International Academy of Pathology
Malaysian Division

FINAL REPORT

QUALITY ASSURANCE PROGRAM
GENERAL DIAGNOSTIC HISTOPATHOLOGY
CYCLE 01/2022

NOTES FROM THE COORDINATOR

1. For this cycle 01/2022, a total of 28 institutions responded online by the closing date of 15 June 2022.

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 01/2022 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. Nurul Akmar Misron, Dr Farveen Merican Bt Abu Bakar, and Dr Yusri bin Yusuf.

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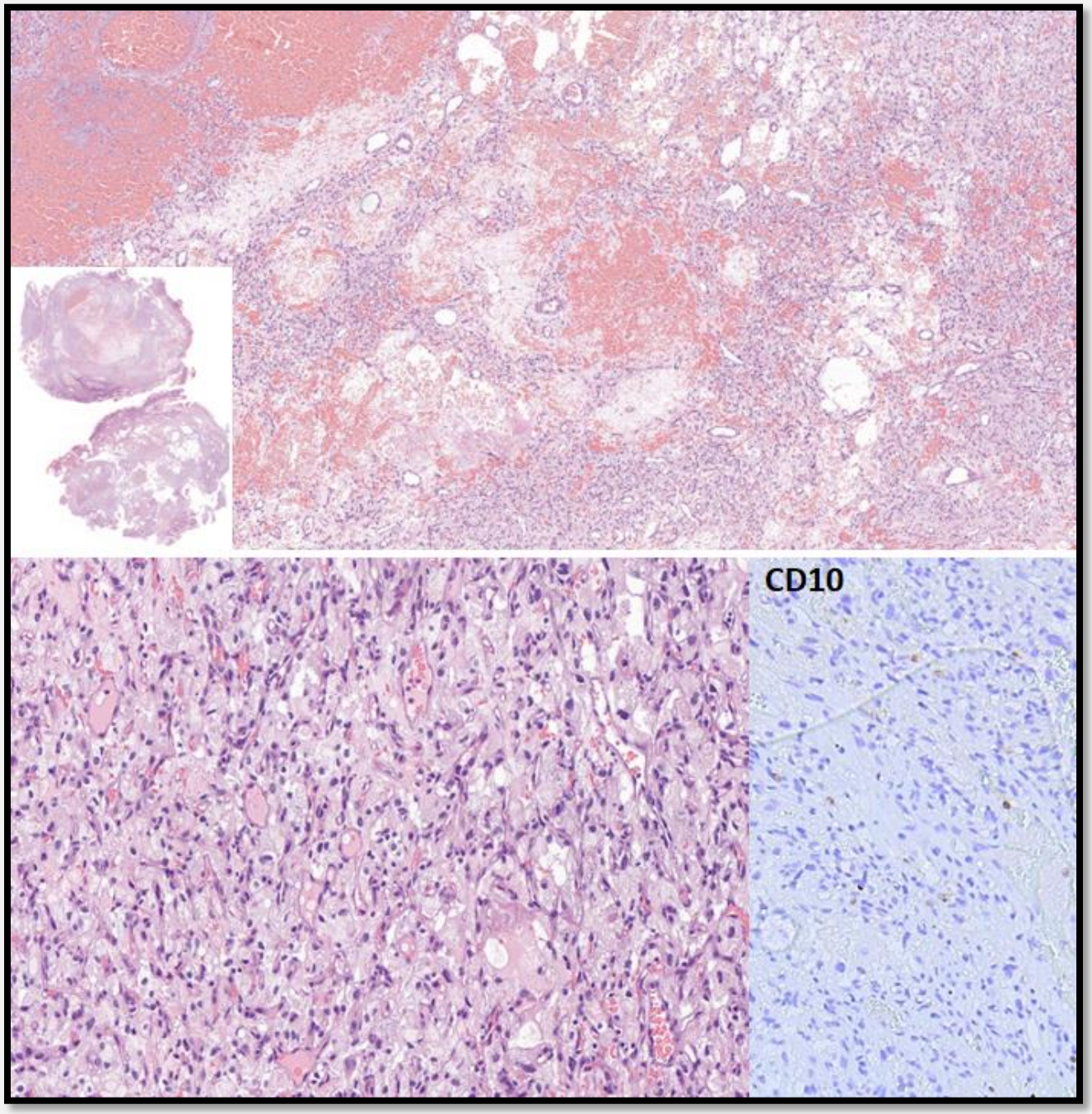
Coordinators for IAP-MD QAP

Case 1

Case 1: A 78-year-old-male presented with a right cerebellar mass. Image of immunohistochemistry for CD10 is attached.

Targeted Diagnosis: **Hemangioblastoma, WHO Grade 1**



Case 1

Submitted Diagnoses by Participating Institutions	Number	
Hemangioblastoma	28	Acceptable

Educational notes:

1. The cerebellar tumor is a hemangioblastoma composed of lobules of large, clear stromal cells containing multiple lipid vacuoles. The stroma cells display mild nuclear atypia and show negative immunohistochemical staining by CD10. There is a rich vascular network, composed mainly of thin-wall capillaries and a few branching, staghorn vessels. Areas of cystic degeneration and hemorrhage are present.
2. Hemangioblastoma is a benign, highly vascularized tumor of the central nervous system (CNS). The diagnosis needs to satisfy either one of the three recently defined WHO essential diagnostic criteria: (1) stromal cell immunopositivity for inhibin, (2) loss or inactivation of the VHL gene, or (3) the diagnosis of Von Hippel Lindau (VHL) disease.
3. Histologically, hemangioblastoma typically displays compact, non-infiltrative growth pattern, which is well-demarcated from the adjacent non-neoplastic tissue; the latter may show reactive changes such as piloid gliosis and Rosenthal fibres. Stromal cells of hemangioblastoma may show degenerative atypia and cytoplasmic hyaline globules, but mitotic figures are either rare or absent. Reticular variant (predominance of capillary vessels over stromal cells) and cellular variant (marked stromal cell predominance) have been described. Other helpful but non-essential features include presence of intratumoral hemorrhage, mast cells, and cyst-like spaces. Extramedullary hematopoiesis may be found in approximately 15% of cases.
4. Several CNS tumors, including those associated with VHL disease, may present as histologic mimics. Presence of abundant clear stromal cells makes metastatic clear cell renal cell carcinoma (ccRCC) a close differential diagnosis. Positivity for α-inhibin, D2-40 and cytoplasmic brachyury expression, coupled with negativity for RCCm, EMA and CD10 are diagnostic of hemangioblastoma.
5. In addition to hemangioblastoma and ccRCC, patients affected by VHL disease may develop VHL-associated neoplasms such as paragangliomas of the head and neck, pheochromocytoma of the adrenal gland, neuroendocrine islet cell tumors of the pancreas, endolymphatic sac tumors of the inner ear, and cystadenomas of the epididymis and broad ligament.

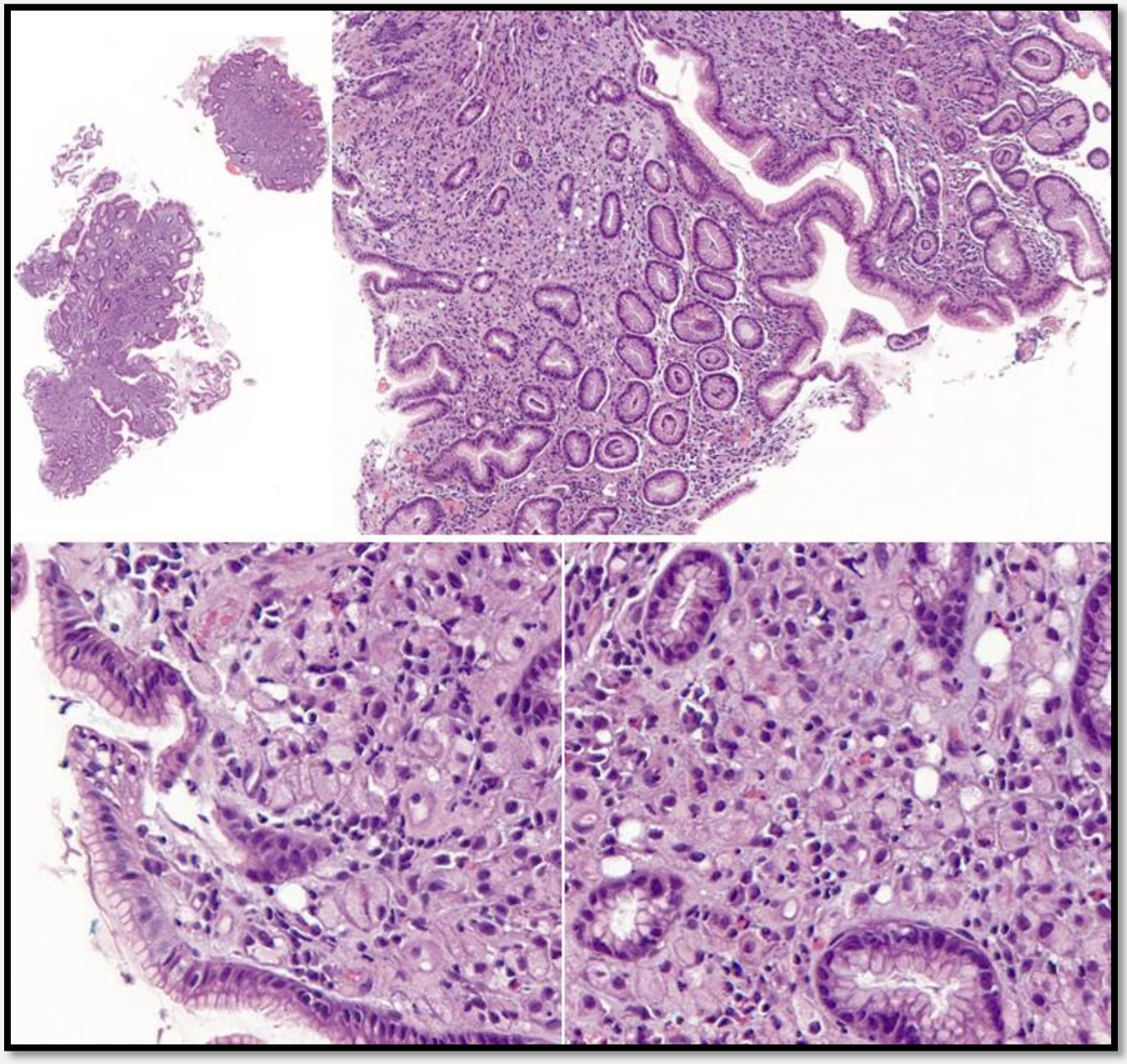
Reference:

1. WHO Classification of Tumours Editorial Board. Central nervous system tumours [Internet]. Lyon (France): International Agency for Research on Cancer; 2021.
2. Neuropathologic features of central nervous system hemangioblastoma J Pathol Transl Med. 2022;56 (3): 115-125.

Case 2

Case 2: A 53-year-old female presented with dyspepsia and epigastric pain. OGDS noted pangastritis and Forrest 3 ulcer at antrum.

Targeted Diagnosis: **Poorly cohesive adenocarcinoma**



Case 2

Submitted Diagnoses by Participating Institutions	Number	
Poorly cohesive carcinoma/ Diffuse type gastric carcinoma/ poorly differentiated adenocarcinoma	16	Acceptable
Atypical cells /Suspicious for adenocarcinoma or malignancy, IHC required.	6	Acceptable
Chronic gastritis with reactive change/ xanthomatous change/ H.Pylori or fungal infection	6	

Educational notes:

1. The gastric biopsy shows an expanded lamina propria diffusely infiltrated by dyscohesive malignant cells admixed with lymphocytes, plasma cells and scattered eosinophils. The malignant cells display enlarged atypical nuclei with irregular nuclear membrane, hyperchromatism, inconspicuous nucleoli, and abundant foamy cytoplasm. Occasional signet-ring cells are present. Mitotic figures are not prominent. There is no destruction of the adjacent gastric glands, which are devoid of intestinal metaplasia or dysplasia.
2. In gastric poorly cohesive carcinoma (PCC), malignant cells may appear as isolated cells or as small aggregates. The signet-ring type is characterized by a central, clear, globoid droplet or cytoplasmic mucin with an eccentrically placed nucleus. Cells of the non-signet-ring type of PCC (PCC-NOS) may appear xanthomatous, lymphocyte-like or have deep eosinophilic cytoplasm. There may be a mixture of different cell types.
3. Expanded lamina propria in gastric biopsies calls for scrutiny and requires judicious use of immunohistochemistry markers especially when a poorly differentiated tumor is suspected. The initial panel should entertain the differential diagnoses of poorly differentiated carcinoma (pankeratin), B-cell lymphoma (CD45/CD20) and melanoma (S100 or SOX10). Other neoplasms to be considered include Langerhans cell histiocytosis, other histiocytic disorders, and rarely, epithelioid gastrointestinal stromal tumor (GIST). Normal background mucosa raises the possibility of metastasis, particularly metastatic lobular breast carcinoma in a woman.
4. Xanthomatous gastritis has an endoscopic appearance of submucosal yellowish lesion. The lesional foamy cells typically display regular, centrally located nuclei in the absence of accompanying goblet cells. CD68 immunostaining confirms its histiocytic origin.

Reference:

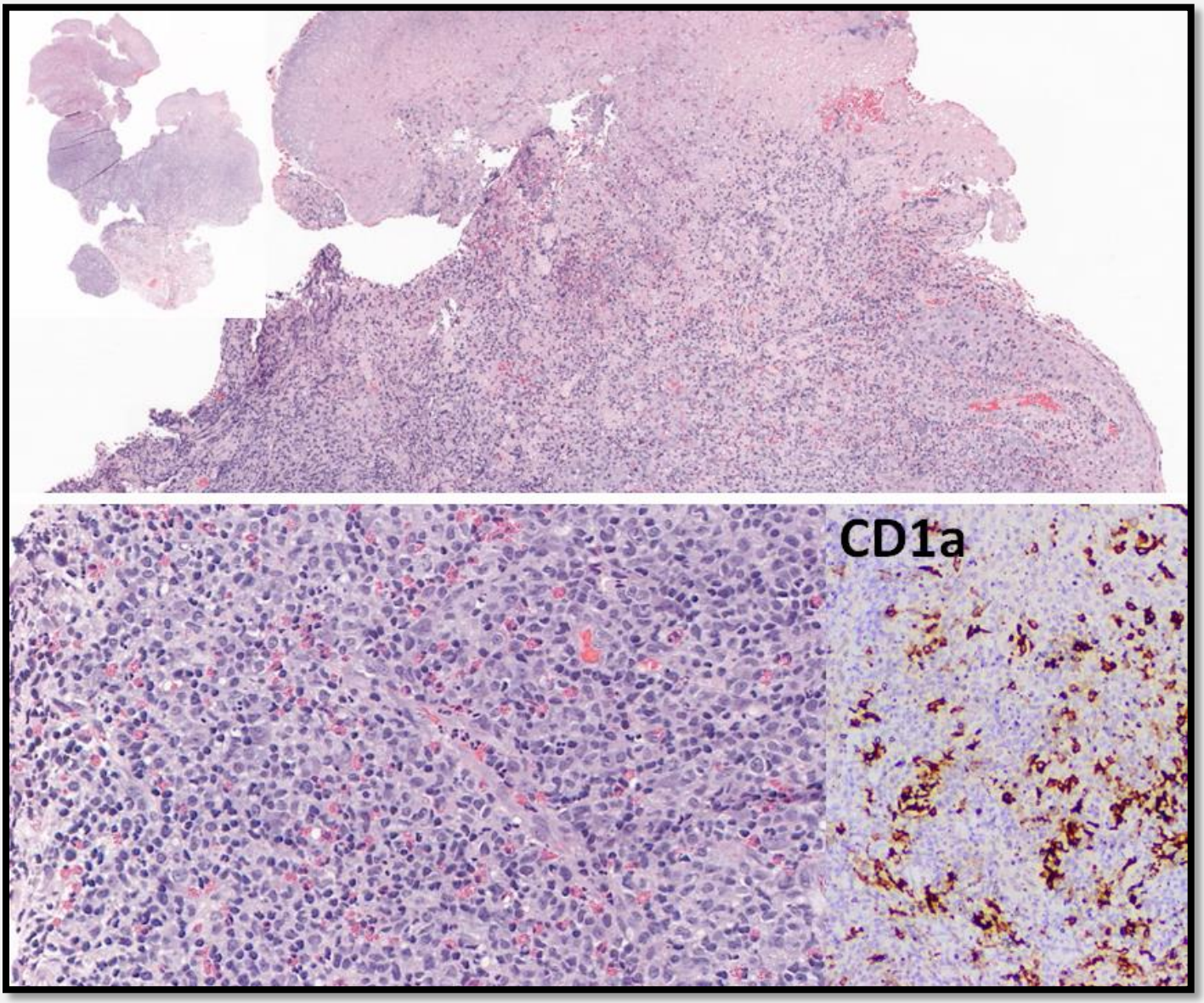
1. WHO Classification of Tumours Editorial Board. Digestive system tumours 5th edition [Internet]. Lyon (France): International Agency for Research on Cancer, 2019.

2. Bellizzi AM, Montgomery EA, Hornick JL. American Registry of Pathology Expert Opinions: Evaluation of poorly differentiated malignant neoplasms on limited samples - Gastrointestinal mucosal biopsies. Ann Diagn Pathol. 2020 Feb;44:151419.

Case 3

Case 3: A 13-year-old female presented with lip ulcer. Image of immunohistochemistry for CD1a is attached.

Targeted Diagnosis: **Traumatic ulcerative granuloma with stromal eosinophilia (TUGSE)**



Case 3

Submitted Diagnoses by Participating Institutions	Number	
Langerhans cell histiocytosis. Differential Diagnosis: Traumatic ulcerative granuloma with stromal eosinophilia (TUGSE)	1	Acceptable
Langerhans cell histiocytosis/ eosinophilic granuloma	27	

Educational notes:

1. The mucosa fragments are ulcerated with fibrinopurulent exudate rich in eosinophils. There are dense inflammatory infiltrates in stroma composed of a mixture of eosinophils, small lymphocytes, large mononuclear cells with round to oval pale nuclei, and histiocytes. CD1a immunohistochemistry highlights scattered CD1a-positive dendritic cells among the inflammatory infiltrates, but not the large mononuclear cells. Further immunohistochemistry shows CD30-positive T cells are admixed. The histological features are that of traumatic ulcerative granuloma with stromal eosinophilia (TUGSE).
2. Traumatic ulcerative granuloma with stromal eosinophilia (TUGSE) is a benign self-limiting lesion usually initiated by trauma. TUGSE has been related to CD30-positive lymphoproliferative disorder and possibly induced by focal Epstein-Barr virus. Clinically, it appears as solitary ulcer in oral soft tissue especially at the lateral and ventral tongue and the buccal mucosa. Histologically, granulation tissue underneath the ulcer is composed of a dense, mixed cellular infiltrate with the predominant large mononuclear cells with pale nuclei harboring small nucleoli. Eosinophils are abundant but may be sparse in cases. The large mononuclear cells have been reported to be CD68 and Factor XIIIa immunoreactive. They are also said to represent predominantly CD30-positive T cells and to a lesser extent, CD3-, CD4-, and CD8-positive T cells. Many TUGSEs resolve without any intervention. Some heal rapidly after biopsy. In the current case, the ulcer heals after biopsy.
3. Histologically, TUGSE resembles Langerhans cell histiocytosis (LCH) due to presence of abundant eosinophils. Nonetheless, clinically, LCH in oral region usually involves the hard tissue, especially the posterior mandible. The bone lesions may be accompanied by soft tissue swelling or ulcer. LCH involving the soft tissue only usually occurs in gingiva and hard palate. Histologically, Langerhans cells have characteristic “coffee bean”-shaped or folded or indented oval nuclei or grooved nuclei with small or absent nucleoli. They are positive for CD1a, CD207/langerin, and S100 protein. However, CD-1a may occasionally be positive in other histiocytic proliferations. Thus, langerin or CD-207 is crucial as it indicates presence of Birbeck granules of dendritic cells.

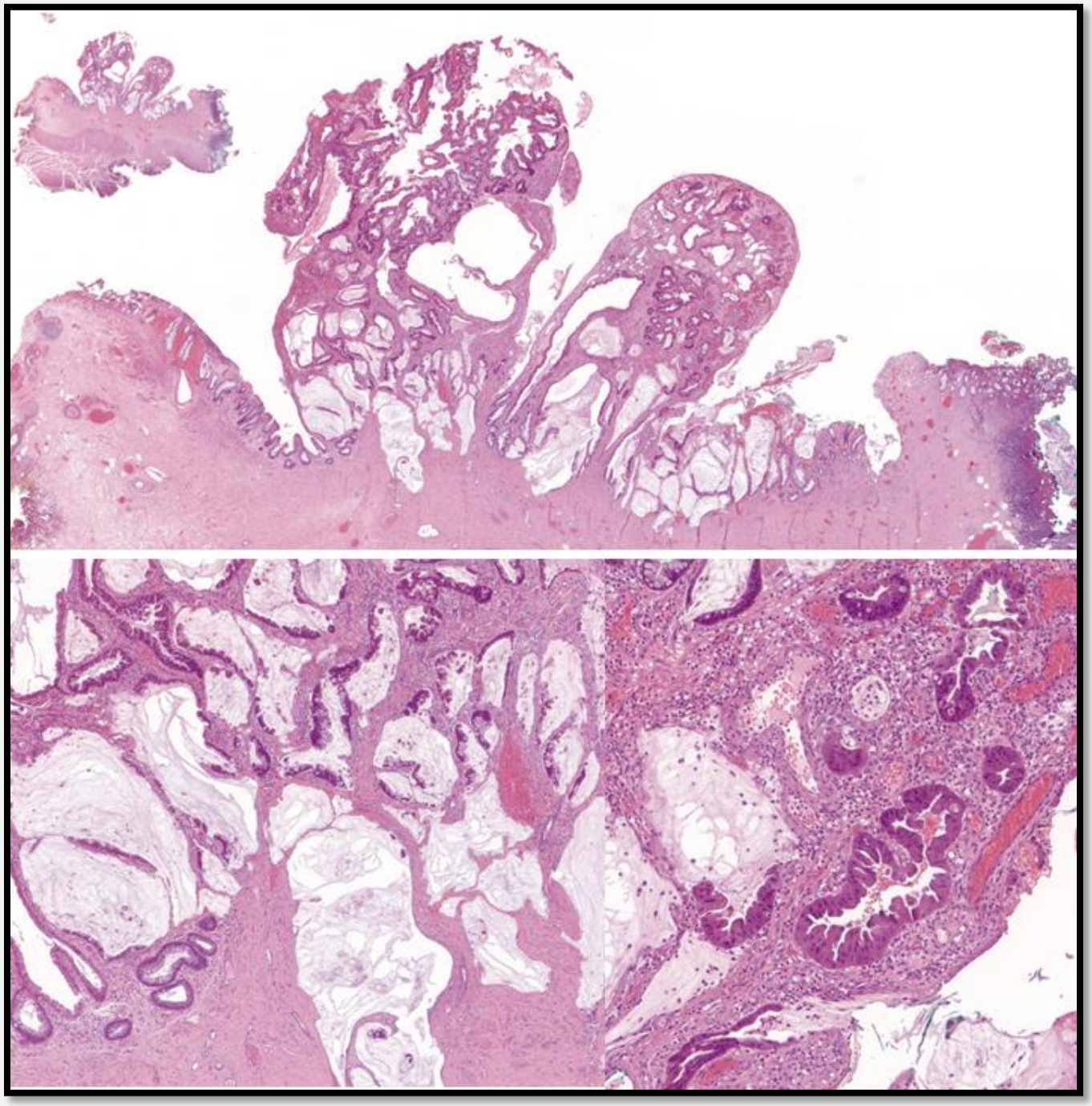
Reference

1. Gnepp's Diagnostic Surgical Pathology of the Head and Neck, 3rd edition, 2020
2. Faustino ISP, Fernandes PM, Pontes HAR, et al. Langerhans cell histiocytosis in the oral and maxillofacial region: An update. J Oral Pathol Med. 2021;50(6):565-571.

Case 4

Case 4: A 66-year-old female presented with passing out mucous and blood in stool. Transanal resection of the rectal polyp was performed.

Targeted Diagnosis: **Mucinous adenocarcinoma, pT1**



Case 4

Submitted Diagnoses by Participating Institutions	Number	
Mucinous adenocarcinoma/Mucinous adenocarcinoma arising from adenomatous polyp or sessile serrated lesion with dysplasia, Haggitt level 4, sm1	17	Acceptable
Adenocarcinoma/ Adenocarcinoma arising from adenomatous polyp or traditional serrated adenoma, Haggitt level 3/4	6	Acceptable
Malignant polyp with mucinous component/ carcinoma (At least pT1)/ Sessile malignant polyp with mucinous adenocarcinoma	3	Acceptable
Traditional serrated adenoma.	1	
Inflammatory cloacogenic polyp; with prominent misplacement of reactive epithelium	1	

Educational notes:

1. This well-differentiated mucinous adenocarcinoma is composed of malignant glands infiltrating superficially into submucosa in the absence of muscularis mucosae (pT1). The malignant glands are lined by low to high-grade dysplastic epithelium with irregular contours and focal serrated appearance. Abundant extracellular mucin is observed. No submucosal lymphovascular invasion is noted. It has complete resection margin (>1mm).
2. Local resection is a curative procedure for early (T1) colorectal cancer. Histological features that predict lymph node metastasis must be assessed for early tumors, i.e. (1) tumor size, (2) degree of differentiation, (3) depth of invasion into the submucosa (4) presence of submucosal lymphovascular invasion, and (5) status of resection margin. Depth of invasion into submucosa has been widely assessed using Kikuchi system for sessile tumors and Haggitt system for polypoid tumors. Ueno system recommends absolute measurement of invasion beyond muscularis mucosae as well as width of tumor invasion. Even though neither one of these systems has good evidence to be recommended, they should be reported as applicable and where possible. Local multidisciplinary team may select the most appropriate for further management decision.
3. Mucinous adenocarcinoma has extracelluar mucin occupying >50% of the lesion. If <50%, the adenocarcinoma is designated as having a mucinous component. Although mucinous adenocarcinomas have no survival advantage compared to adenocarcinomas, NOS, they tend to have higher rate of microsatellite instability. In this case, immunohistochemical evaluation suggests microsatellite-stable tumor.
4. Differentiating epithelial misplacement from true invasion may be problematic. Misplaced glands are identified by the presence of enclosing lamina propria whereas desmoplasia is a reliable criterion for true invasion.

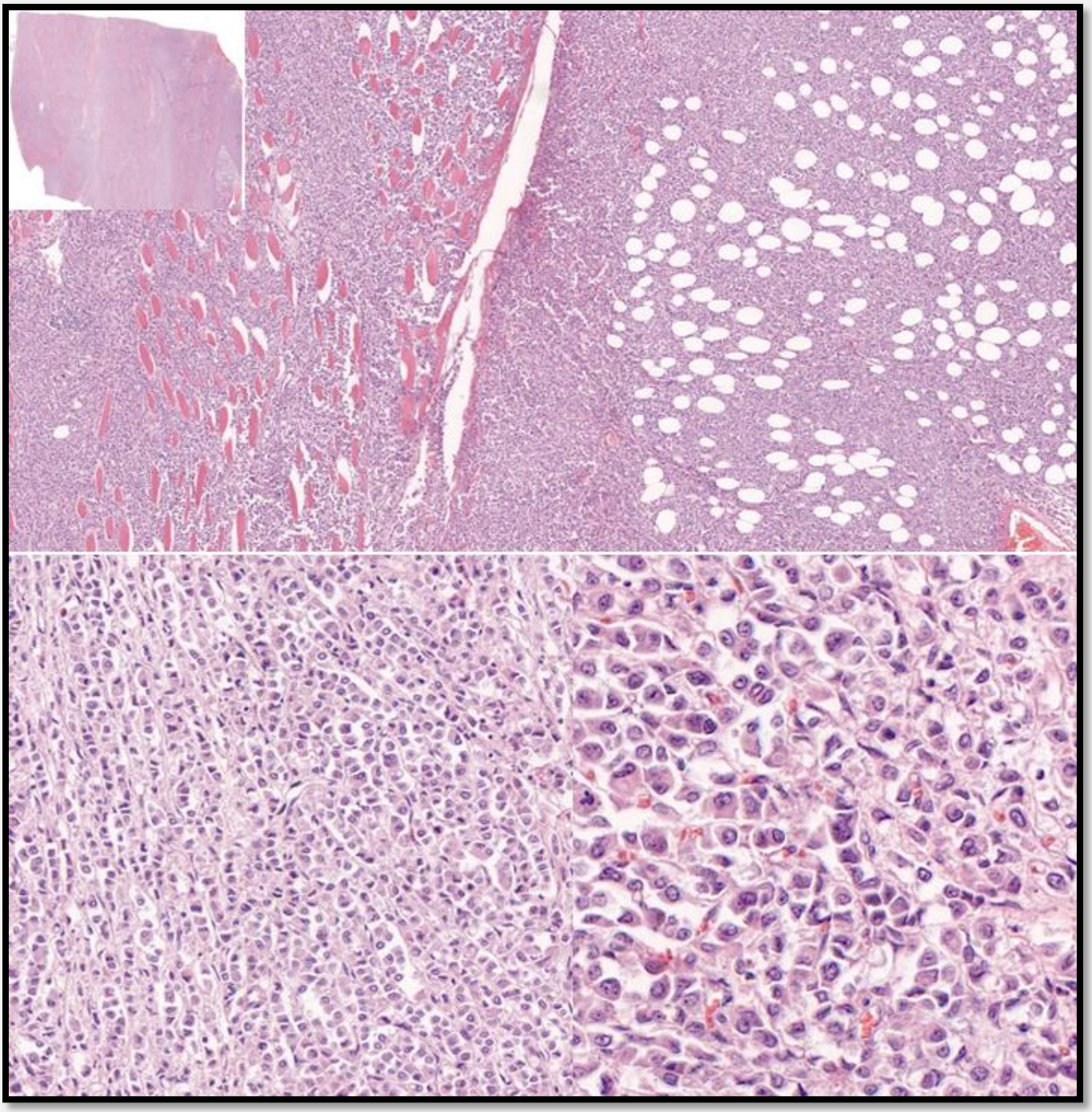
Reference

1. LOUGHREY, Maurice B.; QUIRKE, Philip; SHEPHERD, Neil A. Standards and datasets for reporting cancers Dataset for histopathological reporting of colorectal cancer September 2018.
2. WHO Classification of Tumours Editorial Board. Digestive system tumours 5th edition [Internet]. Lyon (France): International Agency for Research on Cancer, 2019
3. Risio, M. (2012). The natural history of pT1 colorectal cancer. Frontiers in oncology, 2, 22.

Case 5

Case 5: A 55-year-old female presented with right breast mass for 1 year.

Targeted Diagnosis: **Pleomorphic lobular carcinoma**



Case 5

Submitted Diagnoses by Participating Institutions	Number	
Pleomorphic lobular carcinoma	5	Acceptable
Invasive lobular carcinoma	19	Acceptable
Malignant tumor/Poorly differentiated tumor, IHC required	3	Acceptable
Alveolar rhabdomyosarcoma	1	

Educational notes:

1. There is diffuse infiltration by malignant cells arranged mostly in solid sheets, with deep extension into subcutaneous tissue and in between muscle bundles. In focal areas, they form single files. The tumor cells are dispersed and dyscohesive, displaying intermediate to high grade nuclear pleomorphism. They have enlarged nuclei with round to notched nuclear outline and conspicuous nucleoli. The cytoplasm is abundant and appears granular. Occasional signet ring-like cells are present. There is little background host reaction.
2. Pleomorphic lobular carcinoma (PLC) variant differs from classic invasive lobular carcinoma (ILC) that PLC displays greater nuclear pleomorphism with lobulated, indented, and hyperchromatic nuclei, abundant eosinophilic or granular cytoplasm (indicative of apocrine differentiation), and/or rhabdomyoblastoid appearance. Nuclei in PLC are enlarged (>4 times the size of lymphocytes) with frequent mitosis. In contrast, ILC displays smaller cell size, low to intermediate nuclear grade with the size and chromatin quality being fairly constant, scanty cytoplasm, and low mitotic activity.
3. PLC also has a low rate of estrogen receptor (ER) positivity (10%) and may show HER2 overexpression whereas classic ILC is invariably positive for ER and typically HER2 non-amplified. Pleomorphic and solid histological patterns have been reported to have poorer prognosis as compared to the classic ILC.
4. Primary or metastatic alveolar rhabdomyosarcoma of the breast is exceedingly rare, especially in the advanced age group. Most reported cases involved adolescents and young adults. The lesional cells resemble rounded primitive myoblasts with eosinophilic cystoplasm, or present with small, round, blue cell morphology. Immunohistochemistry is vital for definitive diagnosis.

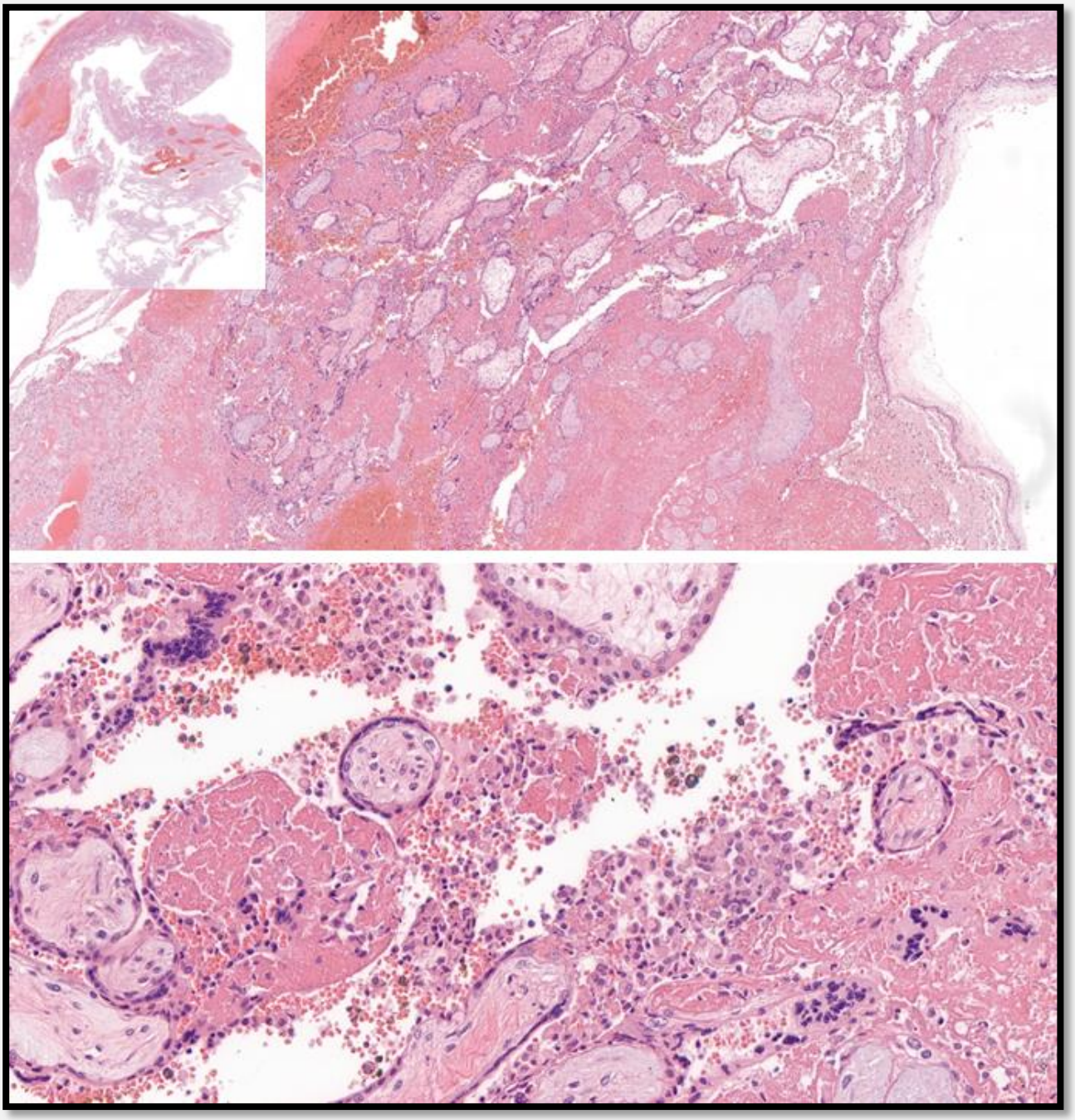
Reference

1. WHO Classification of Tumours Editorial Board. Breast tumours 5th edition [Internet]. Lyon (France): International Agency for Research on Cancer; 2019
2. 2. Christgen, M.; Cserni, G.; Floris, G.; Marchio, C.; Djerroudi, L.; Kreipe, H.; Derksen, P.W.B.; Vincent-Salomon, A. Lobular Breast Cancer: Histomorphology and Different Concepts of a Special Spectrum of Tumors. Cancers 2021, 13, 3695.
3. 3. Trihia HJ, Novkovic N, Provatas I, Mavrogiorgis A, Lianos E. Primary Alveolar Rhabdomyosarcoma of the Breast in an Adult: An Extremely Rare Case. Case Rep Pathol. 2019 Mar 28;2019:6098747.

Case 6

Case 6: A 28-year-old female presented with complete miscarriage at 17 weeks gestation. Products of conception was submitted.

Targeted Diagnosis: **Chronic histiocytic intervilliositis**



Case 6

Submitted Diagnoses by Participating Institutions	Number	
Chronic histiocytic intervilliositis	22	Acceptable
Chronic histiocytic intervillositis. Infectious causes (viral, malaria) need to be ruled out.	1	Acceptable
Chronic histiocytic intervillositis secondary to malarial infection	1	Acceptable
Placental malaria	1	Acceptable
Partial hydatidiform mole	2	
Chronic deciduitis	1	

Educational notes:

1. Placental tissue fragments show maternal decidual tissue and villous parenchyma. The villous parenchyma is composed of hypovascular, fibrotic villi with perivillous fibrin deposits. At areas, there are numerous histiocytic infiltrates in the intervillous spaces. In addition, brown to dark pigments are observed intracellularly and extracellularly. These features are consistent with chronic histiocytic intervilliositis.
2. Chronic histiocytic intervilliositis (CHIV) is a type of chronic placental inflammation defined by infiltration by maternal mononuclear cells in the intervillous space, associated with an increase in perivillous fibrin deposits. Recognizing CHIV is important as it is associated with poor pregnancy outcome such as first-trimester miscarriage, stillbirth, and fetal growth restriction. Moreover, CHIV recurs at the rate of 25-100% that various prophylactic treatment regimens have been tried.
3. Diagnosis of CHIV requires exclusion of infectious causes. Of note, similar histological pattern has been reported in 17% of placental malaria. Although, brown to dark pigments are observed in this case, presence of the pigments in extracellular space suggests those are likely artefactual formalin pigments. Nonetheless, malarial pigments show similar chemical reactions to those of formalin pigments. Confident distinction relies on recognition of intracellular malaria parasites.

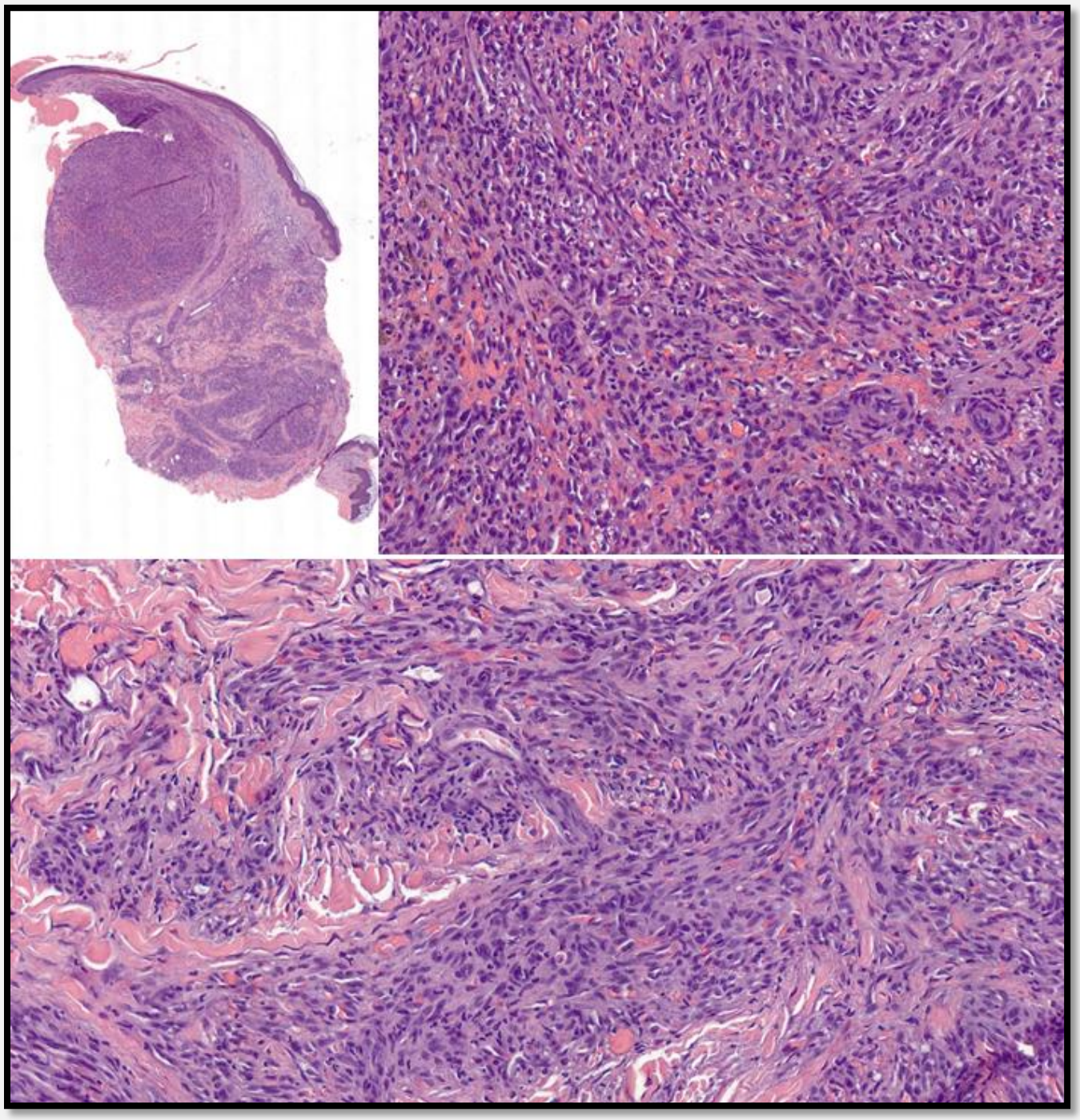
Reference

1. Khong, T. Yee, et al., eds. Pathology of the placenta: a practical guide. New York: Springer, 2019
2. Chatterjee S. Artefacts in histopathology. J Oral Maxillofac Pathol. 2014 Sep;18(Suppl 1):S111-6.

Case 7

Case 7: A 67-year-old male presented with purplish nodules on body and leg.

Targeted Diagnosis: **Kaposi sarcoma**



Case 7

Submitted Diagnoses by Participating Institutions	Number	
Kaposi sarcoma/ Kaposi sarcoma, nodular stage/ Kaposi sarcoma, suggest for HHV-8 stain	25	Acceptable
Malignant vascular neoplasm. Differential diagnosis includes Kaposi sarcoma and angiosarcoma. Suggest for HHV-8 IHC.	1	Acceptable
High grade vascular tumour, consistent with cutaneous angiosarcoma	1	
Myofibroma(tosis)	1	

Educational notes:

1. This biopsy shows the nodular cutaneous Kaposi sarcoma composed of intradermal, circumscribed, cellular nodules of monomorphic spindled cells. The spindled cells are arranged in fascicles with intervening slit-like channels containing erythrocytes. The spindled cells are immunoreactive towards human herpes virus-8 (HHV8).
2. There are four epidemiological forms of Kaposi sarcoma (KS), i.e., classic, African endemic, AIDS-related epidemic and iatrogenic (transplant-related) forms. All forms show similar histological subtypes, i.e., patch-stage, plague-stage, and nodular KS.
3. For nodular KS, other vascular tumors displaying spindled endothelial cells such as spindle cell angiosarcoma, kaposiform hemangioendothelioma (KHE) and spindle cell hemangioma form the main differential diagnoses. Spindle cell angiosarcoma differs from nodular KS as the pleomorphic endothelial cells form anastomosing primitive vascular structures dissecting dermal collagen bundles. KHE and spindle cell hemangioma affect infant and children, and young adults respectively. In KHE, apart from KS-like areas, capillary haemangioma-like areas are observed. In spindle cell hemangioma, the dermal nodules extend into subcutaneous tissue and are composed of cavernous-like vascular spaces accompanied by solid foci of bland spindle cells and epithelioid endothelial cells. All of them differ from KS by negative immunoreactivity towards HHV8.

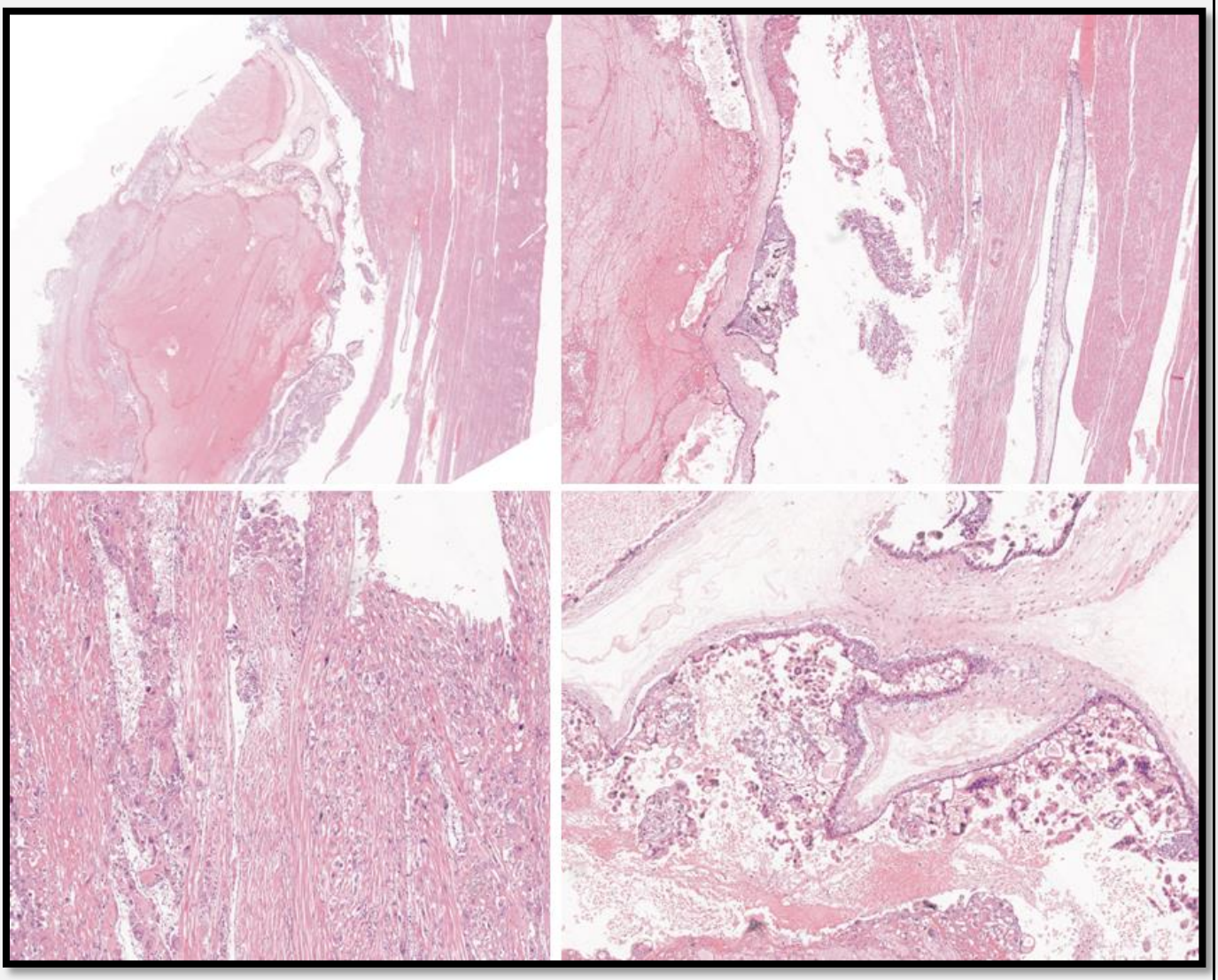
Reference

1. Wadee, R., & Grayson, W. (2022). Cutaneous Kaposi sarcoma and its mimics. Diagnostic Histopathology, 28(1), 38-52.

Case 8

Case 8: A 53-year-old female noted to have raised serum Beta HCG (21 000 000 unit). Computed topography (CT) pelvis showed multi-cystic uterine mass. Her last childbirth was 15 years ago. Hysterectomy was performed.

Targeted Diagnosis: **Invasive hydatidiform mole**



Case 8

Submitted Diagnoses by Participating Institutions	Number	
Invasive hydatidiform mole	26	Acceptable
Choriocarcinoma	2	

Educational notes:

1. Section shows myometrial invasion by complete hydatidiform mole (CHM). The chorionic villi are enlarged and hydropic containing prominent cisternae, accompanied by marked circumferential trophoblastic proliferation with abnormal distribution and loss of polarity. The molar villi invade the myometrium without intervening decidua. Bizarre trophoblasts infiltrate the myometrium as well.
2. Invasive hydatidiform mole is characterized by a hydatidiform mole whereby the molar villi invade the myometrium or its vascular spaces. Most invasive moles are CHM; CHM carries 15-20% risk of persistent gestational trophoblastic disease and 2-3% risk of gestational carcinoma. Less frequently, invasive mole arises from an incomplete mole. Once vascular invasion has occurred, villi may embolize at a distant site, including the vagina, lung, and brain (metastatic hydatidiform mole).
3. Gestational choriocarcinoma displays a characteristic, infiltrative biphasic pattern composed of mononuclear villous cytotrophoblasts and intermediate trophoblasts, and rimming multinucleated syncytiotrophoblasts. The nuclear atypia is striking with frequent mitotic figures. Hemorrhage and necrosis are typically prominent. Presence of chorionic villi is incompatible with the diagnosis of choriocarcinoma, with rare exception of intraplacental choriocarcinomas arising in term placentas. However, invasive mole with exuberant trophoblastic proliferation and scarce villi may be incorrectly diagnosed as choriocarcinoma.

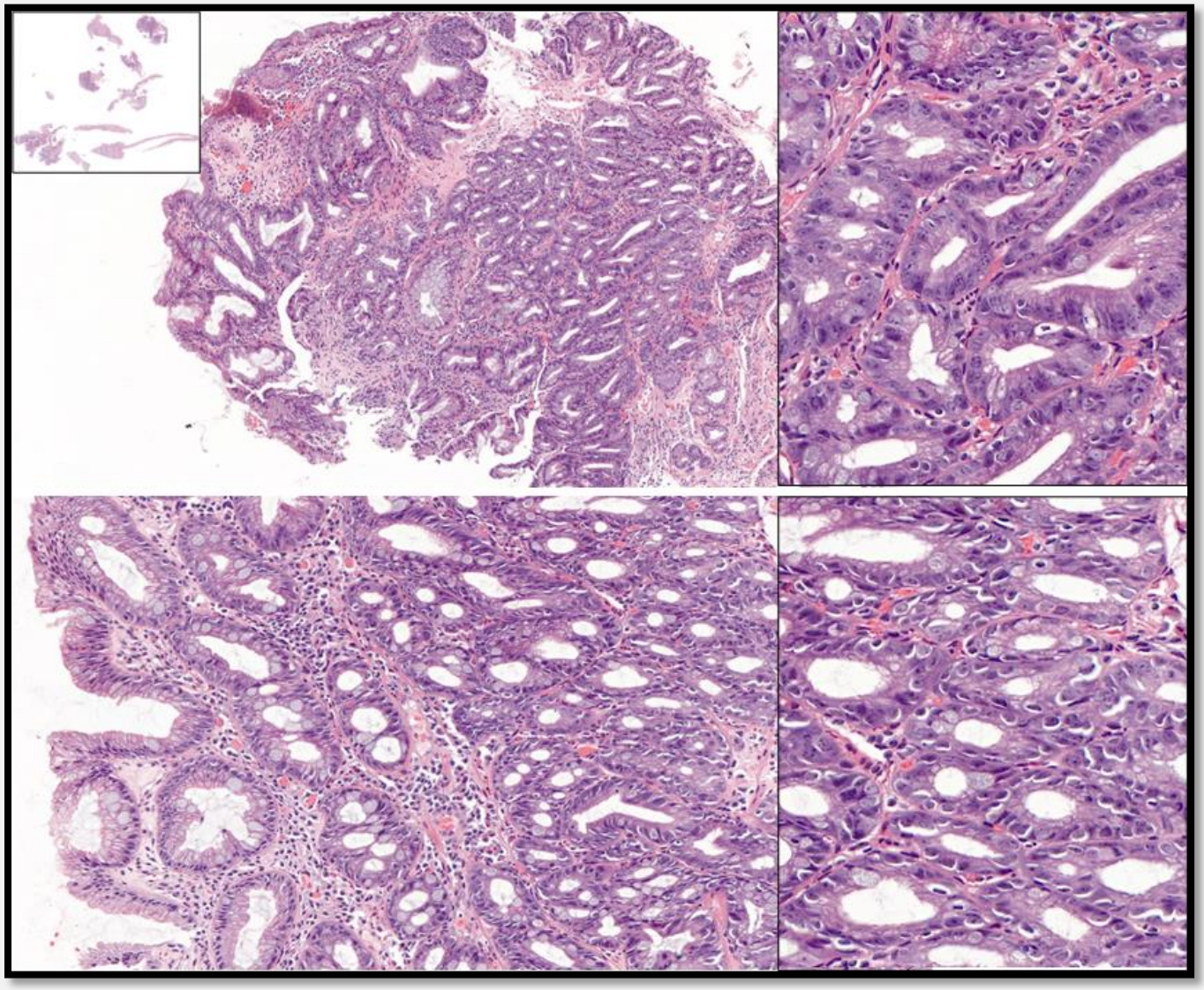
Reference

1. WHO Classification of Tumours Editorial Board. Female Genital Tumours 5th edition [Internet]. Lyon (France): International Agency for Research on Cancer. 2020
2. Crum, C. P., Nucci, M. R., Lee, K. R., & Boyd, T. K. (2011). Diagnostic gynecologic and obstetric pathology. Philadelphia, PA: Saunders/Elsevier.

Case 9

Case 9: A 74-year-old male with salmon-pink patch 2 cm above the esophageal-gastric junction.

Targeted Diagnosis: **Barret esophagus, indefinite for dysplasia**



Case 9

Submitted Diagnoses by Participating Institutions	Number	
Barret esophagus, indefinite for dysplasia	1	Acceptable
Barret esophagus with low grade dysplasia	13	Acceptable
Barret esophagus with high grade dysplasia	7	
Barret esophagus	5	
Barrett's oesophagitis with moderate dysplasia	1	
Barrett esophagus, reactive epithelial changes.	1	

Educational notes:

1. There are fragments of squamocolumnar epithelium displaying intestinal metaplasia. The columnar epithelial component shows compact lobules of regular tubules; there are foci whereby the crypts show nuclear atypia with nuclear crowding and enlargement associated with focal intraepithelial neutrophilic infiltrates. Throughout the fragments, surface maturation is observed. The crypts displaying nuclear atypia does raise the concern of crypt dysplasia, however, presence of intraepithelial neutrophilic infiltrates precludes definite dysplasia. These features are best interpreted as Barret esophagus, indefinite for dysplasia.
2. Dysplasia in Barret esophagus, regardless of grade, involves total crypt and surface epithelium without surface maturation. However, dysplasia has been shown to evolve from the base of crypts, and with time, progress to involve the upper crypts and surface epithelium. Thus, some cases would have been sampled to display crypt dysplasia in the early phase. Nevertheless, the diagnosis of crypt dysplasia remains controversial, especially in the presence of active inflammation that such a diagnosis is best avoided.
3. Indefinite for dysplasia grading category for Barret esophagus is reserved for those cases whereby a definite dysplasia cannot be established. This category represents diagnostic uncertainty due to (1) technical or processing artifact of the samples or (2) pathologists' uncertainty such as confounding effects of inflammation and ulceration that induce overlapping regenerative changes. Cases that showing basal crypt atypia with surface maturation or lack of surface epithelium are acceptably classified under indefinite for dysplasia.
4. Good communication with the clinical counterpart for cases with indefinite for dysplasia is recommended to plan for further management, i.e., an immediate repeat biopsy due to technical or processing artifact, or a 3 to 6-month interval after an aggressive anti-reflux treatment before a repeat biopsy in the presence of confounding effects of inflammation and ulceration.

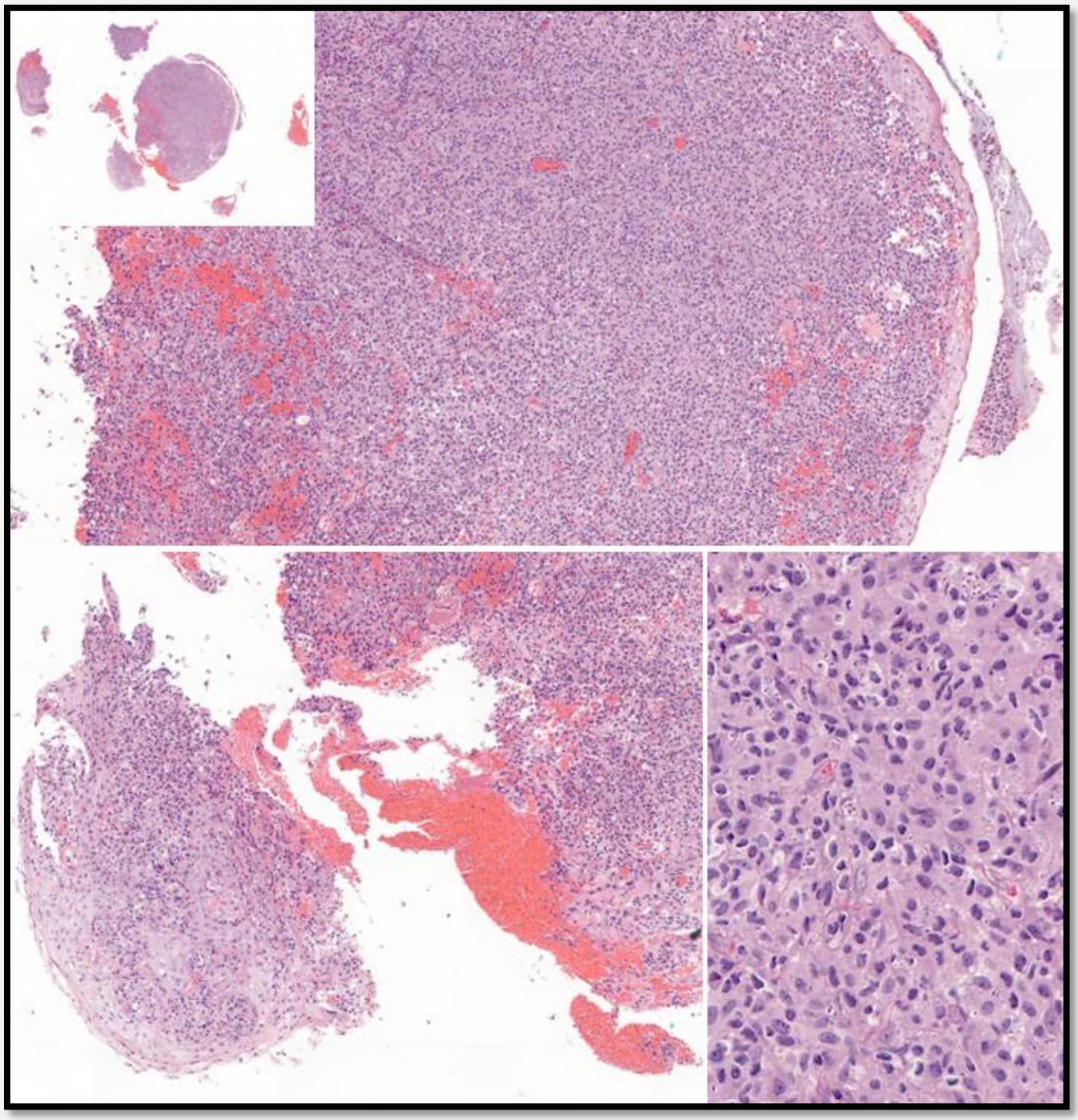
Reference

1. Naini, B. V., Souza, R. F., & Odze, R. D. (2016). Barrett's Esophagus: A Comprehensive and Contemporary Review for Pathologists. The American Journal of Surgical Pathology, 40(5), e45-e66.
2. Gilani, S. M., & Montgomery, E. (2018). Barrett's esophagus: a comprehensive review and update. Diagnostic Histopathology, 24(12), 479-486.
3. Kumarasinghe, M. P., Armstrong, M., Foo, J., & Raftopoulos, S. C. (2021). The modern management of Barrett's oesophagus and related neoplasia: role of pathology. Histopathology, 78(1), 18-38.

Case 10

Case 10: A 60-year-old male with laryngeal mass biopsy.

Targeted Diagnosis: **Histoplasmosis**



Case 10

Submitted Diagnoses by Participating Institutions	Number	
Histoplasmosis / Fungal infection with a differential of histoplasmosis	27	Acceptable
Non keratinizing squamous cell carcinoma	1	

Educational notes:

1. The biopsy shows diffuse stromal infiltration by histiocytes mixed with scattered lymphocytes, plasma cells and eosinophils. Numerous uniform, intracytoplasmic yeasts with characteristic retraction artifacts are observed. No well-formed granuloma or caseous necrosis is seen. The overlying squamous epithelium shows reactive atypia and focal pseudoepitheliomatous hyperplasia. These features are that of histoplasmosis.
2. Primary laryngeal infection by the *Histoplasma capsulatum* is rare, and it generally occurs as the mucocutaneous form of a generalized, disseminated disease. Histopathological spectrum of the lesions reflects the host reactions against *H. capsulatum* and the host's immune status. There are four categories; (1) the tuberculoid form is rich in activated histiocytes and lymphocyte infiltrates as in this case, occurring both in immunocompetent and immunocompromised patients. Well-formed epithelioid granulomas with giant cells and caseous necrosis can be observed, although infrequent. *H. capsulatum* is typically low in number and located intracellularly. (2) The anergic form is described in severely immunocompromised patients in which abundant intracellular and extracellular yeasts are seen. The histiocytes remain inactivated with little tissue response. (3) The mixed form shows a mixture of tuberculoid and anergic reactions, whereas in (4) the sequelae form, fibrosis predominates with little inflammation and rare detectable yeasts.
3. Histoplasmosis can induce pseudoepitheliomatous hyperplasia (PEH) of the overlying epithelium, known to mimic squamous cell carcinoma (SCC) both clinically and histologically. PEH is characterized by exuberant down-growing epithelial proliferation with tongue-like submucosal projections. However, in contrast to SCC, the individual cells of PEH are mature, with little atypia and only occasional dyskeratosis. Invasive epithelial cells in SCC usually demonstrate higher degree of cytologic atypia, including nuclear pleomorphism, maturational atypia, and mitoses.

Reference

1. COUPPIÉ, P., et al. Cytological and Histopathological Spectrum of Histoplasmosis: 15 Years of Experience in French Guiana. Frontiers in Cellular and Infection Microbiology, 2020, 10: 591974-591974.
2. Zarovnaya E, Black C. Distinguishing pseudoepitheliomatous hyperplasia from squamous cell carcinoma in mucosal biopsy specimens from the head and neck. Archives of pathology & laboratory medicine. 2005 Aug;129(8):1032-6
3. Viswanathan, S., Chawla, N., D'Cruz, A., & Kane, S. V. (2007). Head and neck histoplasmosis—a nightmare for clinicians and pathologists! Experience at a tertiary referral cancer centre. Head and Neck Pathology, 1(2), 169-172.