

HISTOPATHOLOGIC AND CLINICAL FEATURES OF RAPIDLY PROGRESSIVE ALK-NEGATIVE CUTANEOUS ANAPLASTIC LARGE T-CELL LYMPHOMA

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Anaplastic large cell lymphoma (ALCL) is a rare type of non-Hodgkin lymphoma (NHL) of the T-cell origin. A diagnosis of ALCL requires tumor biopsy with histopathological verification. The morphological features require T cell immunophenotyping with a positive expression of CD3 or CD4 immunological markers, and CD30 expression in all neoplastic cells is a must. A 46 old male patient with advanced ALK-negative cutaneous ALCL, with a rapidly progressive clinical course, is presented. Given a significant difference in the prognosis between ALK-negative systemic ALCL and cutaneous forms of ALCL, a close collaboration between oncologists/hematologists, pathologists, and dermatologists is the best guarantee for a correct diagnosis and proper treatment. *Acta Medica Medianae* 2017;56(3):55-61.

Key words: lymphoma, large cell, anaplastic, ALK protein, human

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Introduction

Anaplastic large cell lymphoma (ALCL) is a rare type of non-Hodgkin lymphoma (NHL) of the T-cell origin. ALCL comprises about 1% of all NHLs and approximately 16% of all T-cell lymphomas (1). This lymphoma belongs to the large group of peripheral T-cell lymphomas (PTCL) and is characterized by chromosomal aberrations that lead to constitutive activation of anaplastic lymphoma kinase (ALK). The most common is t(2; 5) (p23; q35), which produces a fusion between the nucleophosmin (NPM) and ALK genes, leading to the expression of NPM-ALK fusion protein (1, 2).

ALCL encompasses at least 4 different clinical entities, all sharing the same name, and histologically have also in common the presence of large pleomorphic cells that express CD30 and typical T-cell markers. Two of the ALCL are systemic lymphomas (s-ALCL), which usually present with enlarged lymph nodes in multiple regions of the body, or with tumors outside the lymph nodes (extranodal) such as the bone, intestine, muscle, liver, or spleen. These two subtypes are usually associated with extensive B symptoms (weight loss, fevers and night sweats), and can be lethal if left untreated with chemotherapy (2). The third type of ALCL is the so-called cutaneous ALCL (c-ALCL), and it is a tumor that presents in the skin as ulcers that may persist, or occasionally may involute spontaneously, and commonly recur. This type of ALCL usually manifests in different regions of the body and may extend to regional lymph nodes, i.e., an axillary lymph node if the ALCL presents in the arm (3). A more recently recognized subtype of ALCL is that associated with breast implants. The tumor initially manifests with swelling of the breast due to fluid accumulation around the implant. The disease may progress to invade the tissue surrounding the capsule, and if left untreated may progress to axillary lymph nodes (2, 4).

According to the 4th edition of WHO classification of tumors of hematopoietic and lymphoid tissues, ALCL was divided into ALK-positive and ALK-negative subtypes based on the expression of ALK protein or ALK gene rearrangement (3,

5). ALK/Nucleophosmin (NPM1) gene fusion was the most common genetic alteration. In addition, variant ALK rearrangement patterns have been recognized subsequently, including TPM3 (non-muscle tropomyosin 3 gene), ATIC (5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase/IMP cyclohydrolase) and TFG (TRK-Fused Gene Protein). Mechanically, the rearrangements of these genes result in ALK protein up-regulation (2, 6).

The patients with s-ALCL are divided into 2 groups, depending on whether or not their cells have an ALK protein expression (1, 5). Although both systemic lymphomas are treated as aggressive (fast-growing) lymphomas, the disease course may be different in patients who have ALK-positive ALCL compared with those with ALK-negative ALCL. The ALK-positive form of ALCL responds well to standard chemotherapy treatments, putting most patients into long-term remission. In contrast, while most people with ALK-negative ALCL initially respond to treatment, as well, the disease is more likely to relapse within 5 years in these people than in those with ALK-positive ALCL (7-9). While ALK-positive ALCL usually affects children and young adults, ALK-negative ALCL is more common in patients over the age of 55 years (1, 2). A primary c-ALCL is always ALK-negative (10).

A diagnosis of ALCL requires a biopsy with histopathological verification. Microscopic hallmark cells are of medium size and feature abundant cytoplasm (which may be clear, amphophilic or eosinophilic), kidney shaped or eccentric horse-shoe nuclei, and a paranuclear eosinophilic region (2). Occasional cells may be identified in which the plane of section passes through the nucleus in such a way that it appears to enclose a region of cytoplasm within a ring; such cells are called "doughnut" cells (6). The classification acknowledges the recognition of large cells with pleomorphic nuclei and abundant cytoplasm. The morphological features require immunophenotypic evidence that

the cells are T lymphocytes, such as the expression of immunologic markers CD3 or CD4, but the expression of CD30 in all neoplastic cells is always required (3, 5-7). Out of the 4 types of ALCL, one subtype of systemic ALCL expresses the ALK, and the other types of ALCL do not express ALK (8, 9). Immunohistochemically, tumor cells are characterized by CD30, ALK, CD5, TIA-1, Granzyme B and EMA positive staining, and CD2, CD7, CD8, CD20 and CD79 negative staining (2, 6, 8, 9).

Case report

We present a 46 old male patient with a cutaneous infiltrate of the left arm which was first noticed in November 2014. Since January 2015, in addition to the existing changes, new infiltrates in the area of the left elbow have been registered. By May 2015, further rapid growth of the skin tumor infiltrates was noted, spreading to different body parts including the arms, legs, gluteal skin, upper torso and the back. The clinical diagnosis was lymphoma of the skin. The patient was referred to the Clinic for Plastic and Reconstructive Surgery, Clinical centre Niš, and the biopsy of the lesion from the skin of the left elbow was performed (Figure 1).

At the Centre of Pathology and Pathological Anatomy, Clinical Centre Niš, the specimens underwent the frozen sections diagnosis. The larger biopsy specimen was the skin and the subcutaneous tissue, 5 cm in length, with the tumor formation at the intersection with the maximum size of 3 cm, of yellow-white colour with soft consistency. The second biopsy was the skin with the subcutaneous tissue and the tumor of 1x1.5 cm in size, at the intersection, of the same characteristics as the previous lesion. The microscopic analysis showed that the dermis contained a neoplastic proliferation of pleomorphic cells, hyperchromic polygonal cells in the diffuse arrangement (Figures 2),



Figure 1.: Growth of the skin tumor spreading to different body parts.

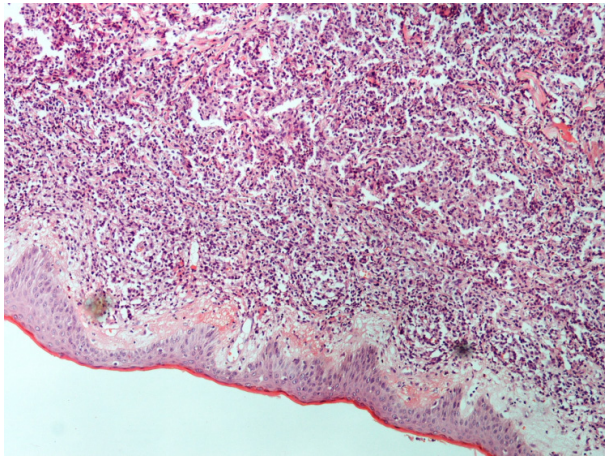


Figure 2.: Skin biopsy, HE staining x10, derm occupy by tumor cells

which could be in favour of the clinical diagnosis, but the definitive diagnosis was made after the immunohistochemical analysis on paraffin slides of subsequent biopsy specimens.

The patient was re-operated on June 1, 2015, and the autologous skin transplantation of the left

upper arm was performed. A circular skin clip of 27 cm in diameter, thickness up to 5 cm, was obtained. In the centre, there were three fused tumor formations, ulcerated, each about 8 cm in diameter. At the same time, the wound swab was taken and the bacteriological analysis found *Escherichia coli* infection, sensitive to β -lactam, cephalosporine, aminoglycoside and fluoroquinolone antibiotics, after which the patient was treated with combined intravenous antibiotic therapy for 10 days.

The skin biopsies were fixed in buffered formalin and embedded in paraffin. A 5 μ -thick section was stained with hematoxylin-eosin (H&E) for routine microscopy. Immunohistochemical (IHC) staining was performed using the DakoAuto-stainer with Envision+ Detection Kit (Glostrup, Denmark) at the Centre for Pathology and Pathological Anatomy, Clinical Centre Niš. Histologically, at high magnification, the majority of tumor cells had pleomorphic nuclei, prominent nucleoli, and brisk mitotic activity. There were small mature-appearing lymphocytes and eosinophils in the background (Figure 3.).

IHC staining showed that the tumor cells were diffusely and strongly positive for LCA, Ki67,

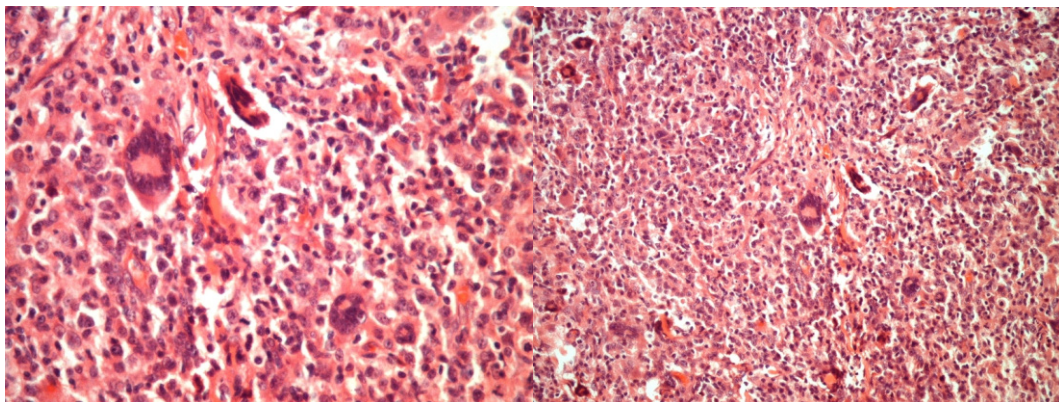


Figure 3.: Skin biopsy, giant tumor cells: (a) HE staining x20 and (b) HE staining x40.

MUM1, CD30 and CD3 staining. Tumor cells were negative for CD20, ALK, cyto-keratin AE1/AE3, desmin, EMA, S100 protein, CD34, CD31 and bcl6 (Figures 4, 5, 6, 7, 8, 9). Based on the morphological features and immunohistochemical profile, ALK negative ALCL of the skin was diagnosed.

The patient was referred to the Clinic of Oncology, Clinical Center Niš, for lymphoma staging procedures and treatment. According to the Ann-Arbour staging system, the patient was staged as I E CS, and no lymph node or visceral organ was involved with the disease. Bone marrow biopsy was not required due to the recommendations of the European Society for Medical Oncology (ESMO) guidelines. The patient had a marfanoid habitus and echocardiography showed aortic aneurysm of 9 cm in diameter. This was con-

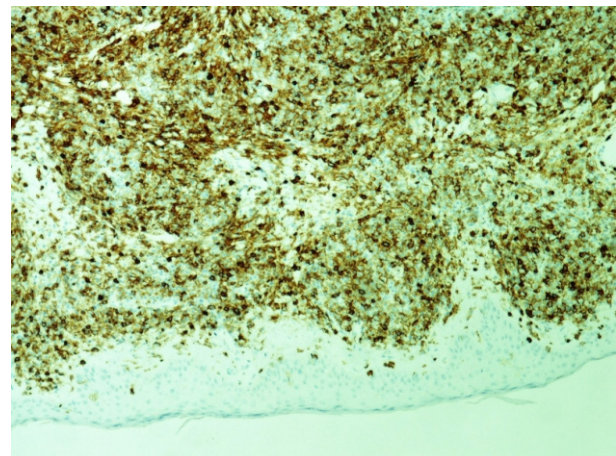


Figure 4.: Positive LCA staining x 20.

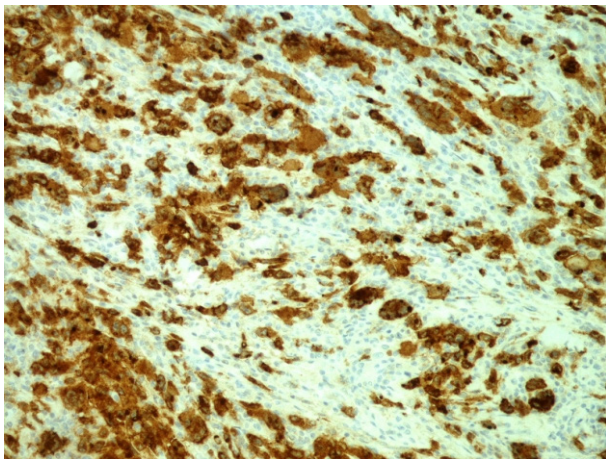


Figure 5. :Positive CD30 staining x20.

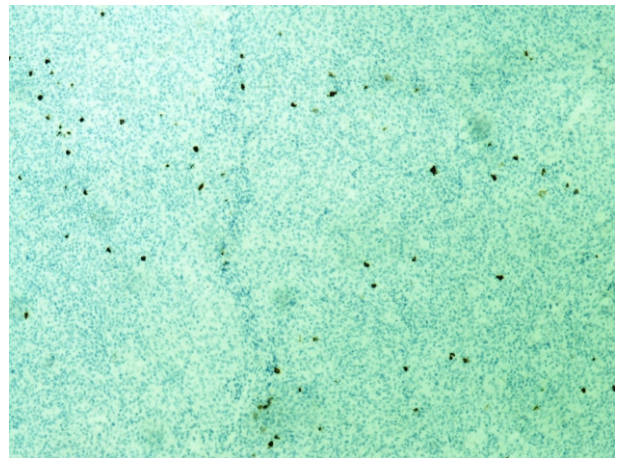


Figure 8.: Rare CD20 positive cells, x10.

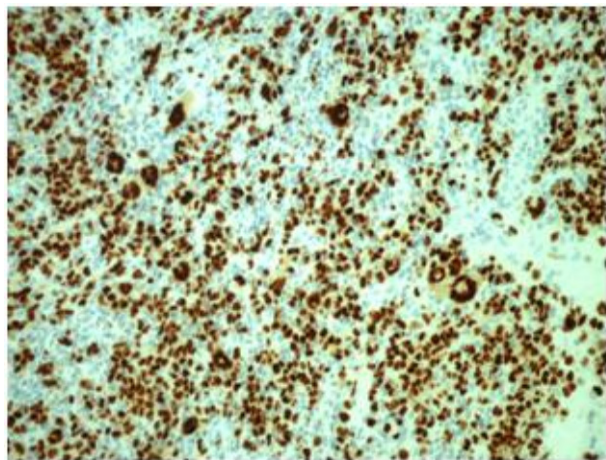


Figure 6. Positive MUM1 staining x40.

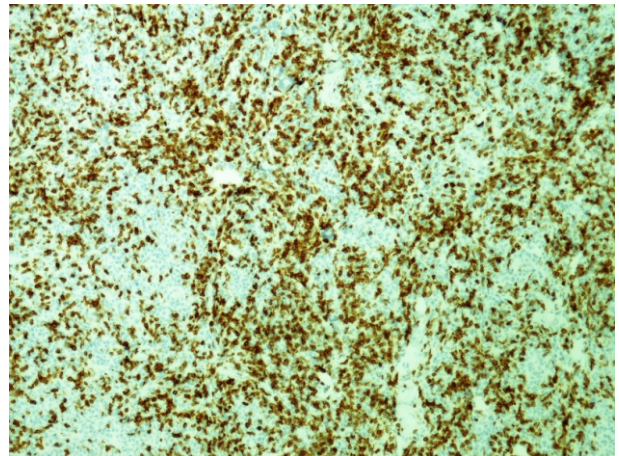


Figure 9. :Positive CD3 staining x10.



Figure 7. Positive Ki67 staining, x20.

firmed by MSCT scan findings. The patient underwent low dose methotrexate (MTX) treatment in 15 consecutive cycles. Disease re-evaluation showed minimal response. During this treatment patient was referred to the Cardiovascular Surgery Clinic for the operation of the aforementioned tho-

racic aneurism. This procedure was not performed due to disease progression which occurred after 15th cycle of MTX. The patient underwent restaging procedure which demonstrated systemic dissemination of the disease in lymph nodes followed by exhausting B symptoms. Skin progression of the disease demonstrated multiple cauliflower-like masses covering over 80% of the skin, as well as the appearance of many exulcerate skin changes and infiltrates within the muscles of the arms. The cyclophosphamide, vincristine, prednisone+epirubicine (CHOP-like) regimen of chemotherapy, was performed in 3 consecutive cycles. However, the patient had short response duration and than he progressed. During the anthracycline treatment, cardiac problems such as excessive tachycardia with arrhythmia developed as a major adverse event. Further treatment was thus abolished. Since the patient had major cardiovascular comorbidity, and no aggressive treatment was the therapeutic option for this specific case, he underwent paliative chemo-treatment with Chlorambucil. The patient is still under treatment with aforementioned medication and has a stable disease without progression after 3 months' treatment.

Discussion

ALCL belongs to peripheral T-cell lymphomas (PTCL), which are characterized by a strong expression of immunological markers CD30 and CD3 (2, 5). According to the expression of ALK, ALCL is divided into 3 categories: primary s-ALK-positive ALCL, primary s-ALK-negative ALCL, and primary c-ALCL. ALK-positive ALCL is sensitive to chemotherapy and has a better prognosis, whereas ALK-negative ALCL usually occurs in elderly patients with a worse prognosis (2, 13). Currently, ALCL comprises approximately 3 % of all NHLs (5, 14).

Despite the ambiguity, the ALK-negative ALCL group comprises approximately 15-20% of all S-ALCL cases (15). Cutaneous ALCL is uniformly ALK-negative. In our case, similar to ALK-negative s-ALCL, c-ALCL tends to express strongly CD30 and T cell markers CD2 and CD3. Microscopically, cutaneous lesions of c-ALCL and ALK-negative S-ALCL both typically demonstrate dermal infiltrates of large lymphoid cells without epidermotropism (16). Whereas the histological presentation of s-ALCL can vary from small cells to large anaplastic cells, almost all cases have the classic "hallmark" cells present. These are large cells with abundant cytoplasm, horseshoe-shaped nuclei, and a brightly eosinophilic region corresponding to the Golgi apparatus. Sometimes the nucleus completely surrounds this region (17).

The treatment paradigm for the most of the PTCL entities (including s-ALCL forms) remains aggressive chemotherapy ("dose-dense" CHOP-like protocols) followed by high dose therapy and autologous stem cell transplantation (auto-SCT) as a consolidation therapy if the disease is responsive and chemo-sensitive. Polychemotherapy is the treatment of choice for both ALK-negative and ALK-positive S-ALCL patients. ALK expression independently predicts the survival difference among s-ALCL patients regardless of the chemotherapeutic regimen (18). Bird et al. described a case of rapidly fatal ALK-negative S-ALCL, highlighting the need for an improved diagnostic classification system that better predicts prognosis

among patients at the time of presentation (19). c-ALCL, if not systemic, should be treated with local radiotherapy in isolated cases or if it has a diffuse pattern, then low-dose MTX should be used. Our patient exhibited advanced cutaneous disease at the time of diagnosis and was similar to previously reported cases and studies of rapidly progressing ALK-negative cutaneous ALCL, except that most of the previously described patients did not demonstrate widespread skin disease (20, 21).

Gene expression studies of ALCLs are relatively scarce due to the rarity of the disease. The largest study performed on 32 patients with s-ALCL (25 ALK-positive and 7 ALK-negative) and 5 cell lines demonstrated the existence of 2 groups corresponding to morphological subgroups (common vs. small cell and mixed variants) (11). Sonic hedgehog (SHH) gene amplification in a subset of ALK positive ALCL has been shown to lead to deregulation of the SHH signaling pathway (1). Given the successes of TKI (tyrosin kinase inhibitor) therapy in chronic myelogenous leukemia and ALK-driven lung cancer, ALK signaling inhibition is a promising therapeutic approach in ALK-positive ALCL (12). With the advent of a more precisely targeted therapy, it may be possible to treat effectively the mutational events underlying ALCL pathogenesis, while reducing the side effects and adverse long-term consequences of therapy. Considering the fact that clinical and histological features of cutaneous lesions are indistinguishable from those seen in s-ALCL, a long-term follow-up of all patients with skin lesions is required. Multi-agent chemotherapy is the only one indicated for the patients who develop extracutaneous disease, and rarely or not at all for those with skin lesions only (22, 23).

Conclusion

Bearing in mind a significant difference in the prognosis between ALK-negative s-ALCL and c-ALCL, a close collaboration between oncologists/hematologists, pathologists, and dermatologists is the best guarantee for a correct diagnosis and proper treatment.

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HISTOPATOLOŠKE I KLINIČKE KARAKTERISTIKE RAPIDNO PROGRESIVNOG ALK NEGATIVNOG ANAPLASTIČNOG KRUPNOĆELIJSKOG T-LIMFOMA KOŽE

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Anaplastični krupnoćelijski limfom (ALCL) je redak tip nehoćinskog limfoma T-ćelijskog porekla. Dijagnoza ALCL-a zahteva biopsiju tumora sa histopatološkom verifikacijom. Morfološke karakteristike zahtevaju imunofenotipizaciju T ćelija sa pozitivnom ekspresijom CD3 ili CD4 markera, a uvek je obavezujuća ekspresija CD30 u svim neoplastičnim ćelijama. Prikazan je četrdesetšestogodišnji muškarac sa uznapredovalom kliničkom formom ALK negativnog kutanog ALCL. S obzirom na značajne razlike u prognozi između ALK negativnih sistemskih ALCL i kožnih oblika ALCL, bliska saradnja onkologa, hematologa, patologa i dermatologa predstavlja najbolju garanciju u postavljanju adekvatne dijagnoze bolesti i primene odgovarajućeg tretmana kod ovih bolesnika. *Acta Medica Medianae 2017;56(3):55-61.*

Ključne reči: limfom, krupnoćelijski, anaplastični, ALK protein, humani

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