Secondary central nervous system involvement in systemic ALK+ anaplastic large cell lymphoma: a case report

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Abstract:

Systemic anaplastic large cell lymphoma is an infrequent form of non-Hodgkin lymphoma determined by the expression of CD30 with different clinical characteristics in its presentation. The majority of patients with anaplastic large cell lymphoma are in an advanced stage of the disease at the time of diagnosis but rarely with a leptomeningeal or central nervous system infiltration. We have presented a young patient with widespread systemic ALK+ anaplastic large cell lymphoma and a secondary central nervous system involvement verified by cytologic examination of the cerebrospinal fluid.

Keywords: anaplastic large cell lymphoma, central nervous system, cerebrospinal fluid, cytology.

Sažetak:

Sekundarna zahvaćenost središnjeg živčanog sustava kod sistemskog ALK+ anaplastičnog velikostaničnog limfoma: prikaz slučaja

Sistemski anaplastični limfom velikih stanica je rijedak oblik ne-Hodgkinovog limfoma determiniran ekspresijom CD30 s različitim kliničkim karakteristikama u svojoj prezentaciji. Većina bolesnika s anaplastičnim limfomom velikih stanica je u uznapredovalom stadiju bolesti u vrijeme postavljanja dijagnoze, ali rijetko s infiltracijom leptomeningea ili središnjeg živčanog sustava. Prikazali smo mladog bolesnika s raširenim sistemskim ALK+ anaplastičnim velikostaničnim limfomom i sekundarnom zahvaćenošću središnjeg živčanog sustava potvrđenom citološkim pregledom cerebrospinalne tekućine.

Ključne riječi: anaplastični velikostanični limfom, središnji živčani sustav, cerebrospinalna tekućina, citologija.

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Introduction

Anaplastic large cell lymphoma (ALCL) named "Ki-1 positive lymphoma" was first described in 1985 by Stein and colleagues as a subset of non-Hodgkin lymphomas (NHLs) with large CD30 (Ki-1) positive anaplastic cells, which cohesively expand and occupied lymph node sinuses (1). As a distinct clinicopathologic subtype of NHLs, ALCL is placed in the revised World Health Organization (WHO) Classification of tumours of hematopoietic and lymphoid tissues. By the definition, "ALK-positive (ALK+) anaplastic large cell lymphoma (ALCL) is a T-cell lymphoma consisting of lymphoid cells that are usually large and have abundant cytoplasm and pleomorphic, often horseshoe-shaped nuclei, with a chromosomal translocation involving the ALK gene and expression of ALK protein and CD30" (2:413). ALK+ ALCL accounts for approximately 3% of adult non-Hodgkin lymphomas and 10-20% of childhood lymphomas; it is most common in the first three decades of life. There is a male predominance in ALK+ ALCL with a male-to-female ratio of 1.5:1 (2). It shows an aggressive behavior with rapidly progressive adenopathy and systemic symptoms especially fever, profuse night sweats, and weight loss.

Currently, four different ALCL entities are recognized in the 2016 WHO classification: systemic ALCL ALK(+), systemic ALCL ALK(–), primary cutaneous ALCL, and breast implant-associated ALCL. ALK(+) ALCL exhibits a wide spectrum of cell morphology ranging from small to large and pleomorphic lymphoma cells, so based on that, there are five morphologic patterns of ALK+ ALCL: common (the most frequent morphological variant), lymphohistiocytic, small cell, Hodgkin-like, and composite pattern. The sheets of large lymphoid cells featuring "hallmark" cells are seen in histological and cytological samples of most patients with the common type of ALCL (3). ALK(+) ALCL has ALK gene rearrangements and infers a better prognosis compared with ALK(-) ALCL but unfortunately, at the time of diagnosis, most patients are in an advanced stage of the disease (III–IV stage) (4).

The reports of systemic ALCL with central nervous system (CNS) involvement are sporadic and diagnosing is sometimes very challenging. The CNS can be affected either at initial diagnosis or letter as a relapse and "secondary CNS T-cell lymphoma" is considered in both forms (5). The prognosis is unfavorable so it is necessary to detect that kind of lymphoma metastasizing as soon as possible with the teamwork of clinicians, neuroradiologists, and cytopathologists.

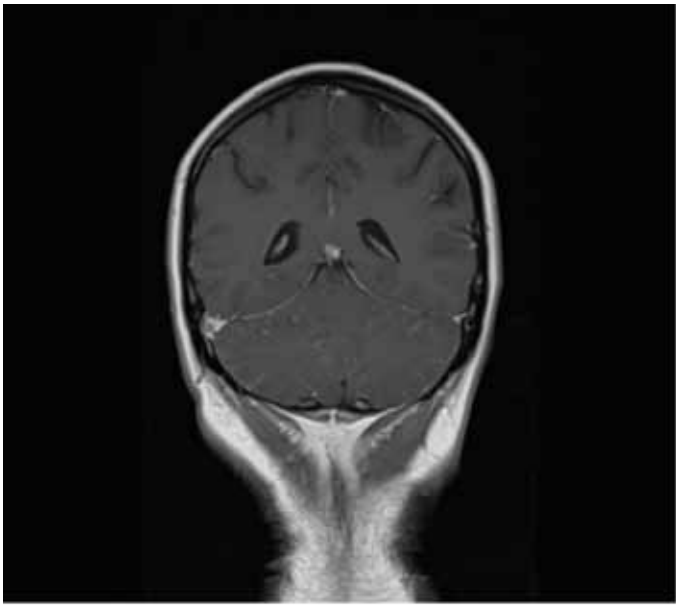
Case Presentation

A 39-year-old woman presented with pain and a lump in the right inguinal region with an on-and-off fever for one month. Ultrasound examination of both inguinal regions revealed enlarged pathological lymph nodes in conglomerates. Contrast-enhanced Computed Tomography (CT) of the thorax and abdomen revealed enlarged bilateral cervical, axillary, mediastinal, retroperitoneal, and inguinal lymph nodes along with mild hepatomegaly and moderate bilateral pleural effusions. After a hematological examination, the cervical node biopsy was performed. Pathohistological findings revealed a total replacement of architecture by a population of large polymorph atypical lymphoid cells, immunohistochemically stained positive with CD30, CD4, CD7, and ALK, so the diagnosis of ALK+ anaplastic large cell lymphoma (common type) was confirmed. The proliferative index Ki 67 was 90%. The bone marrow and peripheral blood examination did not reveal any tumour infiltration. The patient received induction chemotherapy CHOEPx1 and BV-CHEPx1. After one cycle of chemotherapy, the patient complained of severe headaches and vomiting for a few days. A neurological examination followed by contrast-enhanced CT of the brain did not show any significant intracranial pathology.

Because of permanent headache, brain Magnetic Resonance Imaging (MRI) was performed (Figure 1), which showed in the ventral part area of the cingulate gyrus on the right side, corticosubcortically a visible T2 and FLAIR elevated signal, in an area of 13 mm, with the involvement of the corpus callosum where the elevated signal discreetly crosses the central line to the left. Only the cingulate portion up to 8 mm in size showed a post-contrast enhancement, while the signal increase in the corpus callosum is not enhanced by contrast. Also, the cingulate part shows quite discrete diffusion restriction centrally. Discrete post-contrast enhancement is also visible superficially in the sulci next to the cingulate gyrus bilaterally, as a leptomeningeal involvement. Leptomeningeal enhancement is seen also in basal sulci supratentorial and most of the sulci infratentorial, so a secondary CNS lymphoma is therefore considered, and cerebrospinal fluid (CSF) examination was advised.

CSF sampling was obtained to determine levels of protein, glucose, and lactate, cell counts as well cytological analysis. Our patient's CSF sample was slightly cloudy, and xanthochromic; biochemical measurements showed elevated protein (3.32 g/L) and lactate (5.88 mmol/L) levels, and decreased glucose level (1.2 mmol/L) with increased total leukocyte ($80x10^6$/L), and erythrocytes ($3000x10^6$/L) count. The cytocentrifuge preparation of the remaining CSF specimens showed large atypical lymphoid cells with marked pleomorphism and nuclear irregularity, immunocytochemically stained positive with CD30, CD7, and ALK partially as proof of infiltration by ALCL cells (Figure 2). In this case, cytomorphology and immunocytochemical analyses of CSF confirm the presence of anaplastic lymphatic cells.

During the next two weeks after the diagnosis of CNS involvement by anaplastic lymphoma cells was established, despite the therapy, the patient's condition substantially worsened leading to a lethal outcome.



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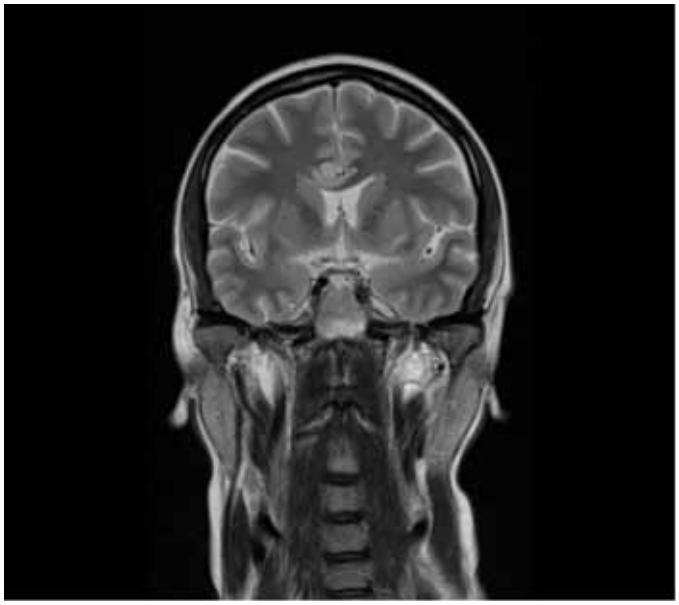

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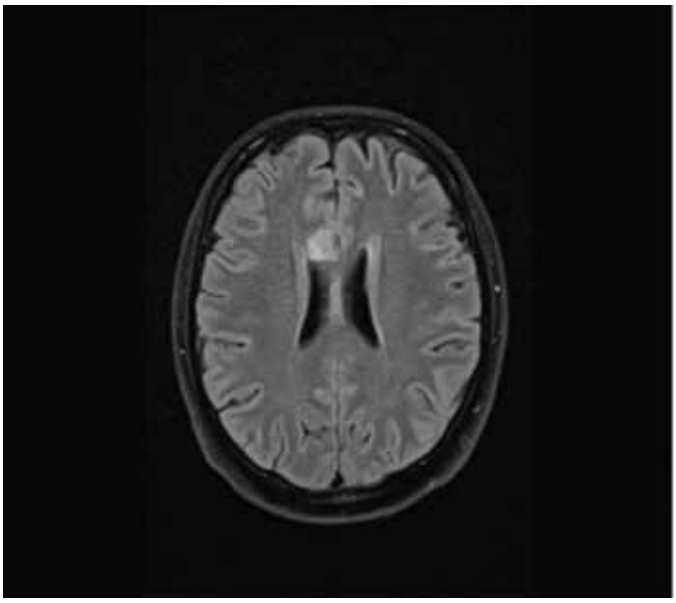

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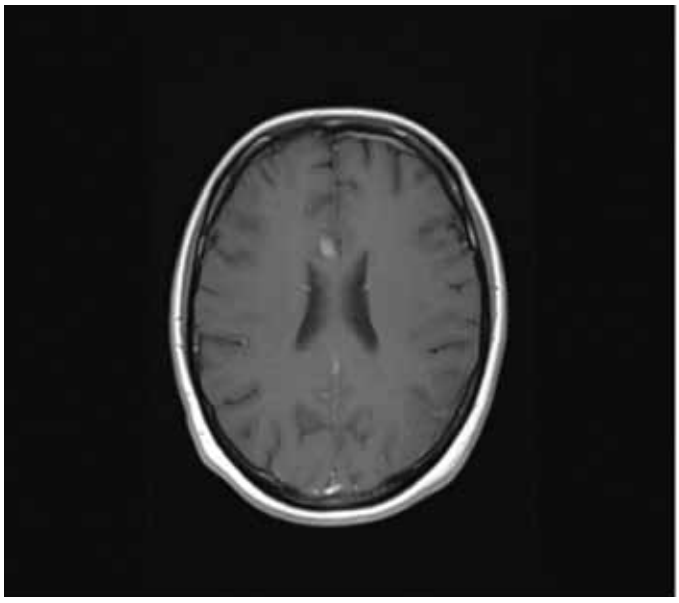

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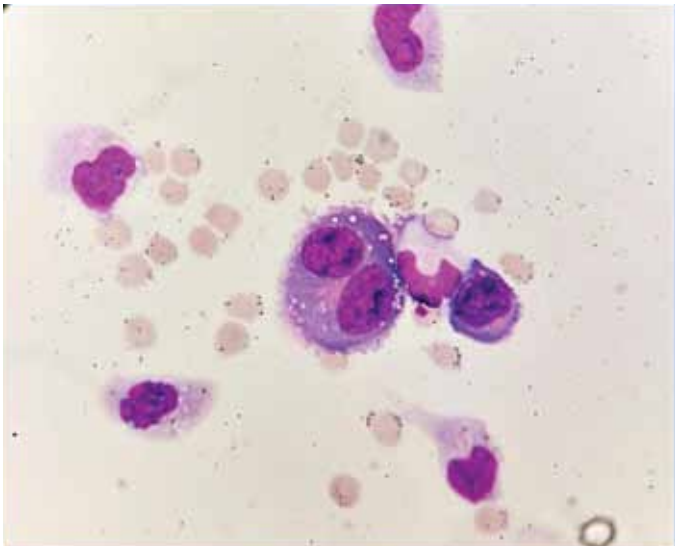
Figure 1. A) T1 postcontrast coronal plane shows leptomeningeal enhancement in basal sulci, supratentorial, and most of the sulci infratentorial; B) T2 coronal plane without contrast shows hyperintense areal in the cingulate gyrus on the right side and in the corpus callosum where it crosses the midline to the left; C) On axial T2 scan hyperintense lesion is seen in the right cingulate gyrus; D) On postcontrast T1 axial scan only the central portion of the lesion shows enhancement.



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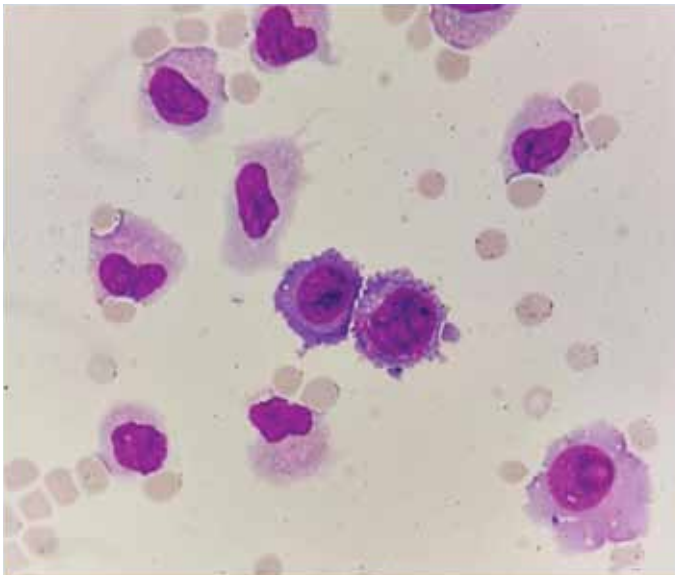

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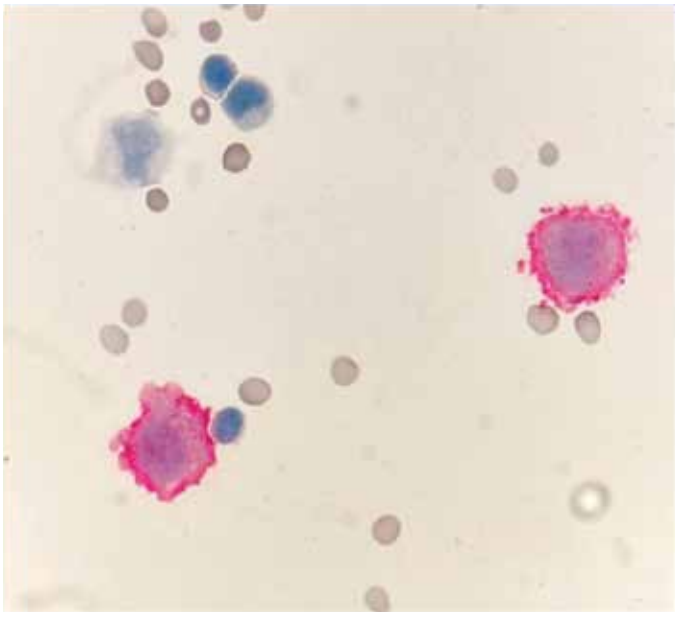

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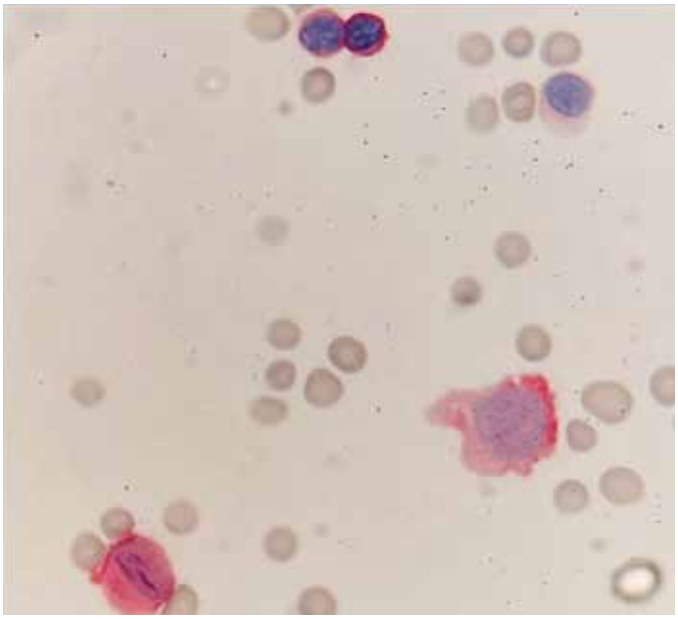

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Figure 2. A-B) Large atypical lymphatic cells in the cerebrospinal fluid sediment of a patient with anaplastic large cell lymphoma, MGG stain, x1000; C) CD30 positive cells in the cerebrospinal fluid sediment of a patient with anaplastic large cell lymphoma, immunocytochemistry, LSAB, x1000; D) CD7 positive cells in the CSF sediment of a patient with anaplastic large cell lymphoma, immunocytochemistry, LSAB, x1000.

Discussion

The reports of systemic ALCL with involvement of the central nervous system (CNS) are very occasional. Most cases reported in the world's literature are primary central nervous system ALCLs. CNS can be affected either at initial diagnosis or at recurrence, and both forms are considered "secondary CNS T-cell lymphoma" (5). Systemic ALCL is primarily a nodal disease, however, extranodal involvement is seen in ~20% of cases, most often involving skin, liver, soft tissues, bone, and bone marrow (7). The primary and secondary sites of the lymphoma can appear in almost any location so physicians should keep oncological alertness. The infiltration of the central nervous system is accompanied by various neurological disorders such as nausea, vomiting, neck stiffness, persistent headaches, diplopia or other visual impairments, different level of cognitive decline, disorientation regarding the time and place, and consciousness level impairment (8). Neuroimaging shows good diagnostic sensitivity but low specificity for distinguishing secondary CNS T-cell lymphomas. Brain CT is usually the first imaging tool due to its availability, however, brain MRI is the method of choice for better investigation of patients with lymphoma (5). Involvement of the CSF in such cases is even more uncommon. CSF cytology and immunocytochemical analyses may help confirm tumour cell presence (6). Detection of atypical lymphoid cells in CSF indicates CNS infiltration in ALCL and brings immeasurably significance both from a prognostic and therapeutic point of view (9). Involvement of the CNS is rare and often associated with a poor prognosis (2). The literature about secondary CNS T-cell lymphoma is sparse, and primarily constituted by single case reports and small case series due to low incidence of this malignancy. However, reported studies similarly suggest high mortality rates related to this unfavorable event (5).
Multiple factors can affect the adverse clinical outcomes of patients with secondary CNS ALCL, including negative ALK expression, monomorphic neoplastic cells, amount of tumour necrosis, multifocal systemic spreading, leukemic phase, size and location of the tumour in the CNS, and other factors such as acute encephalopathy, additional cytogenetic aberrations, and resistance to chemotherapy (10).

Conclusion

Involvement of the central nervous system by systemic anaplastic large cell lymphoma is uncommon but results in an adverse prognosis, therefore prompt examinations are necessary to confirm this type of malignant spreading as early as possible for a more successful treatment. Our case report emphasizes the importance of cerebrospinal fluid cytology in a lymphoma patient with neurologic symptoms for rapid and accurate diagnosis.

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