UNIVERSITY MEDICAL CENTER OF EL PASO

Path-O-Gram

Pathology laboratory news for you!

Department of Pathology

TTUHSC EL PASO
Texas Tech University Health Sciences Center El Paso

Dr. Jude Abadie, Editor | January 2024 | Volume 4 | No. 1

■ Departmental Highlights ■ Surgical Pathology Case Studies ■ Clinical Pathology
■ Test-Your-AP and CP Knowledge ■ Announcements

CONTENTS

I. Department Highlights

A. Residency Program Updates

Our pathology residency program is 6-months old, and we are proud of the progress our PGY-1 residents have made thus far. Their strong performances in anatomic and clinical pathology areas are evident. This Path-o-Gram newsletter highlights some of their work.

About 500 candidates applied to fill 3 slots in the AY 2024-2025 PGY class. While we were only able to interview a portion of our applicants, we are looking forward to match day!

B. Grand opening of Surgical Hospital East

Figure 1. Pathology laboratory at the Surgical Hospital East

On 2 Jan 2024, the UMC Surgical Hospital East (1416 George Dieter) opened its door to provide acute care service, with 40 in-patient rooms, 6 operating room suites, 2 endoscopy suites, 6 emergency room beds.

- Patients who live in east El Paso can now receive care at the surgical hospital without traveling to the main campus.
- Our 24/7 pathology laboratory is equipped to provide general chemistry, hematology, coagulation, and urinalysis testing, as well as blood banking services.
- The pathology laboratory provides services for the cardiac cauterization lab, radiology, gastrointestinal care, as well as orthopedic, gynecological, and ear nose throat surgical procedures.

C. Faculty publications…. since last Path-O-Gram in July 2023

Kirtek T, Chen W, Laczko D, Bagg A, Koduru P, Foucar K, Venable E, Nichols M, Rogers HJ, Tam W, **Orazi A**, Hsi ED, Hasserjian RP, Wang SA, Arber DA, Weinberg OK. Acute leukemias with complex karyotype show a similarly poor outcome independent of mixed, myeloid or lymphoblastic immunophenotype: A study from the Bone Marrow Pathology Group. Leuk Res. 2023 Jul;130:107309.

doi: 10.1016/j.leukres.2023.107309. Epub 2023 May 10.PMID: 37210875

Wang SA, **Orazi A**, Gotlib J, Reiter A, Tzankov A, Hasserjian RP, Arber DA, Tefferi A. The international consensus classification of eosinophilic disorders and systemic mastocytosis. Am J Hematol. 2023 Aug;98(8):1286-1306. doi: 10.1002/ajh.26966. Epub 2023 Jun 7. PMID: 37283522 Review.

Foucar K, Bagg A, Bueso-Ramos CE, George T, Hasserjian RP, Hsi ED, **Orazi A**, Tam W, Wang SA, Weinberg OK, Arber DA. Guide to the Diagnosis of Myeloid Neoplasms: A Bone Marrow Pathology Group Approach.Am J Clin Pathol. 2023 Oct 3;160(4):365-393. doi: 10.1093/ajcp/aqad069. PMID: 37391178

Pardanani A, Tefferi A, Al-Kali A, Patnaik M, Hogan WJ, Begna K, Elliott MA, Khera N, Palmer JM, Gangat N, **Orazi A**, Kelemen K, Reichard KK, Chen D. Reappraisal of mast cell leukemia based on a single institution review of 16 cases: Mast cell morphology determines clinical outcome. Am J Hematol. 2024 Jan;99(1):E1-E4. doi: 10.1002/ajh.27089. Epub 2023 Sep 9. PMID: 37688525

Tefferi A, Pardanani A, Al-Kali A, Alkhateeb H, McCullough K, Patnaik M, Hogan WJ, Begna K, Elliott MA, Khera N, Palmer JM, Gangat N, Kelemen K, **Orazi A**, Chen D, Reichard K. Mast cell cytomorphology and treatment outcome in mast cell leukemia. Am J Hematol. 2024 Jan;99(1):E5-E8. doi: 10.1002/ajh.27105. Epub 2023 Sep 21. PMID: 37732882

Tefferi A, Abdelmagid M, Al-Kali A, Patnaik M, Hogan WJ, Begna K, Gangat N, **Orazi A**, Chen D, Reichard KK, Pardanani A. Granularity in disease classification impacts survival prediction in advanced systemic mastocytosis: A single institution study of 329 informative cases. Am J Hematol. 2024 Jan;99(1):21-27. doi: 10.1002/ajh.27113. Epub 2023 Sep 29. PMID: 37772442

Yin CC, Tam W, Walker SM, Kaur A, Ouseph MM, Xie W, K Weinberg O, Li P, Zuo Z, Routbort MJ, Chen S, Medeiros LJ, George TI, **Orazi A**, Arber DA, Bagg A, Hasserjian RP, Wang SA. STAT5B mutations in myeloid neoplasms differ by disease subtypes but characterize a subset of chronic myeloid neoplasms with eosinophilia and/or basophilia. Haematologica. 2023 Nov 16. doi: 10.3324/haematol.2023.284311. Online ahead of print. PMID: 37981812

Tefferi A, Fleti F, Chan O, Al Ali NH, Al-Kali A, Begna KH, Foran JM, Badar T, Khera N, Shah M, Hiwase D, Padron E, Sallman DA, Pardanani A, Arber DA, **Orazi A**, Reichard KK, He R, Ketterling RP, Gangat N, Komrokji R. TP53 variant allele frequency and therapy-related setting independently predict survival in myelodysplastic syndromes with del(5q). Br J Haematol. 2023 Dec 11. doi: 10.1111/bjh.19247. Online ahead of print. PMID: 38083865

Nazem A, **Jonathan Lavezo**, Abdullaev Z, Aldape K, Quezado M, Cimino PJ, Pratt DW, Jenkins RB, Ida CM. Diffuse hemispheric glioma with H3-3B G34R mutation: Expanding the spectrum of histone H3 genes in diffuse hemispheric glioma, H3 G34-mutant. J Neuropathol Exp Neurol. 2023 Oct 25:nlad089. doi: 10.1093/jnen/nlad089. Epub ahead of print. PMID: 37878797.

Mistry HY, Betancourt D, Schuller D, **Jonathan Lavezo**. Hypoxemic Respiratory Failure Due to Alveolar Pulmonary Sarcoidosis Following COVID-19 Infection. Cureus. 2023 Mar 5;15(3):e35790. doi: 10.7759/cureus.35790. PMID: 37025737; PMCID: PMC10072786.

Jude Abadie, Jesse Qiao. Delayed diagnosis in a 61-year-old Hispanic male with ecchymoses, soft tissue bleeding, and edema. Clinical Chemistry; Volume 69, Issue 8, Aug 2023, 803- 6; https://doi.org/10.1093/clinchem/hvad075

Daniel Bustamante, Jude Abadie. A 6-year-old boy with an atypical liver neoplasm harboring a novel *RPS6KA3* variant. Laboratory Medicine; 2023 2023 Jul 21:lmad061. doi: 10.1093/labmed/lmad061. PMID: 37477894

II.A Anatomic Pathology:

Mucinous metaplasia of fallopian tubes: A surgical pathology case report
Dr. Alex Partida, PGY-1

A 40-year-old female with a chronic history of menometrorrhagia underwent prophylactic total hysterectomy with bilateral salpingo-oophorectomy (TAH-BSO) due to risk of non-epithelial ovarian cancer associated with an *STK11* mutation.

Past medical history:

- Hypertension
- Diabetes Mellitus Type 2
- Ulcerative Colitis (UC)
- Rheumatoid arthritis

- Peutz- Jeghers Syndrome (PJS)

Family history:

- Father with Colorectal Adenocarcinoma
- Mother with endometrial cancer
- Sister with stage IV breast cancer

The patient's cancer screening test were negative for high-grade dysplasia and malignancy:

- Colonoscopy: Benign hyperplastic polyps
- Screening mammogram: Negative (BIRADS 1)
- Endometrial biopsy: Negative for malignancy
- PAP smear: Negative for dysplasia and malignancy

The patient was discharged, and the specimen was sent for histologic evaluation. Gross morphology was unremarkable. Microscopic examination revealed:

- Superficial adenomyosis
- Bilateral ovarian adenofibromas
- Bilateral fallopian tube mucinous metaplasia (Figure 1).

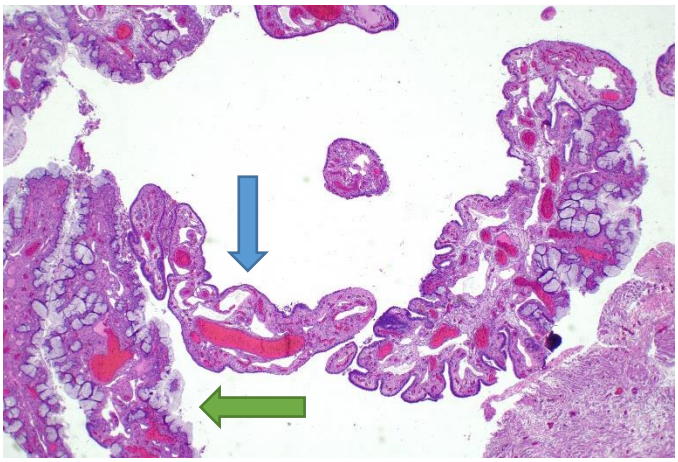


Fig 1: H&E stain (40x) demonstrates ubiquitous areas of transition between the ciliated tubal epithelium (normal, blue arrow) and abnormal intestinal-like mucinous epithelium (green arrow).

Questions to consider:

1. What predisposing factors can lead to metaplastic changes in fallopian tubes?

2. What pathologic, cancerous processes should be ruled-out in patients with mucinous fallopian tube metaplasia?

3. How could differential diagnoses be narrowed to best identify the primary cancer?

4. What would be the most appropriate recommendation(s) for follow-up and cancer prevention in this patient?

Mucinous metaplasia of fallopian tubes is an uncommon, benign, and underreported finding. However, metaplastic changes are usually secondary to an epithelial insult. Two main categories with different predisposing factors are most common in fallopian tube pathology:

- Mucinous metaplasia is the most common type where metaplastic changes resemble an endocervical or gastrointestinal mucinous profile.
    - This involves the distal, fimbriated end of the tube.
    - Pathologic processes in these anatomic locations are often associated with mutations in *STK11* on chromosome 19, such as seen in PJS.

- Transitional cell metaplasia is uncommon when metaplastic cells resemble benign transitional (urothelial) bladder cells.
    - This metaplasia involves only distal fimbriae and is often associated with mechanical irritation, inflammation, or infection.

Mucinous changes in the fallopian tubes can present diagnostic dilemmas.

- Mucinous changes usually arise from a secondary metastatic neoplastic process, especially in patients with PJS.
- These changes can be noted in ovaries, endometrium, appendix, and gastrointestinal tract mucinous tumors.
- Note that mucinous changes in fallopian tubes can occur without mucinous tumor associations.

Considerations for metastatic fallopian tube cancer

Anatomic features:

- Fallopian tube serosal surfaces and fimbriated mucosa are exposed to the peritoneal cavity in a similar fashion to ovary exposure.
- This proximity results in areas that are vulnerable to metastases via transperitoneal spread.
- In contrast, non-fimbriated fallopian tube mucosa is less likely to harbor metastases, except in the setting of disseminated disease.
- This colonization of the non-fimbriated tubal mucosa can occur via direct extension of the tu-

mor from the serosa/fimbrial regions, from submucosal lymphovascular spaces, or via direct deposition of intraperitoneal tumor onto tubal mucosa.

In our patient, microscopic, radiographic, and clinical examination of fallopian tubes, ovaries, and endometrium excluded primary and secondary neoplastic processes. Specifically, appendix and a GI neoplastic origin was excluded with imaging studies, upper endoscopy, and colonoscopy.

Any cytological atypia should raise concern for metastases, and a primary tumor needs to be excluded.

Histologically, the following features indicate a benign, isolated metaplastic change vs. a neoplastic process:

- Metaplasia only at fimbriated end of fallopian tubes
- Abrupt transition between normal tubal epithelium and mucinous gastrointestinal-like epithelium (Figure 2).
- A single layer of mucinous epithelium (i.e., no evidence of pseudostratification)
- No evidence of metaplastic changes in the lamina propria or myosalpinx
- Lack of mucin extravasation (either into the lamina propria or the wall of the tubes)

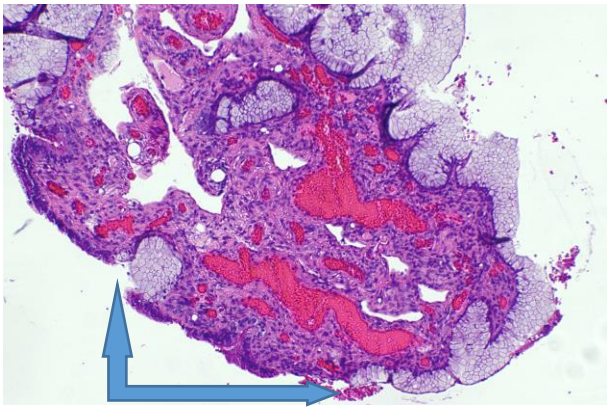


Fig 2: H&E stain (100x) showing abrupt transition between simple columnar ciliated epithelium into mucinous, GI-like epithelium (blue-double arrow).

Figure 3 illustrates bland cytologic features.

- There is absence of nuclear pleomorphism (variability in cell sizes, shapes, and staining) as well as absence of atypical features in nuclei such as mitotic bodies (Figure 3).

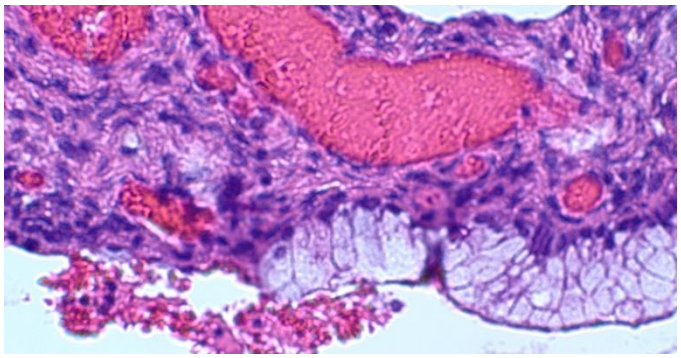


Fig 3: H&E stain (400x) showing bland cytological features and no architectural complexity.

Bland lesions (i.e., lesions without atypical features) can present diagnostic challenges, especially in the context of identifying secondary malignancies such as ovarian, endometrial, or gastrointestinal tract neoplasms.

In general, immunohistochemistry is not helpful in distinguishing metaplasia from metastasis. Therefore, radiological and clinical findings are needed to exclude secondary metastatic processes, such as tubal mucosa infiltration.

The average incidence of mucinous metaplasia of fallopian tubes is up to 0.8% in the general population and is usually identified as an incidental finding [1].

Note the following for TAH-BSO in patients with PJS [2]

- 40% are associated with benign isolated mucinous metaplastic changes.
- 30% are associated with a primary mucinous ovarian carcinoma.
- 10% are associated with a primary seromucinous ovarian carcinoma.
- 10% are associated with adenocarcinoma of the appendix.
- 5% are associated with primary mucinous neoplasms of fallopian tubes.
- 5% are associated with endometrial and breast carcinoma.

Patients with PJS have a significant cumulative cancer risk (93%) [3-5].

- Genetic testing for *STK11* variants should be used to rule in/out of PJS in patients with mucinous metaplasia of fallopian tubes.

The American Society of Clinical Oncologist (ASCO) recommends the following screening in patients with PJS for best practices in diagnosis and prognosis:

- Upper endoscopy: beginning at 12 years old and repeat every 2 to 3 years into adulthood
- Colonoscopy: beginning at 12 years old and repeat at 1 to 3-year intervals (more frequently when polyps are identified)
- Endoscopic ultrasound (for pancreatic cancer): beginning at 25 years old and biennial thereafter
- Breast mammogram: Beginning at 20 years of age and biennial thereafter
- PAP smear: Annually
- Transvaginal ultrasound: Annually beginning at the age of 18 years
- Preventive procedures: TAH-BSO and bilateral prophylactic mastectomy are recommended after childbearing completion

Our patient underwent prophylactic TAH-BSO because of:

- Her positive carrier status
- Increased risk for GYN cancers (e.g., ovarian sex cord tumors with annular tubes), and
- Mucinous tumors of the ovaries and/or the Fallopian tubes

The patient is scheduled next year for prophylactic bilateral mastectomy due to her strong genetic cancer predisposition and positive family history of stage IV breast cancer.

Points to Remember:

- Metaplastic changes of the fallopian tubes are usually findings related either to external stimuli (inflammation, infection, mechanical irritation) and/or mutations in *STK11*).
- Even though such histologic findings have a low incidence, they are related to premalignant somatic pathology seen in PJS.
- In PJS, it is imperative to exclude a secondary malignant process (ovaries, endometrium, appendix, breast), making the cornerstone of management a prophylactic approach proposed by the ASCO screening guidelines.
- Best management approaches can be achieved through collaborative efforts among primary care clinicians, radiologists, and pathologists.

Selected references:

1. Seidman JD. Mucinous lesions of the fallopian tube [A report of seven cases] *Am J Surg Pathol.* 1994;18:1205–1212.
2. Georgia Karpathiou, Celine Chauleur, Melany Venet, Alix Clemenson, Michel Peoc'h; Pathology of the Fallopian Tube: Tubal Involvement by Ovarian Tumors and Incidental Findings in the Non-tumoral Setting. Pathobiology 13 March 2020; 87 (1): 37–44. https://doi.org/10.1159/000505406
3. Giardiello FM, Brensinger JD, Tersmette AC, Goodman SN, Petersen GM, Booker SV, Cruz-Correa M, Offerhaus JA. Very high risk of cancer in familial Peutz-Jeghers syndrome. Gastroenterology. 2000 Dec;119(6):1447-53. doi: 10.1053/gast.2000.20228. PMID: 11113065.
4. Bronte, Monica; Arredondo Montero, Javier; Seara, Maria; Troyas, Rosa. Gastric-phenotype Mucinous Carcinoma of the Fallopian Tube with Secondary Ovarian Involvement in a Woman with Peutz-Jeghers Syndrome: A Case Report. International Journal of Surgical Pathology. Vol.31. April 2023. DOI: 10.1177/10668969221095264.
5. Seidman JD. Mucinous lesions of the fallopian tube. A report of seven cases. Am J Surg Pathol. 1994 Dec;18(12):1205-12. doi: 10.1097/00000478-199412000-00003. PMID: 7977943.

Direct questions to Dr. Alex Partida at alejapar@ttuhsc.edu.

II.B Anatomic Pathology:

Introductory approach to duodenal biopsy interpretation

Dr. Ben Williams, PGY-1 Pathology Resident

Duodenal biopsies are a common and important diagnostic tool for investigating various gastrointestinal disorders. Pathologist meticulously evaluate duodenal biopsies through integrating clinical information with microscopic examination.

This report summarizes fundamental approaches for examining duodenal biopsy based on a landmark publication [1].

Clinical-Pathological Correlation

Establishing a clinical-pathological correlation is essential for evaluating duodenal biopsies. The pathologist begins with a thorough review of the patient's medical record, such as age, sex, symptoms, and medical history. Further, endoscopy reports elucidate critical findings to guide microscopic interpretation.

Histological Evaluation

Histologic examination of the biopsy specimen includes evaluating various aspects of the duodenal mucosa that include:

- **Villi:**
  - Normal villi are elongated with a villous to crypt (V:C) ratio ranging from 3:1 to 5:1.
  - Atrophic villi demonstrate surface flattening due to shortening/blunting of the villi with a decreased V:C ratio.

- **Crypts:**
    - Hyperplastic crypts have increased length, reduced V:C ratio, and increased mitoses.

- **Epithelium:**
    - Duodenal gastric metaplasia: Recognized by foci of gastric-type mucus-secreting cells interspersed between duodenal enterocytes and are associated with gastric acid injury and *H. pylori* infection.

- **Intraepithelial lymphocytes (IELs):**
    - Count
        - 20 IELs per 100 enterocytes (1:5 ratio) is normal.
        - Tip: Avoid counting near lymphoid aggregates.
        - If the IEL count is uncertain or borderline, CD3 immuno-histochemical stain can be used to identify IELs.
    - Distribution
        - Normally there are more IELs at the base of villi than at the tip; increased numbers of IELs at the tips can indicate pathology, such as celiac disease.

- **Lamina Propria**
    - Primarily composed of plasma cells, lymphocytes, scattered lymphoid aggregates, to include blood vessels and lymphatics.
    - If the microscopic slide contains:
        - Increased neutrophils, then consider early celiac disease, active duodenitis, certain infections, or Crohn's disease.
        - Increased eosinophils, then consider celiac disease, food allergy, or eosinophilic duodenitis.
        - Granulomas, then consider Crohn's disease.
        - Duodenal submucosa Brunner's glands, then consider chronic non-specific duodenitis.

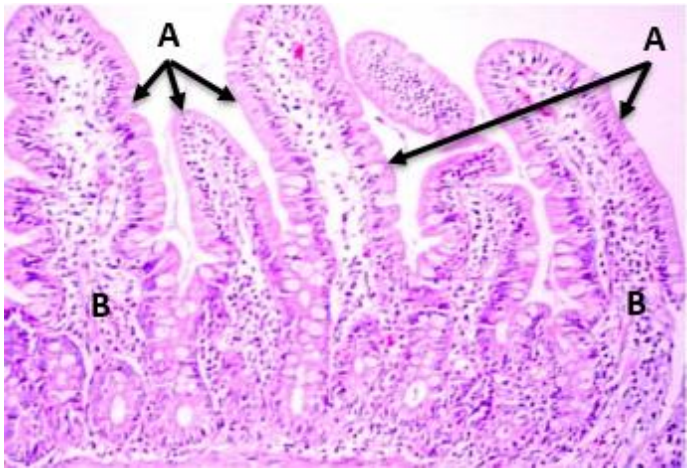


Fig 1. Example of normal duodenal mucosa - Villi: well-formed, with a V:C ratio at least 4:1; Crypts: No hyperplasia; Epithelium (A): No gastric metaplasia evident; IELs: count and distribution appear normal; Lamina propria (B): appropriate number of lymphocytes and without other infiltrates. *Image Source: PathologyOutlines.com.*

<u>Key features of duodenum pathologies</u>

Chronic Non-Specific Duodenitis:

- Histologic features
    - Mild: increased chronic inflammatory cells with widening or flattening of villi.
    - Severe: mixed acute and chronic inflammation, gastric metaplasia, and Brunner gland hyperplasia with prolapse into the lamina propria.
- Can be secondary to *H. pylori* infection or other causes (IBD, celiac disease, medications, other infections).
- Active duodenitis (i.e., neutrophils present) or an associated ulcer, almost always due to *H. pylori*.

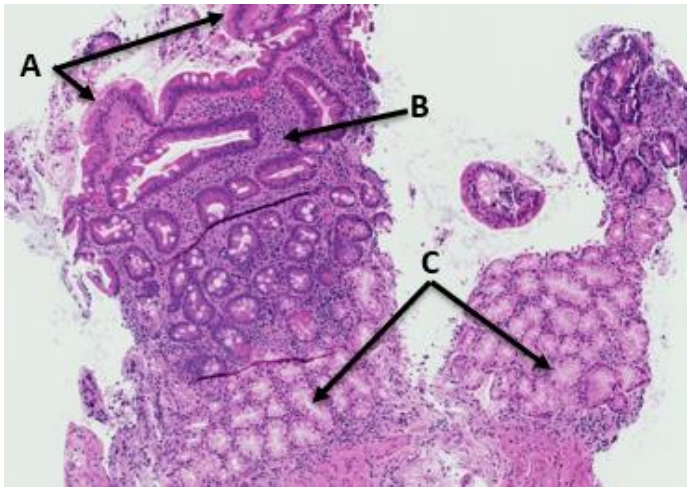


Fig 2. Chronic duodenitis - Surface epithelium with foci of gastric metaplasia (A), lamina propria with increased inflammation (B) and Brunner's glands (C). *Image Source: PathologyOutlines.com*

Celiac Disease:

- Histologic features
    - Increased IELs (> 30 IELs per 100 enterocytes in duodenum)
    - Villous blunting (early) or villous atrophy (late)
    - Crypt hyperplasia
- It is important to correlate findings with the patient's history, clinical presentation, and serology (e.g., tissue transglutaminase, anti-gliadin antibodies)

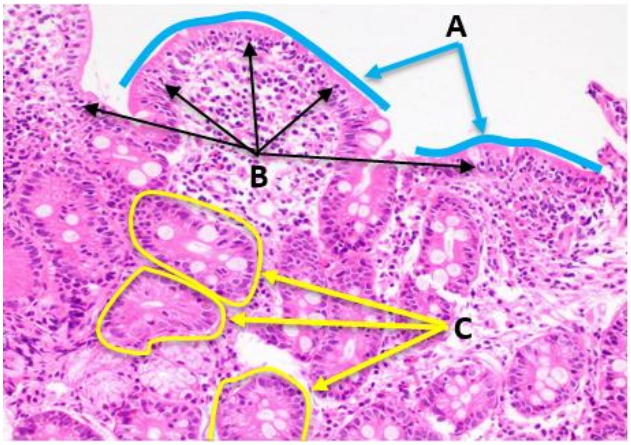


Fig 3. Celiac disease (Marsh 3b) - villous blunting/atrophy (A), increased IELs (B) (>30 per 100 enterocytes), crypt hyperplasia (C). *Image Source: PathologyOutlines.com.*

Crohn's Disease:

- Histologic features
    - Focal acute inflammation (cluster of at least 2 neutrophils, with at least 2-3 foci) adjacent to normal appearing mucosa.
    - Presence of granulomas is variable and may have microaggregates of 5-10 epithelioid cells.
    - IEL count is typically normal.

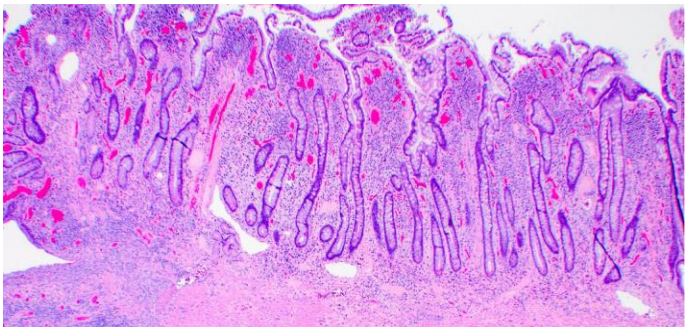


Fig 4. Crohn's disease - Lamina propria with increased inflammation (neutrophils evident on higher power) and granulomas with multi-nucleated giant cells. *Image Source: PathologyOutlines.com*

Other pathologies to note:

- Eosinophilic duodenitis
- Refractory sprue
- Autoimmune enteropathy
- Anteropathy-type intestinal T cell lymphoma

Infectious organisms that can inhabit the duodenum

Giardiasis:

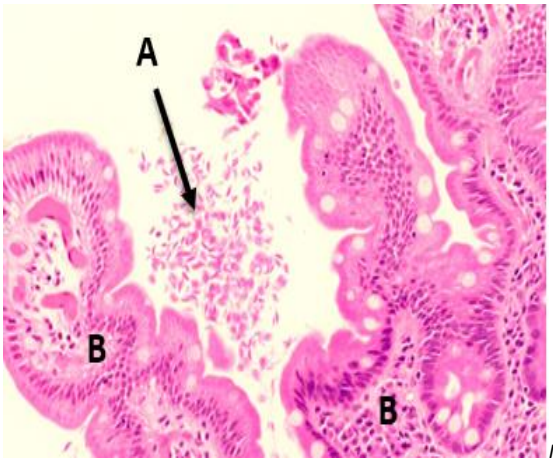


Image Source: PathologyOutlines.com

- Giardia protozoa (A) found among duodenal villi, attached to mucosa without invasion.
- Normal-appearing mucosa (B), with occasional mild villous flattening and mild inflammation of the lamina propria.

Whipple's Disease:

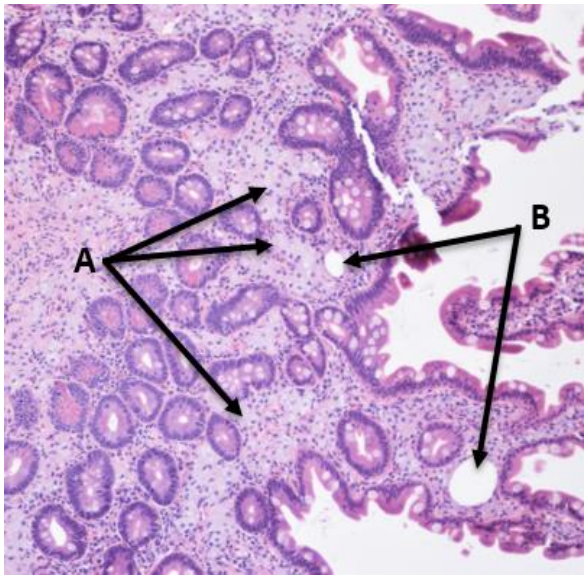
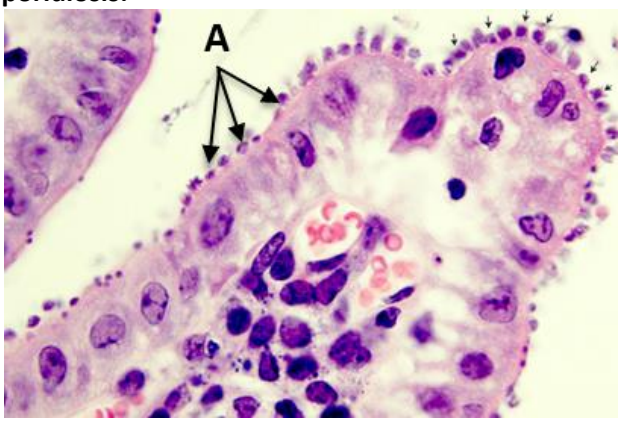


Image Source: PathologyOutlines.com

- Lamina propria packed with foamy macrophages (A) containing numerous and strongly PAS-positive diastase-resistant intracytoplasmic granules.
- Dilated lymphatics, flattened villi (B), increased IEL count, and decreased CD4:CD8 ratio.

Cryptosporidiosis:



- Organisms (A) located along the brush border of the surface and crypt epithelium.
- Other features (not observable in the above image): partial villous atrophy, crypt hypertrophy, increased chronic inflammatory cells in the lamina propria.

Mycobacterium Infections (e.g., MAI):

- Infiltration of pale macrophages packed with acid-fast and DPAS-positive curved bacilli in the lamina propria, resulting in shortened, broad villi.

Cytomegalovirus (CMV) Infection:

- Often seen in ulcers and granulation tissue; identifiable as cytomegaly and intranuclear and inclusion, frequently in endothelial cells.

Other potential infections include microsporidiosis, cyclosporidiosis, and isosporiasis.

Summary

This brief overview demonstrates how a pathologist might approach the interpretation of a duodenal biopsy.

- It is important to remember that a systematic approach is essential in the context of patient history and endoscopic findings.

Reference

1. Serra S, Jani PA. An approach to duodenal biopsies. J Clin Pathol. 2006 Nov;59(11):1133-50. doi: 10.1136/jcp.2005.031260. Epub 2006 May 5. PMID: 16679353; PMCID: PMC1860495.

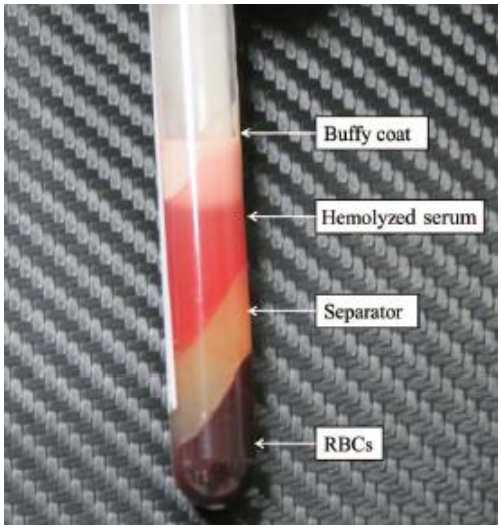
II. Clinical Pathology:

Splenomegaly and milky serum at well-baby visit
Dr. Jude Abadie

The following findings were identified in a 6-month baby during a routine, well-baby medical exam.

- Splenomegaly; 2cm below lower costal margin
- Weight at 99%tile; length 85%tile; head circumference; 99%tile BMI
- Lipomas were noted on the right ear lobe, lateral left eye canthus, abdomen, and back.
- Hepatomegaly was absent, and no other abdominal masses were appreciated.
- Lab results indicated anemia.

A comprehensive metabolic panel could not be resulted due to gross lipemia. Figure 1 below shows the sample after it was centrifuged and stored overnight at 4°C.



Family history

- Maternal grandmother had hypertriglyceridemia (in the thousands) and hypercholesterolemia discovered during pancreatitis episode.

Lipoprotein phenotyping

- Increased TG (661 mg/dL)
- Low total cholesterol (85 mg/dL)
- Low HDL cholesterol (15 mg/dL)
- Presence of chylomicrons with increased pre-β band.

- VLDL and LDL were not calculated due to increased TG.

These results indicated type IV familial hyperlipidemia (isolated hypertriglyceridemia)

- The patient was prescribed dietary fish oil supplementation.
- The patient's mother had a normal lipid profile but the father had hypertriglyceridemia.

Normal lab studies for WBCs, iron studies, bilirubin, alpha-fetoprotein, and uric acid help to rule out the following differential for an infant with splenomegaly:

- Hemolytic anemia
- Portal hypertension
- Malignancy
- Hemophagocytic lympho-histiocytosis
- Glycogen storage disorders

Increased triglycerides (TG) in children are usually secondary to obesity and type 2 diabetes. However, familial hyperlipidemia is an important consideration in very young patients.

Before lipids were used in conjunction with National Cholesterol Education Program guidelines to predict coronary disease, the Fredrickson Classification (FC) was mainly used to characterize lipid disorders *(4)*.

- FC correlates electrophoresis results to clinical disease syndromes and phenotypes.
- Each phenotype is related to disorders affecting the same lipoprotein, demonstrating similar lipid patterns.
- FC uses multiple diagnostic criteria, including serum lipid concentrations, appearance of centrifuged serum, and lipoprotein electrophoresis.

To assess serum, the 'refrigerator test' cools the sample overnight at 4 °C and evaluates the sample for a chylomicron layer (creamy layer on top sample), then IDs the infranate as clear (type I) or turbid (type IV).

Electrophoresis separates by size, with each band representing a different lipoprotein.

- The FC allows differentiates endogenous vs. exogenous hypertriglyceridemia.
- Endogenous hypertriglyceridemia (carbohydrate-induced) increases the TG by increased VLDL production.
- In contrast, exogenous hypertriglyceridemia is fat-induced and caused by the inability to break down chylomicrons. This produces more pronounced chylomicron bands on electrophoresis and a large layer of chylomicrons in the centrifuged sample.

The diagnosis in our case was type IV hyperlipidemia based on the FC. This was based on endogenous hypertriglyceridemia marked by increased TG and normal to slightly increased total cholesterol.

As seen in Fig 1, the patient's plasma had a cloudy appearance due to hyperprebetalipoproteinemia (VLDL). Clear plasma is associated with types I and IIa.

The sample's turbid appearance (phenotype), with chylomicrons, and an increased pre-β band. Because chylomicrons do not indicate type IV hyperlipidemia, their presence may be due to postprandial sampling.

The patient's father had the same lipid profile, suggesting an autosomal dominant inheritance.

While all pathophysiology mechanisms for this lipid dysregulation have not been identified, VLDL TG production is increased in the setting of normal apolipoprotein B synthesis. This leads to the formation of TG- laden VLDL that causes the "milky" appearance of the sample.

Presenting symptoms

- Children with familial hypertriglyceridemia (FH) are often asymptomatic, but can present with colicky pain or failure-to-thrive. A 1983 report of children with FH noted abdominal pain, limb or scrotum swelling, and xanthoma eruption during times of increased plasma TG levels *(1)*.
- Aside from increased TG, anemia may be present due to altered erythrocyte membranes *(2)*.
- Significantly increased TG concentrations also prevent analytical measurement of VLDL and LDL in lipid panels.
- In adults, increased TG levels are known to cause endothelial dysfunction and can accelerate atherosclerotic plaque formation, leading to coronary artery disease.
- As in our patient's family history, markedly increased TG concentrations can precipitate pancreatitis.

Treatment of patients with hypertriglyceridemia begins with lifestyle modifications (i.e., diet and exercise).

- This patient will continue with formula and will subsequently maintain a low-fat diet.
- At 1 year of age, the standard recommendation is to transition from formula to whole milk; however, this patient will instead drink nonfat milk

to promote a low-fat diet with annual lipid monitoring.
- Dietary fish oil supplementation can reduce TG.
- In older children, fibrates can reduce TG *(3)*.

Points to remember:

- Splenomegaly is a physical examination finding of concern for glycogen storage disorder, malignancy, portal hypertension, and hyperlipidemia.
- Laboratory evaluation for these disorders should include a CBC, lipid panel, and abdominal ultrasound.
- The FC characterizes lipid disorders by correlating electrophoresis results to clinical disease syndromes and laboratory phenotypes.
    - Type IV hyperlipidemia is notable for increased TG with relatively normal cholesterol concentrations.
    - Type IV is distinguished as having a negative refrigerator test and an increased pre-β band on electrophoresis, with the plasma appearing cloudy.
    - Patients with FH may be asymptomatic or present with failure-to-thrive and colic.
    - Physical examination may be unremarkable or could note hepatosplenomegaly or xanthomas.

*Sarah Anisowicz and Jude Abadie. A 6-month old boy with "milky" serum. *Clinical Chemistry* Dec 2015.

1. Deckelbaum R, Dupont C, Pencharz P. Primary hypertriglyceridemia in childhood. Am J Dis Child 1983;137:396 – 8.

2. Kavazarakis E, Stabouli S, Gourgiotis, D, Roumeliotou K, Traeger-Synodinos J, Bossios A, et al. Severe hypertriglyceridaemia in a Greek infant: a clinical, biochemical and genetic study. Eur J Pediatr 2004;163:462– 6.

3. Bamba V. Update on screening, etiology, and treatment of dyslipidemia in children. J Clin Endocrinol Metab 2014;99:3093–102.

4. Hansen PS. Familial defective apolipoprotein B-100. Dan Med Bull 1998;45:370 – 82.

Please direct any questions to Dr. Jude Abadie at jude.abadie@ttuhsc.edu

III. i Pathology: Test-Your-Knowledge

Question written & submitted by Dr. Benjamin Williams (PGY-1 pathology resident)

A 7-year-old child presents with a rapidly growing mass in the left thigh. The mass is biopsied, and microscopic examination demonstrates representative histologic features pictured below:

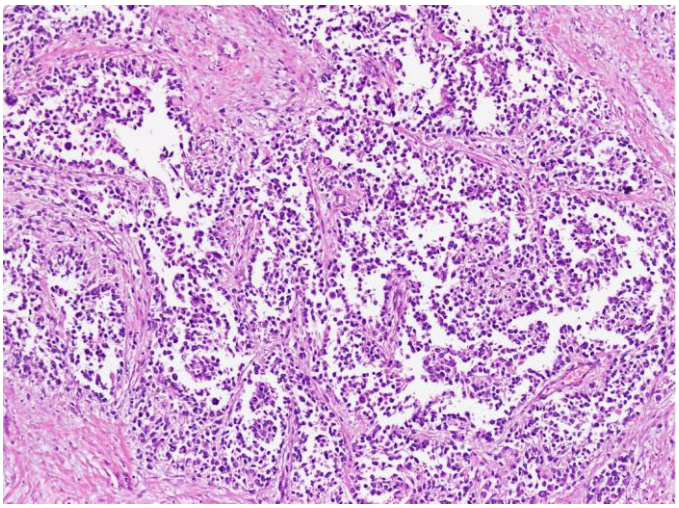


Image source: PathologyOutlines.com

Immunohistochemical staining shows positivity for desmin and myogenin. Based on these findings, which additional feature, if present, would most support the diagnosis?

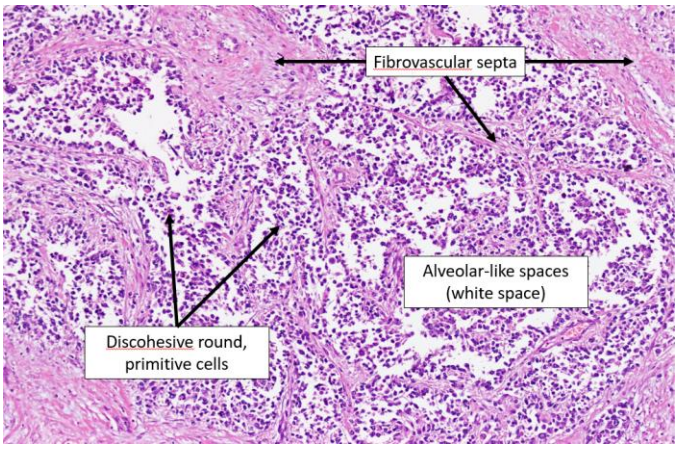
A. Positive staining for CD20
B. Presence of Homer-Wright pseudorosettes
C. Positive staining for synaptophysin
D. Detection of a *PAX3:FOXO1* fusion transcript
E. High levels of serum carcinoembryonic antigen

Case Vignette and Explanation:

Correct Answer: Choice D

This patient's mass is most likely a malignant alveolar rhabdomyosarcoma. Histologic features evident in the image include nests of round blue cells interspersed between prominent fibrovascular septa. The nests demonstrate central loss of cell cohesion, resulting in alveolar-

like spaces. In addition, these nests can show high mitotic activity and cellular necrosis.



These tumors will show positivity for desmin and myogenin on immunohistochemistry (usually with diffuse positive staining). In addition, the majority of alveolar rhabdomyosarcomas are associated with a *PAX3:FOXO1* gene fusion, resulting from a chromosomal translocation involving *PAX3* on chromsome 2 and *FOXO1* on chromosome 13.

Alveolar rhabdomyosarcomas can show positivity for neuroendocrine markers such as synapatophysin, but expression is typically variable and patchy. Positive staining for synaptophysin is not MOST supportive of the diagnosis compared to detection of a *PAX3:FOXO1* fusion.

CD20, a B-cell marker, can be positive in tumors such as lymphomas, but would not be expected to be positive in tumor cells of alveolar rhabdomyosarcoma. Homer-Wright pseudorosettes are seen in tumors such as neuroblastoma or medulloblastoma. Elevated serum levels of carcinoembryonic antigen (CEA) can be associated with malignancies, such as colorectal cancer, but is not associated with alveolar rhabdomyosarcoma.

III. ii Pathology: Test-Your-Knowledge

Question written & submitted by Dr. Alex Partida (PGY-1 pathology resident)

A 62-year-old man with a history of controlled Type 2 Diabetes presented to the ED for hematuria and an 8-day history of perineal pain. He participated in a cycling marathon two weeks prior. Prescription history is unremarkable except for OTC multivitamins. CT scan showed a 3 cm prostate lesion, and immunoassay results for serum PSA was 2.9 ng/mL (ref: < 4.0 ng/mL). A biopsy was revealed prostate cancer. PSA immunoassay results from an annual physical a week after the marathon were unremarkable (3.1 ng/mL).

1. What is the most likely cause of the discordance between the PSA levels and diagnosis?

A) Heterophilic antibodies

B) Biotin interference

C) Antigen excess

D) Exercise induced changes

2. What is the most appropriate next step to resolve the discordance between the immunoassay PSA value and diagnosis?

A. Perform dilution studies.
B. Send the sample to a reference lab.
C. Test the sample using an alternate lab immunoassay.
D. Recalibrate the instruments using CAP standards.

Case Explanation:

Correct Answers: 1. C (Antigen excess) and 2. A (Perform dilution studies)

Explanation: The Hook effect is observed in sandwich immunoassays, where at very high concentrations of the analyte, the assay signal is saturated and leveled off. This phenomenon occurs due to the elevated number of antigen that bind to both the capture and detection Ab, thereby preventing them from forming sandwich immune complexes. In fact, the signal response might decrease at extremely high concentrations and fall in the calibration curve range. This effect then leads to a misleading lower analyte concentration while the actual analyte concentration is much higher (false negative results). The best way to eliminate this antigen excess is by serial diluting the sample.

A) Heterophile antibodies are more commonly associated with false positive results. PSA assays use an anti-PSA animal immunoglobulin, which binds to one site of the PSA molecule, while a second immunoglobulin labeled with a quantifiable tracer binds to the PSA mole-

cule at a separate site. Both immunoglobulins are derived from animals immunized against human PSA. In the case of falsely elevated PSA due to heterophile antibodies, the heterophile antibody itself acts as excess PSA by binding both immunoglobulins resulting in a falsely elevated result. However, an analogous mechanism has not been proposed for a falsely low or undetectable PSA.

B) Biotin has been shown to interfere with the results of streptavidin-based immunoassays. Both the Ortho Clinical Diagnostics and Roche assays are streptavidin-based and biotin has been shown to potentially interfere with both assays. In addition, our patient was taking a daily multi-vitamin with a significantly lower value of biotin (300 µg/day) than the level reported to potentially cause erroneous results (10 mg/day).

D) Exercise like bike riding increases PSA levels through direct trauma to the perineum and prostate. PSA levels usually normalize 48 hours after exercise.

Announcements

Tubing flu and COVID samples to the main pathology laboratory:

- Dry swabs can be sent to the lab via the tube system.
- Previously, swabs in viral-liquid media must be brought to the specimen pick-up ED room for subsequent delivery to the main lab.
- Pathology, in collaboration with Infection Control, validated the process for tubing flu and COVID samples in viral-liquid media.
- The go-live date is 22 Jan 2024.
- As per our pathology laboratory administration policy, the following specimens, considered irretrievable, must be delivered and NOT tubed:
    - CSF, Peritoneal/Abdominal fluid, pleural fluid, pericardial fluid, synovial fluid, bronchial lavage, BAL-CATH, JP-fluid, 24-hour urine.

SpotFire instrument to go-live 22 Jan 2024

- The SpotFire is a PCR test that delivers results within 15 minutes of testing
- The test requires one nasopharyngeal swab that is collected in viral-liquid media.
- The SpotFire testing menu includes:
    - SARS-CoV-2 (COVID-19)
    - Influenza A
    - Influenza B
    - Respiratory Syncytial Virus (RSV)
    - Emtero/Rhino virus

Reminders about coagulation testing:

- INR is usually used to in monitoring patients on warfarin therapy.
- INR also has utility in assessing bleeding and liver function.
- Note that INR does not measure anti thrombotic factors such as Protein C, Protein S, or ATIII.
- ROTEM can be used to assess whole blood clotting formation.
- Remember that fibrinogen is responsible for the initial platelet aggregation and is the substrate for fibrin formation which stabilizes the clot.