CD8-positive Indolent T-Cell Lymphoproliferative Disorder of the Gastrointestinal Tract: Case Report and Literature Review.

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Case Report

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Abstract

Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract (ITLPD-GI), a primary tumor forming in the GI tract, represents a rarely diagnosed clonal T-cell disease with a protracted clinical course. This report presents a 45-year-old male patient with a 6-year history of anal fistula and a more than 10-year history of recurrent diarrhea, who was not rightly diagnosed until the occurrence of complications such as intestinal perforation. Postsurgical histopathological analysis confirmed the diagnosis of CD8+ ITLPD-GI, with a combination of hematoxylin-eosin staining (H&E) staining, immunohistochemistry (IHC) and TCR β/γ clonal gene rearrangement. Individuals with this scarce lymphoma frequently show non-specific symptoms, which are hardly recognized. So far, indolent CD8+ ITLPD-GI has not been comprehensively examined. The current mini-review focused on available reports evaluating indolent CD8+ ITLPD-GI cases, discussing future directions for improved differential diagnosis, genetic and epigenetic alterations, and therapeutic target identification.

Introduction

Indolent T-cell lymphoproliferative disease of the gastrointestinal tract (ITLPD-GI) represents a new entity included in the revised fourth World Health Organization (WHO) classification of lymphoid neoplasms.(1) ITLPD constitutes a low-grade, clonal, non-epitheliotropic T-cell lymphoproliferative disease, consisting of small lymphocytes, which likely emerges from lamina propria lymphocytes and could possibly involve any part of the gut, most frequently the small and large intestines, with fewer cases showing gastric, oesophageal or oral involvement.(2) The disease typically affects adults (median age of 51 years) with a male predilection; however, the etiology and molecular pathogenesis of ITLPD remain unknown.(3)

This report described a rare case of ITLPD-GI with abnormal CD8 expression, who eventually developed into a progressive failure process without overt histologic transformation, and summarized the clinical, pathological and imaging findings alongside a comprehensive literature review to ameliorate awareness of this disorder among health professionals. The patient's informed consent was obtained to report this case.

Case Presentation

A male patient (45 years old) with a history of anal fistula for 4 years and no other remarkable medical/surgical history, presented to our hospital for evaluation because of chronic recurrent diarrhea. The onset of symptoms occurred more than ten years prior to his admission to our hospital. The patient presented with a 6-year history of inflammatory bowel disease (IBD), diagnosed as Crohn's Disease (CD) after several relapses. He was first administered 5-aminosalicylic acid, hormone therapy and azathioprine. Systemic edema appeared during the treatment. Due to poor response to treatment, infliximab was administered twice prior to 2 years ago. He came to our hospital for diarrhea aggravation.

At admission, he had a temperature of 36.6°C, a pulse of 77 beats/min, a blood pressure of 81/46 mmHg and 98% oxygen saturation on room air. Physical exam was normal with the exception of minor edemas on both lower extremities. Laboratory analysis of complete blood count (CBC) showed low hemoglobin at 78 g/L (reference range, 130–175 g/L), whereas leukocyte and platelet counts were unaltered. C-reactive protein (CRP) amounts were 25.4 mg/L (reference range, 0.00–8.00 mg/L). Serum biochemistry showed decreased levels of total protein (57.4 g/L; reference range, 65–85 g/L) and albumin (17.5 g/L; reference range, 40–55 g/L) (Table

1). Fecal calprotectin ($> 1662 \mu\text{g/g}$; reference range, 0–200 g/L), and anti-A2121SCA, anti-AYCA, anti-htTG and anti-gliadin antibodies were positive. EB virus DNA levels were 5.81E^4 (reference range, 0– 5E^3 copies/ml). Allergen detection found that wheat, barley, corn, soybean, peanut and others had levels greater than 400 U/ml. Other blood tests, including carbohydrate antigen, carcinoembryonic antigen and alpha-fetoprotein assessments, were performed. The T-cell spot assay and PPD test for *Mycobacterium tuberculosis* detection were negative. Microbiological stool examination and culture were essentially normal.

MRI of the small intestine showed small intestine thickening in groups 3–6, whole colon and part of the rectum with abnormal enhancement, and enlarged regional lymph nodes at the mesenteries (Fig. 1A). Retroperitoneal B-ultrasound showed multiple enlarged mesenteric lymph nodes, the largest of which was about 3.18×1.3 cm in size (Fig. 1B). The mesenteric lymph nodes were biopsied using an autops biopsy gun under B-ultrasound guidance for further diagnosis with patient consent. Pathological results of lymph node biopsy showed lymphoid tissue hyperplasia with lymphoid sinus dilatation (Fig. 1C). Immunohistochemical staining revealed CD3, CD5, CD20, CD23, CD35, CD43, CD138, CD163, Ki-67 (15%) and Bcl-2 positivity, and CD10, Bcl-6, CyclinD1 and CMV negativity. The analysis of bone marrow aspirates showed obvious hyperplasia of granulocytes and megakaryocytes.

Colonoscopy revealed prominent congestion as well as edema and multiple ulcers involving the entire ileum and colon; two large ulcers were found in the distal ileum and sigmoid colon (Figure. 2A). Pathological analysis of colon specimens demonstrated chronic active inflammation, and immunohistochemical staining revealed CD3, CD20, CD68, Ki-67 and CKpan positivity, and CD21 and CD30 negativity. *In situ* hybridization detected no Epstein-Barr virus-encoded RNA (EBER). In addition, acid-fast staining was also negative (Figure. 2B). Gastroscopy showed chronic atrophic gastritis, and pathological analysis of gastric specimens demonstrated chronic active inflammation with erosion of the gastric antrum and Hp+ (Fig. 2C and 2D).

The patient felt better after 100 mg hydrocortisone was administered twice daily, with enteral and parenteral nutrition maintenance for 1 month. The patient began to develop hematochezia with a total of about 2000 ml; subsequently, interventional hemostasis was performed, and superior mesenteric arteriography showed rupture and hemorrhage of a straight arteriole distal to the ileocolic artery. Fortunately, a good therapeutic effect was obtained (Fig. 3A). After 14 days of observation, the patient developed peritonitis with a small intestinal perforation, and underwent emergency surgery (Fig. 3B). Pathological assessment of resected small bowel specimens revealed persistent small lymphoid infiltrates; immunohistochemical staining revealed CD3, CD5, CD7 and CD8 positivity, CD4, CD20 and CD56 negativity, and less than 10% of infiltrating cells expressed Ki-67 (Fig. 4); TCR β/γ clonal gene rearrangement was detected. *In situ* hybridization showed no EBER. After the diagnosis of CD8 + ITLPD was confirmed, the patient was administered hormone and parenteral nutrition support therapies. Unfortunately, he suffered repeated intestinal perforation and abdominal infection after the operation. The patient had to leave the hospital due to economic reasons. He was still alive 3 months ago, and has since been lost to follow-up.

Discussion

Cancers affecting the gut are common, mostly including adenocarcinomas, with lymphomas representing only 1–4% of all cases. Primary gut T-cell lymphomas (TLs) are aggressive and mainly comprise enteropathy-associated (EATL) and monomorphic epitheliotropic intestinal (MEITL) T-cell lymphomas.(4) Recently, growing

attention has been paid to ITLPD-GI, which represents a rare human primary gastrointestinal TL. ITLPD-GI tumors derive from CD8+/CD4-, CD4+/CD8-, CD8+/CD4+ or CD8-/CD4- cells.(5) ITLPD-GI was firstly reported in 1994 by Carbonnel and colleagues,(6) and subsequently described in small case series and single case reports for its diverse clinicopathological and molecular characteristics.(7–24)

Tsutsumi et al.(8) firstly described a case of CD8 + ITLPDGI in 1996. Cases first show protein-losing enteropathy and malabsorption syndrome, without specific treatment. Subsequently, several studies have provided insights into the properties of CD8 + ITLPD-GI.(8, 11, 15, 19, 20, 23–32) So far, a literature review revealed 15 articles reporting CD8 + ITLPDGI in 29 patients, including 19 male and 10 female cases, averaging 42 years (range, 15–77 years) old. The degree of CD8 + ITLPD-GI involvement varies, but is frequently multifocal; it could affect almost all GI tract segments. In these 29 patients, the small intestine (62.1%), colon (48.3%), stomach (20.7%), oral cavity (13.8%) and esophagus (13.8%) were mostly involved; only five cases have been reported outside the gastrointestinal tract, including two, two and one that involved the bone marrow,(15, 30) lymph nodes,(29, 32) and the uterus.(23) The most common clinical symptoms are chronic abdominal pain (37.9%), diarrhea (48.3%) and weight loss (20.7%). Endoscopic findings described the lesions as thickened intestinal folds, “irregular” or multiple small polyps, according to various reports. Histological examination of biopsies indicated that the lamina propria was nondestructively expanded by an important infiltration of small lymphocytes containing nuclei with slightly irregular shape. Immunophenotyping or IHC showed the lymphocytes always expressed CD8. CD2 and CD7 expression was observed in 17 patients analyzed, and CD5 in 25 cases. TCRαβ (βF1) was detected in 21 patients. The cytotoxic marker TIA1 was expressed by 79.3% (23/29) of ITLPDs but only 13.8% (4/29) were granzyme-B+. Totally 11 and 25 cases expressed no CD30 and CD56, respectively. The Ki-67 proliferation index was normally very low (< 10%). *In situ* hybridization detected no EBER in the 14 cases examined. Molecular analyses indicated clonal rearrangement of the TCR-β/γ chain gene in most cases, with 1 case showing an oligoclonal rearrangement.(23) No cytogenetic analyses were available. Table 2 depicts the features of major CD8 + ITLPD-GI cases.

ITCLD-GI could be transformed into a higher-grade lymphoma.(18, 19, 22, 26, 33, 34) However, the vast majority of CD8 + ITLPD-GI cases show an indolent and lengthy course that lasts for many years or even decades, with a chronic, persistent recurrent or spontaneous remission pattern.(35) Interestingly, Among the 29 reported patients with CD8 + ITLPD-GI, the overall prognosis was good: with survival analysis at 6-324 months of follow-up, only 1 patient died at 324 months;(30) only 4 showed transformation.(19, 26, 30, 32) Sharma et al(19) reported a CD8 + ITLPD-GI case that further had systemic ALK- anaplastic large cell lymphoma (ALCL). Guo and co-workers(26) reported a case of CD8 + TLPD with synchronous diffuse large B-cell lymphoma (DLBCL), who showed continuous periumbilical colic pain and bloating, with intermittent diarrhea for 10 years. The case was administered 8 CHOP chemotherapy cycles and 3 rituximab treatments, and remained well during a follow-up of 6 months. In addition, Wu and collaborators(32) described a 42-year-old man with diarrhea and abdominal pain for two years, who had distant lymph node invasion, eventually leading mixed cellularity-type Hodgkin’s lymphoma. The last case described by Soderquist and colleagues(30) was a 41-year-old man who suffered from abdominal pain, with peptic ulcer disease, *H. pylori* infection and positive Hepatitis B and C serologies. Endoscopy showed mucosal nodularity and decreased duodenal folds, and villous atrophy was observed. The patient lived with the disease for 27 years until he developed large cell transformation. Most previous studies examining large cell transformation focused on CD4 + and CD4-CD8- cells.(10, 18, 22) However, large cell

transformation in CD8 + cells should not be ignored. In the above case, although the patient showed invasion, neither intestinal pathology nor lymph node pathology had confirmed histologic transformation.

Genetic and epigenetic changes related to CD8 + ITLPD-GI have been rarely examined, and only few relevant genetic and epigenetic alterations have been reported. To the best of our knowledge, ITLPD-GI cases almost always have clonal rearrangement of T-cell receptor genes, with half of CD8 + cases showing structural alterations that involve the 3' untranslated region (UTR) of IL2 mRNA.(30) It is not clear whether these changes are related to prognosis, and further research is needed. As dysregulated JAK-STAT signaling is commonly found in multiple T-cell lymphoma types, mainly leading to cytotoxicity, it might play a pathogenetic role in ITLPD-GI; (19, 30, 36) however, these changes were absent in the examined CD8 + cases, with the cytotoxic phenotype as multiple T-cell lymphomas.(30) The STAT3 SH2 domain is mutated in CD8 + T-cell large granular lymphocyte leukemia (LGLL).(37, 38) It may imply that STAT3 SH2 domain mutations are associated with poor prognosis in ITLPD-GI. However, Perry and colleagues(25) detected no STAT3 SH2 domain hotspot mutations in five cases examined by Sanger sequencing, although they were all CD8+. In addition, most CD8 + ITLPD cases displayed the Tc2 phenotype.(39) GATA3 modulates the activation, homeostasis and cytolytic activity of CD8 + T-cells.(40) Soderquist et al.(30) reported positive rates for T-bet of 10%, 20%, 20% and 60% in 4 patients, respectively; meanwhile, GATA3 was positive in all cases. The significance of T-bet/GATA3 co-expression in CD8 + ITLPD remains undefined. Overall, genetic and epigenetic alterations in CD8 + ITLPD-GI need further investigation in order to better predict the prognosis of this disease.

Recently, Wang and colleges(41) reported a case of Epstein-Barr virus-positive T -cell lymphoproliferative (EBV + TLPD) who presented with a 2-month history of intermittently occurring fever, sometimes accompanied by chills, abdominal pain and diarrhea, initially diagnosed as IBD. Colonoscopy showed many discrete ulcers in various segments of the colon and rectum, similar to the current case. Unfortunately, the patient described by Wang and collaborators(41) died 7 months following EBV + TLPD diagnosis. The correct distinction between CD8 + ITLPD and EBV + TLPD cases is achieved by the integration of histopathology and IHC, among others, taking into consideration the clinical history and laboratory analysis of EBV infection. The commonest symptoms of EBV + TLPD include fever, liver dysfunction, enlarged liver and spleen, systemic lymphadenopathy and thrombocytopenia, and the disease progresses rapidly.(42, 43) In addition, EBV + TLPD cases are positive for cytotoxic molecules as well as CD8, GRZB, TIAI, TCRG β and TCR $\gamma\delta$. In the current case, the patient's serum EBV DNA burden was increased, whereas EBV DNA was not detected by multiple pathological biopsies. Furthermore, the case reported here was positive for CD2, CD3, CD5 and CD7 by IHC. Therefore, this case was not related to EBV, but the possibility of this diagnosis should be considered clinically because of the poor prognosis of this type.

IBD is one of the most complex differential diagnoses because such conditions show multiple overlapping characteristics with ITLPD-GI. In 29 previously reported cases, 5 with CD8 + ITLPD-GI allegedly occurred in the setting of IBD,(20, 24, 25, 30) as in our case. They included 2 men and 3 women aged between 27 and 77 years. Two patients were reported by Perry et al.:(25) one of them was 15 years old and initially diagnosed with UC, and underwent colectomy 5 months before diagnosing peripheral T-cell lymphoma (PTCL), which was subsequently revised to ITLPD. More than 3 years following PTCL diagnosis, the patient was administered 3 cycles of cyclophosphamide, vindesine, pirarubicin and prednisolone (CHOP) chemotherapy. Another patient, who had a history of CD, had a diagnosis of PTCL in the mouth 13 years before detecting ITLPD in the small bowel; however, a detailed management of PTCL cases was unavailable. Edison et al.(20) reported a patient with a 15-

year history of IBD based on endoscopy, diagnosed with CD following multiple relapses. The last two patients also had a history of IBD, whereas correct diagnosis could not be determined.(29, 30) There are several reasons that can explain why IBD and CD8 + ITLPD-GIs are indistinguishable. Firstly, ITLPD-GI cases present with relatively non-specific symptoms such as abdominal pain, vomiting, diarrhea and weight loss. In addition, endoscopic characteristics also lack specificity. The mucosa appeared normal or showed slight hyperemia in the current case. Prominent folds, erosions or nodules may be detected. Furthermore, there is only discrete mucosal lymphoid infiltrate, typically limited to the mucosal layer, with the submucosa scarcely involved, and no tumor masses.(35, 44) Such infiltrate could be easily missed, without adequate immunohistochemical and biomolecular assays, as described in the present case. Finally, many clinicians and pathologists are not well aware of ITLPD-GI, which is indeed a rare disease. In the current case, we were unable to diagnose CD because no initial pathological report was obtained before the hospital visit. However, there was no evidence for CD in our subsequent analyses, so we considered CD was a misdiagnosis. Hence, considering the similar signs, symptoms and histological features, both biopsies probably denote the same disease process rather than TLPD development from IBD. This highlights the great challenge of recognizing this entity, indicating that comprehensive clinical and laboratory assays as well as prolonged patient follow-up are warranted in these pathologies.

To date, no standard therapeutic protocol for systemic CD8 + ITLPD-GI is available. Some cases have good prognosis even without drugs, and current guidelines recommend a careful 'watch and wait' strategy.(8, 11) Several cases were administered chemotherapy on the basis of peripheral T-cell lymphoma diagnosis, with little to no therapeutic response. Others underwent IBD treatment, also with no response. To the best of our knowledge, a CD8 + ITLPD-GI case with gastric tumors was treated successfully by involved field radiotherapy (IFRT).(45) Another CD8 + ITLPD-GI case was treated successfully by local operation(23); however, long-term follow-up is essential for the evaluation of this case. Of the remaining patients, 10 were treated by chemotherapy, 5 with biological agents and 6 by hormone therapy; 5 had no treatment and 4 had no mentioned. Biological agents, such as interferons (IFNs) and tumor necrosis factor- α (TNF- α), are used in ITLPD treatment. Edison and collaborators(20) described a rare ITLPD-GI case with resistant CD that occurred following administration of anti-TNF- α treatment with adalimumab. Intriguingly, anti-TNF- α therapy discontinuation resulted in tumor regression. It was hypothesized that the inflammation-associated TNF- α /TNFR1/TNFR2 pathway might contribute to the pathogenetic mechanism of this disorder.(46) Persistent or chronic inflammation might induce unchecked intramucosal CD8 T-cell proliferation in individuals with disturbed TNFR2 signaling, triggering indolent T-LPD.(47) Another case reported by Perry et al.(22) was administered multiple immune-modulating drugs, including thalidomide and intermittent IFX, and showed obvious histologic transformation to PTCL and disease dissemination after CHOP treatment. This observation indicates that anti-TNF- α therapy and ITLPD-GI development may be associated. Although reported in a sporadic case, this finding suggest anti-TNF- α therapy might be avoided in individuals with resistant CD for ITLPD-GI prevention. In the current case, 500 mg/kg TNF- α inhibitor (Infliximab, IFX) was only initiated two times without improvement after therapy. However, whether this treatment promoted disease progression, resulting in bleeding and perforation, remains unknown.

In summary, we described a case of primary small intestinal CD8 + T-cell lymphoma of the gastrointestinal tract that further developed into a progressive failure process with complications of bleeding and perforation, without overt histologic transformation to aggressive lymphoma. The patient was initially misdiagnosed with IBD and

received numerous immune-modulating drugs, including IFX. Whether this treatment promoted disease progression is unclear, but deserves further attention since many previously reported ITLPD patients were administered different therapeutic regimens for initially diagnosed T-cell lymphoma or IBD. In addition, genetic changes related to poor prognosis in CD8 + ITLPD need further investigation, which could not only help predict prognosis, but also provide a precise treatment option for this disorder. In conclusion, many questions remain to be answered about CD8 + ITLPD.

Abbreviations

CD, Crohn's Disease; EATL, Enteropathy-associated T-cell lymphoma; H&E, Hematoxylin-eosin; IBD, Inflammatory bowel disease; IHC, Immunohistochemistry; IFRT, field radiotherapy; ITLPD-GI, Indolent T -cell lymphoproliferative disease of the gastrointestinal tract; MEITL, Monomorphic epitheliotropic intestinal T-cell lymphoma; MRI, Magnetic resonance imaging; TNF- α , Tumor necrosis factor- α ; UC, Ulcerative colitis; WHO, The World Health Organization

Declarations

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Availability of data and materials

The dataset supporting the findings and conclusions of this case report is included within the article and Tables

Authors' contributions

Cheng-Ye, Yi-Hong Fan reviewed the case. Meng Li and Chun-Yan Weng wrote the manuscript. Bin Lu and Chun-Li Zhang edited the manuscript. All authors contributed to discussions and gave final approval of the submitted manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient. A copy of the consent form is available for review by the Editor of this journal.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1

Laboratory findings in the patient at initial presentation

Hematology				Biochemistry				Serology	
Item	Result	Reference range	Unit	Item	Result	Reference range	Unit	Item	Result
WBC	9.2	3.5–9.5	$\times 10^9/L$	TP	57.4	65–85	g/L	HBs Ag	Negative
Neu	70	40–75	%	Alb	17.5	40–55	g/L	HCV Ab	Negative
Lym	21	20–50	%	BUN	7.4	3.1-8.0	mmol/L	HTLV1Ab	Negative
Mono	3	3.0–10.0	%	Cre	57	59–104	$\mu\text{mol/L}$		
Eosino	0.5	0.40-8.0	%	UA	279	208–428	$\mu\text{mol/L}$		
Baso	0.2	0.0–1.0	%	Na	138	137–147	mmol/L		
RBC	4	4.30–5.80	$\times 10^{12}/L$	K	3.8	3.5–5.3	mmol/L		
Hb	78	130–175	g/L	Cl	101.2	99–110	mmol/L		
MCV	84	82–100	fl	Ca	2.13	2.1–2.6	mmol/L		
MCH	27.4	27–34	pg	LDH	128	109–245	U/L		
MCHC	327	316–354	g/L	AST	21	15–40	U/L		
Plt	344	125–350	$\times 10^9/L$	ALT	20	9–50	U/L		
ESR	10	0–15	mm/h	CRP	25.4	0.00–8.00	mg/L		

Due to technical limitations, table 2 docx is only available as a download in the Supplemental Files section.

Figures

Figure 1

Magnetic resonance imaging (MRI) and retroperitoneal B-ultrasound manifestations. (A) Thickened small bowel wall and whole colon, with enlarged regional lymph nodes at the mesenteries. (B) Retroperitoneal B-ultrasound manifestation: multiple retroperitoneal lymph nodes were enlarged. The red arrow points to the largest swollen lymph node. (C) Pathological results of lymph node puncture showing lymphoid tissue hyperplasia with lymphoid sinus dilatation.

Figure 2

Endoscopic and pathologic findings of the stomach and intestines. (A) Colonoscopy manifestation: multiple ulcers were seen in the distal ileum, colon and rectum, with two large ulcerations each in the distal ileum and sigmoid colon (Red arrow). (B) Pathology showed chronic activity with lymphoid tissue hyperplasia in the rectum, colon and terminal ileum. (C) Gastroscopy showed chronic atrophic gastritis. (D) Pathology showed chronic active gastritis with erosion, Hp+.

Figure 3

Superior mesenteric arteriography and perioperative images. (A) Superior mesenteric arteriography showed rupture and hemorrhage of a straight arteriole distal to the ileocolic artery; subsequently, microspring coils were used to embolize the diseased vessels, and repeated angiography showed that the hemorrhagic lesion disappeared 5 minutes later (Red box). (B) A large amount of yellow-green intestinal fluid in the abdominal cavity and ileum perforation were observed during the operation (Red arrow).

Figure 4

Immunohistochemical findings Colonic lymphoid cells underwent immunophenotyping by immunohistochemistry. Lymphoid cells were positive for CD3, CD5, CD7 and CD8, and negative for CD4, CD20 and CD56. The Ki-67 proliferative index was low (<10%). Monoclonal gene rearrangement determined in T-cell receptor-clonality assay by polymerase chain reaction.

Supplementary Files

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- [Table2.docx](#)
- [CAREchecklistEnglish.docx.pdf](#)