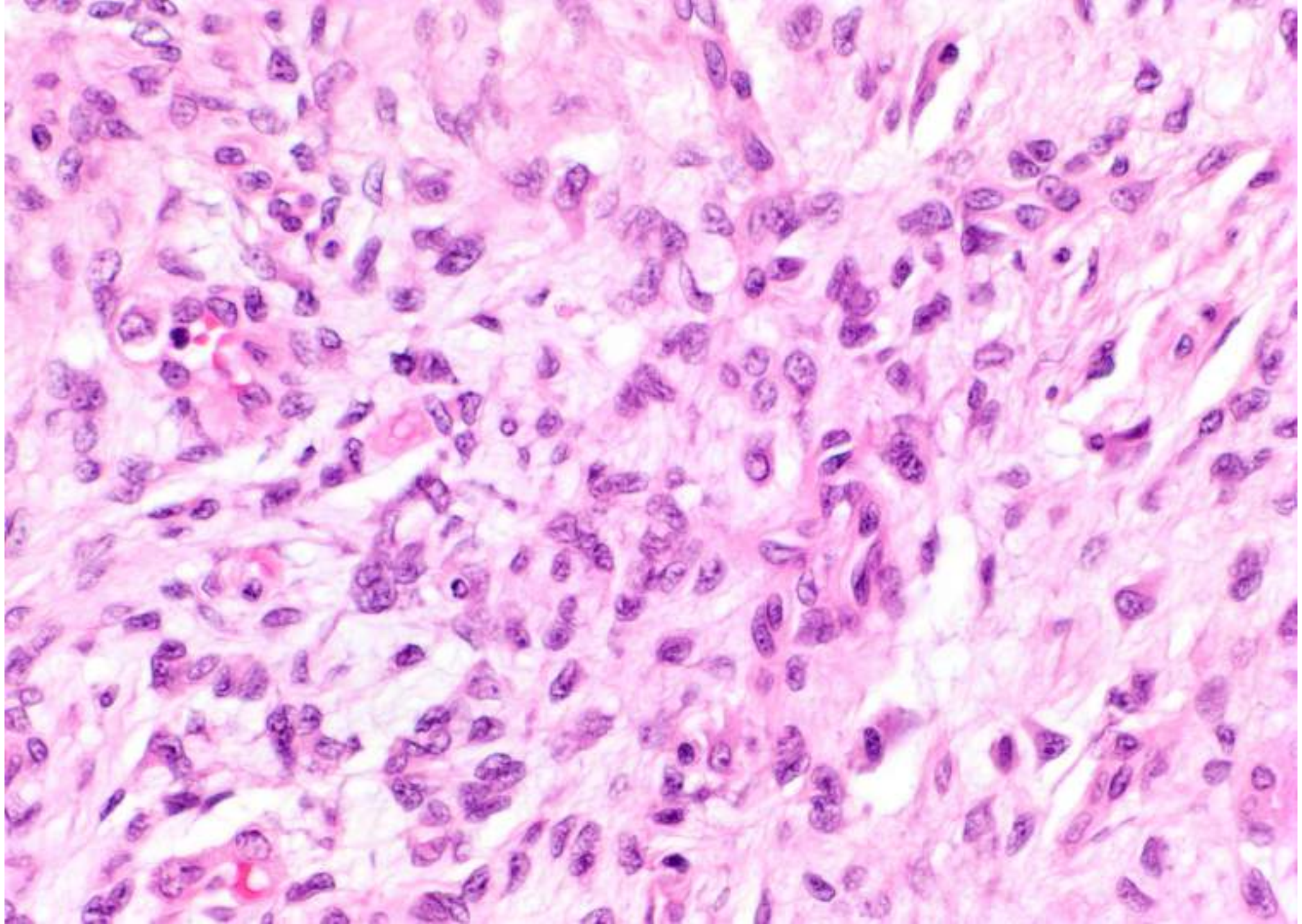


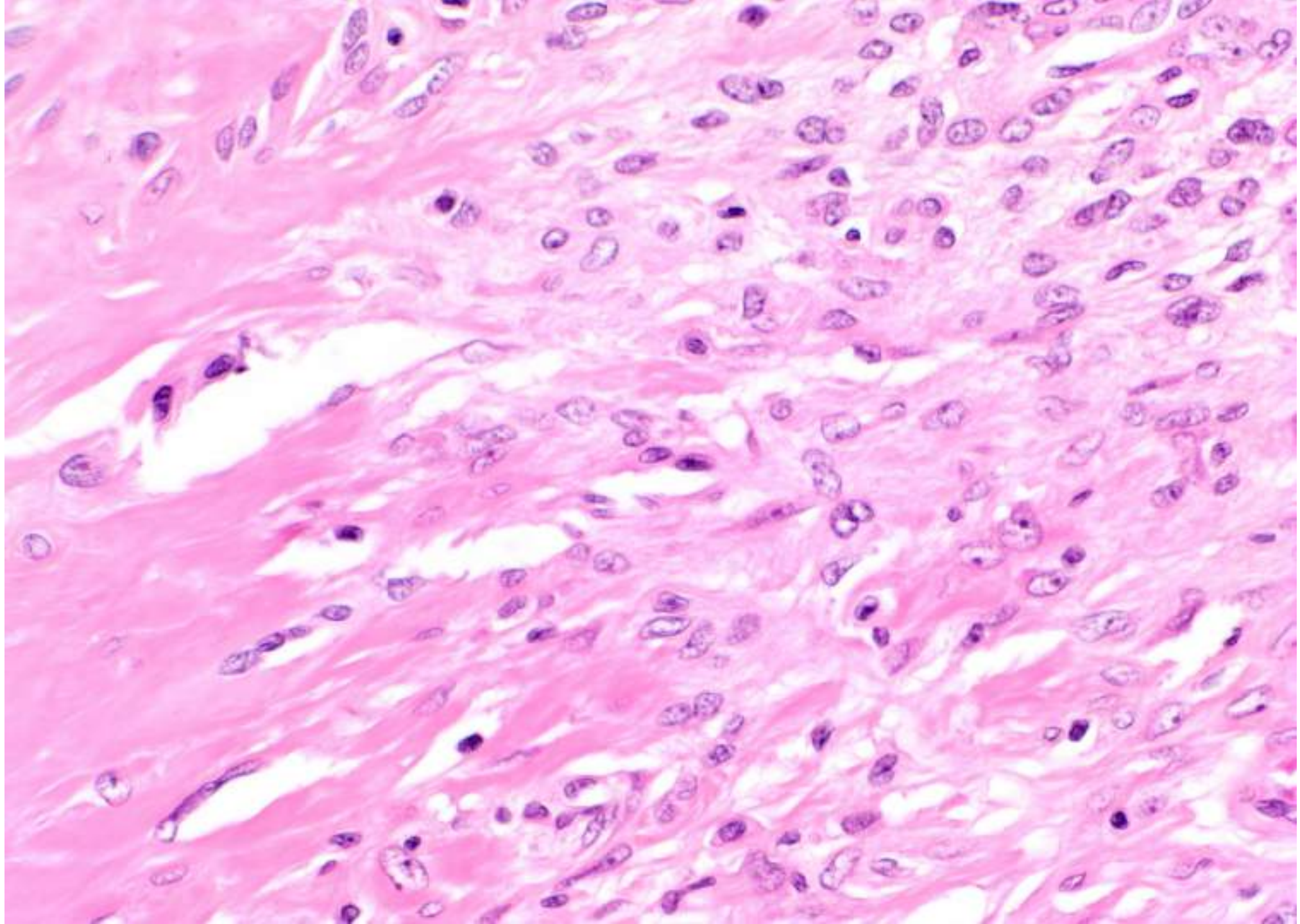






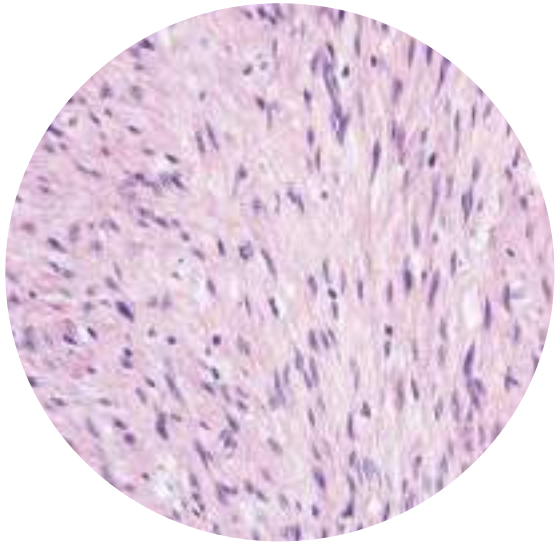




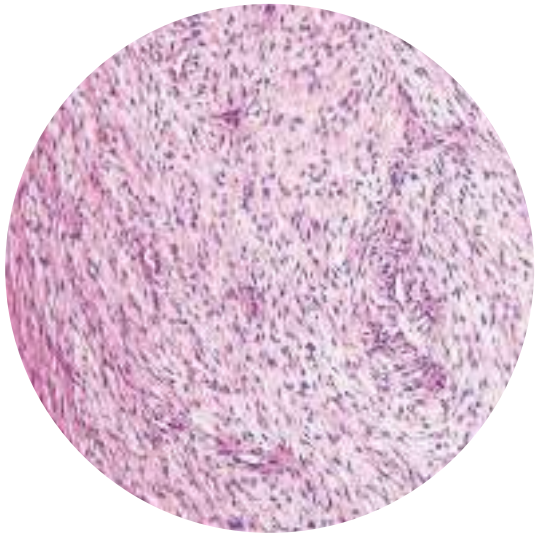


Differential diagnosis

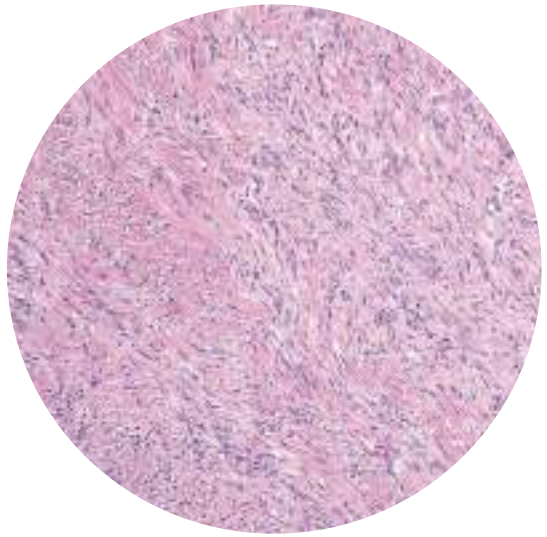
MPNST



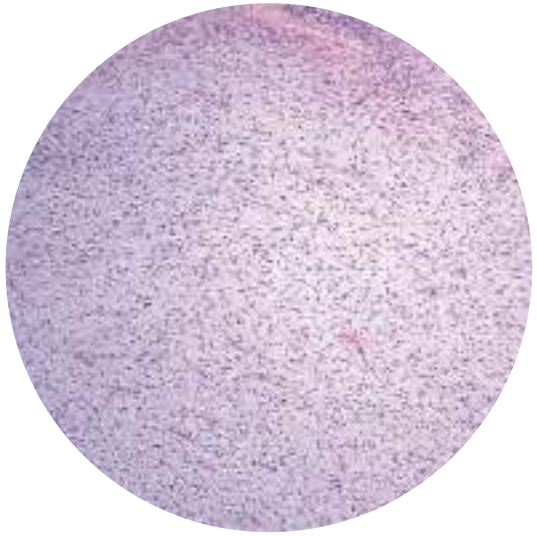
Low-grade fibromyxoid sarcoma



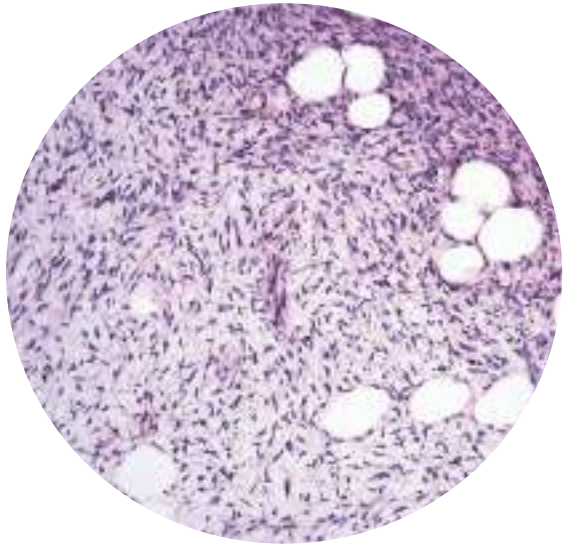
Low grade myxofibrosarcoma



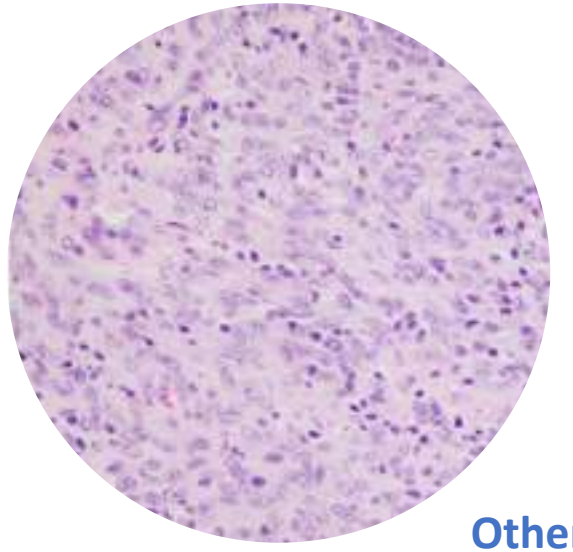
Myxoid Solitary fibrous tumor



Myxoid DFSP



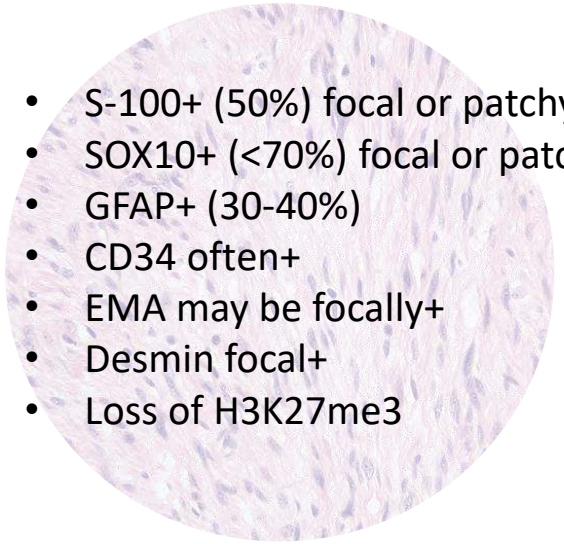
NTRK-rearranged spindle cell neoplasm



Other low grade sarcomas

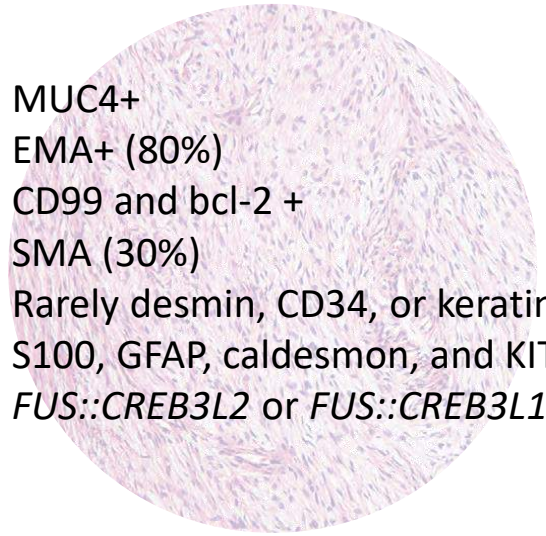
Differential diagnosis

MPNST



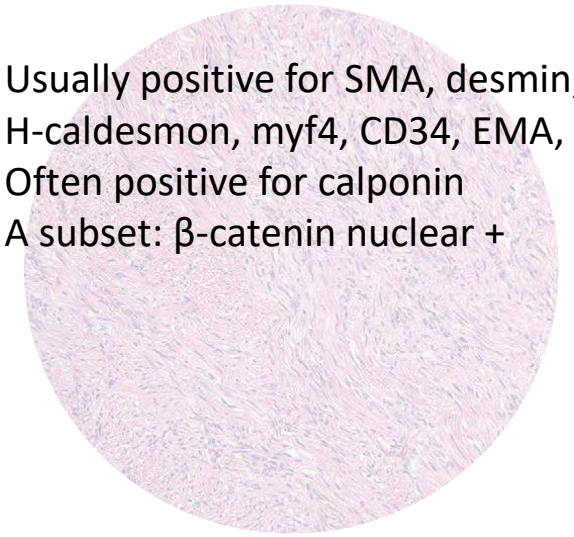
- S-100+ (50%) focal or patchy
- SOX10+ (<70%) focal or patchy
- GFAP+ (30-40%)
- CD34 often+
- EMA may be focally+
- Desmin focal+
- Loss of H3K27me3

Low-grade fibromyxoid sarcoma



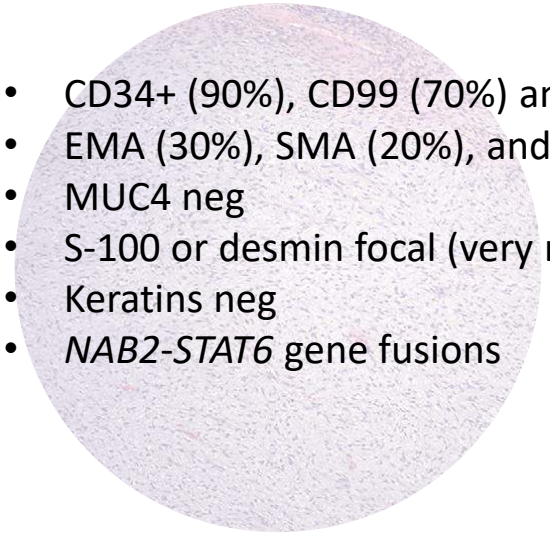
- MUC4+
- EMA+ (80%)
- CD99 and bcl-2 +
- SMA (30%)
- Rarely desmin, CD34, or keratin+
- S100, GFAP, caldesmon, and KIT neg
- *FUS::CREB3L2* or *FUS::CREB3L1*

Low grade myxofibrosarcoma



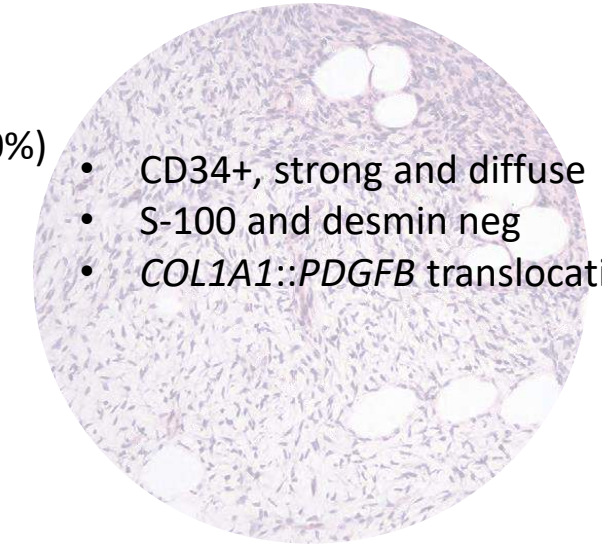
- Usually positive for SMA, desmin, or both
- H-caldesmon, myf4, CD34, EMA, keratins, and S-100 neg
- Often positive for calponin
- A subset: β-catenin nuclear +

Myxoid Solitary fibrous tumor



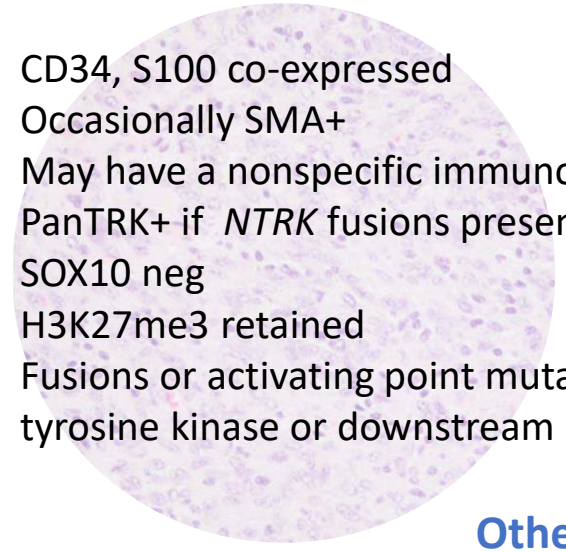
- CD34+ (90%), CD99 (70%) and STAT6
- EMA (30%), SMA (20%), and bcl-2 (30%)
- MUC4 neg
- S-100 or desmin focal (very rare)
- Keratins neg
- *NAB2-STAT6* gene fusions

Myxoid DFSP



- CD34+, strong and diffuse
- S-100 and desmin neg
- *COL1A1*::*PDGFB* translocation

NTRK-rearranged spindle cell neoplasm

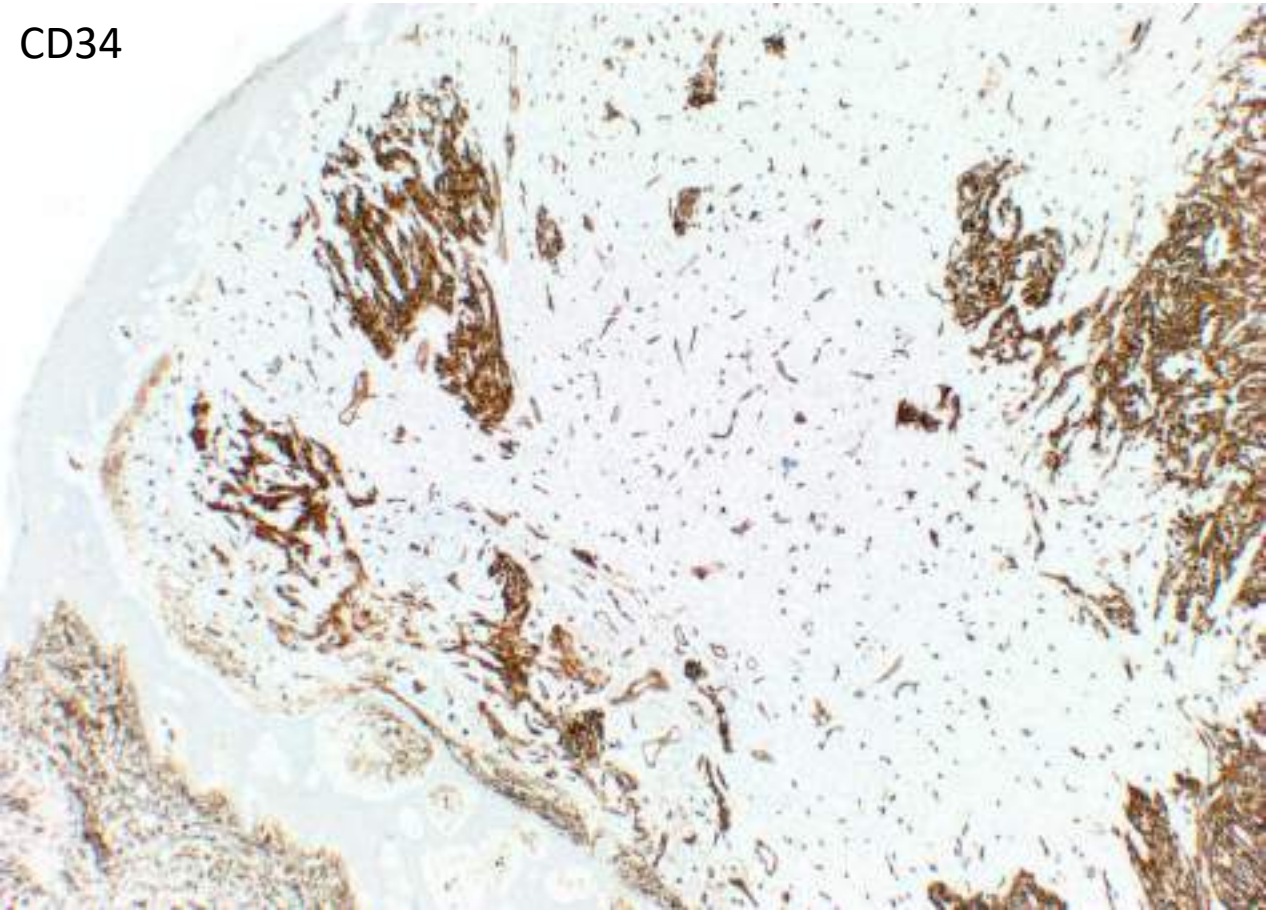


- CD34, S100 co-expressed
- Occasionally SMA+
- May have a nonspecific immunoprofile
- PanTRK+ if *NTRK* fusions present
- SOX10 neg
- H3K27me3 retained
- Fusions or activating point mutations in receptor tyrosine kinase or downstream effector molecule

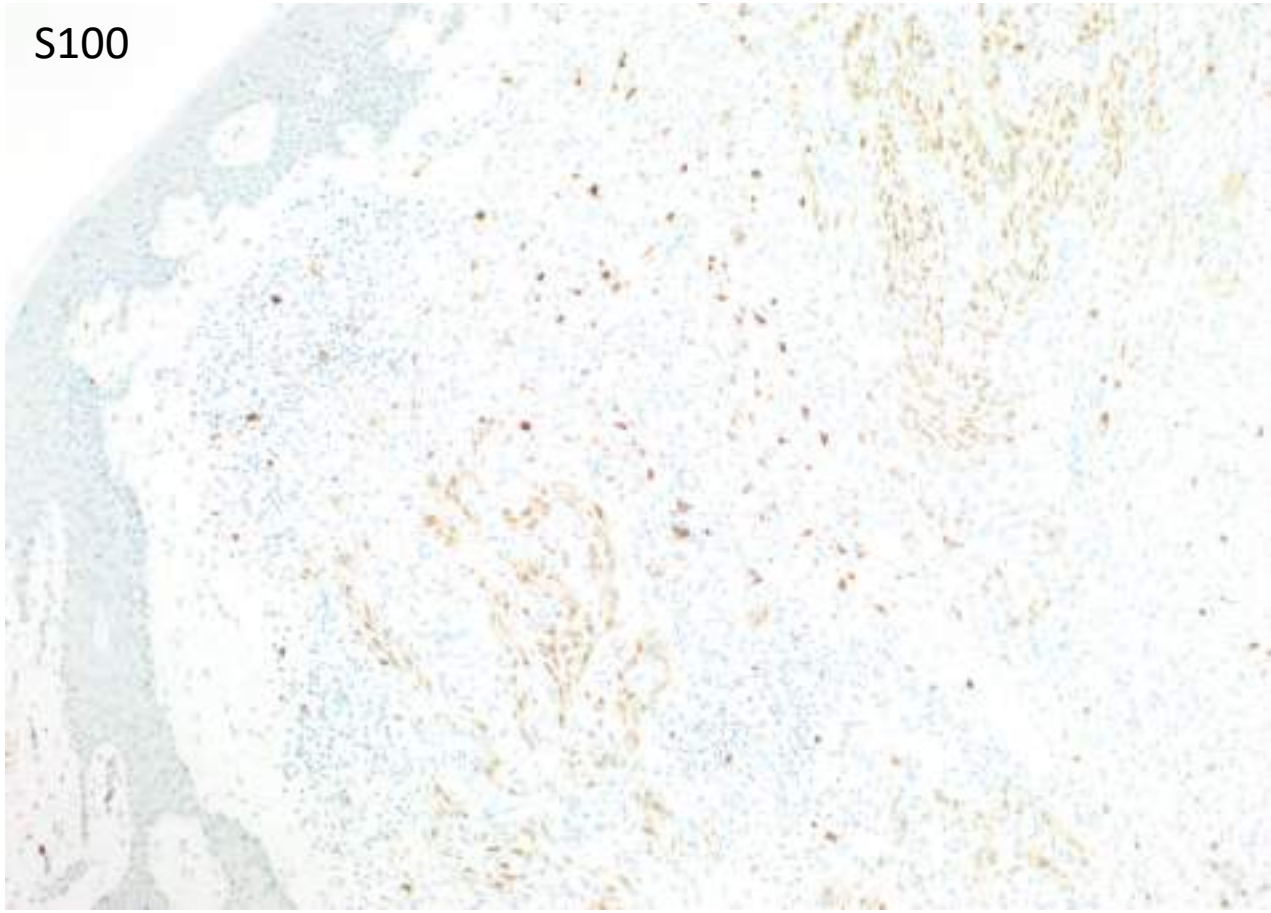
Other low grade sarcomas

Immunoprofile of our case

CD34



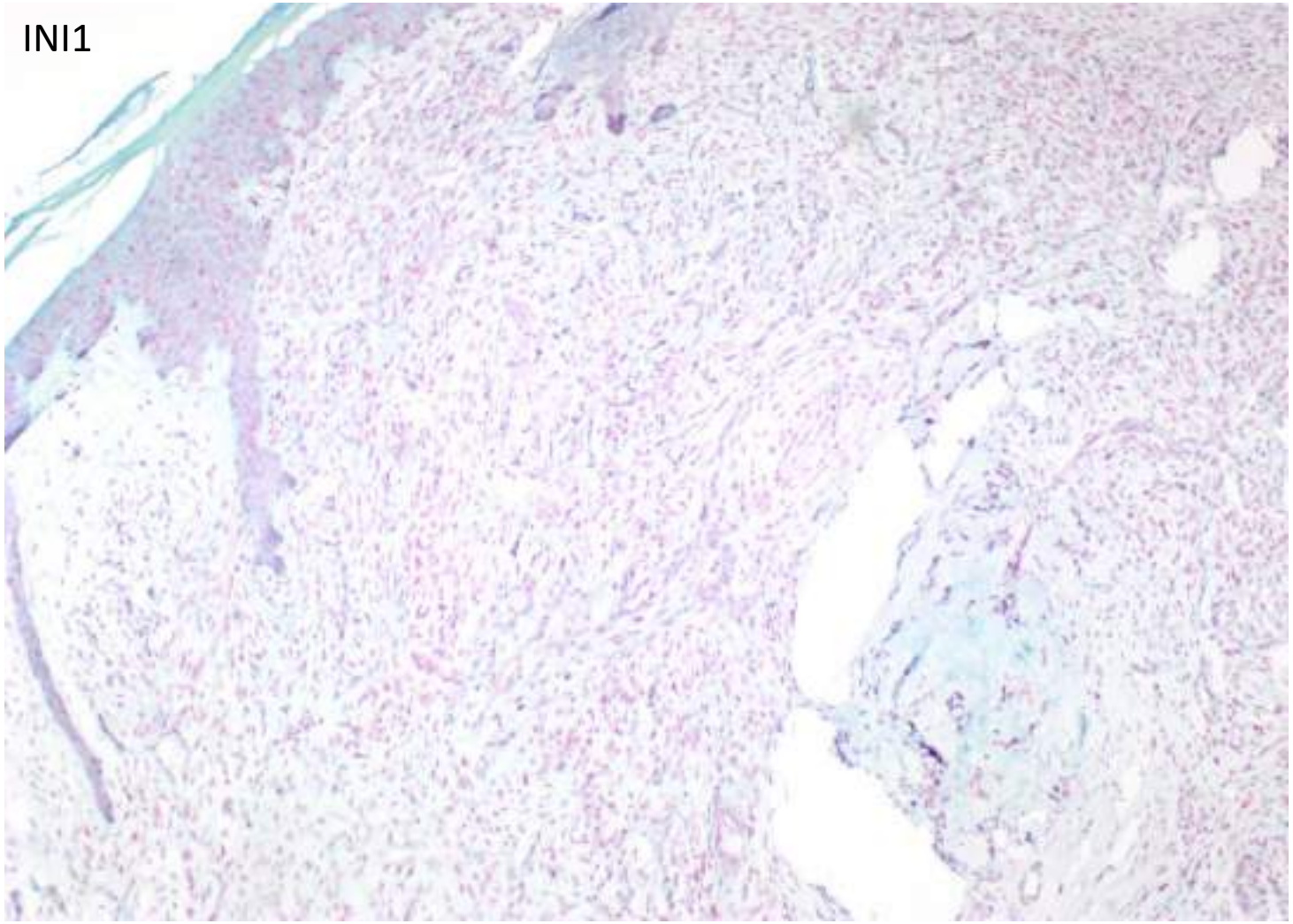
S100



Immunoprofile of our case

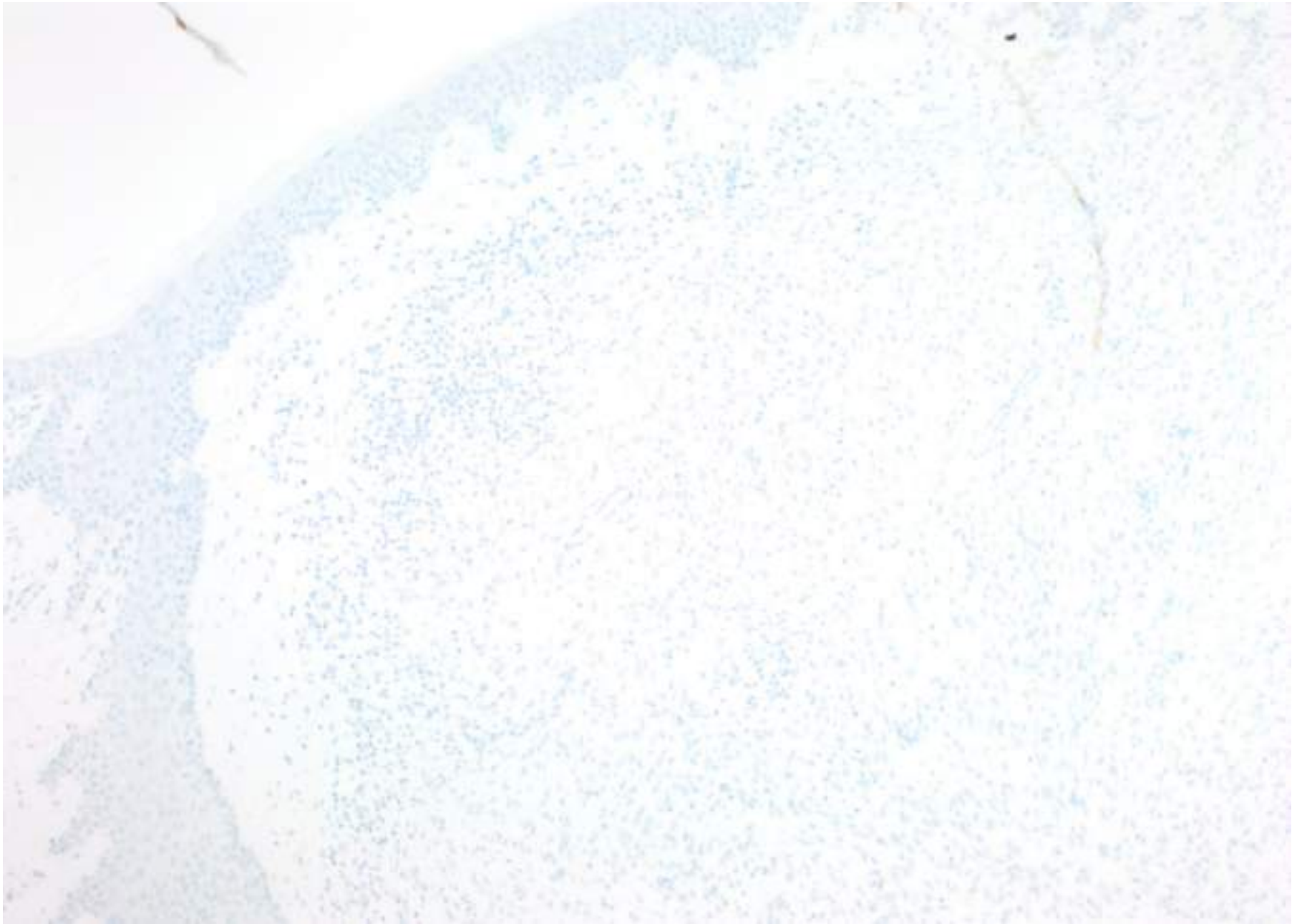
Negative IHC:

- CD68
- CD163
- CD1a
- Langerin
- CK AE1-AE3
- CAM 5.2
- EMA
- P40
- P63
- HMB45
- Melan-A
- SOX10
- GFAP
- Factor XIIIa
- Desmin
- SMA
- H-Caldesmon
- Calponin



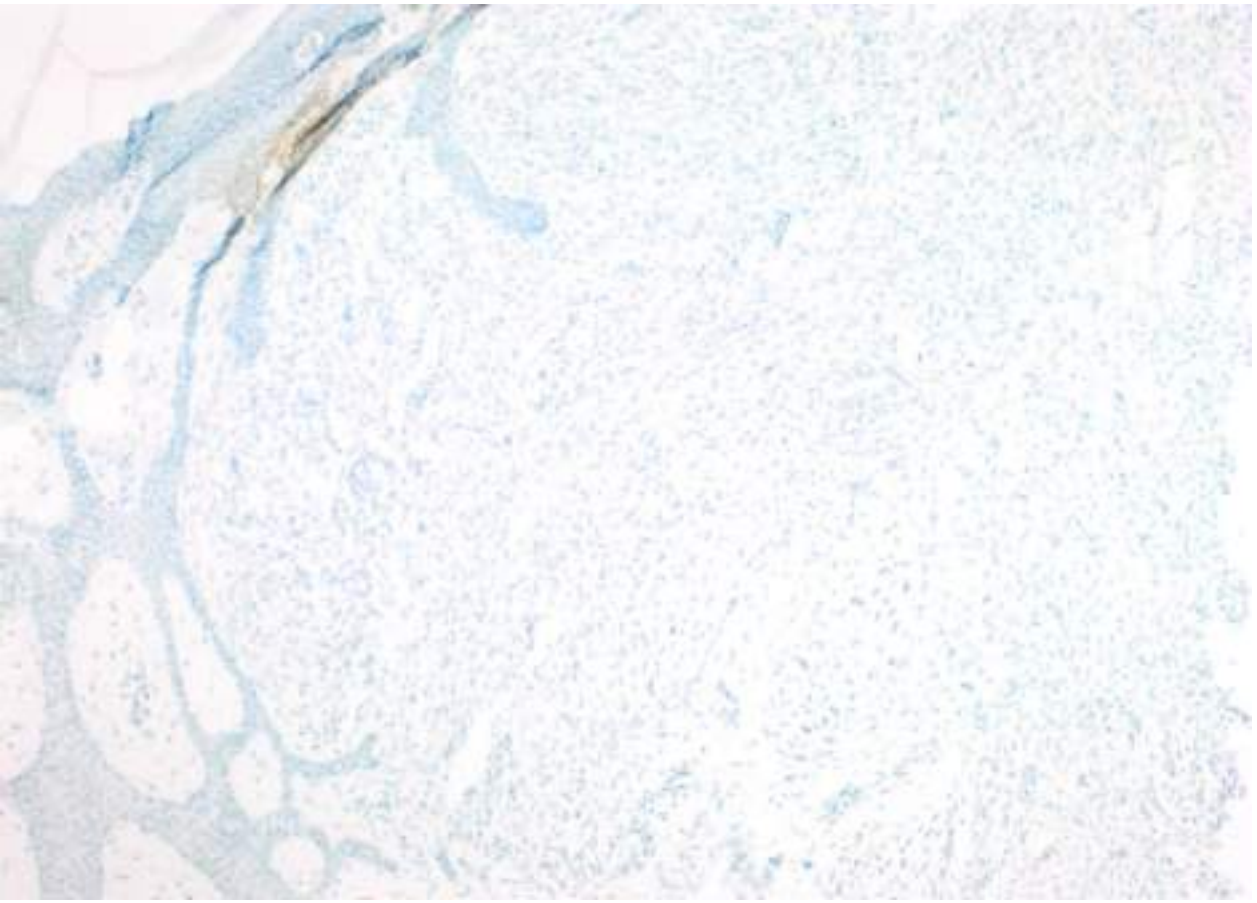
Immunoprofile of our case

panTRK



Immunoprofile of our case

ALK



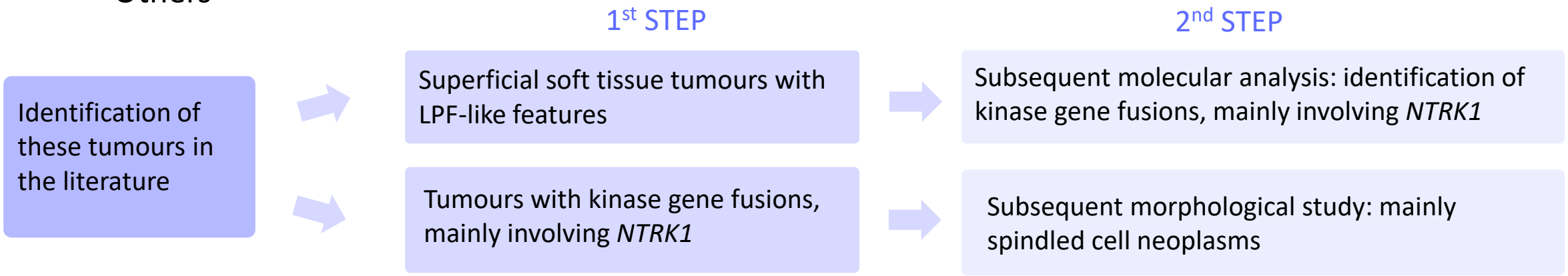
BRAF

Diagnosis:

Similar appearances to
NTRK-rearranged spindle cell neoplasm

NTRK-rearranged spindle cell neoplasm

- Emerging group of molecularly defined rare soft tissue tumours
- Provisional category included in the 5th WHO Classification:
  - Soft Tissue Tumours: Intermediate neoplasms of uncertain differentiation
  - Paediatric tumours: Fibroblastic and myofibroblastic tumours
- Wide spectrum of morphologies:
  - Lipofibromatosis (LPF)-like neural tumours
  - Tumours closely resembling malignant peripheral nerve sheath tumours (MPNST)
  - Infantile fibrosarcoma-like tumours
  - Unclassified spindle cell sarcomas
  - Others



NTRK-rearranged spindle cell neoplasm

Localization

- Mainly located in soft tissue, but also in viscera and central nervous system
- In skin: superficial or deep tumours in the extremities or trunk

Clinical features

- Most tumours present as a palpable, non-tender mass

Epidemiology

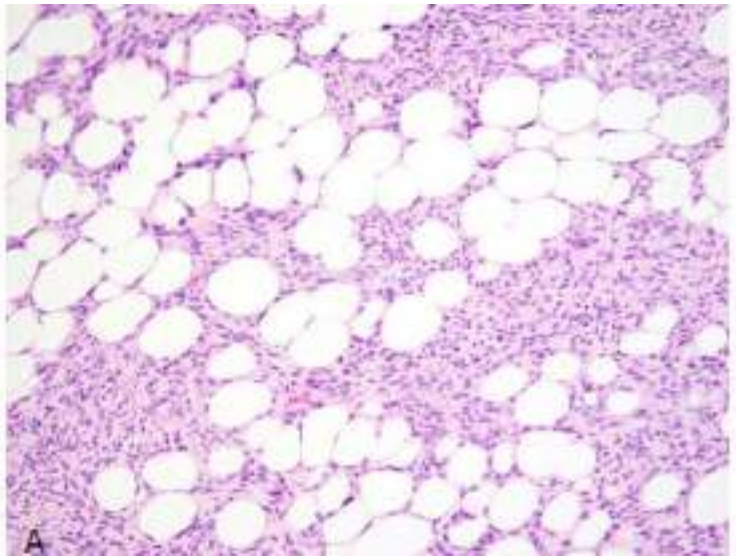
- Majority occur in the first two decades of life
- Majority of lipofibromatosis-like neural tumours and NTRK-rearranged tumours resembling PNSTs present predominantly in children
- Remaining cases: wide age range

No.	Age (y)	Sex	Location
Pure			
1	7	F	Hand
2	4	F	Thigh
3	15	M	Forearm
4	4 m	M	Hip
5	6	F	Hand
6	77	F	Thigh
7	12	M	Arm
8	13	F	Abd. wall
9	1	F	Ankle
10	0	F	Foot
11	64	M	Forearm
12	14	F	Buttock
Hybrid			
13	10	F	Antecubital
14	27	F	Forearm
15	28	F	Flank
16	25	M	Foot
17	38	F	Scalp
18	10	M	Leg
19	12	M	Arm
20	0	M	Lower back
21	5 m	M	Forearm
22	30	M	Scalp
23	0	F	Shoulder
24	23	M	Arm
25	5	M	Leg
26	15	F	Thigh
27	3	F	Sacral area
28	17	M	Thigh
29	6	M	Abd. wall
30	10	M	Abd. wall
31	20	F	Trunk
32	18	M	Knee
33	21	F	Paraspinal
34	3 m	M	Back
35	20	M	Forearm
36	12	M	Thigh

Kao YC et al. Genes Chromosomes Cancer. 2020

NTRK-rearranged spindle cell neoplasm

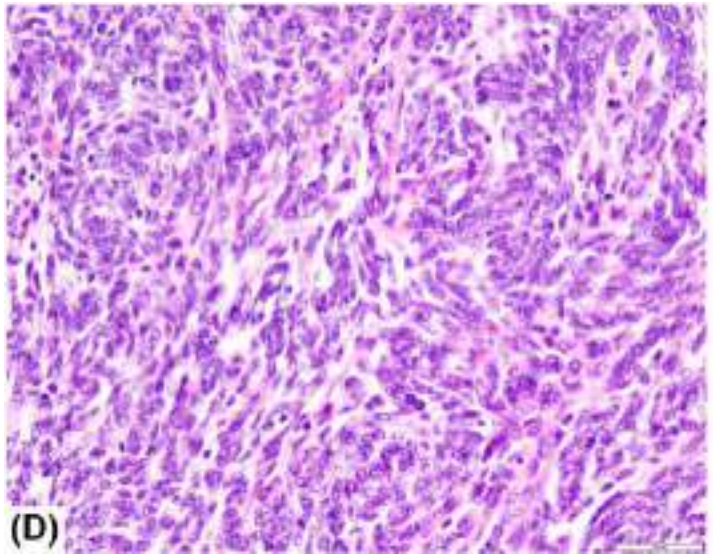
Superficial tumours
Lipofibromatosis-like neural tumour (LPF-like NT)



Spectrum

- Low to high cellularity
- Range of mitotic count

Other tumours
Sheets of spindled cells, myxoid background



Agaram NP et al. Am J Surg Pathol. 2016

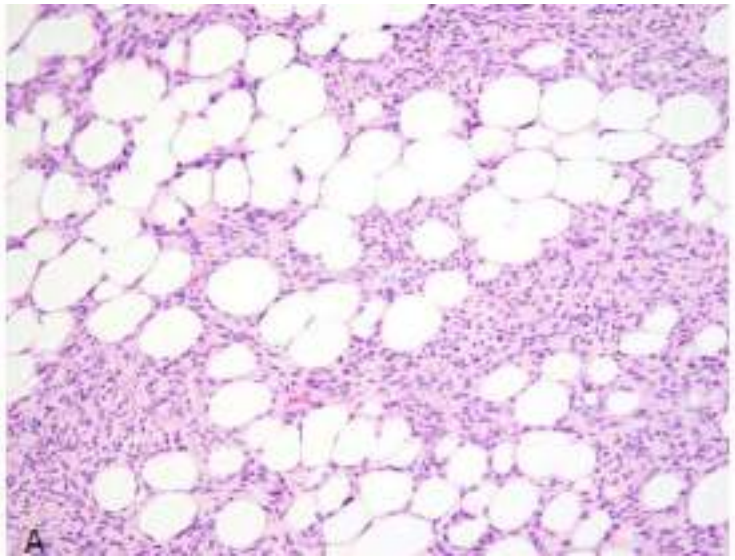
Suurmeijer AJH et al. Genes Chromosomes Cancer. 2018

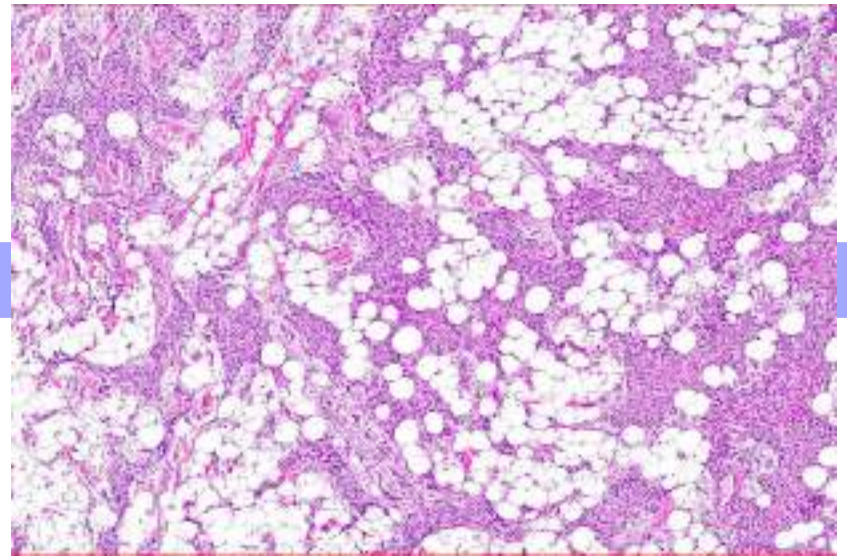
NTRK-rearranged spindle cell neoplasm

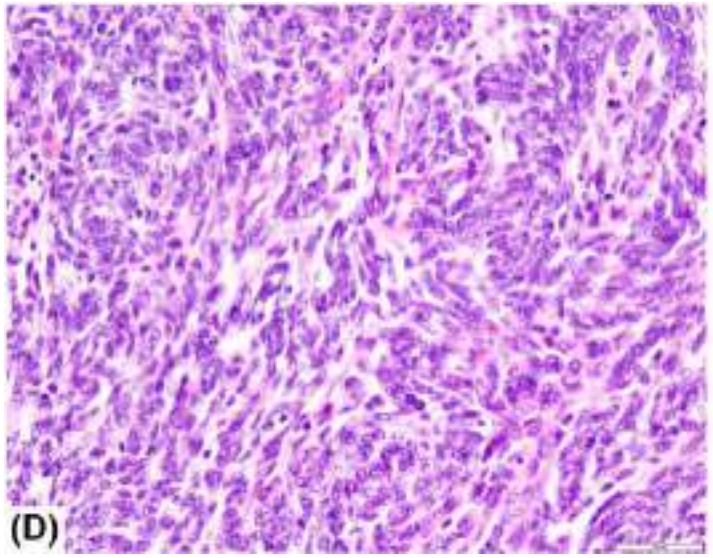
Superficial tumours
Lipofibromatosis-like neural tumour (LPF-like NT)

Commonly hybrid appearance

Other tumours
Sheets of spindled cells, myxoid background







Agaram NP et al. Am J Surg Pathol. 2016

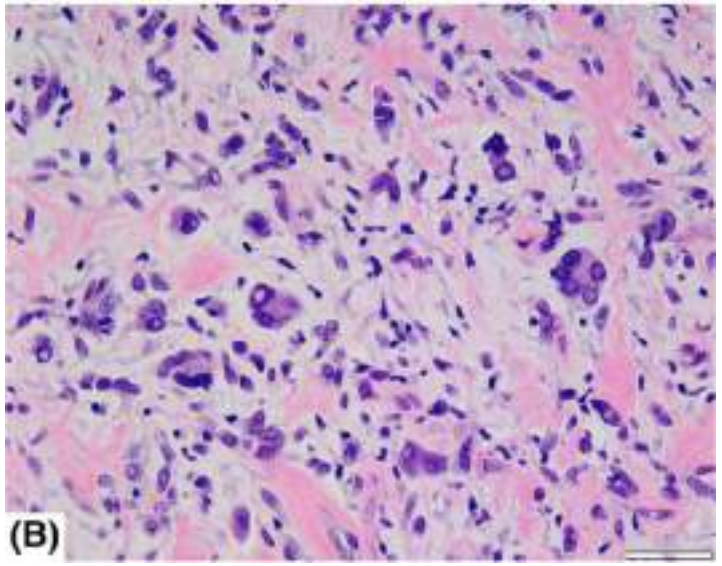
Suurmeijer AJH et al. Genes Chromosomes Cancer. 2018

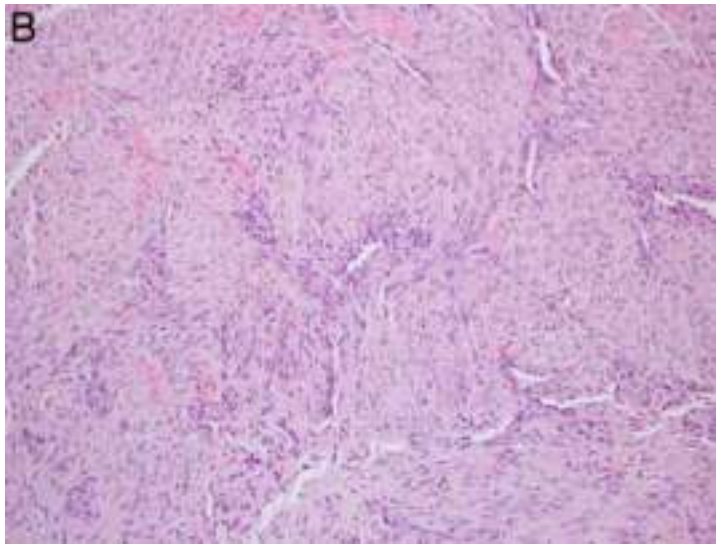
NTRK-rearranged spindle cell neoplasm

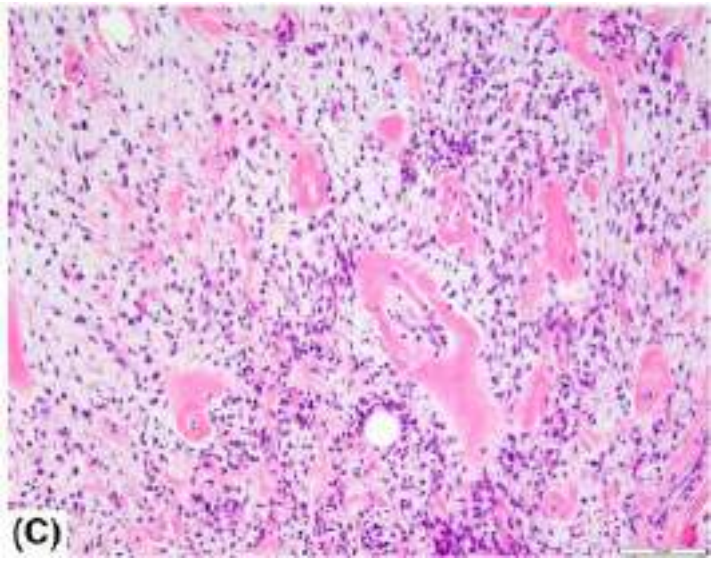
Frequent features
- Hybrid appearance
- Low grade histological features

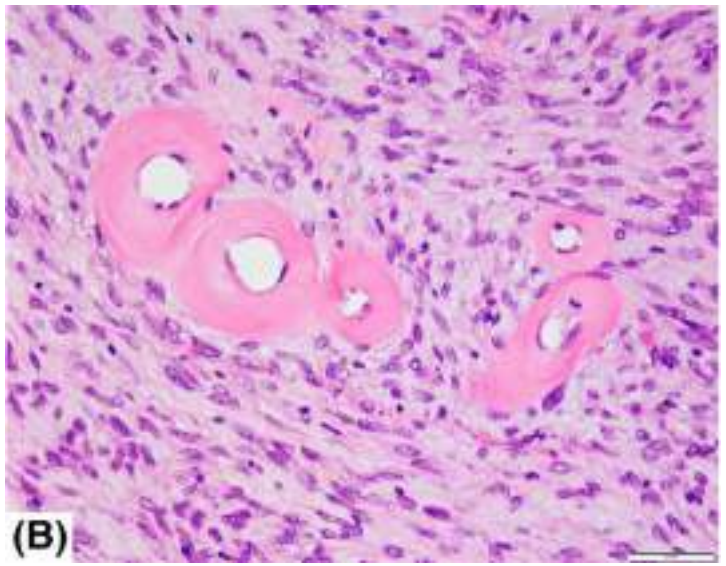
Infrequent features
- Higher-grade histologic features
- High mitotic activity
- Marked nuclear pleomorphism
- Necrosis

Other features
- Lymphocytic infiltrate
- Thin-walled staghorn vessels
- Perivascular hyalinization
- Stromal bands of hyalinized collagen









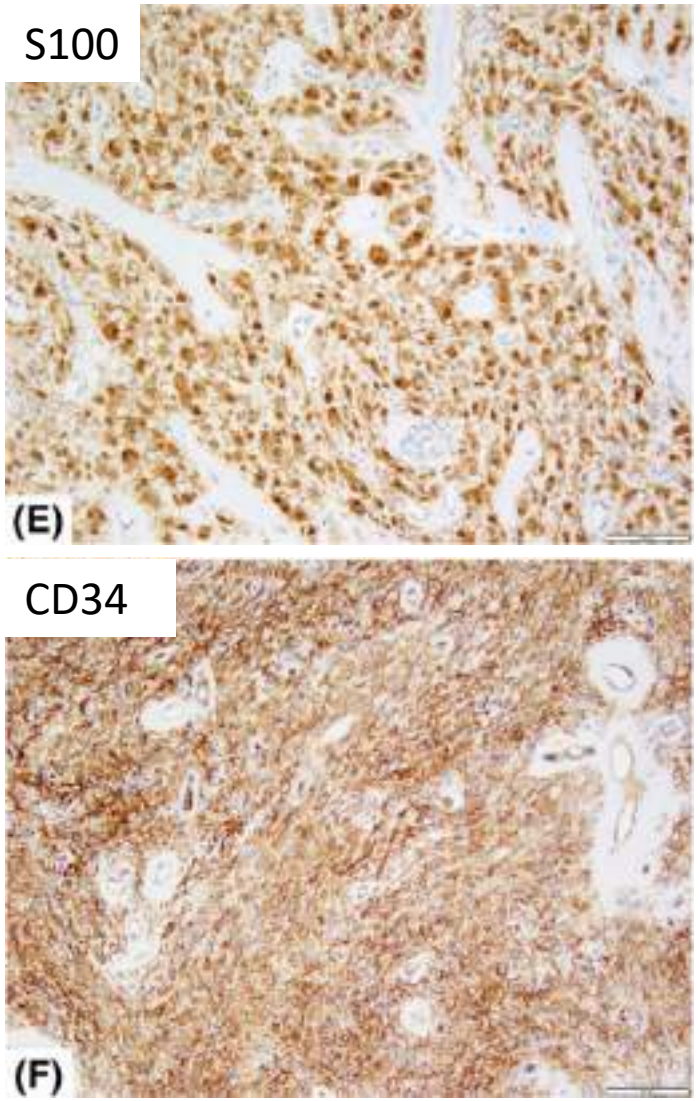
Agaram NP et al. Am J Surg Pathol. 2016

Davis JL et al. Am J Surg Pathol. 2019

Suurmeijer AJH et al. Genes Chromosomes Cancer. 2018

NTRK-rearranged spindle cell neoplasm

- Variable co-expression of CD34, S100, BUT expression of these markers is **not required**
- Occasionally SMA +
- May have a nonspecific immunoprofile

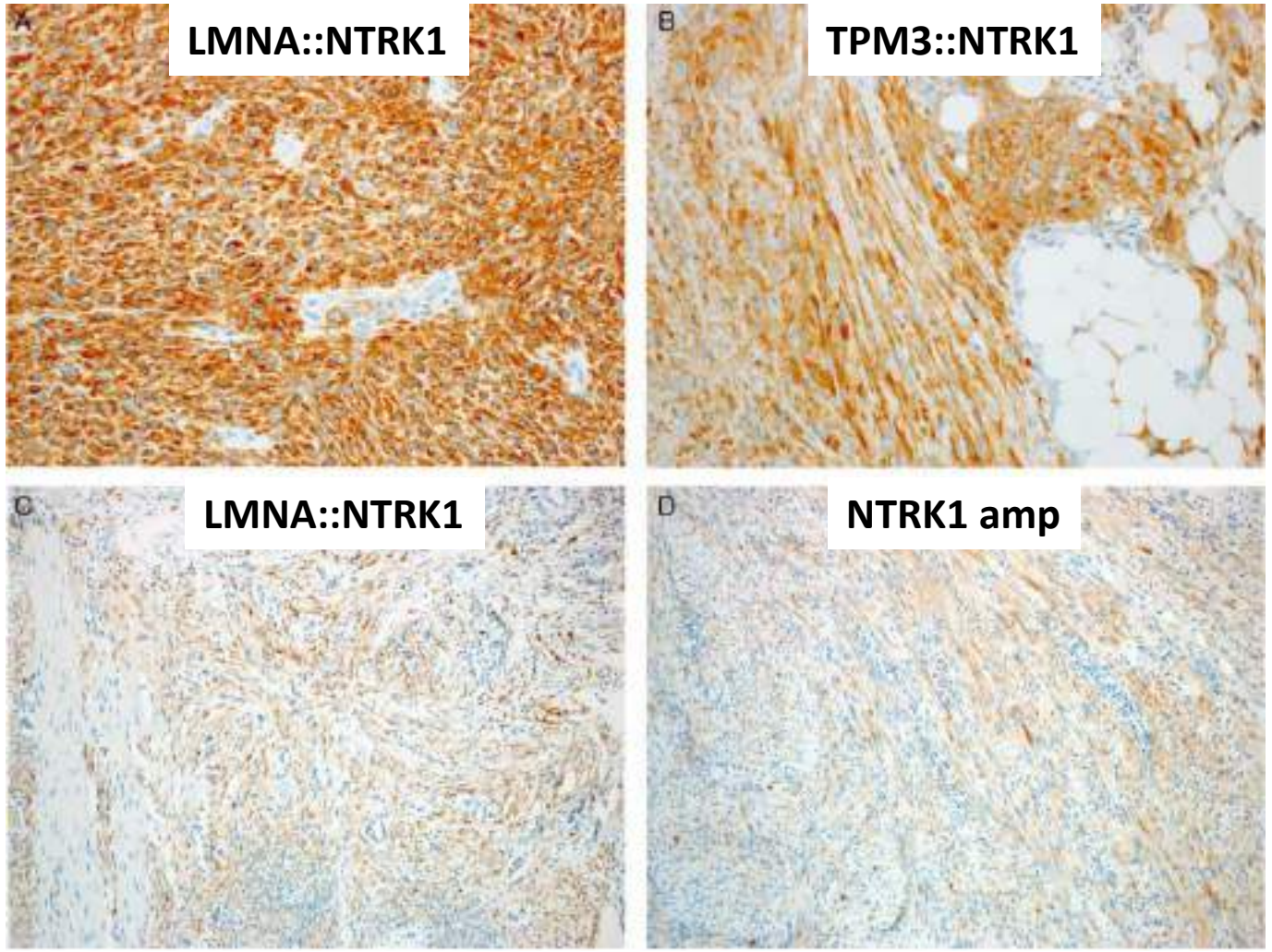


Suurmeijer AJH et al. Genes Chromosomes Cancer. 2018

Kao YC et al. Genes Chromosomes Cancer. 2020

NTRK-rearranged spindle cell neoplasm

- **PanTRK:** usually diffusely expressed in tumours with activating *NTRK* fusions (cytoplasmic positivity, variable intensity)
- SOX10, HMB45, Melan A, desmin negative
- H3K27me3 retained



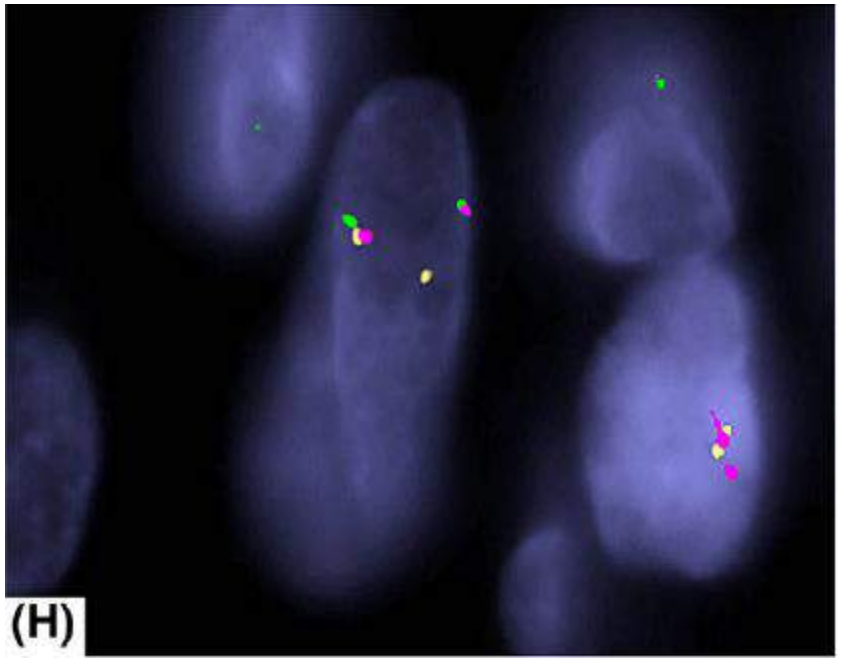
Rudzinski ER et al. Am J Surg Pathol. 2018

Kao YC et al. Genes Chromosomes Cancer. 2020

NTRK-rearranged spindle cell neoplasm

Pathogenesis

- Activation of MAP kinase signaling → mainly through formation of chimeric proteins with *NTRK1* (often **LMNA::NTRK1**, **TPR::NTRK1** or **TPM3::NTRK1**)
- Alternative kinase gene fusions include *NTRK2, NTRK3, RAF1, BRAF, RET, MET, ROS1* or *ALK* with multiple various partners
- Immunohistochemical expression of the protein of the rearranged gene is not always seen



TPM3–NTRK1 fusion

FISH fusion assay: red signal (telomeric 5'-TPM3) comes together with the green signal (telomeric of 3'-NTRK1), while the orange signal (centromeric 5'-NTRK1) breaks away from its green telomeric part

Agaram NP et al. Am J Surg Pathol. 2016

Suurmeijer AJH et al. Genes Chromosomes Cancer. 2018

NTRK-rearranged spindle cell neoplasm

What is needed for a conclusive diagnosis?

- Gene fusion of receptor tyrosine kinase (e.g., *NTRK1/2/3, RET, MET, EGFR, ROS1, ALK*) or downstream effector molecule (*ABL1, BRAF or RAF1*)
- OR
- Activating point mutations

These molecular findings are **required for determination of therapy**

NTRK-rearranged spindle cell neoplasm

Prognosis

- May recur after incomplete resection (highly infiltrative)
- Hybrid tumours have a low rate of metastasis
- The prognostic role of traditional histologic grading features is still unclear

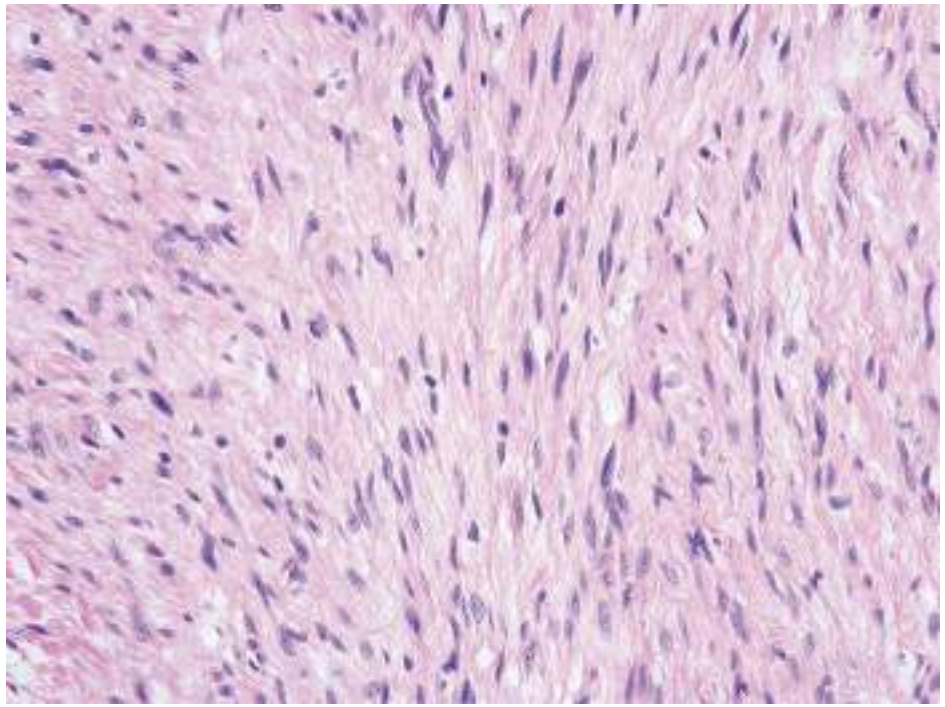
TABLE 1. Clinicopathologic Features and Outcomes

Case	Fusion	Karyotype	Initial Diagnosis	Age (mo)	Sex	Tumor site	Margin Status	Recurrence
1	*TPM3-NTRK1*	Tri 8, 12, 17, 20	IFS	2	M	Arm	POS	2×
2	*TPM3-NTRK1*	Tri 8	LG spindle cell sarcoma	0	M	Thigh	POS	3×
3	*TPM3-NTRK1*	None	LG spindle cell sarcoma/HG at recurrence	0	M	Foot	POS	2×
4	*TPM3-NTRK1*	ND	Unclassified	0	M	Foot	NA	None
5	*TPM3-NTRK1*	Tri 17	IFS	18	M	Flank	POS	None
6	*TPM3-NTRK1*	ND	LG spindle cell tumor	36	F	Axilla	NA	None
7	*TPM3-NTRK1*	ND	Inflammatory spindle and round cell sarcoma	120	M	Pelvic	NA	None
8	*TPM3-NTRK1*	Tri 11	Inflammatory fibroid polyp	2	M	Gastric	POS	Unk
9	*TPM3-NTRK1*	ND	Spindle cell sarcoma	0	M	Pelvic	NA	None
10	*LMNA-NTRK1*	ND	Myxoid DFSP	2	F	Back	NEG	None
11	*LMNA-NTRK1*	ND	IFS	60	F	Shoulder	Unk	None
12	*LMNA-NTRK1*	ND	Cellular schwannoma	36	M	Leg	POS	1×
13	*MIR584F1-NTRK1*	ND	IFS	24	F	Paraspinal	POS	Unk
14	*SQSTM1-NTRK1*	None	Unclassified	2	F	Axilla	POS	1×
15	*TPR-NTRK1*	ND	IFS	5	M	Arm	POS	None
16	*NTRK1*	ND	IFS	10	M	Foot	POS	Unk
17	*STRN-NTRK2*	ND	Unclassified	132	F	Retroperitoneal	POS	1×
18	*EML4-NTRK3*	ND	LG spindle cell sarcoma	0	M	Axilla	POS	None
19	*ETV6-NTRK3**	ND	Unclassified	7	F	Thigh	NA	None
20	*ETV6-NTRK3**	ND	Spindle and round cell sarcoma	5	M	Retroperitoneal	NA	None
21	*ETV6-NTRK3**	ND	IFS	1	F	Hand	POS	None
22	*ETV6-NTRK3**	Tri 11, 17, 20	IFS	2	F	Abdominal wall	POS	None
23	*ETV6-NTRK3*	ND	IFS†	4	F	Dural	NA	None
24	*ETV6-NTRK3*	Tri 11, 15, 17	IFS	4	F	Shoulder	POS	None
25	*ETV6-NTRK3*	ND	LG spindle cell sarcoma	180	M	Lung	POS	1×
26	*ETV6+*	Tri 8, 11	IFS	5	M	Thigh	Unk	Unk
27	*ETV6+*	Tri 8, Tetra 11	IFS	0	F	Thigh	POS	None
28	*ETV6+*	ND	IFS	5	F	Ankle	POS	None
29	*ETV6+*	ND	IFS	0	M	Chest wall	POS	NA
30	*ETV6+*	Tri 8, 17, 10, Tetra 11	IFS	0	F	Foot	POS	None

Davis JL et al. Am J Surg Pathol. 2019

Differential diagnosis

MPNST



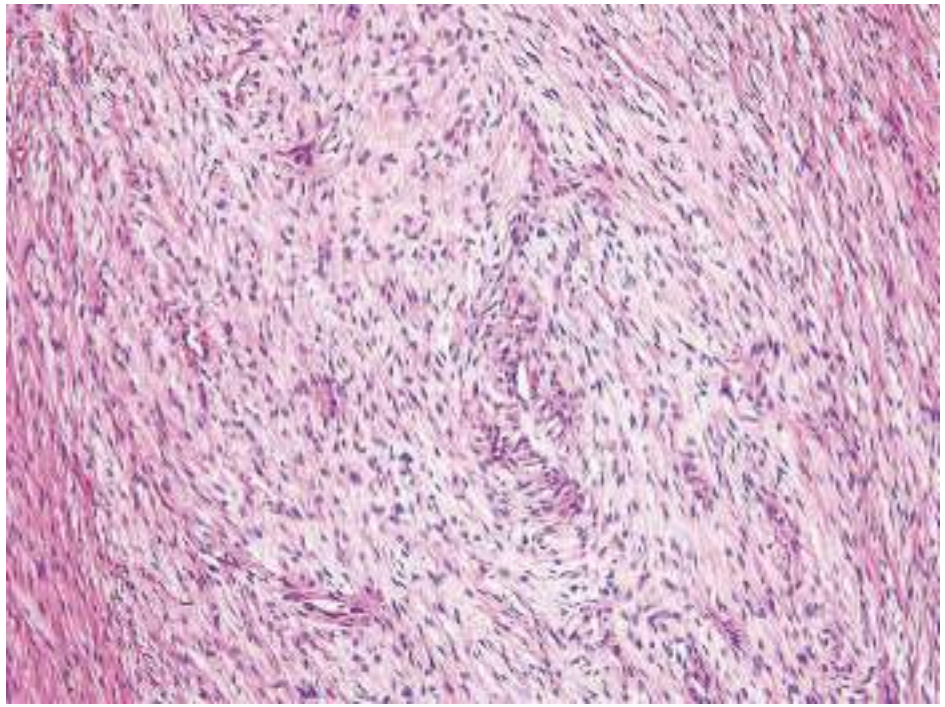
- Hypocellular areas alternating with hypercellular areas
- Extracellular matrix in less cellular areas is usually myxoid
- Well-developed vascular network +/- hemangiopericytoma-like vessels
- Hyperchromatic thin nuclei, with wavy or focally buckled shapes
- Often some degree of nuclear pleomorphism
- Low-grade MPNST: very scarce mitotic activity

IHC

- 50% of tumors express S-100 protein, focal or patchy distribution
- <70% SOX10 positive, focal or patchy
- GFAP is positive in 30% to 40%
- CD34 is often positive
- EMA may show focal staining
- Focal desmin expression
- Complete loss of expression of H3K27me3

Differential diagnosis

Low-grade fibromyxoid sarcoma



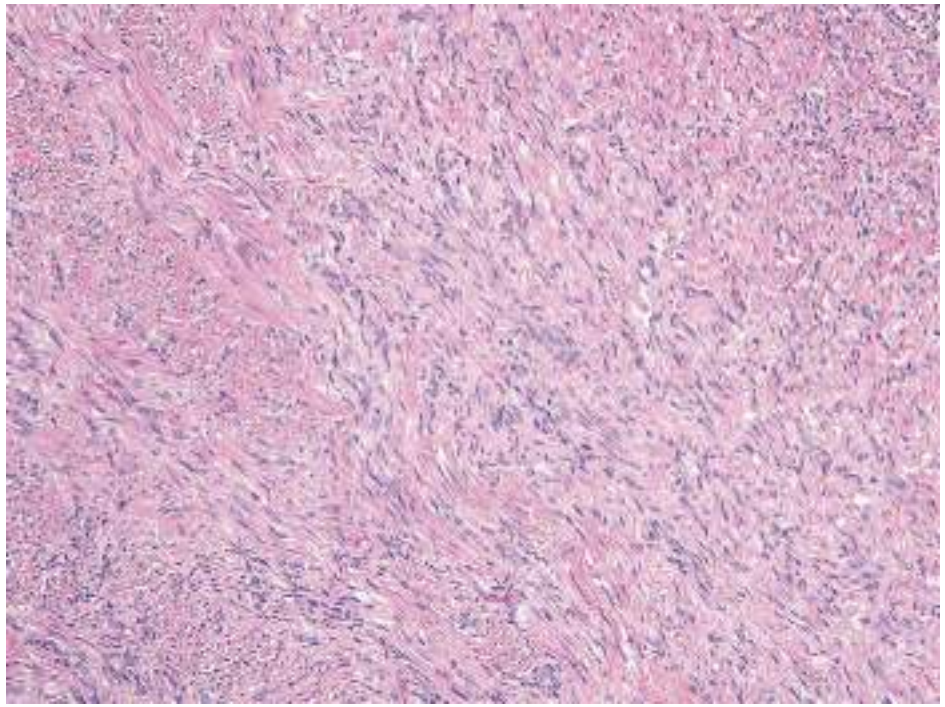
- Sharply demarcated, alternating fibrous and myxoid areas
- Bland monomorphic spindled to ovoid tumor cells
- Fascicular, storiform, or whorled growth pattern
- 10% of tumors contain areas of increased cellularity
- Myxoid areas often contain arcades of elongated blood vessels
- Mitotic activity is usually very low
- Necrosis is uncommon

- **IHC**
- Expression of MUC4, diffuse and strong
- 80% EMA +
- CD99 and bcl-2 +
- Rarely focal expression of SMA (30%), desmin, CD34, or keratin
- negative for S-100, GFAP, caldesmon, and KIT

- *FUS-CREB3L2* or *FUS-CREB3L1* gene fusions

Differential diagnosis

Low-grade myofibroblastic sarcoma

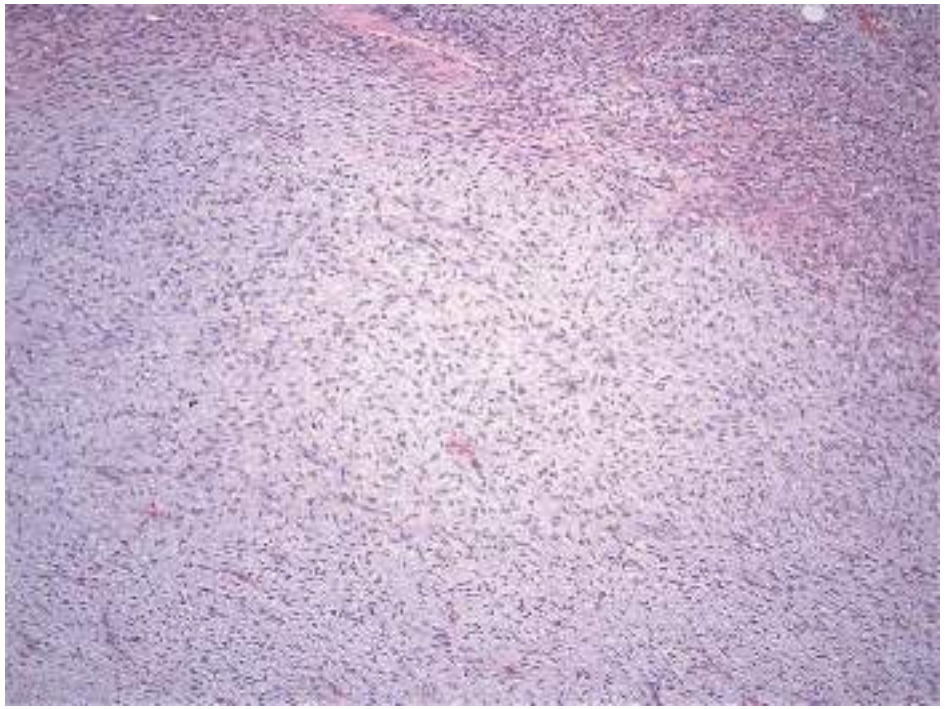


- Long fascicles of relatively uniform spindle cells
- Abundant, palely eosinophilic, fibrillary cytoplasm and ill-defined cell borders
- Stromal collagen is often prominent
- Nuclei are slender or wavy with tapering ends and dispersed chromatin, sometimes with a prominent nucleolus
- Nuclear atypia is usually mild to moderate
- Mitotic activity is typically low
- Infiltrating borders

- **IHC**
- Usually positive for SMA, desmin, or both
- Consistently negative for h-caldesmon, myf4, CD34, EMA, keratins, and S-100
- Often positive for calponin
- A subset shows nuclear staining for β-catenin

Differential diagnosis

Myxoid Solitary fibrous tumor



- Alternating hypercellular and hypocellular fibrous areas
- Patternless architecture
- Prominent stromal collagen
- Hemangiopericytoma-like vessels
- Mitoses are usually sparse
- Necrosis is rare
- Convenctional SFT areas must be found

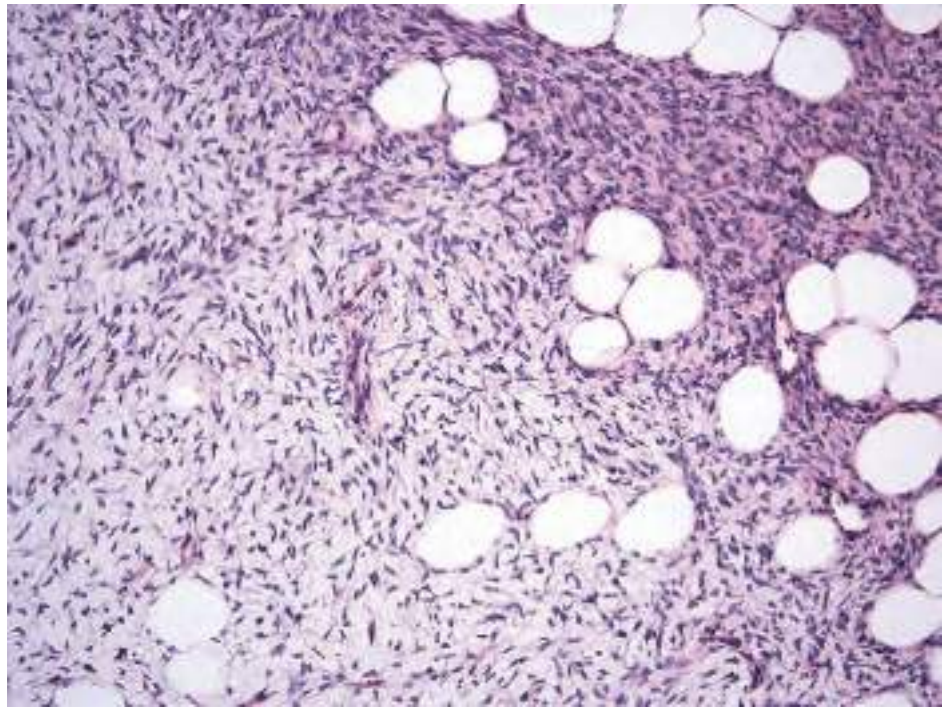
IHC

- Commonly expresses CD34 (90% of cases), CD99 (70%) and STAT6
- Variable expression of EMA (30%), SMA (20%), and bcl-2 (30%)
- MUC4 is negative
- very rare cases show focal staining for S-100 or desmin
- Negative for keratins

- *NAB2-STAT6* gene fusions are pathognomonic

Differential diagnosis

Myxoid DFSP



- This variant usually lack the tight storiform architecture
- Monomorphic proliferation of small spindle cells embedded in a myxoid matrix
- Ill-defined and diffusely infiltrative
- Lacelike or honeycomb appearance in transitional area with subcutaneous tissue
- Nuclear pleomorphism is absent
- Mitotic activity is low
- Necrosis is uncommon
- Conventional DFSP areas should be found

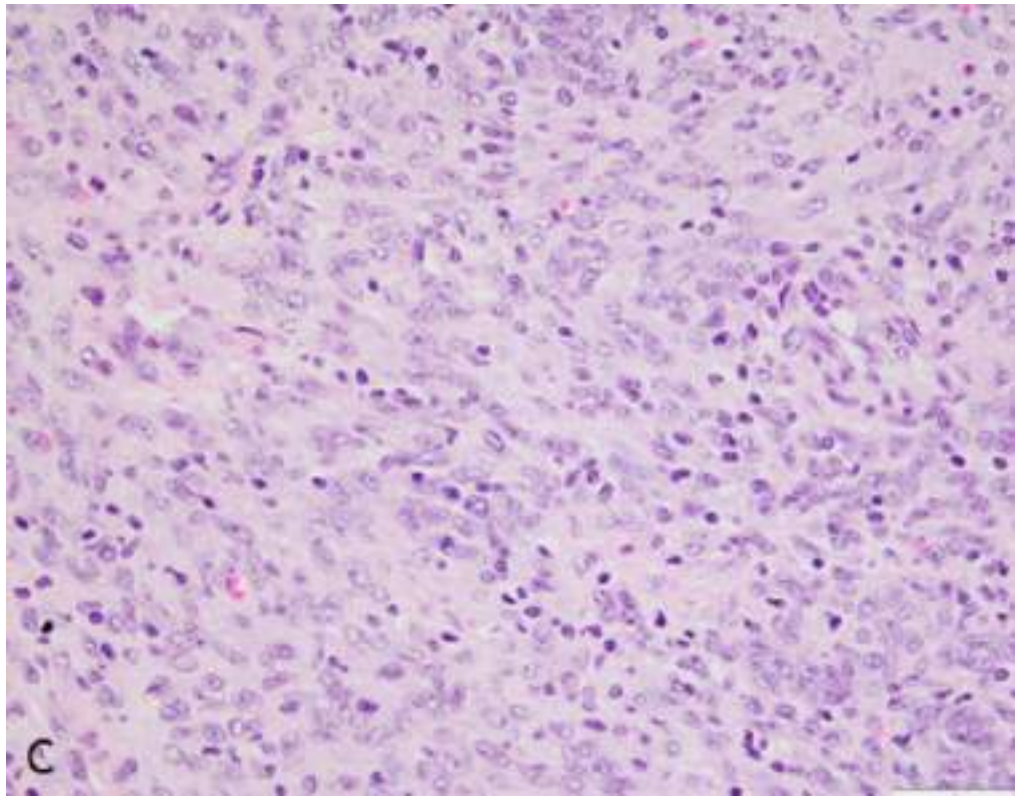
IHC

- Strongly and diffusely positive for CD34
- S-100 and desmin are not expressed

- *COL1A1*::*PDGFB* translocation

Differential diagnosis

NTRK-rearranged spindle cell neoplasm



- Wide spectrum of morphological patterns
- Superficial tumours show a pattern reminiscent of lipofibromatosis
- Other tumours may be more celular with a myxoid background
- Hybrid appearance is common
- Range of cellularity and mitotic counts (frequently low)

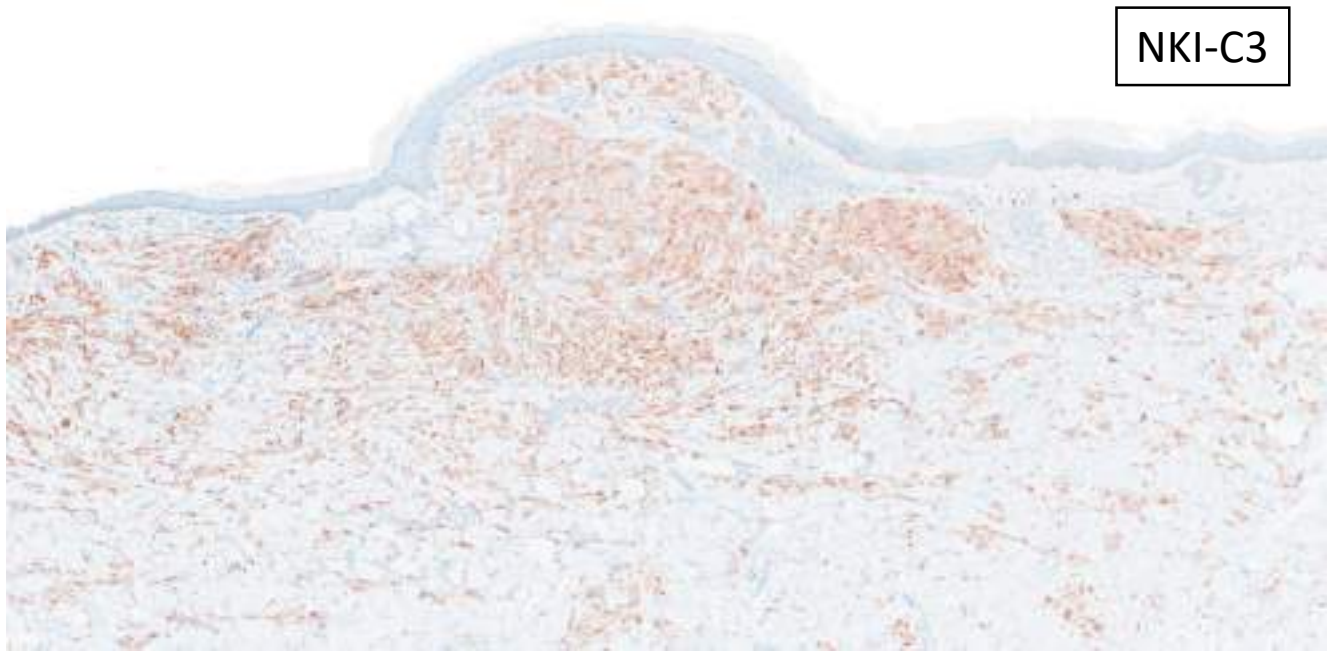
- **IHC**
- co-expression of CD34, S100 and occasionally SMA
- May have a nonspecific immunoprofile
- PanTRK is usually diffusely expressed in tumours with activating *NTRK* fusions
- SOX10 is typically absent
- H3K27me3 retained

- Fusions or activating point mutations in receptor tyrosine kinase or downstream effector molecule

Immunohistochemistry

Positive

- NKI-C3
- CD10
- S100A6



Negative

- S100
- GFAP

Variable

- MITF
- CD99
- NSE
- CD68
- SMA
- Muscle specific actin

PRAME expression in cellular neurothekeoma: A study of 11 cases

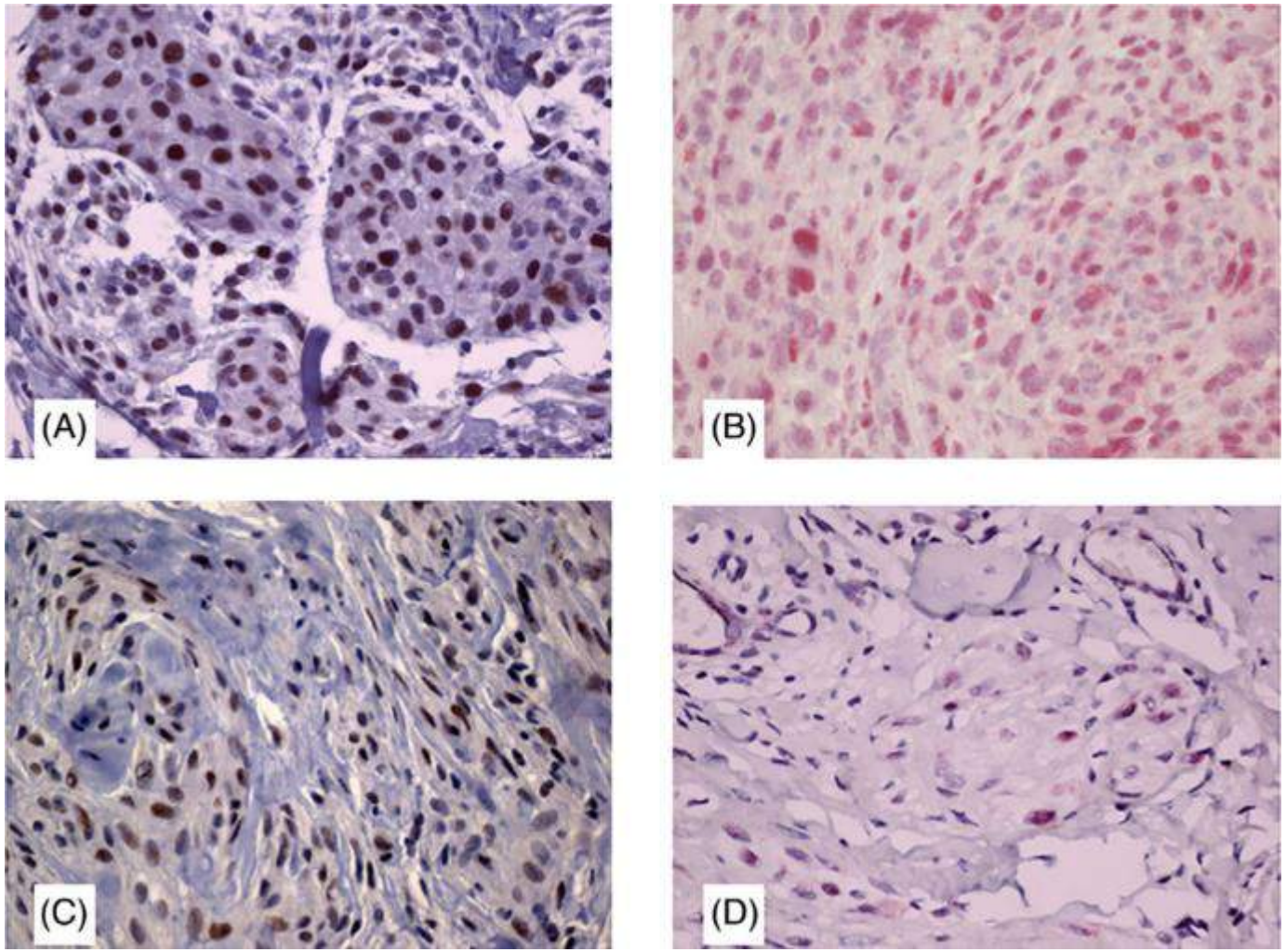


FIGURE 2 Moderate and diffuse nuclear staining for PRAME in a case of NTK (A) and a case of atypical NTK (B). Two cases of NTK with focal (C) and faint nuclear staining (D)

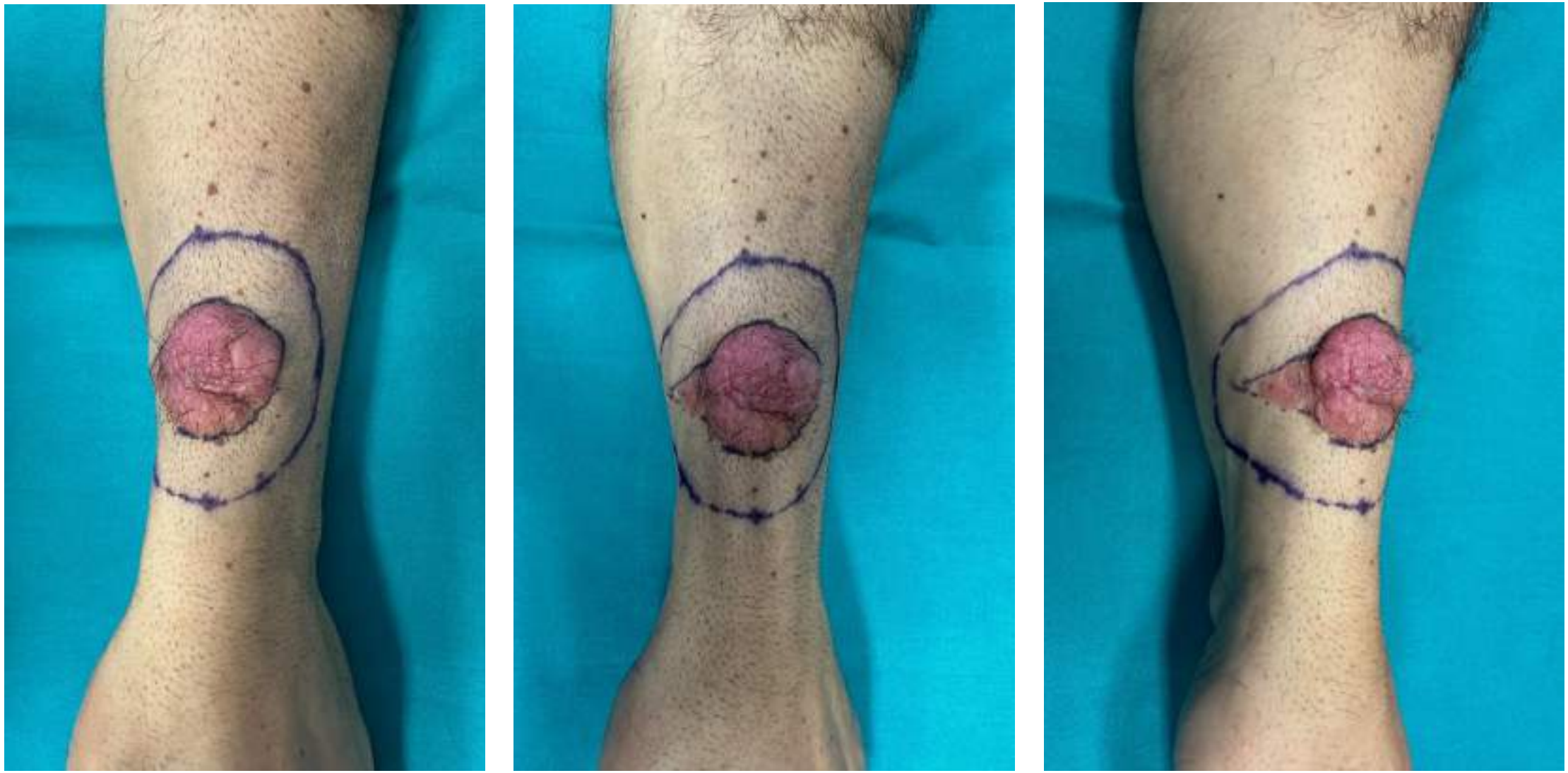
- Expression of PRAME, albeit focally, in all 11 cases of NTK studied, whereas staining was completely negative in three cases of Nerve sheath myxoma. This finding could represent an aid in differentiating the myxoid variant of NTK from NSM.
- Plexiform fibrous histiocytoma were negative

Cesinaro AM et al. PRAME expression in cellular neurothekeoma: A study of 11 cases. J Cutan Pathol. 2022 Apr;49(4):338-342.

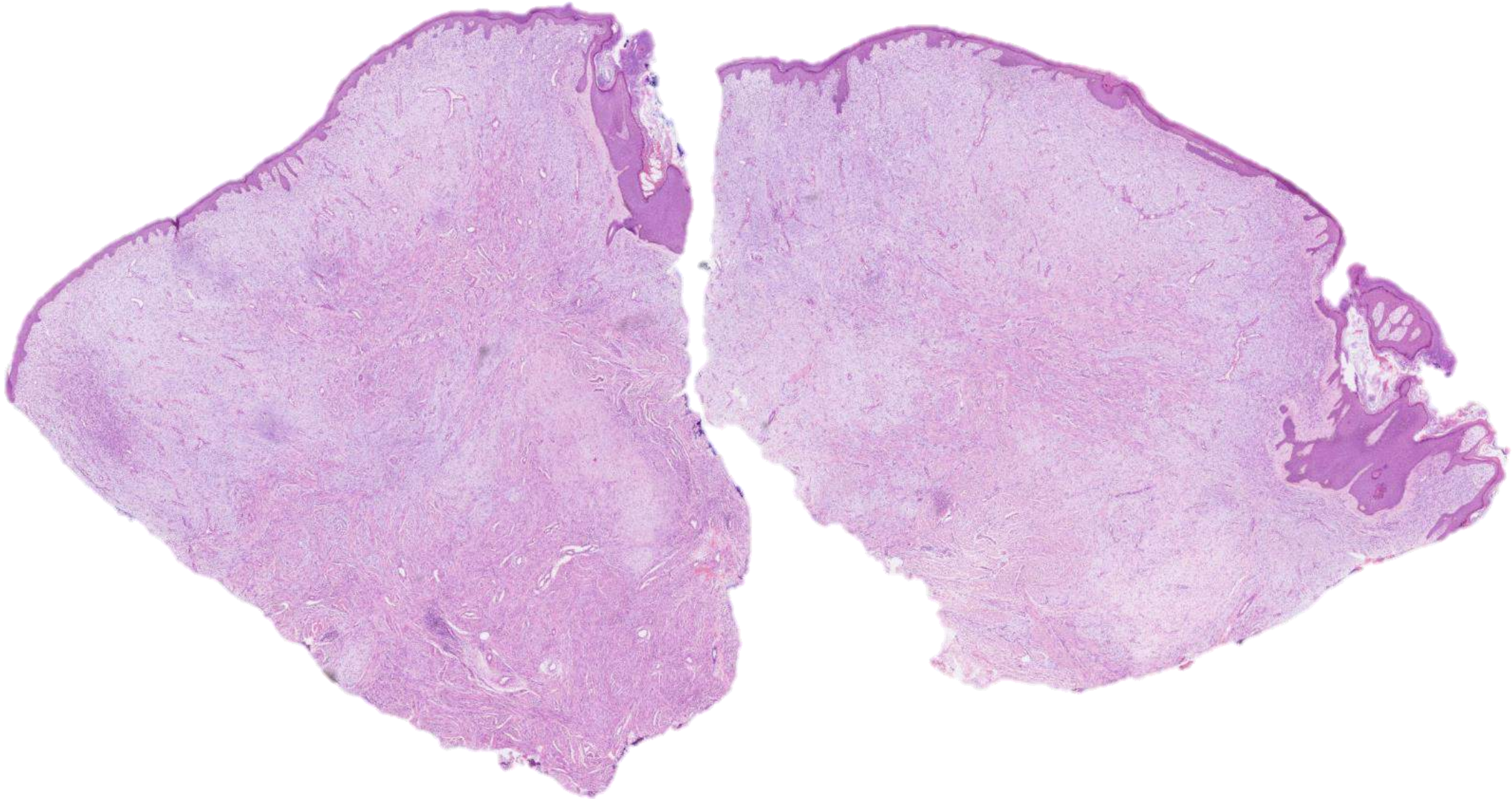
Differential diagnosis

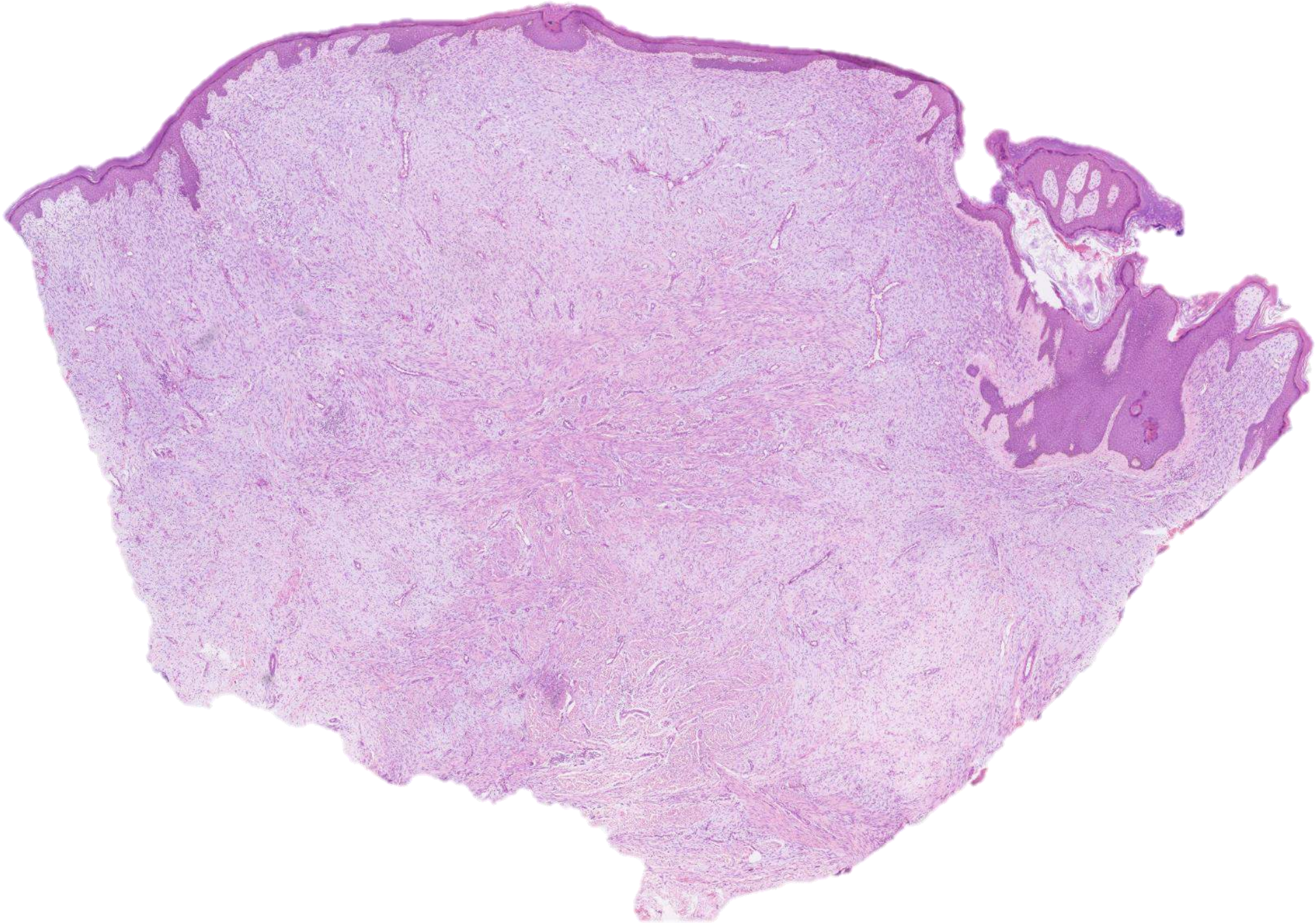
- Melanocytic lesions, intradermal Spitz
- Plexiform fibrohistiocytic tumour
- Nerve sheath myxoma

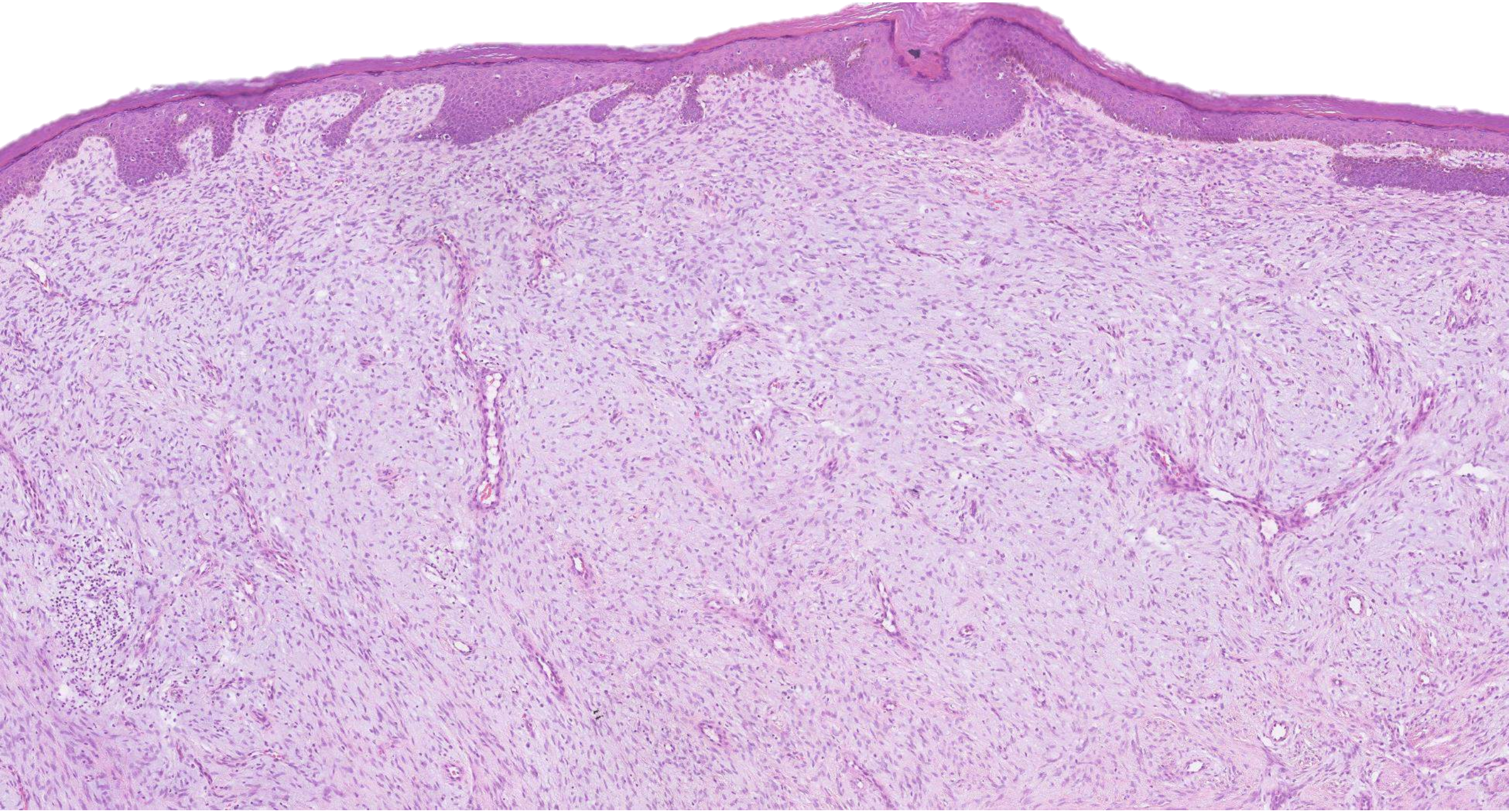
Male, recurrent lesion, diagnosed in 2014 as dermatomyofibroma

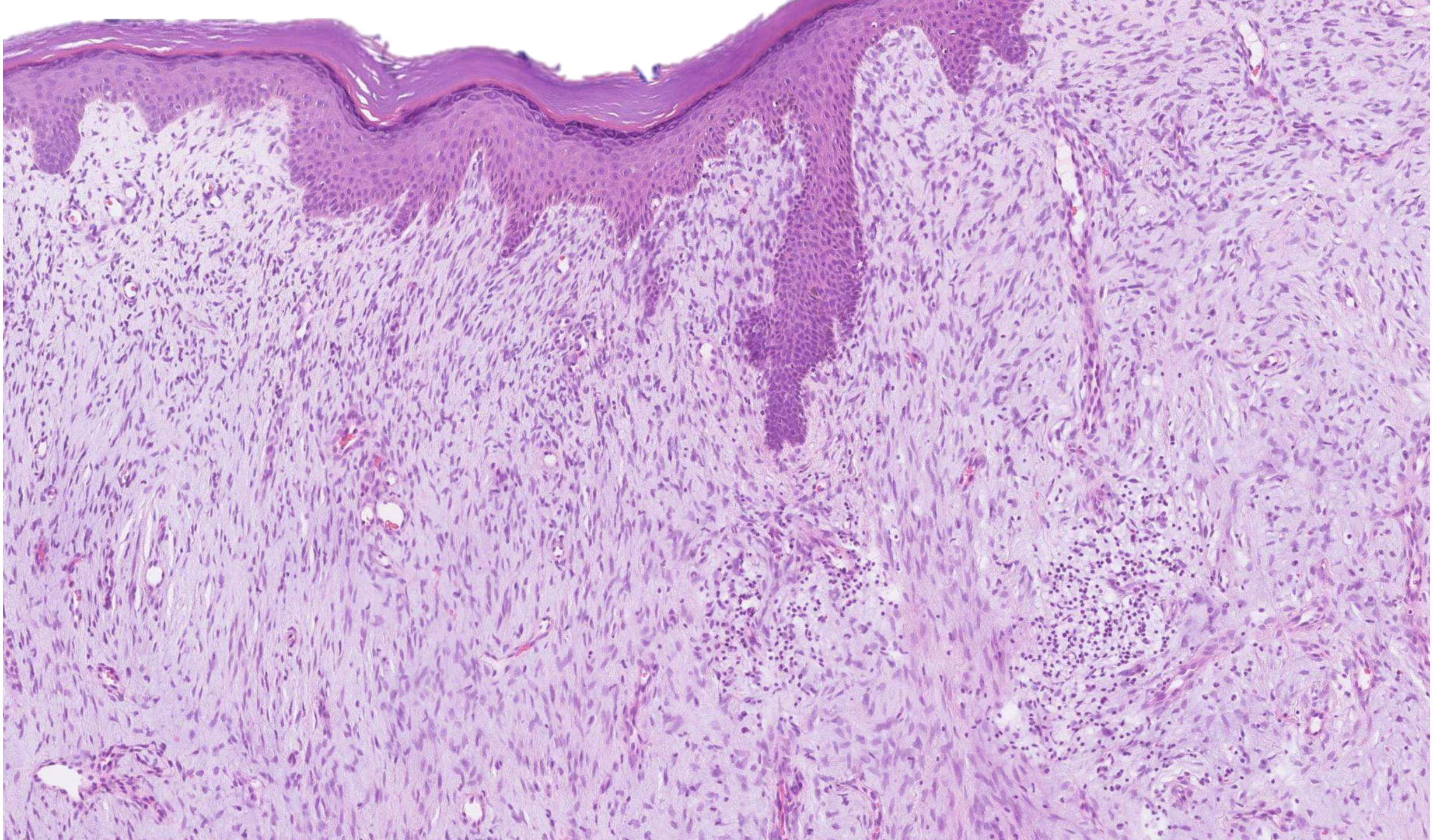


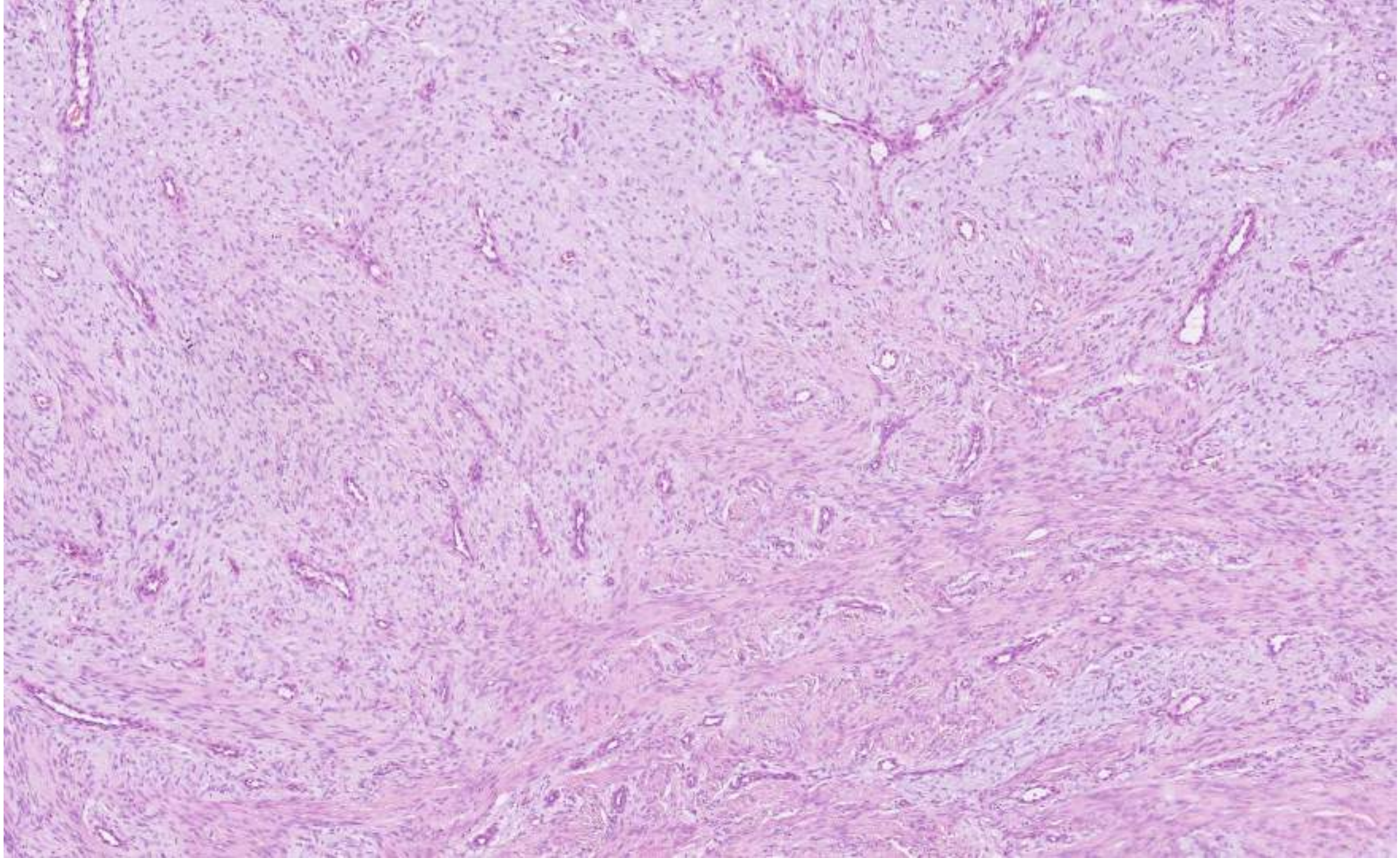
Picture courtesy of Prof Carla Di Loreto, md, Udine, Italy

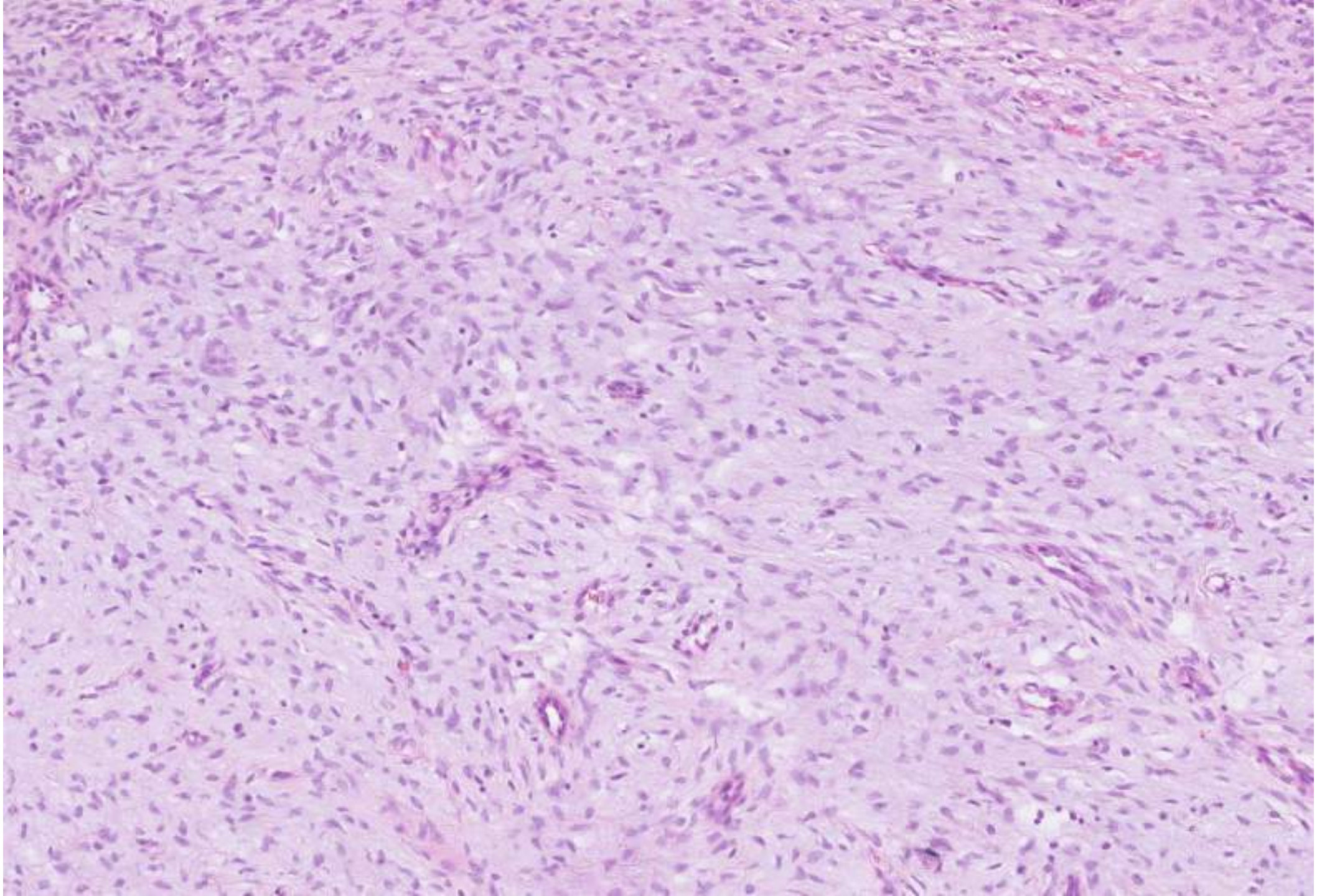


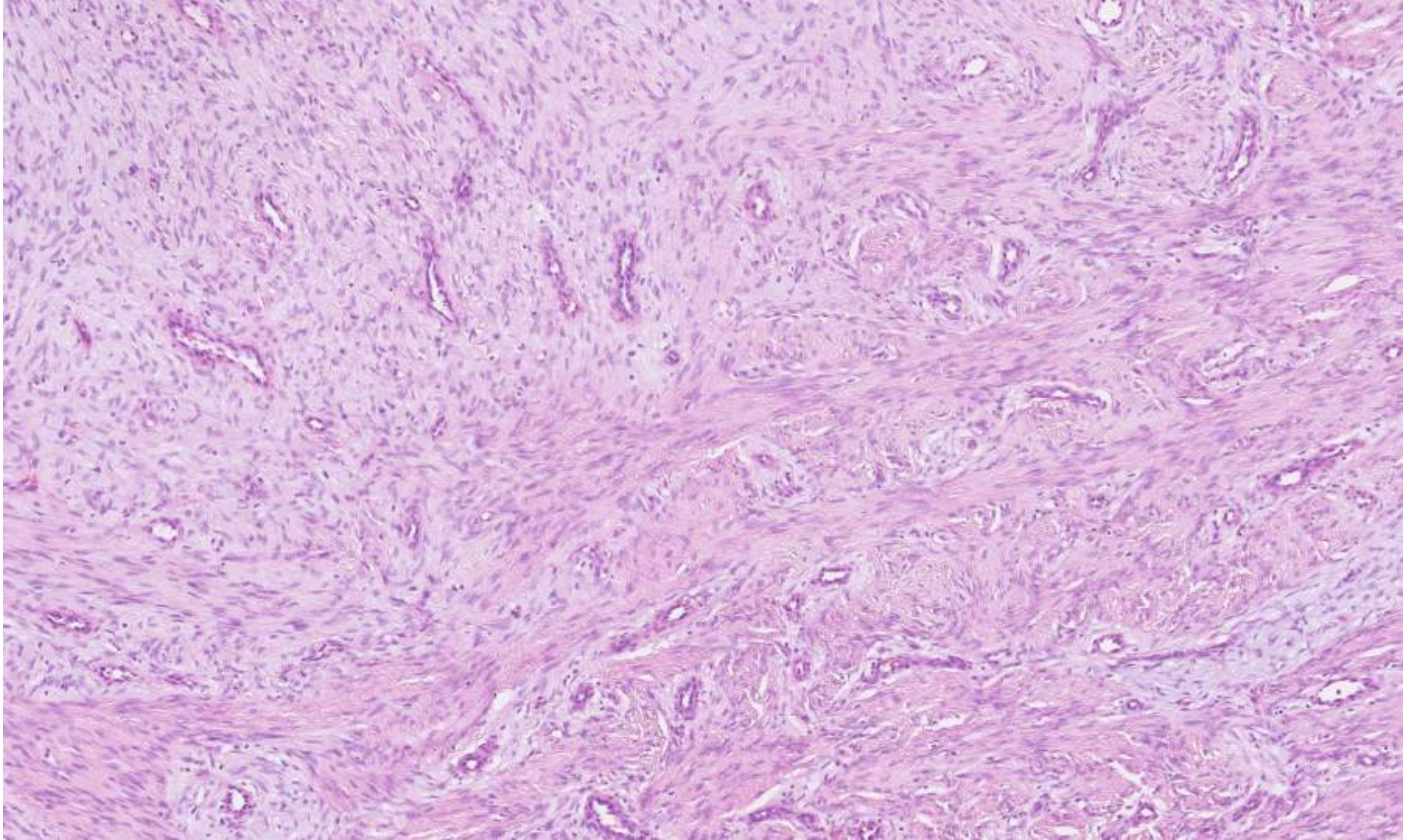


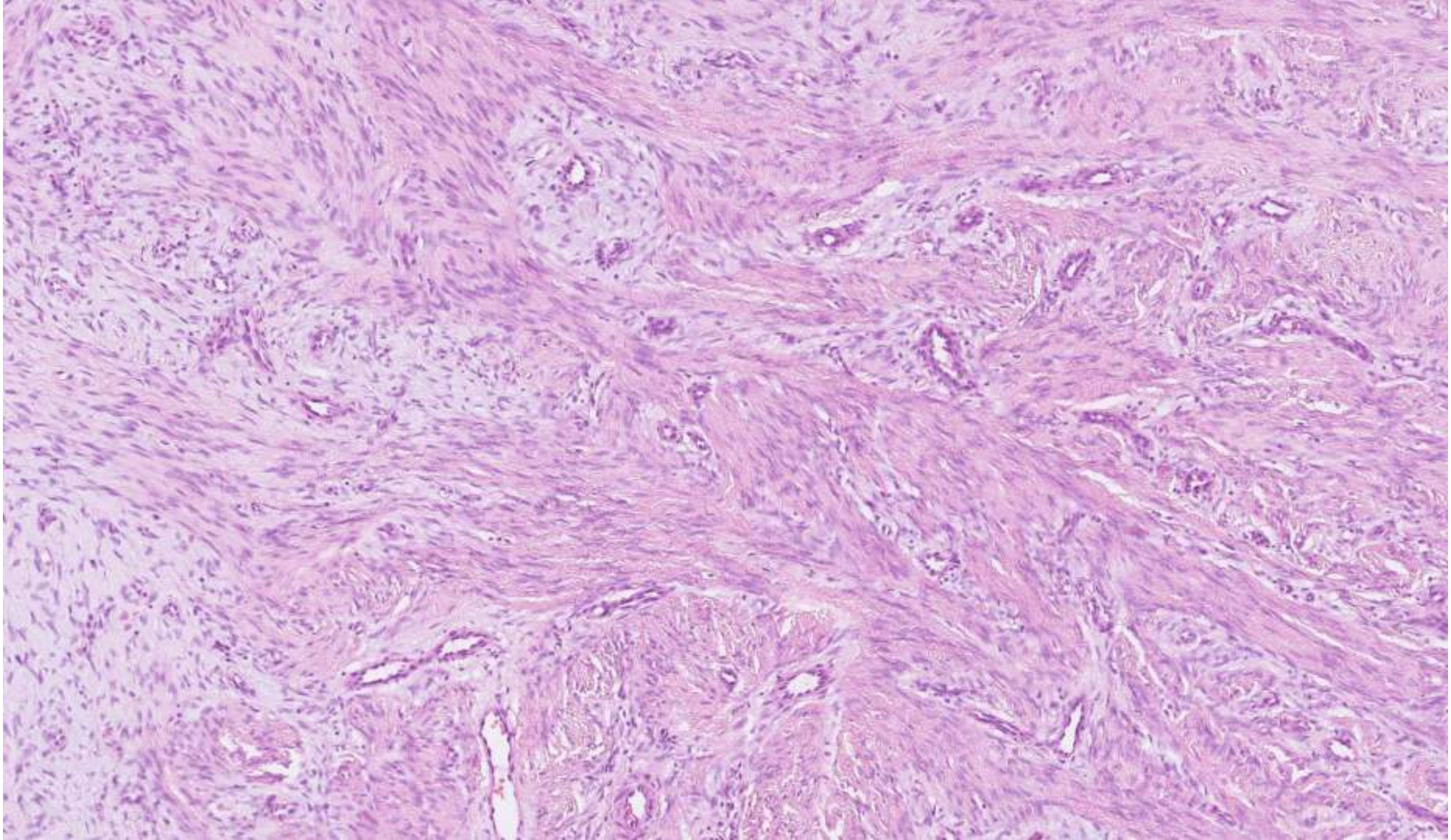


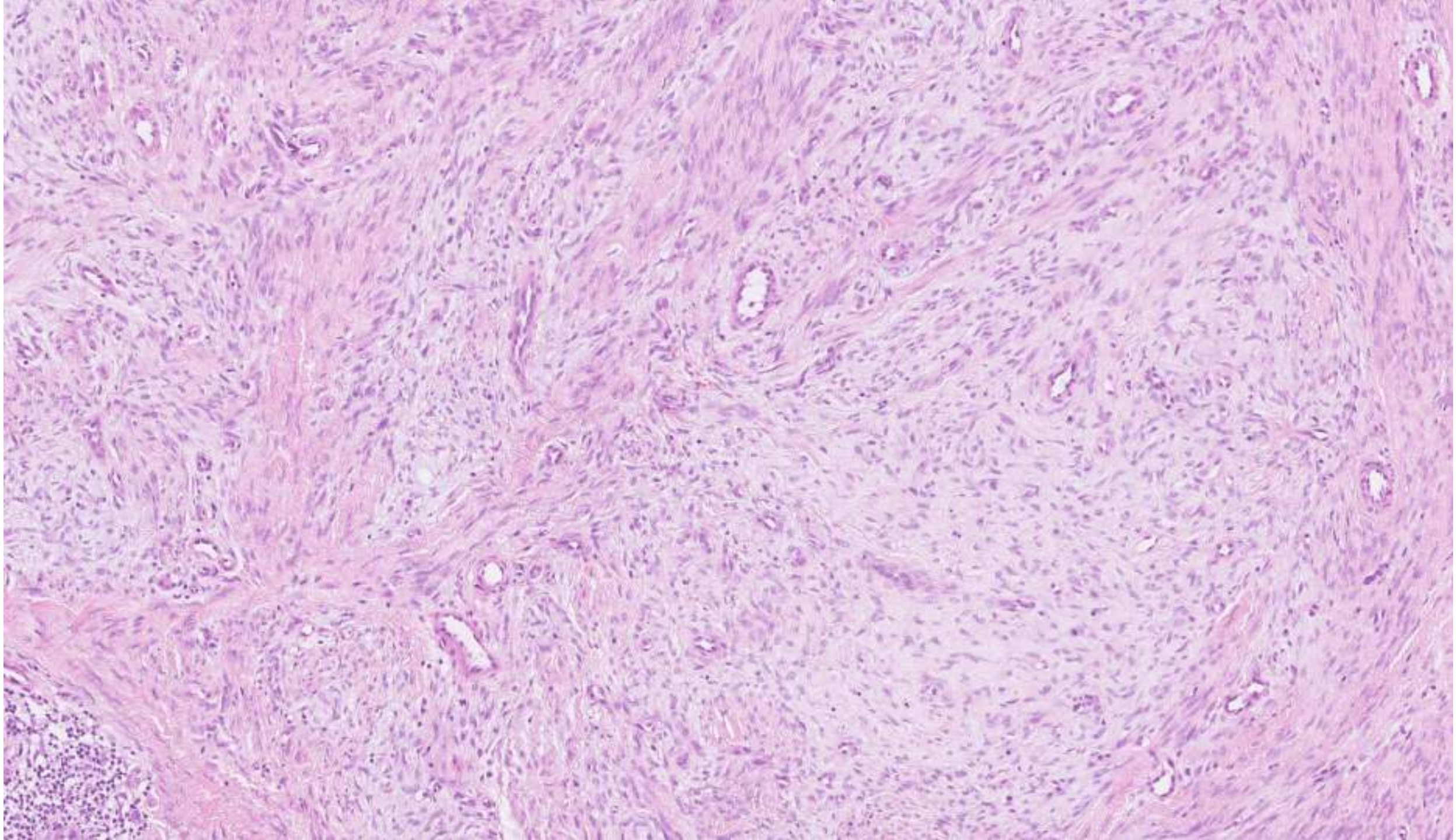


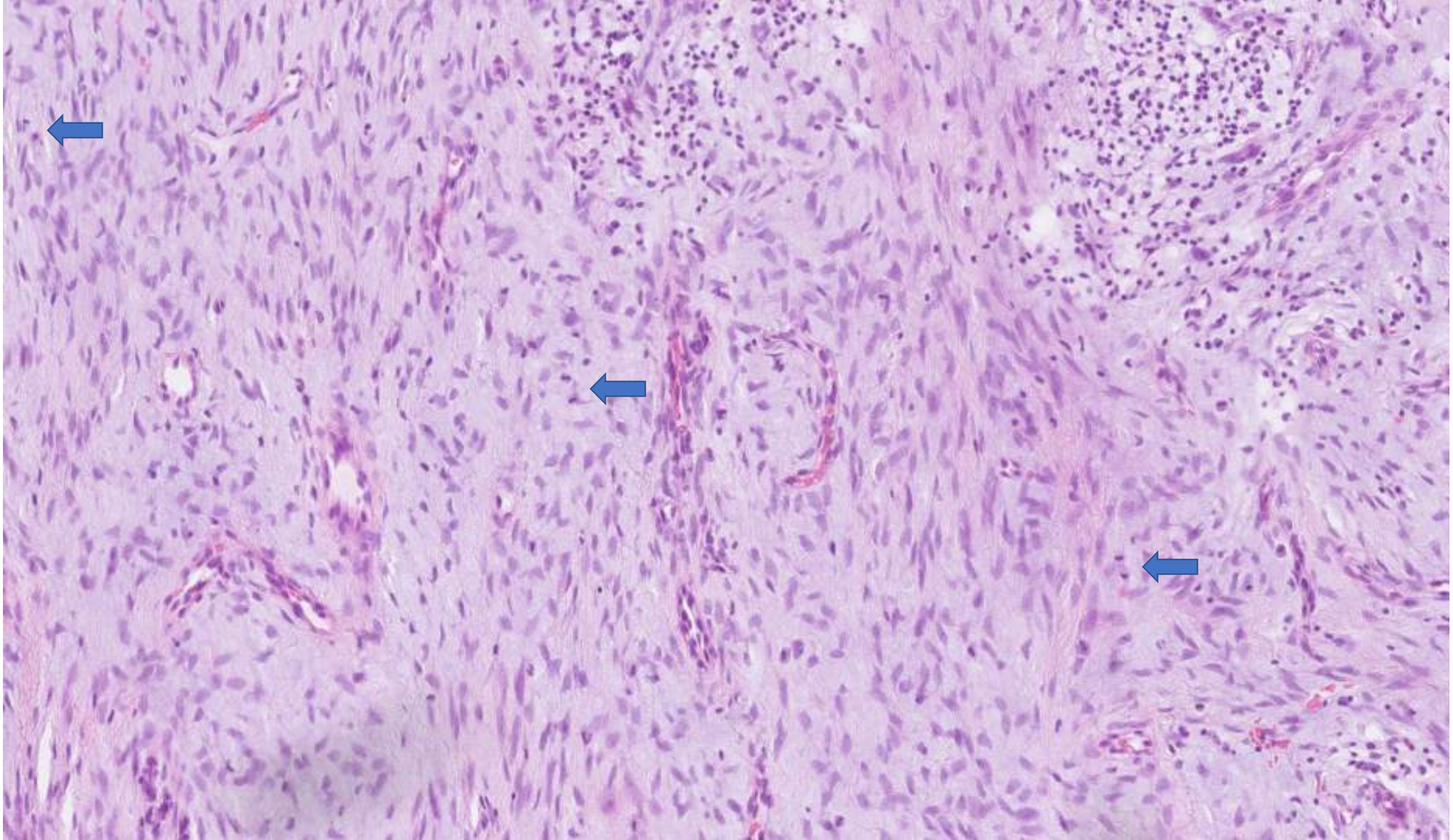


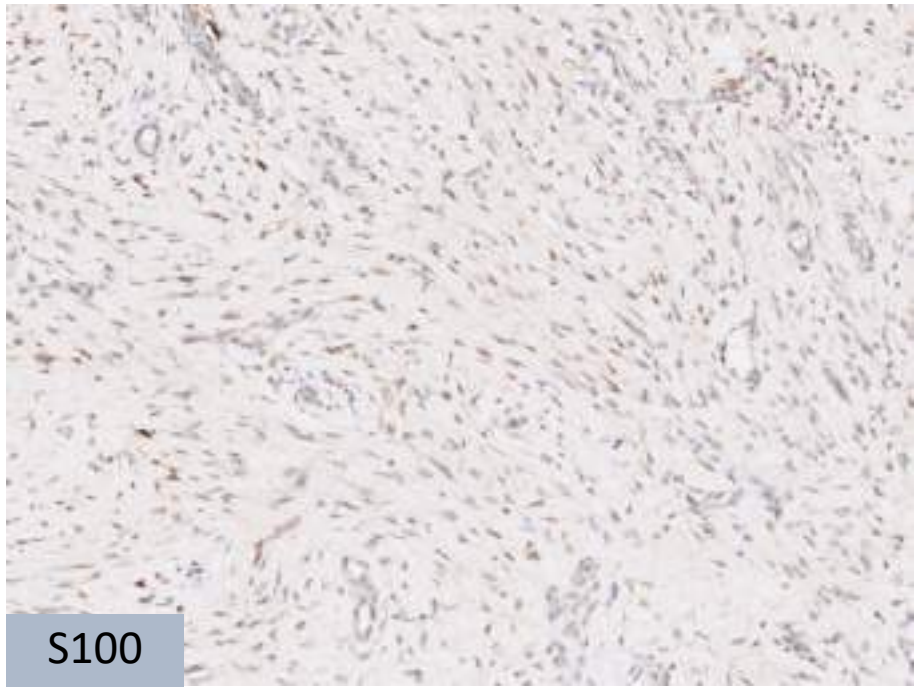


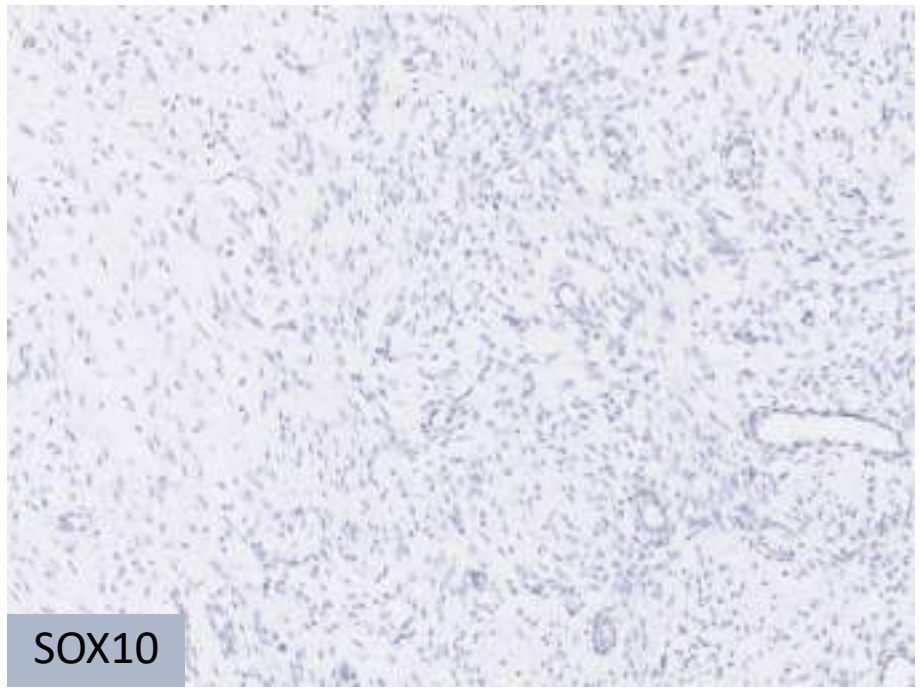


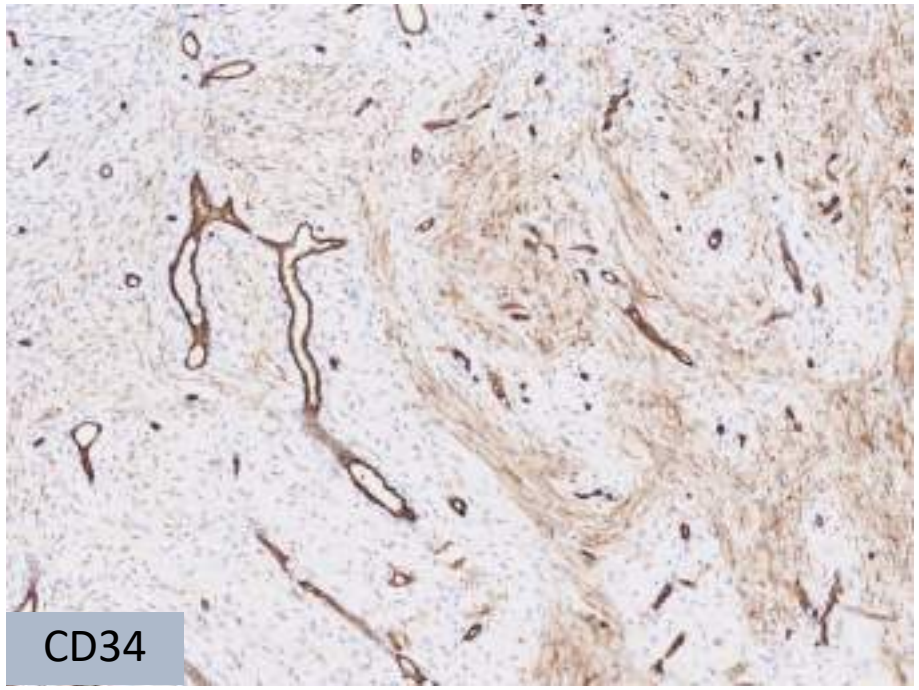


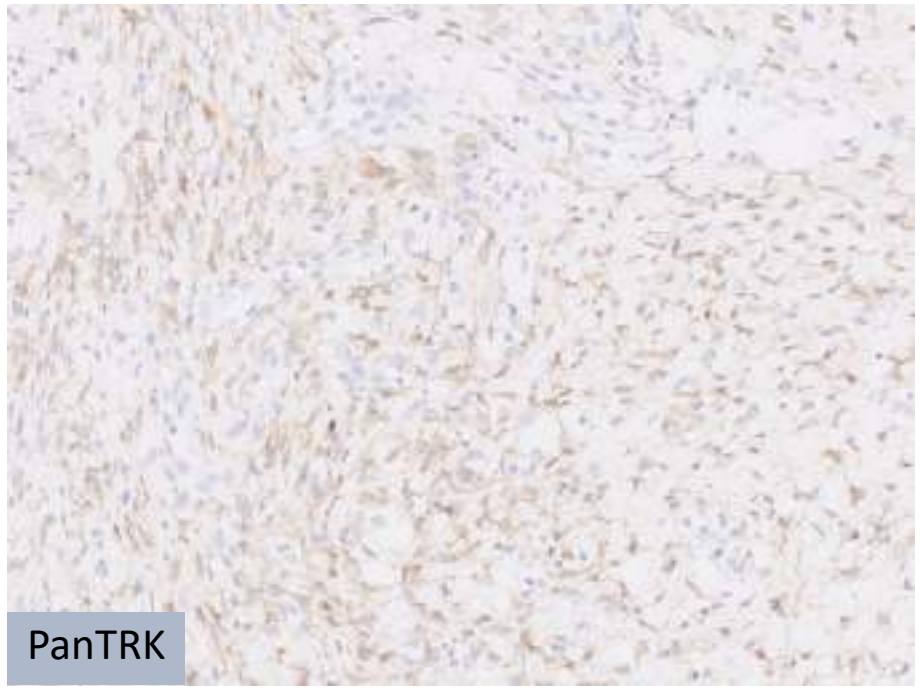





S100


SOX10


CD34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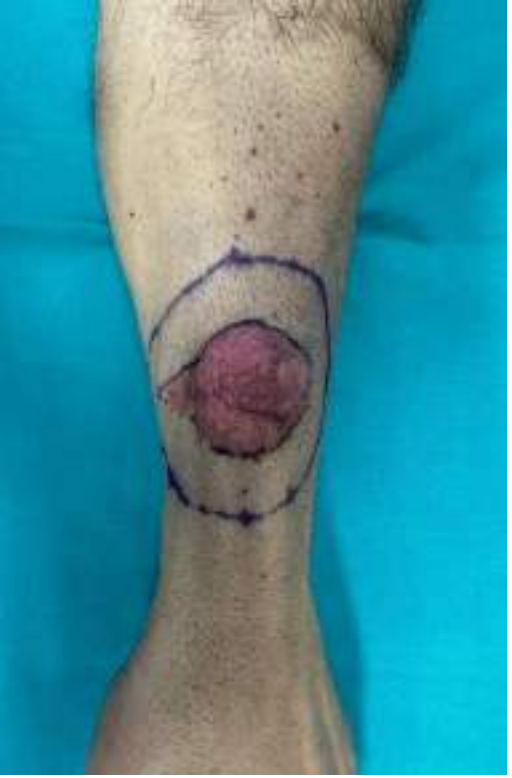

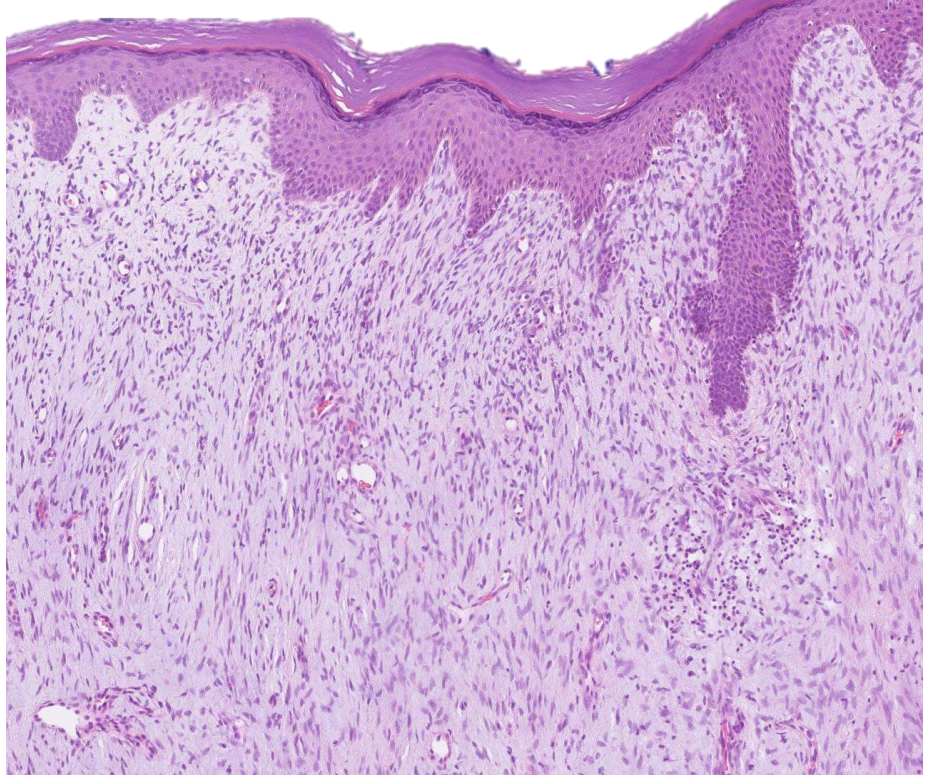

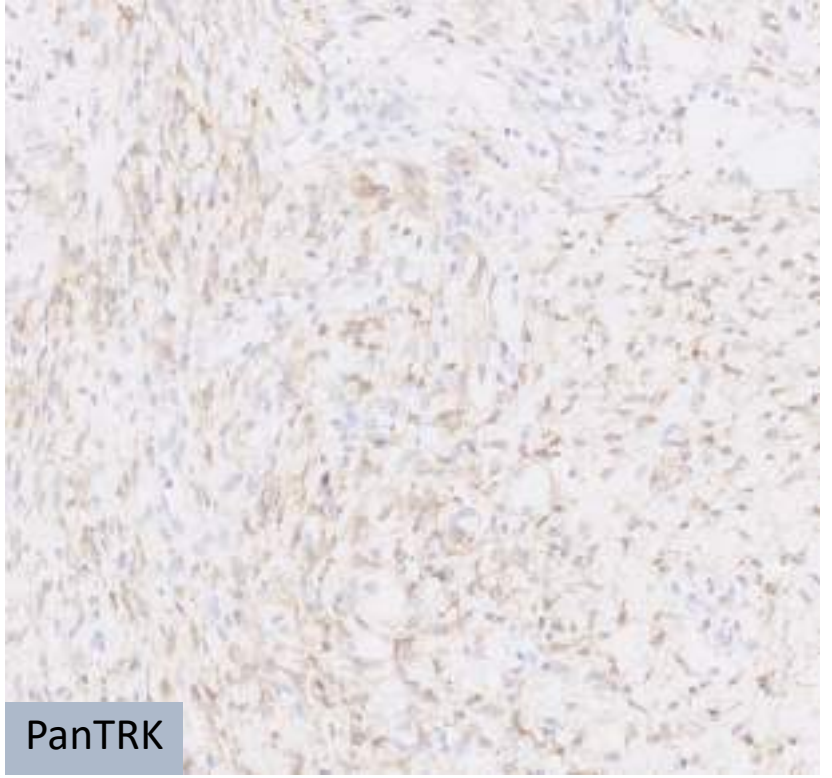
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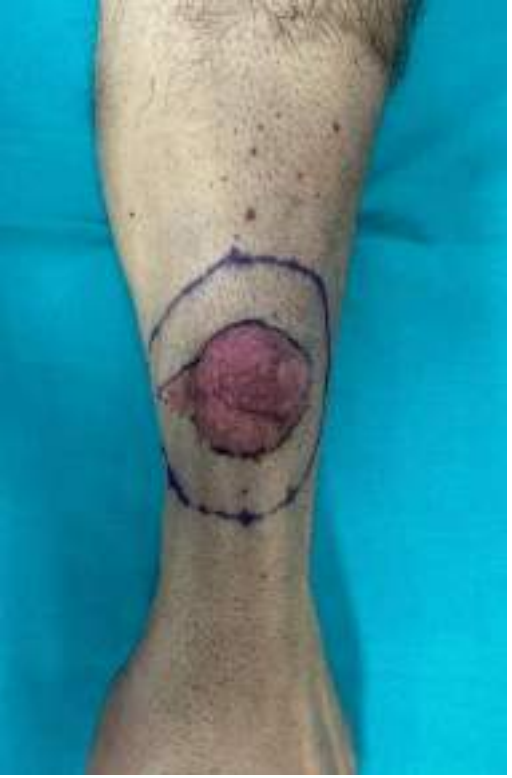
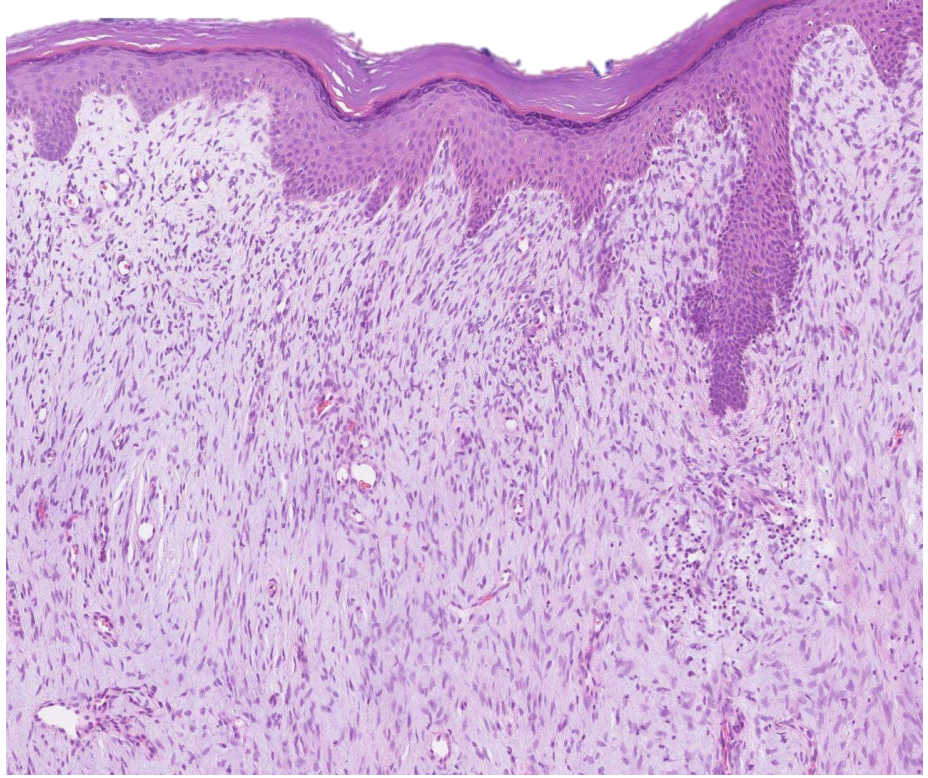
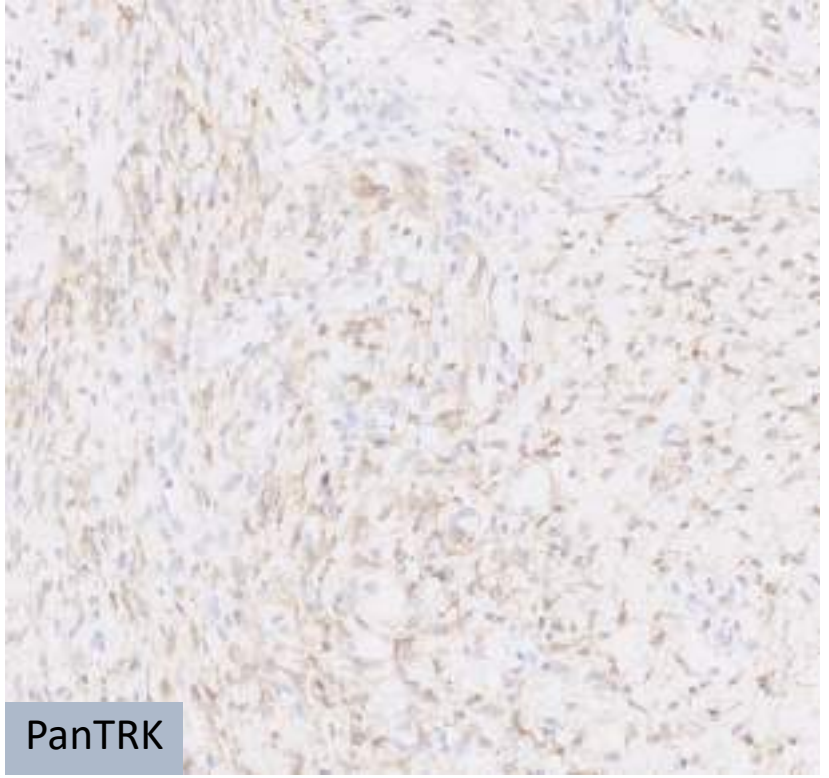






REZULTAT

Fusions detected:

- PPFIBP1 (exon 12) :: NTRK3 (exon 14), with a frequency 51.3%

Genomic location of the breakpoint PPFIBP1 - chr12:27817370 (+) and NTRK3 - chr15:88576276 (-).

- PPFIBP1 (exon 12) :: NTRK3 (exon 14), with a frequency 17.6%

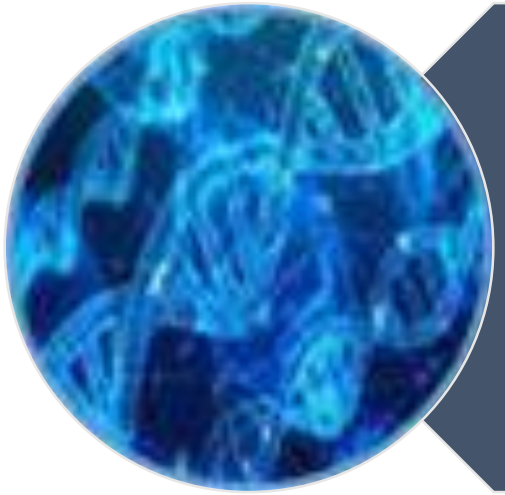
Genomic location of the breakpoint PPFIBP1 - chr12:27817379 (+) and NTRK3 - chr15:88576276 (-).

JP

INTERPRETACIJA

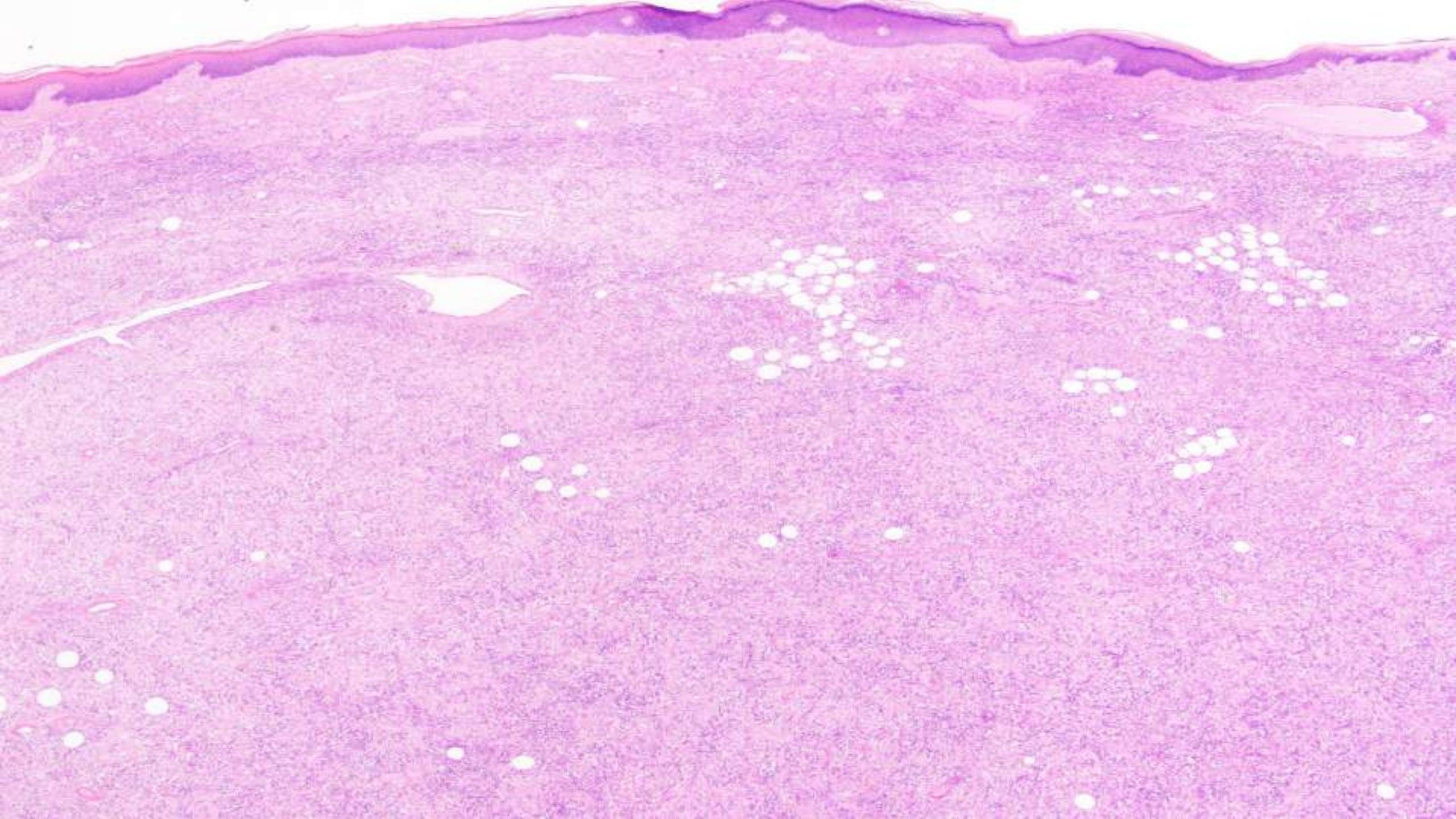
Detected alteration in the tumour: **PPFIBP1::NTRK3 fusion.**

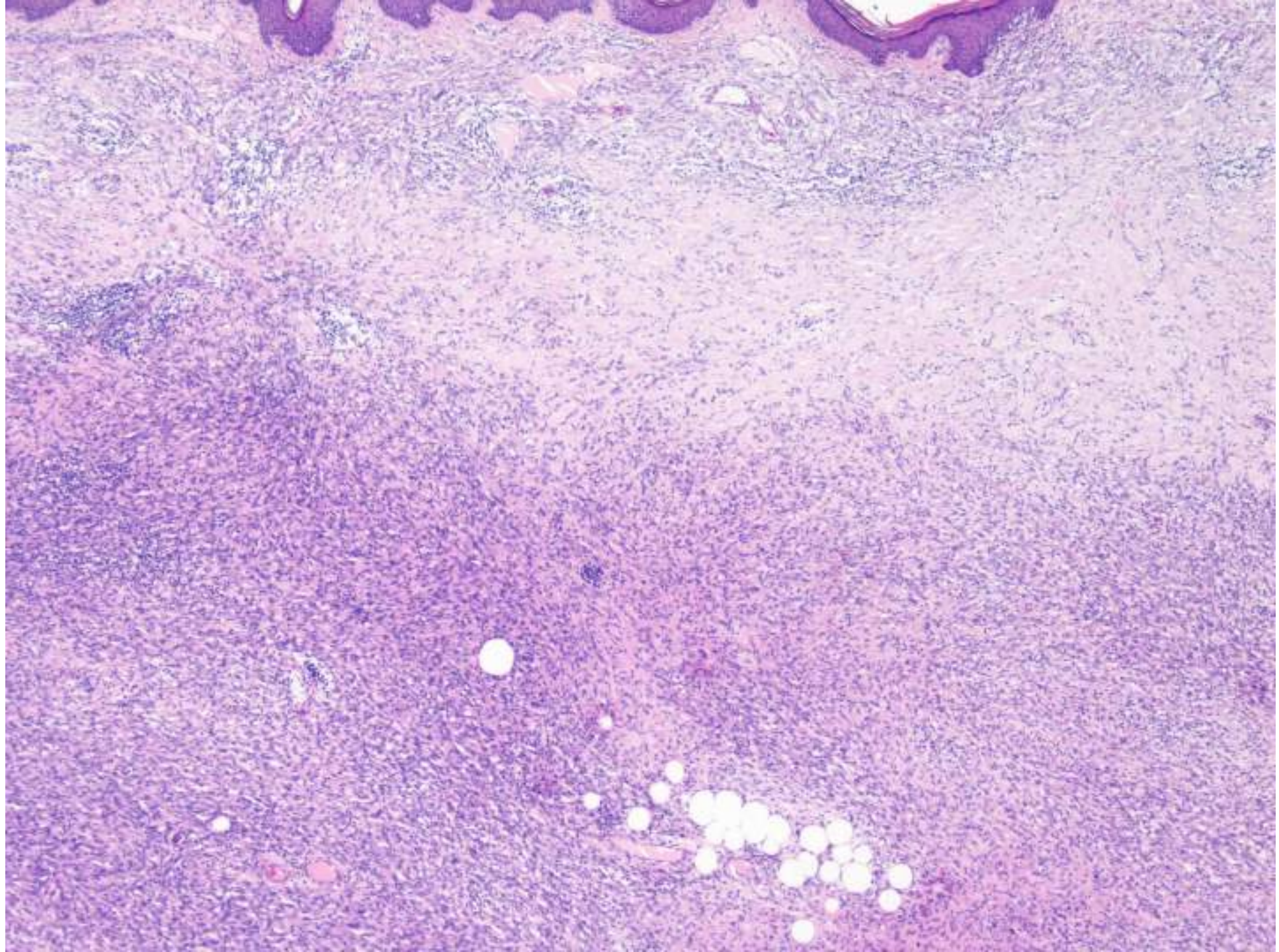
CASE 1
- *DIAGNOSIS* -

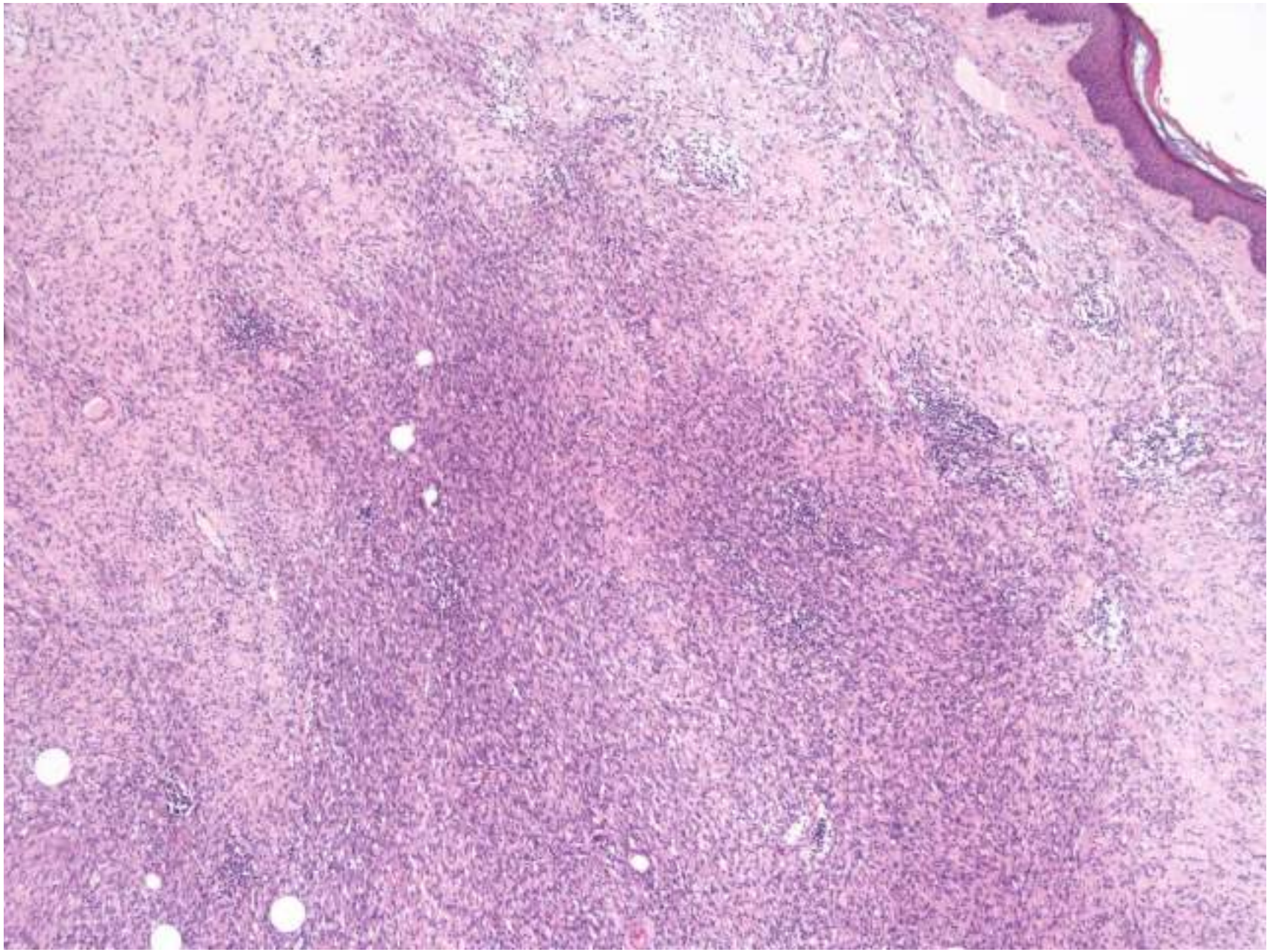


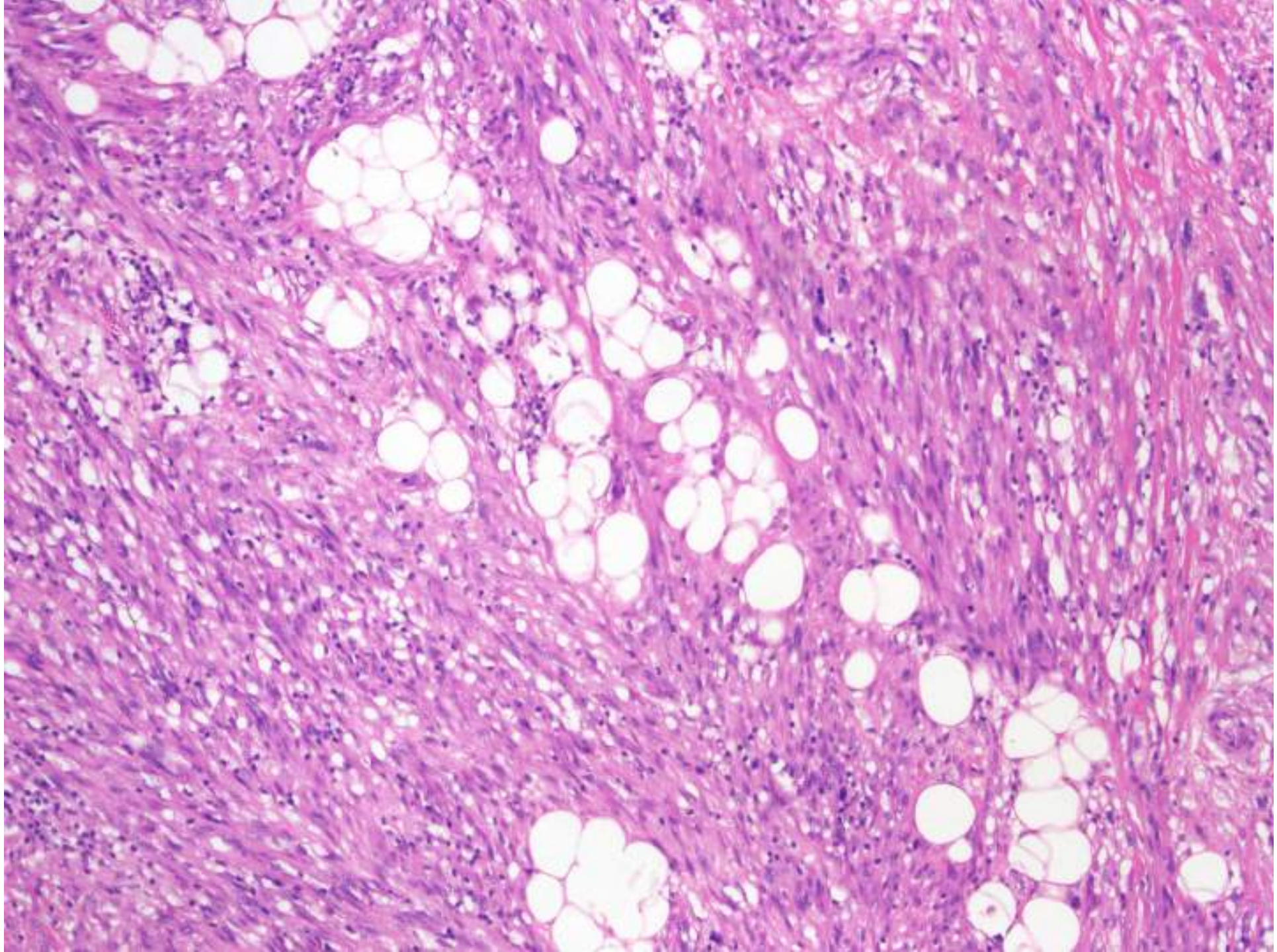
SPINDLE CELL TUMOUR WITH *PPFIBP1::NTRK3* FUSION

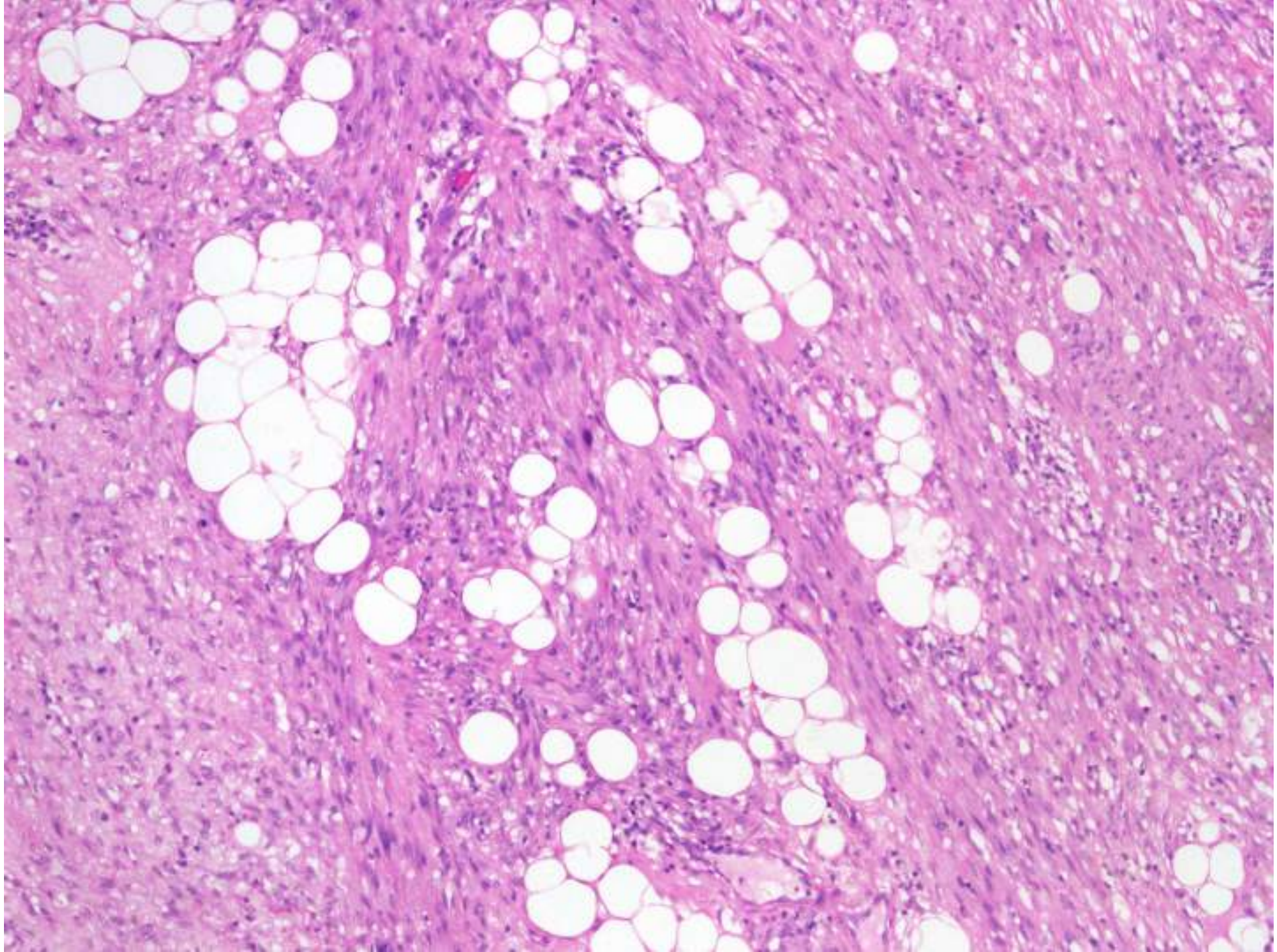
CASE 2

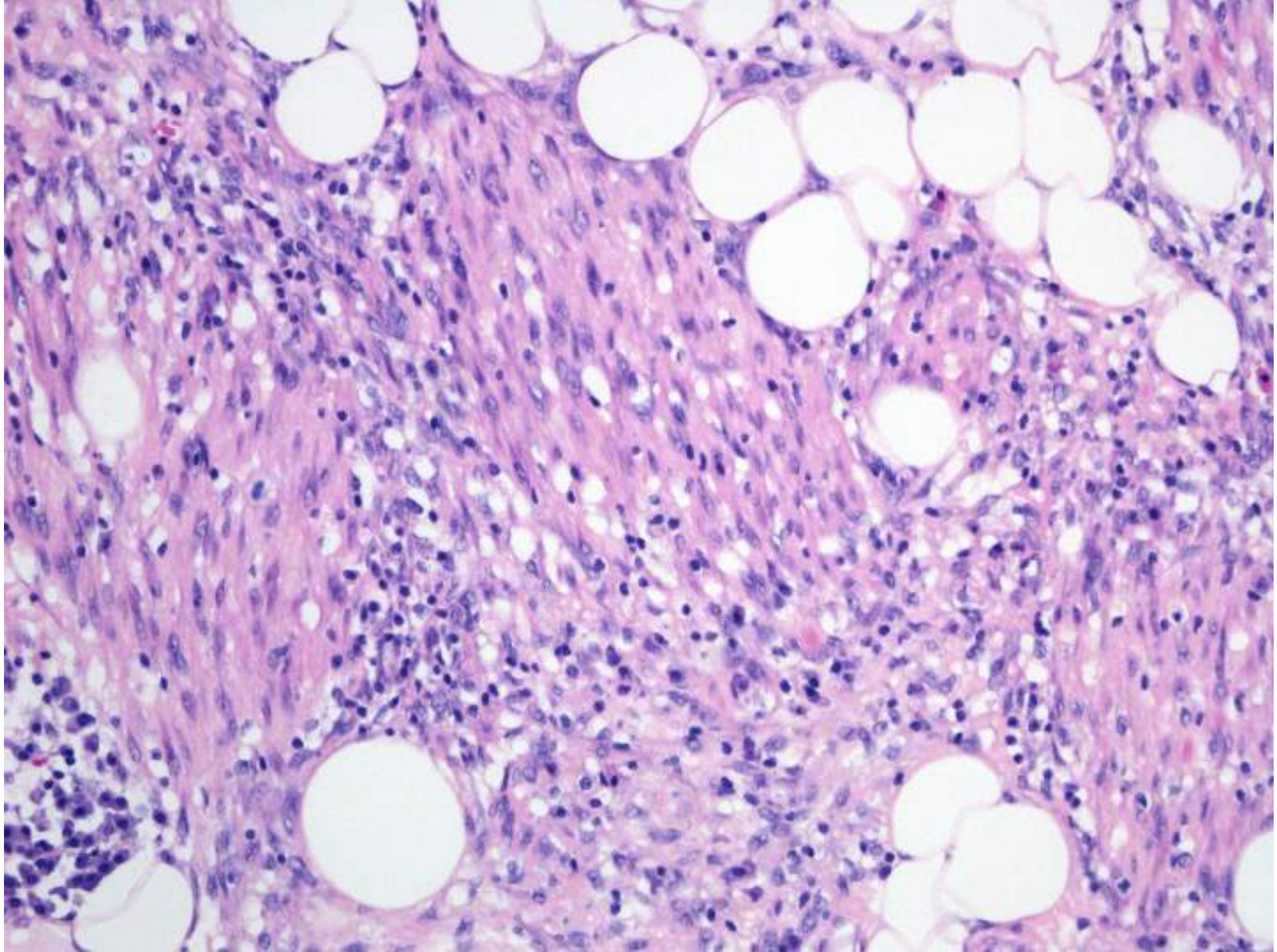


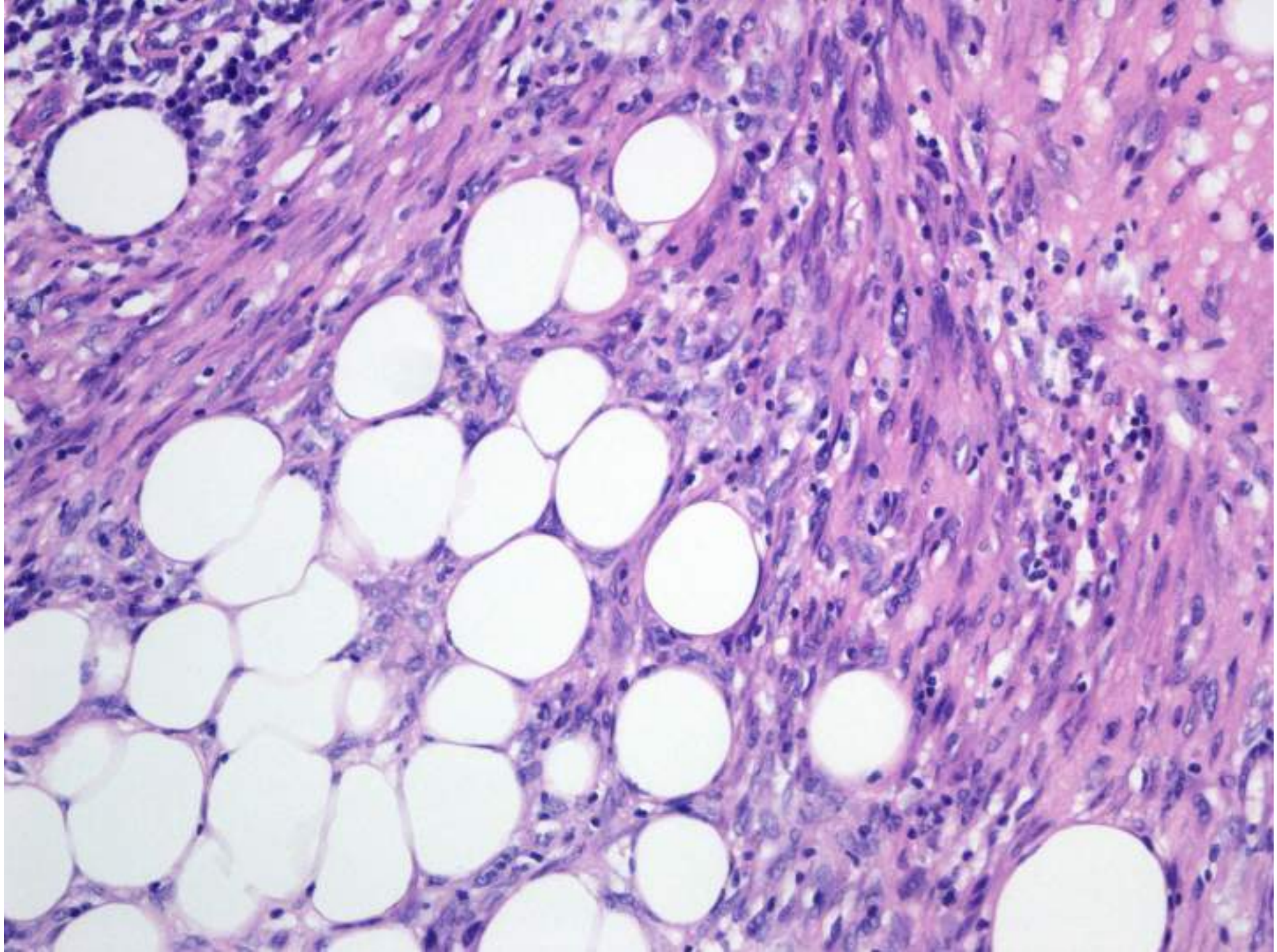


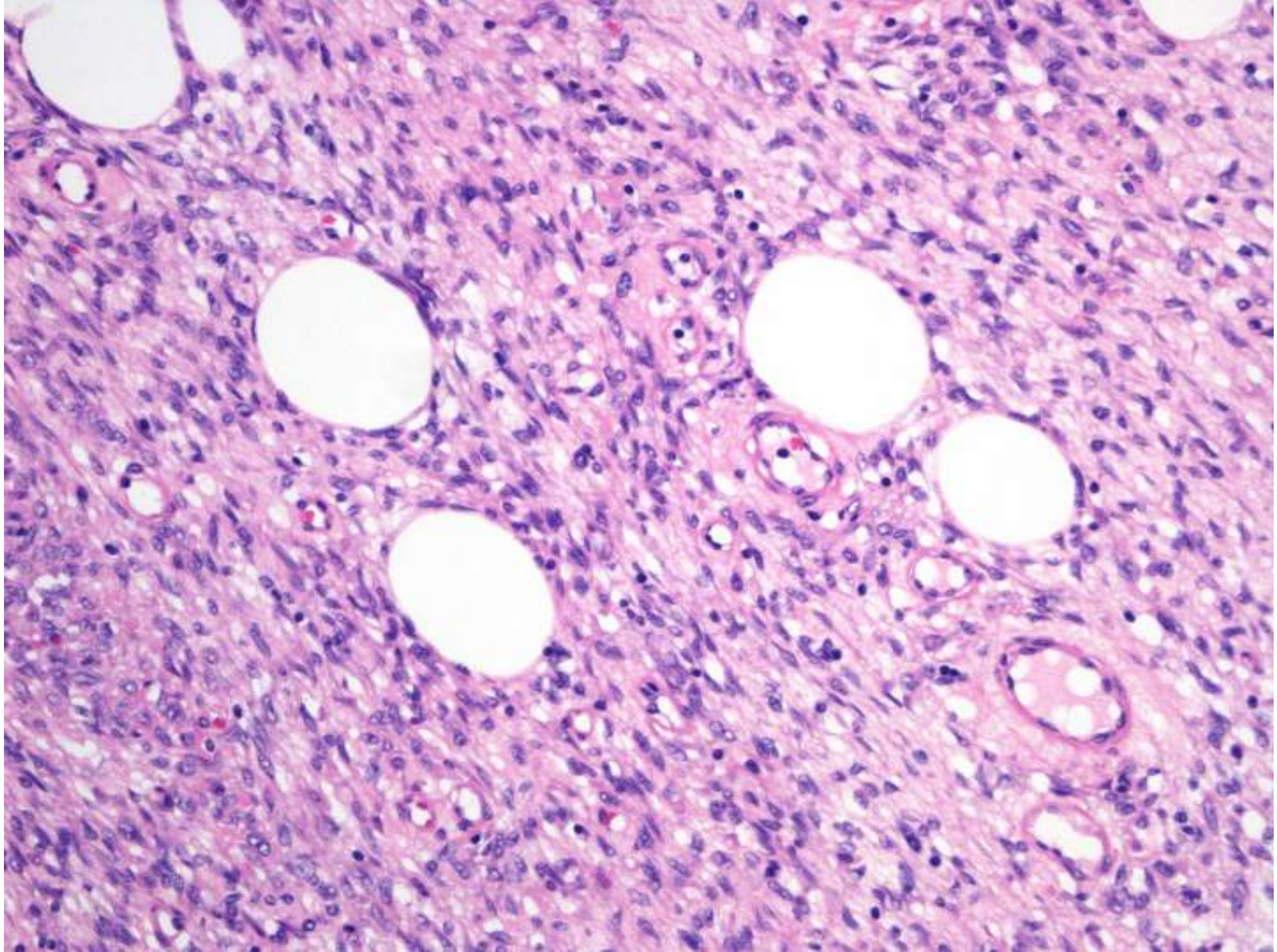


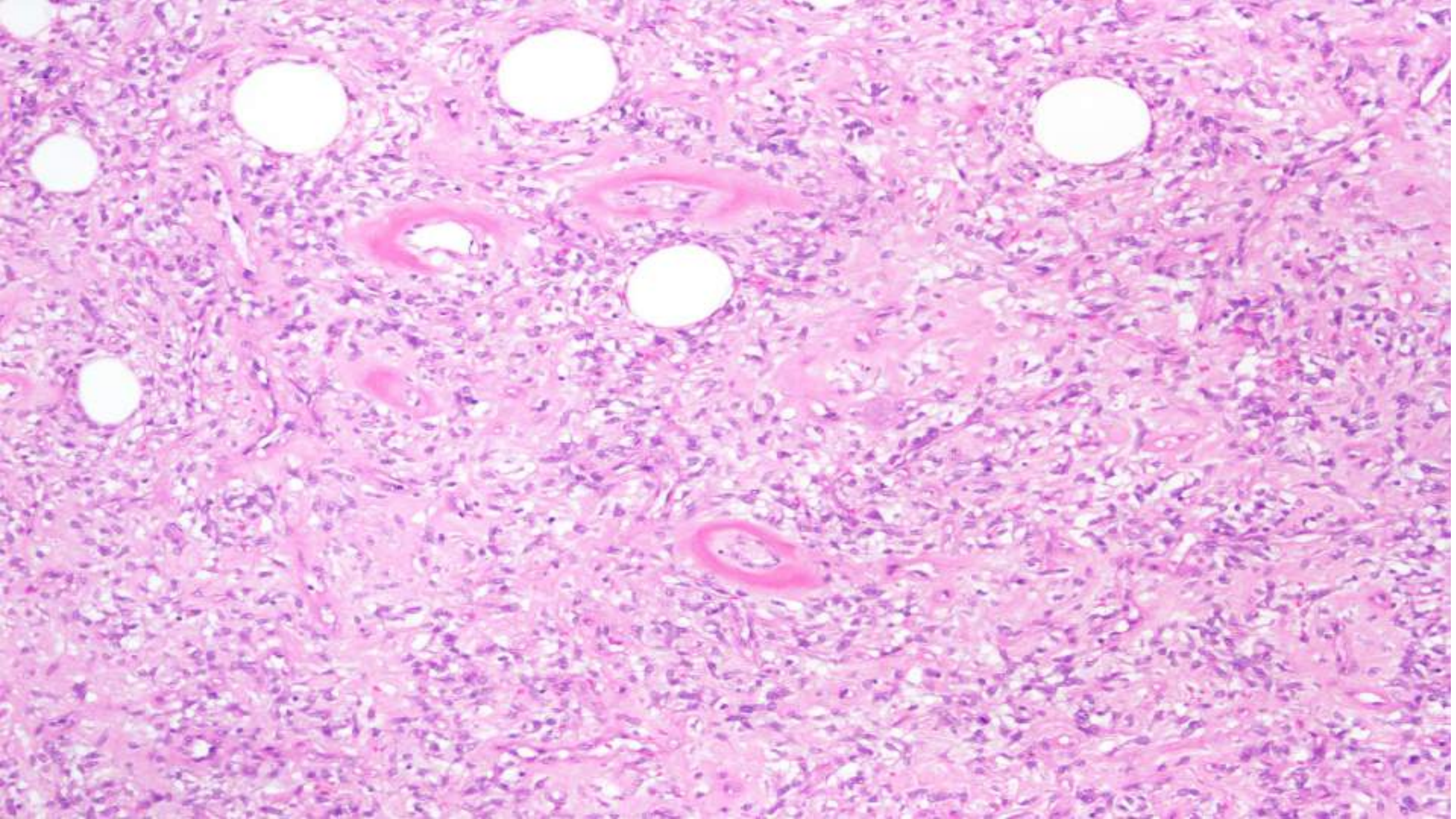


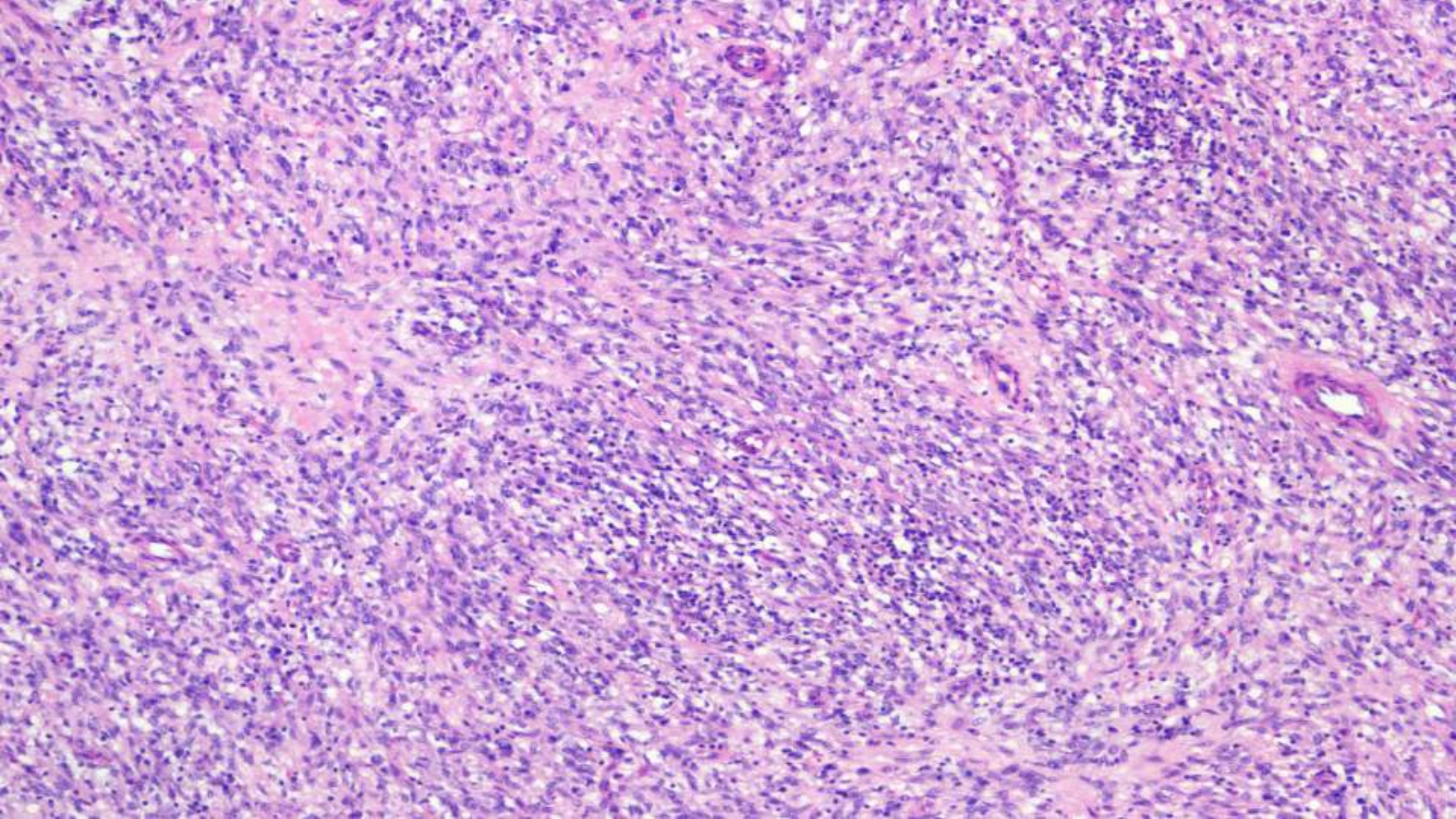


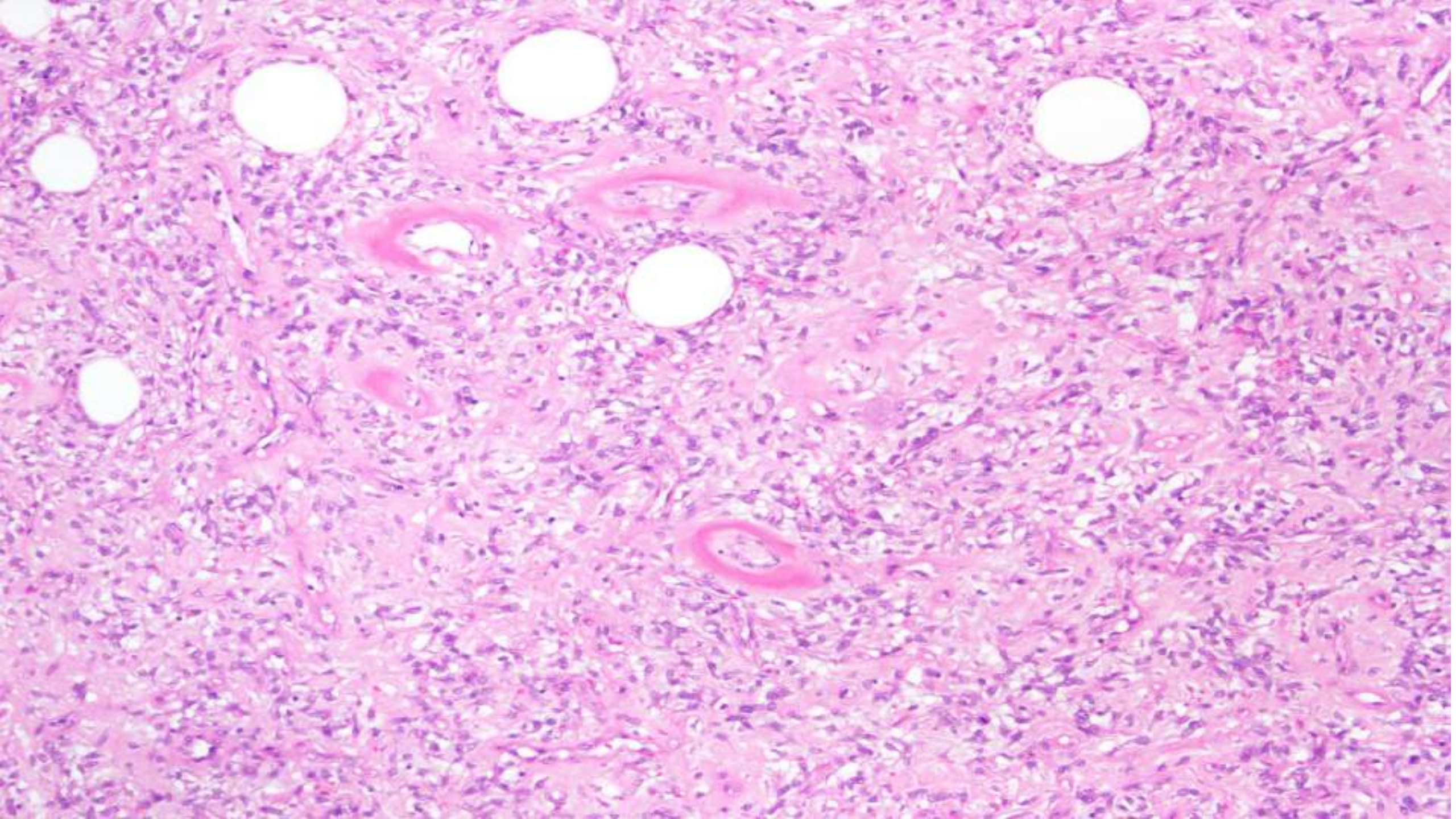


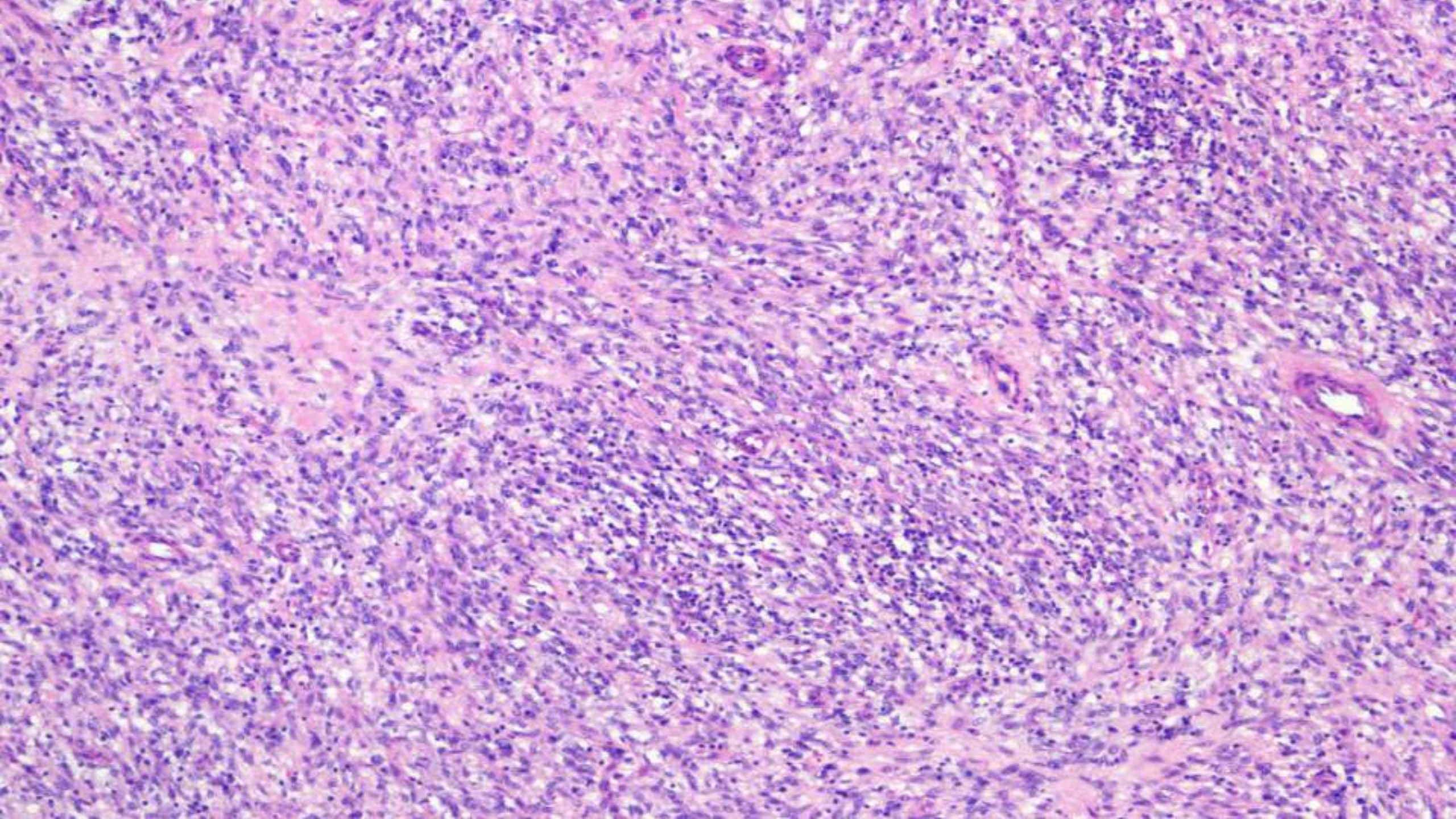


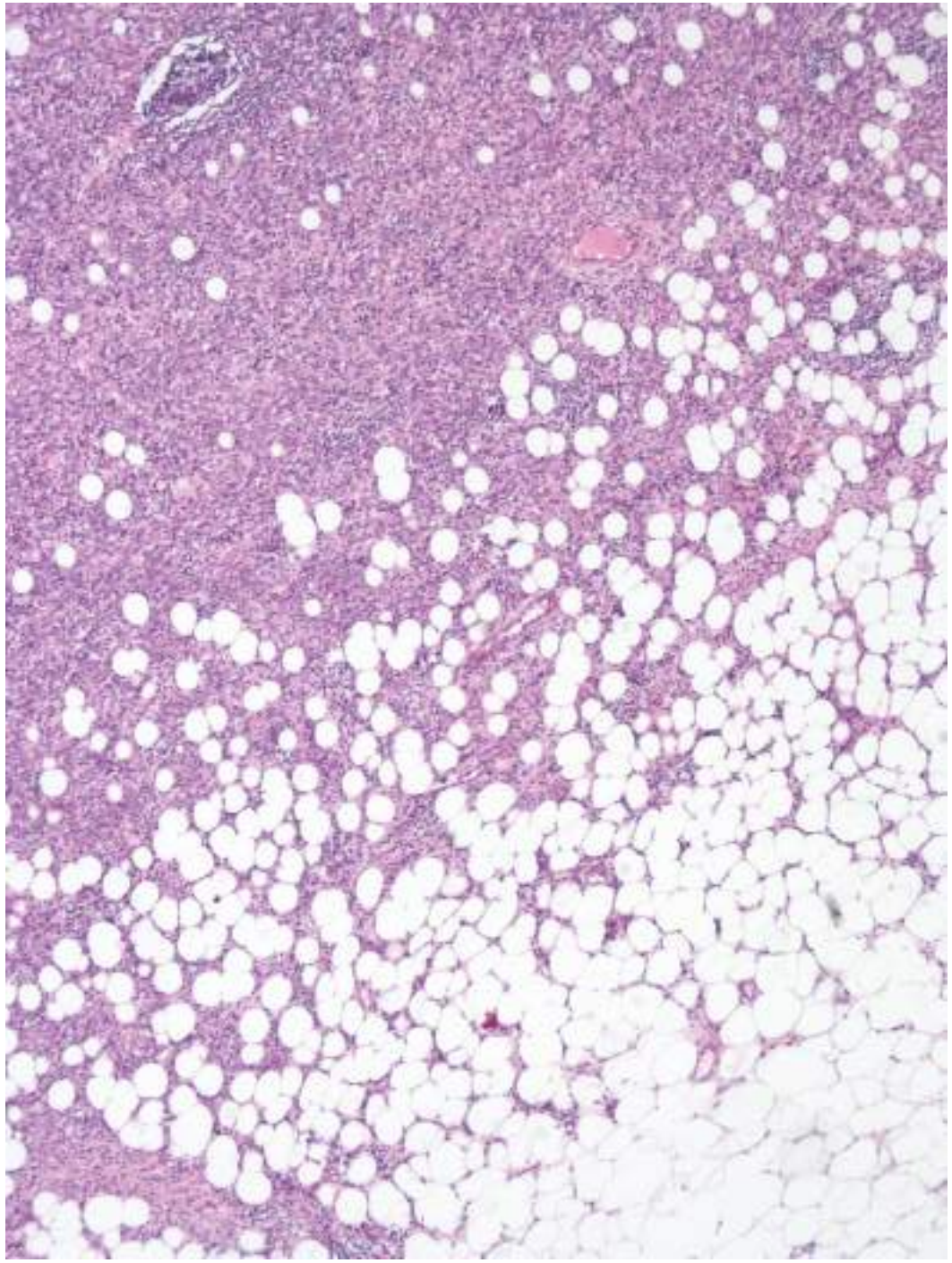


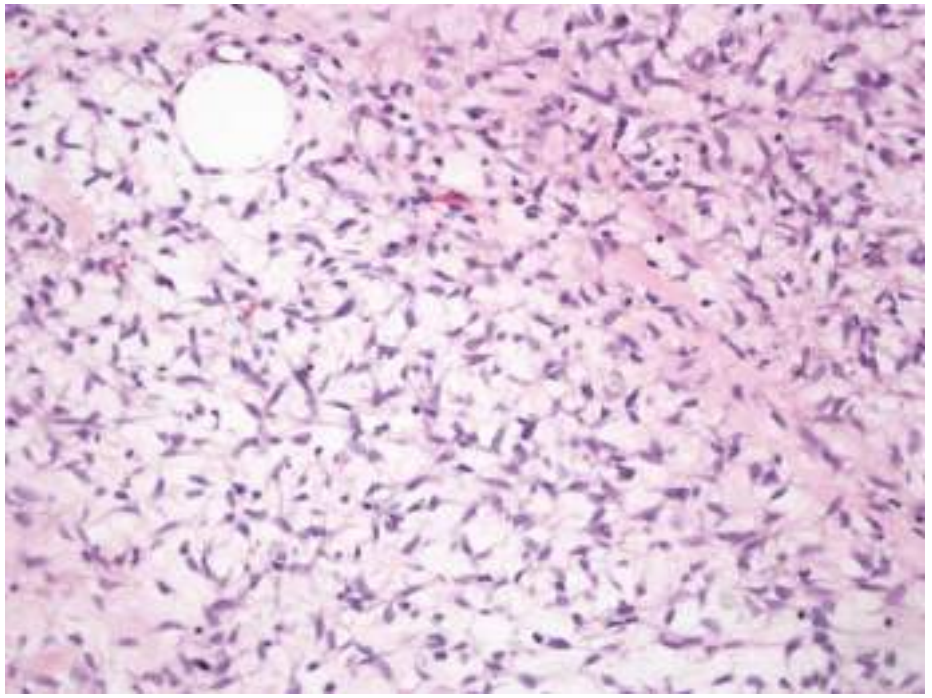


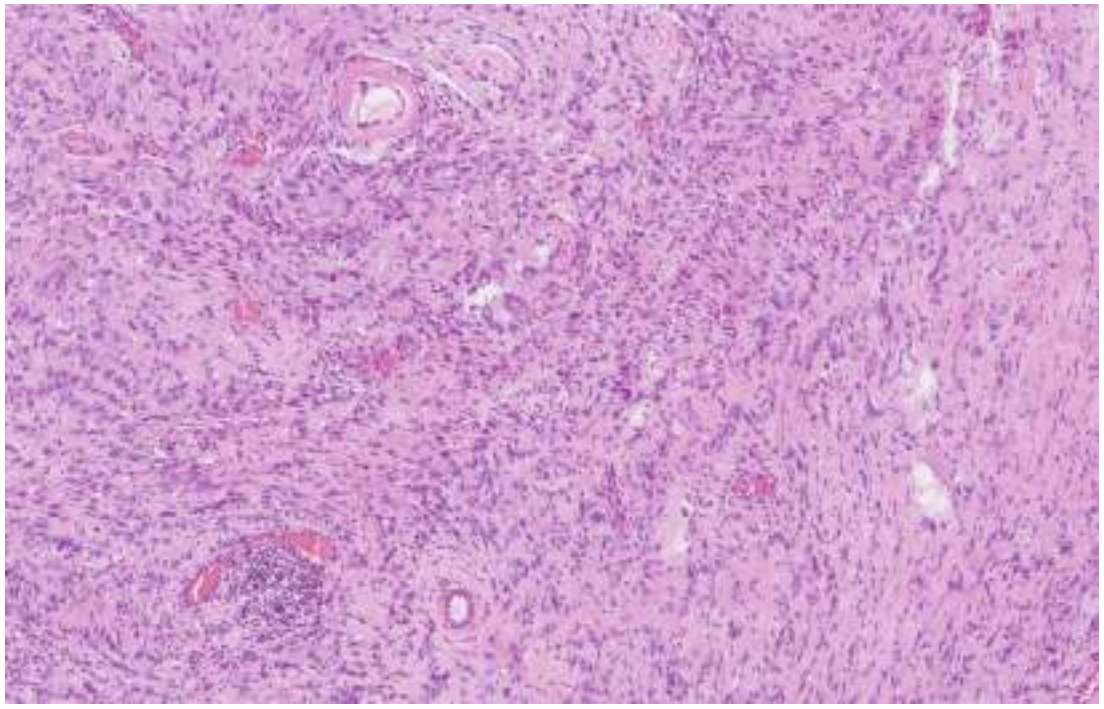




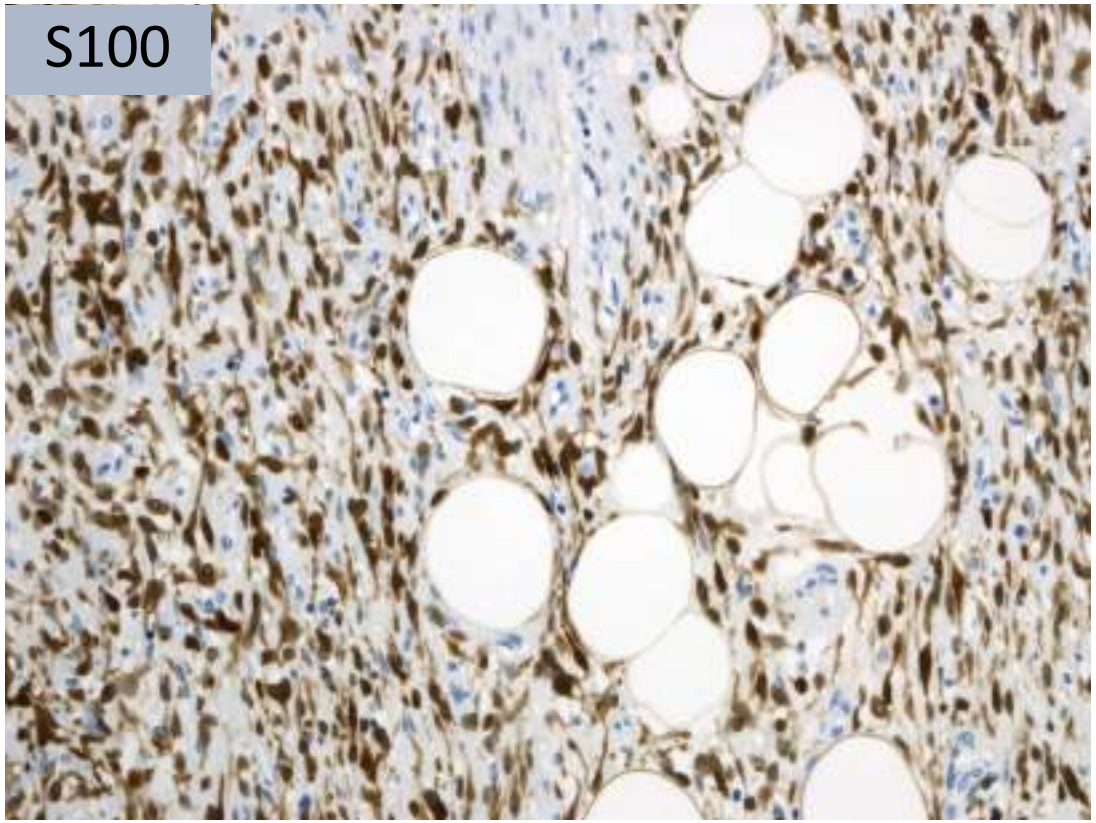


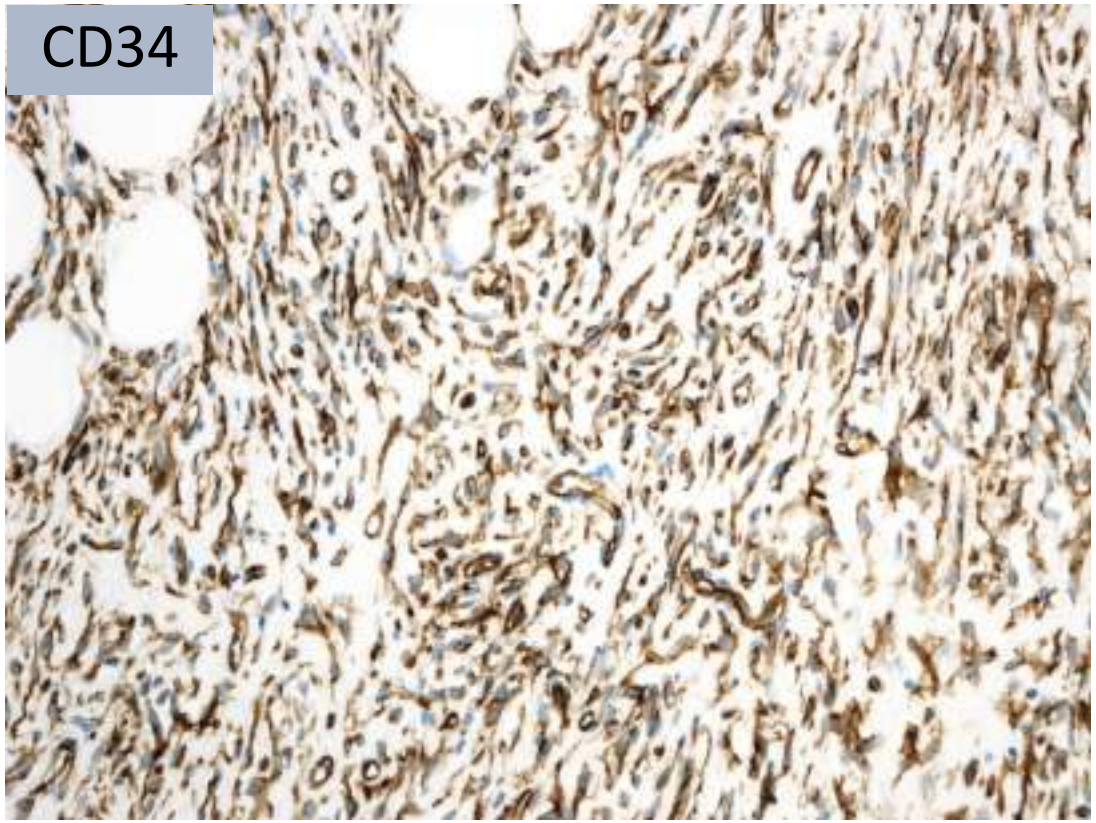






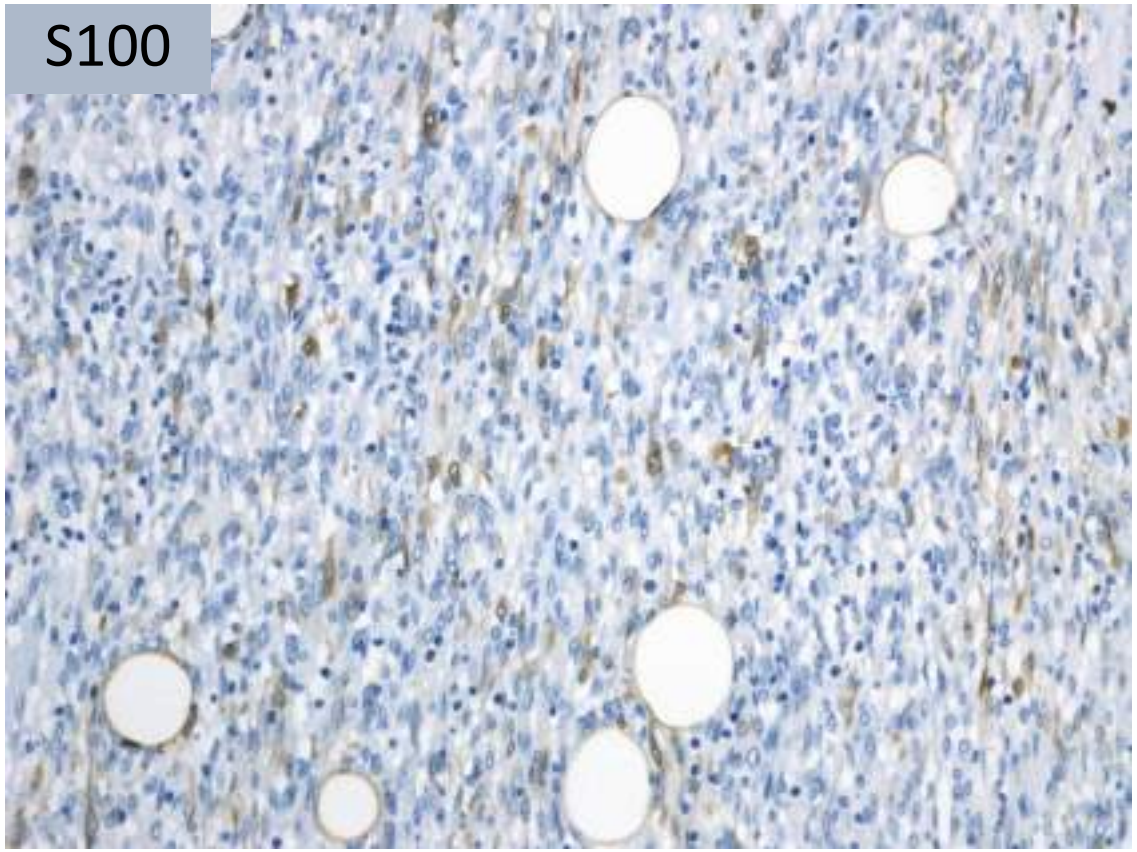
CASE 2
- *IMMUNOHISTOCHEMISTRY* -



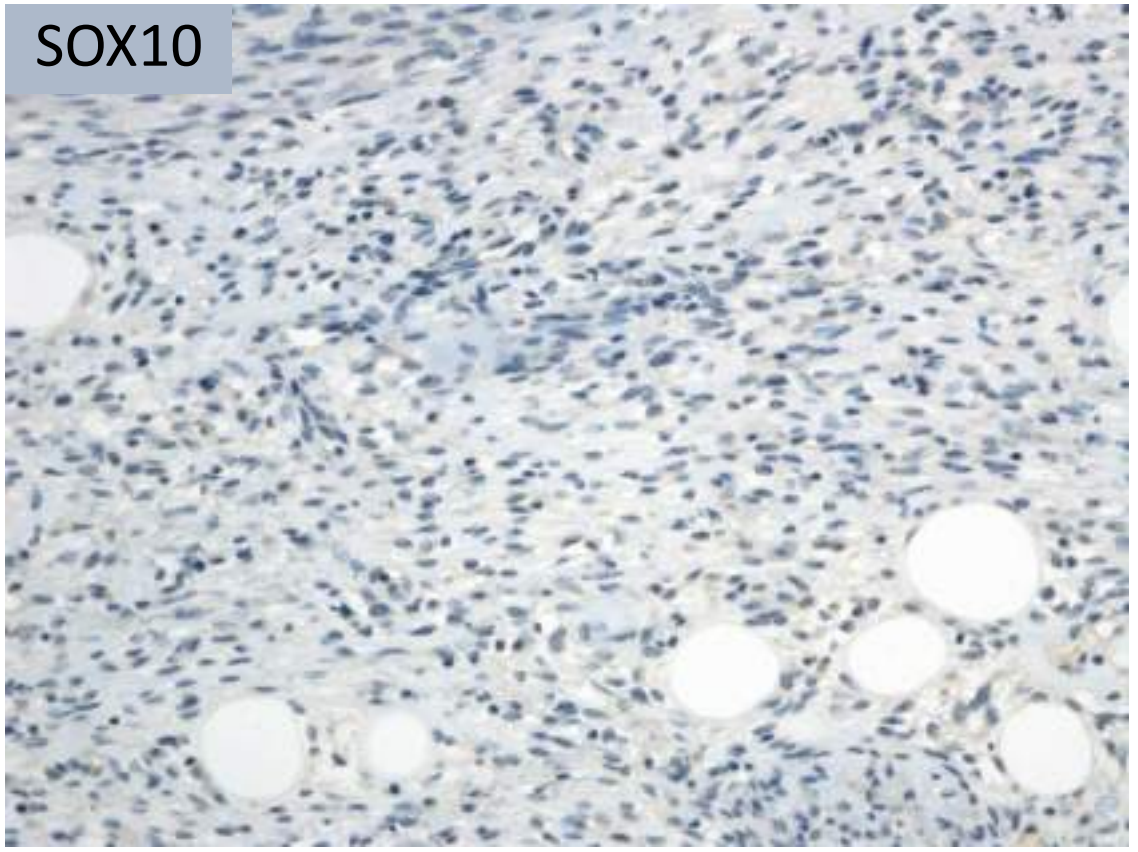


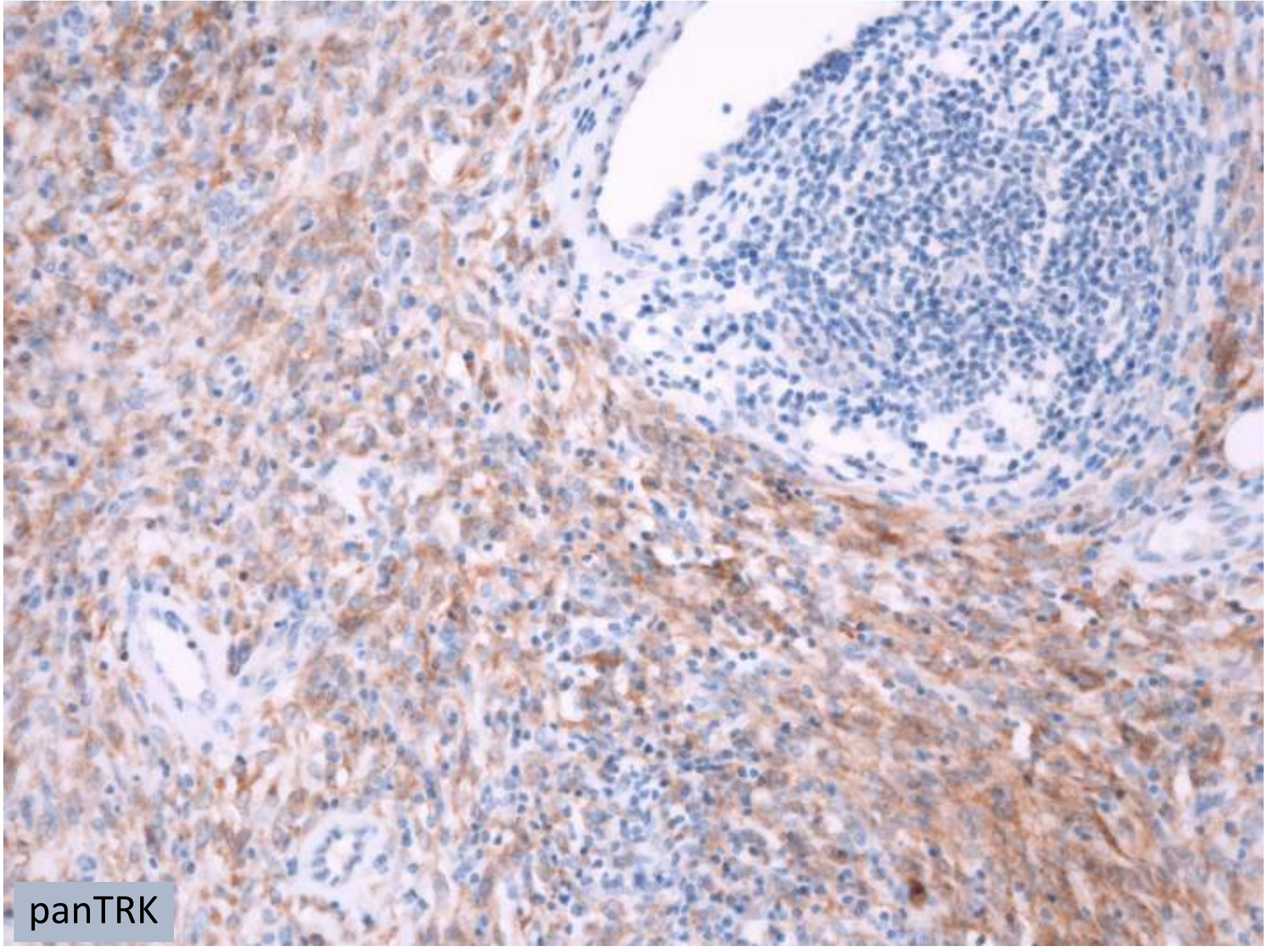
CASE 2
- *IMMUNOHISTOCHEMISTRY* -

S100



SOX10

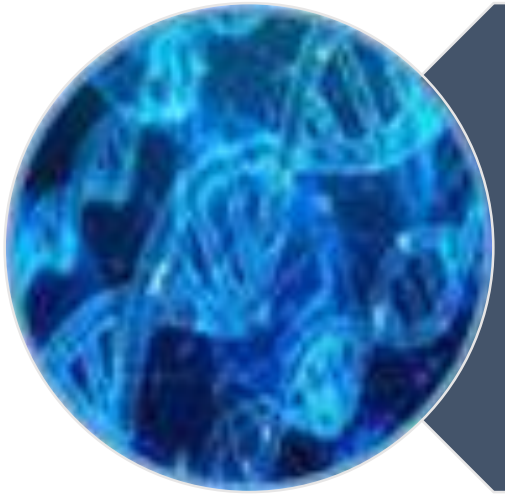



panTRK

CASE 2
- *RNA sequencing* -

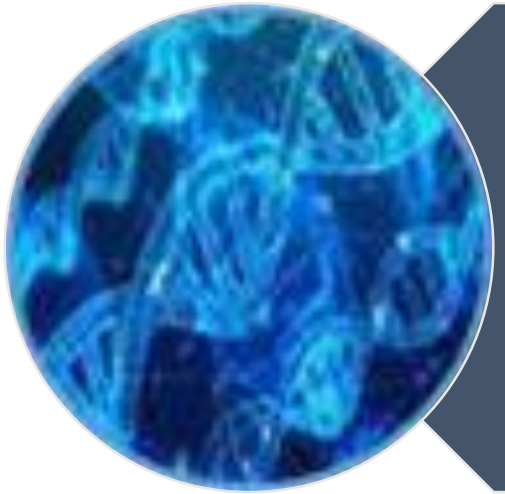
TPR::NTRK3
FUSION

CASE 2
- *DIAGNOSIS* -



CD34+ S100+ SPINDLE CELL TUMOUR WITH

TPR::NTRK3 FUSION



EWSR1::SMAD3

REARRANGED FIBROBLASTIC TUMOUR

EWSR1::SMAD3 REARRANGED FIBROBLASTIC TUMOUR

- *BACKGROUND* -

Novel *EWSR1-SMAD3* Gene Fusions in a Group of Acral Fibroblastic Spindle Cell Neoplasms

Yu-Chien Kao, MD, Uta Flucke, MD, PhD,† Astrid Eijkelenboom, PhD,† Lei Zhang, MD,‡ Yun-Shao Sung, MSc,‡ Albert J.H. Suurmeijer, MD, PhD,§ and Cristina R. Antonescu, MD‡*

Abstract: Benign/low-grade fibroblastic tumors encompass a broad spectrum of tumors with different morphologies and molecular genetic abnormalities. However, despite significant progress in recent genomic characterization, there are still tumors in this histologic spectrum that are difficult to classify, lacking known molecular characteristics. Triggered by a challenging congenital spindle cell neoplasm arising in the heel of a 1-year-old boy, we applied RNA sequencing for genetic discovery and identified a novel *EWSR1-SMAD3* gene fusion. On the basis of the index case superficial acral location and fibroblastic appearance with a nonspecific immunophenotype, we searched our files for similar cases and screened them by fluorescence in situ hybridization for these abnormalities. Thus an identical *EWSR1-SMAD3* fusion was identified in 2 additional spindle cell tumors with similar clinicopathologic features. Both cases occurred in the feet of adult women (58 and 61 y old) and were characterized by distinctive nodular growth with zonation pattern of peripheral hypercellular areas arranged in short fascicles, transitioning to hypocellular central areas of hyalinization and infarction. Focal stippled calcification in the collagenous area was present in 1 case. All 3 tumors had similar immunoprofiles, being negative for SMA, CD34, CD31, and S100, but showing consistent ERG positivity of uncertain significance. Follow-up information was available in 2 patients who developed local recurrences after incomplete initial excisions, at 5 and 14 months, respectively. None developed metastatic disease. In summary, we report a group of locally recurrent superficial acral tumors, characterized by bland spindle cell fascicular growth, occasional zonation pattern, ERG positivity, and recurrent *EWSR1-SMAD3* gene fusions.

Key Words: EWSR1, SMAD3, ERG, spindle cell tumor, fibroblastic tumor, acral

(*Am J Surg Pathol* 2018;42:522–528)

Benign/low-grade fibroblastic tumors are a diverse group of tumors with overlapping morphologies and clinical presentations that can pose diagnostic challenge due to their rarity and lack of a specific immunoprofile. In recent years, with the advent of next-generation sequencing, novel genetic alterations, including mutations or recurrent gene fusions, have been unraveled, increasingly refining the classification of fibroblastic and myofibroblastic neoplasms. Few examples in this morphologic spectrum with newly described genetic abnormalities include: calcifying aponeurotic fibroma showing recurrent *FN1-EGF* fusions,[1] fibrous hamartoma of infancy with *EGFR* internal tandem duplications,[2] myofibroma/myopericytoma with *PDGFRB* mutations,[3,4] and lipofibromatosis-like neural tumors with recurrent *NTRK1*-related gene fusions.[5] Triggered by a challenging congenital fibroblastic lesion, which did not fit in any of the known pathologic entities, we have applied whole transcriptome sequencing for further genomic characterization. Thus a novel *EWSR1-SMAD3* fusion was identified and found to be recurrent in 2 additional cases with similar acral clinical presentation and immunoprofile, suggesting the possibility of a new subtype of fibroblastic lesions with propensity for local recurrence.

EWSR1-SMAD3–rearranged Fibroblastic Tumor

An Emerging Entity in an Increasingly More Complex Group of Fibroblastic/Myofibroblastic Neoplasms

Michael Michal, MD,†‡ Ryan S. Berry, MD,§ Brian P. Rubin, MD,§ Scott E. Kilpatrick, MD,§ Abbas Agaimy, MD,‖ Dmitry V. Kazakov, MD,*‡ Petr Steiner, MD,*‡ Nikola Ptakova, MSc,*‡ Petr Martinek, PhD,*‡ Ladislav Hadravsky, PhD,¶ Kvetoslava Michalova, PhD,*‡ Zoltan Szep, PhD,# and Michal Michal, MD*‡*

Abstract: Three cases of superficial acral fibroblastic spindle cell neoplasms with *EWSR1-SMAD3* fusion have been recently reported. Their differential diagnosis is broad, primarily comprising rare tumors from the fibroblastic/myofibroblastic category. The aim of this report is to present 4 new cases of this entity and to discuss the appropriate differential diagnosis. Also, as the ERG antibody seems to be a characteristic marker for these tumors, we analyzed ERG immunostaining characteristics in potential mimics of this entity. All cases in our cohort occurred in women aged 5 to 68 years (mean, 36.5 y). Two were located on the hand, 1 on foot, and the last case arose on the calf. The tumor size ranged from 1 to 1.5 cm in the greatest dimension, with a mean size of 1.2 cm. Except for one recent case, follow-up was available, ranging from 7 to 18 years (mean, 11.7 y), with a recurrence noted in 1 case after 10 years. All tumors were subcutaneous and showed 2 main components. One consisted of bland, spindled cells with elongated nuclei which were round when observed on the cross-section. These cells mostly grew in relatively hypercellular, well-organized, and intersecting fascicles. The second component was prominently hyalinized and paucicellular, but lacked calcifications. Both components showed either a distinct zonation pattern, or they were randomly intermingled with each other. In all 3 analyzable tumors, next-generation sequencing showed *EWSR1-SMAD3* gene fusion in each case. By fluorescence in situ hybridization, one tested case also revealed unbalanced rearrangement of the *EWSR1* gene. All 4 cases showed strong, diffuse nuclear expression of ERG, whereas none of the mimics stained with this antibody except for weak to moderate staining in calcifying aponeurotic fibromas (W10 cases). Two tumors showed focal weak to moderate expression of SAT-B2. The 4 herein presented cases further broaden the clinicopathologic spectrum of tumors with *EWSR1-SMAD3* gene fusion. They also confirm that they represent a novel entity for which we propose the name *EWSR1-SMAD3*–rearranged fibroblastic Tumor. Our study also proves that in the context of fibroblastic/myofibroblastic tumors, ERG immunohistochemistry is a relatively specific marker for these neoplasms.

Key Words: soft tissues, acral fibroblastic spindle cell neoplasm, *EWSR1-SMAD3*–rearranged fibroblastic tumor, ERG, lipofibromatosis, lipofibromatosis-like neural tumor, myofibroma, fibromatosis, calcifying aponeurotic fibroma

(*Am J Surg Pathol* 2018;42:1325–1333)

Although several new entities have been defined or redefined during the last few decades, still there are mesenchymal neoplasms which elude precise classification. This is particularly true for soft tissue neoplasms featuring

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An Emerging Entity in an Increasingly More Complex Group of Fibroblastic/Myofibroblastic Neoplasms

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Abstract: Three cases of superficial acral fibroblastic spindle cell neoplasms with *EWSR1-SMAD3* fusion have been recently reported. Their differential diagnosis is broad, primarily comprising rare tumors from the fibroblastic/myofibroblastic category. The aim of this report is to present 4 new cases of this entity and to discuss the appropriate differential diagnosis. Also, as the ERG antibody seems to be a characteristic marker for these tumors, we analyzed ERG immunostaining characteristics in potential mimics of this entity. All cases in our cohort occurred in women aged 5 to 68 years (mean, 36.5 y). Two were located on the hand, 1 on foot, and the last case arose on the calf. The tumor size ranged from 1 to 1.5 cm in the greatest dimension, with a mean size of 1.2 cm. Except for one recent case, follow-up was available, ranging from 7 to 18 years (mean, 11.7 y), with a recurrence noted in 1 case after 10 years. All tumors were subcutaneous and showed 2 main components. One consisted of bland, spindled cells with elongated nuclei which were round when observed on the cross-section. These cells mostly grew in relatively hypercellular, well-organized, and intersecting fascicles. The second component was prominently hyalinized and paucicellular, but lacked calcifications. Both components showed either a distinct zonation pattern, or they were randomly intermingled with each other. In all 3 analyzable tumors, next-generation sequencing showed *EWSR1-SMAD3* gene fusion in each case. By fluorescence in situ hybridization, one tested case also revealed unbalanced rearrangement of the *EWSR1* gene. All 4 cases showed strong, diffuse nuclear expression of ERG, whereas none of the mimics stained with this antibody except for weak to moderate staining in calcifying aponeurotic fibromas (W10 cases). Two tumors showed focal weak to moderate expression of SAT-B2. The 4 herein presented cases further broaden the clinicopathologic spectrum of tumors with *EWSR1-SMAD3* gene fusion. They also confirm that they represent a novel entity for which we propose the name *EWSR1-SMAD3*–rearranged fibroblastic Tumor. Our study also proves that in the context of fibroblastic/myofibroblastic tumors, ERG immunohistochemistry is a relatively specific marker for these neoplasms.

Key Words: soft tissues, acral fibroblastic spindle cell neoplasm, *EWSR1-SMAD3*–rearranged fibroblastic tumor, ERG, lipofibromatosis, lipofibromatosis-like neural tumor, myofibroma, fibromatosis, calcifying aponeurotic fibroma

(*Am J Surg Pathol* 2018;42:1325–1333)

Although several new entities have been defined or redefined during the last few decades, still there are mesenchymal neoplasms which elude precise classification. This is particularly true for soft tissue neoplasms featuring

EWSR1::SMAD3 REARRANGED FIBROBLASTIC TUMOUR

- *BACKGROUND* -

Novel *EWSR1-SMAD3* Gene Fusions in a Group of Acral Fibroblastic Spindle Cell Neoplasms

Yu-Chien Kao, MD, Uta Flucke, MD, PhD,† Astrid Eijkelenboom, PhD,† Lei Zhang, MD,‡ Yun-Shao Sung, MSc,‡ Albert J.H. Suurmeijer, MD, PhD,§ and Cristina R. Antonescu, MD‡*

Abstract: Benign/low-grade fibroblastic tumors encompass a broad spectrum of tumors with different morphologies and molecular genetic abnormalities. However, despite significant progress in recent genomic characterization, there are still tumors in this histologic spectrum that are difficult to classify, lacking known molecular characteristics. Triggered by a challenging congenital spindle cell neoplasm arising in the heel of a 1-year-old boy, we applied RNA sequencing for genetic discovery and identified a novel *EWSR1-SMAD3* gene fusion. On the basis of the index case superficial acral location and fibroblastic appearance with a nonspecific immunophenotype, we searched our files for similar cases and screened them by fluorescence in situ hybridization for these abnormalities. Thus an identical *EWSR1-SMAD3* fusion was identified in 2 additional spindle cell tumors with similar clinicopathologic features. Both cases occurred in the feet of adult women (58 and 61 y old) and were characterized by distinctive nodular growth with zonation pattern of peripheral hypercellular areas arranged in short fascicles, transitioning to hypocellular central areas of hyalinization and infarction. Focal stippled calcification in the collagenous area was present in 1 case. All 3 tumors had similar immunoprofiles, being negative for SMA, CD34, CD31, and S100, but showing consistent ERG positivity of uncertain significance. Follow-up information was available in 2 patients who developed local recurrences after incomplete initial excisions, at 5 and 14 months, respectively. None developed metastatic disease. In summary, we report a group of locally recurrent superficial acral tumors, characterized by bland spindle cell fascicular growth, occasional zonation pattern, ERG positivity, and recurrent *EWSR1-SMAD3* gene fusions.

Key Words: EWSR1, SMAD3, ERG, spindle cell tumor, fibroblastic tumor, acral

(*Am J Surg Pathol* 2018;42:522–528)

3 CASES

EWSR1-SMAD3–rearranged Fibroblastic Tumor

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4 CASES

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EWSR1::SMAD3 REARRANGED FIBROBLASTIC TUMOUR

- *BACKGROUND* -

Received: 30 June 2020 | Revised: 23 August 2020 | Accepted: 31 August 2020
DOI: 10.1111/cup.13870

ORIGINAL ARTICLE

JCP WILEY

EWSR1-SMAD3 rearranged fibroblastic tumor: Case series and review

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Abstract

We report the largest series to date (N = 6) of *EWSR1-SMAD3* rearranged fibroblastic tumor. Initially described in 2018, the tumor features a marked female predominance (F:M, 5:1, mean age 44-years, median age 45.5 years; range 27-57), with most cases (5/6, 83%) arising in acral locations (4 on foot/toe, 1 on hand). One case presented on the lower extremity. The lesions presented as nodules and were composed of short, variably cellular, intersecting fascicles of uniform spindled cells in a collagenous to myxoid stroma. In four cases, the tumor abutted the epidermis without a grenz zone. In one case, there was an abrupt transition to a central, acellular hyalinized area. Two other cases had admixed smaller collagenous areas, reminiscent of collagen rosettes. One had a concentric arrangement of tumor cells around blood vessels. Mitotic activity was low (<1/10 HPFs). All were positive for ERG by immunohistochemistry and negative for CD34 (6/6). An *EWSR1-SMAD3* fusion was identified in three cases tested by next-generation sequencing (3/3). Rearrangement of *EWSR1* by fluorescence in situ hybridization was showed in 1/1 case. Our series reaffirms prior findings and expands the known histopathologic spectrum of this emerging entity.

6
CASES

EWSR1::SMAD3 REARRANGED FIBROBLASTIC TUMOUR

- *CLINICAL FEATURES* -

WIDE AGE DISTRIBUTION
(INFANCY TO ELDERLY)

FEMALE PREDOMINANCE
(80%)

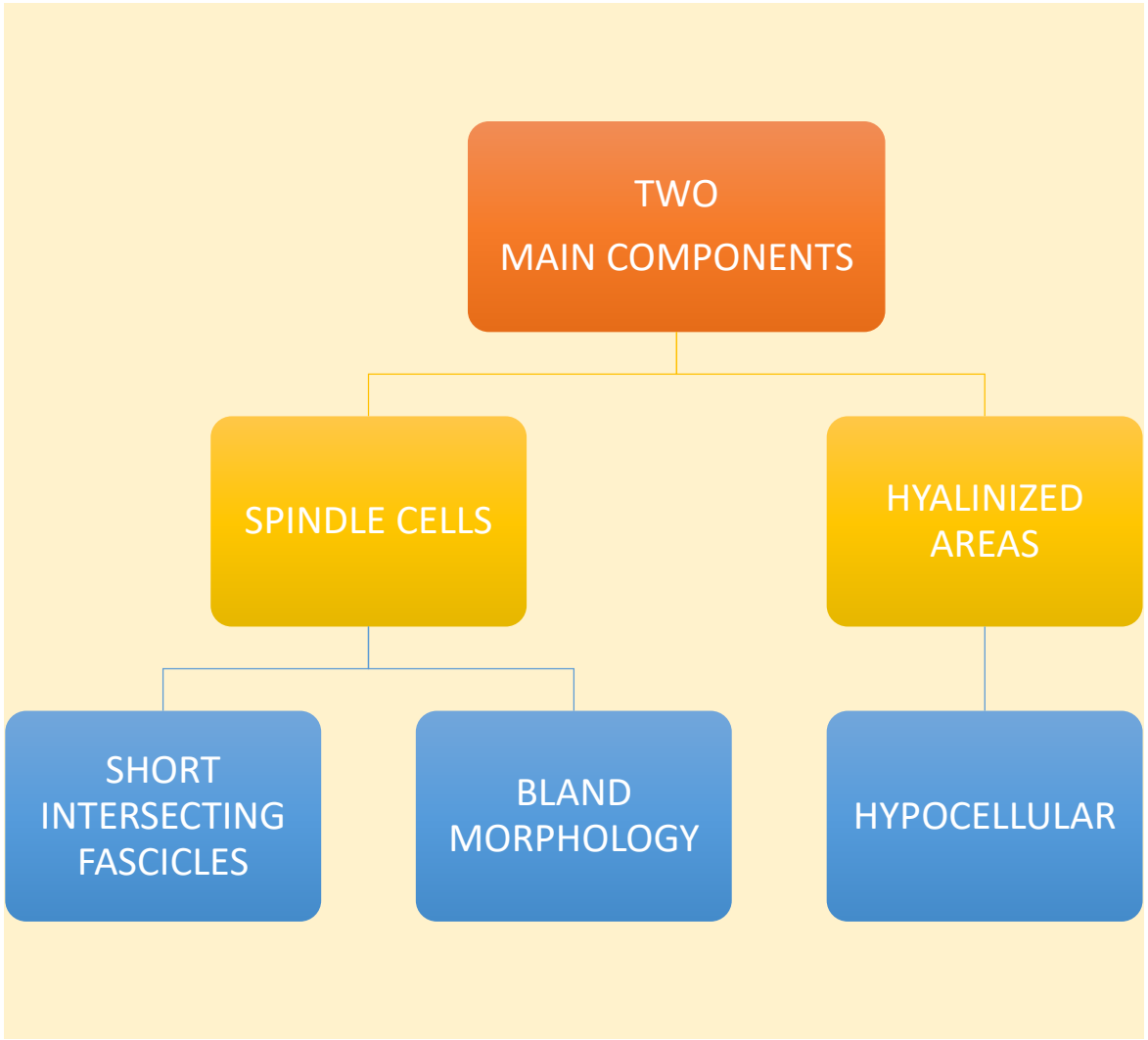
LESS THAN 20 CASES

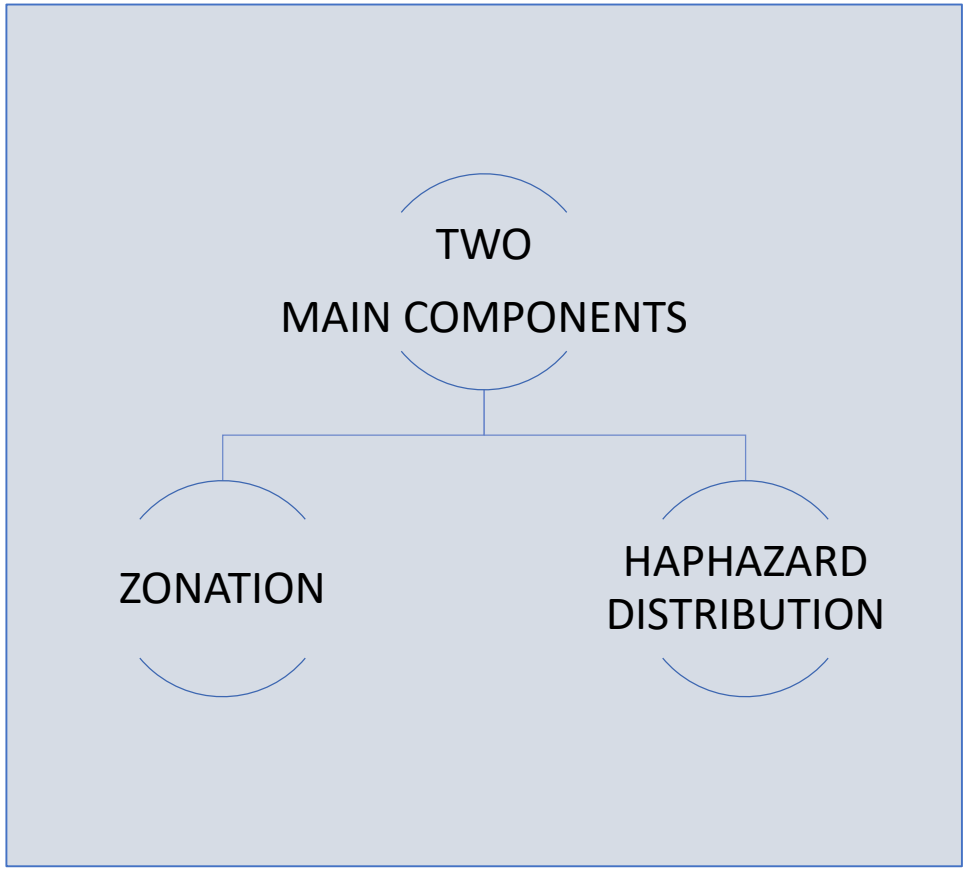
ACRAL LOCATION
(>80%)

NON-ACRAL SITES:
EXTREMITIES, BONE

EWSR1::SMAD3 REARRANGED FIBROBLASTIC TUMOUR

- *HISTOLOGICAL FEATURES* -



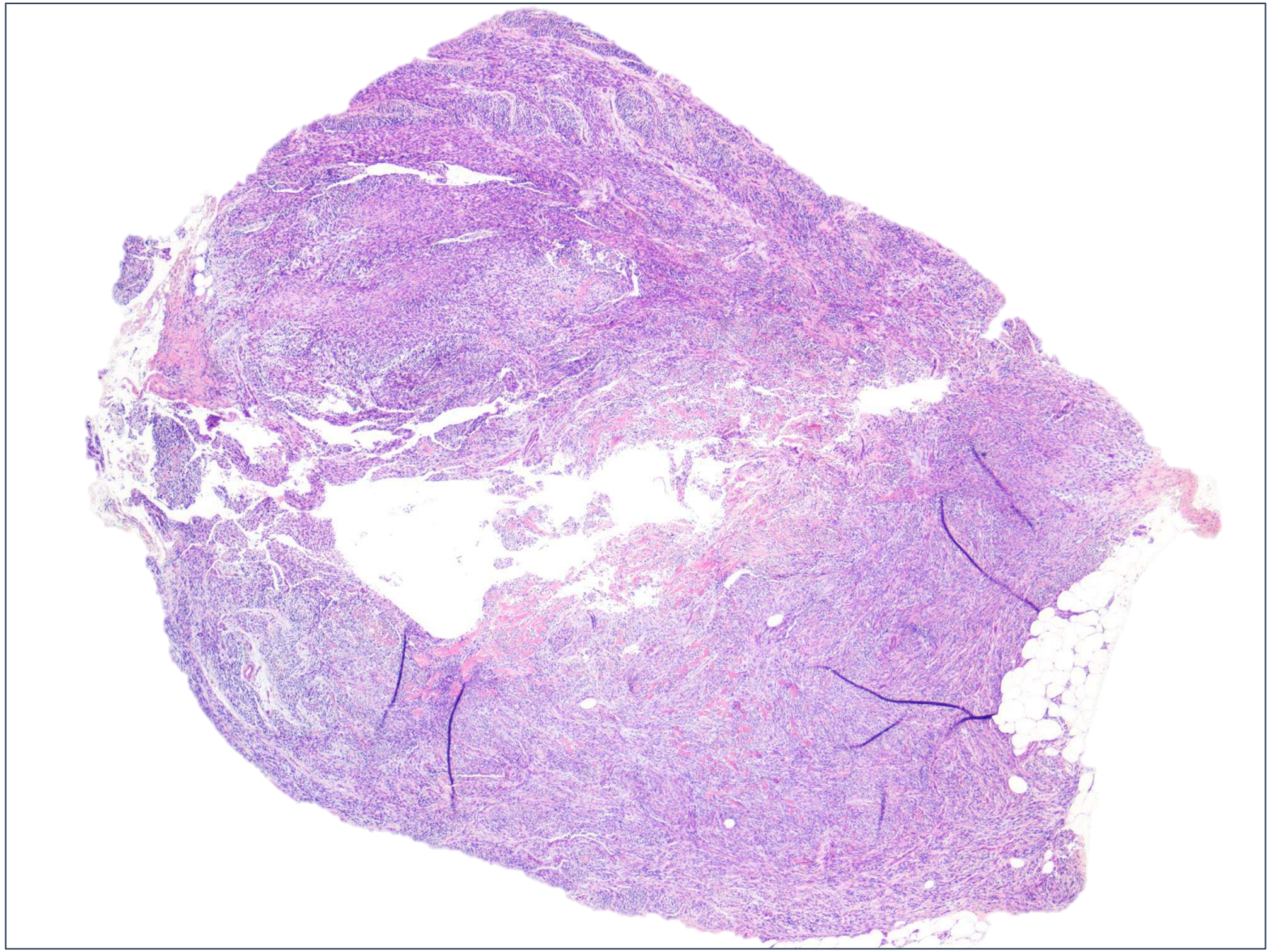


EWSR1::SMAD3 REARRANGED FIBROBLASTIC TUMOUR

- *HISTOLOGICAL FEATURES* -

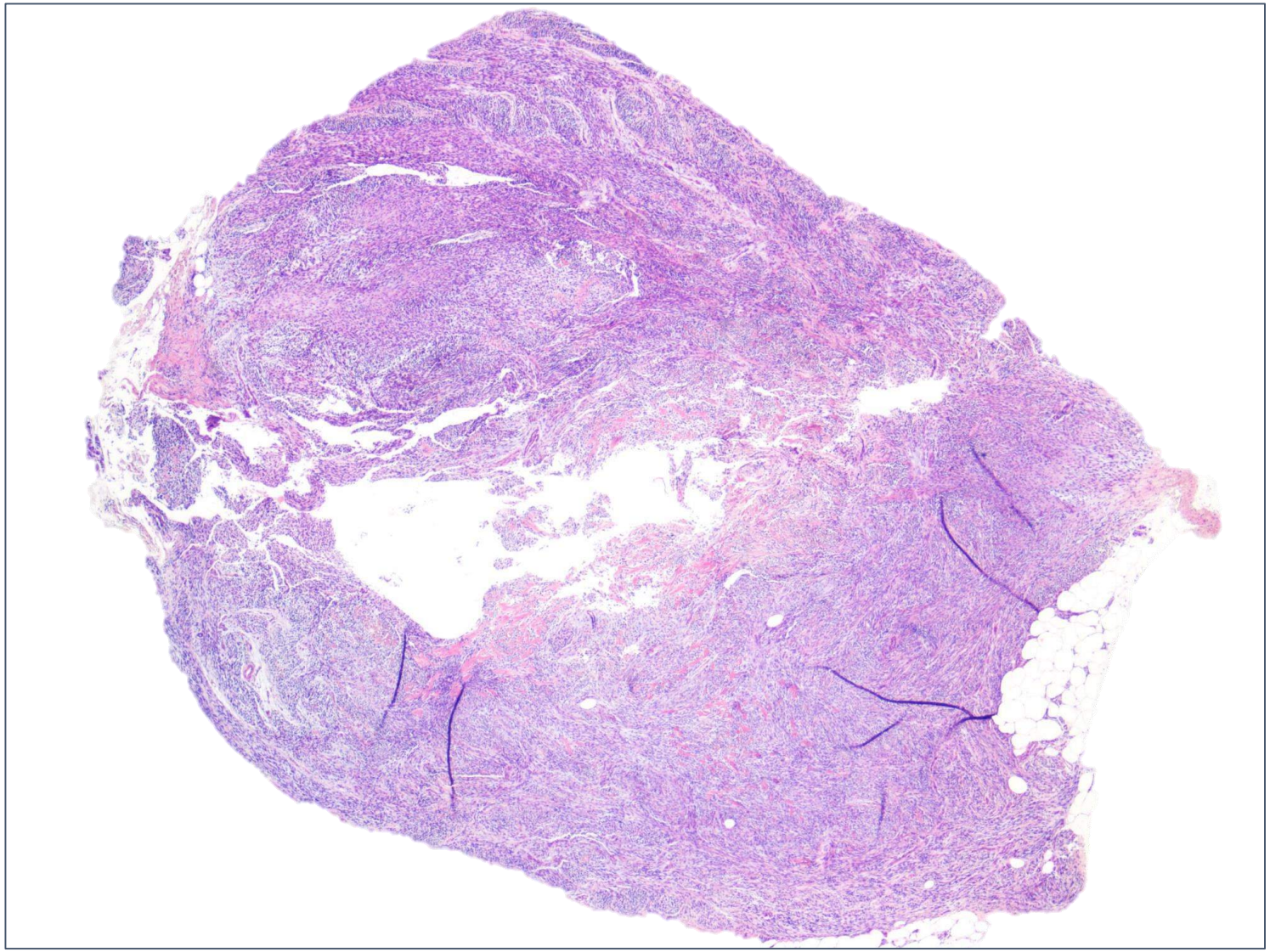
DERMIS AND SUBCUTIS

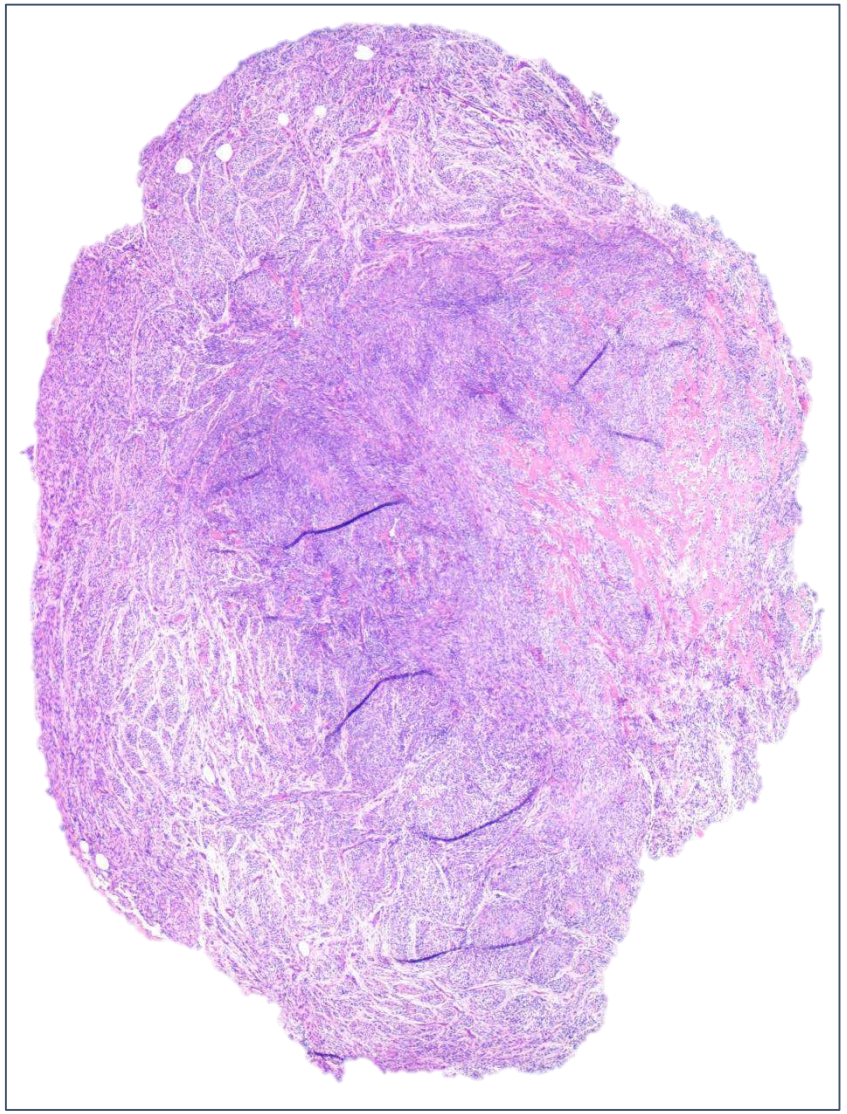
NODULAR YET INFILTRATIVE AREAS



EWSR1::SMAD3 REARRANGED FIBROBLASTIC TUMOUR

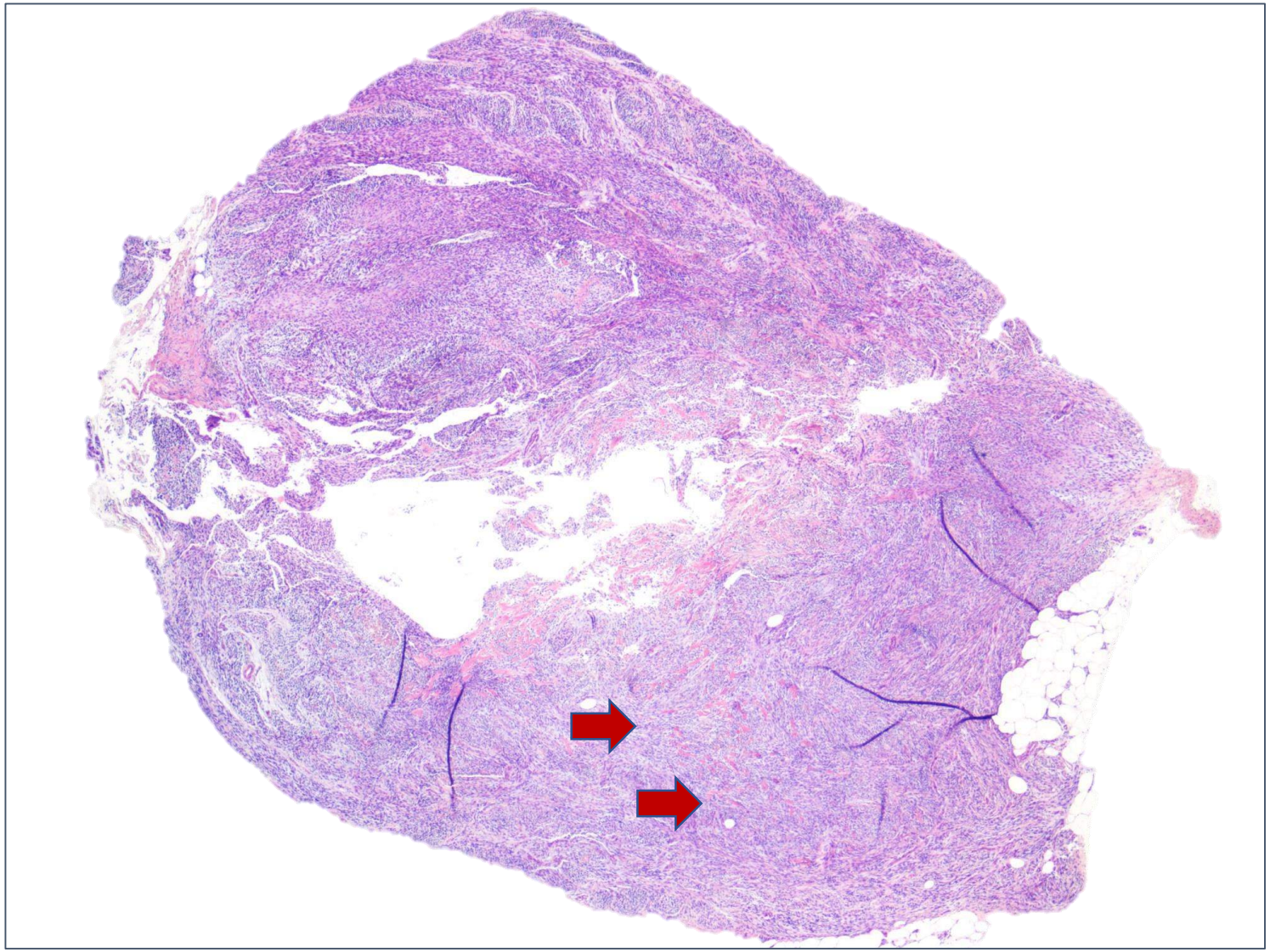
- *HISTOLOGICAL FEATURES* -

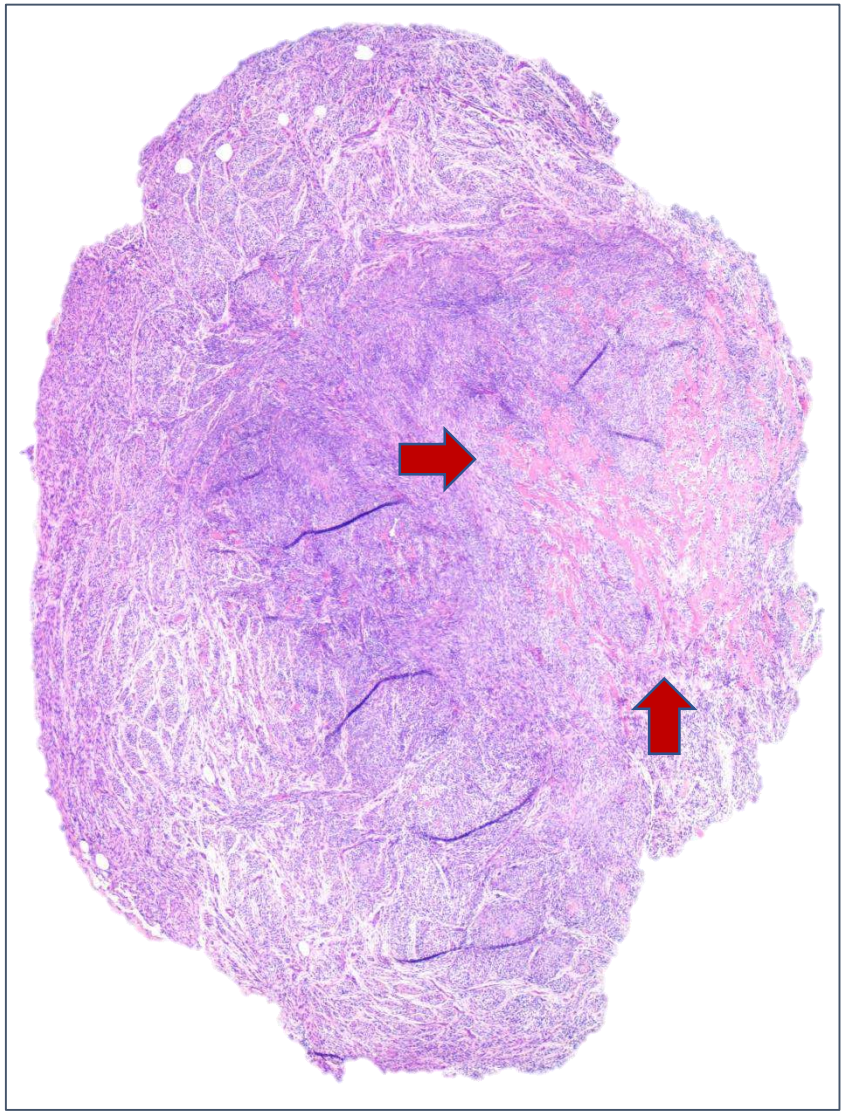




EWSR1::SMAD3 REARRANGED FIBROBLASTIC TUMOUR

- *HISTOLOGICAL FEATURES* -





EWSR1::SMAD3 REARRANGED FIBROBLASTIC TUMOUR

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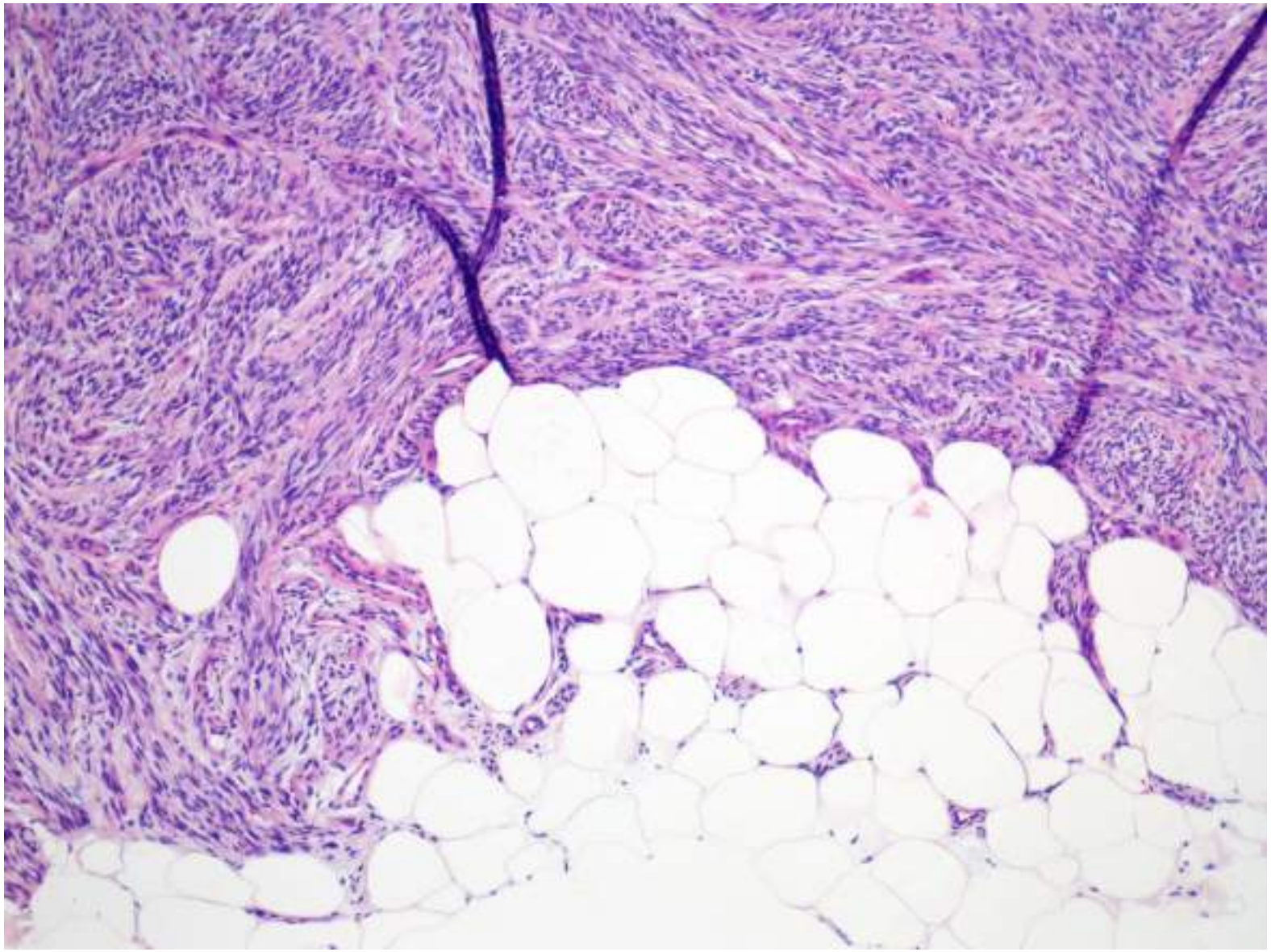

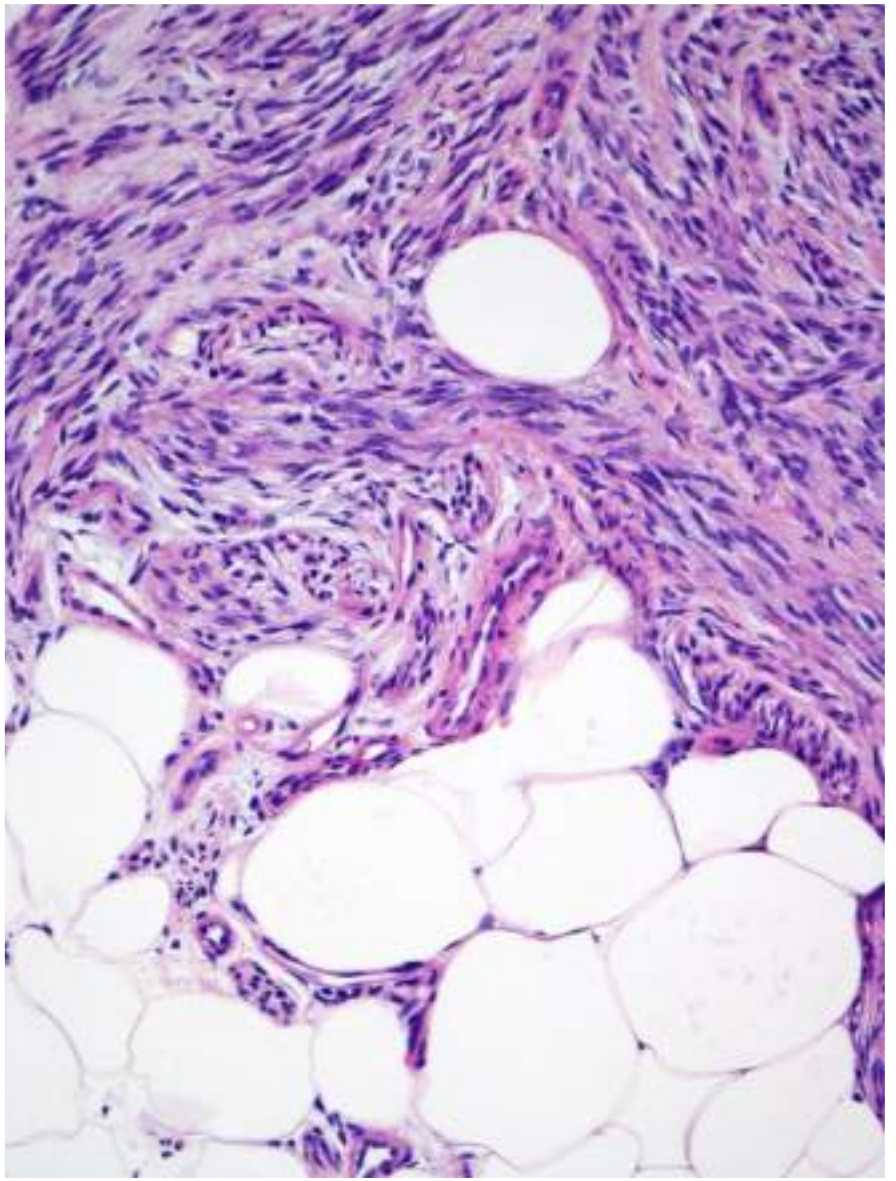

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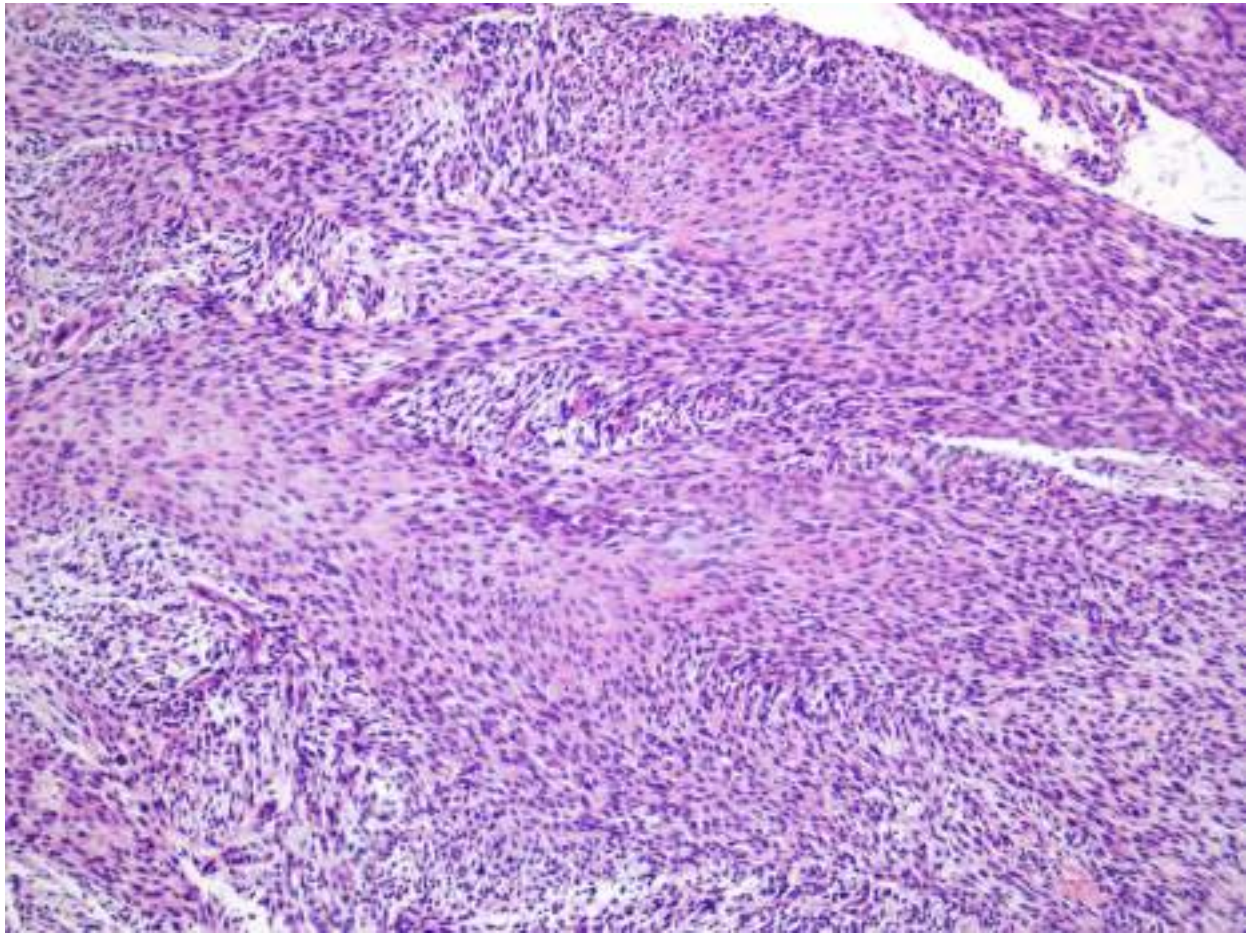

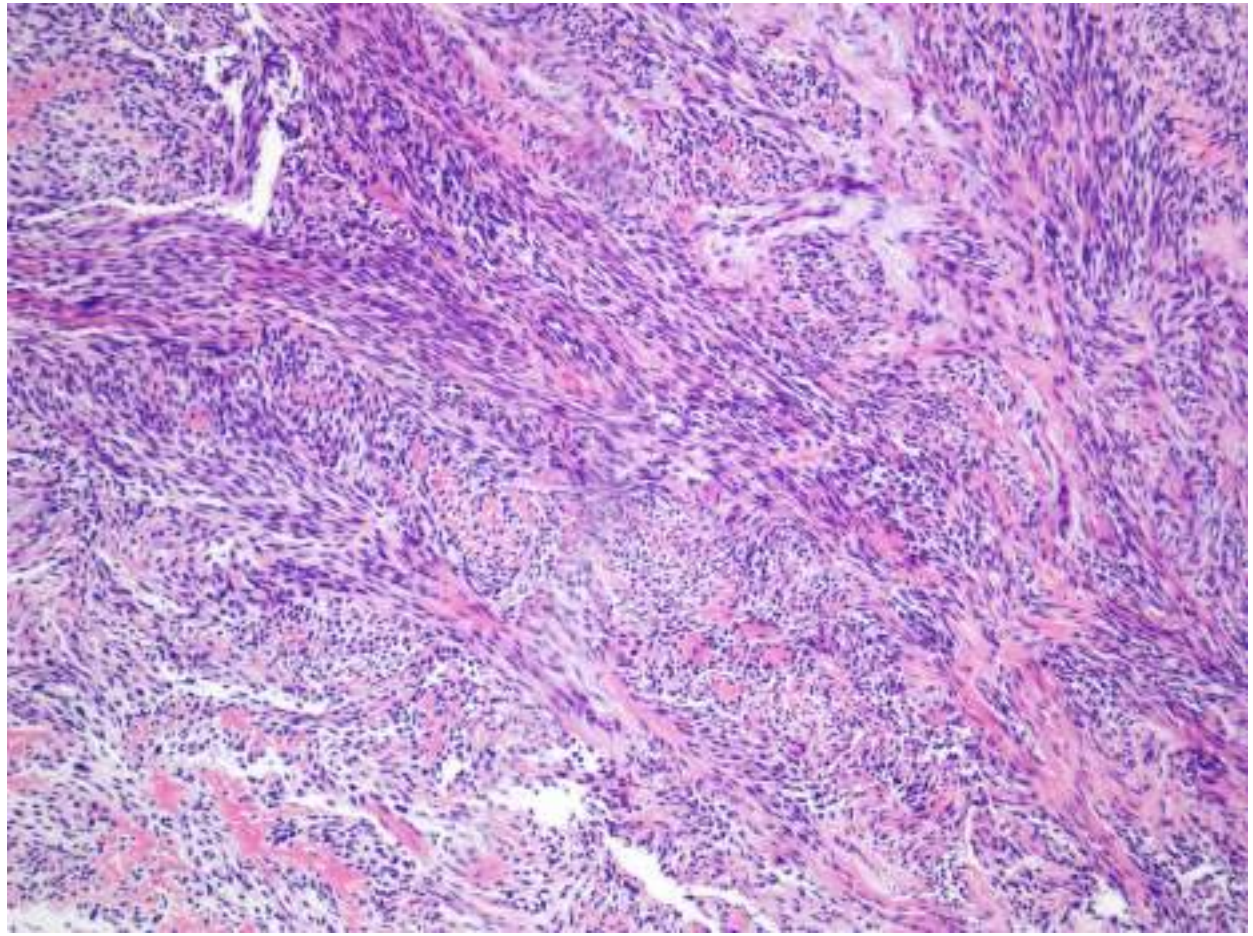

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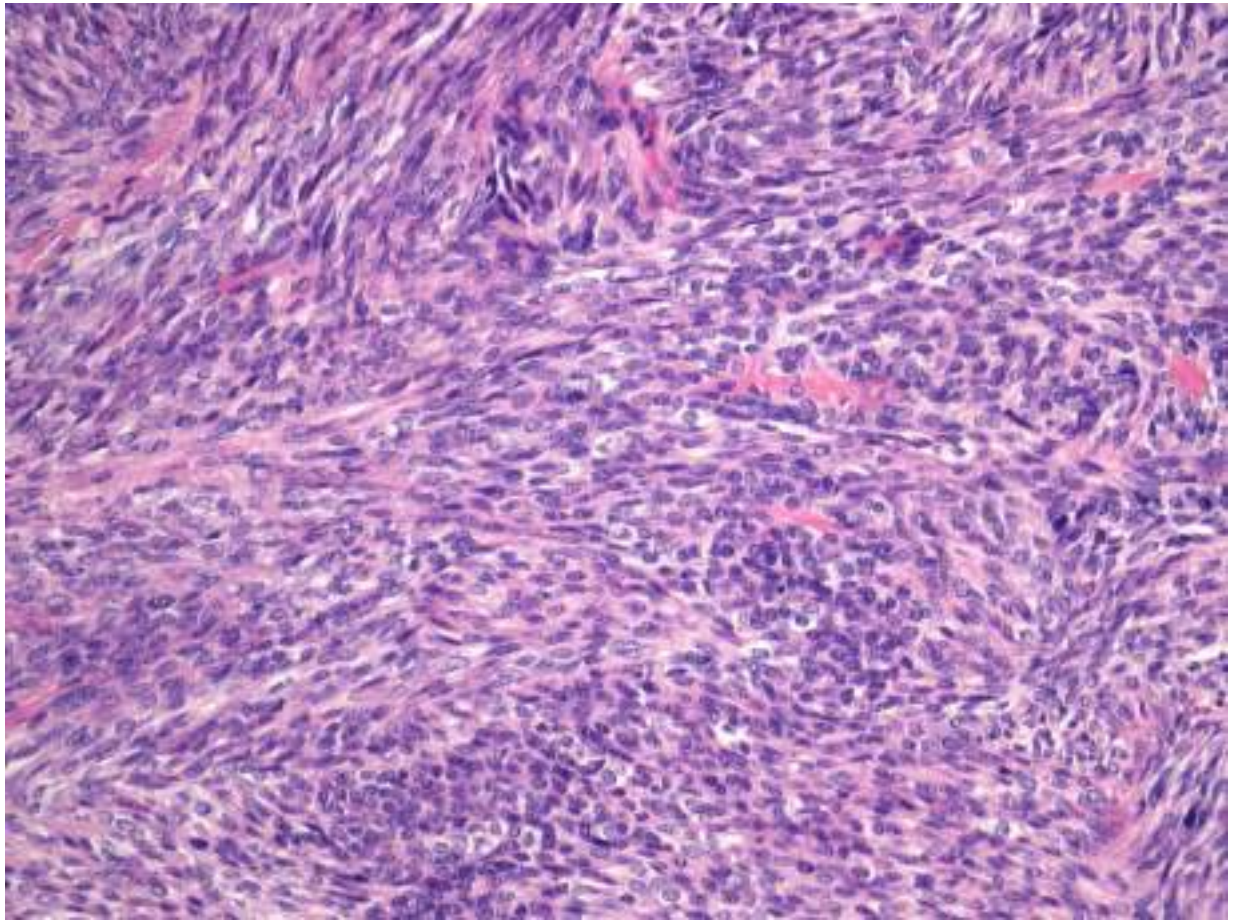

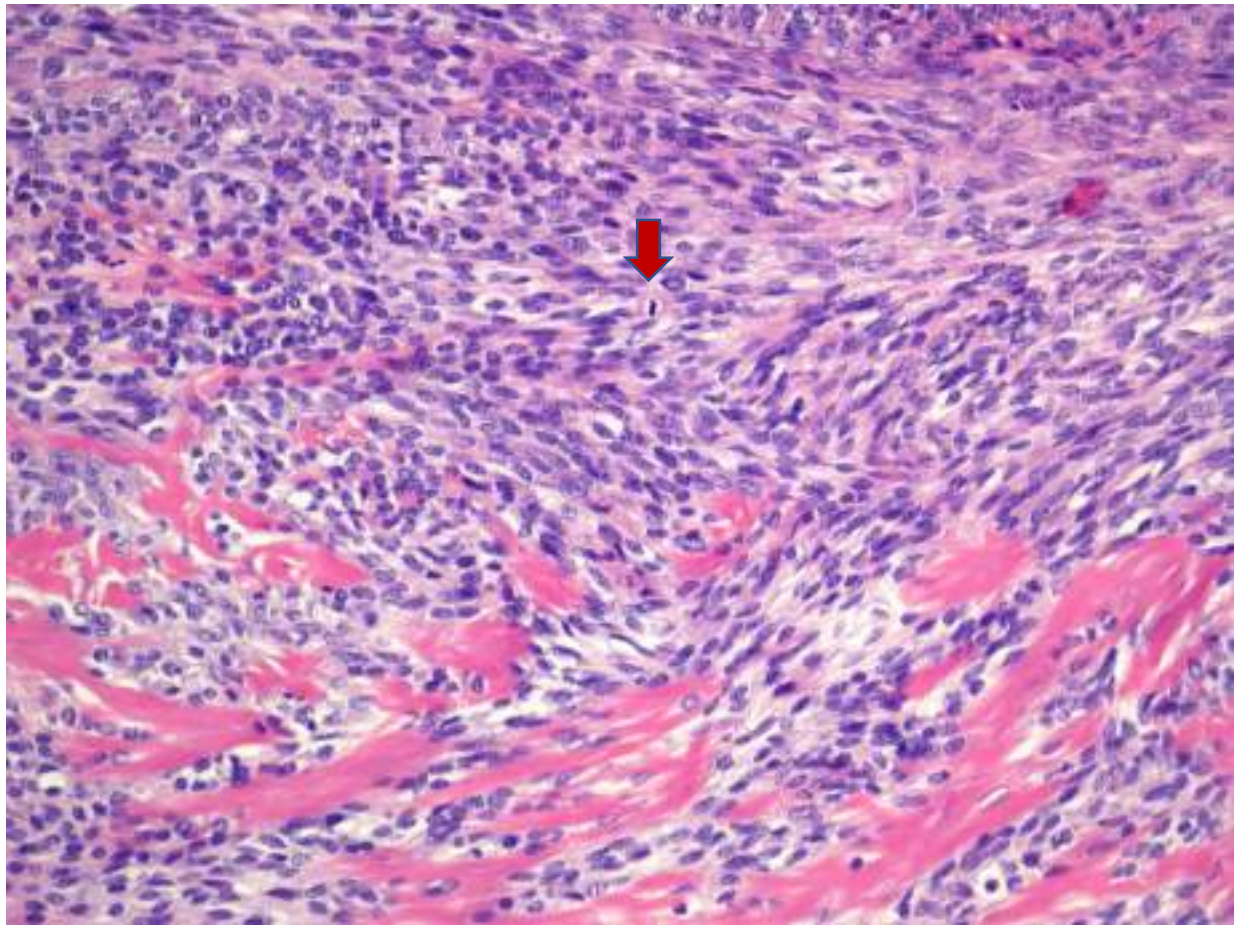

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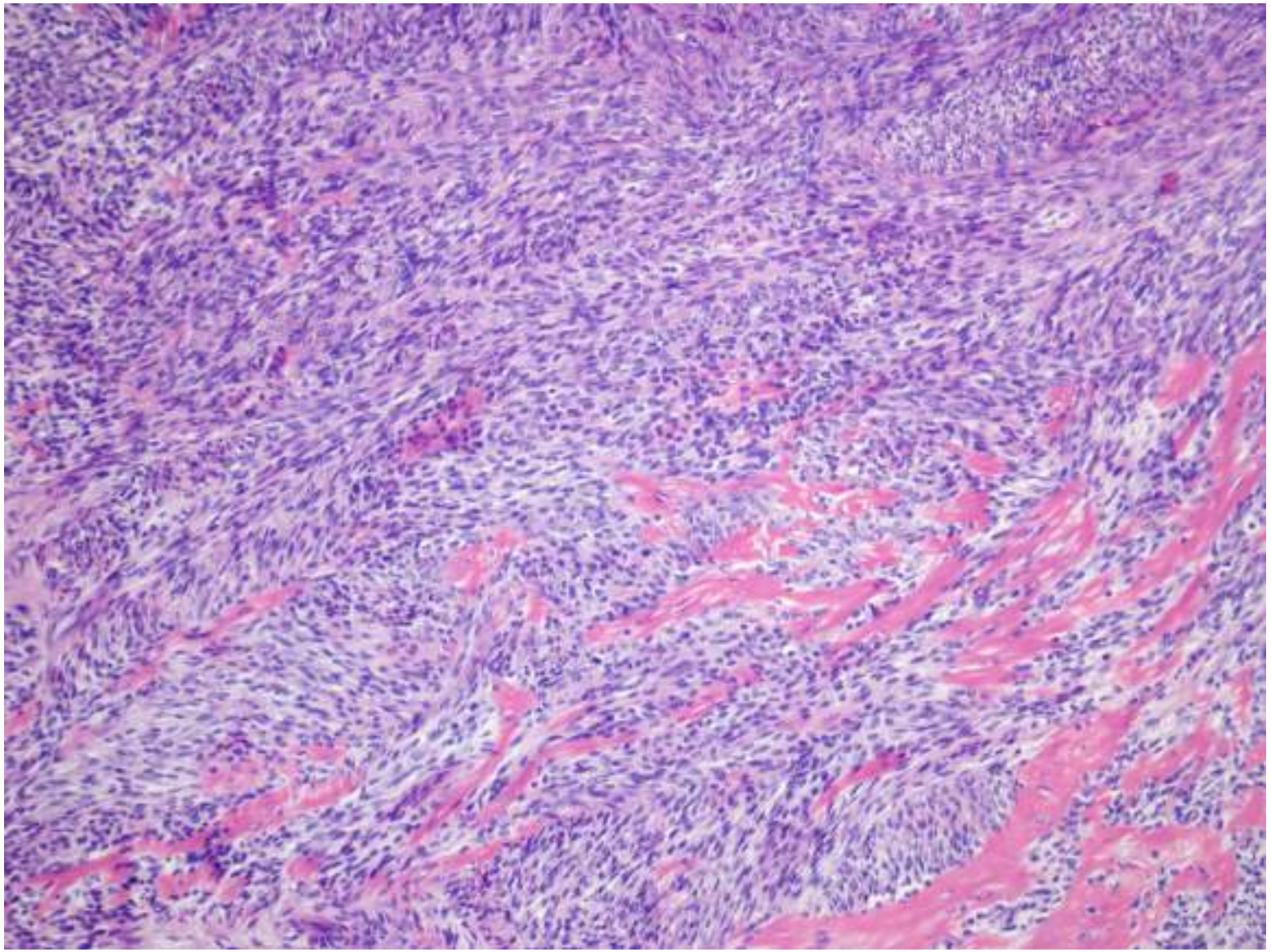
- *HISTOLOGICAL FEATURES* -



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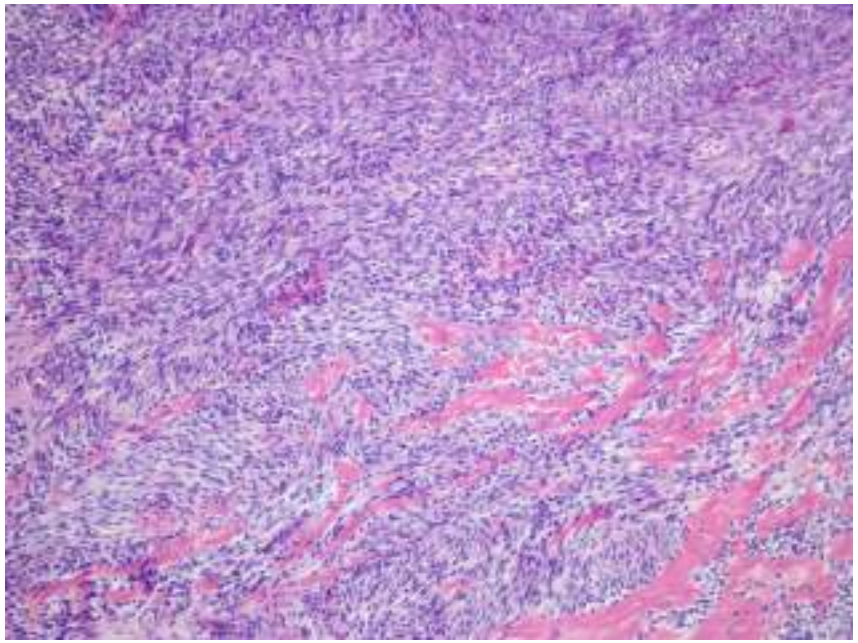
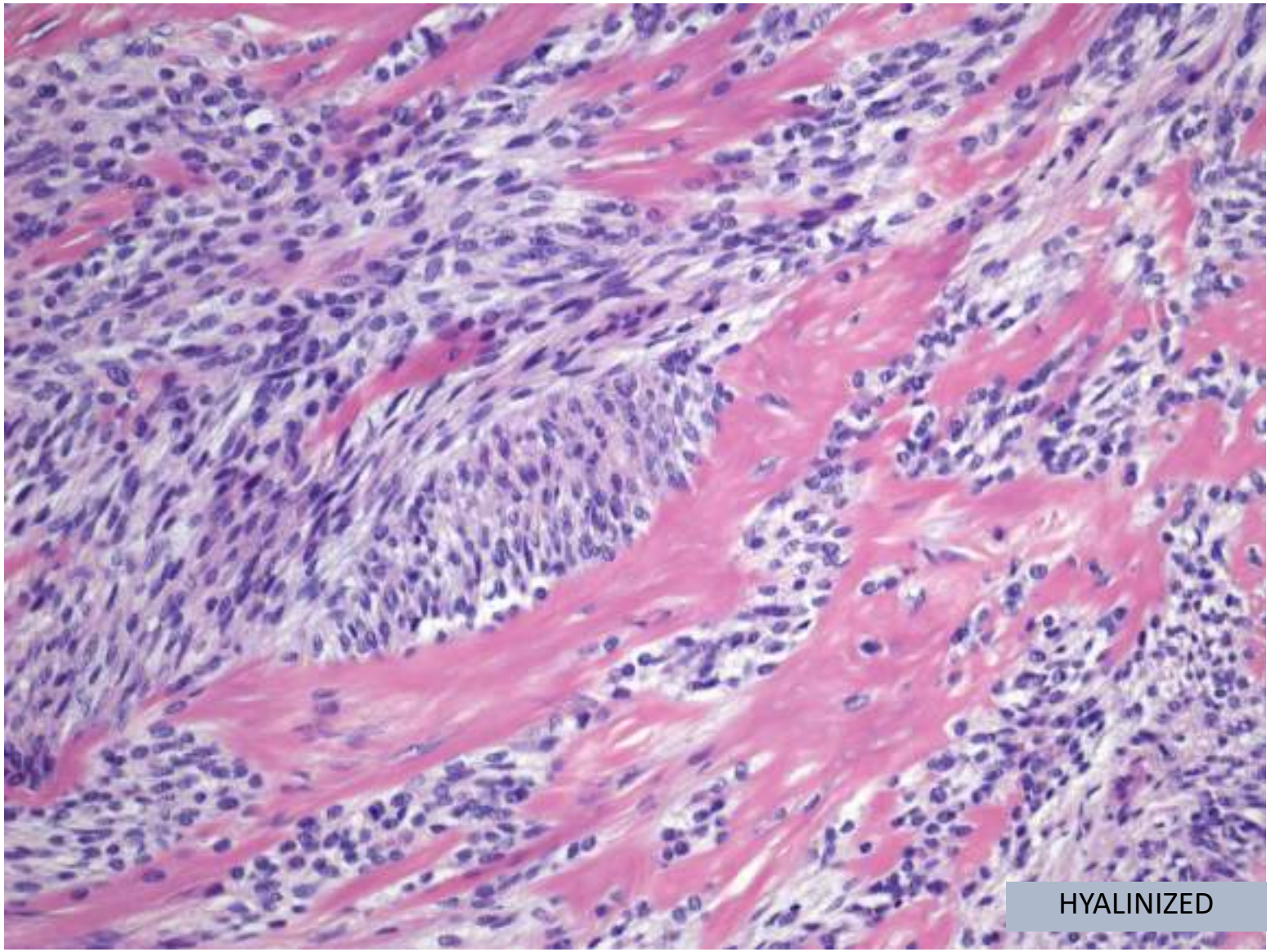
- *HISTOLOGICAL FEATURES* -





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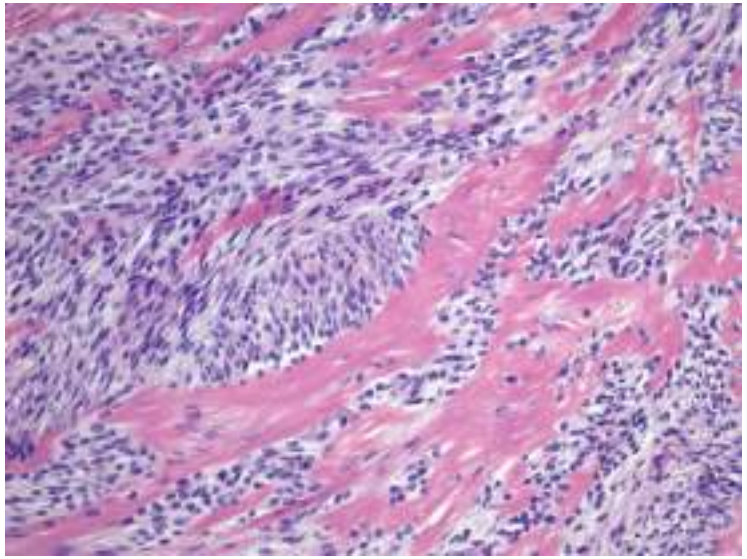
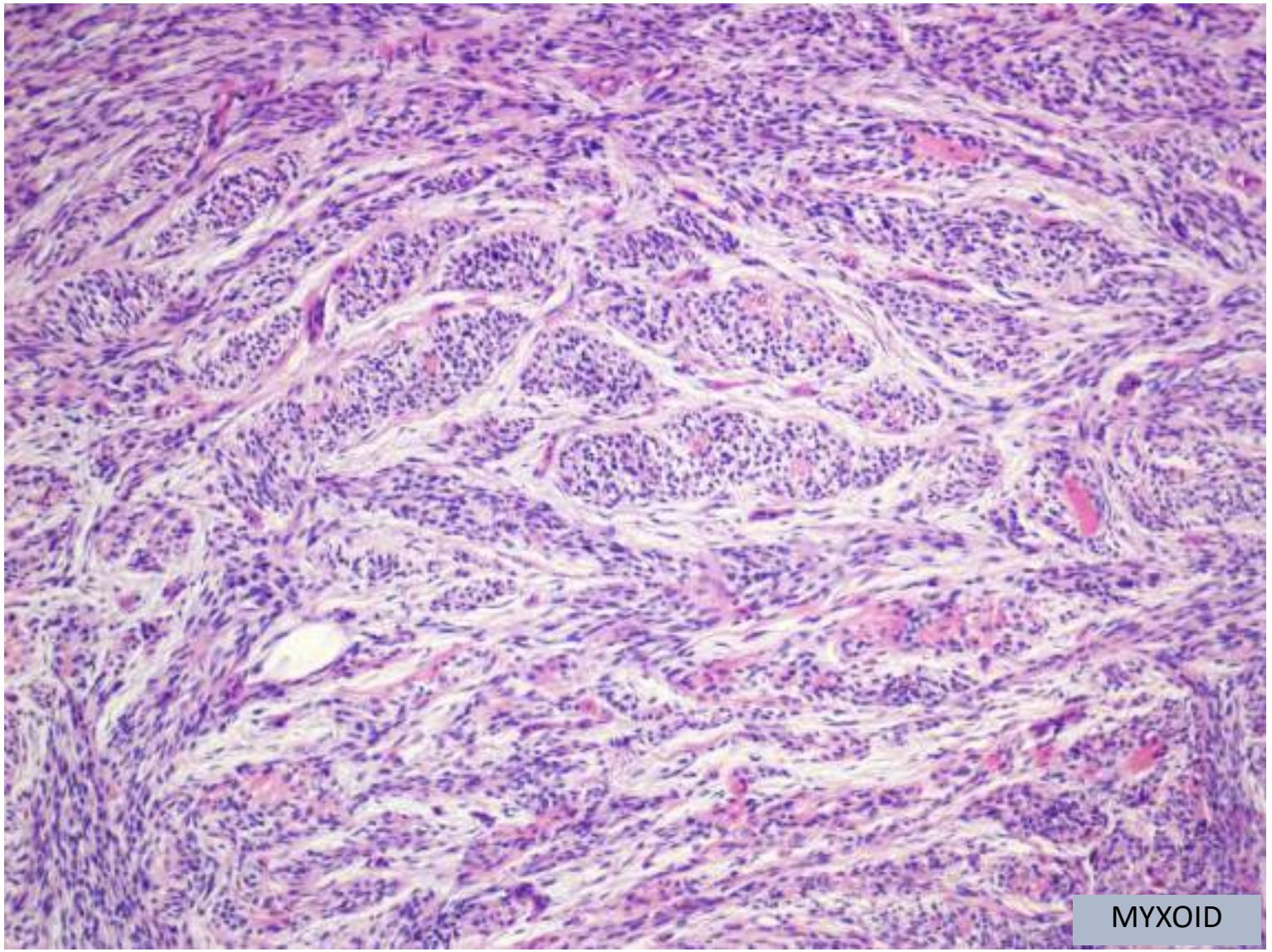
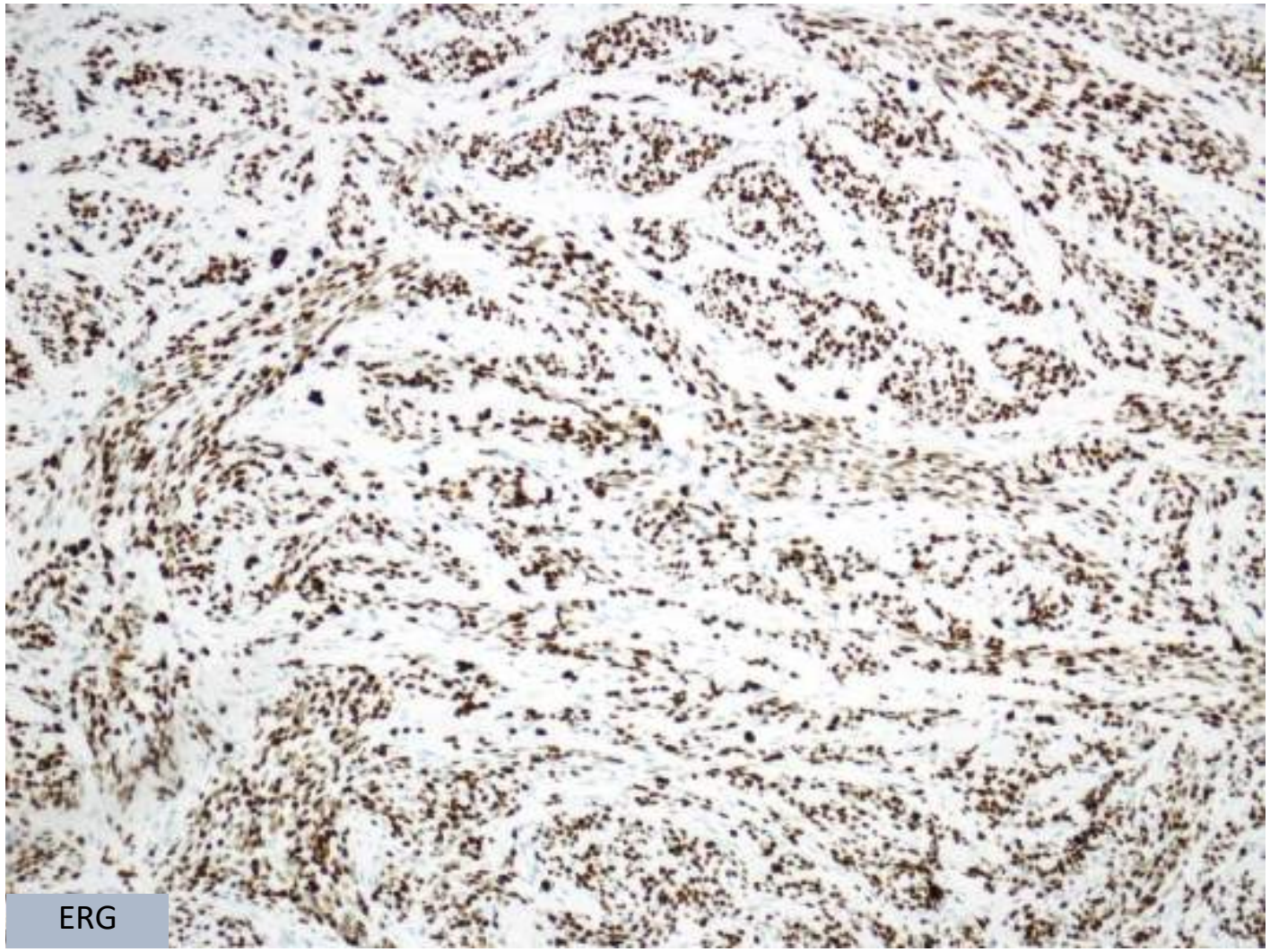
- *HISTOLOGICAL FEATURES* -





MYXOID

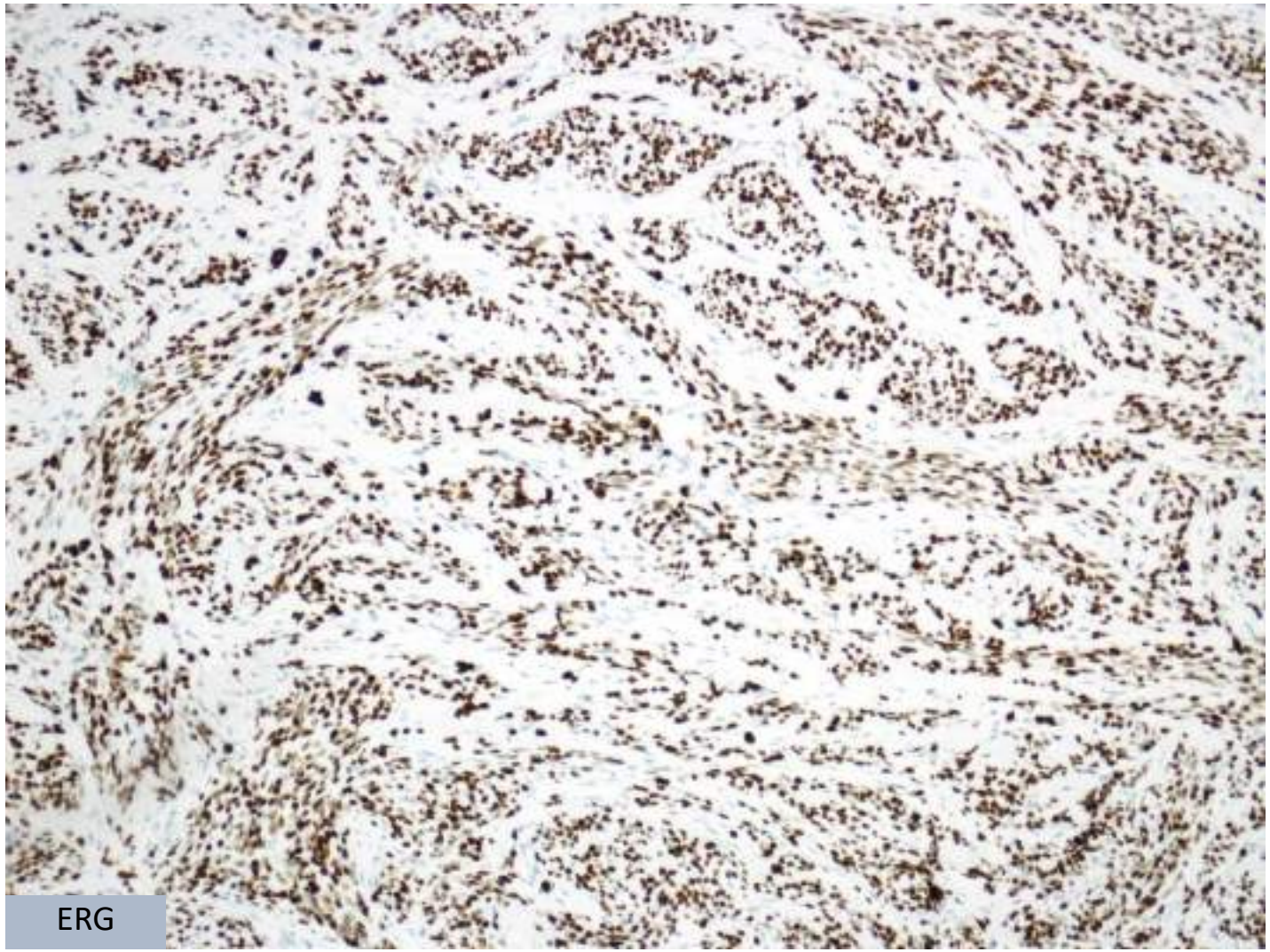
EWSR1::SMAD3 REARRANGED FIBROBLASTIC TUMOUR
- *IMMUNOHISTOCHEMICAL FEATURES* -


ERG

\+
- ERG

\-
- S100
- CITOKERATIN
- SOX10
- DESMIN
- SMA
- CD34

EWSR1::SMAD3 REARRANGED FIBROBLASTIC TUMOUR
- *IMMUNOHISTOCHEMICAL FEATURES* -



+ ERG

HIGH LEVELS OF *ERG* mRNA

NO GENE AMPLIFICATION

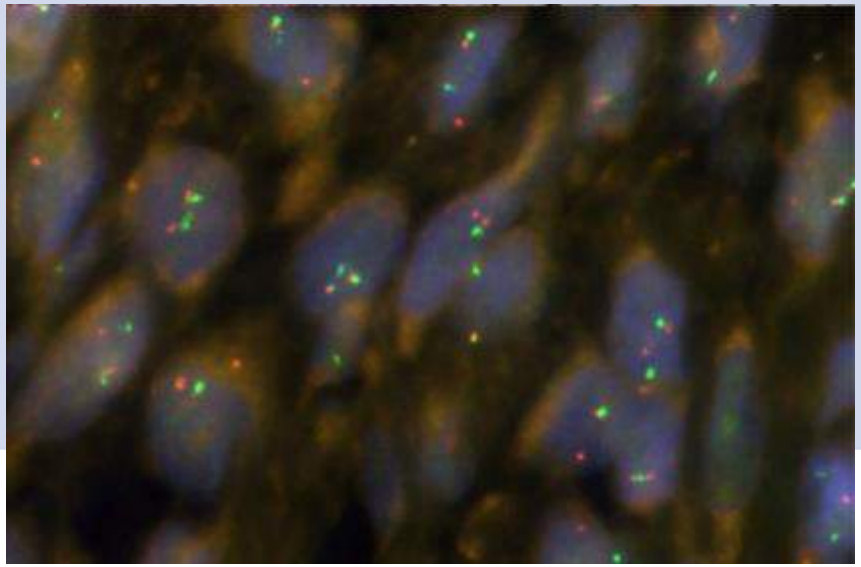
NO GENE REARRANGEMENT

MECHANISM FOR ABERRANT ERG EXPRESSION ELUSIVE

EWSR1::SMAD3 REARRANGED FIBROBLASTIC TUMOUR
- *DIAGNOSTIC TOOLS* -

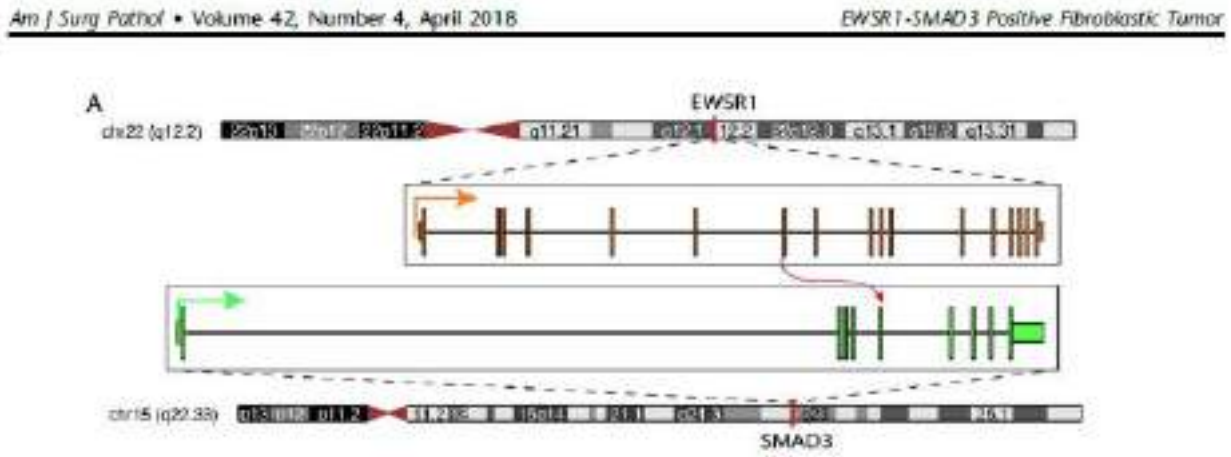
FISH

- *EWSR1* REARRANGEMENT



NEXT GENERATION SEQUENCING

- *EWSR1*(exon 7)::*SMAD3* (exon 5 or 6)



EWSR1::SMAD3 REARRANGED FIBROBLASTIC TUMOUR
- *MOLECULAR GENETIC FEATURES*-

EWSR1::SMAD3

OVEREXPRESSION OF *FIBRONECTIN* (*FN1*)

- SUGGESTS FIBROBLASTIC LINEAGE
- OTHER TUMOURS WITH *FN1*-RELATED GENE FUSIONS
  - CALCIFYING APONEUROTIC FIBROMA
  - PHOSPHATURIC MESENCHYMAL TUMOUR (CAN BE ERG+)

EWSR1::SMAD3 REARRANGED FIBROBLASTIC TUMOUR
- *PROGNOSIS*-

BENIGN

LOCAL RECURRENCES COMMON

- INCOMPLETE/MARGINAL EXCISION

COMPLETE EXCISION CURATIVE

EWSR1::SMAD3 REARRANGED FIBROBLASTIC TUMOUR
- *DIFFERENTIAL DIAGNOSIS* -

SPINDLE CELL SARCOMAS

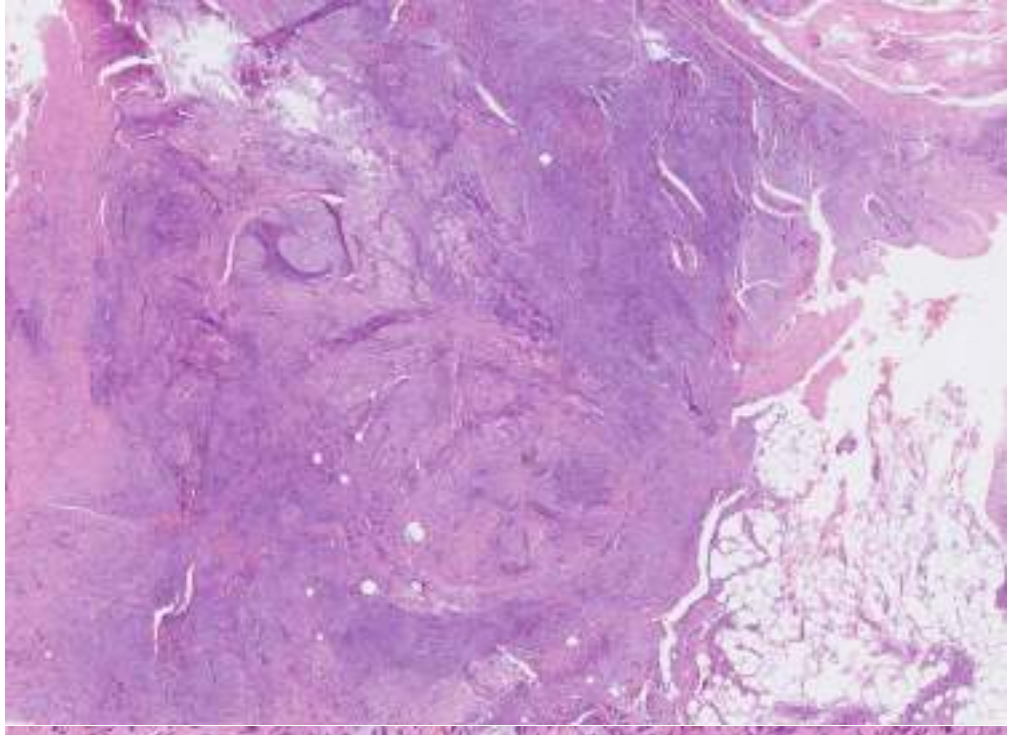
- SYNOVIAL SARCOMA, MONOPHASIC
- DERMATOFIBROSARCOMA PROTUBERANS
- LOW-GRADE FIBROMYXOID SARCOMA

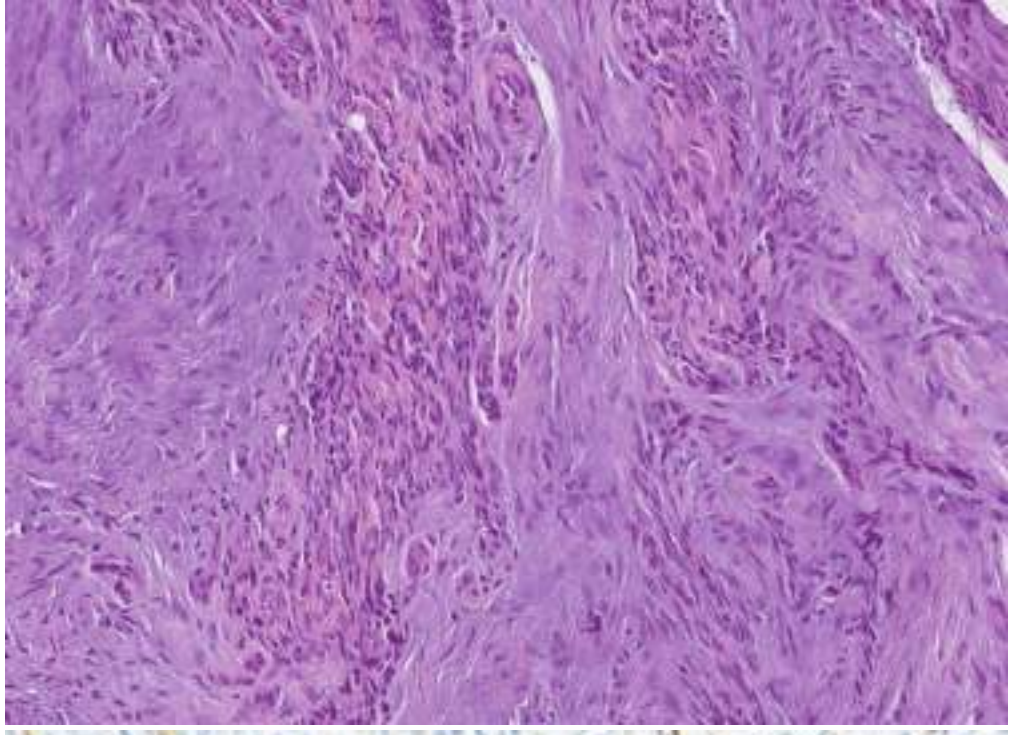
EWSR1::SMAD3 REARRANGED FIBROBLASTIC TUMOUR
- *DIFFERENTIAL DIAGNOSIS* -

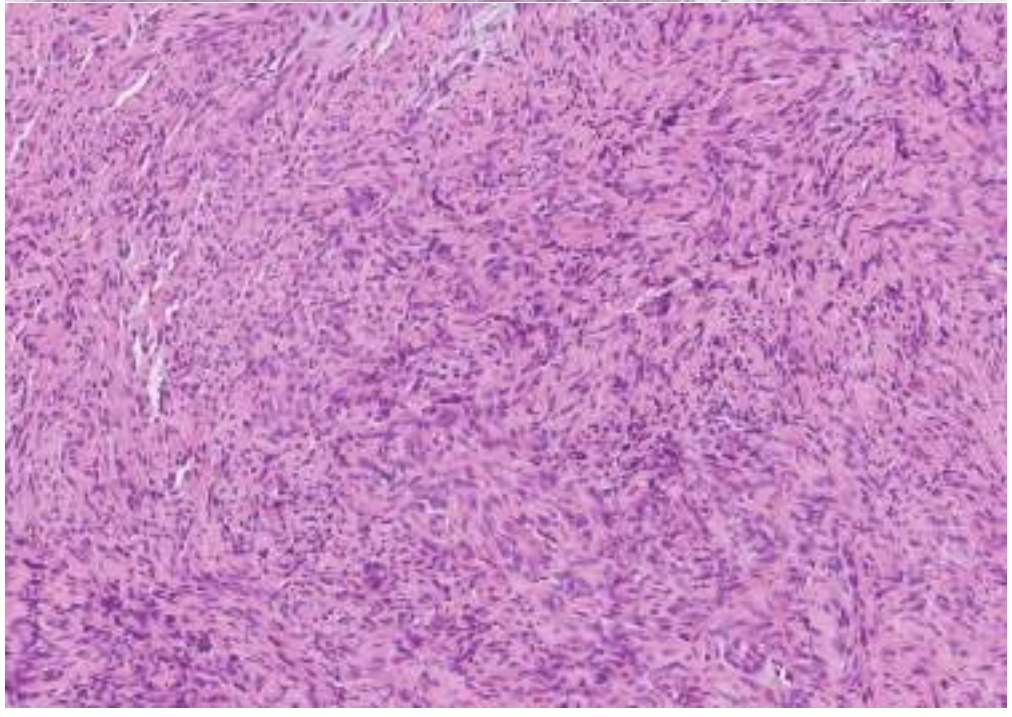
SPINDLE CELL SARCOMAS

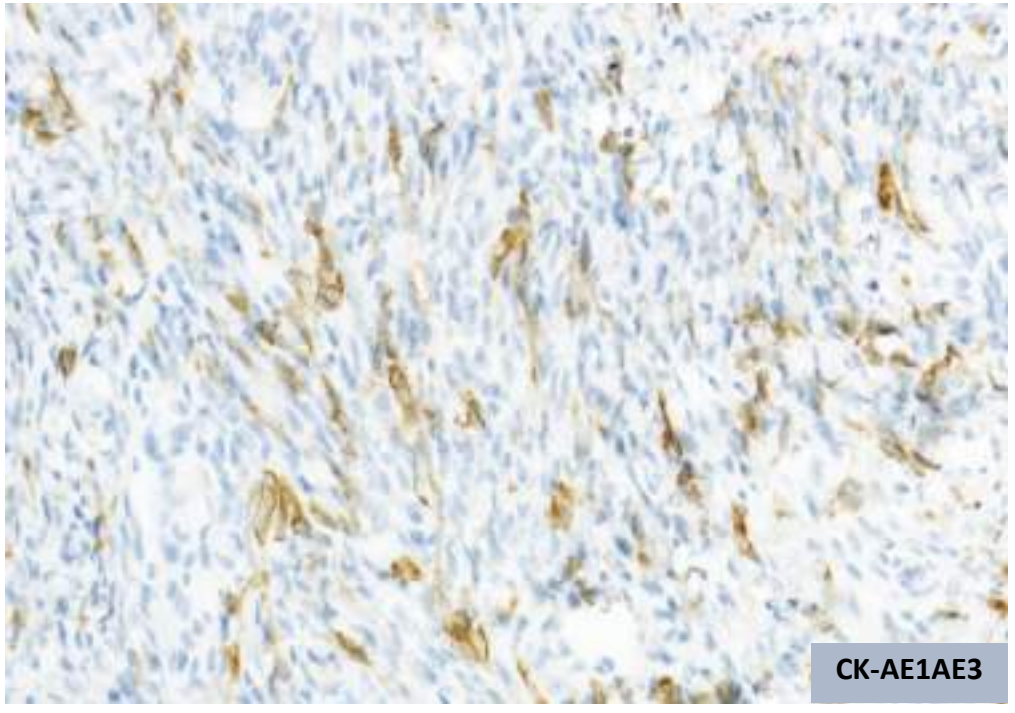
- SYNOVIAL SARCOMA, MONOPHASIC
- DERMATOFIBROSARCOMA PROTUBERANS
- LOW-GRADE FIBROMYXOID SARCOMA

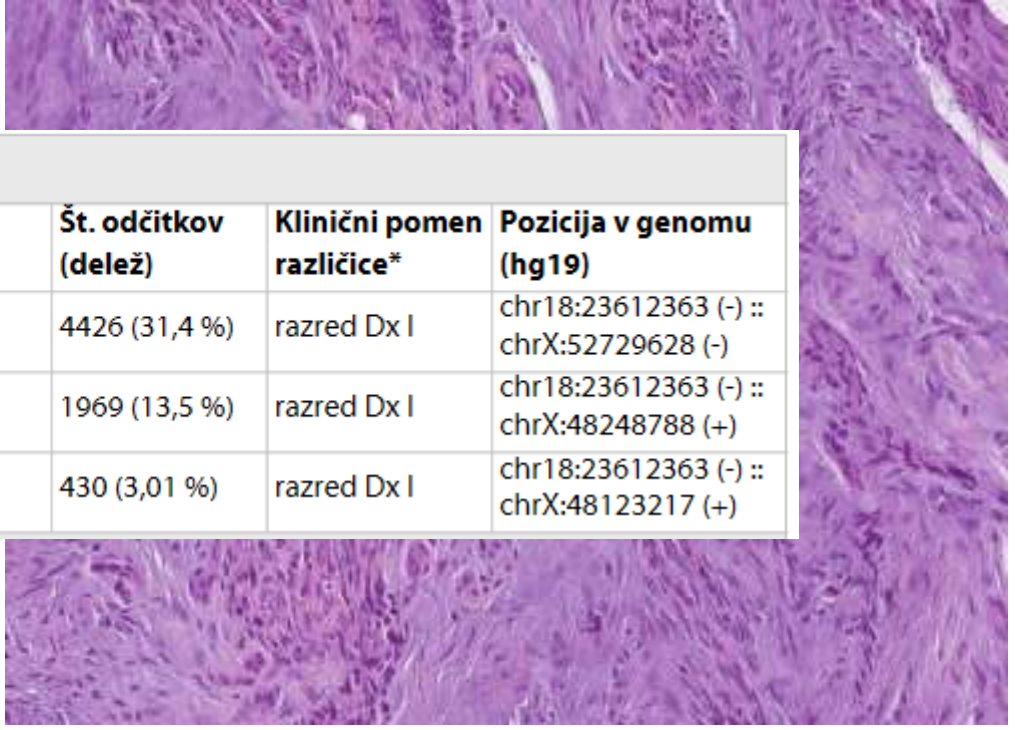
DIFFERENT IMMUNOHISTOCHEMISTRY → DIFFERENT GENETIC BACKGROUND



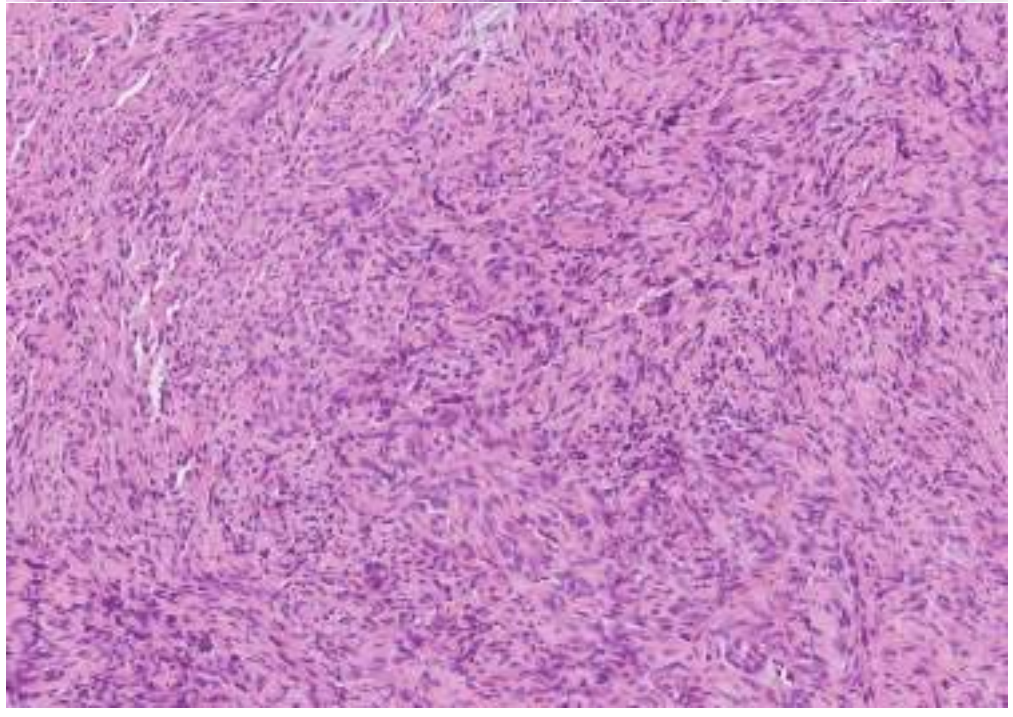


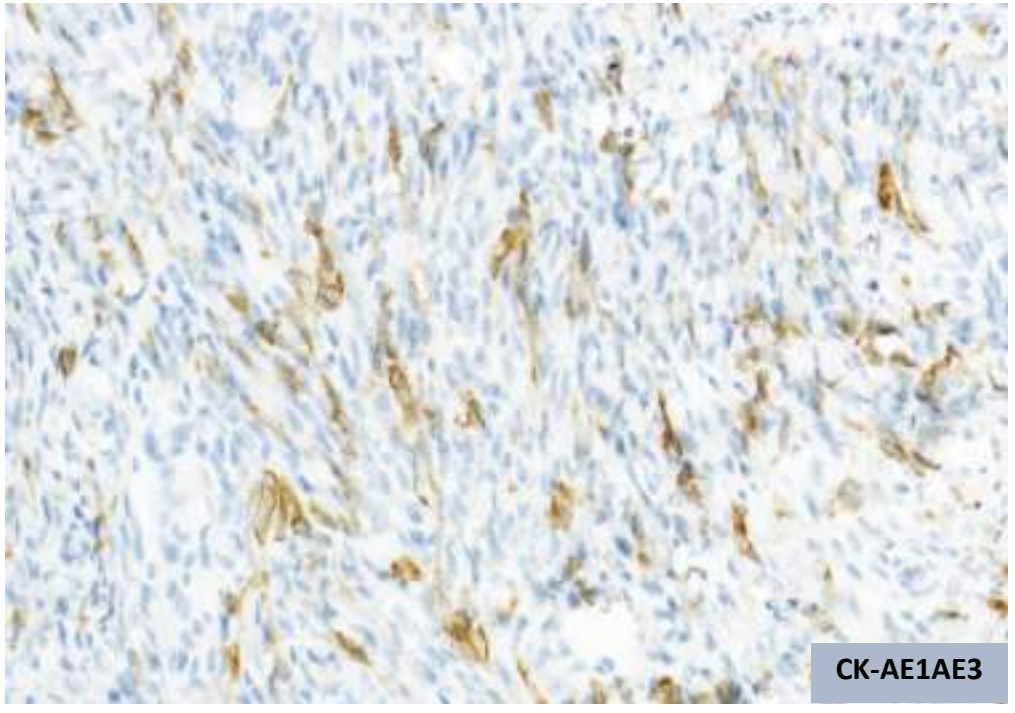



CK-AE1AE3



FUZIJE				
Gen	**Vključeni geni (eksoni)**	**Št. odčitkov (delež)**	**Klinični pomen različice***	**Pozicija v genomu (hg19)**
SS18	SS18 (ekson 9) :: SSX2 (ekson 6)	4426 (31,4 %)	razred Dx I	chr18:23612363 (-) :: chrX:52729628 (-)
	SS18 (ekson 9) :: SSX4 (ekson 6)	1969 (13,5 %)	razred Dx I	chr18:23612363 (-) :: chrX:48248788 (+)
	SS18 (ekson 9) :: SSX1 (ekson 6)	430 (3,01 %)	razred Dx I	chr18:23612363 (-) :: chrX:48123217 (+)

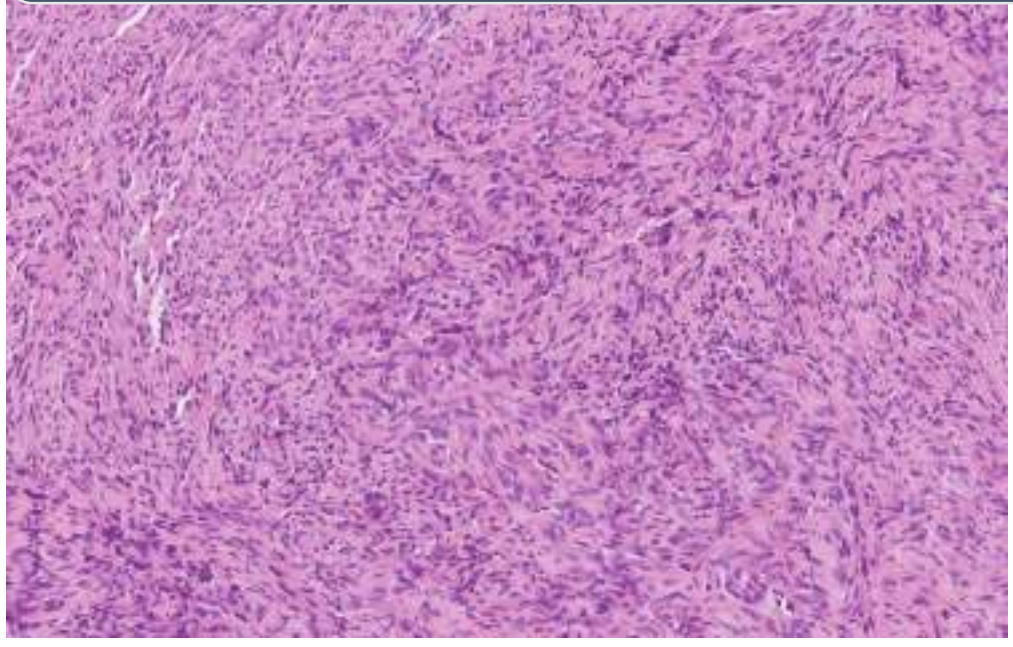


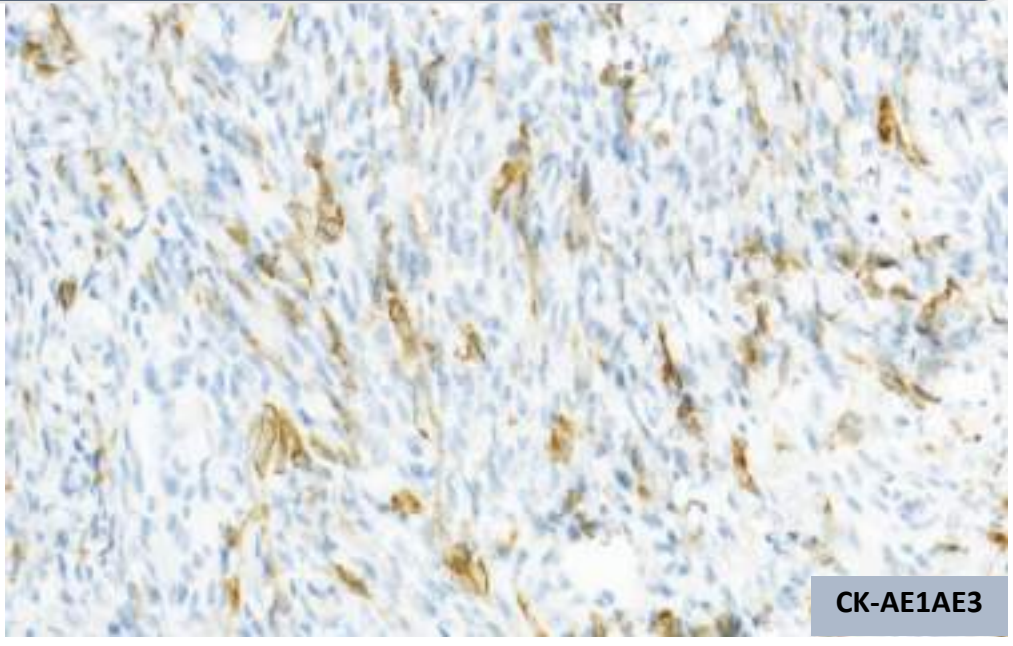


CK-AE1AE3

FUZIJE				
Gen	**Vključeni geni (eksoni)**	**Št. odčitkov (delež)**	**Klinični pomen različice***	**Pozicija v genomu (hg19)**
SS18	SS18 (ekson 9) :: SSX2 (ekson 6)	4426 (31,4 %)	razred Dx I	chr18:23612363 (-) :: chrX:52729628 (-)
	SS18 (ekson 9) :: SSX4 (ekson 6)	1969 (13,5 %)	razred Dx I	chr18:23612363 (-) :: chrX:48248788 (+)
	SS18 (ekson 9) :: SSX1 (ekson 6)	430 (3,01 %)	razred Dx I	chr18:23612363 (-) :: chrX:48123217 (+)

MINUTE SYNOVIAL SARCOMA





CK-AE1AE3

EWSR1::SMAD3 REARRANGED FIBROBLASTIC TUMOUR
- *DIFFERENTIAL DIAGNOSIS* -

BENIGN SPINDLE CELL TUMOURS (FIBROBLASTIC/ MYOFIBROBLASTIC)

- LIPOFIBROMATOSIS
- LIPOFIBROMATOSIS-LIKE NEURAL TUMOR
- MYOFIBROMA/MYOFIBROMATOSIS
- CALCIFYING APONEUROTIC FIBROMA
- PALMAR/PLANTAR FIBROMATOSIS

EWSR1::SMAD3 REARRANGED FIBROBLASTIC TUMOUR
- *DIFFERENTIAL DIAGNOSIS* -

BENIGN SPINDLE CELL TUMOURS (FIBROBLASTIC/ MYOFIBROBLASTIC)

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- MYOFIBROMA/MYOFIBROMATOSIS
- CALCIFYING APONEUROTIC FIBROMA
- PALMAR/PLANTAR FIBROMATOSIS

DIFFERENT IMMUNOHISTOCHEMISTRY

DIFFERENT GENETIC BACKGROUND

EWSR1::SMAD3 REARRANGED FIBROBLASTIC TUMOUR
- *DIFFERENTIAL DIAGNOSIS* -

BENIGN SPINDLE CELL TUMOURS (FIBROBLASTIC/ MYOFIBROBLASTIC)

- LIPOFIBROMATOSIS
- LIPOFIBROMATOSIS-LIKE NEURAL TUMOR
- MYOFIBROMA/MYOFIBROMATOSIS
- CALCIFYING APONEUROTIC FIBROMA
- PALMAR/PLANTAR FIBROMATOSIS
- CELLULAR FIBROUS HISTIOCYTOMA

Received: 6 January 2021 | Revised: 19 March 2021 | Accepted: 6 April 2021

DOI: 10.1111/cup.14024

JCP JOURNAL OF CUTANEOUS PATHOLOGY WILEY

NOTES AND COMMENTS

Pitfall regarding expression of ETS-related gene (ERG) in fibrohistiocytic neoplasms

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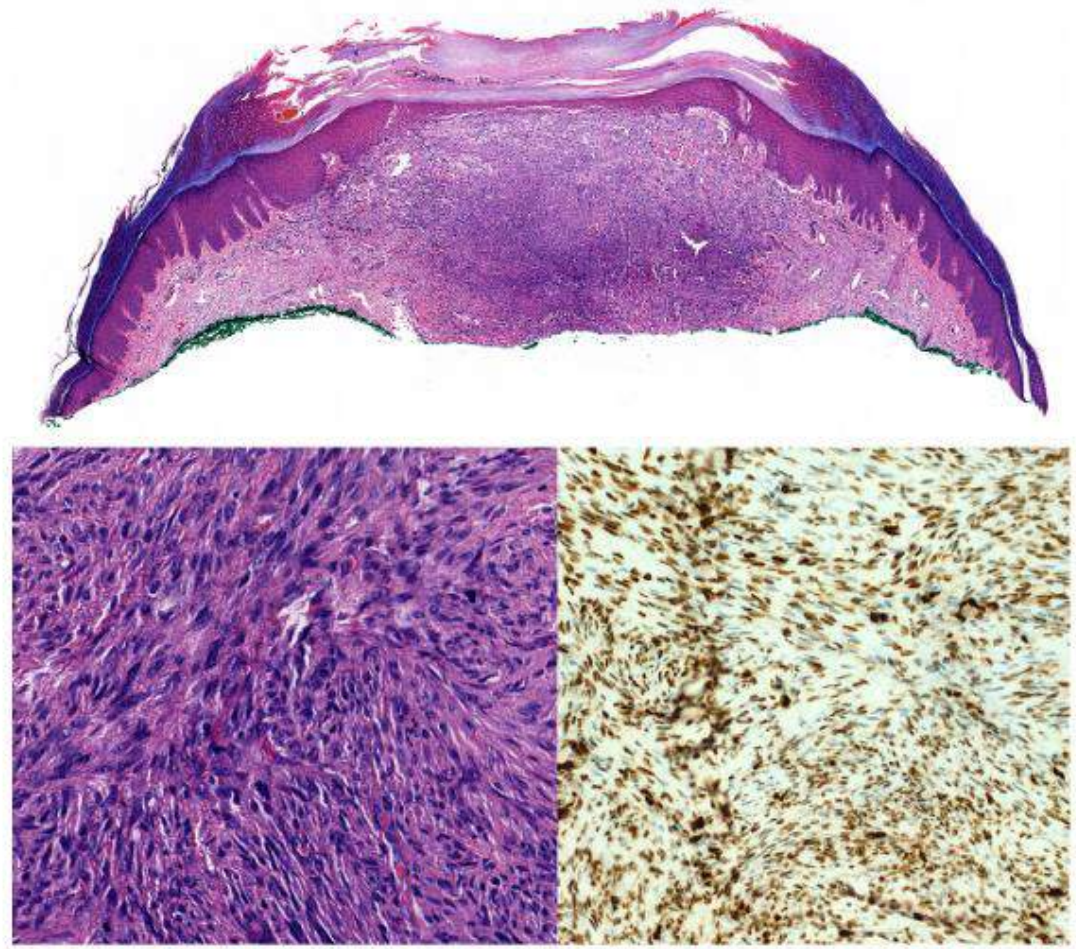
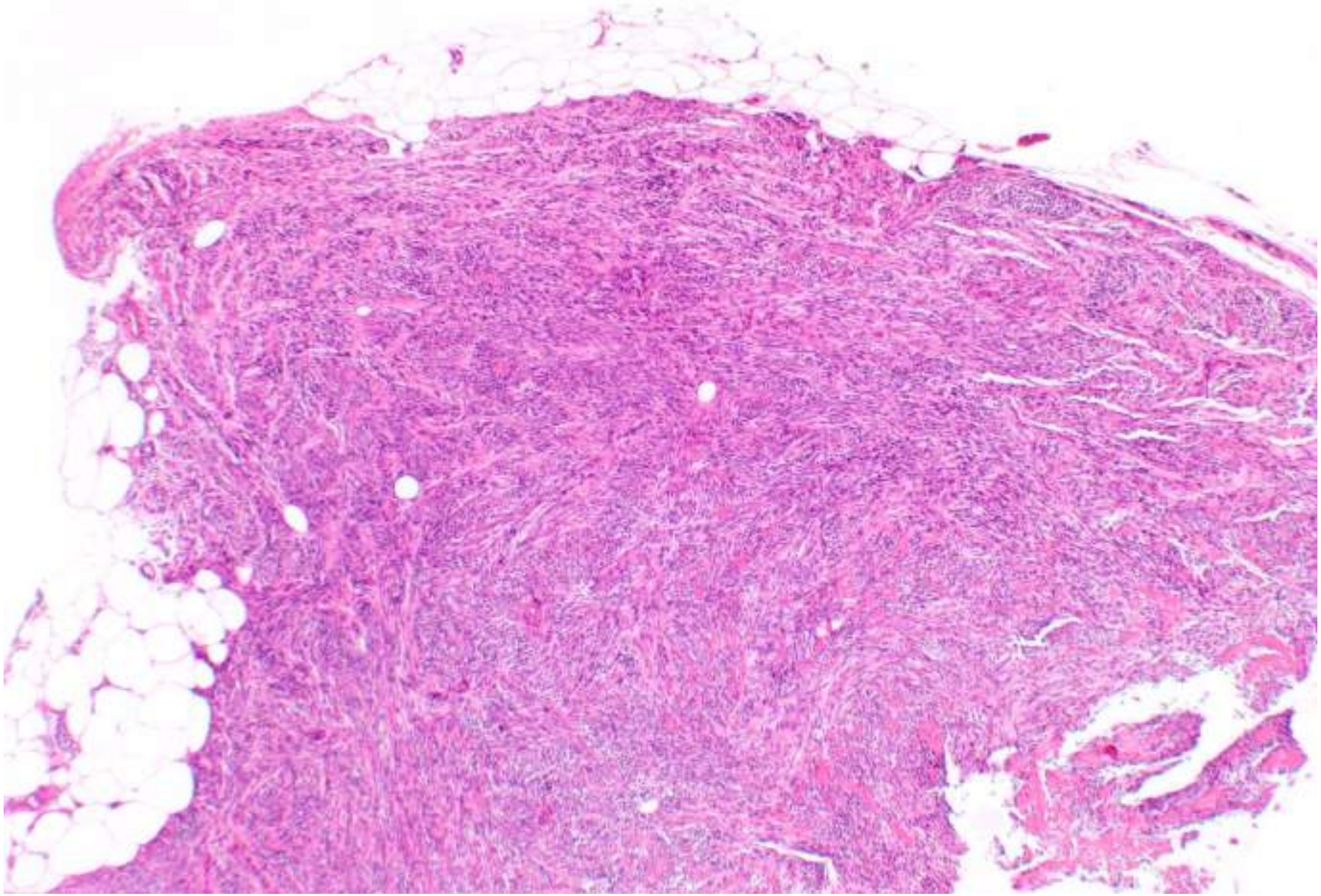


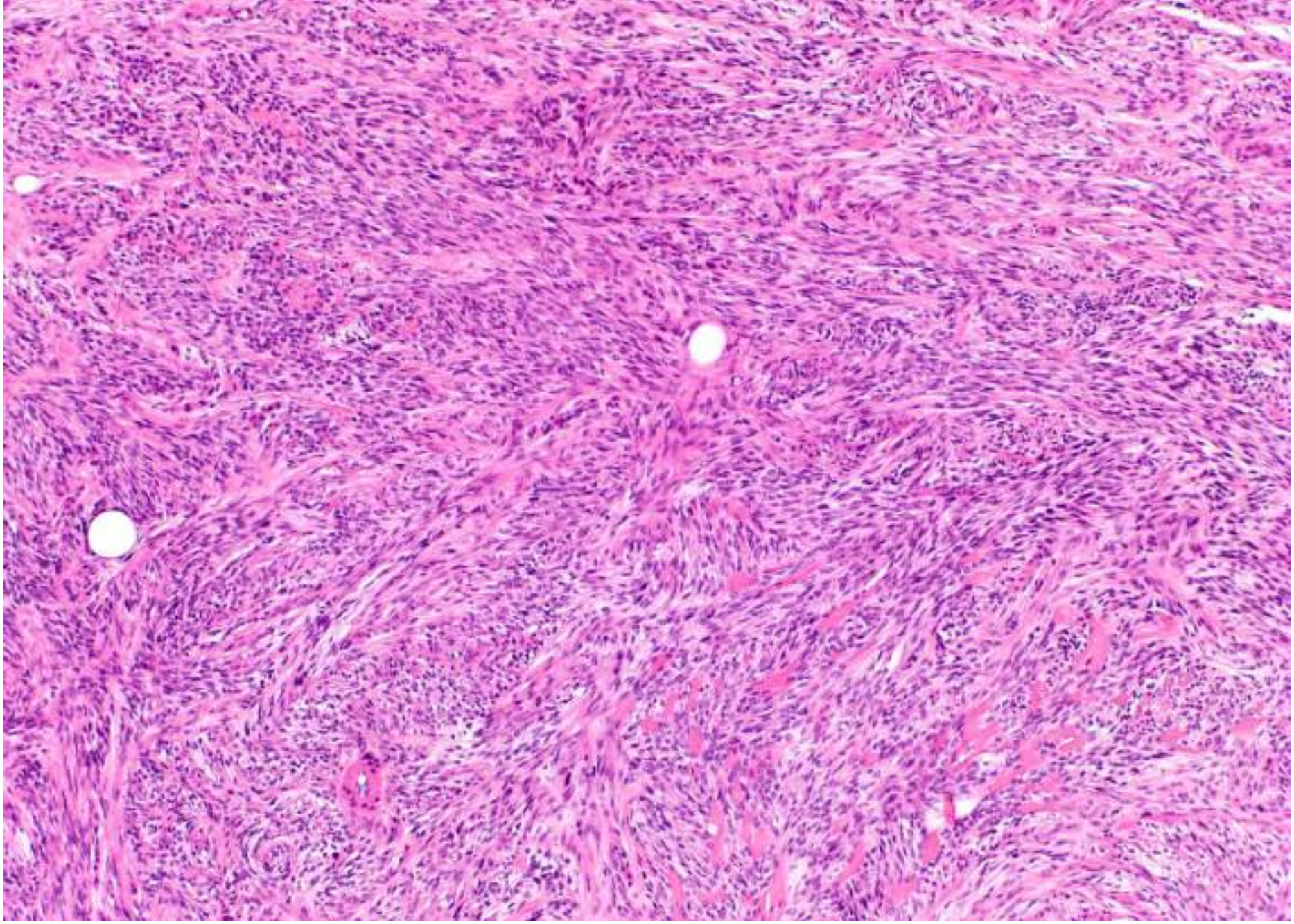
FIGURE 1 Top panel demonstrates a dermal-based proliferation of spindled cells in fascicles pressed up against the epidermis with peripheral collagen trapping (hematoxylin and eosin [H&E], ×40, original magnification). Lower right panel shows relatively monomorphous plump spindled cells in hypercellular fascicles (H&E, ×200, original magnification). Lower left panel shows intense expression of ERG (H&E, ×200, original magnification)

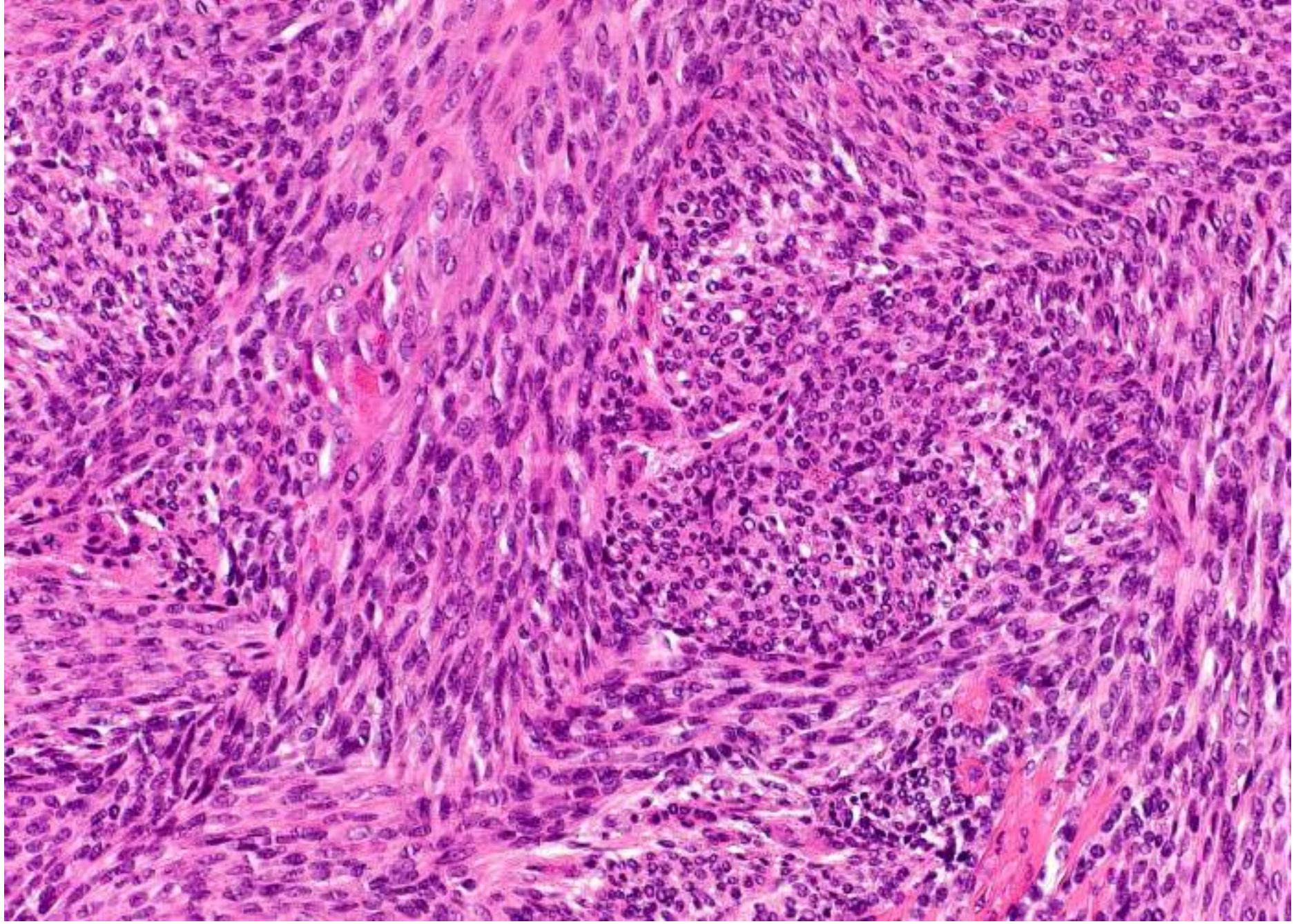
Thank You For your Attention!

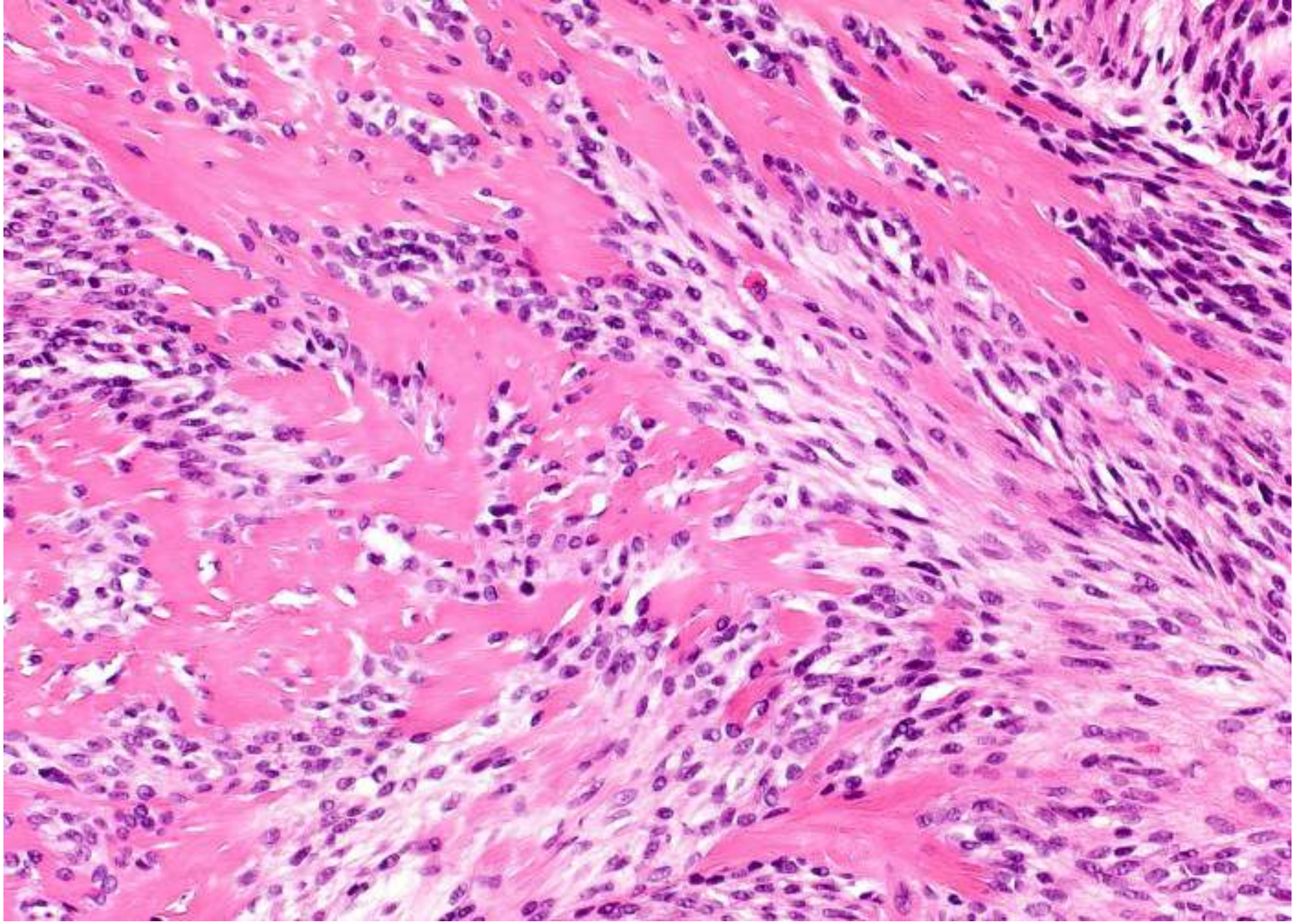
Case presentation

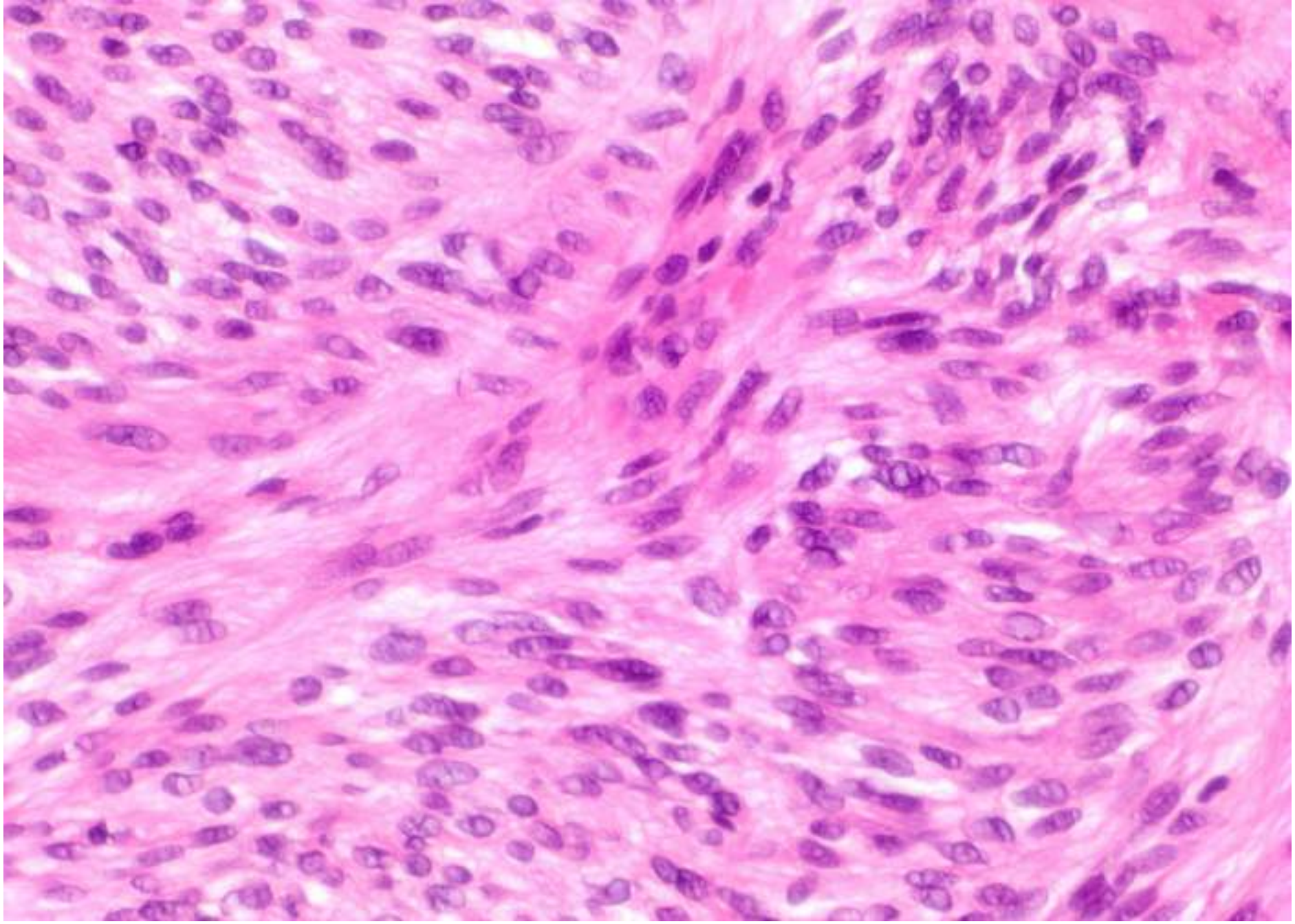
- 39 yo female
- Nodule on dorsal aspect of 3rd metatarsophalangeal joint
- ? Dermoid inclusion cyst











Differential diagnosis

- Paediatric patient
- Acral lesion
- Fascicular pattern
- Spindled cells
- Lack of atypia and mitotic activity

Minute synovial sarcoma (monomorphic variant)

Michal M et al. Am J Surg Pathol. 2006

- Young patients (median age 29 yo)
- Hands and feet
- Favorable outcome if completely excised

EWSR1::SMAD3 rearranged fibroblastic tumour

Habeeb O et al. J Cutan Pathol. 2021

- Wide age range (1-68 yo)
- Hands and feet
- Benign neoplasm, but local recurrence if incompletely excised

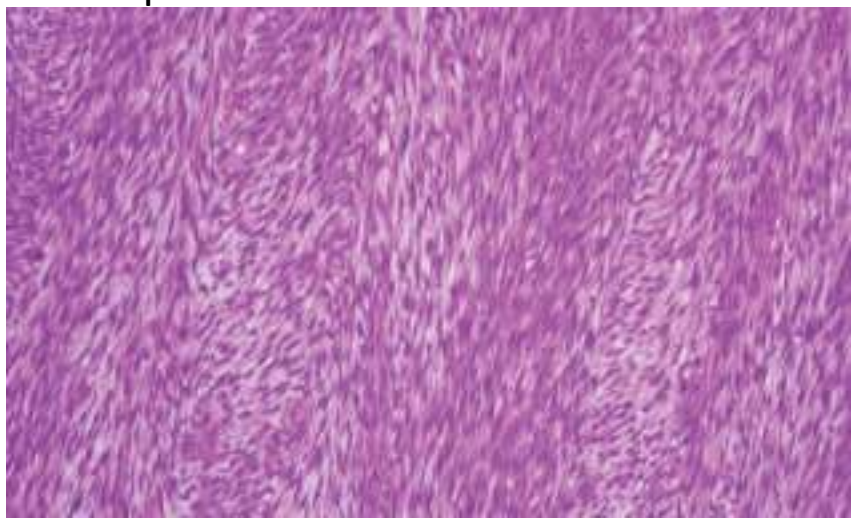
Differential diagnosis

Minute monomorphic synovial sarcoma

- Capsule, pseudocapsule or infiltrating margin
- Uniform, tapered spindle cells with variably collagenous stroma
- Mitotic activity: 0-3 mitosis/10 HPF
- No atypical mitosis

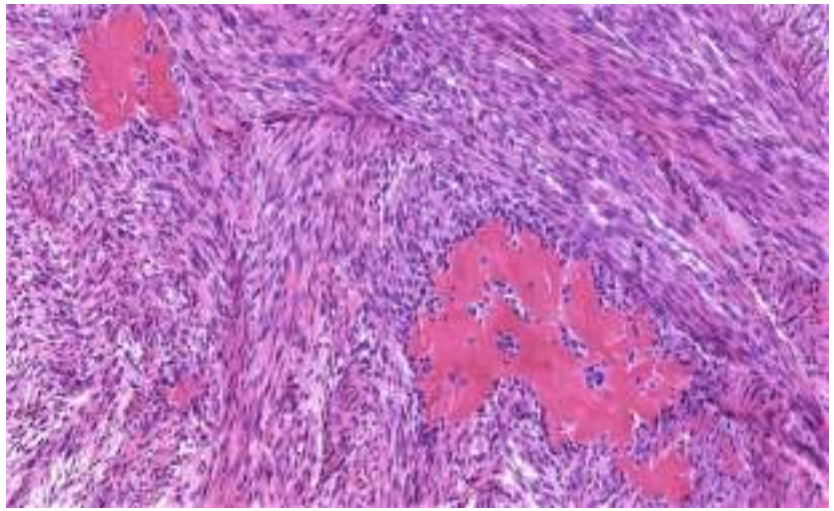
Michal M et al. Am J Surg Pathol. 2006

Monophasic SS



EWSR1::SMAD3 rearranged fibroblastic tumour

- Well demarcated, but can infiltrate subcutaneous fat
- May show zonation pattern:
  - Intersecting cellular fascicles in the periphery
  - Hyalinized acellular centre
- Fibroblastic spindle cells within collagenous to more myxoid stroma
- Lack nuclear pleomorphism, hyperchromasia, prominent nucleoli and mitotic activity



Habeeb O et al. J Cutan Pathol. 2021

Differential diagnosis

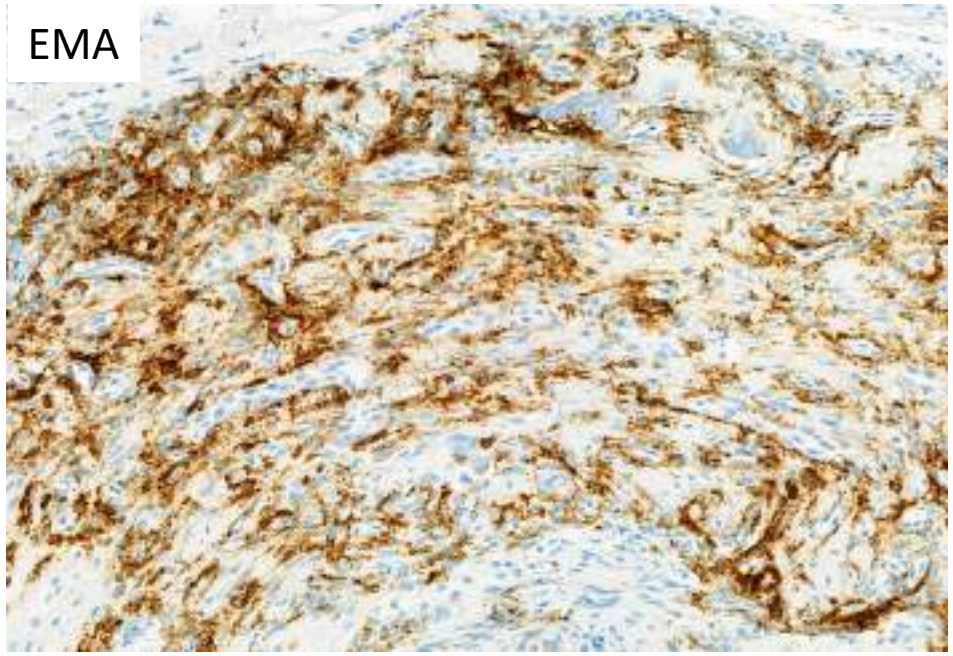
Minute monomorphic synovial sarcoma

- EMA +
- CK AE1-AE3: + in isolated or clustered cells
- S100: scattered small nerve twigs
- Can have *SYT-SSX* fusion transcripts

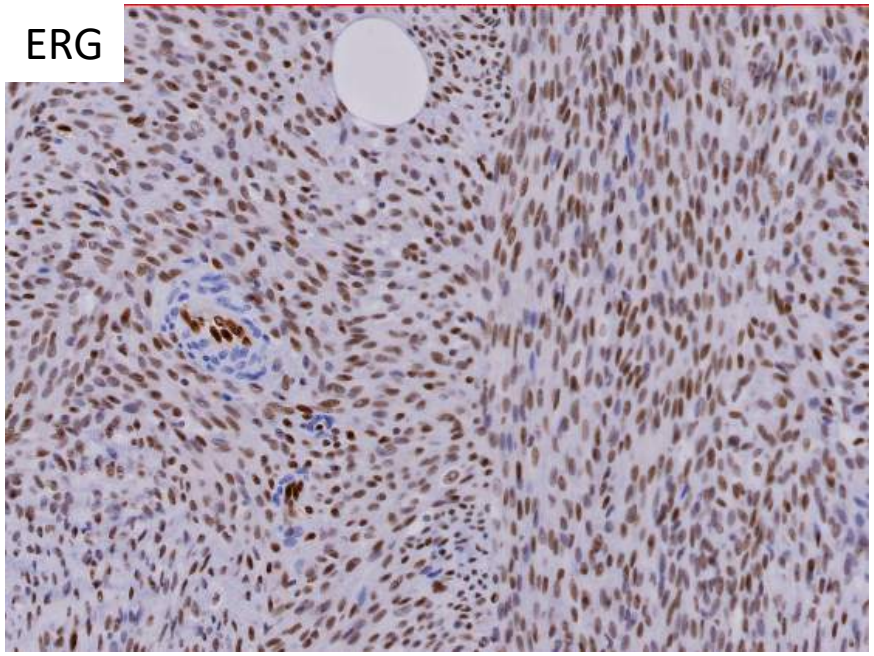
EWSR1::SMAD3 rearranged fibroblastic tumour

- Strong diffuse nuclear ERG expression
- SMA and CD34 are negative
- CK, EMA, S100 and SOX10: negative
- *EWSR1* rearrangement

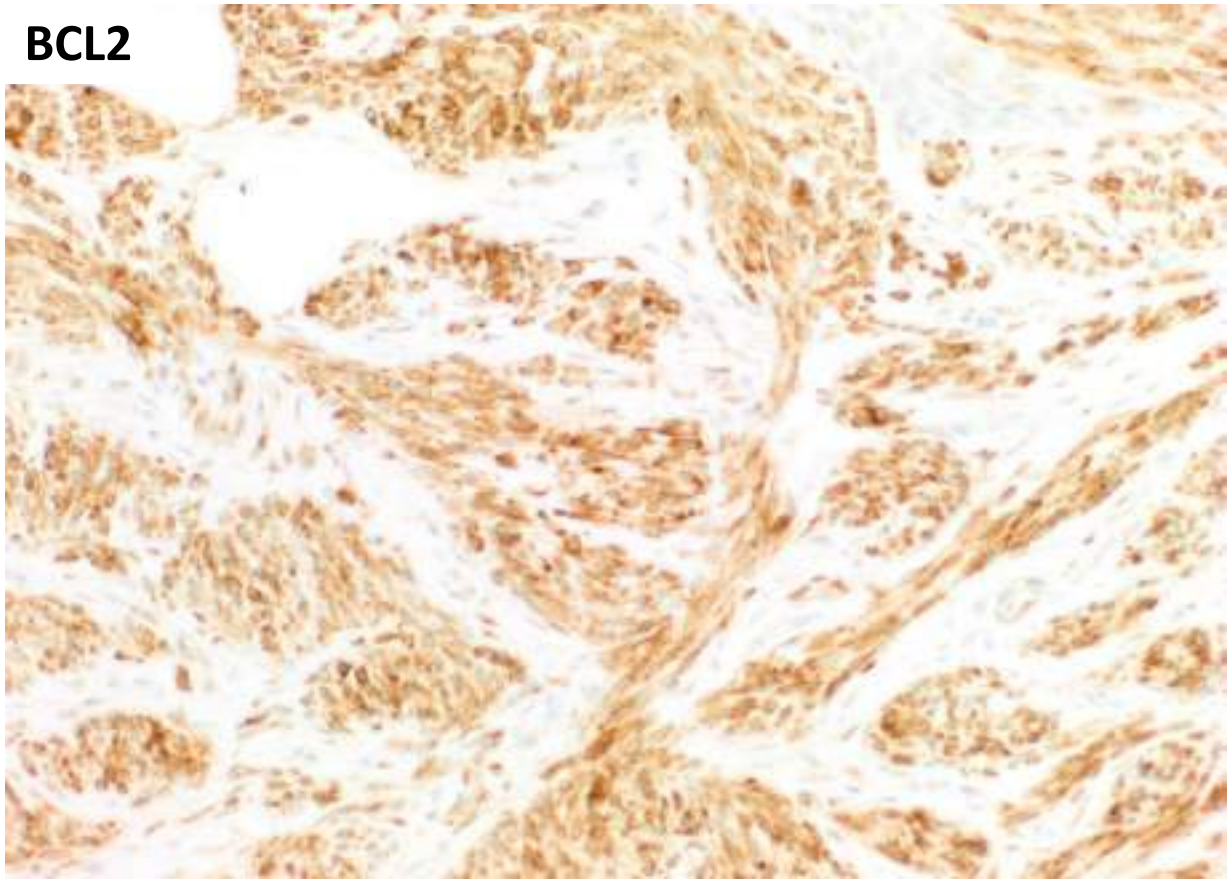
EMA

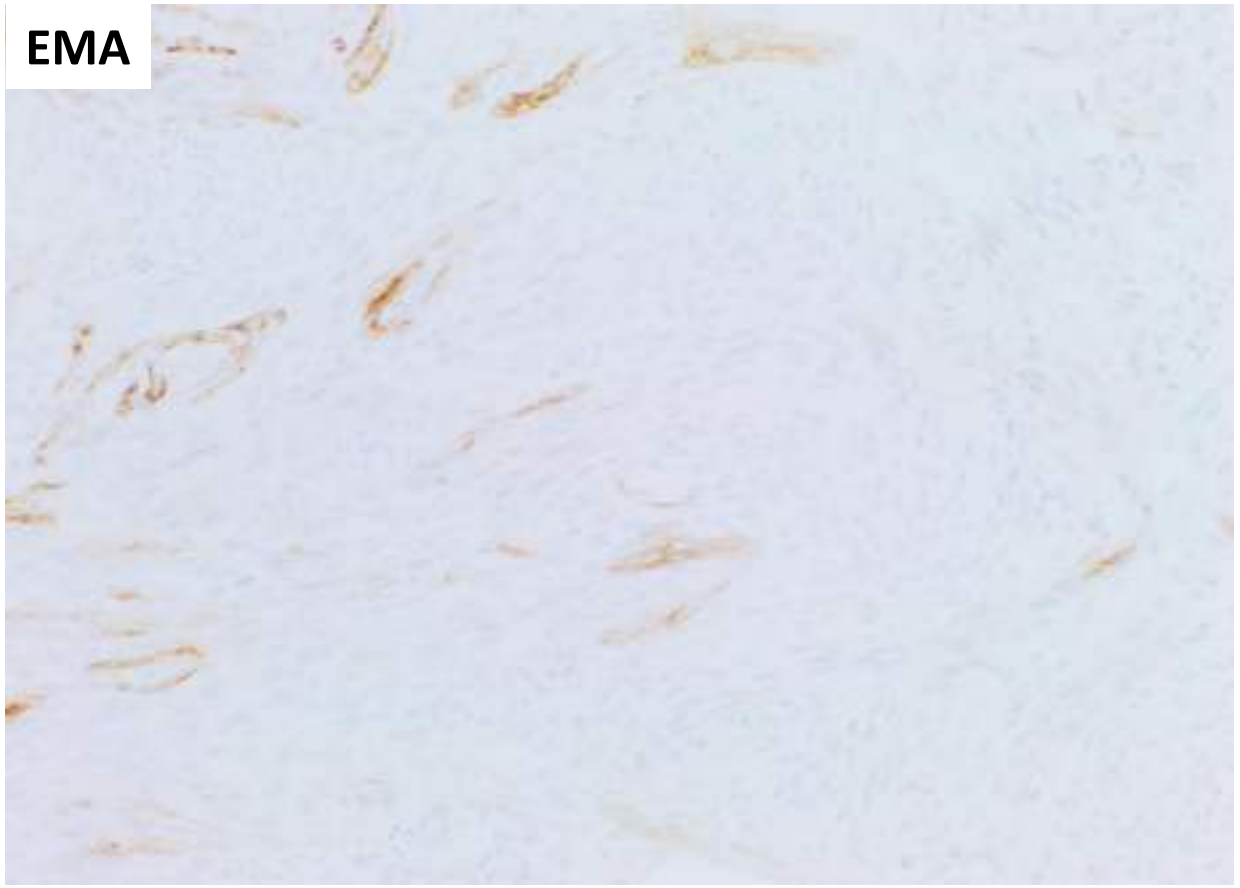


ERG



Our case





Positive:

- BLC-2 and CD99: diffuse

Partially positive:

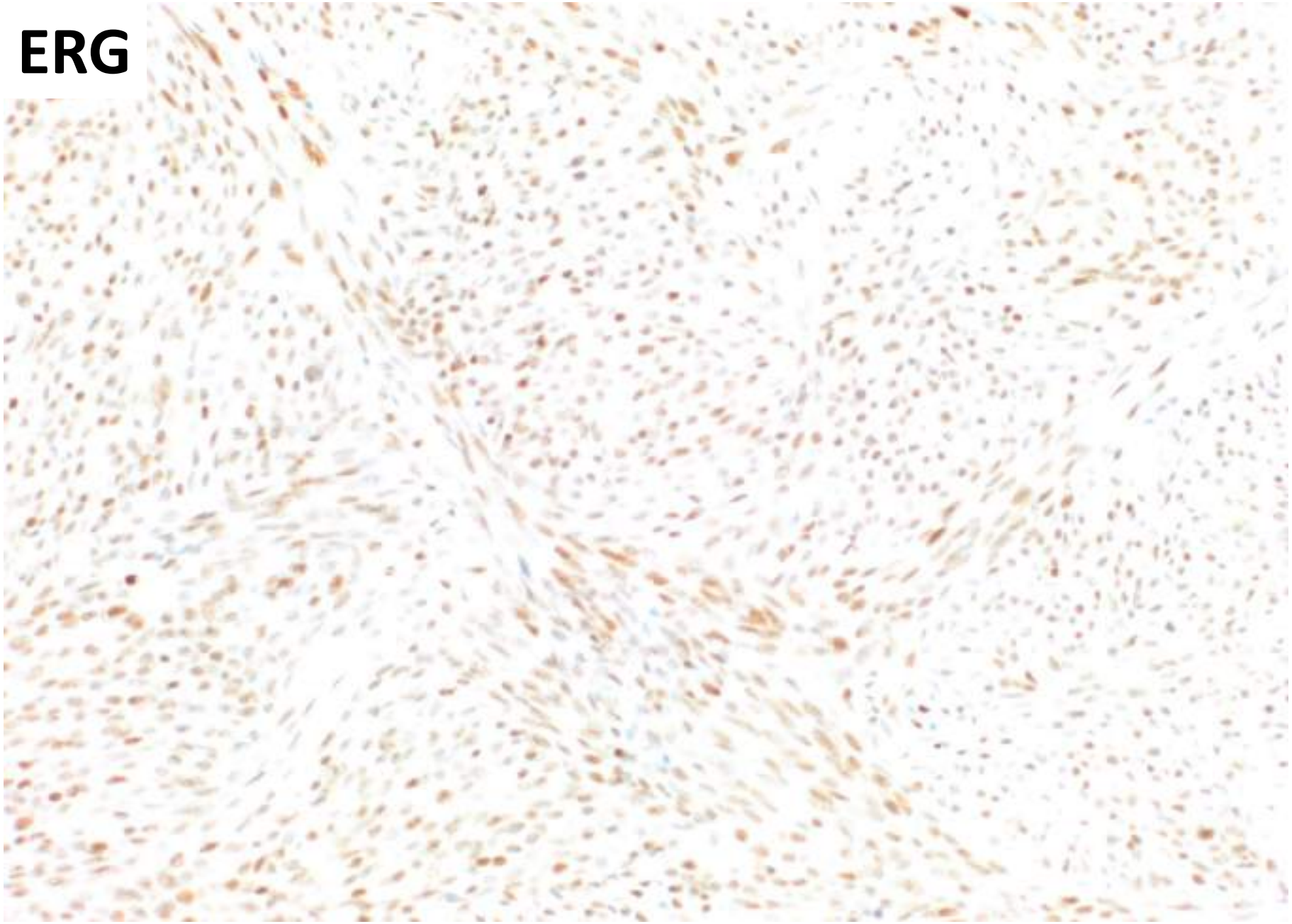
- EMA and CD34: peripheral cells/bundles
- S100 and SOX10: scattered cells

Negative:

- CK AE1/AE3, CK5 and CAM5.2
- Desmin and SMA

Our case

ERG



Differential diagnosis

Minute monopmorphic synovial sarcoma

In favour:

- EMA +, BUT very focal

Not supportive:

- CK AE1-AE3: negative

EWSR1::SMAD3 rearranged fibroblastic tumour

In favour:

- ERG +
- Zonation pattern

Not supportive:

- EMA focal +

EWSR1::SMAD3 rearranged fibroblastic tumour

Subsequent molecular study…

Presence of EWSR1::SMAD3 fusion

Molecular analysis performed by Bostjan Luzar

EWSR1::SMAD3 rearranged fibroblastic tumour

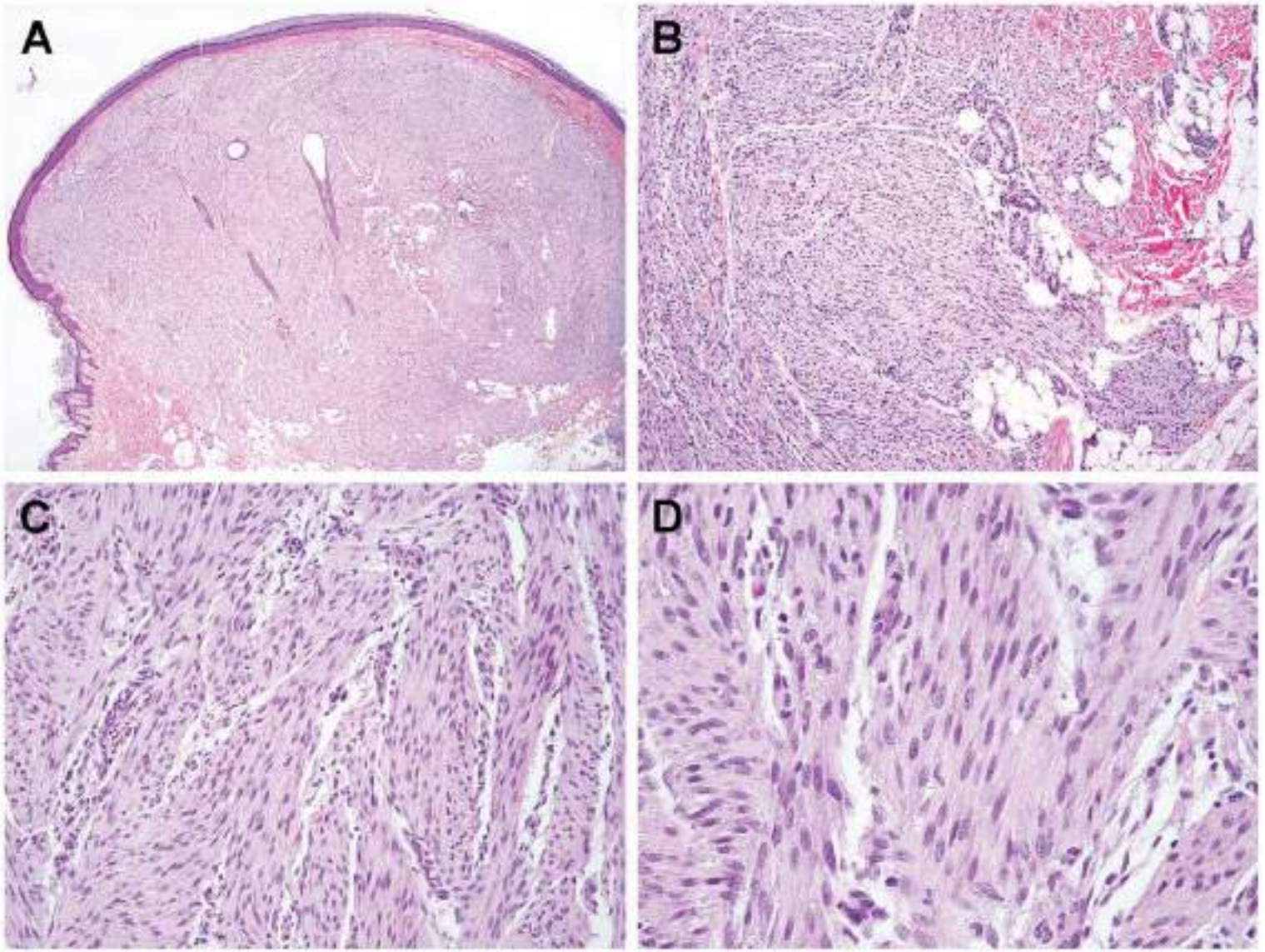
- Initially described in 2018
- Benign fibroblastic neoplasm
- Female predominance
- Size ranged from 0.3 to 1.7 cm
- Painless superficial tumour with strong predilection for hands and feet
- Superficially located within the dermis and/or subcutaneous fat

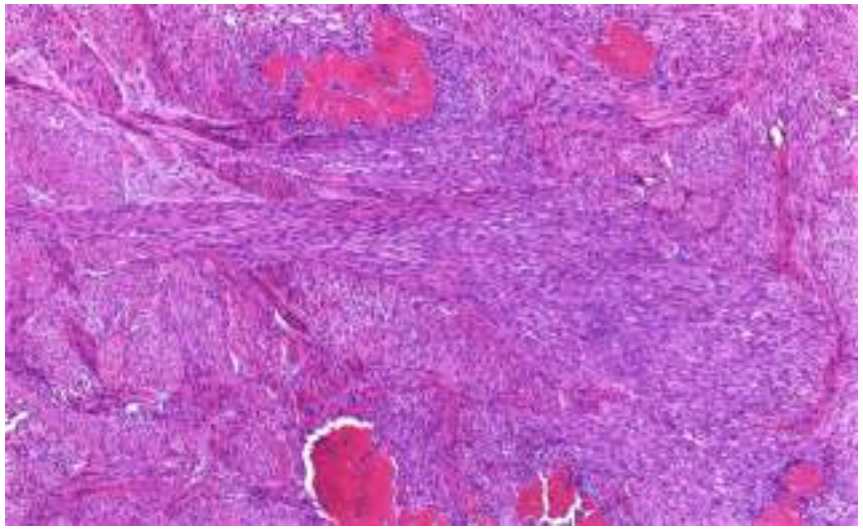
Case	Age [y] / Sex	Site	Size [mm]	Key Histological Features†	IHC+	IHC-‡	FISH	NGS
1	27/F	L lower extremity	17 X 13 X 8	Abuts epidermis. Polypoid, mostly superficial dermis.	ERG, vimentin	AE1/3, EMA, SMA, S-100, Melan-A, SOX-10, Factor XIIIa	NP	*EWSR1-SMAD3* [exon 7-exon 6]
2	35/F	L 4th/5th finger webspace	7 X 3 X 2	Deeper dermis. Small hyalinized areas, reminiscent of small rosettes.	ERG, SMA [weak, focal]	AE1/3, EMA, SOX-10, Factor XIIIa	NP	NP
3	45/F	R plantar forefoot	9 X 7 X 2	Abuts epidermis. Mostly superficial and dermal.	ERG	EMA, CD10, CD63, CD117, SMA, Melan-A, SOX-10	*EWSR1* rearranged [64%]	NP
4	46/F	L 4th toe	3 X 2 X 2	Abuts epidermis. Superficial dermis. Small collagenous nodules, similar to rosettes.	ERG	SMA, S-100	NP	NP
5	54/M	L foot	5 X 3 X 3	Abuts epidermis. Superficial dermis. Myopericytomatous pattern focally.	ERG	AE1/3, SMA, S-100, STAT-6, Factor XIIIa	NP	*EWSR1-SMAD3* [exon 7-exon 6]
6	57/F	L 5th toe	14 X 12 X 6	Deep dermis/ subcutis. Peripheral circumscription, with abrupt central hyalinization.	ERG	Cytokeratin, EMA, SMA, CD10, CD68, MUC-4, S-100	NP	*EWSR1-SMAD3* [exon 7-exon 5]

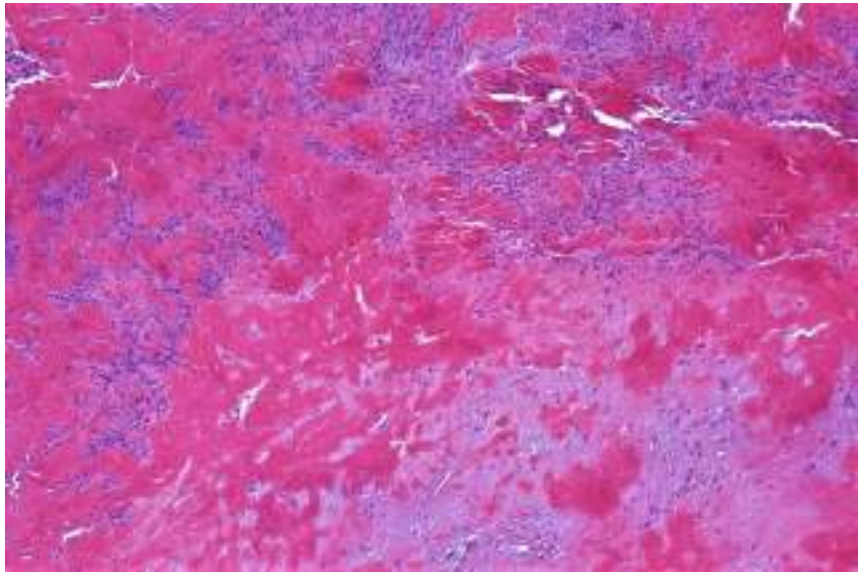
Table 1. Clinicopathologic characteristics of *EWSR1-SMAD3* rearranged fibroblastic tumor in the series.

Habeeb O et al. J Cutan Pathol. 202

EWSR1::SMAD3 rearranged fibroblastic tumour







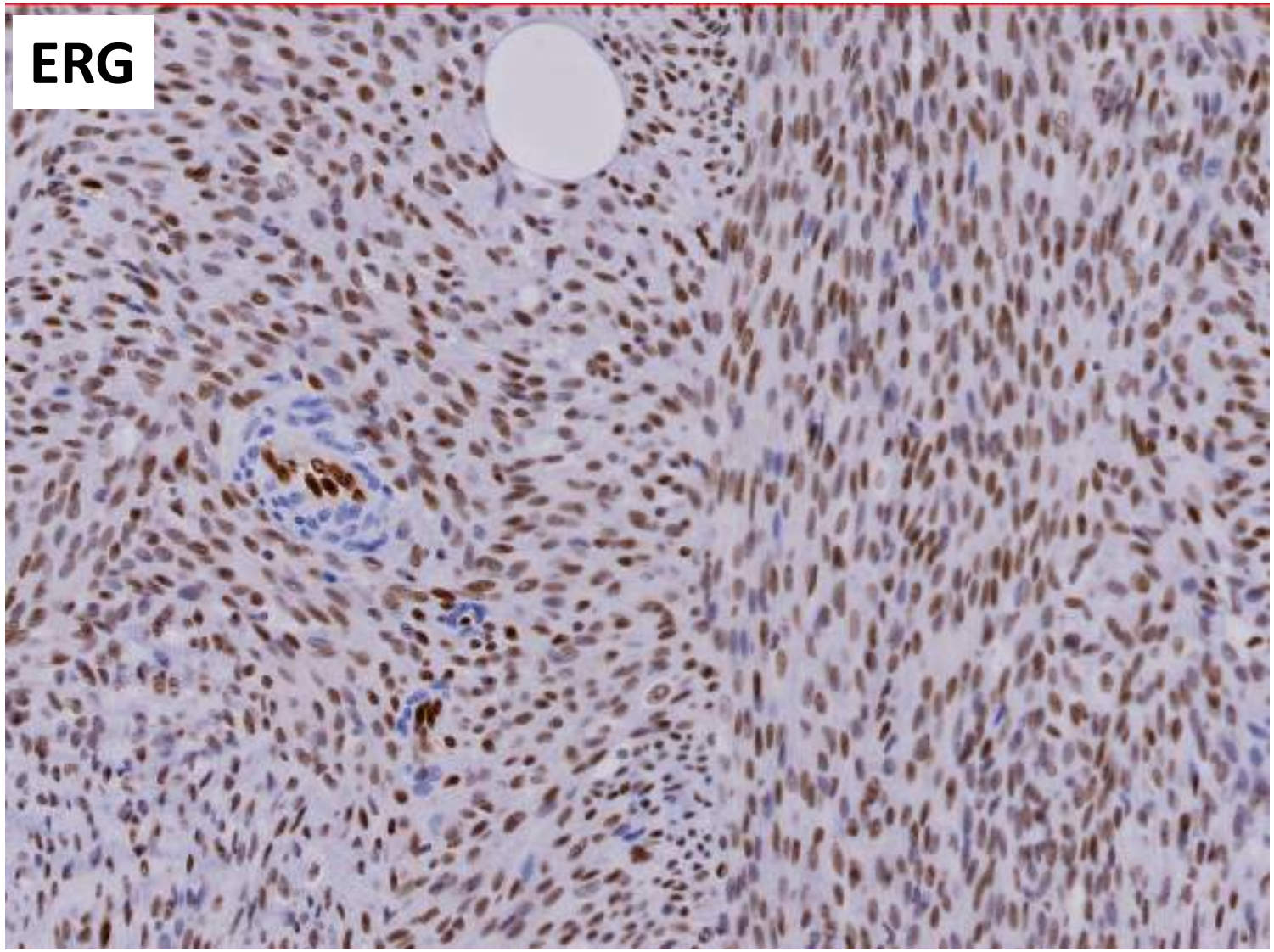
Kao YC et al. Am J Surg Pathol. 2018

WHO Classification of tumours Online, 5th Ed

EWSR1::SMAD3 rearranged fibroblastic tumour

- Strong diffuse nuclear ERG expression

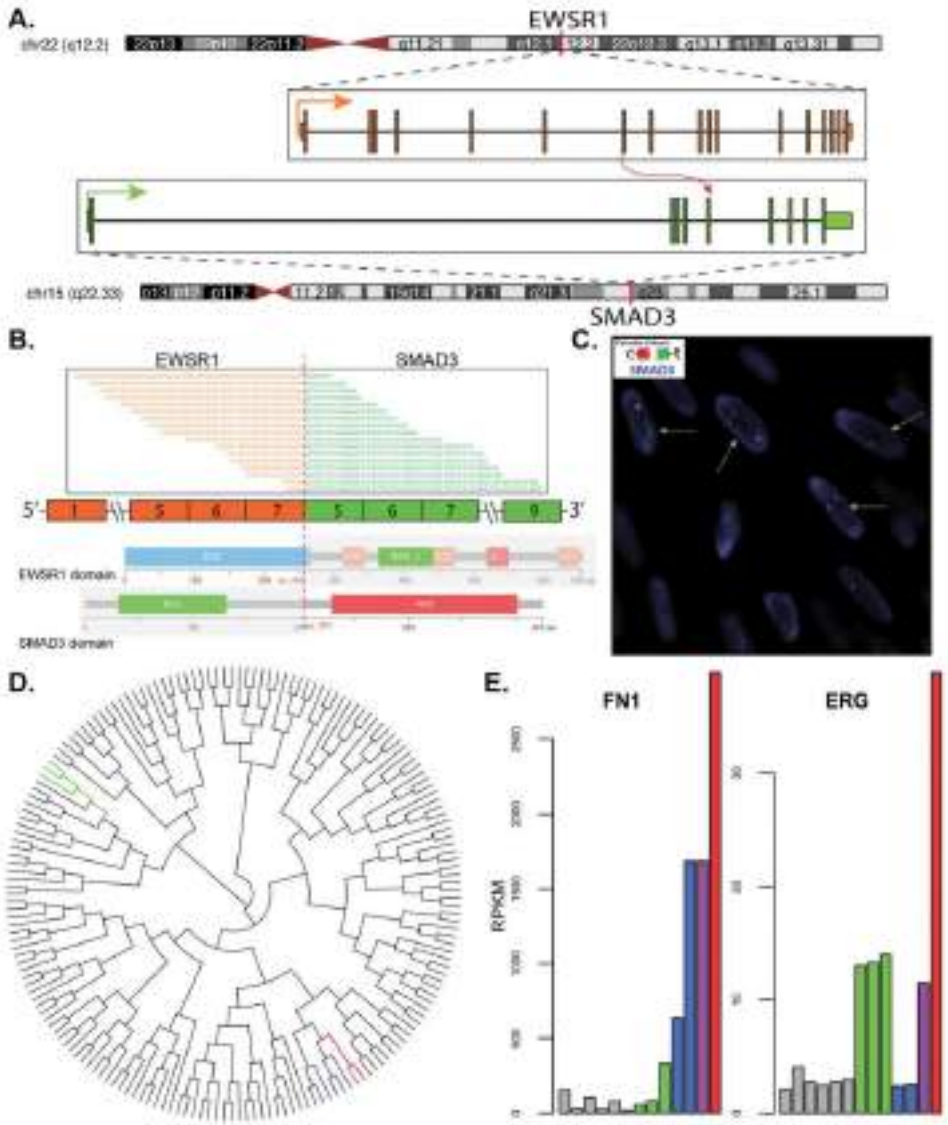
- SMA, CD34, CK, EMA, S100 and SOX10: negative



WHO Classification of tumours Online, 5th Ed

EWSR1::SMAD3 rearranged fibroblastic tumour

- Defined by a fusion of exon 7 of *EWSR1* with exon 5 or exon 6 of *SMAD3*
- NGS or validated by break-apart FISH assays
- *SMAD3:* signal transducer in the TGF-β/Smad signaling pathway
- Involved in extracellular matrix synthesis by fibroblasts



Kao YC et al. Am J Surg Pathol. 2018

EWSR1::SMAD3 rearranged fibroblastic tumour

- Benign but local recurrence may occur after incomplete excision

Clinicopathologic Features of Cases with *EWSR1-SMAD3* Fusions

Case#	Age/Sex	Location	Depth	Size (cm)	Immunohistochemistry				Follow-up
					ERG	CD34	SMA	S-100	
1	1/M	Heel	Dermis & Subcutis	1.0	+	–	–	–	LR (14 mon)
2	61/F	Foot	Subcutis	2.0	+	–	–	–	NA
3	58/F	Toe	Dermis & Subcutis	1.1	+	–	–	–	LR (5 mon)

M, male; F, female; LR, local recurrence; mon, months

Kao YC et al. Am J Surg Pathol. 2018

Minute Synovial Sarcomas of the Hands and Feet

A Clinicopathologic Study of 21 Tumors Less Than 1 cm

Michal Michal, MD, Julie C. Fanburg-Smith, MD,† Jerzy Lasota, MD,† John F. Fetsch, MD,† Jack Lichy, MD,‡ and Markku Miettinen, MD†*

Abstract: Synovial sarcoma, one of the most common types of soft tissue sarcomas, usually presents in the proximal or middle portions of the extremities, often as a large mass with an aggressive clinical behavior. Gland-forming biphasic and spindle cell fibrous monophasic tumors are the most common subtypes. In this study, we evaluated 21 minute synovial sarcomas, < 1 cm in diameter, from the hands and feet. These tumors occurred in 14 females and 7 males with a median age of 29 years (range, 8–60 years). Clinically, all tumors were thought to be benign processes such as a ganglion cyst or glomus tumor, and on microscopic examination, they were also often initially misinterpreted as benign lesions such as nerve sheath or (myo) fibroblastic tumors. Histologically, 7 tumors were biphasic and 14 were monophasic spindle cell variants. Microscopic calcifications were present in 8 cases and were prominent in 3 tumors. All monophasic tumors tested had elements positive for EMA, and all but one had reactivity for a keratin cocktail. S-100 protein-positive neuroma-like neural proliferations were commonly present in the monophasic but not in biphasic tumors. SYT-SSX fusion transcripts were demonstrated in 5 cases studied by polymerase chain reaction assay. All tumors were enucleated, followed by local reexcision of the site, and often combined with postoperative radiation. Three patients had amputation of the involved digit or metatarsal. Four patients had local recurrences, 2 of which were successfully treated; 2 of these patients were lost to follow-up. Despite some variation in treatment, all 12 patients with complete follow-up were alive and well, 2 to 32.2 years after surgery (median, 14.7 years), including 2 patients who received neither amputation nor postoperative radiation. Minute synovial sarcomas of hands and feet are clinically favorable tumors if completely excised; there is some evidence to suggest that they may be managed more conservatively than larger tumors. These tumors should be recognized as part of the spectrum of synovial sarcomas.

Key Words: monophasic synovial sarcoma, biphasic synovial sarcoma, keratins, prognosis, S-100 protein, SYT-SSX fusion, PCR

(*Am J Surg Pathol* 2006;30:721–726)

Synovial sarcoma comprises up to 10% of soft tissue sarcomas. It usually occurs in the extremities, especially the thigh, but it can present in a wide variety of locations. Most examples are large when diagnosed: 85% are > 5 cm. Occasional reports exist on very small tumors, but the clinicopathologic profile and prognosis of this subgroup have not been defined, as none of the recent synovial sarcoma series have included tumors < 1 cm in maximum diameter.[2,11,12] The purpose of this study is to report the AFIP experience with minute (< 1 cm) synovial sarcomas of the hands and feet.

MATERIALS AND METHODS

Case Material and Follow-up

Synovial sarcomas of the hands (n = 57) and feet (n = 125) were reviewed from the AFIP files from 1970–1998, and tumors measuring < 1 cm (n = 21, 11.5% of all examples of hands and feet) were selected for further study. Follow-up was obtained from contributors, tumor registries, or in some cases, from patients themselves.