International Academy of Pathology
Malaysian Division

FINAL REPORT

QUALITY ASSURANCE PROGRAM
GENERAL DIAGNOSTIC HISTOPATHOLOGY
CYCLE 02/2018

NOTES FROM THE COORDINATOR

1. For this cycle 02/2018, a total of 23 sets of DVDs had been circulated. 21 institutions responded by the closing date of 15 November 2018.

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 01/2018 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. Norizal Mohd Noor, Dr. Yusri Yusuf, Dr. Fazilah Hassan, Dr. Faizah Ahmad, and Dr. Nurul Akmar Misron.

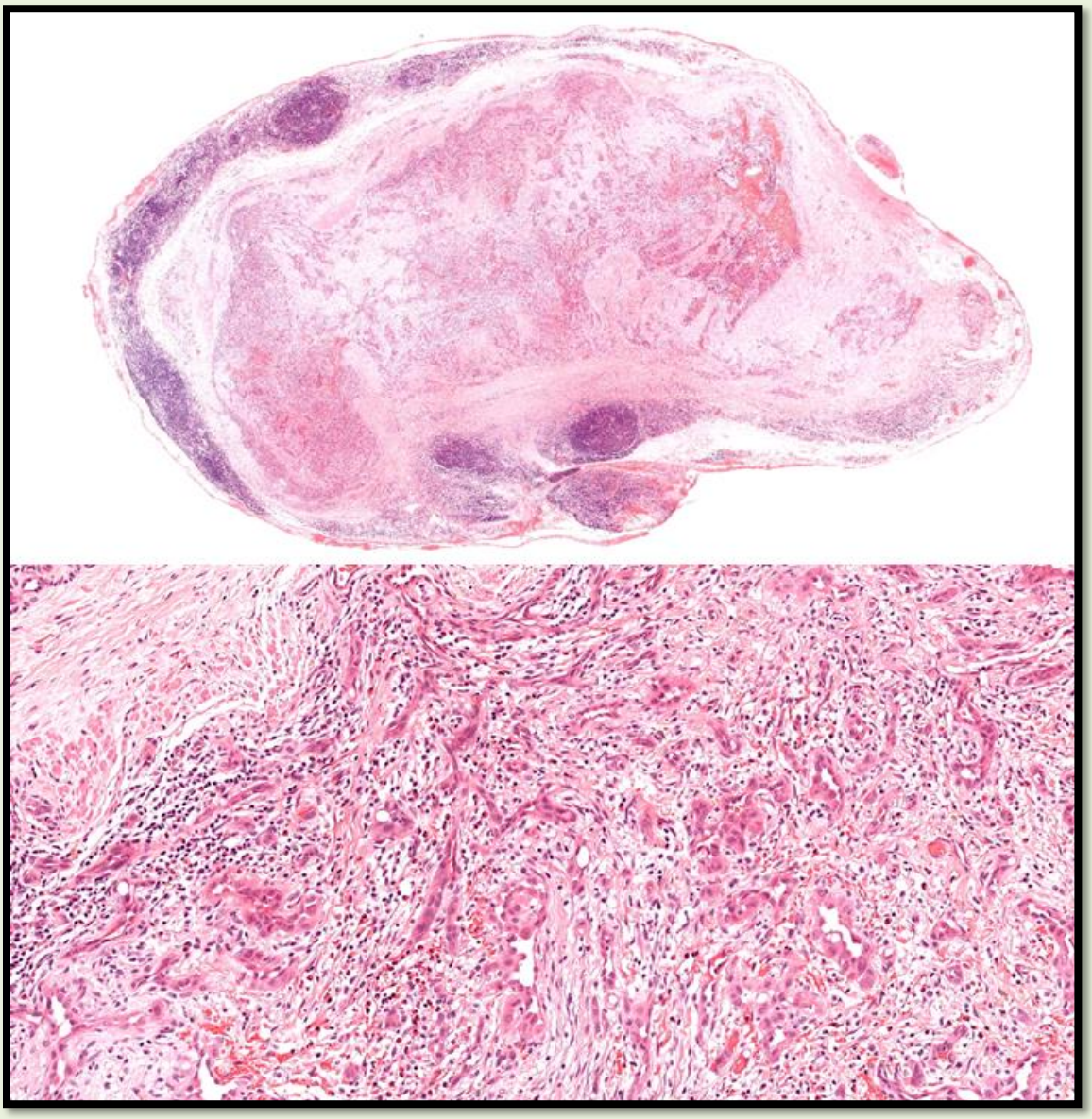
Prepared by,

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

Case 11

Case 1: 25 y.o., male, forehead nodule. One representative section.

Targeted Diagnosis: **Angiolymphoid hyperplasia with eosinophilia AKA Epithelioid hemangioma**



Case 11

Submitted Diagnoses by Participating Institutions	Number	
Angiolymphoid hyperplasia with eosinophilia / Epithelioid hemagioma	20	Acceptable
Masson tumor	1	

Educational notes:

1. The well-circumscribed nodule shows angiolymphoid hyperplasia with eosinophilia (ALHE) A.K.A. epithelioid hemangioma. Lymphoid reaction with lymphoid follicles is observed at the periphery of the nodule. At the center, proliferation of small blood-vessels lined by epithelioid endothelial cells is noted. There is no obvious cytological atypia of the epithelioid endothelial cells. Numerous eosinophils and lymphocytes are scattered in the fibromyxoid stroma.
2. Histologically ALHE resembles Kimura's disease. Kimura's disease also shows prominent lymphoid follicles with inflammatory cell infiltrates including eosinophils. However, in Kimura's disease, the proliferating vessels are high endothelial venules. Eosinophil microabscesses and infiltration of germinal centers by eosinophils are characteristics of Kimura's disease.
3. ALHE is differentiated from epithelioid hemangioendothelioma and epithelioid angiosarcioma. Epithelioid hemangioendothelioma shows infiltrative growth pattern with myxoid to hyaline stromal matrix. Significant cytological atypia with macronucleoli and mitoses are observed in epithelioid angiosarcoma.

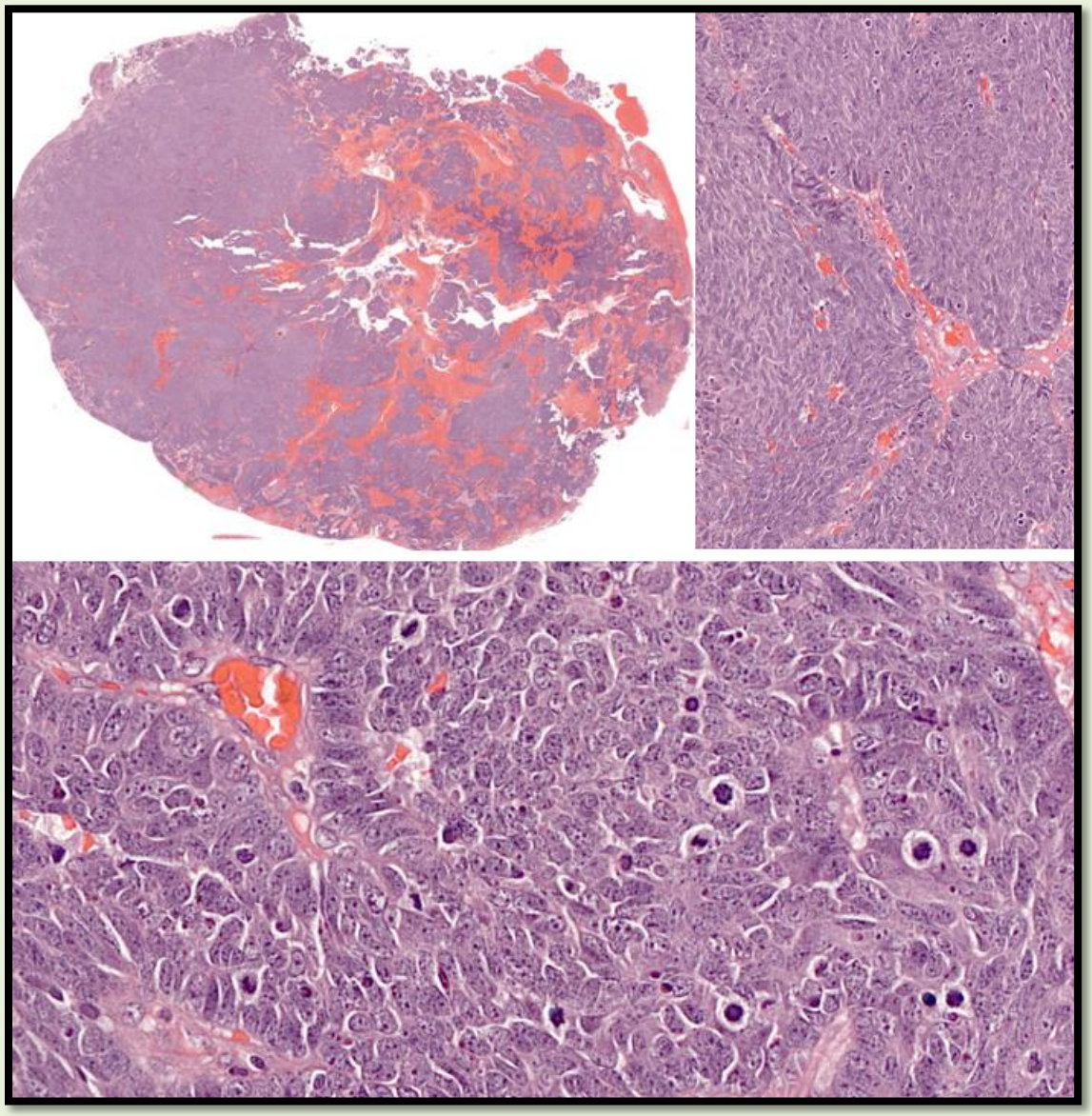
Reference:

1. McKee's Pathology of the Skin with Clinical Correlations. 4th Edition. Elsevier/Saunders, 2012

Case 12

Case 12: 23 y.o., female, cervical polyp. One representative section.

Targeted Diagnosis: **Small cell neuroendocrine carcinoma**



Case 12

Submitted Diagnoses by Participating Institutions	Number	
High grade neuroendocrine carcinoma	2	Acceptable
Small cell carcinoma, Small cell neuroendocrine carcinoma	5	Acceptable
Neuroendocrine carcinoma	4	Acceptable
Large cell neuroendocrine carcinoma	2	Acceptable
Neuroendocrine carcinoma, small cell type. Differential diagnosis is Basaloid SCC. Need IHC study to confirm/ High grade carcinoma in favor of neuroendocrine carcinoma, to confirm with IHC/ Neuroendocrine carcinoma favoring small cell carcinoma. CD56, Synaptophysin, Chromogranin, Ki67 and pan CK for confirmation/ Differentials: 1. Neuroendocrine carcinoma, 2. Non-keratinizing SCC, 3. Angiosarcoma; To do IHC	5	Acceptable
Poorly differentiated carcinoma: DDx 1) Large cell neuroendocrine carcinoma 2) Basaloid SCC	1	Acceptable
Papillary squamotransitional carcinoma	1	
Basaloid squamous cell carcinoma	1	

Educational notes:

1. The cervical polyp is a small cell neuroendocrine carcinoma (SCNEC). It displays sheets of malignant cells characterized by high nucleocytoplasmic ratio with scanty cytoplasm, nuclei with salt-and-pepper chromatin pattern, nuclear molding, and a high mitotic rate with scattered apoptotic bodies.
2. SCNEC, also known as high-grade neuroendocrine carcinoma, small cell type, resembles its counterpart in the lung. SCNEC is diagnosed based on its morphological appearance, although immunohistochemistry for neuroendocrine markers (chromogranin, synaptophysin, CD56) may provide support for the diagnosis. Nevertheless, some SCNECs may be totally negative for neuroendocrine markers. Among the neuroendocrine markers, CD56 and synaptophysin are more sensitive as compared to chromogranin A.
3. TTF-1 does not differentiate between SCNECs of the cervix and metastatic small cell carcinomas of the lung as both are positive. SCNECs have to be differentiated from lymphomas and basaloid squamous cell carcinomas. Basaloid squamous cell carcinomas are usually diffusely positive for p63.
4. The management of SCNECs also draws on data for treating small cell carcinoma of the lung that it may include specific neuroendocrine-based systemic chemotherapy and radiation therapy including axial sites (whole brain radiation).

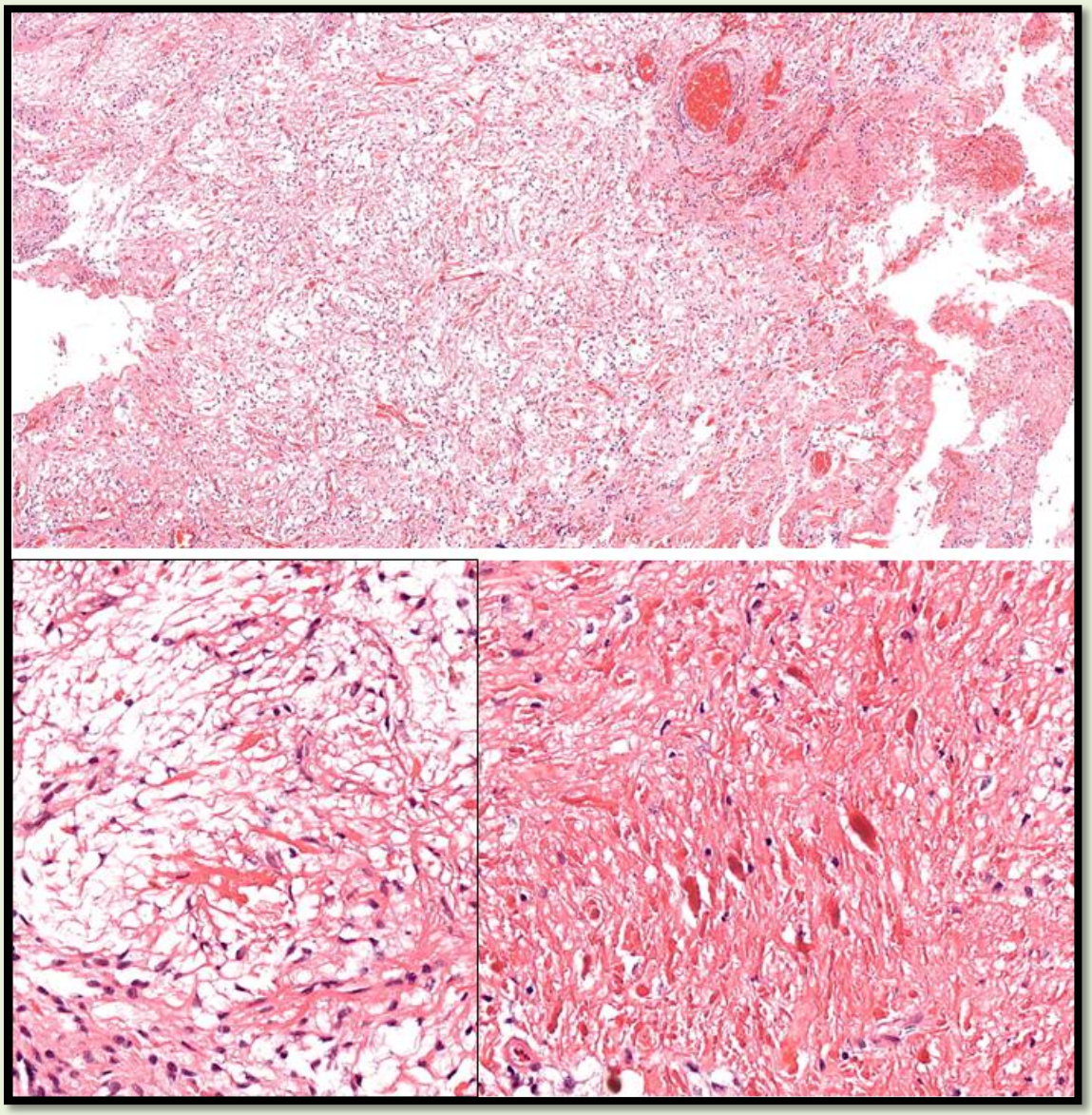
Reference

1. Kurman, R. J., Carcangiu, M. L., Herrington, C. S., & Young, R. H. (2014). WHO classification of tumours of female reproductive organs. Lyon: International Agency for Research on Cancer.

Case 13

Case 13: 17 y.o., male, left thalamic tumor. One representative section

Targeted Diagnosis: **Pilocytic astrocytoma, WHO grade 1**



Case 13

Submitted Diagnoses by Participating Institutions	Number	
Pilocytic astrocytoma - WHO grade 1	19	Acceptable
Pilomyxoid astrocytoma - WHO grade 2	1	
Low grade glial tumor	1	

Educational notes:

1. Section shows fragments of pilocytic astrocytoma, WHO grade 1, composed of loose-textured areas and more dense areas. The cellularity is generally low. The tumor cells are small bipolar cells or multipolar cells. Rosenthal fibres are easily observed, especially at the compact piloid tissue. The tumor tissue fragments are in rich in vascularity. Reactive gliotic tissue is admixed.
2. Pilocytic astrocytoma is the most common glioma in childhood and adolescence with predilection occurring in cerebellum and cerebral midline structures. Radiologically it is circumscribed and usually cystic with enhancing mural nodule. Enhancement in a paradoxically low grade astrocytoma is thought to be related to the high vascularity in pilocytic astrocytoma.
3. Classic pilocytic astrocytoma shows biphasic pattern histologically, i.e. dense fibrillary and loose/microcystic components. Rosenthal fibres and eosinophilic granular bodies are helpful diagnostic features, but they are not specific for pilocytic astrocytoma. Incorporating radiological findings with histological findings will help distinguish pilocytic astrocytoma from diffuse astrocytoma.
4. Pilomyxoid astrocytoma, a higher grade variant of pilocytic astrocytoma, shows markedly myxoid background, monomorphous bipolar cells, and a predominantly angiocentric arrangement. Rosenthal fibres and eosinophilic granular bodies are absent.

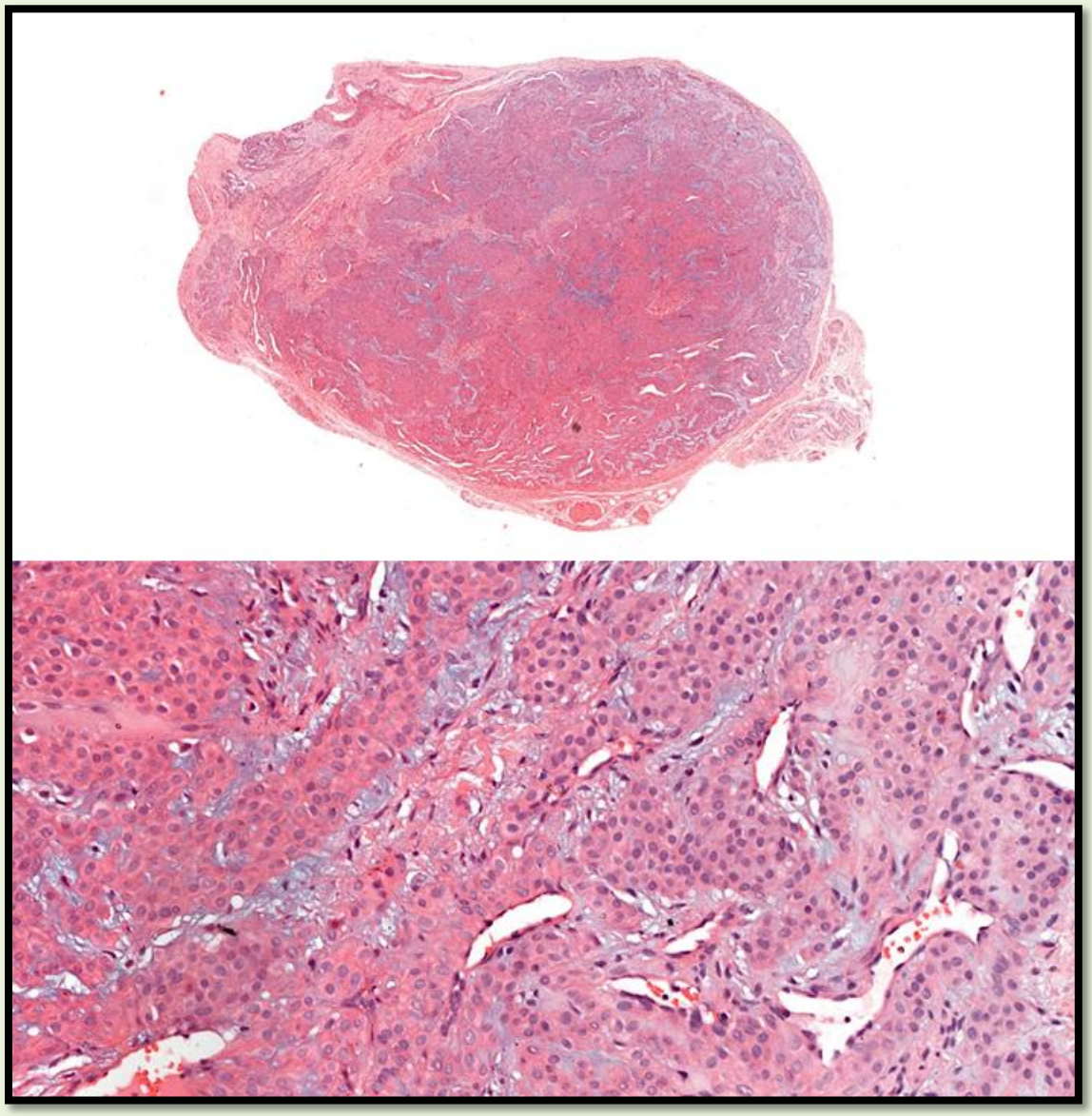
Reference

1. Louis, D. N., Ohgaki, H., Wiestler, O. D. & Cavenee, W. K (2016). WHO Classification of Tumours of the Central Nervous System. Lyon: International Agency for Research on Cancer.

Case 14

Case 14: 31 y.o., male, right finger nodule. One representative section

Targeted Diagnosis: **Glomus tumor**



Case 14

Submitted Diagnoses by Participating Institutions	Number	
Glomus tumor	17	Acceptable
Glomangioma	2	Acceptable
Glomus tumor / glomangioma.	1	Acceptable
Glomus tumor. S100, SMA and H-caldesmon for confirmation	1	Acceptable

Educational notes:

1. Section shows a well circumscribed glomus tumor composed of nests and trabeculae of uniform cells surrounding the capillary. Myxoid change of the stroma is observed.
2. Solid glomus tumors comprise about 75% of cases. Glomangiomas (Glomovenous malformations) show presence of cavernous haemangioma-like vascular structures. Glomangiopericytoma contains hamangiopericytoma-like vasculature. Cells in glomangiomyomas are more elongated, resembling mature smooth muscle.
3. Glomus tumors of uncertain malignant potential are those glomus tumors showing atypical features such as more than 2 cm in size and deep location. Malignant glomus tumor should display either marked nuclear atypia and any level of mitotic activity, or atypical mitotic figures.
4. Glomus tumors of all types typically express SMA and h-caldesmon.

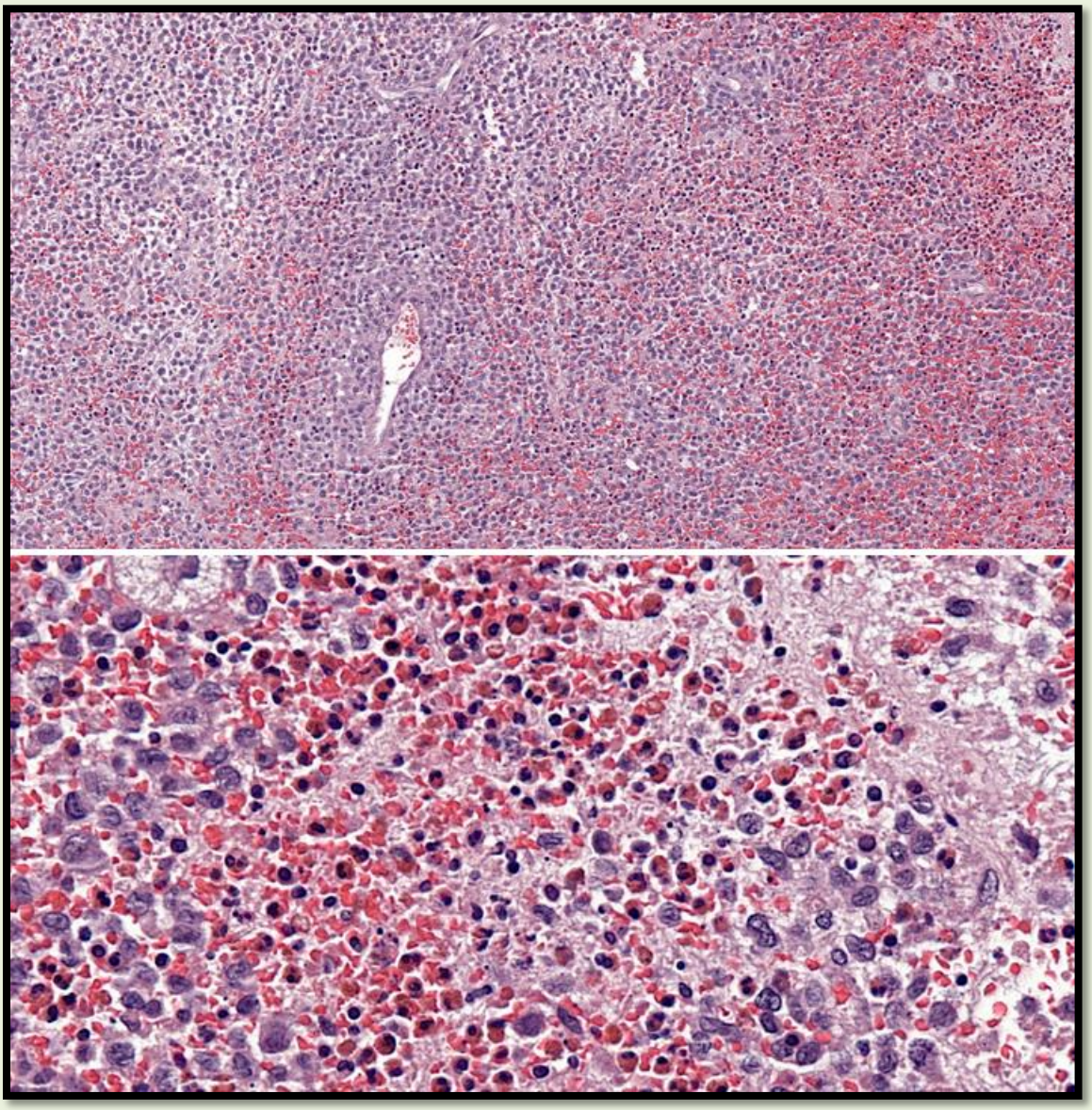
Reference

1. Christopher, D. M., Fletcher, J. A., & Bridge, P. C. (2013). WHO classification of tumours of soft tissue and bone. International agency for research on cancer. 4th edition. Lyon.

Case 15

Case 15: 1 y.o., male, supraorbital swelling. One representative section

Targeted Diagnosis: **Langerhans cell histiocytosis**



Case 15

Submitted Diagnoses by Participating Institutions	Number	
Langerhans cell histiocytosis	20	Acceptable
Langerhans cell histiocytosis. CD1a, S100, CD68 and Langerin for confirmation.	1	Acceptable

Educational notes:

1. The supraorbital swelling is composed of sheets of mononuclear cells showing characteristic grooved, indented, folded nuclei with fine chromatin and inconspicuous nucleoli. The cytoplasm is moderately abundant. In the background, predominantly eosinophils are observed. These features are diagnostic of Langerhans cell histiocytosis (LCH).
2. LCH mostly occurs in childhood. It can present as a "single site" disease, "multiple sites in a single organ system" disease or "multiple organ systems" disease; these different extents of disease determine the prognosis of the patients.
3. LCH cells express CD1a, langerin , and S-100 protein. Langerin and CD1a might be helpful in detecting bone marrow involvement in bone marrow biopsy.
4. In adults, pulmonary LCH is mostly related to smokers. Unlike in children, Langerhans cell sarcoma has to be excluded in all forms of adult LCH. Langerhans cell sarcoma shows overt cytological malignant features.

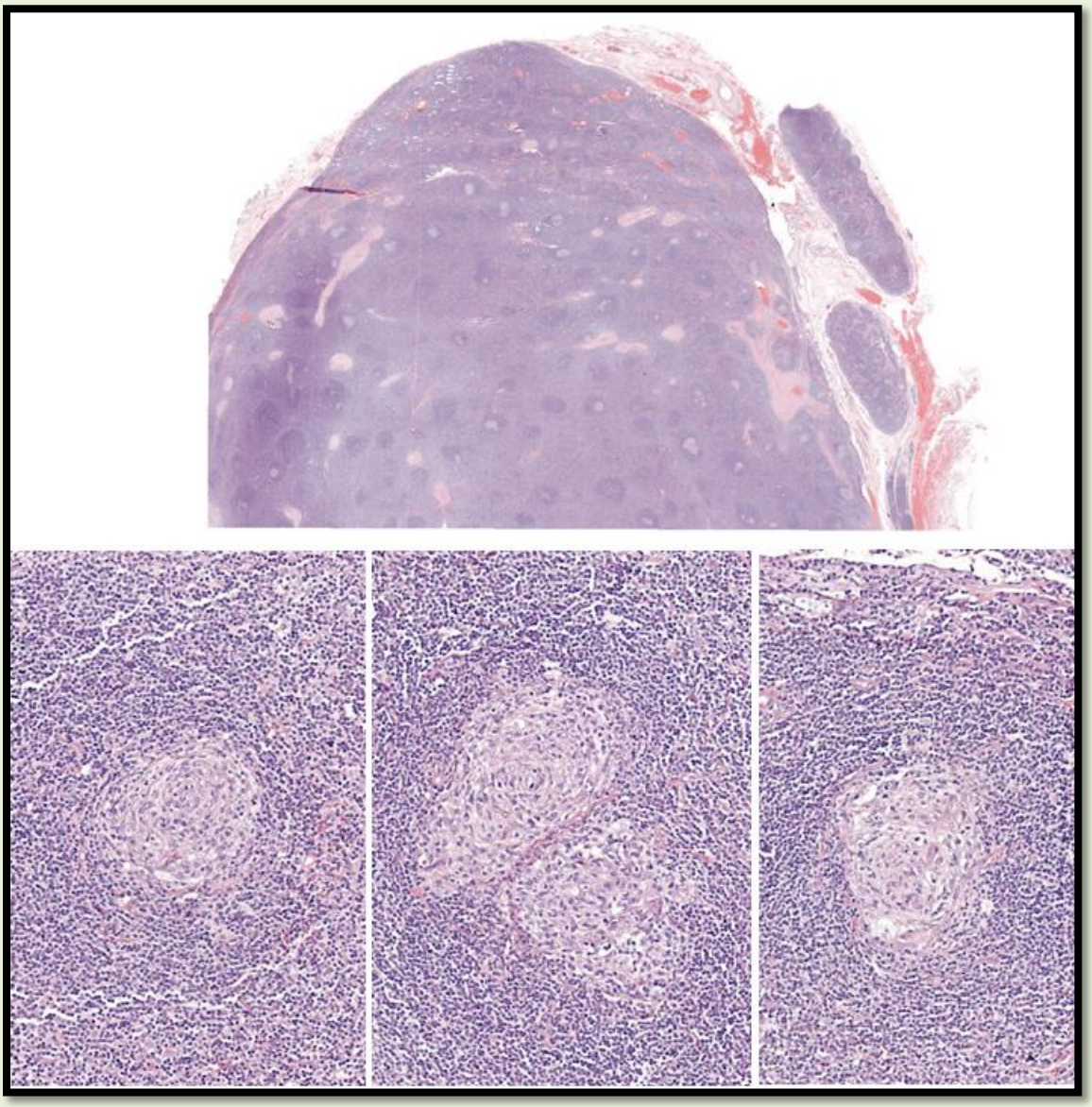
Reference

1. Swerdlow, S. H., Campo, E., Harris, N. L., Jaffe, E. S., Pileri, S. A., Stein, H., & Thiele J. (2017). WHO Classification of tumors of haematopoietic andlymphoid tissues. Lyon, France IARC.

Case 16

Case 16: 12 y.o., male, left cervical lymph node. One representative section

Targeted Diagnosis: **Hyaline-vascular variant Castleman disease**



Case 16

Submitted Diagnoses by Participating Institutions	Number	
Castleman disease, hyaline vascular type	12	Acceptable
Castleman disease	7	Acceptable
Progressive transformation of germinal centers	2	

Educational notes:

1. The lymph node shows distorted architecture with scattered small atrophic follicles both in the cortex and medulla. The germinal centers of the follicles are composed of mainly follicular dendritic cells with hyaline deposits. Twinning of germinal centers is noted. The mantle zones are expanded. The interfollicular regions show small lymphocytes rich in vascular network. Dense bands of sclerosis are observed. These features are that of hyaline-vascular variant Castleman disease (HVCD).
2. Castleman disease (CD) is histologically categorized into hyaline-vascular (HV) variant, plasma cell (PC) variant. It may be unicentric (localized) or multicentric disease clinically. Multicentric CD is mostly plasma cell variant histologically.
3. In HVCD, characteristic follicular changes include fairly uniform-sized lymphoid follicles distributed throughout the lymph node, germinal centers depleted of small lymphocytes but rich in dendritic follicular cells, onion skin pattern of mantle zones, "lollipop lesions" with radially penetrating blood vessels, and "twinning" of germinal centers in a lymphoid follicle. The interfollicular regions show high-endothelial venules with small lymphocytes and plasma cells.
4. In PCCD, confluent sheets of plasma cells are observed in the interfollicular regions. Some of the lymphoid follicles show hyaline vascular changes.
5. The histology of atrophic lymphoid follicles in HVCD can also be seen in late phase of the HIV infection and primary immunodeficiencies. Clinical and serologic findings can help in these distinctions.

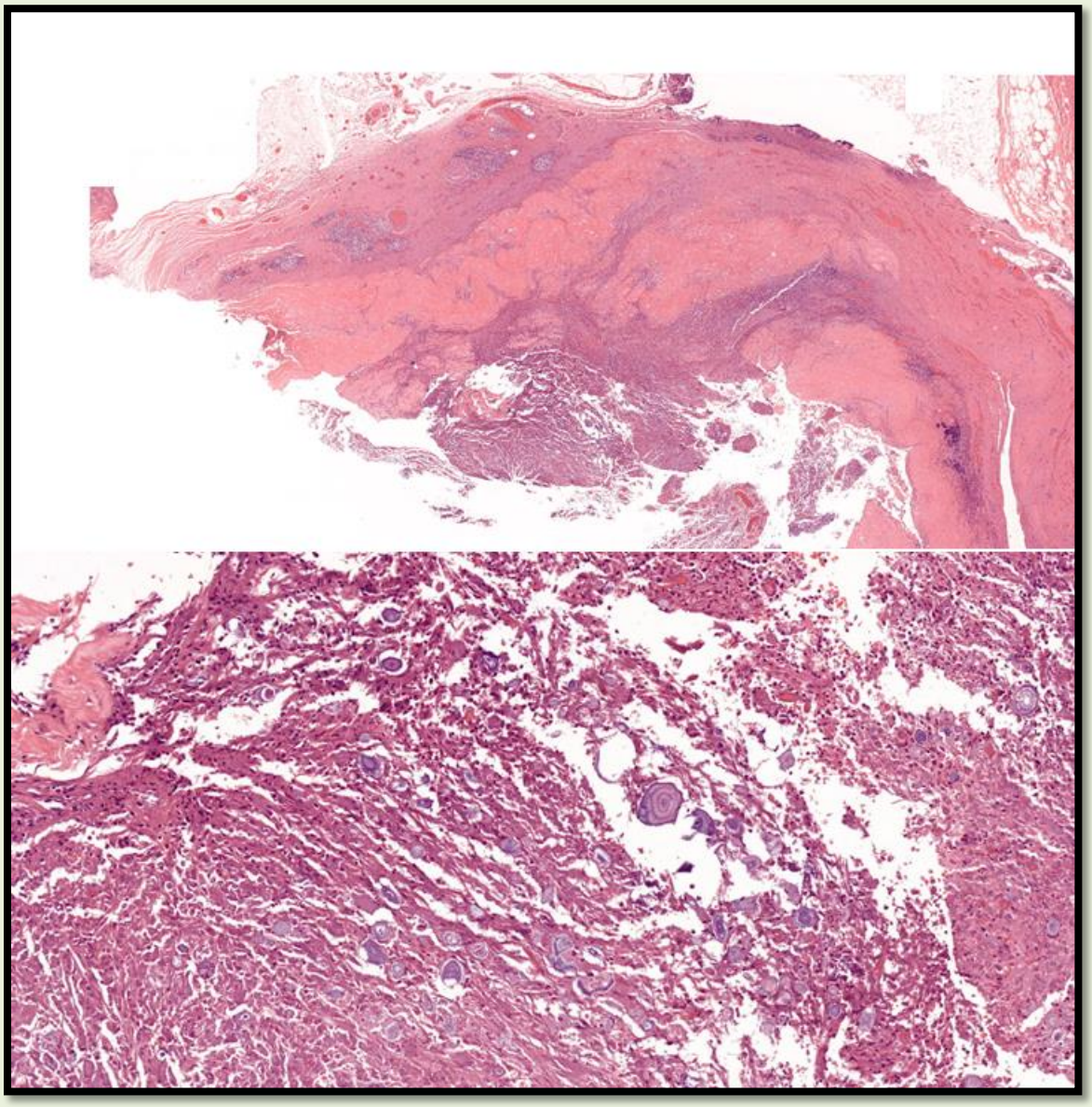
Reference

1. Ioachim, H. L., & Medeiros, L. J. (Eds.). (2009). Ioachim's lymph node pathology. Lippincott Williams & Wilkins.

Case 17

Case 17: 44 y.o., female, jaundice and right hypochondria pain, cholecystectomy. One representative section

Targeted Diagnosis: **Marked chronic cholecystitis with calcified bodies**



Case 17

Submitted Diagnoses by Participating Institutions	Number	
Schistosomiasis/ Acute on chronic cholecystitis with parasitic infestation, morphology suggestive of Schistosomiasis, For future identification and special stain.	4	Acceptable
Chronic cholecystitis with parasitic infestation/ Chronic cholecystitis with calcified material, suspicious of parasitic infestation/ Parasitic infestation. Need to confirm with culture and serological testing/ Parasitic cholecystitis (helminth)/ Parasitic cholecystitis with empyema/ Parasitic cholecystitis	11	Acceptable
Ascariasis cholecystitis	1	Acceptable
Parasitic infestation ? Chlonorchis sinensis	1	Acceptable
Parasitic infestation, favouring liver fluke / fasciola hepatica / Parasitic infestation, possibility of liver fluke.	2	Acceptable
Malakoplakia and amyloidosis/ Malakoplakia	2	Acceptable

Educational notes:

1. The gallbladder wall shows extensive fibrosis and mostly ulcerated mucosa replaced by sheets of histiocytes, lymphoplasmacytic infiltrates and neutrophils. Within these inflammatory infiltrates, round to oval basophilic calcified bodies are observed. These calcified bodies are mostly extracellular. Many of them are laminated with a targetoid appearance. The sizes vary from 8um to 60um.
2. Marked chronic cholecystitis is observed associated with calcified bodies. The differential diagnoses of the calcified bodies include Michaelis–Gutmann bodies of malakoplakia, calcified parasitic ova and microlithiasis.
3. Michaelis–Gutmann bodies are usually intracellular or extracellular laminated basophilic bodies of the size of a red blood cell (2-10um). Parasitic Infestation of the gallbladder by *Schistosoma mansoni, Paragonimus westermani, Ascaris lumbricoides, Fasciola hepatica* and *Clonorchis sinensis* has been previously documented. Calcified ova of parasites are uniform and larger in sizes, which are usually surrounded by fibrosis.
4. In this case, the variation in sizes of the calcified bodies with laminated and targetoid appearance is more consistent with microlithiasis. Similar calcified bodies are also found in testicular microlithiasis and pulmonary aveolar microlithiasis.

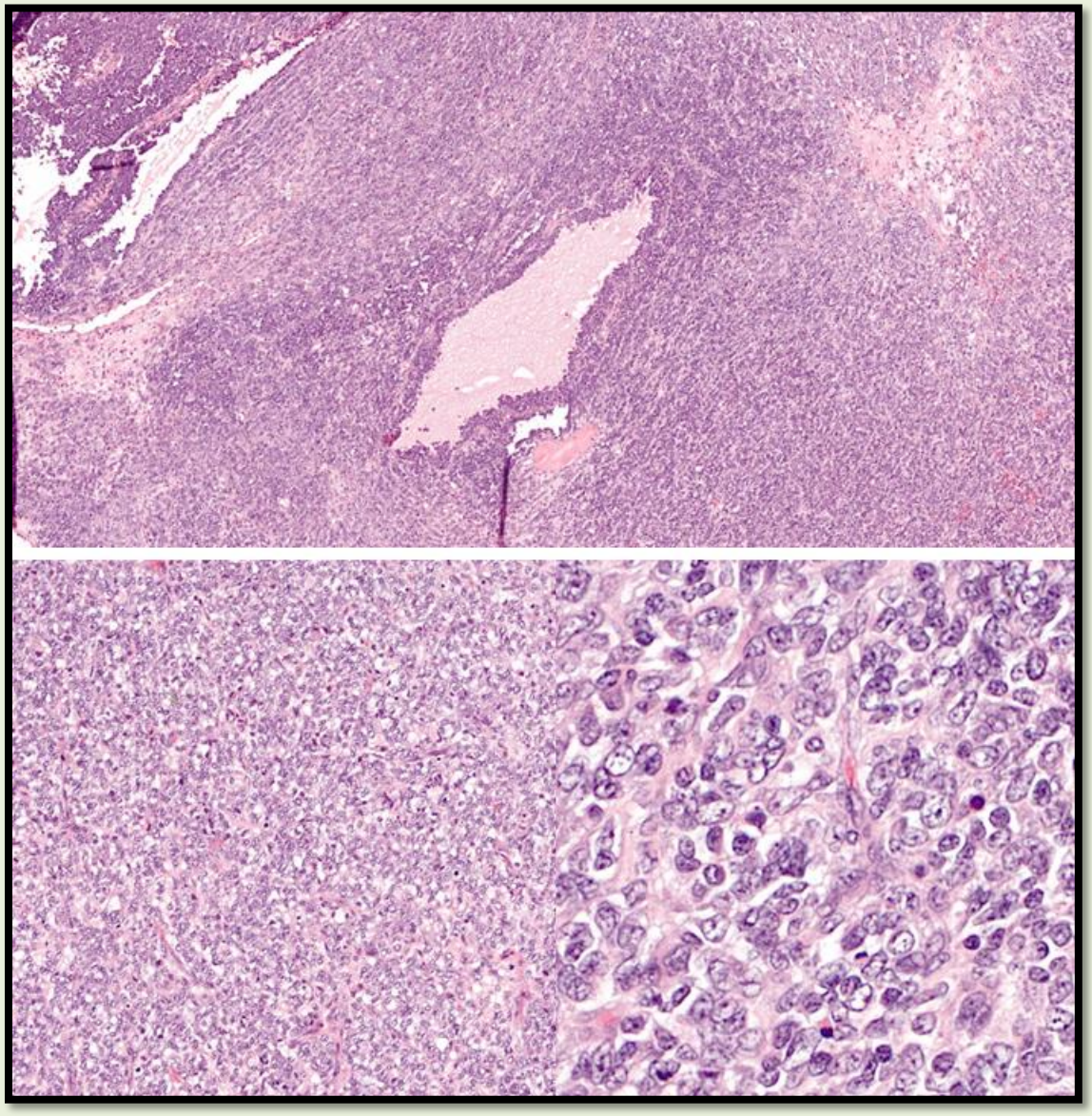
Reference

1. Lack, E. E. (2003). Pathology of the pancreas, gallbladder, extrahepatic biliary tract, and ampullary region. Oxford University Press
2. Bostwick, D. G., & Cheng, L. (2014). Urologic surgical pathology. Elsevier Health Sciences.

Case 18

Case 18: 16 y.o, female, abdominal mass, left ovary, high serum calcium.
One representative section.

Targeted Diagnosis: **Small cell carcinoma of hypercalcemic type**



Case 18

Submitted Diagnoses by Participating Institutions	Number	
Small cell carcinoma of hypercalcemic type	16	Acceptable
Small cell carcinoma of ovary, hypercalcemic type. Close differential is juvenile granulosa cell tumour/ Malignant neoplasm; differential diagnosis includes small cell carcinoma of hypercalcaemic type vs granulosa cell tumour. To do IHC: Inhibin, EMA	2	Acceptable
Juvenile granulosa cell tumor/ Granulosa cell tumour	3	

Educational notes:

1. The left ovarian mass is composed of diffuse growth of small cells showing irregular round to oval nuclei with small nucleoli. The cytoplasm is scanty. Mitoses are scattered. At focal areas, cystic spaces containing light eosinophilic secretion is observed. These small cells are focally immunoreactive towards CK MNF116, CD10, calretinin, EMA, and synaptophysin. They are diffusely positive for WT1. They are negative for chromogranin and inhibin.
2. Morphologically, the ovarian mass is composed of undifferentiated small cells with a high mitotic count. Small cell carcinoma of hypercalcemic type of the ovary (SCCHT) and granulosa cell tumor of the juvenile type (JGCT) are the main differential diagnoses in this young female patient.
3. In JGCT, follicle-like spaces containing eosinophilic or basophilic secretions are more numerous. JGCT may have fibrous septa and fibrothecomatous component. In contrast, SCCHT has focal follicle-like spaces with scanty stroma. The most useful immunohistochemical marker to differentiate between these two is inhibin whereby it is positive in JGCT but negative in SCCHT.
4. Clinically, SCCHT is usually associated with hypercalcemia whereas JGCT with estrogenic manifestations.
5. JGCT mostly presents at stage I with excellent prognosis whereas SCCHT is a highly aggressive tumor with a poor prognosis (almost all patients with a stage higher than stage Ia died of disease)

Reference

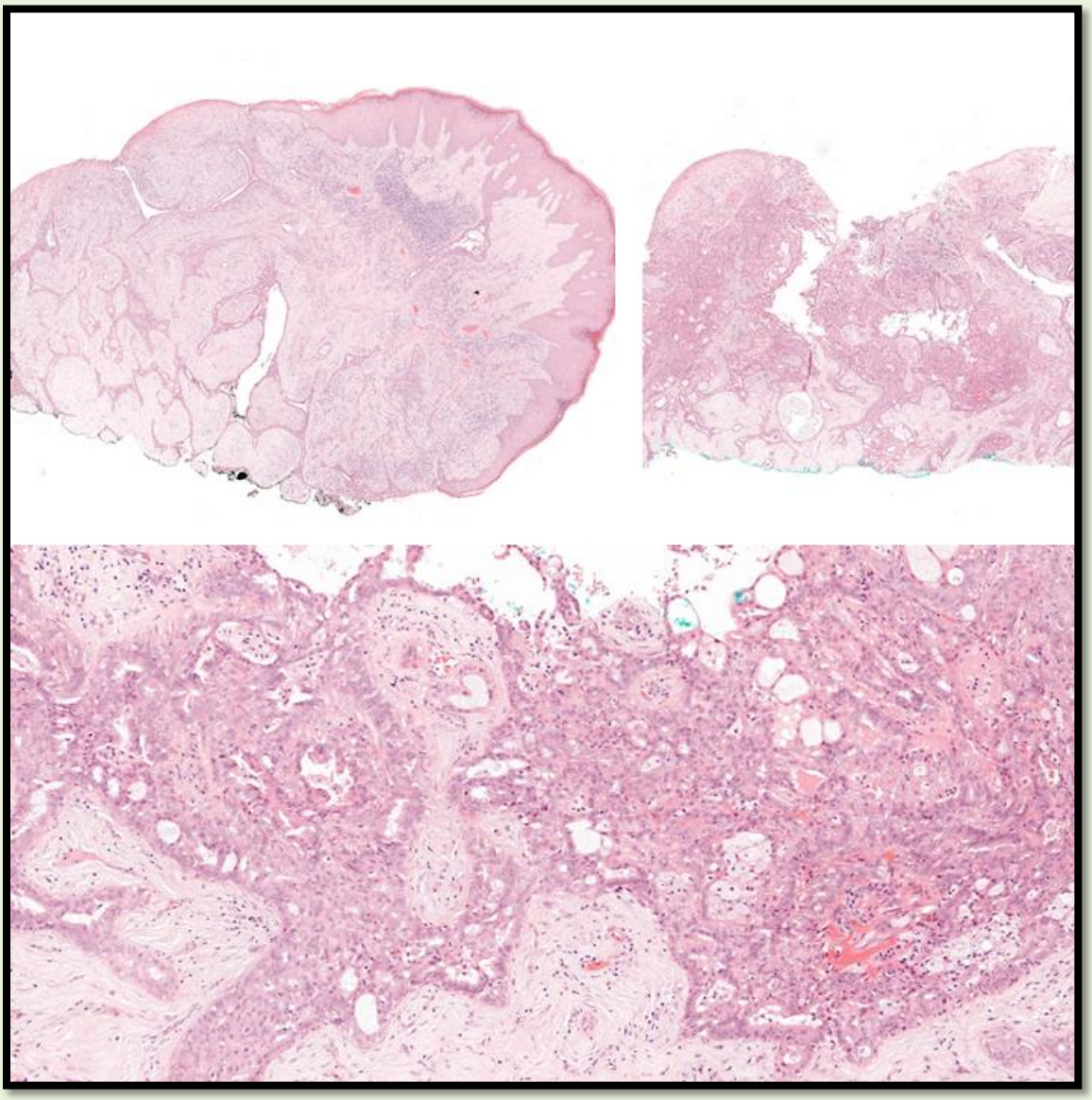
1. Soslow, R. A., & Tornos, C. (Eds.). (2011). Diagnostic pathology of ovarian tumors. Springer Science & Business Media.

2. Kurman, R. J., Carcangiu, M. L., Herrington, C. S., & Young, R. H. (2014). WHO classification of tumours of female reproductive organs. Lyon: International Agency for Research on Cancer.

Case 19

Case 19: 32 y.o., female, nipple erosion. One representative section.

Targeted Diagnosis: **Nipple adenoma (florid papillomatosis of the nipple)**



Case 19

Submitted Diagnoses by Participating Institutions	Number	
Nipple adenoma/ Florid papillomatosis of the nipple/ Nipple adenoma with florid epitheliosis	18	Acceptable
Papillary adenoma of the nipple. For p63 to support diagnosis.	1	Acceptable
Benign breast lesion, suggestive of nipple adenoma with fibroadenoma	1	Acceptable
Syringocystadenoma papilliferum	1	

Educational notes:

1. Section from the nipple shows anastomosing ducts and glands ulcerating the overlying epidermis. These ducts and glands show presence of myoepithelial cells. Areas of florid usual ductal hyperplasia forming irregular fenestrations are observed. p63-immunostaining shows preserved myoepithelial cells. Mosaic pattern with CK5/6 immunostaining at the florid usual ductal hyperplasia is noted.
2. Histologically, nipple adenoma is a proliferative lesion with several morphological patterns, namely, sclerosing adenosis, papillomatosis, usual ductal hyperplasia and pseudoinfiltrative pattern, which can overlap. The unifying feature is the bi-layered architecture of luminal epithelial cells and myoepithelial cells that can be demonstrated by immunohistochemistry. Immunostaining for CK5/6 shows a mosaic pattern (a mixture of positively stained myoepithelial cells and negatively stained luminal epithelial cells).
3. Nipple adenomas are benign lesions that may recur if incompletely excised.

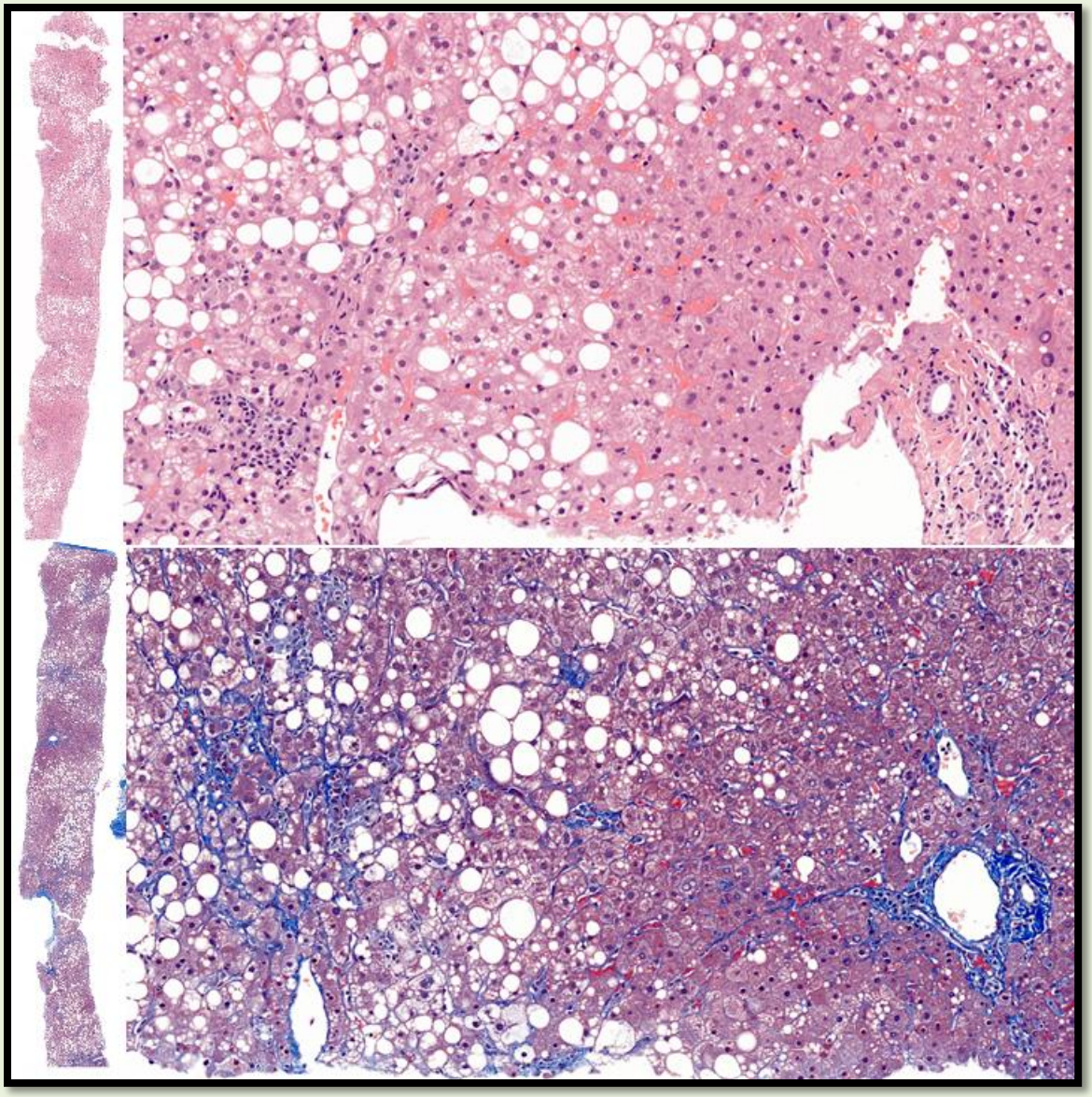
Reference

1. Lakhani, S. R. (Ed.). (2012). WHO Classification of Tumours of the Breast. International Agency for Research on Cancer.

Case 20

Case 20: 20 y.o., female, deranged liver function test: ALT 100-140 U/L (reference range:7-48), AST 60-70 U/L(reference range: 7-44). BMI 30. No significant medical history. No alcohol use. ANA: Positive (1 in 80); ASMA, anti-LKM, AMA: negative; IgG: 13.9 g/L (reference range: 4-16); Viral hepatitis, Wilson's disease screening: negative. One representative section and one MT.

Targeted Diagnosis: **Steatohepatitis, consistent with non-alcoholic steatohepatitis (NASH)**



Case 20

Submitted Diagnoses by Participating Institutions	Number	
Non-alcoholic steatohepatitis	11	Acceptable
Non-alcoholic steatohepatitis (grade 2)	1	Acceptable
Non-alcoholic steatohepatitis, Grade 1, Stage 1	1	Acceptable
Steatohepatitis consistent with non-alcoholic steatohepatitis	2	Acceptable
Non-alcoholic steatohepatitis. Features suggestive of Non-alcoholic Fatty Liver Disease (NAFLD). Modified histological activity index : Grade: score 3 Stage : Score 1	1	Acceptable
Steatohepatitis	1	Acceptable
Steatohepatitis favour NASH. Need to exclude alcohol cause.	1	Acceptable
Steatohepatitis with Zone 3 pericellular/perisinosoidal fibrosis.	1	Acceptable
Non-alcoholic fatty liver disease	2	

Educational notes:

1. The strips of liver tissue show moderate macrovesicular steatosis. Moderate lobular inflammation associated with hepatocyte ballooning and occasional Mallory–Denk body formation is observed. Glycogenated nuclei of hepatocytes are noted. The portal inflammation is mild. Masson's trichrome stain highlights the sinusoidal collagen deposition in the perivenular zones (zone 3). These features are that of steatohepatitis; incorporating the clinical information, these features are consistent with non-alcoholic steatohepatitis (NASH).
2. In this case, a positive ANA is documented. Autoimmune hepatitis is a valid clinical differential diagnosis that a liver biopsy maybe indicated for confirmation. Nonetheless, positive ANA or/and ASMA is not incompatible with NASH as low titers of ANA could be observed in NASH.
3. Steatohepatitis should be considered in any liver tissue with steatosis and inflammation associated with hepatocyte damages i.e. hepatocyte ballooning. Pericellular fibrosis as highlighted in the trichrome stain is a helpful diagnostic feature for steatohepatitis especially in equivocal cases of hepatocyte damages. Steatohepatitis is usually categorized into alcoholic and non-alcoholic steatohepatitis; however histological features alone cannot reliably distinguish these two.
4. Wilson disease sometimes mimics steatohepatitis; zone 3 pericellular fibrosis should be absent in Wilson disease. Although mild portal inflammation can be seen in adult steatohepatitis, a more prominent portal inflammation might be seen in cases with advanced fibrosis. A substantial chronic portal and periportal inflammation in the

absence of advanced fibrosis raises the possibility of chronic hepatitis such as viral, drug-induced or autoimmune hepatitis as an alternative diagnosis or co-existing pathology.

5. The term "nonalcoholic fatty liver disease (NAFLD)" refers to the spectrum of steatosis, steatohepatitis and cirrhosis. NASH CRN scoring system is one of the systems developed for evaluation of NAFLD in terms of necroinflammatory activity (grade) and fibrosis architectural alterations (stage). NAFLD activity score evaluates steatosis, lobular inflammation and hepatocellular ballooning in order to determine the presence of NASH (Score ≥5). Nonetheless, cases with score ⩾5 without hepatocyte damages are equivocal for NASH.
6. The choice and use of the scoring systems in routine practice may be tailored to specific clinical and research needs.

Reference

1. Hubscher, S. G., Burt, A. D., Portmann, B. C., & Ferrell, L. D. (2011). MacSween's Pathology of the Liver. Elsevier Health Sciences.