Primary ALK-1 negative anaplastic large cell lymphoma of the brain: Case report and review of the literature

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Abstract

Anaplastic large cell lymphoma (ALCL) is a type of non-Hodgkin lymphoma composed of CD30 positive cells. Anaplastic large cell protein (ALK) -1 positive ALCL frequently involves both lymph nodes and extranodal sites. While primary extranodal involvement of ALK-1 negative ALCL is rare, this case is quite unique in that we describe a case of primary ALK-1 negative ALCL of the brain. A 79-year-old man presented with dementia-like symptom. Neuroimaging revealed a well-enhanced mass in the left parietooccipital region. The tumor was excised and histological diagnosis of primary ALK-1 negative anaplastic large cell lymphoma was made. Primary ALK-1 negative ALCL showed aggressive clinical behavior and fatal consequence. It is of great importance to avoid any delay in reaching an accurate diagnosis, as even primary ALCL of brain is too seldom suspected clinically.

keywords: ALK-1, anaplastic large cell lymphoma, brain, CD30

Introduction

Anaplastic large cell lymphoma (ALCL) was firstly described by Stein in 1985 for the feature of CD30 positivity.[1] ALCL is defined as T-cell lymphoma consisting of lymphoid cells with abundant cytoplasm and pleomorphic, often horseshoe-shaped nuclei. The cells are CD30 positive and mostly express cytotoxic granule-associated proteins.[2, 3] Most ALCLs express T-cell antigens, and the less common "null cell" tumors often show genetic evidence of T-cell lineage.[2-8]

The majority of ALCLs present as nodal disease, but primary involvement and secondary spread to extranodal sites is frequent.[2, 8, 9] The majority (60-85%) of ALCL are associated with a characteristic t(2;5) (p23;q35) chromosome

translocation that causes the anaplastic lymphoma kinase (ALK) gene on chromosome 2 to fuse with the nucleoplasmin (NPM) gene on chromosome 5, which results in ALK-1 protein expression. Generation of monoclonal antibodies to the aberrantly expressed ALCL tyrosin kinase or ALK-1 can be diagnostically used and have led to improve definition of the diagnostic entity with important clinical and prognostic implications. Expression of the ALK-1 protein is generally associated with younger age and better prognosis in conventional nodal and extranodal ALCL. Fifteen to fifty percent of systemic CD30-positive ALCLs are ALK-1 negative. While the ALK-1 positive lymphomas have relative homogenity, the ALK-1 negative lymphomas are a more heterogeneous group.[2, 7] ALK-1 negativity has been reported to correlate with epithelial membrane antigen immunonegativity, bcl-2 immunopositivity, occasional EBV positivity, elder patient age, and a worse prognosis than ALK-1 positive tumors.[2, 7, 9-12] Five-year survival in ALK-1 negative lymphomas is only 30-40%, while that in ALK-1 positive lymphomas is 80%; that makes ALK-1 status the most important single prognostic feature of ALCL.[2, 9]

ALCL arising in the central nervous system (CNS) is extremely rare.[2] Secondary spread of primary nodal or systemic ALCL to the CNS is also rare.[2-5, 7-9, 13-17] Primary systemic ALK-1 positive ALCL frequently involves both lymph nodes and extranodal sites; however, extranodal involvement of ALK-1 negative ALCL is extremely rare.[2] We report a case of primary cerebral ALK-1 negative ALCL and review the literature to date.

Clinical Summary

A 79-year-old immunocompetent man was admitted with a 2-week history of dementia-like symptom. He presented with

sensory dominant aphasia, dressing ataxia, agraphia and acalculia. Magnetic resonance imaging (MRI) revealed a well-enhanced mass in the left parietooccopital region with surrounding high intensity area on T2-weighted image (Fig. 1). Laboratory data showed increased serum soluble interleukin (IL) -2 receptor level of 830 U/ml (normal range: 3-59 U/ml). Serological test was negative for human immunodefiency virus (HIV) -1. Surgical resection was performed.

The mass increased in size in 2 months after the first surgery and second excision was performed. Unfortunately, neither irradiation nor chemotherapy was performed due to his poor performance status. The patient deceased from local recurrence 4 months after the first surgery and autopsy findings revealed no lymphomatous tissue involvement.

Pathological findings

Photomicroscopic examination revealed pleomorphic multi-nucleated giant cells with coagulative necrosis (Fig. 2 A). Immunohistological studies were performed using routinely fixed/processed archival tissues. Monoclonal antibodies specific to the following antigens were used: CD3, CD56, 1:50 (Novocastra Laboratories, Newcastle-on-Tyne, UK); CD5, CD 20 (L26), 1:100; CD30 (BerH2) 1:5; EMA (E29) 1:20; ALK-1, 1:25 (DAKO, Kyoto, Japan); Genzyme B, 1:30 (Monosan, Ueden, the Netherlands). A presenting heat-induced antigen retrieval method was used. Reactivity was detected by an avidin-biotin immunoperoxidase method. ALK-1 was negative for tumor cells (Fig. 2 C). Immunohistochemical staining showed CD 3, CD30 and CD45RO (UCLH 1) and EMA positivity of the tumor cells (Fig. 3 A-D) and negativity for CD20 (Fig.3 E). Table 1 summarizes the result of immunohistochemical stainings. Southern blot analysis with using restriction enzymes Bam HI in lane 1, Eco RV in 2, and Hind □ in 3 revealed the rearrangement of TCR C□1 (Fig. 3).

Discussion

ALCL accounts for approximately 3% of adult non-Hodgkin lymphoma and frequently involves both lymph nodes and extranodal sites. Extranodal sites commonly involve include skin, bone, soft tissue and liver. Primary CNS lymphoma has a close relationship with immunosupression, especially under circumstances of acquired immune deficiency syndrome.[1] But, primary CNS involvement of lymphoma in immunocompetent population is extremely rare.[2] To the best of our knowledge only thirteen cases of primary CNS ALCL have been previously reported in the literature.[18-27] Table 2 summarizes the clinicopathological findings of the patients previously reported and the present case of primary ALCL of brain. There seemed to be a bimodal age distribution in adolescents and aged population (range 4.5-79, median 34.5 years-old). There were 6 men and 8 women. The results of ALK-1 protein expression

were available in eleven cases. ALK-1 positive and negative groups consisted of 5 and 6 patients, respectively. The ALK-1 positive group was composed from the children and adolescent patients (range 4.5-18, median 12.5 years-old) and the ALK-1 negative group from the elder patients (range 22-79, median 55.6 years-old). Tumors were located in the supratentorial compartment in all cases except one which was located in the cerebellum. T-cell phenotype was identified in 11 out of 14 cases. The others showed null cell lineage.

Three of five ALK-1 positive patients showed no evidence of disease after treatment, the period ranging from 2 to 6.1 years. Another ALK-1 positive one showed remission, though died of chemo-sepsis 6 months after chemotherapy. One patient with ALK-1 positivity in this series (case 3) shortly died of disease. Case 3 was a 13-year-old boy presented with a 3-month history of headache and vomiting. Initially, he was treated with antitubercurosis because of the results of CSF examinations and normal CT findings. Without clinical improvement, following MRI revealed an abnormal signal in the parietal lobe and two masses in the frontal lobe. Biopsy

yielded ALCL and chemotherapy was performed, but he took fatal course.[18] Multiple foci seem to be an unfavorable outcome factor or implicate more progressed stage at the diagnosis because five of six patients presented with multifocal foci took fatal sequelae.

Five of six ALK-1 negative patients were fatal after excision, ranging from 4 days to 4 months. But there have been reported the only one ALK-1 negative case of 46-year-old woman who had achieved no evidence of disease after radiotherapy of 40 Gy for the whole brain and 60 Gy for the tumor bed following surgery. Her tumor cells expressed CD30 and CD43, but they were negative for CD3, CD45RO CD20, nor CD79a and surrounded by the reactive histiocytes and eosinophils.[21]

Overall nine out of fourteen (64%) CNS ALCL patients took a rapidly fatal clinical course with a tumor-associated mortality. The high mortality suggests that the CNS ALCL is more aggressive than other extra-nodal ALCL excluding CNS, for which an overall 5-year survival is reported from 62 to 77%.[10, 28] The mortality rate of CNS ALCL is greater than that of CNS lymphoma in general, for which the initial response rate of

85% was reported.[29]

In general, ALCL is the most common in the pediatric, adolescent, and young age group, and ALK-1 reactivity is a favorable prognostic factor as shown in ALCL of nodal and extranodal sites excluding bone. Aggressive and fatal clinical course has been previously reported in the primary CNS ALCL in adult patients.[19, 23] The overall 5-year survival rate was 80% and 40% in ALK-1 positive and negative cases, respectively.[2] The present case had unfavorable prognostic factors such as an elderly person and negative ALK-1 expression.

Primary CNS ALCL is an exceedingly rare tumor with aggressive clinical behavior and fatal consequence. Owing to the scarcity of available case records the relationship between ALK-1 reactivity and its prognosis has not been clarified yet. Further studies are required to determine whether ALK-1 positivity is a favorable prognostic factor for the patients with primary CNS ALCL or not. And it is of great importance to avoid any delay in reaching an accurate diagnosis, even as primary CNS ALCL is too seldom suspected

clinically.

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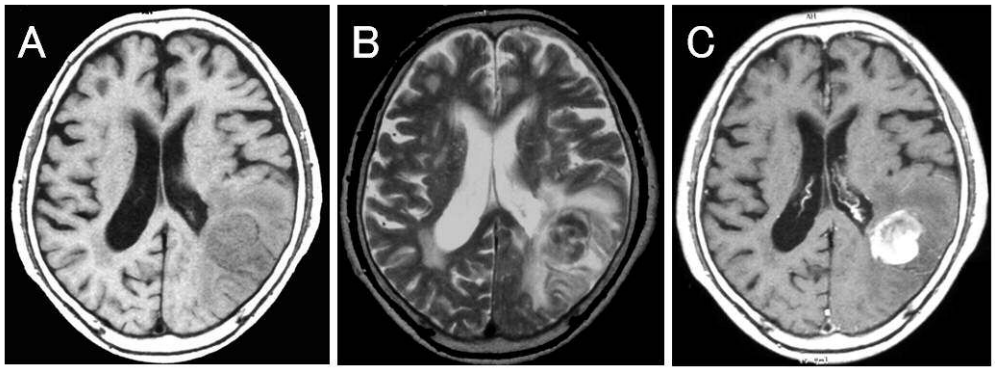
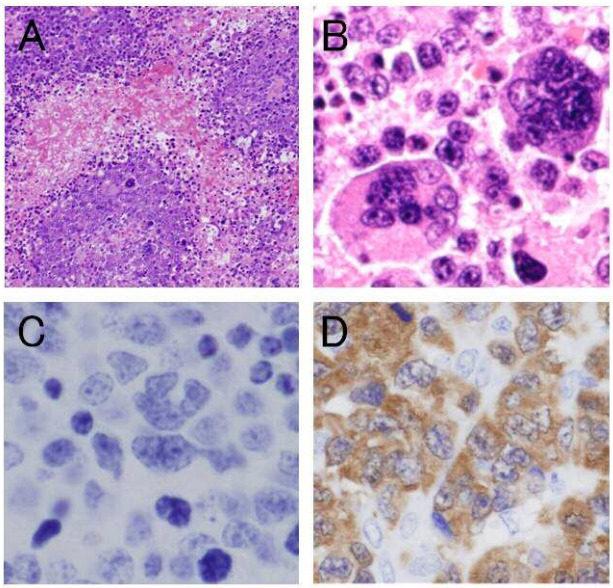
Fig. 1



Preoperative MRI scans. A, T1, B, T2, and C, postogadolinium T1-weighted images on axial section. A well-enhanced lesion with T2 high intensity area in the left parietal region is demonstrated.

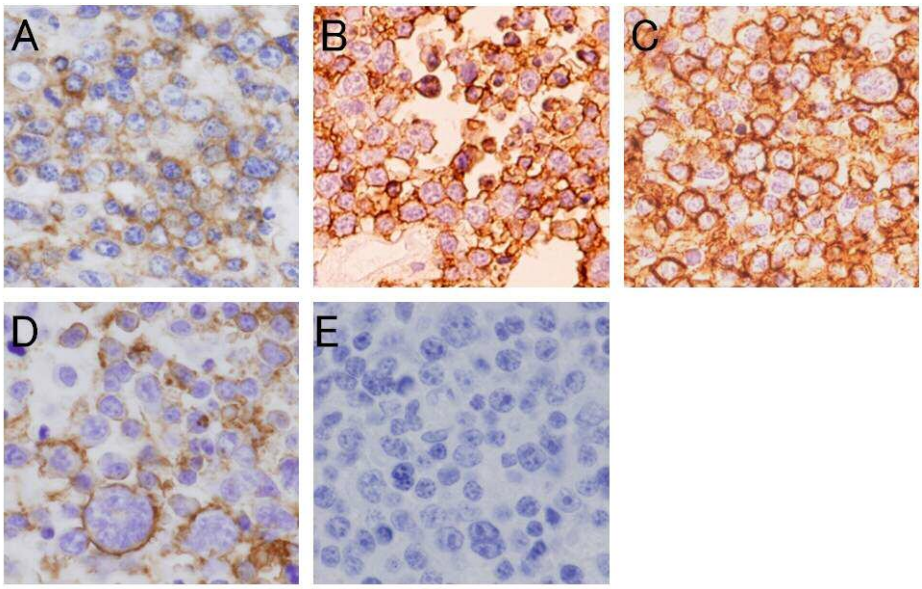
275x190mm (96 x 96 DPI)

Fig. 2



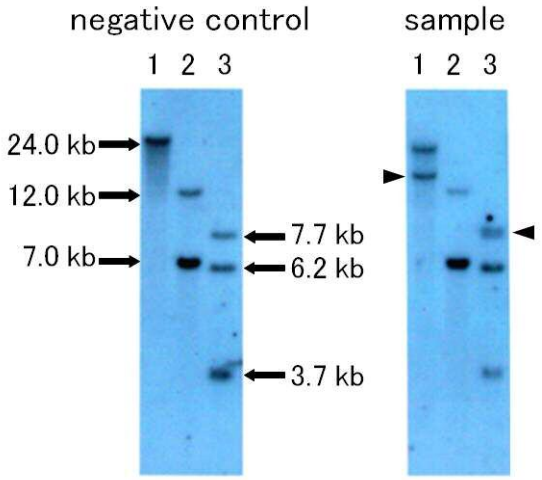
Photomicrographs of the excised tumor. Hematoxylin and eosin (H&E) staining showing pleomorphic multi-nucleated lymphoma cells (A, x40, B x100). ALK-1 immunohistichemical staining demonstrating the negativity for ALK-1 (C, x100) and positive control of ALK-1 (D, x100).
275x190mm (96 x 96 DPI)

Fig. 3



Immunohistichemical stainings showing the positivity for CD3 (A), CD30 (B), CD45RO (C) and EMA (D), negativity for CD20 (E). A-E, original magnification: x100.
275x190mm (96 x 96 DPI)

Fig. 4



275x190mm (96 x 96 DPI)

Table 1 Results of immunohistochemical staining

CD 3□	+
CD 5	+
CD15	-
CD20	-
CD30	+
CD45RO (UCLH 1)	+
CD56	-
CD79a	+
granzyme B	+
EMA	+
EBER-ISH	-
ALK-1	-

Table 2 literature review

Case	Age (yr)/sex	Location	Positive T-cell markers	Treatment	Outcome
ALK-1 positive cases					
1 Havlioglu *et al*.[18, 19] 1995	4.5/F	Multifocal brain brain stem, spinal cord	-	Ex, R, C	NED at 6.1years
2 Buxton *et al*.[18, 20] 1998	10/F	Parietal, falx	CD3, CD45RO	Ex, R, C	Dead at 6 months from post chemo sepsis in remission
3 Abdulkader *et al*.[18, 21] 1999	13/M	Frontal, parietal	CD3, CD45RO	Biopsy, C	Dead shortly after chemotherapy
4 George *et al*.[18] 2003	17/M	Parietal dura	CD3, CD43, CD45RO	Ex, R	NED at 4.8 years
5 George *et al*.[18] 2003	18/F	Temporal, dura	CD45RO	Ex, R, C	NED at 5.2 years
ALK-1 negative cases					
6 George *et al*.[18] 2003	22/F	Cerebellum + 4 additional infra and supratentorial	CD3, CD8	Ex, supportive	Dead at 11 days
7 Chuang *et al*.[22] 2001	46/F	Parietoccipital	CD43, TIA-1, ganzyme B	Ex, R	NED at 25 months
8 George *et al*.[18] 2003	50/F	Parietal + 2 additional supratentorial	-	Ex, R	Dead at 2 months
9 Paulus *et al*.[18, 23] 1994	63/M	Frontal, parietal	CD3, CD45RO	Ex, R	Dead at 11 weeks
10 Nuckols *et al*.[18, 24] 1994	66/F	Temporal	CD3	Ex, supportive	Dead at 4 days

11	Present case	79/M	Parietooccipital	CD3, CD45RO	Ex, supportive	Dead at 4 months
Cases ALK-1 not reported						
12	Bergmann and Edel [25] 1991	12/F	Occipital	-	Ex, R, C	Dead a t 4 months
13	Feldges *et al.* [26] 1992	20/M	Parietal	CD3, CD45RO	Ex, R, C	NED at 24 months
14	Goldbrunner *et al.* [27] 1996	63/M	Frontal, parietal	CD3, CD45RO	Ex, R	Dead at 3 months

NED, no evidence of disease, Ex: excision, C: chemotherapy, R: radiotherapy, TIA-1: T-cell intracellular antigen 1