Primary Epstein-Barr Virus–Associated Hodgkin Disease of the Ileum Complicating Crohn Disease

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• We describe a case of primary Hodgkin disease of the terminal ileum in a 38-year-old man with Crohn disease of 24 years' duration. The infiltrate was located in an ulcerated fistula involving the terminal ileum and urinary bladder. Reed-Sternberg cells and their variants were characteristically positive for CD15, fascin, and CD30 and showed focal positivity for CD20. Epstein-Barr virus messenger RNA was also detected in the neoplastic cells. Staging revealed no evidence of other lymph node or organ involvement. Although rare, primary gastrointestinal Hodgkin disease arising in the setting of Crohn disease may have a stronger association with Epstein-Barr virus infection than conventional Hodgkin disease.

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Primary extranodal Hodgkin disease unassociated with lymphatic tissue is extremely rare. It accounts for less than 1% of all Hodgkin disease cases. The most common site of involvement is the gastrointestinal tract, followed by (in order of descending frequency) the pulmonary system, thyroid, skin, genitourinary system, and central nervous system.[1–3]

Patients with chronic inflammatory bowel disease are at increased risk for gastrointestinal malignancies, such as adenocarcinoma and non-Hodgkin lymphoma. However, an association of primary gastrointestinal Hodgkin disease with Crohn disease is controversial, because only a few such cases with limited immunohistochemical and/or molecular investigations have been reported in the literature.[4–9] Here we describe an additional case of primary Hodgkin disease arising in the terminal ileum in a 38-year-old man with Crohn disease of 24 years' duration.

REPORT OF A CASE

The patient was a 38-year-old man with a history of Crohn disease diagnosed at age 14. He was treated with azathioprine and low-dose prednisone. In June 1999, he presented with gastrointestinal obstruction and internal fistula formation, and underwent terminal ileum and ascending colon resection. At surgery, multiple fistulas were noted involving small bowel, colon, and urinary bladder. Macroscopically, the specimen consisted of a portion of terminal ileum, cecum, and a portion of ascending colon with severe adhesions and formation of multiple fistulas. Grossly, the mucosal surface was flattened and had focal areas of polyp formation. Histologically, sections of the terminal ileum and the ascending colon showed characteristic changes seen in idiopathic chronic inflammatory bowel disease with active inflammation. Interestingly, sections from the fistula involving the terminal ileum and urinary bladder showed a nodular proliferation of atypical lymphocytic cells separated by bands of collagen fibers in the submucosa (Figure, A). Within the nodules were numerous Reed-Sternberg cells and their variants in a mixed inflammatory background (Figure, B), characteristic of Hodgkin disease. By immunohistochemical staining, the neoplastic cells were positive for CD15 (Leu-M1) (Becton Dickinson, San Jose, Calif), CD30 (Ki-1), and fascin (Dako Corporation, Carpinteria, Calif) (Figure, C through E). The tumor cells were focally positive for CD20 (L26) (Dako), but negative for CD45RB (leukocyte common antigen) (Dako), epithelial membrane antigen (Dako), or other T- or B (CD79a)-cell surface markers. Most of the surrounding lymphocytes were T cells, as demonstrated by UCHL-1 (CD45RO) (Dako) and CD3 (Dako) immunostaining (not shown). The Reed-Sternberg cells and their variants were strongly positive for Epstein-Barr virus (EBV) messenger RNA (mRNA), as demonstrated by in situ hybridization (Novocastra, Newcastle Upon Tyne, United Kingdom) (Figure, F).

Multiple sections of the mesenteric lymph nodes failed to reveal any evidence of Hodgkin or non-Hodgkin lymphoma. On physical examination, the patient had no evidence of peripheral lymphadenopathy. Computed tomographic scan showed no visceral lymph node enlargement or hepatosplenic lesions. A complete blood cell count and white cell differential were within normal range. A bone marrow biopsy was negative for involvement. All these clinical and laboratory findings supported the diagnosis of stage IE primary Hodgkin disease of the terminal ileum with Crohn disease.

After surgery, the patient received 4 cycles of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine). He had no evidence of disease at last follow-up, 8 months after the diagnosis of Hodgkin disease.

COMMENT

Primary gastrointestinal Hodgkin disease in association with Crohn disease is a rare entity. To date, only 9 cases (including the current report) have been described in the literature (Table). The majority of the patients were men (8 men and 1 woman) in their 30s (average age of 38.8 years at the time of lymphoma diagnosis). The duration of Crohn disease at the time of lymphoma diagnosis ranged from 2 to 24 years with an average of 8.9 years. All patients described received treatment with azathioprine, prednisone, or both for their Crohn disease. Intestinal obstruction and the appearance of a palpable mass were the most common presenting signs and symptoms. All reported tumors arose at sites of active inflammatory bowel disease, with a predilection for the small bowel (5

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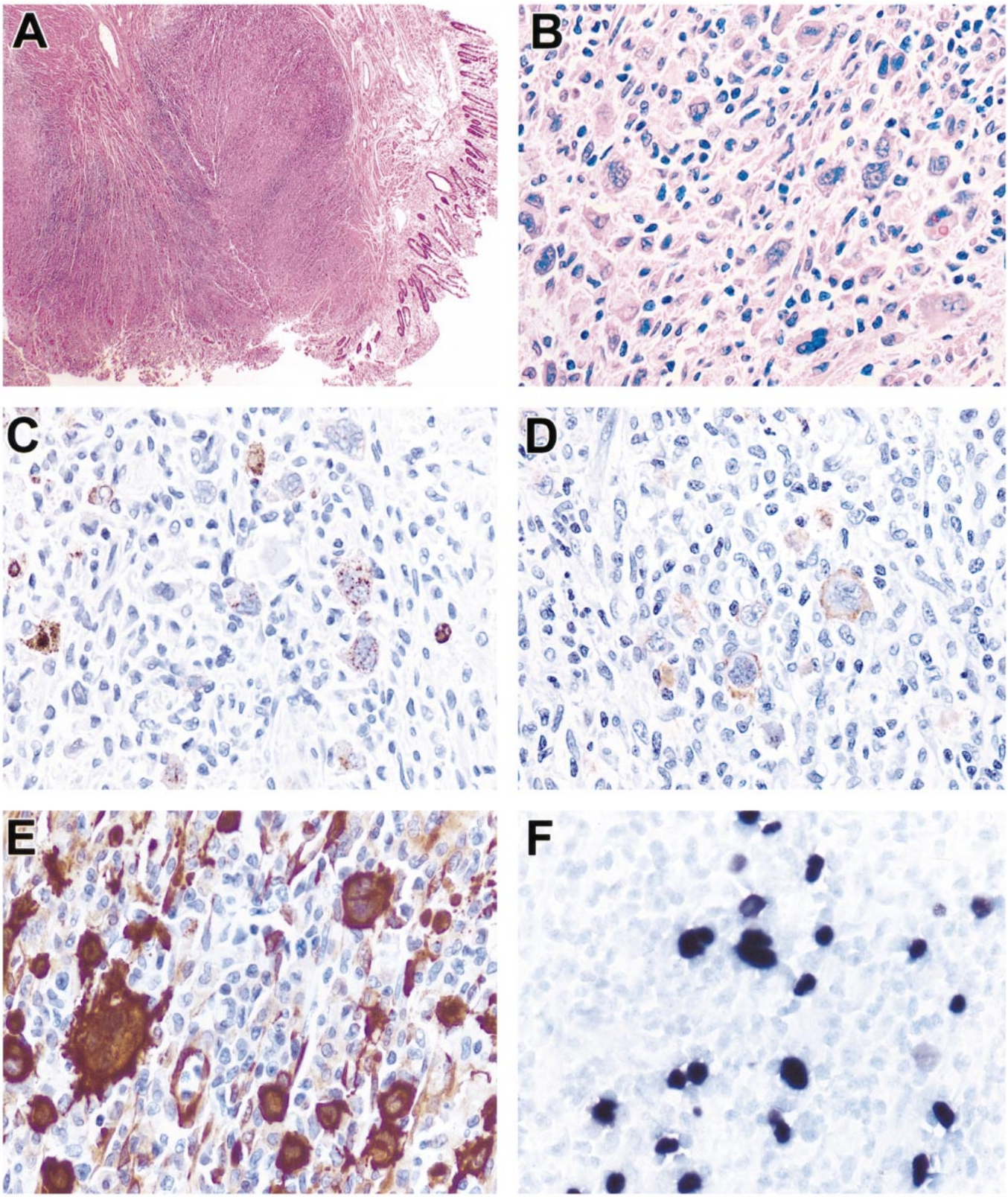

A, Low-power view of a dense, atypical, lymphocytic infiltrate in the submucosa of the terminal ileum (hematoxylin-eosin, original magnification ×40). B, High-power view of the Reed-Sternberg cells and their variants in a mixed background of lymphocytes (hematoxylin-eosin, original magnification ×400). C, CD15 expression in Reed-Sternberg cells and their variants (immunoperoxidase, original magnification ×400). D, CD30 expression in Reed-Sternberg cells and their variants (immunoperoxidase, original magnification ×400). E, Fascin expression in Reed-Sternberg cells and their variants (immunoperoxidase, original magnification ×400). F, Detection of Epstein-Barr virus mRNA in Reed-Sternberg cells and their variants by in situ hybridization (original magnification ×400).

Summary of Primary Gastrointestinal Hodgkin Disease Complicating Crohn Disease*

Source, y	Age at HD Diagnosis, y/Sex	Duration of Crohn Disease, y	Site of Involvement	Histologic Diagnosis	Immunohistochemistry	EBV Status
Hecker et al,[4] 1978	32/M	12	Small bowel and colon with node and marrow involvement	HD, MC	NT	NT
Morrison and Whittaker,[5] 1982	22/F	7	Large bowel	HD, MC	NT	NT
Shaw and Mulvaney,[6] 1982	39/M	2	Small bowel with node and liver involvement	HD, MC	NT	NT
Vanbockrijck et al,[7] 1993	34/M	3	Small bowel	HD, NS	$CD15^+$, $CD30^+$	NT
Kelly et al,[8] 1995	31/M	7	Small bowel with node involvement	HD, NS	$CD15^+$, $CD30^+$	NT
Kumar et al,[9] 2000	79/M	9	Colon with node and liver involvement	HD, MC	$CD15^+$, $CD30^+$, $CD20^{\pm}$ in all 3 cases	Positive in all 3 cases
	30/M	8	Colon with node involvement	HD, NS		
	44/M	8	Small bowel	HD, MC		
Current report	38/M	24	Small bowel	HD, NS	$CD15^+$, $CD30^{+,}$ $Fascin^+$, $CD20^{\pm}$	Positive

* HD indicates Hodgkin disease; MC, mixed cellularity; NS, nodular sclerosis; NT, not tested; and EBV, Epstein-Barr virus.

in small bowel, 1 in both small and large bowel, and 3 in large bowel only). All patients were treated with primary excisional surgery, sometimes followed by radiation therapy, chemotherapy, or both.

Because primary gastrointestinal Hodgkin disease cases are so rare, and those arising in Crohn disease are even rarer, the diagnosis should only be made following strict histologic and other criteria proposed by Dawson et al[10]: (*a*) no superficial lymphadenopathy should be present at the time of diagnosis; (*b*) chest radiological studies should indicate no involvement of mediastinal lymph nodes; (*c*) the complete blood count and white cell differential should be within normal limits; (*d*) gastrointestinal lesion should predominate with or without positive adjacent lymph nodes; and (*e*) liver and spleen should be free of disease at the time of diagnosis.

Among the 9 cases described in the literature, 3 reports were published before the advent of newer lymphoma classification systems using modern techniques, such as immunohistochemical studies.[4–6] In 1977, Codling et al[11] reported a case of Hodgkin disease complicating Crohn colitis. On further review in 1989, however, this case was reclassified as high-grade non-Hodgkin lymphoma of equivocal phenotype.[12] Although the majority of Hodgkin disease cases can be diagnosed with confidence on morphology alone, confirmatory immunohistochemical studies should be performed in cases of Hodgkin disease arising from unusual extranodal locations, such as gastrointestinal tract or central nervous system.

Our case fulfills the criteria of Dawson et al[10] and the immunohistochemical criteria for the diagnosis of primary gastrointestinal Hodgkin disease. The Reed-Sternberg cells and their variants demonstrated a typical immunohistochemical profile (membrane and cytoplasmic staining with dotlike Golgi enhancement of CD30, moderate cytoplasmic staining of CD15 in the Golgi area, diffuse cytoplasmic staining for fascin, focal membrane staining of CD20 of $<10\%$ of neoplastic cells, and CD45RB and epithelial membrane antigen negativity).

In the patients with primary Hodgkin disease complicating Crohn disease reported by Vanbockrijck et al[7] and Kelly et al,[8] immunohistochemical studies with antibodies to CD15 and CD30 confirmed the diagnosis of Hodgkin disease, but the presence of EBV was not investigated. In the largest series of primary gastrointestinal Hodgkin disease in association with chronic inflammatory bowel disease reported by Kumar et al,[9] all 3 cases showed evidence of EBV infection. In our case, the neoplastic cells were also strongly positive for EBV mRNA (Figure F). Although the number of cases is limited, it appears that the association of EBV infection with primary gastrointestinal Hodgkin disease in the setting of Crohn disease is stronger than that with conventional Hodgkin disease.[13]

It has been postulated that altered immunologic status associated with Crohn disease and ongoing chronic inflammation predispose patients to develop Hodgkin disease. All 9 patients received treatment with azathioprine, prednisone, or both therapies for a long period prior to the development of Hodgkin disease, suggesting an additional risk factor from immunosuppressive therapy in these patients. The demonstration of EBV in Reed-Sternberg cells and their variants in all 4 cases studied to date strongly supports a pathogenic role for the virus in Hodgkin disease in this clinical setting, analogous to Hodgkin disease arising in other immunodeficiency states, such as human immunodeficiency virus infection and after transplantation.

In summary, we have described an additional case of primary EBV-associated Hodgkin disease of the ileum in a 38-year-old man with Crohn disease, further supporting the possible association between primary gastrointestinal Hodgkin disease and Crohn disease. Our findings also suggest that EBV infection, in the setting of treatment-related immunosuppression, is important in the pathogenesis of primary gastrointestinal Hodgkin disease.

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