

Case Report

Brain metastasis of ALK positive anaplastic large cell lymphoma after a long-term disease free survival in an old adult

Cai-Xia Wang^{1*}, Hai Wang^{1*}, Jie Li², Heng-Hui Ma¹, Bo Yu¹, Shan-Shan Shi¹, Xiao-Jun Zhou¹, Qun-Li Shi¹

¹Department of Pathology, ²Department of Neurosurgery, Jinling Hospital, Medical School of Nanjing University, Nanjing, Jiangsu, China. *Equal contributors.

Received December 18, 2013; Accepted December 23, 2013; Epub February 15, 2014; Published March 1, 2014

Abstract: Anaplastic large cell lymphoma (ALCL) is a subtype of non-Hodgkin lymphoma composed of CD30-positive cells and now recognized as three different entities: primary cutaneous ALCL, primary systemic anaplastic lymphoma kinase (ALK)-positive (ALK+) ALCL and primary ALK-negative (ALK-) ALCL. ALK+ ALCL is supposed to have a better prognosis than ALK- ALCL. It is rarely metastasized to other sites, especially to the central nervous system (CNS). Herein, we present a rare case of systemic ALK+ ALCL which metastasized to the brain after a long-term disease free survival in an adult. Neuroimaging revealed a well-enhanced mass in the left frontal lobe. And it was completely resected. The results of the pathological and immunohistochemical studies were consistent with the metastasized ALK+ ALCL. The clinical findings, pathologic characteristics and treatment are described.

Keywords: ALCL, ALK-positive, CNS, metastasis

Introduction

Anaplastic large cell lymphoma (ALCL), which was first described by Stein in 1985 as a feature of CD30 positivity, is now acknowledged as a distinct subset of T-cell non-Hodgkin lymphomas (NHL) [1]. It accounts for approximately 3% of adult non-Hodgkin's lymphoma while constitutes as many as 30%-40% of pediatric large-cell lymphomas [2].

ALCL tumors frequently show a positive immunohistochemical reaction to the presence of anaplastic lymphoma kinase (ALK) — the tumor cell product of a fused gene which comes from a chromosomal translocation t(2; 5) (p23;q35) on chromosome. And most of the translocations are linked to the nucleophosmin (NPM-ALK) [3].

Due to the heterogeneity in the cytology and clinical features in patients with ALCL, several subtypes which based on the morphologic, immunophenotypic and clinical characteristics were generated. In addition to primary cutaneous ALCL, the primary systemic ALK positive

ALCL (ALK+ ALCL) and the provisional entity of primary systemic ALK-negative ALCL (ALK-ALCL) were classified as two new diseases in the 4th edition of the World Health Organization (WHO) Classification of the Tumors of Hematopoietic and Lymphoid Tissues in 2008 [4, 5]. As is widely reported, ALK expression in ALCL patients is generally associated with younger age and a favorable outcome with overall survival of 71%-83% [6, 7].

Though vast majority of ALCLs present as nodal disease, primary involvement of extranodal sites is not uncommon, among which the most frequent involvement is skin (21%) followed by bone (17%) and soft tissues (17%) [7]. Primary involvement in the CNS of ALK+ ALCL is a rare event and metastasis of primary systemic ALK+ ALCL to the central nervous system (CNS) is much rarer. To the best of our knowledge, most cerebral ALK+ ALCL reported are primarily involved and there are few about the spread of the primary systemic ALK+ ALCL to CNS.

In the present report, we described a case of CD30+ ALCL with a T-cell immunophenotype

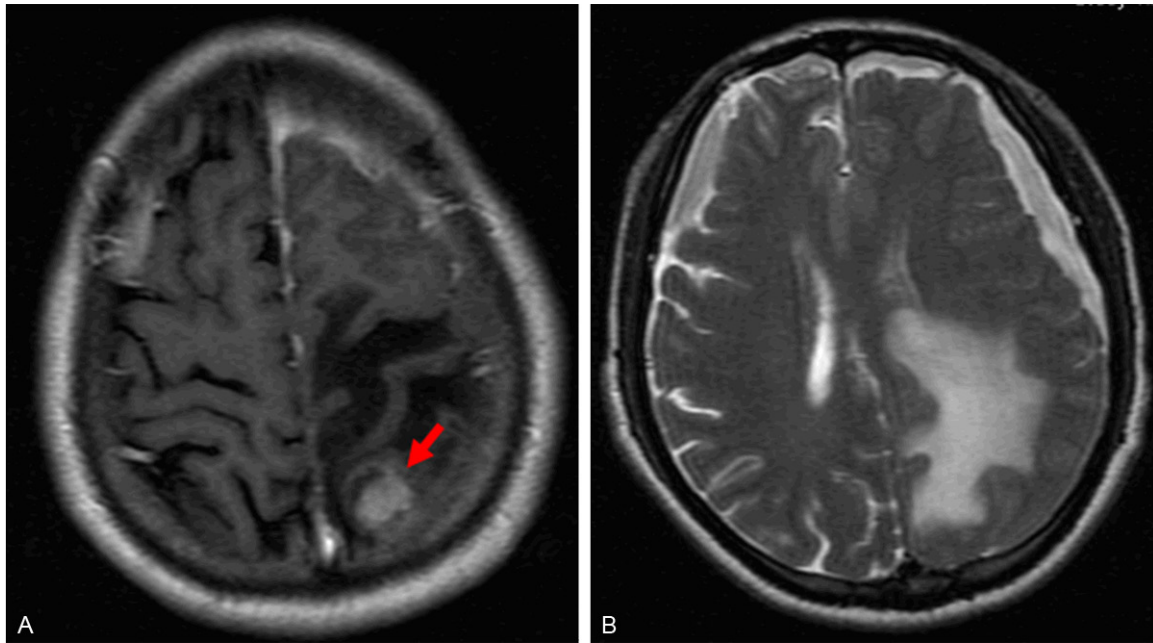


Figure 1. A. Axial T1-weighted imaging with contrast medium demonstrated a well-enhancing mass in the left frontal lobe. B. Axial T2 weighted image reveals the presence of a frontal cortical hypo-isointense lesion with significant edema and a mass effect on median structure.

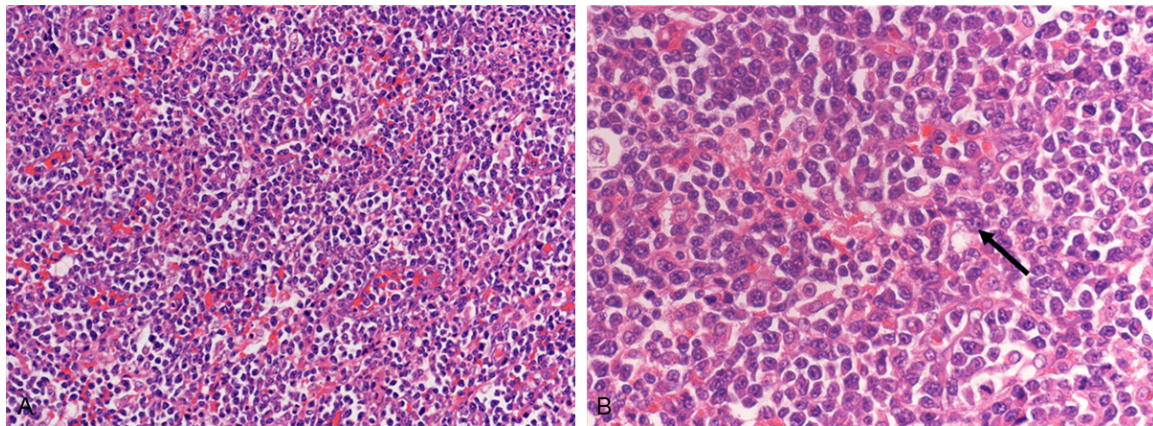


Figure 2. A. The tumor cells were diffusely presented with many fibrovascular in the interstitium (×100). B. The neoplastic population was composed of medium-to-large cells with irregular nuclei (×400). Large atypical cells with horseshoe shaped nuclei were also observed (arrow).

metastasized to the CNS in an old immuno-competent adult who had a long medical history of ALCL and literature on ALK+ ALCL occurring in the CNS to-date were also reviewed.

Case report

A 59-year-old man presented fever, headache and weakness in his right leg. He stated a medical history of retroperitoneal ALCL in his

retroperitoneum. About 10 years ago, a mass was found in his retroperitoneum, and it had been proved to be a ALK+ ALCL by the pathologic analysis. After the surgery, he received a systemic chemotherapy and neither recurrence nor evidence of metastasis had been detected during follow-up for the subsequent 10 years. Until recently, he referred to our hospital and the magnetic resonance imaging (MRI) of his brain delineated a well-enhanced mass in the

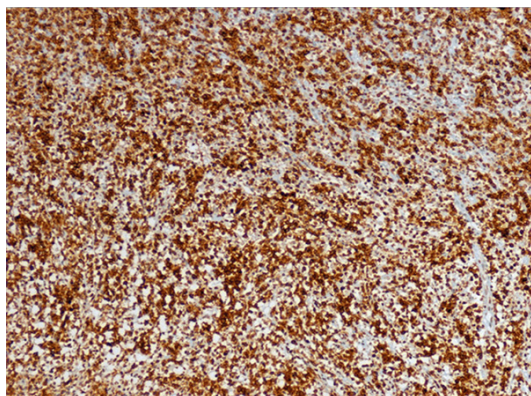


Figure 3. The lymphocytes were diffusely and strongly immunostained positive for CD30 ($\times 100$).

left frontal lobe with surrounding high-intensity area on T2-weighted images (**Figure 1A** and **1B**). Serological tests suggested negative reaction to both human immunodeficiency virus (HIV)-1 and Epstein-Barr virus (EBV). Further evaluation of the patient showed no palpable lymph nodes. CT scan of his abdomen and chest failed to show any lesion suggesting tumor involvement, and a bone marrow analysis did not reveal any abnormalities. Then, a total surgical resection of the tumor was performed and a diagnosis of metastasized ALK+ ALCL was made.

Photomicroscopic examination revealed that the brain tissue was diffusely infiltrated by numerous medium-to-large sized neoplastic cells (**Figure 2A**). These cells had round to irregular nuclei, coarse chromatin and a moderate amount of cytoplasm. In some areas, large atypical cells with slightly horseshoe- or kidney-shaped nuclei, which are characteristic “hall mark” cells of anaplastic large cell lymphoma, could also be identified (**Figure 2B**). The mitotic reactivity which included the atypical mitotic figures was prominent. Focal necrosis and a slight inflammatory infiltrate on the background were present as well.

By immunohistochemistry, the large tumor cells showed diffuse and strong immunoreactivity for CD30 (**Figure 3**) and CD43, weakly stained for epithelial membrane antigen (EMA), while negative for CD20, CD79a, CD15, MPO and TdT. ALK was expressed in many large cells and the immunohistochemical reactivity was in a cytoplasmic pattern (**Figure 4A**). Nuclear staining was not observed (**Figure 4B**). The Ki-67 pro-

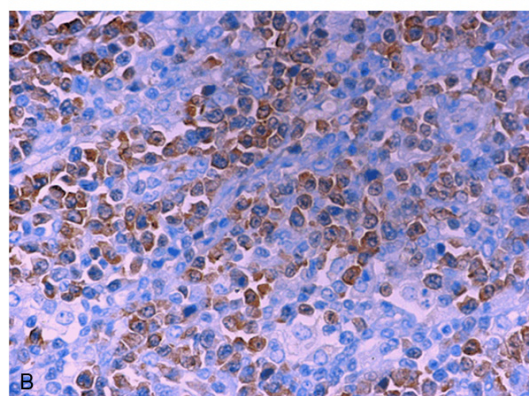
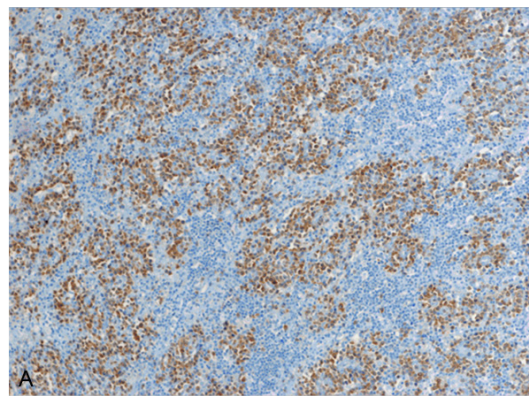


Figure 4. A. Immunoreactivity for ALK was focally present in the tumor cells of the ALCL ($\times 100$). B. Tumor cells were only positively immunoreacted in cytoplasm and nuclear staining was not observed ($\times 400$).

liferation index was more than 80% (**Figure 5**). These findings were consistent with diagnosis of anaplastic large cell lymphoma of T-cell phenotype with ALK reactivity.

For fluorescence in situ hybridization (FISH) analysis, cytospin preparations were denatured and hybridized with the LSI ALK break-apart probe set (Vysis, Downer's Grove, IL) to the ALK gene at the chromosome 2 region (2p23) according to the manufacturer's specifications. Images were acquired using MacProbe Software (Applied Imaging, San Jose, CA) on a Zeiss Axiophot microscope. Tumor proportion of the tested tissues was 90%. At least 60 tumor cells were counted. Splitting of the red and green signals and isolated red signals which were associated with ALK rearrangement were detected in tumor cells (**Figure 6**).

Discussion

It is admitted that patients with ALK+ ALCL often affects young male patients within the

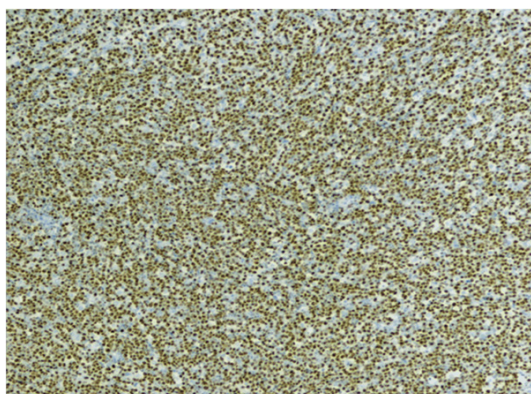


Figure 5. Ki-67 immunostaining showed a high proliferative index of around 80% ($\times 100$).

first three decades in their lives. They frequently present with aggressive stage 3 or 4 diseases, often accompanied by multiple extranodal sites of involvement. To the best of our knowledge, CNS involvement of ALK+ ALCL is very rare and the vast majority of them documented were primarily occurred with only one affected by cutaneous ALK+ ALCL [8]. Primary systemic ALK+ ALCL metastasizing to the brain is rarely related, especially after a long-term disease free survival.

As were summarized by Park JS in 2013, only 9 cases of primary CNS ALK+ ALCL were reported to date and all occurred in young patients with the oldest one of 31 years old [9]. Generally, they were morphologically characterized by the presence of large, pleomorphic cells with moderate cytoplasm and eccentrically located, kidney-shaped nuclei, coarse chromatin and variably sized nucleoli. In terms of immunohistochemistry, these cases were all positive for CD30 and ALK and have a T- or null cell phenotype. Most of them demonstrate EMA reactions and no one shows B cell markers. Our case was T-cell phenotype with CD43 strongly stained and immuno-negativity for B cell markers. As is reported, vast of ALK+ ALCLs display immunoreactivities both the nucleus and cytoplasm which are consistent with the characteristic chromosomal translocation involving the NPM gene located at 5q35 and the ALK gene on 2p23. However, in our case, the ALK only expressed in the cell cytoplasm and the FISH result shows a translocation involving ALK gene, demonstrating that the ALK domain activated in our case is likely to be

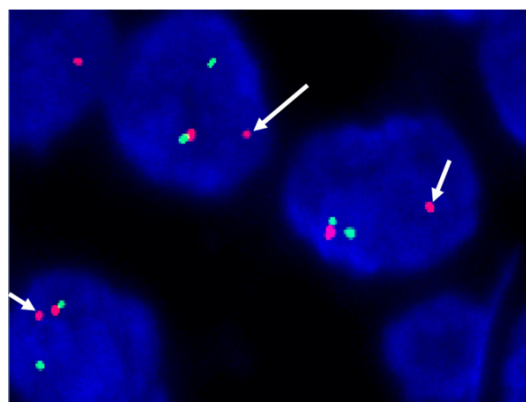


Figure 6. Break apart anaplastic lymphoma kinase (ALK) fluorescence in situ hybridization (FISH) assay. Splitting of the red and green signals and isolated red signals (arrows) are associated with ALK rearrangement.

involved in the other type neoplastic transformation. Whether the ALK+ ALCLs with other type gene transformation are more potentially active to metastasize to other lesions even after a long time survival is still unclear. The patient reported here developed the cerebral ALK+ ALCL after the retroperitoneal ALK+ ALCL was diagnosed 10 years ago.

As was acknowledged, the various ALK fusions increase the cell migration and invasion rate of lymphoid cells by modulating cytoskeletal rearrangements. Also, ALK modulates the activity of Rho family GTPases, resulting in RAC1 activation, thus increasing migration and invasion [10]. In addition, blood brain barrier (BBB) impairment should be considered as a high risk of neoplasm invading CNS. Malignant cells appeared to enter the CNS through the deficient BBB of the subarachnoid vessels [11]. Preceding BBB damage may predispose to brain metastases. The parenchymal dissemination of malignant cells was similar to that in primary CNS lymphoma and it followed the same spreading pathways as the extracellular fluid. Both these factors possibly give an explanation for the cerebral metastases of the lymphoma.

Given that the tumor was firstly suggested in the left frontal lobe of the brain and primary ALK+ ALCL can also be involved in the brain, diagnosis of metastasized CNS ALK+ ALCL must be made by the exclusion of the primary one. Primary CNS involvement in lymphoma

has a close relationship with immunosuppression, especially under circumstances of acquired immune deficiency syndrome. When it occurred, it is usually a B-cell lymphoma, often associated with either primary or secondary immunodeficiency states and EBV related. However, the patient presented here was negative for EBV, HIV and cytomegalovirus in serological tests. The patient was a middle-aged male, during which age group cancers are highly probable to be developed and thus kinds of transferred cancers must also be excluded before we get the right diagnosis. Histologically, carcinoma cells are more likely to be stuck together forming characteristic patterns of nests, clusters or cords. And immunohistochemical studies often show positive reactivity for epithelial markers.

The presentation of clinical symptoms such as high fever and vomiting often mimic that of an infectious, immunologic or rheumatologic etiology and thus makes the diagnosis challenging, especially when the overwhelming reactive cellular milieu on histology presented. Fortunately, in our patient, the iconographical information of the brain MRI depicted a solid mass which ruled out the possibility of infections.

To date, owing to its great clinical scarcity, treatment specifically for CNS ALK+ ALCL has not been established. Currently, the combined systemic and intrathecal chemotherapy without cranial radiotherapy are suggested to be safer and more efficient than the traditional combination of systemic chemotherapy and CNS radiation by some researches [12, 13].

Though primary systemic ALK+ ALCL is more responsive to chemotherapy leading to better prognosis than its counterpart, things seem different in the primary CNS ALK+ ALCL. To the best of our knowledge, of all the cases reported, only 2 patients died within the follow-up periods, 6 survived with no evidence of disease and 1 was alive [9]. However, larger sample size is required to determine whether or not ALK+ is a favorable prognostic factor for patients with primary CNS ALCL. After the complete resection, the patient reported received a standard chemotherapy consisting of cyclophosphamide, doxorubicin, vincristine and prednisone and he survived without relapse within the consequent 6 month follow-up.

Conclusion

In conclusion, to the best of our knowledge, this is the first reported case of systemic ALK+ ALCL metastasized to brain after a long period survival in an adult. Early detection is of vital importance in terms of both mortality and morbidity. Though systemic ALK+ ALCL has a favorable prognosis overall, physicians should take the possibility of metastasized ALK+ ALCL into consideration in a patient who had a good follow-up. Clinical data, pathologic results and iconographic information are suggested to be combined when the diagnosis was made.

Address correspondence to: Dr. Qunli Shi, Department of Pathology, Jinling Hospital, Medical Clinical School of Nanjing University, Nanjing, Jiangsu 210002, China. Tel: 025-80861291; E-mail: shiqunli2011@126.com

References

- [1] Stein H, Mason DY, Gerdes J, O'Connor N, Wainscoat J, Pallesen G, Gatter K, Falini B, Delsol G, Lemke H, et al. The expression of the Hodgkin's disease associated antigen Ki-1 in reactive and neoplastic lymphoid tissue: evidence that Reed-Sternberg cells and histiocytic malignancies are derived from activated lymphoid cells. *Blood* 1985; 66: 848-858.
- [2] Sandlund JT, Pui CH, Roberts WM, Santana VM, Morris SW, Berard CW, Hutchison RE, Ribeiro RC, Mahmoud H, Crist WM, et al. Clinicopathologic features and treatment outcome of children with large-cell lymphoma and the t(2;5)(p23;q35). *Blood* 1994; 84: 2467-2471.
- [3] Fiorani C, Vinci G, Sacchi S, Bonaccorsi G and Artusi T. Primary systemic anaplastic large-cell lymphoma (CD30+): advances in biology and current therapeutic approaches. *Clin Lymphoma* 2001; 2: 29-37; discussion 38-29.
- [4] Campo E, Swerdlow SH, Harris NL, Pileri S, Stein H and Jaffe ES. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. *Blood* 2011; 117: 5019-5032.
- [5] Sabattini E, Bacci F, Sagromoso C and Pileri SA. WHO classification of tumours of haematopoietic and lymphoid tissues in 2008: an overview. *Pathologica* 2010; 102: 83-87.
- [6] Reiter A, Schrappe M, Tiemann M, Parwaresch R, Zimmermann M, Yakisan E, Dopfer R, Bucsky P, Mann G, Gadner H, et al. Successful treatment strategy for Ki-1 anaplastic large-cell lymphoma of childhood: a prospective

Brain metastasis of ALK positive anaplastic large cell lymphoma

- analysis of 62 patients enrolled in three consecutive Berlin-Frankfurt-Munster group studies. *J Clin Oncol* 1994; 12: 899-908.
- [7] Falini B, Pileri S, Zinzani PL, Carbone A, Zagonel V, Wolf-Peters C, Verhoef G, Menestrina F, Todeschini G, Paulli M, Lazzarino M, Giardini R, Aiello A, Foss HD, Araujo I, Fizzotti M, Pelicci PG, Flenghi L, Martelli MF and Santucci A. ALK+ lymphoma: clinico-pathological findings and outcome. *Blood* 1999; 93: 2697-2706.
- [8] Rannan-Eliya YF, Pulford K, Johnson R, Peart I, Kokai G, Baillie C, Ait-Tahar K and Pizer B. Isolated cutaneous anaplastic large cell lymphoma progressing to severe systemic disease with myocardial involvement and central nervous system infiltration. *Pediatr Blood Cancer* 2008; 50: 879-881.
- [9] Park JS, Park H, Park S, Kim SJ, Seol HJ and Ko YH. Primary central nervous system ALK positive anaplastic large cell lymphoma with predominantly leptomeningeal involvement in an adult. *Yonsei Med J* 2013; 54: 791-796.
- [10] Chiarle R, Voena C, Ambrogio C, Piva R and Inghirami G. The anaplastic lymphoma kinase in the pathogenesis of cancer. *Nat Rev Cancer* 2008; 8: 11-23.
- [11] Aho R, Vaittinen S, Jahnukainen K and Kalimo H. Spread of malignant lymphoid cells into rat central nervous system with intact and disrupted blood-brain barrier. *Neuropathol Appl Neurobiol* 1994; 20: 551-561.
- [12] Taga T, Sakaue Y, Anzai Y, Takeuchi Y and Ohta S. Pediatric primary leptomeningeal lymphoma treated without cranial radiotherapy. *Pediatr Blood Cancer* 2007; 48: 477-478.
- [13] Felice MS, Zubizarreta PA, Rossi JG, Rose A, Alfaro EM and Sackmann-Muriel F. Diagnosis and successful treatment of childhood primary leptomeningeal lymphoma. *Med Pediatr Oncol* 2000; 34: 361-363.