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Title: ALK-positive large B-cell lymphoma with strong CD30 expression; a diagnostic pitfall and resistance to brentuximab and crizotinib

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This work highlights a rare diagnostic pitfall and reports lack of efficacy of brentuximab and crizotinib in ALK positive large B-cell lymphoma

We report a case of ALK positive large B-cell lymphoma (ALK-LBCL) with strong CD30 expression, initially misdiagnosed as anaplastic large cell lymphoma (ALCL), ALK positive. These two lymphomas differ in response to chemotherapy and prognosis making accurate diagnosis essential.

A 23-year old female presented with a 3-month history of B symptoms and enlarging lymphadenopathy. She subsequently developed abdominal pain and jaundice with a palpable swelling in the right upper abdominal quadrant. Blood tests revealed obstructive liver function tests, a pancytopenia and an elevated LDH. A computed tomography (CT) scan revealed lymph node masses at the level of the porta hepatis and in the retroperitoneum and a positron emission tomography (PET)-CT scan confirmed widespread FDG avid nodal and extra-nodal disease.

A bone marrow (BM) aspirate showed multiple clusters of large mononuclear cells with abundant basophilic, vacuolated cytoplasm. (Fig 1A, B). The BM trephine showed infiltration by sheets of large atypical cells with prominent nucleoli. These cells were diffusely positive for ALK (cytoplasmic and perinuclear) and CD30, but negative for B-cell, T-cell and myeloid markers (Fig 2 A-C). Fluorescence in situ hybridisation on the BM aspirate using a break-apart probe demonstrated a rearrangement of the *ALK* gene (Fig 1C). The lymph node biopsy showed replacement by sheets of large atypical cells with irregular nuclei and multiple nucleoli. Immunohistochemistry demonstrated strong positive staining for CD30 (cytoplasmic), ALK (cytoplasmic and paranuclear), CD45 and EMA (epithelial membrane antigen) as

well as Bcl-6, CD10 and CD15. Ki67 was 95%. The cells did not express pan B-cell or T-cell markers. Thus, a diagnosis of anaplastic large cell lymphoma, ALK positive with a 'null phenotype' was made.

The patient was treated using the paediatric ALCL 99 protocol[1], following the algorithm for high-risk disease. Following 2 cycles of chemotherapy the patient had progressive disease. Given the CD30 expression, a trial of brentuximab vedotin (BV) was commenced. Although there was a transient response with a fall in LDH levels, after 2 cycles the disease progressed (Fig 1D). A single course of gemcitabine and oxaliplatin chemotherapy was tried without effect. The presence of an *ALK* translocation prompted a two-week trial of crizotinib, an ALK inhibitor, through a company access program. There was an initial fall in LDH levels (Fig 1D) but the patient rapidly deteriorated with circulating tumor cells and died 4 months following initial diagnosis.

Given the unexpected treatment refractory nature of the disease, a review of the diagnostic biopsy was undertaken. Further immunohistochemical stains on the BM trephine showed positivity for CD138 and lambda light chain restriction confirming the B-cell origin of the tumour, more in keeping with ALK-LBCL (Fig 2D, E).

ALK-LBCL is a rare variant of diffuse large B-cell lymphoma (DLBCL), first described in 1997[2]. Since then, fewer than 100 cases have been described. The lymphoma has a bimodal age distribution with primarily nodal involvement and displays an aggressive behavior resulting in a median survival of 12 months[3]. ALK-LBCL is characterised by the presence of immunoblastic or plasmablastic cells with strong ALK protein expression that is frequently associated with t(2;17)(p23;q23) and more rarely the t(2;5)(p23;q35). Immunohistochemistry

reveals a distinct profile, including a lack of B- and T-cell markers, but expression of CD138 and CD38 and usually cytoplasmic IgA with light chain restriction. CD30 expression is rare, usually focal and weak, with one case series reporting positivity in 11% of cases[3].

BV is an anti-CD30 monoclonal antibody conjugated to monomethyl auristatin E..Variable CD30 expression has been demonstrated, in DLBCL. A study of BV in relapsed/refractory CD30 positive DLBCL reported a response rate of 44%[4]. There are no data reporting the use of BV in ALK-LBCL.

There are limited experimental and clinical data to suggest that ALK inhibitors may be efficacious in ALK-LBCL. Crizotinib, the small molecule dual inhibitor of the MET and ALK receptor tyrosine kinases, has been reported to produce short-term clinical response[5,6].

This case highlights that the diagnosis of ALK-LBCL can pose a challenge, especially when it is CD30 positive. It also demonstrates the chemorefractory nature of the disease and the dismal prognosis. However, there is hope that a targeted therapy combined with chemotherapy may improve prognosis in the future.

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1. VM collected clinical history, investigation results, obtained morphology pictures and wrote the initial manuscript.
2. RI and CS reviewed the pictures
3. SD, RM, PP and DY were involved in the care of the patient
3. SK and SP edited the manuscript for final submission

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Figure Legends :

Figure 1

a) BM aspirate (MGG stain) shows clusters of large atypical pleomorphic mononuclear cells with vacuolated basophilic cytoplasm and eccentric immature nuclei-immunoblastic morphology.
b) BM aspirate with hypercellular particles and trails with some clustering of tumour cells.
c) FISH on BM aspirate: Break-apart probe confirming ALK gene rearrangement (separate red & green signal).
d) Trends in LDH as a bio-marker correlating with disease activity. Note transient decline in LDH when treated with novel agents, suggestive of some response.

Figure 2: BM Trephine:

a) H&E section (x 40 magnification).
b) ALK stain positive.
c) CD30 stain positive.
d) CD138 stain positive.
e) Surface lambda Light chain positive.