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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1. Takeuchi K, Yokoyama M, Ishizawa S, *et al*. Lymphomatoid gastropathy: a distinct clinicopathologic entity of self-limited pseudomalignant NK-cell proliferation. *Blood* 2010; 116: 5631−7.
2. Swerdlow SH, Campo E, Harris NL, *et al*. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. Revised 4th ed. Lyon: IARC Press, 2017.
3. 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.
4. Koh J, Go H, Lee WA, *et al*. Benign indolent CD56-positive NK-cell lymphoproliferative lesion involving gastrointerestinal tract in an adolescent. *Korean J Pathol* 2014; 48: 73−6.
5. Hwang SH, Park JS, Jeong SH, *et al*. Indolent NK cell proliferative lesion mimicking NK/T cell lymphoma in the gallbladder. *Hum Pathol Case Rep* 2016; 5: 39−42.
6. Ishibashi Y, Matsuzono E, Yokoyama F, *et al*. A case of lymphomatoid gastropathy: a self-limited pseudomalignant natural killer (NK)-cell proliferative disease mimicking NK/T-cell lymphomas. *Clin J Gastroenterol* 2013; 6: 287−90.
7. Ogawa S, Imai Y, Inokuma T. Mimicking gastric natural killer/T-cell lymphoma. *Gastroenterology* 2017; 153: e22−3.
8. Vivier E, Tomasello E, Baratin M, *et al*. Functions of natural killer cells. *Nat Immunol* 2008; 9: 503−10.

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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

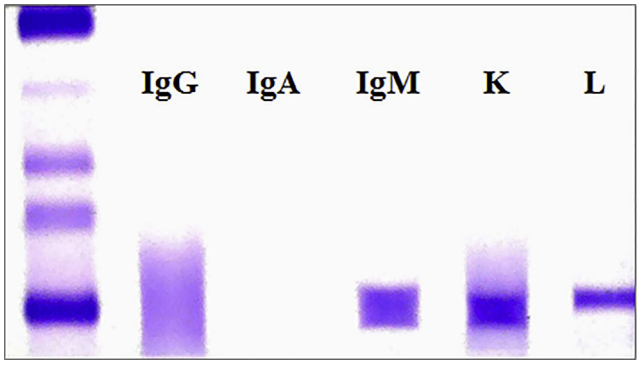

Fig. 1 Serum immunofixation study shows two paraproteins, IgM kappa and IgM lambda.

standardised uptake value (SUV) up to 5.3 as well as multiple small retroperitoneal and mesenteric lymph nodes with a SUV of 4.0. There was no evidence of splenomegaly but the spleen showed mild diffuse hypermetabolic activity with a SUV up to 4.8. Hypermetabolic activity was also observed in the axial skeleton with a maximum SUV of 5.8.

Bone marrow biopsy showed an atypical lymphoid infiltrate composed of many small lymphocytes and scattered plasma cells in an interstitial and focally diffuse pattern (Fig. 2). By immunohistochemistry, the lymphocytes were predominantly B cells positive for CD20. The anti-CD138 antibody highlighted scattered plasma cells and light chain antibodies showed kappa restriction. Flow cytometric analysis showed an aberrant B cell population, positive for CD19, CD20 and monotypic surface kappa, and negative for CD5 and CD10 (data not shown). A small kappa-restricted plasma cell population was also detected by flow cytometric analysis (data not shown). Molecular study using PCR and a quantitative pyrosequencing method detected a *MYD88 L265P* mutation with a mutation rate of 16.5%.

Lymph node excisional biopsy showed that the nodal architecture was effaced by lymphoma in a vaguely nodular pattern (Fig. 3). The lymphoma was composed of sheets of small lymphocytes and scattered to loosely clustered plasma cells. Immunostain for CD20 highlighted sheets of B cells and CD138 highlighted scattered plasma cells. Kappa and lambda immunostains showed that neoplastic cells were lambda restricted. The concurrent flow cytometric immunophenotyping studies of the lymph node showed an aberrant B-cell population, positive for CD19, CD20 and monotypic surface lambda, and negative for CD5 and CD10 (data not shown). Molecular study detected *MYD88 L265P* mutation with a mutation rate of 40%.

We assessed the lymphoma cells in bone marrow and lymph node for a clonal relationship by performing next generation sequencing (NGS) analysis to study the patterns of gene rearrangements for *IGH* and *IGK* using the LymphoTrack assay (Invivoscribe, USA). In the bone marrow, *IGH* rearrangement showed a dominant clone that utilised VH3-J4 (Fig. 4A). This same clone was also identified in the lymph node but was significantly smaller; instead a different dominant clone was identified which utilised VH3-J5 (Fig. 4B). Sequence comparison showed no similarity between these two dominant clones. Analysis of the rearranged *IGK* in bone marrow and lymph node also showed different dominant clones (Fig. 4C versus 4D). Further analysis of the dominant *IGK* clone from lymph node revealed the kde rearranged to the Jk-Ck intron (IGKintr-IGKdel, Fig. 4D). The rearrangement involving kde has been shown to inactivate the *IGK* allele through deletion of the entire Jk-Ck area or the Ck region only.[3] The inactivation of *IGK* triggered subsequent *IGL* rearrangement and lambda light chain expression in the lymph node.

LPL/WM is believed to be a monoclonal process arising from a single transformed progenitor cell which proliferates and differentiates into a heterogeneous population composed of lymphocytes, plasmacytoid lymphocytes and plasma cells. Similar to other haematopoietic diseases, however, clonal heterogeneity and clonal evolution from a common ancestor clone have been described in LPL/WM.[4] In addition, two unrelated clones present in bone marrow and peripheral blood from the same patient have been rarely described.[5–7] Here we

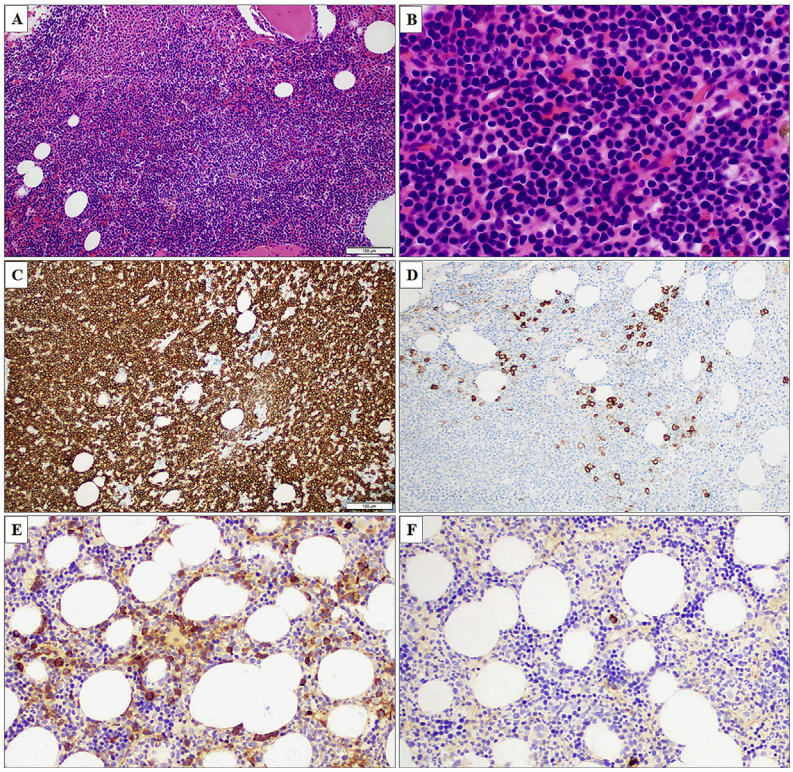

Fig. 2 (A) Bone marrow core biopsy shows an atypical lymphoid infiltrate in an interstitial and diffuse pattern. (B) Lymphocytes are small with occasional plasma cells. (C) Immunostains show the lymphoid infiltrate is composed of many B cells (anti-CD20) and (D) scattered plasma cells (anti-CD138). (E) Kappa and (F) lambda immunostains show plasma cells are kappa light chain restricted.

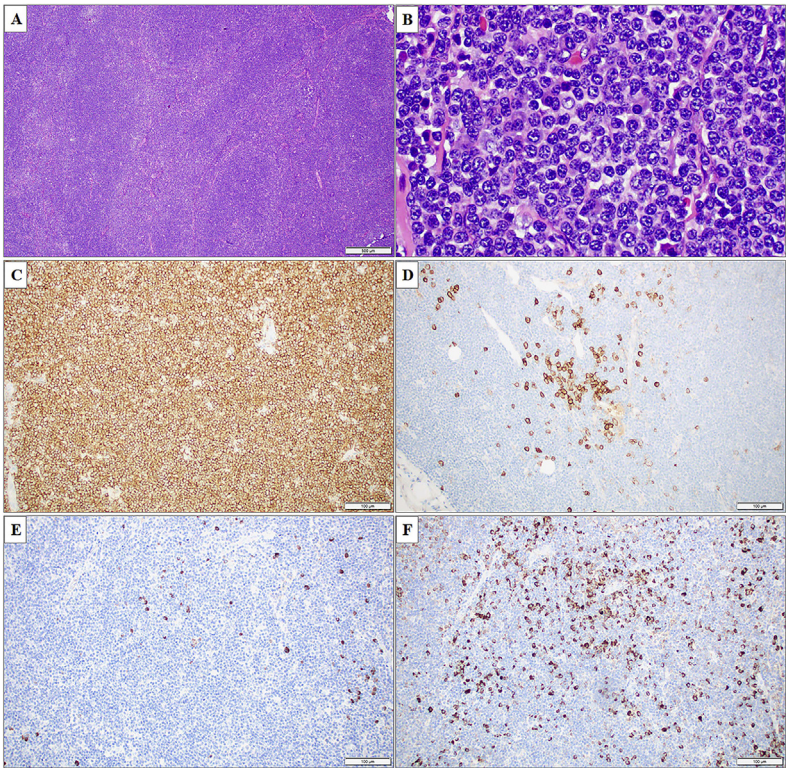

Fig. 3 (A) At low power, the lymph node architecture is effaced by a vaguely nodular lymphoid proliferation. (B) At high power, the lymphoid infiltrate is composed of a mixture of small lymphocytes (predominant) and plasma cells (scattered). (C) Anti-CD20 highlights sheets of lymphocytes and (D) anti-CD138 highlights scattered and clustered plasma cells. Plasma cells are lambda light chain restricted by (E) kappa and (F) lambda immunostains. In addition to plasma cells, lambda immunostain also highlights plasmacytoid lymphocytes.

have presented a unique case of biclonal LPL/WM with different clones located in bone marrow and lymph node, respectively. Biclonality was shown at both the protein and molecular levels. Although two paraproteins (IgM kappa and IgM lambda) were detected in the serum, the predominant paraprotein was IgM kappa which was derived from neoplastic cells in bone marrow. The presence of two different clones carrying the same *MYD88 L265P* mutation raises the possibility that the *MYD88* mutation occurred before VDJ rearrangements, although the emergence of two *MYD88 L265P* mutations independently later after VDJ rearrangements can not be completely excluded.

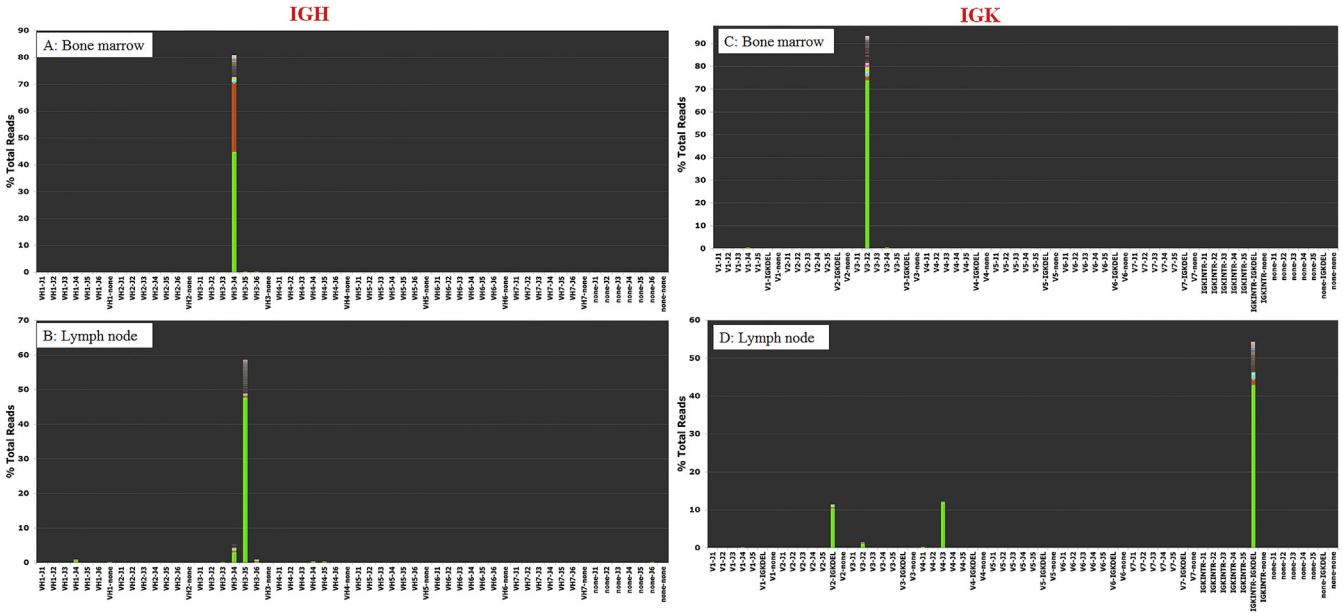

Fig. 4 (A,B) LymphoTrack IGH assay. (A) In bone marrow the predominant clone is VH3-J4, whereas (B) in lymph node the predominant clone is VH3-J5. The VH3-J4 sequence identified in bone marrow is still present in lymph node specimen but with a significantly lower percentage. (C,D) LymphoTrack IGK assay. (C) Bone marrow shows one dominant clone. (D) Lymph node shows several clones and the predominant one (IGKintr-IGKdel) shows a deletion.

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1. Swerdlow S, Cook J, Sohani A, *et al*. Lymphoplasmacytic lymphoma. In: Swerdlow S, Campo E, Harris N, *et al*., editors. *Who Classification of Tumours of Haematopoietic and Lymphoid Tissues*. Lyon: IARC Press, 2017; 232–5.
2. Shaheen SP, Talwalkar SS, Lin P, *et al*. Waldenstrom macroglobulinemia: a review of the entity and its differential diagnosis. *Adv Anat Pathol* 2012; 19: 11–27.
3. Gonzalez D, van der Burg M, Garcia-Sanz R, *et al*. Immunoglobulin gene rearrangements and the pathogenesis of multiple myeloma. *Blood* 2007; 110: 3112–21.
4. Ciric B, VanKeulen V, Rodriguez M, *et al*. Clonal evolution in waldenstrom macroglobulinemia highlights functional role of B-cell receptor. *Blood* 2001; 97: 321–3.
5. Bonewald L, Virella G, Wang AC. Evidence for the biclonal nature of a Waldenstrom's macroglobulinemia. *Clin Chim Acta* 1985; 146: 53–63.
6. Schulz R, David D, Farkas DH, *et al*. Molecular analysis in a patient with waldenstrom's macroglobulinemia reveals a rare case of biclonality. *Mol Diagn* 1996; 1: 159–66.
7. Kriangkum J, Taylor BJ, Treon SP, *et al*. Molecular characterization of Waldenstrom's macroglobulinemia reveals frequent occurrence of two B-cell clones having distinct IGH VDG sequences. *Clin Cancer Res* 2007; 13: 2005–13.

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