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ALK-negative anaplastic large cell lymphoma with extensive peripheral blood and bone marrow involvements manifested as "leukemic phase"

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ABSTRACT

CD30-positive anaplastic large cell lymphoma (ALCL) is a distinctive malignant large cell lymphoma of T-cell lineage, often presenting in lymph node or extranodal sites. ALCL cases with extensive bone marrow and peripheral blood involvement manifested as "leukemic phase" are extremely rare and the most of those cases reported are anaplastic large cell lymphoma kinase (ALK) positive ALCL in childhood population. Here we report four adult cases of ALK-negative ALCL with extensive bone marrow and peripheral blood involvement manifested as "leukemic phase". Circulating large lymphoma cells varied from 20 to 80% in peripheral blood and bone marrow biopsy showed various nodular or interstitial infiltrates. By reviewing the clinicopathologic data of previously reported ALCL cases with extensive bone marrow and peripheral blood involvement, there appears to be of large variations in regard to the patient's age, morphologic variants, immunophenotypic or genotypic characteristics of the disease. While most cases of ALCL with peripheral blood and bone marrow involvement were ALK-positive or carrying t(2;5) translocation, rare ALK-negative cases were also present. Leukemic ALCL patients usually have unfavourable prognosis, regardless of ALK expression.

1. Introduction

Anaplastic large cell lymphoma (ALCL) was first described in 1985 as a neoplasm of highly pleomorphic lymphoid cells in a predominantly sinusoidal pattern involved in lymph nodes [1]. Virtually all tumor cells were subsequently found to strongly express CD30 antigen and a high percentage of them was identified to have an unique, balanced chromosomal translocation t(2;5)(p23;q35) [2,3]. It was recognized as a distinct entity of mature T-cell lymphoma with T- or null-cell immunophenotype by the most recent World Health Organization (WHO) classification [4]. ALCL comprises approximately 3% of all non-Hodgkin's lymphomas. The primary systemic ALCL cases commonly involve lymph nodes, with or without involvement of a variety of extranodal sites. The disease has a bimodal age distribution with one peak in children and the second in older adults [4]. Morris et al. [5] identified a NPM/ALK fusion gene, as a consequence of t(2;5) translocation, which results in a translation of an unique chimeric NPM/ALK protein with altered tyrosine kinase activity. A monoclonal antibodies specific to ALK protein can be used diagnostically, thus leading to the definition of this distinctive entity with important clinical and prognostic implications [6].

Although ALK-positive ALCL has been studied extensively [7–10], approximately 15–20% of systemic ALCL cases are ALK-negative [6], which is less well characterized. Unlike a distinctive ALK-positive ALCL entity, those ALK-negative ALCL cases are considered to be more heterogeneous based on their clinical and epidemiologic features [6]. It is morphologically composed of larger and more pleomorphic cells with some characteristic "hallmark" cells, which are either T- or null-cell immunophenotype, and are uniformly positive for CD30. The older median age and more aggressive clinical course of ALK-negative ALCL compared to ALK-positive ones support the notion that they may represent two different clinical and pathologic entities, as defined by the current 2008 WHO classification [4].

ALCL cases with extensive bone marrow and peripheral blood involvement manifested as "leukemic phase" are extremely rare and have been occasionally reported with the majority being ALK-positive ALCL cases in pediatric population [11–14]. We report here four adult cases of ALK-negative ALCL with extensive peripheral

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Table 1
Clinical features of the current ALK-negative ALCL cases with extensive bone marrow and peripheral blood involvements.

Case no.	Age/sex	Initial symptoms	Site of involvement	Therapies	Time to relapse (months)	Survival (months)
1	46/M	Fever, fatigue, headache	LN, BM, PB, CSF	CHOP	3	5
2	38/M	Groin cyst	LN, BM, PB,	CHOP	N/A	31
3	61/F	Fever, fatigue, weight loss,	LN, BM, PB, spleen, liver	CHOP, APBSCT	N/A	>18
4	46/M	Thrombocytopenia	LN, BM, PB, spleen	CHOP	2	2

LN: lymph node; BM: bone marrow; PB: peripheral blood; CSF: cerebral spinal fluid; CHOP: cyclophosphamide, adriamycin, vincristine, prednisone; APBSCT: autologous peripheral blood stem cell transplant; N/A: not available.

blood (>20% circulating lymphoma cells) and bone marrow involvement. One case also showed leptomeningeal spreading, complex cytogenetic karyotypes and associated with short survival time. This is the first report of ALK-negative ALCL case with central nervous system involvement.

2. Materials and methods

2.1. Clinical case selection and the literature review

Four cases of anaplastic large cell lymphoma with extensive bone marrow and peripheral blood involvement manifested as "leukemic phase" were identified by searching pathology files from City of Hope National Medical Center and Duke University Medical Center. ALCL cases with "leukemic phase" in the current study are defined as more than 20% circulating lymphoma cells of total white blood cells in peripheral blood specimens. ALCL cases with less than 20% circulating lymphoma cells were excluded. The pathologic diagnosis was made according to the most recent WHO classification [4]. In addition, we also reviewed ALCL cases with peripheral blood and bone marrow involvement manifested as "leukemic phase" reported in the literature.

2.2. Histomorphologic and immunophenotypic studies

Peripheral blood smears, bone marrow aspirate and tough preparations were stained with standard Wright–Giemsa staining (WG) for morphologic examination. Tissue biopsy specimens of lymph nodes and bone marrow core were fixed in formalin and then rapidly decalcified. The specimens were then processed routinely, embedded in paraffin, and stained with hematoxylin and eosin (H&E) stain. For immunohistochemistry, 4-μm sections from paraffin-embedded blocks were immunostained with ALK (1:100, Dako Corporation, Carpinteria, CA, USA), CD3 (1:800, Dako), CD20 (1:40, Novacastra, Burlingame, CA, USA), CD30 (1:2000, Dako), EMA (1:40, Boehringer Mannheim Biochemica, Indianapolis, IN, USA), granzyme B (1:50, Monosan, USA), and perforin (1:30, Vector, Burlingame, CA, USA), using the streptavidin–biotin complex method with automated staining equipment (Dako autostainer; Dako, Carpinteria, CA, USA). In Case 1, cyto-spin of CSF was stained with Wright–Giemsa (WG) and brain tissue was fixed in formalin and then embedded in paraffin, and stained with hematoxylin and eosin (H&E) stain. In two cases, immunophenotyping was performed by four-color flow cytometric analysis of bone marrow aspirate with a Coulter Epics XL cytometer (Beckman Coulter, Miami, FL). Related flow cytometry panels were followed: CD2, CD3, CD4, CD5, CD7, CD8, CD10, CD19, CD20, CD22, CD34, CD33, and CD45.

2.3. Cytogenetic analysis

Cytogenetic analysis was performed on peripheral blood or bone marrow specimens using standard techniques. GTG banding was used to identify the individual chromosomes.

3. Results

3.1. Clinical features of the present cases

The clinical features of the present four "leukemic phase" ALCL cases were summarized in Table 1. They were included one female and three male patients, all adults, with a median age of 48 years. Two patients presented with B symptoms such as fever, fatigue and weight loss, while Case 4 initially presented with thrombocytopenia. All of them had lymphadenopathy with various but extensive peripheral blood and bone marrow involvement. Case 1 also had severe headache and the cytology of lumbar puncture demonstrated central nervous system involvement by lymphoma cells. Case 3 and Case 4 presented with splenomegaly, suggesting ALCL involvement at initial diagnosis. All 4 patients had received CHOP based chemotherapy and three of them failed to have good response. Case 1 and Case 4 were expired within 6 months after initial diagnosis, Case 2 had an initial response after chemotherapy, but did not reach complete clinical remission. Case 3 appeared to have good response to chemotherapy, but was lost in follow-up 18 months after initial diagnosis, right after an autologous stem cell transplant (Table 1).

3.2. Cytomorphologic and immunophenotypic findings of the present cases

The lymph node biopsies in all four cases showed sheets or large clusters of pleomorphic cells in a characteristic sinusoidal pattern in the lymph nodes. Many large anaplastic cells contained large irregular nuclear contours and often harbored eccentric kidney shape nuclei, consistent with so-called hallmark cells (Fig. 1A and D).

Table 2
Pathologic features of the current ALK-negative ALTL cases with extensive bone marrow and peripheral blood involvements.

Case no.	CBC	Circulating lymphoma cells	Immunophenotype (on lymph node or bone marrow)	Cytogenetics (bone marrow)
1	WBC 7.6×10^9/L, Hb 104 g/L, Plt 27×10^9/L	Large cells 40%	IHC: CD30+, EMA focal+, CD3+, CD20−, ALK−	LN(CC): 86–93, X, +X, Y, del(1) (p32)×2, add(3)(p21)×2, del(6)(q21)×2, −7, add(7)(q32)×2, +8, −9, −10, −11,? del(12q), add(19)(p13.3), add(19)(q13.4), −20, +7, −10mar[cp10]/46, XY[18]
2	WBC 110×10^9/L, Hb 76 g/L, Plt 29×10^9/L	Large cells 50%	IHC: CD30+, CD45+, CD4+, CD3+, ALK−; FC: CD4+, CD5+, CD45+, CD7−, CD8−, CD10−, CD19−, CD20−, CD22−	46, XY
3	WBC 22.3×10^9/L, Hb 89 g/L, Plt 163×10^9/L	Large cells 20%	IHC: CD30+, CD2+, CD4+, CD3−, CD5−, CD7−, ALK−; FC: CD4+, CD2+, CD7−, CD5−	N/A
4	WBC 7.1×10^9/L, Hb 120 g/L, Plt 183×10^9/L	Large cells 80%	IHC: CD30+, CD2+, CD45+, CD3−, CD5−, CD7−, EMA−, ALK−	46, XY

IHC: immunohistochemistry; FC: flow cytometry.