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ABOUT COVER

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CASE REPORT

CD8-positive indolent T-Cell lymphoproliferative disorder of the gastrointestinal tract: A case report and review of literature

Chun-Yan Weng, Cheng Ye, Yi-Hong Fan, Bin Lv, Chun-Li Zhang, Meng Li

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Abstract

BACKGROUND

Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract (ITLPD-GI), a primary tumor forming in the gastrointestinal (GI) tract, represents a rarely diagnosed clonal T-cell disease with a protracted clinical course.

CASE SUMMARY

This report presented 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 correctly diagnosed until the occurrence of complications such as intestinal perforation. Postsurgical histopathological analysis, combined with hematoxylin-eosin staining, immunohistochemistry and TCRβ/γ clonal gene rearrangement test, confirmed the diagnosis of CD8+ ITLPD-GI.

CONCLUSION

Individuals with this scarce lymphoma frequently show non-specific symptoms that are hard to recognize. So far, indolent CD8+ ITLPD-GI has not been comprehensively examined. The current mini-review focused on evaluating indolent CD8+ ITLPD-GI cases based on existing literature and discussing future directions for improved differential diagnosis, detection of genetic and epigenetic alterations, and therapeutic target identification.

Key Words: Indolent T-cell lymphoproliferative disease; Gastrointestinal tract; Inflammatory bowel disease; Immunohistochemistry; Case report

Core Tip: Here we presented a case report of a patient with a history of anal fistula and chronic recurrent diarrhea. This case was easily misdiagnosed as inflammatory bowel disease, enteropathy associated T-cell lymphoma and other diseases due to the lack of characteristic manifestations, which posed great challenges to clinicians and pathologists.

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INTRODUCTION

Indolent T-cell lymphoproliferative disease of the gastrointestinal tract (ITLPD-GI) represents a new entity included in the revised fourth edition of 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 that likely emerges from lamina propria lymphocytes. It 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, which 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 the awareness of this disorder among health professionals.

CASE PRESENTATION

Chief complaints

The subject was a 45 years male with a chief complaint of chronic recurrent diarrhea.

History of present illness

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), and was diagnosed as Crohn's Disease (CD) after several relapses. He first received 5-aminosalycilic acid, hormone therapy and azathioprine. Systemic edema appeared during the treatment. Due to poor response to treatment, infliximab was administered twice 2 years ago. He came to our hospital for diarrhea aggravation.

History of past illness

The patient denied cigarette smoking and consumption of alcohol. He had a history of anal fistula for 4 years.

Personal and family history

The patient denied family history.

Physical examination

Physical exam was normal with the exception of minor edemas on both lower extremities.

Laboratory examinations

Laboratory analysis of complete blood count showed low hemoglobin level at 78 g/L (reference range, 130–175 g/L), whereas leukocyte and platelet counts were unaltered. C-reactive protein concentration was 25.4 mg/L (reference range, 0.00–8.00 mg/L). Serum biochemistry showed decreased levels of total proteins (57.4 g/L; reference range, 65–85 g/L) and albumin (17.5 g/L; reference range, 40–55 g/L), and high fecal calprotectin level (> 1662 μg/g; reference range, 0–200 g/L). Serum EBV viral load was 5.81E × 4 (reference range, 0-5E × 3 copies/mL). Other blood tests including carbohydrate antigen, carcinoem-

bryonic antigen and alpha-fetoprotein assessments were performed. The results of T-cell spot assay and postpartum depression (PPD) test for Mycobacterium tuberculosis detection were negative. Microbiological stool examination and culture were essentially normal.

Imaging examinations

Magnetic resonance imaging 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 (Figure 1A). Retroperitoneal B-ultrasound showed multiple enlarged mesenteric lymph nodes, the largest of which was about 3.18 cm × 1.3 cm in size (Figure 1B). The mesenteric lymph nodes were biopsied using an autobiopsy gun under B-ultrasound guidance for further diagnosis with the patient's consent. Pathological results of lymph node biopsy showed the destruction of lymph node structure and diffuse proliferation and infiltration of tumor cells in the paracortical area and medullary sinus (Figure 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, and two large ulcers were found in the distal ileum and sigmoid colon (Figure 2A). Gastroscopy showed chronic atrophic gastritis (Figure 2B).

FINAL DIAGNOSIS

CD8+ ITLPD.

TREATMENT

Based on the above related examinations and results, the patient was first given prednisone 45 mg once a day, azathioprine tablets 50 mg every other day, and 5 d later, azathioprine tablets 50 mg once a day. Unfortunately, the patient developed hematochezia and was treated with hemostasis and related medications. The patient felt better after hydrocortisone 100 mg was administered twice daily, with enteral and parenteral nutrition maintenance for 1 mo. The patient began to develop hematochezia with a total volume 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 (Figure 3A). After 14 d of observation, the patient developed peritonitis with a small intestinal perforation, and underwent emergency surgery (Figure 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 (Figure 4). TCRβ/γ clonal gene rearrangement was detected (Figure 5). *In situ* hybridization showed no Epstein-Barr encoding region (EBER). After the diagnosis of CD8+ ITLPD was confirmed, the patient underwent hormone and parenteral nutrition support therapies.

OUTCOME AND FOLLOW-UP

He suffered repeated intestinal perforations and abdominal infections after the operation. The patient had to leave the hospital due to economic reasons. He was still alive 3 mo ago, and has since been lost to follow-up. However, we will continue and track the patient's situation.

DISCUSSION

Cancers affecting the gut are common, mostly including adenocarcinomas,and lymphomas only represent 1%–4% of all cases. Primary gut T-cell lymphomas are aggressive and mainly comprise enteropathy-associated and monomorphic epitheliotropic intestinal 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 was 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. This case first presented with protein-losing enteropathy and malabsorption syndrome, without specific treatment. Subsequently,

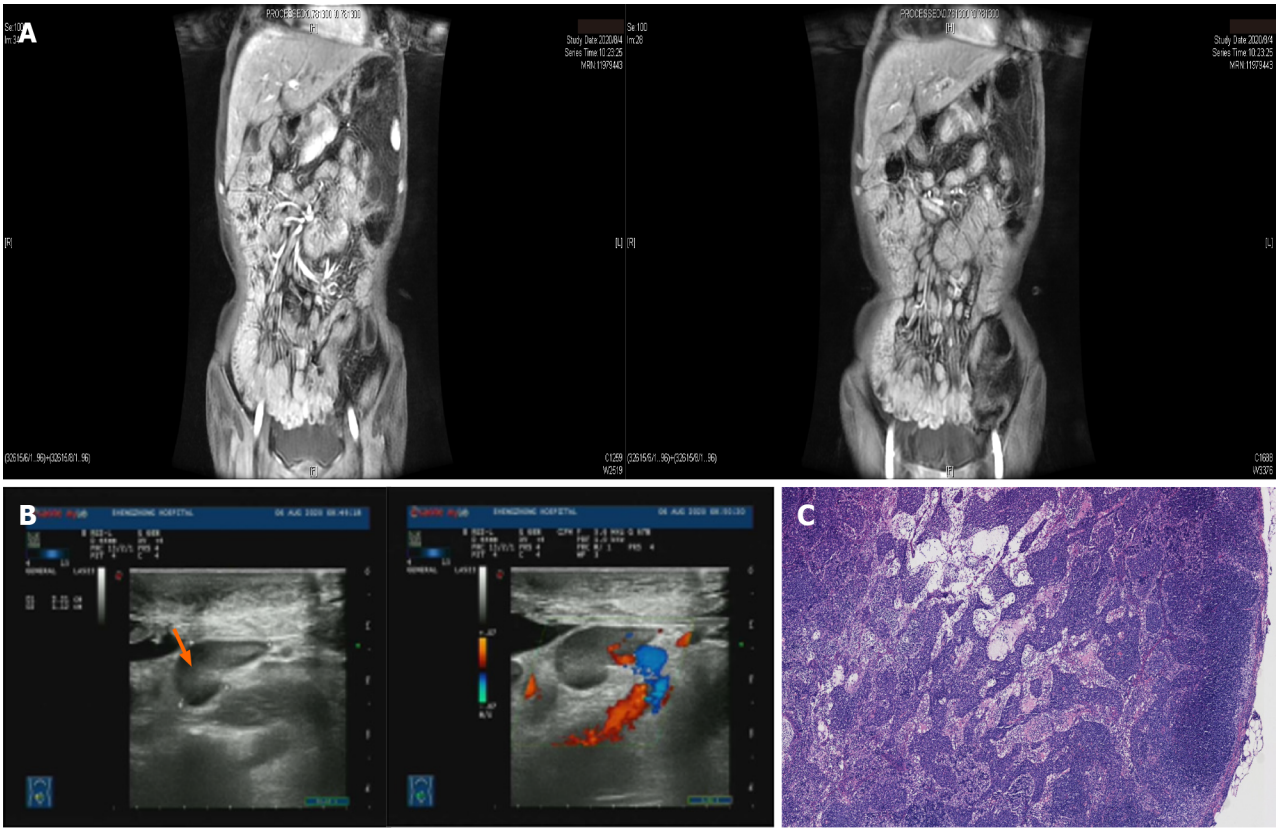

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Figure 1 Magnetic resonance imaging and retroperitoneal B-ultrasound manifestations. A: Thickened small bowel wall and whole colon, with enlarged regional lymph nodes at the mesenteries; B: Retroperitoneal B-ultrasound manifestation: Multiple retroperitoneal lymph nodes are enlarged. The orange arrow points to the largest swollen lymph node; C: Pathological results of lymph node puncture showing the destruction of lymph node structure and diffuse proliferation and infiltration of tumor cells in the paracortical area and medullary sinus.

several studies have provided insights into the properties of CD8+ ITLPD-GI[8,11,15,19,20,24-31]. So far, a literature review revealed 15 articles reporting CD8+ ITLPDGI in 29 patients, including 19 males and 10 females, averaging 42 years old (range, 15-77 years). The degree of CD8+ ITLPD-GI involvement varies, but it is frequently multifocal, and almost all GI tract segments could be affected. 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 cases that involved the bone marrow[15,30], lymph nodes[29,32], and the uterus, respectively[23]. The most common clinical symptoms were 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 slightly irregularly shaped nuclei. Immunophenotyping or Immunohistochemistry (IHC) showed the lymphocytes always expressed CD8. CD2 and CD7 expression was observed in 17 patients assessed, and CD5 expression was seen in 25 cases. TCRαβ (βF1) was detected in 21 patients. The cytotoxic marker TIA1 was expressed in 79.3% (23/29) of ITLPD cases, 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 very low (< 10%). In situ hybridization detected no EBER in the 14 cases evaluated. 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 1 and Table 2 depict 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. Survival analysis at 6-324 mo of follow-up showed that only 1 patient died after 324 mo[30], and only 4 showed transformation[19,26,30,32]. Sharma *et al*[19] reported a CD8+ ITLPD-GI case who further developed systemic ALK- anaplastic large cell lymphoma. Guo *et al*[26] reported a case of CD8+ TLPD with synchronous diffuse large B-cell lymphoma who showed continuous periumbilical colic pain and bloating, with intermittent diarrhea for 10 years. The patient received 8 CHOP chemotherapy cycles and 3 rituximab treatments, and remained well during a follow-up period of 6 mo. In addition, Wu and

Table 1 Case reports of CD8+ Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract

Ref.	Country	Age	Gender	Involved sites	Clinical presentation	Endoscopic findings	IHC/ Phenotype/molecular		Molecular/Genetic alterations		Treatment	Follow-up (mo)
							Positive	Negative	Rearrangement	Other gene		
Tsutsumi *et al* [8], 1996	Japan	48	Male	Small bowel	Abdominal distension, diarrhea, weight loss, leg edema	Irregular granular mucosa	CD2, CD3, CD5, CD8, TCRβ, HLA-DQ, HLA-DR	CD4, CD20, TCRδ, EBER	Q3-1 region	NA	None	AWD (12)
Ranheim *et al* [11], 2000	United States	35	Male	Palate, small bowel, colon, rectum	Recurrent oropharyngeal ulcer, rectal bleeding	Small erosions in colonic mucosa	CD3, CD5, CD8, TCRαβ	CD4, CD56, TIAI	TCRγ	NA	None	AWD (108)
Leventaki *et al* [15], 2013	United States	42	Male	Esophagus, stomach, small bowel, colon, bone marrow	Peptic ulcer	Nodular gastric and duodenal mucosa	CD2, CD3, CD8, GRZB (subset), Ki67 < 10%	CD4, CD5, CD56, CD57	TCRβ/γ	NA	IFN, Ia, Ster	AWD (237.6)
Perry *et al* [25], 2013	United States	15	Female	Small intestine (jejunum, ileum), colon	Abdominal pain, diarrhea	Numerous small polyps, erosions	CD2, CD3, CD5, CD7, CD8, TIA1, TCRβ; Ki67: 5%-10%	CD30, CD56, GRZB, EBER	TCRγ	STAT3 mutation(-)	CHOP (3)	AWD (52)
		31	Male	Small intestine (ileum), colon	Diarrhea	Numerous small polyps, erythema	CD2, CD3, CD5, CD7, CD8, TIA1, Ki67: 5%-10%	CD30, CD56, GRZB, EBER			NA	AWD (17)
		35	Male	Oral cavity, small intestine (ileum), colon	Oropharyngeal ulcers, rectal bleeding	NA	CD3, CD5, CD8, TIA1, TCRβ	CD56, TCRG, EBER			None	AWD (156)
		38	Male	Esophagus, stomach, small intestine (duodenum, ileum), colon	Abdominal pain, diarrhea, food intolerance	Stomach: unremarkable; duodenum: thickend folds	CD2, CD3, CD5, CD7, CD8, TIA1, TCRβ, Ki67: 5%	CD30, CD56, TCRG, EBER			NA	AWD (14)
		52	Female	Stomach	Abdominal pain, vomiting, diarrhea	NA	CD3, CD5, CD8, TIA1, Ki67: 5%	CD7, CD56, GRZB, EBER			Unknown chemothery	AWD (24)
		52	Male	Colon	Abdominal pain, bloody diarrhea	Congestion, erythema and friable mucosa	CD3, CD5, CD8, T1A1, TCRβ, Ki67: 5%	CD7, CD30, CD56, GRZB, TCR-G, EBER			CHOP (4)	AWD (175)
		59	Female	Small intestine (duodenum)	Abdominal bloating, diarrhea, foul stools; hypocalcemia, hypoka, hyp	"Irregular" appearace of duodenal mucosa	CD2, CD3, CD5, CD7, CD8, Ki67: 5%	CD30, CD56, GRZB			None	AWD (23)
		77	Female	Oral cavity, small intestine (ileum)	Oropharyngeal ulcers; history of	NA	CD2, CD3, CD5, CD7, CD8, TIA1, GRZB, TCR β	CD30, CD56, EBER			NA	AWD (168)

					Crohn disease		, Ki67: 5%					
Edison N *et al* [20], 2016	Israel	27	Female	Sigmoid colon, ascending colon, cecum	History of IBD	Consistent with IBD	CD2, CD3, CD5, CD7, CD8, TCRβ, TIA1	CD56, CD57, GRZB	TCRG, TCRB	NA	5Aa, Ster, Aza, Ada	NA
Wang *et al*[21], 2017	China	39	Male	Colitis, caecum, rectum, renal	Chronic diarrhoea, loss of weight, poly arthralgia, intermittent fever	Erythema and friable mucosa	CD2, CD3, CD7, CD8, TIA1, TCRβ	CD4, CD10, CD20, CD56, TCRγ, CD30, GRZB, ALK1, EBER	TCRγ	NA	Bas, Tac, Ster, Aza, Ami, Mes	NA
Sharma *et al* [19], 2018	United States	47	Female	Stomach, duodenum, jejunum, ileum	NA	NA	CD3, CD5, CD8, T1A1, TCRβ, Ki67: 5%, P-STAT5 (Y694)	CD4, CD7, CD56, GRZB, TCRγδ	NA	STAT3-JAK2 fusion (-)	NA	NA
		39	Male	Stomach, duodenum, jejunum, ileum, colon	NA	NA	CD3, CD5, CD7, CD8, T1A1, TCRβ	CD4, CD56, GRZB, TCRγδ				
		74	Female	Duodenum, jejunum	NA	NA	CD3, CD5, CD7, CD8, T1A1, TCRβ, P-STAT1 (Y694)	CD4, CD56, GRZB, TCRγδ				
		57	Male	Ileum	NA	NA	CD3, CD5, CD7, CD8, T1A1, TCRβ	CD4, CD56, GRZB, TCRγδ				
Guo L *et al*[26], 2019	China	46	Male	Intestine	Paraumbilical colic pain, bloating, occasional diarrhea	Diffuse small nodular hyperplasia, irregular ulcers and intestinal stricture, granulate mucosa and redness	CD2, CD3, CD5, CD8, CD43, Ki67: 5%	CD4, CD20, CD56, GB	TCRγ	NA	CHOP (8), Rit (3)	AWD (6)
Kohri M *et al* [27], 2019	Japan	52	Male	Colon	Diarrhea	Diffuse edematous lesions with multiple aphtha	CD3, CD5, CD7, CD8, TIA1, Ki67 < 10%	CD4, CD56, EBER	NA	NA	CyclOBEAP	AWD (79)
Moreno *et al* [29], 2019	Spain	68	Female	None	History of IBD/IBS	Normal	CD2, CD3, CD5, CD7, CD8, TIA1, TCRβ, GRZB (subset), CD103 (subset), EBER, Clonal TCR, Ki67 < 10%	NA	NA	STAT3-JAK2 fusion (-)	Aza, Anti, Ster, CHOP	NA
Saggini A *et al* [28] 2020	Italy	65	Male	Oral, tongue, larynx, colon	2-cm-wide infiltrated, enlarging, non-ulcerated plaque	NA	CD2, CD3, CD5, CD8, CD20, TIA1, TCRβ, Ki-67 < 5%	CD4, CD56, PAX5, CD79a	TCRγ	NA	Cor	AWD (36)
		36	Male	Intestinal and lymph node	Malabsorption, weight loss	NA	CD3, CD5, CD7, CD8, TIA1, Ki67 < 5%	CD4, CD56, EBER Clonal TCR	NA	STAT3-JAK2 fusion (-)	Aza, Anti, Ster, CHOP	NA
Soderquist *et al* [30] 2020	United States	38	Male	Duodenum, jejunum, ileum,	Diarrhea, abdominal pain, vomiting	Mucosal nodularity, decreased, duodenal	CD2, CD3, CD5, CD7, CD8, CD103, TCRαβ,	CD4, CD30, CD56, TIA1,	NA	IL2-RHOH	None	AWD (252)

				colon		folds, gastric erythema	Ki-67 < 5%, GATA3	TCRγδ, T-bet, GRZB				
		38	Male	Duodenum, ileum, colon	Diarrhea, weight loss, abdominal pain	Mucosal nodularity, erythema, friability	CD2, CD3, CD5, CD7, CD8, CD103, TIA1, TCRαβ, Ki-67 < 5%, GATA3, T-bet	CD4, CD30, TCRγδ	NA	IL2 3′ UTR deletion, IL2-TNIP3	CP, Dox, VCR, Bud, Pred, Etop, AGS67E	AWD (84)
		41	Male	Duodenum, stomach, bone marrow	Abdominal pain	Mucosal nodularity, decreased duodenal folds	CD2, CD3, CD8, TIA1, TCRαβ, Ki-67 < 5%, GATA3	CD4, CD5, CD30, CD56, CD103, GRZB, TCRγδ	NA	None identified	IFN, CP, Dox, VCR, Pred, Gem	Dead (324)
		49	Male	Duodenum, jejunum	Diarrhea weight loss, abdominal pain, Crohn's disease	Flattened small bowel mucosa, gastric erythema	CD2, CD3, CD5, CD7, CD8, TIA1,TCRαβ, Ki-67 < 5%, GATA3	CD4, CD30, CD103, TCRγδ, T-bet	NA	None identified	CP, Dox, VCR, Pred, Mes, Aza	AWD (228)
Takahashi *et al* [31], 2020	Japan	70	Female	Stomach	Mild epigastralgia, weight loss	Multiple erosions in the lower body	CD3, CD5, CD8, CD43, TIA1, GRZB, TCRβ, Ki-67: 10%	CD4, CD56, EBER	NA	NA	IFRT	NA
Thomas SJ *et al* [23], 2020	United Kingdom	31	Female	Uterine corpus	Menorrhagia, anemia	NA	CD2, CD3, CD5 CD7, CD8, TCRβ, TIA1	CD5, CD10, CD21, CD23, CD56, ALK1, EBER	NA	Oe	Local lesection	NA
Wu *et al*[32], 2020	China	42	Male	Rectum, colon	Dental ulcers, abdominal pain, and diarrhea	Rough, hyperemic, mucosa, multifocal deep ulcers	CD3, CD8, CD43, TIA1, Ki-67: Approximately 5%–10%	CD4, CD5, CD20, CD56, TdT, EBER	TCRγ	NA	Mes, Cg, Pcb	AWD (12)

5Aa: 5-Aminosalycilic acid; Ada: Adalimumab; Cg: Compound glutamine; AGS67E: Ant, antibiotics Anti-CD37 monoclonal antibody AGS67E; Ami: aminosalicylate sulfasalazine; AWD: Alive with disease; Aza: Azathioprine; Bas: Basiliximab; Bud: Budesonide; CHOP: Chronic abdominal pain; Cor: Corticosteroids; CP: Cyclophosphamide; CyclOBEAP: Cyclophosphamide, doxorubicin, vincristine, etoposide, bleomycin and prednisone; Dox: Doxorubicin; EBER: Epstein-Barr virus-encoded RNA; Etop: Etoposide; GRZB: Granzyme B; Gem: Gemcitabine; Hyp: Hypozincemia associated with paraesthesias, confusion; Hypoka: Hypokalemia; Ia: Isotretinoic acid; IFN: Interferon; IFRT: Involved field radiotherapy; ITLPD-GI: Indolent T-cell lymphoproliferative disease of the gastrointestinal tract; Mes: Mesalamine; Oe: Oligoclonal expansion; Pcb: Probiotic cocktail Bifico; Pred: Prednisone; Rit: Rituximab; Ster: Steroid; Tac: Tacrolimus; TCR-BF1: T-cell receptor b F1; TCRG: T-cell receptor g; VCR: Vincristine; NA: Not available.

collaborators[32] described a 42-year-old man with diarrhea and abdominal pain for two years, who had distant lymph node invasion, eventually leading to mixed cellularity-type Hodgkin' s lymphoma. The most recent 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 that examined 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 tumor 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 (Punit, 2015 #2104) 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

Table 2 The number and proportion of case reports

Age		Gender		Involved sites	Number	Proportion	Clinical presentation	Number	Proportion	IHC/ Phenotype/Molecular		
											Positive	Negative
< 45	15	Male	19	Small intestine	18	62.10%	Chronic abdominal pain	11	37.90%	CD2	17	0
										CD3	29	0
				Colon	14	48.30%				CD4	0	18
							Diarrhea	14	48.30%	CD5	25	3
				Stomach	6	20.70%				CD7	17	3
≥ 45	14	Female	10							CD8	29	0
				Oral cavity	4	13.80%	Weight loss	6	20.70%	CD56	0	25
										TCRαβ	21	0
				Esophagus	4	13.80%				T1A1	23	2
										EBER	1	14

IHC: Immunohistochemistry; EBER: Epstein-Barr encoding region.

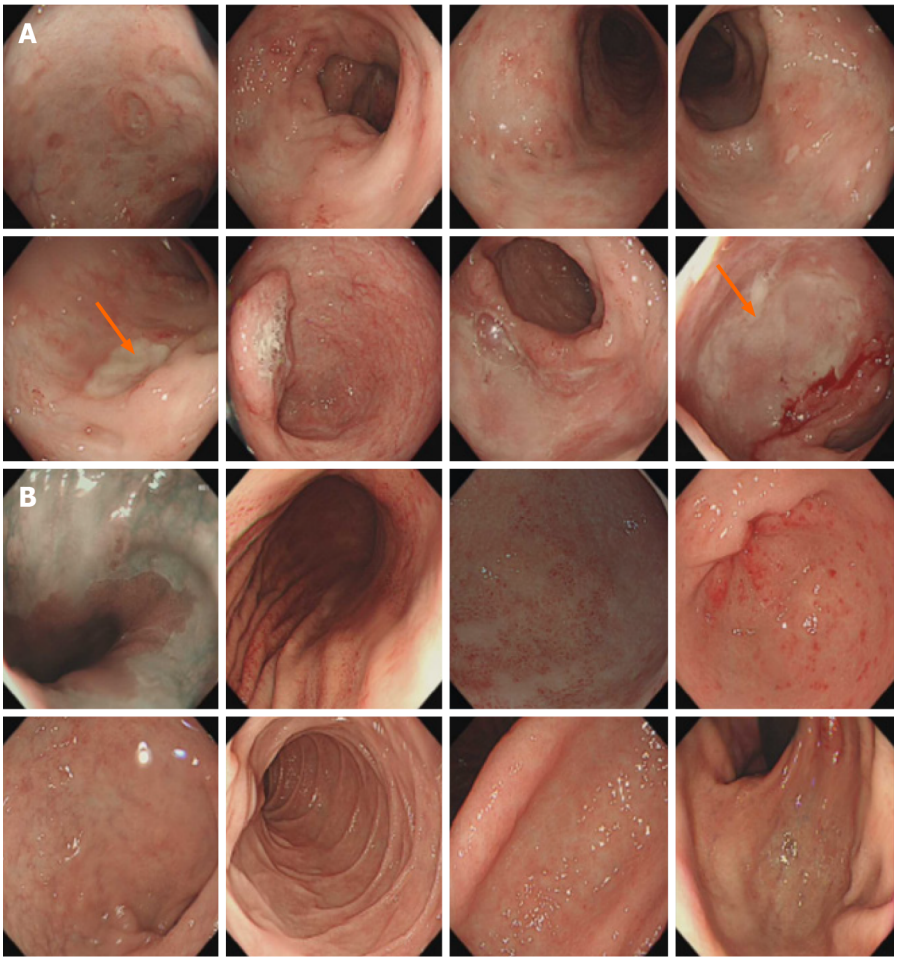

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Figure 2 Endoscopic and pathologic findings of the stomach and intestines. A: Colonoscopy manifestation: multiple ulcers are seen in the distal ileum, colon and rectum, with two large ulcerations each in the distal ileum and sigmoid colon (Orange arrow); B: Gastroscopy shows chronic atrophic gastritis.

of CD8+ cases showing structural alterations that involve the 3′ untranslated region of IL2 mRNA[30]. It is not clear whether these changes are related to prognosis, and further research is needed. Dysregulated JAK-STAT signaling is commonly found in multiple T-cell lymphoma types, mainly leading to

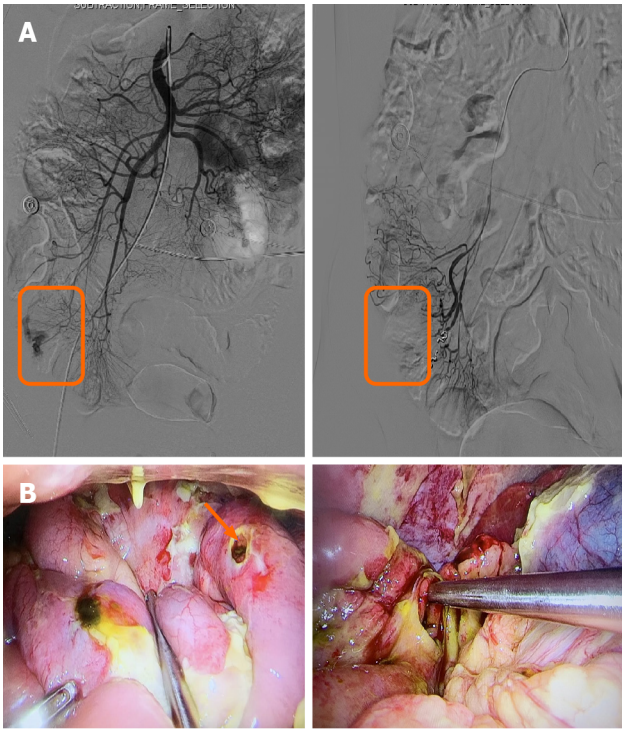

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Figure 3 Superior mesenteric arteriography and perioperative images. A: Superior mesenteric arteriography shows rupture and hemorrhage of a straight arteriole distal to the ileocolic artery; subsequently, microspring coils are used to embolize the diseased vessels, and repeated angiography shows that the hemorrhagic lesion disappears 5 minutes later (Red box); B: A large amount of yellow-green intestinal fluid in the abdominal cavity and ileum perforation are observed during the operation (Orange arrow).

cytotoxicity, which 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], which may imply that STAT3 SH2 domain mutations are associated with poor prognosis of ITLPD-GI. However, Perry and colleagues[25] detected no STAT3 SH2 domain hotspot mutations in five cases undergoing Sanger sequencing, although they were all CD8+ ITLPDs. 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 *et al*[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 (2010 #604;, 2010 #604). Colonoscopy showed many discrete ulcers in various segments of the colon and rectum, similar to the current case. Unfortunately, the patient described by Wang *et al*[41] died 7 mo following EBV+ TLPD diagnosis. The correct distinction between CD8+ ITLPD and EBV+ TLPD cases is achieved by integrating histopathology and IHC, and among others, taking into consideration the clinical history and laboratory analysis of EBV infection. The most common 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, for EBV+ TLPD cases, cytotoxic molecules as well as CD8, GRZB, TIAI, TCRGβ and TCRγδ are positive. 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 showed positivity 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 in clinic practice due to 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 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 15-year-old patient was initially diagnosed with UC and underwent colectomy 5 mo before the diagnosis of peripheral T-cell lymphoma (PTCL), which was subsequently revised to ITLPD. More than 3 years following PTCL

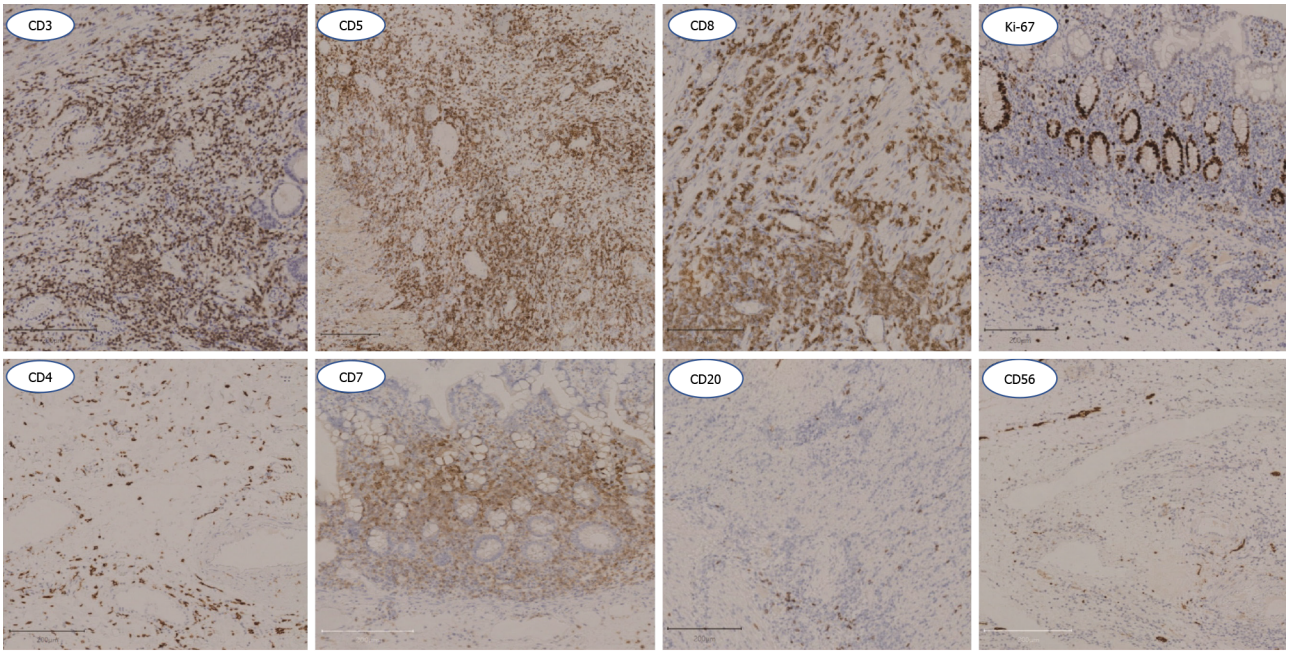

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Figure 4 Immunohistochemical findings. Colonic lymphoid cells undergo immunophenotyping by immunohistochemistry. Lymphoid cells show positivity for CD3, CD5, CD7 and CD8, and negativity for CD4, CD20 and CD56. The Ki-67 proliferative index is low (< 10%). Monoclonal gene rearrangement is determined in T-cell receptor-clonality assay by polymerase chain reaction.

diagnosis, the patient recevived 3 cycles of cyclophosphamide, vindesine, pirarubicin and prednisolone (CHOP) chemotherapy. Another patient with a CD history 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 who was diagnosed with CD following multiple relapses. Another study suggested that 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 infiltration, typically confined to the mucosal layer, with the submucosa scarcely involved, and no tumor masses are found[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 patient's 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 denoted 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 received 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)[31]. 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 were not mentioned. Biological agents, such as interferons (IFNs) and tumor necrosis factor-α (TNF-α), are used in ITLPD treatment. Edison *et al*[20] described a rare ITLPD-GI case with resistant CD that occurred following anti-TNF-α treatment with adalimumab. Intriguingly, anti-TNF-α therapy discontinuation resulted in tumor regression. It was hypothesized that the inflammation-associated TNF-a/TNFR1/TNFR2 pathway might contribute to the pathogenetic mechanism of this disorder[45]. Persistent or chronic inflammation might induce unchecked intramucosal CD8 T-cell proliferation in individuals with disturbed TNFR2 signaling, triggering indolent T-LPD[46]. Another case reported by Perry *et al*[22] was administered multiple immune-

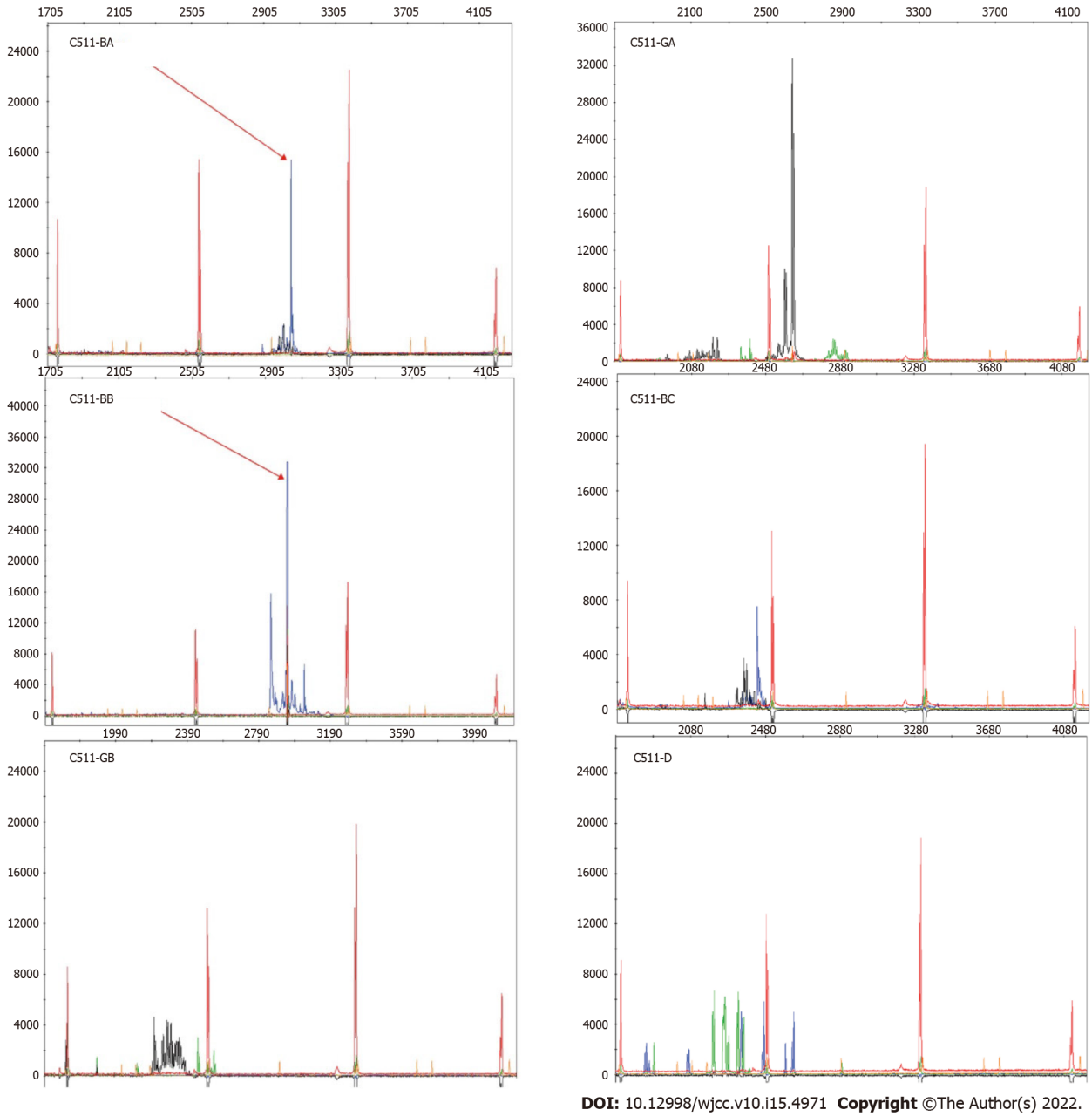

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Figure 5 TCRβ/γ clonal gene rearrangement. TCRβ/γ clonal gene rearrangement test by PCR and Capillary Electrophoresis. The results shows positivity for C511-BA, C511-BB, and negativity for C511-GA, C511-BC and C511-GB and C511-D.

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 may be associated with ITLPD-GI development. Although reported in a sporadic case, this finding suggests that 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.

CONCLUSION

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 was unclear, but deserved further attention since many previously reported ITLPD patients received different therapeutic regimens for initially

diagnosed T-cell lymphoma or IBD. In addition, genetic changes related to poor prognosis of 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+ ILTLD.

FOOTNOTES

Author contributions: Weng CY, Fan YH reviewed the case; Li M and Weng CY wrote the manuscript; Lv B and Zhang CL edited the manuscript; all authors contributed to discussions and gave final approval of the submitted manuscript.

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