## Case History

A 74 year old man with no significant past medical history presents with abdominal pain for over one year. Imaging studies revealed duodenitis and bilateral renal cysts. Fat stranding was noted around the second portion of the duodenum with mural thickening. No other detectable lesions in other sites were identified through additional imaging studies. No other lymph nodes or masses are known. He has no cancer history and is not immunosuppressed.

At endoscopy, a 2.5 cm ulcer was identified in the second portion of the duodenum. Biopsies were taken and sent for histology.

Histologic sections of the lesion are depicted below along with selected immunohistochemical stains. Additional immunohistochemical stains (not depicted) showed the cells of interest were negative for CD15, BOB1, and ALK1. Stains for infectious microorganisms (Helicobacter pylori, acid fast bacilli, CMV, GMS, spirochetes) were all negative.

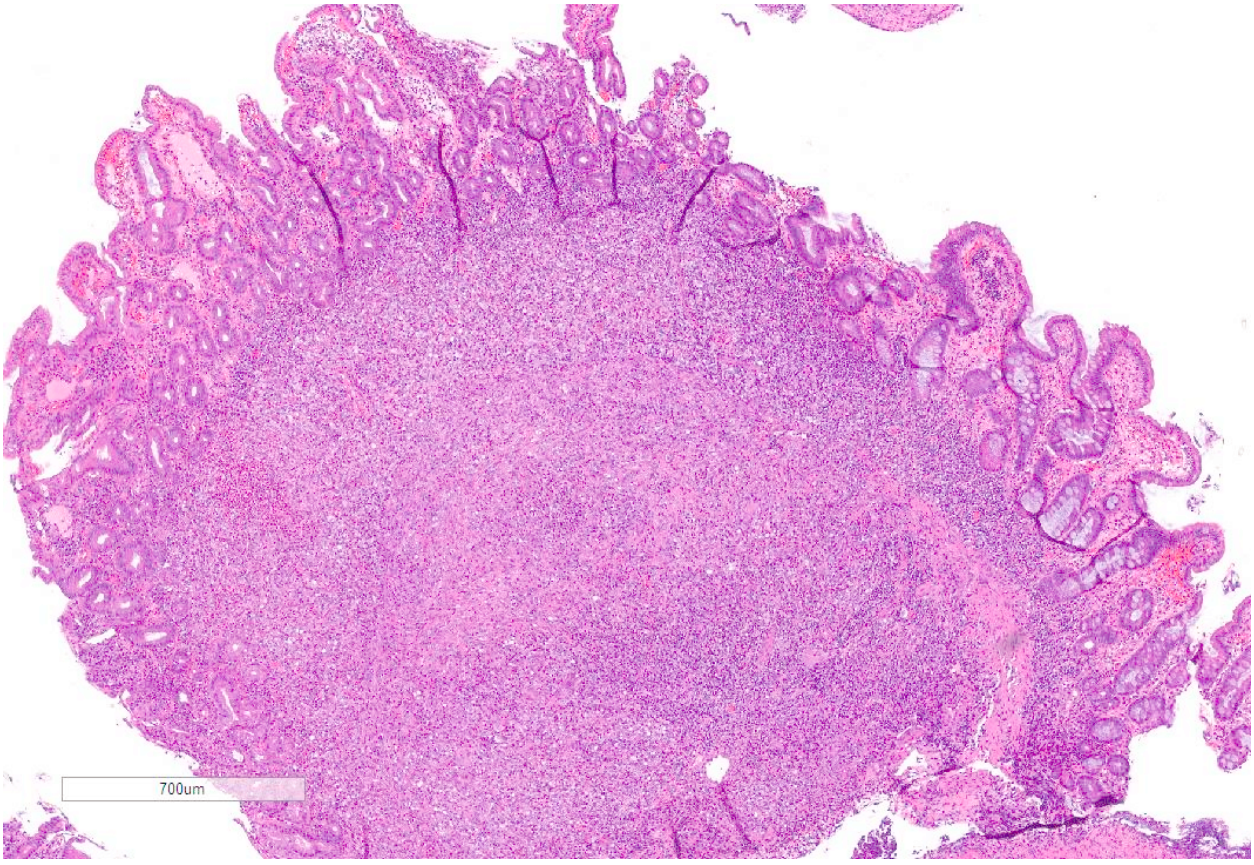


**Figure 1**: H&E stain, 2x magnification.

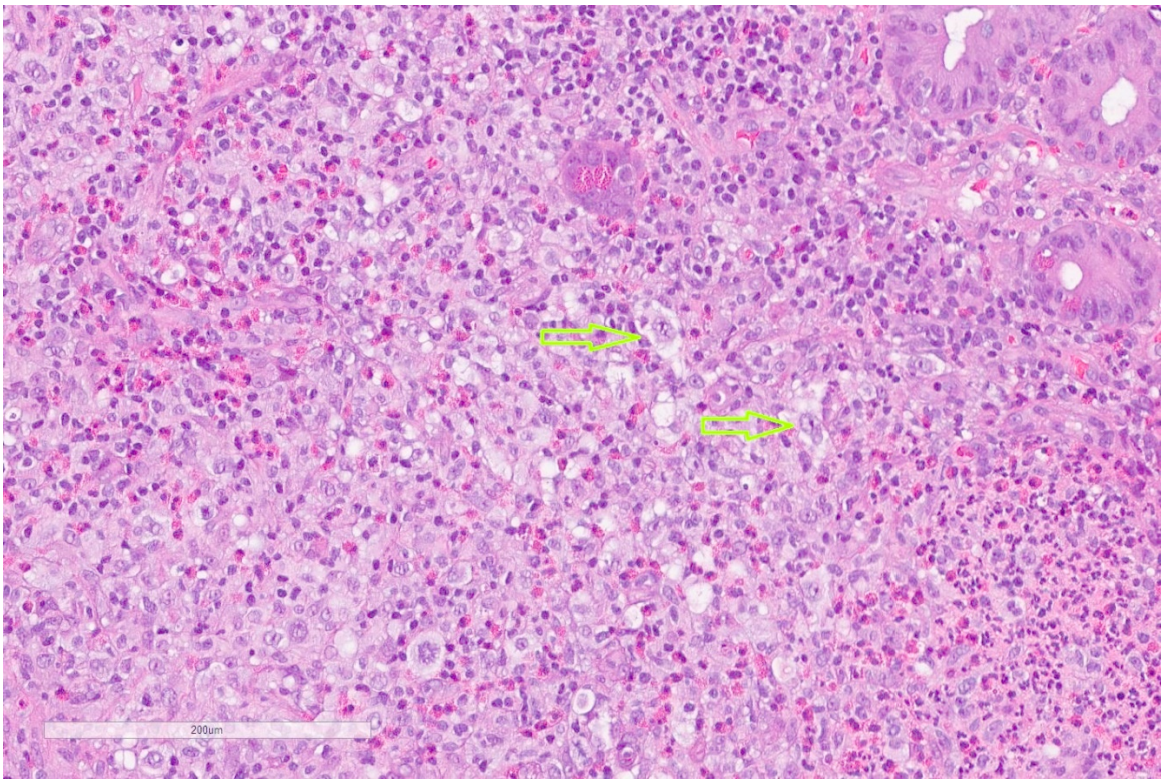


**Figure 2**: H&E stain, 20x magnification.

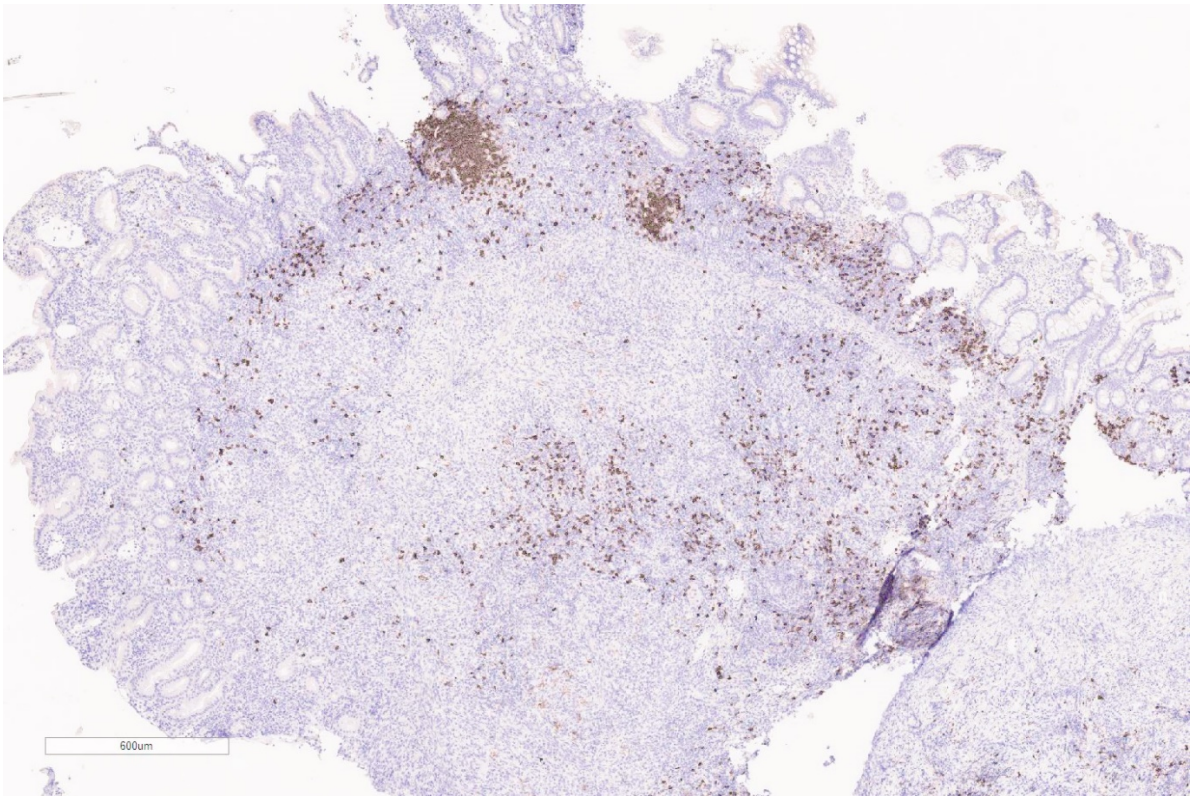


**Figure 3:** CD20

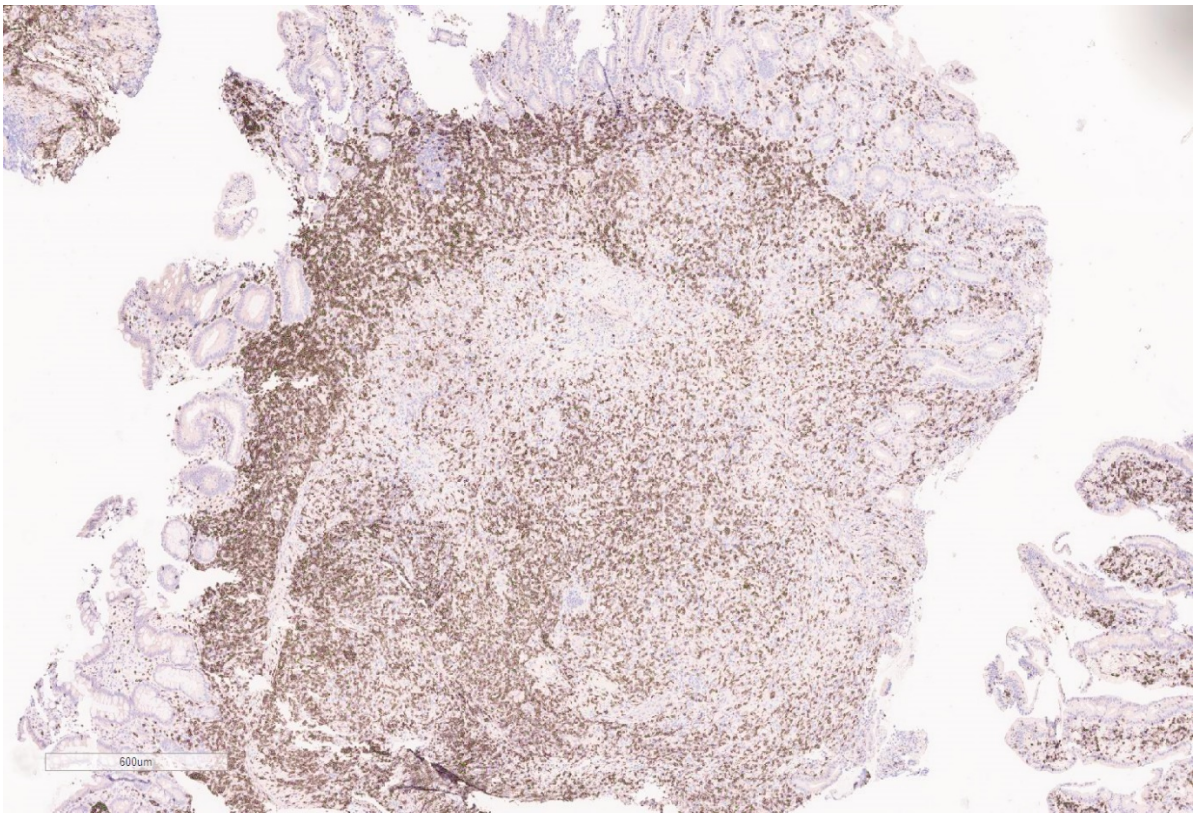


**Figure 4**: CD3

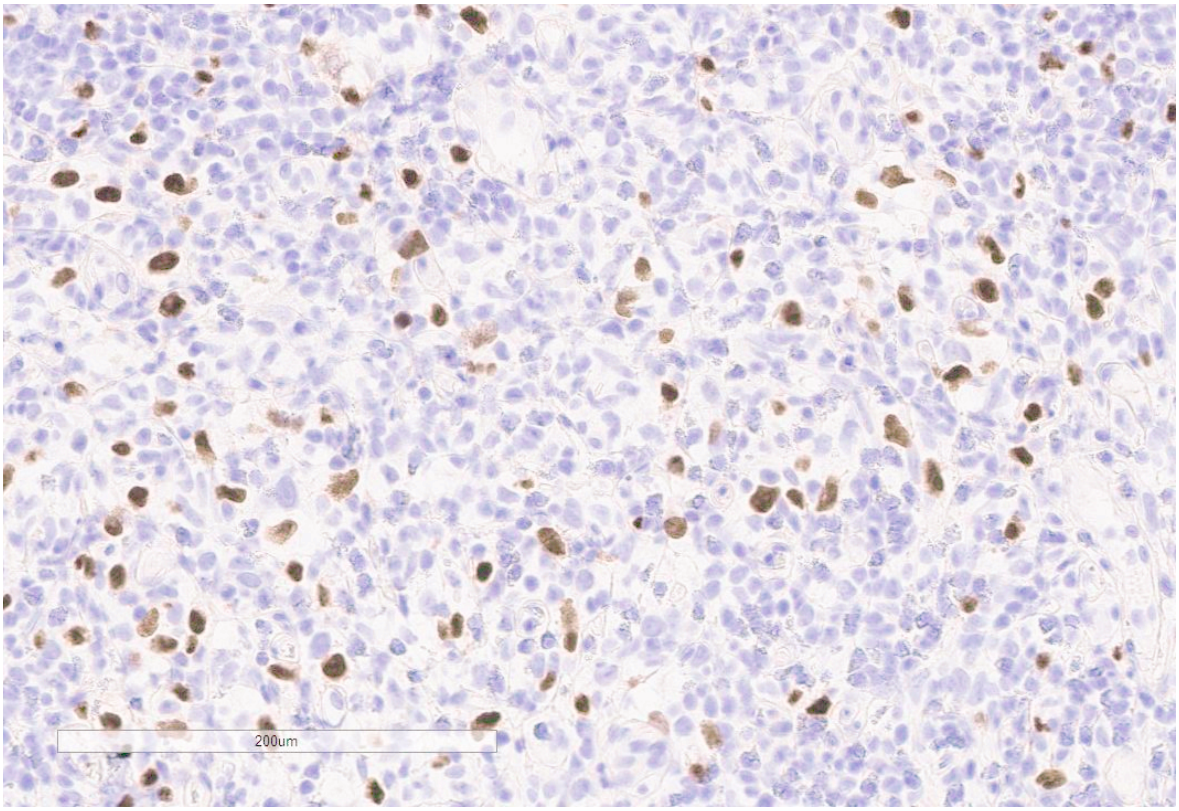


**Figure 5**: PAX5

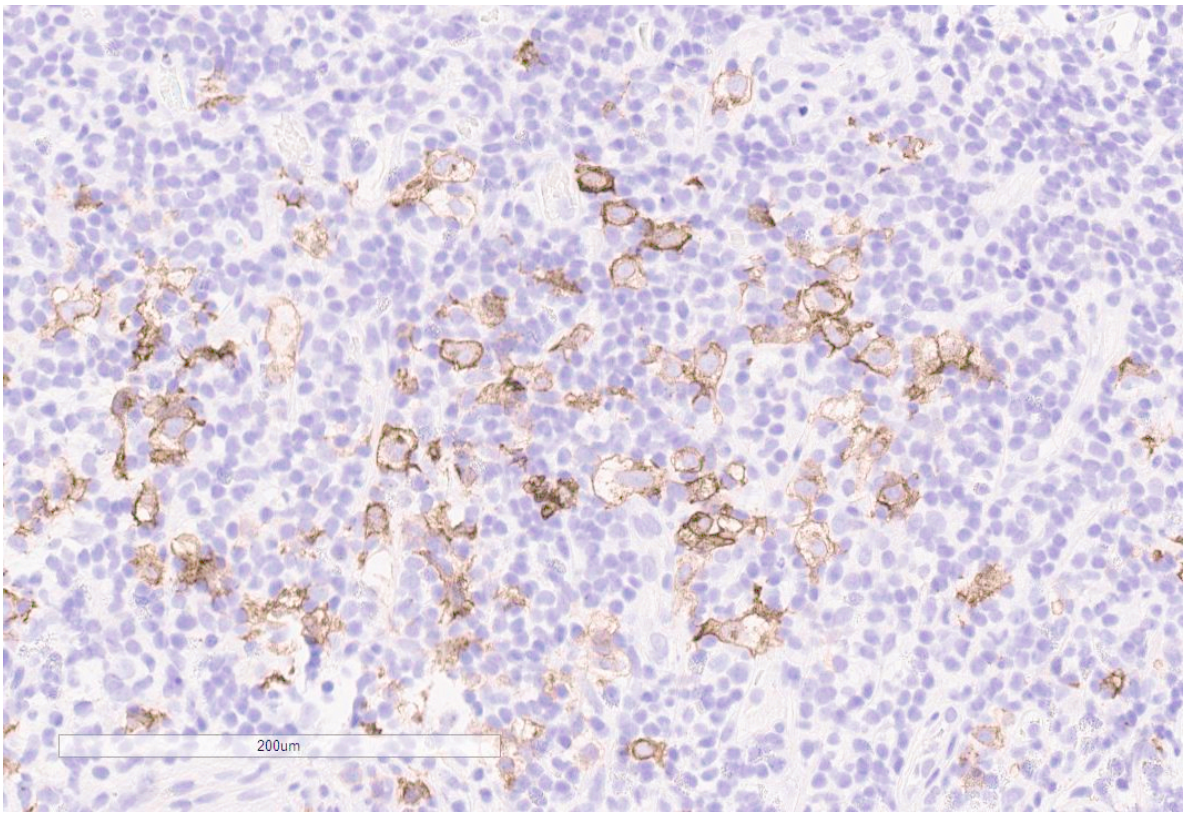


**Figure 6**: CD30

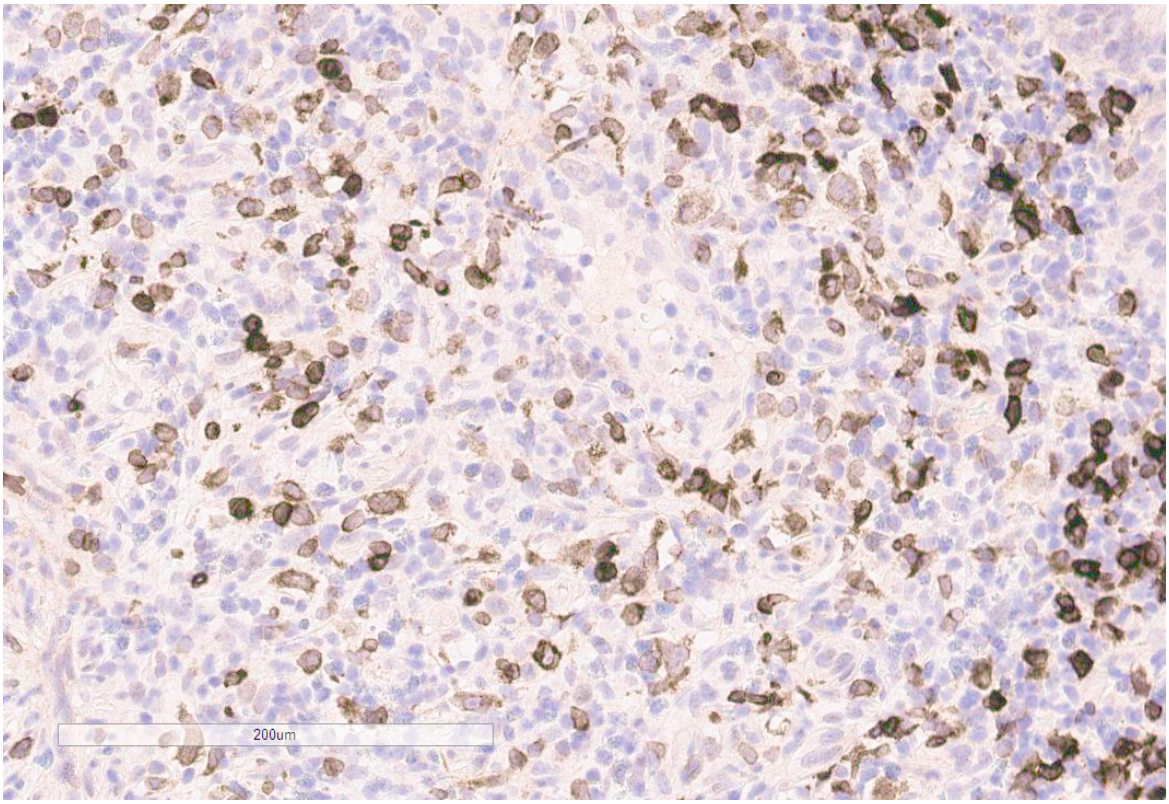


**Figure 7**: CD79a

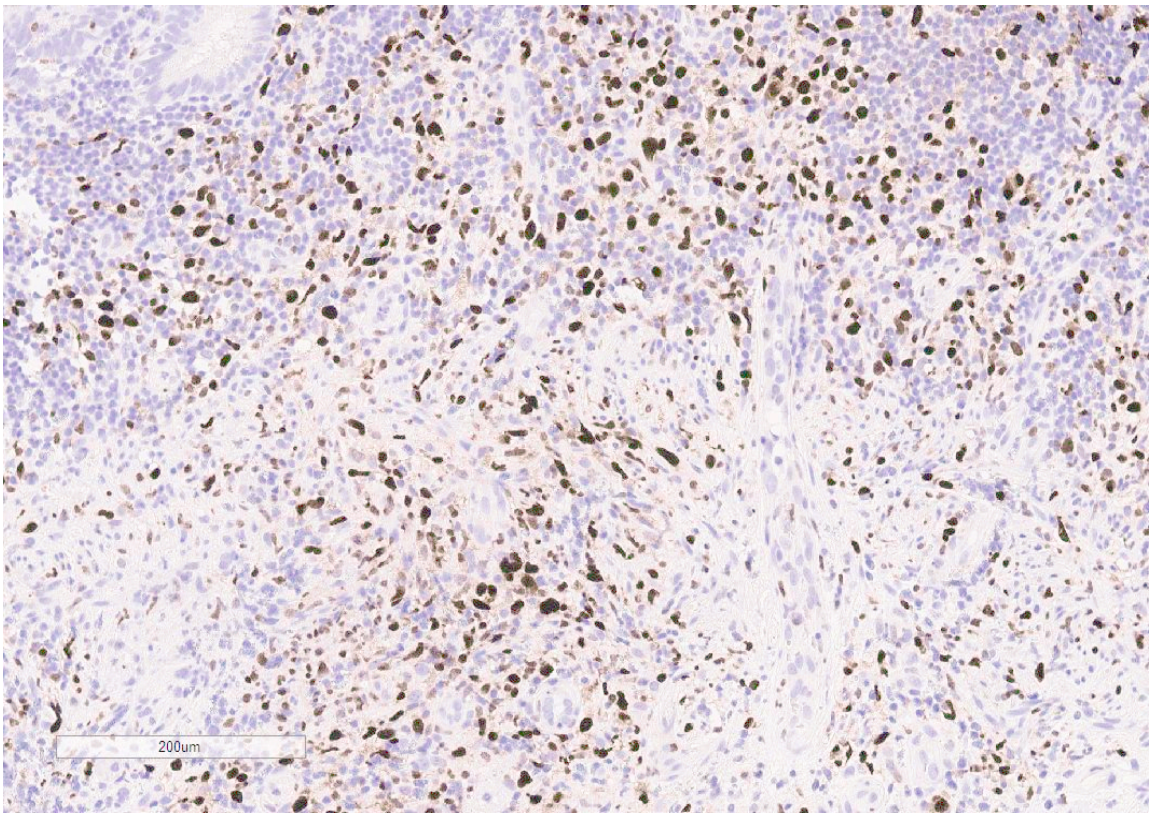


**Figure 8**: MUM1

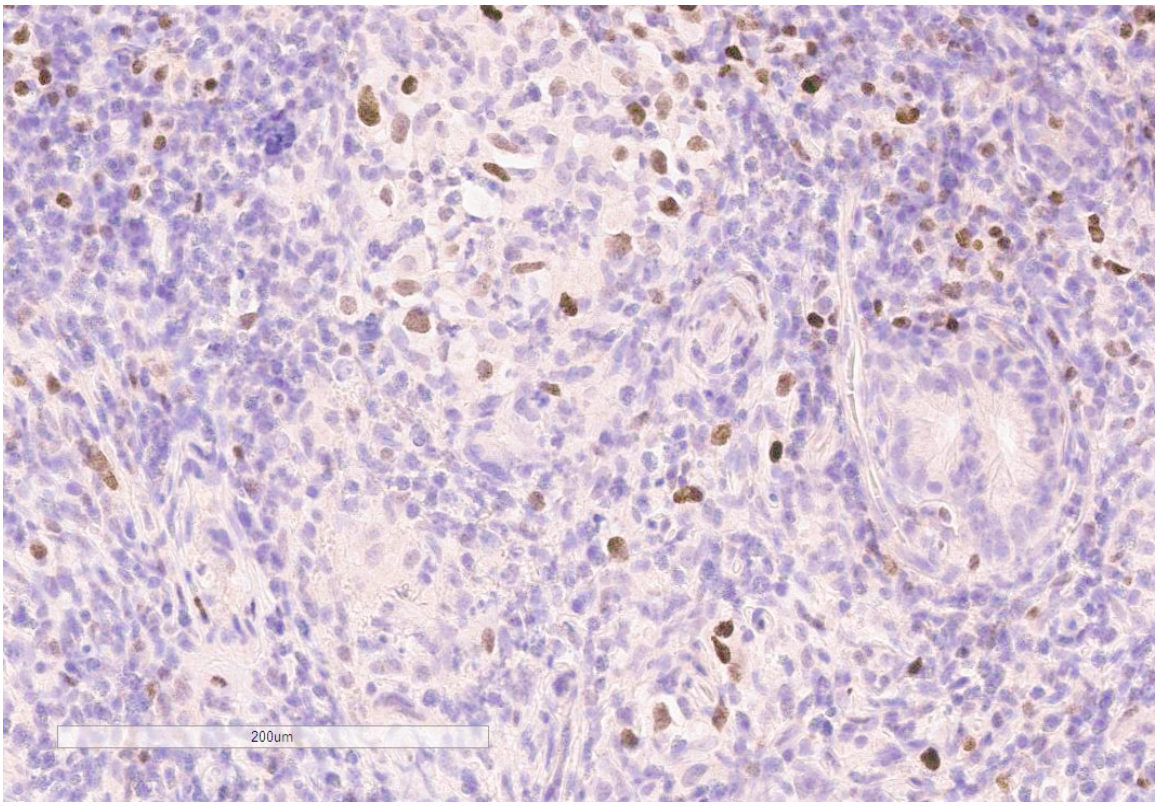


**Figure 9**: OCT2

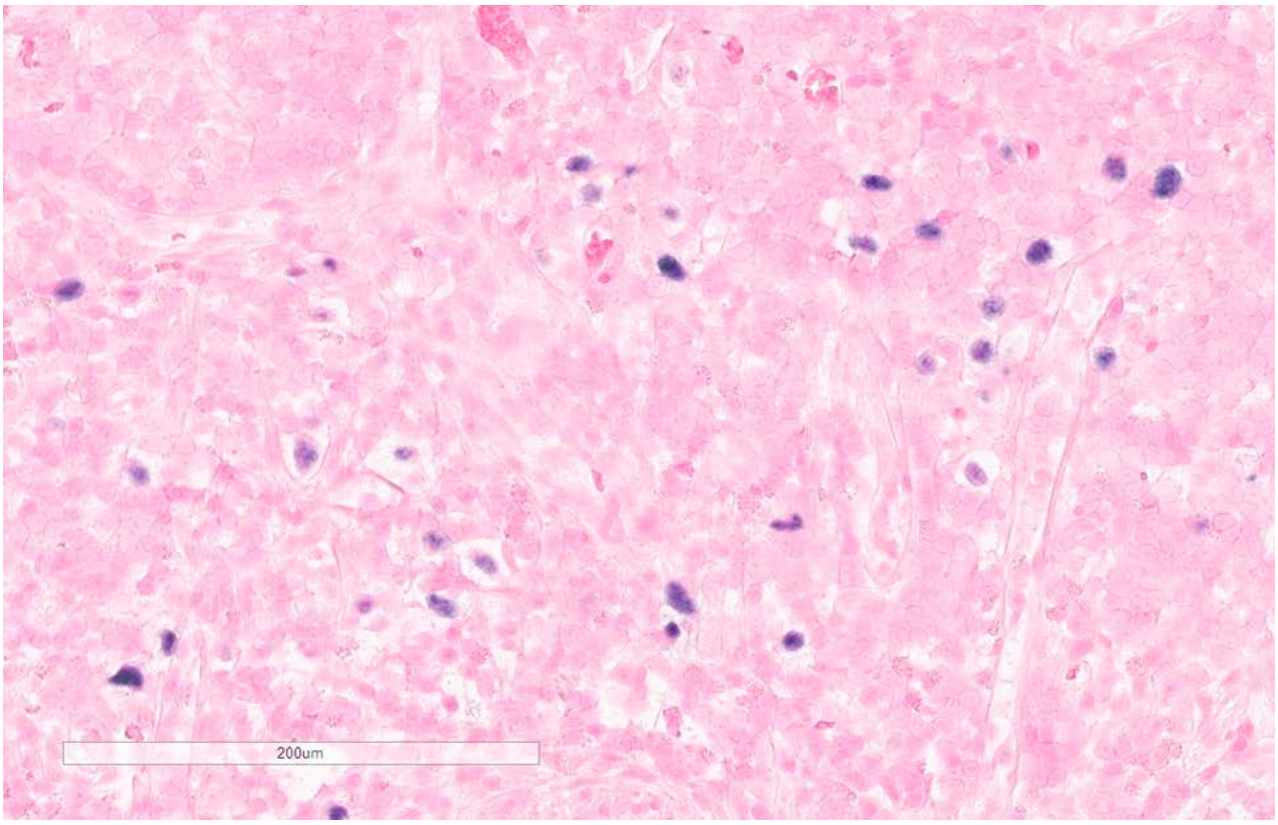

**Figure 10**: EBER in situ hybridization

**What is the most likely diagnosis?**

A. EBV positive mucocutaneous ulcer
B. Classical Hodgkin lymphoma
C. Post-transplant lymphoproliferative disorder (PTLD)
D. Diffuse large B cell lymphoma, activated B cell type
E. EBV positive Diffuse large B cell lymphoma

**Answer: A. EBV positive mucocutaneous ulcer**

Histologic sections show duodenal mucosa with large nodules of polymorphous inflammatory cells. The inflammatory cells are composed of small lymphocytes, histiocytes, plasma cells, and numerous eosinophils. CD3 and CD20 highlight a polymorphous lymphocytic infiltration with B and T cells. Among the inflammatory cells, large neoplastic cells are identified and some have vesicular chromatin, prominent nucleoli, and large amount of “clear” cytoplasm (Hodgkin-like cells).

Immunohistochemical stains reveal these large neoplastic cells are positive for PAX5, CD30, MUM1, CD79a (weak), OCT2, and negative for CD20, CD45, CD15, BOB1, and ALK1. EBER by in situ hybridization is positive in some large cells as well in some small cells.

EBV+ mucocutaneous ulcer is a lymphoproliferative disorder that typically occurs in patients with immunosuppressed states and advanced age. Patients can present with ulcerated lesions of skin, of mucosal sites such as the GI tract, or of other sites such as the oral cavity. The EBV+ lesional cells sometimes resemble Reed-Sternberg cells/Hodgkin-like cells and variants, with a similar immunophenotype to that of Hodgkin lymphoma (CD30+, CD15−/+, CD20 +/ −, CD45+/−, PAX5+, MUM1+). Additionally, the polymorphous background of reactive cells can also potentially mimic classic Hodgkin lymphoma. Although there are some Hodgkin-like cells, the patient’s advanced age, presentation of isolated well circumscribed ulcerative mass involving GI mucosa, and immunophenotype such as PAX5+ (relatively strong), CD15-, CD79a+, are unusual for classic Hodgkin lymphoma. In this patient's clinical setting, this tumor is best classified as EBV+ MUCOCUTANEOUS ULCER.

The disease usually behaves in an indolent manner. Thus, distinguishing this entity from an aggressive lymphoma remains important.

B. Classical Hodgkin lymphoma (incorrect)

Classical Hodgkin lymphoma can present in the GI tract, but it is extremely uncommon. The sites involved, in descending order, typically include the stomach, small intestine, and colon. Upper abdominal pain and nonhealing ulcers are the typical clinical presentation in patients with gastric or duodenal tumors. Classic Hodgkin lymphoma typically shows Reed-Sternberg cells and variants in a background of small lymphocytes, histiocytes, eosinophils, and/or plasma cells, without medium-sized atypical cells or immunoblasts. Immunochemical profiles of Reed-Sternberg cells are positive for CD15 and CD30; focally CD20+ or CD20−; and negative for CD3, CD79a, and CD45. Neoplastic cells are positive for EBV by in situ hybridization. In the present case, the relatively strong PAX5 expression, CD15-, and CD79a+, are unusual for classic Hodgkin lymphoma.

C. Post-transplant lymphoproliferative disorder (incorrect)

Post-transplant lymphoproliferative disorders (PTLD) are identified in transplant patients. Though they can occur at any time, they are most frequently diagnosed within six months of transplantation. In majority of cases, they are usually polymorphic, EBV+ B-cell proliferations, with the small intestine being affected more than the stomach and colon. Polymorphic PTLDs produce destructive mass lesions and show the full range of B-cell differentiation, with lymphocytes, plasma cells, immunoblasts, plasmablasts, and cells resembling follicle center cells. Though PTLD is an important diagnostic consideration in this case, the patient's lack of transplantation essentially excludes this possibility.

D. Diffuse large B cell lymphoma, activated B cell type (incorrect)

When Diffuse large B cell lymphoma involves the gastrointestinal tract, it often takes the form of a solitary infiltrative mass with ulceration of the mucosa. The morphology is similar to nodal disease with sheets of large cells with high proliferation index. Tumor cells are large and resemble centroblasts/immunoblasts with expression of one or more B-cell markers (CD19, CD20, CD79a, PAX5). The activated B cell type (ABC), which is associated with a poorer prognosis than the Germinal center B-cell (GCB) DLBCLs, shows expression with MUM-1 and absence of CD10. BCL6 can be positive or negative (either CD10−, BCL6+, MUM1+ or CD10−, BCL6−). GCB immunophenotype, on the other hand, lacks MUM1 expression and expresses BCL6. CD10 can be absent or expressed (CD10+ or CD10−, BCL6+, MUM1−). Though this is important to consider in the differential, the inflammatory infiltrate in this case was polymorphous with a combination of lymphocytes, histiocytes, eosinophils and plasma cells. CD3 and CD20 both demonstrated a polymorphous lymphocytic population rather than a monoclonal B cell infiltrate, making DLBCL an unlikely choice.

E. EBV positive Diffuse large B cell lymphoma (incorrect)

EBV positive Diffuse large B cell lymphoma is defined by a diffuse infiltrate of atypical large lymphoid cells (immunoblasts/centroblasts) that demonstrate immunoreactivity for B-lineage markers (CD20, CD79a), MUM1 as well as immunoreactivity for EBV. As stated previously in part D, the demonstration of a polymorphous (rather than monoclonal) inflammatory infiltrate precludes this as the diagnosis, despite the expression of EBV with in situ hybridization.

**References:**

1. Dojcinov SD, Venkataraman G, Raffeld M, et al. EBV positive mucocutaneous ulcer-a study of 26 cases associated with various sources of immunosuppression. Am J Surg Pathol. 2010; 34:405-417.

2. Hart M, Thakral B, Yohe S, et al. EBV-positive mucocutaneous ulcer in organ transplant recipients: a localized indolent posttransplant lymphoproliferative disorder. Am J Surg Pathol. 2014 Nov;38(11):1522-9
3. Devaney K, Jaffe E: The surgical pathology of gastrointestinal Hodgkin's disease. Am J Clin Pathol. 95:794-801 1991
4. Solez K Racusen L Billingham M Pathology and rejection diagnosis in solid organ transplantation. 1994 Marcel Dekker Philadelphia 277-301
5. Harris N, Ferry J, Swerdlow S: Posttransplant lymphoproliferative disorders: summary of society for hematopathology workshop. Sem Diagn Pathol. 14:8-14 1997
6. Chadburn A, Cesarman E, Knowles D: Molecular pathology of posttransplantation lymphoproliferative disorders. Sem Diagn Pathol. 14:15-26 1997
7. Odze, R. D., Goldblum, J. R. (2015). Odze and Goldblum surgical pathology of the GI tract, liver, biliary tract, and pancreas.
8. International Agency for Research on Cancer. (2019). WHO classification of tumours of the digestive system. Lyon: International Agency for Research on Cancer.

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