CASE REPORTS

Crohn’s Disease Complicated by Primary Gastrointestinal Hodgkin’s Lymphoma Presenting with Small Bowel Perforation

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Abstract

An increased incidence of non-Hodgkin’s lymphoma has been reported in patients with inflammatory bowel disease, particularly in those receiving immunosuppressive therapy. Rare cases of Hodgkin’s lymphoma have been reported in a setting of inflammatory bowel disease. The mechanism underlying the apparent association is unclear, but alterations in immune surveillance could play a role. In this report we describe the clinicopathological features of primary gastrointestinal Hodgkin’s lymphoma diagnosed in a patient with Crohn’s ileocolitis who had been receiving therapy with immunomodulator and biologic therapies.

Keywords

Introduction

Patients with Crohn’s disease are at an increased risk of developing neoplasms of the gastrointestinal tract. Adenocarcinomas of the intestinal tract are the most common complications in the course of this chronic inflammatory condition [1].

The association between Crohn’s disease and non-Hodgkin’s lymphoma remains controversial. It has been suggested that alterations in the immunologic state of IBD predispose to development of lymphoma. Large population based studies have failed to identify a significant association between lymphoma and inflammatory bowel disease (IBD) [2]. In contrast, a recent published meta-analysis showed a fourfold increased risk of non-Hodgkin’s lymphoma in a subgroup of IBD patients treated with azathioprine and/or 6-mercaptopurine [3].

In a meta-analysis of 9 randomized trials, patients with rheumatoid arthritis receiving therapy with anti-Tumor Necrosis Factor (TNF) were not found to be at an increased risk of developing non-Hodgkin’s lymphoma [4]. However, the clinical trials did not provide an adequate period of observation. The development of Hodgkin’s lymphoma as a complication in the clinical course of Crohn’s disease is rare. Only a limited number of cases have been reported [5-7].

In this report we describe the case of a 59 year old man with Crohn’s disease complicated by the development of primary gastrointestinal Hodgkin’s lymphoma.

Case Report

A 66 year-old man with Crohn’s ileocolitis presented with complaints of worsening diarrhea and lower abdominal pain over a two week period. He denied experiencing any fever, chills, nausea, vomiting or weight loss.

The patient’s past medical history was significant for peripheral arthritis diagnosed 8 years before presentation that had not responded to conventional non steroidal antinflammatory agents. The patient was then treated with methotrexate 15 mg orally once weekly and achieved symptomatic relief for a period of two years followed by a recurrence of symptoms. He was then started on leflunomide 20 mg orally once daily with minimal relief of symptoms. Therapy was continued for one year when symptoms of diarrhea and abdominal pain developed. An evaluation with computed tomography scan and colonoscopy with biopsy revealed findings consistent with Crohn’s ileocolitis. Methotrexate and leflunomide were discontinued and the patient was started on therapy with infliximab 5 mg/kg infusions every 8 weeks with improvement of symptoms.

Over the course of the next five years the patient experienced multiple symptomatic relapses with abdominal pain and diarrhea which were treated with prednisone tapers along with titration of the infliximab dosage up to 10 mg/kg every four weeks. During the last two years of this five year period he became steroid dependent and was started and maintained on 6-mercaptopurine (1.5 mg/kg) therapy which allowed for a modest reduction in the prednisone dosage.
At the time of presentation a colonoscopy revealed minimal inflammation of the terminal ileum. Within 3 days of the procedure, the patient developed severe abdominal pain with rebound tenderness. He underwent explorative laparotomy which revealed a thickened and severely inflamed terminal ileum which was resected with the cecum. Gross examination of the specimen revealed a perforation 60 cm proximal to the ileocecal valve. Histologic examination in the region of perforation evidenced numerous highly atypical lymphoid cells (Fig. 1). These atypical cells had the morphological appearance and immunohistochemical profile of Reed Sternberg (RS) cells (Fig. 2), demonstrating co-expression of CD20, CD79a and CD30 (Fig. 3). The RS cells were found to be EBER1-positive by in situ hybridization (Fig. 4). A total of five regional mesenteric lymph nodes were analyzed all of which revealed the presence of Hodgkin’s lymphoma.

The findings were consistent with a diagnosis of Hodgkin’s lymphoma mixed cellularity type, stage II E.

Imaging findings revealed no evidence for other nodal or hepatosplenic involvement. A bone marrow smear and biopsy showed no infiltration by Hodgkin’s lymphoma cells. Infliximab and 6-mercaptopurine treatment were discontinued. The patient recovered well post-operatively and is currently awaiting initiation of systemic chemotherapy with the combination of adriamycin, bleomycin, vinblastine and dacarbazine (ABVD).

**Discussion**

In this report we describe the clinicopathologic features of primary gastrointestinal Hodgkin’s lymphoma that developed in a patient with Crohn’s disease receiving immunosuppressive therapy for at least 5 years.
The mechanism underlying the apparent association between Crohn’s disease and lymphoma is unclear. Other chronic inflammatory conditions, including Hashimoto thyroiditis, myoepithelial sialadenitis, Helicobacter pylori associated gastritis, rheumatoid arthritis and Sjögren’s syndrome are thought to predispose to the development of lymphoma [8]. Controversy exists as to whether this association is due primarily to disease activity or an effect of medical therapy. It has been suggested that the altered immunologic state in IBD predisposes to the development of lymphoma [8]. Patients receiving treatment for Crohn’s disease are considered to be immunosuppressed as prednisone, 6 mercaptopurine, azathioprine and, more recently, anti-TNF therapy are frequently used to treat the disease.

Epstein-Barr virus (EBV) has been linked to most post-transplant lymphoproliferative disorders (PTLD), with a near 100% association in the early-occurring cases (within a year) and in PTLD-associated Hodgin lymphoma [9]. Epstein-Barr virus (EBV) encodes latency membrane proteins that are involved in cell signaling preventing apoptosis of RS-cell and indicating that infection by EBV may play an important role in the proliferation of Hodgkin lymphoma.

Higher EBV-positive rates are typically seen in HIV-positive and in immunosuppressed Hodgkin lymphoma patients [10]. Patients with Crohn’s disease receiving immunosuppressive therapy may be at increased risk for EBV reactivation and infection.

The case presented here and most of those reported in the literature are associated with EBV infection [5-7].

It appears that many factors may be involved in the development of lymphoma in patients with Crohn’s disease. Chronic inflammation in a setting of immunosupression by cytotoxic agents and biologic therapy may, theoretically, promote the proliferation of EBV-positive neoplastic clones. However, given the rarity of the development of lymphoma in patients with Crohn’s disease, the benefits of therapy with immunomodulators and biologic agents largely outweigh the risk of developing treatment related complications such as lymphoma.

References
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