Case Report

Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract managed conservatively with corticosteroids: A case report

Tyler McKechnie BSc[1], Haroon Yousuf MD FRCPC[2], Stephen Somerton MD FRCPC[3]

1 Michael G. DeGroote School of Medicine, McMaster University, Hamilton, Ontario, Canada.

2 Department of Medicine, McMaster University, Hamilton, Ontario, Canada.

3 Department of Gastroenterology, Brant Community Healthcare System, Brantford, Ontario, Canada.

Abstract

Introduction: Indolent T-cell lymphoproliferative disorder (TCLPD) of the gastrointestinal (GI) tract is recognized as a provisional entity under the World Health Organization. It most often presents with chronic diarrhea. The diagnosis relies on clinical and endoscopic (macroscopic and microscopic) findings. Treatment regimens are variable but often include chemotherapeutic agents.

Case: An 82-year-old female presented with a 4-week history of abdominal pain, weight loss, diarrhea, and nausea. A complete infectious workup was negative. Her computed tomography (CT) scan showed no pathologic changes and her esophagogastroduodenoscopy (EGD) showed mucosal erosion in the duodenum. Her duodenal biopsies demonstrated a marked increase in intra-epithelial lymphocytes and her immunohistochemistry was consistent with indolent TCLPD of the GI tract.

Management: She was started on high dose prednisone three months after the onset of her symptoms. She gradually improved with complete resolution of erosive changes on her repeat EGD. The prednisone was gradually tapered over three months. One month following the completion of the taper, she had recurrent symptoms. She was thus kept on low dose prednisone for two months.

Conclusions: She is the oldest known patient to be diagnosed with indolent TCLPD of the GI tract, thus prompting reconsideration of patient populations most at risk of this disease. Moreover, she represents the first case with complete resolution of macroscopic disease with corticosteroid treatment alone.

Keywords: Internal Medicine, Gastroenterology, Oncology, Geriatrics

Corresponding author: tyler.mckechnie@medportal.ca
ISSN
DOI

Introduction

Lymphoma is the malignant transformation of lymphocytes. Primary gastrointestinal (GI) lymphomas are generally aggressive neoplasms that carry significant morbidity and mortality. (1) Recently, however, cases of primary GI indolent lymphomas have been described. These entities are less aggressive and likely do not require the same aggressive chemotherapeutic approaches that primary GI lymphomas do.(2) It is now recognized as a provisional entity in the World Health Organization (WHO) under lymphoid neoplasms.(3) Indolent T-cell lymphoproliferative disorder (TCLPD) of the GI tract may present with abdominal pain, diarrhea, vomiting, or dyspepsia.(2) The exact pathophysiology is yet to be determined but it is thought to be related to immune dysregulation.(1) The diagnosis of indolent TCLPD relies on identifying clinical features consistent with the diagnosis (e.g. abdominal pain, diarrhea), macroscopic endoscopic findings (e.g. mucosal erythema or ulceration), and microscopic endoscopic findings (e.g. intra-epithelial lymphocytes (IELs), low rate of proliferation, CD4/8 staining).(1) Current treatment modalities include cytotoxic agents (e.g. cyclophosphamide, vinblastine, gemcitabine) and corticosteroids.

Case Report

Mrs. EA is an 82-year-old female with a 4-week history of diffuse abdominal pain, weight loss, diarrhea, and nausea without vomiting. She described experiencing up to 15-20 clay-coloured stools, with no rectal bleeding, hematochezia, melena stool, or nocturnal diarrhea. She reported decreased oral intake secondary to nausea. Her past medical history was significant for dyslipidemia, hypertension and squamous cell carcinoma of the lip, which was resected in 2013. Her only medications were hydrochlorothiazide and telmisartan for her hypertension. Her family and social history were non-contributory.

She was admitted to hospital and given intravenous rehydration. A complete infectious workup including stool Clostridium difficile and norovirus PCR, stool culture and stain (C&S), and stool ova and parasites (O&P) was negative. The only abnormalities on routine blood work were a low potassium of 3.2mmol/L (normal 3.5-5mmol/L), an elevated erythrocyte sedimentation rate (ESR), an elevated C-reactive protein (CRP), and an elevated lactate dehydrogenase (LDH). She was initially trialed on a gluten-free diet for one month with no abatement of symptoms. She was then restarted on a gluten-containing diet and her celiac markers and anti-nuclear antibody (ANA) were measured. They failed to demonstrate any abnormalities. Her computed tomography (CT) scan of the abdomen and pelvis showed no obvious pathology. Due to her weight loss of close to 12lbs, she was started on total parenteral nutrition (TPN). She subsequently had an esophagogastroduodenoscopy (EGD) which showed erosive damage in the duodenum and a colonoscopy which was normal.

Her duodenal biopsy showed inflammation with marked increase in intra-epithelial lymphocytes (IEL). The immunohistochemistry demonstrated lymphocytes positive for CD3, CD4, CD8 and negative for CD56 and CD57 with a monoclonal gene rearrangement of the T-cell gamma receptor (Figure 1). The macroscopic and microscopic mucosal abnormalities ruled out the important differential diagnoses of inflammatory bowel disease (IBD) and Celiac disease (CD), while the CD staining ruled out peripheral T-cell lymphoma (PTCL). Thus, these findings were most consistent with a diagnosis of indolent TCLPD of the GI tract. She was started on high dose prednisone roughly three months after the onset of her symptoms. She was subsequently prescribed a slow prednisone taper over three months and her symptoms gradually improved. Her repeat EGD displayed grossly normal duodenum and resolution of the previous erosive changes. One month following completion of the taper, she experienced recurrence of her nausea and diarrhea. A low dose prednisone was started, and she again experienced resolution of her symptoms. She was kept on low dose prednisone for two months, after which she tolerated a taper without recurrent symptoms.

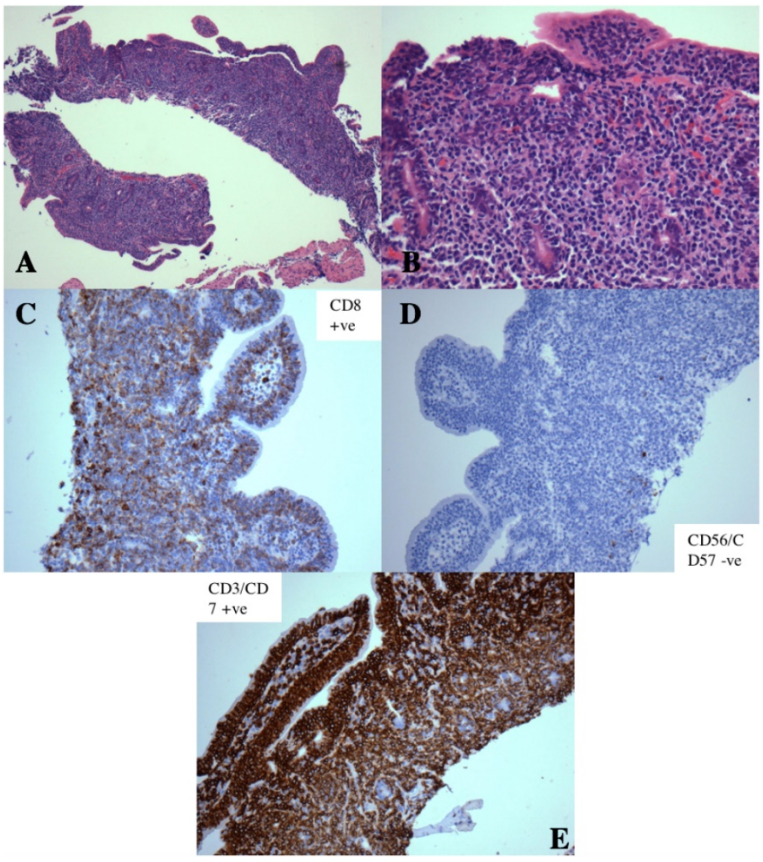

Figure 1. Hematoxylin and eosin (H&E) stains demonstrating dense infiltration of atypical lymphocytes in mucosa (A,B) and immunohistochemistry of these lymphocytes (C,D,E).

Discussion

Indolent CD4+/CD8+ TCLPD of the GI tract is a rare clinical entity, with 33 cases diagnosed and reported in the literature over the past 26 years (Table 1). The relatively recent description of this entity is likely a result of advancing diagnostic approaches (i.e. high-definition endoscopy, specific immunohistochemistry staining). (1) Currently the pathogenesis is unknown, but it is speculated that this disease is related to immune dysregulation, inflammation, and persistent antigenic stimulation.(1) The lymphocytic derangements in this disease are consistent with this, given the immunomodulating effect of CD8 T-cells in the GI tract.(4) The diagnosis of indolent TCLPD of the GI tract can be challenging as chronic diarrhea effects up to 5% of North Americans at any given time and has a vast differential diagnosis.(5) This was evident in this patient's case, as her diagnosis of indolent TCLPD of the GI tract was made three months after symptom onset. Indolent TCLPD of the GI tract is often initially diagnosed as PTCL, IBD, or CD. (2) Distinguishing indolent TCLPD from these entities is important as it can prevent unnecessary therapy and potential adverse effects related to the therapy. For example, 50% of patients with indolent TCLPD of the GI tract in one case series received chemotherapy that did not change their disease course, yet exposed them to potential adverse effects such as hair loss, immunosuppression, and anemia (see Table 1 for a full list of treatments).(2)

This case of indolent TCLPD of the GI tract is unique for a number of reasons. First, she is one of three patients treated with corticosteroids alone.(5) The previous two cases did not have complete resolution of their macroscopic GI tract abnormalities. Although corticosteroids carry risk of adverse events, the severity and frequency of these side effects are less than in chemotherapy. For example, cyclophosphamide, a chemotherapeutic agent used in the management of previously reported cases of indolent TCLPD of the GI tract, is associated with severe adverse effects that steroids are not, such as hemorrhagic cystitis, alopecia, and febrile neutropenia.(6) Moreover, the clinical response is likely comparable between the two.(5) These considerations served as the basis for treating her solely with corticosteroids, and are important discussion points for future physicians when managing this disease. Second, Mrs. EA was 84 years old on presentation, making her the oldest reported patient with indolent TCLPD of the GI tract. The mean age in previously reported cases was 46.9 (range: 15-77). Third, indolent TCLPD of the GI tract affects a larger proportion of males – of the 33 cases reported, 22 have been male. Taken together, this case serves as a reminder that demographic factors alone (i.e. age, gender) do not preclude the diagnosis of indolent TCLPD of the GI tract.

Mrs. EA's immunohistochemistry results were also remarkable. The results demonstrated marked intra-epithelial lymphocytes (IELs), which was only observed in three other patients with indolent TCLPD.(2,7,8) Thus, increased IELs on immunohistochemistry, although less common in indolent TCLPD of the GI tract, does not rule out the diagnosis altogether.

Whether this clinical entity is truly a rarity or simply underdiagnosed is yet to be determined.(5) Regardless, it is necessary that clinicians consider the diagnosis of indolent TCLPD of the GI tract in patients with chronic diarrhea once more common pathologies (eg. PTCL, IBD, CD) have been ruled out. Investigations should include endoscopy (EGD and colonoscopy) with

biopsy and immunohistochemistry. While endoscopic investigations (i.e. EGD and colonoscopy) are often performed in the initial workup of patients presenting chronic diarrhea, the threshold for biopsy and immunohistochemistry should be low in patients with duodenal mucosal abnormalities. Such an approach may reduce the time to diagnosis and decrease patient exposure to unnecessary therapy. Therapy with corticosteroids alone is likely sufficient in managing this disease, thus correct diagnosis early within the course of the disease may limit exposure to more aggressive therapies such as chemotherapy. It is likely, however, that a long course of corticosteroids (i.e. longer than 3 months) is required for sufficient resolution of GI tract abnormalities and symptoms. Further investigation is required to elucidate the pathogenesis of this disease in order to develop more targeted treatment.

Table 1. Summary of previous TCLPD case reports

Author, Year	**Patient(s)**	**Endoscopy Findings**	**Histology**	**Immuno-histochemistry**	**Management**
Mendes et al. (2014)(7)	1 Female; 59 years of age; clinical presentation of diarrhea, weight loss	N/A	• Partial villous atrophy • Small lymphocytes in LP of stomach, SI, and colon • IELs increased	CD4+, CD8-, CD2+, CD3+, CD7+, CD103-	Gemcitabine, prednisone
Malamut et al. (2014)(9)	5 Males, 5 Females; 22-68 years of age; clinical presentation of diarrhea, weight loss	N/A	• Subtotal villous atrophy • Small lymphocytes in LP of stomach, SI, and colon • IELs not increased	CD3+, CD4+, CD8-	Anti-CD52, vinblastine
Perry et al. (2013)(2)	6 Males, 4 Females; 15-77 years of age; clinical presentation of diarrhea (8/10), abdominal pain (6/10), oral ulcers (4/10)	Numerous small polyps, erosions, and erythema in duodenum	• Dense, non-destructive lymphoid infiltrate in LP of stomach, small bowel, and colon • IELs increased in 1/10 patients	10/10 CD3+, CD4-, CD56-; 8/10 CD8+, CD5+; 7/7 CD2+	• Watch and wait (4/10) • Multiple bowel resections (1/10) • CHOP (5/10)
Margolskee et al. (2013)(5)	2 Males, 1 Female; 37-53 years of age; clinical presentation of diarrhea (3/3), weight loss	Nodular mucosa in duodenum	• Partial villous atrophy and small lymphocytes in the LP of the stomach, small bowel, and colon	CD2+, CD3+, CD4+, CD8-	• Budesonide (3/3) • Azathioprine (1/3) • Prednisone (1/3)

	(3/3), night sweats (1/3)		• IELs not increased		
Leventaki et al. (2013)(10)	1 Male; 42 years of age; clinical presentation of gastritis symptoms	Atrophy of small bowel mucosa	• Small lymphocytes in the LP of esophagus, stomach, small bowel, and colon • IELs not increased	CD2+, CD3+, CD8+, CD4-, CD5-, CD56-	Interferon isotretinoic acid, steroids
Zivny et al. (2004)(11)	1 Male; 60 years of age; clinical presentation of diarrhea, weight loss	Gastric and duodenal erythema	• Villous blunting, and small lymphocytes in the LP of the stomach and small bowel • IELs not increased	CD3+, CD4+, CD8-, CD103-	Prednisone, vincristine, cyclophosphamide
Tsutsumi et al. (1996)(12)	2 Male; 48-68 years of age; clinical presentation of diarrhea, weight loss, leg edema	Irregular granular mucosa in small bowel	• Small lymphocytes in LP of small bowel • IELs not increased	CD2+, CD3+, CD5+, CD8+, CD4+/- (1/2 patients were CD4+, CD8+)	None
Hirakawa et al. (1996)(13)	1 Male; 47 years of age; asymptomatic	Polypoid gastric and small bowel mucosa, aphthoid lesions in the large bowel	• Normal mucosa • Small lymphocytes in LP of small bowel, colon, and rectum • IELs not increased	CD2+, CD3+, CD4+, CD8-, CD103+	Cyclophosphamide, vindesine, pirarubicin, prednisone
Egawa et al. (1995)(8)	1 Male: 51 years of age; clinical presentation of relapsing oral and colorectal ulcers, periumbilical abdominal pain	Small ulcers in oropharynx, terminal ileum, and colon	• Diffuse and dense infiltration of small lymphocytes in LP of oral cavity, colon, and rectum • IELs increased	CD3+, CD4+, CD8-	Prednisone, salicylazosulfa-pyridine
Carbonnel et al. (1994, 1999)(14,15)	3 Males and 1 Female; 28-59 years of age; clinical presentation of	No gross findings	• Extensive infiltration of small lymphocytes in LP of stomach and small bowel	CD2+, CD3+, CD4+, CD5+, CD7+, CD8-, CD56-, CD57-, CD103-	MACOP-B, holoxane, etoposide, teneposide, doxorubicin, chlorambucil

	diarrhea, weight loss		• IELs not increased		

(N/A, not applicable; LP, lamina propria; IEL, intra-epithelial lymphocyte; CD, cluster of differentiation; CHOP, cyclophosphamide, doxorubicin, hydrochloride, vincristine, prednisone; MACOP-B, methotrexate, leucovorin, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin)

References

1. Matnani R, Ganapathi KA, Lewis SK, Green PH, Alobeid B, Bhagat G. Indolent T- and NK-cell lymphoproliferative disorders of the gastrointestinal tract: A review and update. Hematol Oncol. 2017;35(1):3–16.

2. Perry AM, Warnke R a, Hu Q, Gaulard P, Copie-bergman C, Alkan S, et al. Indolent T-cell lymphoproliferative disease of the gastrointestinal tract Indolent T-cell lymphoproliferative disease of the gastrointestinal tract. Blood. 2013;122(22):3599–606.

3. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2017;127(20):453–62.

4. Grdic D, Hörnquist E, Kjerrulf M, Lycke NY. Lack of local suppression in orally tolerant CD8-deficient mice reveals a critical regulatory role of CD8+ T cells in the normal gut mucosa. J Immunol. 1998;160(2):754–62.

5. Margolskee E, Jobanputra V, Lewis SK, Alobeid B, Green PHR, Bhagat G. Indolent small intestinal CD4+ T-cell lymphoma is a distinct entity with unique biologic and clinical features. PLoS One. 2013;8(7).

6. Fraiser L, Kanekal S, Kehrer J. Cyclophosphamide Toxicity. Drugs. 1991;42:781–95.

7. Mendes L, Attygalle AD, Cunningham D, Benson M, Andreyev J, Gonzales-de-Castro D, et al. CD4-positive small T-cell lymphoma of the intestine presenting with severe bile-acid malabsorption: A supportive symptom control approach. Br J Haematol. 2014;167(2):265–9.

8. Egawa N, Fukayama M, Kawaguchi K, Hishima T, Hayashi Y, Funata N, et al. Relapsing oral and colonic ulcers with monoclonal T-cell infiltration. A low grade mucosal T-lymphoproliferative disease of the digestive tract. Cancer. 1995;75(7):1728–33.

9. Malamut G, Meresse B, Kaltenbach S, Derrieux C, Verkarre V, Macintyre E, et al. Small intestinal CD4+ T-cell lymphoma is a heterogenous entity with common pathology features. Clin Gastroenterol Hepatol [Internet]. 2014;12(4):599-608.e1. Available from: http://dx.doi.org/10.1016/j.cgh.2013.11.028

10. Leventaki V, Manning JT, Luthra R, Mehta P, Oki Y, Romaguera JE, et al. Indolent peripheral T-cell lymphoma involving the gastrointestinal tract. Hum Pathol [Internet]. 2014;45(2):421–6. Available from: http://dx.doi.org/10.1016/j.humpath.2013.08.003

11. Zivny J, Banner BF, Agrawal S, Pihan G, Barnard GF. CD4+T-cell lymphoproliferative disorder of the gut clinically mimicking celiac sprue. Dig Dis Sci. 2004;49(4):551–5.

12. Tsutsumi Y, Inada KI, Morita K, Suzuki T. T-cell lymphomas diffusely involving the intestine: Report of two rare cases. Jpn J Clin Oncol. 1996;26(4):264–72.

13. Hirakawa K, Fuchigami T, Nakamura S, Daimaru Y, Ohshima K, Sakai Y, et al. Primary gastrointestinal T-cell lymphoma resembling multiple lymphomatous polyposis. Gastroenterology. 1996;111(3):778–82.

14. Carbonnel F, D'Almagne H, Lavergne A, Matuchansky C, Brouet JC, Sigaux F, et al. The clinicopathological features of extensive small intestinal CD4 T cell infiltration. Gut. 1999;45(5):662–7.

15. Carbonnel F, Lavergne A, Messing B, Tsapis A, Berger R, Gralian A, et al. Extensive small intestinal T-cell lymphoma of low-grade malignancy assocaited with a new chromosomal translocation. Cancer. 1994;73(4):1286–91.

Acknowledgements: N/A

Support: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Consent: Informed consent was obtained for this written report and the publication of the attached clinical images