Histopathology

Histopathology 2024 DOI: 10.1111/his.15161

Lesson of the Month

A wolf in sheep's clothing: enteropathy associated T-cell lymphoma involving a nasal polyp masquerading as primary mucosal CD30-positive T-cell lymphoproliferative disorder

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Case Summary

An 81-year-old woman presented with nose bleeds and a left anterior nasal septal polyp. Excision biopsy revealed a mucosal lymphoid infiltrate with features of anaplastic large-cell lymphoma (ALCL) (Figure 1A). The neoplastic cells were positive for CD45, CD30, EMA (focal), CD3 (variable), CD2, CD25, pSTAT3, TIA1 (focal), and granzyme-B (focal), but negative for ALK, CD5, CD7, CD4, CD8, TCRβ, CD103, and B-cell markers. There was weak and patchy LEF1 expression. Ki67 proliferation approached 100%. EBV encoded small RNA was negative by *in situ* hybridisation (ISH). Fluorescent ISH analysis did not detect *DUSP22* or *TP63* rearrangements. In view of the clinically localized disease, the proffered diagnosis was mucosal $CD30^+$ T-cell lymphoproliferative disorder (T-LPD) akin to primary cutaneous $CD30^+$ T-LPD, with the caveat that imaging should confirm localized disease to exclude systemic ALK-negative ALCL.

Staging a positron emission tomography (PET) / computed tomography (CT) scan highlighted two areas of jejunal thickening with a standardized uptake value (SUV) max of 17.4, but no disease elsewhere (Figure 1B). The possibility of enteropathy-associated T-cell lymphoma (EATL) with nasal involvement was considered, and serology for coeliac disease (CD) and jejunal biopsy were recommended. CD was confirmed on serology. Further questioning revealed a history of weight loss and anaemia for which an upper gastrointestinal endoscopic biopsy performed 3 years previously at another institution had suggested CD. Jejunal resection showed a necrotic ulcerated tumour with typical histology of EATL and background refractory coeliac disease type 2 (RCD2) (Figure 1C). The EATL was CD30-positive, but unlike the nasal polyp, was diffusely positive for CD7, CD103, and cytotoxic granules. Background mucosa displayed typical RCD2 changes, including villous atrophy and a marked increase of $CD3^+$, $CD8^-$, $CD103^+$, and $CD7^+$ intraepithelial lymphocytes (IELs). The nasal polyp diagnosis was revised to disseminated EATL.

Clonality analysis showed identical sized clonal TRG products (184 bp, 191 bp) in the nasal polyp, EATL, and RCD2 lesions well-separated from the main tumour. Targeted next-generation sequencing of 185 T-cell lymphoma genes identified variants in *HLA*-A (c.1017delA, p.R339fs), *POT1* (c.G199A, p.E67K), *PTPTD* (c.C1750T, p.R584C), *SOCS1* (c.213_223del, S71fs; c.494delC, p.P165fs), *STAT3* (c.G1981C, p.D661H), and *TET2* (c.A1606T, p.K536X) in all three sites at different variant allele frequencies, reflecting their tumour cell contents (Figure 2). Although none of these mutations is pathognomonic, their combination favours a diagnosis of EATL rather than ALK-negative ALCL.[1,2]

The patient received two cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone but died of disease 9 months after the initial presentation.

Comment

ALK-negative ALCL is a heterogeneous entity harbouring different genetic abnormalities with prognostic implications. Histologically, it shows characteristic strong and uniform CD30 expression and is morphologically indistinguishable from ALK+ ALCL. Diagnosis of 'triple negative' ALCL, i.e. lacking *ALK*, *DUSP22*, and *TP63* rearrangements, requires clinical correlation to exclude mimics that have similar histological features but different clinical outcomes. While systemic ALK-negative ALCL is usually disseminated, localized mucosal disease of the head and neck points to the recently recognized primary mucosal $CD30^+$ T-LPD, analogous to primary cutaneous $CD30^+$ T-LPD, and amenable to localized therapy.[3]

EATL, an aggressive primary intestinal T-cell lymphoma of IELs, is also often strongly and uniformly CD30-positive with a similar cytotoxic T-cell immunoprofile. It typically occurs in those with CD and may show stepwise evolution from RCD2, a clonal precursor lesion composed of phenotypically aberrant IELs. CD may precede or be diagnosed simultaneously with EATL.[4] Rarely, EATL may disseminate to a single extraintestinal site, typically either concurrently or following diagnosis of RCD, EATL, or CD.[5,6] Verbeek *et al.* report a case of RCD2 with unusual

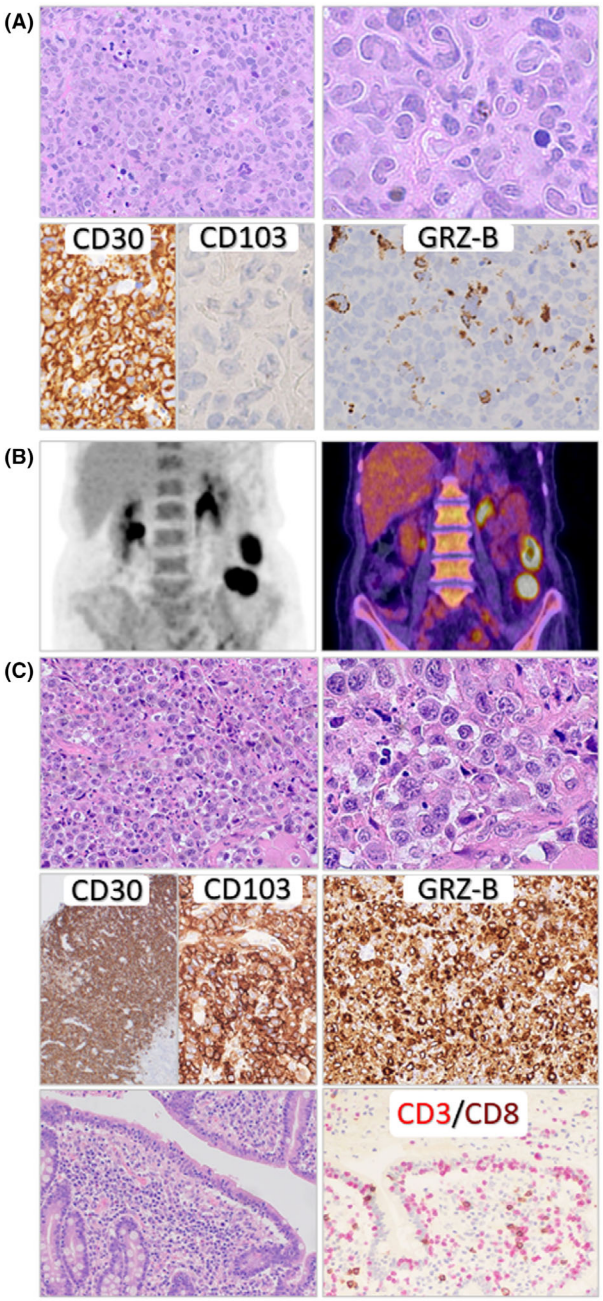

Figure 1. Clinical and histological presentation. **A**:– Histology and immunoprofile of the nasal polyp. Haematoxylin and eosin (H&E) stain shows a diffuse infiltrate of large, atypical cells with abundant eosinophilic cytoplasm and atypical, often indented nuclei with frequent mitoses (top left, top right). The tumour is strongly and diffusely positive for CD30 (bottom left, left panel). CD103 is negative (bottom left, right panel) and granzyme B shows focal positivity (bottom right). **B**:– Positron emission tomography (PET) / computerized tomography (CT) scan. Two jejunal lesions detected on PET/CT, coronal inverse grey scale PET (left) and fused PET/CT (right) with a standardized uptake value (SUV) max of 17.4. **C**:– Histology and immunoprofile of jejunal enteropathy associated T-cell lymphoma (EATL) (top and middle rows) and background refractory coeliac disease type 2 (RCD2) (bottom row). H&E stain, focally transmural partly necrotic large cell lymphoma composed of pleomorphic, anaplastic large cells including multinucleate forms with frequent mitoses (top left, top right). CD30 shows strong and diffuse positivity (middle left, left panel right). CD103 is strongly and diffusely positive (middle left, right panel), as is granzyme B (middle right). H&E stain of RCD2 shows villous atrophy and an increase in intraepithelial lymphocytes (IELs) (bottom left), while CD3 (red)/CD8(brown) double stain illustrates the aberrant CD3-positive, CD8-negative phenotype of the IELs.

cutaneous lesions containing RCD2-type aberrant T-cells, which subsequently developed intestinal EATL.[7] Bisig *et al.* describe *DUSP22*-rearranged CD30$^+$ cutaneous lesions in a case of long-standing CD, disseminated lymphadenopathy on scan, and subsequent clonally related EATL lacking the *DUSP22*-rearrangement, suggesting their divergent differentiation from RCD2.[8]

Solitary extraintestinal mucosal dissemination presenting prior to clinical suspicion or diagnosis of RCD or EATL is a potential pitfall with significant clinical impact. To the best of our knowledge, this is the first report of such a case. Initial misdiagnosis is attributed to the unusual presentation with no information on CD and the undue reliance on histopathology for diagnosis. CD103, an integrin αE subunit involved in lymphocyte homing to epithelia, is positive in normal IELs, RCD2, and in most cases of EATL. Lack of CD103 in the nasal polyp, as previously reported at other extraintestinal sites,[8,9] was misleading. The phenotypic discordance between nasal polyp and RCD2/EATL, mutation profiles, and clonality studies provide no insight into pathogenesis, whether stepwise progression or divergent evolution from RCD2.

In conclusion, EATL may rarely present at a solitary extraintestinal mucosal site with no prior clinical suspicion of RCD or EATL. Histopathology, even when combined with genetics, may not enable an accurate diagnosis. CD103, although a useful clue when expressed, may be absent in extraintestinal disease. Awareness and correlation with relevant clinical details and imaging are essential to prevent misdiagnosis as the far less aggressive primary cutaneous/mucosal CD30$^+$ T-LPD.

Author contributions

ADA, KMV, and ACW reviewed histology. ADA and MQD analysed the data and co-wrote the article. CZ

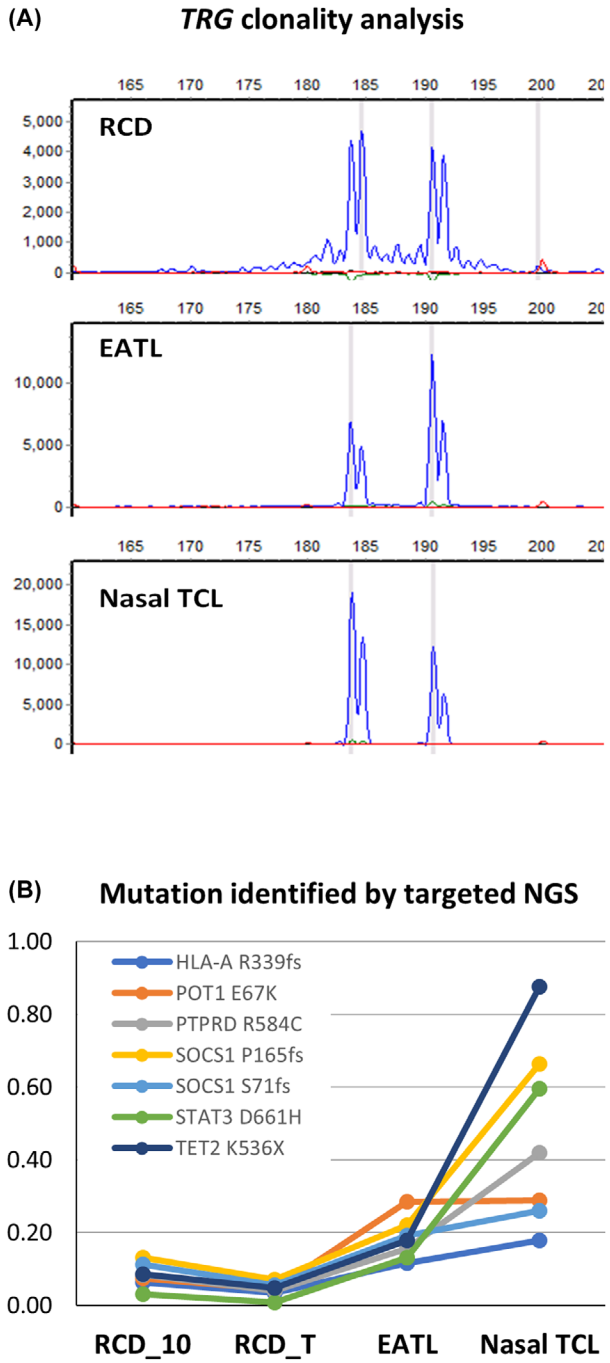

Figure 2. Clonality and mutation analysis. **A**:– Clonality analysis of the rearranged TR genes shows identical sized clonal TRG products (184 bp, 191 bp) in the nasal polyp, EATL, and RCD2 lesions well-separated from the main tumour, indicating their common clonal identity. **B**:– Targeted next-generation sequencing of 185 T-cell lymphoma genes reveals the same mutations among the nasal polyp, EATL, and RCD2 lesions well-separated from the main tumour.

designed the NGS panel and EM, MMT, and ZC performed the NGS analysis. BS reviewed the radiology. SR performed clonality studies and SC performed cytogenetics. EJA provided clinical input and KMV, ACW, BS, MMT, CZ, ZC, EJA, SR, and SC revised the article critically.

Funding information

The research in MQD's lab was supported by grants from Blood Cancer UK (19010, 22011), Cancer Research UK (C8333/A29707), MMT was supported by a BBSRC DTP PhD studentship (BBSRC BB/M011194/1). We acknowledge support from the NIHR RM/ICR Biomedical Research Centre and CRUK.

Conflict of interest

The authors have no conflicts of interest to declare.

Ethical statement

There was no direct involvement of the patient in this study, no patient identifying information was used, and therefore patient consent was not required. The study was a clinical diagnostic investigation and additional molecular work was based on redundant tissue materials after diagnosis. This met with conditions approved by the Ethics Committees of the involved institutions (05-Q1604-10).

Data availability statement

Data sharing is not applicable to this article, as no datasets were generated or analysed during the current study.

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