

CASE REPORT

Pediatric mediastinal ALK- negative anaplastic large cell lymphoma (Hodgkin-like pattern) in a 13-year-old girl: a case report and review of literature

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Abstract

Anaplastic large-cell Lymphoma (ALCL) is a rare type of non-Hodgkin lymphoma that is characterized by an entity of large neoplastic cells labeled by the Ki-1 antibody. It constitutes ~2% of all lymphoid neoplasms and is divided into two main categories: anaplastic large-cell kinase (ALK)+ALCL and ALK–ALCL that is recognized by the absence of ALK expression and mostly affects men at older ages. Thus, in this report we present a rare case of ALK-negative ALCL (ALK–ALCL) that was described and diagnosed in a 13-year-old girl in the mediastinum. Highlighting the rarity of manifestation at younger ages and the importance of using immunohistochemical staining in the differential diagnosis of this lymphoid neoplasm.

INTRODUCTION

Anaplastic large-cell lymphoma (ALCL) is a rare type of non-Hodgkin lymphoma that was first identified by Stein *et al.* in 1985 as a neoplastic entity of large cells with abundant cytoplasm and kidney-shaped nuclei. ALCL affects both nodal and extra nodal sites and constitutes ~15% of pediatric NHL [1].

Systemic ALCL is the most common type and mostly affects men [2]. It's categorized into two main subtypes according to the expression of a protein called anaplastic large-cell kinase (ALK): ALK-positive ALCL which is more common in young adults,

while ALK-negative ALCL tends to affect older males with a worse prognosis [2, 3].

Herein, we report a rare case of a 13-year-old girl who was diagnosed with an ALK-negative ALCL in the mediastinum with regards to pathological and immunohistochemical features of this neoplasm.

CASE REPORT

We report a case of a 13-year-old Syrian girl who was admitted to the hospital on 16/7/2018 due to dysphagia, dyspnea, edema in the face, pallor and asthenia. Clinical examination revealed large

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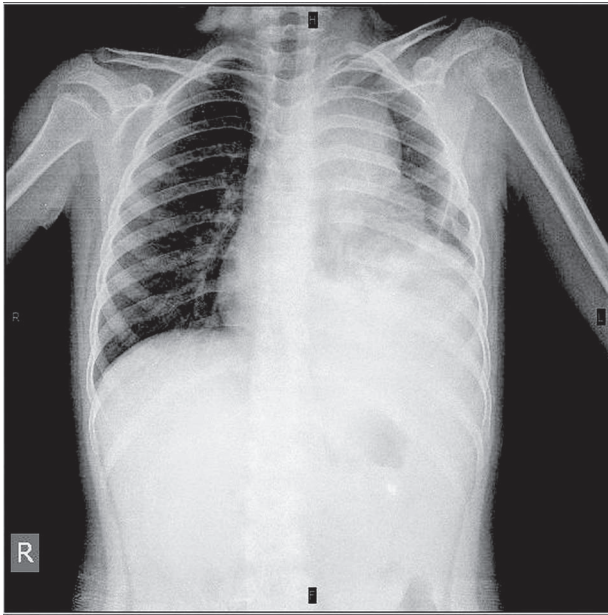


Figure 1: A chest radiography demonstrates an abnormal shadow in the mediastinum extending to the pulmonary hilar region.

masses in the mediastinum causing symptoms of superior vena cava syndrome. Blood examination showed WBC count $6 \times 10^9/L$, lymphocyte count 48%, neutrophil count 42%, hemoglobin count 85 g/L and CRP 117.

Chest radiography revealed an abnormal shadow in the mediastinum extending to pulmonary hilar region (Fig. 1). Furthermore, CT scan demonstrated large masses in the anterior mediastinum (Fig. 2) with no other masses elsewhere. Thus, our patient underwent surgery on 30 July 2018 for complete resection of the mediastinal lesions to remove the symptoms. Gross examination revealed that the resected masses were 10 enlarged lymph nodes measuring 3–7 cm. Microscopic examination revealed cohesive sheets of diffuse large pleomorphic cells effacing the nodes architecture (Fig. 3A and B), characterized by abundant cytoplasm and kidney-shaped nuclei with abnormal mitotic figures and Reed–Sternberg-like cells (Fig. 3C and D). Thus, differential diagnosis included ALCL, classical Hodgkin lymphoma (CHL), peripheral T-Cell lymphoma and diffuse large B-cell lymphoma (DLBCL).

Immunohistochemical stainings showed strong CD30 positivity for large and Reed–Sternberg-like cells (Fig. 4A and B), whereas CD15, CD3, CD20, ALK, CD45Ro and EMA were negative (Figs 4 and 5). These results confirmed the diagnosis of ALK–ALCL.

The patient received chemotherapy based on NHL-BFM 90 Protocol for ALCL. Thus treatment regimen was based on alternating courses that included dexamethasone, cyclophosphamide, methotrexate, cytarabine, vincristine, etoposide, doxorubicin, ifosfamide and prednisolone.

The last chest and abdomen CT scan on 18 March 2019 showed complete response and the patient is currently in remission on maintenance therapy of Vinblastine 10 mg/m².

DISCUSSION

ALCL is an aggressive rare type of non-Hodgkin lymphoma that's characterized by pleomorphic cells labeled by Ki-1 antibody [4].

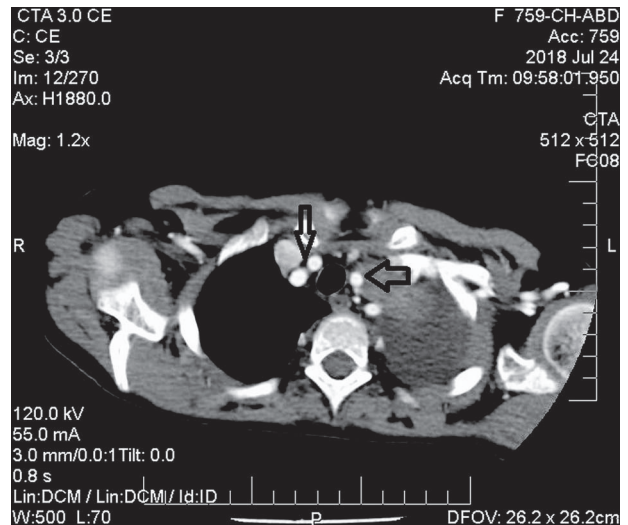


Figure 2: CT scan of the upper thoracic region demonstrate enlarged lymph nodes (Black Arrows) in the anterior mediastinum.

It constitutes nearly 15% of pediatric NHL and 2% of all NHL. Furthermore, about 15–20% of ALCL cases affect patients under 20 years old mostly males [4, 5], our rare case, however, was described in a 13-year-old female.

According to the revised fourth edition of the WHO classification (2017), ALCL is defined as a CD30-positive neoplasm of T or null cell lineage, as these tumors are distinguished by their anaplastic cytology and constant membrane expression of CD30 antigen [5, 6].

There are two subsets of ALCL: Primary cutaneous ALCL which is confined to the skin, and Systemic ALCL that affects all organs mostly the lymph nodes, with involvement of extra nodal sites including bone marrow, skin, soft tissues, lung and liver [2]. The mediastinum is involved in ~10% [7], and as it is a common site in CHL, we have faced more challenges adding CHL to differential diagnosis.

Furthermore, systemic ALCL is categorized into two main subtypes according to the expression of a protein called ALK: ALK-positive ALCL which constitutes 50–80% and is more common in young adults with a survival rate of 70–90% for 5 years, while ALK-negative ALCL represents 20–50% and tends to affect older adults with a worse prognosis and a survival rate of 40–60%. Male predominance (60%) is seen in both subtypes [8, 9].

Diagnosing ALCL can be challenging. Cytomorphologic findings, immunohistochemistry and clinical data were critical as there are certain similarities between ALCL, Hodgkin lymphoma, peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) and DLBCL. These features include the proliferation of large pleomorphic cells with abundant cytoplasm and large atypical nuclei. And this gives an essential role for immunohistochemistry [9, 10].

Morphologically in ALCL, we see cohesive sheets of large pleomorphic cells with abundant cytoplasm and kidney-shaped nuclei surrounded by an inflammatory background [10]. Neoplastic cells resemble Reed–Sternberg cells raising the difficulty in differentiating it from CHL.

However, CHL lacks cohesive growth pattern and has classical Reed–Sternberg cells with an inflammatory background and band-like fibrosis. Likewise, DLBCL can be distinguished with its

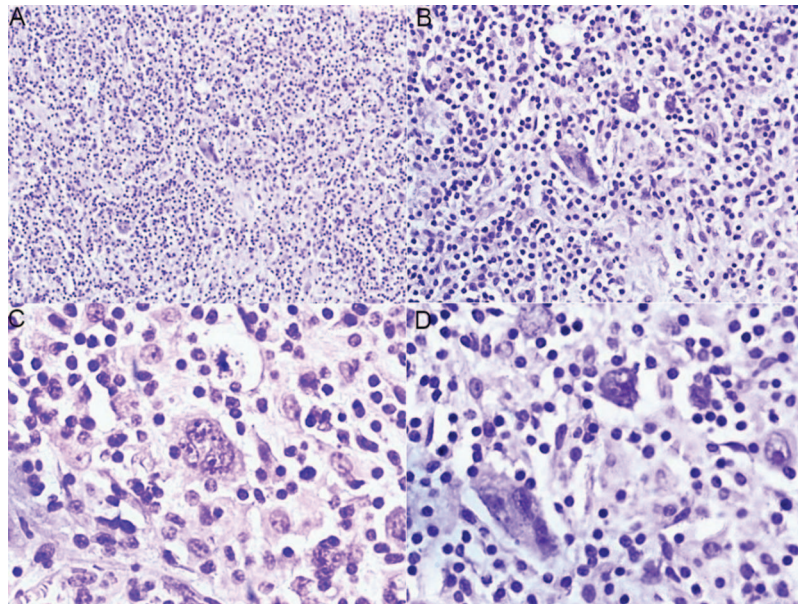


Figure 3: H&E sections of resected lymph nodes demonstrating: (A and B) cohesive sheets of diffuse pleomorphic cells effacing the nodes architecture; (C and D) neoplastic cells characterized by abundant cytoplasm and kidney-shaped nuclei with multiple abnormal mitotic figures in addition to Reed-Sternberg like cells

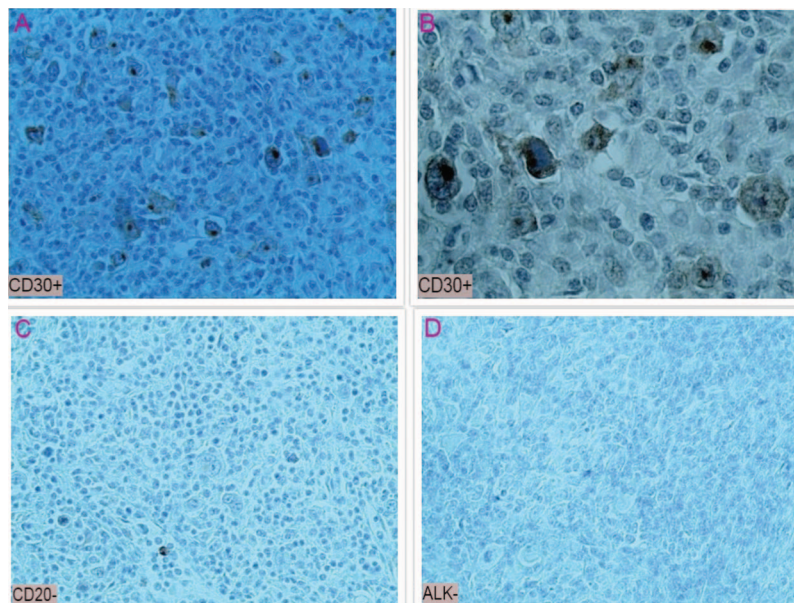


Figure 4: Immunohistochemistry of the lymph nodes: (A and B) strong CD30 positivity for large and Reed-Sternberg-like cells; (C) negativity for CD20; (D) negativity for ALK.

large B-cells lineage, while PTCL-NOS is recognized with small clusters of epithelioid histiocytes resembling granulomas [8, 10].

In addition, IHC stainings for ALK, CD30, CD3, CD15, CD20, CD45Ro and EMA are valuable in the differential diagnosis. In ALK-ALCL, cells show strong positivity for CD30, usually in Golgi region and at the cell membrane. Our case also showed negativity for CD15 excluding CHL. Without forgetting negativity for CD20 and EMA excluding DLBCL and negativity for CD3 and CD15 excluding PTCL-NOS.

Molecularly, detecting ALK protein correlates with a chromosomal translocation that involves NPM gene on chromosome 5q35 and ALK gene on chromosome 2p23. Furthermore, ALK+ALCL is characterized by overexpression of HIF1- α target

genes as well as interleukin10 and H-ras/K-ras induced genes, while ALK-ALCL is enriched for TMOD1, TNFRSF8, GATA3, MYC, IRF4 target genes and PI3K pathway-regulated genes. Studies also revealed that DUSP22 and P63 rearrangement were present in 30% and 8% of ALK-ALCL cases respectively, but absent in ALK+ALCL [10]. Nevertheless, molecular testing has been largely replaced by immunohistochemistry. In addition, these tests were not available in our country, thus the diagnosis was based on immunohistochemical and cytomorphologic findings.

Furthermore, although studies showed correlation between the presence of ALK/Ki1 antigen and young ages, our case was ALK-negative presenting in a 13-year-old patient.

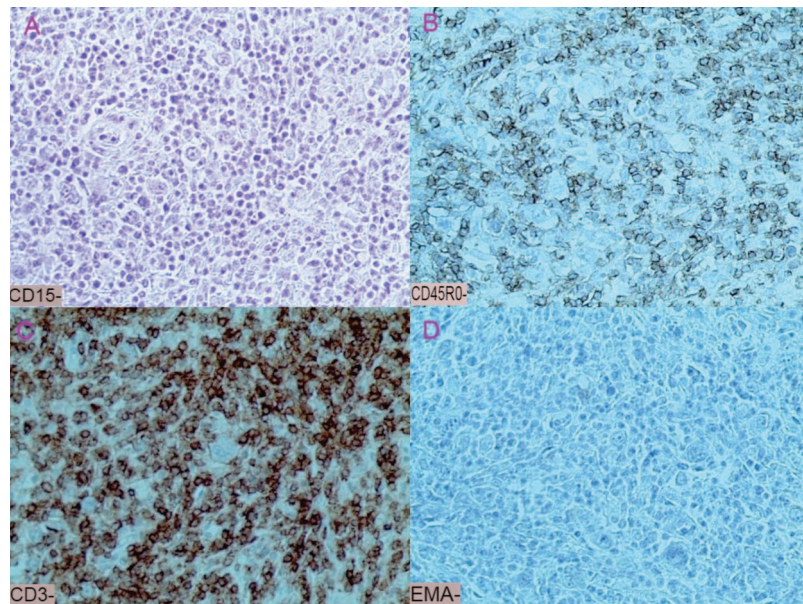


Figure 5: Immunohistochemistry of the lymph nodes: (A) CD15 is negative; (B) CD45Ro is negative; (C) CD3 is negative; (D) EMA is negative.

In conclusion, diagnosing ALK-ALCL represented a hard challenge due to rarity of presenting in young ages, male predominance and difficulties in diagnosis. However, with proper immunohistochemical stainings and detailed cytomorphologic observation, diagnosis was confirmed in our case.

CONFLICT OF INTEREST STATEMENT

Not applicable.

CONSENT

Consent Form was obtained from the patient's guarantor (Patient's father). A copy of the consent form is available with the editor.

GUARANTOR

Dr. Z.A.-S. (one of the co-authors) is the Guarantor of the manuscript.

REFERENCES

- Alessandri AJ, Pritchard SL, Schultz KR, Massing BG. A population-based study of pediatric anaplastic large cell lymphoma. *Cancer* 2002;**94**:1830-5.
- Medeiros LJ, Elenitoba Johnson K. Anaplastic large cell lymphoma. *Am Soc Clin Pathol* 2007;**127**:707-22.
- Boi M, Zucca E, Inghirami G, Bertoni F. Advances in understanding the pathogenesis of systemic anaplastic large cell lymphomas. *Br J Haematol* 2015;**168**:771-83.
- Stein H, Mason DY, Gerdes J, O'Connor N, Wainscoat J, Pallesen G et al. The expression of the Hodgkin's disease associated antigen Ki-1 in reactive and neoplastic lymphoid tissue: evidence that reed-Sternberg cells and histiocytic malignancies are derived from activated lymphoid cells. *Blood* 1985;**66**:848-58.
- Prokoph N, Larose H, Lim MS, Amos Burke GA, Turner S. Treatment options for Paediatric anaplastic large cell lymphoma (ALCL): current standard and beyond. *Cancers* 2018;**10**:99.
- Ferreri A, Govi S, Pileri S, Savage K. Anaplastic large cell lymphoma, ALK-negative. *Crit Rev Oncol Hematol* 2013; **85**:206-15.
- Kayao J, Tamaru J, Wakita H, Saitou T, Kuzuu Y, Mikata A et al. Anaplastic large CELL lymphoma of the mediastinum diagnosed by Transbronchial scratch cytology. *Acta Cytol* 2002;**46**:405-11.
- Savage KJ, Harris NL, Vose JM, Ullrich F, Jaffe E, Connors J et al. ALK- anaplastic large-cell lymphoma is clinically and immunophenotypically different from both ALK+ ALCL and peripheral T-cell lymphoma, not otherwise specified: report from the international peripheral T-cell lymphoma project. *Blood* 2008;**111**:5496-550.
- Brugières L, Le Deley M-C, Rosolen A, Williams D, Horibe K, Wrobel G et al. Impact of the methotrexate administration dose on the need for intrathecal treatment in children and adolescents with anaplastic large-cell lymphoma: results of a randomized trial of the EICNHL group. *J Clin Oncol* 2009;**27**:897-903.
- Hapgood G, Savage KJ. The biology and management of systemic anaplastic large cell lymphoma. *Blood* 2015; **126**:17-25.