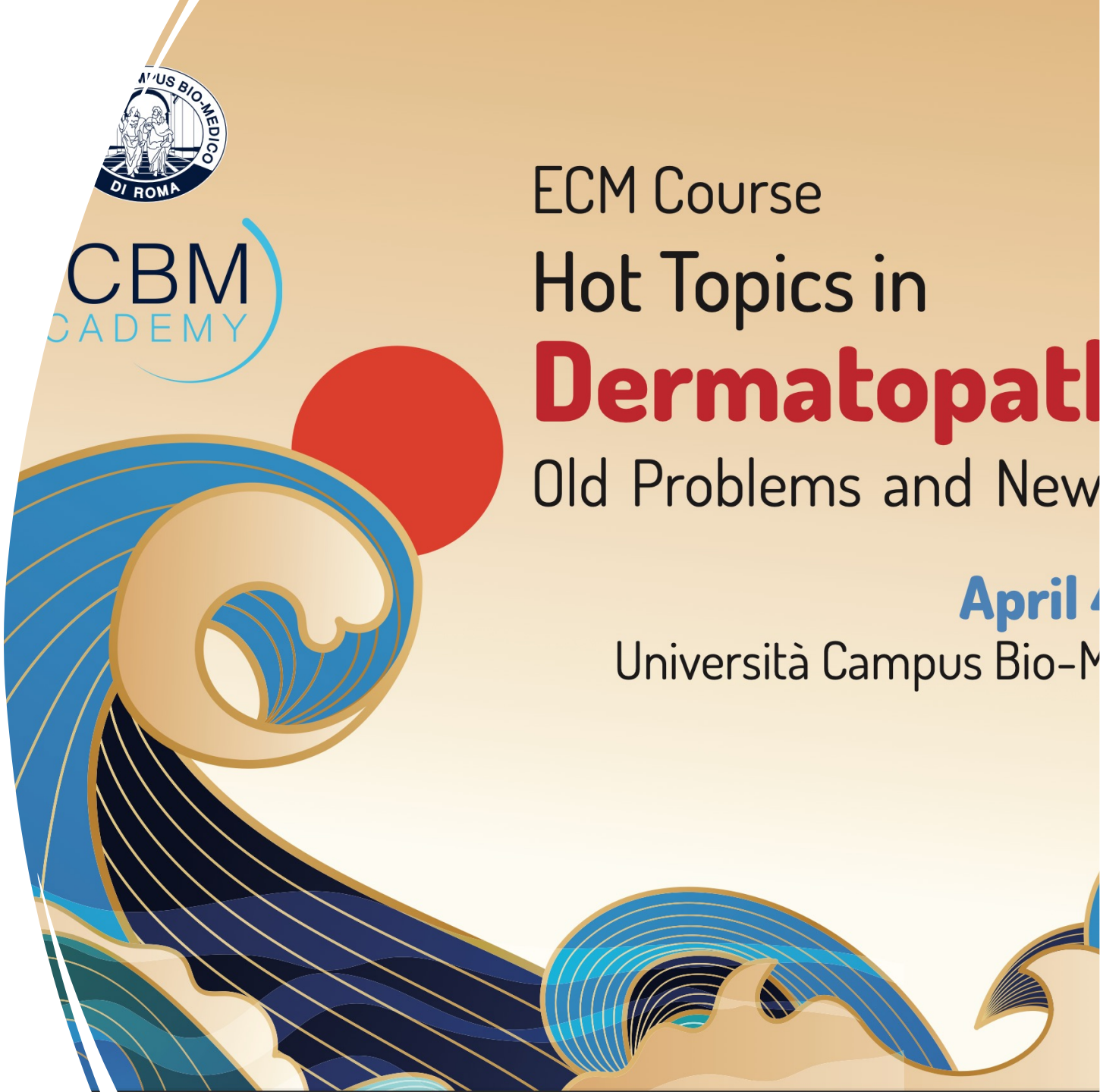
BAP1 inactivated melanocytoma: morphology and beyond.

D. Kazakov, M. Donati



The Times-Picayune
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State emphasizes need for shots

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COVID-19 IN VANDERBURGH COUNTY

163 new cases reported in one day

Doyle and Sarah Loesch

The seven-day positivity rate was 9.1% with the date range of July 17-23. The cumulative positivity rate was 8.9%.

Hatfield said he can't say for sure whether or not numbers would be different with a change in vaccine rates, but "who knows where we would be if

"I think what you're going to find is individual companies, corporations, institutions, creating rules on their

www.nature.com/modpathol

ARTICLE

Novel insights into the *BAP1*-inactivated melanocytic tumor

Michele Donati[1,2], Petr Martinek[3], Petr Steiner[3], Petr Grossmann[3], Tomas Vanecek[3], Liubov Kastnerova[2,3], Isabel Kolm[4], Martina Baneckova[2,3], Pietro Donati[5], Irina Kletskaya[6], Antonina Kalmykova[7], Josef Feit[8], Petr Blasch[9], Diana Szilagyi[10], Alfonso Baldi[11], Paolo Persichetti[12], Anna Crescenzi[1], Michal Michal[2,3] and Dmitry V. Kazakov[2,4]✉

BAP1-inactivated melanocytic tumor (BIMT) is a group of melanocytic neoplasms with epithelioid cell morphology molecularly characterized by the loss of function of *BAP1*, a tumor suppressor gene located on chromosome 3p21, and a mutually exclusive mitogenic driver mutation, more commonly *BRAF*. BIMTs can occur as a sporadic lesion or, less commonly, in the setting of an autosomal dominant cancer susceptibility syndrome caused by a *BAP1* germline inactivating mutation. Owing to the frequent identification of remnants of a conventional nevus, BIMTs are currently classified within the group of combined melanocytic nevi. "Pure" lesions can also be observed. We studied 50 BIMTs from 36 patients. Most lesions were composed of epithelioid melanocytes of varying size and shapes, resulting extreme cytomorphological heterogeneity. Several distinctive morphological variants of multinucleated/giant cells were identified. Some hitherto underrecognized microscopic features, especially regarding nuclear characteristics included nuclear blebbing, nuclear budding, micronuclei, shadow nuclei, peculiar cytoplasmic projections (ant-bear cells) often containing micronuclei and cell-in-cell structures (entosis). In addition, there were mixed nests of conventional and BAP1-inactivated melanocytes and squeezed remnants of the original nevus. Of the 26 lesions studied, 24 yielded a *BRAF* mutation, while in the remaining two cases there was a *RAF1* fusion. *BAP1* biallelic and singe allele mutations were found in 4/22 and 16/24 neoplasms, respectively. In five patients, there was a *BAP1* germline mutation. Six novel, previously unreported *BAP1* mutations have been identified. *BAP1* heterozygous loss was detected in 11/22 lesions. Fluorescence in situ hybridization for copy number changes revealed a related amplification of both *RREB1* and *MYC* genes in one tumor, whereas the remaining 20 lesions studied were negative; no *TERT-p* mutation was found in 14 studied neoplasms. Tetraploidy was identified in 5/21 BIMTs. Of the 21 patients with available follow-up, only one child had a locoregional lymph node metastasis. Our results support a progression of BIMTs from a conventional *BRAF* mutated in which the original nevus is gradually replaced by epithelioid BAP1-inactivated melanocytes. Some features suggest more complex underlying pathophysiological events that need to be elucidated.

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Review

Beyond typical histology of *BAP1*-inactivated melanocytoma☆

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Multinucleated polypoid giant cells
Entosis

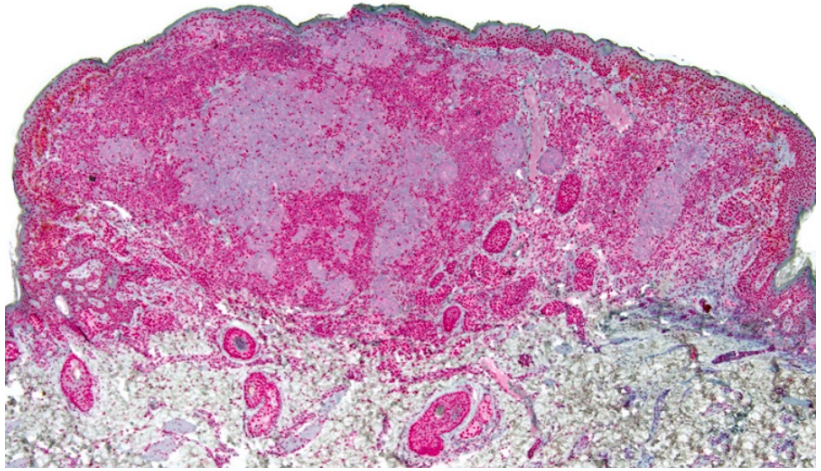
ABSTRACT

BAP1-inactivated melanocytoma (BIM) is a novel subgroup of melanocytic neoplasm listed in the 5th edition of WHO classification of skin tumor. BIM is characterized by two molecular alterations, including a mitogenic driver mutation (usually *BRAF* gene) and the loss of function of *BAP1*, a tumor suppressor gene located on chromosome 3p21, which encodes for BRCA1-associated protein (BAP1). The latter represents a nuclear-localized deubiquitinase involved in several cellular processes including cell cycle regulation, chromatin remodeling, DNA damage response, differentiation, senescence and cell death. BIMs are histologically characterized by a population of large epithelioid melanocytes with well-demarcated cytoplasmic borders and copious eosinophilic cytoplasm, demonstrating loss of BAP1 nuclear expression by immunohistochemistry. Recently, we have published a series of 50 cases, extending the morphological spectrum of the neoplasm and highlighting some new microscopic features. In the current article, we focus on some new histological features, attempting to explain and link them to certain mechanisms of tumor development, including senescence, endoreplication, endocycling, asymmetric cytokinesis, entosis and others. In light of the morphological and molecular findings observed in BIM, we postulated that this entity unmasks a fine mechanism of tumor in which both clonal/stochastic and hierarchical model can be unified.

BAP1 inactivated melanocytoma:

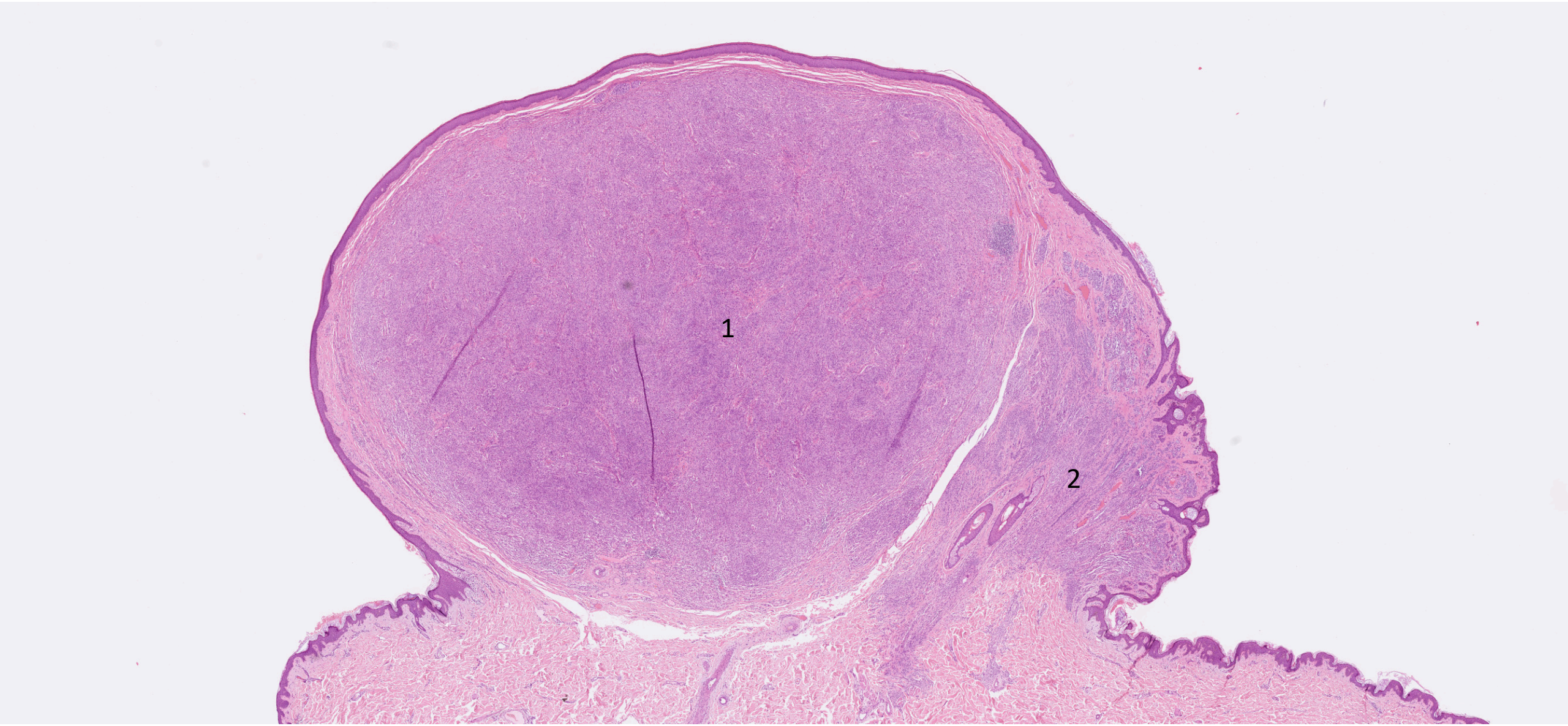
Two molecular alterations:

1) a mitogenic driver mutation
2) loss of function of the BAP1 gene.



1) Mostly BRAF mutations (rarely NRAS mutation or RAF1 fusion)

2) Inactivating mutation of the BAP1 gene following by the loss of heterozygosity in the 3p21 locus.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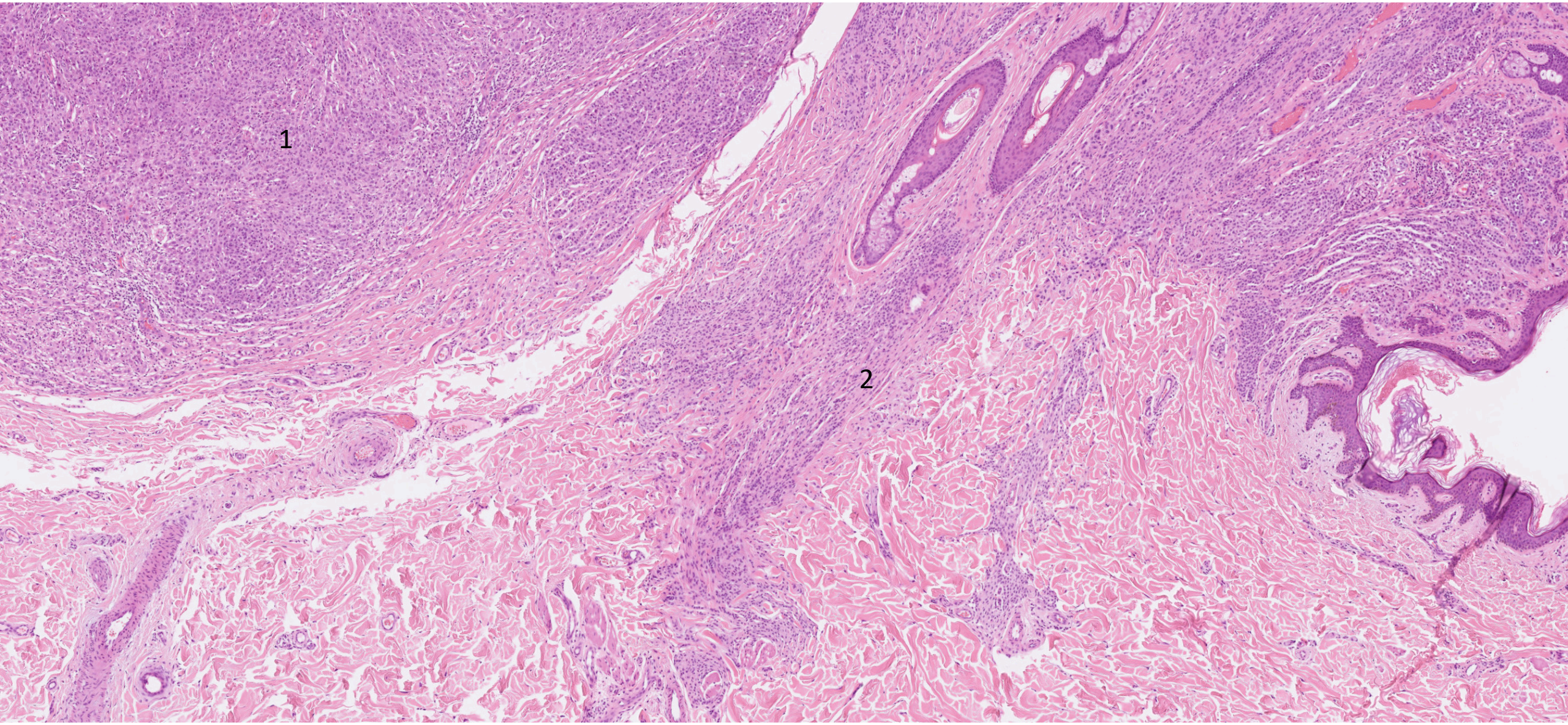
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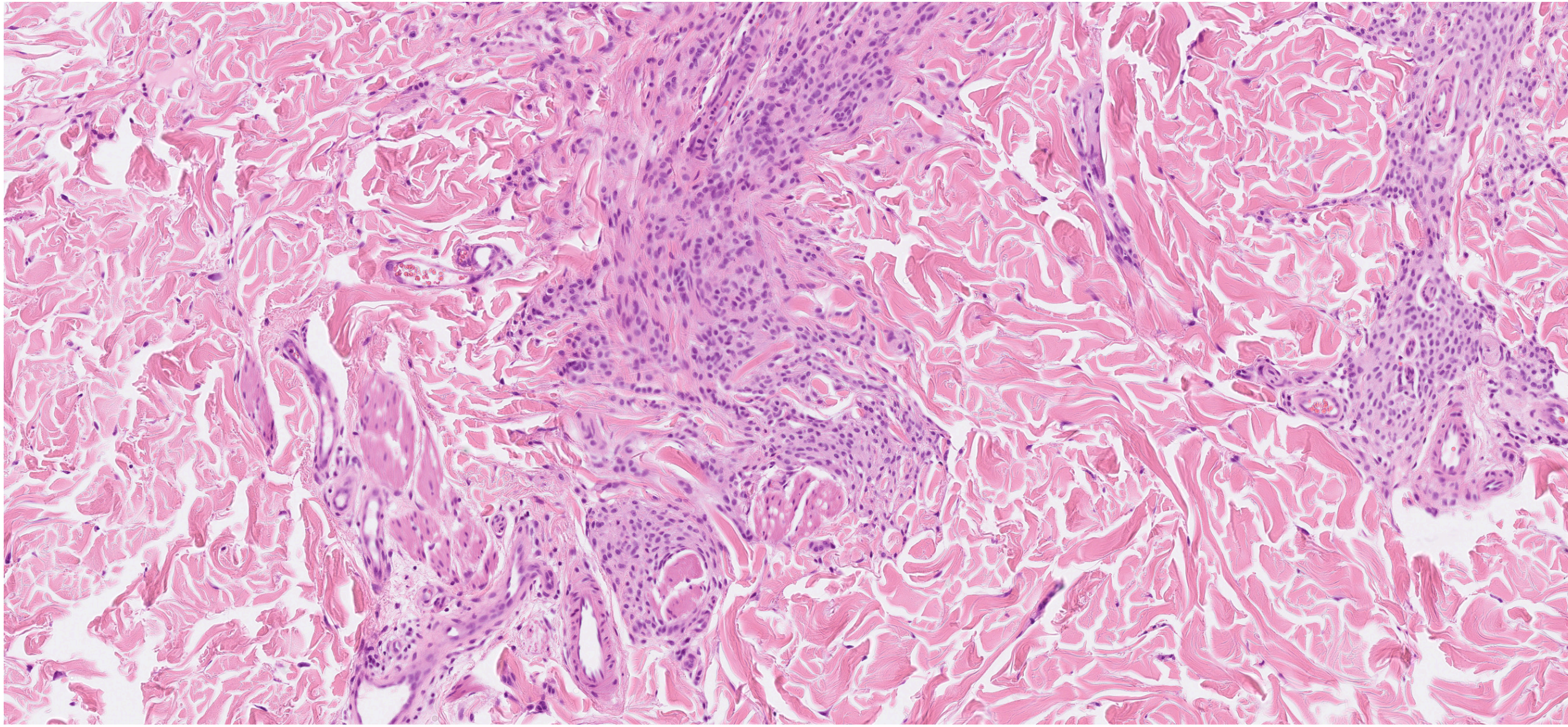
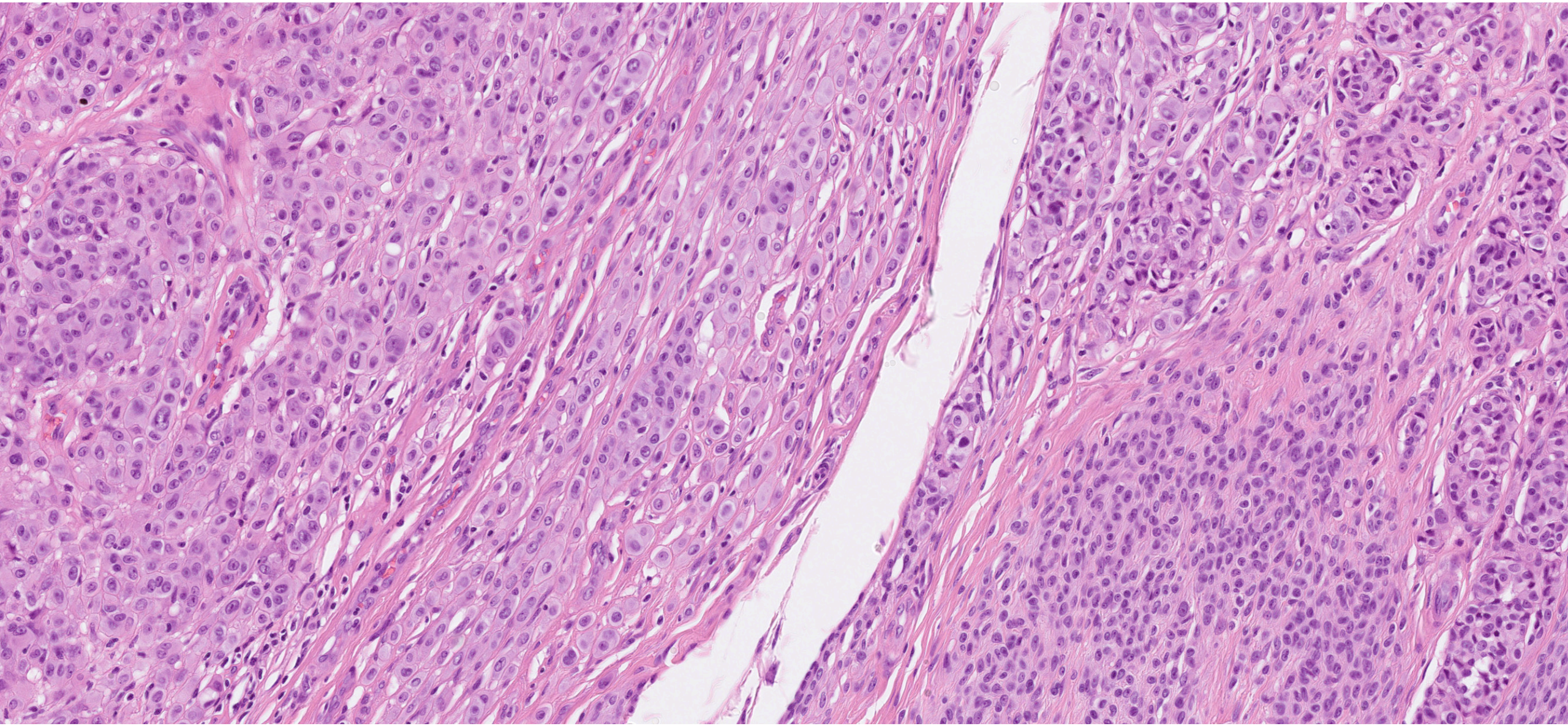
2

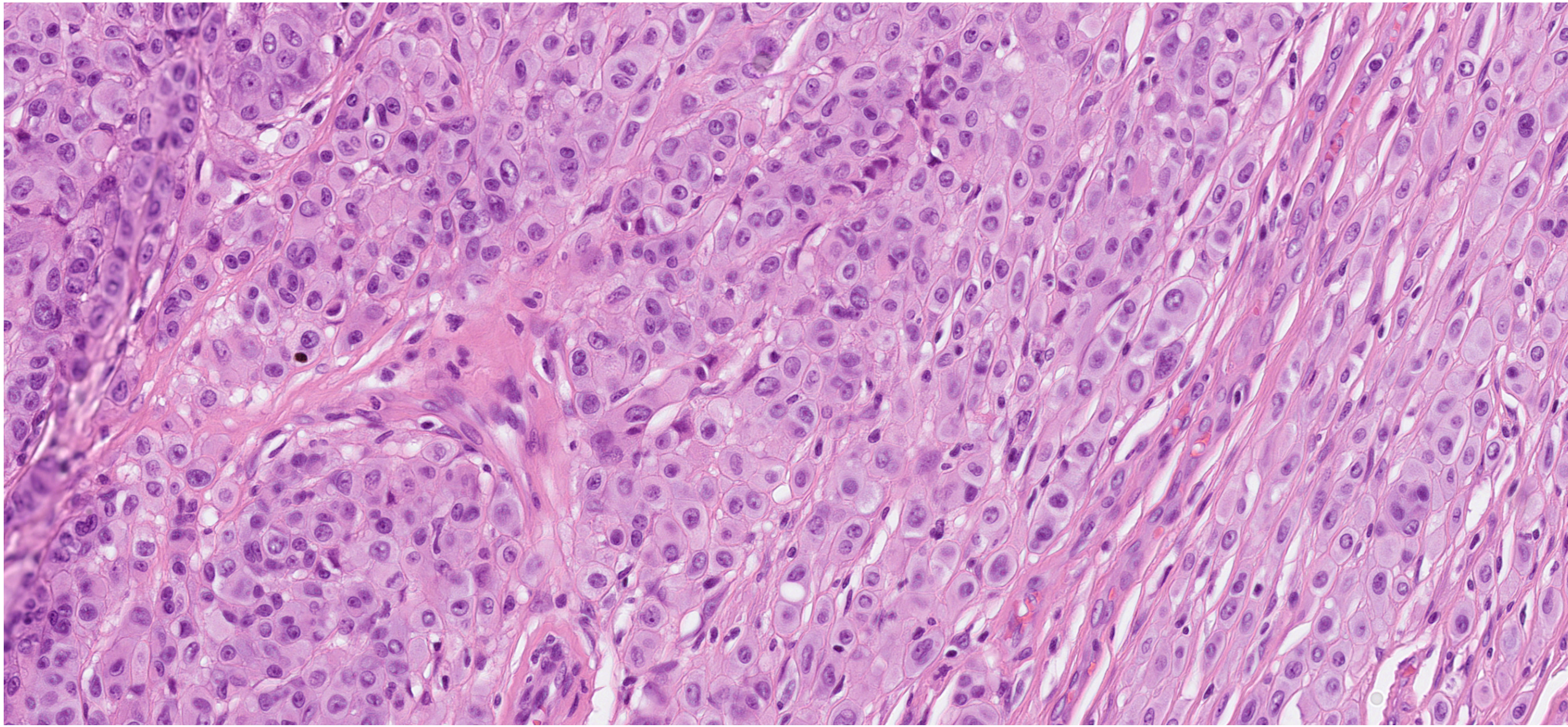
Congenital pattern : 52%



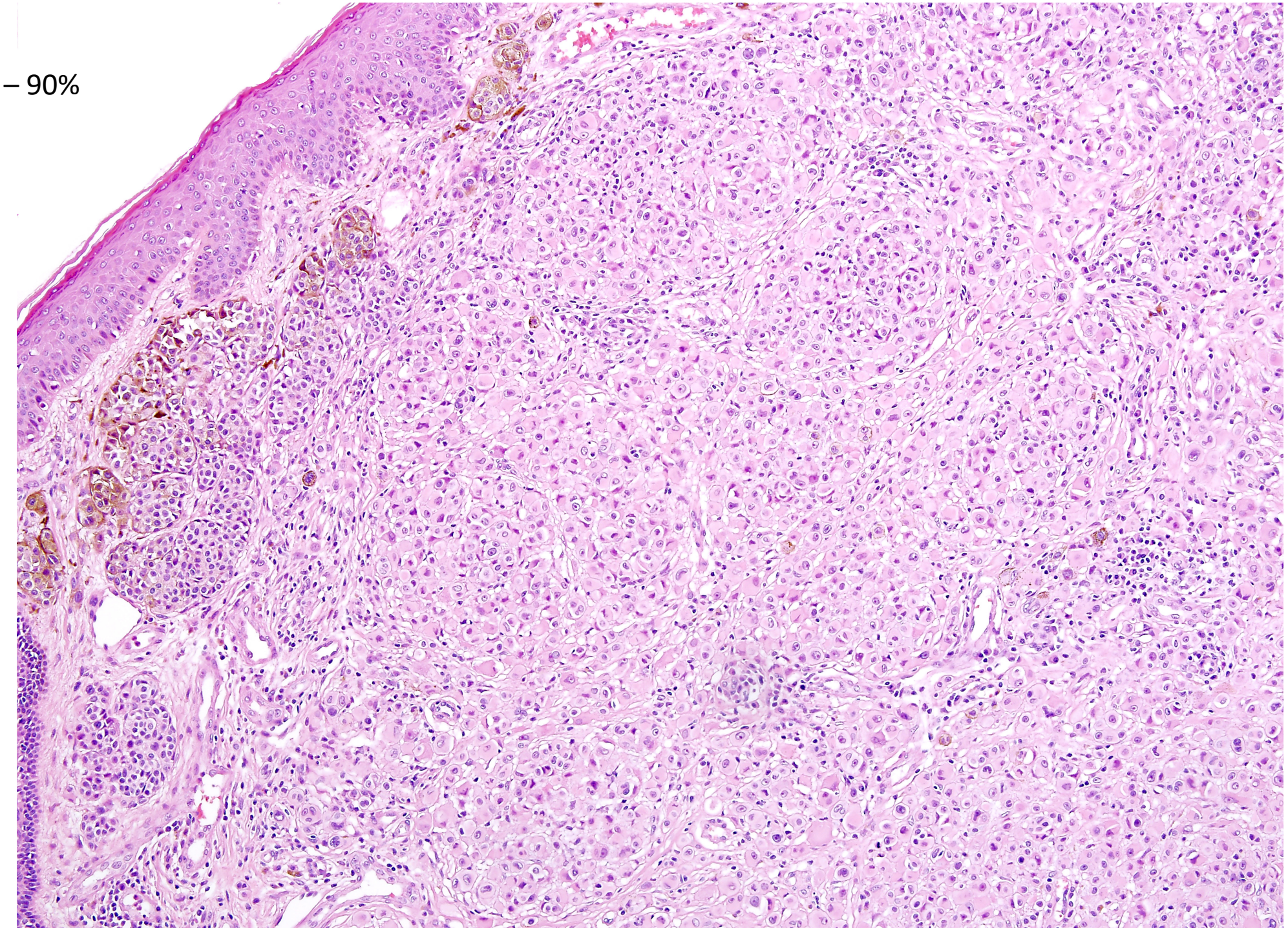
Large epithelioid melanocytes with well-demarcated cytoplasmic borders and copious eosinophilic cytoplasm



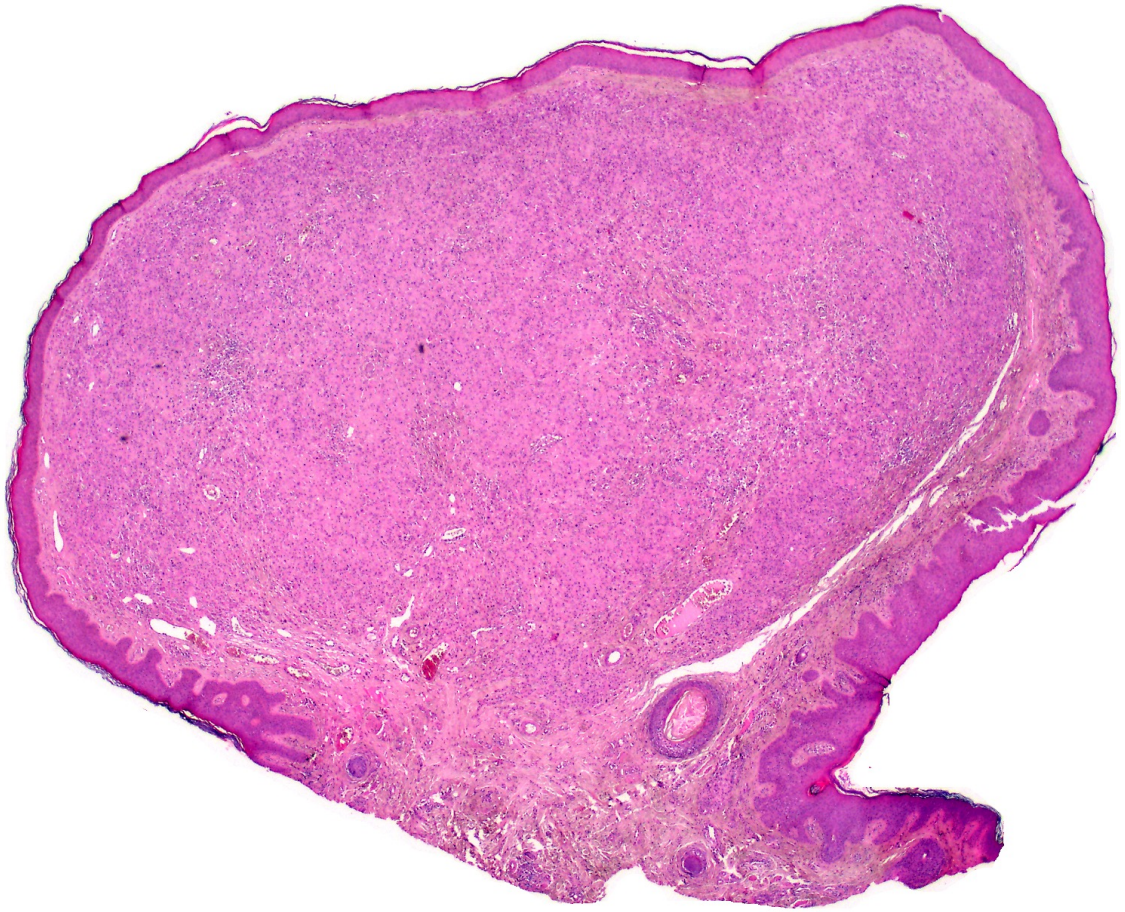
Large epithelioid melanocytes with well-demarcated cytoplasmic borders and copious eosinophilic cytoplasm

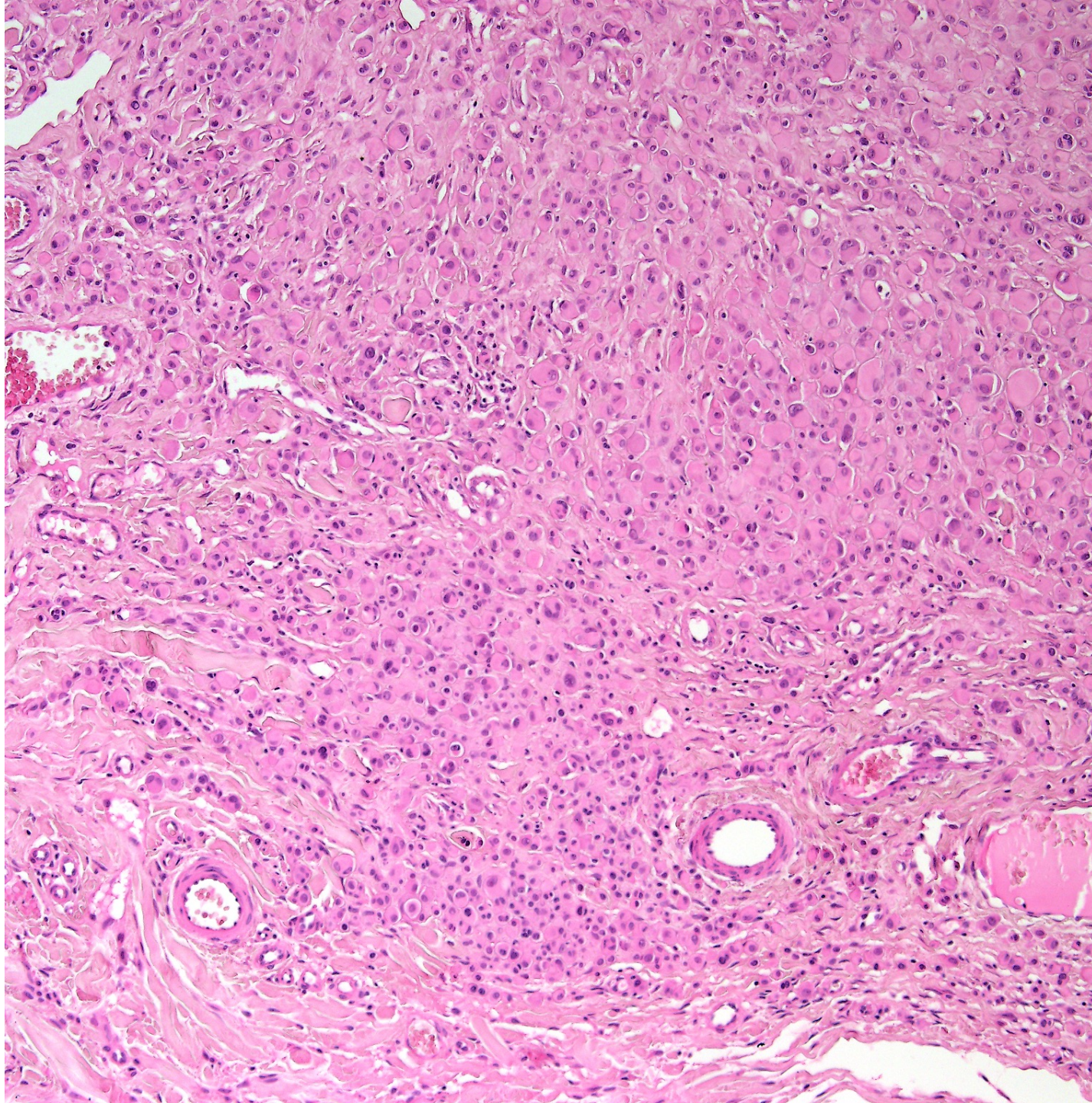


«Mixed» lesions – 90%

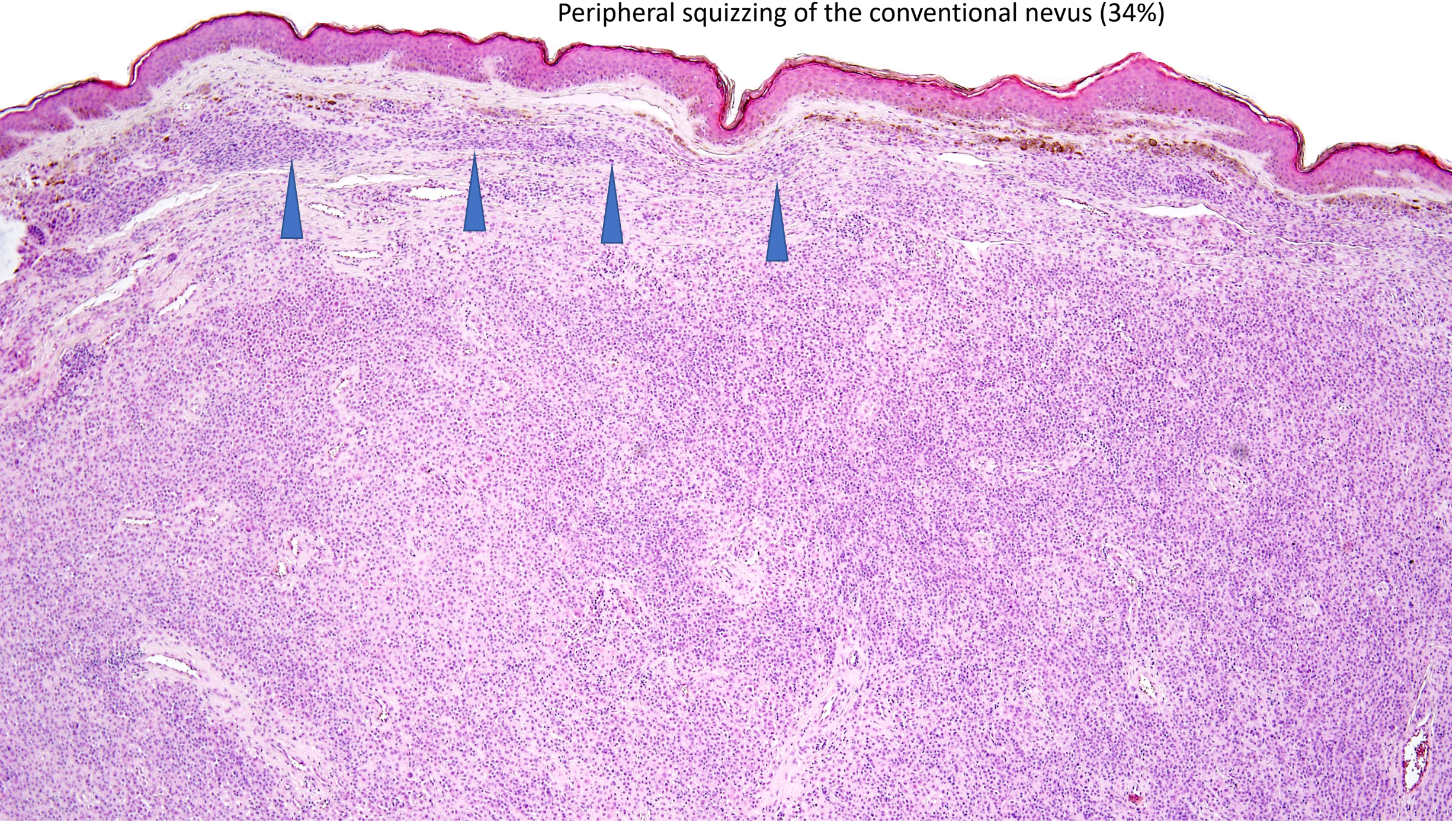


Pure type: no conventional melanocytes (10%)

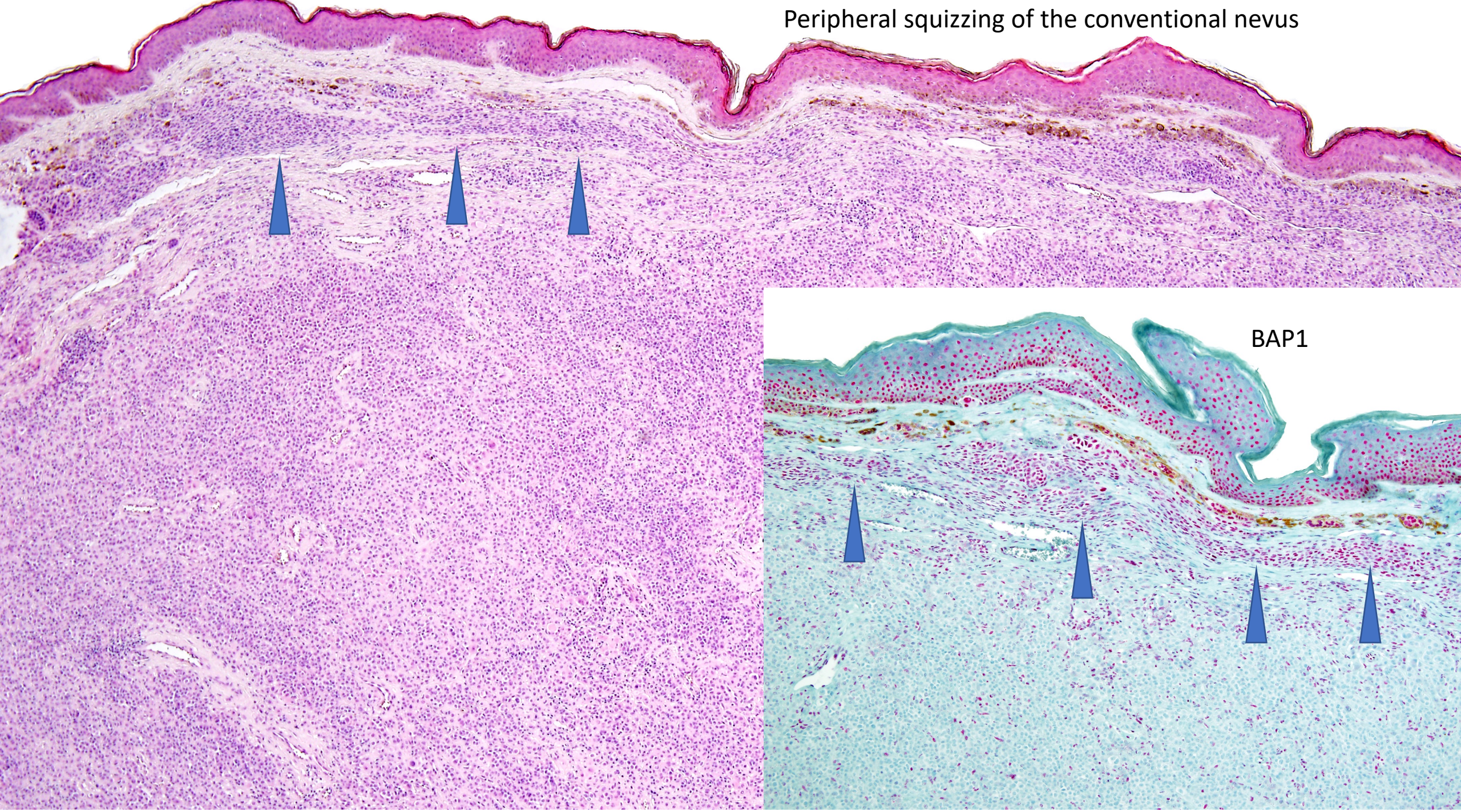




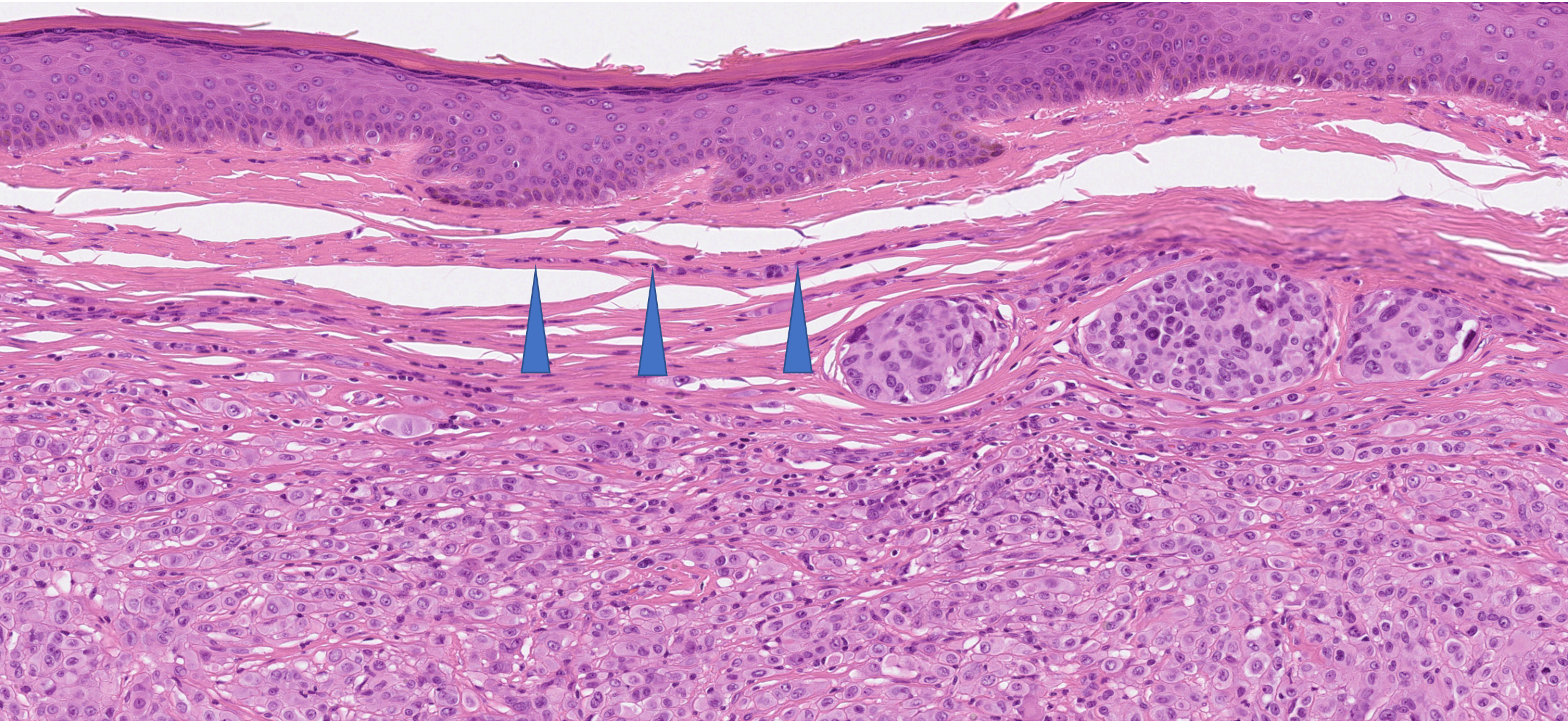
Peripheral squizzing of the conventional nevus (34%)



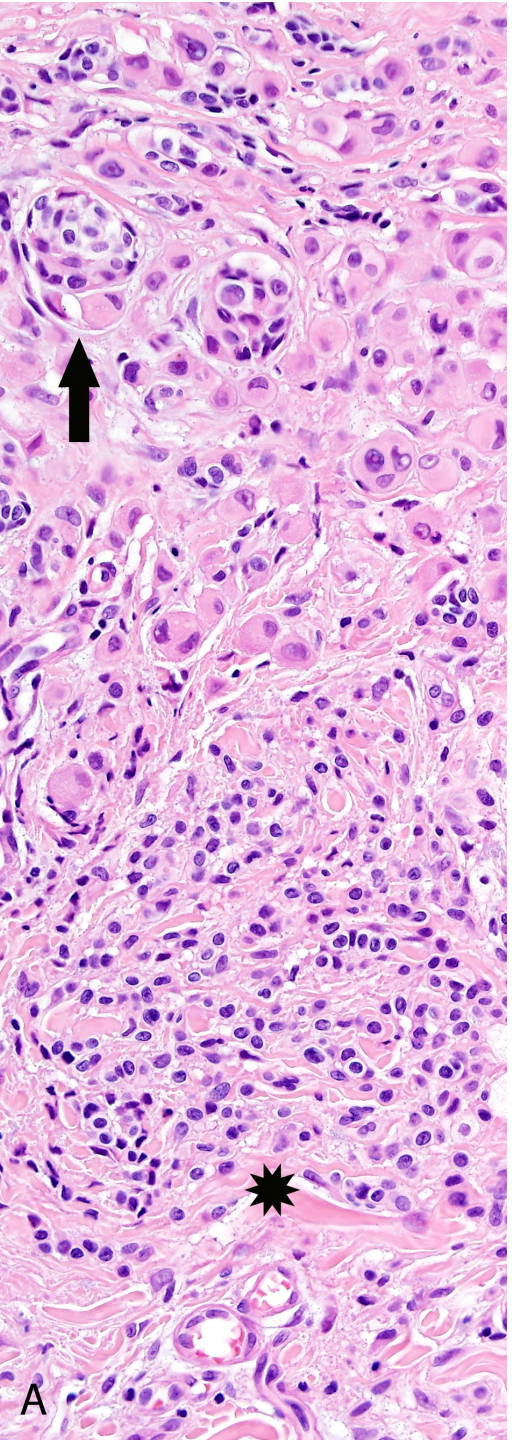
Peripheral squizzing of the conventional nevus

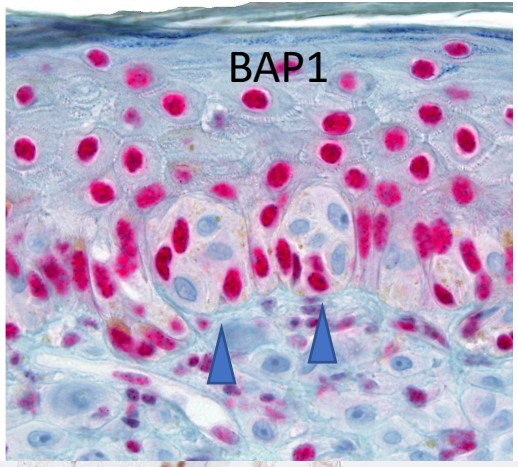


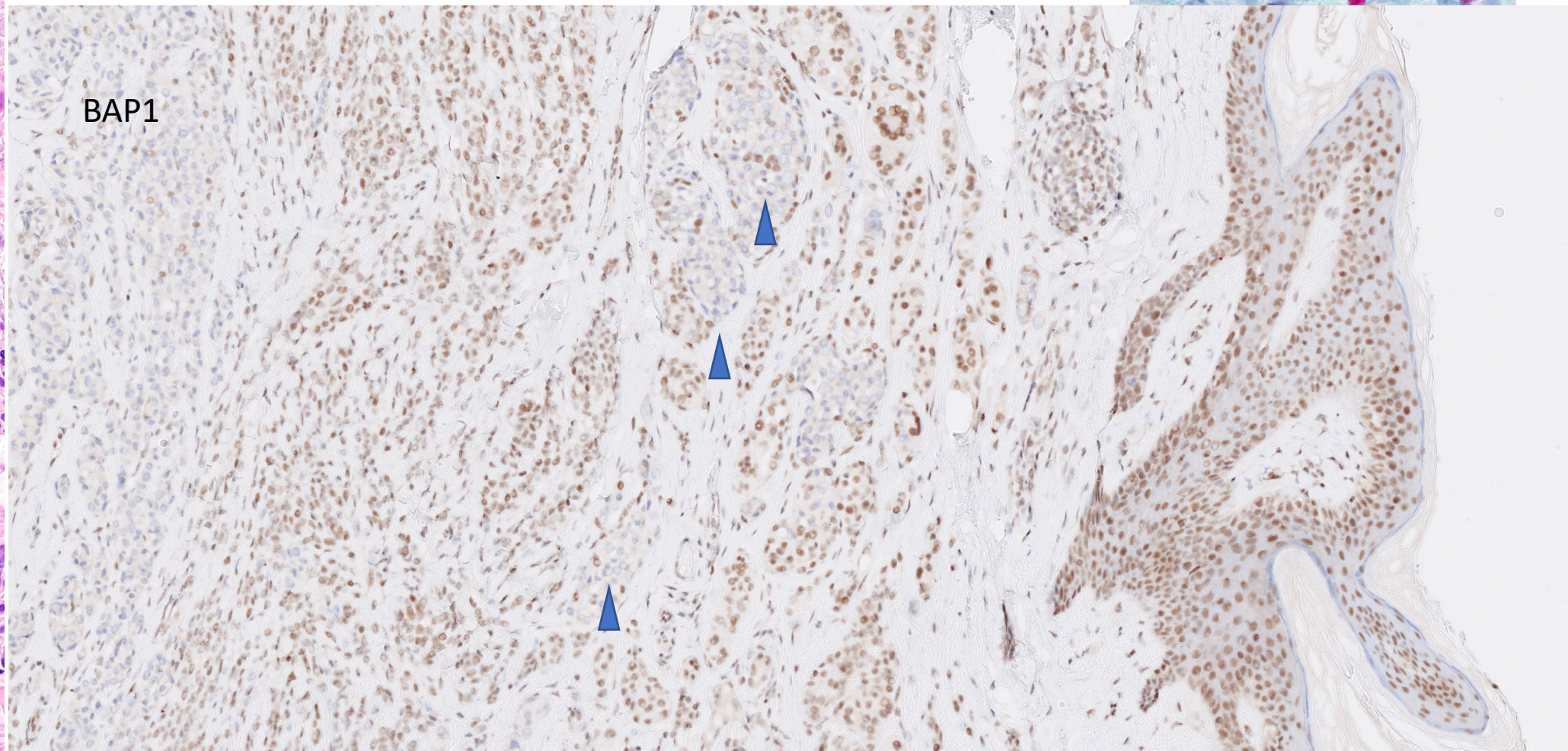
Peripheral squizzing of the conventional nevus



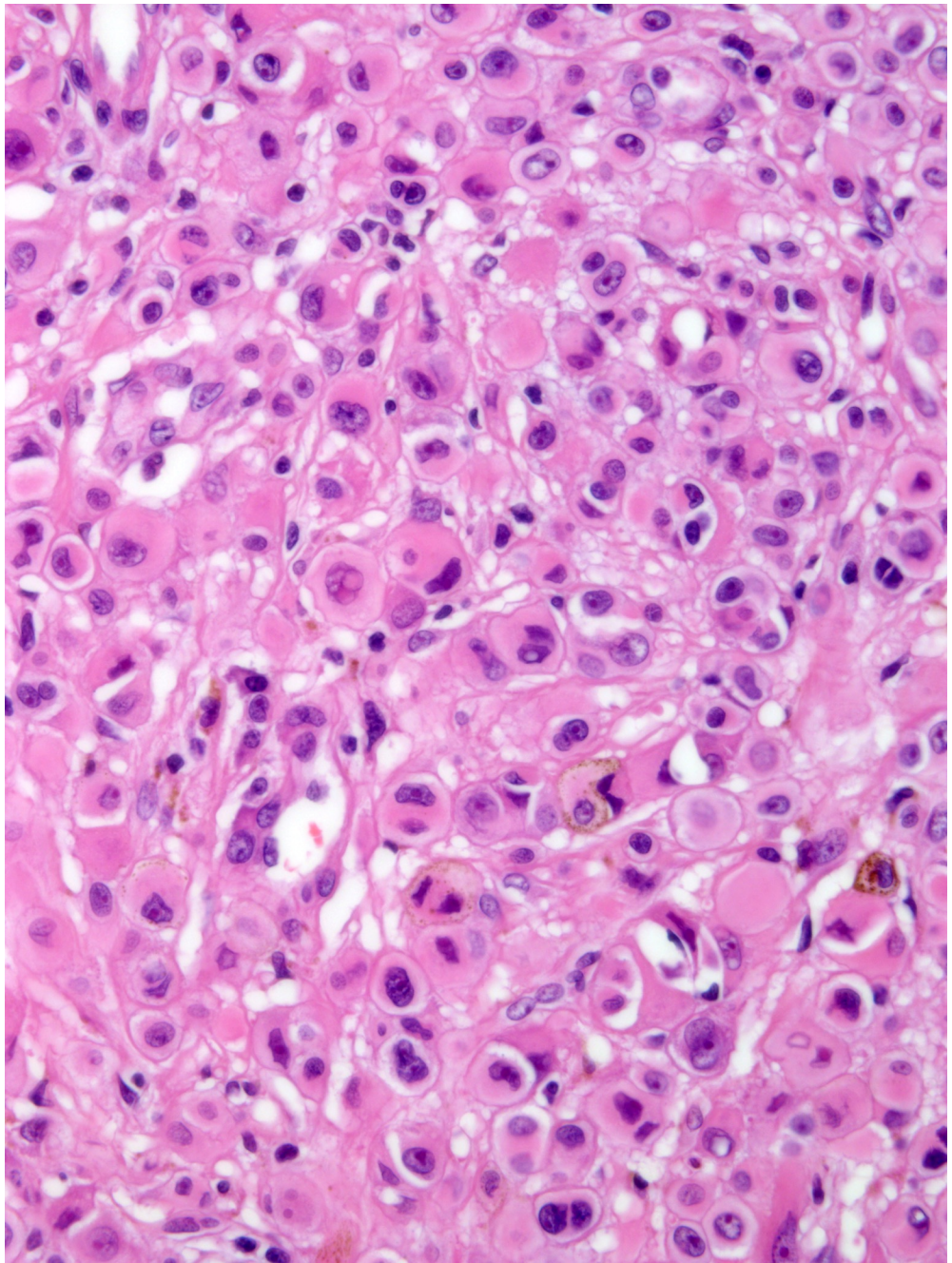
Mixed nests composed of both BAP1-inactivated epithelioid and BAP1-positive conventional melanocytes at the junction (36%) or in the dermis (54%)

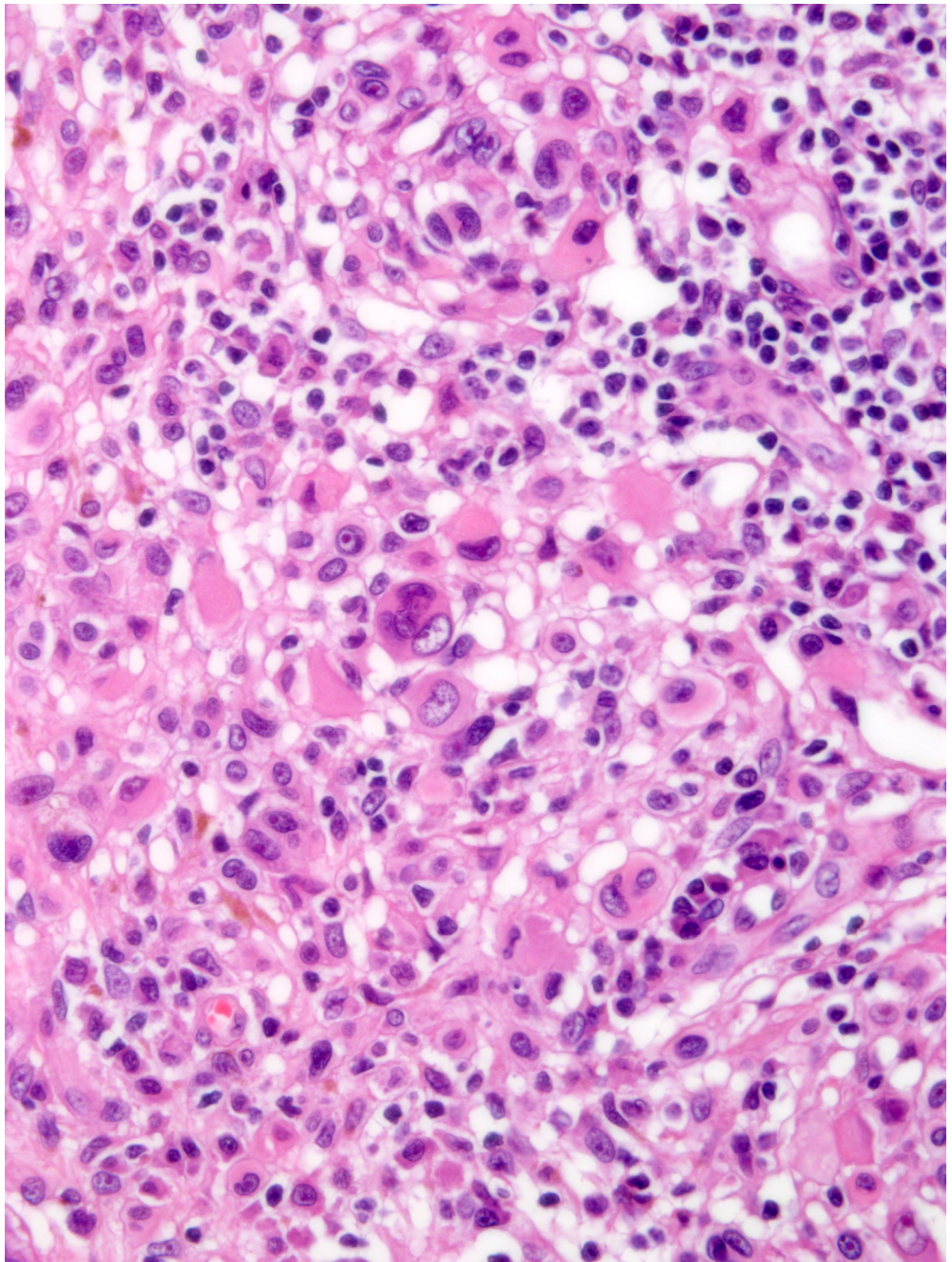




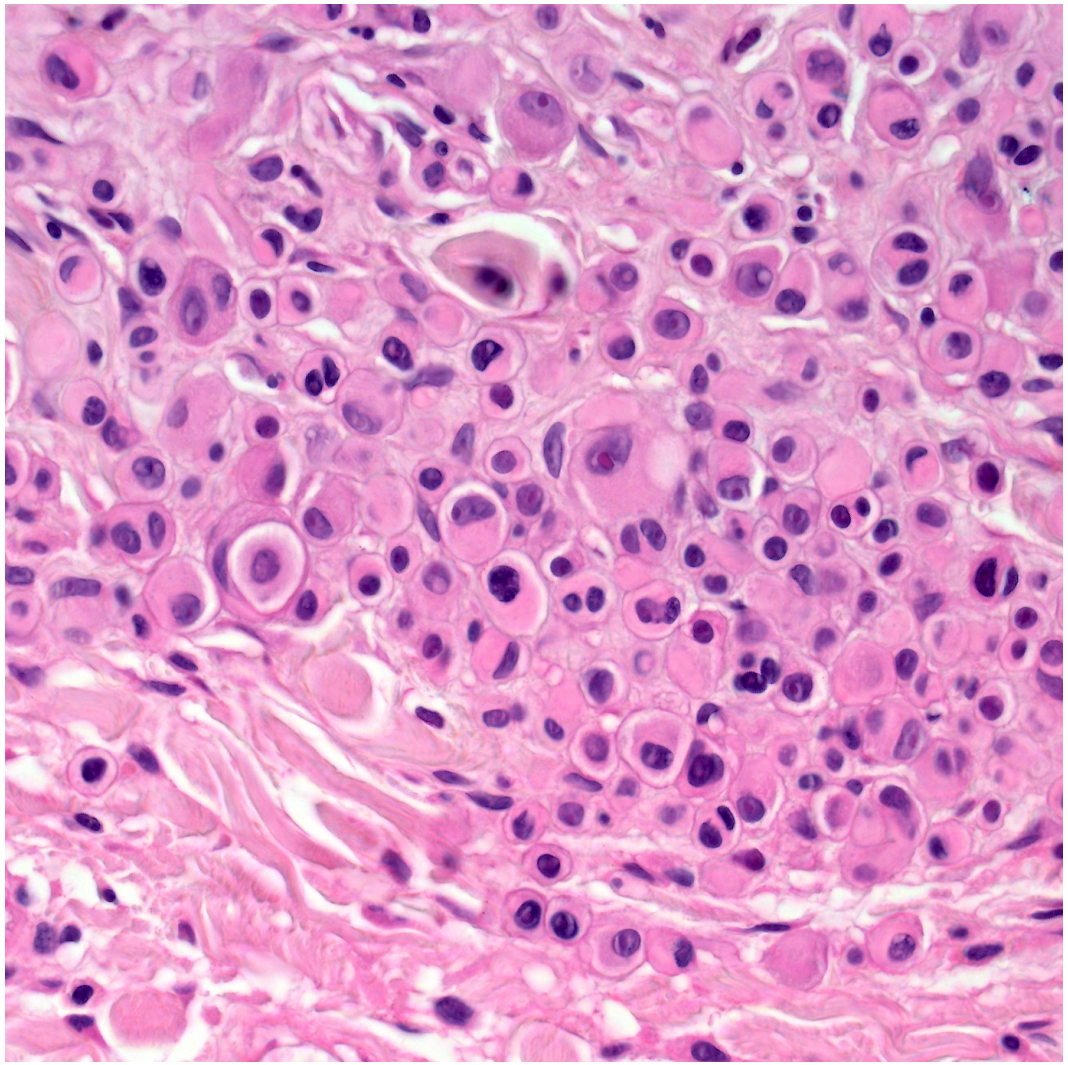


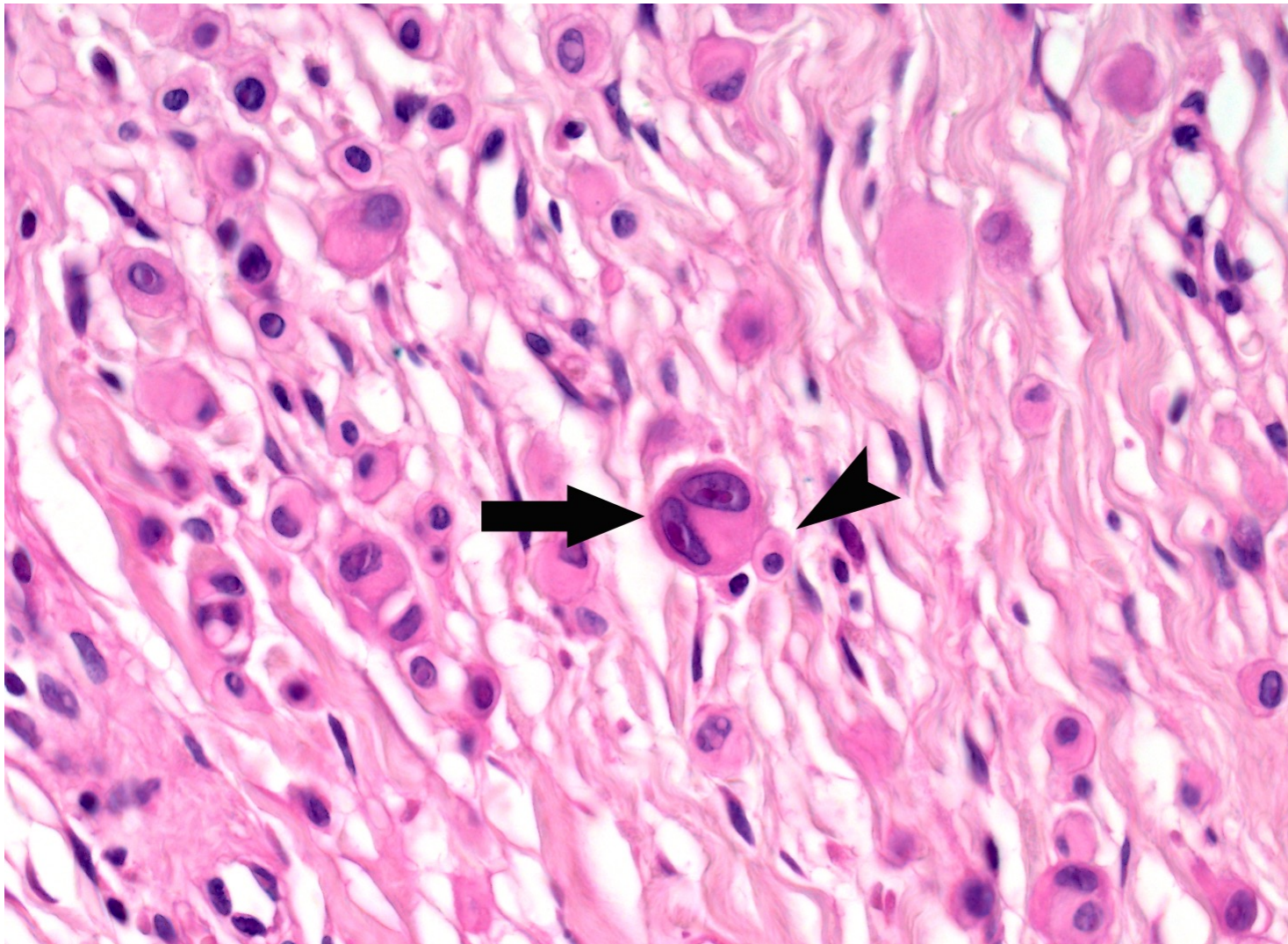
Marked intratumoral heterogeneity with few if any mitoses and intratumoral lymphocytes





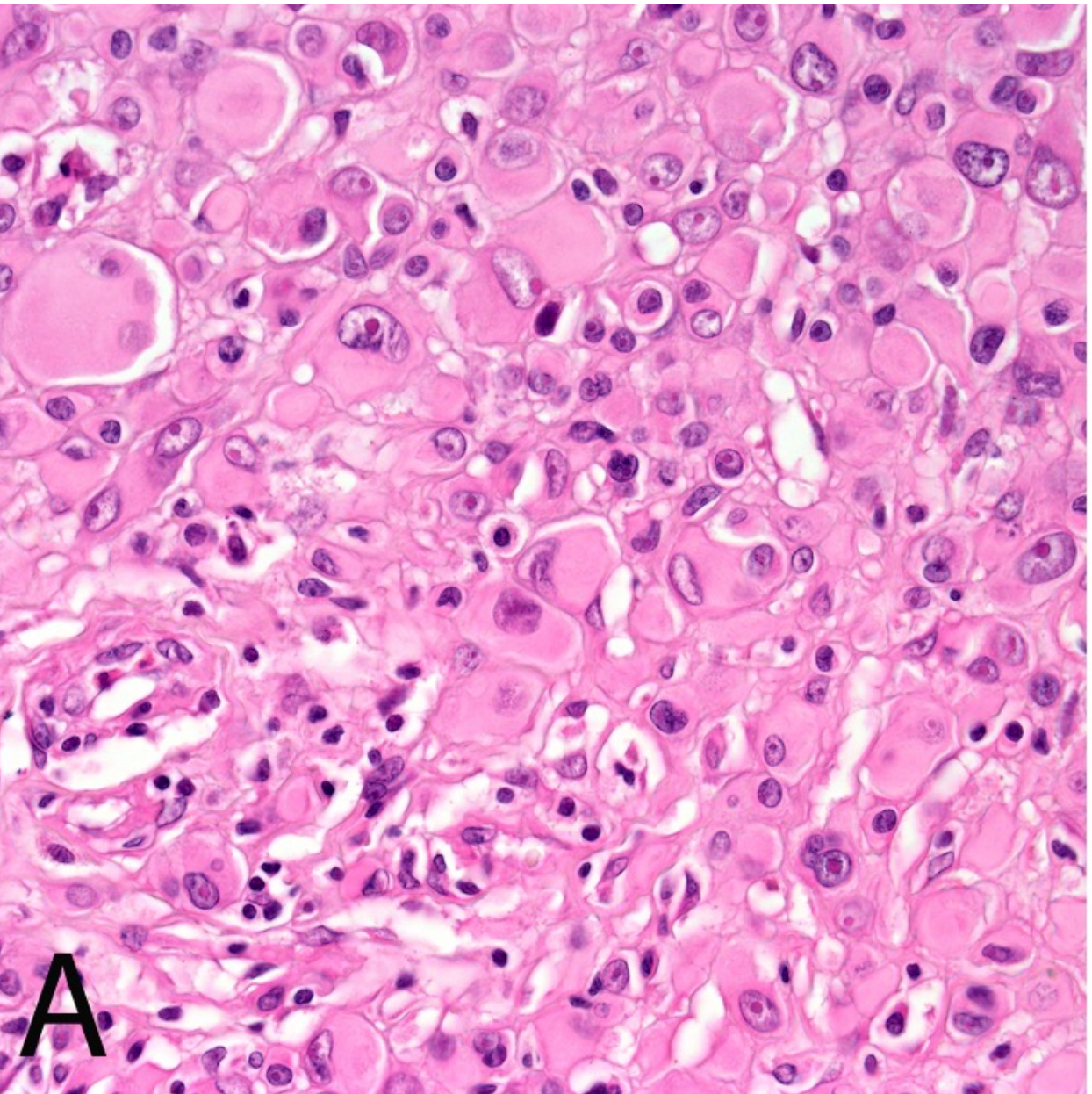
Cell size variation

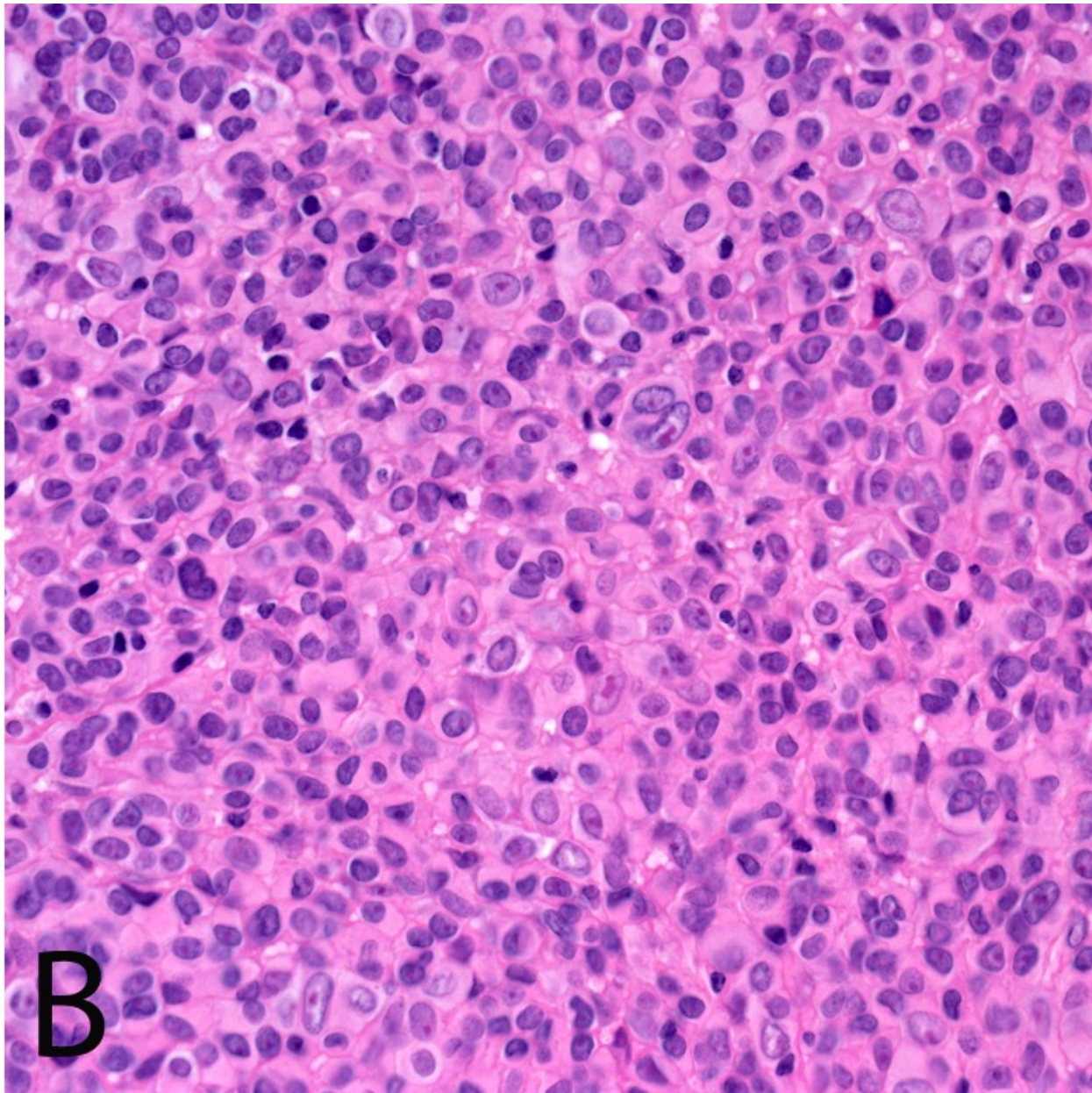




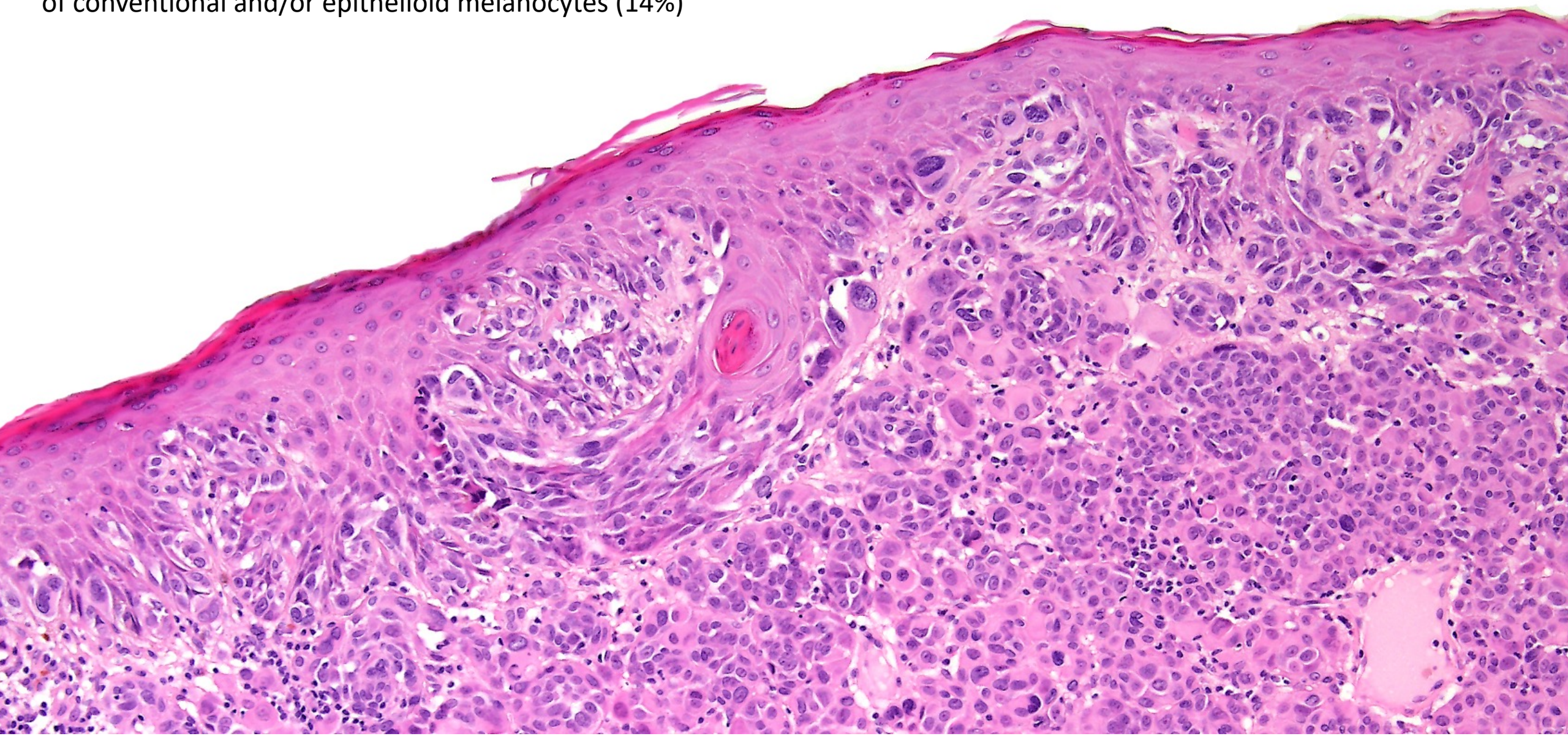
Most cases shows small to large cells

Some cases are predominantly composed of small epitehlioid cells (32%)

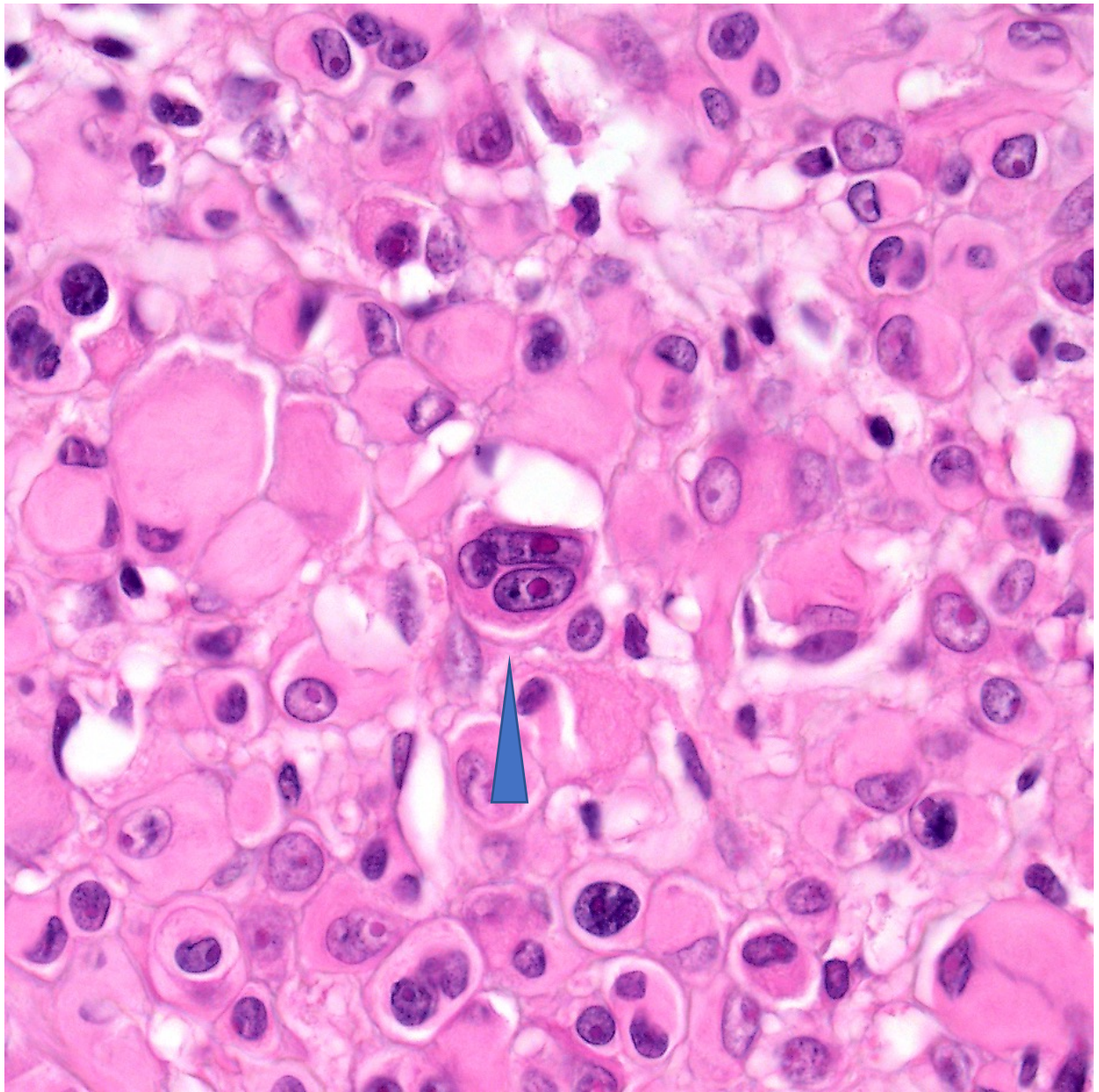


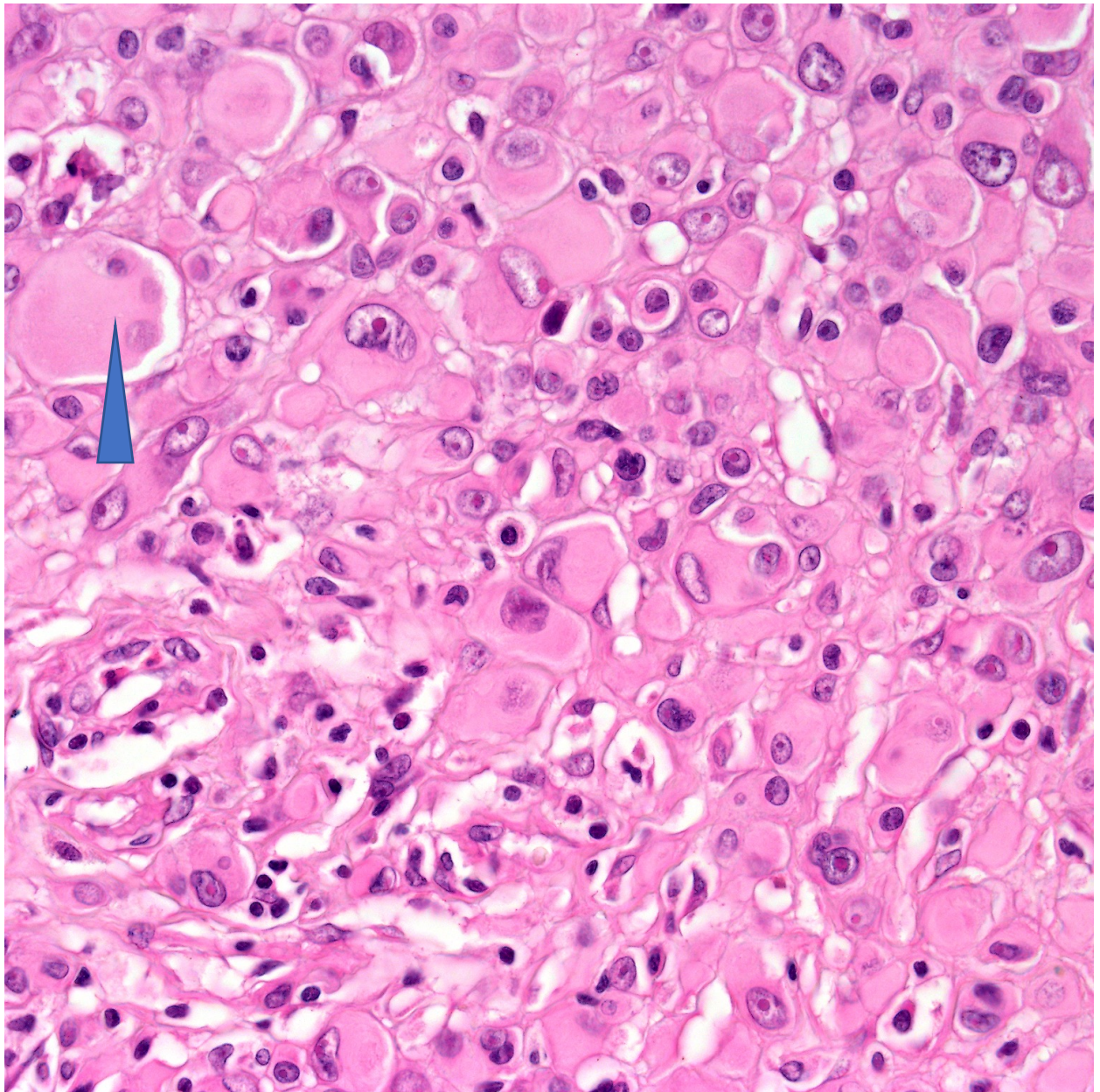


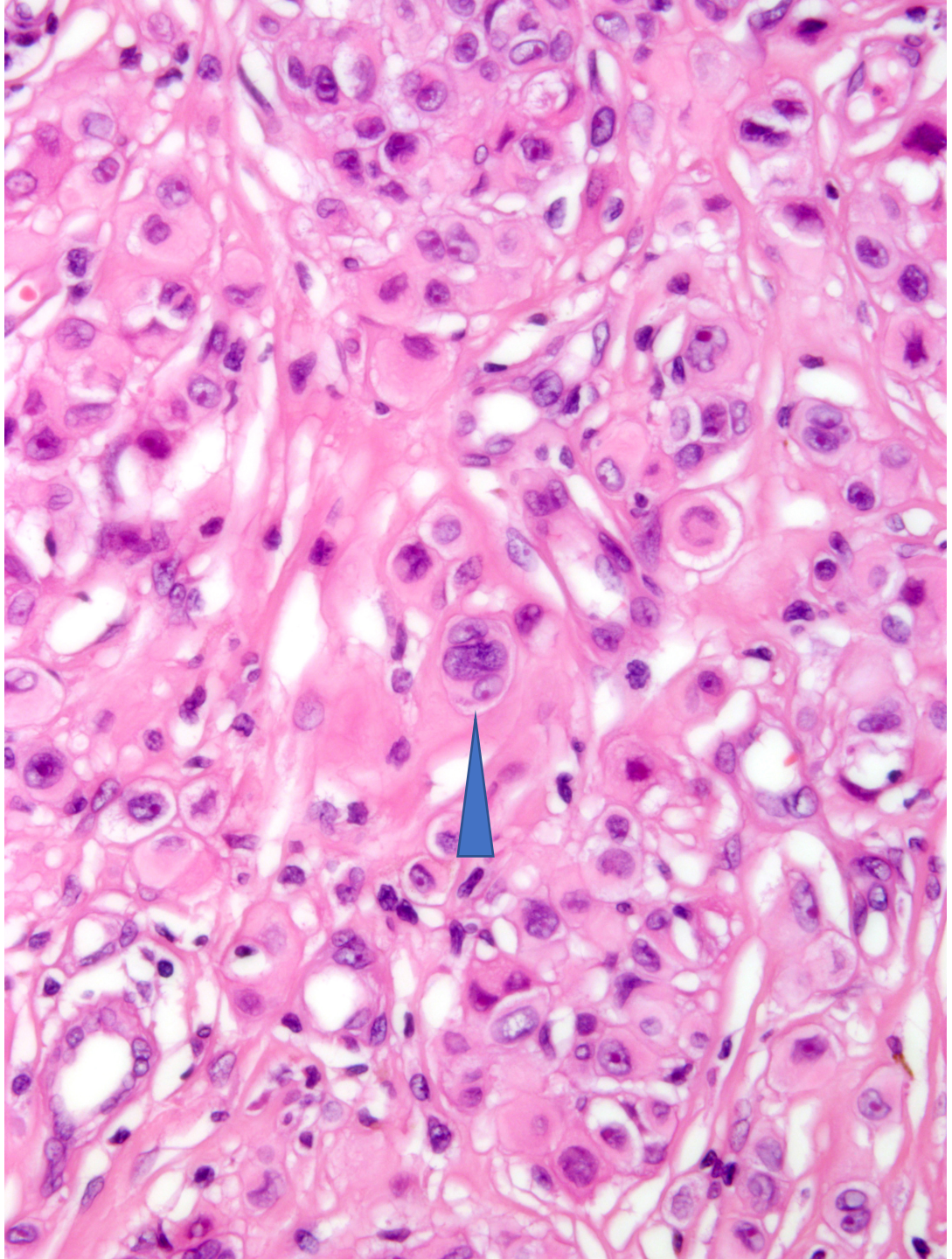
Dysplastic features: Bridging of the adjacent junctional, horizontally arranged nests of conventional and/or epithelioid melanocytes (14%)

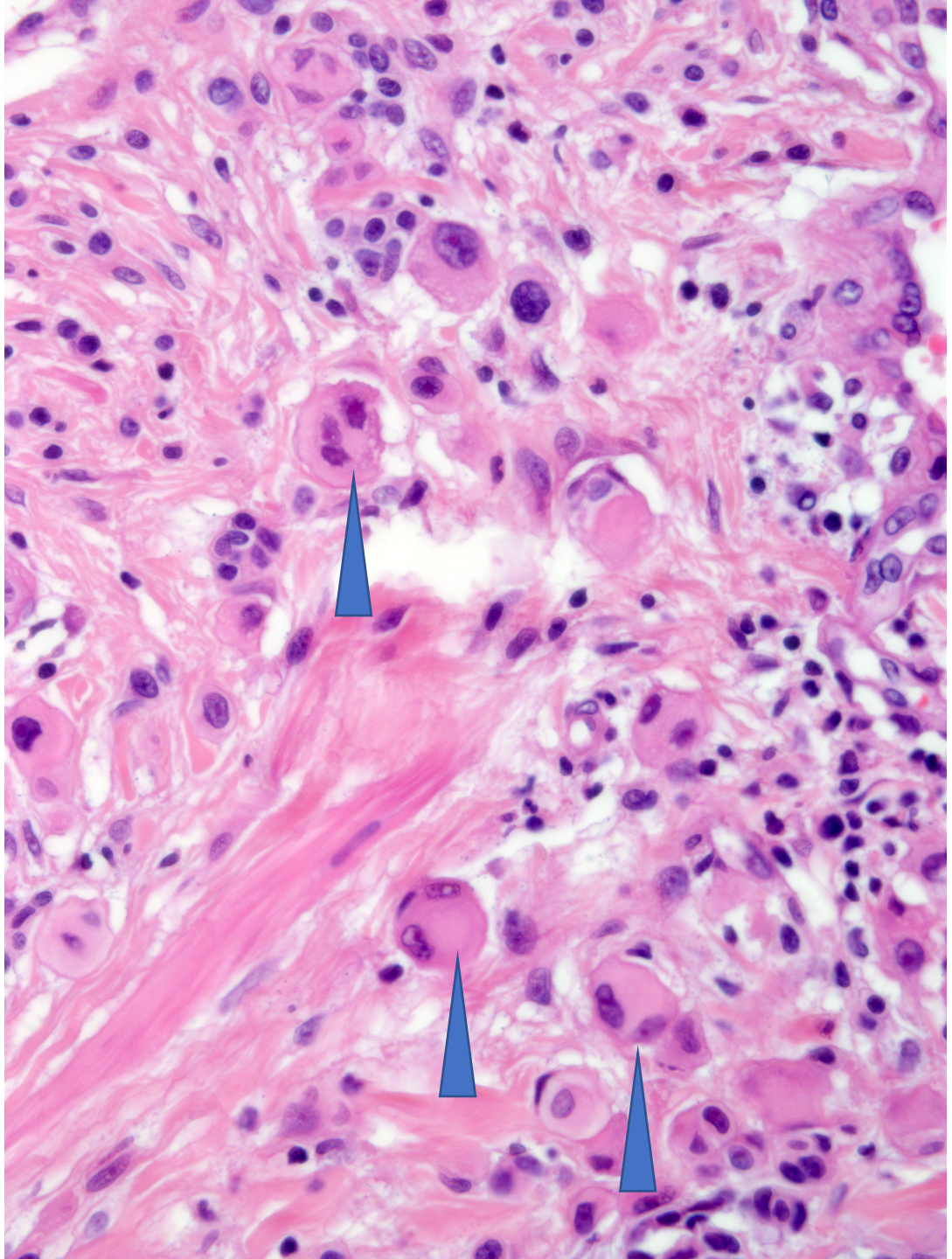


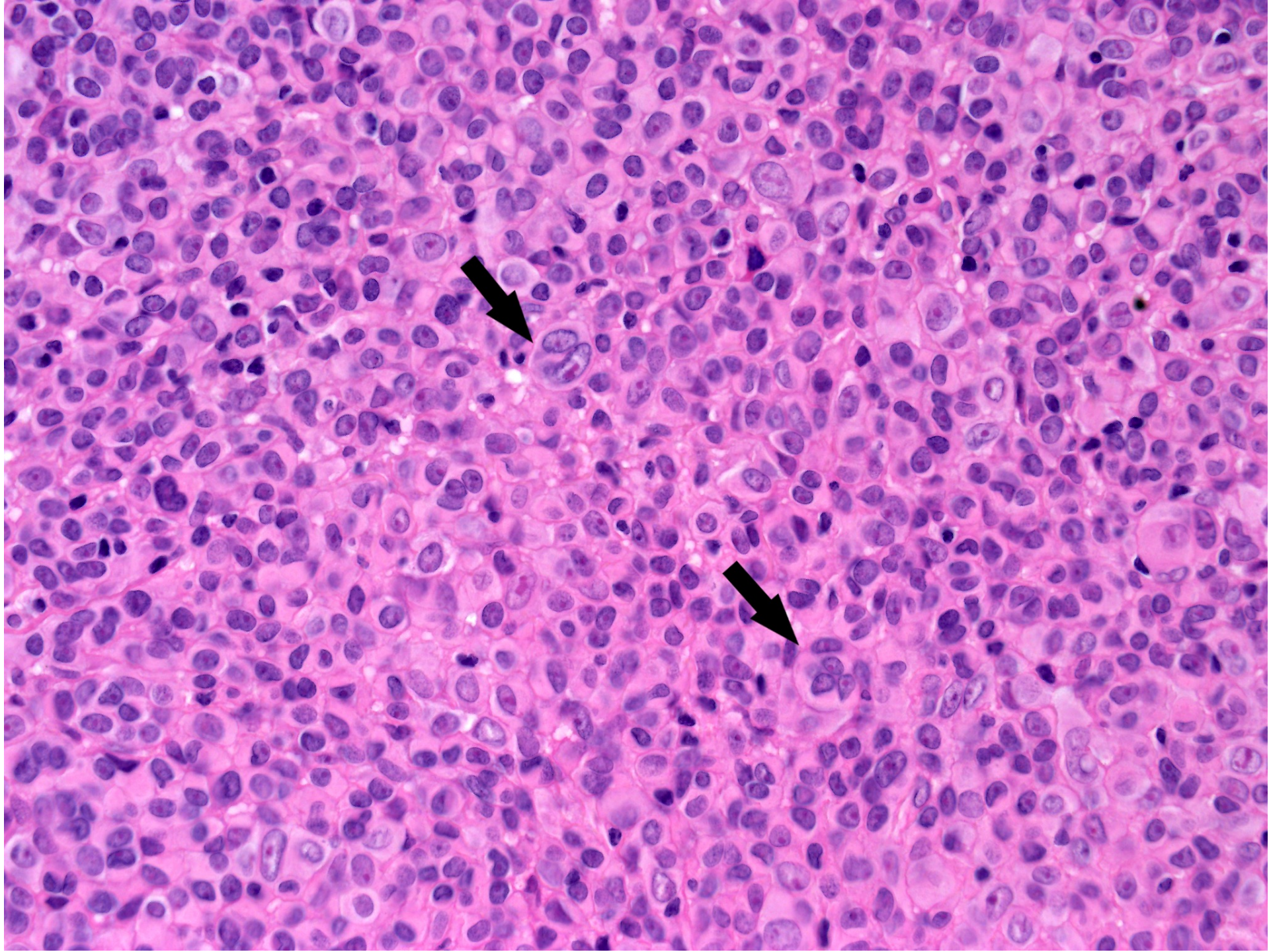
Multinucleated cells are very typical (98%)



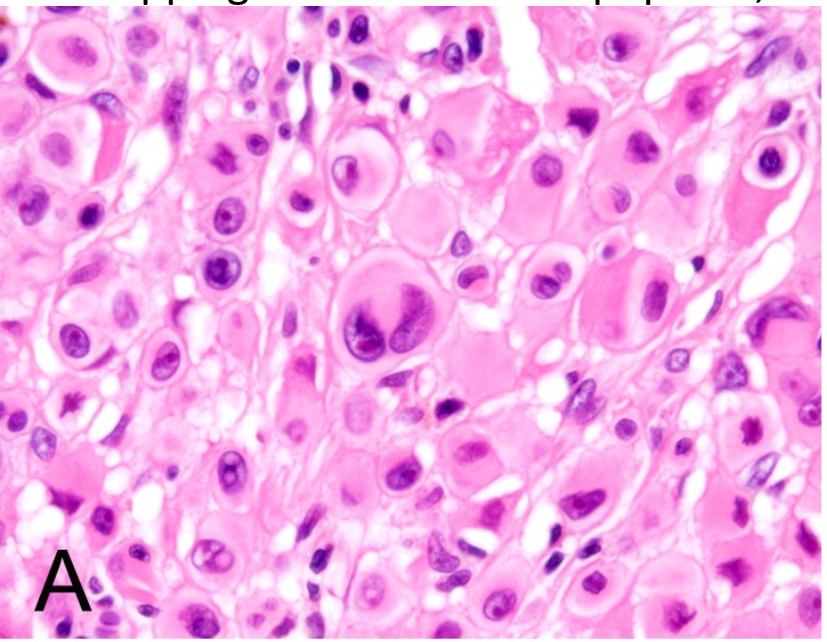


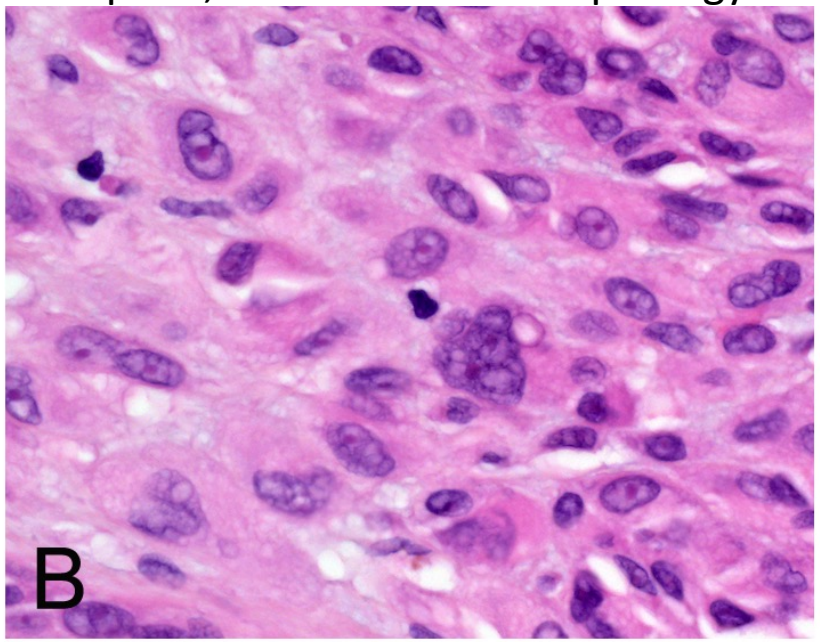


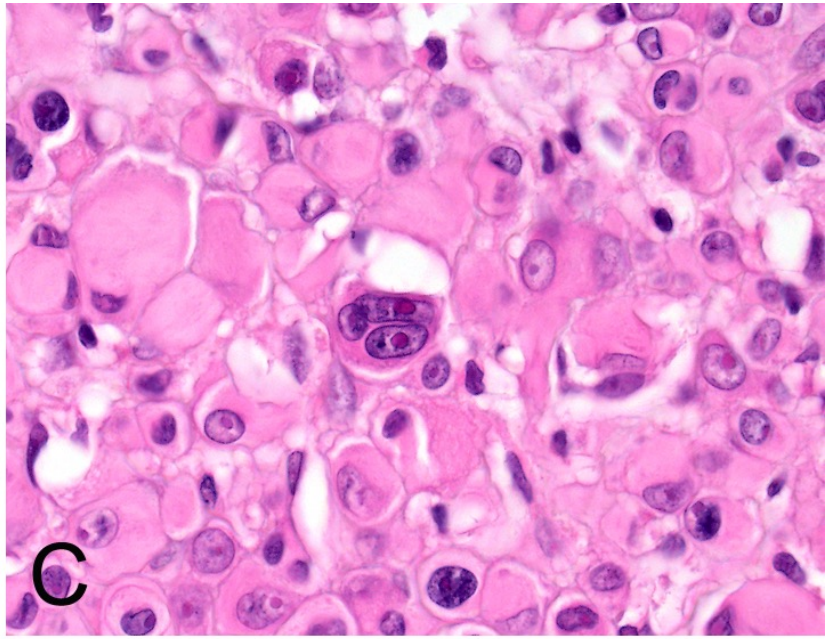


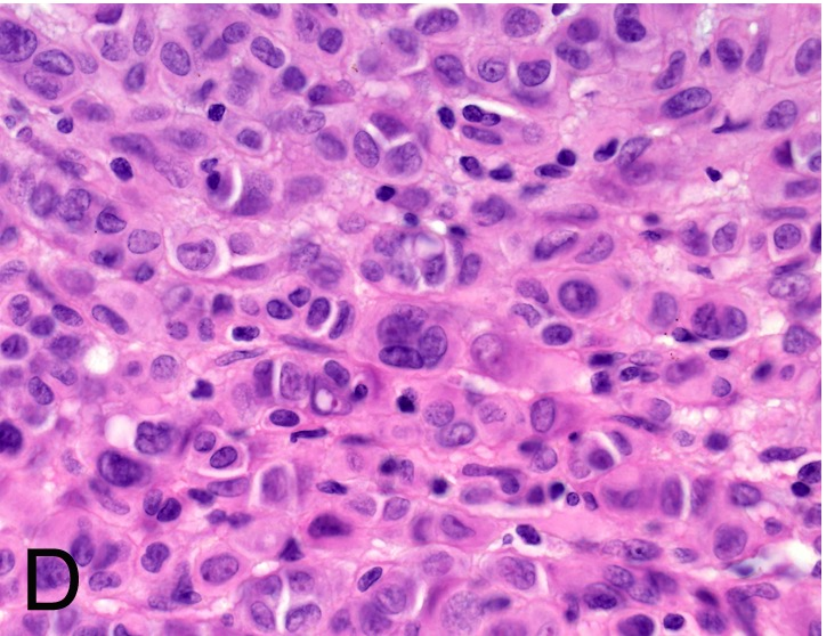


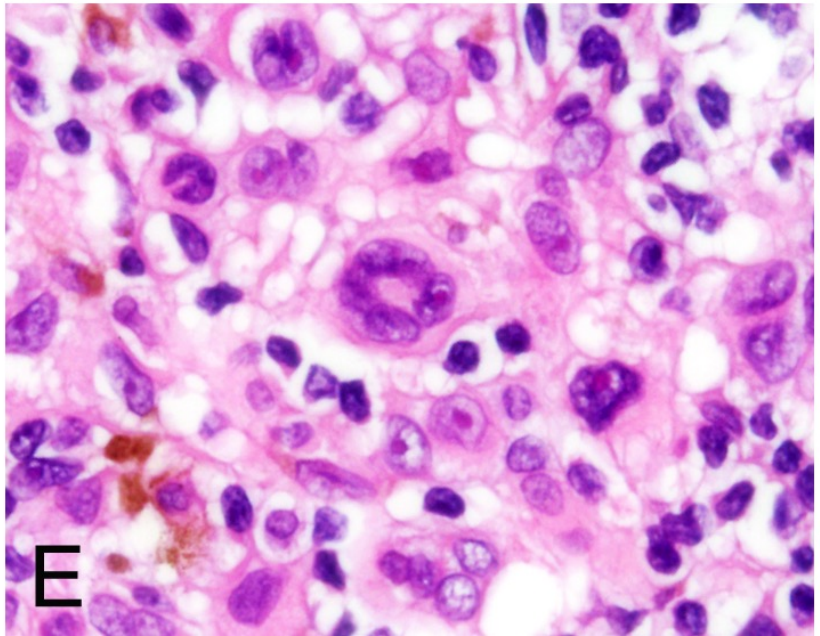
Various types of multinucleated cells: binucleated cells resembling Reed-Sternberg cells, multinucleated/giant cells with overlapping nuclei result in a popcorn, coin-on-a-plate, or wreath-like morphology

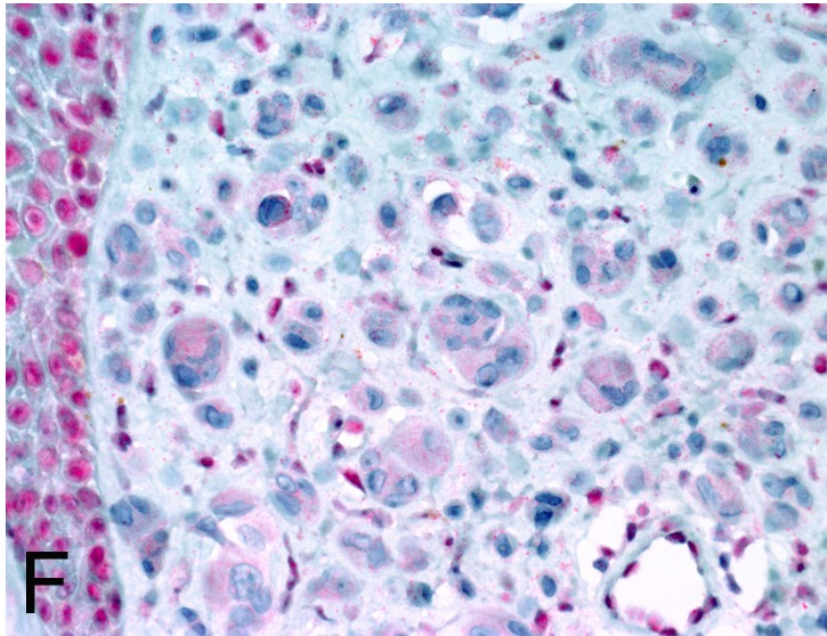




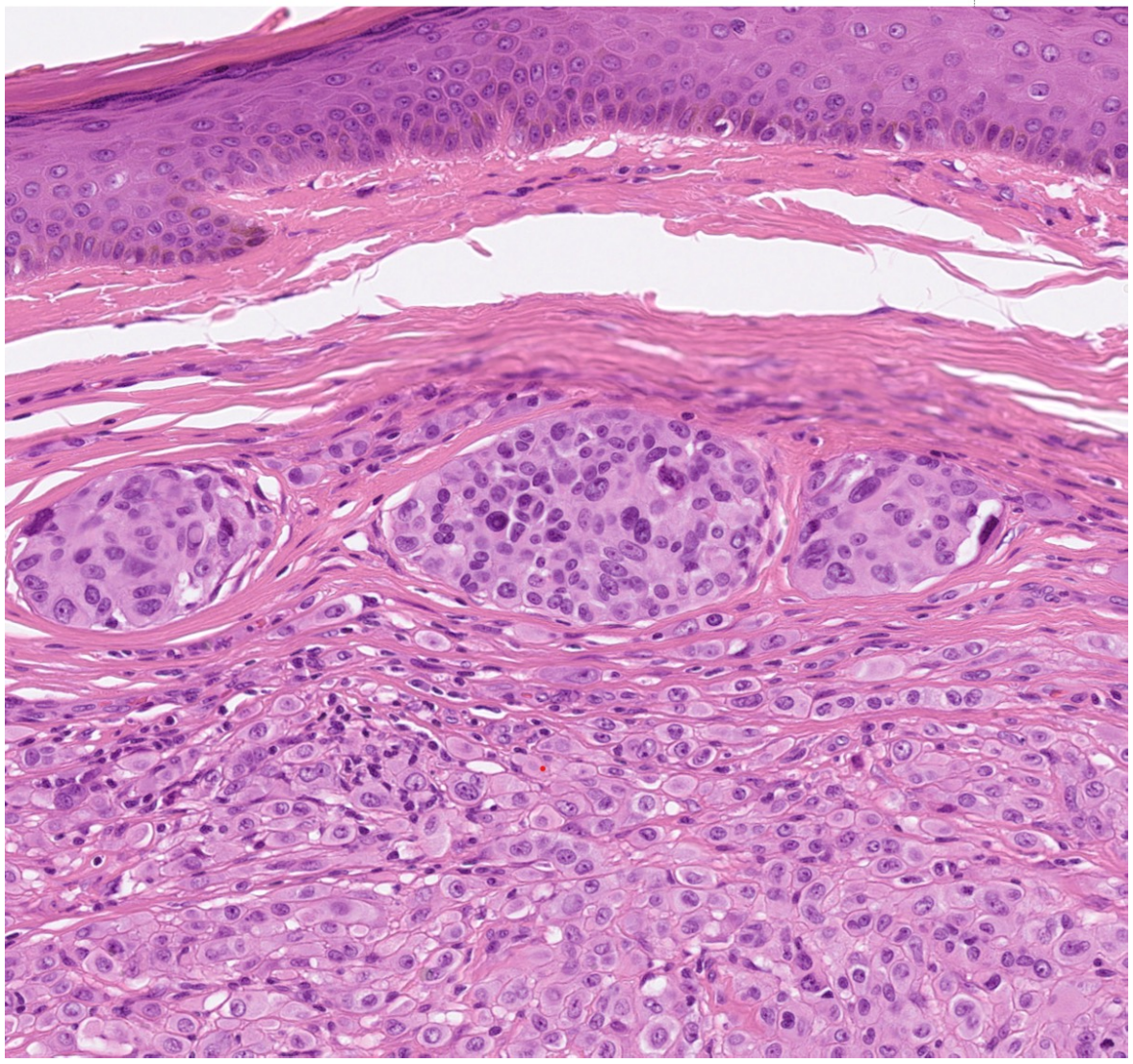


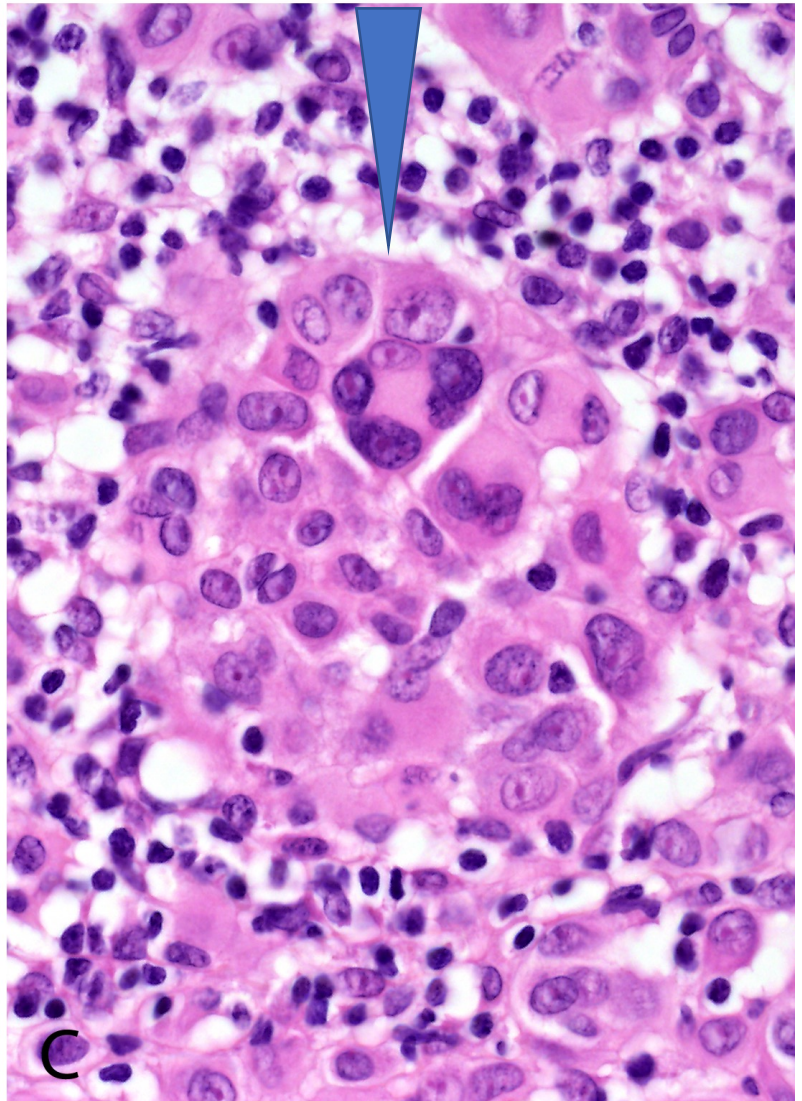


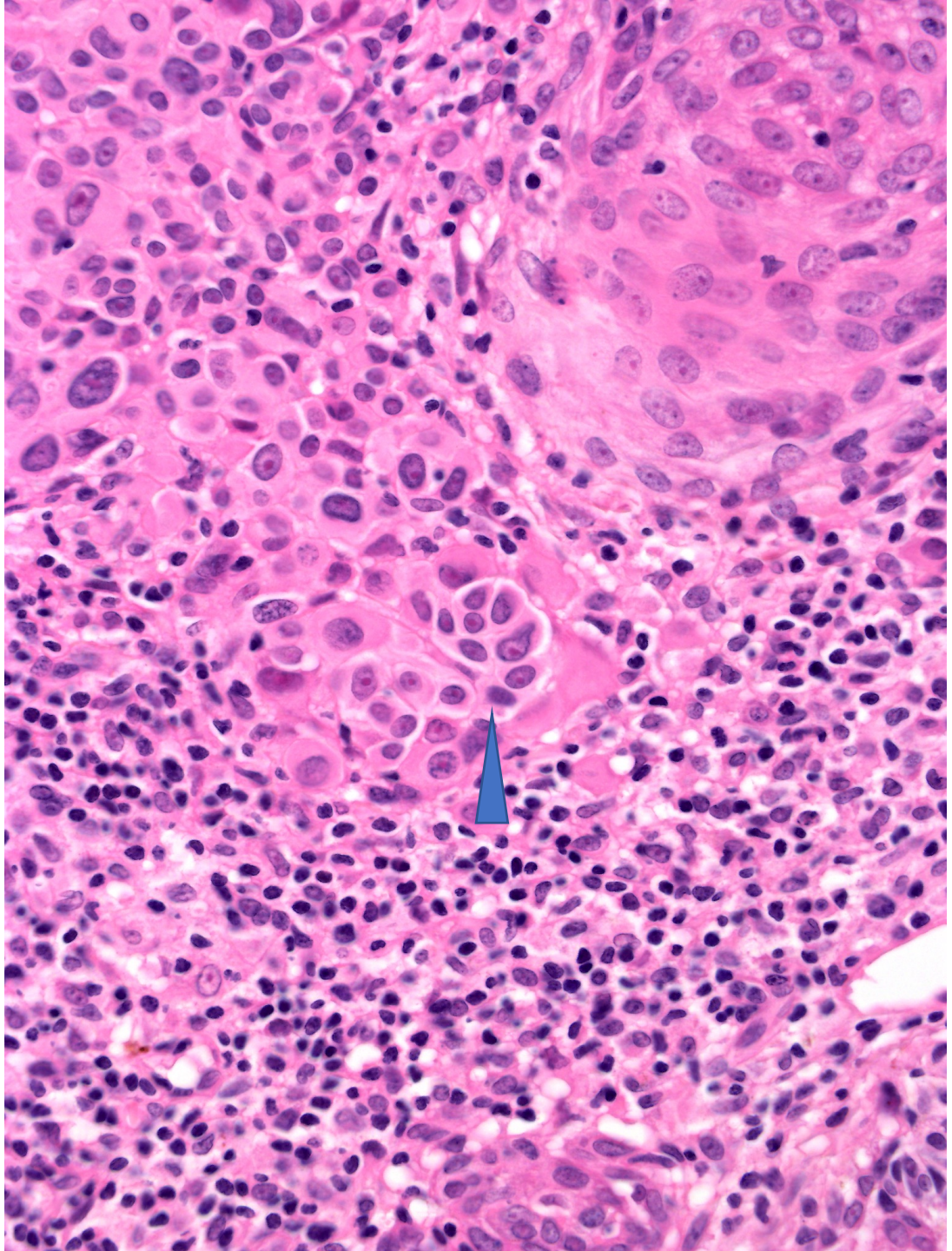


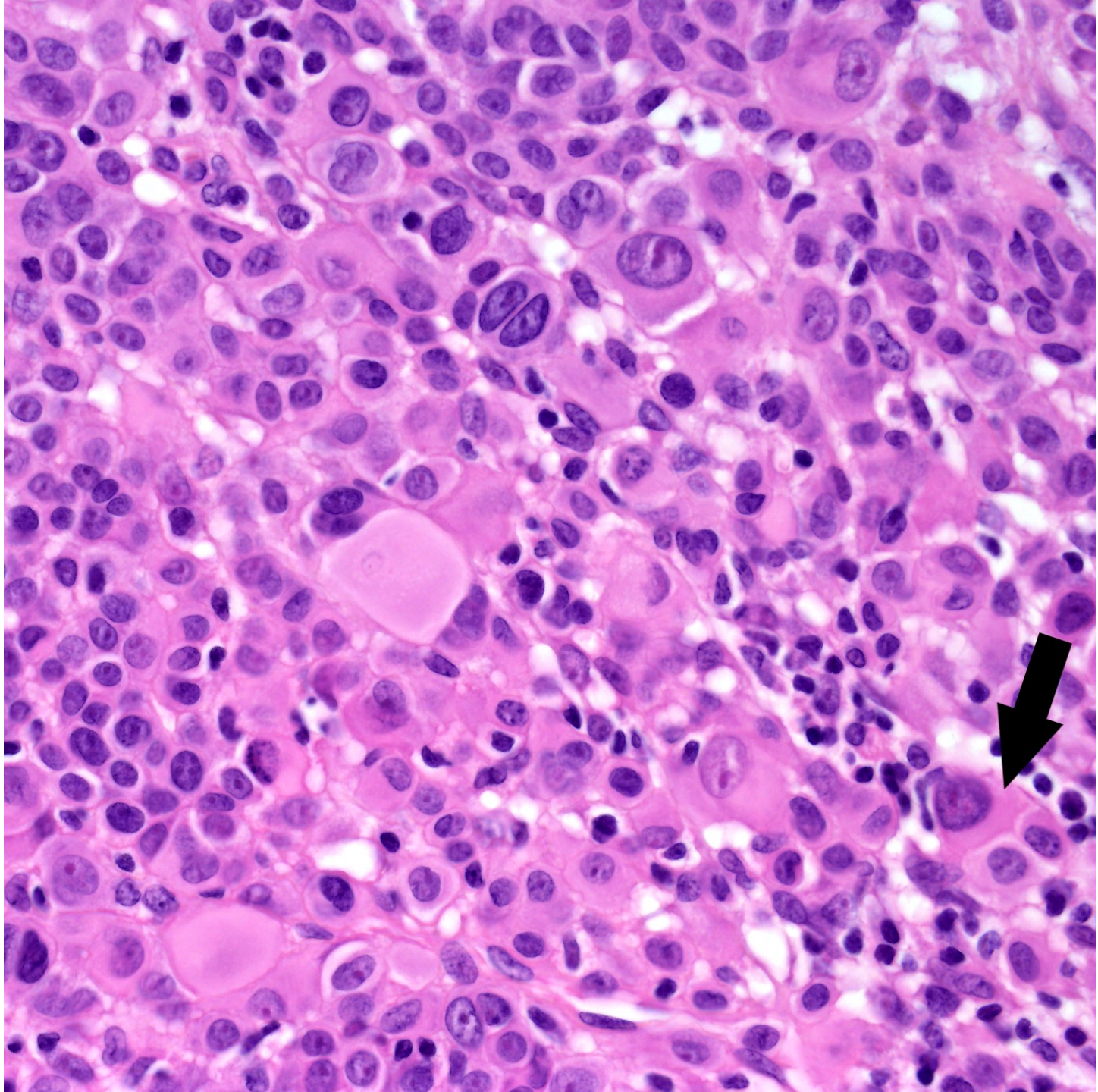


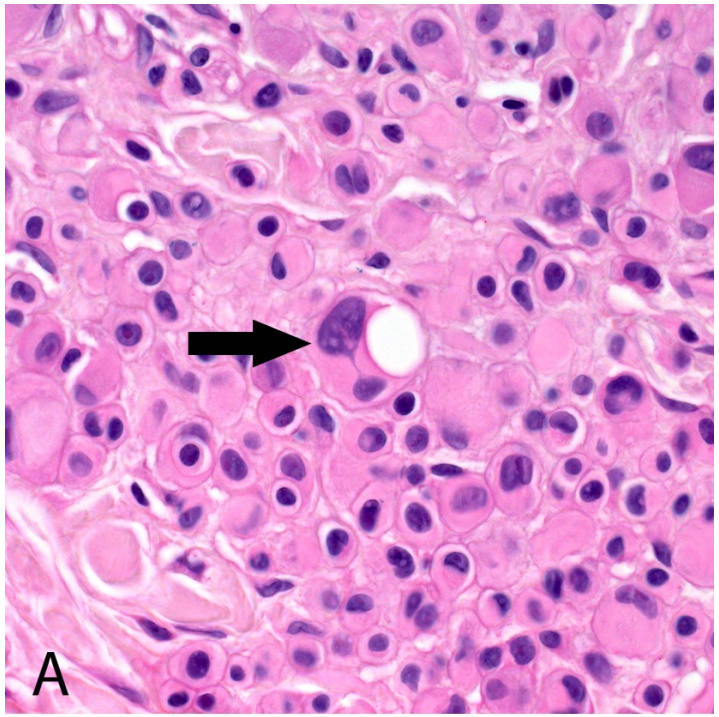
Discohesive nests of epithelioid cells (88%)

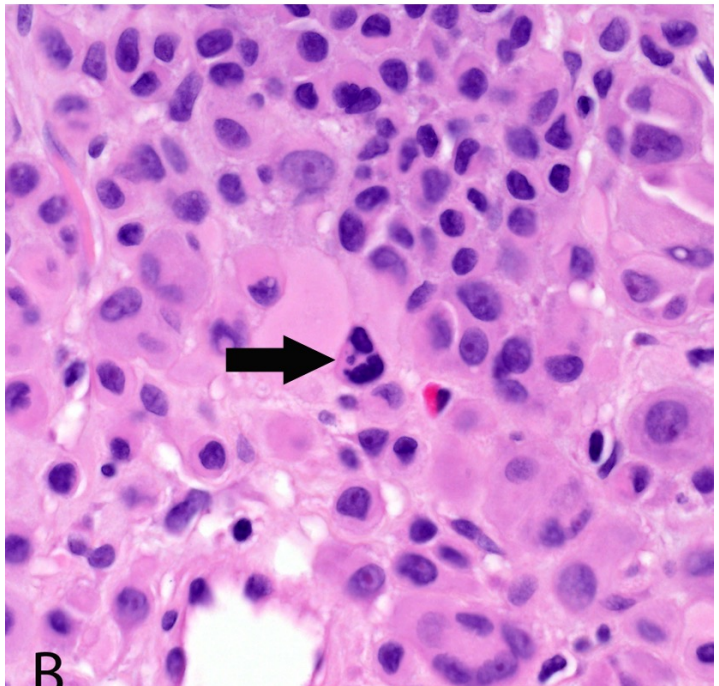






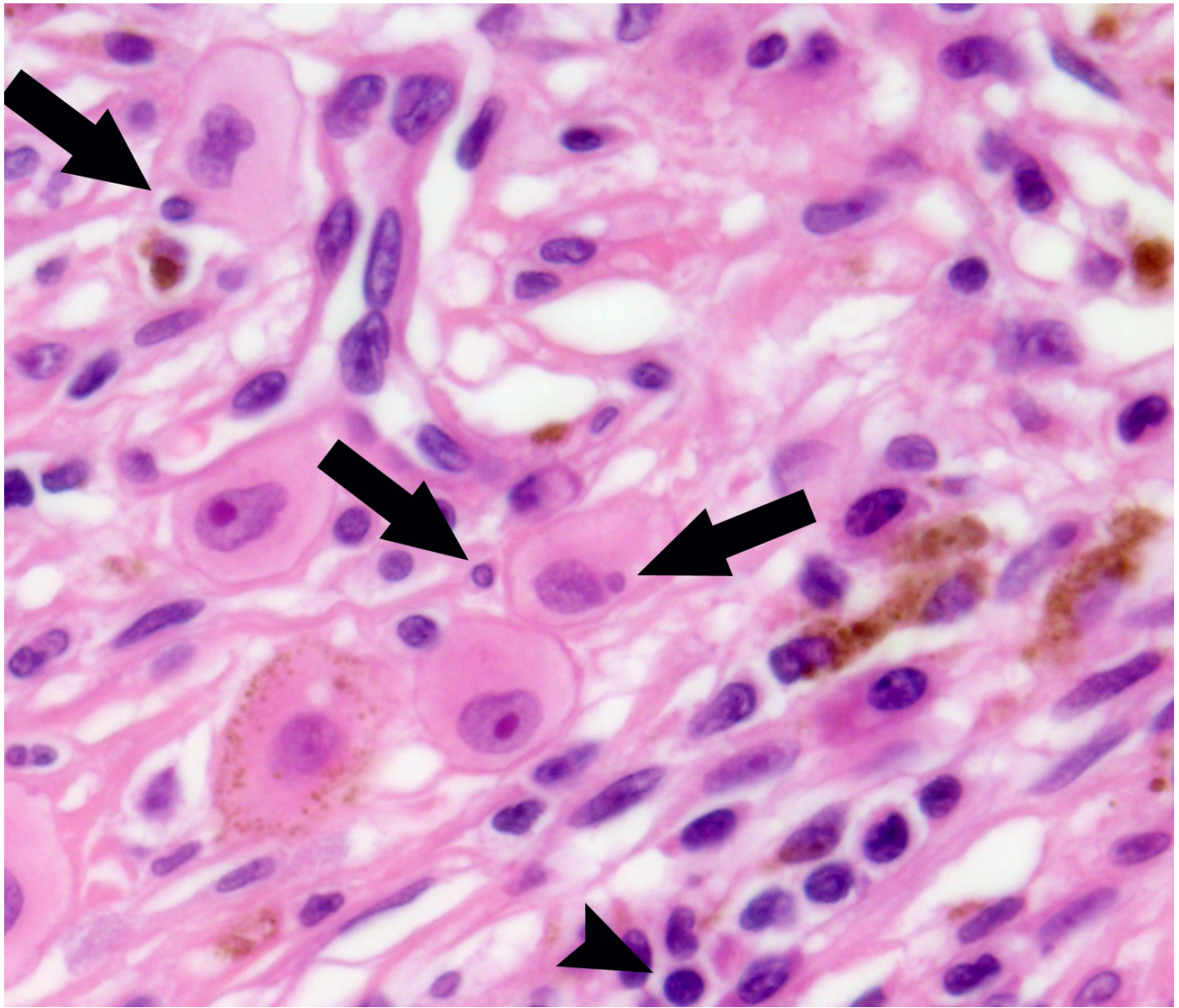




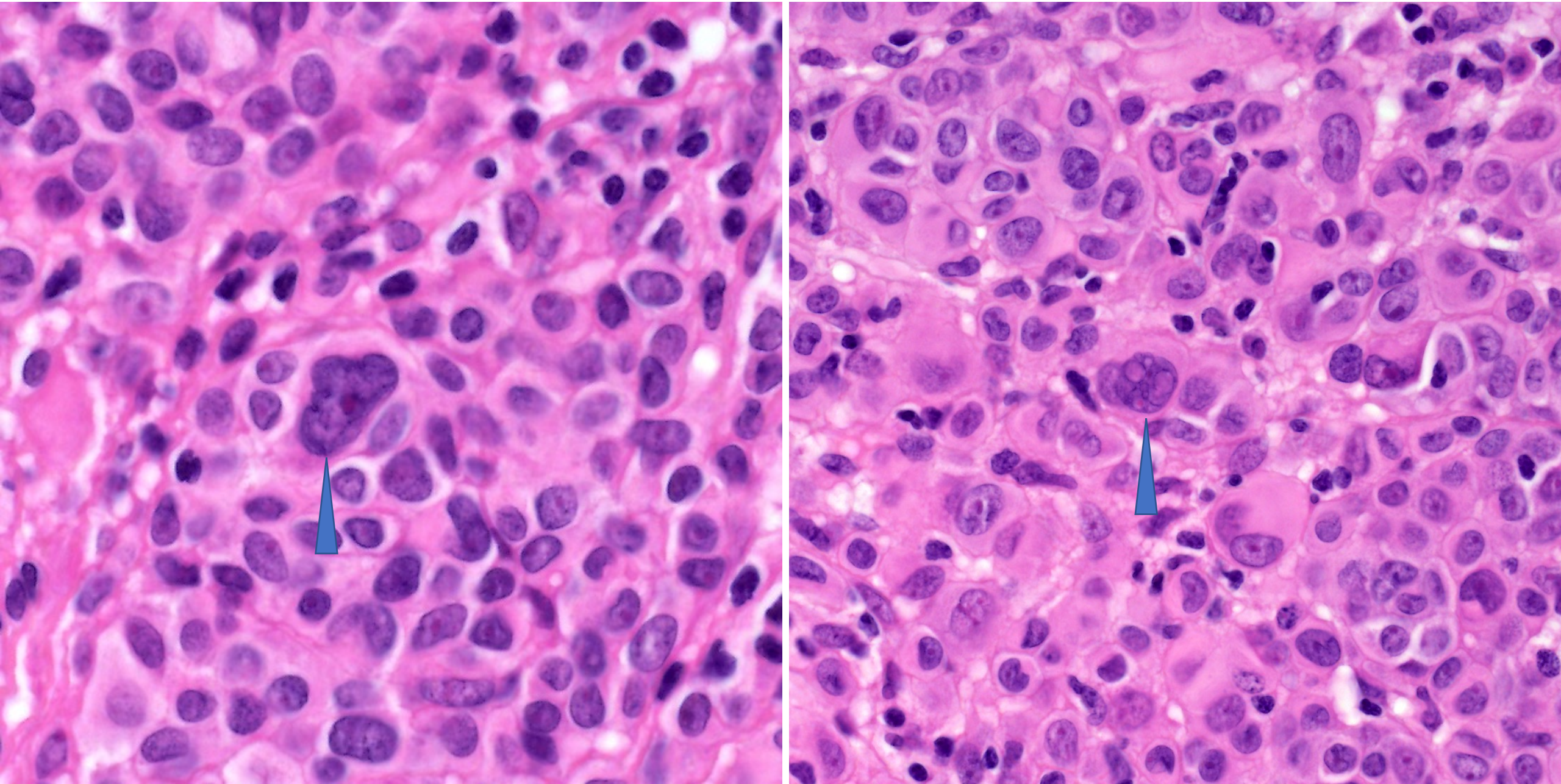


Nuclear bridging
Nuclear budding: nuclear buds of variable dimension detaching from the main nucleus (98%)

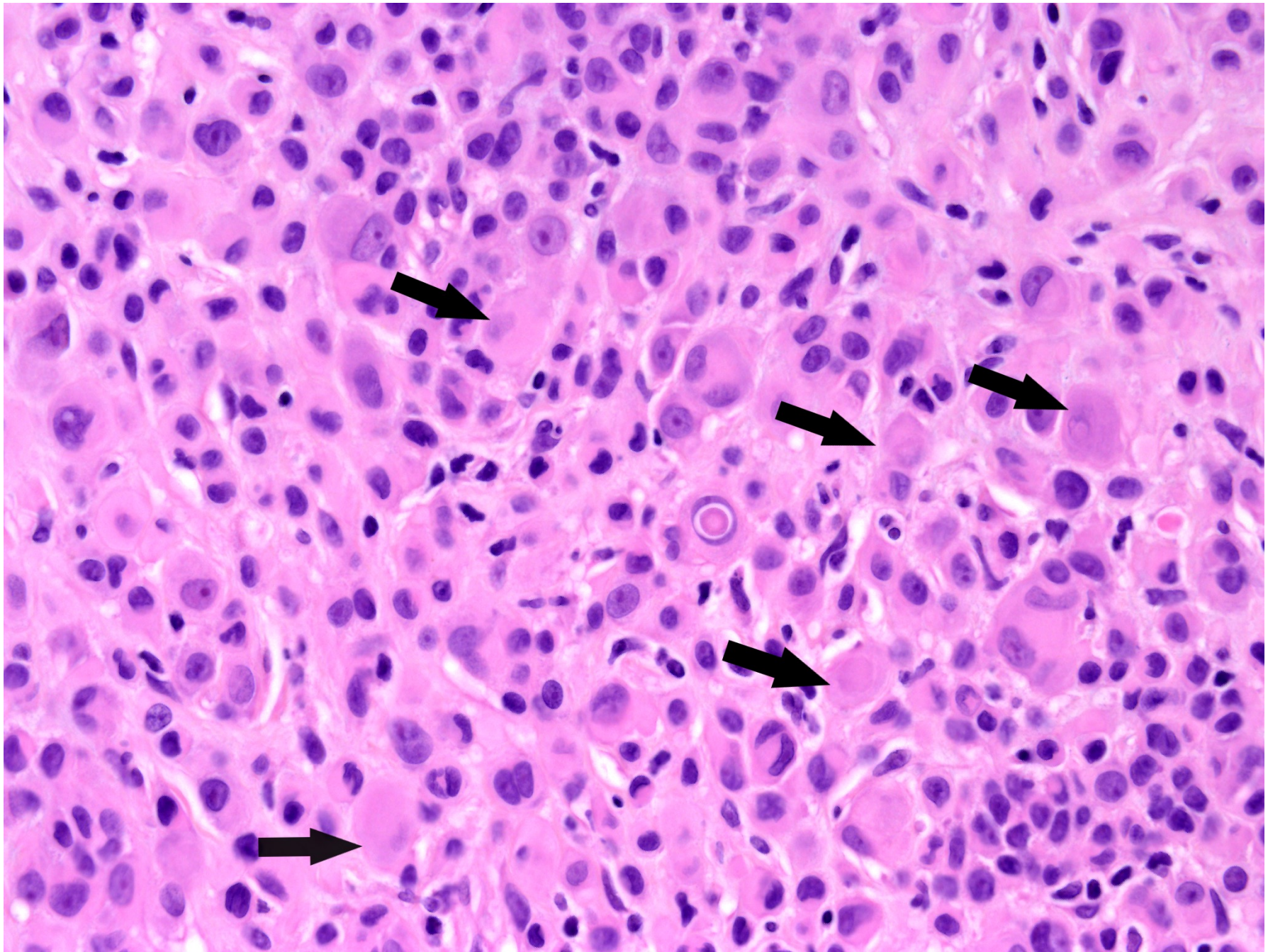
Micronuclei: a small nucleus or nuclear buds being 1/3 or smaller compared to the main nucleus presented with a similar or slightly lighter non-refractile staining intensity (80%)



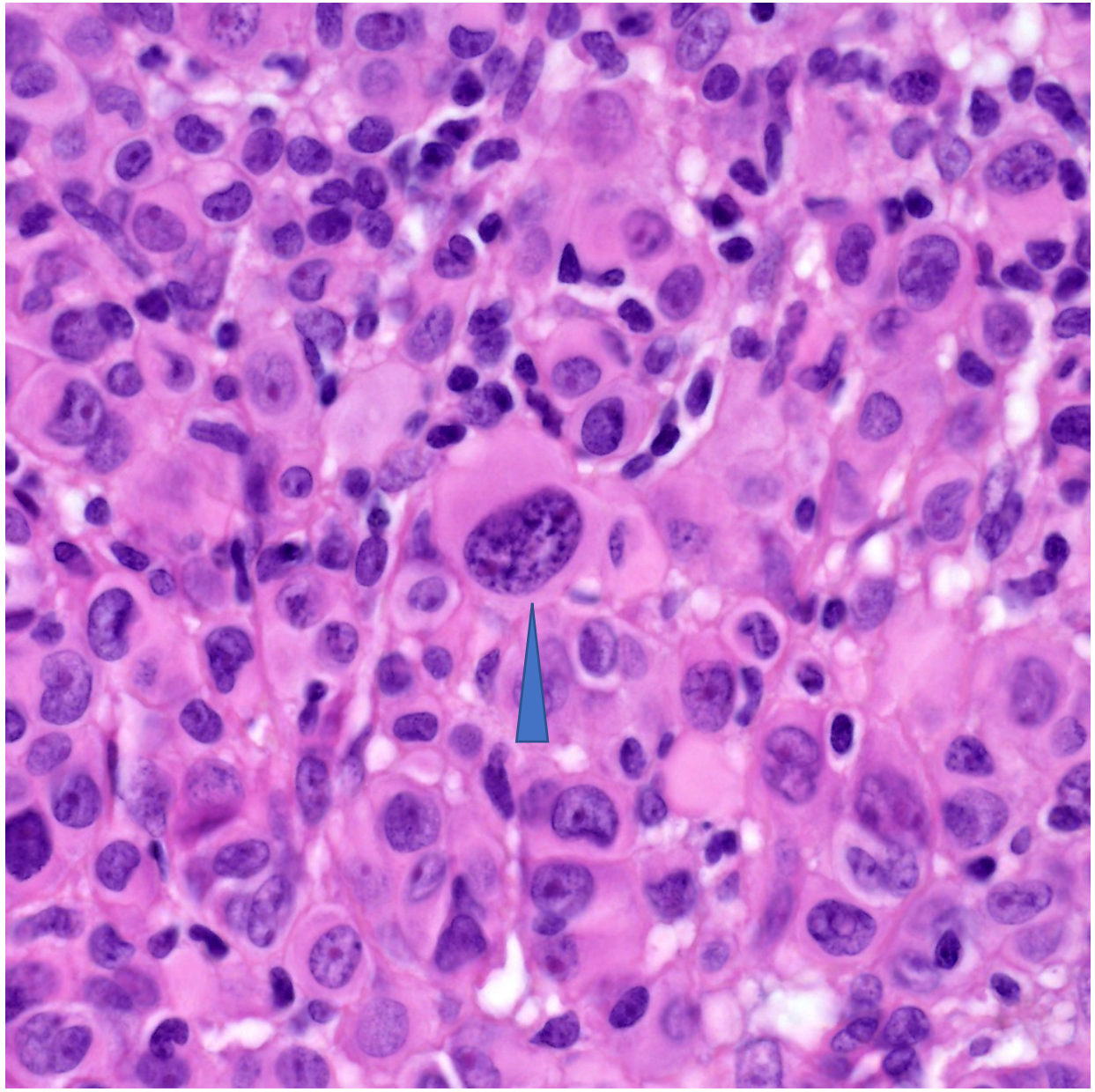
Cells with large irregular nuclei resembling blebbing (98%).



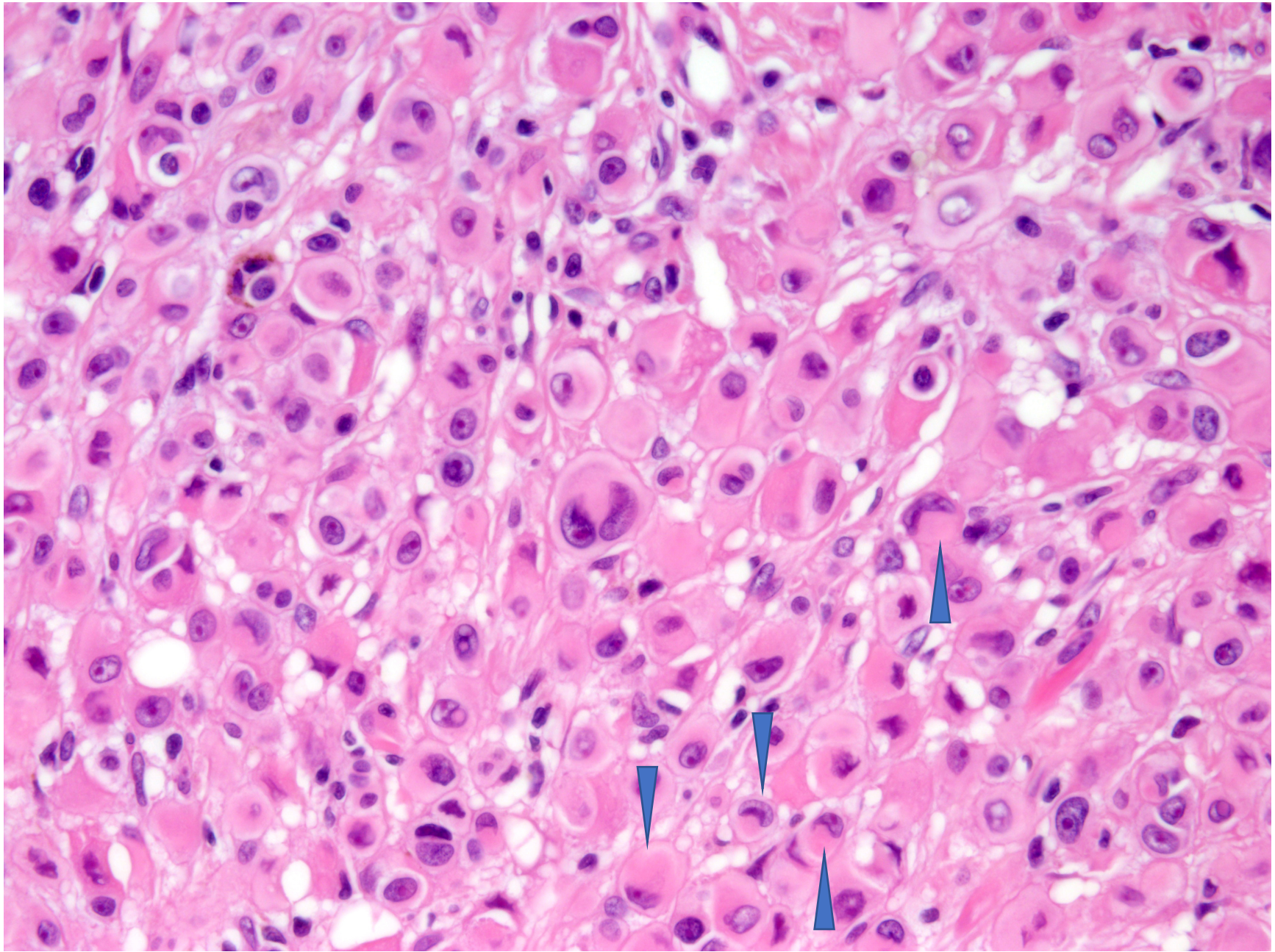
“Ghosts” cells: cells are exclusively composed of large eosinophilic cytoplasm with only a shadow/vestige of a nucleus (90%).

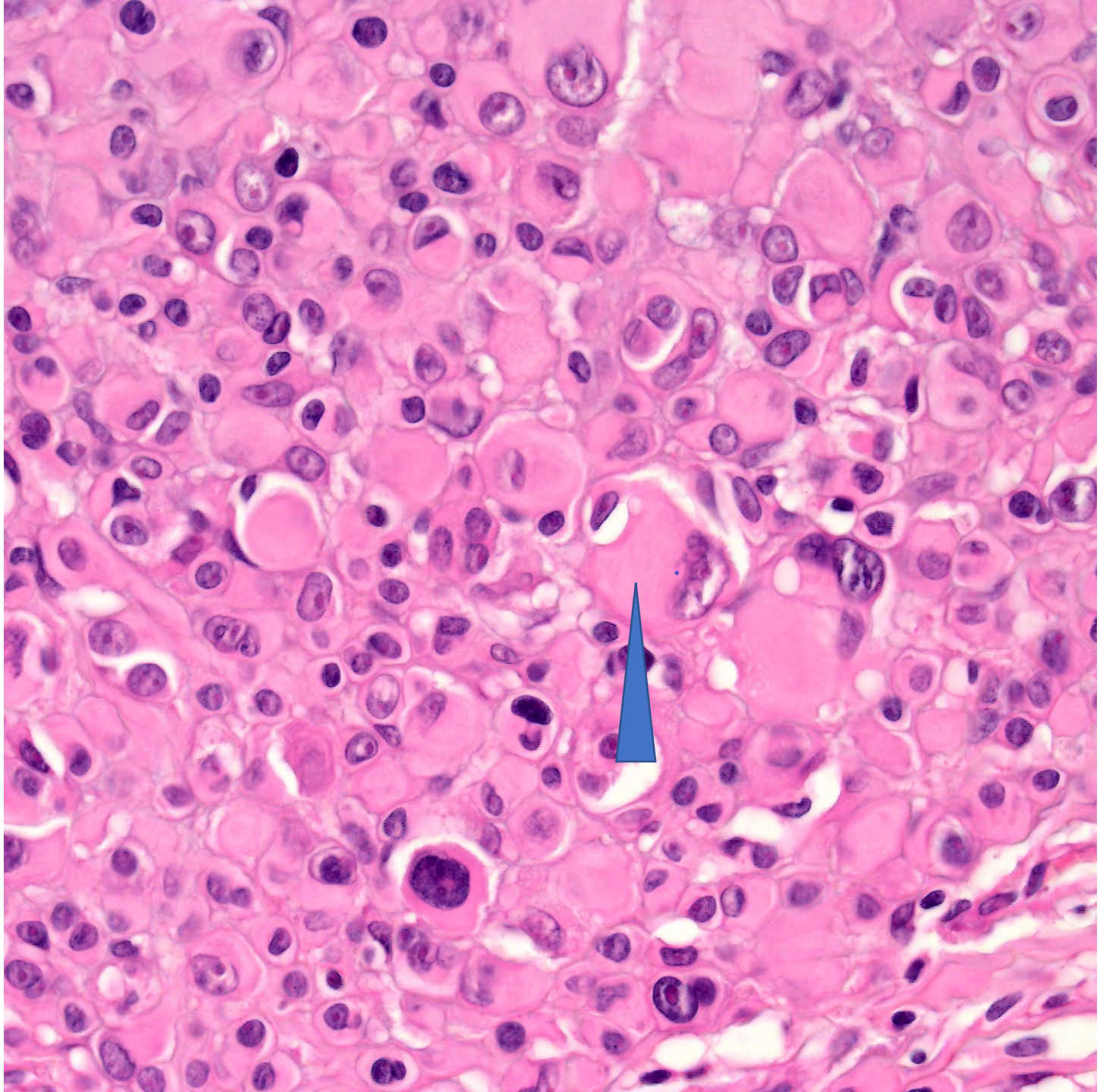


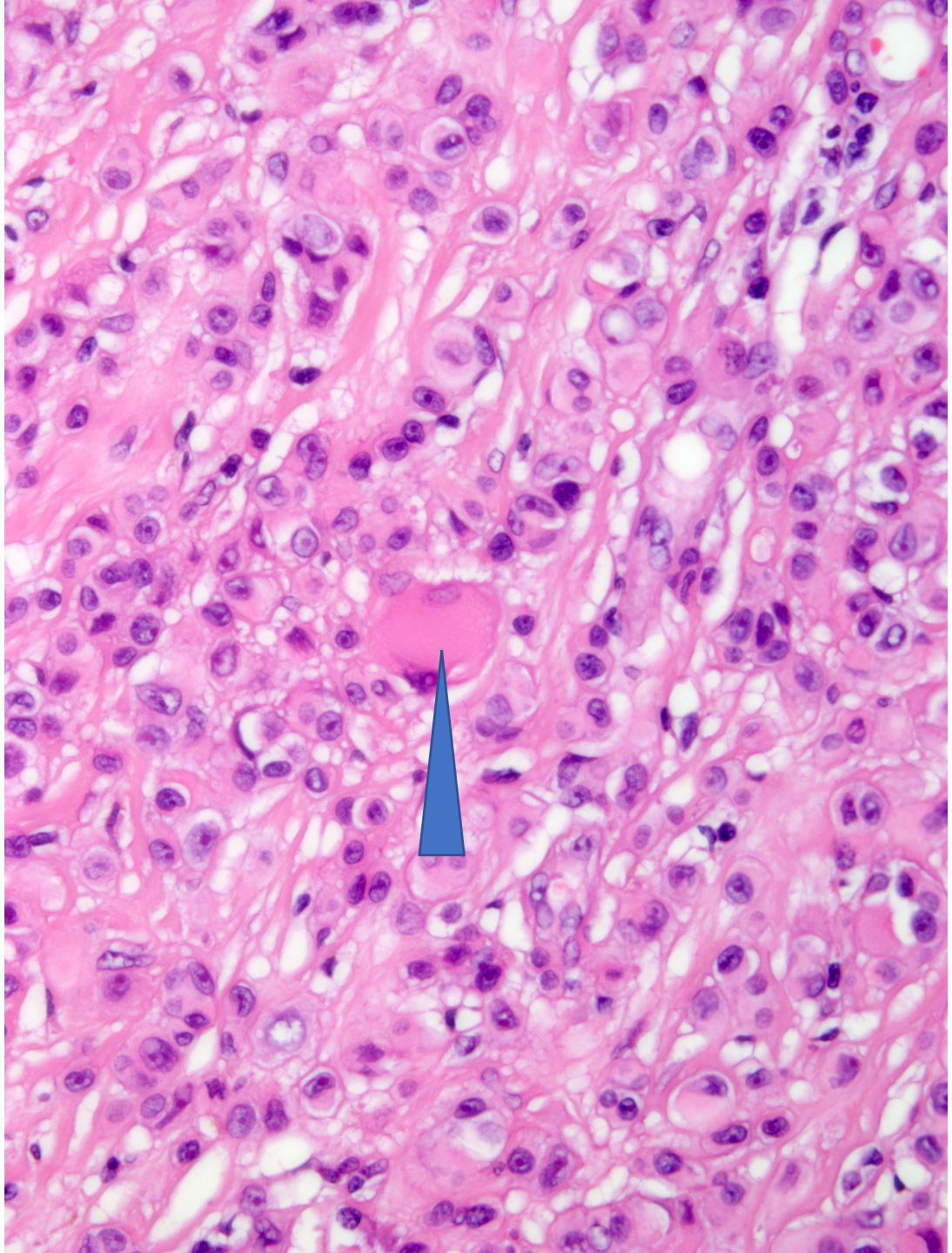
Large epithelioid melanocytes with enlarged nuclei showing clumped chromatin



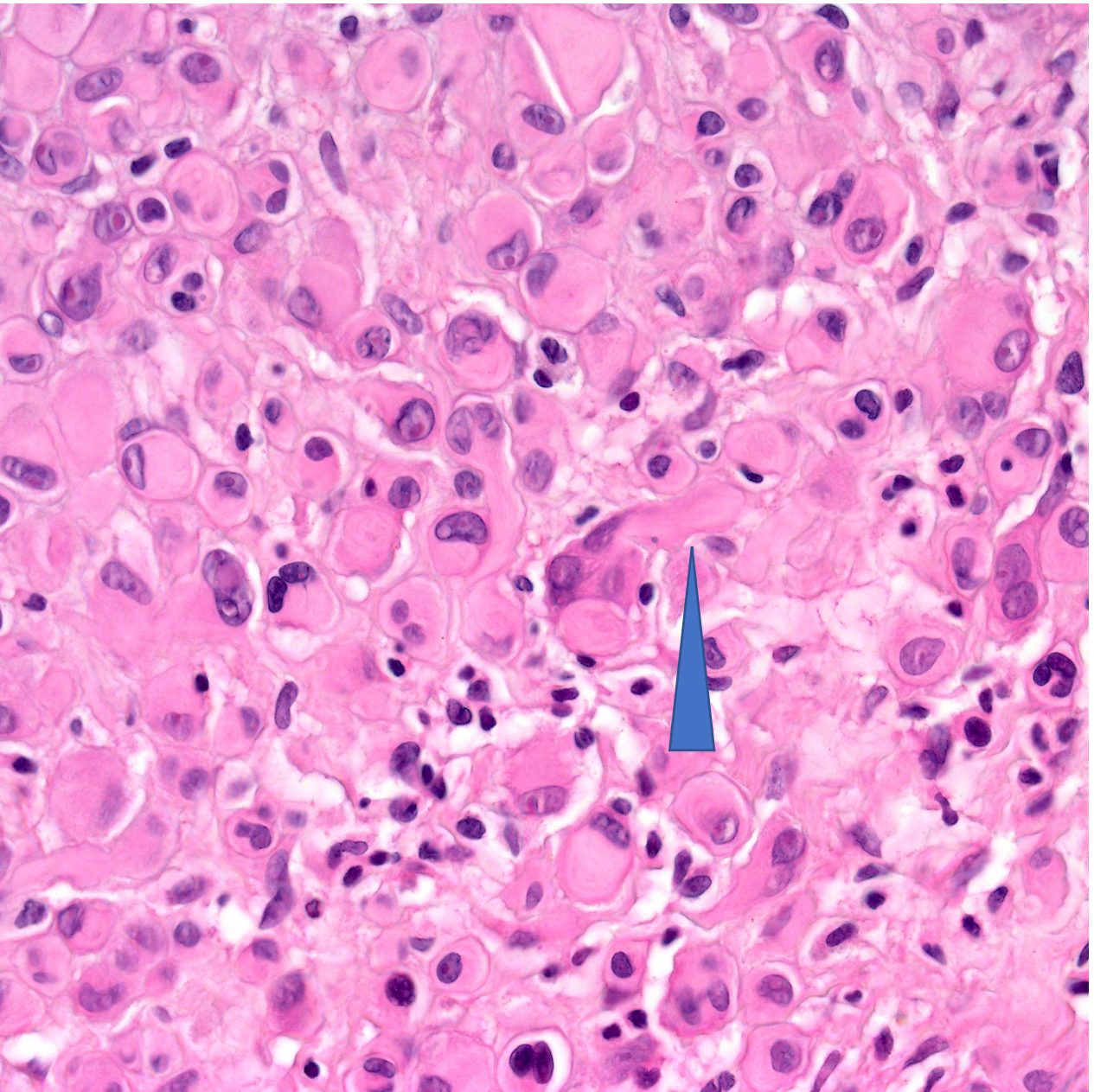
Polarized cells: cells with dislodged nucleus toward the peripehry (58%)

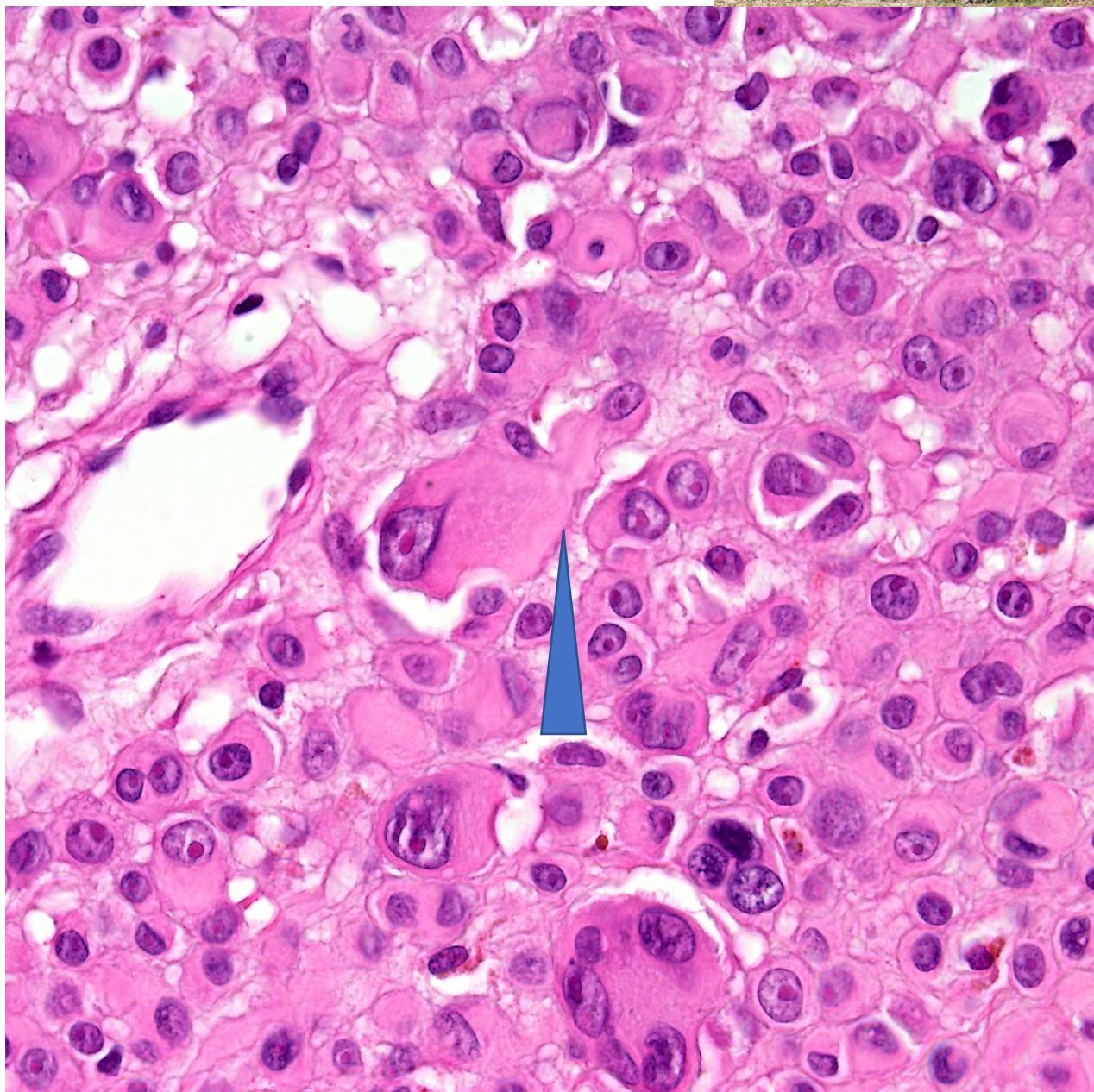




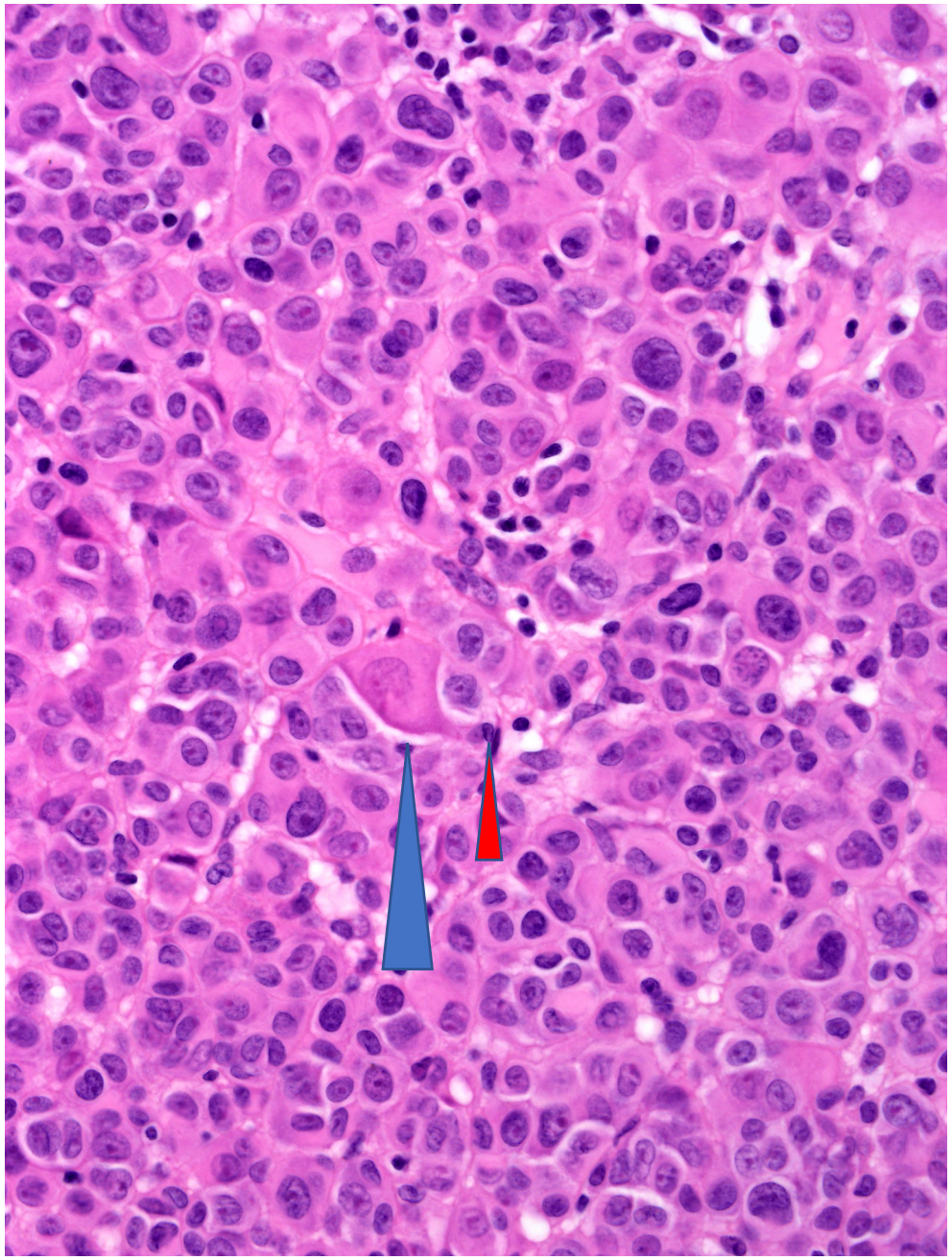


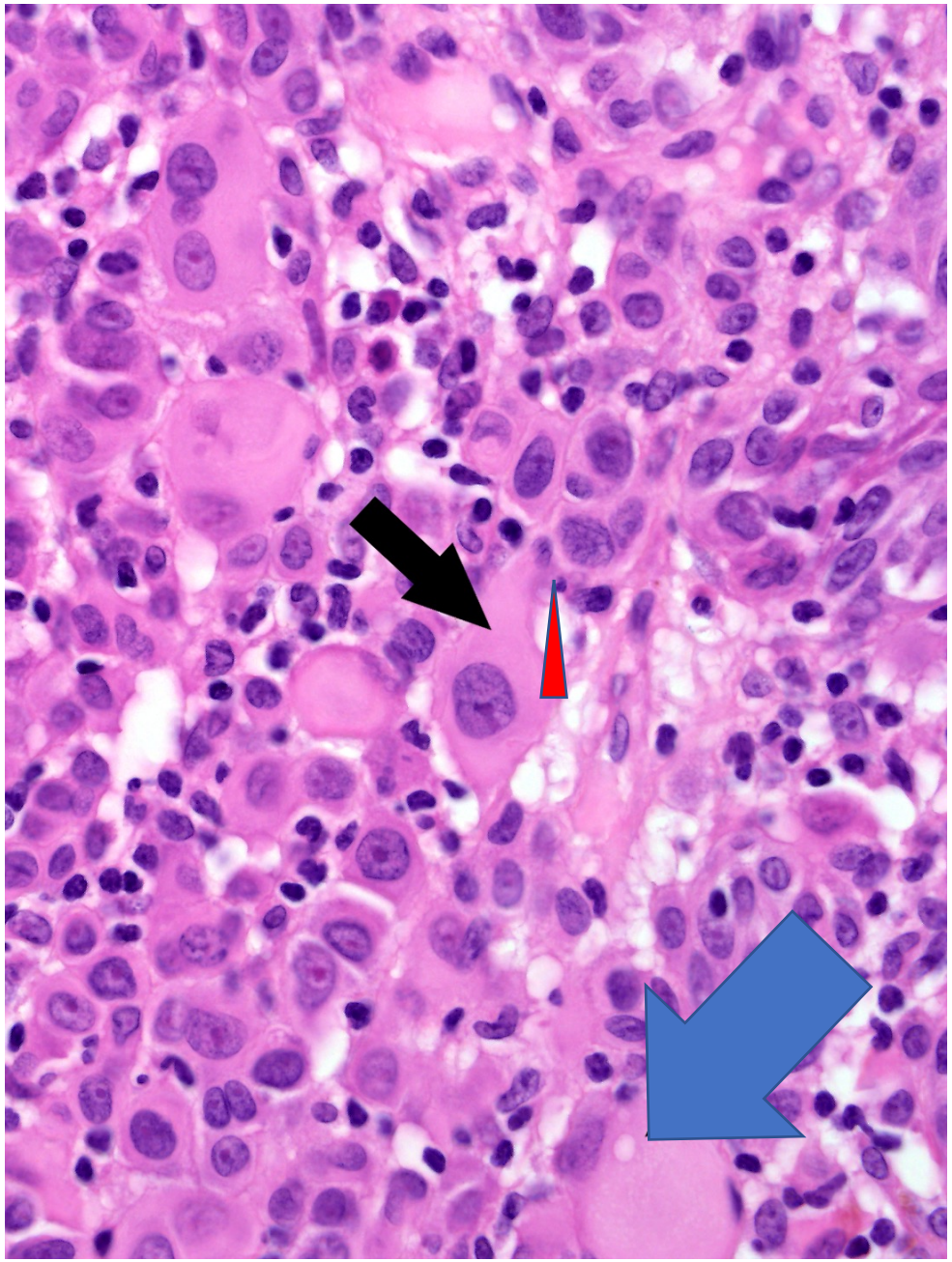
Large epithelioid melanocytes with cytoplasmic protrusions resembling proboscis (ant-bear cells).

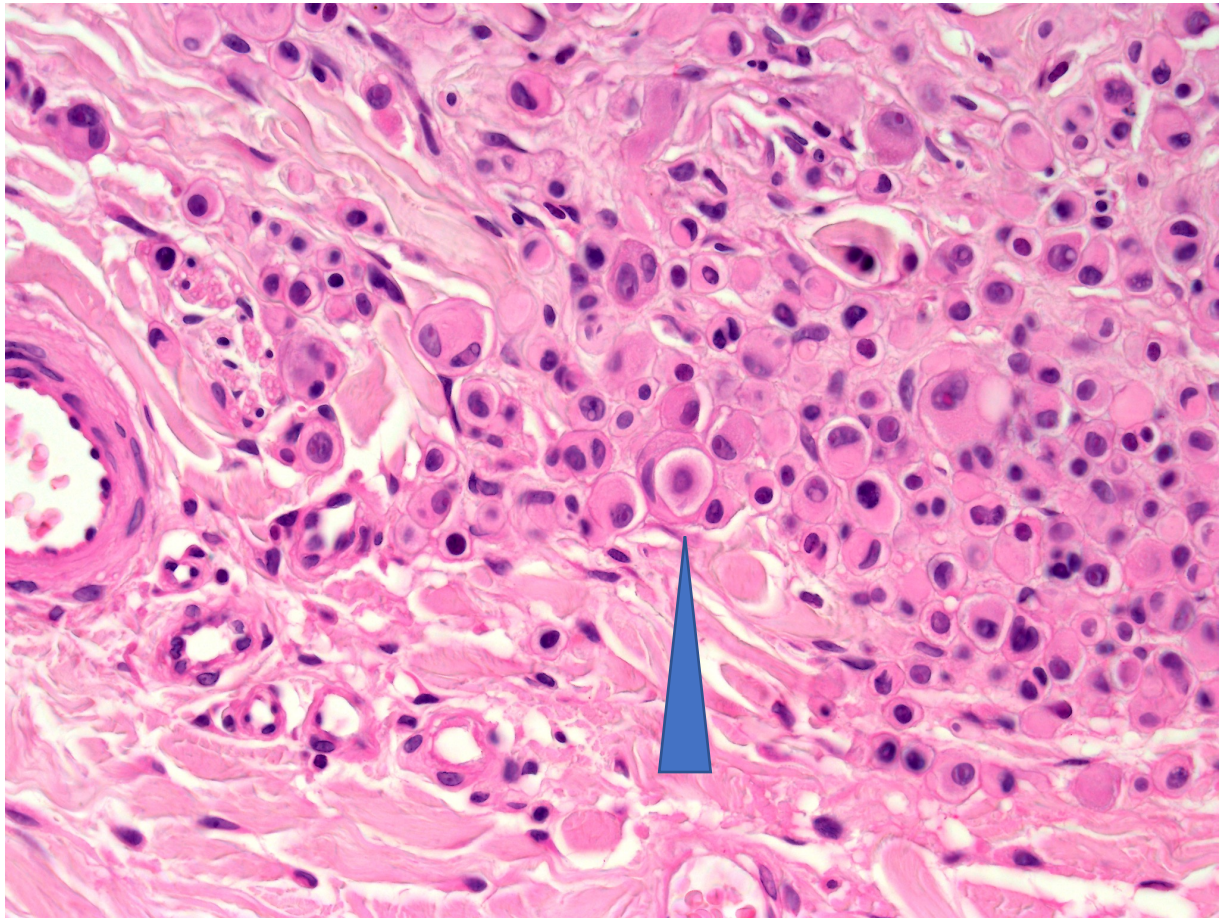


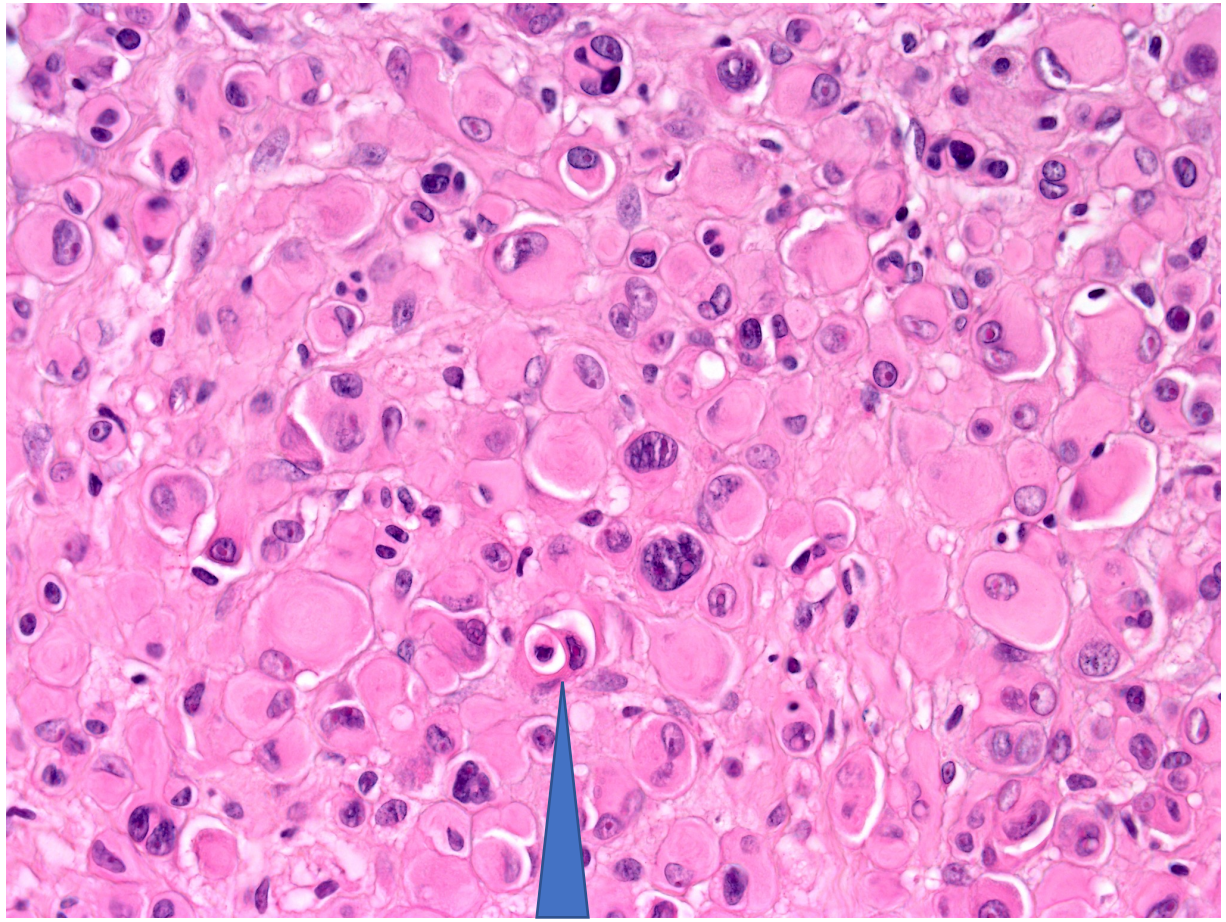


Ant-bear cells









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Melanocytic "ball-in-mitts" and "microalveolar structures" and their role in the development of cellular blue nevi

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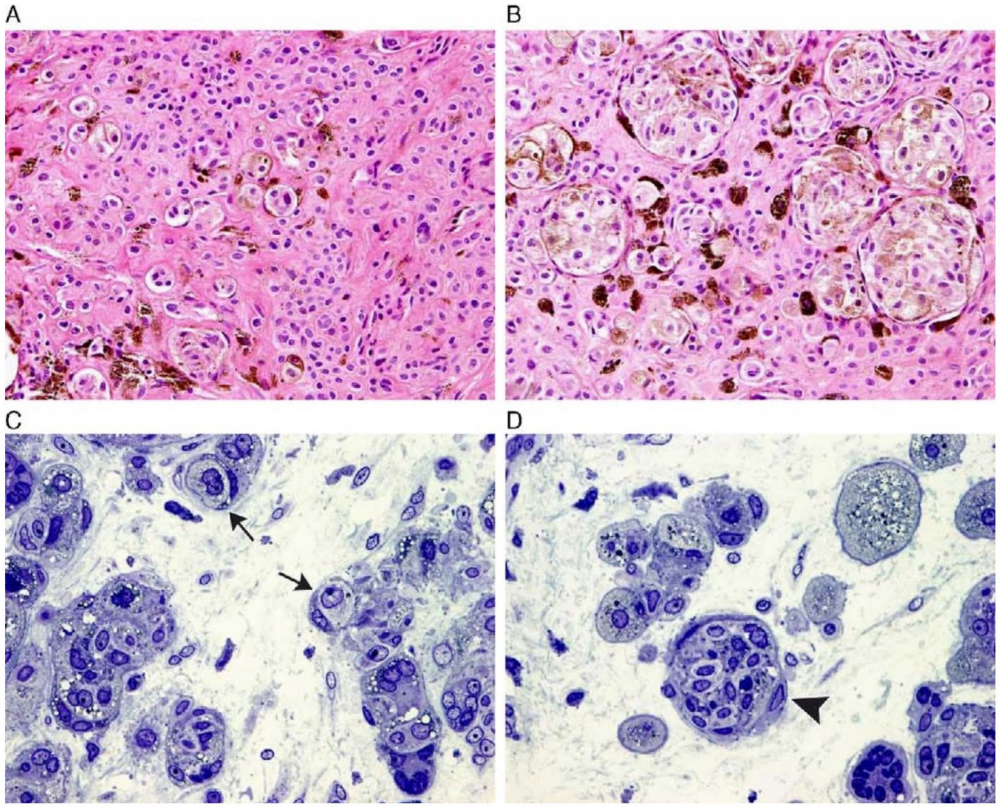

Fig. 1. Ball-in-mitt and microalveolar structures appearance on H&E-stained slides (A, B) and semithin sections (C, D). A *ball-in-mitt structure* is composed of a single centrally placed melanocyte with a round to oval nucleus (the ball cell) and a clear, dusty, or pigmented cytoplasm encircled by a single dendritic cell (the mitt cell) with an oval to spindle-shaped nucleus and slender bipolar processes containing melanin (arrow, C). A *microalveolar structure* is defined as a group of 2 to 10 centrally placed melanocytes with round to oval nuclei and clear, dusty, or pigmented cytoplasm (balls) surrounded by one or more cells (mitts) with spindle-shaped nuclei and slender bipolar processes containing melanin (arrowhead, D).

Intracytoplasmic vacuoles