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. Ki67 proliferation approached 100%. EBV encoded small RNA was negative by in situ hybridisation. Fluorescent in situ hybridisation analysis did not detect DUSP22 or TP63 rearrangements. In view of the clinically localised disease, the proffered diagnosis was mucosal CD30+ T-cell lymphoproliferative disorder (T-LPD) akin to primary cutaneous CD30+ T-LPD, with the caveat imaging should confirm localised disease, excluding systemic ALK-negative ALCL.

Staging PET/CT scan highlighted two areas of jejunal thickening with a standardised 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 gastro-intestinal 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 marked increase of CD3+, CD8-, CD103+, CD7+ intra-epithelial lymphocytes (IELs). Nasal polyp diagnosis was revised to disseminated EATL.

Clonality analysis showed identical sized clonal TRG products (184bp, 191bp) 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 these lesions 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 (PMID: 30829413, PMID: 28424246).

Patient received 2 cycles of cyclophosphamide, doxorubicin, vincristine and prednisone but died of disease 9-months after 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 the common 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, localised mucosal disease of the head and neck points to the recently recognised primary mucosal CD30+ T-LPD, analogous to primary cutaneous CD30+ T-LPD, and amenable to localised therapy.1
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. Rarely EATL may disseminate to a single extra-intestinal site, typically either concurrently or following diagnosis of RCD, EATL or CD. Veerbeek et al report a case of RCD2 with unusual cutaneous lesions containing RCD2-type aberrant T-cells, which subsequently developed intestinal EATL. 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 but lacking the DUSP22-rearrangement, suggesting their divergent differentiation from RCD2.

Solitary extraintestinal mucosal dissemination presenting prior to clinical suspicion or diagnosis of RCD or EATL is a potential pitfall with significant clinical impact, as exemplified in this case report. Its 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, 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 a correct 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.
References

1. Feldman AL, Li X-Q, Ko Y-H, Pileri SA, Boy S. Primary mucosal CD30 positive T-cell lymphoproliferative disorder. 5th ed. Online: IARC.

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Authors’ Contributions

ADA, KMV and ACW reviewed histology. ADA and MQD analyzed the data and co-wrote the paper. CZ designed the NGS panel and EM, MMT, and ZC performed the NGS analysis. BS reviewed the radiology. SR and AM performed cytogenetics. EJA and JB provided clinical input. KMV, ACW, BS, EJA, JB, MMT, CZ, ZC, SR and AM revised the manuscript critically.
Figure legends

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). The tumour is strongly and diffusely positive for CD30 (top right). CD103 is negative (bottom left) and granzyme B shows focal positivity (bottom right).

B. Positron emission tomography (PET)/computerised tomography (CT) scan

Two jejunal lesions detected on CT (left) and PET scan (right), with a standardised 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, x600 magnification of the focally transmural partly necrotic large cell lymphoma composed of pleomorphic, anaplastic large cells including multinucleate forms with frequent mitoses (top left). CD30 shows strong and diffuse positivity (top right). CD103 is strongly and diffusely positive (middle left) as is granzyme B (middle right). H&E stain of RCD2 shows villous atrophy and an increase in intra-epithelial lymphocytes (IELs) (bottom left) while CD3 (red)/CD8(brown) double stain illustrates the aberrant CD3 positive, CD8 negative phenotype of the IELs.

Figure 2: Clonality and mutation analysis.

A. Clonality analysis of the rearranged TR genes shows identical sized clonal TRG products (184bp, 191bp) 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.