A Case of Central Nervous System Metastasis of Anaplastic Lymphoma Kinase Positive Anaplastic Large Cell Lymphoma Manifested as Central Nervous System Vasculitis

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Abstract

Introduction: Anaplastic Large Cell Lymphoma (ALCL) is a rare distinct subset of T-cell non-Hodgkin lymphomas (T-cell NHL). Anaplastic Lymphoma Kinase (ALK), which induces neoplastic transformation is the tumor cell product of a fused gene that comes from a chromosomal translocation t (2; 5) (p23;q35) on chromosome or a rearrangement of the ALK gene with various partner genes [2-6]. In the World Health Organization (WHO) classification of tumors of the hematopoietic and lymphoid tissues, ALCL is grouped into three distinct clinical sub-entities, the primary cutaneous ALCL, the primary systemic ALK + ALCL and the primary systemic ALK-ALCL, according to organ distribution and the expression of ALK [7]. As is well known, ALK + ALCL patients are generally associated with younger age and have a better prognosis with overall survival of 71%-83% [8,9]. Besides the vast majority of ALCL present as nodal disease, ALCL can also involve in skin (21%), bone (17%) and soft tissues (17%) [9]. Compared with B-cell non-Hodgkin lymphomas, T-cell NHL affecting Central Nervous System (CNS) is much rare. T-cell NHL account for less than 4% of the primary involvement in the CNS NHL [10,11]. ALCL is an even rarer variant of T-cell lymphoma primary involving the CNS, most of which is associated with meningeval lesions [12]. Vasculitis can be secondary to lymphoma or the treatment. Some lymphoma can even present as vasculitis [13]. Vessel injury may occur as a direct result of infiltrating neoplastic cells [14]. However, there were rare reports about lymphoma and CNS vasculitis. Furthermore, no report about ALK + ALCL and CNS vasculitis. In the present report, we first describe a case of ALK + ALCL metastasized to the CNS in a 17-year-old teenage who presented as CNS vasculitis in the beginning. We also reviewed the literature on ALK + ALCL occurring in the CNS and relevance with CNS vasculitis.

Conclusion: We first present a case of CNS metastasis of systemic ALK + ALCL accompanied with CNS vasculitis. When an ALK + ALCL patient had CNS symptoms while imaging revealed CNS vasculitis, we need to be vigilant that the patient may have CNS involvement.

Keywords: Anaplastic large cell lymphoma • Anaplastic lymphoma kinase • Central nervous system metastasis • Central nervous system vasculitis

Introduction

Anaplastic Large Cell Lymphoma (ALCL) is a rare distinct subset of T-cell non-Hodgkin lymphomas (T-cell NHL). The CD30 antigen expressing large cell lymphoma was first described in 1985 by Stein [1]. Anaplastic Lymphoma Kinase (ALK), which induces neoplastic transformation is the tumor cell product of a fused gene that comes from a chromosomal translocation t (2; 5) (p23;q35) on chromosome or a rearrangement of the ALK gene with various partner genes [2-6]. In The World Health Organization (WHO) classification of tumors of the hematopoietic and lymphoid tissues, ALCL is grouped into three distinct clinical sub-entities, the primary cutaneous ALCL, the primary systemic ALK + ALCL and the primary systemic ALK-ALCL, according to organ distribution and the expression of ALK [7]. As is well known, ALK + ALCL patients are generally associated with younger age and have a better prognosis with overall survival of 71%-83% [8,9]. Besides the vast majority of ALCL present as nodal disease, ALCL can also involve in skin (21%), bone (17%) and soft tissues (17%) [9]. Compared with B-cell non-Hodgkin lymphomas, T-cell NHL involving Central Nervous System (CNS) is much rare. T-cell NHL account for less than 4% of the primary involvement in the CNS NHL [10,11]. ALCL is an even rarer variant of T-cell lymphoma primary involving the CNS, most of which is associated with meningeal lesions [12]. Vasculitis can be secondary to lymphoma or the treatment. Some lymphoma can even present as vasculitis [13]. Vessel injury may occur as a direct result of infiltrating neoplastic cells [14]. However, there were rare reports about lymphoma and CNS vasculitis. Furthermore, no report about ALK + ALCL and CNS vasculitis. In the present report, we first describe a case of ALK + ALCL metastasized to the CNS in a 17-year-old teenage who presented as CNS vasculitis in the beginning. We also reviewed the literature on ALK + ALCL occurring in the CNS and relevance with CNS vasculitis.

Case Report

In January, 2020, a 17-year-old boy presented with persistent fever accompanied with diffuse maculopapular rashes and mild chest pain. When the patient was admitted to the Department of Infection of the First Affiliated Hospital, Zhejiang University School of Medicine, a mass was found in the left clavicle area of the neck. The mass turned out to be enlarged Lymph nodes by ultrasound and Computerized Tomography (CT). Positron Emission Tomography-Computed Tomography (PET-CT) showed that there were multiple enlarged lymph nodes in the left clavicle area, the entrance of the left thoracic cavity, the left anterior superior mediastium, and the posterior margin of the left sternum. The lesions in the left clavicle area were fused into a mass and the Fluorodeoxyglucose (FDG) metabolism was significantly increased. Multiple small lymph nodes in the left parapharyngeal space, the left lower neck, and the lower margin of the left parotid gland had slight metabolic increase. Lesions with increased FDG metabolism were also found in skin, subcutaneous nodules, bone, left kidney and lung. While no abnormal increase of FDG metabolism was found in CNS. Lymph node biopsy was conducted. Immunohistochemistry studies showed CD3 (partly + ), CD20 (-), Ki-67 (+, 40%), CD30 (+), CD5 (-), CD10 (+), Bcl-2 (+), Bcl-6 (+, 25%), MUM1 (+, 20%), PAX-5 (-), CD21 (-), Cyclin D1 (-), c-Myc (+, 12%), ALK (+), EBER (-), CD23 (-), CD2 (partly +), CD4 (+), CD7 (-), CD8 (-), CD56 (-), TIA-1 (+), TDT (-), MPO (-), CK (pan) (-), CD34 (-), CD117 (-). Thus, a diagnosis of ALK + ALCL was made. The patient was referred to the hematology department and underwent six courses of systemic chemotherapy of CHOP (cyclophosphamide, doxorubicin, vincristine, and dexamethasone). The original symptoms were relieved. Repeated imaging of the neck showed significant reduction of the lymph nodes.

In May, 2020, about 1 week after the sixth cycle of chemotherapy, the patient developed symptoms of fever, headache and a short convulsion with...
unconsciousness. He was admitted to the Department of Infection. When he was admitted, the pathologic signs of nervous system examination were negative. Initial laboratory evaluation showed that blood routine examination had no obvious abnormality, erythrocyte sedimentation rate was 16 mm/1 h and C-reactive protein was slightly elevated (10.5 mg/L). Lactate dehydrogenase was 306 U/L and ferritin was 1098.6 ng/mL. Blood culture was free of bacteria. The DNA of Epstein-Barr virus and Cytomegalovirus was negative. Anti-nuclear antibodies and antineutrophil cytoplasmic antibody were negative. The cranial CT showed no lesions. Lumbar puncture was performed; the pressure was 250 mm H2O. Cerebrospinal Fluid (CSF) examination showed 25 μl nucleated cells. The CSF glucose, chlorine and protein were in normal range. And CSF adenosine deaminase, lactate dehydrogenase was normal. The Flow cytometry detection of CSF showed no atypical lymphocytes. High-throughput sequencing of DNA and RNA sequences in CSF did not find bacteria, fungi, viruses, parasites, mycoplasma, chlamydia or mycobacterium. Antibiotic therapy was ineffective. So, we excluded infection. The Color Doppler sonography of vessels demonstrated severe stenosis in the M1 segment of the right middle cerebral artery and the terminal segment of the right internal carotid artery, mild stenosis of Basilar artery and moderate stenosis of left anterior cerebral artery (Figure 1). No stenosis was found in peripheral vessels. The severe stenosis of CNS arteries suggested CNS vasculitis. During the patient's hospitalization, the patient had persistent fever accompanied with headache, dizziness and palpitations. And he also underwent epileptic seizures and developed the symptoms of paroxysmal slurred speech, slight deviation of mouth, numbness and weakness of left upper limb. We gave priority to CNS vasculitis and treat the patient with methylprednisolone, and all the symptoms were relieved.

However, the cranial MR showed lesions in right parietal temporal cortex (Figure 2). We conducted another PET-CT, and it showed FDG metabolism in the right parietal lobe, right frontal lobe and left temporal lobe was higher than contralateral (Figure 3). Compared with the previous PET-CT, the original enlarged lymph nodes were significantly reduced and partially disappeared, FDG metabolism was significantly reduced, and the original skin and

Figure 1. The Color Doppler sonography of vessels demonstrated severe stenosis in the M1 segment of the right middle cerebral artery (A) and the terminal segment of the right internal carotid artery (B), and moderate stenosis of left anterior cerebral artery (C).

Figure 2. The gadolinium enhanced cranial MRI. There were lesions in the right parietal temporal cortex, it was low density in T1W1 (A), high density in T2W2 (B), high density in DWI (C), and enhanced in T1W1-weighted imaging (D).
subcutaneous nodules, bone, left kidney and lung lesions were not found this time. According to the presence of cranial nerve palsy and the demonstration of lesions on MRI as well as PET-CT, we considered CNS metastasis of ALCL. The patient was discharged from the First Affiliated Hospital, Zhejiang University School of Medicine and got admitted to Huashan Hospital affiliated to Fudan University. Their Flow cytometry detection of CSF showed a nucleated cell count of 18 × 10^6/L, small lymphocytes accounting for about 40% (CD3 + 84.9%, CD4 + 37.6%, CD 8 + 41.4%). Atypical large lymphocytes accounted for 20.1%, expressing positive markers (CD45 + cyCD3 + CD7 + CD4 + CD30 + 52.9%) and negative markers (CD2- CD3- CD5- CD6- CD10- CD1a- TdT-). Cellular morphology of CSF showed that clusters of atypical lymphocytes were visible. They had large, round or irregular shapes, a large amount of cytoplasm, irregular 1-3 nucleoli, purplish red granules, multiple vacuoles in the cytoplasm and most of them have pseudopodia. Therefore, CNS metastasis of ALCL was diagnosed. No brain autopsy was performed.

**Discussion**

CNS metastasis in T-cell NHL is rare and has a dismal prognosis [15]. In adult peripheral T-cell NHL patients, the reported median time to CNS involvement was 3.44 to 6.06 months and median overall survival time from relapse or progression to CNS was disappointing, which ranged from 1.1 to 2.83 months [15-18]. Extramedulillary involvement >1 site, International Prognostic Index (IPI) ≥ 3, skin and gastrointestinal involvement, elevated LDH level and involvement of the paranasal sinus were reported to be risk factors [15-18]. Among all the risk factors, Extramedulillary involvement >1 site was reported in multiple analyses [15-18]. ALCL seemed to have high proportion of T-cell NHL involving CNS [17]. A retrospective analysis showed that of a total of 74 peripheral ALK + ALCL patients, the 5-year cumulative incidence of CNS relapse was 5.4%, higher than ALK-ALCL or any other types of peripheral T-cell lymphoma. In addition, ALK + ALCL patients who had extramedulillary involvement >1 had very high risk of CNS relapse, whose one-year cumulative incidence was 17% and they all occurred within six months after diagnosis. Thus, evaluation of CNS involvement at the time of diagnosis was necessary and possible CNS-directed prophylaxis shall be considered [18]. A report about neuro-meningeal relapse in a large population of ALK + ALCL children in Europe showed that CNS involvement at first or subsequent relapse was reported in 26/818 patients. Median interval between initial diagnosis and first CNS involvement was 8 months. The 5-year cumulative risk of CNS involvement was 4%. Peripheral blasts, bone marrow involvement, and CNS involvement at diagnosis were reported to be high risk factors. The median survival after relapse to CNS was 23.7 months, and three-year overall survival after CNS relapse was 48.70%, which seemed to have a better prognosis than peripheral T-cell NHL in adult patients [19]. In addition, it was recommended that intensified CNS prophylaxis based on a last-generation ALK-inhibitor should be evaluated as part of front-line treatment in patients with high risk factors, while patients with no risk factors could undergo chemotherapy with minimal CNS prophylaxis [19]. Patient in this case had risk factors including >1 extra nodal site, IPI ≥ 3, elevated LDH level and skin involvement, without peripheral blasts, bone marrow involvement, or initial CNS involvement.

Vasculitis can occur secondary to lymphoma or the treatment. Intravascular lymphoma even presents as vasculitis [13]. A case of systemic ALK-ALCL associated with hypereosinophilia, granulomatous myositis and vasculitis was reported [20]. Another case reported that recurrent ALK-ALCL presenting as ulcerating skin lesions, and the biopsy revealed a necrotizing vasculitis which resulted from the infiltration of neoplastic cells [14]. However, there were rare reports about lymphoma and CNS vasculitis. Furthermore, no report about ALK + ALCL and CNS vasculitis. Carlo Salvareani found that lymphoma without involving the CNS can be diagnosed in the meantime with primary CNS vasculitis, which may suggest an immunologic paraneoplastic mechanism [21]. Pathology report confirmed that intravascular large B-cell lymphoma can present as CNS vasculitis [22]. A patient with Burkitt Lymphoma carrying a SH2D1A mutation developed fatal central nervous system vasculitis 6 months after completing treatment for lymphoma was reported [23]. Another case report described a patient diagnosed with primary CNS lymphoma developed severe leukocytoclastic vasculitis, which might due to high-dose methotrexate toxicity [24]. High-resolution vessel wall MRI appearance of biopsy-proven intravascular lymphoma can mimic CNS vasculitis [25]. Till now, there was no report about CHOP associated CNS vasculitis. As is well known, vasculitis is more associated with systemic leukemia. And researches confirmed that vessel injury can be a product of infiltration by neoplastic tumor cells instead of a paraneoplastic phenomenon mediated by benign inflammatory cells [16]. So, the CNS vasculitis in this patient might be caused by benign inflammatory cells mediated by ALK + ALCL or resulted from the infiltration of ALK + ALCL, which could not be confirmed for the patient refused to conduct a brain biopsy.

**Conclusion**

We first present a case of a systemic ALK + ALCL patient who presented as CNS vasculitis but eventually it turned out to be CNS metastasis of ALK + ALCL. The CNS vasculitis might result from benign inflammatory cells mediated by ALK + ALCL, or ALK + ALCL might infiltrate CNS vessels. Therefore, when an ALK + ALCL patient had CNS symptoms while imaging revealed CNS vasculitis, we need to be vigilant that the patient may have CNS involvement.

**References**


