Classical Hodgkin Lymphoma Presenting as a Sigmoid Mass

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Abstract

Primary classical Hodgkin lymphoma (CHL) in the colon is exceedingly rare and shares many histologic features with other lymphoproliferative disorders in the gastrointestinal tract. Here we report a case of CHL forming a sigmoid mass. An elderly man with a past medical history of mantle cell lymphoma presented with constipation. Imaging revealed an ulcerated, circumferential mass in the sigmoid colon. Endoscopic biopsy of the mass showed ulcerated colonic mucosa with an underlying diffuse mixed inflammatory infiltrate admixed with Hodgkin and Reed-Sternberg cells. Immunohistochemistry was performed to characterize these cells. They were weakly positive for Pax-5, strongly positive for CD30, variably positive for CD15, and negative for CD45, CD20, CD3, and SOX-11. *In situ* hybridization was positive for Epstein-Barr virus (EBV) and negative for cytomegalovirus or herpes simplex virus. This immunophenotype is diagnostic for CHL in the clinical context of a large mass. It is not possible in this case to determine whether this is *de novo* CHL or progression from a precursor lesion like EBV-positive mucocutaneous ulcer. Since diagnosis, this patient underwent colectomy followed by chemotherapy and has remained in complete remission.

Keywords: Hodgkin lymphoma; EBV; Gastrointestinal lymphoma; EBV-positive mucocutaneous ulcer

Introduction

The gastrointestinal (GI) tract is a relatively uncommon location for primary extra-nodal lymphomas. Upon endoscopic biopsy, entities such as diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, and mucosa-associated lymphoid tissue (MALT) lymphoma are the most common diagnoses [1]. Primary classical Hodgkin lymphoma (CHL) involving the GI

tract is exceedingly rare [2]. In previous cases where CHL is identified within the GI tract, it has been linked to clinical histories such as non-Hodgkin lymphoma, inflammatory bowel disease, and immunosuppression [3, 4]. A newly described entity, Epstein-Barr virus-positive mucocutaneous ulcer (EBVMCU), shows features which overlap with CHL [5, 6]. Differentiation of these two diagnoses is critical for guiding appropriate treatment decisions as EBVMCU may respond to reduction in immunosuppressant while CHL may need chemotherapy. Here we report a case of primary CHL presenting as a sigmoid mass.

Case Report

Investigations

The case was an 84-year-old man with a past history of mantle cell lymphoma. Four years ago, he presented to an outside facility with weight loss, fatigue, and a left axillary mass. The 5-cm axillary mass was excised and diagnosed as mantle cell lymphoma, stage 4B (an advanced stage with mass formation and non-nodal involvement). Fluorescent *in situ* hybridization (FISH) detected an IGH/CCND1 fusion rearrangement, supporting the diagnosis of mantle cell lymphoma. The patient was treated for his mantle cell lymphoma, but the exact treatment and remission status is unknown.

More recently, he presented to an outside hospital with worsening constipation. Imaging by positron emission tomography/computed tomography (PET/CT) showed increased radiotracer uptake in his GI tract, which was greatest in the distal colon without significant nodal or splenic uptake. Subsequent colonoscopic evaluation revealed a 10-cm in length circumferential, ulcerating and infiltrative mass in the sigmoid colon and no obstruction. This mass was biopsied, and the biopsy material was sent to our institution for diagnostic consultation.

Diagnosis

The biopsy fragments showed ulcerated colonic tissue. The mucosal and submucosal tissue was distorted by a diffuse infiltrate of mixed inflammation consisting of predominantly neutrophils with scattered eosinophils, lymphocytes, histiocytes, and plasma cells (Fig. 1a). Glandular dysplasia or carcinoma were not present within the biopsied material. Most of
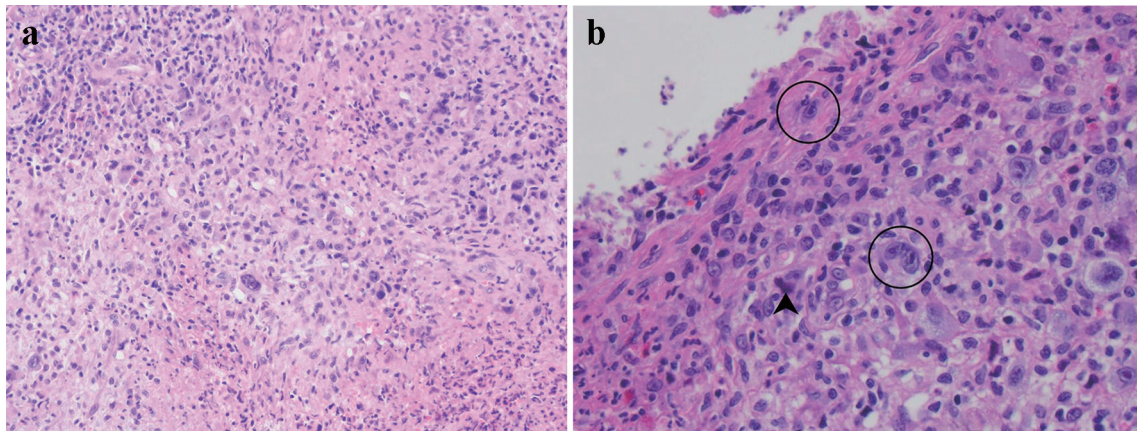
Figure 1. Histological evaluation of lesional tissue by hematoxylin and eosin (H&E) stain: (a) the lesion consists primarily of a destructive infiltrate of large, atypical cells mixed in a background of neutrophils, small lymphocytes, and eosinophils (× 100 magnification); (b) the large atypical cells resemble Hodgkin or Reed-Sternberg cells (circled) with 1 - 2 nuclei featuring vesicular chromatin and prominent inclusion-like nucleoli (× 400 magnification). Mummified cells are also depicted (arrowhead).

the small lymphocytes were T cells by immunohistochemistry. Also scattered throughout the lesion were large, atypical cells morphologically resembling Hodgkin or Reed-Sternberg cells. These atypical cells demonstrated abundant pale cytoplasm, fine chromatin, and a single inclusion-like prominent nucleolus in each nucleus (Fig. 1b). Occasionally, these atypical cells were bi- or multi-nucleated. Mitotic activity within the lesion was predominantly observed within these large cells. Also scattered within the inflammatory milieu was a second population of large, atypical cells which showed condensed cytoplasm and blurred nuclei (so-called "mummified cells").

Immunohistochemistry was performed to characterize the large, atypical neoplastic cells (Fig. 2). These cells were negative for CD45/leukocyte common antigen (Fig. 2a), CD20 (Fig. 2b), CD3 and other T-cell markers, SOX-11, Bcl-6, cyclin-D1, and ALK. They were weakly positive for Pax-5 (Fig. 2c), CD79a, Bcl-2, OCT-2, and MUM-1. They were positive for CD30 (Fig. 2d) and variably positive for CD15 (Fig. 2e). They did not express kappa and lambda surface or cytoplasmic light chains by chromogenic *in situ* hybridization (CISH). CISH revealed that these large atypical cells were positive for EBV (Fig. 2f) and negative for cytomegalovirus and herpes simplex virus. The overall immunophenotype and CISH EBV result supported an EBV-positive B-cell neoplasm with abundant reactive T cells, features of CHL. Due to the rarity of this entity, this case has been reviewed at an intradepartmental consensus conference, and a consensus diagnosis of CHL, mixed cellularity variant was made given the clinical presentation of large colonic mass and the above immunophenotype.

Treatment and outcomes

In this case, the patient developed life-threatening lower GI tract hemorrhage. He underwent colectomy for this deep and large ulcerating mass. He responded well to adjuvant chemotherapy, achieving complete remission 5 months after the initial diagnosis.

Discussion

The imaging and endoscopic findings of the sigmoid lesion in this case were highly concerning for a primary colonic malignancy, the top differential diagnosis being colonic adenocarcinoma. Prominent lymphoid response to colonic adenocarcinoma can occur, and when lymphoproliferation masks underlying carcinoma, the carcinomatous cells may be identified using cytokeratin and CDX2 immunostains [7]. However, the biopsy fragments in this case clearly showed a lymphoproliferative tumor based on the histomorphology and immunophenotype. The destructive lesion primarily involved the submucosa with limited extension into the mucosa. There was no evidence of chronic colitis, epithelial dysplasia, or carcinoma.

The biopsy showed a diffuse infiltrate of mixed inflammation consisting of predominantly neutrophils with scattered eosinophils, lymphocytes, histiocytes, and plasma cells. The scattered large atypical cells showed morphologic features compatible with Hodgkin/Reed-Sternberg cells or so-called mummified cells. Mitotic activity within the lesion was predominantly observed within these large cells rather than the accompanying inflammatory milieu. Immunohistochemical staining and CISH revealed that these large atypical cells were EBV-infected, CD30-positive and CD15 variably positive B lymphocytes lacking expression of CD45 and CD20. Most of the small lymphocytes were T cells by immunohistochemical staining. These features are most consistent with CHL, mixed cellularity variant.

The most common non-Hodgkin B-cell lymphomas in the colon include DLBCL, MALT lymphoma, and follicular lymphoma [8]. While T-cell rich DLBCL can mimic CHL, the large, atypical lymphocytes in DLBCL express CD20 and strong Pax-5 [9], unlike this case. MALT lymphoma tends to form lymphoepithelial lesions rather than causing ulceration and destruction of the surrounding tissue, and the predominant cell type would be small CD20-positive B cells [10]. High-grade follicular lymphoma can present with a more diffuse infiltrative pattern; however, this would not be T-cell rich, and the lesional
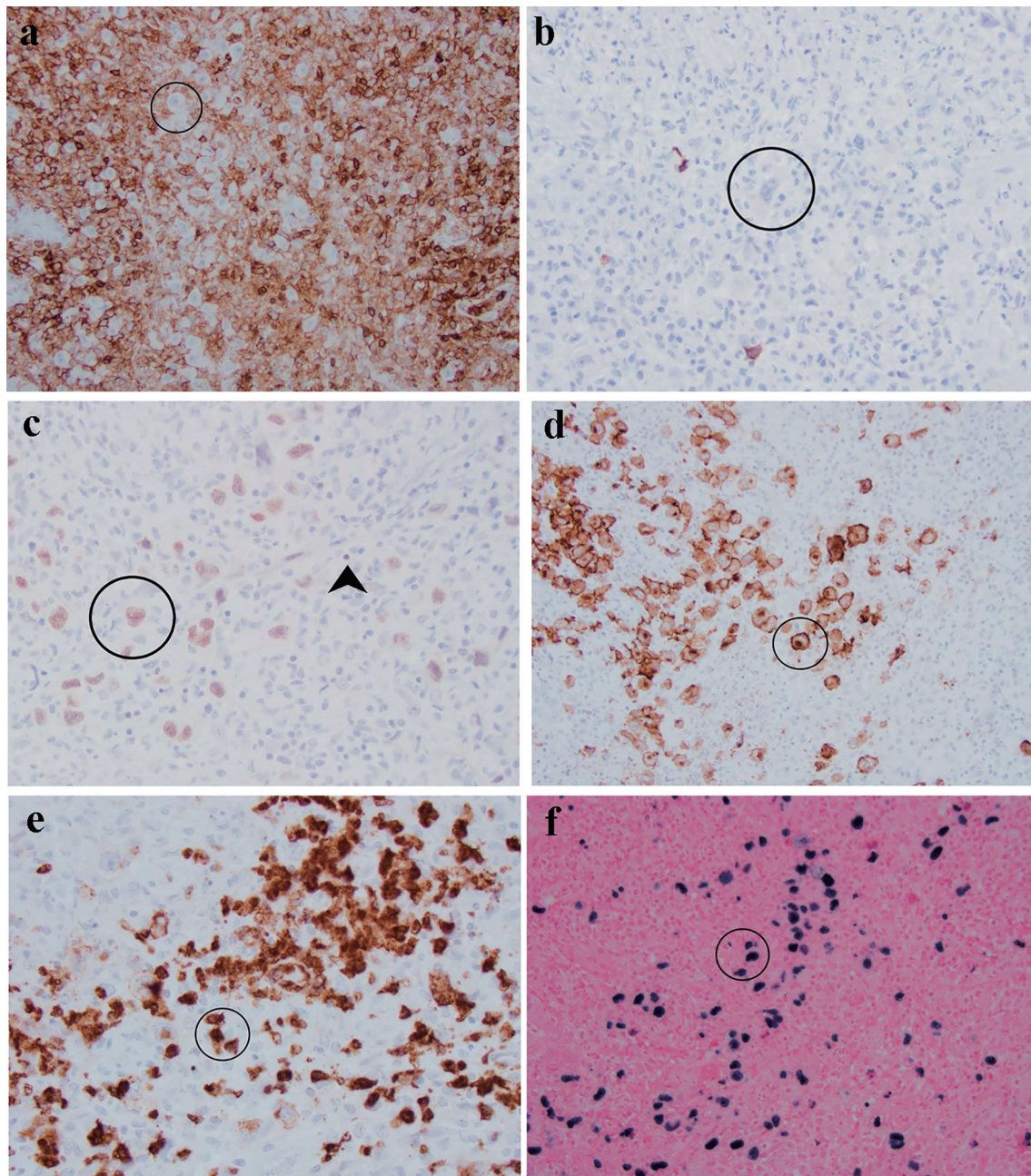
Figure 2. Characterization of atypical cells (circled) in this sigmoid mass by immunohistochemistry and *in situ* hybridization: (a) CD45 is negative in comparison with surrounding lymphocytes; (b) CD20; (c) Pax-5 is weak in Reed-Sternberg cells in comparison with strong staining in background B cells (arrowhead); (d) CD30 highlights membrane and Golgi bodies; (e) CD15 is positive in approximately 75% of Reed-Sternberg cells; (f) Epstein-Barr virus is positive in large cells rather than background small lymphocytes.

cells would be CD45- and CD20-positive and co-express Bcl-2 and Bcl-6 [11]. Given the morphologic and immunohistochemical patterns in this biopsy specimen, none of these common B-cell lymphomas are likely diagnoses over CHL.

Given the patient's prior history, another possibility was extranodal recurrence of mantle cell lymphoma. In particular, the large, atypical cells could represent the more aggressive pleomorphic variant. The large cells in pleomorphic mantle cell lymphoma should stain positively for CD20, CD5, and SOX-11 [12, 13], which was not seen in this case. While this lymphoma was not recurrence of mantle cell lymphoma, it is possible that immunosuppression from induction or maintenance treatment in this patient contributed to the pathogenesis of CHL.

Peripheral T-cell lymphomas (PTCLs) can also mimic CHL in the GI tract. In these instances, cells morphologically

similar to Reed-Sternberg cells are present and share an identical immunophenotype as the neoplastic T cells. Additionally, CHL can arise within tissue involved by a T-cell lymphoma due to the immunosuppressive effects of the underlying PTCL [12]. In either setting, the background T cells should aberrantly lose expression of T-cell markers such as CD3, CD4, CD7, and CD8, and may aberrantly express CD10 or Bcl-6. Complete differentiation from CHL requires molecular studies for T-cell clonality [12, 14, 15]. In our case, immunohistochemical stains showed no abnormal patterns among the background T cells, making underlying T-cell lymphoma unlikely.

Primary CHL in the colon is exceedingly rare and has been associated with immunosuppression and inflammatory bowel disease [4]. In most cases of CHL in the GI tract, colonic involvement represents metastasis from a nodal primary or Richter transformation from chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) [16, 17]. This patient's PET/CT scan did not show lymphadenopathy or foci of significant radiotracer uptake within lymph nodes or the spleen, making extranodal metastasis unlikely in this case. In Richter transformation, the Reed-Sternberg cells can be positive for EBV [18] and tend to be positive for MUM-1 [12]. Due to the immunohistochemical staining pattern and lack of areas morphologically resembling CLL/SLL in other fragments in the biopsy, primary CHL is more likely than transformation of a previous lymphoma. Histological review of the colectomy specimen would be helpful to completely rule out this possibility, but the surgery was performed at an outside hospital and the colectomy specimen was not available to us to review.

EBVMCU is a newly described entity presenting as a small ulcer rather than a large mass. EBVMCU is usually associated with immunosuppression or immune senescence. The lesions in EBVMCU are reported to be well circumscribed and superficial [5, 6, 19]. They can mimic CHL with Reed-Sternberg-like (RSL) cells admixed with infiltrating B lymphocytes. These RSL cells are positive for CD45, CD20 and EBV, and can also express CD15 and CD30 [5, 6, 19]. Most of these cases have an indolent clinical course and often resolve without treatment; however, complications such as luminal obstruction have been described [20]. Given the large size of the patient's mass lesion, EBVMCU is less likely than CHL in this case. Whether our current case represents a *de novo* CHL or progression from an EBVMCU is not clear. Recently, a case of colonic EBVMCU progressing to CHL, mixed cellularity variant in less than 2 years was reported in a patient with Crohn's disease [21]. It is possible that our case is immunodeficiency (immunosuppression or immune senescence)-related given the patient's age of 84 years and a clinical history of mantle cell lymphoma which has been treated.

In summary, when biopsy of a colonic mass shows atypical cells in a mixed inflammatory milieu, a diagnosis of CHL of the GI tract must be in the differential, although primary CHL of the GI tract is extremely rare. Immunohistochemistry using a panel of antibodies helps rule out non-Hodgkin lymphomas such as DLBCL, MALT lymphoma, follicular lymphoma, and PTCL. Primary CHL of the GI tract can only be established after GI tract (extra-nodal) involvement by nodal CHL and transformation into CHL from low-grade lymphomas are ruled out by clinicopathologic correlation. It is essential to distinguish CHL from EBVMCU as treatments are different. CHL may need chemotherapy and in some cases surgery, while EBVMCU may respond to reduction in immunosuppression in cases secondary to immunosuppressant treatment.

Acknowledgments

Financial Disclosure

Conflict of Interest

None to declare.

Informed Consent

Per Institutional Review Board guidelines, informed consent is not required for this de-identified, single patient case report.

Author Contributions

Conceptualization: XL; investigation: HC, AI, LY, and XL; resources: HC and XL; writing original draft preparation: HC; writing review and editing: AI, LY, and XL; visualization: HC; supervision: XL; project administration: XL. All authors have read and agreed to the published version of the manuscript.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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