

CASE REPORT

Diffuse large B-cell lymphoma of the small intestine in a patient with refractory coeliac disease

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Abstract

Introduction: Coeliac disease enteropathy is associated with an increased risk of lymphomas. Enteropathy-associated T-cell lymphoma is the principal malignancy related to coeliac disease. However, studies have shown that other types of lymphoma such as diffuse large B-cell lymphoma may also be associated with coeliac disease. **Case Report:** We report a 54-year-old Caucasian man who presented with chronic diarrhoea and weight loss. He was diagnosed with coeliac disease based on positive serology results and duodenal, jejunal, and ileal biopsies that showed villous atrophy. Despite adherence to a gluten-free diet, there was no clinical remission and enteropathy-associated T cell lymphoma was suspected. Repeated endoscopic biopsy showed persistent mucosal disease but no evidence of lymphoma. Several weeks later he presented with a perforated jejunum. Histology of the resected jejunum showed diffuse infiltration of submucosa and muscularis propria by malignant lymphoid cells sparing the mucosa. The cells expressed CD20, CD79 α , CD10 and BCL6 and ki67 of 80%, consistent with diffuse large B-cell lymphoma. **Discussion:** It is suspected that the undetected lymphoma may have contributed to the persistent malabsorption syndrome rendering the patient unresponsive to treatment. Despite thorough clinical and endoscopic evaluation and multiple biopsies, histologic diagnosis of DLBCL was only confirmed following resection of the perforated jejunum.

Keywords: Diffuse large B-cell lymphoma, refractory coeliac disease, small intestine, perforation

INTRODUCTION

Coeliac disease is a chronic immune-mediated enteropathy which is induced by dietary gluten in genetically susceptible individuals.¹ It has a worldwide distribution and commonly affects the European populations with a prevalence of about 1%.¹ It is associated with complications such as osteopenia, infertility, autoimmune diseases, immune deficiencies, infections and malignancies.² The risk factors for developing complications include persistent exposure to dietary gluten, chronic mucosal inflammation and genetic factors.² There is a strong association between coeliac disease and lymphoma, particularly the rare enteropathy-associated T-cell lymphoma (EATL) type 1 which accounts for about 30% of the cases.^{3,4,5} However, some studies have suggested that other types of lymphomas are more frequently associated with coeliac disease.^{3,4} These lymphomas include

unspecified peripheral T-cell lymphoma, diffuse large B-cell lymphoma (DLBCL) and mucosa-associated lymphoid tissue (MALT) lymphoma.^{3,4} Here, we report a case of DLBCL of the small intestine arising in a patient with refractory coeliac disease.

CASE REPORT

A 54-year-old Caucasian man presented to our centre with generalised lethargy, weight loss and persistent diarrhoea for one year. He was pre-morbidly well and had been in Malaysia for the past 20 years. There was no family history of coeliac or other autoimmune diseases. Clinically, he was cachexic and had bilateral pedal oedema. Oral aphthous ulcers, skin rashes, peripheral neuropathy as well as other features to suggest autoimmune disease were absent. His blood investigations showed low total protein [35 g/L (normal range: 64-83

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TABLE 1: Summary of the intestinal biopsies performed: Microscopic findings and pathological diagnoses

No.	Biopsy	Indication	Microscopic findings	Interpretation
1.	Terminal ileal biopsy at diagnosis	To confirm the diagnosis of coeliac disease	Moderate mucosal damage with partial villous atrophy and crypt destruction. Intraepithelial lymphocytosis was present. IHC showed reactive T and B cells (retrospective).	Coeliac disease, Modified Marsh Classification Type 3a
2.	Duodenal biopsy 12 months after diagnosis	To re-assess the mucosal disease following gluten-free diet	Severe active duodenitis with partial villous blunting. There was increased intraepithelial lymphocytes. <i>Helicobacter pylori</i> was present. IHC showed reactive T and B lymphocytes.	Superimposed <i>H. pylori</i> infection on an underlying coeliac disease
3.	Jejunal biopsy 12 months after treatment	Suspected lymphoma, to exclude EATL	Partial villous blunting and flattening. No abnormal lymphocytes seen. IHC showed reactive and non-neoplastic T and B lymphocytes.	Consistent with refractory coeliac disease. No evidence of EATL.

Note: In view of high suspicion of lymphoma, immunohistochemical study for B- and T-cells was performed on the three biopsies to look for evidence of lymphoma. However, immunohistochemical study results showed that there was no evidence of lymphoma in all the biopsy samples. Abbreviation: IHC, immunohistochemistry; EATL, enteropathy-associated T-cell lymphoma.

g/L)] and serum albumin [17 g/L (normal range: 35-50 g/L)] levels, normochromic normocytic anaemia [haemoglobin 10 g/dL (normal range: 13.5-17.4 g/dL)] with a normal iron status. His IgM, IgA and IgG levels were also low. Serum endomysial and anti-tissue transglutaminase antibodies were not performed. A colonoscopy was performed for chronic diarrhoea and showed

a typical mosaic appearance of the small bowel mucosa consistent with coeliac disease. An ileal biopsy was performed at this point (Table 1, Fig. 1) which revealed villous atrophy consistent with Modified Marsh Classification Type 3a coeliac disease.

The patient was subsequently started on gluten-free diet. However, his symptoms

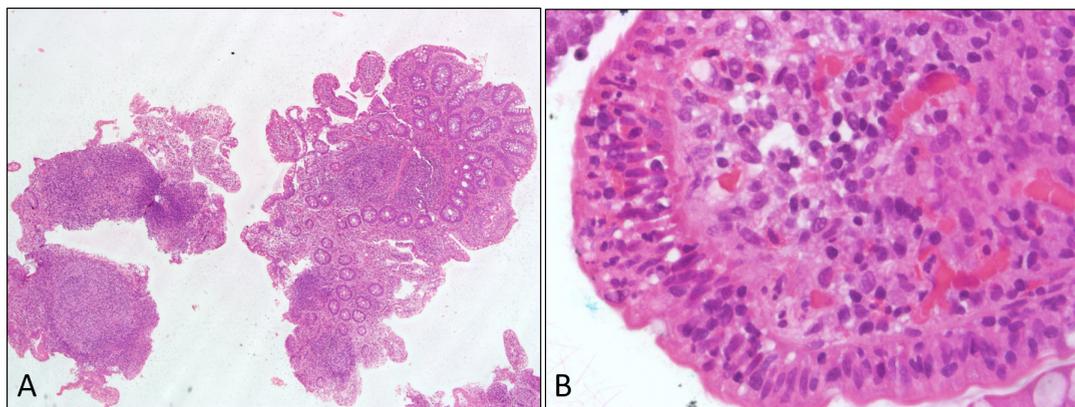


FIG. 1: Ileal biopsy showed (A) moderate mucosal damage with partial villous atrophy and crypt destruction and (B) increased number of intraepithelial lymphocytes.

persisted despite 12 months of strict compliance with gluten-free diet. Gastroendoscopy revealed mucosal atrophy of the duodenum (Table 1) with superimposed *Helicobacter pylori*. A diagnosis of chronic active duodenitis on underlying coeliac disease was made. At this time a magnetic resonance enterography (MRE) was performed and showed thickening of the small bowel wall at the level of proximal and mid-jejunum with multiple enlarged mesenteric lymph nodes measuring up to 2.0 cm. These findings were compatible with small bowel lymphoma. It was thus concluded that the patient had refractory coeliac disease and that the findings of the MRE were strongly suspicious that there was also EATL of the small intestine. An oral-route double balloon enteroscopy was performed and the suspicious jejunal lesion was biopsied (Table 1).

The biopsy showed mucosal damage but no evidence of EATL or any malignancy. Five weeks later, he developed an acute abdomen due to a perforated jejunum. An emergency laparotomy was performed and the perforated jejunum was resected.

Pathological findings

The resected jejunum measured 250 mm in length and 40 mm in diameter with attached mesenteric fat. The wall was thickened around the perforation site. A small polyp measuring 10 mm greatest area dimension was also present. Microscopically, diffuse malignant lymphoid cells comprised medium to large cells were seen mainly within the submucosa with infiltration into the serosa (Fig. 2). In areas, there was spillage of the tumour cells into the lamina

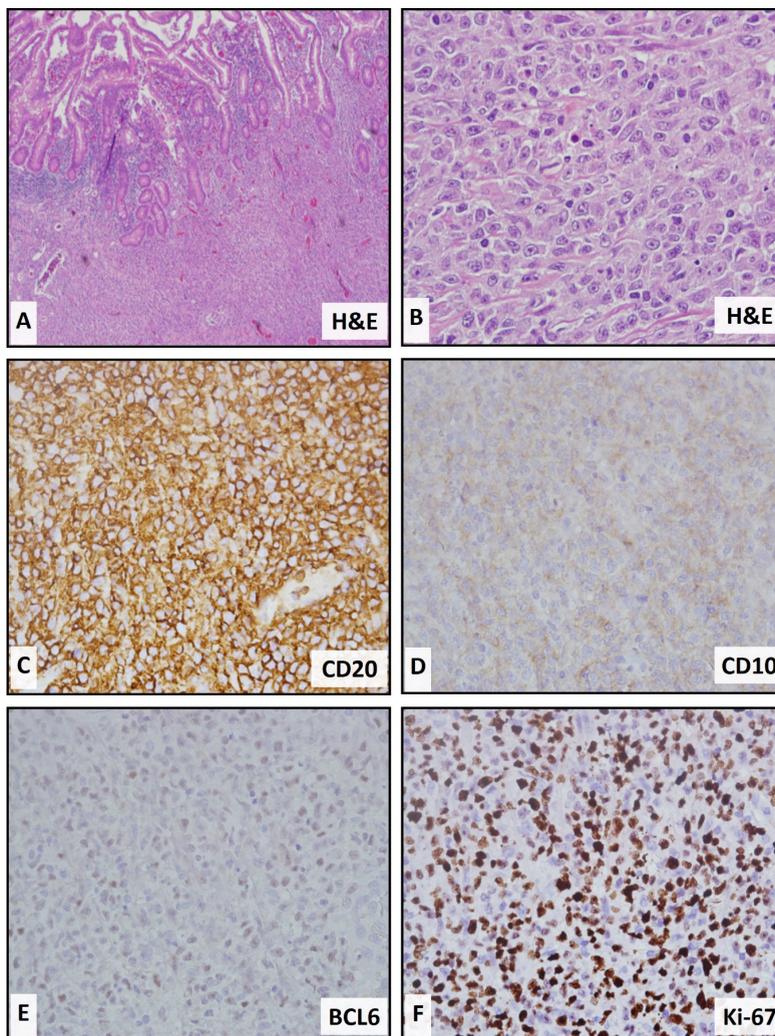


FIG. 2: (A) Diffuse infiltration of malignant lymphoid cells predominantly the submucosa. (B) The cells were composed of medium to large cells and displayed pleomorphic nuclei with prominent nucleoli and scant cytoplasm. The cells expressed (C) CD20, (D) CD10 (weak), and (E) BCL6. (F) The proliferative index (Ki-67) was 80%.

propria. Malignant lymphoid cells were also seen within the small polyp. The cells displayed large and pleomorphic nuclei with prominent nucleoli and scant cytoplasm. Mitoses were numerous with areas of necrosis were observed. Immunohistochemical studies showed that the malignant lymphoid cells expressed CD20, CD79 α , CD10 (weak) and BCL6. Ki-67 showed a high proliferative index (80%) (Fig. 2). These cells were negative for CD3, CD5, CD7, CD8, TIA-1, MUM1, cyclin D1 and CD56. A diagnosis of DLBCL was made. Twenty-one lymph nodes were identified and none of the lymph nodes showed malignant infiltration. Elsewhere the mucosa showed focal blunting of the villi with increased intraepithelial lymphocytes.

Clinical course

Post-operatively, he developed intra-abdominal sepsis secondary to anastomotic leak and underwent a second laparotomy for further small bowel resection and double-barrel stoma creation. A positron emission tomography-computed tomography (PET-CT) did not show any active disease elsewhere. Bone marrow biopsy showed normocellular marrow with no evidence of lymphomatous infiltration. He was diagnosed with stage I disease and was counselled for chemotherapy.

He was given gluten-free diet supplemented with parenteral nutrition. His adherence of gluten-free diet was monitored and his general condition improved. Subsequently, he underwent reversal of ileostomy and was finally discharge after three months of hospitalisation.

DISCUSSION

The association between sprue-like syndrome and lymphoma was first described by Fairley and Mackie in 1937.⁶ Recent studies demonstrated a three- to six-fold increased risk of lymphoma incidence which is much lower than the earlier estimates of risk.^{3,4} This decline may have been due to early detection and treatment of coeliac disease.⁷ More than half of the lymphoma cases in coeliac disease were of primary gastrointestinal origin while the remaining were extraintestinal.³ Patients with coeliac disease and small intestinal lymphoma present with non-specific symptoms such as abdominal pain, diarrhoea, weight loss and rarely presented with complications such as perforation, haemorrhage and obstruction.^{1,4,8} The jejunum is the most common site of coeliac disease-associated gastrointestinal lymphoma

followed by ileum, stomach and colon.^{4,8}

The present patient showed lack of initial response to gluten-free diet. Although radiological examination was highly suspicious of lymphoma, initial biopsies failed to show the lymphoma cells. The main reason the biopsies did not show the malignant cells was because they were superficial (mucosal layer only) whereas the malignant lymphoid cells were predominantly in the submucosa. Repeated biopsies are frequently necessary before the correct diagnosis is finally made.⁹ In such difficult cases, full thickness laparoscopic biopsies are sometimes required.⁸

The commoner type of lymphoma associated with coeliac disease is EATL type 1. EATL type 1 frequently shows a large-cell and pleomorphic morphology. In contrast, EATL type 2 which is less frequently associated with coeliac disease has a more monomorphic cytology.¹⁰ Recent studies have found an increased risk for B-cell neoplasm commonly DLBCL.^{3,4} Histologically, both EATL type 1 and DLBCL display medium-sized to large cells with vesicular nuclei, prominent nucleoli and moderate to abundant pale cytoplasm. Immunohistochemical profile of the tumours is clearly distinct. In EATL, the tumour cells express CD3, CD7, CD103 and TIA-1 with loss of CD5, CD4 and CD8 expression. However, in DLBCL the neoplastic cells express pan B-cell markers such as CD20 and CD79 α with further subgrouping by combination of immunomarkers CD10, BCL6 and MUM1. Both tumours show high proliferative index by Ki-67 staining and may be positive for CD30.¹¹ Clinically, patients with B-cell lymphoma have better survival rate than those with T-cell lymphoma.^{3,4}

CONCLUSION

We described a case of DLBCL of the jejunum in a patient with refractory coeliac disease where initial biopsies failed to detect the tumour. Diagnosis of lymphoma was only achieved on the resected jejunum following intestinal perforation. This case illustrates the need for careful clinical and pathological evaluation of patients with non-responsive coeliac disease for the possibility of underlying lymphoma.

ACKNOWLEDGEMENT

This case report was presented as a poster in the 3rd Annual Scientific Meeting 2016 of the International Academy of Pathology (Malaysian Division) in Penang, Malaysia in October 2016.

Conflict of interest: The authors declared no conflict of interest.

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