International Academy of Pathology
Malaysian Division

FINAL REPORT

QUALITY ASSURANCE PROGRAM
GENERAL DIAGNOSTIC HISTOPATHOLOGY
CYCLE 01/2018

NOTES FROM THE COORDINATOR

1. For this cycle 01/2018, a total of 24 sets of DVDs had been circulated. 21 institutions responded by the closing date of 15 June 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, and Dr. Nurul Akmar Misron.

Prepared by,

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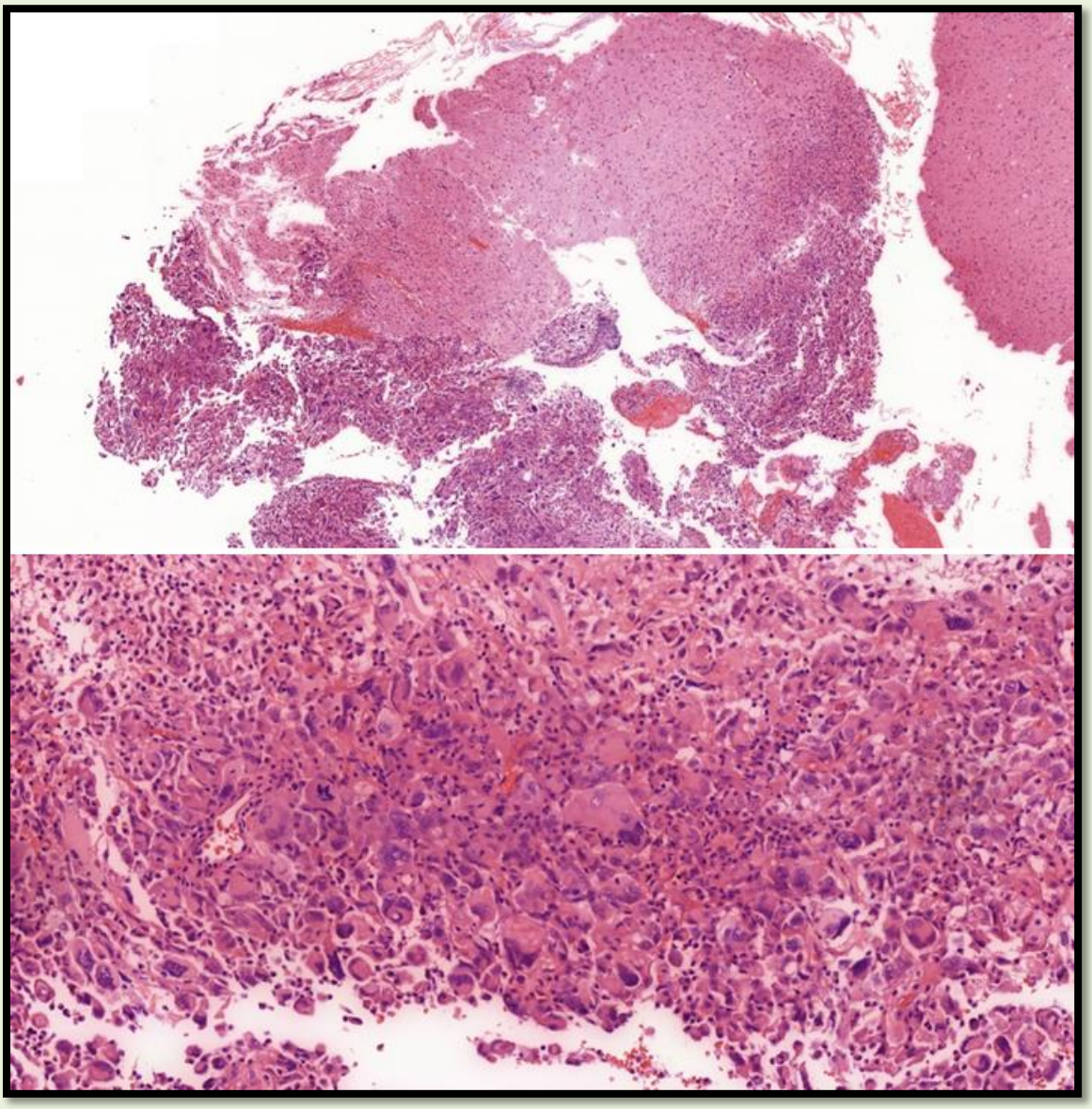
Coordinator for IAP-MD QAP

Case 1

Case 1: 32 y.o., female, multiple hyperdense lesions on the right parietal region. One representative section.

Targeted Diagnosis: **Giant cell glioblastoma, WHO grade IV**



Case 1

Submitted Diagnoses by Participating Institutions	Number
Giant cell glioblastoma/ Giant cell glioblastoma, WHO grade IV/ Glioblastoma-giant cell type (WHO grade 4)	9
Glioblastoma/ Glioblastoma multiforme/ Glioblastoma multiforme WHO Grade IV	7
High-grade glial tumour, differentials include 1) Anaplastic Pleomorphic Xanthoastrocytoma, WHO Grade III 2) Glioblastoma, WHO Grade IV/ Anaplastic astrocytoma	2
Metastatic carcinoma, Differential diagnosis Giant cell glioblastoma. Need to do immunohistochemical stain i.e GFAP, Pancytokeratin & beta HCG)/ Giant cell glioblastoma (would like to exclude metastasis by immunohistochemistry)/ Anaplastic or Pleomorphic astrocytoma. Differential includes metastases.	3

Educational notes:

1. Section shows tumor tissue fragments composed of bizarre malignant cells with angulated hyperchromatic nuclei and abundant cytoplasm. Numerous multinucleated tumor giant cells are admixed. Mitoses are easily observed. The adjacent glial tissue is focally infiltrated by malignant cells. Immunohistochemistry shows the malignant cells are positive for GFAP and negative for pan-cytokeratin and HMB-45. Histological findings are consistent with giant cell glioblastoma, WHO grade IV. (Note: Without IDH evaluation, a diagnosis of glioblastoma, NOS, is more appropriate, *vide infra*)
2. The 2016 World Health Organization Classification of Tumors of the Central Nervous System employs integrated phenotypic and genotypic parameters for tumor classification. Glioblastomas are classified into (1) **glioblastoma, IDH-wildtype** (about 90 %), which corresponds to the clinically defined primary or de novo glioblastoma in older patients; (2) **glioblastoma, IDH-mutant** (about 10 %), which corresponds to secondary glioblastoma with a history of prior lower grade diffuse glioma in younger patients, and (3) **glioblastoma, NOS**, a diagnosis for those tumors that IDH evaluation cannot be performed.
3. Along with gliosarcoma and epithelioid glioblastoma, giant cell glioblastoma is a variant under the umbrella of glioblastoma, IDH-wildtype. Histologically, it is characterized by bizarre, multinucleated giant cells and an occasionally abundant reticulin network. Palisading and large ischaemic necroses are observed. Atypical mitoses are frequent. Microvascular proliferation is not common. Giant cell glioblastoma has a somewhat better prognosis than ordinary glioblastoma.

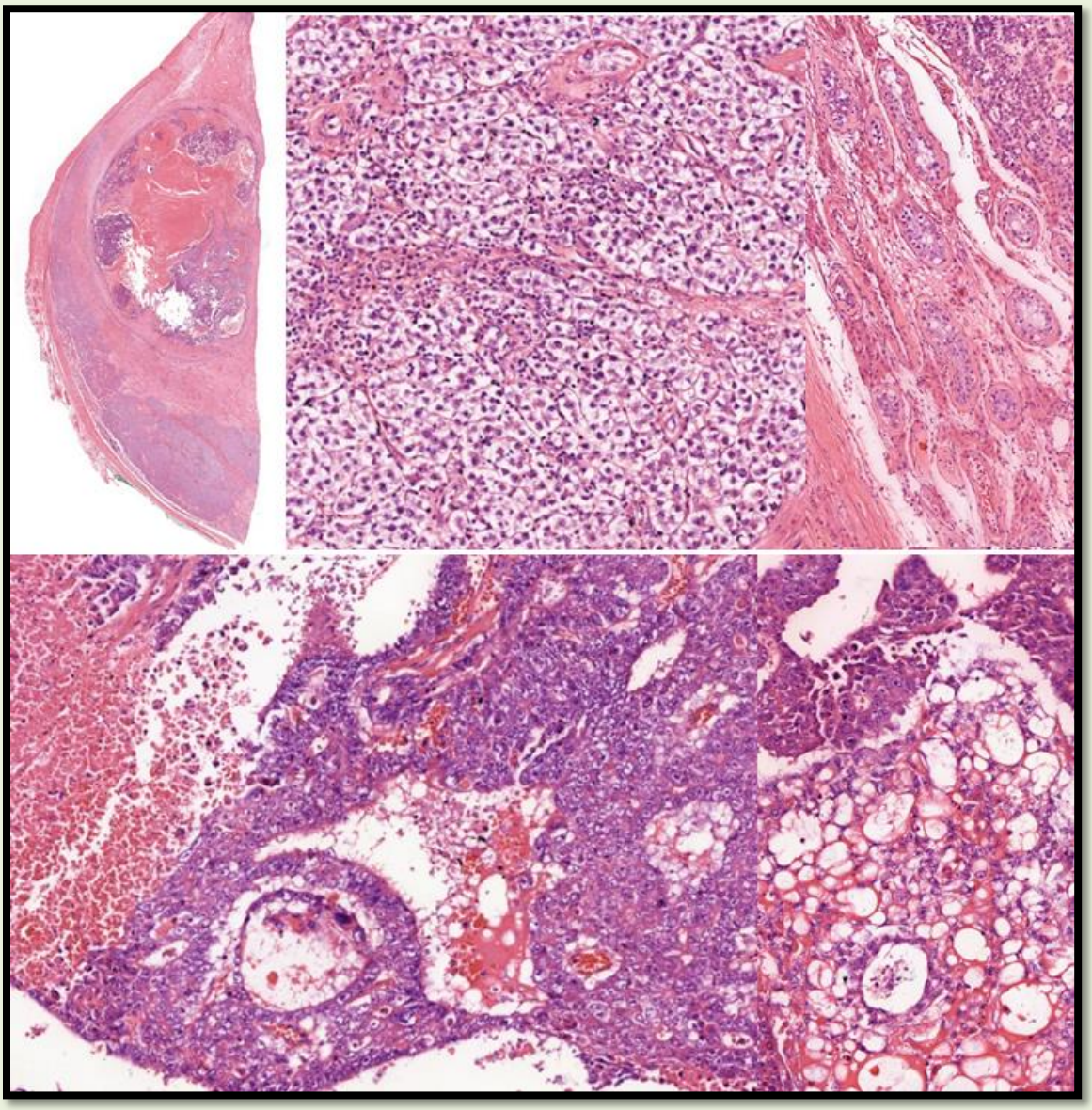
Reference:

1. World Health Organization. (2016). WHO Classification of Tumours of the Central Nervous System Revised 4th Edition. David N. Louis, (Ed.). Internat. Agency for Research on Cancer.

Case 2

Case 2: 22 y.o., male, left testicular mass. One representative section.

Targeted Diagnosis: **Mixed germ cell tumor (seminoma 40%, embryonal carcinoma 55%, yolk sac tumor 5%)**



Case 2

Submitted Diagnoses by Participating Institutions	Number
Mixed germ cell tumor (seminoma, embryonal carcinoma and yolk sac tumor)/ Mixed germ cell tumour (yolk sac tumour, embryonal carcinoma & seminoma). Need to do immunohistochemical stain to support the type of tumour i.e CD117, CD30 and alpha-fetoprotein	4
Mixed germ cell tumor (seminoma and embryonal carcinoma)	4
Mixed germ cell tumour (seminoma with embryonal carcinoma and Germ cell neoplasia in situ)/ Mixed germ cell tumor (seminoma and embryonal carcinoma) with intratubular germ cell neoplasia	2
Mixed germ cell tumor (seminoma and yolk sac tumor)/ Mixed Germ Cell Tumour (Seminoma & Yolk Sac). Suggest for IHC for confirmation of diagnosis	8
Mixed germ cell tumour (yolk sac tumour and Seminoma) and intratubular germ cell neoplasia	1
Mixed germ cell tumour/ Mixed germ cell tumours with seminoma and non seminomatous component. For CD30, Inhibin, Glypican 3, AFP, CD117 for typing of non seminomatous component.	2

Educational notes:

1. This testicular mass is a mixed germ cell tumor composed of seminoma (40%), embryonal carcinoma (55%) and yolk sac tumor (5%). The embryonal carcinoma shows malignant cells with pleomorphic vesicular nuclei with macronucleoli and dense amphophilic cytoplasm associated with tumor necrosis. The focal yolk sac tumor component displays vacuolated tumor cells in loose meshwork with a few eosinophilic hyaline globules. At the periphery, germ cell neoplasia in situ is noted. Immunohistochemistry shows that seminoma, embryonal carcinoma and yolk sac tumor are reactive towards CD117, CD30 and AFP respectively.
2. Mixed germ cell tumors are regarded as nonseminoma for clinical management. Different components and their proportions may have clinical implications that enumeration of the percentages of all non-necrotic tumor components is required. This may be facilitated by a limited panels of antibodies directed against OCT4, CD117, CD30, and glypican3: [Seminoma OCT4+ve, CD 117+ve, CD30-ve], [Embryonal carcinoma OCT4+ve, CD30+ve, CD117-ve], [Yolk sac tumor OCT4-ve, glypican3+ve, AFP+ve], and [Choriocarcinoma OCT4-ve, glypican3+ve, hCG+ve]. Embryonal carcinoma and yolk sac tumor are closely associated; the later component is often missed. Rises in serum markers AFP and hCG reflect the presence of yolk sac tumor and trophoblastic components respectively. These components may present in metastatic sites even though they are absent in the primary tumor.

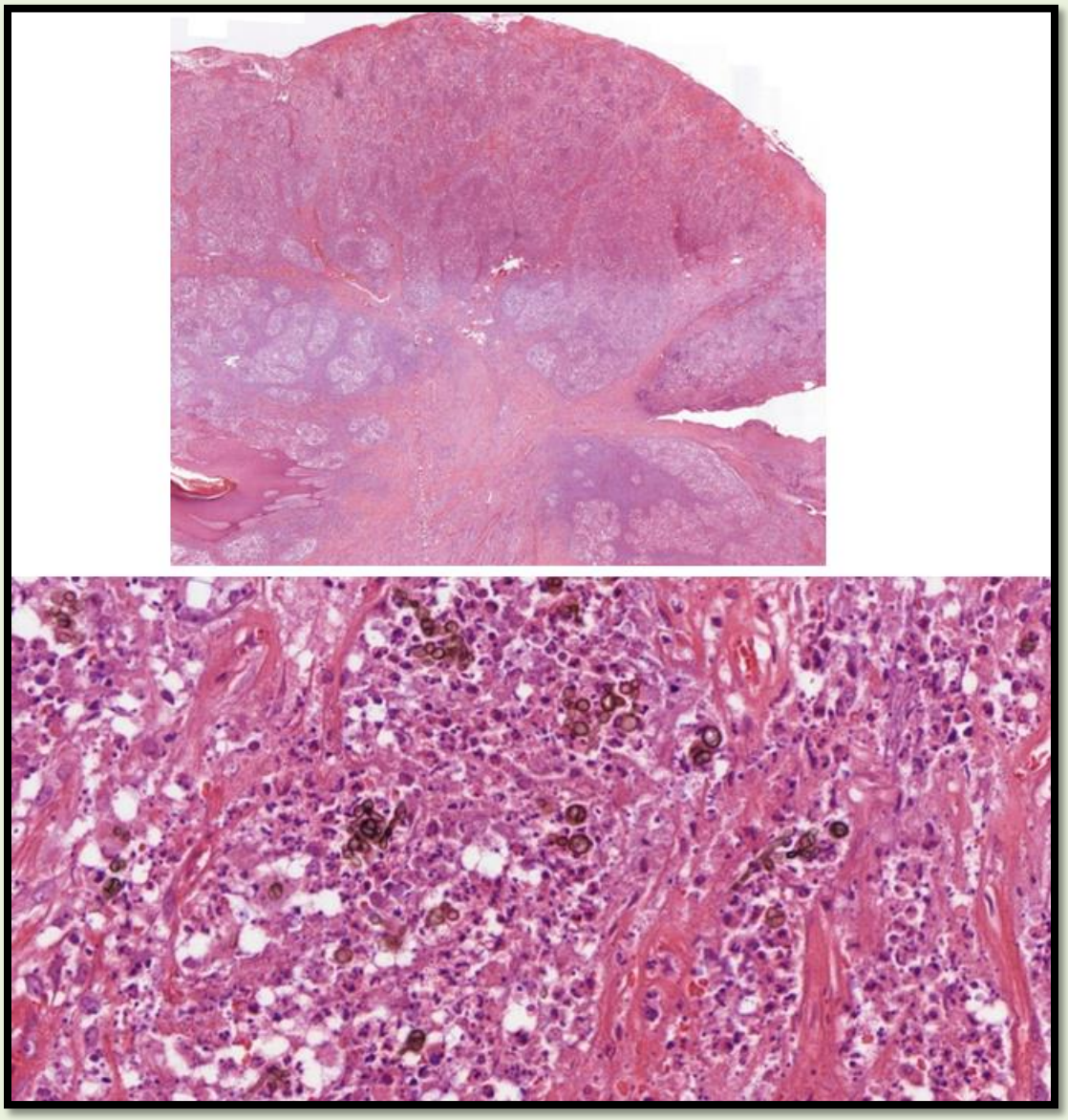
Reference:

1. World Health Organization. (2016). WHO Classification of Tumours of the Urinary System and Male Genital Organs. Fourth edition. Moch, H (Ed.). Internat. Agency for Research on Cancer.

Case 3

Case 3: 87 y.o., male, right plantar swelling. One representative section.

Targeted Diagnosis: **Chromoblastomycosis**



Case 3

Submitted Diagnoses by Participating Institutions	Number
Chromoblastomycosis/ chromomycosis	20
Cryptococcosis	1

Educational notes:

1. This nodular ulcerated skin lesion shows suppurative granulomatous inflammation with dense neutrophils and histiocytic infiltrates. Multinucleated giant cells are scattered. Fungal bodies are noted, comprised of round to polyhedral, golden brown to chestnut brown fungal cells that divide by septation.
2. Dematiaceous fungi (naturally pigmented molds) primarily cause skin and soft tissue infections that are preceded by trauma or environmental exposure, and they can give rise to three clinical entities: eumycetoma, chromoblastomycosis, and phaeohyphomycosis.
3. As in this case, chromoblastomycosis forms darkly pigmented, thick-walled, round to polyhedral fungal bodies with septation, or descriptively, "copper pennies". Eumycetomas produces grains, which are interwoven mycelial aggregates that are lined with intense eosinophilic material (Splendore-Hoeppli phenomenon). Fungal bodies in phaehyphomycosis are budding yeast and hyphal elements that may be septate or branching or may exhibit pseudohyphae. A Fontana-Masson stain may be needed to demonstrate presence of melanin (pigmentation).

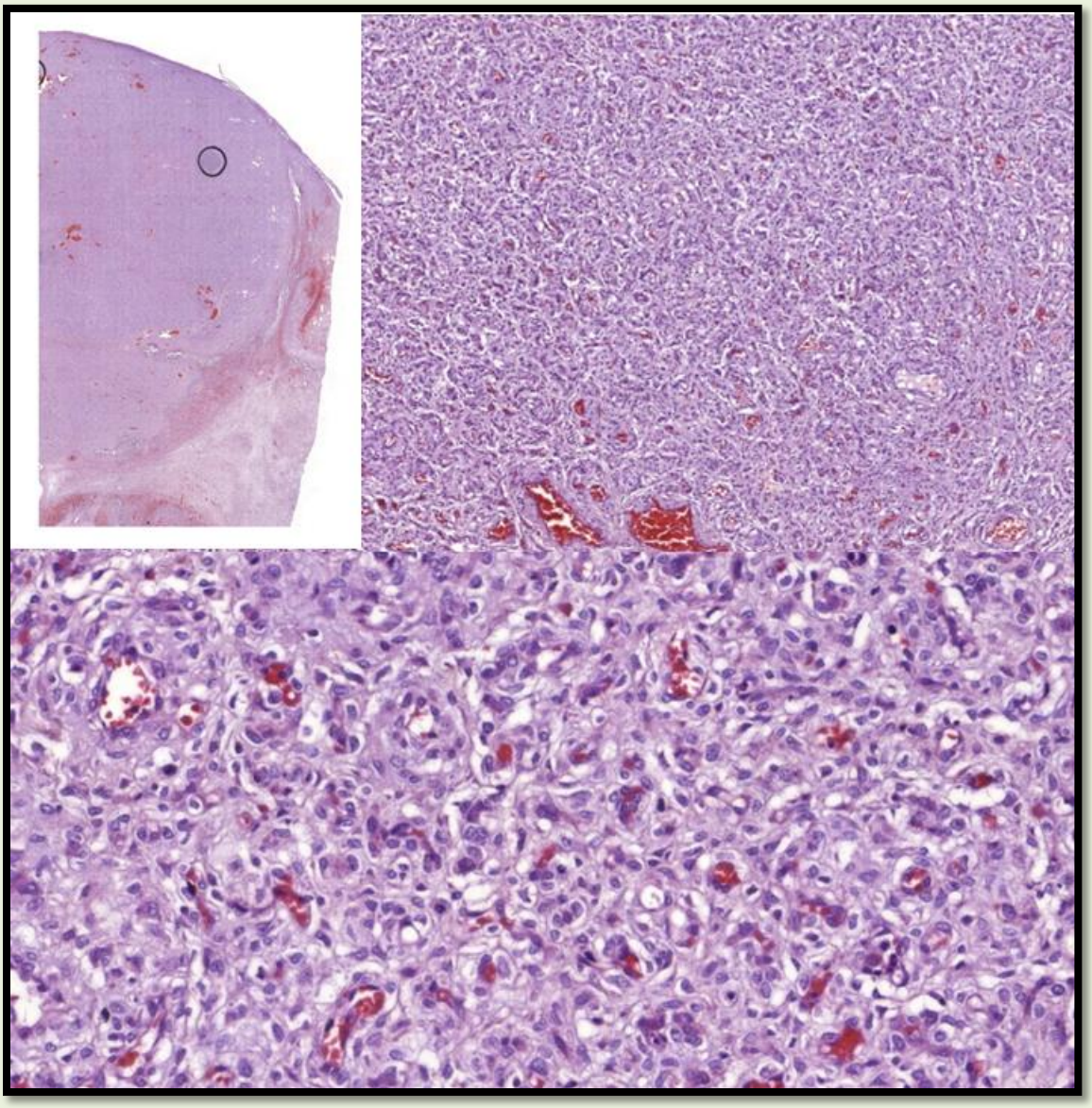
Reference:

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

Case 4

Case 4: 34 y.o., female, placenta. One representative section.

Targeted Diagnosis: **Chorangioma**



Case 4

Submitted Diagnoses by Participating Institutions	Number
Chorangioma/ Chorioangioma	21

Educational notes:

1. This chorangioma shows a mixed proliferation of capillaries and stromal cells forming nodular sheets. At areas, the vessels are sinusoidal. Microcalcifications are noted. The surface is covered by trophoblasts.
2. Chorangiosis, chorangiomatosis and chorangioma are related lesions in placentas. There is an increase in villous capillaries in chorangiosis and chorangiomatosis. In chorangiosis, the process involves terminal villi. In contrast, chorangiomatosis involves immature intermediate villi and stem villi, sparing terminal villi.
3. Chorangioma is the most common benign tumor in placenta, has been named alternately as chorioangiomas, angiomyxomas, fibroangiomyxomas and fibromas. It is characterized by proliferation of capillaries and stroma forming an expansile nodule. Relative composition of the capillaries and the stroma gives rise to a number of variants, which are clinically irrelevant as the clinical outcome depends more on the size of the mass.
4. Large chorangiomas are known to be associated with hydramnios, hydrops, anemia, thrombocytopenia, growth restriction and stillbirth.

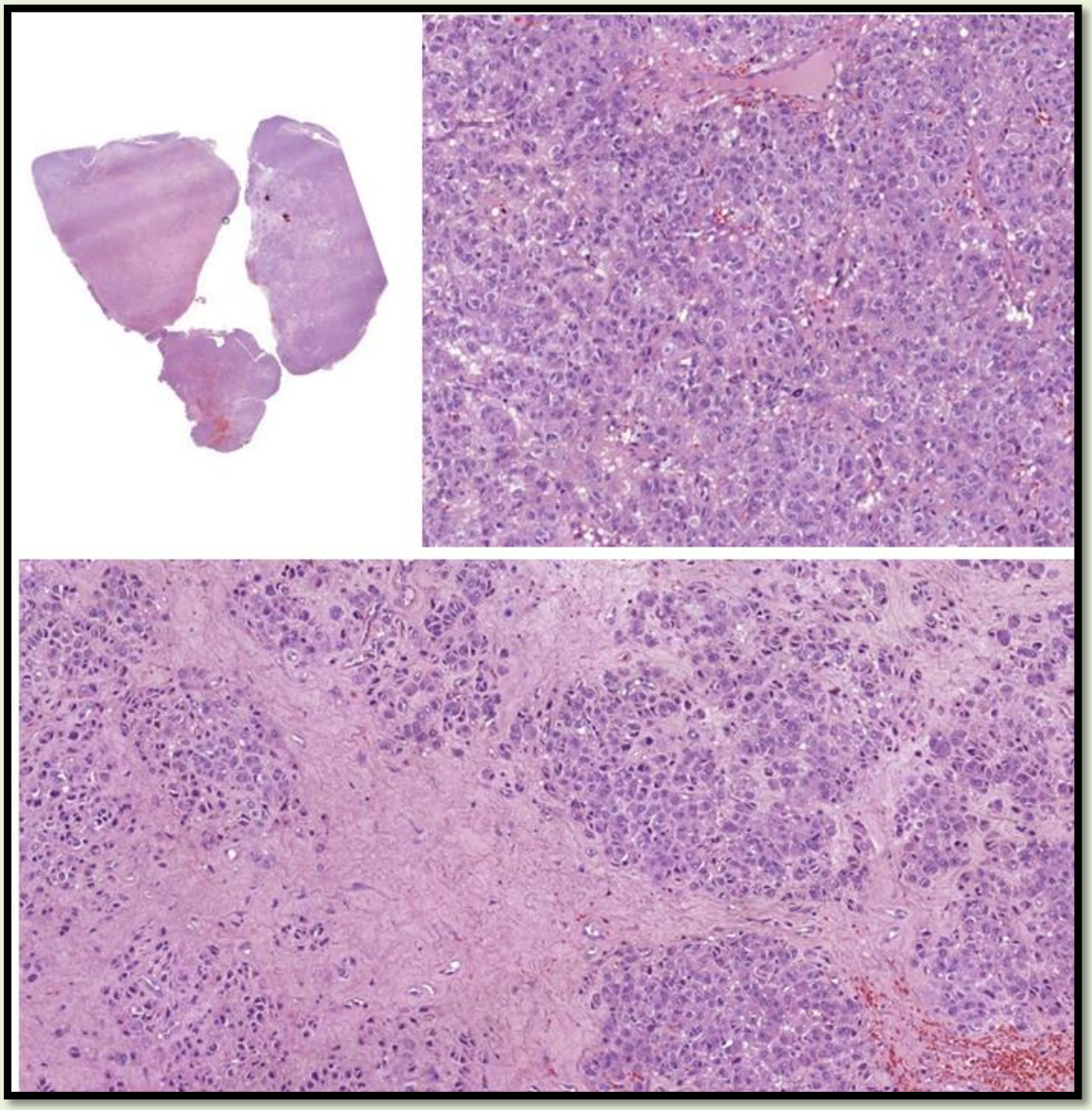
Reference:

1. Baergen, Rebecca N. Manual of Benirschke and Kaufmann's pathology of the human placenta. Springer Science & Business Media, 2005.

Case 5

Case 5: 19 y.o.,female, PCOS, high testosterone levels, right ovary. One representative section.

Targeted Diagnosis: **Steroid cell tumor, NOS**



Case 5

Submitted Diagnoses by Participating Institutions	Number
Steroid cell tumor	7
Leydig cell tumor/ Steroid cell tumour, most likely Leydig cell tumour/ Sex-cord stromal tumour favouring Leydig cell tumour	4
Sertoli - Leydig cell tumour/ Sertoli-Leydig cell tumor, moderately differentiated/ Sex-cord stromal tumour favouring Sertoli Leydig cell tumour, moderately differentiated	4
Sex cord stromal tumour/ mixed sex cord stromal tumour	3
Sex-cord stromal tumour. DDx; 1) Leydig cell tumour 2) Sclerosing stromal tumour. Suggest for IHC for confirmation of diagnosis/ Suggestive of sclerosing stromal tumour. DDx: Sertoli Leydig tumour.	2
Sclerosing stromal tumour	1

Educational notes:

1. Two of tissue fragments show sheets and nests of tumor cells displaying round vesicular nuclei with nucleoli and abundant eosinophilic cytoplasm. No obvious cytoplasmic Reinke crystals are noted. Mitosis is absent. At areas, the stroma is hyalinized, separating the cells in pseudo-lobules. The other fragment is predominantly fibrotic. Immunohistochemistry shows the neoplastic cells are positive for inhibin and calretinin.
2. This ovarian tumor belongs to the sex cord-stromal tumors of pure stromal tumors as it lacks sex cord derivatives (granulosa and Sertoli cells). The round tumor cell morphology suggests steroid cell tumors. Steroid cell tumors are further sub-classified into steroid cell tumor, NOS and Leydig cell tumor based on presence or absence of Reinke crystals and tumor location. Without Reinke crystals, a diagnosis of "steroid cell tumor, probably Leydig cell tumor" is rendered based on hilar location and characteristic tumor features of nuclear clustering, fibrinoid necrosis of vessels and associated hilus cell hyperplasia. By default, this ovarian tumor is designated as steroid cell tumor, NOS, lipid poor type in the absence of aforementioned features of Leydig cell tumor.
3. In Sertoli-Leydig cell tumors of moderate differentiation, two populations of cells - Sertoli cells (cellular lobules with darkly stained nuclei and scant cytoplasm) and Leydig cells (larger cells with abundant cytoplasm) are admixed.
4. In sclerosing stromal tumor, cellular lobules composed of a mixture of spindle and rounded cells in a background of hypocellular collagenous or edematous stroma are observed.
5. Inhibin and calretinin stain most sex cord-stromal tumors except fibromas. But these markers are of little help in differentiating one from another sex cord-stromal tumor.

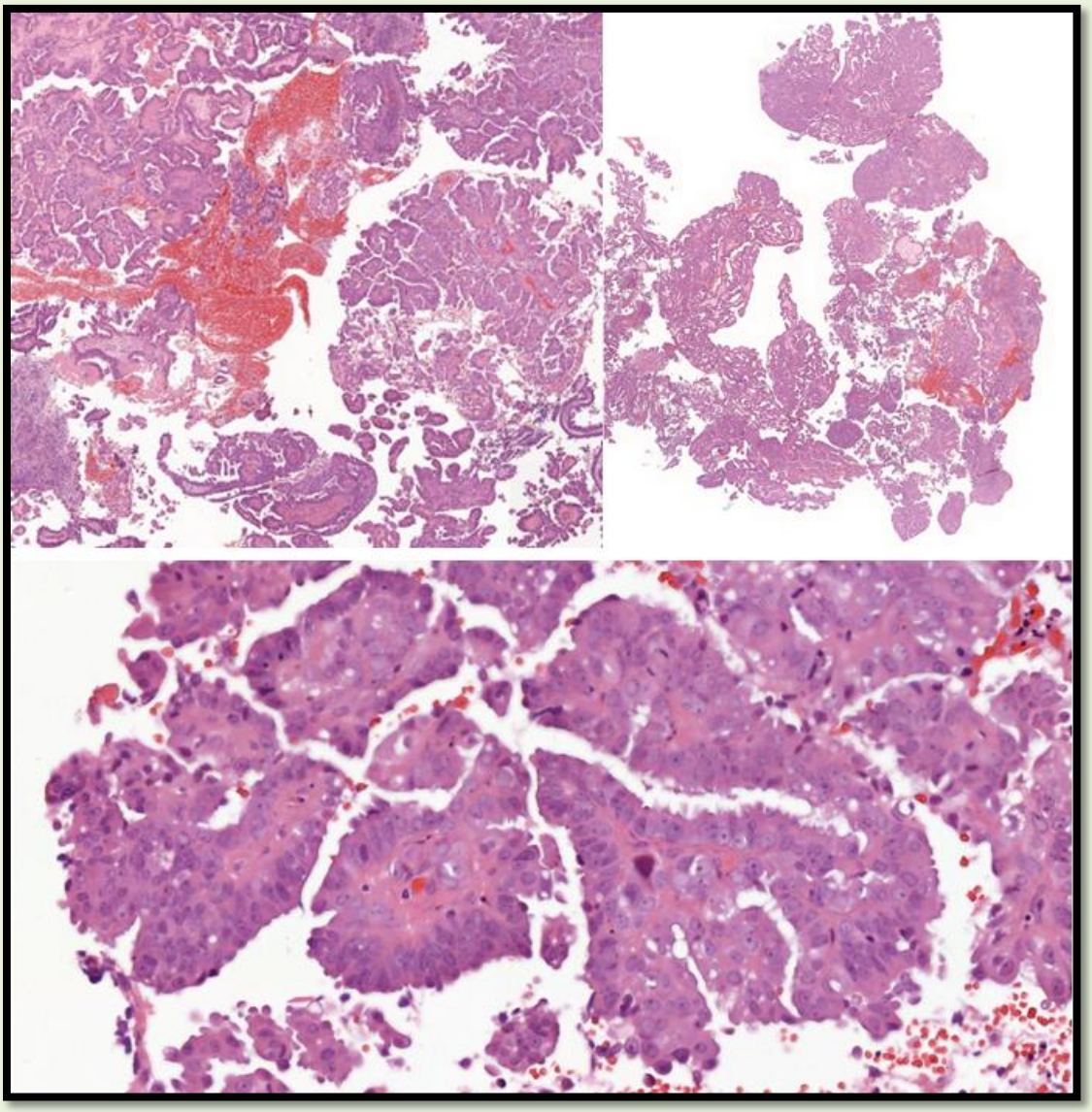
Reference:

1. World Health Organization. (2014). WHO classification of tumours of female reproductive organs. R. J. Kurman (Ed.). Internat. Agency for Research on Cancer.
2. Reichert, R. A. (2012). Diagnostic gynecologic and obstetric pathology: an atlas and text. Lippincott Williams & Wilkins.

Case 6

Case 6: 73 y.o., female, postmenopausal bleeding. One representative section.

Targeted Diagnosis: **Serous carcinoma**



Case 6

Submitted Diagnoses by Participating Institutions	Number
Serous carcinoma/ Serous cell carcinoma/ High grade serous papillary carcinoma/ Uterine papillary serous carcinoma/ High grade endometrial adenocarcinoma favouring serous carcinoma	19
Serous carcinoma, need to confirm with p53 and PTEN immunostains	1
Clear cell carcinoma	1

Educational notes:

1. This serous carcinoma is composed of multiple tumor tissue fragments with malignant cells arranged in papillae and micropapillae. The malignant cells show marked nuclear pleomorphism with prominent nucleoli.
2. Uterine serous carcinoma is prototypical type II (estrogen-independent) tumor. Its immediate precursor is serous endometrial intraepithelial carcinoma (SEIC), which shows similar cytological features without invading surrounding stroma. Nonetheless, SEIC can shed cells and metastasize widely to extra-uterine sites. SIEC is considered as pT1a.
3. Uterine serous carcinoma is high grade by definition and has more frequent extra-uterine spread at presentation. It shows aberrant p53 expression (intense and diffuse staining of at least 75% of the tumor cells or complete absence of p53 immunoreactivity), and diffuse strong p16 immunostaining. This immunochemistry profile could be helpful to distinguish serous carcinoma from high-grade endometrioid carcinoma and clear cell carcinoma.
4. Uterine serous carcinoma may present with adnexal mass. Presence of SEIC supports primary endometrial origin. WT-1 staining is weak/focal or negative in uterine serous carcinoma whereas it is strong and diffuse in tubo-ovarian high-grade serous carcinoma.

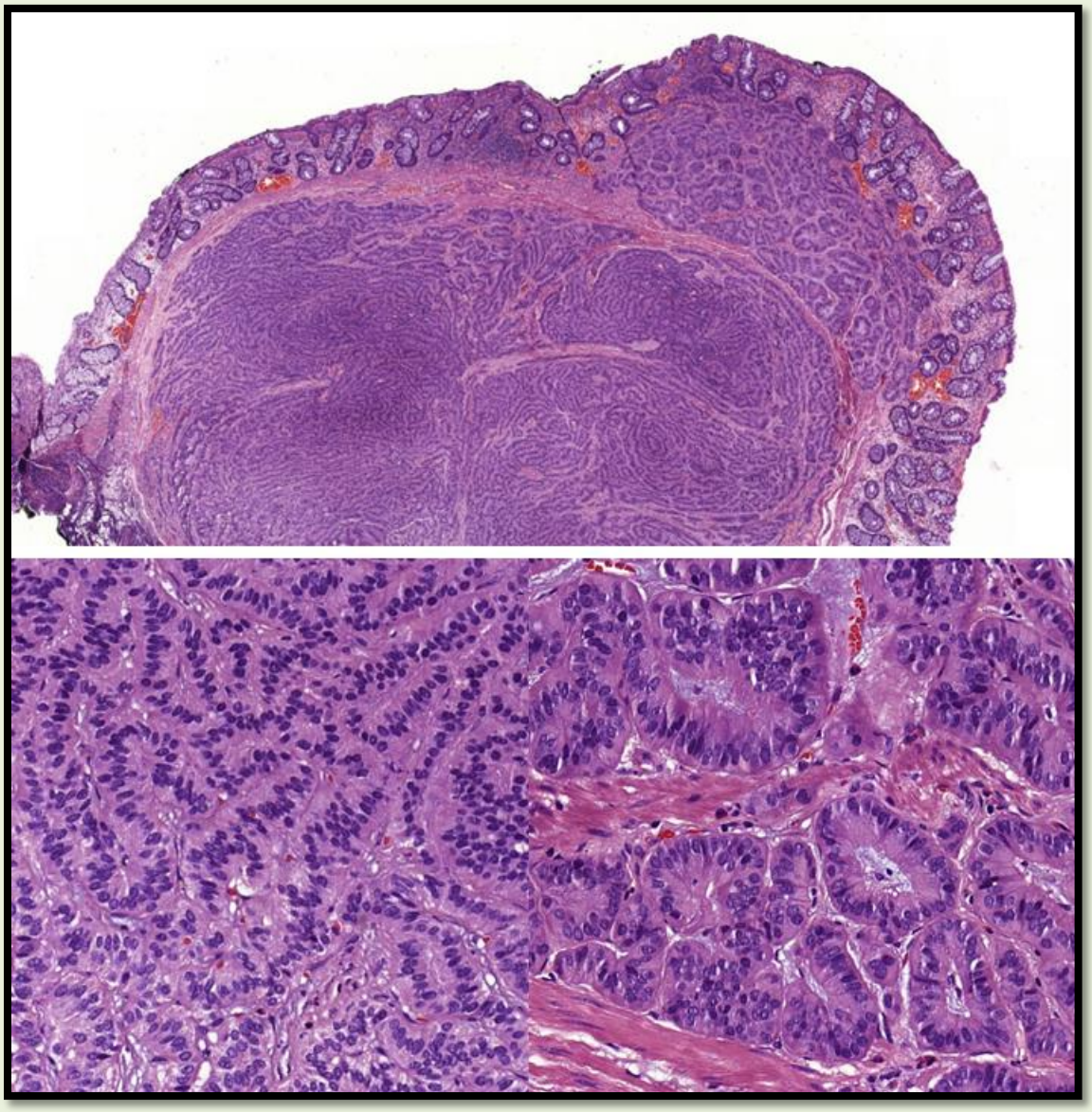
Reference:

1. World Health Organization. (2014). WHO Classifi cation of Tumours of Female Reproductive Organs. Robert J. Kurman (Ed.). Internat. Agency for Research on Cancer.
2. College of American Pathologists (CAP)(2017). Protocol for the Examination of Specimens From Patients With Primary Tumors of the Ovary, Fallopian Tube, or Peritoneum

Case 7

Case 7: 54 y.o., male, rectal polyp. One representative section.

Targeted Diagnosis: **Neuroendocrine tumor, grade 1**



Case 7

Submitted Diagnoses by Participating Institutions	Number
Neuroendocrine tumor, well differentiated/ Neuroendocrine tumour, grade I/Neuroendocrine tumour, Grade 1, base of polyp is involved by tumour/ Neuroendocrine tumour (NET) G1, transected edges involved by tumour.	14
Neuroendocrine tumor	3
Neuroendocrine tumour well differentiated Grade 2	1
Carcinoid tumor	1
Neuroendocrine tumour, Grade I Comment: Ki67 for proliferative index is required/ Neuroendocrine tumour, Need to do Ki67 for the grading of tumour.	2

Educational notes:

1. This polyp shows neuroendocrine tumor (NET), grade 1. In the submucosal layer, nodular proliferation of small glands and maze-like trabeculae of neoplastic cells is observed. The neoplastic cells show uniform oval nuclei displaying characteristic salt-and-pepper chromatin. Mitotic rate is low (1/10HPF) without tumor necrosis. Immunohistochemically the neoplastic cells are weak positive for chromogranin and dot-like positive for CK AE1&3.
2. NETs of the colon can be either serotonin (enterochromaffin, EC) cell NETs (in the caecum and ascending colon) or L cell (glucagon-like peptide-producing and PP/PYY-producing) NETs (in the more distal colon and rectum). Histologically, solid nests predominate in the EC cell NETs whereas trabecular pattern admixed with tubuloacini or broad, irregular trabeculae with rosettes in L cell NETs.
3. Grading of neuroendocrine neoplasms of gastrointestinal tract is based on morphological criteria and assessment of proliferation fraction. Neuroendocrine carcinoma (NEC) of small cell or large cell type is G3 with >20/10HPF mitotic rate and/or Ki-67 index >20%. G1 and G2 NETs are separated by a cutoff of 2/10HPF mitotic rate and/or Ki-67 index 2%.

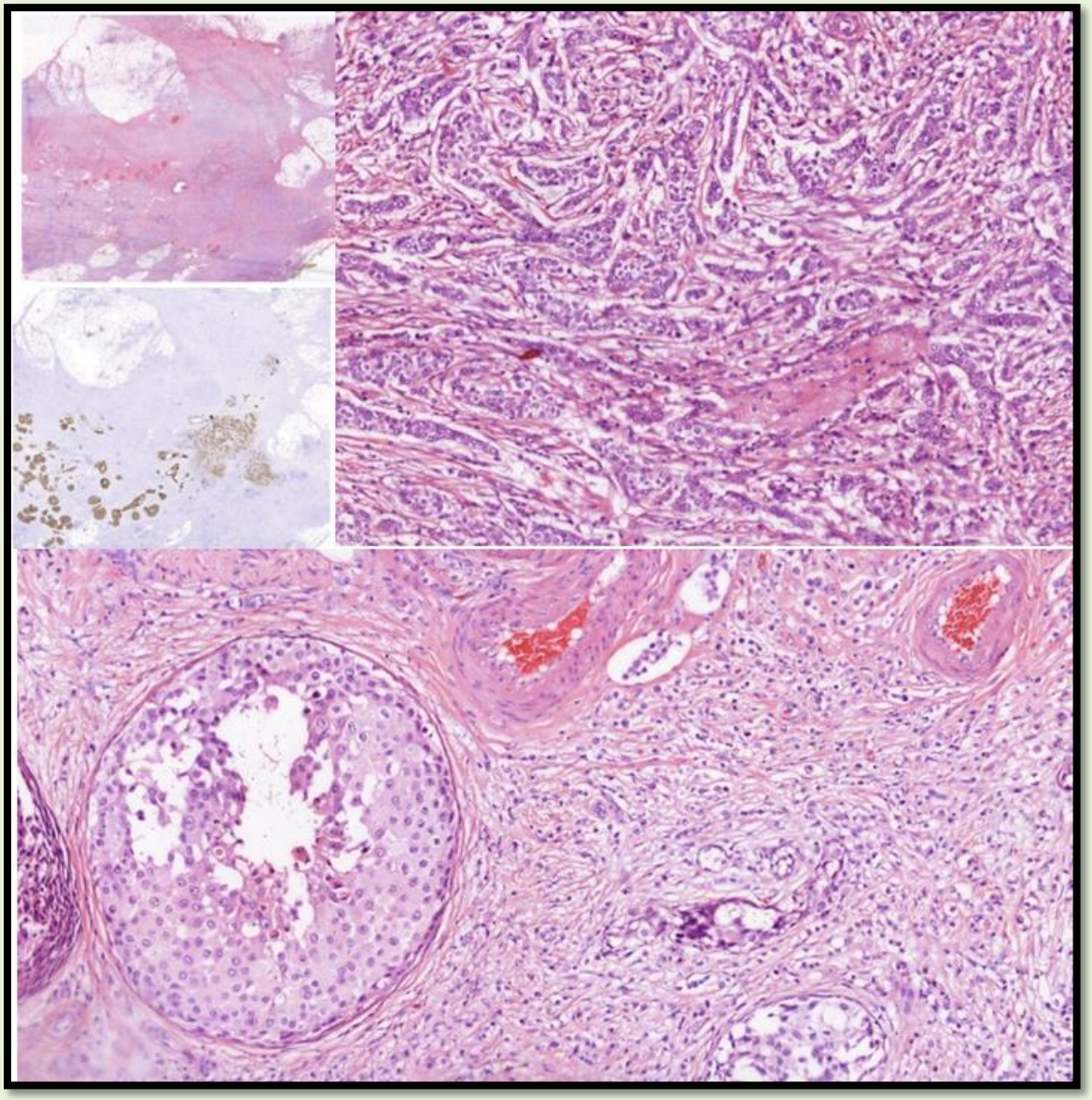
Reference:

1. World Health Organization. (2010). WHO classification of tumours of the digestive system. Fred. T. Bosman (Ed.). Internat. Agency for Research on Cancer.

Case 8

Case 8: 58 y.o, female, left breast lump, mastectomy. One representative section and one IHC for e-cadherin.

Targeted Diagnosis: **Mixed invasive lobular carcinoma (60%) and invasive carcinoma, NST (40%), and ductal carcinoma in situ (high grade)**



Case 8

Submitted Diagnoses by Participating Institutions	Number
Mixed invasive carcinoma, NST and lobular carcinoma with high-grade DCIS (comedo-type)/ Mixed ductal-lobular with high grade DCIS	3
Invasive carcinoma, NST with invasive lobular carcinoma and intermediate grade DCIS (Bloom and Richardson Grade II)	3
Mixed invasive carcinoma NST and invasive lobular carcinoma and ductal carcinoma in situ.	4
Mixed ductal and pleomorphic lobular carcinoma in the background of lobular carcinoma in situ/ Mixed invasive No Special type (NST) and lobular carcinoma with lobular neoplasia	3
Mixed ductal and lobular carcinoma with in situ component.	1
Mixed invasive ductal carcinoma and invasive lobular carcinoma/ Mixed invasive lobular and carcinoma (NST)/ Invasive mixed ductal NST and lobular carcinoma, Grade 2	6
Invasive carcinoma with ductal and lobular features	1

Educational notes:

1. This is a mixed invasive lobular carcinoma (ILC) (60%) and invasive carcinoma, NST (IDC) (40%). The former is negative for E-cadherin and the latter is positive. Both components are grade 3 (score 8 out of 9). High grade ductal carcinoma in situ of solid and comedo types are observed, which is also E-cadherin positive.
2. Invasive carcinoma, NST may have combined morphology as a tumor of "hybrid" morphology or a "mixed" pattern with two or more distinctive histological types. The former is best represented by invasive carcinoma, NST with lobular features (IDC-L) whereas the latter is mixed invasive lobular carcinoma and invasive carcinoma NST (Mixed ILC-IDC).
3. IDC-L although in part resembles ILC with its infiltrative growth pattern, it is positive for E-cadherin. Treatment for IDC-L and ILC does not differ, nonetheless, it may be more difficult to archive negative surgical margin for both IDC-L and ILC as compared to IDC due to their infiltrative growth pattern. Mixed ILC-IDC is defined as a carcinoma with a predominant ILC with a minor component of IDC (10%-49%). Mixed ILC-IDC may have distinctive biological behavior as compared to IDC or ILC.

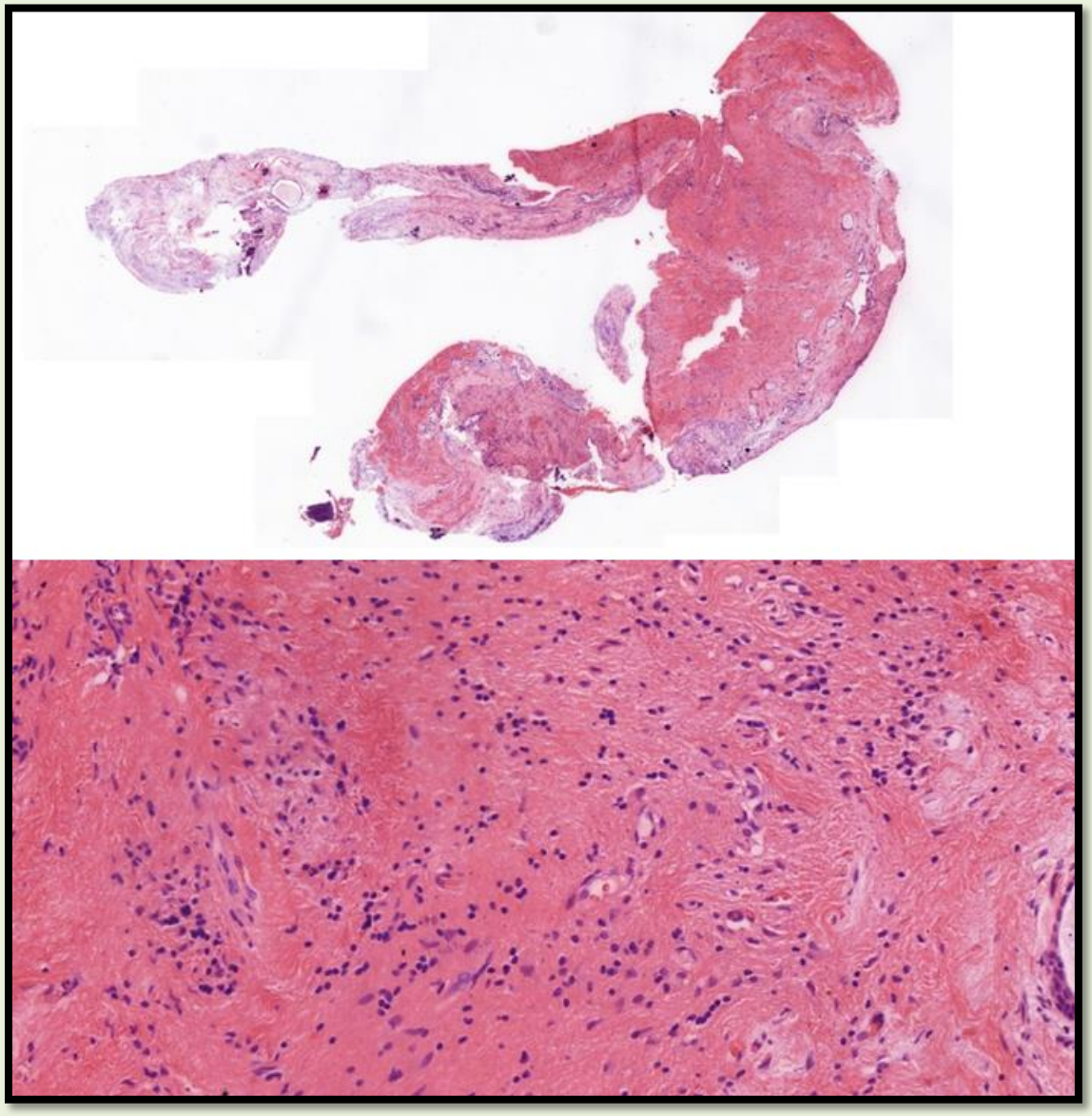
Reference:

1. World Health Organization. (2012). WHO classification of tumours of the Breast. Sunil R. Lakhani (Ed.). Internat. Agency for Research on Cancer.
2. Ishikawa, M. K., Pinsky, R. W., Smith, L. B., & Jorns, J. M. (2015). Morphologic mimics of invasive lobular carcinoma. Archives of pathology & laboratory medicine, 139(10), 1253-1257

Case 9

Case 9: 61 y.o., female, right middle ear cleft biopsy. One representative section.

Targeted Diagnosis: **Neuroglial heteropia**



Case 9

Submitted Diagnoses by Participating Institutions	Number
Glial heterotopia/ Glial choristoma/ Neuroglial choristoma/ Glial tissue heteropia	17
Glial choristoma. Comment: Bony deficit with herniation of brain tissue should be rule out by imaging.	1
Acoustic neuroma	1
Glioma	2

Educational notes:

1. A fragment of glial tissue with gliosis, which is positive for GFAP, is noted. There are scattered foci of dystrophic calcification.
2. Middle ear neuroglial heterotopia is rare. The differential diagnosis includes acquired encephalocele - herniation of brain into the middle ear and mastoid via compromised tegmen due to trauma, surgery, otitis media or congenital defect. Radiologic imaging is required to rule out the connection to the central nervous system or presence of defect.

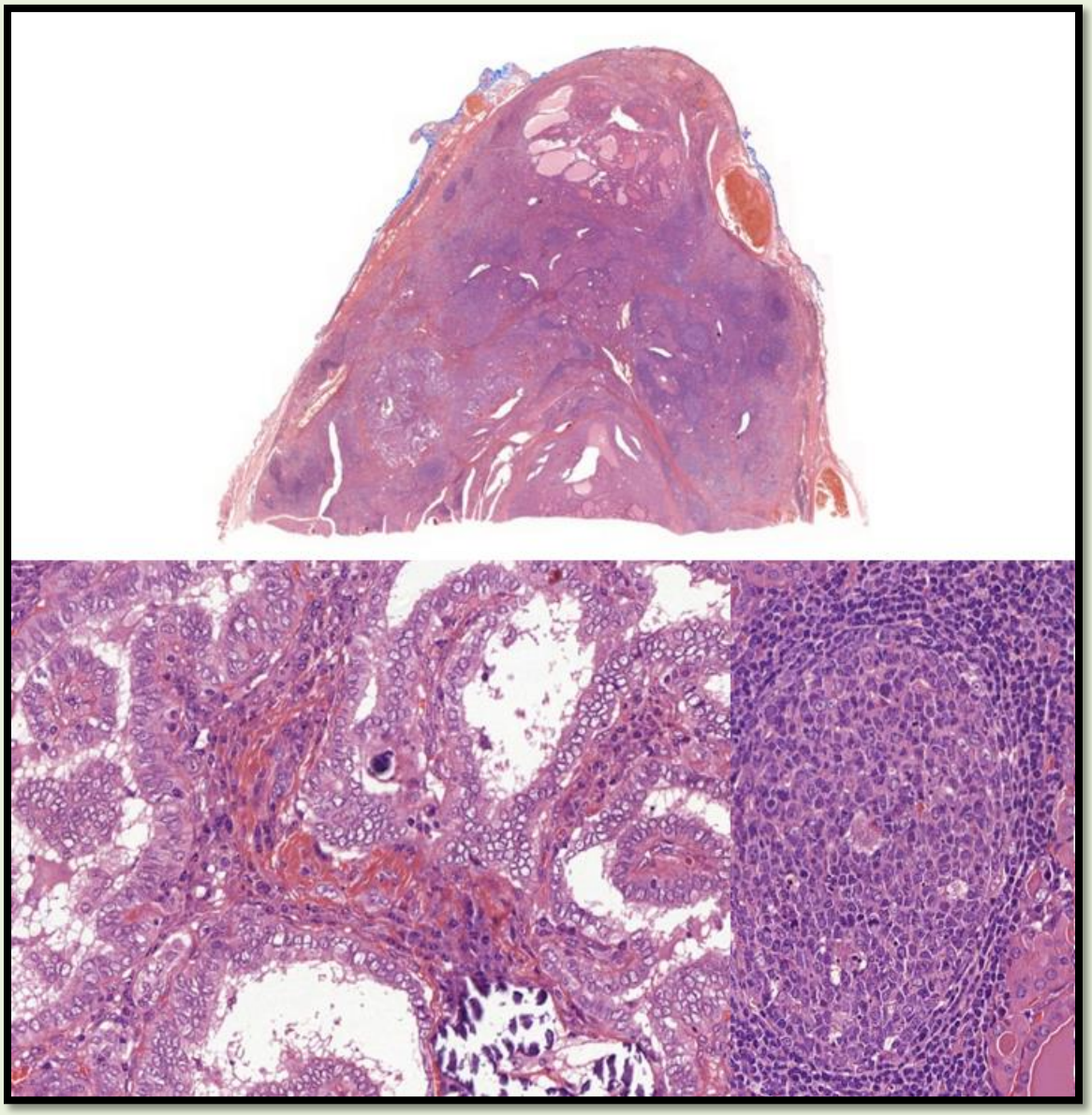
Reference:

1. Wenig, Bruce M. Atlas of Head and Neck Pathology. Elsevier Health Sciences, 2015.

Case 10

Case 10: 38 y.o., female, left solitary thyroid nodule. One representative section.

Targeted Diagnosis: **Hashimoto thyroiditis with papillary microcarcinoma**



Case 10

Submitted Diagnoses by Participating Institutions	Number
Papillary thyroid microcarcinoma in the background of Hashimoto thyroiditis/ Micropapillary carcinoma with background of Hashimoto's thyroiditis/ Papillary microcarcinoma in a background of lymphocytic thyroiditis.	6
Papillary thyroid carcinoma with background Hashimoto's thyroiditis/ Papillary thyroid carcinoma in a background of lymphocytic thyroiditis.	10
Papillary thyroid microcarcinoma	1
Papillary carcinoma	3
Papillary thyroid carcinoma in a background of Hashimoto's thyroiditis and nodular hyperplasia	1

Educational notes:

1. In the background of Hashimoto thyroiditis characterized by lymphoid follicles with germinal centers associated with Hurthle cell change, there is a focus of papillary microcarcinoma (4mm). This microcarcinoma displays tubulopapillae lined by follicular cells with characteristic nuclear crowding, nuclear clearing and irregular nuclear membrane. Microcalcifications are observed.
2. Papillary microcarcinoma measures ≤ 1cm and shows general attributes of a papillary carcinoma. It has excellent prognosis but there are rare exceptions. Histological markers of potential aggressiveness that should be examined in papillary microcarcinomas are: (i) multifocal and/or bilateral (ii) upper half of the size range, i.e. ≥ 6 mm in diameter (iii) extrathyroidal extension (iv) desmoplastic fibrosis and/or infiltrative growth pattern (v) poorly differentiated component and (vi) lymphovascular invasion.
3. Lymphocytic thyroiditis and Hashimoto thyroiditis represent the spectrum of autoimmune thyroiditis. Both are characterized by lymphocytic infiltration associated with germinal center formation. Morphological separation between the two depends on the extent of parenchyma (i.e. thyroid follicles) damage. Lymphocytic thyroiditis is designated when the thyroid follicles are relatively normal whereas in Hashimoto thyroiditis, severely damaged follicular cells show extensive oncocytic change. Complications of Hashimoto thyroiditis include thyroid lymphoma, oncocytic (Hurthle cell) neoplasms, and papillary carcinoma.

Reference:

1. Rosai and Ackerman's Surgical Pathology, John R. Goldblum (ed.) 11th Edition, Elsevier, 2017
2. Dataset for thyroid cancer histopathology reports. The Royal College of Pathologists. 2014