CASE REPORT

Atypical blood and bone marrow lymphocytes in ALK-positive anaplastic T-cell lymphoma: important lessons

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SUMMARY

A 42-year-old man presented with a short history of fever, significant weight loss and bilateral neck swelling. A CT scan revealed widespread lymphadenopathy and hepatosplenomegaly. Lymph node morphology and immunohistochemistry confirmed a diagnosis of anaplastic lymphoma kinase (ALK)-positive anaplastic T-cell non-Hodgkin's lymphoma. Both the peripheral blood (PB) and bone marrow (BM) revealed atypical lymphocytes with cleaved nuclei, vacuolation and granulation, suggestive of disease involvement at both sites. However, BM and PB immunophenotyping and immunohistochemistry did not reveal typical markers (ALK and CD30) at either site. All features resolved with a short remission after conventional chemotherapy. Despite salvage chemotherapy and an autologous stem cell transplant, a relapse of the PB and BM features with stable radiological findings was noted. Rapid decline followed with pancytopenia resulting in death 12 months after the initial diagnosis.

BACKGROUND

Anaplastic lymphoma kinase (ALK)-positive anaplastic T-cell lymphoma generally conveys a favourable prognosis responding well to conventional chemotherapy. Peripheral blood (PB) and bone marrow (BM) involvement with the presence of positivity for CD30 and ALK confer a significantly poorer prognosis. Morphology in both sites was typical of disease involvement in the absence of typical immunohistochemistry and immunophenotyping findings. Such morphological findings may correlate with a poorer prognosis and warrant the need to undertake detailed cytogenetic analysis.

CASE PRESENTATION

A 42-year-old man presented to his general practitioner with a 2-month history of a progressive bilateral neck swelling associated with persistent fever and over 5 kg weight loss. Clinical examination confirmed bilateral cervical swelling but with no other palpable lymphadenopathy or hepatosplenomegaly. An unprovoked above knee deep vein thrombosis was noted in his medical history for which he completed a 3-month course of warfarin 9 months prior to presentation.

INVESTIGATIONS

Initial investigations showed a leucocytosis with a neutrophilia and lymphocytosis (haemoglobin 129 g/L, white cell count $23.4 \times 10^9/L$, platelet

$352 \times 10^9/L$, lymphocyte $7.3 \times 10^9/L$, neutrophil $13.6 \times 10^9/L$). The lactate dehydrogenase was moderately elevated at 314 IU/L. The PB film confirmed a lymphocytosis with atypical cleaved nuclei, occasional cytoplasmic vacuolation and granulation (figure 1). PB immunophenotyping (figure 2) showed the majority of the lymphocytes to have variable CD5 expression ranging from negative to brightly positive. Some lymphocytes had an abnormal T-cell phenotype (CD2+/CD3-/CD7+/CD4weak/CD16-/CD56-/CD57-). CD30 analysis of the peripheral blood was not undertaken.

A CT scan revealed infra and supra-diaphragmatic lymphadenopathy with moderate splenomegaly of 15 cm (figure 3). The histology of an axillary lymph node core biopsy showed infiltration of large

Figure 1 Peripheral blood film ($\times 1000$ H&E) showing (A) atypical lymphocytes with cleaved nuclei, pale blue cytoplasm and vacuolation with eosinophilic granules and (B) large granular lymphocytes with coarse eosinophilic granules ($\times 1000$ H&E).

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Figure 2 Flow cytometry dot plots of abnormal T-cell population. (A) Slightly larger T cells, weak CD45 expression, (B) CD2+/CD3–/CD7+/CD5 variable, (C) CD4+/CD8–/CD57–/CD16–/CD56– and (D): abnormal CD3 expression: surface CD3–/cytoplasmic CD3+.

pleomorphic blasts, some displaying vacuolated cytoplasm. Immunohistochemistry was positive for CD5, CD7, CD2, CD30, CD43 and ALK and negative for CD20 and CD15. A BM

trephine showed marked hypercellularity and a diffuse infiltrate of large atypical lymphoid cells (figures 4 and 5). Immunohistochemistry staining for CD30 and ALK was negative.

A diagnosis of ALK-positive anaplastic T-cell non-Hodgkin's lymphoma was made (stage IVb).

TREATMENT

The patient was promptly started on CHOP (cyclophosphamide, vincristine, doxorubicin and prednisolone) with a complete clinical resolution of his cervical swelling and B symptoms after two cycles. An interim CT scan after four cycles of chemotherapy revealed a complete radiological response. He received a total of eight cycles of CHOP with four intrathecal methotrexate courses as primary central nervous system prophylaxis maintaining a clinical and radiological remission.

OUTCOME AND FOLLOW-UP

Three months after the completion of chemotherapy, he presented to the clinic with a right-sided neck swelling and low grade fever. Apart from a mild normocytic normochromic anaemia, his blood count including PB morphology was normal

Figure 3 CT scan at presentation with bilateral cervical lymphadenopathy.

Figure 4 Bone marrow aspirate ($\times 1000$ H&E) showing (A) atypical lymphocyte with binucleate form, (B) large granular lymphocytes (black arrow) and left shifted neutrophil (yellow arrow).

Figure 5 Bone marrow trephine biopsy showing (A) marked hypercellularity with patchy lymphoid infiltrate ($\times 40$ H&E) and (B) population of atypical lymphocytes ($\times 1000$ H&E).

(haemoglobin 92 g/L, white cell count 7.1×10^9 /L, platelet 135×10^9 /L, lymphocyte 0.9×10^9 /L, neutrophil 5.8×10^9 /L).

A CT scan showed recurrence with infra-diaphragmatic and supra-diaphragmatic lymphadenopathy (figure 6). He received two cycles of etoposide, methylprednisolone, cytarabine and cisplatin (ESHAP) as salvage treatment resulting in a gratifying partial radiological response with only residual lymphadenopathy noted in the paratracheal, retroperitoneal and mesenteric regions (figure 7A). This was followed by a BEAM (carmustine, etoposide, cytarabine and melphalan) autologous stem cell transplant.

Only 1 month after his BM transplant, he was admitted to the haematology ward with nausea and fever. A rapidly progressing pancytopenia developed over the course of 3 weeks (haemoglobin 81 g/dL, white cell count 2.8×10^9 /L, platelet 9×10^9 /L, lymphocyte 1.6×10^9 /L, neutrophil 1×10^9 /L). A viral screen including parvovirus was negative. The PB film revealed a recurrence of his atypical lymphocytes with cleaved nuclei being a predominant feature. A BM trephine showed large atypical lymphoid cells, negative for ALK and CD30 on immunohistochemistry. Interestingly, a repeat CT scan (figure 7B) revealed similar appearances prior to his autologous stem cell transplantation.

He became increasingly transfusion dependent with persistent fever despite multiple courses of intravenous antibiotics. Despite high dose prednisolone (1 mg/kg) he died approximately 12 months after the initial diagnosis.

Figure 6 CT scan at relapse post-CHOP chemotherapy with (A) bilateral axillary lymphadenopathy and (B) intra-abdominal lymphadenopathy.

Figure 7 CT scan showing minimal change in intra-abdominal lymphadenopathy at (A) post-salvage (ESHAP) chemotherapy and (B) at second relapse post-autologous stem cell transplant.

DISCUSSION

The hallmark of anaplastic lymphoma is a genetic translocation between chromosomes 2 and 5 forming a fusion gene between ALK and nucleophosmin (NPM) gene sequences.

Anaplastic lymphoma generally conveys a more favourable prognosis in comparison to other T-cell lymphomas. However, it is ALK positivity that accounts for this observation, with 5-year overall survival in positive as well as negative cases of 71% and 15%, respectively.¹

However, it is now understood that ALK positivity alone is not the primary prognostic factor in anaplastic lymphoma. Patients with early disease relapse have significantly worse outcomes. The 3-year disease-free survival after first relapse (<12 months) is 28% vs 68% for late relapse.¹ BM and PB involvement should also be considered in defining prognosis. One study in paediatric and adolescent patients identified by quantitative PCR NPM-ALK showed the incidence of BM and PB involvement to be 48% and 52%, respectively.² Positivity also correlated with advanced disease and early disease relapse.

Onciu *et al* reported three cases of children with chemoresistant disease and leukaemic PB involvement. All showed the presence of atypical medium- and large-sized lymphoid cells with a minority displaying azurophilic granules and markedly irregular, cerebriform and cloverleaf-shaped nuclei.³ Interestingly, in this

case series all showed immunophenotypic evidence of T-cell differentiation and positivity for ALK and CD30.

The current literature excludes adult cases of either BM or PB involvement or the impact on overall prognosis. Despite the lack of ALK and CD30 positivity in PB as well as BM, the morphological features and mature T-cell phenotype demonstrated high-grade lymphomatous involvement. We hypothesised that such morphological features in addition to early disease relapse accounted for the poor outcome observed. Such morphological PB features also correlate with cases in the paediatric population. In patients with ALK-positive anaplastic lymphoma, with atypical morphology in the PB and BM (ALK/CD30 negative) there may be a benefit from further investigation with molecular studies such as PCR NPM-ALK.

Learning points

- ▶ Generally, anaplastic lymphoma kinase positivity in anaplastic lymphoma conveys a favourable prognosis.
- ▶ This is overcome by evidence of early disease relapse, peripheral blood and bone marrow involvement.
- ▶ Accurate morphological, immunohistochemistry and immunophenotyping analysis of the bone marrow and peripheral blood are vital in providing patients with an accurate prognosis, independent of anaplastic lymphoma kinase positivity.
- ▶ This case suggests typical morphological features in the absence of characteristic immunohistochemical and immunophenotypic findings in the peripheral blood and bone marrow is partly sufficient in conferring worse outcomes.

Contributors AJM was the main author and obtained patient consent; NE undertook background literature review and acted as co-author; HO reviewed the paper; and IT reviewed and obtained histological images.

Competing interests None.

Patient consent Obtained.

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