

Indolent T-cell lymphoproliferative disease with synchronous diffuse large B-cell lymphoma

A case report

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Abstract

Rationale: Indolent T-cell lymphoproliferative disease (T-LPD) of gastrointestinal tract is a rare recently described disease that seldom progresses. We report a case of T-LPD with synchronous diffuse large B-cell lymphoma (DLBCL) that cause aggravation of disease.

Patient concerns: A 46-year-old Chinese male presented with intermittent paraumbilical colic pain, bloating, and occasional diarrhea for 10 years. His condition aggravated with partial bowel obstruction recently. The patient was diagnosed as T-LPD initially based on histological result and T-cell receptor-gamma clonal gene rearrangement test. The patient was followed without chemotherapy. His condition stabilized for 1 year and then deteriorated with small intestine perforation.

Diagnosis: The patient was diagnosed as indolent T-LPD and DLBCL finally.

Interventions: The patient had surgery for intestine perforation and received chemotherapy for DLBCL and T-LPD afterward.

Outcomes: At 6 months follow-up, the patient continued to have resolution of his symptoms.

Lessons: Early detection of high-grade transformation of T-LPD or the coexistence of aggressive lymphoma is essential for the patient. DLBCL may coexist in the indolent course of T-LPD. The diagnosis of T-LPD should be made cautiously in case with progressing symptoms such as intestinal obstruction.

Abbreviations: ANA = antinuclear antibodies, ANCA = antineutrophil cytoplasmic antibodies, CMV = cytomegalovirus, CTE = computed tomography enterography, DLBCL = diffuse large B-cell lymphoma, EATL = enteropathy associated T-cell lymphoma, EBV = Epstein Barr virus, HIV = human immunodeficiency virus, IBD = inflammatory bowel disease, PTCL = peripheral T cell lymphoma, TCR- γ = T-cell receptor-gamma, T-LPD = indolent T-cell lymphoproliferative disease.

Keywords: diffuse large B-cell lymphoma, indolent T-cell lymphoproliferative disease, intestinal obstruction, intestine perforation

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Find the patient and get the idea: ZW, YW.

Collect the information of the patient: LJG, ZW, YW.

Diagnosis and treatment for the patient: ZW, YW.

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1. Introduction

Indolent T-cell lymphoproliferative disease (T-LPD) of gastrointestinal tract is a rare recently described disease. It was first proposed by Perry et al^[1] who reported a series of 10 cases in 2013. The 2016 revision of the World Health Organization classification of lymphoid neoplasms added it as a new indolent provisional entity to emphasize the indolent clinical course and differentiation from the aggressive T-cell lymphomas.^[2] Indolent T-LPD usually has a favorable clinical course. In our knowledge, no report of indolent T-LPD with synchronous DLBCL has been reported before. Hereby, our case may help better understand the pathogenesis of T-LPD.

2. Case presentation

A 46-year-old Chinese male presented with intermittent paraumbilical colic pain, bloating, and occasional diarrhea for 10 years. He did not have fever or hematochezia. The findings of gastroscopy, colonoscopy, abdominal ultrasound, and CT scan were normal. One year ago, the symptoms recurred and the patient underwent capsule endoscopy at local hospital. However, the patient's condition aggravated gradually and was diagnosed as partial small bowel obstruction 2 weeks after the capsule endoscopy examination. His symptoms improved after fasting and nasogastric decompression. He was transferred to our hospital after 2 months of capsule retention. Physical examination only revealed slight epigastric tenderness and no hepatosplenomegaly

was detected. Complete blood cell, hepatic, and renal function was unremarkable. Erythrocyte sedimentation rate was 62 mm/h. CRP was 4.6 mg/L. Serum albumin level was 26.9 g/L. Interferon-gamma release assay for tuberculosis was positive. Serological tests were negative for Epstein Barr virus (EBV), cytomegalovirus (CMV), and human immunodeficiency virus (HIV). Antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA) were negative. Single-balloon enteroscopy by oral route revealed diffuse small nodular hyperplasia, irregular ulcers, and intestinal stricture about 150 cm distal to pylorus (Fig. 1A, B). The endoscopy could not pass through the stenosis in jejunum. Enteroscopy by anal route found redness and granulate mucosa in ileum (Fig. 1C, D). Capsule was retrieved in the process (Fig. 1E). Computed tomography enterography (CTE) showed thickness of small bowel wall and stricture of jejunum in the left upper quadrant with no sign of lymph node enlargement (Fig. 1F).

Jejunum biopsy showed dense diffuse small lymphoid cells infiltration in mucosa (Fig. 2A, B). Atypical lymphocytes were CD8-positive and CD4-partial positive (Fig. 2C, D). This case was positive for CD2, CD3, CD5, and CD7 (Fig. 3A–D). The cells were negative for CD20, CD56, Granzyme B, or TdT (Fig. 3E–H). EBV encoded RNA-in situ hybridization showed no evidence of EBV infection (Fig. 3I). The Ki-67 proliferative index was about 3% (Fig. 3J). T-cell receptor-gamma (TCR- γ) clonal gene rearrangement was detected (Fig. 3K). Bone marrow biopsy revealed no monoclonal hyperplasia. He was diagnosed as indolent T-LPD initially.

After careful consideration, the patient demanded to be followed without chemotherapy. Partial enteral nutrition was given. His condition stabilized for 1 year with no abdominal pain, almost normal stool, and weight gain. However, the second single-balloon enteroscopy examination during this period did

not show any improvement. Endoscopic appearance and biopsy results were similar. One month after the enteroscopy, the patient had sudden abdominal pain and bowel perforation was found at the jejunum about 80 cm distal to Treize ligament during surgery. Postoperative pathological examination showed DLBCL in the center of the sample with indolent T-LPD on the margin. Immunohistochemistry of T-LPD part showed CD2(+), CD3(+), CD4(-), CD8(+), CD5(+), CD20(-), CD43(+), CD56(-), GB(-), TIA(partial +), Ki67/MIB-1(+, 5%), and TCR γ clonal gene rearrangement was detected. On histology, the DLBCL part was shown (Fig. 4A). Immunohistochemistry was positive for CD20 and negative for CD3 (Fig. 4B, C). The Ki-67 proliferative index was about 90% (Fig. 4D).

Now the patient has received 8 circles of CHOP chemotherapy and 3 times of Rituximab. His condition remains stable and the PET-CT afterward shows no sign of metastasis at 6 months follow-up.

3. Discussion

The GI tract is the most commonly involved extranodal site of Non-Hodgkin lymphoma. Most lymphomas in GI tract are originated from B-cell line, and only up to 15% are from T cells. The most common type of primary T-cell lymphomas in GI tract is enteropathy associated T-cell Lymphoma (EATL).^[2] However, the recently described new entity of indolent T-LPD of GI tract is different. It usually has an indolent clinical course and a long survival.

Previous reports have provided insight into the features of indolent T-LPD of the GI tract.^[1,3] The majority of patients were young to middle-aged, predominantly males. The most common symptoms are diarrhea, abdominal pain, and weight loss. Any

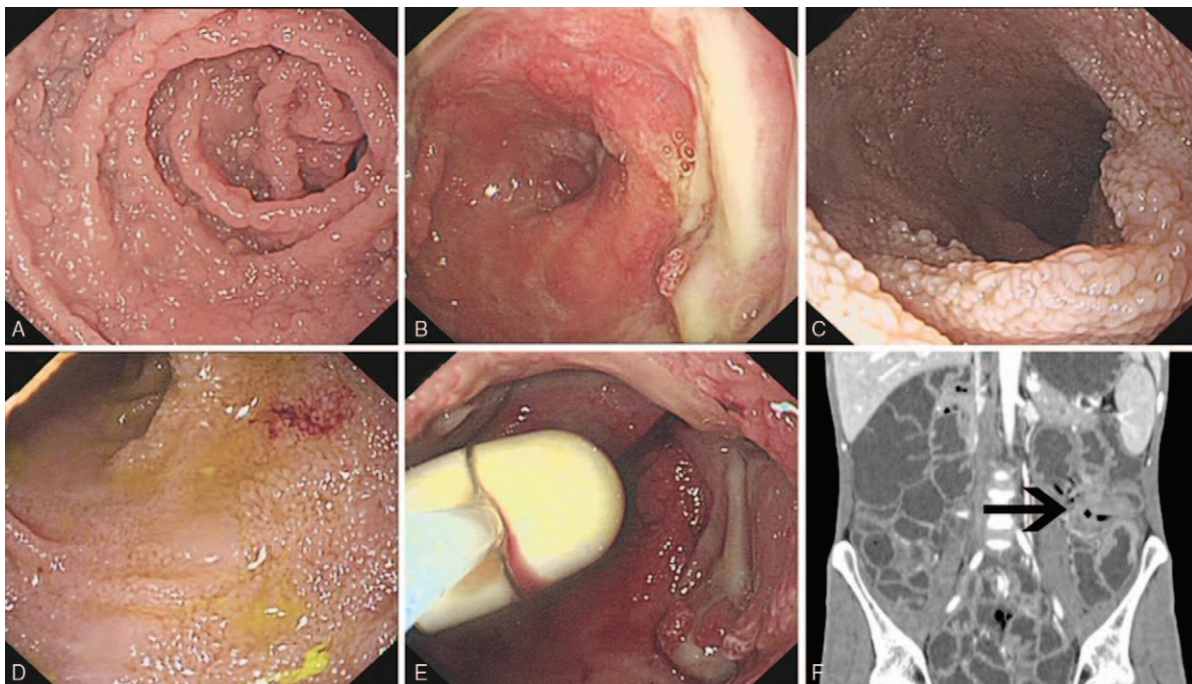


Figure 1. Single-balloon enteroscopy revealed diffuse small nodular hyperplasia (A), irregular ulcers and intestinal stricture (B) in jejunum, granulate mucosa (C) and redness (D) in ileum. Capsule was retrieved in the process (E). Computed tomography enterography (CTE) showed thickness of small bowel wall and stricture of jejunum in the left upper quadrant (F).

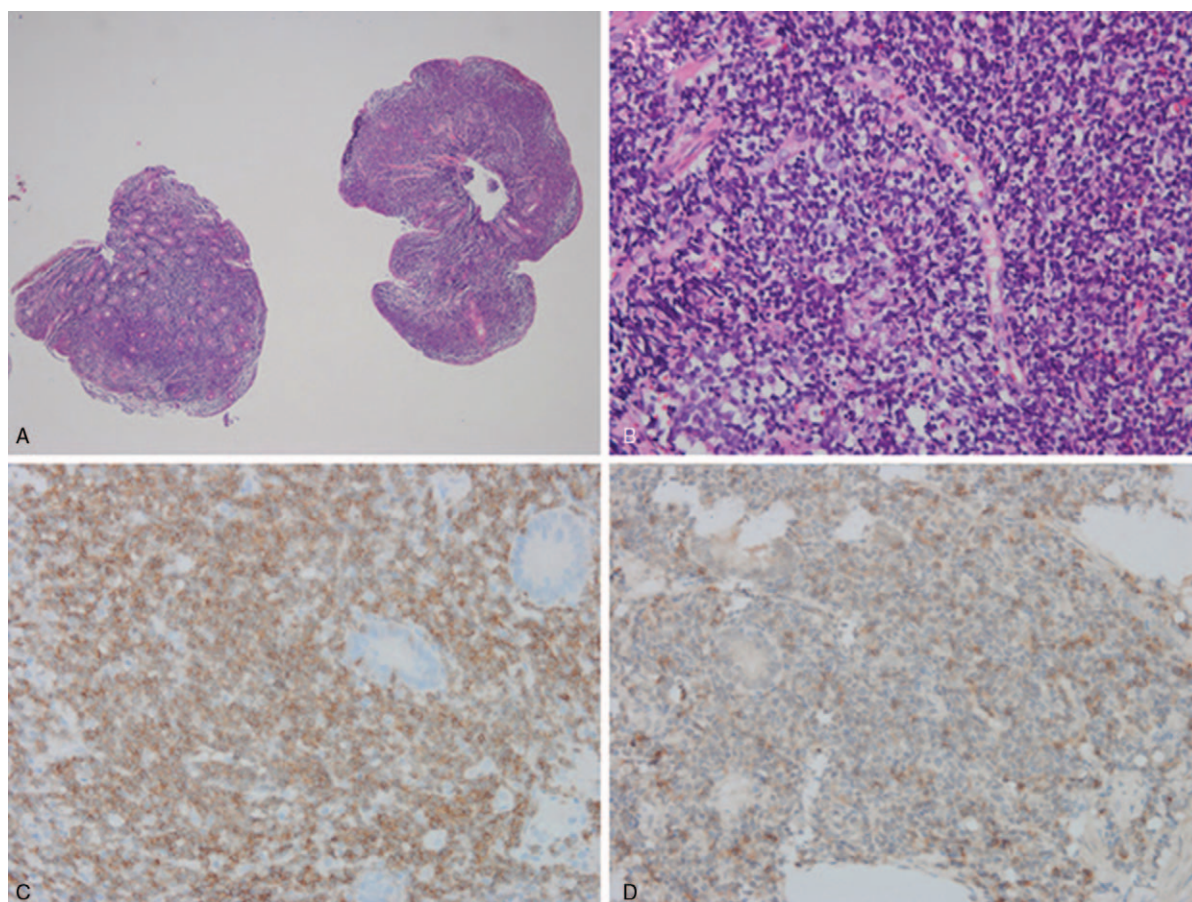


Figure 2. Jejunum biopsy showed dense diffuse small lymphoid cells infiltration in mucosa. A and B, Atypical lymphocytes were CD8-positive (C) and CD4-partial positive (D).

part of the GI tract can be involved, while small bowel was the most common site. Endoscopic finding included numerous small polyps, diffuse nodules, erythema, erosions, and shallow mucosal ulcers. Lesions can be continuous or multifocal. Lesions can be confluent in some cases mimicking endoscopic appearance of inflammatory bowel disease (IBD). Histological features include predominantly infiltration of small, monotonous T lymphoid cells with scant cytoplasm in mucosa/lamina propria. Sometimes the infiltration extends into the submucosa, but does not usually involve the full thickness of the bowel and does not form tumor masses. The immunophenotype is variable. It can be CD8-positive/CD4-negative, CD4-positive/CD8-negative, or the other double negative for CD4 and CD8. Most reports show these indolent proliferations are commonly CD8-positive. TCR- γ clonal gene rearrangement invariably shows clonal rearrangement.^[1]

The patient in our case was diagnosed as indolent T-LPD at first, however, indolent T-LPD usually only involves the mucosa and submucosa layer, it is unlikely to cause stricture and perforation later. DLBCL in our case was found 16 months after the diagnosis of indolent T-LPD. This unique situation raises several interesting questions. Was DLBCL transformed from indolent T-LPD? Or was DLBCL coexisted with T-LPD at the very beginning?

The etiology of indolent T-LPD of the GI tract still remains unclear. Margolske et al^[3] reported aberrations were found in

2 indolent T-LPD patients (8q gain in one and monosomy X in another). The meaning of this aberration is not clear now. Immune or inflammatory processes probably play a role in disease pathogenesis. Gattazzo et al^[4] verified that persistent antigenic stimuli possibly resulted in an ultimate clonal T-cell selection. Some reported cases occurred in patients with Crohn disease after following TNF- α inhibitor therapy (Adalimumab and Certolizumab).^[5] A hypothesis has been proposed that an inflammation-related TNF- α / TNFR1/TNFR2-pathway may be involved in the pathogenesis of this disease entity. TNF-receptor 2 (TNFR2) has been shown susceptibility to IBD by controlling expression of genes that regulate CD8 T-cells.^[6] Edison reported the link between the inflammatory process and the CD8-positive T-cells infiltrates. The CD8 T-cells in the lamina propria play an important role against inflammation.^[7] Persistent or repeated inflammation may stimulate unrestricted proliferation of intra-mucosal CD8 T-cells in the patients with disturbance of TNFR2 signaling and then indolent T-LPD may be triggered.^[8]

Transformation from T-cell lineage lymphoproliferative disorders to DLBCL has not been reported before. Since DLBCL and T-LPD are originated from B and T cells respectively, it is unlikely that DLBCL is transformed from T-LPD. Indolent T-LPD with synchronous DLBCL is more convincing. Persistent inflammatory stimuli might trigger both B cells and T cells proliferation at the same time.

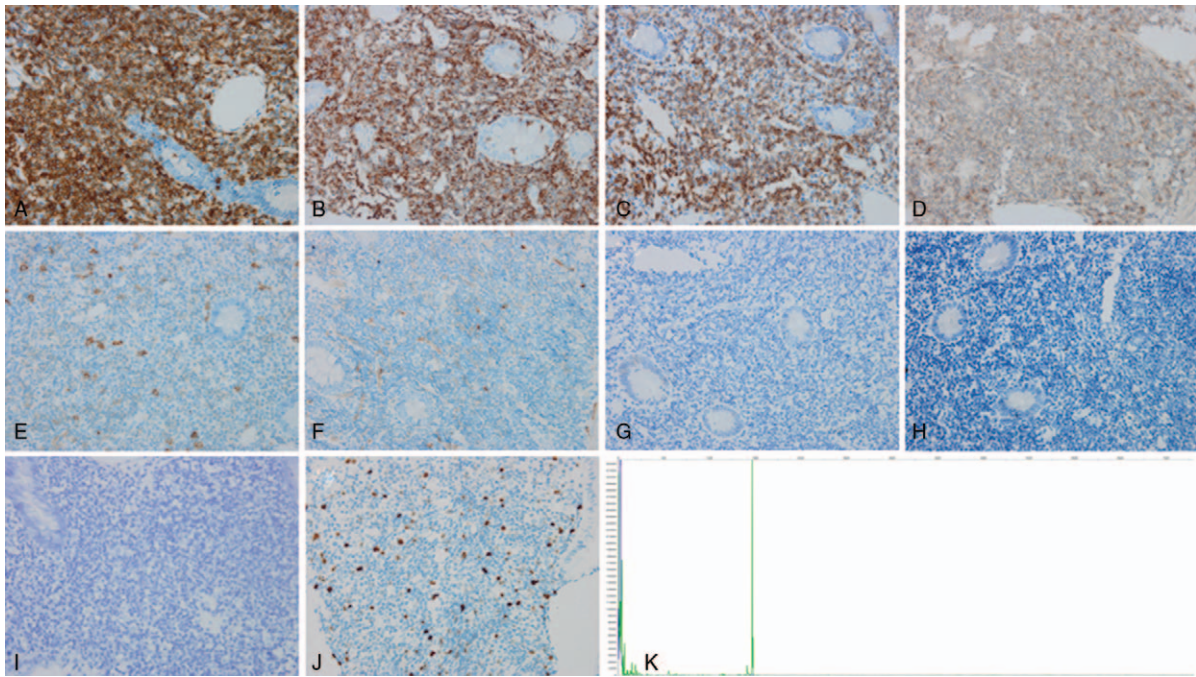


Figure 3. Immunohistochemistry showed positive for CD2 (A), CD3 (B), CD5 (C), CD7 (D), and negative for CD20 (E), CD56 (F), Granzyme B (G), and TdT (H). EBV encoded RNA-in situ hybridization showed no evidence of EBV infection (I). The Ki-67 proliferative index was about 3% (J). T-cell receptor-gamma (TCR- γ) clonal gene rearrangement was detected (K).

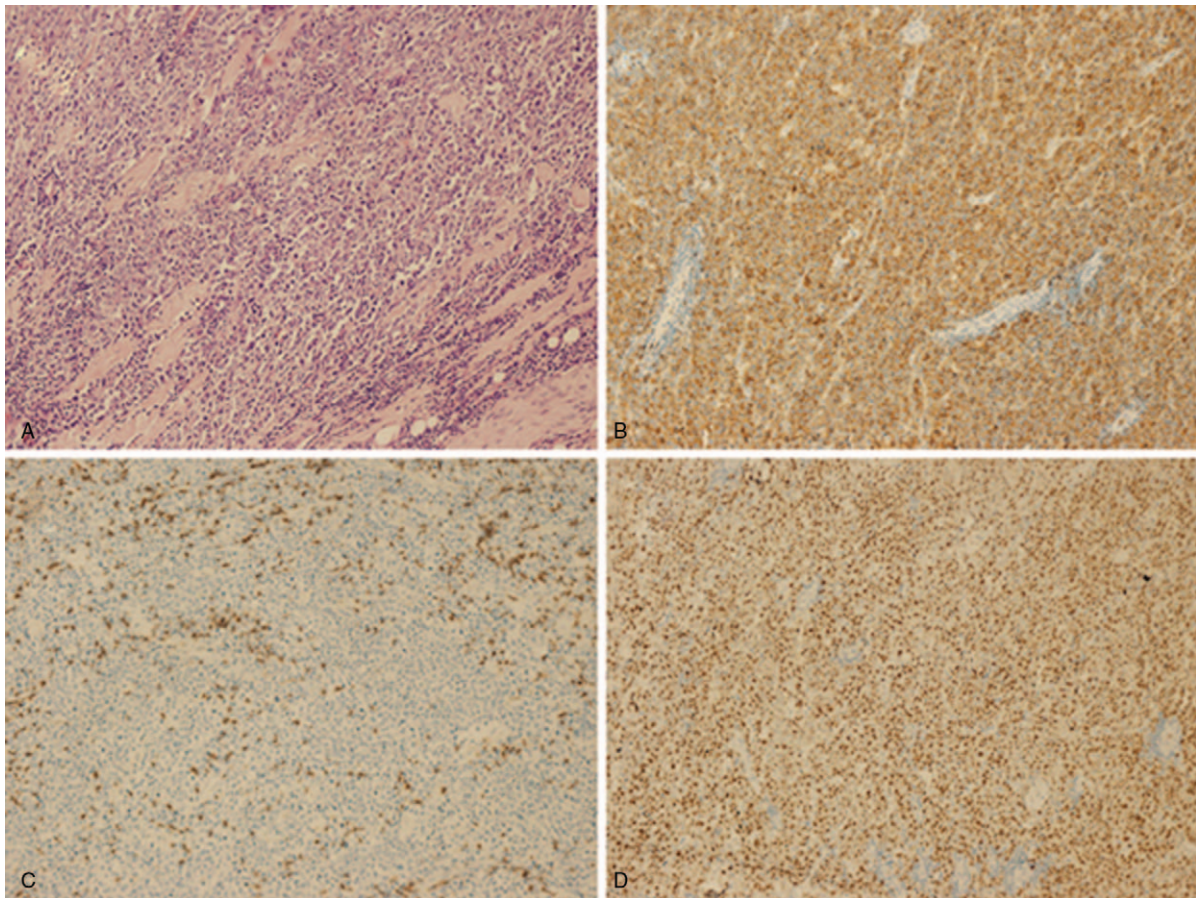


Figure 4. Histopathological examination showed the DLBCL part (A). Immunohistochemistry was positive for CD20 (B) and negative for CD3(C). The Ki-67 proliferative index was about 90% (D).

The clinical outcome for T-LPD is usually benign and does not require aggressive treatment. Careful clinical follow-up with minimal therapy might be sufficient. T-LPD patients who underwent chemotherapy were reported to have little or no response.^[1] DLBCL, on the other hand, is very aggressive and has poor prognosis.^[2] There is no standard treatment for patients with both T-LPD and DLBCL. We mainly adopted the treatment of DLBCL with CHOP chemotherapy and Rituximab for this case.^[9] The patient's condition was stable at 6 months follow-up.

Cautious differentiation should be made in the diagnosis of indolent T-LPD.^[3,10] Since in contrast to aggressive lymphoma, the optimal treatment for indolent T-LPD may only require careful follow-up plus low-dose chemotherapy.^[2,11] Early detection of high-grade transformation of T-LPD or the coexistence of aggressive lymphoma may change the treatment regimen and provide better prognosis for the patient.

Author contributions

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Writing – review & editing: linjie guo, Zhonghui Wen, Xueying Su, Shuyuan Xiao, Yufang Wang.

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