International Academy of Pathology
Malaysian Division

FINAL REPORT

QUALITY ASSURANCE PROGRAM
GENERAL DIAGNOSTIC HISTOPATHOLOGY
CYCLE 01/2021

NOTES FROM THE COORDINATOR

1. For this cycle 01/2021, a total of 21 institutions responded online by the closing date of 15 June 2021.

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 01/2021 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. Wan Syahira Ellani, Dr. Zahrah Tawil, Dr Malisalaora Mohamed, Dr. Chew Bee See, Dr.Faezahtul Arbaeyah Hussain and Dr. Mariani Hashim.

Prepared by,

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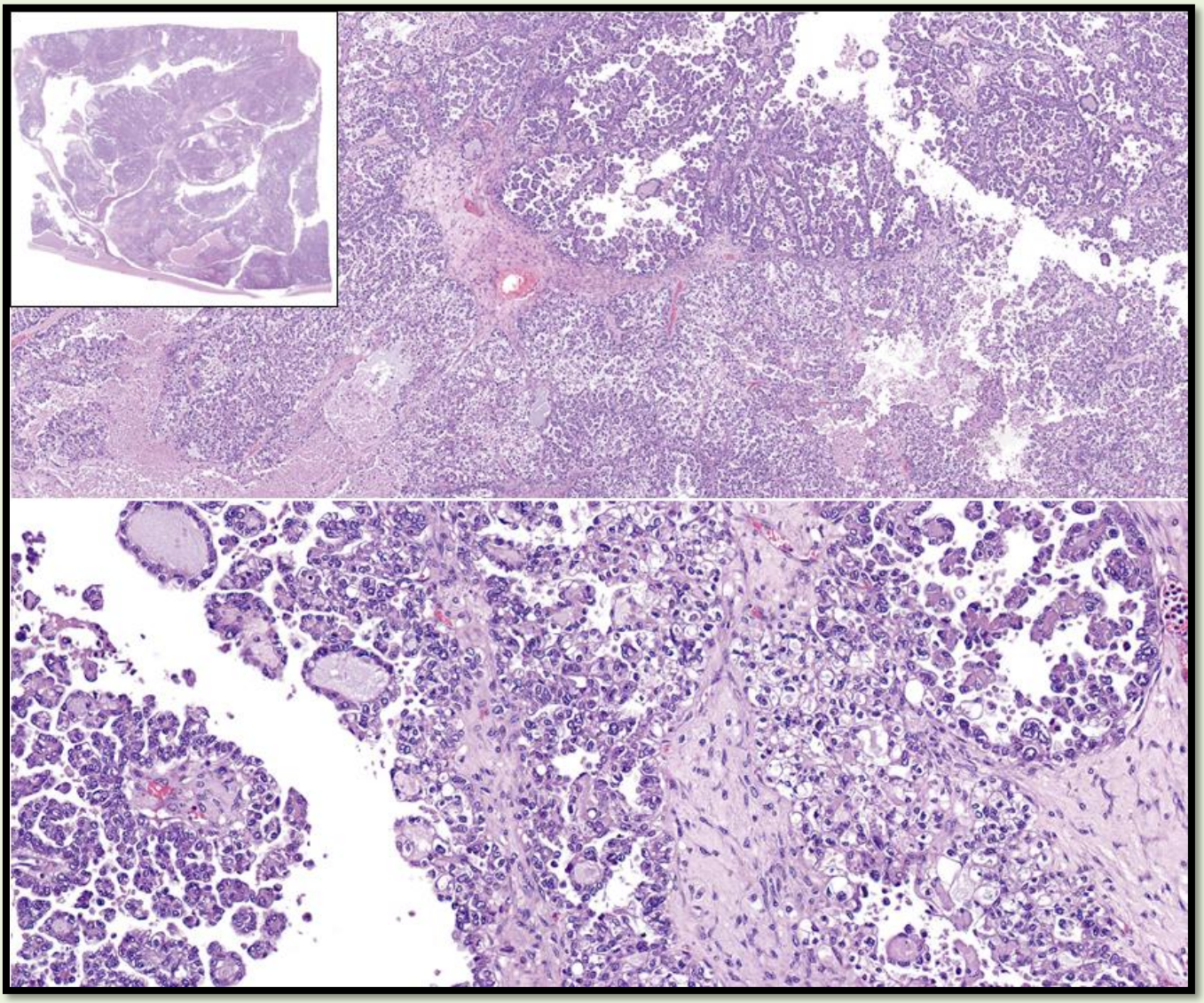
Coordinator for IAP-MD QAP

Case 1

Case 1: A 56-year-old lady presented with a left ovarian mass. One representative section.

Targeted Diagnosis: **Clear cell carcinoma of the ovary**



Case 1

Submitted Diagnoses by Participating Institutions	Number	
Clear cell carcinoma of the ovary/ High grade carcinoma, suggestive of clear cell carcinoma. Advice IHC stains.	18	Acceptable
High grade serous carcinoma/ Papillary serous cystadenocarcinoma/ Mixed serous and clear cell adenocarcinoma	3	Acceptable

Educational notes:

1. The ovarian mass is a clear cell carcinoma composed predominantly of non-hierarchically branched papillae covered by one- or two-layers of cuboidal, high-grade malignant cells displaying clear to light eosinophilic cytoplasm. The papillae have fibrous, hyalinized or edematous stromal cores. Eosinophilic hyaline globules are noted.
2. Clear cytoplasm is not specific nor characteristic of clear cell carcinoma of the ovary as not all clear cell carcinomas have clear cytoplasm, and other primary ovarian carcinomas and metastatic carcinomas may have clear cytoplasm. Histological features aid in the diagnosis of clear cell carcinoma includes (1) admixture of papillary, tubulocystic and solid patterns, (2) stromal hyalinization (3) relatively uniform high-grade nuclei with low mitotic count (<8/10HPF), and (4) presence of endometriosis.
3. Serous carcinoma as one of the differential diagnoses shows high grade pleomorphic nuclei with a high mitotic count (>10/10HPF) and cellular stratification. Immunohistochemistry aids in differentiating clear cell carcinoma from high-grade serous carcinoma as the former is positive for Napsin A and negative for WT1 and ER, whereas the latter shows the reverse pattern of immunoreactivity.
4. Mixed carcinoma of the ovary is diagnosed when there are two or more different histologies irrespective of their percentages and supported by ancillary testing. The most common combination is endometrioid and clear cell carcinomas, supported by PR expression in the former component and Napsin A expression in the latter component. However, a diagnosis of clear cell carcinoma should be retrained if areas unequivocally showing high-grade serous carcinoma are present, as many high-grade serous carcinomas can contain clear cells.

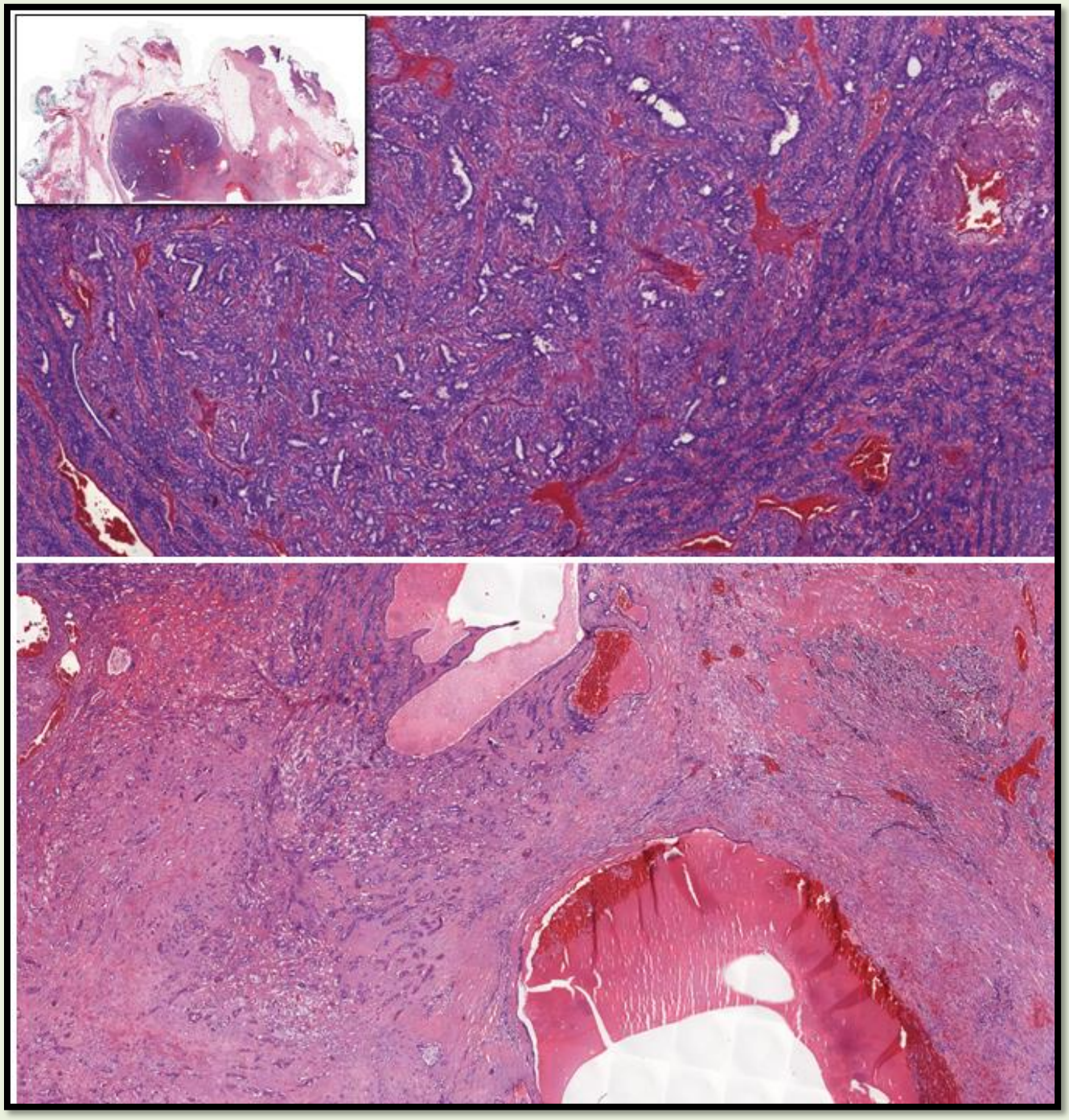
Reference:

1. WHO Classification of Tumours Editorial Board. Female Genital Tumours: WHO Classification of Tumours, 5th ed.; IARC: Lyon, France (2020).

Case 2

Case 2: A 50-year-old lady was noted to have a breast mass on mammography. A lumpectomy was performed following an abnormal biopsy finding. One representative section.

Targeted Diagnosis: **Intraductal papilloma with post-biopsy changes**



Case 2

Submitted Diagnoses by Participating Institutions	Number	
Intraductal papilloma/ Intraductal papilloma with sclerosing adenosis. Comment: Immunohistochemistry (e.g. p63, ER and PR) for confirmation.	8	Acceptable
Intraductal papilloma with florid hyperplasia. Suggest IHC stains for myoepithelial layer.	1	Acceptable
Adenomyoepithelioma/ Adenomyoepithelioma with infarction. Suggest for p63 and CK 5/6 stains.	2	Acceptable
Benign breast lesion (differential diagnoses include: 1) adenomyoepithelioma; 2) intraductal papilloma) with adjacent sclerosing adenosis	1	Acceptable
Intraductal papillary neoplasm. p63 IHC/ Papillary neoplasm, with suspicious of invasion. Require confirmation with p63.	2	Acceptable
Encapsulated papillary carcinoma/ Encapsulated papillary carcinoma, suspicious of invasion. p63 IHC to exclude invasion/ Encapsulated papillary carcinoma/ Encapsulated papillary carcinoma with post procedural changes	5	
Solid papillary carcinoma	1	
Invasive breast carcinoma with atypical intraductal papilloma	1	

Educational notes:

1. There is an intraductal mass composed of compact arborizing papillae with fibrovasular cores. They are lined by ductal epithelial cells with underlying myoepithelial cells. Myoepithelial cells are prominent at areas. There is an area of fibrosis with entrapped small glands and surrounding chronic inflammatory cells and hemosiderin-laden histiocytes, consistent with post-biopsy changes.
2. The dual populations of ductal epithelial cells and myoepithelial cells in this intraductal mass are recognized, excluding a malignant process such as encapsulated papillary carcinoma. The differential diagnosis includes intraductal papilloma and adenomyoepithelioma with a papillary architecture. The distinction maybe difficult as adenomyoepithelioma may represent variants of intraductal papilloma; adenomyoepithelioma usually has numerous, plumper, and prominent myoepithelial cells as compared to the intraductal papilloma.
3. Hemorrhage, infarction, and fibrosis/ sclerosis may occur in intraductal papilloma following needle core biopsy or due to torsion of fibrovascular cores. Epithelial glands and nests maybe entrapped or displaced in the fibrotic area, which warrants careful interpretation to avoid misinterpretation as an invasive carcinoma. These entrapped or displaced epithelial glands and nests retain myoepithelial cells at least focally, assuring the benignity.

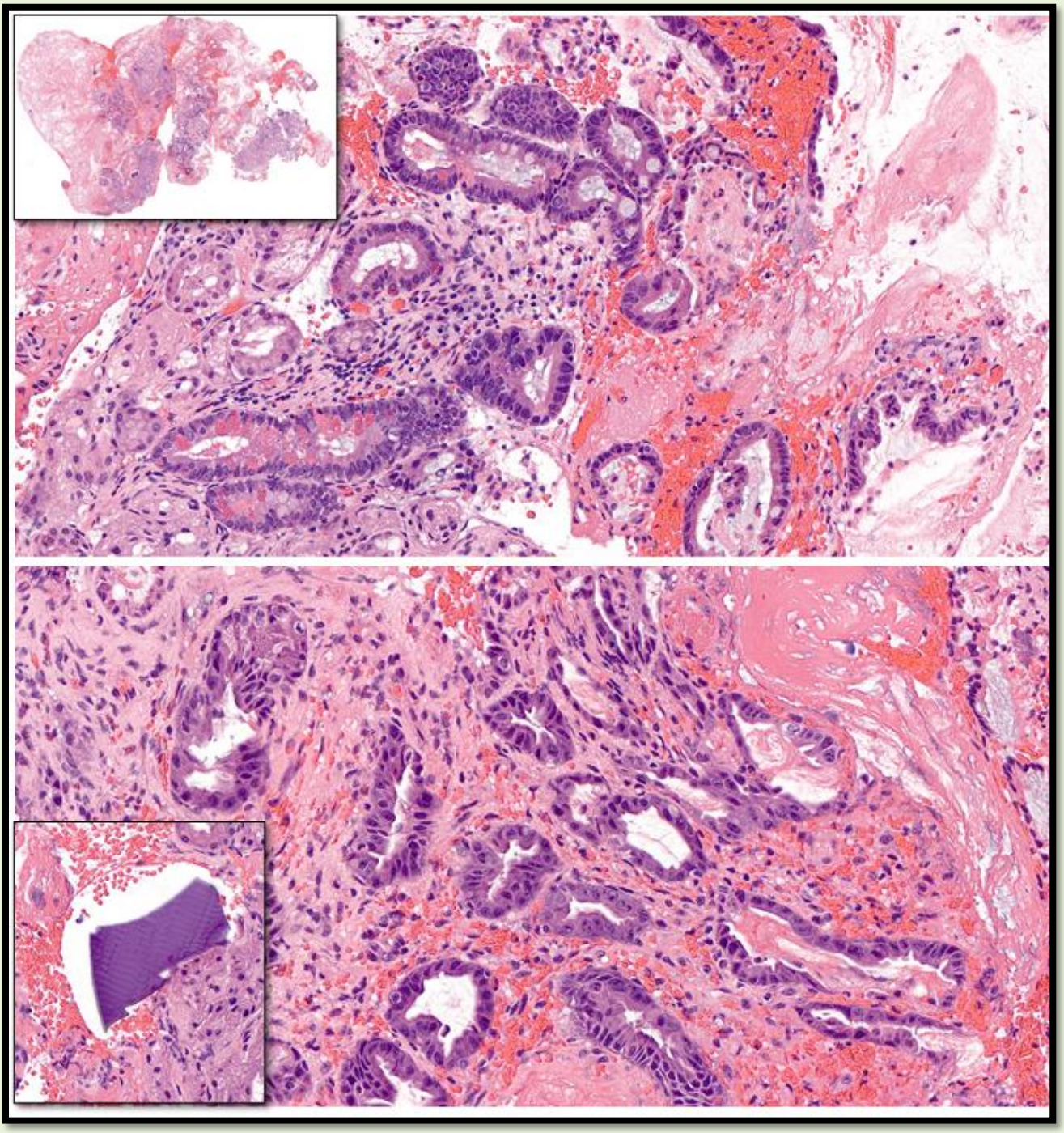
Reference

1. WHO Classification of Tumours Editorial Board. Breast Tumours: WHO Classification of Tumours, 5th ed.; IARC: Lyon, France (2019).

Case 3

Case 3: A 55-year-old man diagnosed with perforated stomach ulcer. Biopsy was taken from ulcer site. One representative section.

Targeted Diagnosis: **Acute erosive/hemorrhagic gastritis in the background of chronic gastritis with intestinal metaplasia, Kayexalate-associated; Indefinite for dysplasia**



Case 3

Submitted Diagnoses by Participating Institutions	Number	
Chronic gastritis with intestinal metaplasia, ulcer and associated with kayexalate/ Benign ulcer edge with intestinal metaplasia and kayexalate changes/ Benign ulcer with reactive chemical gastropathy, likely kayexalate induced/ Kayexalate-associated injury with intestinal metaplasia/ Reactive gastropathy with intestinal metaplasia, likely related to Kayexalate	7	Acceptable
Acute mucosal injury secondary to kayexalate/resin induced and indefinite for dysplasia/ Benign ulcer edge with intestinal metaplasia and regenerative atypia/ Benign ulcer with intestinal metaplasia and indefinite dysplasia/ Chronic gastritis with intestinal metaplasia, indeterminate for dysplasia. Kayexalate changes are present	4	Acceptable
Chronic gastritis with intestinal metaplasia/ Reactive (chemical) gastropathy in the background of chronic gastritis	2	
Ulcer edge with high grade dysplasia and intestinal metaplasia and background kayexalate crystals/ High grade dysplasia and intestinal metaplasia/ High grade dysplasia, in a background of intestinal metaplasia and atrophic gastritis/ Ulcer edge with dysplasia and intestinal metaplasia.	6	
High grade dysplastic glands, adjacent adenocarcinoma cannot be totally excluded/ Chronic gastritis with intestinal metaplasia and high-grade dysplasia with areas suspicious for invasion	2	

Educational notes:

1. There are fragments of eroded gastric mucosa associated with fibrin and hemorrhage. Complete intestinal metaplasia of the glands is observed with presence of goblet cells, absorptive cells, and Paneth cells. Some glands are haphazardly arranged without complex architecture; they are lined by a layer of short columnar to cuboidal cells displaying atypical nuclei with prominent nucleoli. These cytologically abnormal glands do not extend to the surface epithelium. A focus of kayexalate crystals, which are basophilic with a "fish scale" appearance, is noted. The lamina propria contains focal lymphoplasmacytic infiltrates.
2. Kayexalate crystals are likely a contributing factor for this erosive/hemorrhagic gastritis. The biopsy also shows underlying chronic gastritis with complete intestinal metaplasia. Interpretation of the glands with atypical nuclei poses diagnostic challenge in differentiating bona fide dysplasia from regenerative/reparative atypia. Bona fide dysplasia should extend to the surface of the gastric mucosa for both intestinal and foveolar-type dysplasia. Presence of superimposed erosion/ulcer should be a caveat not to overinterpret the cytological atypia. In cases where cytological atypia is worrisome but not certain for dysplasia, “indefinite for dysplasia” is rendered. Subsequent endoscopic evaluation and biopsy is recommended.

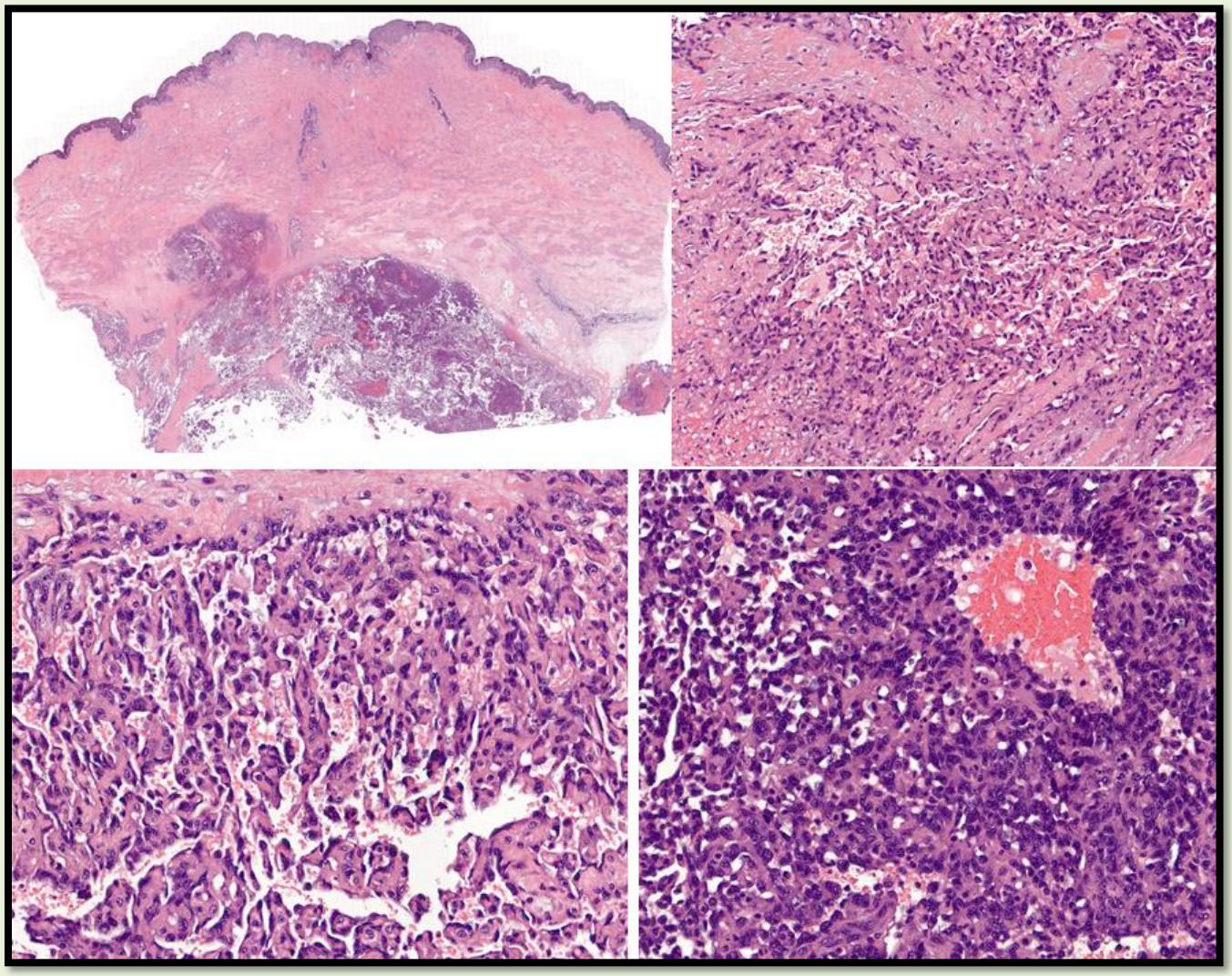
Reference

1. Lamps, L. W., Bellizzi, A. M., Frankel, W. L., Owens, S. R., & Yantiss, R. K. (2015). Neoplastic Gastrointestinal Pathology: An Illustrated Guide. Springer Publishing Company.

Case 4

Case 4: A 42-year-old lady presented with an enlarging right breast mass. Mastectomy was performed. One representative section.

Targeted Diagnosis: **Primary angiosarcoma of the breast, intermediate grade**



Case 4

Submitted Diagnoses by Participating Institutions	Number	
Angiosarcoma, intermediate grade/ Angiosarcoma, high grade/ Angiosarcoma	20	Acceptable
Invasive micropapillary carcinoma.	1	

Educational notes:

1. There is an infiltrative tumor in the breast parenchyma involving the deep dermis. This tumor shows a vasoformative growth pattern with anastomosing vascular channels dissecting the collagenous stroma. These vascular channels are lined by markedly pleomorphic endothelial cells forming papillary projections and focal solid multi-layering pattern.
2. Angiosarcoma of the breast arises de novo or post-radiation. De novo primary breast angiosarcomas are usually deeply located with or without cutaneous involvement. Post-radiation angiosarcomas are predominantly dermal based tumors with variable degrees of invasion into the subcutaneous tissue. Both types of angiosarcoma show a range of well, intermediate to poorly differentiated morphologies. Immunohistochemically, strong MYC expression is observed in the post-radiation angiosarcoma due to *MYC* gene amplification whereas MYC is not expressed in de novo primary breast angiosarcoma.

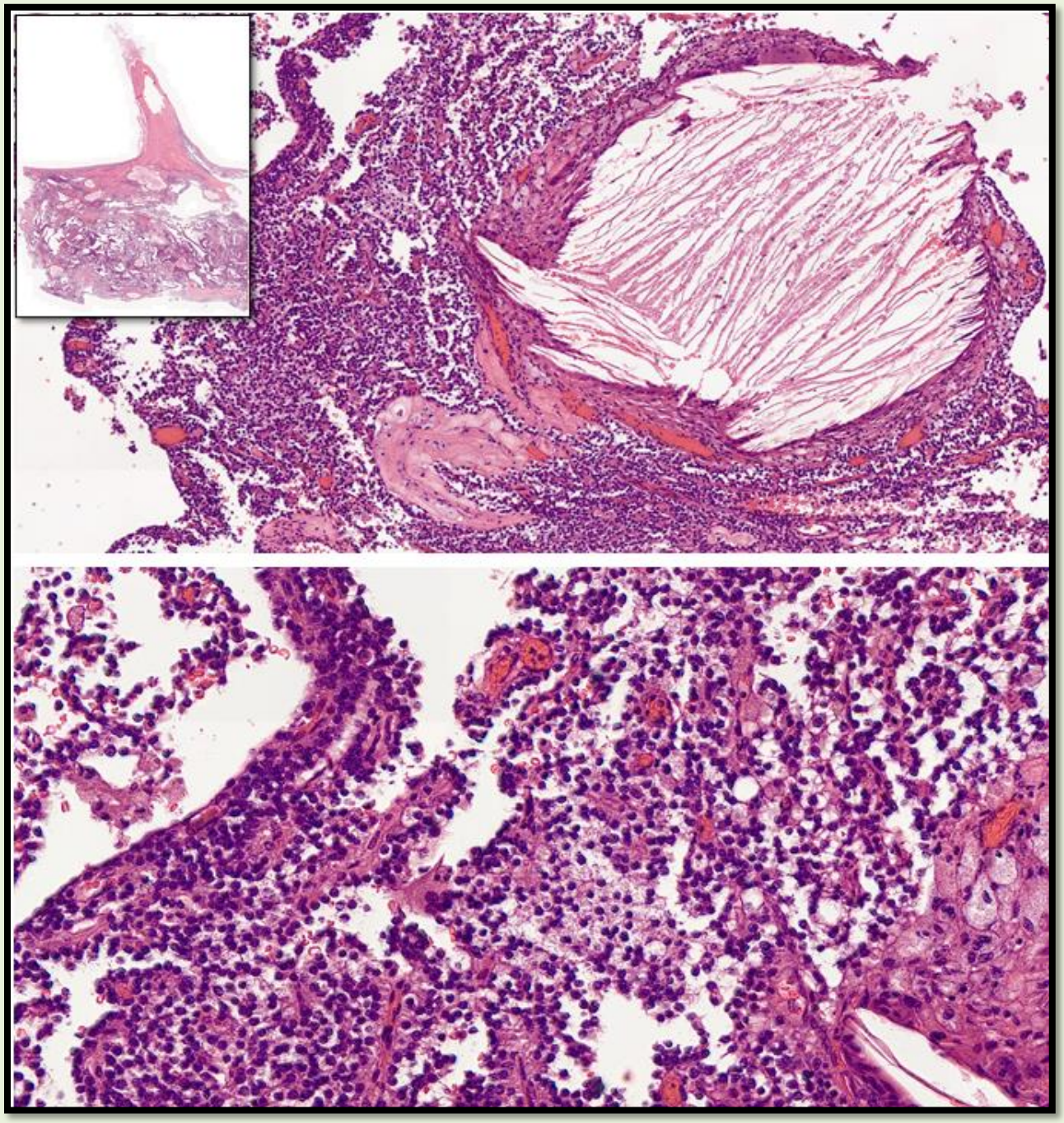
Reference

1. WHO Classification of Tumours Editorial Board. Breast Tumours: WHO Classification of Tumours, 5th ed.; IARC: Lyon, France (2019).

Case 5

A 26-year-old woman presented with maternal pyrexia. Radiological imaging showed a mass on the body and tail of the pancreas.

Targeted Diagnosis: **Solid pseudopapillary neoplasm of the pancreas**



Case 5

Submitted Diagnoses by Participating Institutions	Number	
Solid pseudopapillary neoplasm of the pancreas	20	Acceptable
Angiosarcoma	1	

Educational notes:

1. This tumor mass is circumscribed with cystic spaces. The tumor cells are loosely cohesive, forming pseudopapillae and surrounding hyalinized broad fibrovascular cores. The tumor cells are monomorphic with small hyperchromatic nuclei. There are secondary changes of cholesterol crystals and foamy histiocytes. These histological features are that of solid pseudopapillary neoplasm (SPN) of the pancreas.
2. 90% of SPNs occur in adolescent girls and young women. They are discovered incidentally by imaging or due to abdominal discomfort. They are not associated with functional endocrine syndrome.
3. Morphologically, SPN may need to be differentiated from well-differentiated neuroendocrine neoplasm or acinar cell carcinoma due to its solid appearance and monomorphic cellular feature. In contrast to neuroendocrine neoplasm or acinar cell carcinoma, SPN expresses nuclear beta-catenin and are negative for chromogranin A, trypsin and/or BCL-10.
4. Although the long-term prognosis for SPN is excellent with long disease-free survival for localized, metastatic or recurrence disease after treatment, SPN is regarded as a low-grade malignant neoplasm as there were a few patients died of metastatic SPNs.

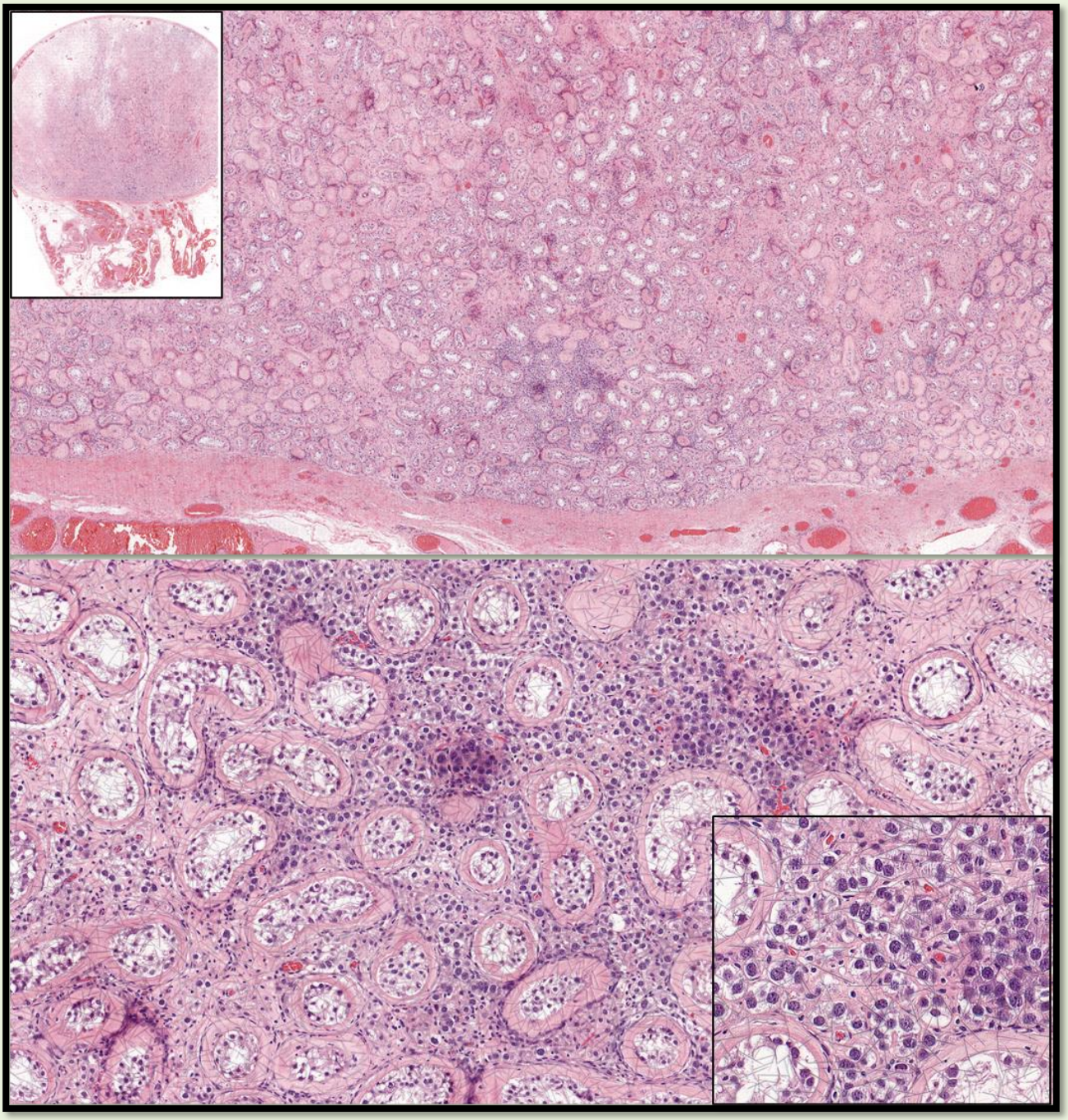
Reference

1. WHO Classification of Tumours Editorial Board. Digestive System Tumours: WHO Classification of Tumours, 5th ed.; IARC: Lyon, France (2019).

Case 6

Case 6: A 29-year-old man with an incidental finding of undescended testis, diagnosed during investigation for scrotal inguinal hernia.

Targeted Diagnosis: **Seminoma (exclusively intertubular growth pattern), focal intratubular seminoma, and germ cell neoplasia in situ in an atrophic testis**



Case 6

Submitted Diagnoses by Participating Institutions	Number	
Seminoma with germ cell neoplasia in situ/Seminoma with germ cell neoplasia in situ (GCNIS) and tubular atrophy/ Intertubular seminoma with focal intratubular seminoma. Comment: For SALL4 and CD117 for confirmation/ Germ cell neoplasia in situ (GCNIS) with invasion/ Germ cell neoplasia in situ (GCNIS) with invasion	19	Acceptable
Testicular atrophy with intratubular germ cell neoplasia.	2	

Educational notes:

1. The testis is atrophic, composed of widely separated seminiferous tubules characterized by marked thickened basement membrane. In the interstitium, there are infiltrating large neoplastic cells showing round nuclei with small nuclei and a small rim of clear to pale cytoplasm. Similar neoplastic cells are observed completely filling a few seminiferous tubules and lining the seminiferous tubules in single or multi-layered pattern. These histological features are consistent with seminoma with exclusively intertubular growth pattern without mass formation apart from intratubular seminoma and germ cell neoplasia in situ.
2. Seminoma with intertubular growth pattern is common at the periphery of mass-forming seminoma. However, seminoma with exclusively intertubular growth pattern is exceedingly rare and might be overlooked due to lack of an expansile lesion. This variant of seminoma is usually associated with cryptorchidism or infertility.
3. Clue to recognition of this variant of seminoma with exclusively intertubular growth pattern is the presence of diffuse germ cell neoplasia in situ, which requires close examination of cytological features for enlarged nuclei with nucleoli and clear cytoplasm. One should hold a low threshold for infiltration by similar neoplastic cells in the interstitium and not to disregard as Leydig cells or inflammatory cells. Immunohistochemistry for c-Kit (CD117), OCT3/4 and SALL4 would be helpful to highlight these neoplastic cells.
4. Seminoma with exclusively intertubular growth pattern is regarded as a variant of seminoma seemingly to have behavior comparable to classic seminoma. Cases presented with metastases have been previously documented.

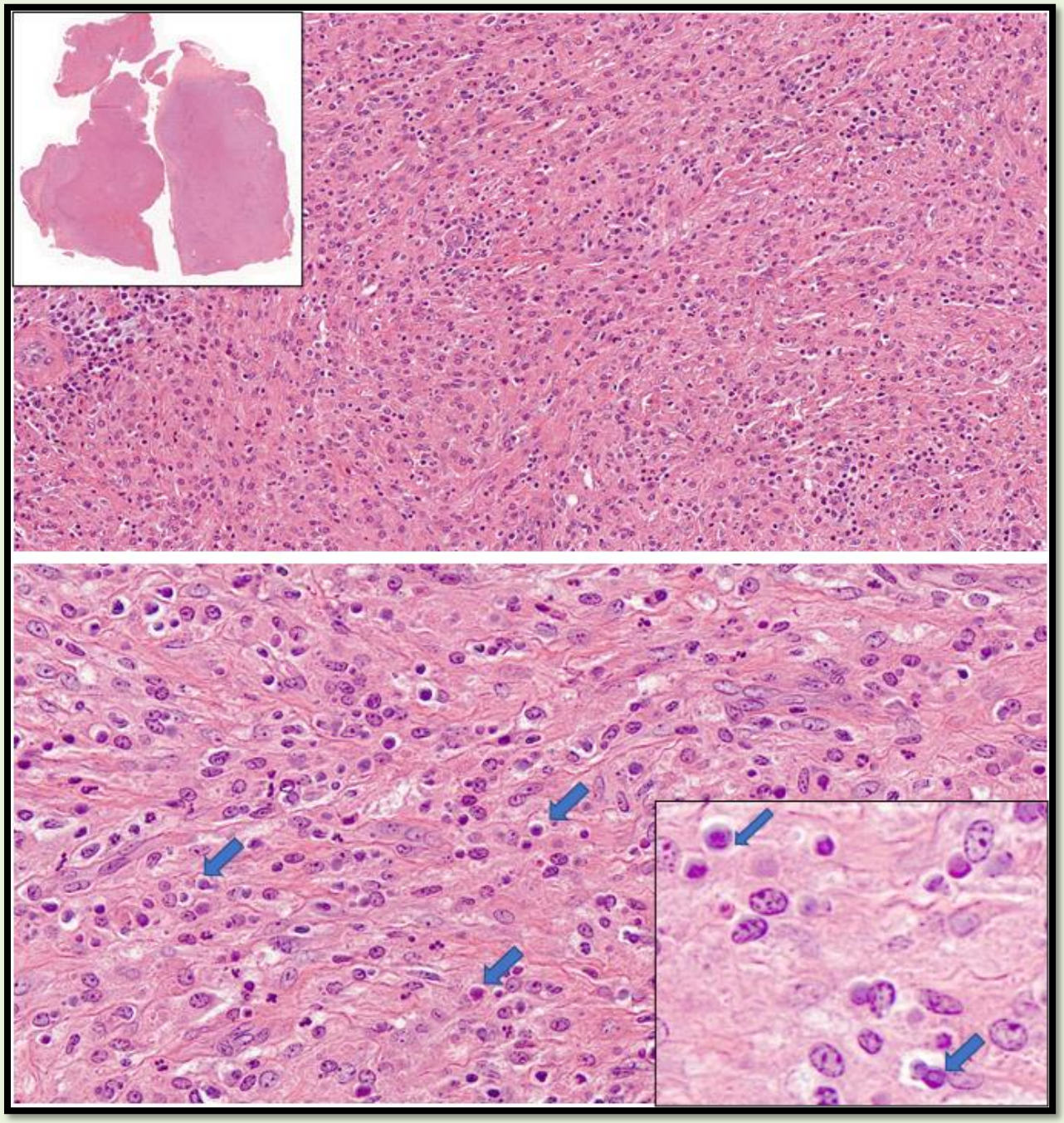
Reference:

1. Chu, Y. H., Huang, W., & Hu, R. (2018). Exclusively intertubular seminoma arising in undescended testes: Report of two cases. Human Pathology: Case Reports, 11, 15-18.

Case 7

Case 7: A 46-year-old lady with underlying Systemic Lupus Erythematosus, presented with a right perinephric mass. One representative section.

Targeted Diagnosis: **Malakoplakia**



Case 7

Submitted Diagnoses by Participating Institutions	Number	
Malakoplakia	17	Acceptable
Differential could be Malakoplakia, Angiomyolipoma etc	1	Acceptable
Inflammatory myofibroblastic tumour	2	
Histoplasmosis	1	

Educational notes:

1. There are sheets of histiocytoid cells admixed with neutrophils, lymphocytes, and plasma cells. Within the eosinophilic cytoplasm of histiocytoid cells, round basophilic inclusions characterized by concentric laminations surrounded by a halo are observed. These inclusions represent Michaelis-Gutmann bodies and the lesion is consistent with malakoplakia.
2. Malakoplakia is most frequently observed in the urinary tracts as a complication of recurrent infections. The pathogenesis of malakoplakia is related to the impairment of mononuclear cells in degrading phagocytosed bacteria.
3. Morphologically, malakoplakia is characterized by sheets of histiocytes with granular eosinophilic cytoplasm (von Hansemann cells) and small basophilic intracytoplasmic inclusions (Michaelis-Gutmann bodies). Michaelis-Gutmann bodies are said to be formed via precipitation of calcium or iron on bacteria or bacterial fragments. Michaelis-Gutmann bodies could be highlighted by von Kossa stain for calcium and Perl's Prussian blue stain for iron. Careful search for Michaelis-Gutmann bodies is needed to avoid overlooking malakoplakia, especially when Michaelis-Gutmann bodies are relatively few in the fibrosing phase of the disease.

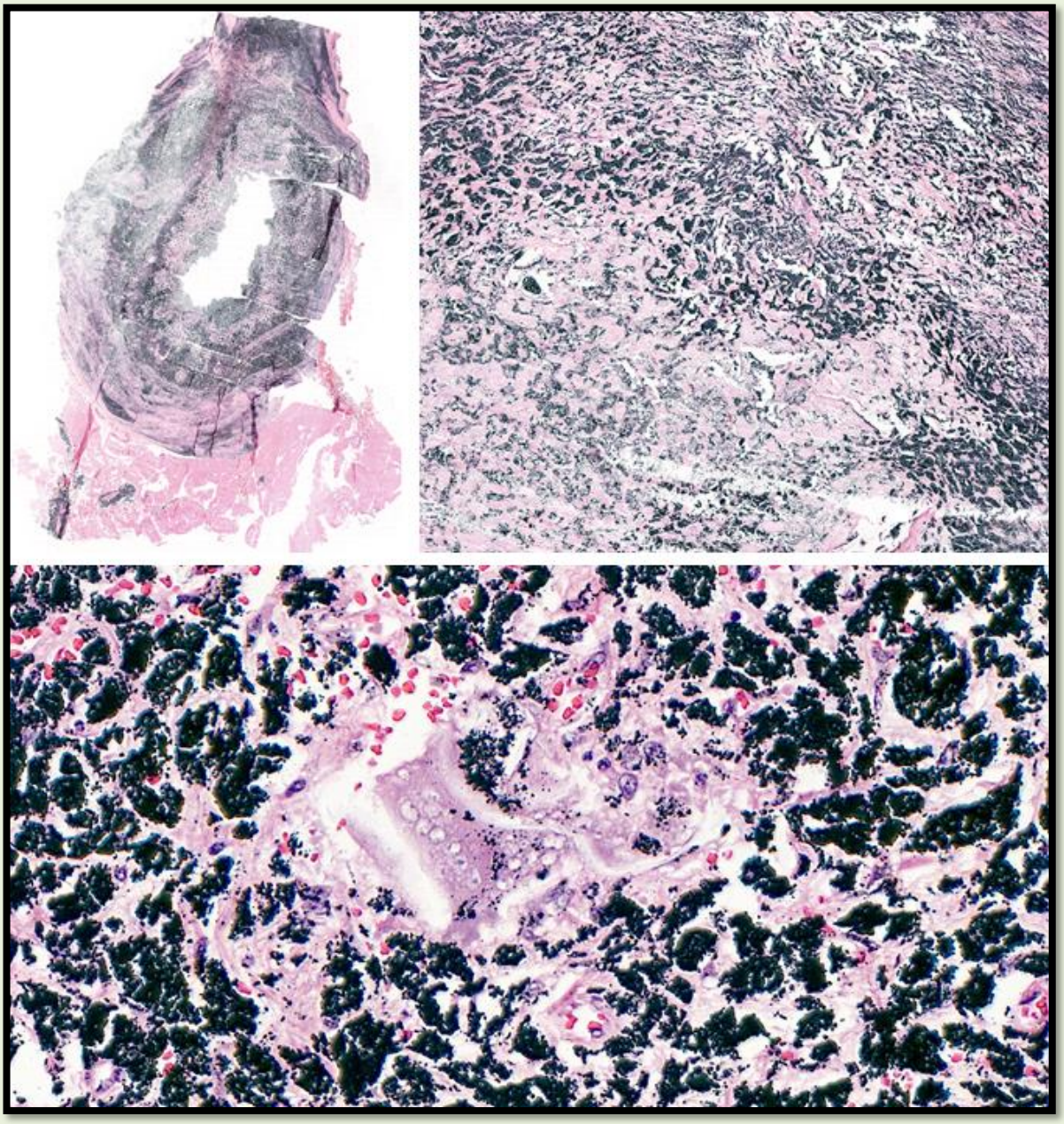
Reference

1. Amin, M. B., Eble, J., Grignon, D., & Srigley, J. (2014). Urological pathology. Lippincott Williams & Wilkins.

Case 8

Case 8: A 32-year-old man with a past medical history of left distal femur endoprosthesis due to osteosarcoma. He presented with left knee pain and difficulty walking. Pseudocapsule removal was performed. One representative section.

Targeted Diagnosis: **Metallosis/ Periprosthetic membrane of the wear particle induced type**



Case 8

Submitted Diagnoses by Participating Institutions	Number	
Implant-associated metallosis/ Metallosis or metal-induced synovitis	18	Acceptable
Implant-related changes	1	Acceptable
Local argyria	1	
Ochronosis	1	

Educational notes:

1. Section shows infiltration by histiocytes in the fibrotic tissue. The histiocytes are heavily laden with fine dark particles. Focal multinucleated giant cells are noted. Lymphocytic infiltrates are scanty. This represents periprosthetic membrane of the wear particle induced type (type I) with non-ferrous metal particles.
2. Several terminologies are used to describe non-infectious implant failure. Adverse local tissue reactions (ALTR)/ adverse reactions to metallic debris (ARMD) are umbrella terms used to describe adverse reaction to particulate wear debris. Metallosis is used to describe accumulation of metallic wear debris in periprosthetic tissue of large and small joints, and metallic fixation devices.
3. A revised histopathological consensus classification of joint implant related pathology includes four major histological patterns as follows:

Periprosthetic membrane of the wear particle induced type (type I)	Infiltration of macrophages and multinuclear giant cells in which prosthesis wear can be detected.
Periprosthetic membrane of the infectious type (type II)	Infection of low or high grade characterized by the presence of neutrophils. Various cutoffs of the number of neutrophils per field of vision have been proposed to define low grade periprosthetic joint infection.
Periprosthetic membrane of the combined type (type III)	Histological features of both type I and type II.
Periprosthetic membrane of the indeterminate type (type IV)	Paucicellular connective tissue rich in collagen fibers.

4. Prosthesis wear particles could be identified based on light microscopical features, optical properties under polarized light and special stains such as Prussian blue reaction according to the histopathological particle algorithm as laid out in the consensus.

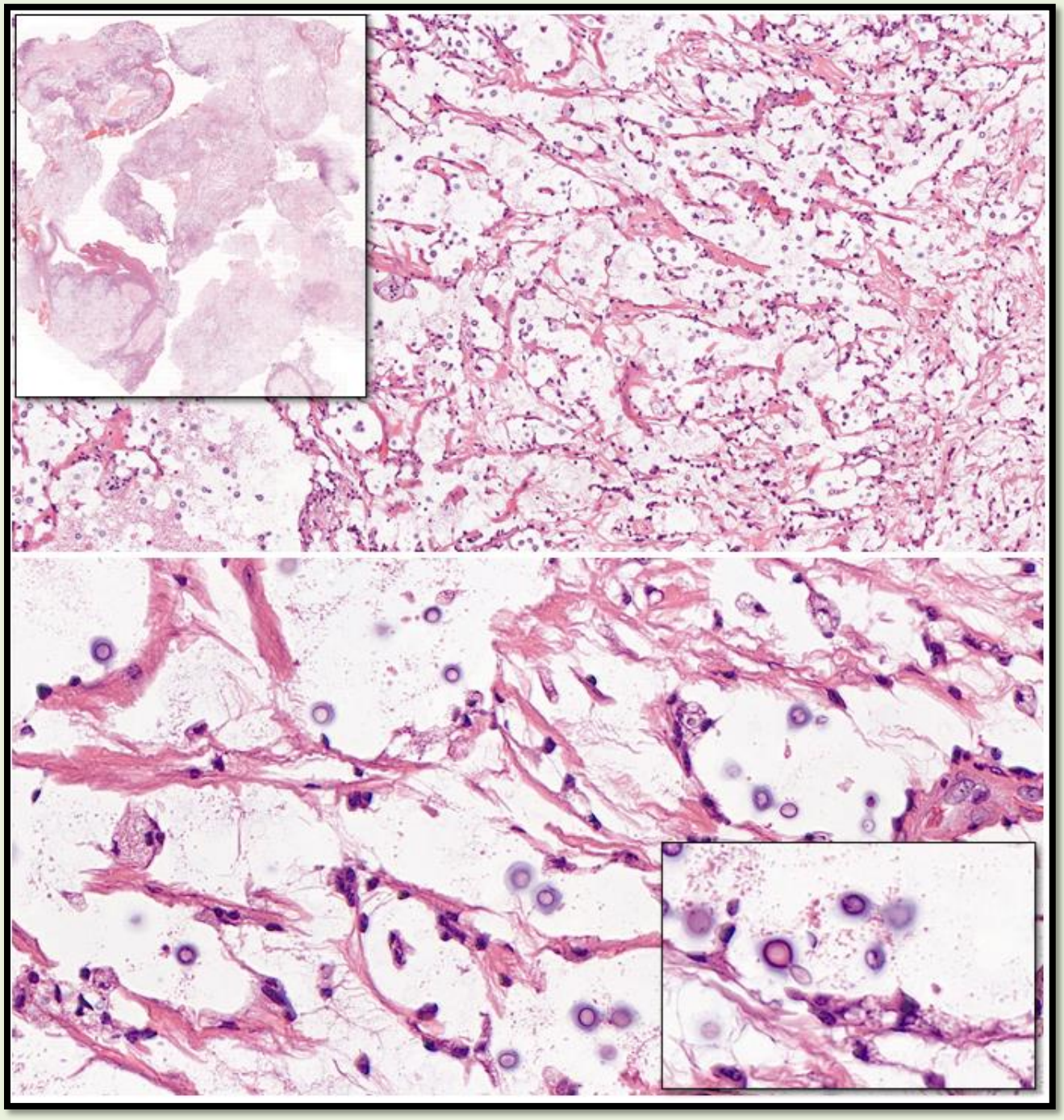
Reference

1. Krenn, V., Morawietz, L., Perino, G., Kienapfel, H., Ascherl, R., Hassenpflug, G. J., ... & Gehrke, T. (2014). Revised histopathological consensus classification of joint implant related pathology. Pathology-Research and Practice, 210(12), 779-786.

Case 9

Case 9: A 50-year-old man underwent brain biopsy for an intracranial lesion. One representative section.

Targeted Diagnosis: **Cryptococcosis**



Case 9

Submitted Diagnoses by Participating Institutions	Number	
Cryptococcosis/ Cryptococcal encephalitis/ Cryptococus neoformans.	21	Acceptable

Educational notes:

1. There are multiple fragments of edematous tissue fragments displaying many scattered fungal bodies with minimal inflammatory infiltrates. These fungal bodies appear as narrow-based budding yeasts with the size larger than the red blood cells. They show a thick fibrous capsule. These features are consistent *cryptococcus spp.*
2. Cryptococcosis is caused by several *Cryptococcus* species such as *C. neoformans* and *C. gattii*. Lung is the primary site due to inhalation of cryptococcal yeasts or basidiospores. Majority display pneumonia, cryptococcomas, or pleural effusions. The frequency of dissemination from the lung to the central nervous system (meningitis or cryptococcomas), skin, bones, or other tissues depends on the immune status of the patients.
3. Histological reactions range from well-formed granulomas to minimal inflammation. Cryptococci are identified as encapsulated, spherical to oval yeasts, measuring 5 to 10 µm in diameter. They have narrow-based budding and a thick capsule. The capsule is stained positive with Alcian blue stain, mucicarmine stain, Grocott or Gomori methenamine silver satin, PAS stain and Fontana-Masson stain. Fontana-Masson stain will help to differentiate cryptococci from other yeasts of similar size, such as *Candida spp*. or *Histoplasma* in cases whereby capsule of cryptococci appears thinner.

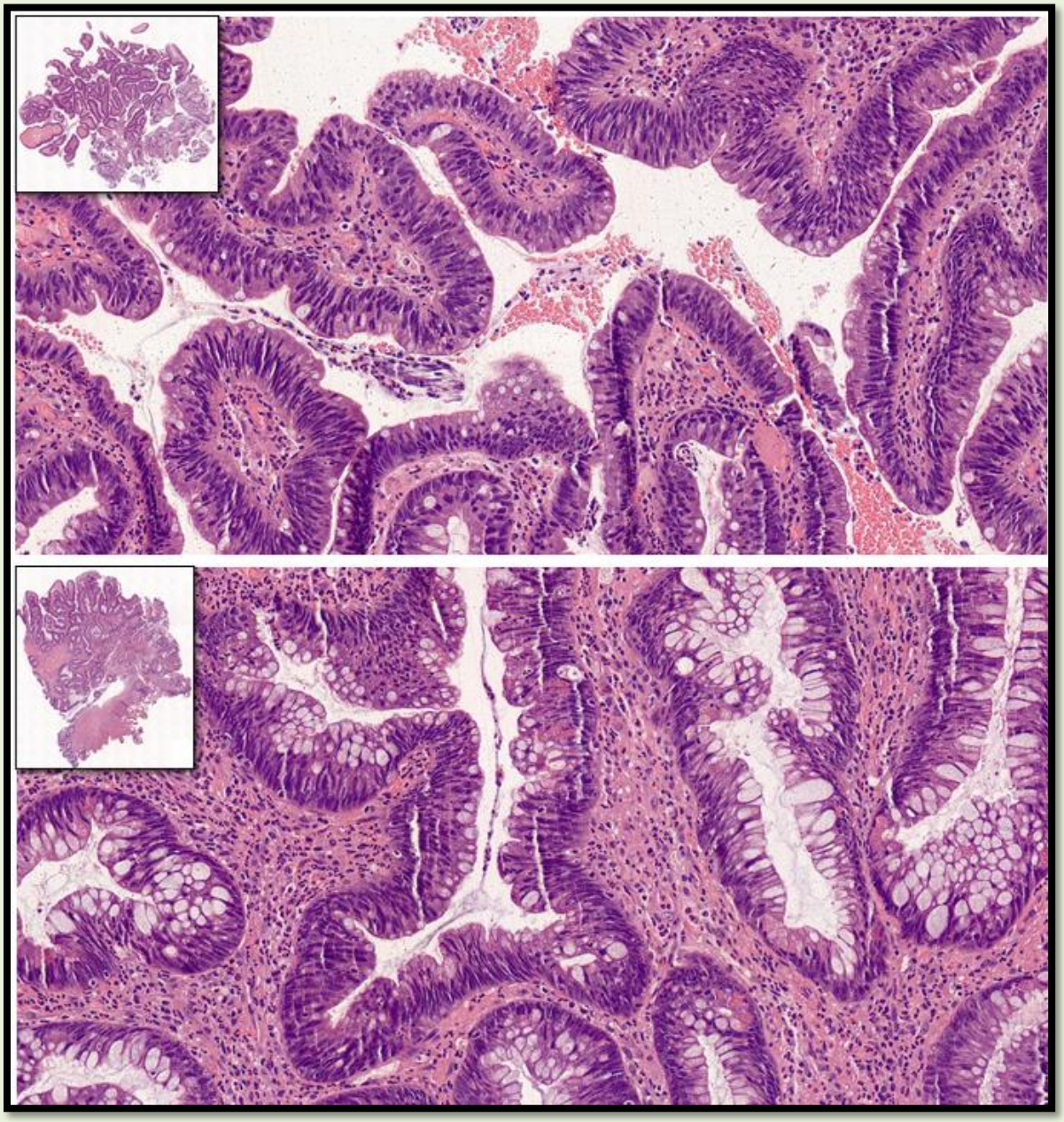
Reference

1. Guarner, J., & Brandt, M. E. (2011). Histopathologic diagnosis of fungal infections in the 21st century. Clinical microbiology reviews, 24(2), 247-280.

Case 10

Case 10: A 78-year-old man was noted to have a small bladder lesion on cystoscopy. He had a past medical history of adenocarcinoma of the colon. Biopsy of the bladder lesion was performed. One representative section.

Targeted Diagnosis: **Cystitis glandularis of intestinal type with low grade dysplasia/ villous adenoma of the bladder**



Case 10

Submitted Diagnoses by Participating Institutions	Number	
Cystitis cystica et glandularis with low grade dysplasia/ Villous adenoma with low grade dysplasia in background of cystitis cystica et glandularis (intestinal-type metaplasia).	2	Acceptable
Villous adenoma, low grade dysplasia/ Villous adenoma	8	Acceptable
Tubulovillous adenoma with low grade metaplasia/ Tubulovillous adenoma of bladder. Need IHC to exclude colonic origin/ Primary tubulovillous adenoma with moderate dysplasia	3	Acceptable
Villous adenoma, low grade dysplasia with a focus of cauterized artifact, suspicious of invasion; repeat biopsy	1	Acceptable
Cystitis with goblet cell and intestinal metaplasia/ Cystitis glandularis with intestinal metaplasia	2	
Adenocarcinoma arising from villous adenoma (high grade). Correlate clinically in view of past medical history of colon adenocarcinoma./ Adenocarcinoma, enteric type. A primary bladder tumour or adjacent invasion from colorectal carcinoma has to be excluded/ Invasion of well-differentiated colorectal adenocarcinoma/ Adenocarcinoma enteric-type/ Adenocarcinoma (? primary intestinal type, ?metastatic for IHC).	5	

Educational notes:

1. These two fragments of tissue display tubulovillous architecture lined by intestinal-type epithelium with goblet cells and focal Paneth cells. The intestinal-type epithelium however exhibits diffuse low-grade adenomatous dysplasia characterized by enlarged, hyperchromatic and pencillate nuclei arranged in a stratified configuration along the basement membrane. These features are best regarded as cystitis glandularis of intestinal type with low grade dysplasia (CGLGD)/ villous adenoma (VA) of the bladder.
2. The histological features of these fragments resemble biopsies derived from the lower gastrointestinal tract with evidence of diffuse low dysplasia characterized by pencillate nuclei arranged in a stratified configuration along the basement membrane. Dysplastic glands in both VA and CGLGD show similar cytological features; nonetheless, VA is usually diagnosed when the villous architecture is more apparent, composed exclusively of dysplastic glands, whereas CGLGD is diagnosed when intestinal-type glands without dysplasia is also recognized within the lesion. In addition, earliest case reports have documented VA arising from cystitis glandularis. Thus, the destination of VA and CGLGD seems to depend on the percentage of dysplastic glands in a lesion.
3. Recognition of dysplasia in this lesion is important as both VA and CGLGD may be associated with adenocarcinoma. Distinction from adenocarcinoma is based on histological features of infiltrative glands associated with stromal reaction as well as muscularis propria invasion.

Reference

1. McKenney, J. K. (2019). Precursor lesions of the urinary bladder. Histopathology, 74(1), 68-76.
2. Amin, M. B., Eble, J., Grignon, D., & Srigley, J. (2014). Urological pathology. Lippincott Williams & Wilkins.