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ALK negative Anaplastic Large Cell Lymphoma with granulomatous reaction in a pediatric patient: Report of a rare case

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Abstract: Anaplastic Large Cell Lymphoma (ALCL) represents a generally recognized group of large cell lymphomas. Defining features consist of a proliferation of predominantly large lymphoid cells with strong expression of the cytokine receptor CD30 and a characteristic growth pattern. Granulomatous reaction is a rare presentation in NHL (Non Hodgkin's Lymphoma)-ALCL type. Here, we present a rare case of ALK (Anaplastic Lymphoma Receptor Tyrosine Kinase) negative ALCL with granulomatous reaction in a pediatric patient.
Keywords: ALCL (Anaplastic large cell lymphoma); ALK (anaplastic lymphoma receptor tyrosine kinase); granuloma; pediatric

INTRODUCTION

During the last 25 years, anaplastic large cell lymphoma (ALCL) has evolved from a tumor often misdiagnosed as metastatic carcinoma, melanoma, or malignant histiocytosis to a distinct molecular pathologic entity.[1]ALCL (Anaplastic Large Cell Lymphoma) accounts for <5% of all lymphomas. Incidence of ALCL is 20-50% of all large cell lymphomas in children and they occur as 2-8% cases of all NHL(Non Hodgkin Lymphoma) in adults. Peak incidence is in childhood, accounting for approximately 40% cases of NHLs with a male predominance. Broadly, there are two main clinical forms: primary cutaneous variant and systemic variant and two main groups: ALK positive with good prognosis and ALK negative with worse prognosis. Most of the ALCLs in children are ALK-positive.

ALK expression is caused by chromosomal translocations, most commonly t (2; 5). ALK positive ALCLs are NHLs of T cell lineage having broad spectrum of histologic features and expression of CD 30(Ki-1) and ALK. ALCL cases positive for ALK predominantly affects young male patients and, if treated with chemotherapy, has a favorable prognosis. ALK negative patients have a far worse prognosis. [2]

Epithelioid cell granuloma has been reported in association with a wide range of neoplasms including malignant lymphomas. Among lymphomas, this occurs more often in Hodgkin's disease and T cell derived Non-Hodgkin's Lymphoma where a granulomatous reaction is probably evoked by aberrant cytokine production in the tumor cells or other cells composing the tumor background.[3]However, not many reports are available in literature on the association of granuloma with ALCL, especially in our part of geographical location.

CASE REPORT

A three and a half year old boy was brought to our hospital with chief complaints of fever, difficulty in breathing and two episodes of hematemesis.

History dates back to 2 months when child started having fever, which was of moderate grade, not associated with rigor and chills and without diurnal variation. He also developed cough which was non productive and not associated with hemoptysis. There was no history of significant weight loss. On examination, the child had bilateral, multiple ,discrete, non tender cervical lymph nodes varying in size from 0.5 to 1.2 cm. Patient was kept on intravenous fluids, antipyretics and antibiotics. Still, his condition kept on deteriorating from date of admission. Relevant investigations were as follows:

Peripheral blood film showed 10% atypical or activated lymphocytes and on flow cytometry they presented as lymphocytes predominantly T cells. Bone marrow aspiration and biopsy revealed atypical or activated lymphocytes (CD 3, CD 5 and CD 30 positive) and epithelioid cell granulomas. Lymph node aspiration was done and it showed ill formed epithelioid

cell granulomas and atypical cells (CD 3, CD 5 and CD 30 positive) which was confirmed on lymph node biopsy. Immunohistochemistry panel was applied which revealed that the atypical cells were positive for CD 3, CD 5 and CD 30 while they were negative for CD 15, ALK and CD 68.

After all the investigations, immunohistochemistry and other relevant diagnostic tests, the final diagnosis was rendered as Non- Hodgkin lymphoma (anaplastic large cell type) with granulomatous reaction. Patient was given treatment but despite that he died 7 months after the initial diagnosis.

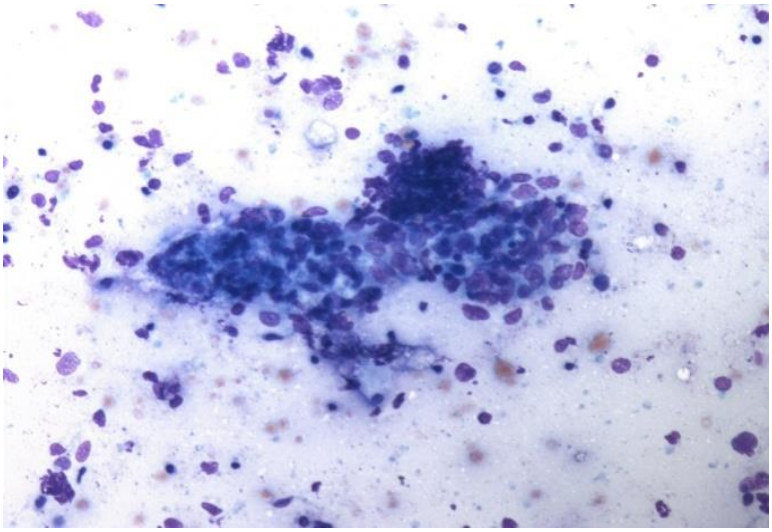

Fig-1: FNAC cervical lymph node showing ill formed granuloma and atypical cells in the Background

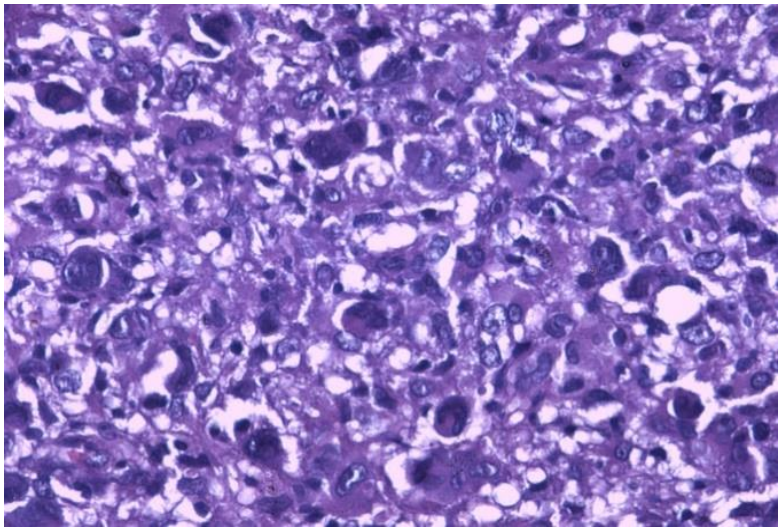

Fig-2: Large pleomorphic atypical cells with high N:C ratio, multinucleation and horse shoe shaped nuclei

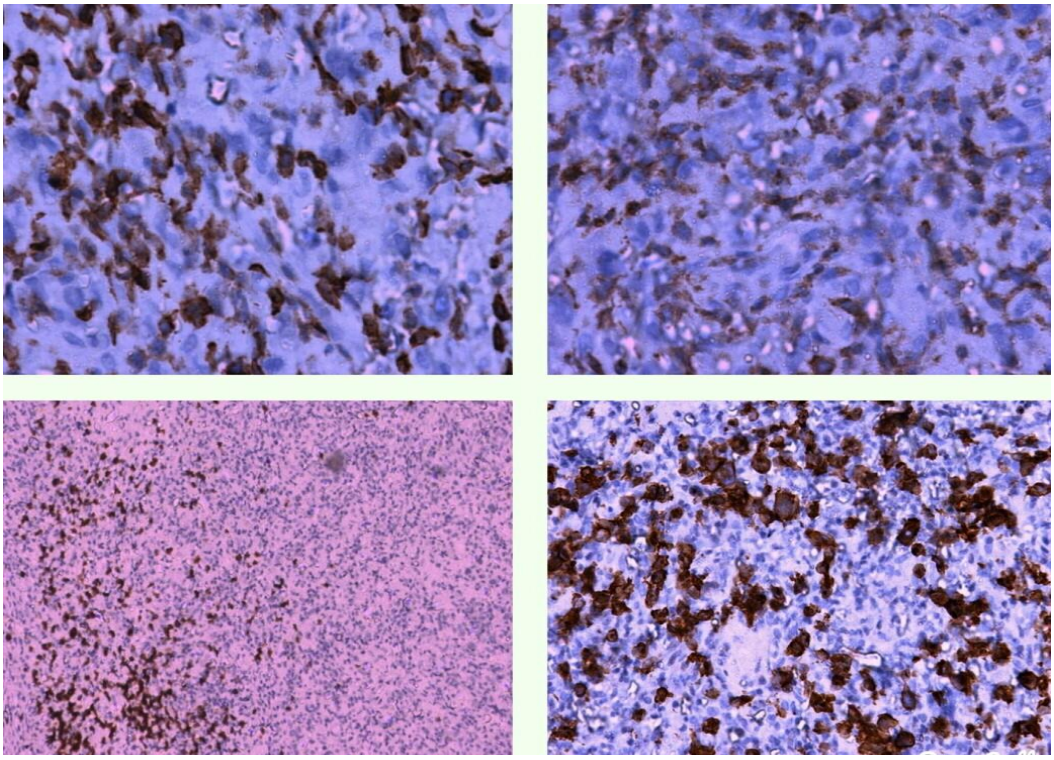

Fig-3: Clockwise from above left corner: CD 3 and CD 5 positive in atypical cells; CD 20 positive in residual cells; CD 30 positive in tumor cells.

DISCUSSION

Ana plastic large cell lymphoma is most common in children and young adults but has a bimodal age distribution and can occur in older adults.[4]Anaplastic large cell lymphoma represents approximately 10% to15% of pediatric/adolescent non-Hodgkin lymphomas, as compared to 2% of adult non-Hodgkin lymphomas and 30% to 40% of pediatric large cell lymphomas. The median age at diagnosis for pediatric patients is approximately10.2 to 11.0 years,26–28 and ALCL rarely occurs in infants.[5] Approximately 60% to 70% of patients have advanced stage III/IV disease due to peripheral and abdominal lymphadenopathy. Mediastinal adenopathy is present in approximately 5% to 40% of patients. Extra nodal disease is frequent with skin, bone, and soft tissue being the most common sites. [6]

ALCL, named after its morphologic variant first recognized by Stein et al, [7] includes a variety of histologic appearances that have in common the presence of a variable proportion of hallmark anaplastic large tumor cells and the expression of CD30 (Ki-1) and ALK.ALK expression aids in the differential diagnosis with other types of lymphoma and inflammatory lesions and permits recognition of tumors with an unusual phenotype as a part of this same category of disorders. It's prognosis depends on the ALK marker positivity. Cases with ALK translocation positive have a more favorable prognosis and survival rate. Immuno phenotyping and cytogenetic characterization largely eliminates much of the confusion for us and helps to make a final diagnosis. ALCL is characterized by sheets of largelymphoid cells with large, somewhat eccentric, chromatin-poor horseshoe-shaped nuclei containing multiple nucleoli[2]. Cells with these cytologic features have been called hallmark cells because they are encountered in all ALCL variants, including the small cell and lymphohistiocytic variants. Multinucleated large cells (often wreathlike) are frequently present and can have larger, more eosinophilic nuclei, thus resembling Reed-Sternberg cells. The cytoplasm is abundant and often has denser focal staining in the perinuclear, Golgi region of the cytoplasm[1]. Diagnosis of ALK+ ALCL of the common type has become straightforward owing to the widespread availability of reliable anti-ALK antibodies.

ALCL has been clinically subdivided into a primary form (de novo) and a secondary form (anaplastic transformation from another lymphoma). Among the primary ALCLs, systemic and cutaneous categories have been recognized both in immunocompetent patients and in HIV-positive patients (rarely). Primary systemic ALCL is the most frequent sub form, accounting for 2% to 8% of non-Hodgkin lymphomas in adults [8] and approximately 20%-30% of large cell lymphomas in children[9].

Our patient was a young child who presented with lymphadenopathy. Numerous investigations were performed and he was finally diagnosed with ALK negative ALCL. This usually is a rare occurrence in children and has a very bad prognosis.

Sarcoid-like granulomas may occur in association with Hodgkin's disease and Non-Hodgkin's Lymphoma [10]. The granulomas may be concomitant and so extensive that they may obscure the malignant process. In addition, a sarcoidosis-lymphoma syndrome has been described in which there appears to be a relationship between sarcoidosis and the development of a lymphoproliferative disorder[11]. However, this patient had no diagnostic clinical evidence of sarcoidosis. But granuloma formation was found in the FNAC of lymph node. The relationship between the exuberant epithelioid granulomas and the underlying neoplastic lymphoid proliferation is not clear [10]. Regardless of whether it represents a distinct clinic pathological entity, recognition of this remarkable association has important practical implications since the lesions may be erroneously interpreted by the pathologist.

ALCL is a less frequently occurring type of NHL which is a diagnostic challenge for clinicians and pathologists. Granulomatous reaction is also a rare occurrence in this tumor but if florid can obscure the entire malignant picture and it is mostly due to aberrant cytokine production. Although the first description of ALCL and it' sub forms was done about 15 years ago, there are still a lot of unanswered questions about the disease and it's presentation. The answers to those will definitely go a long way in improving diagnosis and therapeutic out comes for patients.

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