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NK-cell enteropathy, a potential diagnostic pitfall of intestinal lymphoproliferative disease

Sir,

NK-cell enteropathy is a rare and clinically indolent lymphoproliferative disorder involving the gastrointestinal tract. The disease, which is characterised by an atypical proliferation of CD56 expressing NK-cells within the mucosa, is a recently described unique clinicopathological entity which has also been coined 'lymphomatoid gastropathy'.[1] Patients experience a benign or indolent clinical course with persistent local disease or spontaneous regression punctuated by occasional relapses. Here, we present a case of NK-cell enteropathy which was diagnosed in an asymptomatic patient undergoing routine colonoscopic surveillance. Our case highlights the importance of recognising this entity in order to avoid misdiagnosis of an aggressive enteric NK/T cell lymphoma which would result in unnecessary treatment burden for the patient.

Our patient was an otherwise well 58-year-old man, referred for colonoscopic assessment due to anxiety about bowel cancer after a recent diagnosis in a friend. He denied any rectal bleeding or recent weight loss and his medical history was unremarkable. His family history was remarkable only for a maternal aunt who was diagnosed with bowel cancer in her mid-60s. Colonoscopy revealed a 10 mm semi-sessile polyp in the lower third of his rectum (Fig. 1) with abnormal submucosal vasculature. The endoscopic impression at the time was that of a solitary rectal ulcer. The polyp was snared and submitted for histological examination.

Haematoxylin and eosin (H&E) stained sections of rectal mucosa deep to submucosa revealed lamina propria expansion by a relatively monomorphous infiltrate of intermediate sized lymphoid cells with irregular nuclear borders, finely clumped nuclear chromatin, small indistinct nucleoli and moderate to abundant pale cytoplasm with a somewhat histiocytoid appearance (Fig. 2A). Some cells contained striking intracytoplasmic eosinophilic granules (Fig. 2B). Mitoses were inconspicuous and there was no necrosis. Epitheliotropism and intraepithelial lymphocytosis were not identified and there was no evidence of angiocentric or angiodestructive growth. The atypical lymphoid infiltrate formed variably sized nodular aggregates which were rimmed by small mature lymphocytes and a polymorphous population of inflammatory cells composed of eosinophils, plasma cells, and histiocytes. Scattered reactive lymphoid follicles were present in the adjacent mucosa.

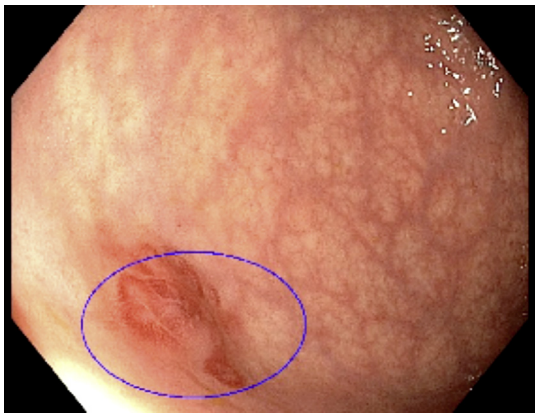

Fig. 1 Colonoscopic appearance of the semi-sessile rectal polyp with abnormal submucosal vasculature.

On immunohistochemistry, the atypical lymphoid cells showed strong diffuse cytoplasmic expression for CD45, CD56, granzyme B and cytotoxic granule-associated RNA binding protein TIA1 (Fig. 2C,D). There was variable expression for T-cell markers, with CD3 and CD7 detected, while CD4, CD5 and CD8 were absent. TCR-βF1 was negative, as was *in situ* hybridisation for EBV-RNA. CD20 highlighted the rim of small mature lymphocytes surrounding the atypical infiltrate as well as adjacent reactive lymphoid follicles with well formed germinal centres. Ki-67 proliferation index was low.

The immunophenotypic findings revealed an NK/T-cell lineage lymphoproliferative disease. We considered the possibility of an enteric NK/T cell lymphoma such as extranodal NK/T-cell lymphoma or monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL; previously called Type II enteropathy-associated T-cell lymphoma[2]); however, the absence of high grade features (e.g., tumour cell necrosis and apoptosis), lack of epitheliotropism and angiocentric/angiodestructive growth, and absence of detectable EBV-RNA, were incompatible with either diagnosis. Moreover epitheliotropism was not identified in the adjacent mucosa. The overall findings therefore were most in keeping with NK-cell enteropathy.

Following the diagnosis, the patient was referred to a haematologist and had full lymphoma workup, including a bone marrow biopsy, a staging CT scan of his chest, abdomen and pelvis, as well as a PET scan, which were all negative. He remained asymptomatic 6 months after the diagnosis (at the time of this case report).

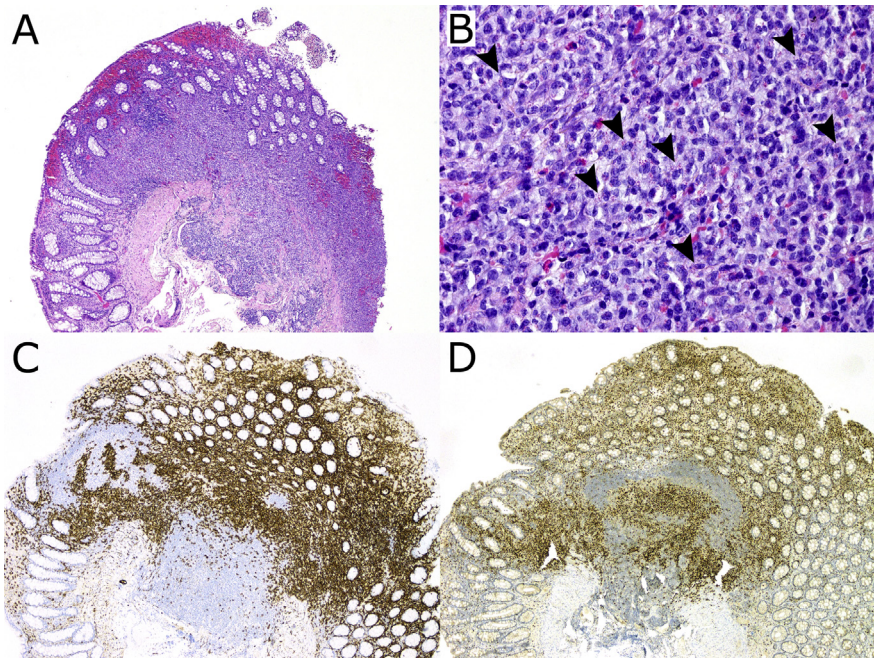

Fig. 2 H&E and immunohistochemistry of NK-cell enteropathy. (A) Scanning magnification showed a diffuse atypical lymphoid infiltrate in the lamina propria of the rectal polyp. (B) Some cells contained striking intracytoplasmic eosinophilic granules (arrow head). The atypical lymphoid cells showed strong diffuse cytoplasmic expression for CD56 (C) and cytotoxic granule-associated RNA binding protein TIA-1 (D).

The term 'NK-cell enteropathy' was first proposed by Mansoor *et al.*[3] in 2011, in their case series of eight patients with atypical NK-cell lymphoproliferative lesions which mimicked NK- or T-cell lymphoma on histology but which followed a clinically indolent course. In the year prior to Mansoor and colleagues' paper, Takeuchi *et al.*[1] reported ten similar cases of a pseudomalignant disorder caused by an unrecognised atypical NK-cell proliferation in the stomach, for which they proposed the term 'lymphomatoid gastropathy'. Since the publication of these two major studies, there has been occasional individual case reports describing similar findings.[4–7] The lack of a significant body of literature on this condition attests to the rarity of NK-cell enteropathy and its potential for underdiagnosis or overdiagnosis. As the disease can involve any gastrointestinal site, we prefer the term 'NK-cell enteropathy'.

NK-cell enteropathy appears to affect both men and women in the adult age group, although one case report describing the disease in a 14-year-old boy exists.[4] Most patients are asymptomatic, undergoing elective endoscopy for various unrelated reasons, while others report vague abdominal symptoms. The lesions are found most commonly in the stomach, duodenum, and colon, with extra-gastrointestinal involvement (of the gallbladder) described in one case report.[5] Endoscopic appearances range from superficial erythematous lesions, erosions, superficial ulcerations, and flat elevations to sub-centimetre sized polyps.

The histology of this disease is distinctive yet similar across all reported cases. Takeuchi *et al.*[1] noted the presence of variable proportions of cells (ranging from 20% to 90%) with intracytoplasmic eosinophilic granules which were also present in our case. These large eosinophilic cytoplasmic granules have not been previously described in extranodal lymphoma of NK/T cell lineage and may represent a characteristic cytomorphological feature of NK-cell enteropathy. Future studies will be needed to investigate this further.

The immunohistochemical profile for NK-cell enteropathy is characteristic; the atypical cells express CD56 and cytotoxic cell markers (e.g., TIA-1, and/or granzyme B), with variable expression for T-cell markers (typically positive for CD7 and cytoplasmic CD3, and negative for CD5, CD4, CD8, CD10, CD20, CD30, and TCRβF1). EBER-RNA *in situ* hybridisation is negative and the Ki-67 proliferation index is relatively low. Polymerase chain reaction for T-cell receptor gene rearrangement typically fails to identify evidence of a clonal process. As most cases are identified incidentally (as was ours for polyp surveillance), it is not always possible to rely on flow cytometric analysis of fresh tissue.

The aetiology of NK-cell enteropathy remains undefined. NK cells are a subset of lymphoid cells associated with the innate immunity which demonstrate cytotoxic activity against viruses and tumour cells.[8] As the lesional cells in NK-cell enteropathy show consistently strong expression for granzyme B and/or TIA-1, it has been postulated that these atypical populations arise in the setting of chronic inflammation which trigger a cytotoxic response such as autoimmunity or viral infection.[3] At this point in time, it is difficult to determine if NK-cell enteropathy is a truly neoplastic process, given the absence of detectable monoclonality. Further elucidation by gene expression profiling using next generation sequencing technologies await discovery.

The prognosis of NK-cell enteropathy appears to be promising with all reported cases behaving in a benign manner. None of the patients in the case series reported by Mansoor *et al.*[3] developed progressive disease or died of lymphoma (median follow-up of 30 months) regardless of whether aggressive follow-up treatment was instituted. In our review of the published literature including individual

case reports to date (where follow-up data was available), all patients were either alive with persistent disease or there was spontaneous regression with occasional local relapses.

In summary, we describe NK-cell enteropathy in the rectum presenting as endoscopically visible polypoid mucosa in an asymptomatic adult patient. The lesion is characterised by a diffuse atypical lymphoid infiltrate in the lamina propria with CD56 and cytotoxic molecule expression. Tests for Epstein−Barr virus (EBV) are typically negative, and importantly, T-cell monoclonality is not detected. It is important to consider this differential in the workup of any gastrointestinal non-B-cell lymphoma as it can be misdiagnosed as an aggressive lymphoma such as MEITL or extranodal NK/T-cell lymphoma. In the case series by Mansoor and colleagues,[3] three patients were initially misdiagnosed as malignant lymphoma and received aggressive chemotherapy (followed by autologous bone marrow transplantation in two). Of the ten patients described by Takeuchi *et al.*,[1] six patients were initially misdiagnosed as malignant lymphoma or suspected malignant lymphoma, while one patient was misdiagnosed as poorly differentiated adenocarcinoma and treated with partial gastrectomy. We emphasise that clinicopathological and haematological correlation is necessary in the workup of unusual lymphoid diseases of the gastrointestinal tract.

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Biclonal presentation of lymphoplasmacytic lymphoma/ Waldenström macroglobulinaemia

Sir,

Lymphoplasmacytic lymphoma/Waldenström macroglobulinaemia (LPL/WM) is a lymphoid neoplasm involving bone marrow associated with an IgM paraprotein. It is composed of small lymphocytes, plasmacytoid lymphocytes and plasma cells in variable proportions.[1] About 10−20% of patients with LPL/WM have involvement of lymph nodes, spleen or other extranodal sites.[2] This neoplasm is monoclonal and usually derives from a single transformed B-cell progenitor. In this study, we present an interesting case of LPL/WM with two different clones identified in bone marrow and lymph node, respectively. Whereas *MYD88 L265P* mutation was detected at both anatomical sites, flow cytometric immunophenotypic analysis and immunohistochemical studies demonstrated kappa light chain restricted cells in the bone marrow but lambda light chain restricted cells in the lymph node. Correspondingly, serum protein electrophoresis and immunofixation studies showed two paraproteins, IgM kappa and IgM lambda. To determine whether these two neoplastic populations in bone marrow and lymph node, respectively, were derived from the same clone, we performed next generation sequencing analysis to study immunoglobulin heavy chain (*IGH*) chain and kappa light chain (*IGK*) gene rearrangements. We found that neoplastic cells from bone marrow and lymph node had different V(D)J rearrangements, indicating they were independent clones. Analysis of rearranged *IGK* sequences from the lymph node revealed the kappa deleting element (kde), which led to inactivation of the *IGK* allele; as a result, lambda light chain (*IGL*) was rearranged and transcribed, as demonstrated by lambda light chain expression by lymphoma cells in the lymph node.

The patient was a 62-year-old man who presented with anemia (red blood cells 3.68 × 10^6/μL, haemoglobin 10 g/dL). The white blood cell and platelet counts were normal. Serum studies showed an elevated free kappa/lambda ratio of 8.7 with free kappa of 63 mg/L (3.3−19.4 mg/L) and free lambda of 7.26 mg/L (5.7−26.3 mg/L). IgM was elevated at 3407 mg/dL. Protein electrophoresis and immunofixation studies showed two paraproteins; one was IgM lambda (0.6 g/dL) and another was IgM kappa (2.3 g/dL) (Fig. 1). Positron emission tomography-computed tomography (PET-CT) scan showed right axillary lymphadenopathy (up to 4/4 cm) with a

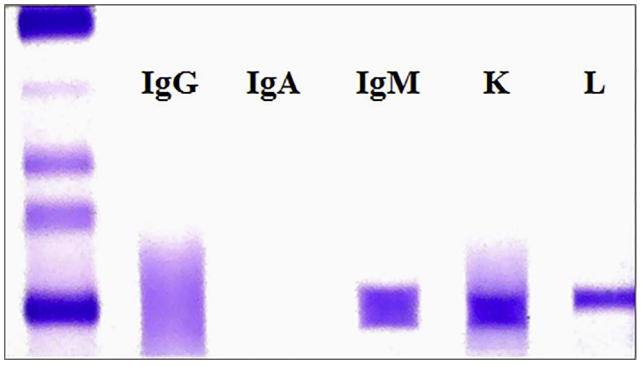

Fig. 1 Serum immunofixation study shows two paraproteins, IgM kappa and IgM lambda.