Primary Intestinal Lymphoma in Crohn’s Disease: Minute Tumor with a Fatal Outcome

Patricia M. Perosio, M.D., John J. Brooks, M.D., Schott H. Saul, M.D., and Daniel G. Haller, M.D.

Department of Pathology, University of Michigan Medical Center, Ann Arbor, Michigan; Department of Pathology and Laboratory Medicine, and Section of Hematology-Oncology, Department of Medicine, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania; and Department of Pathology, Chester County Hospital, West Chester, Pennsylvania

A 54-yr-old man with a 22-yr history of Crohn’s disease was found to have a microscopic focus of immunoblastic lymphoma within a segment of small bowel resected to relieve intestinal obstruction. There was no other clinically evident disease. Thirty months later, he developed axillary adenopathy with recurrent lymphoma of the same immunophenotype (IgA lambda) and was given combination chemotherapy, with complete clinical response. Lymphoma recurred 6 months later in the axilla and progressed rapidly over the next 3 months, despite chemotherapy. He developed extensive mediastinal, mesenteric, and retroperitoneal disease with malignant ascites and died 39 months after diagnosis of the incidentally discovered bowel mucosal primary tumor.

INTRODUCTION

Primary malignant lymphoma of the gastrointestinal tract is uncommon (1, 2). Most occur in the stomach, although, less often, the small bowel and colon are involved. There is a known association between intestinal adenocarcinoma and inflammatory bowel disease (3, 4). However, primary intestinal lymphoma is rare in these patients. Approximately 20 cases of malignant lymphoma of the gastrointestinal tract arising in Crohn’s disease have been reported. There have been reports of nearly twice that number of cases of colonic malignant lymphoma in association with ulcerative colitis (5). Of those with an adequate pathologic description, all have produced grossly evident tumors. The present case is unique in that the primary small intestinal lymphoma consisted of a minute focus confined predominantly to the mucosa, which was discovered incidentally in a segment of small bowel resected to relieve chronic intermittent obstructive symptoms. Although the patient remained well for 2½ yr without further therapy, his lymphoma subsequently relapsed in axillary lymph nodes. This initially responded to chemotherapy, but eventually became widespread, causing the patient’s demise. We report on the clinical and pathologic data of this case and review the previously reported cases of primary gastrointestinal lymphoma arising in the setting of Crohn’s disease.

CASE REPORT

A 54-yr-old man with a 22-yr history of Crohn’s disease, who had been treated intermittently with corticosteroids and azulfadine and who had multiple prior admissions for intermittent small bowel obstruction, was admitted with malnutrition and recurrent symptoms of obstruction. Exploratory laparotomy was performed, and a 3-foot segment of terminal ileum with multiple foci of stricture and dilatations was resected. Dilation of the proximal small bowel was noted, the colon appeared normal, and the spleen was enlarged. No adenopathy was evident. No further clinical staging evaluation or treatment was rendered at that time.

The patient was well for 30 months, at which time, he presented with right axillary adenopathy. A biopsy was performed. Computerized tomography (CT) of the chest and abdomen revealed no further adenopathy. He was treated with MACOP-B (methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin) for 12 wk, resulting in complete resolution of the adenopathy. Six months later, he developed recurrent right axillary adenopathy which was again biopsied and showed lymphoma. Repeat CT scans revealed no other adenopathy. He was treated initially with cyclophosphamide and doxorubicin, but his adenopathy progressed on this therapy. His regimen was changed to bleomycin, vincristine, etoposide, cytosine arabinoside, procarbazine, and prednisone for one cycle, but was stopped because of persistent thrombocytopenia and leukopenia, presumed to result in part from splenic sequestration. He subsequently underwent splenectomy. In the perioperative period, his disease rapidly progressed to involve the chest wall, as well as the mediastinum, by CT scan. He resumed therapy...
with procarbazine, etoposide, cytosine arabinoside, CCNU, and prednisone and was discharged from the hospital. He was readmitted with dehydration and anasarca 1 month later. CT scan showed extensive retroperitoneal and mesenteric adenopathy, massive ascites, and bilateral pleural effusions. The patient developed sepsis and died several days after admission, 39 months after diagnosis of primary bowel lymphoma.

Pathologic findings

**Small bowel.** The 70-cm length of terminal ileum showed multiple dilatations and strictures with thickening of the bowel wall, serosal edema, and cobblestoning of the mucosa. No tumor was evident grossly. The attached cecum was unremarkable. Histologic sections of the small bowel showed active chronic idiopathic inflammatory bowel disease characterized by increased mucosal chronic inflammation with focal cryptitis and crypt abscesses, as well as submucosal and serosal lymphoid aggregates. Multiple deep fissuring ulcers were seen. Although we saw no epithelioid granulomas, the histology was consistent with active Crohn's disease of the small bowel; there was no evidence of colonic involvement.

In a random section of small bowel within the inflamed area, several adjacent villi were distended by a monomorphic population of large lymphocytes with abundant amphophilic cytoplasm and prominent nucleoli (Fig. 1). Occasional tumor cells also were seen in the adjacent submucosa. The lesion was approximately 2 mm in size. Multiple additional sections of this area, as well as the remaining small bowel, failed to reveal any similar foci. Eleven mesenteric lymph nodes showed no evidence of lymphoma. Immunohistochemical staining of paraffin-embedded sections showed strong diffuse reactivity for IgA heavy and lambda light chain within this focus (Fig. 2). This was consistent with immunoblastic lymphoma of IgA, lambda type, pathologic stage I.

**Axillary lymph nodes.** Both biopsies showed an enlarged lymph node effaced by a similar population of large lymphoid cells with amphophilic cytoplasm, eccentric nuclei, and prominent nucleoli consistent with immunoblastic lymphoma (Fig. 3). Repeat immunohistochemistry on the first lymph node biopsy again showed a predominance of IgA and lambda expression within this tumor. Flow cytometric analysis for lymphoid subset markers was not done on this biopsy because of poor specimen preservation. Flow cytometry was performed on tissue from the second lymph node biopsy (with identical histology), and it showed that most large lymphocytes were strongly positive for the combination of B lymphocyte markers CD 19 and lambda (88%); only a minority of CD 19 and kappa-positive cells were seen (7%).

**Spleen.** The spleen weighed 1.1 kg and, on histologic

---

**Fig. 1.** Adjacent small intestinal villi expanded by a monotonous infiltrate of immunoblastic lymphoma. This was a solitary, minute focus. No further disease was evident in the adjacent bowel or lymph nodes (hematoxylin and eosin, ×10).

**Fig. 2.** Immunohistochemical staining of the primary intestinal immunoblastic lymphoma shows strong and diffuse reactivity for IgA (a) and lambda light chain (b). This is in contrast to IgM (c) and kappa (d), which react with occasional trapped plasma cells only. (Immunohistochemical stain, ×100).

**Fig. 3.** Immunoblastic lymphoma within an axillary lymph node. Morphologically and immunophenotypically, this was similar to the prior focus within the resected small bowel (hematoxylin and eosin, ×100).
section, showed only red pulp congestion. There was no evidence of involvement by malignant lymphoma.

**DISCUSSION**

The association of chronic idiopathic inflammatory bowel disease (CIIBD) and gastrointestinal adenocarcinoma is well known (3, 4, 6, 7). The risk of colorectal carcinoma in patients with ulcerative colitis increases with more extensive bowel involvement and colitis of longer duration. It is estimated that the cumulative risk of carcinoma after 25 yr of extensive colitis is 12% (8). In Crohn’s disease, prior reports emphasized that the low risk of carcinoma is low; however, more recent series have suggested that the frequency approaches that of ulcerative colitis (9).

Primary gastrointestinal lymphoma only rarely has been reported in association with CIIBD. In a review of primary colorectal lymphoma complicating CIIBD, Shepherd et al. (5) reported on 32 cases associated with ulcerative colitis and six cases associated with Crohn’s disease. Cases of lymphoma arose in patients with longstanding colonic disease (mean duration of colitis, 12 yr). Compared with sporadic cases of colorectal lymphoma, those that arose in the setting of ulcerative colitis were more often multiple, left-sided, high grade, and at an advanced stage at presentation. Of the 26 cases from which staging could be determined, 22 either extended through the muscle wall or involved mesenteric lymph nodes.

In Table 1, we review the clinicopathologic features of 20 cases reported in the literature as Crohn’s disease complicated by malignant lymphoma. As in patients with ulcerative colitis, many of these patients had a long history of inflammatory bowel disease prior to development of lymphoma, although the majority had disease for less than 10 yr. The patient we currently report is at the extreme, with a 22-yr history of intermittently active Crohn’s disease.

This patient is also unique in that the initial tumor consisted of a single microscopic focus of immunoblastic lymphoma confined predominantly to the mucosa, with only a few cells extending into the submucosa. The adjacent lymph nodes were not involved. Although it was considered possible that this minute lesion represented the first manifestation of a generalized lymphoma, it appeared unlikely because of the lack of detectable disease at the time of initial work-up and the subsequent 30-month disease-free hiatus. Of the 12 cases in the literature from which the extent of lymphoma could be determined, only one had disease limited to the mucosa and submucosa. This case, reported by Kini et al. (22), was a large, ulcerated superficial tumor in the stomach associated with noncaseating granulomas in the adjacent stomach and lymph nodes. There was neither prior history of inflammatory bowel disease nor other evidence of Crohn’s disease in this patient. In the absence of follow-up, the diagnosis of associated Crohn’s disease may be questioned.

Histologically, most of the cases reported in the literature have been classified as large cell non-Hodgkin’s lymphomas. Several have been classified only as high grade B or T cell lymphomas. Of the four originally classified as Hodgkin’s disease, one was reclassified as non-Hodgkin’s lymphoma. The others probably also represent pleomorphic non-Hodgkin’s lymphomas. Another case of immunoblastic lymphoma, histologically similar to the present case, was reported by Kwee et al. (21), and arose in the sigmoid of a patient with a 4-yr history of Crohn’s disease.

In our patient, the immunohistochemical typing of the original small intestinal focus, as well as the recurrent axillary tumor, revealed the same immunophenotype, a predominance of IgA, and lambda staining in the malignant cells. This is consistent with a B cell lymphoma showing restricted immunoglobulin heavy and light chain expression. This finding was supported by the flow cytometric analysis on the second lymph node recurrence, which again showed a predominant population of B cells expressing lambda light chain.

Malignant lymphoma of the gastrointestinal tract may not be suspected clinically in patients with a history of Crohn’s disease, because it may cause symptoms similar to those of active inflammatory bowel disease. Gastrointestinal lymphoma has been discovered at laparotomy in patients presenting with abdominal pain, bloody diarrhea, or tenesmus (5, 14, 20). Others may present with intestinal obstruction, fistulization, or stricture formation mimicking the complications of active Crohn’s disease (5, 12, 15, 19). In a patient described by Wyburn-Mason (12), malignant lymphoma obstructing a surgical anastomotic site was discovered 7 yr after resection of an adjacent segment of ileum obstructed by active inflammatory bowel disease. When our patient’s lymphoma was first diagnosed, symptoms were referable to intestinal obstruction, which was the result of active inflammatory bowel disease. The focus of small bowel lymphoma was an incidental microscopic finding.

As in our patient, most of those reported in the literature developed lymphoma either within active inflammatory bowel disease or at the site of prior activity. This suggests that chronic inflammation and stimulation of the immune response may provoke malignant degeneration, not only of the damaged and regenerating epithelium, but also of the responding lymphocytes. This is analogous to the situation in the small intestine in patients with gluten-sensitive enteropathy. Chronic lymphocytic inflammation and mucosal injury result not only in malabsorption but, also, are associated with
an increased risk of small intestinal adenocarcinoma and malignant lymphoma (25).

In summary, this is a unique case of a patient with a long history of Crohn’s disease who was found to have a microscopic focus of immunoblastic lymphoma in a portion of small bowel resected for relief of bowel obstruction. Although it remained inapparent for many months after surgery, it eventually recurred in axillary lymph nodes with an identical immunophenotype and, despite chemotherapy, later disseminated, resulting in the patient’s death.

Reprint requests and correspondence: John J. Brooks, M.D., Department of Pathology and Laboratory Medicine, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104.

REFERENCES


This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.