International Academy of Pathology
Malaysian Division

FINAL REPORT

QUALITY ASSURANCE PROGRAM
GENERAL DIAGNOSTIC HISTOPATHOLGY
CYCLE 01/2017

NOTES FROM THE COORDINATOR

1. For this cycle 01/2017, a total of 35 sets of DVDs had been circulated. Twenty-seven institutions responded by the closing date of 15 June 2017.

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 01/2017 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. Suhaila Abdullah, Dr. Fazilah Hassan, Dr. Pavitratha Puspanathan, and Dr. Nurul Akmar Misron.

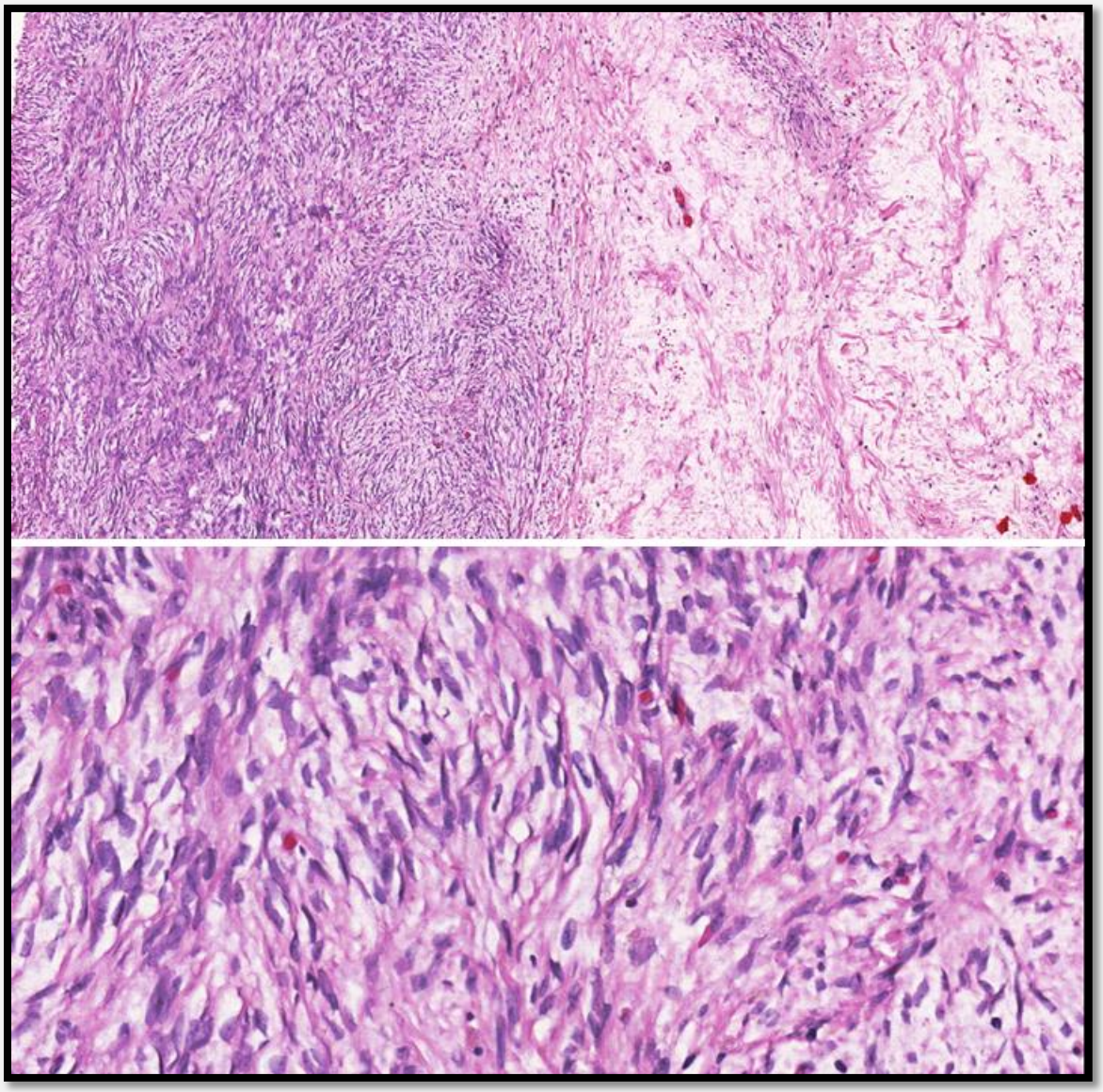
Prepared by,

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

Case 1

81-year-old female, ovarian mass (11cm). One representative section.

Targeted Diagnosis: **Ovarian fibroma**



Case 1

Submitted Diagnoses by Participating Institutions	Number
Fibroma/ Ovarian fibroma/ Fibroma with edema	20
Sclerosing stromal tumor	2
Massive ovarian oedema/ Ovarian stromal edema	2
Ovarian fibrothecoma with massive oedema	1
Thecoma. Differential dx: sclerosing stromal tumour	1
Myxoma	1

Educational notes:

1. This is an ovarian fibroma composed of spindle cells arranged in fascicles and a storiform pattern with massive areas of stromal edema.
2. About 10% of ovarian fibromas are densely cellular, which are termed as cellular fibroma. In mitotically active cellular fibromas, a high mitotic rate (>4/10HPF) could be encountered in the absence of cytological atypia.
3. Differential diagnoses include thecoma, sclerosing stromal tumor and massive ovarian edema.
4. Thecomas, by definition, are stromal tumors containing a significant number of cells resembling theca cells. These theca cells are uniform cells with oval to round nuclei and pale pink cytoplasm with ill-defined borders.
5. "FIbrothecoma" has been used as the distinction between thecomas and fibromas is difficult. This term is best avoided. These tumors are best regarded as fibromas in the absence of appreciable numbers of theca cells.
6. Sclerosing stromal tumors mostly occur in young females (mean age: 27 years). These tumors show cellular lobules in a background of hypocellular collagenous or edematous stroma. However, the cellular lobules are composed of a mixture of spindle and rounded cells.
7. This ovarian fibroma is distinguished from massive ovarian edema as the latter always encompasses follicles, corpora lutea, and corpora albicantia.

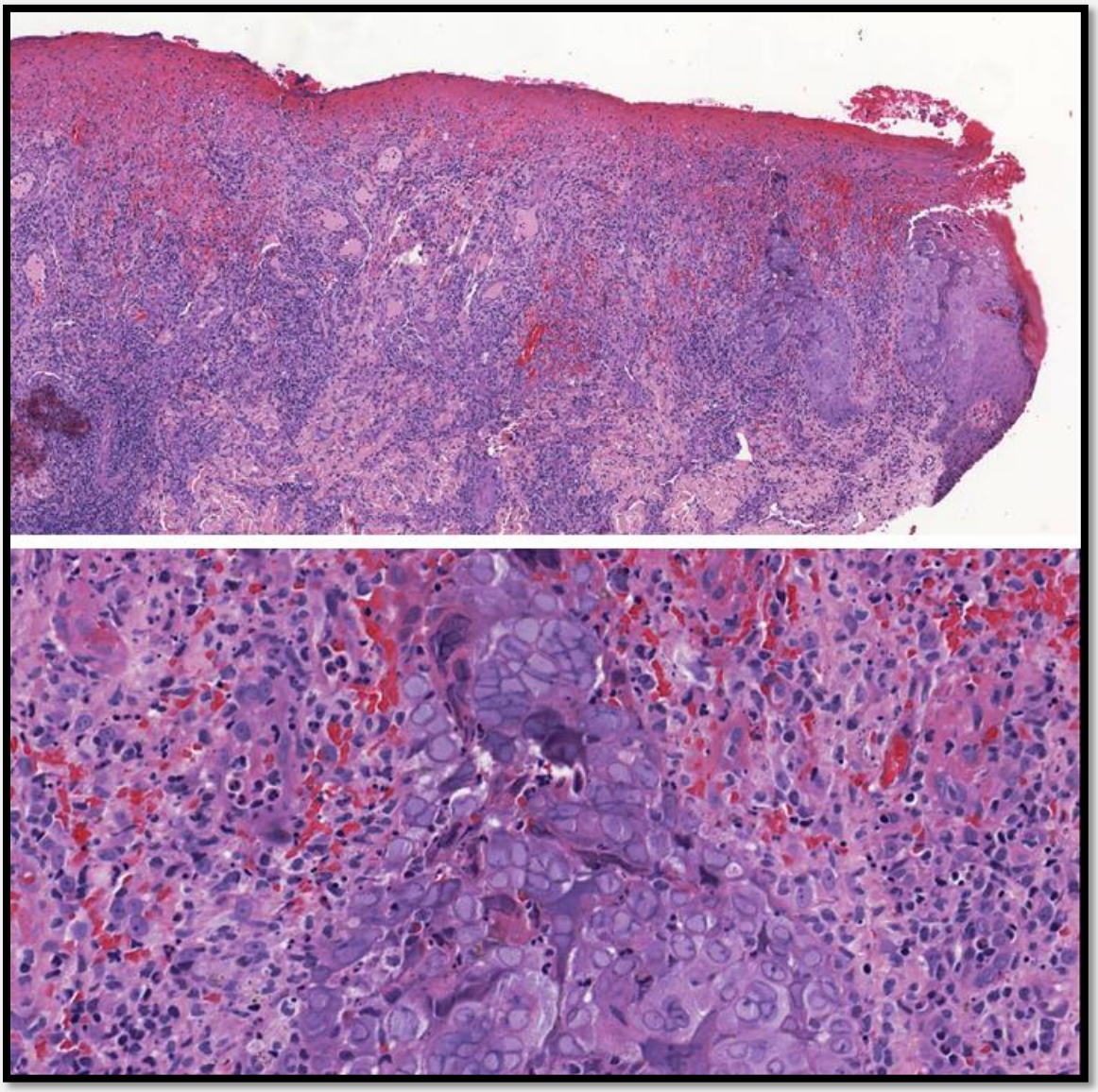
Reference:

1. Clement, P. B., & Young, R. H. (2014). Atlas of gynecologic surgical pathology. London: Saunders, 2014.
2. World Health Organization. (2014). WHO classification of tumours of female reproductive organs. R. J. Kurman (Ed.). Internat. Agency for Research on Cancer.

Case 2

25-year-old male, perianal ulcer edge biopsy.

Targeted Diagnosis: **Herpes simplex virus infection**



Case 2

Submitted Diagnoses by Participating Institutions	Number
Herpes simplex virus infection	21
Herpes virus infection	2
Herpetic/Herpes Zoster infection	1
Herpes simplex virus colitis	1
Leukocytoclastic vasculitis and dermoid cyst	1
Basosquamous carcinoma	1

Educational notes:

1. This biopsy shows extensive ulceration with dense mixed inflammatory infiltrates. At the ulcer margins, there are keratinocytes with characteristic nuclear features: steel-gray nuclei with marginated chromatin. Characteristic multinucleated giant cells are formed by fused keratinocytes.
2. The herpesvirus family consists of herpes simplex virus, varicella zoster virus, cytomegalovirus, herpes viruses 6 and 7, Epstein-Barr virus (EBV) and human herpesvirus (HHV) type 8.
3. Both herpes simplex virus (HSV) infection and varicella zoster virus (VZV) infection shows similar characteristic nuclear features as described above, which are indistinguishable without immunostains.
4. However, clinical findings would help in this distinction. HSV type 1 typically involves face (lips, perioral, perinasal); HSV type 2 involves genital region. VZV primary infection results in chickenpox, whereas reactivation of VZV results in shingles (herpes zoster), which has a dermatomal distribution.

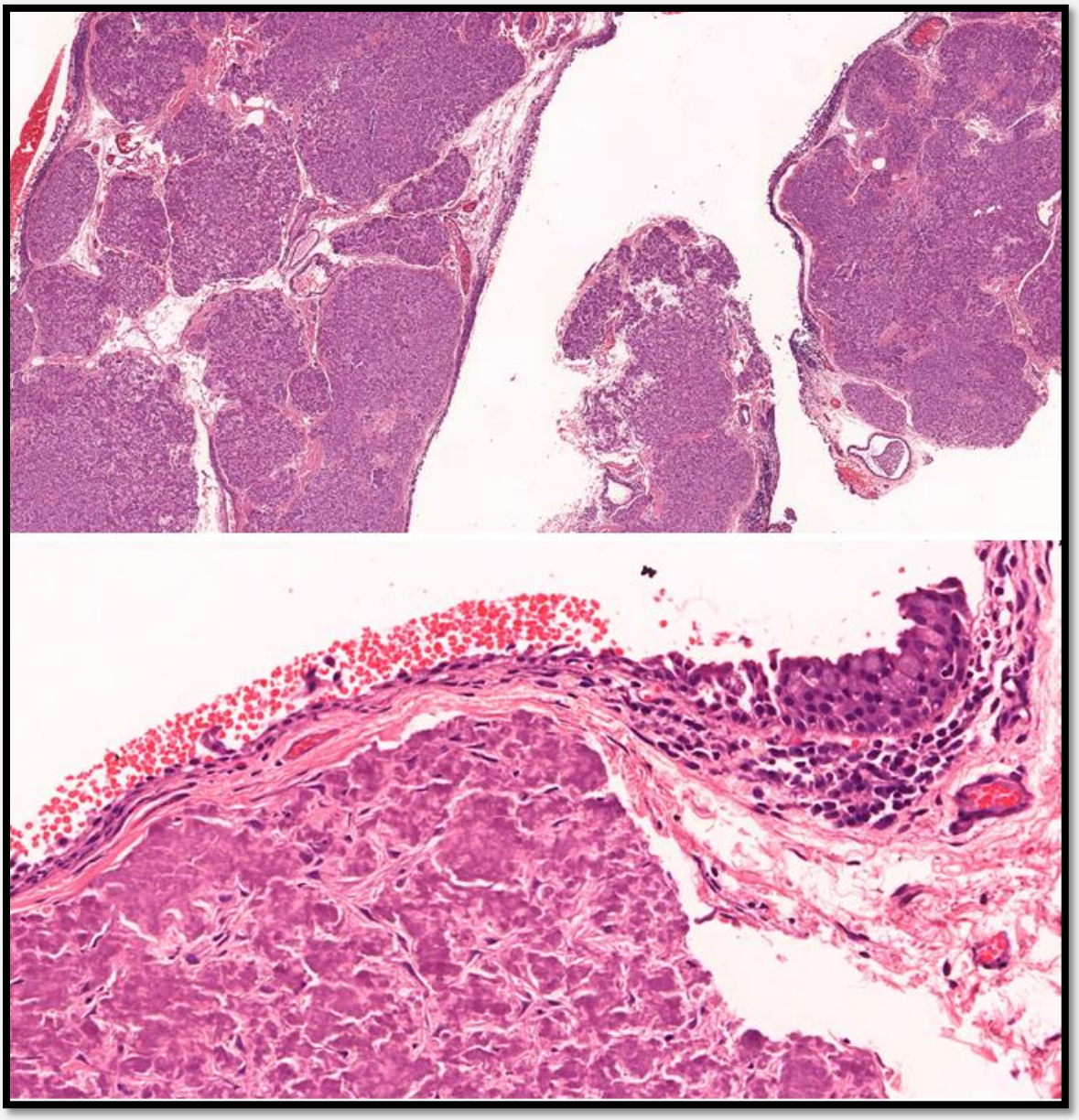
Reference:

1. Busam, K. J. (2016). Dermatopathology: A Volume in the Series Foundations in Diagnostic Pathology

Case 3

49-year-old female, right ptosis with conjunctival mass at eyelid.

Targeted Diagnosis: **Amyloidosis**



Case 3

Submitted Diagnoses by Participating Institutions	Number
Conjunctival calcinosis/Subconjunctival calcium deposition	3
Calcinosis cutis	7
Calcinosis/ Tumoral calcinosis	6
Calcinosis cutis. Require special stain to rule out amyloid.	1
Calcified nodule	1
Amyloidosis/ Conjunctival amyloidosis	4
Amorphous deposition, favour amyloidosis. Need special stain for proper histological confirmation	1
Molluscum contagiosum	1
Conjunctival concretion (Hordeolum)	1
Pinguecula	1
Basophilic acellular material? foreign material deposition. Requires further history (?any previous procedure to the site etc)	1

Educational notes:

1. The conjunctival mucosa is composed of non-keratinizing squamous epithelium admixed with goblet cells. There are extensive subepithelial nodular depositions of amorphous material, which appear basophilic in this biopsy.
2. The IAP-MD QAP evaluation panel agreed that the differential diagnoses include calcinosis and amyloidosis, which require special stains for confirmation.
3. In practice, calcinosis could be demonstrated by Von Kossa calcium special stain that highlights the black-stained calcium. Congo red special stain highlights the presence of amyloid in orange red, which is apple green birefringent after polarization.
4. This biopsy was concluded as amyloidosis. Conjunctival amyloidosis is uncommon; it usually occurs as primary localized amyloidosis without systemic amyloidosis except in rare instances.

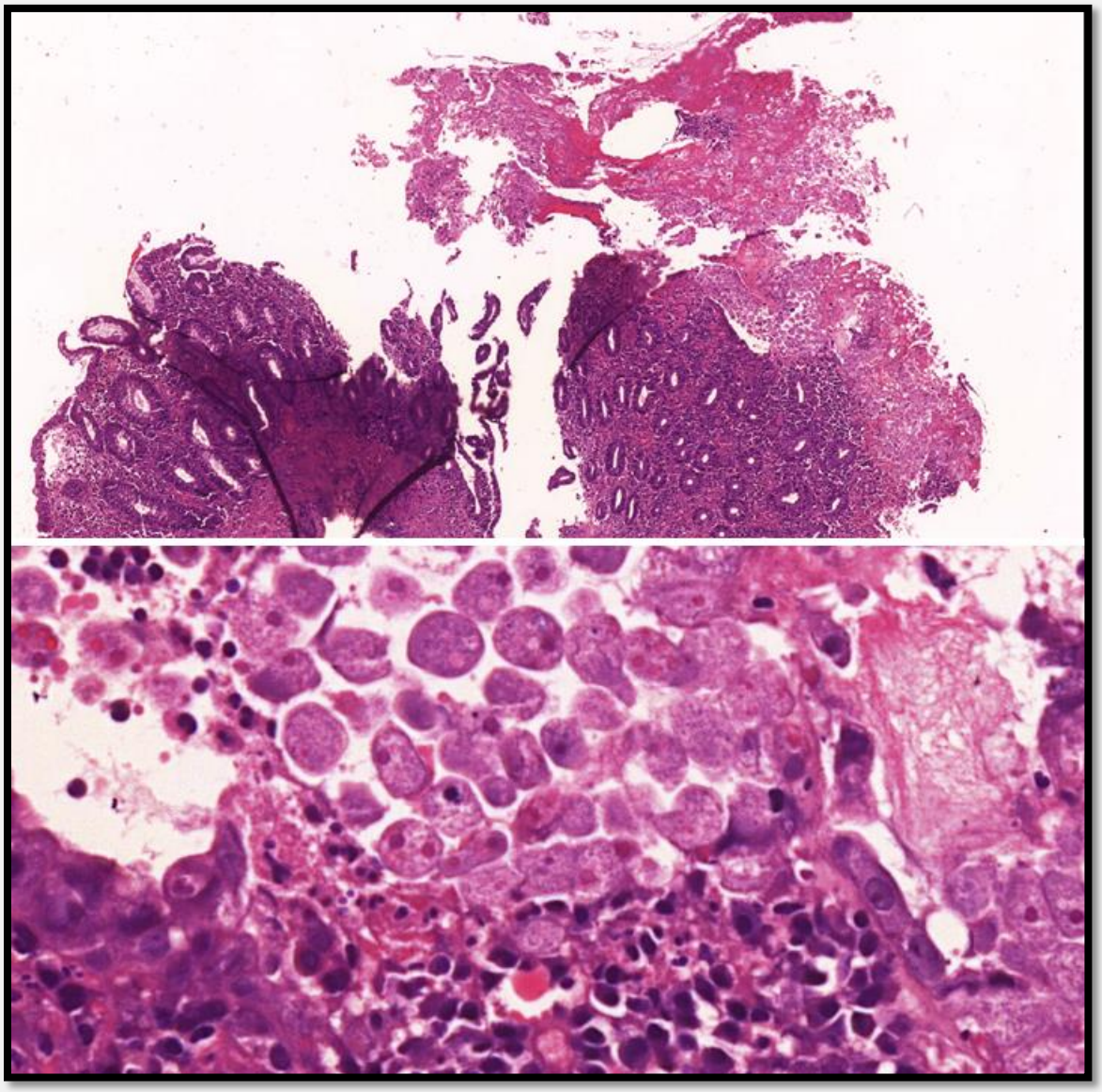
Reference:

1. Heegaard, S., & Grossniklaus, H. (Eds.). (2014). Eye pathology: An illustrated guide. Springer.

Case 4

57-year-old-male, prolonged diarrhea and abdominal pain, colonic biopsy.

Targeted Diagnosis: **Amebic colitis**



Case 4

Submitted Diagnoses by Participating Institutions	Number
Amebiasis/ Amebic colitis	27

Educational notes:

1. There are multiple relatively intact colonic tissue fragments. One fragment shows ulceration capped by clusters of trophozoites of *E. histolytica* mixed with eosinophilic debris at the luminal surface.
2. (i)Noninvasive infection occurs when trophozoites remain confined to the intestinal lumen of asymptomatic carriers. (ii) Intestinal disease and (iii) extraintestinal disease (such as liver, lung and brain) manifest when the trophozoites invade the intestinal mucosa and spread through the bloodstream.
3. Trophozoites of *E. histolytica* have foamy cytoplasm and distinct cytoplasmic membrane. They have round, eccentrically placed nuclei with marginated chromatin and a central karysome. Ingestion of red blood cells is pathognomonic of *E. histolytica*.
4. Trophozoites of *E. histolytica* are densely PAS-positive.

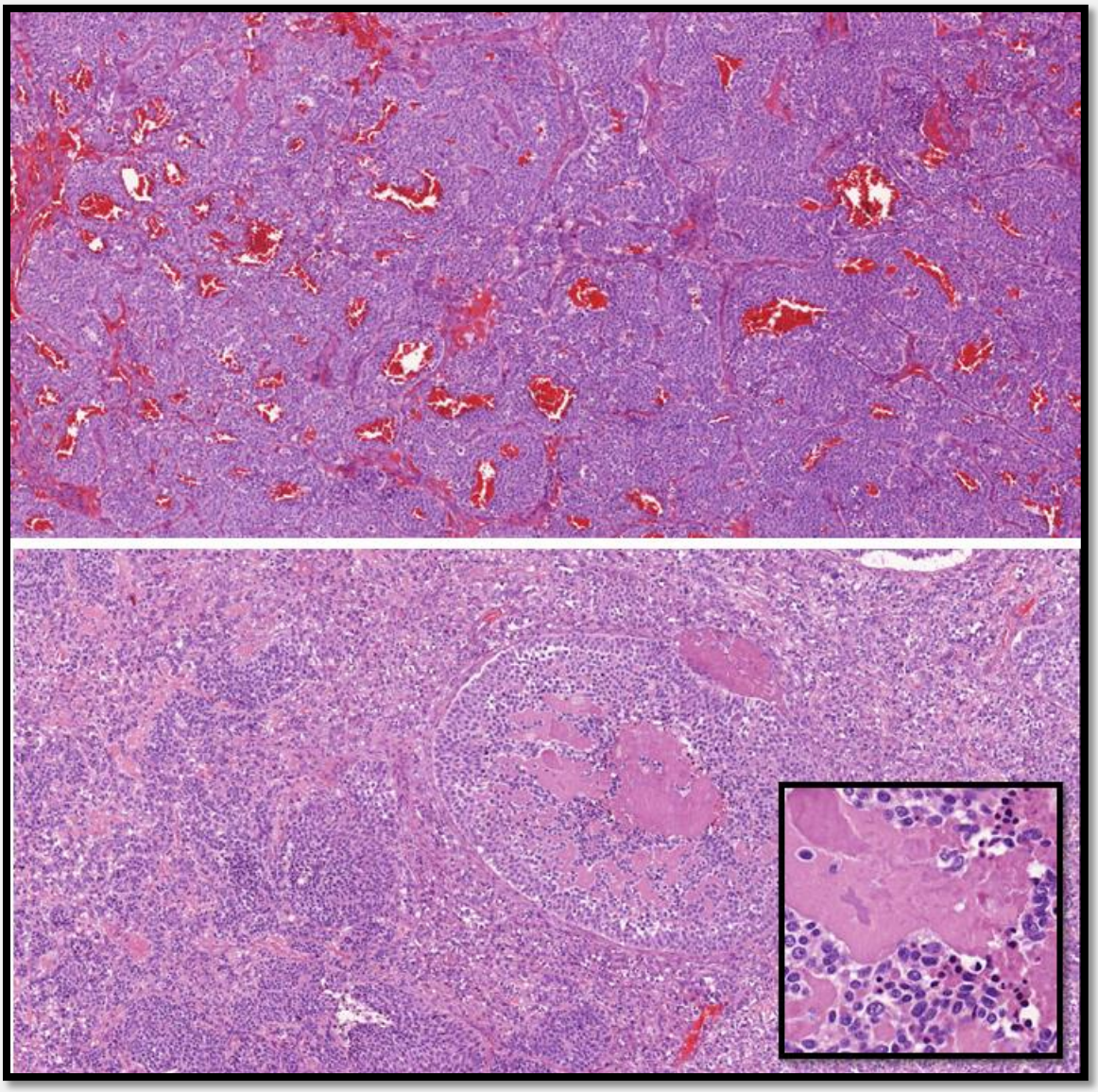
Reference:

1. Parasites - Amebiasis - Entamoeba histolytica Infection, https://www.cdc.gov/parasites/amebiasis/index.html
2. Laura W. Lamps. (2009). Surgical Pathology of the Gastrointestinal System: Bacterial, Fungal, Viral, and Parasitic Infections. Springer.

Case 5

61-year-old male, thyroid swelling with a mass (6cm). One representative section.

Targeted Diagnosis: **Medullary thyroid carcinoma**



Case 5

Submitted Diagnoses by Participating Institutions	Number
Medullary carcinoma of thyroid	21
Medullary carcinoma with colloid	1
Medullary thyroid carcinoma, paraganglioma-like variant	1
Medullary thyroid carcinoma with perithyroidal soft tissue involvement and possible lymphovascular invasion. Differential diagnosis of poorly differentiated carcinoma. Need immunohistochemistry (Calcitonin, thyroglobulin, CEA and neuroendocrine markers)	1
Poorly differentiated thyroid carcinoma (insular carcinoma)	1
Follicular carcinoma	1
Paraganglioma	1

Educational notes:

1. This tumor shows predominantly nested pattern separated by thin fibovascular septa. The tumor cells are polygonal in shape with relatively uniform nuclei displaying characteristic salt-and-pepper chromatin pattern. Amyloid deposits are evident.
2. Histopathological features of medullary thyroid carcinoma are variable and at least 12 histologic variants have been described, such as papillary or pseudopapillary, glandular, giant cell, spindle cell, and paraganglioma-like.
3. Amyloid deposits are observed in about 80% of medullary thyroid carcinoma, which are helpful in the diagnosis of medullary thyroid carcinoma; nonetheless, they are also present in non-C-cell derived thyroid lesions.
4. Diagnosis of medullary thyroid carcinoma is aided by immunopositivity for calcitonin, chromogranin A, synaptophysin, CEA and low molecular weight cytokeratin.
5. Caveat: medullary thyroid carcinoma is also positive for TTF-1. Sustentacular cells in medullary thyroid carcinoma can be numerous and they are positive for S-100 protein. Distinction from paraganglioma is possible as cytokeratin is negative in the former.

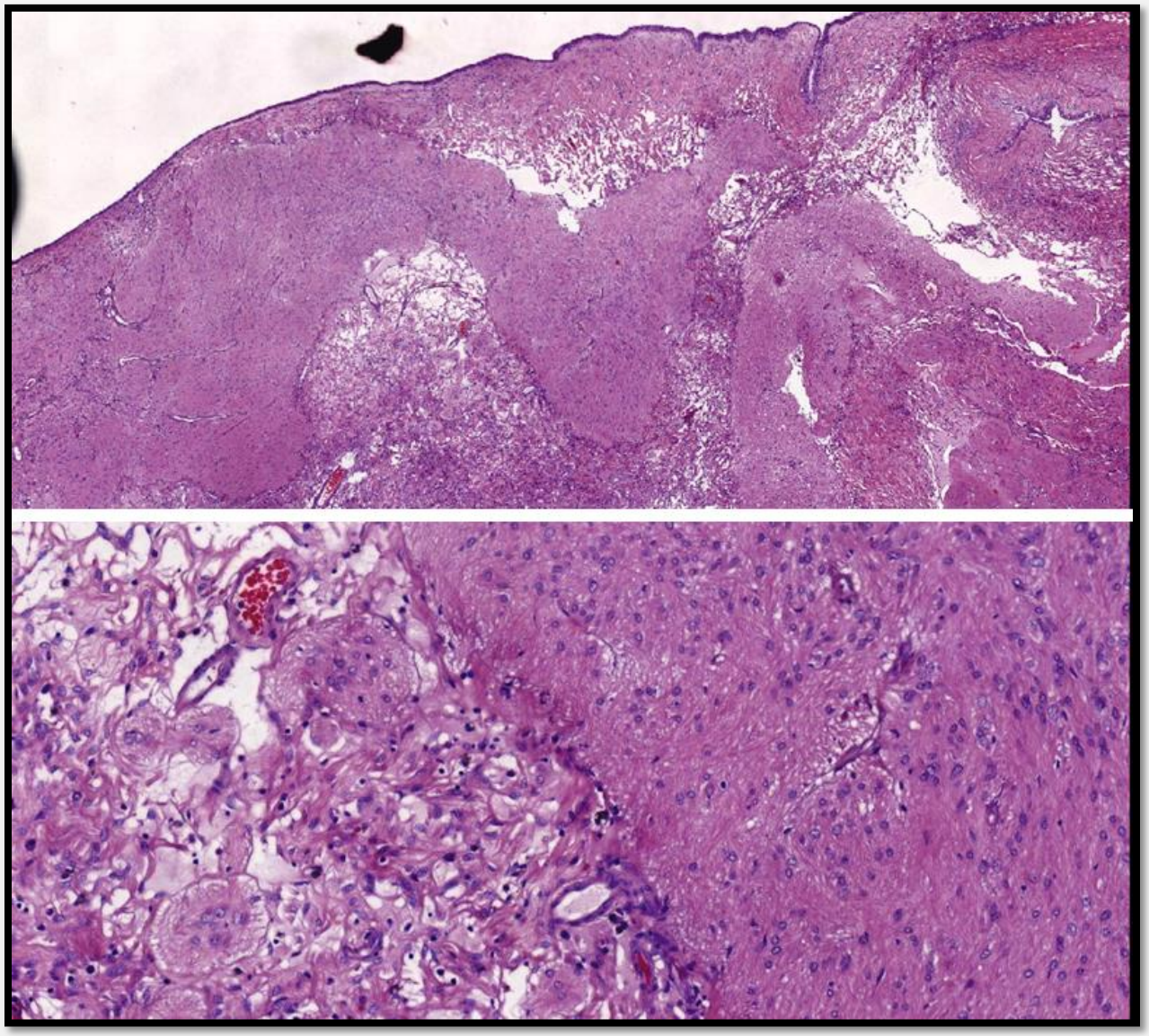
Reference:

1. Schmid, K. W. (2015). Histopathology of C Cells and Medullary Thyroid Carcinoma. In Medullary Thyroid Carcinoma (pp. 41-60). Springer International Publishing.

Case 6

1-year-old female, left nasal mass. One representative section.

Targeted Diagnosis: **Glial heterotopia**



Case 6

Submitted Diagnoses by Participating Institutions	Number
Glial heterotopia/ nasal glioma	23
Meningoencephalocoele	1
Glial heterotopia/ encephalocoele	1
Encephalocoele	1
Ganglioglioma	1

Educational notes:

1. The polypoid tissue fragments are partially covered by respiratory epithelium. These fragments are composed of disorganized fibrillary neuroglial tissue in lobular architecture.
2. Nasal glioma is a misnomer as glial heterotopia is a non-neoplastic condition.
3. In glial heterotopia, neuroglial tissue is congenitally displaced without connection to the central nervous system. This occurs most commonly at the subcutaneous tissue of the nose and inside the nasal cavity.
4. In contrast, connection to central nervous system is maintained in encephalocele as brain tissue herniates beyond the cranial cavity. Connection to central nervous system should be assessed pre-operatively. Encephalocele appears as more organized brain tissue histologically and have leptomeningeal elements; distinction from glial heterotopia requires clinico-radiological correlation.

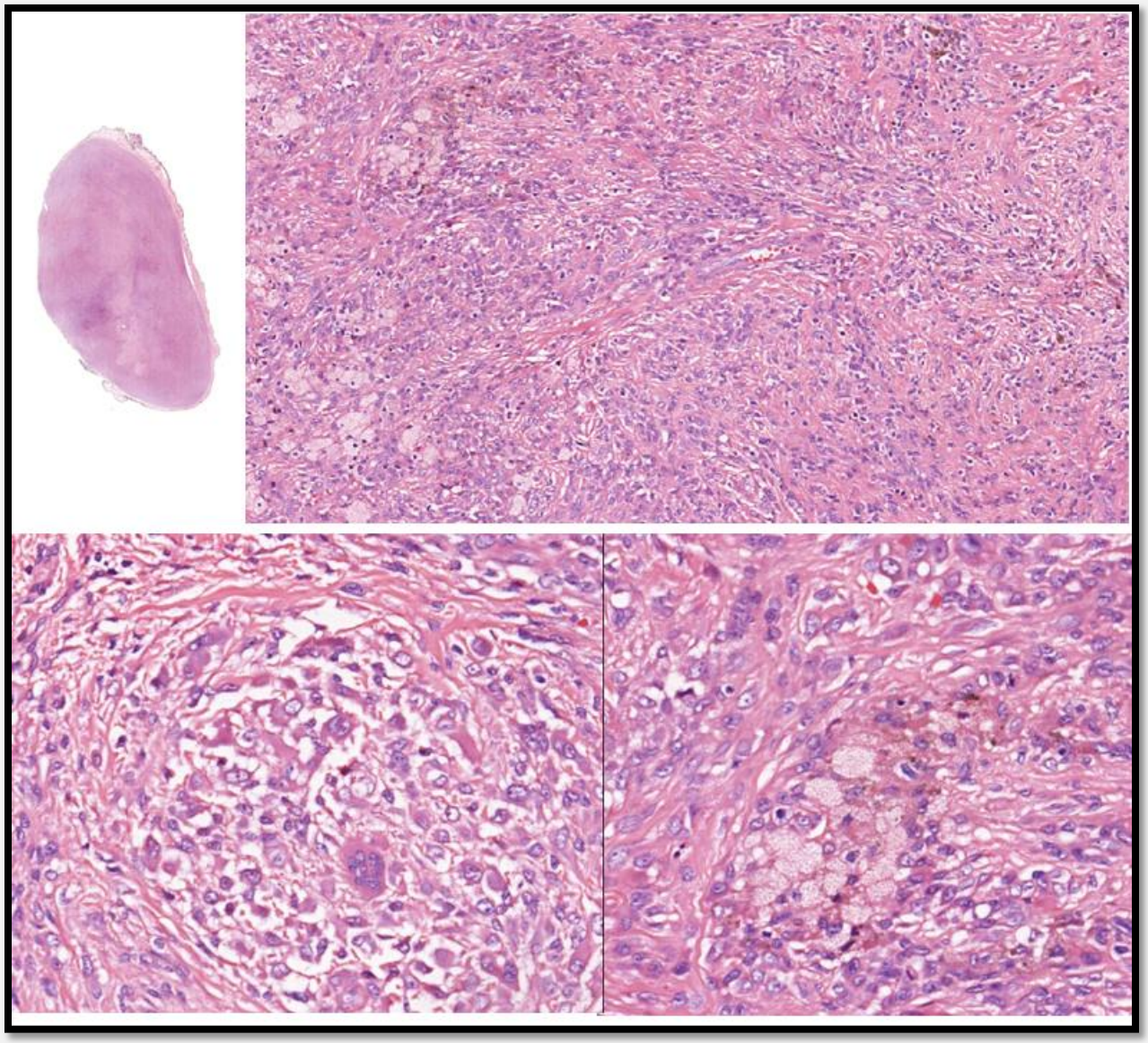
Reference:

1. Cardesa, A., Slootweg, P. J., Gale, N., & Franchi, A. (Eds.). (2017). Pathology of the Head and Neck. Springer.

Case 7

68-year-old male, right knee soft tissue mass. One representative section.

Targeted Diagnosis: **Tenosynovial giant cell tumor, localized type**



Case 7

Submitted Diagnoses by Participating Institutions	Number
Tenosynovial giant cell tumor, localized type/ Giant cell tumor of tendon sheath, localized type	2
Tenosynovial giant cell tumor/ Giant cell tumor of tendon sheath/ Nodular tenosynovitis	11
Tenosynovial giant cell tumor, diffuse type/ Giant cell tumor of tendon sheath, diffuse type	2
Giant cell tumor	7
Giant cell tumor of soft tissue	5

Educational notes:

1. This tumor is well-circumscribed with a partial fibrous capsule. Mononuclear tumor cells, multinucleated giant cells, foamy macrophages, siderophages and lymphocytes admix in the variably fibrotic stroma.
2. According to WHO classification of tumors of the soft tissue and bone (2012), the so-called fibrohistiocytic tumor group includes the following entities: (i)tenosynovial giant cell tumor, localized type, (ii) tenosynovial giant cell tumor, diffuse type, (iii) deep benign fibrous histiocytoma, (iv) plexiform fibrohistiocytic tumor, and (v)giant cell tumor of soft tissue.
3. Tenosynovial giant cell tumor, localized type is a benign well-circumscribed neoplasm. In contrast, tenosynovial giant cell tumor, diffuse type is infiltrative with diffuse expansive sheets. It is a locally aggressive but non-metastasizing neoplasm.
4. Giant cell tumor of soft tissue is a rarely metastasizing neoplasm and has similar clinicopathological features with giant cell tumor of the bone. Histologically, there are usually cellular nodules separated by fibrous septa. The cellular nodules are composed of a mixture of mononuclear cells and multinucleated giant cells in the richly vascularized stroma.

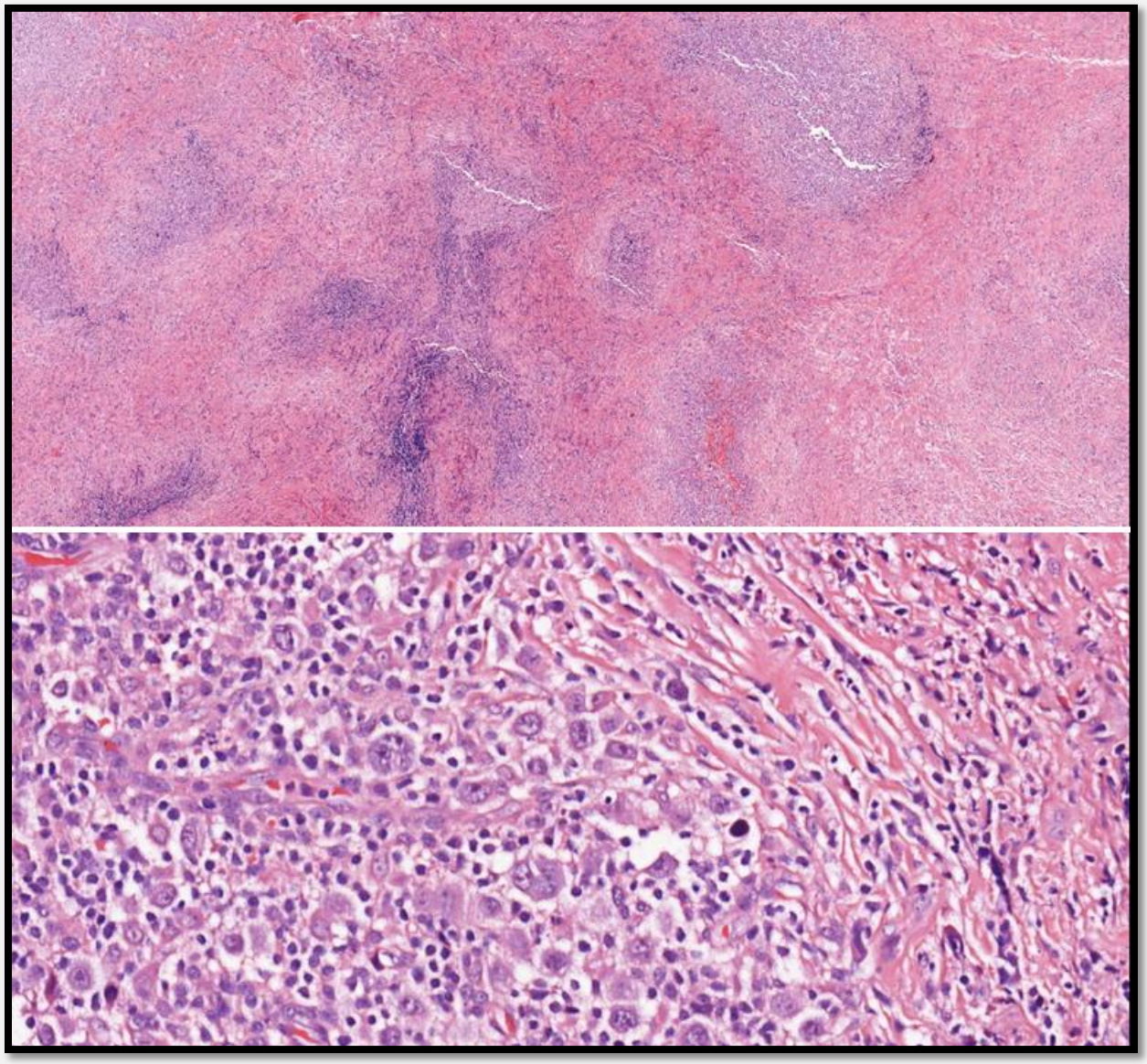
Reference:

1. World Health Organization (2012). WHO classification of tumours of soft tissue and bone. Christopher D. M. Fletcher (Ed.). Internat. Agency for Research on Cancer.

Case 8

43-year-old female, lobulated upper lobe lung mass. One representative section.

Targeted Diagnosis: **Hodgkin lymphoma, classical nodular sclerosis**



Case 8

Submitted Diagnoses by Participating Institutions	Number
Hodgkin lymphoma, nodular sclerosis	20
Hodgkin's Disease, nodular sclerosing, I would like to do IHC for confirmation.	1
Hodgkin lymphoma/ Classical Hodgkin lymphoma	3
Malignant lymphoma, favor Hodgkin Lymphoma. Requires immunohistochemistry.	1
Angiolymphoid hyperplasia with eosinophilia.	1
Inflammatory myofibroblastic tumour	1

Educational notes:

1. This tumor shows broad bands of collagenized fibrosis encasing cellular nodules. The cellular nodules are composed of a mixture of many atypical mononuclear cells (Hodgkin cells), scattered binucleate or multinucleate Reed–Sternberg cells, mummified Hodgkin cells, small lymphocytes and scattered eosinophils.
2. Hodgkin lymphoma comprises two distinct disease entities: nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) and classical Hodgkin lymphoma (CHL). CHL is further divided into four subtypes: nodular sclerosis, mixed cellularity, lymphocyte-rich and lymphocyte-depleted.
3. NLPHL is characterized by nodular and diffuse proliferation of LP [lymphocyte-predominant] cells (also known as popcorn cells or L&H [lymphocytic and/or histiocytic Reed-Sternberg cell variants] cells). LP cells are positive for CD20 and CD79a but usually lack of CD15 and CD30 expression.
4. On the other hand, CHL shows reactive infiltrates in the background with scattered typical Hodgkin cells and Reed-Sternberg cells, which are usually negative for CD20 and CD79a but positive for CD15 and CD30. They are positive for PAX5/BSAP, a B-cell marker.
5. Reed–Sternberg like cells are atypical immunoblasts resembling Reed–Sternberg cells; they are present in a number of lymphadenitis such as infectious mononucleosis. These atypical immunoblasts are positive for CD20 and CD79a as well as CD30.

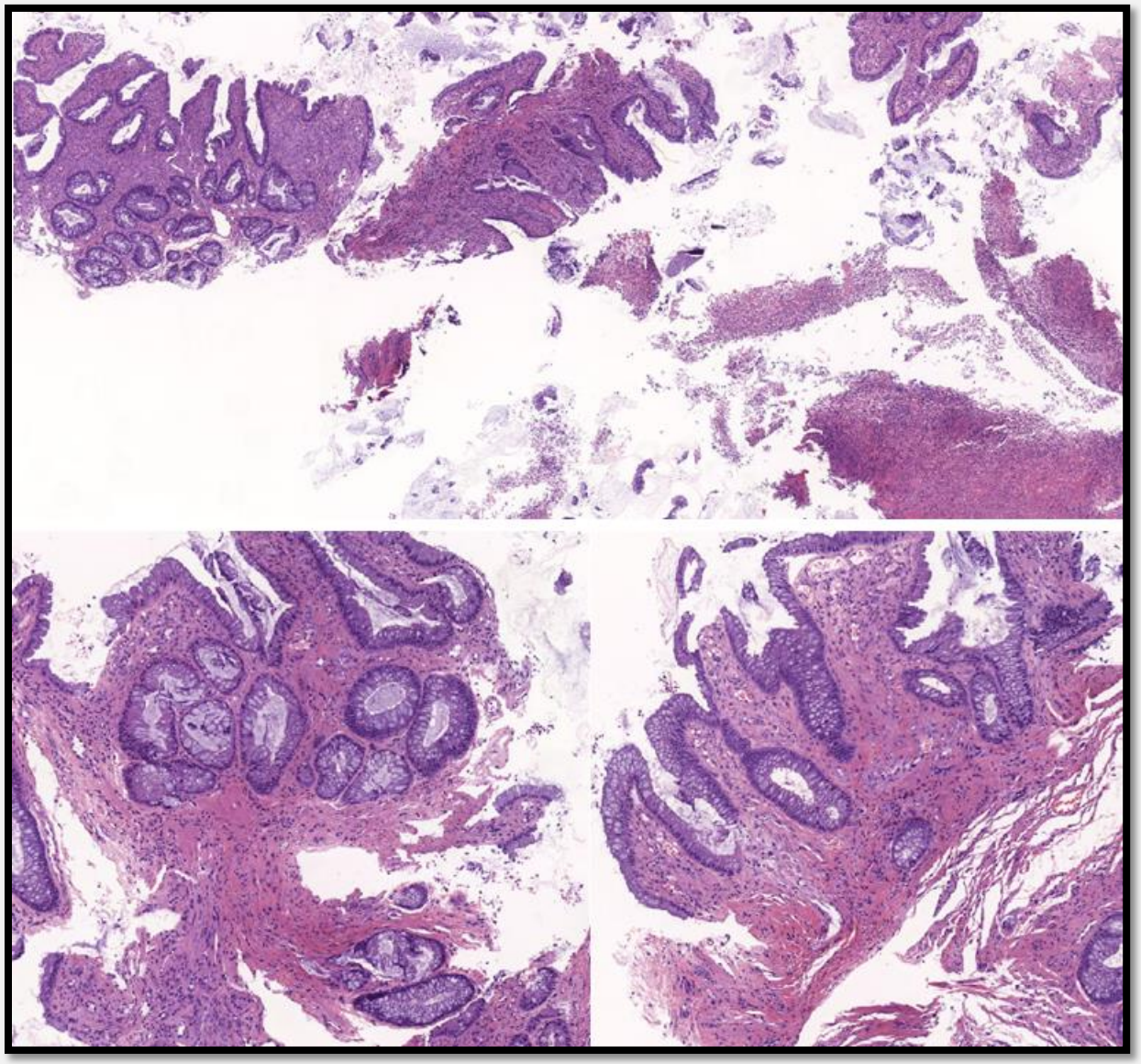
Reference:

1. World Health Organization (2008). WHO classification of tumours of haematopoietic and lymphoid tissues. S. H. Swerlow (Ed.). Internat. Agency for Research on Cancer.

Case 9

57-year-old-male, colonoscopy: ulcerated tumor, ulcer biopsy.

Targeted Diagnosis: **Mucosal prolapse syndrome (solitary rectal ulcer)**



Case 9

Submitted Diagnoses by Participating Institutions	Number
Solitary rectal ulcer/ mucosal prolapse syndrome	14
Ulcer with hyperplastic reactive changes. Requires further history and determine exact site (eg rectum - solitary rectal ulcer etc)	1
Benign ulcer/ Benign chronic ulcer with vasculitic changes	2
Solitary rectal ulcer syndrome. Vacular proliferation in lamina propria noted, probably reactive, need to exclude vascular neoplasm.	1
Low grade vascular neoplasm DD: Solitary rectal ulcer	1
Features favour benign vascular tumour. I would like to do IHC and suggest for a rebiopsy for confirmation.	1
? infective colitis (aetiology) /Infective colitis (fungal infection) /Chronic colitis with ulceration favouring infective etiology (suspicious for Mucormycosis). Request PAS/GMS for confirmation.	3
Giardia infection	1
Inflammatory bowel disease possible UC	1
Ischaemic colitis	2

Educational notes:

1. There are small colonic tissue fragments and pieces of ulcerative tissue with cellular debris and fibrin. The colonic tissue fragments show variably placed crypts with distortion. Fibromuscular obliteration of the lamina propria and vascular ectasia are evident.
2. Mucosal prolapse syndrome describes a group of benign disorders sharing similar histopathological features whereby chronic mucosal prolapse is the underlying mechanism. This includes several entities such as rectal prolapse, solitary rectal ulcer syndrome, inflammatory cloacogenic polyp, and proctitis cystica.
3. The shared histopathological features are superficial ulceration, crypt distortion, surface serration, fibromuscular obliteration of the lamina propria and vascular ectasia underneath the surface epithelium. The last two features are the most significant changes.
4. Caveat: Misplacement of epithelium in mucosal prolapse syndrome may mimic invasive carcinoma. Recognition of this entity with emphasis on lack of desmoplastic reaction and cytological atypia would help to avoid misdiagnosis.

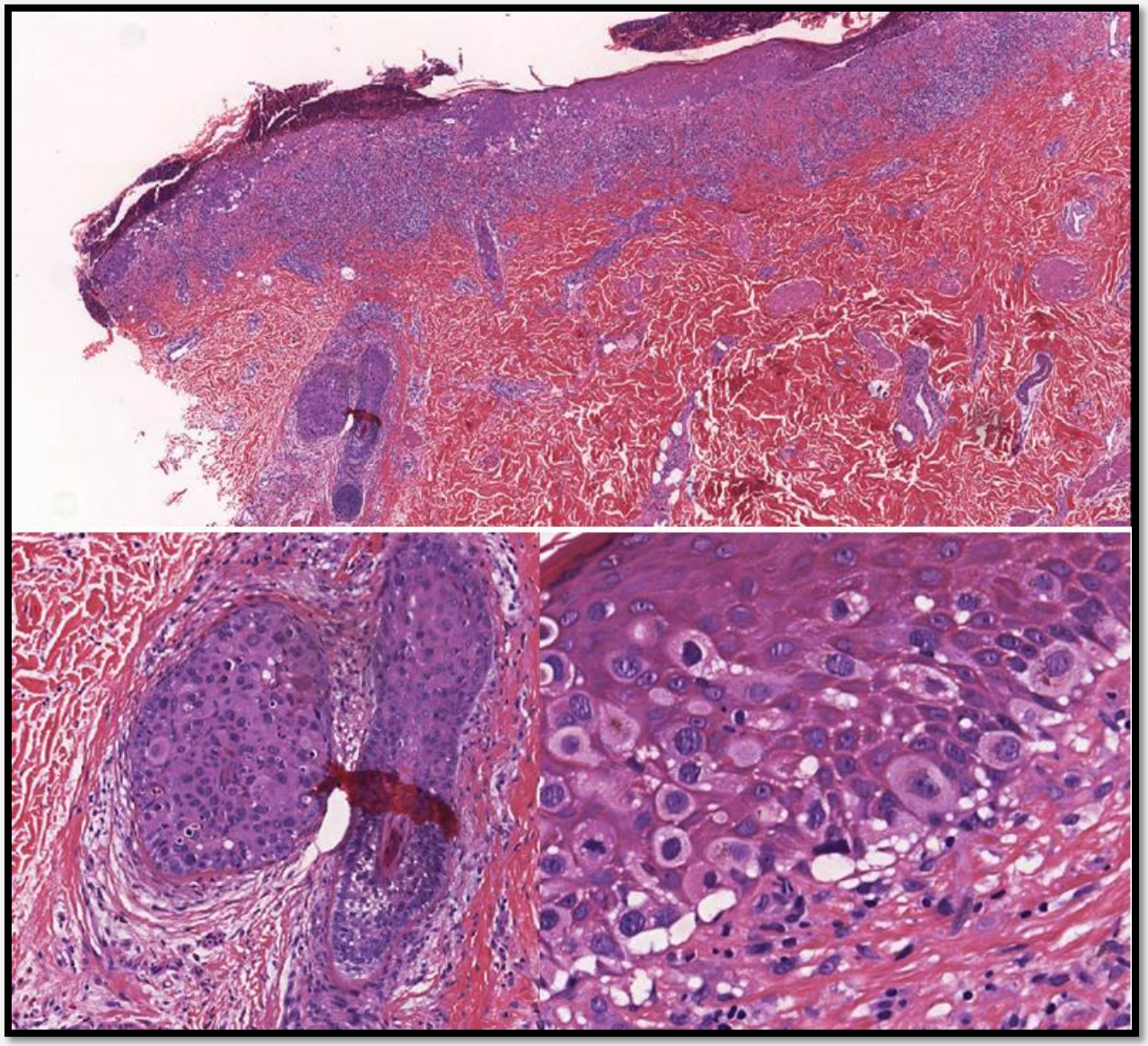
Reference:

1. Odze, R. D., & Goldblum, J. R. (2015). Surgical pathology of the GI tract, liver, biliary tract, and pancreas. Elsevier Health Sciences.

Case 10

59-year-old female, eroded right nipple, nipple biopsy.

Targeted Diagnosis: **Paget disease of the breast**



Case 10

Submitted Diagnoses by Participating Institutions	Number
Paget disease of the breast/nipple	24
Paget disease of the breast/nipple associated with DCIS/high grade DCIS/ intermediate grade DCIS	3

Educational notes:

1. This nipple biopsy shows ulceration and dense inflammatory infiltrates. Pagetoid spread of malignant epithelial cells in the epidermis is noted. These malignant epithelial cells show high grade nuclei with ample amphophilic cytoplasm. Colonization of the skin appendages by the malignant cells is observed.
2. Differential diagnoses include melanoma and squamous cell carcinoma in situ, which also show pagetoid spread. Immunohistochemistry would be helpful as malignant cells in Paget disease of the breast are typically positive for CK7 and EMA. They always over-express Her-2 and contain mucicarmine.
3. Toker cell hyperplasia of the nipple also shows pagetoid spread of clear cells, which are however negative for Her-2 and Ki-67.
4. 87 to 100% of Paget disease of the breast is associated with underlying DCIS or infiltrating carcinoma, NST or both.

Reference:

1. Dabbs, D. J. (2012). Breast pathology. Elsevier Health Sciences.