Case Report

Hypocellular/Lymphohistiocytic Variant of Anaplastic Large Cell Lymphoma of Lymph Node, Mimicking Granulation Tissue

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Abstract

Anaplastic Large Cell Lymphoma (ALCL) is a subgroup of T/null cell non-Hodgkin lymphoma (NHL) in WHO classification. Lymphohistiocytic (LH) variant constitutes about 10% of all ALCLs and characterized by presence of abundant reactive histiocytes that can mask the neoplastic nature of the lesion, leading to misdiagnose as "reactive lymphadenopathy". Here we introduce a 16-year-old female patient, diagnosed as hypocellular LH variant ALCL with unusual histologic feature including granulation tissue- like appearance. We emphasize that in young patients with unusual- looking reactive lymphadenopathy, ALCL should be considered as one of differential diagnoses. A brief review of the nature of the lesion and differential diagnoses is also included.

Keywords: Anaplastic large cell lymphoma, hypocellular, lymphohistiocytic variant, reactive lmphadenopathy

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Introduction

Anaplastic Large Cell Lymphoma (ALCL) is a subgroup of T/null cell non-Hodgkin lymphoma (NHL) in WHO classification, described by Stein in 1985 for the first time.[1–5] It is characterized by a sheet- like growth pattern of large atypical lymphoid cells with pleomorphic reniform or horseshoe shaped nuclei, called "hallmark cells", predominantly involve intrasinusoidal and para-cortical areas of lymph node.[1,6,7] Frequently affected site is lymph node followed by skin, bone, and soft tissue.[1,8] This entity exhibits a broad spectrum of morphologic features[6] and can be sub-classified into common(classic) type, lymphohistiocytic (LH) variant, small cell variant, and some other rare patterns.[1]

LH variant constitutes 10% of all ALCLs and was first introduced by Pileri, et al. (1990).[5,9] The characteristic feature of this variant, according to WHO classification, is the presence of abundant reactive histiocytes that can mask the neoplastic cells. Since the tumor cells may make up only a minor component of the neoplasm, this variant poses a great problem in diagnosis and can be easily misdiagnosed as "reactive lymphadenopathy".[3,6,9]

Here we introduce a hypocellular LH variant of ALCL presented with epigastric pain and briefly review the diagnostic challenges in this condition.

Case Report

A 16-year-old female patient was presented with complaint of an epigastric pain. There was a three-month history of intermittent fever, night sweats, and significant weight loss. On physical examination, neither hepatosplenomegaly nor superficial lymphadenopathy noted. Imaging studies revealed multiple abdominal and retroperitoneal lymph nodes ranging from 1 to 4 cm, with the greatest one located in the liver hilum. Following laparoscopic evaluation, representative samples including pieces of tan rubbery tissue measuring 2 × 2 × 1cm were taken, fixed in 10% buffered formalin, and sent for pathologic evaluation. The whole specimen processed and 4µm thick sections cut from each paraffin block and stained with Hematoxylin and Eosin. On microscopic examination, the lymph node architecture was totally effaced and appeared like granulation tissue at low power. On higher magnification, sheets of histiocytes having eccentric nuclei and pinkish cytoplasm admixed with large atypical cells with marked pleomorphism, horseshoe shaped nuclei, and multiple prominent eosinophilic nucleoli were evident.

Immunohistochemistry, using antibodies listed in Table 1, was performed. A positive immunoreaction of anaplastic cells to LCA, CD3, CD8, and CD30 was noted. Granzyme B showed specific paranuclear staining and ALK protein revealed both nuclear and cytoplasmic staining. The background histiocytes were positive for CD68. Other markers such as CD20, CD34, CD1a, MPO, and CD117 were negative in neoplastic cells.

According to histologic and immunohistochemical findings, the final diagnosis was ALCL (hypocellular/lh variant).

Discussion

ALCL constitutes approximately 10% – 15% of all NHLs,[7,10–15] and 20% – 30% of large cell lymphomas in children.[7,13,16] Only T or null cell phenotypes are included in ALCL.[1] According to clinical and molecular features, this entity is subclassified into three dominant categories: primary ALK+, primary ALK−, and primary cutaneous ALCL.[1] ALK protein is expressed in 53% to 84% of ALCLs.[6,17–21] The wide range depends on criteria for patient selection. While there is no significant morphologic difference between ALK+ and ALK− ALCLs, the clinical, genetic,

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Table 1. Antibodies used for immunohistochemical studies

Target protein	Clone	Source
LCA*	2B11+ PD7126	DAKO
CD3	Polyclonal	DAKO
CD8	C8/144B	DAKO
CD30	Ber-H2	DAKO
CD68	PG-M1	DAKO
CD20	L26	DAKO
CD34	QB End10	DAKO
MPO**	Polyclonal	DAKO
ALK1***	ALK1	DAKO
Granzyme B	GrB-7	DAKO
CD1a	010	DAKO
CD117	Polyclonal	DAKO

*Leukocyte Common Antigen; **Myeloperoxidase; *** Anaplastic Lymhoma Kinase.

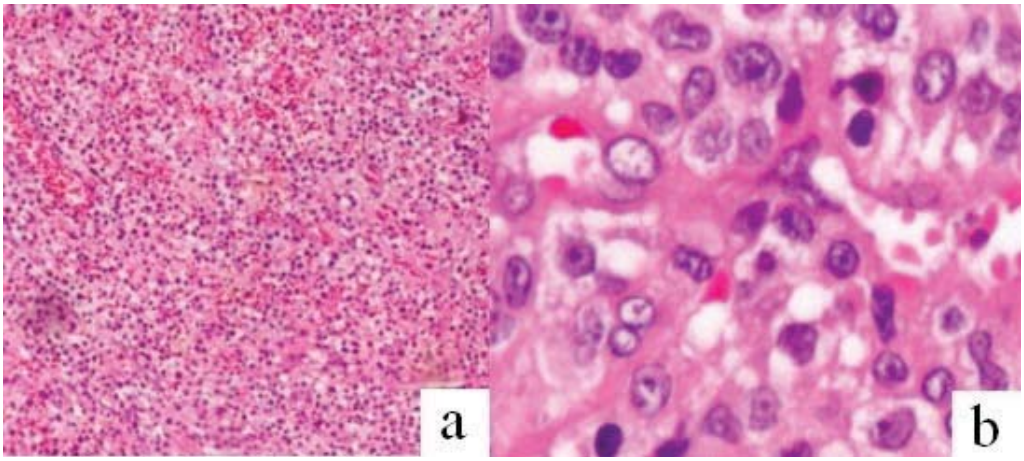

Figure 1. a) Granulation tissue- like appearance in lymph node (H&E X40), **b)** Large atypical cells with marked pleomorphism showing perivascular cuffing and mixed with histiocytes (H&E X400).

and immunohistochemical features vary.[22] The ALK+ subgroup has emerged as a category with primary systemic disease, predominant occurrence in males, and at first three decades of life. It usually manifests in advanced stages III or IV with presence of B symptoms,[6,23,24] whereas ALK− primary systemic ALCL is more common in older population and shows less frequent involvement of extranodal sites compared to ALK+ ALCL.[23,25] Primary cutaneous ALCL is almost always ALK negative.[6,26]

Most ALK+ ALCLs harbor t (2;5) (p23;q35) chromosomal aberration[27–30] and the remaining 15% – 20% show variant fusion partners with different immunohistochemical pattern from the first group (cytoplasmic pattern without nuclear staining vs cytoplasmic and nuclear pattern).[27] ALK+ ALCL, including variant ALK fusions appears to have better response to chemotherapy and more favorable outcome.[27,31]

Based on morphologic features, variants of ALCL consist of common type, monomorphic, small cell, mixed cell, LH, giant cell, and sarcomatoid.[5,6,9,17–19,32–33] Among different morphologic features, LH variant is the one which poses great problem in diagnosis and can be easily misdiagnosed as reactive process.[6] Although the presence of characteristic "hallmark cells" defined as large cells with reniform or horseshoe shaped nuclei and multiple small nucleoli[1,6] can be a useful guide to correct diagnosis, but here the neoplastic cells are usually smaller than common type.[6] Furthermore, reactive histiocytes may include the dominant population and mask the tumor cells.[3,9] Reactive histiocytes have eccentric dense nuclei with acidophilic cytoplasm and sometimes show evidence of erythrophagocytosis.[1,2,9,34] An important diagnostic clue to LH variant of ALCL is perivascular cuffing of the tumor cells, that can be reinforced by CD30 or ALK staining.[1] The neoplastic cells are mostly reactive for EMA and negative for histiocytic markers.[1] Positive CK staining with occasional negative reaction to LCA can make undifferentiated carcinoma as one of differential diagnoses.[1] Hypocellularity, a growth pattern rather than a specific subtype, can be seen in various morphologic types of ALCL,[6] including LH variant.

In LH-ALCL, being hypocellular in addition to some unusual morphologic features like sarcomatoid pattern, myxoid stroma, presence of spindle cells or granulation tissue- like appearance (like the present case) make too difficult to differentiate LH-ALCL from reactive process or even can be misdiagnosed as inflammatory pseudotumor.

In our patient, on microscopic evaluation, dilated and congested blood vessels and capillary structures in addition to myxoid hypocellular stroma in a young patient mimicked the granulation tissue appearance and directed one towards reactive process on first impression. Despite this morphologic feature, in our opinion, the total effacement of lymph node was the important point reminding to search more in order not to miss any serious pathology. Presence of atypical lymphoid cells, especially clustering around blood vessels constitute another diagnostic hint directed us toward correct diagnosis. By using ALK and CD30 antibodies we were

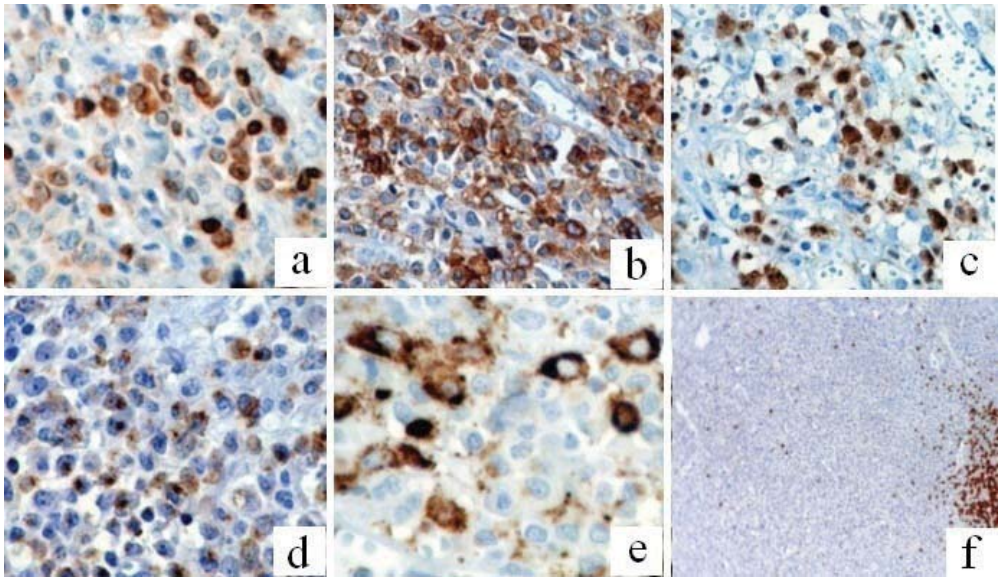

Figure 2. IHC staining for **a)** CD3 (X200), **b)** CD30 (X200), **c)** ALK-1 (X200), **d)** Granzyme-B (X200), **e)** CD68 (X400), **f)** CD20 (X40)

able to highlight the neoplastic cells.

In contrast to hypocellular ALCL, the lymph node parenchyma is relatively preserved and neither spindle cells nor lymphoid cells show atypia in inflammatory pseudotumor.[6]

Finally, we emphasize that ALCL can present as hypocellular myxoid lesion with congested blood vessels and granulation tissue- like appearance, mimicking reactive process. Therefore, in every young patient with unusual looking reactive lymphadenopathy simulating granulation tissue, ALCL should be considered as one of the differential diagnoses in order not to miss the chance of appropriate treatment for the patient.

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