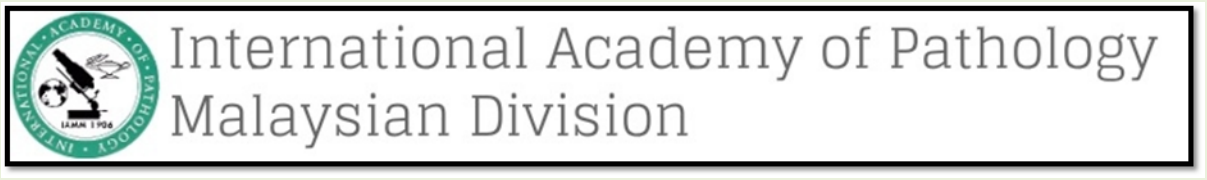


FINAL REPORT

QUALITY ASSURANCE PROGRAM
GENERAL DIAGNOSTIC HISTOPATHOLOGY
CYCLE 01/2019

NOTES FROM THE COORDINATOR

1. For this cycle 01/2019, a total of 22 institutions responded online by the closing date of 15 June 2019.

2. Excerpts of previously circulated information about this quality assurance program are reproduced here:
    - IAP-MD QAP provides a platform via the evaluation reports to compare and identify diagnostic insufficiency based on the outcomes of submitted diagnoses and targeted diagnoses.
    - In the evaluation reports of each cycle, the targeted diagnosis for each case is provided, followed by a tabulated list of diagnoses submitted by participating laboratories and followed by discussion and possible differential diagnoses on the case.
    - Evaluation of performance of each laboratory is conducted by participating laboratory by comparing own submitted diagnoses with the diagnoses provided in the evaluation reports. Evaluation of performance shall be the responsibility of each participating laboratory.

3. Any queries regarding this final report for cycle 01/2019 could be directed to Dr. Ch'ng Ewe Seng, e-mail: iapmdqap@gmail.com.

4. The coordinator would like to acknowledge the contributions from Prof. Dr. Nor Hayati Othman, Dato Dr. Norain Karim, Dr. Hakimah Mahsin, Datin Dr. Nik Raihan Nik Mustapha, Dr. Yusri Yusuf, Dr. Fazilah Hassan, Dr. Suhaila Abdullah and Dr. Nurul Akmar Misron.

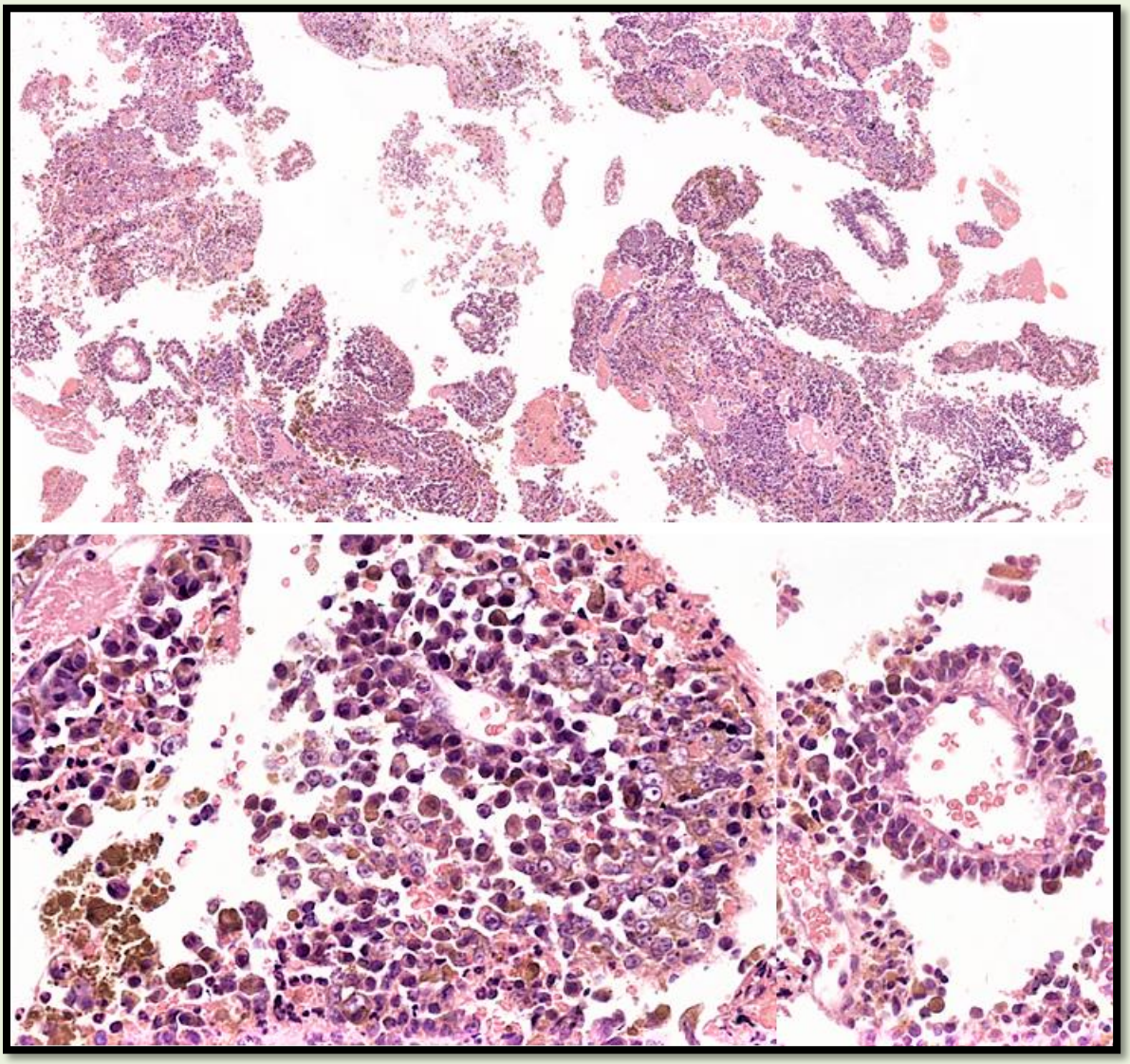
Prepared by,

Ch'ng Ewe Seng, MD, MPath, FIAC
Coordinator for IAP-MD QAP

Case 1

Case 1: 8-year-old male. Underlying diffuse cutaneous melanosis. Pontine enhancing mass. Brain tumor biopsy. One representative section.

Targeted Diagnosis: **Melanoma**



Case 1

Submitted Diagnoses by Participating Institutions	Number	
Melanoma/ Neurocutaneous melanosis with melanoma	12	Acceptable
Metastatic melanoma	3	Acceptable
Malignant Melanoma. Differential could be atypical neurocutaneous melanosis. Suggest Ki-67 stain to look for hot spot	1	Acceptable
Neoplasm with melanotic differentiation. Differential diagnosis: Malignant melanoma and melanocytoma	1	
Melanocytoma	2	
Intermediate grade melanocytic neoplasm	1	
Melanosis/ Neurocutaneous melanosis.	2	

Educational notes:

1. The biopsy shows fragments of discohesive, markedly pleomorphic malignant cells displaying vesicular nuclei with prominent nucleoli and cytoplasmic melanin. Necrosis and perivascular pseudorosettes are observed. These features are diagnostic of melanoma.
2. Leptomeningeal melanocytic tumors in WHO classification 2016 are classified as follows:

Diffuse tumor	Benign	Melanosis
	Malignant	Melanomatosis
Localized tumor	Benign	Melanocytoma
	Intermediate grade	Intermediate grade melanocytic neoplasm
	Malignant	Melanoma

3. Although the history provided was "diffuse cutaneous melanosis", this patient was likely to have large congenital melanocytic nevi. Patients with large cutaneous congenital nevi are at risks of development of neurocutaneous melanosis, a condition characterized by large cutaneous congenital nevi associated with benign proliferation of the melanocytes involving the leptomeninges (melanosis). These patients also have significant risks for subsequent development of cutaneous and leptomeningeal melanomas.
4. Localized central nervous system melanocytic tumors with bland cytology and low mitotic count (<1/10HPF) are classified as melanocytoma. Those tumors with tissue invasion and elevated mitotic count but cytologically bland are regarded as intermediate grade melanocytic neoplasms. Melanomas are anaplastic cytologically and they are associated with elevated mitotic count, tissue invasion or coagulative necrosis.

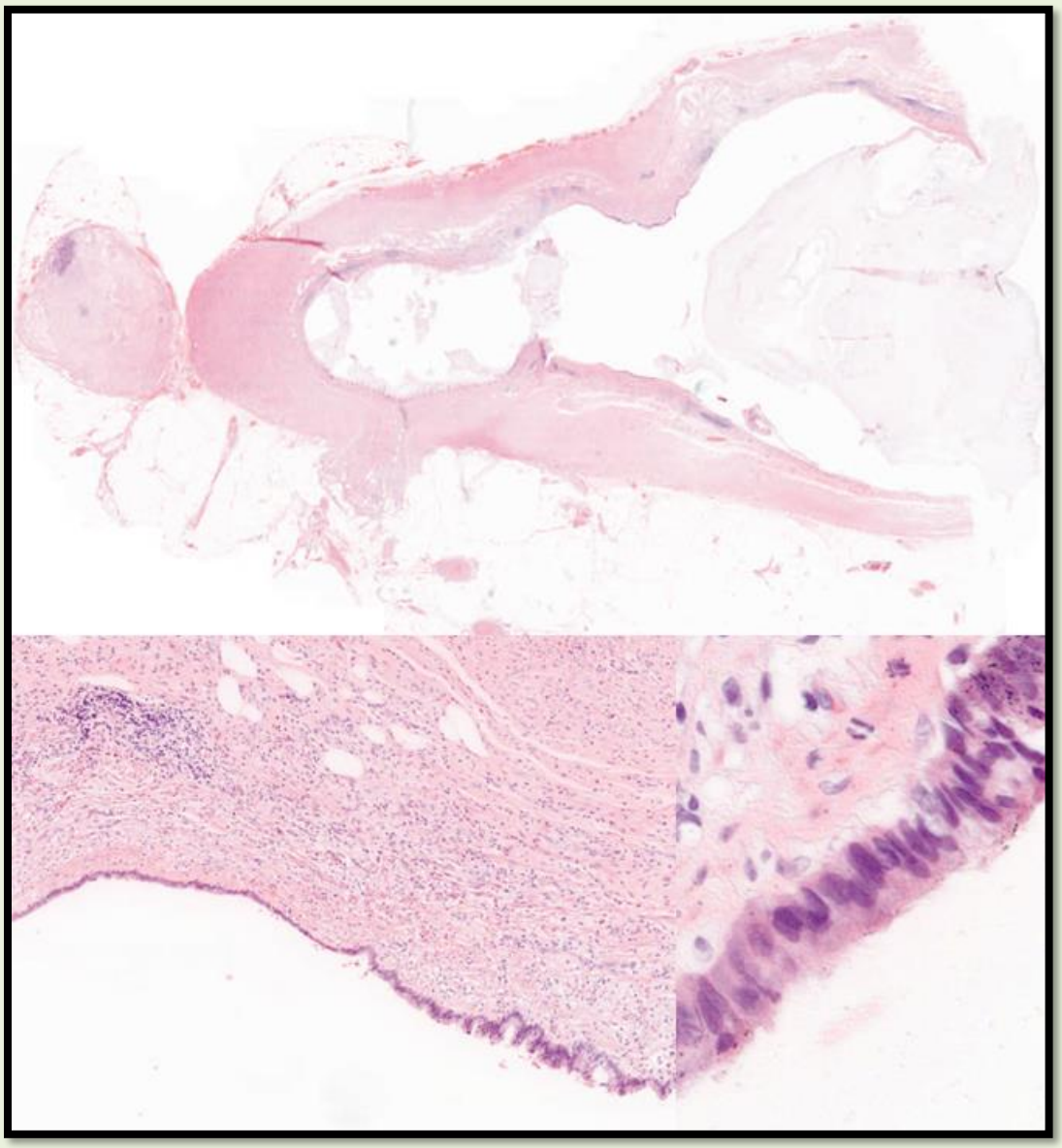
Reference:

1. WHO Classification of Tumours of the Central Nervous System, 4th Edition, revised, 2016

Case 2

Case 2: 70-year-old male. Right iliac fossa pain. Appendicectomy. One representative section.

Targeted Diagnosis: **Low grade appendiceal mucinous neoplasm**



Case 2

Submitted Diagnoses by Participating Institutions	Number	
Low grade appendiceal mucinous neoplasm	18	Acceptable
Low grade appendiceal mucinous neoplasm and eosinophilic appendicitis/ Low grade appendiceal mucinous neoplasm (LAMN) and fibrous obliterans/ Low grade appendiceal mucinous neoplasm with acute appendicitis	3	Acceptable
Mucinous adenoma	1	

Educational notes:

1. The appendix is dilated and filled with mucin. A layer of columnar epithelium is attached to the appendiceal fibrotic submucosa without intervening lamina propria and muscularis mucosae. This columnar epithelium shows low grade dysplasia with basally located pseudostratified enlarged nuclei and occasional pencillate nuclei. These features are diagnostic of low grade appendiceal mucinous neoplasm (LAMN).
2. Peritoneal Surface Oncology Group International (PSOGI) defines LAMN as mucinous neoplasm with low-grade cytology and any of the following: loss of the lamina propria and muscularis mucosae, fibrosis of the submucosa, "pushing" diverticulum-like growth into the wall, dissection of acellular mucin in the wall, or mucin and/or neoplastic cells outside of the appendix. LAMN that is confined within muscularis propria is staged as pTis(LAMN) and it carries no risk of recurrence. pT1 and pT2 do not apply to LAMN as LAMN usually lacks lamina propria and muscularis mucosae for evaluation, and invasion into muscularis propria by LAMN does not affect prognosis.
3. When acellular mucin or neoplastic mucinous epithelium extends into the subserosa or mesoappendix without involvement of the visceral peritoneal surface, it is staged as pT3 with unknown risk of recurrence. Acellular mucin involvement of peritoneal surface in pT4a carries 3% of risk whereas neoplastic epithelium involvement of peritoneal surface in pT4a carries 36% of risk of recurrence.
4. Peritoneal involvement by LAMN is termed as low-grade mucinous carcinoma peritonei. In contrast, the term "pseudomyxoma peritonei" is a clinical condition characterized by accumulation of gelatinous material in the abdominal and/or pelvic peritoneal cavity; it is not a histopathological diagnosis.

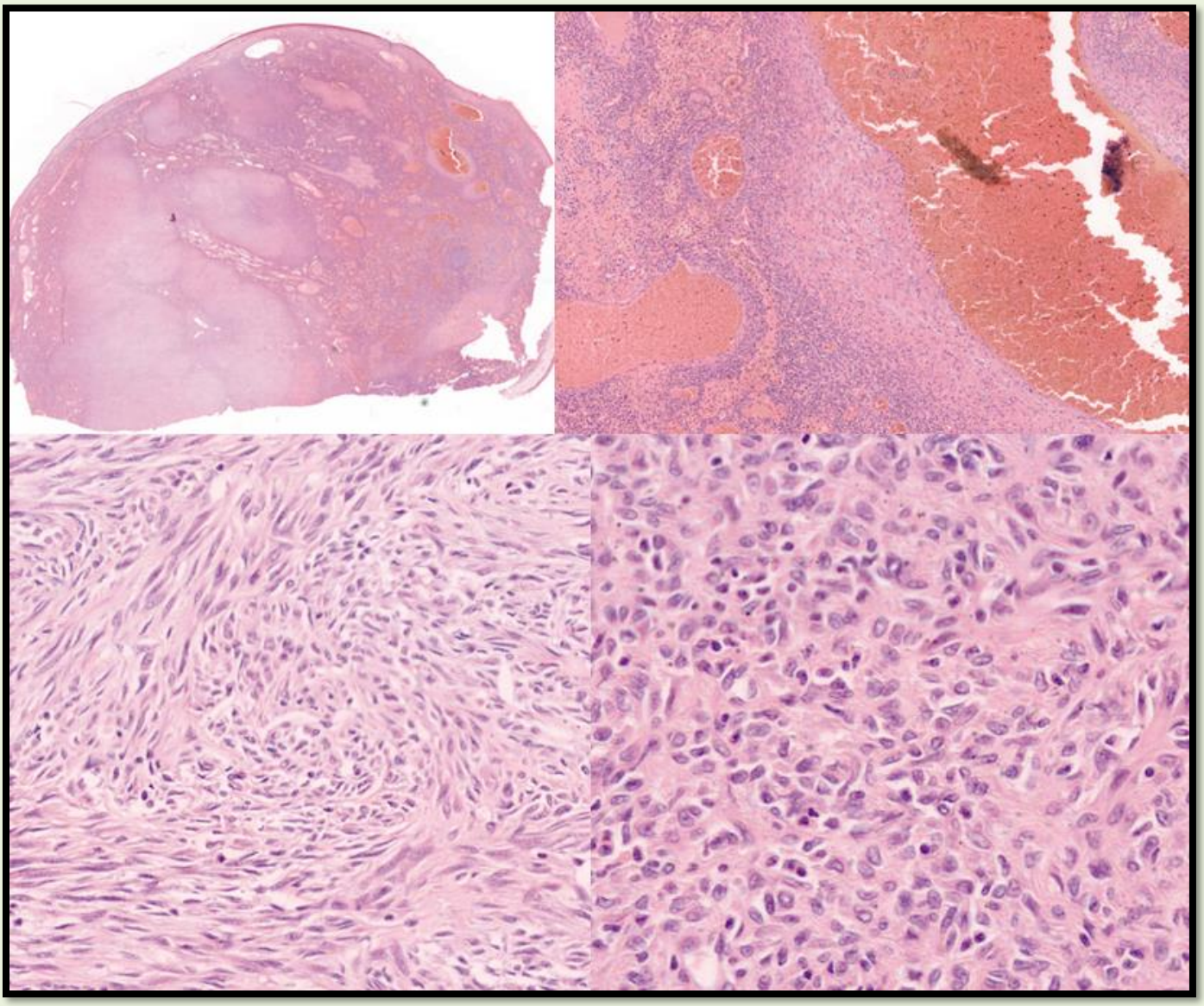
Reference

1. Valasek, M. A., & Pai, R. K. (2018). An update on the diagnosis, grading, and staging of appendiceal mucinous neoplasms. Advances in anatomic pathology, 25(1), 38-60.

Case 3

Case 3: 20-year-old male. Right proximal arm, 30mm-swelling. One representative section.

Targeted Diagnosis: **Aneurysmal fibrous histiocytoma with a differential diagnosis of angiomatoid fibrous histiocytoma**



Case 3

Submitted Diagnoses by Participating Institutions	Number	
Aneurysmal benign fibrous histiocytoma/ Benign fibrous histiocytoma/ Dermatofibroma, cellular / aneurysmal variant/ Angiomatoid dermatofibroma	11	Acceptable
Angiomatoid fibrous histiocytoma	4	Acceptable
Benign to intermediate spindle cell tumor (myofibroma, aneurysmal benign fibrohistiocytoma, solitary fibrous tumor, leiomyoma; to rule out Kaposi sarcoma and melanocytic tumour) / Differentials: synovial sarcoma, angiomatoid fibrohistiocytoma/ Differentials: dermatofibroma, spindle cell hemangioendothelioma, myopericytoma/ Differentials : solitary fibrous tumor, dermatofibrosarcoma protuberance, aneurysmal fibrous histiocytoma. for IHC: STAT6, CD34, factor XIIIa, NKIC3.	4	Acceptable
Spindle cell hemangioma	1	
Low grade spindle cells tumour with vascular formation	1	
Angioleiomyoma	1	

Educational notes:

1. The polypoid mass shows spindled and epithelioid cells in the dermis. At larger vague nodular areas, they are arranged in short fascicles with storiform pattern. Blood filled pseudoangiomatous cystic spaces are scattered. There are collections of hemosiderin-laden histiocytes. Lymphocytic infiltrates are minimal. There is a thin Grenz zone with focal extension of the tumor cells into the papillary dermis. Thinning of the overlying epidermis is noted. The tumor cells are focally positive for CD68, EMA and SMA. They are negative for S100, desmin and CD34. This fibrohistiocytic tumor in the dermis is compatible with aneurysmal fibrous histiocytoma (FH).
2. Differential diagnoses for this tumor include aneurysmal FH and angiomatoid FH. Aneurysmal FH is usually a dermal-based tumor showing peripheral collagen fiber entrapment. In contrast, angiomatoid FH is usually located in the subcutis with a thick fibrous pseudocapsule accompanied by dense lymphoplasmacytic infiltrate or cuff, which are lacking in this case. Of note, there is no specific immunoprofile for angiomatoid FH although 50% of them co-express EMA and desmin. Ideally, a definite exclusion of angiomatoid FH requires molecular cytogenetic study to demonstrate absence of specific translocations in angiomatoid FH (EWSR1-CREB1, EWSR1-ATF1 or FUS-ATF1 fusion genes). Clinical follow up in either situation is recommended as both have risk of local recurrence. In addition, angiomatoid FH has smaller risk of distant metastasis.

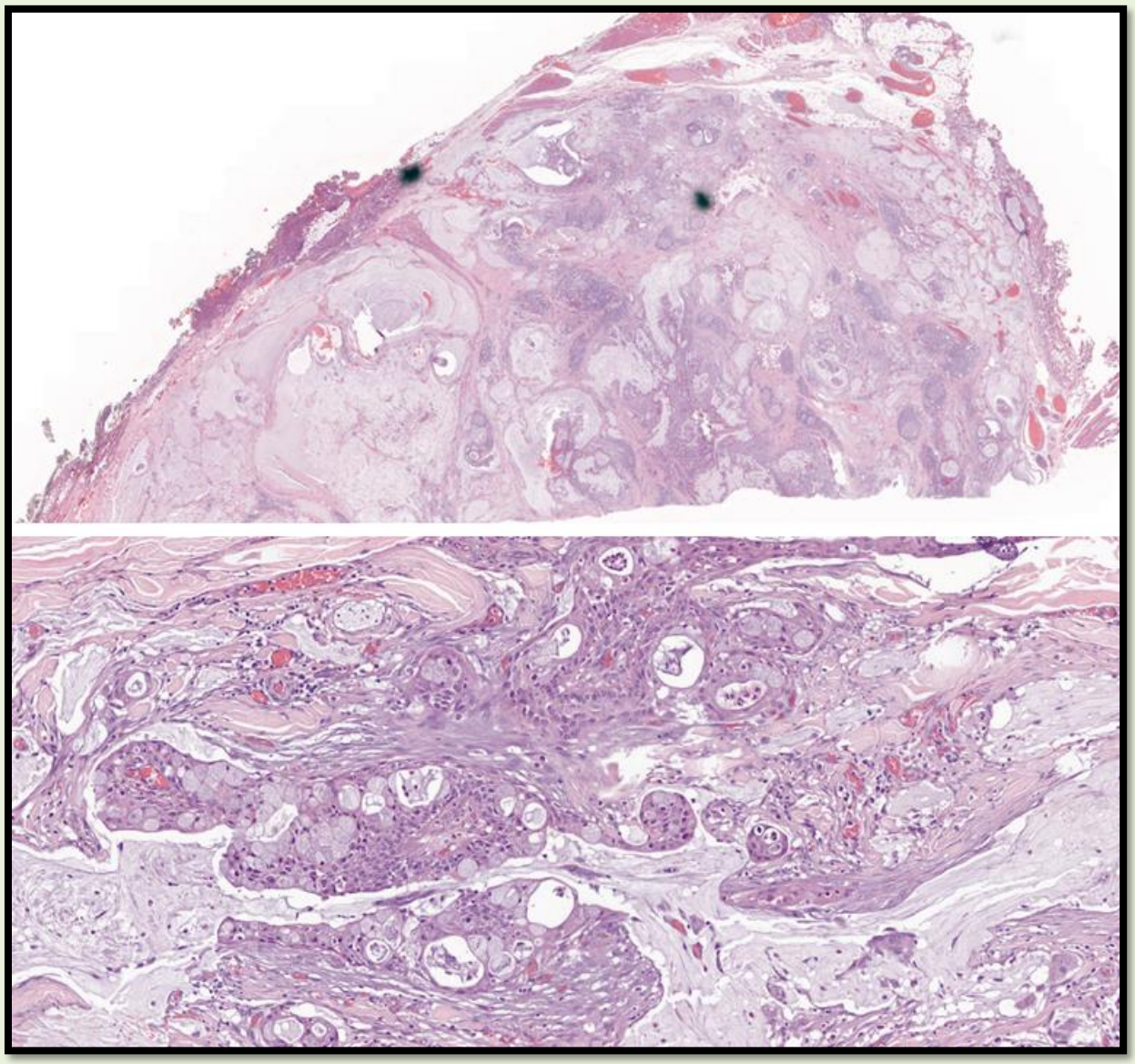
Reference

1. Thway, K., & Fisher, C. (2015). Angiomatoid fibrous histiocytoma: the current status of pathology and genetics. Archives of Pathology and Laboratory Medicine, 139(5), 674-682. El-Naggar, A. K. (Ed.). (2017). WHO Classification of Head and Neck Toumours. International Agency for Research on Cancer.

Case 4

Case 4: 32-year-old male. Parotid swelling. One representative section.

Targeted Diagnosis: **Mucoepidermoid carcinoma, low grade**



Case 4

Submitted Diagnoses by Participating Institutions	Number	
Mucoepidermoid carcinoma, low grade	15	Acceptable
Mucoepidermoid carcinoma	5	
Mucoepidermoid carcinoma. Differential includes primary mucinous adenocarcinoma of salivary gland.	1	
Mucoepidermoid tumor	1	

Educational notes:

1. Section shows a well-circumscribed tumor displaying multiple mucin-containing cystic spaces. There are areas harboring epithelial lining cells composed of mainly mucus-secreting cells mixed with intermediate cells and squamoid cells. These histological features are those of low grade mucoepidermoid carcinoma.
2. Mucoepidermoid carcinoma is the most common malignant salivary gland tumor in children and young adults. It is most common located at parotid gland followed by palate and submandibular gland. Histologically, mucoepidermoid carcinoma is characterized by a mixture of mucus-secreting cells, intermediate cells and squamoid cells showing solid and cystic growth pattern.
3. Although several grading systems are applied for mucoepidermoid carcinoma, current WHO classification does not endorse a specific grading system. Grading is however important for management as low grade mucoepidermoid carcinoma is usually followed up after complete surgical resection. For intermediate and high grade mucoepidermoid carcinoma, post-resection radiotherapy is considered.
4. Histological features of high grade carcinoma in AFIP system are: less than 20% cystic component, nuclear anaplasia, increase in mitosis (>=4/10HPF), perineural invasion and necrosis.

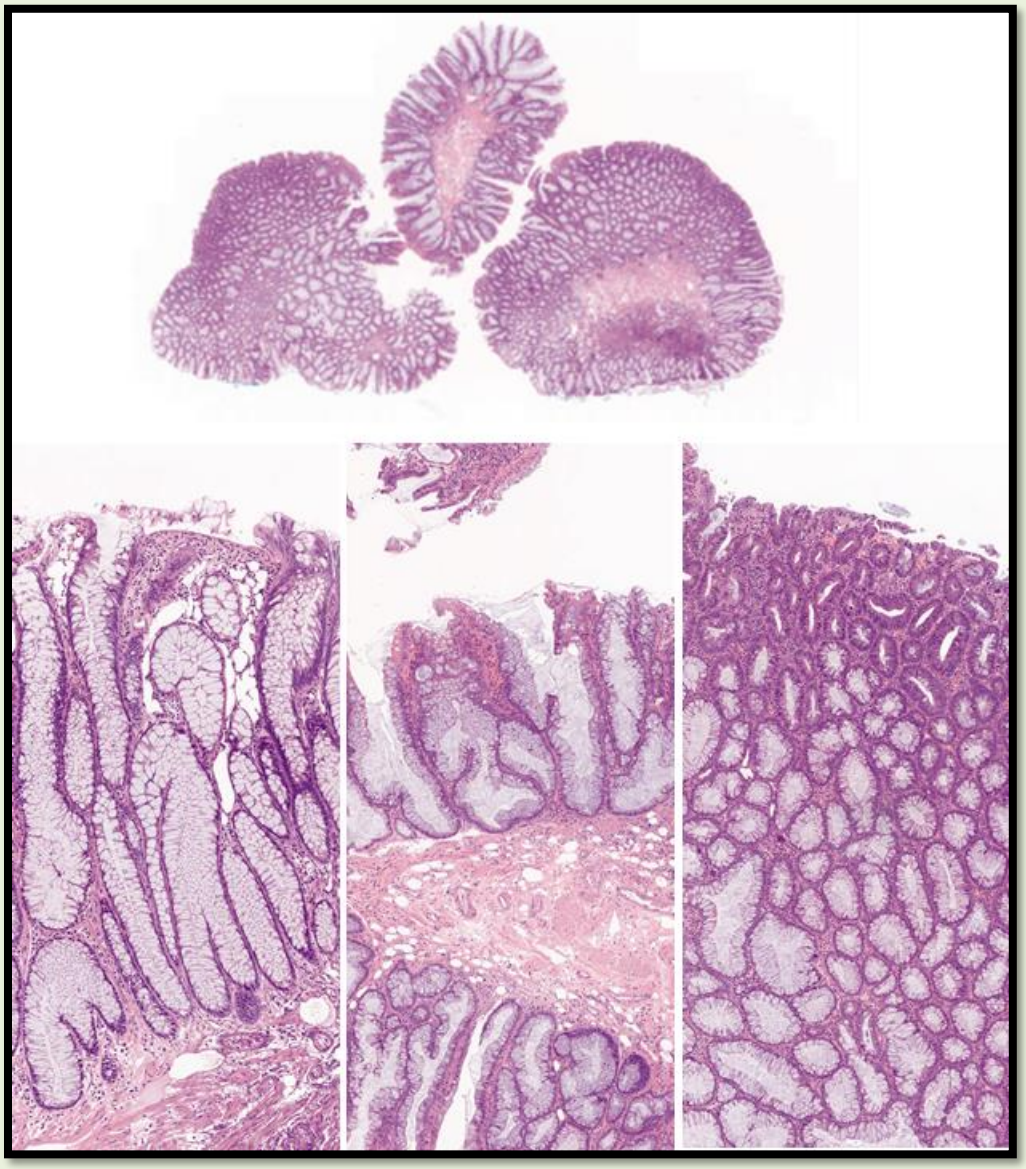
Reference

1. Goode, R. K., Auclair, P. L., & Ellis, G. L. (1998). Mucoepidermoid carcinoma of the major salivary glands: clinical and histopathologic analysis of 234 cases with evaluation of grading criteria. Cancer: Interdisciplinary International Journal of the American Cancer Society, 82(7), 1217-1224.
2. El-Naggar, A. K. (Ed.). (2017). WHO Classification of Head and Neck Toumours. International Agency for Research on Cancer.

Case 5

Case 5: 63-year-old male. iFOBT positive. Colonoscopy: 3 rectal polyps up to 14mm in size. One representative section.

Targeted Diagnosis: **Sessile serrated polyp/adenoma with dysplasia**



Case 5

Submitted Diagnoses by Participating Institutions	Number	
Sessile serrated adenoma/polyp with low grade dysplasia/ Sessile serrated adenoma/polyp with dysplasia/ Serrated adenoma, low-grade dysplasia/ Sessile serrated lesion with adjacent low grade dysplasia	11	Acceptable
Tubular adenoma with low grade dysplasia and sessile serrated polyp/ Sessile serrated adenoma with tubular adenoma, low grade/ Tubular adenoma with focal high grade dysplasia and sessile serrated adenoma / polyp	5	
Tubular adenoma with serrated features, low grade/ Adenomatous polyp, low grade dysplasia/ Mixed hyperplastic adenomatous polyp/ Tubulovillous adenoma	5	
Traditional serrated adenoma	1	

Educational notes:

1. There are three colonic polyps composed of closely packed elongated glands with obvious crypt abnormalities such as irregularly shaped crypts and crypt dilation. Focal serration is observed on the surface. In addition, two of the colonic polyps show adenomatous dysplasia of the glands on the upper part of the polyps.
2. Serrated colorectal polyps are generally classified into hyperplastic polyp (HP), sessile serrated polyp/ adenoma (SSA/P), SSA/P with dysplasia, and traditional serrated adenoma (TSA). HP and SSA/P do not manifest conventional adenomatous dysplasia. SSA/P is distinguished from hyperplastic polyp by the distorted crypts usually near the base involving at least 2 or 3 contiguous crypts. If cytological dysplasia is recognized in SSA/P in addition to crypt abnormalities, the polyp is termed as SSA/P with dysplasia. Currently two types of dysplasia are recognized in SSA/P with dysplasia: the adenomatous dysplasia and the serrated dysplasia. TSA is characterized by a complex villiform architecture lined by dysplastic cells showing tall columnar shape with pencillate nuclei and eosinophilic cytoplasm. The morphology differs from the conventional adenomatous dysplasia. Another defining feature of traditional serrated adenoma is presence of ectopic crypts that are detached from the muscularis mucosae.
3. SSA/P and SSA/P with dysplasia are polyps usually carrying BRAF gene activating mutation; they are considered more immediate precursors to BRAF-serrated pathway colorectal carcinoma. Regardless of polyp size and degree of dysplasia, SSA/P with dysplasia is regarded as advanced polyp carrying clinical significance similar to conventional adenomas with high grade dysplasia.

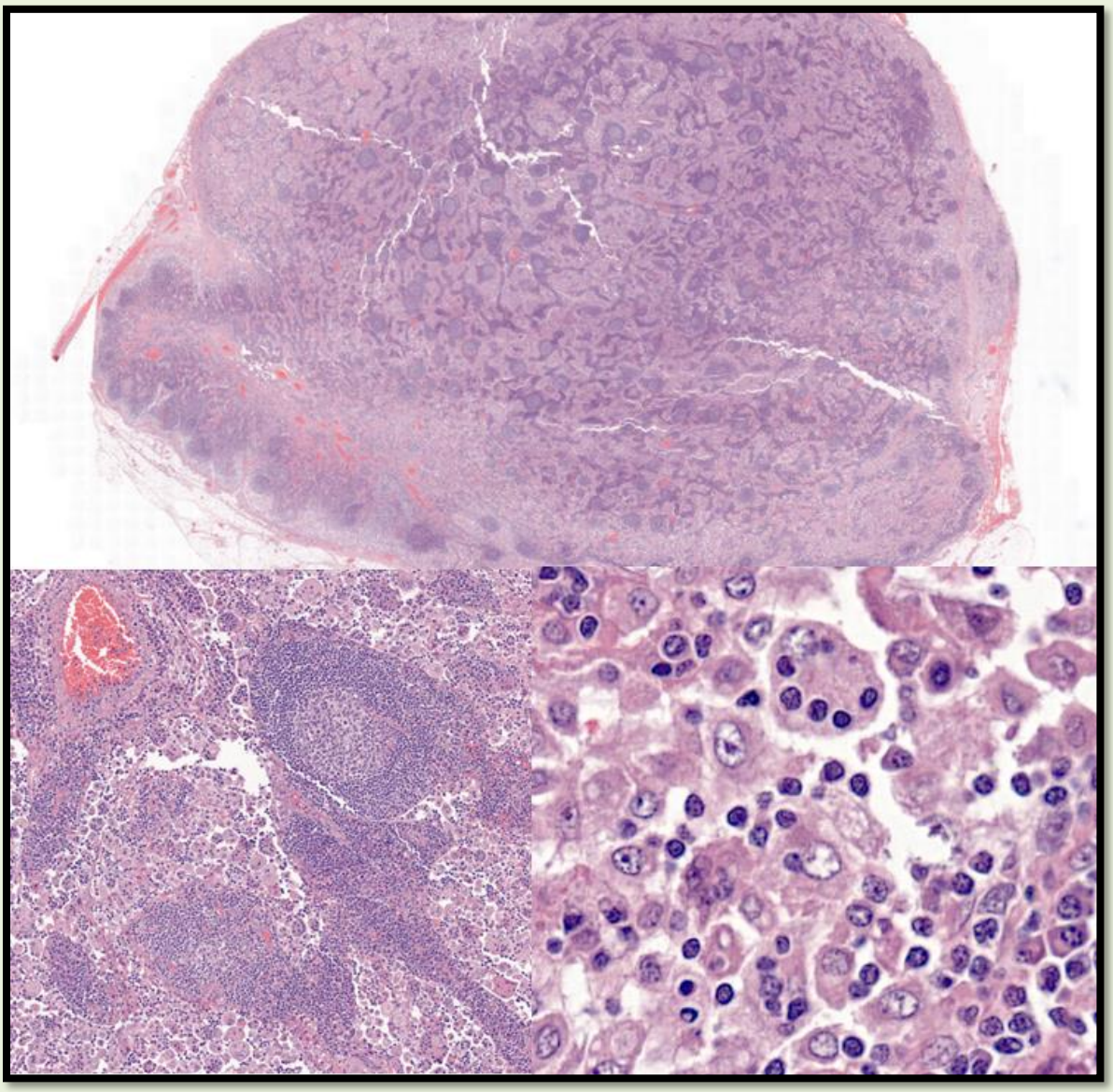
Reference

1. Bosman, F. T., Carneiro, F., Hruban, R. H., & Theise, N. D. (2010). WHO classification of tumours of the digestive system (No. Ed. 4). World Health Organization.

Case 6

Case 6: 9.y.o. male. Right cervical lymph node. One representative section.

Targeted Diagnosis: **Rosai–Dorfman disease**



Case 6

Submitted Diagnoses by Participating Institutions	Number	
Rosai-Dorfman disease/ Sinus histiocytosis with massive lymphadenopathy	22	Acceptable

Educational notes:

1. The lymph node is effaced with prominent expansion of the sinuses. The sinuses are filled with histiocytes displaying foamy cytoplasm and vesicular nuclei with prominent nucleoli. Emperipolesis is evident with lymphocytes passing through the cytoplasm of the histiocytes. Many plasma cells and reactive germinal centers are noted. These features are diagnostic of Rosai- Dorfman disease.
2. Histiocytes are disorders characterized by accumulation of cells derived from dendritic cells or macrophages and currently categorized into 5 different groups. Rosai-Dorfman disease (RDD) belongs to the "R" group.
3. Classic sporadic RDD involves lymph nodes but extranodal involvement of skin, nasal cavity, bone and soft tissue is documented in about 40% of the cases. RDD occurs frequently in children and young adults and is often self-limiting with a good prognosis. Nonetheless, 5 to 11% of patients may die of the disease.
4. Histologically, RDD is characterized by accumulation of large histiocytes with abundant emperipolesis. These histiocytes are positive for S100 protein, CD68 and CD163 but negative for CD1a and CD207, which differentiates RDD from CD1a-positive Langerhans cell histiocytosis.

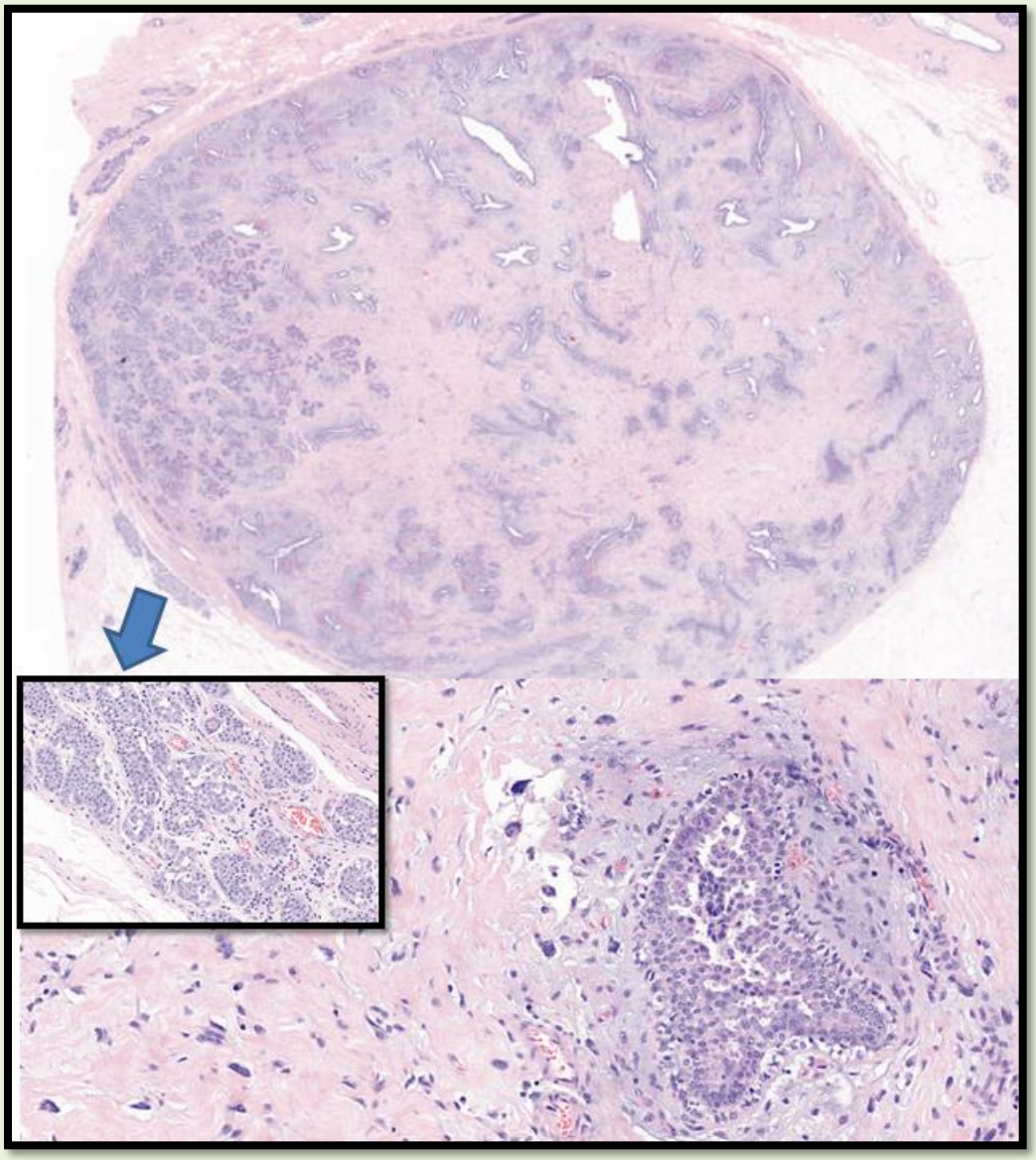
Reference:

1. Emile, Jean-François, et al. "Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages." Blood 127.22 (2016): 2672-2681.

Case 7

Case 7: 44-year-old female. Right breast lump. One representative section.

Targeted Diagnosis: **Fibroadenoma with bizarre stromal giant cells and lobular neoplasia(LCIS)**



Case 7

Submitted Diagnoses by Participating Institutions	Number	
Fibroadenoma with multinucleated stromal giant cells/ Fibroadenoma with pleomorphic stromal giant cells/ Fibroadenoma with bizarre stromal giant cells/ Fibroadenoma with atypical stromal giant cells/ Fibroadenoma	20	
Fibroadenoma with pseudoangiomatous stroma.	1	
Pseudoangiomatous stromal hyperplasia with nuclear atypia and columnar cell changes. Need to exclude low grade angiosarcoma and phyloides tumour	1	

Educational notes:

1. Section shows a well-circumscribed fibroadenoma composed of scattered mammary ducts and the surrounding fibrotic stroma. There are occasional bizarre stromal giant cells; some of them are multinucleated. There are two foci of mammary acini distended by a monotonous population of rather discohesive cells in the adjacent tissue, consistent with lobular neoplasia (lobular carcinoma in situ). E-cadherin immunostaining is negative at these foci.
2. Multinucleated giant stromal cells with bizarre nuclei can be observed in the interlobular stroma of the breast as well as within the stroma of the fibroadenoma and phyllodes tumor. Their significance is unknown but should not be regarded as a mark of malignancy.
3. Lobular neoplasia (atypical lobular hyperplasia and lobular carcinoma in situ (LCIS) depending the extent of acini involvement) is usually an incidental finding in breast biopsies performed for another abnormality. Differentiating LCIS from ductal carcinoma in situ sometimes poses difficulties based on morphology alone. This however could be resolved by demonstrating loss of E-cadherin in LCIS. LCIS is now considered a proliferative lesion associated with risk for future development of breast cancer. It is no longer staged as pTis(LCIS) in AJCC TNM staging system 8th edition.

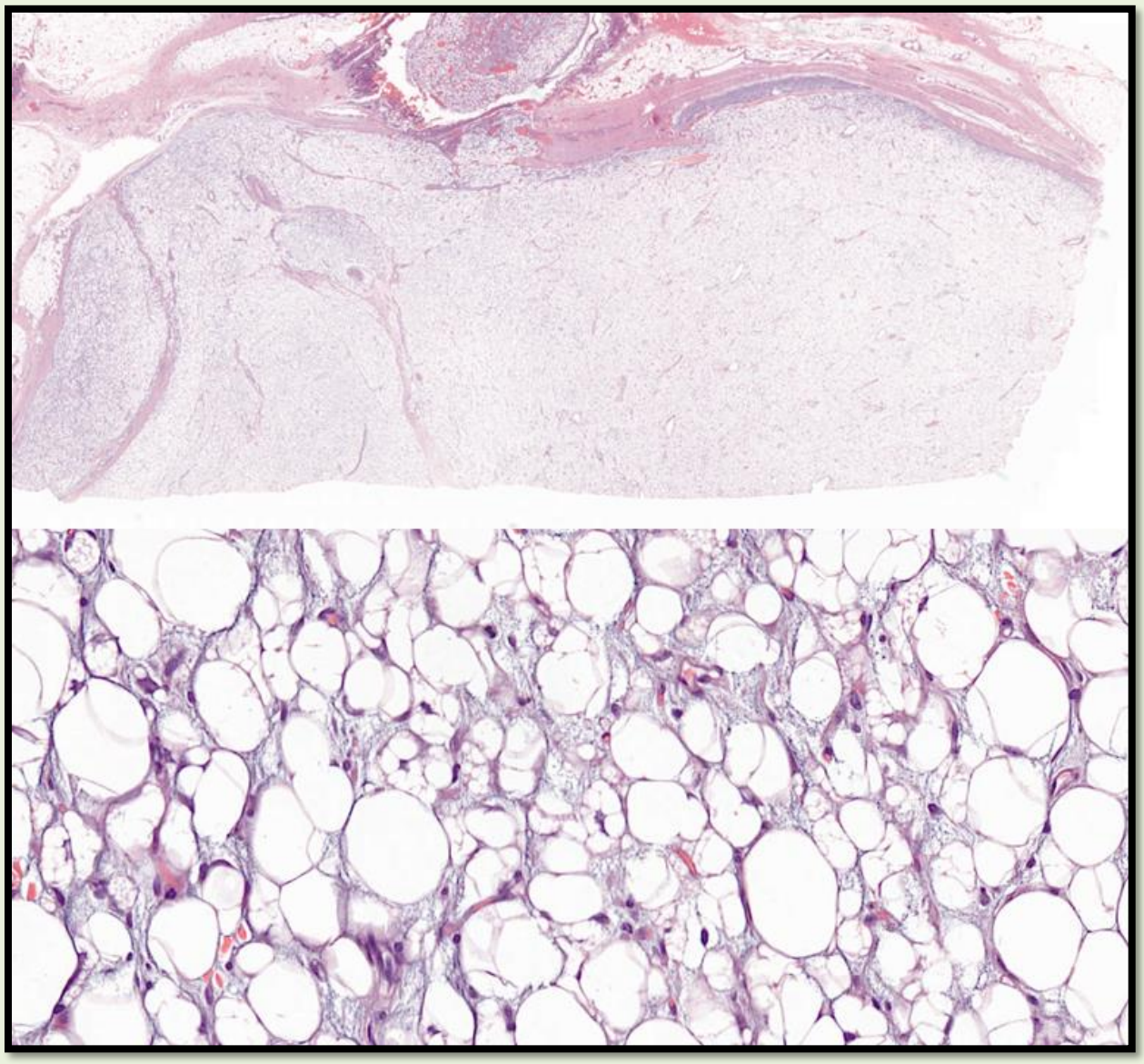
Reference

1. Biopsy interpretation of the breast. 3rd edition.
2. AJCC Cancer Staging Manual. 8th edition

Case 8

Case 8: 1-year-old male. Gluteal swelling since the age of 6 months. One representative section.

Targeted Diagnosis: **Lipoblastoma**



Case 8

Submitted Diagnoses by Participating Institutions	Number	
Lipoblastoma	21	Acceptable
Liposarcoma. Differential could be myxoid liposarcoma or pleomorphic liposarcoma. Extensive arborizing blood vessel is not feature of atypical lipomatous tumour. Suggest MDM2 study	1	

Educational notes:

1. Section shows a well-circumscribed lipomatous tumor surrounded a fibrous capsule. There are thin fibrous septa within this tumor. This lipomatous tumor shows a mixture of mature adipocytes, multi-vacuolated lipoblasts and scattered immature spindle cells. Myxoid stromal change is focally noted. The blood vessel network is not prominent. These histological features are consistent with a lipoblastoma.
2. Lipoblastoma is a benign adipocytic tumor of infancy whereby 90% occur at the age of less than 3 years. Histologically, lipoblastoma is composed of a mixture of preadipocytes (immature spindle cells), lipoblasts and mature adipocytes arranged in lobules separated by fibrovascular septa.
3. Myxoid stromal change associated with plexiform vascular network rarely occurs in lipoblastoma, mimicking myxoid liposarcoma. However, myxoid liposarcoma rarely occurs in less than 10 years old and lacks the lobular architecture of lipoblastoma. In difficult cases, distinction between these two depends on fluorescence in situ hybridization (FISH) demonstration of DDIT3 gene rearrangement in myxoid liposarcoma but not in lipoblastoma.
4. Lipoblastomatosis, in contrast to lipoblastoma, shows diffuse proliferation with infiltrative growth pattern.

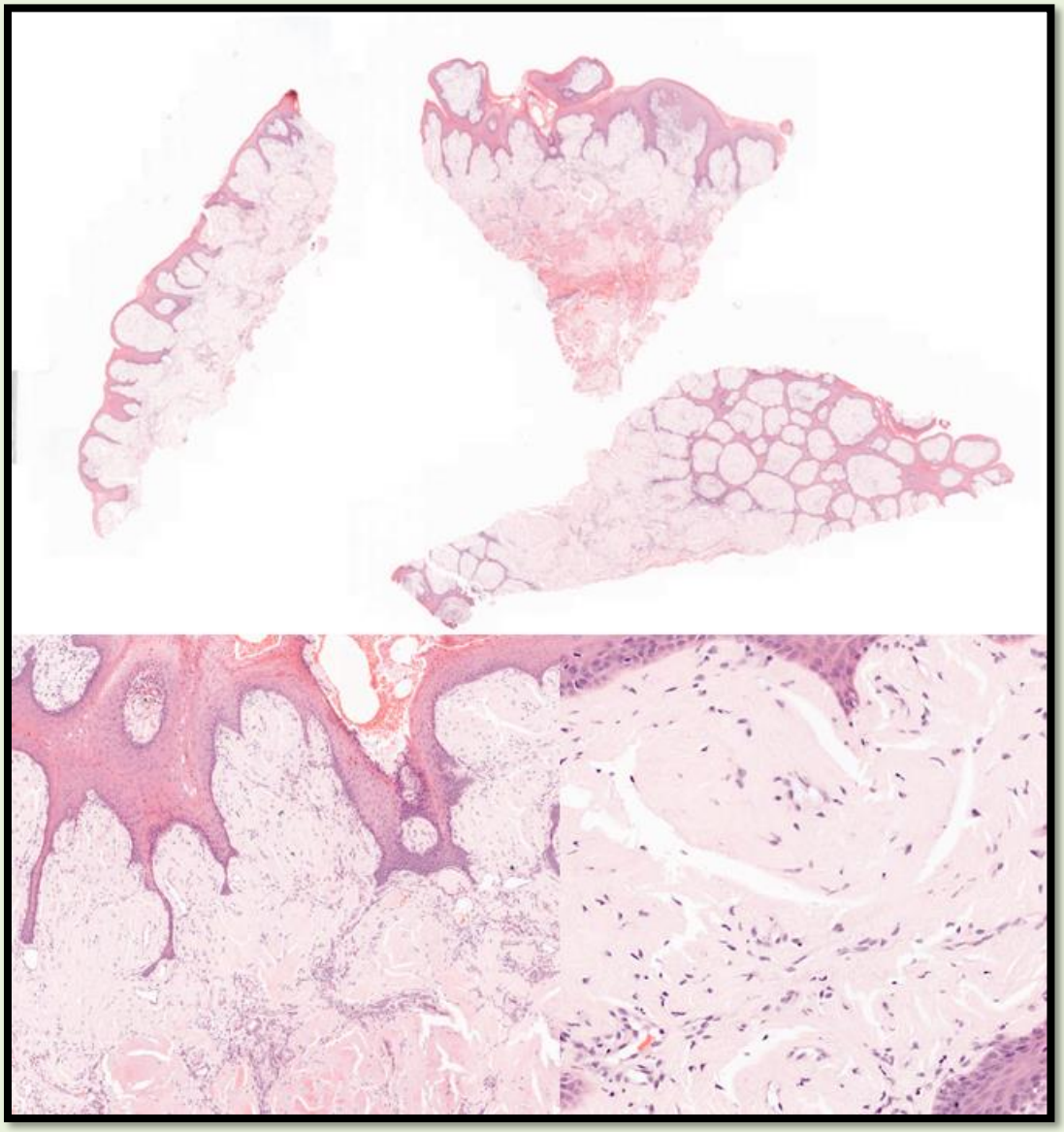
Reference

1. Christopher D.M. Fletcher, Julia A. Bridge, Pancras C.W. Hogendoorn, Fredrik Mertens (Eds.): WHO Classification of Tumours of Soft Tissue and Bone. IARC: Lyon 2013
2. Practical Soft Tissue Pathology: A Diagnostic Approach, 2nd Edition

Case 9

Case 9: 52-year-old female. Right tongue mass. One representative section.

Targeted Diagnosis: **Amyloidosis of the tongue**



Case 9

Submitted Diagnoses by Participating Institutions	Number	
Amyloidosis of the tongue/ Amyloid deposition/ Amyloidosis - need Congo red special stain to confirm.	20	Acceptable
Benign fibrocollagenous lesion; differentials are amyloidosis or submucosal fibrosis.	1	Acceptable
Benign tongue lesion. 1)Lymphangioendothelioma 2) Lymphangioma	1	

Educational notes:

1. The biopsy shows fragments of tongue mucosa. There are abundant amorphous eosinophilic materials deposited extracellularly in the submucosa, highly suggestive of amyloid. Congo red staining confirms the finding.
2. Amyloid is a pathological extracellular deposited proteinaceous material formed predominantly by amyloid fibrils. The amyloid fibrils are rigid, non-branching fibrils about 10nm in diameter; they bind the dye Congo red and exhibit apple-green birefringence under polarized light. They show a characteristic cross beta diffraction pattern by X-ray diffraction. To date, there are 36 different proteins that are accepted as major amyloid-fibril proteins.
3. Amyloidosis of the tongue may be localized or secondary to systemic disease. Large amount of deposits may result in macroglossia or a localized tumor. Diagnosis of amyloidosis of the tongue should trigger further workup for systemic causes of amyloid deposition, especially multiple myeloma as the underlying cause.

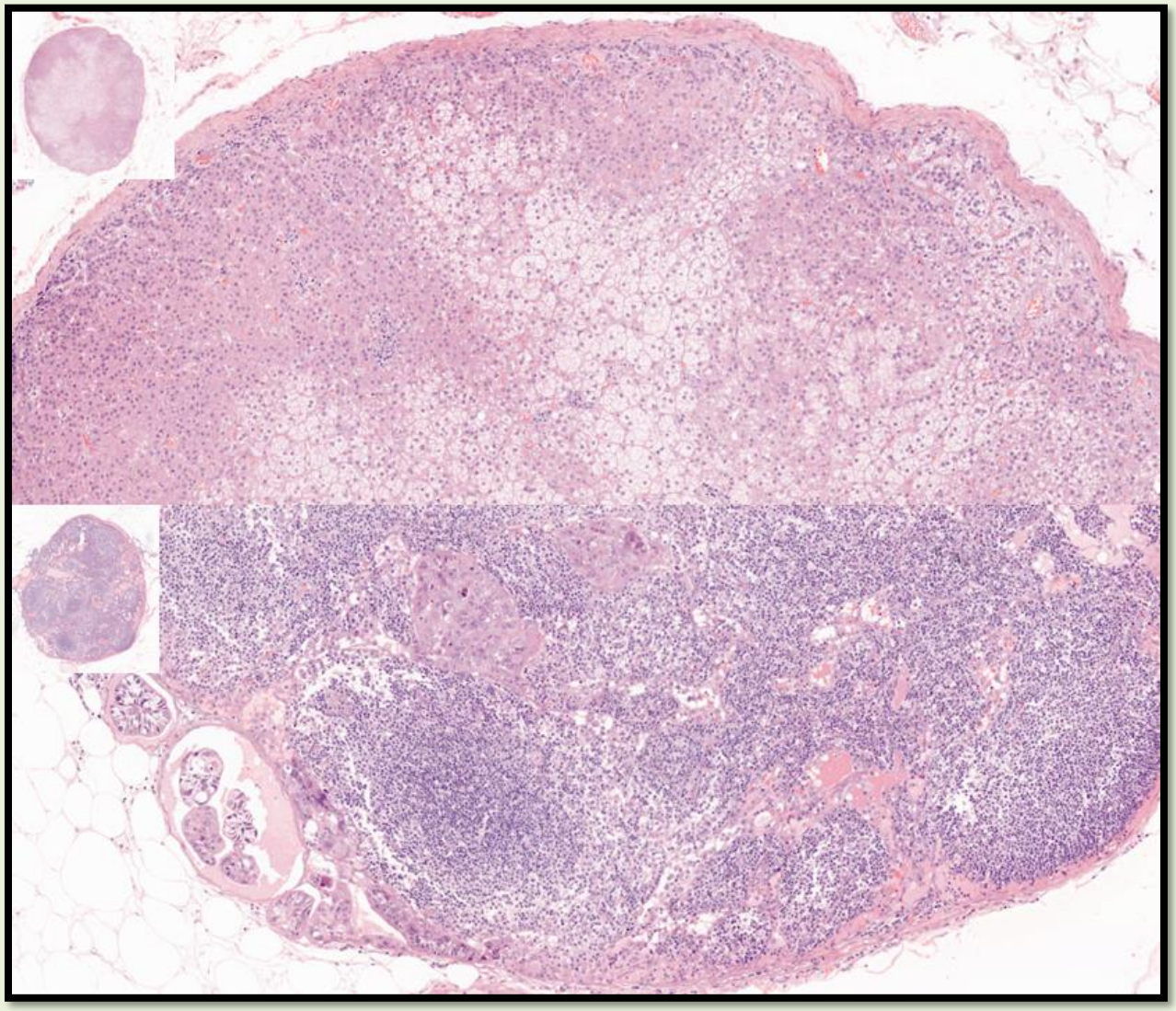
Reference

1. Rosai and Ackerman's Surgical Pathology, 11th edition
2. Sipe, Jean D., et al. "Amyloid fibril proteins and amyloidosis: chemical identification and clinical classification International Society of Amyloidosis 2016 Nomenclature Guidelines." Amyloid 23.4 (2016): 209-213.

Case 10

Case 10: 65-year-old female. female. Pericolic lymph nodes in colectomy specimen for rectosigmoid tumor. One representative section.

Targeted Diagnosis: **Metastatic adenocarcinoma and heterotopic (accessory) adrenal cortical tissue**



Case 10

Submitted Diagnoses by Participating Institutions	Number	
Metastatic adenocarcinoma and ectopic adrenal tissue/ adrenal cortical rest/ adrenal cortical nodule	18	Acceptable
Metastatic adenocarcinoma and adrenal heterotopia. Differential: Hibernoma	1	Acceptable
Metastatic carcinoma	2	
Metastatic renal cell carcinoma	1	

Educational notes:

1. There are two small lymph nodes; one of them harbors a metastatic adenocarcinoma. Another small heterotopic (accessory) adrenal cortical tissue fragment composed predominantly of zona glomerulosa and zona fasciculata is observed.
2. For colorectal carcinomas, any lymph node with a tumor deposit measuring $\geqslant$0.2 mm is considered an involved node and is staged as pN1. Lymph nodes with only isolated tumor cells or tumor cell groups <0.2 mm are considered negative and staged as pN0; this requires diligent search for additional lymph nodes to exclude significant tumor deposit.
3. Heterotopic (accessory) adrenal cortical tissue is commonly found in the retroperitoneal space along the course of urogenital ridges. It usually contains no medulla except those located in the region of celiac ganglia. The zonal architecture of the adrenal cortical tissue distinguishes this accessory tissue from other clear cell tumors such as metastatic renal cell carcinoma.

Reference
1. Dataset for histopathological reporting of colorectal cancer, September 2018, The Royal College of Pathologists
2. Mills, S. E., Carter, D., Greenson, J. K., Reuter, V. E., & Stoler, M. H. (2012). Sternberg's diagnostic surgical pathology. Lippincott Williams & Wilkins.