

# Tonsillar Extraintestinal Enteropathy-Associated T-Cell Lymphoma in a Patient With Celiac Disease

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## ABSTRACT

Enteropathy-associated T-cell lymphoma (EATL) is a rare but serious complication of celiac disease. Diagnosis is challenging. Patients can present with weight loss, abdominal pain, and diarrhea or acutely with bowel perforation or obstruction. Patients often present with advanced disease. Malnutrition further limits treatment options. Early diagnosis is important to start aggressive treatment strategies. However, even with prompt diagnosis, prognosis remains poor with a high mortality rate. We report the first documented case of sole tonsillar involvement, a rare extraintestinal and extranodal site of disease, leading to EATL diagnosis. We also highlight some of the challenges in diagnosing EATL.

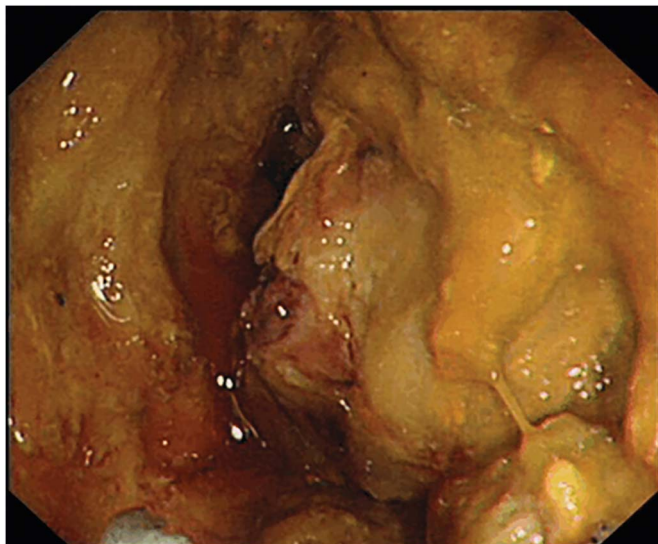
## INTRODUCTION

Celiac disease (CD) is an immune-mediated enteropathy affecting 0.6% of the Western population.<sup>1</sup> Although prognosis is usually excellent, a proportion of individuals develop serious complications including refractory CD type I and type II (RCD I and RCD II), ulcerative jejunitis, and enteropathy-associated T-cell lymphoma (EATL).<sup>2</sup> EATL is a rare complication, affecting 0.04% of adult-onset CD patients.<sup>2</sup> Patients often present with advanced disease, and by this stage, their nutritional deficits limit chemotherapeutic options.<sup>3,4</sup>

## CASE REPORT

A 57-year-old woman was reviewed in the gastroenterology clinic with a 3-month history of abdominal pain, vomiting, and a 6-kg weight loss. She was diagnosed with CD 6 years earlier but reported nonadherence to a gluten-free diet. She took lansoprazole 30 mg, had no relevant family history, abstained from alcohol, and was an ex-smoker. Weight was 62 kg, body mass index was 22.23 kg/m<sup>2</sup>, and physical examination was unremarkable.

Laboratory investigations revealed normal full blood count, renal function, and liver function. Anti-tissue transglutaminase antibody was raised at 256 U/mL (normal value < 7 U/mL). Immunoglobulin levels were normal. Gastroscopy revealed gastritis, but otherwise normal appearances to the second part of the duodenum (D2). D2 biopsies demonstrated flattened villi, an increase in inflammatory cells in the lamina propria, and an increase in intraepithelial lymphocytes. These features were consistent with CD but without evidence of dysplasia or neoplasia. Computed tomography (CT) of the chest, abdomen, and pelvis with intravenous contrast was unremarkable. Investigations were consistent with untreated CD. She was referred to a specialist dietician and commenced on a strict gluten-free diet.



**Figure 1.** An irregular, circumferential tumor in the jejunum on enteroscopy.

Three months later, she was admitted with intractable vomiting, a further 9-kg weight loss, and acute kidney injury. Tissue transglutaminase antibody had improved (62 U/mL), and lactate dehydrogenase (LDH) was normal (188 U/L). Repeat gastroscopy revealed stagnant fluid to the third part of the duodenum (D3); no obstructing lesion was seen. D2 biopsies were consistent with adherence to a gluten-free diet. Magnetic resonance imaging of the small bowel revealed a thickened 7-cm loop of proximal jejunum. Multiple, deep, jejunal ulcers were seen on capsule endoscopy, confirmed by push enteroscopy. Histology reported ulceration only, with no features of neoplasia and normal immunohistochemistry. She was started on prednisolone 20 mg for possible ulcerative jejunitis. She clinically improved, tolerated a liquid diet, and her weight increased.

Two months later, repeat surveillance enteroscopy revealed interval progression with a 5-cm circumferential jejunal tumor (Figure 1). Histology showed inflammatory and necrotic debris, again with no malignant cells. Repeat CT revealed mural thickening and aneurysmal dilatation of 8 cm of the proximal jejunum with surrounding lymphadenopathy (Figure 2). Positron emission tomography-CT showed uptake only in the jejunal mass. Laparotomy and jejunal resection were performed.

She developed a sore throat postoperatively. Examination revealed a left tonsillar mass, and tonsillectomy was performed. Tonsillar histology revealed high-grade T-cell lymphoma, in keeping with the simultaneous results from the jejunal resection specimen, which confirmed type 1 EATL.

She was referred to the hemato-oncology team for management of EATL, Ann Arbor Stage III. She received 6 cycles of cyclophosphamide, doxorubicin, vincristine, and prednisolone chemotherapy, followed by salvage chemotherapy with 4 cycles of gemcitabine, cisplatin, and methylprednisolone, and then a lomustine, etoposide, cytarabine, and melphalan-conditioned

autologous stem cell transplant. Currently, she remains in remission under annual hematology surveillance with interval positron emission tomography (PET) scanning.

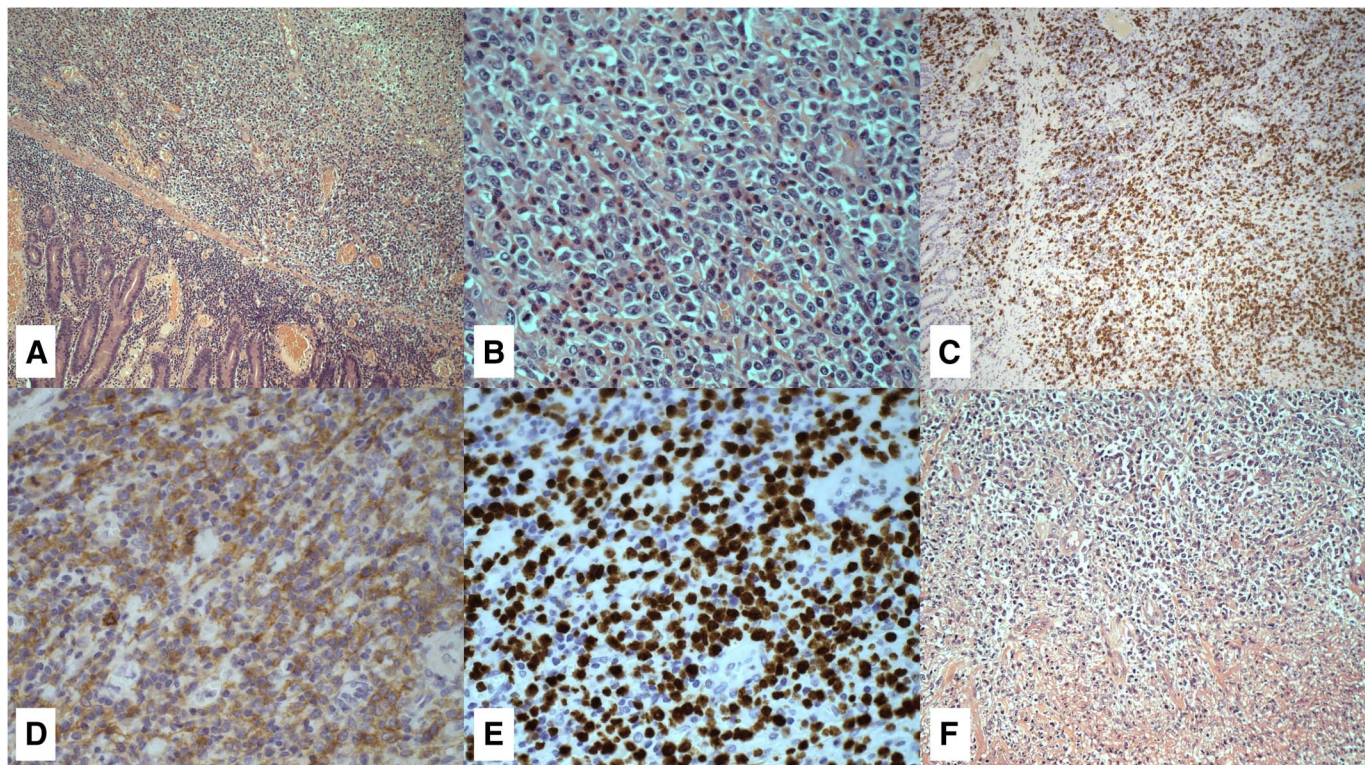
## DISCUSSION

EATL is a peripheral non-Hodgkin T-cell lymphoma subdivided into type 1 EATL (comprising 80%–90% of cases and associated with CD) and Type II EATL (a monomorphic disease variant).<sup>5</sup> The median age of diagnosis is 60 years. The jejunum and ileum are the most frequent sites of disease.<sup>6</sup> 30%–50% of EATL cases are observed in CD patients with preexisting RCD II and result from the neoplastic transformation of aberrant intraepithelial T lymphocytes.<sup>7</sup> “De novo” EATL (46%) occurs in patients with uncomplicated CD or RCD I; the pathogenesis remains uncertain.<sup>8</sup>

Risk factors for EATL include poor adherence to a gluten-free diet, late diagnosis of CD, and HLA-DQ2 homozygosity.<sup>9</sup> EATL presents a diagnostic challenge; symptoms are diverse and include vomiting, night sweats, abdominal pain, and weight loss.<sup>3</sup> Investigations comprise magnetic resonance imaging of the small bowel, capsule endoscopy, PET, and biopsy. Biopsy can be obtained endoscopically; however, initial histological confirmation of EATL from endoscopic biopsy specimens is as low as 36.4%,<sup>10</sup> and therefore, laparotomy may be required for full-thickness biopsy specimens in cases of diagnostic uncertainty.<sup>3</sup> However, approximately 50% of patients present acutely with obstruction, perforation, or gastrointestinal hemorrhage<sup>11</sup> and at a late stage with advanced disease.<sup>3</sup> Diagnosis is then made at emergency laparotomy, which demonstrates ulcerating intestinal



**Figure 2.** A coronal view of the proximal jejunal mass on CT scan (mass identified by white arrow). CT, computed tomography.



**Figure 3.** Histological slides demonstrating the characteristic features of type 1 enteropathy-associated T-cell lymphoma (EATL). (A) Malignant lymphoid cell infiltration in the distal duodenum (hematoxylin and eosin [H&E] stain 100× magnification). (B) Pleomorphic lymphoid cells with a high nuclear-cytoplasmic (N/C) ratio, vesicular nuclei, ill-defined cytoplasm, and numerous eosinophils in the distal duodenum (H&E stain 400× magnification). (C) CD3 expression in neoplastic lymphoid cells in the distal duodenum (CD3 stain 100× magnification). (D) CD30 expression in neoplastic lymphoid cells in the distal duodenum (CD30 stain 400× magnification). (E) MIB-1 showing a proliferation fraction of approximately 90% in the distal duodenum (MIB-1 stain 400× magnification). (F) Diffuse infiltration by sheets of pleomorphic medium-to-large-sized lymphoid cells mixed with eosinophils in ulcerated tonsil (H&E stain 200× magnification).

mucosal masses.<sup>12</sup> Histology reveals large lymphoid cells with areas of necrosis and an increase in eosinophils and histiocytes.<sup>13</sup>

Treatment centers on surgical resection, chemotherapy, and autologous stem cell transplantation.<sup>4,7</sup> Surgical debulking is often undertaken as the first step because of perforation or obstruction at diagnosis, or to reduce the risk of bowel perforation during chemotherapy.<sup>14</sup>

EATL carries a high mortality rate. The clinical disease stage is usually advanced at diagnosis.<sup>6</sup> The poor nutritional state and performance status of many patients at presentation limit chemotherapeutic options. Five-year survival ranges from 8% to 60% depending on suitability for more aggressive treatment.<sup>4,14</sup>

We report the development of EATL in a patient without RCD II but with a history of gluten-free diet nonadherence. Our patient presented with advanced disease, in keeping with the literature.<sup>3</sup>

We report the first documented case of tonsillar involvement of EATL related to CD. Delabie et al<sup>6</sup> studied a cohort of 62 patients with EATL from 22 centers. Jejunal and ileal tumors accounted for 90% of the cases, followed by the colon (16%) and

stomach (8%). The mesenteric (35%) and para-aortic or iliac (11%) lymph nodes were also frequently involved. Extranodal extraintestinal disease was rare; lung, skin, bone marrow, and paranasal sinuses were involved in 5%, 5%, 3%, and 2% of the cases, respectively.<sup>6</sup> Another infrequent, but devastating, extranodal site of involvement is the central nervous system.<sup>15</sup> Case reports have also described cardiac<sup>16</sup> and intraocular involvement.<sup>17</sup>

We report a case of EATL in a patient with known CD and gluten-free diet nonadherence. This case highlights the diagnostic challenge of EATL, especially when our patient experienced a partial response and clinical improvement with the introduction of a gluten-free diet and steroid prescription. Our case emphasizes the need for repeat biopsies when histology is inconclusive and suggests that laparotomy is appropriate in cases of diagnostic uncertainty. Clinical suspicion must remain high to allow for diagnosis at an earlier stage of disease and better performance status to allow aggressive treatment options.

## DISCLOSURES

Author contributions: The article was written by VT Kronsten and C. Gosson. The article was critically revised by A. Al-

Khatib, I. Bagwan, T. Worthington, S. Muthalali, M. Ethell, G. Lim, and P. Youd. VT Kronsten, T. Worthington, S. Muthalali, M. Ethell, G. Lim, and P. Youd were involved in the care of the patient. All coauthors approved the final submitted article. VT Kronsten is the guarantor of the article.

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