



Fatal anaplastic lymphoma kinase positive anaplastic large cell lymphoma presenting with cutaneous lesions: A case report

Deri lezyonları ile prezente olan fatal anaplastik lenfoma kinaz pozitif anaplastik büyük hücreli lenfoma: Bir olgu sunumu

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Abstract

Anaplastic large-cell lymphoma (ALCL) is a CD30-positive non-Hodgkin lymphoma of T-cell origin. It comprises approximately 3% of all non-Hodgkin lymphomas. The skin may be the primary involvement site (primary cutaneous) or systemic ALCL may affect the skin as cutaneous metastasis. In systemic ALCL, 80-85% of cases exhibit anaplastic lymphoma kinase-1 (ALK). However, primary cutaneous ALCL is typically ALK-negative. The most important prognostic marker in systemic ALCL is the expression of ALK. Positive ALK is associated with a favourable prognosis in systemic ALCL. Here, we report a case of ALK-positive ALCL with a very aggressive clinical course. Our case was evaluated for brown-violaceous nodules appearing on the trunk, groin and arm for about 3-4 weeks. In a few days after the diagnosis of ALCL, the patient died because of sepsis which was thought to be associated with ALCL.

Keywords: Anaplastic, large cell lymphoma, CD30, anaplastic lymphoma kinase, primary cutaneous

Öz

Anaplastik büyük hücreli lenfoma (ABHL), T hücre kökenli CD30 pozitif bir non-Hodgkin lenfomadır. Non-Hodgkin lenfomaların yaklaşık %3'ünü oluşturur. ABHL'de deri primer tutulum yeri olabileceği gibi (primer kutanöz ABHL), sistemik ABHL'nin deri metastazı şeklinde de deri tutulumu görülebilir. Sistemik ABHL'de olguların %80-85'i anaplastik lenfoma kinaz (ALK) pozitifliği göstermektedir. Primer kutanöz ABHL ise tipik olarak ALK negatiftir. Sistemik ABHL'nin en önemli prognostik belirteci ALK pozitifliğidir. ALK pozitifliği sistemik ABHL'de iyi prognozu gösterir. Burada gövde, inguinal bölge ve kolda 3-4 haftadır gelişen kahverengi-viyolase nodüler lezyonlar nedeniyle kliniğimizde değerlendirilerek ABHL tanısı koyulan ve günler içerisinde ABHL'ye bağlı geliştiği düşünülen sepsis nedeniyle kaybedilen çok agresif klinik seyirli ALK pozitif bir ABHL olgusu sunulmaktadır.

Anahtar Kelimeler: Anaplastik, büyük hücreli lenfoma, CD30, anaplastik lenfoma kinaz, primer kutanöz

Introduction

Anaplastic large cell lymphoma (ALCL) is a CD30-positive non-Hodgkin lymphoma of T-cell origin^{1,2}. It comprises approximately 3% of all non-Hodgkin lymphomas³. The skin may be the primary involvement site (primary cutaneous) or systemic ALCL may secondarily affect the skin (primary nodal)^{1,2}. In systemic ALCL, 80-85% of cases exhibit anaplastic lymphoma kinase-1 (ALK)⁴. However, primary cutaneous ALCL is typically ALK-negative^{1,2}. Here, we report a case

of ALK-positive ALCL with a very aggressive clinical course presenting with cutaneous lesions.

Case Report

A 64-year-old man presented to our clinic with purplish swellings appearing on the skin for the last 3-4 weeks. Dermatological examination of the patient revealed brown-violaceous hard nodules located on the right groin, right

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and left site of the trunk, left upper arm with desquamation upon the lesions (Figures 1, 2). The inguinal lymph nodes were palpable and were stiff as rubber. The lesions were asymptomatic. The patient had used various kinds of topical antibiotics previously, but did not benefit from these treatments. The history of the patient revealed that he had no illnesses except for nephrolithiasis and cholelithiasis. When the history of the present illness was investigated more rigorously, it was explored that the patient has experienced unintentional weight loss and night sweats for the last few months. The biopsy of the nodular lesions revealed infiltration of atypical lymphoid cells with large eosinophilic cytoplasm, large irregular, occasionally oval shaped nuclei spreading out from upper dermis to the deeper layer of the dermis (Figure 3). Immunohistochemical study showed that the neoplastic lymphoid cells were CD30, CD2, CD4, CD43, granzyme and ALK-positive, MUM-1-negative (Figures 4, 5). The diagnosis was ALCL and we intended to survey the systemic involvement because of the widespread ALK expression.

Notable laboratory findings were as follows: hemoglobin: 10.74 g/dL (n=14-18), monocytes to leukocytes ratio: 12.4% (n=3-8%), erythrocyte sedimentation rate: 78 mm/h (n=0-15), lactate dehydrogenase (LDH): 343 U/L (n=0-248), serology for viral markers: negative, tumor markers: negative, ferritin: 956.9 ng/mL (n=30-400).

In a few days, while the work-up on the disease was maintained, the patient was referred to hospital because of right flank pain. The patient

died due to rapidly progressive sepsis and multiorgan dysfunction syndrome which was supposed to be associated with lymphoma.

Discussion

Histopathologically, ALCL has anaplastic morphology, which is characterized by a diffuse infiltrate composed of large sized T lymphocytes with round, oval or irregular nuclei, prominent eosinophilic nucleoli and abundant cytoplasm. These so called "hallmark cells" with eccentric horse shoe or kidney shaped nuclei are present in all the ALCL variants^{5,6}. The clinical features, course and prognosis of the disease may be different in ALCL variants^{1,2}.

Primary cutaneous ALCL is one of the CD30-positive lymphoproliferative diseases without systemic involvement at the time of diagnosis and in the next six months². The incidence of primary cutaneous ALCL among other types of peripheral T cell non-Hodgkin lymphomas is 1.7%⁷. It reaches an overall peak in the sixth decade of life and an average of 50% of cases are diagnosed in patients aged 61². Localized nodules, papules



Figure 1. Brown-violaceous nodule on the trunk



Figure 2. Brown-violaceous nodule with desquamation on the right site of the trunk

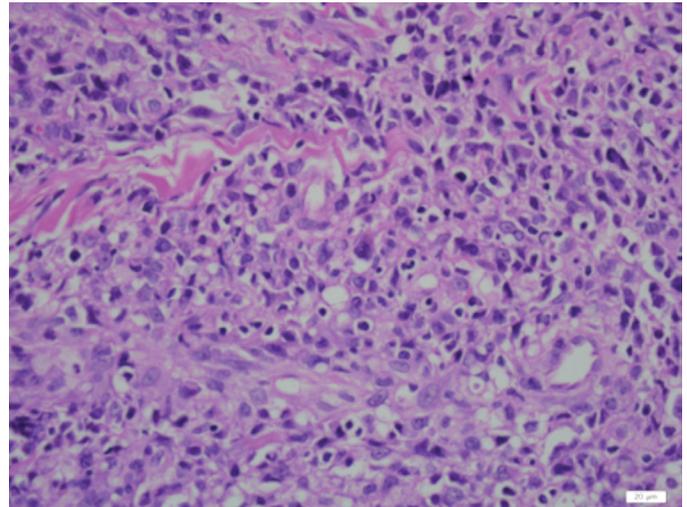


Figure 3. Lymphoid cell infiltration of partly anaplastic morphology with large cytoplasm and large irregular nuclei including eosinophilic nucleolus (hematoxylin&eosin x200)

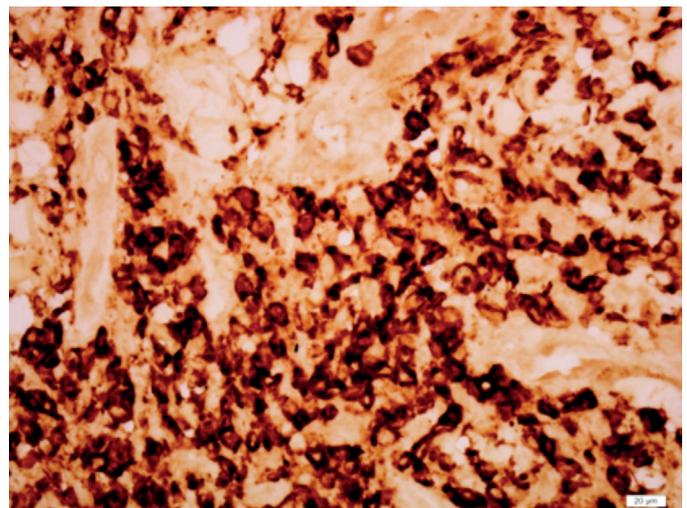


Figure 4. Widespread CD30 positive painting of atypical lymphoid cells (CD30, x200)

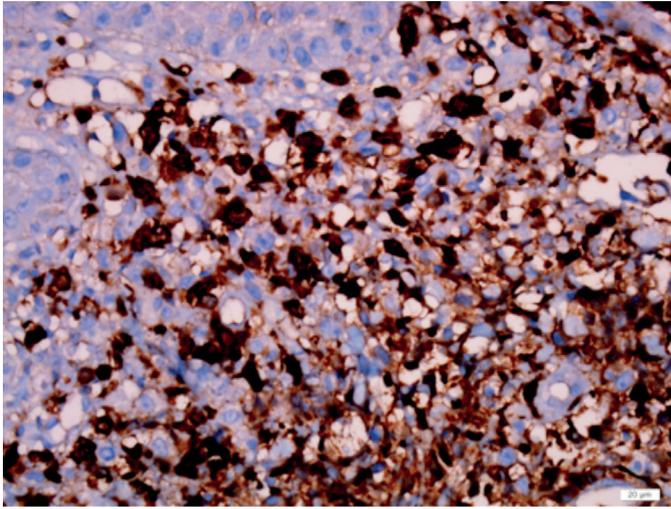


Figure 5. Widespread anaplastic lymphoma kinase positive painting of atypical lymphoid cells (anaplastic lymphoma kinase, x200)

or plaques are usually seen clinically, however, up to 20% of patients may have multiple lesions. The lesions are mostly asymptomatic and they may occur on the trunk, face extremities and buttocks². One of the most important histological characteristics of cutaneous ALCL is the absence of epidermotropism despite the extensive dermal infiltration of T lymphocytes with anaplastic morphology which is unlike the most common cutaneous T cell lymphoma, namely mycosis fungoides^{1,2,5,8}. Primary cutaneous ALCL is typically an ALK-negative disease; also the anaplastic cells express CD30 and the T cell markers CD2, CD3 resembling ALK-negative systemic ALCL¹. However, some cells may have lost their T cell-associated antigens and thus they may show null cell phenotype³. In addition, MUM-1, a member of the interferon regulatory factor family, is observed in primary cutaneous ALCL and lymphomatoid papulosis⁹. Primary cutaneous ALCL has a favourable prognosis and the prognosis does not depend on lymphatic invasion⁶. The overall 5-year survival rate is 83-100%⁶. Recurrences are frequent. Systemic involvement is rare¹⁰. A study revealed systemic involvement in 12% of cutaneous ALCL cases⁸. Spontaneous regression is seen in 25% of patients⁶.

Systemic ALCL comprises of 30% of non-Hodgkin lymphomas in adults. It is more common in young men under 35 years old, presenting with the disease in stage 3 or 4 with lymphadenopathy. B symptoms, which are characterized by fever, night sweats, and weight loss, are seen in 75% of patients. The skin is the most frequent involvement site after the lymph nodes^{1,5,6}. Cutaneous involvement occurs in approximately 20% of patients with systemic ALCL^{6,7}. The most important prognostic marker in systemic ALCL is the expression of ALK which exists in 85% of cases¹. In systemic ALCL, *nucleophosmin 'NPM'* gene located on chromosome 5 translocates to ALK gene located on chromosome 2, which results in ALK exhibition¹¹. Positive ALK is associated with a favourable prognosis in systemic ALCL. The 5-year survival for ALK-positive systemic ALCL ranges from 71% to 100% compared to only 15-45% for ALK-negative systemic ALCL^{1,12}. Other indicators of poor prognosis in systemic ALCL include skin or peripheral blood involvement⁵. A point to emphasize is the necessity for distinguishing between primary cutaneous ALCL and ALK negative systemic ALCL as they have very different clinical outcomes despite their very similar clinical and histopathological

findings. A work-up for systemic involvement is needed in all patients with cutaneous lesions of ALCL^{5,7}.

In primary cutaneous ALCL, the most common treatment modality for localized lesions is surgical excision or localized radiation therapy^{6,8}. Favourable outcomes have also been reported with intralesional methotrexate¹³. Multiagent systemic chemotherapy is not recommended for localized primary cutaneous ALCL because response rates are similar to local directed therapies with more significant side effects⁸. Systemic biologic therapies such as interferon 2 α and oral bexarotene treatments may be considered as initial therapy in generalized primary cutaneous ALCL⁸. If there is no satisfactory response to these treatments or in systemic ALCL, systemic multiagent chemotherapy regimens are applied².

Our patient without any known previous systemic diseases presented to our clinic because of his cutaneous lesions. He was diagnosed with ALCL and widespread ALK expression, MUM-1 negativity of the skin biopsy, elevated LDH and ferritin levels, anemia, and the presence of B symptoms mainly gave an impression of ALK-positive systemic ALCL with cutaneous metastasis. In fact, our patient was in his sixth decade of life which corresponded to the peak incidence of primary cutaneous ALCL, but ALK status and such a poor prognosis were not consistent with primary cutaneous ALCL. The clinical course with rapidly progressive sepsis and multiorgan dysfunction syndrome also indicates the systemic involvement. Strikingly, although it is emphasized in the literature that ALK is associated with favourable prognosis in systemic ALCL, our case had a very aggressive clinical course. An investigation including lymph node biopsy, bone marrow biopsy, and computed tomography of the chest, abdomen, and pelvis which were planned to reveal the systemic involvement could not be performed. For the diagnosis of our case was made initially after the evaluation of the cutaneous lesions and the fatal clinical course, we found it noteworthy to submit. Additionally, we aimed to study the diagnosis and the classification of ALCL which rarely involves the skin.

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.B.E., E.A., N.A., M.A.G., Concept: F.B.E., Design: F.B.E., E.A., Data Collection or Processing: F.B.E., Analysis or Interpretation: F.B.E., E.A., N.A., M.A.G., Literature Search: F.B.E., Writing: F.B.E.

Conflict of Interest: No conflict of interest was declared by the authors.

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