CASE REPORT

Enteropathy-associated T-cell lymphoma: An extremely rare cause of chronic diarrhoea

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SUMMARY

Chronic diarrhoea in tropical countries may be due to a myriad of causes from infective to non-infective. This case report illustrates the challenges faced in the investigation of a middle-age Chinese gentleman who presented with chronic diarrhoea and weight loss. The diagnosis of type II enteropathy-associated T-cell lymphoma (EATL) was finally made. The diagnosis of EATL was least suspected as the condition is almost unheard of in this part of the world. The epidemiology, presentation, diagnosis, management and prognosis of this rare condition are discussed.

KEY WORDS:

Enteropathy-associated T-cell lymphoma; EATL; type II enteropathy-associated T-cell lymphoma; type II EATL; small bowel lymphoma; chronic diarrhoea

CASE REPORT

A 50-year-old Chinese man with no previous medical illness was admitted to the Gastroenterology Ward with a history of chronic diarrhoea for six months. He had 6-7 bowel movements a day, including nocturnal diarrhoea. The stool was watery, non-bloody and varied from small to large amounts. He also reported weight loss of 17kg within the same duration. There was no febrile episode and no significant travel history. His symptoms were investigated in another medical centre two months earlier. At that time, computed tomography (CT) scan of thorax, abdomen and pelvis and oesophagogastroduodenoscopy were unremarkable. On examination, his hydration was fair, blood pressure 102/68 mmHg and pulse rate 80 beats per minute. The abdomen was soft and non-tender with no organomegaly. Relevant investigation results are summarized in Table I.

He was commenced on intravenous hydration and correction of electrolyte imbalance. Colonoscopy was normal. Push enteroscopy using paediatric colonoscope (Olympus, Tokyo, Japan) revealed pale-looking small bowel mucosa with loss of villous appearance. Histopathological examination of small bowel biopsy revealed mucosal blunting with intra-epithelial and lamina propria lymphoid infiltrate, which was reported as consistent with celiac disease. However, he tested negative for anti-tissue transglutaminase antibody. In view of the watery diarrhoea and severe hypokalaemia, the possibility of a VIPoma was considered. Endoscopic ultrasonography did not show any lesion in the pancreas. Serum chromogranin A was raised but serum vasoactive intestinal peptide (VIP) level was normal. A positron emission tomographic (PET) scan showed an active lesion in the peritoneum. CT scan was repeated and showed a well-defined enhancing mass measuring 5.0cm x 7.9cm x 8.9cm in the mesentery adjacent to an area of thickened jejunum.

He was started on supplemental parenteral nutrition and was planned for surgery. However, he developed vomiting, abdominal distension and pain, and showed signs of peritonism. Emergency laparotomy showed a hard mesenteric mass and adjacent small bowel perforation with two litres of haemoserous fluid. Partial resection of small bowel with primary anastomosis and peritoneal wash-out was done (Figure 1a–1b). Histopathological examination of the resected small bowel revealed a tumour composed of monotonous, small to intermediate-sized lymphoid cells which displayed round to slightly irregular nuclei with condensed chromatin and scanty cytoplasm. The tumour cells were strongly immune-reactive for CD3, CD8 and CD56, and negative for CD4, CD5, CD30 and EBV encoded RNA (EBER) (Figure 2a–2h). A diagnosis of type II EATL was made. He made an uneventful recovery post-surgery and his diarrhoea resolved. He received two cycles of combination chemotherapy consisting of cyclophosphamide, hydroxydaunorubicin, oncovin and prednisolone, which were complicated with febrile neutropenia on both occasions despite granulocyte colony-stimulating factor. A repeat PET scan showed disease progression with recurrence at the small bowel anastomotic site with ascites, lung opacities with pleural effusion, and splenic involvement. Bone marrow aspiration and trephine biopsy showed bone marrow involvement as well. He was then given a cycle of ifosfamide, carboplatin and etoposide. His condition deteriorated and he died of massive gastrointestinal bleeding four months from the time of diagnosis.

DISCUSSION

EATL is a rare primary gastrointestinal T-cell lymphoma in which the classical type is strongly associated with celiac disease and is thus more common in those areas with high

This article was accepted: 3 February 2016

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Table I Relevant investigation results

Parameters	Levels
Hemoglobin	12.5 g/dL
White cell count	4.5 x 10^9/L
Platelet	132 x 10^9/L
Sodium	136 mmol/L
Potassium	1.9 mmol/L
Urea	2.6 mmol/L
Creatinine	94 µmol/L
Albumin	22 g/L
Erythrocyte sedimentation rate	20 mm/hour
C-reactive protein	1.3 mg/dL
T4	19.1 pmol/L
Thyroid-stimulating hormone	0.83 mIU/L
Serum iron	8.2 µmol/L
Serum ferritin	825.5 µg/L
Serum folate	18 nmol/L
Serum vitamin B12	288 pmol/L
Anti-nuclear factor	Negative
Human immunodeficiency virus serology	Negative
Peripheral blood film	Normochromic, normocytic anemia, lymphopenia and thrombocytopenia
Stool examination	Negative for ova, cysts and Clostridium difficile toxins
Stool culture	Negative for Shigella, Salmonella and Clostridium difficile

prevalence of celiac disease, in particular northern Europe.[1] The other rarer type, known as type II EATL, lacks association with celiac disease and is thought to constitute most if not all cases of EATL in Chinese and probably also amongst most Asians.[2] In a retrospective study by Chan and colleagues that included several hospitals in Hong Kong, only 18 cases of type II EATL were identified over a 12-year period, attesting to the rarity of the condition.[2] Another multi-centre retrospective study by Tse and colleagues of the Asia Lymphoma Study Group identified only 38 patients with EATL over a 19-year period in which all the cases were type II EATL.[3] Tan and colleagues have proposed that type II EATL is a separate entity from classical type EATL and to be renamed epitheliotropic intestinal T-cell lymphoma.[4]

Colorectal cancer should be suspected in a middle-age Chinese patient with altered bowel habit and weight loss, and the diagnosis was excluded by a normal colonoscopy in this case. A normal colonoscopy also makes gut tuberculosis unlikely since the condition usually affects the ileocecal junction, and especially in the absence of fever and elevated erythrocyte sedimentation rate. Other causes of chronic diarrhoea such as hyperthyroidism, human immunodeficiency virus infection and giardiasis should be considered and were excluded with blood and stool tests. Careful examination of the small bowel and obtaining biopsies for histopathological examination is important in patients with chronic diarrhoea when baseline investigations have failed to identify the cause. Although balloon-assisted enteroscopy allows a more complete evaluation of the small bowel, examination of the duodenum and proximal jejunum can be easily achieved by push enteroscopy using a paediatric colonoscope. In our patient, subtle abnormalities that included pale-looking mucosa with loss of villous appearance could be appreciated. Although histopathological examination of small bowel mucosal biopsies was consistent with celiac disease, anti-tissue transglutaminase antibody, which has high sensitivity and specificity for celiac disease, was negative in our patient. In the study by Chan and colleagues, intra-epithelial lymphocytosis zones could be identified in contiguous or distant small bowel mucosa in all their type II EATL patients. The histological changes were merely enteropathy-like and did not represent manifestation of celiac disease.[2] Similarly, on retrospect, we do not think our patient had celiac disease and believe that the histologic changes were part of the manifestation of type II EATL. Newer modalities such as magnetic resonance enteroclysis and video capsule endoscopy can be useful in the investigation of suspected small bowel pathology but both lacks the ability to obtain tissue for histopathological examination. Nevertheless, they can serve as initial investigation before the more invasive deep enteroscopy is considered. The presence of watery diarrhoea and severe hypokalaemia prompted investigations to look for VIPoma. VIPoma is a type of neuroendocrine tumour that secretes vasoactive intestinal polypeptide and arises from the pancreas in 90 % of cases but may also be found in many other extra-pancreatic sites. Endoscopic ultrasound did not reveal any pancreatic lesion and the diagnosis of VIPoma was effectively ruled out by the normal serum VIP level.

In two case series, bowel perforation (39-72%) and abdominal pain (22-59%) were the most common presentations for EATL. Chronic diarrhoea was seen in 6-28%.[2, 4] The diagnosis of EATL is usually made by histopathological examination of small bowel resected due to obstruction or perforation. In the classical type, tumour cells are pleomorphic, medium to large-sized and typically express CD3, CD7 and CD103 but not CD4, CD5, CD8 and CD56. In type II EATL, tumour cells are monomorphic, small to medium-sized, and typically express CD3, CD8, CD56 and TCRβ but not CD4.[2] The neoplastic cells are derived from intraepithelial T-lymphocytes (IEL) which express a cytotoxic phenotype such as TIA-1 positivity.[3] Type II EATL also differ from classical EATL in which chromosomal gains in 1q and 5q are less common while 8q24 (MYC) amplifications are more common.[5] Other differential diagnoses for type II EATL

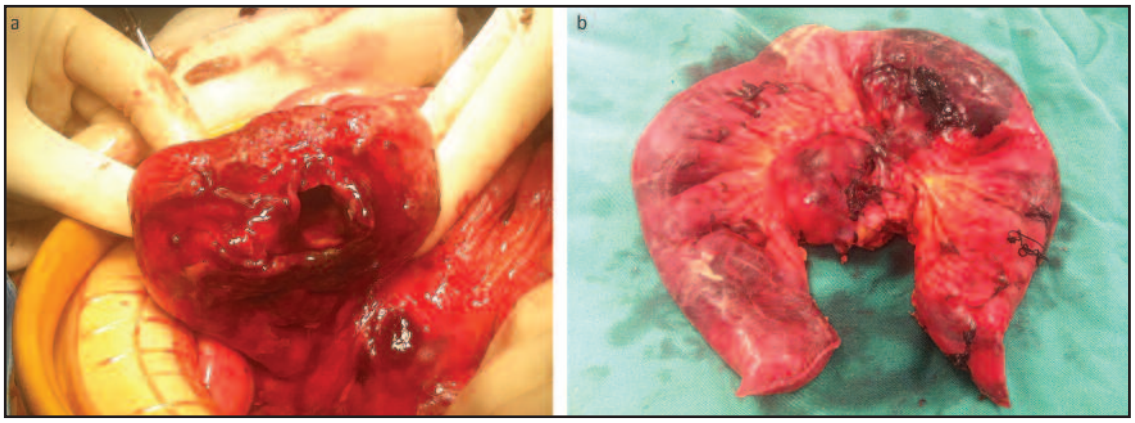

Fig. 1: (a) Emergency laparotomy showed a hard mesenteric mass and adjacent small bowel perforation (b) The resected small bowel with the adjacent mesenteric mass

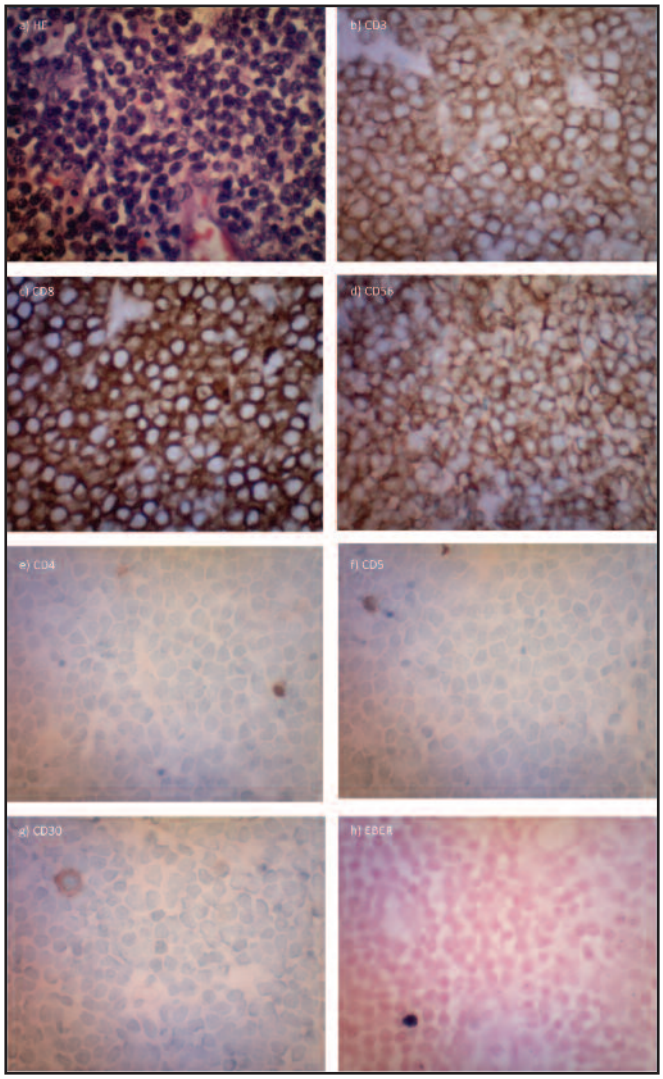

Fig. 2: Histopathological examination of the resected small bowel revealed a tumour composed of monotonous, small to intermediate-sized lymphoid cells which display round to slightly irregular nuclei with condensed chromatin and scanty cytoplasm (3a, HE stain). The tumour cells were strongly immune-reactive for CD3, CD8 and CD56, and negative for CD4, CD5, CD30 and EBV encoded RNA (EBER) (3b – 3h). All slides are 40x.

are extranodal NK/T-cell lymphoma and peripheral T-cell lymphoma. Extranodal NK/T-cell lymphoma consists of small, medium and large neoplastic cells with large area of necrosis and is negative for CD8. In situ hybridization for EBER demonstrates virtually all lymphoma cells in extranodal NK/T-cell lymphoma are labelled for EBV. On the other hand, peripheral T cell lymphoma more commonly has nodal than extra-nodal involvement, tends to involve the bone marrow, spleen, liver, lung and skin instead of the small intestine, and in most cases, the tumour cells are positive for CD4.

A standard treatment for patients with EATL, both type I and II, has not been established. [1] The role of surgery is limited to management of complications e.g. perforation, and debulking of masses posing high risk of obstruction. Combination chemotherapy used for other aggressive T-cell lymphomas are employed.[5] Unfortunately, patients are often malnourished and have poor performance status at the time of diagnosis, and may not be able to commence on or complete chemotherapy. Moreover, up to 80% of chemotherapy-responsive patient may relapse. Autologous bone marrow transplant has been suggested for those patients with good performance status and chemotherapy-sensitive disease, as it may be potentially curative.[5] That said, EATL is an aggressive lymphoma with poor overall prognosis with a median overall survival of seven months and progression-free survival of a month in one cohort.[3]

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