


Primary central nervous system ALK-positive anaplastic large cell lymphoma with CD56 abnormally expression in a Chinese child: Challenge in diagnostic practice

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Abstract

Anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALK + ALCL) is most frequent in youth and possesses a broad morphologic spectrum. However, involvement in central nervous system (CNS) is definitely rare. The case we presented was a 12-year-old Chinese male who presented with headache and emesis for a couple of days. The neoplastic component was smaller cells resembling starry-sky growth pattern and immunohistochemical stained positively for CD30, ALK1, and CD56. Monoclonal T-cell receptor (TCR γ) gene rearrangement and gene translocation involving ALK identified by fluorescence in situ hybridization (FISH) using ALK break apart probe supported the diagnosis of ALK + ALCL. This case showed ALK + ALCL occur in a rare site with an abnormal CD56 expression. Awareness of this entity is important to distinguish it from other intracranial lymphoma.

Keywords

ALK + anaplastic large cell lymphoma (ALK + ALCL), CD56, central nervous system (CNS)

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Introduction

Anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALK + ALCL) is a T-cell lymphoma that has been recognized as a distinct entity in World Health Organization (WHO) classification of hematopoietic neoplasms. It is most frequent in youth. It involves both lymph nodes and extranodal sites, but rarely be found in central nervous system (CNS).¹ Besides, ALK + ALCL shows a broad morphologic spectrum, such as the common, small cell, lymphohistiocytic, Hodgkin-like, and occasional alveolar growth patterns.^{2,3} All cases contain a variable proportion of characteristic hallmark cells with expression of ALK protein and CD30 facilitating accurate diagnosis. However, other lymphoid tumors such as

some diffuse large B-cell lymphoma and NK/T-cell lymphoma can express CD30, and the latter mainly possess CD56-positive tumor cells, it's definitely challenging in such situation. Herein, we reported a case of primary CNS ALK + ALCL without typical

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Table 1. Clinicopathologic features of primary central nervous system ALK + ALCL reported in the literature.

References	Age(y), sex	Site	Phenotype	ALK-I	Therapy	Outcome
George et al. ⁶	17/M	R. parietal dura	T cell	+	rtx	NED at 4.8 years
	18/F	L. tempora, dura	T cell	+	ctx + rtx	NED at 5.2 years
Havlioglu et al. ⁷	4/F	Multifocal brain, brainstem, spinal cord: intra-axial and meningeal	Null cell	+	ctx + rtx	NED at 6.1 years
Buxton et al. ⁸	10/F	R.parietal, falx	T cell	+	ctx + rtx	Dead at 6 months from postchemo sepsis; in remission
Abdulkader et al. ⁹	13/M	R.parietal, r. frontal ×2: intra-axial and meningeal	T cell	+	ctx	Dead shortly after diagnosis
Karikari et al. ¹⁰	4/M	Frontal, parietal, pineal region	T cell	+	ctx + rtx	Alive, ED
Merlin et al. ¹¹	13/M	Frontal, leptomeninges	T cell	+	ctx + rtx	Dead form multiple organ failure
Furuya et al. ¹²	11/M	Parietal, leptomeninges	Null cell	+	ctx + rtx	Alive
Present case	12/M	R.occipital, falx	Null cell	+	untreated	Dead shortly after diagnosis a month later

NED: no evidence of disease; ED: evidence of disease; ctx: chemotherapy; rtx: radiotherapy.

large hallmark cells, but abnormally expressing CD56 in a 12-year-old Chinese male.

Case presentation

A 12-year-old male presented with headache, emesis for 10 days. Head magnetic resonance imaging (MRI) examination showed a mass effect from right occipital lobe to falx cerebrum with large area cerebral edema and partial cystis degeneration (Figure 1(a)). He had no trauma history and physical examination didn't find any enlarged lymph nodes. The patient received open craniotomy and biopsy of some gray white tissues of right occipital lobe. The mass was poorly circumscribed, gray white like fish with cystis degeneration and partially suppurative discharge.

The surgically resected specimen was fixed in 10% neutral buffered formalin and embedded in paraffin. Hematoxylin-eosin staining and immunohistochemical analysis were performed on 4- μ M-thick paraffin-embedded sections. Microscopic examination revealed no evidence of normal cerebral histomorphology. The neoplastic component was lymphoid cells showing a diffuse monotonous growth pattern. Focal or sheets of necrosis and starry-sky mimicking presented (Figure 1(b)). The neoplastic lymphoid cells were not large cells obviously. Nuclei of most tumor cells were subtle irregular-shaped and contain multiple basophilic nucleoli. The cytoplasm were abundant pale or basophilic. Many mitoses could be easily found (Figure 1(c)).

Immunohistochemical staining showed that neoplastic cells stained strongly for CD30 on the cell membrane and in the Golgi region (Figure 1(d)) and ALK1 (Figure 1(e)). The cells lacked expression CD2, CD3, CD5 and CD7, but Granzyme B and TIA-1 expression was seen. In addition, the tumor cells were positive for CD56, MUM-1, EMA, and negative for glial fibrillary acidic protein (GFAP), PLAP, CD34, CD45, CD20, CD79a, TdT, CD99, BCL-2, BCL-6 and CD10. Few tumor cells were positive for CD4. Ki-67 index was up to 95%. In situ hybridization for Epstein-Barr virus-encoded small RNAs (EBER) was negative. Monoclonal T-cell receptor (TCR γ) gene rearrangement was detected. Gene translocation involving ALK was identified by fluorescence in situ hybridization (FISH) using ALK break apart probe (Figure 1(f)). In conclusion, the final diagnosis as ALK + ALCL was made. Unfortunately, the patient died without any further treatment in one month.

Discussion

As we know, primary CNS lymphoma is an extremely unusual type of non-Hodgkin lymphoma. More than 90% of primary CNS lymphomas are diffuse large B-cell lymphomas (DLBCLs), only 2% of all are of T-cell origin.^{4,5} ALK + ALCL is a T-cell lymphoma which accounts for approximately 10%–20% of childhood lymphomas.² However, primary CNS ALK + ALCL is distinctly rare in children. Only 8 patients were reported in English literature (Table 1).^{6–12} The age of these

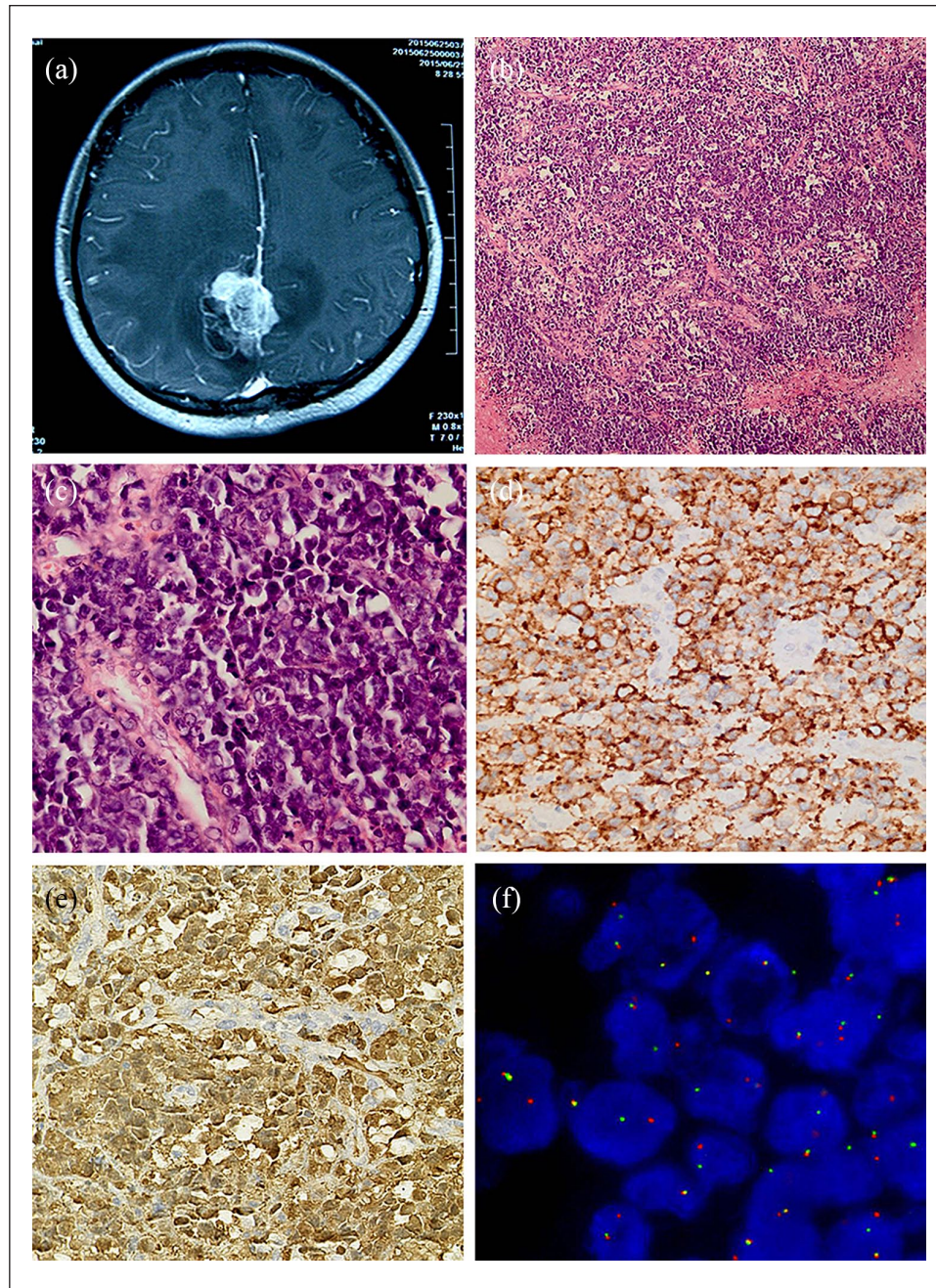


Figure 1. Primary central nervous system ALK-positive anaplastic large cell lymphoma. (a) The tumor effect from right occipital lobe to falx cerebri with large area cerebral edema and partial cystic degeneration. (b) Tumor cells were arranged in diffuse monotonous growth pattern with focal necrosis and starry-sky mimicking presented. (c) The neoplastic lymphoid cells were not large cells obviously. Nuclei of most tumor cells were subtle irregular-shaped and contain multiple basophilic nucleoli. The neoplastic cells stained strongly for CD30 on the cell membrane and in the Golgi region. (d) and ALK1 (e, f) FISH identified ALK gene break apart.

patients ranged from 4 to 18 years (mean 9.1 years). The majority of cases had evidence of dual/meningeal tumor, usually with simultaneous brain involvement.¹³ The clinical symptoms of primary CNS ALCLs were nonspecific, include headache, dizziness, hemiparesis, seizure and dementia. The prognosis of these patients was variable. All of the

eight patients had received chemotherapy and/or radiotherapy, five patients were alive with or without evidence of disease, and three of them with tumor-free survival beyond 3 years (4.8–6.1 years), other three patients died from lymphoma or chemotherapy-related sepsis. Our patient died from the aggressive disease without any adjuvant therapy in

short order. Unlike the favorable prognosis observed with ALK + ALCL occurring outside the CNS, the majority of CNS ALCL pursued a rapidly fatal course.⁶

Since primary CNS ALK + ALCL is distinctly rare and characteristic, the diagnosis is absolutely challenging, especially presenting abnormal morphology and immunophenotype. The case herein we reported is ALK + ALCL with relatively small-sized neoplastic cells, focal or sheets of necrosis and starry-sky mimicking pattern, instead of prominent hallmark cells. As to the immunophenotype of ALK + ALCL, the great majority of tumor cells express one or more T-cell antigens. CD3 is negative in > 75% of the cases. However, due to loss of several pan-T-cell antigens, only few tumor cells were positive for CD4. This case may have an apparent so-called null-cell phenotype, but show evidence of a T-cell lineage at the genetic level.²

CD56, a neural cell-adhesion molecule, which is expressed on natural killer (NK) cells and a subset of T cells and monocytes. Its expression is well recognized in hematolymphoid malignancies of NK-cell lineage, but also in some types of T- and B-cell lymphoma. Suzuki et al.¹⁴ reported that approximately 25 of 140 cases (18%) of ALCL expressed CD56, the incidence of expression of CD56 in ALK-positive group (18%) and ALK-negative group (20%) was almost the same. As we once analyzed, extranodal NK/T-cell lymphoma, nasal type (ENKTCL-NT) was the most common subtype mature T- and NK-cell neoplasm in our Southwest China. Up to 30.9% of extranodal lymphoma is ENKTCL-NT only second to diffuse large B-cell lymphoma.¹⁵ By definition, ENKTCL-NT possesses distinctive morphology and immunophenotype including atypical lymphoid tumor cells with prominent necrosis, cytotoxic phenotype, which should be differentiated from ALCL.² The key point of distinction ALCL from ENKTCL-NT is association with Epstein-Barr virus (EBV) other than CD56 expression. Moreover, the ALK expression in the current case exhibited a classic pattern with cytoplasmic and nuclear staining, which suggests the presence of a t(2:5)(NPM1-ALK) translocation.² In short, typical CD30 expression, ALK1 expression, monoclonal TCR gene rearrangement, gene translocation involving ALK, and negative for

EBER substantiated the authentic diagnosis of this challenging case.

It should be noticed that CD56 is an independent prognostic factor in ALCL. CD56 expression in ALCL indicates a worse prognosis overall, as well as in both ALK positive and ALK negative subgroups, including multiple recurrences, CNS involvement, and an increased incidence of bone involvement.¹⁴ So, abnormal CD56 expression not only casts showdown on making diagnosis but also promotes the prognosis evaluation. Primary CNS ALCL shows histologic, immunophenotypic, and some clinical features that are similar to ALCL occurring outside the CNS, but its clinical behavior appears to be more aggressive. Young age of patient, unifocal tumor, lack of necrosis, and ALK positivity of tumor cells have been proposed as favorable prognostic factors. Instead, a high mortality have been found to correlate with older age, multifocal tumor, extensive necrosis, and ALK negativity.⁶

Conclusion

In summary, we herein report a rare case of pediatric ALK + ALCL occur in uncommon site with an abnormal CD56 expression. The patient present with aggressive course and poor prognosis. More cases need to be studied to observe such clinicopathologic features.

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Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

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Informed consent

Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

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