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Enteropathy-associated T-cell lymphoma (type II): a Brazilian case report

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ABSTRACT

Enteropathy-associated T-cell Lymphoma (EATL) is a rare form of aggressive T-cell lymphoma. It is more prevalent in men over 60 years and the prognosis is very poor. EATL is classified into two groups based on morphology, immunohistochemistry, and genetic profile. EATL type I is highly associated with celiac disease and is more common in Western countries. EATL type II predominates over type I in Asia, where celiac disease is uncommon. We report a case of a 78-year-old previously healthy white male who presented with a 2-month history of diarrhea, weight loss and edema. The abdomen was distended and painful, and a tumor mass was palpable in the hypogastrium. Laboratory tests showed hypoalbuminemia. Serological tests for HIV, viral hepatitis and HTLV-1 were negative. The chest radiography showed pneumoperitoneum, and an exploratory laparotomy revealed perforation of the small bowel. An advanced stage (Ann Arbor IV B/Lugano IIE2B) EATL type II was diagnosed. Four cycles of chemotherapy were interspersed with several complications (anthracycline-induced cardiotoxicity, chemotherapy-induced neutropenic fever and severe sepsis). Performance status progressively worsened and he died 6 months after the diagnosis. This is an illustrative report of a rare and aggressive primary intestinal lymphoma. To the best of our knowledge, this is the first report of EATL type II in Brazil.

Keywords: Enteropathy-Associated T-Cell Lymphoma; Celiac Disease; Lymphoma, Non-Hodgkin; Intestinal Perforation; Lymphoma, T-Cell.

CASE REPORT

A 78-year-old previously healthy white male patient sought medical care with a 2-month history of diarrhea accompanied by 20 kg of weight loss. He denied fever or night sweats. One month

prior the hospital admission a slight lower-limb edema started, which progressively worsened reaching the thighs. An erythematic eruption also appeared on the anterior surface of both legs. On

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the day of hospital admission he referred an intense and diffuse abdominal pain radiating to the back.

The physical examination revealed an ill-looking, pale, and dehydrated patient. The pulse rate was 120 beats per minute and blood pressure was 90/50 mmHg. The lower limbs were edematous, with bullous lesions over an erythematous skin (consistent with erysipela) on the anterior surface of both legs. The heart and lungs examination was unremarkable. The abdomen was distended, painful, and a tumor mass was palpable in the hypogastrium. Bowel sounds were absent and the rebound tenderness (Bloomberg sign) was positive.

Laboratory tests are shown in Table 1. Serological tests for HIV, hepatitis (B and C) and HTLV-1 were negative.

The chest radiography showed the image of pneumoperitoneum. The patient underwent an exploratory laparotomy, which revealed a large amount of enteric fluid in the abdominal cavity and perforation of the small intestine at 15 cm and 220 cm from the Treitz angle. The two perforated segments were resected. The post-operative follow up was marked by generalized edema and hypoalbuminemia.

Gross examination of enterectomy specimens revealed two segments of jejunum (42 cm length each). Each segment presented a

5.5 cm ulcerated, infiltrated, whitish and soft tumor (Figure 1). Tumor perforation was detected in one segment as well as suppurative serositis. Whitish and soft enlarged lymph nodes (up to 3.0 cm) adhered to the segment. Surrounding mucosa and bowel wall were somewhat thickened and rubbery.

On microscopic examination, tumor masses invaded through the wall of the intestine (Figure 2A) and were composed by cells with medium-sized round or irregular, darkly staining nuclei with a rim of pale or eosinophilic cytoplasm (Figure 2B). Frequent mitotic figures and some enlarged nucleoli were seen. Intestinal crypts and surface epithelium were diffusely infiltrated by malignant cells. Villous atrophy and crypt hyperplasia were also present (Figure 2C and 2D). Two adjacent lymph nodes were invaded by tumor cells. No other foci of infiltration were detected.

On immunohistochemistry analysis, neoplastic cells were CD3+, CD8+ and CD56+, which was consistent with a natural killer like (NK-like) T cell or even NK phenotype (Figure 3A and C). Immunostaining for CD20, CD30, ALK, CD4 and CD5 were all negative. Proliferation index by Ki67 was 60-70%. Pancytokeratin immunostaining with AE1+AE3 highlighted villous atrophy and intraepithelial infiltration by both individual and clusters of tumor cells (Figure 3D). These findings were consistent with enteropathy-associated T-cell lymphoma type II (EATL type II).

Table 1 – Laboratory work up

Exam	Result	RV	Exam	Result	RV
Hemoglobin	13.2	12.3-15.3 g/dL	Creatinine	1.4	0.4-1.3 mg/dL
Hematocrit	40	36.0-45.0%	Urea	57	10-50 mg/dL
Leukocytes	9.1	4.4-11.3×10 ³ /mm ³	Ionized Ca ⁺	1.07	1.15-1.35 Mmol/L
Promyelocytes	1	0	Sodium	138	136-146 mEq/L
Myelocytes	3	0	Potassium	5.3	3.5-5.0 mEq/L
Metamyelocytes	5	0	AST	20	10-31 IU/L
Bands	25	1-5%	ALT	21	9-36 IU/L
Segmented	50	46-75%	Alkaline phosphatase	83	10-100 IU/L
Eosinophils	0	1-4%	γGT	46	2-30 IU/L
Basophils	0	0-2.5%	Total bilirubin	0.7	0.3-1.2 mg/dL
Lymphocytes	15	18-40%	Total protein	3.7	6.0-8.0 g/dL
Monocytes	1	2-9%	Albumin	1.0	3.0-5.0 g/dL
Platelets	509×10 ³	150-400×10 ³ /mm ³	LDH	168	120-246 IU/L

ALT = alanine aminotransferase, AST = aspartate aminotransferase, γGT = gamma-glutamyl transferase, LDH = serum lactate dehydrogenase, RV = reference value.

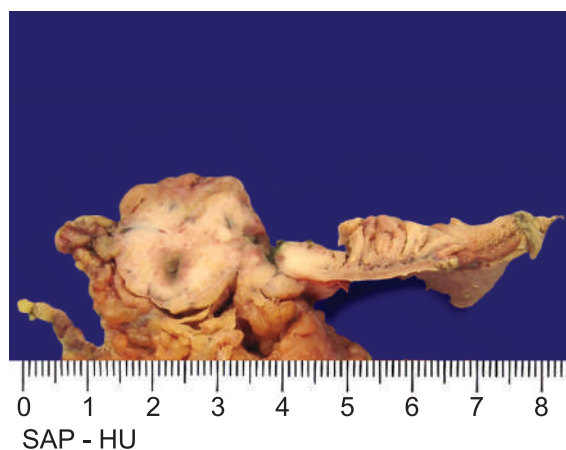


Figure 1 – View of a section through small bowel EATL type II.

Post-operative abdominal computed tomography (CT) revealed the presence of confluent lymph nodes, near the superior mesenteric vascular bundle, measuring up to 2.5 cm with homogeneous enhancement by the contrast medium. Neck and chest CT did not detect lymphadenopathy.

The patient developed nosocomial pneumonia, which delayed the start of the specific treatment. After clinical improvement he was referred to an oncology center. Bone marrow biopsy revealed no lymphoma infiltration. Disease was staged Ann Arbor IV B/Lugano IIE2B. Treatment started with CHOP chemotherapy and was changed to COP scheme after 2 cycles. The patient developed anthracycline-induced cardiotoxicity, chemotherapy-induced neutropenic fever and severe sepsis. Performance status progressively worsened and he died 6 months after the diagnosis. Postmortem examination was not requested.

DISCUSSION

The gastrointestinal tract is the most common location of extranodal lymphomas. The stomach is the most frequent site of involvement (mainly due to *Helicobacter pylori* associated mucosal associated lymphoid tissue - MALT – lymphoma), followed by the small intestine.^{1,2} Primary large bowel and rectum lymphomas are much less common.³

Most gastrointestinal primary lymphomas are of B phenotype (MALT lymphoma, large B cell lymphoma, mantle cell lymphoma, follicular

lymphoma, Burkitt lymphoma and immunoproliferative small intestinal disease- IPSID).⁴

Primary gastrointestinal tract T-cell lymphomas are mostly associated with malabsorption, as a complication of celiac sprue. These cases have been designated as “enteropathy-associated T-cell lymphoma” (EATL) and they are characterized by prominent intraepithelial lymphomatous spread and villous atrophy of uninvolved mucosa. T cells show varying degrees of transformation, frequently with an inflammatory background.^{5,6,7}

EATL is considered a rare form of aggressive T-cell lymphoma accounting for less than 1% of non-Hodgkin lymphomas. The estimated annual incidence rate is 0.5-1 per million people in Western countries. It is more prevalent in men over 60 years.^{8,9} The outcome is very poor with an overall survival rate of 15-20% in 2-year.¹⁰

Based on morphology, immunohistochemistry and genetic profile EATL can be divided into two groups. EATL type I is a large-size cell lymphoma which is highly associated with celiac disease and mostly, presents with malabsorption, weight loss and celiac disease-related symptoms. Geographic distribution follows that of celiac disease, with a high prevalence in Northern Europe. Most patients show adult onset celiac disease, sometimes with an initial period of refractory disease and ulcerative jejunitis. Tumor cells are typically CD3+, CD5–, CD7+, CD8+/, CD4–, CD30+ and contain cytotoxic granule associated proteins by immunohistochemistry.^{7,11}

EATL type II comprises about 10-20% of EATL and is composed of monomorphic, small to medium-sized cells. Obstruction or perforation of the small bowel is common. EATL type II is not associated with celiac disease and may occur sporadically. The immunophenotype is somewhat different from EATL type I (CD3+, CD4–, CD8+, CD56+).^{5,12,13} Prognosis of EATL type II seems to be even worse, with median overall survival of 7 months and progression-free-survival of 1 month.¹⁴

Other T-cell lymphomas may also develop in the intestine and sometimes simulate the histologic pattern of EATL.¹⁵ T-cell lymphomas can involve any part of the gastrointestinal tract, especially in patients in the Far East, where most cases are peripheral T-cell lymphomas, not otherwise specified (NOS),

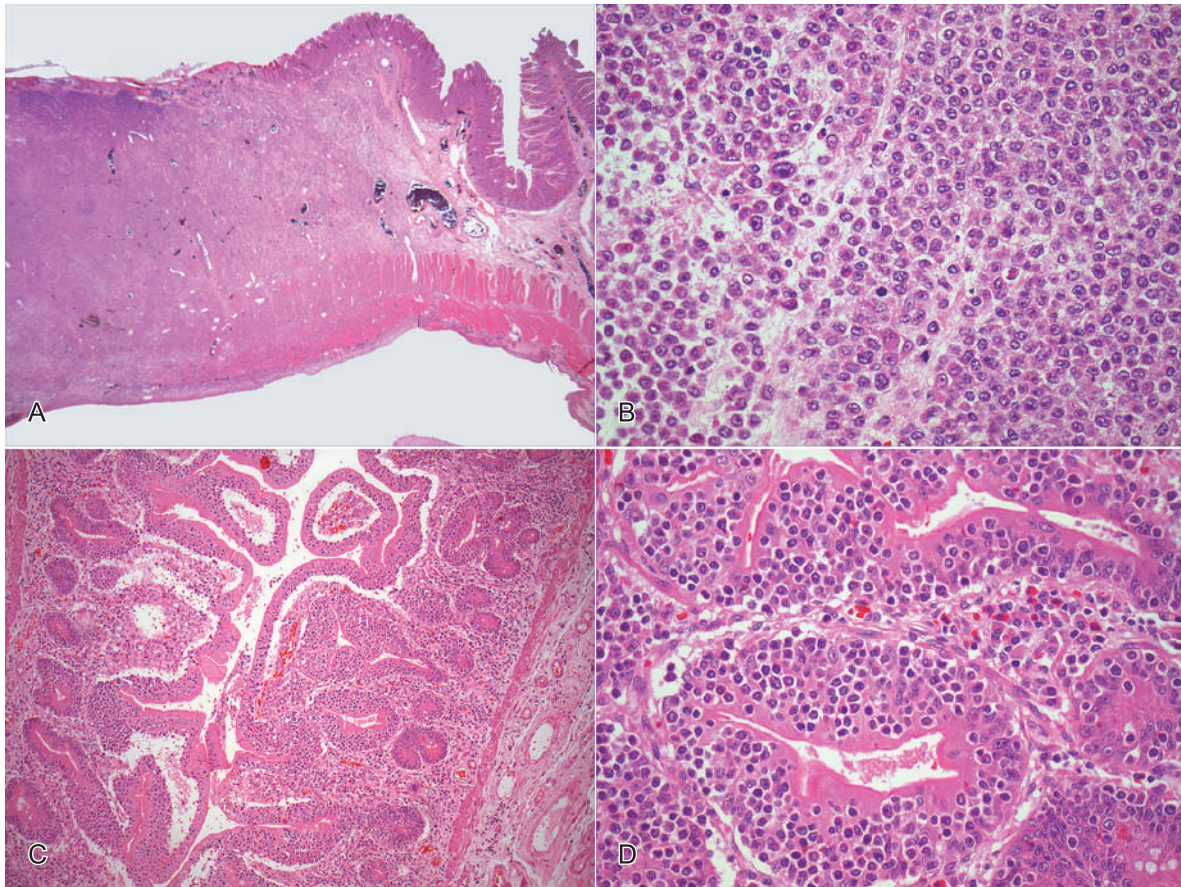


Figure 2 – Photomicrography – small bowel surgical pathology specimen. **A** - (H&E, 12.5x) Tumor cells invade through the entire bowel wall. Serosal exudate secondary to perforation can be seen at the bottom; **B** - (H&E, 400x) Lymphoma cells with medium-sized round or irregular, darkly staining nuclei with a rim of pale or eosinophilic cytoplasm; **C** - (H&E, 100x) Villous atrophy and crypt hyperplasia; **D** - (H&E, 400x) Marked intraepithelial infiltration by lymphoma cells.

NK/T-cell lymphomas of nasal type, and cases linked with the HTLV-1 virus.¹⁶⁻²¹

NK-cell enteropathy has recently been described as an entity that mimics EATL, especially the type II. In the case series reported by Mansoor et al., 8 patients presented with vague gastrointestinal symptoms and a mucosal infiltrate of atypical cells with an NK-cell phenotype. No patient developed progressive disease or died of lymphoma. In contrast with EATL type II, NK-cell enteropathy cells are CD8- and do not show marked epitheliotropism. Furthermore, clonal T-cell gene rearrangement is absent in NK-cell enteropathy.²²

Differential diagnosis could also include IPSID, which is an uncommon type of gastrointestinal B cell lymphoma that tends to manifest as malabsorption, presents in the duodenum or proximal jejunum, and exhibits villous atrophy as well as plasma cell infiltration of the adjacent intestine.²³ Formerly

known as Mediterranean lymphoma or α heavy chain disease, it mainly occurs in the Middle East and arises in association with a morphologically benign-appearing infiltrate, often characterized by a dense, plasma cell proliferation in the intestinal mucosa.²⁴

This patient did not have a history of celiac disease. Actually, this was a quite recent onset with a clinical history of 2 months, which is consistent with EATL type II. Despite that, the patient presented with severe diarrhea and malabsorption, hypoalbuminemia and peripheral edema. In a recent large multicenter analysis of 38 patients with EATL type II, diarrhea and hypoalbuminemia were present in 21% and 90% of the cases, respectively.¹⁴

In summary, this is an illustrative report of a rare and aggressive primary intestinal lymphoma. To the best of our knowledge, this is the first report of EATL type II in Brazil.

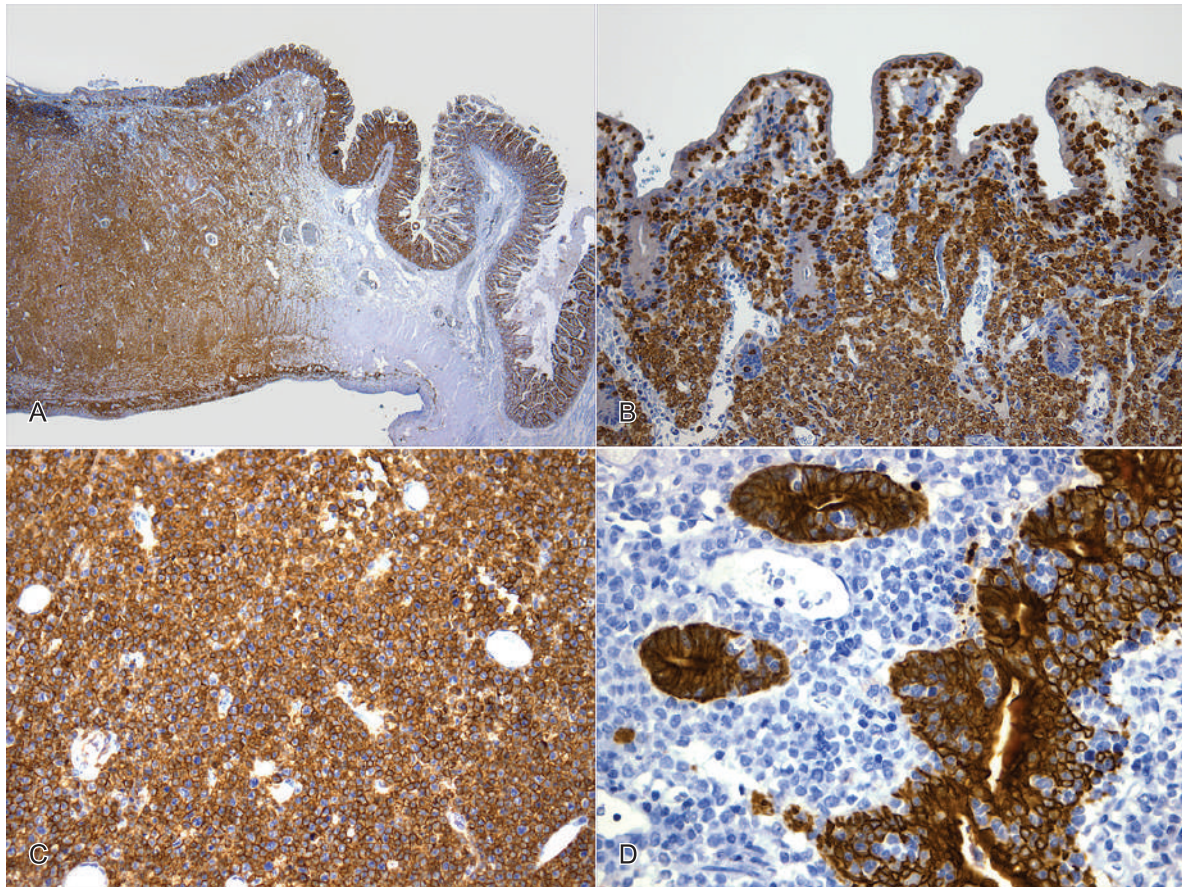


Figure 3 – Photomicrography – Immunohistochemistry. **A** - (CD3, 12.5x) CD3+ T-cells invade through the entire bowel wall; **B** - (CD3, 200x) Striking intraepithelial infiltration by CD3+ lymphoma cells; **C** - (CD56, 200x) CD56+ cells featuring EATL type II; **D** - (AE1+AE3, 400x) Pan-cytokeratin stains intestinal epithelium, highlighting clusters of intraepithelial lymphoid cells.

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