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CASE REPORT

Intestinal Perforation Complicating Type II Enteropathy-associated T-cell Lymphoma

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Type II enteropathy-associated T-cell lymphoma (Type II EATL) is only rarely reported in Asia, especially in Taiwan and is known to be associated with a high bowel perforation rate. We described a case of Type II EATL with fatal perforation of the small intestine during his first cycle of chemotherapy. Conventional treatment for enteropathy-associated T-cell lymphoma consists of combination chemotherapy used for aggressive T-cell lymphoma (e.g., cyclophosphamide, adriamycin, vincristine, prednisone). Perforation of intestine often occurs at the time of diagnosis or in the early days of the first cycle of chemotherapy in these patients. To rescue and treat patient promptly, intestinal perforation should always be kept in mind as a differential diagnosis of acute abdominal pain in these patients. This case report highlights the potential pitfall in managing patients with gastrointestinal lymphoma and the need for maintaining a low threshold for prechemotherapy surgical intervention in patients diagnosed with type II EATL.

Key words: T-cell lymphoma, enteropathy, intestinal perforation

INTRODUCTION

Primary lymphomas of the gastrointestinal (GI) tract are rare, whereas secondary GI tract involvement is more common. The GI tract is in fact a predominant site of extranodal involvement by non-Hodgkins lymphomas (NHLs).[1] However, primary lymphomas of the GI tract are also a clinically important entity, since there are key issues pertaining to the diagnosis, treatment, and prognosis that are distinct from lymphomas of other sites and cancers of the GI tract. Primary NHLs of the GI tract account for around 1-4% of malignancies arising in the stomach, small intestine, or colon.[2] Two case series looking at GI tract lymphoma have reported the small bowel as being the second most frequent site of involvement by these lymphomas,[3,4] although their distribution appears to vary among populations. Primary small intestinal lymphoma maybe broadly categorized into three groups including immunoproliferative small intestinal disease (IPSID) lymphoma, enteropathy-associated T-cell lymphoma (EATL) and other western-type non-IPSID lymphomas. Primary small intestinal lymphomas account for 20-40% of primary GI tract lymphomas in western populations with survival data indicating that T-cell lymphomas carry the worst prognosis.[5] Primary T-cell GI lymphomas are relatively rare and the only well-defined clinicopathological entity is EATL.[6]

Enteropathy-associated T-cell lymphoma accounts for <5% of all GI tract lymphomas and <1% of all NHLs. It is usually associated with celiac disease. The mean age at diagnosis is 64-year and approximately 65% of cases are diagnosed in men.[7] Patient with untreated celiac disease have a substantially increased risk of developing EATL, especially among those diagnosed at an older age.[8] EATL only rarely develops in patients diagnosed with celiac disease early in life and patients with EATL rarely have a long clinical history of celiac disease.[9]

Type II enteropathy-associated T-cell lymphoma is a subset of EATL which does not appear to be associated with celiac disease and therefore has a broader geographic distribution.[10] To the best of our knowledge, cases of primary intestinal lymphoma from Taiwan have been reported in three case series of which there was only one case of Type I EATL.[11] We present a case of Type II EATL patient from Taiwan who was diagnosed and managed at our institution.

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CASE REPORT

A 46-year-old male presented with a 3-week history of intermittent epigastric dull pain, belching, and fullness of abdomen. He also reported poor appetite and general malaise and had lost ten kilograms of body weight over the last 2 months. In addition, he had low grade fever with chills intermittently during this time, although no nausea, vomiting or diarrhea were noted. He had no significant physical findings on examination except for some local tenderness over the epigastric and the left lower abdomen quadrant without peritoneal signs. Colonoscopy and abdominal sonogram done earlier were also unrevealing. However, upper GI panendoscopy showed erosive gastritis of antrum and a duodenal ulcerative lesion which was biopsied. The pathologic findings showed atypical lymphoid cells immunoreactive to CD3 and overexpression to P53 and Ki-67, indicative of intestinal T-cell lymphoma. He was admitted for further staging and treatment.

Pertinent laboratory findings included mild anemia with Hb: 11.0 g/dL, mean corpuscular volume: 88.5 fl, mean corpuscular hemoglobin concentration: 33.1%, white blood cell: 12.8 × 10^3/uL, with neutrophil: 75.0%, lymphocyte: 12.3%, monocyte: 11.4%. The platelet count was 552 × 10^3/uL. Lactic dehydrogenase was 321 U/L, total calcium 7.8 mg/dL, total protein 5.5 mg/dL, serum albumin 2.7 g/dL, glucose 132 mg/dl, sodium 135 mmol/L, potassium 2.8 mmol/L, C-reactive protein 9.35 mg/dL. Stool routine revealed strong positive occult blood test and red blood cell stool. Other biochemical studies were all within normal limits.

Further investigations for staging of lymphoma included bone marrow aspiration and biopsy study, computed tomography (CT) of abdomen and pelvis [Figure 1a] and whole body positron emission tomography (PET) [Figure 1b]. The CT showed lymphoma involving diffusely the intestine with multiple enlarged lymph nodes. The PET scan was consistent with disseminated lymphoma within the abdomen cavity. There was no lymphoma involvement in the bone marrow. The patient was therefore staged as Stage II two intestinal T-cell lymphoma.

Early during the hospitalization, the patient developed fever and night sweats which were attributed to his lymphoma. He reported episodes of worsening abdominal pain, but was treated symptomatically with conservative measures after abdominal imaging including CT scan failed to show any acute changes or any evidence of perforation. His symptoms subsided with narcotic analgesic and steroid therapy and systemic chemotherapy was initiated with the COP regimen. We chose to hold anthracycline during the first cycle, given patient's debilitated condition with the intervention of adding it with subsequent cycles.

Later that evening, patient developed severe abdominal pain, which did not respond to the usual symptomatic treatment. He now developed peritoneal signs and rapidly evolved into sepsis with hypotension, azotemia, and acidosis. At this point, emergent exploratory laparotomy was performed, which revealed multiple small bowel perforations (duodenum, jejunum and terminal ileum mesenteric root) through areas of macroscopic lymphomatous involvement. Biopsy specimens taken from these sites were sent for histopathologic and immunohistochemical analysis [Figures 2 a-f] which confirmed the diagnosis of Type II EATL.

Needless to say, any further systemic chemotherapy for the lymphoma had to be placed aside. Although the patient recovered from the acute perforation, he expired a month later from progressive lymphoma.

DISCUSSION

Patients with EATL generally present with abdominal pain, often associated with intestinal obstruction, perforation, or bleeding. Many patients are diagnosed with celiac disease at the time of presentation with EATL. EATL most commonly involves the proximal jejunum and less frequently the rest of the small intestine, stomach or colon.[12] On gross observation of the intestine, multiple circumferentially-oriented jejunal ulcers are typically present and are often associated with gut perforation. There may or may not be a mass.[13] Microscopically, the tumor cells are variable in

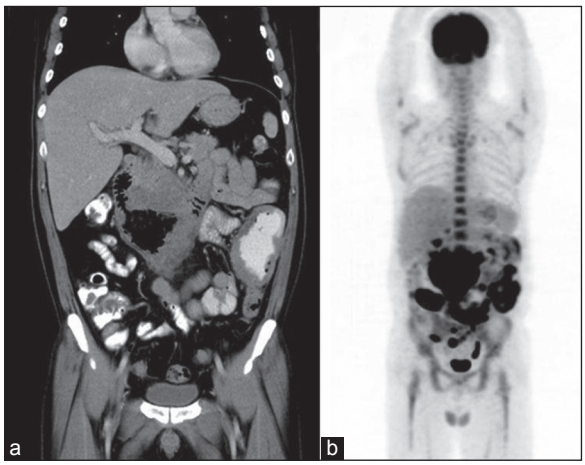

Figure 1. (a) Computed tomography of abdomen (coronal view) showing diffuse lobulated intestinal wall thickening over the second, third and partial fourth portion of duodenum, distal jejunum and proximal ileum with multiple enlarged lymph nodes in the adjacent small bowel mesentery, hepatoduodenal and para-aortic spaces. (b) Whole body positron emission tomography scan showing several fluorodeoxyglucose-avid lesions within abdomen, including mid abdomen (>12 cm), right lower quadrant (>6.0 cm), left lower quadrant (>7.0 cm) and also several smaller ones at different sites involving the bowel loops

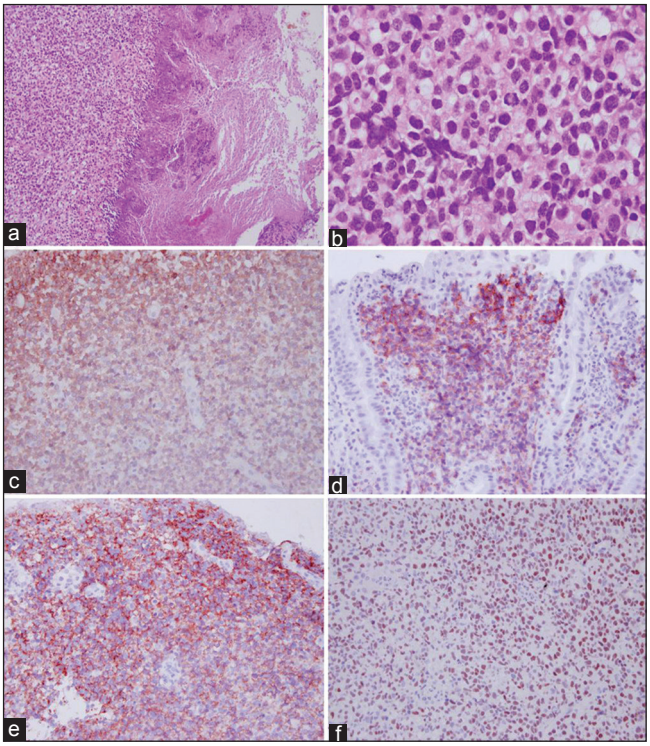

Figure 2. Histologic sections from the intestinal tissue show diffusely infiltrating monotonous lymphoid cells with enlarged and pleomorphic nuclei in an extensive ulcerative background (a) and (b). Immunohistochemical studies reveal that the tumor cells are positive immunoreactive for CD3 (c), CD8 (d), CD56 (e), and p53 (f)

size and morphology in Type I EATL, which accounts for 80-90% of cases. In Type II EATL, which accounts for 10-20% of cases.[10,14] the tumor cells are monomorphic and small to medium in size with infiltration of the intestinal crypt epithelium. The immunophenotype of Type I EATL typically shows $CD3^+$, $CD4^-$, $CD5^-$, $CD8^-$, $CD56^-$. Type II EATL shows $CD3^+$, $CD4^-$, $CD5^-$, $CD8^+$, $CD56^+$.[14-16]

In this case, immunohistochemical studies reveal that the tumor cells are positive immunoreactive for CD3, CD8, CD56, and p53. The result is compatible with the diagnosis of Type II EATL. Tumor suppressor p53 is nonspecific and mutated in approximately half of human cancers, resulting in inactivation and often an accumulation of the protein in the tumor cells.

At present, there are no standardized diagnostic or treatment protocols for EATL and no therapeutic distinction is made between the two types. Conventional treatment of EATL consists of combination chemotherapy used for other aggressive T-cell lymphomas such as CHOP. The 5-year overall survival (OS) rate with anthracycline-based chemotherapy alone is approximately 10-20%.[13,17,18] Autologous hematopoietic cell transplantation (HCT) may be benefitial for patient in first remission, although data regarding its use for EATL mostly come from case reports and case series.[19-22] A retrospective study of 26 patients with EATL treated with an intensive chemotherapy regimen (ifosfamide, vincristine, etoposide, and methotrexate) followed by autologous HCT rescue reported rates of progression-free survival and OS at 5-year of 52% and 60%, respectively.[22] For patients with EATL who have a good performance status and chemotherapy sensitive disease, treatment with intensive chemotherapy followed by autologous HCT rather than chemotherapy alone are suggested. Intra-abdominal perforation, fistula formation, and infection frequently complicate management in these patients and worsen prognosis.[23]

Our patient who presented with abdominal pain and body weight loss and was initially diagnosed as an intestinal T-cell lymphoma based on biopsy of a duodenal lesion found on upper GI panendoscopy. He was therefore treated as such with a CHOP like regimen. His abdominal pain was managed symptomatically given negative findings on physical examination and imaging studies. The patient had GI perforation shortly thereafter with sepsis and had to undergo emergent surgery. He succumbed to progressive disease before he could adequately recover from the surgery to receive systemic chemotherapy.

High perforation rates of 23% (7/31) at diagnosis and of 17% (4/24) in patients who underwent chemotherapy for Type II EATL have been reported. For patients who received chemotherapy, bowel perforation mostly occurred in the first cycle of treatment and was usually fatal.[13] Studies from Japan and Korea have showed Type II to be the most prevalent subtype of EATL in Asia with a high perforation rate of 80% (4/5) being noted in this subset in one of these studies.[24,25] Due to concern of high risk of intestinal perforation during treatment in Type II EATL, surgical intervention prior to chemotherapy may be beneficial and deserves consideration in the treatment planning for these patients. A recent series also reported sustained complete response in 66% of EATL patients who underwent surgical resection followed by combination chemotherapy and autologous HCT.[21] The type and extent of surgery needs to be planned very carefully in these patients to minimize the risk of acute perforation, while allowing sufficiently rapid recovery postoperative in order to start chemotherapy in a timely fashion.

In retrospect, had we been aware of the diagnosis of Type II EATL, we would have had a lower threshold for electively intervencing with surgery followed by a more intensive chemotherapy regimen (ifosfamide, vincristine, etoposide, and methotrexate) with possible autologous HCT at a later time.

Type II EATL is an uncommon GI lymphoma with a fairly aggressive phenotype including a high propensity for bowel perforation. A multi-disciplinary approach to planning

management of these patients with these caveats in mind is therefore critical to optimizing therapeutic outcomes.

DISCLOSURE

The authors declare that they have no conflict of interest.

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