

Infant ALK-Positive Anaplastic Large Cell Lymphoma with Unfavourable Prognostic Features and Neutrophilia at Presentation

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Abstract

Anaplastic large cell lymphoma (ALCL) is an uncommon form of non-Hodgkin lymphoma in younger patients, accounting for less than 15% of cases. It is exceedingly rare in infants, with a median age at diagnosis of 12 years. Various treatment strategies have been studied in pediatric ALCL, however the long-term event free survival is approximately 70% regardless of treatment approach. We present the case of six month old infant with anaplastic lymphoma kinase (ALK) positive ALCL with unfavourable prognostic features. We elected to treat with upfront brentuximab in addition to combination chemotherapy. This achieved a clinical and molecular remission of the disease. The treatment was well tolerated.

Keywords: ALCL; Child; Pediatric; Infant; MDD; ALK titre

Introduction

Anaplastic large cell lymphoma (ALCL) is an uncommon form of non-Hodgkin lymphoma in younger patients, accounting for less than 15% of cases. It is exceedingly rare in infants, with a median age at diagnosis of 12 years. Various treatment strategies have been studied in pediatric ALCL, however the long-term event free survival is approximately 70% regardless of treatment approach [1,2]. Outcomes for infants with this disease have been reported to be inferior to that of older children [3]. The emergence of novel biological agents on the therapeutic landscape in ALCL has provided opportunities for new treatment modalities in an effort to improve long term outcomes in pediatric patients, with agents targeting either CD30 or the anaplastic lymphoma kinase (ALK) protein being added to chemotherapy regimens for newly diagnosed patients. These agents have been studied in patients with recurrent ALCL [4]. Furthermore, the use of minimal residual disease technology to detect minimally disseminated disease (MDD) before therapy and minimal residual disease (MRD) after therapy has recently been shown to be of prognostic significance in pediatric ALCL [5,6]. Until recently, risk stratification of children with ALCL was based on clinical parameters alone [7]. Here, we describe a case of ALCL in an infant, with a high risk of relapse based on disease assessment by recently described biological parameters, meriting up front treatment with novel biological agents.

Case Report

A 6-month-old girl presented with a 3-week history of fever, irritability, generalised lymphadenopathy and palpable splenomegaly. Laboratory data showed a leucocytosis of $34.6 \times 10^9/l$ with a neutrophilia (66%), and an elevated LDH (1069 U/L (310-790)). Radiological investigations corroborated clinical findings and did not show any

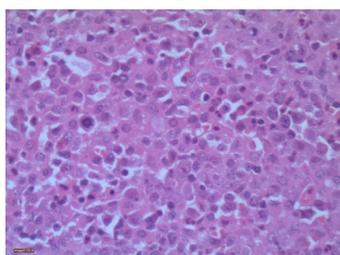


Figure 1: Histological examination of an axillary node showed total effacement of the lymph node, with a background of lymphocytic cells and plasma cells.

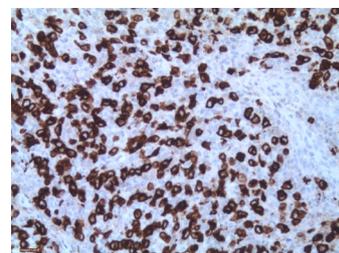


Figure 2: The CD30 immunostain showed strong cytoplasmic Golgi staining with CD68 highlighting background histiocytes.

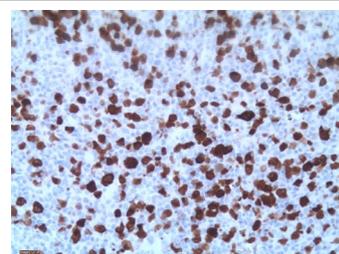


Figure 3: Anaplastic lymphoma kinase (ALK) stain is strongly positive in both nuclear and cytoplasmic regions. CD3 and CD5 are positive in the large ALK-positive cells within the effaced lymph node.

additional visceral abnormalities. Bone marrow cytomorphology showed granulocytic hyperplasia with left shift and a myeloid erythroid ratio of 15:1. Histological examination of an axillary node showed total effacement of the lymph node, with a background of lymphocytic cells and plasma cells (Figure 1). The CD30 immunostain showed strong cytoplasmic Golgi staining (Figure 2) with CD68 highlighting

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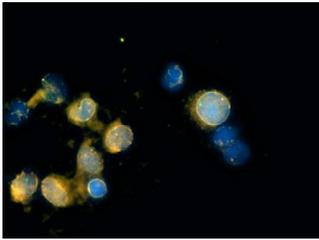


Figure 4: Interphase FISH analysis on a touch prep with an ALK probe shows a rearrangement involving this locus.

background histiocytes. Anaplastic Lymphoma Kinase (ALK) stain is strongly positive in both nuclear and cytoplasmic regions (Figure 3). CD3 and CD5 are positive in the large ALK-positive cells within the effaced lymph node. Interphase FISH analysis on a touch prep with an ALK probe shows a rearrangement involving this locus (Figure 4). *NPM-ALK* fusion-gene specific reverse transcriptase detected minimally disseminated disease (MDD) in the bone marrow and a low anti-ALK antibody titre (<1/750) was found in her blood.

The patient was induced with dexamethasone and vinblastine and demonstrated prompt resolution of lymphadenopathy and neutrophilia. As there is no gold standard for the treatment of very high-risk ALCL, we decided to administer multiagent chemotherapy with the addition of brentuximab vedotin, an antibody-drug conjugate containing an anti-CD30 monoclonal antibody linked to a tubulin inhibitor (monomethylauristatin E). We considered the use of crizotinib, a protein kinase inhibitor with activity against the ALK fusion protein, however its capsule formulation precluded its use in an infant. MRD assessment after induction will aid further prognostication in this patient.

Discussion

Over 90% of child and adolescent ALK-positive ALCL carry the translocation t(2;5) that results in the *NPM-ALK* chimeric fusion product and subsequent ALK expression [8,9]. Expression of ALK-fusion genes is unique to the lymphoma cells, allowing the analysis of minimal disseminated disease (MDD) and minimal residual disease (MRD) in blood and bone marrow. MDD is generally defined as submicroscopic bone marrow involvement at diagnosis. Patients with ALK-positive ALCL produce antibodies to ALK and the anti-ALK antibody titre has been shown to inversely correlate with the risk of relapse [10]. The combination of a lympho-histiocytic histological variant (negative prognostic factor [11,12], positive MDD and a low ALK antibody titre stratifies our patient to have high-risk disease, with a progression free survival in the region of approximately 25% [5]. The availability of novel biological targeting agents hold promise for improved treatment outcomes in this group of high-risk patients with easily measurable biological parameters, and are currently being studied in children with newly diagnosed ALCL. ALK inhibitors have been shown to be effective in relapsed and refractory disease, however

two cases of prompt disease relapse on withdrawal of crizotinib have been recently reported, demonstrating that quiescent neoplastic cells that evaded detection by PCR testing measuring levels of *NPM-ALK* have the ability to reappear abruptly and cause overt clinical relapse of disease.¹² Improvement in outcome in children with ALCL may also be achieved with the application of novel risk stratification approaches to treatment incorporating MRD and ALK antibody titres. Cancer in infancy is inherently a rare event; non-Hodgkin lymphoma and specifically ALCL is exceedingly rare.

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