Management of Enteropathy-Associated T-Cell Lymphoma: An Algorithmic Approach

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Key Words

Celiac disease · Lymphoma · Small bowel · T cell

Abstract

Perforation of the small intestine is the most lethal complication following induction chemotherapy for enteropathy-associated T-cell lymphoma (EATL). We report a case of EATL with a near perforated jejunal ulcer, and suggest a novel approach towards its management. Surgical resection followed by aggressive chemotherapy should limit chemotherapy-associated gastrointestinal toxicity, thus allowing patients to receive adequate dose and duration of chemotherapy. The presented case highlights potential benefits of surgical intervention prior to chemotherapy for EATL.

Introduction

Recent epidemiologic studies have shown that celiac disease (CD) is more common than previously thought and may affect approximately 1% of the general population [1]. Enteropathy-associated T-cell lymphoma (EATL), a rare but well-documented complication of CD, is a high-grade T-cell non-Hodgkin lymphoma (NHL) of the small intestine that is specifically associated with CD [2]. This potentially treatable tumor, which may be a significant subtype of NHL (fifth most common cancer in the United States) [1], has attracted renewed interest. Small bowel obstruction (SBO) is a rare initial presentation of intestinal lymphoma or CD, and it is even rarer in the case of EATL [1]. In most cases, these lymphomas behave aggressively, and their prognoses are typically grim which may be related to delayed diagnoses due to non-specific symptoms, lack of conclusive imaging and a low index of clinical suspicion.

Case Report

At our hospital, we performed an exploratory laparotomy and segmental small bowel resection in a 72-year-old man with a high-grade SBO. Intraoperatively, a near perforated ulcerative tumor in the proximal jejunum was identified as the obstructive etiology. Histopathology of the bowel adjacent to the tumor showed effacement of normal villous architecture (villous atrophy), the degree of which was consistent with long-standing but asymptomatic CD. The tumor was a high-grade NHL that was comprised of highly atypical lymphoid cells confirmed as T cells (immunostaining: positive for CD3 and CD45RO; negative for B-cell markers CD20 and CD30). Serological tests yielded strong evidence of anti-human tissue transglutaminase IgA, anti-endomysial IgA, and antigliadin IgG and IgA-findings consistent with untreated CD. Postoperatively, the patient was administered intensive chemotherapy consisting of 8 courses of CHOP (cyclophosphamide, adriamycin, oncovin and prednisolone). Re-staging with computed tomography (CT) scan, small bowel contrast study and upper gastrointestinal (UGI) endoscopy with random biopsies at 6-month intervals have revealed no evidence of recurrence. A repeat PET scan demonstrated an ongoing complete response. At 3½-years of follow-up, the patient remains disease-free.

Discussion

The term EATL was first introduced by the International Lymphoma Study Group (ILSG) to denote its association with CD, and EATL is classified as ‘enteropathy-type intestinal T-cell lymphoma’ by the World Health Organisation (WHO) [3]. EATL, a rare form of T-cell lymphoma (<1% of all NHLs), usually occurs in the setting of refractory CD (RCD) with an incidence that is about 20 times higher than that for the general population [4, 5]. This corresponds to an incidence rate of 7–10% in patients with long-standing CD [6]. However, patients with CD who are adherent to a gluten-free diet for at least 1–5 years and have recovered small bowel architecture have an EATL lifetime-risk comparable to that of the normal population [7].

Occasionally, CD is identified following the diagnosis of lymphoma since the disease remains asymptomatic [1, 2]. The median age at diagnosis of EATL is 60 years, and there is a slight male preponderance. Patients with CD typically suffer from chronic or recurrent abdominal pain, diarrhea, or weight loss; whereas some may manifest non-specific symptoms for years or present with an acute bowel perforation, obstruction, or hemorrhage. Since EATL is often disseminated at diagnosis, extraintestinal manifestations of the disease are seen in about 20% of cases. EATL usually presents as multifocal, circumferential ulcers localized to the jejunum or proximal ileum. The neoplastic cells are neither cytologically abnormal nor do they form tumor masses, which may cause a delayed diagnosis [8, 9]. Typically, EATLs reveal tumor cells that are CD3+, CD5–, CD7+, CD8–/+, CD4– and CD103+. Many cases contain a varying population of cells that are CD30+. In tumors with a high proportion of small and medium-sized cells, the cells are CD3+, CD8+ and CD30–.

The natural history of EATL is generally unfavorable. Approximately 50% of patients require laparotomy for complications of hemorrhage, perforation, or obstruction [10]. The high risk of intestinal perforation is especially seen with the commencement of standard anti-lymphoma chemotherapy due to the multifocal nature of bowel disease, poor nutrition and tissue integrity.

The suspicion of EATL should prompt an extensive diagnostic work-up that may include small bowel series, CT scan with enteroclysis, and total endoscopy – push or wireless video-capsule endoscopy (VCE) [11]. VCE is vital in the diagnostic work-up of complicated CD, particularly in cases with suspected RCD or EATL. VCE enables assessment of the extent of small bowel involvement and detection of overt though often

small neoplasms. It also assists in planning further diagnostic procedures, particularly enteroscopy, which are necessary to achieve a precise tissue diagnosis [12]. A prospective study comparing ^{18}F -FDG PET scan to conventional CT for the detection of EATL in patients with RCD showed that ^{18}F -FDG PET was better at discriminating between RCD and EATL and more sensitive and specific than CT scan (100 vs. 87% and 90 vs. 53%, respectively) [13].

Anthracyclin-based chemotherapy is the mainstay treatment of overt EATL, and CHOP or CHOP-like regimens were used most commonly in the 2 largest reported series [10, 14]. However, the outcomes of both series were poor with 1-year and 5-year survival rates in the range of 31–39% and 11–20%, respectively. In a prospective study of 35 intestinal T-cell lymphoma patients treated with 6 cycles of CHOP, the cumulative 2-year survival was 28% [15], and in another series of EATL patients the survival at 30 months was only 13% [16]. In most EATL cases, multimodal therapy comprising of chemotherapy, radiation, and surgery can result in improved survival rates. Our review of literature revealed an association between intestinal perforations at the tumor site and initiation of chemotherapy, which may be related to lack of vigorous desmoplastic response in lymphoma. Four studies [14, 15, 17, 18] evaluating management options in EATL and other intestinal lymphomas have documented intestinal perforations upon commencement of primary chemotherapy in a high percentage of cases.

Gale et al. [14] reported the largest series of 31 patients with EATL. Twenty-four patients underwent combination chemotherapy, and grade 3 and 4 toxicities restricted more than half of the patients from completing chemotherapy. In 3 out of 4 patients who suffered small bowel perforation, it occurred after the first cycle of chemotherapy (at 1, 2, and 4 days) and proved fatal, and after 3 cycles in the fourth. In addition, a gastrointestinal bleed, a postoperative wound infection and an enterocolic fistula occurred in 3 separate patients, and 6 others encountered episodes of neutropenic sepsis following initiation of chemotherapy. Wöhrer et al. [17] reported that 2 out of 10 EATL patients initiated on CHOP regimen underwent emergent surgeries for intestinal perforations. In the series by Wada et al. [18], emergency operations performed following spontaneous gastrointestinal perforations that had occurred within 2 weeks of initiating chemotherapy in lymphoma patients were successful in 2, whereas the third succumbed to severe sepsis. In another study by Daum et al. [15], 80% (28 of 35) of all intestinal T-cell lymphomas were associated with histologic features of enteropathy in the uninvolved small bowel, hence were classified as EATL. Sixteen of these 28 patients (57.1%) required an emergent laparotomy. Jantunen et al. [19] initiated combination high-dose chemotherapy with bone marrow transplant in five EATL patients – two died from transplant-related gastrointestinal toxicities and each of the surviving three relapsed/progressed within 0–14 months.

Bowel perforation is the second most common presentation (28.6%), after abdominal pain (66%), in primary intestinal lymphomas [20]. Uniquely, the high rate of chemotherapy-associated bowel perforation reported in patients with EATL makes it reasonable to consider surgery as the initial therapeutic modality prior to chemotherapy administration. The rarity of EATL accounts for the lack of a standard management scheme, and based on our experience and review of the literature we offer a novel algorithm (fig. 1). We suggest a multimodal approach that includes curative or debulking surgery to resect gross disease in all cases of EATLs, if tolerable, *prior to* chemotherapy. This may avoid chemotherapy-related bowel perforation, thus allowing completion of chemotherapy in most cases. Chemotherapy should be reserved as an adjuvant following resection, and long-term survival can be expected with its use. A recent series reported

sustained complete response in 66% of EATL patients who underwent surgical resection followed by combination chemotherapy and autologous stem cell transplant [21]. Follow-up must include UGI endoscopy and random biopsy at 6-month intervals. PET scan offers significant advantage in surveillance due to its ability to detect both nodal and extra-nodal involvement, including focal bone involvement [22]. A prospective clinical trial is needed to assess the survival benefit from our proposal; however, the rarity of this disease makes that unlikely.

Fig. 1. Proposed management algorithm for EATL.

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