CASE REPORT

The first report of a previously undescribed EBV-negative NK-cell lymphoma of the GI tract presenting as chronic diarrhoea with eosinophilia

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SUMMARY

A 74-year-old man presented with a 2-month history of watery diarrhoea. His complete blood count showed lymphopaenia and marked eosinophilia. Investigations for common infectious causes including *Clostridium difficile* toxin, stool culture, ova and parasites were negative. Endoscopy revealed extensive colitis and a CT of the abdomen identified numerous large abdominal lymph nodes suspicious for lymphoma. Multiple tissue samples were obtained; colon, mesenteric lymph node and bone marrow biopsy, as well as pleural fluid from a rapidly developing effusion, confirmed the presence of metastatic lymphoma with an immunophenotype most consistent with an aggressive variant of Epstein-Barr virus (EBV)-negative natural killer (NK)-cell lymphoma. The patient's clinical condition rapidly deteriorated and he died shortly following diagnosis. To the best of our knowledge, this is the first case report of a primary gastrointestinal EBV-negative NK-cell lymphoma, and its clinical presentation highlights the importance of a broad differential in the management of chronic diarrhoea.

primary NK-cell lymphoma of the GI tract not associated with Epstein-Barr virus (EBV) infection.

CASE PRESENTATION

A 74-year-old man presented to the emergency department (ED) for the third time in 2 months, with a primary symptom of diarrhoea. He described the diarrhoea as watery, non-bloody and non-mucoid, occurring every hour and present even while fasting. This was associated with cramping abdominal pain that was relieved with bowel movement. He had one episode of bright red blood per rectum 1 week before presentation, which resolved without recurrence. He had lost approximately 10 kg over 1 month but denied other constitutional symptoms. He also denied fever, had no symptoms suggestive of infection and had no relevant exposures (ie, recent travel, sick contacts or consumption of undercooked food). There were no systemic symptoms including rash, arthralgias or vision changes. There was no history of dietary intolerance and no known family history of chronic medical illness.

The patient's medical history was notable for persistent atrial fibrillation, hypertension, hyperlipidaemia and benign prostatic hyperplasia. There had been no changes to his medication regimen and, in particular, he had not recently been started on any diarrhoeagenic medications.

Physical examination revealed an unwell appearing patient who was alert and oriented with no focal neurological deficits. His blood pressure was 139/83 mm Hg and his heart rate was 140–150 bpm and irregularly irregular. There was no palpable lymphadenopathy. Cardiac examination was normal and respiratory examination revealed absent breath sounds in the right lung base. His abdomen was distended but soft and non-tender to palpation. There were no palpable masses and no organomegaly. Digital rectal examination was normal. There were no active joints or rashes. His diarrhoea had been unresponsive to two outpatient courses of empiric antibiotics (ciprofloxacin and amoxicillin) as well as loperamide and cholestyramine.

INVESTIGATIONS

A complete blood count showed elevated white cell counts (14.50×10^9 cells/L) with an abnormal differential including lymphopaenia (0.67×10^9 cells/L) and eosinophilia (3.89×10^9 cells/L). The patient was hyponatraemic (120 mmol/L) but had

BACKGROUND

Chronic diarrhoea, broadly defined as unformed stools lasting more than 4 weeks, is a common presentation to general practitioners, internists and gastroenterologists, with a prevalence of 3–5% in the USA.^{1 2} It is a clinical manifestation of a wide array of gastrointestinal (GI) illnesses that span infection, autoimmune inflammation, malabsorption and malignancy. Often, an underlying aetiology is not found on clinical examination or routine investigations, necessitating radiographic or endoscopic intervention for definitive diagnosis.^{3 4} GI malignancy is a rare cause for chronic diarrhoea and this report highlights a case of a unique natural killer (NK)-cell lymphoma with GI infiltration manifesting as diarrhoea. Diagnosis was initially made with colonic biopsy, and confirmed with immunohistochemical and flow cytometry assessment of tissue from a lymph node biopsy, bone marrow biopsy and pleural effusion cytology. The diagnosis was ultimately delayed by repeated infectious work ups and trials of empiric medication, likely prompted by the finding of eosinophilia despite the absence of infectious risk factors. This case therefore highlights the importance of considering malignancy as an uncommon but life-threatening cause of chronic diarrhoea. It is also notable for being the first report, to the authors' knowledge, of an aggressive

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Figure 1 Colonoscopy images showing extensive colitis extending from the sigmoid colon to the caecum. The colon showed evidence of mucosal erythema, touch friability and congestion.

an otherwise normal metabolic profile including normal thyroid function tests. At each of his three (ED) visits, a sample of his stool was assayed for *Clostridium difficile* toxin, bacterial culture, and presence of ova and/or parasites. Each assessment was negative. Blood cultures were also negative. HIV, hepatitis B and hepatitis C testing was negative. Tissue transglutaminase IgA was 1 U/mL (negative <15 U/mL) and serum antineutrophil cytoplasmic antibody was not detectable.

Chest X-ray revealed a right-sided pleural effusion and atelectasis. The patient underwent colonoscopy, which revealed extensive colitis with erythema, friability, oedema and congestion from the rectum (spared) to the caecum (figure 1). The terminal ileum was normal. The findings were non-diagnostic but follow-up CT of the abdomen with intravenous contrast was recommended to assess for ischaemic colitis. Biopsies were obtained at the time of colonoscopy.

Abdominal CT revealed extensive colitis predominantly involving the right colon, with no evidence of ischaemia. An incidental finding of multiple enlarged, retrocrural, para-aortic, aortocaval, retrocaval and mesenteric lymph nodes was identified and deemed suspicious for lymphoma (figure 2). CT of the thorax and a bone scan were negative for metastasis. Colonic biopsies identified diffuse infiltration of monomorphous lymphoma cells (figure 3A).

Figure 2 Coronal (left) and axial (right) CT of the abdomen and pelvis, with intravenous and oral contrast demonstrating multiple enlarged intra-abdominal lymph nodes suspicious for lymphoma.

Figure 3 (A) H&E stain of colon tissue identifying large lymphoma cells diffusely infiltrating the lamina propria. Single cells are also seen in the glandular epithelium (objective lens $\times 40$). (B) Anti-CD3 immunohistochemistry reveals weak CD3 expression in the cytoplasm of the lymphoma cells but no surface expression. Some scattered small lymphocytes in the stroma strongly express CD3 (objective lens $\times 40$).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for chronic diarrhoea in an elderly patient is broad and can be the primary manifestation of many diseases. Initial narrowing of this expansive list can be predicated on stool characteristics, often categorised as watery, fatty or inflammatory.¹ Watery diarrhoea is associated with the broadest differential, encompassing medication reactions, endocrinopathies and functional disease among other diagnoses. Fatty stools are characteristic for malabsorptive and maldigestive conditions and present as foul-smelling and oily diarrhoea. Inflammatory stool, often described as bloody or purulent, encompasses inflammatory bowel disease as well as a number of malignant, ischaemic and infectious aetiologies including *C. difficile*.¹

Our patient's clinical picture biased us towards an inflammatory presentation, primarily guided by an episode of bright red blood per rectum in combination with an elevated white cell count. His age, clinical history and the absence of systemic findings were not consistent with a diagnosis of inflammatory bowel disease. Furthermore, his diarrhoea lasted longer than would be expected for most GI infections and he lacked obvious infectious exposures. Finally, he had multiple negative infectious work ups and failed two courses of antibiotics, making an infectious cause less likely.

Our differential was aided by the finding of peripheral eosinophilia, which escalated during this patient's admission. In the context of chronic diarrhoea, a finding of eosinophilia limited our differential to parasitic disease, eosinophilic gastroenteritis, autoimmune vasculitides and malignancy.^{5–7} Eosinophilia is a common finding in haematological malignancies and, in particular, lymphoid malignancy.⁸

OUTCOME AND FOLLOW-UP

Colon biopsy revealed diffuse infiltration of large, atypical lymphoma cells into the lamina propria and submucosa. Only minimal epitheliotropism was seen (figure 3A). Immunophenotypic characterisation of the lymphoma by immunohistochemistry and flow cytometry revealed cytoplasmic (but no surface) CD3 (figure 3B) and cytotoxic granule markers, but absence of all T-cell surface markers (CD4, CD5, CD7, CD8 and T-cell receptor (TCR) β) and also lacked expression of CD30, CD56 and EBER. Genotypic analysis according to the BIOMED-2 protocol revealed absence of clonal TCR γ and TCR β gene rearrangements. Analysis of the bone marrow, mesenteric lymph nodes and the patient's pleural effusion, the latter including flow cytometry, confirmed metastatic spread of the lymphoma with an identical morphology and immunophenotype (table 1). An immunocytochemistry study for proliferation was performed and showed up to 98% of nuclei staining positive for MIB1, suggesting highly aggressive disease. Bone marrow biopsy was notable for marked eosinophilia (approximately 35% of total cells). Taken together, the absence of T-cell markers and absence of TCR gene rearrangements was consistent with a unique case of an aggressive, primary GI, EBV-negative NK-cell lymphoma.

Table 1 Immunophenotype markers for tumour cells isolated from the colon, mesenteric lymph nodes and pleural effusion

	Colon biopsy	Mesenteric LN	Pleural effusion
CD2 (FC/IHC)	–	–	+
sCD3 (FC)	NA	–	–
cCD3 (IHC)	+	+	+
CD4 (FC/IHC)	–	–	–
CD5 (FC/IHC)	–	–	–
CD7 (FC/IHC)	–	–	–
CD8 (FC/IHC)	–	–	–
CD10 (FC/IHC)	–	–	–
CD11c (FC/IHC)	NA	–	+
CD19 (FC)	NA	–	–
CD20 (FC)	NA	–	–
CD25 (FC/IHC)	–	–	–
CD30 (FC/IHC)	–	–	±
CD34 (FC)	NA	–	–
CD38 (FC)	NA	–	–
CD56 (FC/IHC)	–	–	–
CD57 (FC)	NA	–	–
TCR α/β (FC/IHC)	–	–	–
TCR γ/δ (FC)	NA	–	–
Granzyme B (IHC)	+	+	+
TIA-1 (IHC)	+	+	+
FOXP3 (IHC)	–	–	–
EBER (ISH)	–	NA	–
MIB1 (IHC)	80%	NA	98%

Samples were tested using a combination of FC, IHC and ISH.

FC, flow cytometry; IHC, immunohistochemistry; ISH, in situ hybridisation; LN, lymph node; NA, not applicable.

A course of high-dose corticosteroids was offered and initiated while awaiting final tissue pathology to determine an optimal chemotherapeutic approach. Unfortunately, the patient's disease progressed aggressively and he died shortly after diagnosis. Blood cultures were positive for *Candida albicans* post-mortem likely reflecting profound immunosuppression.

DISCUSSION

Lymphomas of the GI tract are well characterised although a critical distinction must be made between primary GI lymphomas, a rare entity and more commonly seen secondary infiltration from metastatic spread.⁹ The incidence of primary GI lymphoma has been increasing, particularly in westernised countries.¹⁰ There is no absolute consensus on the clinical definition of primary GI lymphoma, but commonly cited criteria require predominant intestinal involvement with associated GI symptoms on clinical presentation.^{9–11} An older, and more restrictive, set of criteria was described in 1961 by Dawson and colleagues, and requires: (1) absence of superficial lymphadenopathy on presentation, (2) absence of mediastinal lymphadenopathy on chest radiographs, (3) normal white cell count and differential, (4) a predominantly intestinal lesion with lymph node disease limited to sites of drainage and (5) absence of hepatosplenic disease.^{9–12} Both criteria are outdated and untested, leaving little consensus on a unified diagnostic classification. With the exception of an abnormal white cell count, the patient described in this case report meets the diagnosis of a primary GI lymphoma by both criteria and would be reasonably treated as such.

Although the GI tract is the most common site of extranodal lymphoma, these malignancies account for only 5–10% of primary GI malignancies.¹³ GI lymphomas predominantly affect the proximal tract (stomach, small intestine) with only 10% presenting in the colon.¹³ All primary GI lymphomas are non-Hodgkin lymphomas and, of these, nearly half are diffuse large B-cell lymphomas with marginal zone, mantle cell and follicular lymphoma frequently identified as well.^{10–13} The most commonly identified T-cell phenotype is the enteropathy-associated T-cell lymphoma, a rare but well-characterised disease of the small intestine.^{14–15}

NK cells are phenotypically identified by cytotoxic molecule expression, cell markers (ie, CD2, cytoplasmic CD3, CD56 and CD57) and lack of T-cell and B-cell markers, as well as lack of TCR gene rearrangements (including both α/β and γ/δ receptors).¹⁶ There is a very strong association between EBV infection and aggressive NK-cell malignancy, although the presence of EBV is not a pre-requisite to identifying an NK-cell lymphoproliferative disease. The three major entities comprising the spectrum of NK malignancy are NK-cell enteropathy, extranodal NK/T-cell lymphoma (ENTL)-nasal type and aggressive NK-cell lymphoma.^{16–17} NK-cell enteropathy, a clinically indolent disorder characterised by a self-limiting lymphoproliferation in the GI tract, is inconsistent with the morphology and aggressive features of the cells characterised in this case.¹⁵ NK-cell enteropathies are routinely identified in the absence of EBV infection.¹⁷ The ENTL-nasal type, however, is an aggressive disease that, as the name suggests, is mostly localised to the upper aerodigestive tract.^{15–18–19} These lymphomas, by definition, require EBV infection as a pre-requisite for diagnosis, and are very occasionally found elsewhere in the GI system.^{20–22} Aggressive NK-cell lymphoma, also known as aggressive NK-cell leukaemia, is a fulminant form of the disease, and manifests in the third to fourth decade of life, with multiorgan involvement, rapid disease progression and a prognosis in the order of weeks.²³ These cancers are routinely associated with EBV infection and CD56

expression, distinguishing it from the lymphoma described in this case.²⁴ Furthermore, a literature review could not identify primary GI involvement as a manifestation of aggressive NK-cell lymphoma.

In the absence of EBV infection, which was confirmed in our case by EBER in situ hybridisation on three independent samples, the NK-cell origin of the lymphoma was identified by the lack of T-cell surface marker expression and absence of TCR gene rearrangements. EBV negativity is common in indolent NK-cell disease, such as NK-cell enteropathies and chronic lymphoproliferative disorders, but has never been reported in an aggressive NK-cell process.^{16 17} In summary, we report a unique case of aggressive EBV-negative NK-cell lymphoma of the GI tract manifesting as chronic diarrhoea with eosinophilia.

Learning points

- ▶ Chronic diarrhoea is a common presentation that requires a broad differential diagnosis.
- ▶ Eosinophilia in the context of diarrhoea provides guidance for disease aetiology, and malignancy is a rare but serious potential diagnosis in these patients.
- ▶ In the absence of revealing clinical findings or normal routine investigations, one should consider timely endoscopy with tissue biopsy for diagnosis.
- ▶ Lymphoma with gastrointestinal involvement often reflects aggressive disease, and prompt diagnosis with appropriate therapy impacts prognosis and outcome.

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REFERENCES

- 1 Juckett G, Trivedi R. Evaluation of chronic diarrhea. *Am Fam Physician* 2011;84:1119–26.
- 2 [No authors listed]. American Gastroenterological Association medical position statement: guidelines for the evaluation and management of chronic diarrhea. *Gastroenterology* 1999;116:1461–3.
- 3 Genta RM, Sonnenberg A. The yield of colonic biopsy in the evaluation of chronic unexplained diarrhea. *Eur J Gastroenterol Hepatol* 2015;27:963–7.
- 4 Shen B, Khan K, Ikenberry SO, et al. The role of endoscopy in the management of patients with diarrhea. *Gastrointest Endosc* 2010;71:887–92.
- 5 Pagnoux C, Mahr A, Cohen P, et al. Presentation and outcome of gastrointestinal involvement in systemic necrotizing vasculitides: analysis of 62 patients with polyarteritis nodosa, microscopic polyangiitis, Wegener granulomatosis, Churg-Strauss syndrome, or rheumatoid arthritis-associated vasculitis. *Medicine* 2005;84:115–28.
- 6 Baig MA, Qadir A, Rasheed J. A review of eosinophilic gastroenteritis. *J Natl Med Assoc* 2006;98:1616–19.
- 7 Roufosse F, Weller PF. Practical approach to the patient with hypereosinophilia. *J Allergy Clin Immunol* 2010;126:39–44.
- 8 D'Souza A, Pardanani A, Tefferi A. Lymphoma-associated versus lymphocytic-variant hypereosinophilia. *Leuk Lymphoma* 2012;53:2103–4.
- 9 Chang ST, Menias CO. Imaging of primary gastrointestinal lymphoma. *Semin Ultrasound CT MR* 2013;34:558–65.
- 10 Howell JM, Auer-Grzesiak I, Zhang J, et al. Increasing incidence rates, distribution and histological characteristics of primary gastrointestinal non-Hodgkin lymphoma in a North American population. *Can J Gastroenterol* 2012;26:452–6.
- 11 Lewin KJ, Ranchod M, Dorfman RF. Lymphomas of the gastrointestinal tract: a study of 117 cases presenting with gastrointestinal disease. *Cancer* 1978;42:693–707.
- 12 Dawson IM, Cornes JS, Morson BC. Primary malignant lymphoid tumours of the intestinal tract. Report of 37 cases with a study of factors influencing prognosis. *Br J Surg* 1961;49:80–9.
- 13 O'Malley DP, Goldstein NS, Banks PM. The recognition and classification of lymphoproliferative disorders of the gut. *Hum Pathol* 2014;45:899–916.
- 14 Delabie J, Holte H, Vose JM, et al. Enteropathy-associated T-cell lymphoma: clinical and histological findings from the international peripheral T-cell lymphoma project. *Blood* 2011;118:148–55.
- 15 Foukas PG, de Leval L. Recent advances in intestinal lymphomas. *Histopathology* 2015;66:112–36.
- 16 Kwong YL. Natural killer-cell malignancies: diagnosis and treatment. *Leukemia* 2005;19:2186–94.
- 17 Mansoor A, Pittaluga S, Beck PL, et al. NK-cell enteropathy: a benign NK-cell lymphoproliferative disease mimicking intestinal lymphoma: clinicopathologic features and follow-up in a unique case series. *Blood* 2011;117:1447–52.
- 18 Al-Hakeem DA, Fedele S, Carlos R, et al. Extranodal NK/T-cell lymphoma, nasal type. *Oral Oncol* 2007;43:4–14.
- 19 Tse E, Kwong YL. How I treat NK/T-cell lymphomas. *Blood* 2013;121:4997–5005.
- 20 Fujiwara H, Akiyama T, Nishimura H, et al. Primary intestinal NK-cell lymphoma with a CD8+ CD56+ immunophenotype: a case report. *Pathol Int* 2013;63:138–40.
- 21 Chuang SS, Jung YC. Natural killer cell lymphoma of small intestine with features of enteropathy but lack of association with celiac disease. *Hum Pathol* 2004;35:639–42.
- 22 Chim CS, Au WY, Shek TW, et al. Primary CD56 positive lymphomas of the gastrointestinal tract. *Cancer* 2001;91:525–33.
- 23 Lima M. Aggressive mature natural killer cell neoplasms: from epidemiology to diagnosis. *Orphanet J Rare Dis* 2013;8:95.
- 24 Zhang H, Meng Q, Yin W, et al. Adult aggressive natural killer cell leukemia. *Am J Med Sci* 2013;346:56–63.

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