SJIF Impact Factor: 5.464

WORLD JOURNAL OF ADVANCE HEALTHCARE RESEARCH

ISSN: 2457-0400
Volume: 6.
Issue: 3
Page N. 01-05
Year: 2022

Case Report www.wjahr.com

SYSTEMIC ALK-NEGATIVE ANAPLASTIC LARGE CELL LYMPHOMA: A CASE REPORT OF AN ASYMPTOMATIC PATIENT FROM SYRIA

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Received date: 28 December 2021 **Revised date:** 18 January 2022 **Accepted date:** 08 February 2022

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ABSTRACT

Anaplastic large cell lymphomas (ALCLs) are uncommon malignancies; they include a group of CD30-positive Non-Hodgkin T-cell lymphomas that share similar morphologic and immunophenotypic features. The World Health Organization identifies 3 entities: primary cutaneous ALCL, anaplastic lymphoma kinase (ALK)-positive ALCL, and ALK-negative ALCL. ALK-negative ALCL is known for its aggressive behaviour and poor prognosis. It usually affects males at a median age of 55-60 years old. The majority of patients are presented with B symptoms and stage III–IV of the disease. Medical literature has reported very few cases of systemic ALK-negative ALCL. Here we demonstrate a unique case of a 47-year-old male, with no systemic symptoms, diagnosed with a stage IV, CD30+, ALK-negative ALCL presented with several tender, enlarged, inguinal lymph nodes and extranodal involvement in the skin, lung, liver and the bone marrow.

KEYWORDS: Anaplastic large T-cell lymphoma, ALK-negative, extranodal involvement, bone marrow.

INTRODUCTION

Lymphoma is a malignant disease of the lymphatic system characterized by the proliferation of B cells, T cells, or natural killer (NK) cells. It is categorized into two broad groups: Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL). Anaplastic large cell lymphoma (ALCL), a sub-type of T-cell Non-Hodgkin lymphomas (NHLs), forms 2% to 3% of all NHLs and 12% of all T-cell lymphomas.[1] The WHO classification, according to the most recent update in 2016, identifies 3 distinct types: ALK-positive ALCL, ALK-negative ALCL and primary cutaneous ALCL (PC-ALCL).[2]

ALK-negative anaplastic large cell lymphoma was first recognized by Stein and colleagues in 1985.[3] It is a rare, challenging systemic type of CD30-positive T-cell lymphoma.[4] Anaplastic large cell lymphoma (ALCL) can imitate several other hematologic and non-hematologic malignancies by morphology and immunohistochemistry.[4] Therefore, it must be distinguished from classical Hodgkin lymphoma, primary cutaneous ALCL and other subtypes of CD30+ T or B-cell lymphoma with anaplastic features.[5] It generally affects adults, and it's slightly more predominant in males than in females. The median age of diagnosis fluctuates between 55–60 years. About 70% of patients present with B symptoms and stage III–IV of the disease. Typically, it involves lymph nodes (49% of cases) and infrequently extranodal sites (20% of cases), while bulky disease and bone marrow involvement are uncommon.[5,6] Here we present an unusual case of an advanced stage, CD30-positive, ALK-negative ALCL, with extranodal involvement in the skin, lung, liver and the bone marrow.

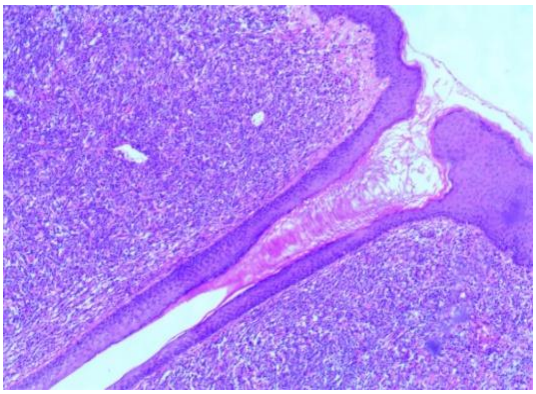
CASE REPORT

A 47-year-old man, with a medical history of percutaneous coronary intervention (PCI), presented to a local clinic, reporting a two-month history of multiple, slightly tender, enlarged inguinal lymph nodes accompanied with a slight swelling in the root of the penis. Other than that, the patient was asymptomatic, he had no fever, weight loss or night sweats. His family history is unremarkable except for his brother who has a past medical history of psoriasis. The abdomen and pelvic ultrasound showed bilateral, low-density,

enlarged, inguinal lymph nodes as well as several low-density foci on the liver, both highly suggestive of metastatic origin. Consequently, the patient was referred to the hematology/oncology department at Tishreen University Hospital for further investigation.

Initial laboratory work-up showed the following results: WBC: 8800, HGB: 13.2 g/dL, PLT: 361000, a remarked increase in Lactate Dehydrogenase (LDH) levels of 980 U/l (normal ranges are between 250-450 U/l) and in C - reactive protein (CRP) concentration of 22 mg/L (normal ranges are up to 6 mg/L). His liver and renal function tests were within normal limits. Human Chorionic Gonadotropin (Beta-HCG) and Alpha-Fetoprotein were also normal.

Following that, an excisional biopsy of a right inguinal lymph node and the regional edematous skin was obtained. Microscopic examination revealed atypical dermal and subcutaneous lymphoid infiltration of solid, cohesive sheets of large pleomorphic neoplastic cells with eccentric, horseshoe-shaped, or kidney-shaped nuclei and sometimes containing prominent nucleoli, and occasional mitotic figures. Fig. (1). This is consistent with malignant Non-Hodgkin lymphoma, and therefore immunohistochemical analysis was recommended.



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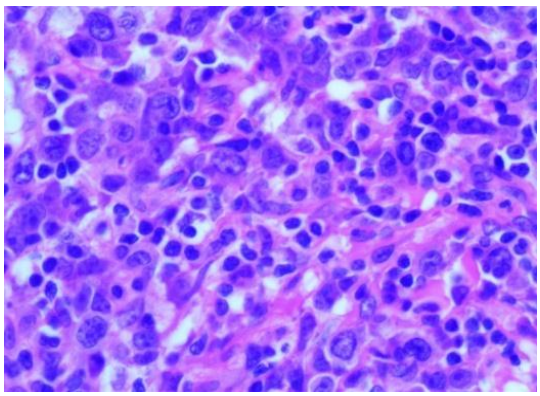
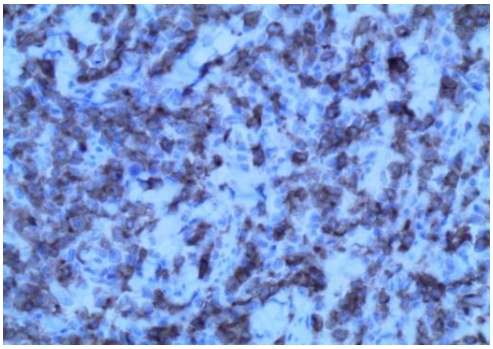


(B)

Fig. (1): Histopathologic examination demonstrates atypical dermal and subcutaneous lymphoid infiltration. H&E x 100 (A), x 600 (B).

The pathology report confirmed high-grade CD30-positive, ALK-negative T-cell lymphoma. Immunostaining supported the diagnosis with the positivity of CD3 and CD30, high Ki67 proliferation activity marker (80%) and a negative expression for ALK1 marker. **Fig. (2)**.



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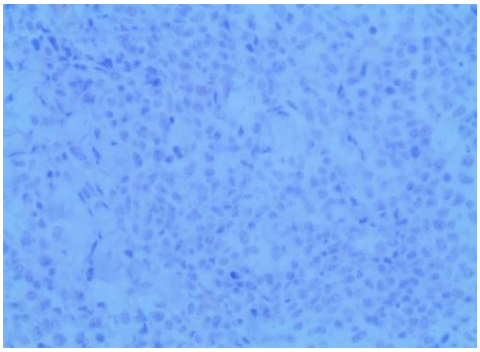

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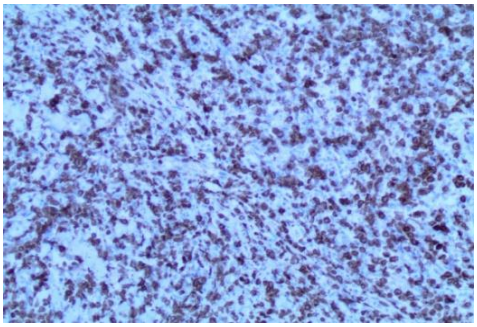
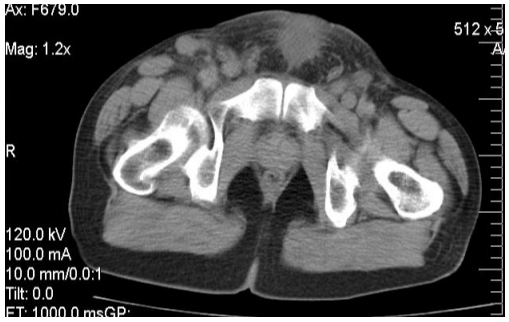


(C)

Fig. (2): Lymph node immunohistochemical staining: (A) CD30 positive, (B) ALK1 negative, (C) CD3 positive.

Afterwards, the patient was referred for a complete computed tomography (CT) scan with contrast for staging. It showed bilateral pulmonary parenchymal nodules, the largest being 12 mm, as well as a number of bilateral necrotic lymph nodes in the inguinal region, the right iliac area and anteriorly to the abdominal aorta bifurcation, measuring 56, 50 and 20 mm respectively, and multiple low-density hepatic foci measuring 30 mm; all of these are highly suggestive of metastatic disease. Fig. (3).



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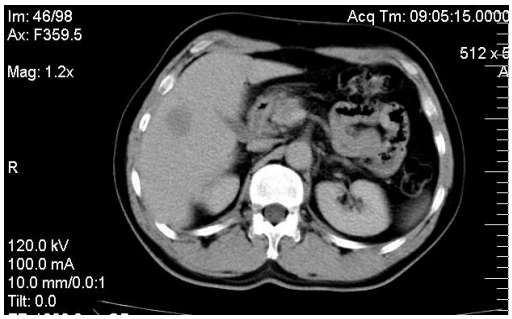
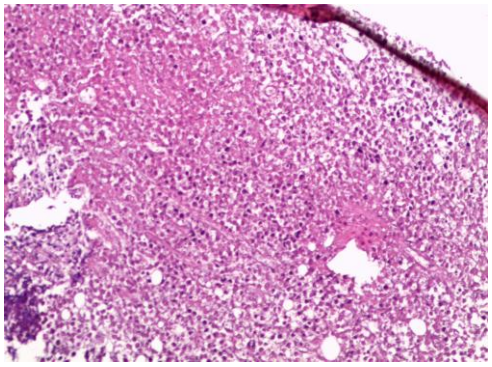


(B)

Fig. (3): CT scan with IV contrast, axial view, of the: (A) Pelvis, shows several bilateral enlarged inguinal lymph nodes, (B) Abdomen, shows liver metastases.

While bone marrow involvement is known to be uncommon, bone marrow biopsy of our patient showed diffuse infiltration of atypical lymphocytes. **Fig. (4).**



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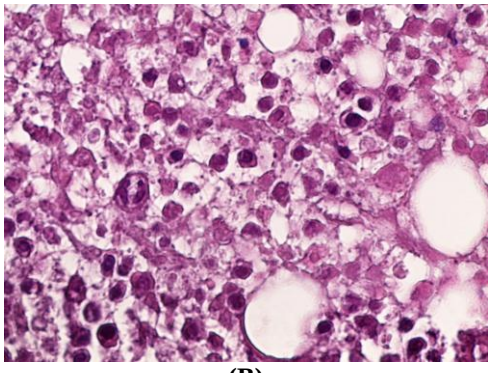

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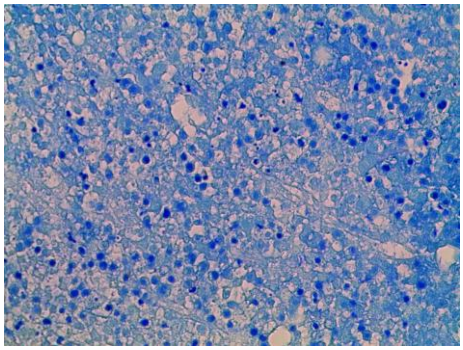

(C)

Fig. (4): Histopathologic examination demonstrates diffuse infiltration of atypical lymphocytes in bone marrow biopsy. H&E x 100 (A), x 400 (B), immunohistochemical staining shows negative ALK staining (C).

Regarding that the patient had no systemic symptoms, the lymphoma was classified as stage IV A, according to COSTWOLD modification of the Ann Arbor staging system[7] with high-intermediate risk (score of 3) according to the International Prognostic Index (IPI) and group 1 (score of 1) according to the Prognostic Index for T-cell lymphoma (PIT) Table (1).

Table (1): The International Prognostic Index (IPI) and the Prognostic Index for T-cell lymphoma (PIT).

PTCL
Prognostic Indices (IPI and PIT)

The Prognostic Index for PTCL (PIT) was developed to better define prognosis than the IPI[2]

Risk factor	IPI	Age-adjusted IPI (age ≤60 years)	PIT
Age >60 years	•		•
Serum LDH >1x normal	•	•	•
Performance status 2–4	•	•	•
Stage III or IV	•	•	
Extranodal involvement >1 site	•		
Bone marrow involvement			•

# of risk factors*	IPI	Age-adjusted IPI (age ≤60 years)	PIT
0	Low	Low	Group 1
1		Low intermediate	Group 2
2	Low intermediate	High intermediate	Group 3
3	High intermediate	High	Group 4
4	High	N/A	
5			N/A

* Each risk factor has a relative value of 1; LDH = lactate dehydrogenase.

1. International Non-Hodgkin's Lymphoma Prognostic Factors Project. *N Eng J Med*. 1993;329:987–994; 2. Gallamini A, et al. *Blood*. 2004;103:2474–2479.

The patient is currently started on CHOEP regimen (Cyclophosphamide 750 mg/m^2, Doxorubicin 50 mg/m^2, Vincristine 2 mg on day 1, Etoposide 100 mg/m^2 on days 1-3 and prednisone 100 mg orally on days 1-5) with a 3-week interval for six cycles.

DISCUSSION

The systemic type of ALCL represents nearly 2% to 3% of all NHLs.[8] Approximately 15% to 20% of systemic ALCL are ALK-negative.[9] No predisposing agents or risk factors have yet been correlated with ALCL. The association between ALCL and immunologic disorders, such as psoriasis, hasn't been well identified yet.

Nevertheless, it was found that breast implants could be considered as an independent risk factor of ALCL.[4]

Systemic ALK-negative ALCL patients typically present with painless lymphadenopathy and around two thirds of patients with systemic ALCL are likely to have B symptoms with advanced stage (lll or lV) upon admission. Extranodal sites such as the skin, the lung, and the liver may be involved, but this occurs in ALK-negative ALCL less frequently than in ALK-positive ALCL, while bone marrow involvement is very rare.[1,8,9] Our patient experienced no systemic symptoms and had normal complete blood count despite the advanced stage of the disease and the existence of lung and liver metastases and the secondary involvement of the skin and the bone marrow. Through the past two decades, only few cases of systemic ALK-negative anaplastic large T-cell lymphoma with similar presentation were reported in the literature.

Multiple pathologic patterns were presented at the WHO classification including common, lymphohistiocytic, small cell and Hodgkin-like. All patterns of ALCL resemble by demonstrating a specific cell type referred to as the "hallmark cell": a large cell of an ample cytoplasm and a unique nuclei in the shape of a kidney or a horseshoe with a centralized Golgi zone. The nucleus may sometimes appear in the shape of a doughnut when it surrounds the Golgi apparatus.[1,4]

The strong diffuse expression of CD30 is the most important stain in the diagnosis of ALK-negative ALCL. Routinely, one T-cell antigen at a minimum is detected. B-cell lineage markers are absent.[4] ALK-negative ALCL can resemble other non-hematologic malignancies cytologically and pathologically, including sarcomas, carcinomas, melanomas and germ cell tumors. Other multiple lymphoid malignancies could be variably CD30 positive, such as diffuse large B-cell lymphoma, classical Hodgkin lymphoma, enteropathy associated T-cell lymphoma (type 2), Peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), extranodal NK/T-cell lymphoma, and transformed mycosis fungoides.[4] Despite that several entities might express CD30, these entities don't usually have the diffuse and strong pattern of ALCL. The accurate diagnosis of primary cutaneous ALCL demands clinicopathologic correspondence to exclude a secondary involvement of a systemic ALCL. The immunophenotyping of primary cutaneous ALCL and systemic ALK-negative ALCL is almost identical.[4] The most seen genetic abnormalities in both malignancies are DUSP22. The prognosis of ALK-negative ALCL is worse than ALK-positive ALCL; 5-year overall survival rate (49%) versus (70%), yet it's better than peripheral T-cell Lymphoma-NOS (32%).[4]

No ideal therapy was found yet for ALK-negative ALCL, and this could be attributed to disease infrequency, heterogeneity of clinical presentation, and low numbers of randomized trials focused solely on this lymphoma. ALK-negative ALCL is usually studied with other T-cell lymphomas, that's why very few past studies concentrated independently on adult patients with ALK-negative ALCL.[5] Through the years, CHOP is still widely used as a front-line regimen for newly diagnosed patients with peripheral T-cell lymphoma. CHOP plus Etoposide (CHOEP) is the most front-line regimen thought to provide more benefit over CHOP, as it showed better survival outcomes.[10] The 3-year overall survival rate (76%) in anthracycline/Etoposide-based treatment group was higher than the anthracycline-based treatment group (56%); according to the T-Cell Project cohort study in 2021.[6]

CONCLUSION

ALK-negative ALCL might present with a wide range of clinical pictures, and this case shows that the absence of symptoms doesn't rule out the diagnosis. Thus, it's highly recommended for the clinicians to keep the diagnosis in mind in suspected patients even if they were asymptomatic. This raises the probability of identifying this neoplasm early and therefore, obtaining better outcome.

Conflict of interest

The authors declare no conflict of interest.

Patient consent form

Written informed consent was obtained from the patient.

ACKNOWLEDGEMENTS

We would like to thank Dr. Michael Georgeos and Dr. Zuheir Al-Shehabi for their support and guidance through this work.

Sources of funding

There are no sources of funding.

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