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CASE REPORT

Anaplastic large cell lymphoma, ALK-positive in very young children: A long-term follow-up of two cases and a review of the literature

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Abstract

Anaplastic large cell lymphoma, ALK-positive is a mature T-cell neoplasm that accounts for 10-20% of paediatric non-Hodgkin lymphoma. Its frequency in infants and very young children is exceedingly rare and was rarely documented in the literature. The disease prognosis in this age-group is unknown. We report two male patients who were diagnosed with ALCL-ALK(+) at the ages of 12 and 14 months, both presented with fever and leukemoid reaction, one was in stage I and the other in stage IV diseases. They were treated with APO-based chemotherapy and remained in complete remission for more than 7 years. To our knowledge, this is the first report that describes the long-term survival of ALCL-ALK(+) at very young age.

Keywords: anaplastic large cell lymphoma; ALK; lymphoma; infants; non-Hodgkin lymphoma

INTRODUCTION

Anaplastic large cell lymphoma, ALK-positive (ALCL-ALK(+)) is a systemic mature T-cell neoplasm, characterised by bright and diffuse CD30 expression and chromosome 2p.23.2/ ALK rearrangements that result in ALK-protein expression. The cells are usually large and cohesive, with abundant cytoplasm, pleomorphic nuclei and the tendency to proliferate in lymph node sinuses. The disease is more common in males and peaks in the first three decades of life with an exception of infants, in whom the disease is very rare. Most patients present with B-symptoms and are in advanced-clinical stage.[1] On very rare occasions, the disease might appear very early in life, and the prognosis in these patients is unknown. Herein, we report two cases of ALCL-ALK(+) arising in very young age and describe the long-term outcome.

CASE REPORT

Case 1

A previously healthy 12-month-old male infant presented in November 2013 with fever of unknown origin for 45 days that was unresponsive to antibiotics. Physical examination revealed generalised lymphadenopathy and hepatosplenomegaly. Complete blood count (CBC) test revealed WBC count of 48 x 10^9/L (68% neutrophils, 23% lymphocytes and 5% monocytes), haemoglobin concentration (Hg) of 99 g/L and platelets count of 551 x 10^9/L. Blood film examination showed toxic changes of neutrophils, left shift but no definite malignant cells. Excisional biopsy from the cervical lymph node confirmed the diagnosis of ALCL-ALK(+) of conventional type (Fig. 1). Computerised Tomography (CT) scan with contrast revealed pretracheal, hilar, para-aortic lymph nodes enlargement and hepatosplenomegaly. Brain CT without contrast was normal. Blood culture was negative. Bone marrow trephine biopsy showed few CD30-positive cells, qualifying for stage-IV disease. Serum lactate dehydrogenase (LDH) level was elevated (12.2 μkat/L). Cytogenetic study was not available in the facility. The International Prognostic Index (IPI) score was 3, qualifying for high-intermediate risk. The patient was started on APO regimen (doxorubicin, prednisone, vincristine, 6-mercaptopurine and methotrexate) for induction and maintenance as previously described.[2] The course of the disease was uneventful and the patient remained in

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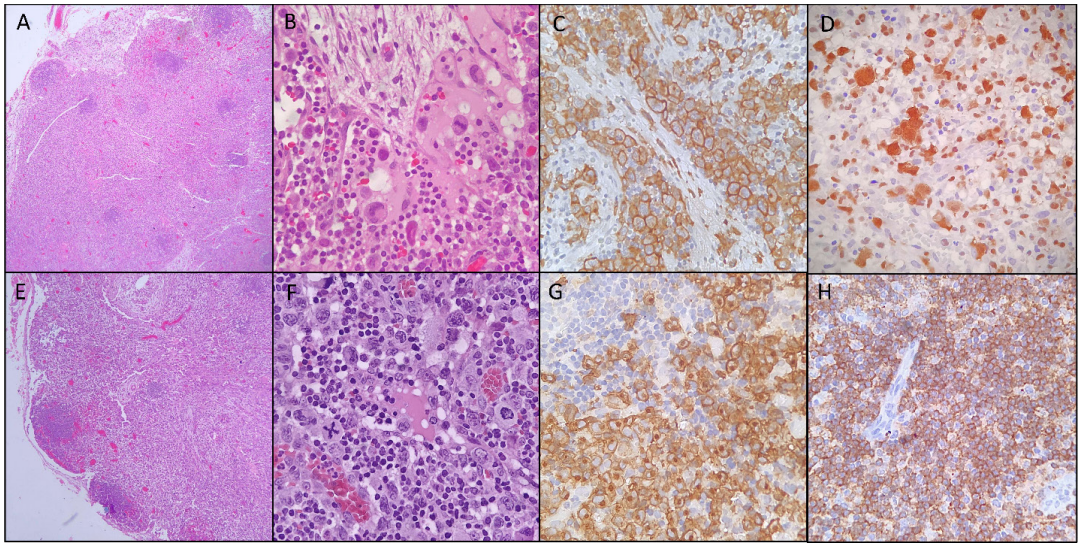

FIG. 1. Excisional lymph node biopsy from both patients. A, Low-power view shows marked sinusoidal expansion and disturbed nodal architecture (hematoxylin and eosin, original magnification, x20). B, High-power view reveals perisinusoidal proliferation of large cells with eosinophilic cytoplasm and curved nuclei, characteristic of "Hallmark cells" (hematoxylin and eosin, original magnification, x400). C, the lymphoma cells are positive for membranous CD30 (original magnification, x400) and D, nuclear positivity for ALK immunohistochemical stains (original magnification, x400). E, Similarly, the architecture of lymph node in the second case is effaced showing residual follicles only (hematoxylin and eosin, original magnification, x20). F, there is exuberant proliferation of anaplastic lymphocytes with prominent and atypical mitotic figures (hematoxylin and eosin, original magnification, x400). G, CD30 immunohistochemical stain is bright and diffusely positive, note the Golgi-pattern (original magnification, x400). H, ALK immunohistochemical stain shows cytoplasmic positivity, indicating an variant mutation (original magnification, x400).

complete remission (CR) for 94 months.

Case 2

In January 2014, a 14-month-old male baby had a corrective surgery for complicated intussusception. During the operation, he was found to have a mesenteric lymphadenopathy that was excised and sent for histopathology. The diagnosis came as ALCL-ALK(+), (Fig. 2). Following the surgery, the patient developed sepsis and acute respiratory distress syndrome, necessitating intubation and intravenous antibiotic treatment. His condition improved and he was extubated after one week.

At the time of biopsy, the patient's CBC test was as the following: Hg: 116 g/L, WBC count: 80.9 x 10^9/L (85.9% neutrophils, 8.75% monocytes, 4.3% lymphocytes) and platelets count: 171 x 10^9/L. Blood film examination showed toxic changes in neutrophils, shift to left and reactive lymphocytes. Bone marrow biopsy for staging was performed and was negative for lymphoma. Serum LDH was normal (3.1 μkat/L). Hence, the patient was in stage I disease, had IPI score of 1, qualifying for Low-risk. He received APO regimen similar to the first patient and remained again in complete remission for 92 months.

DISCUSSION

Cancer in children is rare and lymphoma represents 16% of childhood malignancies.[3] The incidence of non-Hodgkin lymphoma (NHL) tends to increase with age and the frequency of subtypes varies according to age groups,[4] but it is exceedingly rare in infants; a study of 2084 children with NHL revealed only 20 were infants (<1%).[5] ALCL-ALK(+) in infants is exceptionally rare and has been documented in few reports, with virtually all cases resulting from a genetic translocation involving the ALK gene; no definite risk factors are known yet, but a potential association with insect bites has been proposed.[1] The frequency of ALCL-ALK(+) among childhood NHL ranges from 10-20% to as low as <5% according to different studies.[5,6]

A thorough electronic search using National Center for Biotechnology Information/National

Table 1: Literature review of reported cases of ALCL-ALK(+) in infants with relevant clinicopathologic features

	Year	Reference	Sex	Age*	Site	Stage	Histology	Follow up*	Additional findings
1	1993	[7]	Ma	4	LN, BM	IVB	Small cell	Died of relapse after 10m, received MACOP-B & aBMT (x2)	
2	2003	[8]	Fe	9	PB, BM, LN	IVB	Small cell	Died of relapse after 9m, received steroid, cy, vb, then received dxa, cy, da, asp & intrathecal mtx, then received ara-C, eto, vb	Leukemoid & leukaemic cells
3	2005	[9]	Ma	5	Skin, LN	NA	Conventional	CR after 4m, relapsed after FAB LMB 96-regimen B (x4), then salvage of comustine, vb & bl, time of follow up is NA	
4	2007	[5], case 2	Fe	11	Neck LN	I	NA	Died of sepsis during NHL-BFM90	
5		[5], case 4	Fe	8	Neck LN	I	NA	CR after NHL-BFM90, time of follow up is NA	
6		[5], case 6	Ma	6	Mediastinum, neck and abdominal LN	III	NA	CR after NHL-BFM95, time of follow up is NA	
7		[5], case 11	Ma	2	Lung, abdominal LN	III	NA	Died of relapse after 3m, received NHL-BFM95	
8		[5], case 15	Ma	6	Neck and inguinal LN	III	NA	CR after NHL-BFM95, time of follow up is NA	Wiskott-Aldrich syndrome
9	2007	[10]	Fe	2	LN, BM, PB	IV	Conventional	Died of sepsis during ALCL–99-EICNHL regimen	Leukemoid & leukaemic cells
10	2009	[11]	Ma	8	Generalized LNs	III	Conventional	NA	HLH
11	2016	[12]	Fe	6	Generalized LNs	IIIB	Conventional	CR after dxa, vb and brn, time of follow up is NA	Leukemoid reaction
12	2019	[13]	Ma	0.03	Axillary LN, BM	IV	Conventional	CR after APO (x10), time of follow up is NA	HLH
13	2021	Our case, 1	Ma	12	Cervical & visceral LNs, BM	IVB	Conventional	CR after APO (x15) for 84m	Leukemoid reaction
14	2021	Our case, 2	Ma	14	Mesenteric LN	I	Conventional	CR after APO (x15) for 82m	Leukemoid reaction

*Age and follow up are reported in months

Abbreviations: aBMT: autologous bone marrow transplant. APO: prednisone, vincristine, doxorubicin. Ara-C: cytarabine. Asp: Asparaginase. Bl: bleomycin. BM: bone marrow. Brn: brentuximab. CR: complete remission. Cy: cyclophosphamide. Da: daunorubicin. Dx: diagnosis. Dxa: dexamethasone. Eto: Etoposide. Fe: female. FAB LMB 96 protocol, regimen B: intermittent combination of cyclophosphamide, vincristine, prednisolone, methotrexate, doxorubicin and cytarabine. HIV: human immunodeficiency virus. HLH: haemophagocytic lymphohistiocytosis. LN: lymph node. m: months. Ma: male. MACOP-B: methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin. NA: not available. PB: peripheral blood. Vc: vincristine. Vb: vinblastine. X: number of cycles.

Institutes of Health Website Pubmed (https://www.ncbi.nlm.nih.gov/pubmed) showed 12 cases (Table 1). When combined with our cases, the characteristics of patients are as follows: there were 9 boys and 5 girls (M:F=1.8); Histologic subtype was described in 9 patients, 7 (78%) was conventional and 2 (22% was small cell variant; clinical stage was available in 13 patients, as advanced clinical stage (III, IV) was evident in 10/13 (77%) cases; B-symptoms were apparent in 4/14 (29%) cases; accompanied conditions included leukemoid reaction in 5/14 (36%) patients, haemophagocytic lymphohistiocytosis (HLH) in 2/14 (14%) cases and immunodeficiency in 1/14 (7%) case; death occurred in 5/13 (38%) patients in a period of less than 10 months (3 died of disease progression and 2 of sepsis). Finally, the remaining 8 patients (62%) reached CR, one of which had a disease relapse after initial chemotherapy regimen. IPI score and the long-term survival were not provided in any of the previously reported cases.

Patients with ALCL-ALK(+) occasionally develop leukemoid reaction and the leukocyte count may be very high. It is characterised by marked neutrophilia with toxic changes and left shift. In some cases, leukaemic lymphoma cells appear. This condition was most often reported in small-cell variant of disease and carried a poor outcome.[14] Routine detection of leukaemic cells can be challenging if they carry a null-immunophenotype or if they were of small cell variant and accompanied by leukocytosis. Interestingly, more than one third of the reported cases in infants, including our cases, had leukemoid reaction. Among those, true leukaemic lymphoma cells were confirmed in two cases only, one of which was of small cell variant.[8,10]

The prognosis of pediatric ALCL-ALK(+) is generally good, as the 5-year survival rate reaches 80%. Approximately 30% of treated patients develop relapse and about half of them respond well to additional therapy.[1] Infants, however, represent a peculiar subgroup of children and haematolymphoid tumours in this age group might show a different scenario. For instance, acute leukaemia is characterised by a unique clinicopathologic pattern in infants and carries an unfavourable prognosis compared with older children.[5] The impact of infancy-onset lymphoma on clinical outcome is largely unknown due to its exceptional rarity and the shortage of clinical data. For ALCL-ALK(+), preliminary results pointed to an inferior prognosis when the disease affected children younger than 4 years, but no data is available about infants.[5] Our study is the first that documents an excellent long-term prognosis in infants with ALCL-ALK(+), irrespective of clinical stage at presentation.

In short, the incidence of ALCL-ALK(+) in infants and very young children is extremely rare. By reviewing all reported cases in the literature, the disease shares some features with older age groups such as male predominance and advanced clinical stage. The accompanied leukemoid reaction appears to be more common and is not restricted to the small-cell variant. Although the mortality rate in infants is slightly higher in the first two year of diagnosis, our two cases showed an excellent response to chemotherapy and the long-term survival is comparable to older age groups. We hope this report brings light to this peculiar incident and helps characterise it.

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