

Anaplastic large cell lymphoma in the African child presenting with cervical lymphadenopathy: A report of two cases from the pediatric oncology unit of Gabriel Toure Hospital.

Summary

Anaplastic large cell lymphoma is a rare malignancy of childhood. Equally rare are publications of the disease in African children. We report on two cases successfully treated by chemotherapy in the pediatric oncology unit at Gabriel Touré Hospital in Bamako, Mali. The clinical course and therapeutic outcomes of the disease in these two children, presented similarly to cases described in the medical literature from other areas of the world. However, further study with a larger number of cases is needed to confirm these results.

Key words: Anaplastic large cell lymphoma, children, Mali.

Introduction

Anaplastic large cell lymphoma (ALCL) is a type of non-Hodgkin lymphoma. This relatively new classification, often confused in the past with malignant histiocytosis, carcinoma, sarcoma or melanoma, was first recognized in 1985 by Stein [1]. The term anaplastic lymphoma is based on the characteristic histologic appearance. The malignant cells are universally positive for CD30 [2]. Clinically, ALCL has an insidious presentation with lymphadenopathy, fever and weight loss [3].

ALCL accounts for only 10%-15% of all childhood non-Hodgkin's lymphomas [4, 5] and it is a heterogeneous group of diseases, differing in their histology, phenotype, cytogenetics, and clinical course[6, 7]. Primary ALK-positive systemic ALCL frequently involves both lymph nodal and extra-nodal sites. Extra-nodal lesions commonly include skin (21%), bone (17%), soft tissue (17%), lung (11%) and liver (8%), while central nervous system involvement is rare [8].

Cutaneous manifestations of primary systemic ALCL are usually solitary or multiple red papules or nodules [9, 10]. Like the other childhood lymphomas, ALCL are highly chemosensitive with complete remission rates ranging from 66%—100% with various multi-agent chemotherapy regimens in childhood [11-12]

As the disease is rare, reports on the treatment and outcome of ALCL are limited in number and usually involve small series of patients.

No cases of anaplastic large cell lymphoma successfully treated in African children have been previously reported in the medical literature in sub-Saharan Africa. We report on two children treated with anaplastic large cell lymphoma at our center, in 2012 (from March to May).

45 **Case No.1**

46 A 4 year old girl presented with cervical lymphadenopathy, fever and weight loss. The
47 parents noted the cervical lymph node enlargement two months prior to presentation to the
48 hospital. Due to progressive cervical node enlargement, weight loss and persistent fever they
49 sought medical attention.

50 On arrival to the pediatric oncology unit, her weight was 15 kg, her height was 114 cm, with
51 a temperature of 38.8°C.
52 Clinical examination revealed a temperature of 38.8⁰ C, pallor, splenomegaly extending 5 cm
53 below the costal margin, cervical and bilateral axillary non-mobile and matted
54 lymphadenopathy measuring about 4 to 5cm in diameter. There were no skin lesions,
55 hepatomegaly or pulmonary involvement by chest x-ray. HIV1 and HIV2 serology were
56 negative; liver and kidney function tests were normal.

57 The first blood count demonstrated leukocytosis to 28 G / L with a predominance of
58 neutrophils, microcytic anemia (Hb: 6.2 g / dl, MCV: 74 fl). There was no bone marrow
59 infiltration as demonstrated by negative bilateral bone marrow aspirates and biopsies.
60 Abdominal ultrasound showed multiple abdominal lymphadenopathy, with the largest
61 measuring 3 cm in diameter. A lymph node biopsy was performed, which confirmed the
62 diagnosis of anaplastic large cell lymphoma. The patient therefore had stage III ALCL per the
63 Ann-Arbor classification.

64 She was treated on modified European protocol 99 for ALCL, standard risk arm 3 with
65 replacement of ifosfamide by cyclophosphamide. The protocol consists of alternating cycles
66 of regimens AM and BM for a total of 6 cycles (tables 1 & 2). The treatment was well
67 tolerated with minimal nausea or vomiting. Antiemetic treatment was provided by
68 metopimazine and methylprednisolone. After completion of treatment, clinical and
69 radiological assessment showed complete remission that continues to date.

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71 **Clinical case 2**

72 An eleven-year-old boy was referred by the ENT department of our hospital for evaluation of
73 cervical lymphadenopathy. He is a previously well child who five months prior to
74 presentation when he developed enlarged left cervical lymph nodes that gradually increased
75 in size.

76 Given the failure of prolonged traditional treatment, the parents consulted the local health
77 facilities, who then referred the child to our department.

78 On his arrival, he weighed 27 kg with a height of 131 cm. His axillary temperature was 36.4 °
79 C.

80 His chest examination was normal; abdomen was soft without hepatomegaly or
81 splenomegaly. He had no neurologic symptoms to suggest central nervous system
82 involvement. His exam was remarkable for a left submandibular lymphadenopathy measuring
83 7 cm, hard and non-tender. Staging work-up including chest radiograph, abdominal

84 ultrasonography and bilateral bone marrow aspiration and biopsies were negative. Liver and
85 kidney function tests as well as HIV1 and HIV2 serologies were negative.

86 Lymph node biopsy was consistent with stage 1 anaplastic large cell lymphoma. As with
87 clinical case 1, the patient was treated with six alternating cycles of regimen AM and BM.

88 Metopimazine and methylprednisolone were administered before each cycle as anti-emetic
89 therapy with very good effect. The chemotherapy was very well tolerated. The patient had
90 complete radiologic response at the end of protocol therapy.

91 **Discussion**

92 Anaplastic large cell lymphoma is a rare malignancy in western medical literature,
93 representing 10 to 15% of all cases of non-Hodgkin lymphoma. It is characterized by a
94 proliferation of large pleomorphic cells of T or null phenotype, which tends to invade the
95 sinuses of the lymph nodes and express CD30 (formerly KI-1).[13] The CD 30 is a
96 transmembrane receptor member of the super family Tumor Necrosis Factor (TNF),
97 expressed on activated T cells but its role in the pathogenesis of ALCL is currently unknown
98 [13].

99 Both cases expressed CD30, a marker consistently expressed in anaplastic large cell
100 lymphoma. These are the only two cases of ALCL diagnosed in our department, which is the
101 largest pediatric oncology center in Mali, to date. The average age of our two patients was 7
102 years. In the European Pediatric Deley case series, the average age of presentation was 10.2
103 years [14]. An insidious progression characterized both of these cases as described in the
104 literature [15]. Our first patient had systemic symptoms (persistent fever, weight loss) as was
105 the case in 75% of the patients in the Italian Falini report [16]. Both of our patients presented
106 with lymphadenopathy of one nodal region, which is characteristic of ALCL. In the Falini
107 cases, 40% of patients had only one lymph node enlargement.

108 The current treatment of anaplastic large cell lymphoma is based on protocols containing
109 adriamycin. These protocols induce complete remission in 95% of patients, but relapse occurs
110 in over 30% of the cases [17, 18].The response to chemotherapy was favorable in our two
111 patients, reflecting the high chemo sensitivity of this disease. CD30 expression could be
112 associated with better overall survival in patients with advanced disease [19]. In a study of
113 the French Pediatric Oncology Society (SFOP) on 82 pediatric patients, 95% of patients
114 achieved complete remission but 21 patients eventually of relapsed [20].

115 Our second patient had stage I ALCL based on the Ann Arbor classification, while the first
116 patient had stage III.

117 The very slow progression of the disease explains why our second patient was still in the
118 earlier stage of the disease. Close monitoring of both patients is necessary to quickly detect
119 any relapse.

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Conclusion:

Anaplastic large cell lymphoma in these two African children presented here have the same clinical manifestation, therapeutic response and clinical course as described in literature. A study involving a larger number of cases would provide more specific information on the epidemiology of this disease in African children. Close follow-up will be needed for our patients.

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216 **Table 1**
217 **AM Treatment**
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Days	1	2	3	4	5
Dexamethasone	X X	X X	X X	X X	X X
Methotrexate	X				
Cyclophosphamide	X	X	X	x	X
Cytarabine				X X	X X
VP16				X	X

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220 Dexamethasone 10 mg / m² / day in 2 doses from D1 to D5 (IV or oral)
221 Methotrexate 3 g / m 3 h infusion on day 1
222 Folinic acid 15 mg / / m orally every 6 h (12 outlets total) to start within 24 h after the start of
223 the methotrexate infusion.
224 Cyclophosphamide 250 mg / m² infusion D1 to D5
225 Cytarabine 150 mg / m² / dose in one hour infusion every 12 h, D4 and D5
226 VP 16: 100 mg / m 2-hour infusion, after infusion of Cytarabine D4 and D5
227 Dilution: 0.4 mg / ml.
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229 Hydration: alkaline hyper hydration particularly for methotrexate for 48 hours. After the
230 specific hydration of methotrexate, continue hydration of 2 l / m² up to 12 h after the last dose
231 of cyclophosphamide.
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Table 2
MB Treatment

Days	1	2	3	4	5
Dexamethasone	° °	° °	° °	° °	° °
Methotrexate	°				
Cyclophosphamide	°	°	°	°	°
Adriamycin				°	°

Dexamethasone: 10 mg / m² / day in 2 doses from D1 to D5 (IV or PO)

Methotrexate: 3 g / m³ (m²?) h infusion on day 1

Folinic acid 15 mg / m² PO every 6 hours (12 or less taken a total based on circulating levels of methotrexate) to start within 24 hours after the start of the methotrexate infusion.

Cyclophosphamide: 200 mg / m² infused over one hour, D1, D5

Adriamycin: 25 mg / m² infused over one hour D4 and D5

Hydration: alkaline hyperhydration particular methotrexate for 48 hours.

After the specific hydration of methotrexate, continue hydration of 2 l / m² (IV or oral) to 12 hours after the last dose of cyclophosphamide.