Primary Central Nervous System ALK-Positive Anaplastic Large Cell Lymphoma: Clinicopathologic and Prognostic Features

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Abstract

Background

Primary CNS anaplastic lymphoma kinase-positive (ALK+) anaplastic large cell lymphoma (ALCL) is extremely rare and only few cases have been reported. Due to its rarity, the clinicopathologic features and the prognosis of primary CNS ALK + ALCL have not been well characterized.

Methods

We retrospectively analyzed the clinicopathologic and prognostic features of 3 cases of primary CNS ALK + ALCLs among 337 cases of primary CNS lymphomas during the past 14 years in our cancer center with review of an additional 20 cases from the literature.

Results

Primary CNS ALK + ALCL accounted for 0.9% (3/337) of all primary CNS lymphomas during the study period in our cancer center. The ages of patients ranged from 4 to 43 years, with a median age of 18 years. There was a predominance of males, with the male-to-female ratio of 6.7:1. Most (87%, 20/23) of cases had intracerebral mass(es), and among these cases, 25% (5/20) of cases were accompanied by involvement of spinal cord and (or) leptomeninges; rare cases (3/23, 13%) were confined to the spinal cord and (or) leptomeninges. A solitary mass and multiple tumors were present in 56.5% (13/23) and 43.5% (10/23) of cases, respectively. Of the 22 patients with survival data, 31.8% (7/22) of patients died of the disease during the follow-up period (median follow-up, 24 months; range, 0.5–87 months). The 2-year overall survival (OS) of patients with primary CNS ALK + ALCL was 69%. Patients under 18-years old had worse 2-year overall survival, but the difference did not reach statistical significance ($p = 0.115$). No statistical significance was found between patients with solitary mass and multiple tumors ($p = 0.940$).

Conclusions

Primary CNS ALK + ALCL is an extremely rare disease and tends to occur in young adults with a male preponderance. Patients with this disease have relatively favorable outcome than other types of primary CNS lymphomas. Accurate diagnosis, as well as timely and optimal treatment for patients with this disease is important.

Background

Primary central nervous system lymphoma (PCNSL) is a relatively rare disease accounting for 2.4-3% of all brain tumors(1). The most majority histological type of PCNSL is diffuse large B-cell lymphoma (DLBCL) and patients with CNS DLBCL have remarkably worse outcome than do patients with systemic DLBCL(2). Other types of lymphoma have just occasionally been seen in CNS.

Primary CNS anaplastic large cell lymphomas (ALCLs) are rare, most of which are ALK+, while only a minority of cases are ALK-1 negative(3). Up to date, only few cases of primary CNS ALK + ALCL have been reported, mainly as case reports rather than as study series(4–20). Because of its rarity, the clinicopathologic and prognostic features of primary CNS ALK + ALCL have not been well illuminated. In an attempt to expand the current knowledge of the occurrence, clinicopathologic characteristics and prognosis of this rare tumor, we retrospectively analyzed 3 cases of primary CNS ALK + ALCL among 337 cases of primary CNS lymphomas during the past 14 years in our cancer center with review of an additional 20 cases from the literature.

Materials And Methods

Case Selection

All cases of PCNSLs diagnosed in the Department of Pathology, Sun Yat-sen University Cancer Center, Guangzhou, China, were retrospectively analyzed during the period from January, 2007 to December, 2020. Primary CNS ALK+ ALCL cases were collected. The inclusion criterions of this retrospective study were as followings: (1) patient was without a history of lymphoma; (2) CNS lesion was as the initial presentation without extra CNS or lymph node manifestations at presentation; (3) lymphoma of the dura, intravascular lymphoma, lymphomas with evidence of systemic disease or secondary lymphomas, and all immunodeficiency-associated lymphomas were excluded. The clinical data collected for analysis included age, location, clinical presentation, treatment regimens, and survival data. All patients provided written informed consent for the collection and publication of their medical information during the first visit to the hospital.

We also performed an extensive literature search for the reported cases of primary CNS ALK+ ALCL in PubMed (www.ncbi.nlm.nih.gov/pubmed/) using different combinations of key words in the title/abstract field, including “primary,” “CNS,” “central nervous system,” “ALK,” “ALK1,” “ALCL,” and “anaplastic large cell lymphoma”. Cases in the English literature were carefully reviewed to extract essential clinicopathologic data and to combine the cases that were repeatedly studied in different papers. A total of 20 cases of primary CNS ALK+ ALCL were retrieved from the literature and were included in our review.

Immunohistochemical Staining and In Situ Hybridization

The specimens of these 3 cases of primary CNS ALK+ ALCL cases were formalin fixed and paraffin embedded (FFPE) and then sectioned at 4.0 mm thickness. The sections were stained using hematoxylin and eosin staining or were used for immunohistochemical examination. The immunohistochemical stains were performed on a Leica Autostainer (BOND-MAX, M495644) with Bond Polymer Refine Detection Kit (Leica Biosystems Newcastle Ltd, Catalog No.: DS9800). Appropriate negative and positive controls were performed with satisfactory staining. The pretreatment methods, primary antibodies, and their working dilutions are listed in Table 5.

The EBV Probe In Situ Hybridization Kit (ISH- 6021, Zhongshan Golden Bridge Biotechnology Co. Ltd, Beijing, China) was used to detect EBV-encoded small RNAs (EBERs) according to the manufacture's protocol. The main protocols were published in our previous paper(21). The positive signals were a brownish-yellow color and localization in the nuclei.

Molecular Assays for Gene Rearrangements

Genomic DNA was extracted from FFPE tissue using the QIAamp DNA FFPE Tissue Kit (Qiagen, Hilden, Germany). A commercial BIOMED-2 multiplex PCR system (Invivoscribe Technologies, San Diego, CA) was used to detect the gene rearrangements of T cell receptor (TCR) and immunoglobulin (Ig) in Case #1 and #2 according to previously published methods(22). Gene scanning was performed on ABI 3500XI Genetic Analyzer using GeneMapper Software (version 4.1; Life Technologies Corporation, Carlsbad, CA, USA) with appropriate positive and negative controls. Interpretation of clonal peak was carried out as per the EuroClonality guideline and the manufacturer's protocol.

Statistical Analysis

Among these 23 cases of primary CNS ALK+ ALCL, survival data of 22 cases were available for analyses, including 3 cases from present study and 19 cases in the literature. Survival was defined as years from first diagnosis of primary CNS ALK+ ALCL to death or last follow-up. Those alive at last follow-up were treated as censored. The Kaplan-Meier method was used to estimate overall distributions, and the log-rank test was used to compare survival distributions by patient groups. P-values <0.05 (2 sided) were considered to be statistically significant. The Life Table method was used to estimate overall distributions. SPSS software (version 26.0 for Mac; Statistical Product and Service Solutions; IBM, Armonk, NY) was used for analysis.

Results

Occurrence and Patient's Clinical Characteristics

Primary CNS ALK+ ALCL accounted for 0.9% (3/337) of all primary CNS lymphomas during the study period in our cancer center. The major clinical features of the 3 cases of primary CNS ALK+ ALCL are summarized in Table 1. All 3 patients were males and ranged from 12 to 27 years with a median age of 16 years at diagnosis. All patients were Chinese without a history of lymphoma. The average clinical course was 4 months (range, 2 to 6 months). All patients initially presented with headache and vomiting or dizziness. Patient 1# and 2# had a single lesion located in right frontal lobe (Fig.1) and right parieto-occipital lobe, respectively, whereas Patient 3# had multiple lesions mainly located in cerebellum.

Pathology Findings

Histology

Histopathologically, normal brain architectures were replaced by lymphoid cells (Fig. 2A). The tumors had a diffuse growth pattern largely effacing the brain tissues, and some neoplastic cells often clustered around blood vessels in all 3 cases (Fig. 2B). Cytologically, the lymphomas were composed predominantly of large sized cells with abundant cytoplasm and irregular nuclei in all cases. The nuclear chromatin was finely clumped or dispersed, with prominent nucleoli (Fig. 2C-2D). The mitotic figures were visible. All these 3 cases were of common type.

Immunophenotype

The results of immunohistochemistry and EBER in situ hybridization (ISH) are summarized in Table 2. All 3 cases showed that neoplastic cells were stained strongly for CD30 on the cell membrane and in the Golgi region (Fig. 3A). ALK-1 positivity was identified in all cases, with staining in both cytoplasm and nucleus (Fig. 3B). All cases were positive for MUM1 (Fig. 3C) and the cytotoxic antigens (TIA1, granzyme B) (Fig. 3D). Two available cases were positive for EMA (Fig. 3E) and CD43, CD2, CD3ε and CD7 were partially positive in one available case, respectively. All cases were negative for B cell markers, including CD20 and CD79a. The Ki-67 proliferation fraction ranged from 60% to 80% (Fig. 3F). In situ hybridization for EBER was negative for all 3 cases.

Gene Rearrangements

PCR assays for TCR and IG gene rearrangements were performed on Case 1# and Case 2#. Both showed monoclonal T-cell receptor (TCRγ) gene rearrangement, but without IG gene rearrangement.

Treatment and Outcome

All 3 patients underwent surgical resection and chemotherapy (treatment regimens for each case was listed in Table 1). In addition, Case 2# and Case 3# received whole brain radiotherapy. All patients were successfully followed-up. The median follow-up interval was 52 months (range, 18 to 98 mo). All

patients survived without diseases during the follow-up period, and of note, patient 3# survived for 98 months.

Review of 23 Cases of Primary CNS ALK+ ALCL

After an extensive search of the English literature, we found 20 cases of primary CNS ALK+ ALCL(4-20). Some cases were included in two articles with different study purposes, and the data from these cases were carefully extracted and combined. The brief clinicopathologic features of these cases and those from the present study are summarized in Table 3. The ages of patients ranged from 4 to 43 years, with a median age of 18 years. There was a predominance of males, with the male-to-female ratio of 6.7:1. Most (87%, 20/23) of cases had intracerebral mass(es), and among these cases, 25% (5/20) of cases were accompanied by involvement of spinal cord and (or) leptomeninges; rare cases (3/23,13%) were confined to the spinal cord and (or) leptomeninges. A solitary mass and multiple tumors were present in 56.5% (13/23) and 43.5% (10/23) of cases, respectively. Of the 22 patients with survival data, 31.8% (7/22) of patients died of the disease during the follow-up period (median follow-up, 24 months; range, 0.5-87 months). The 2-year overall survival (OS) of patients with primary CNS ALK+ ALCL was 69% (Fig. 4A). Patients under 18-years old had worse 2-year overall survival, but the difference did not reach statistical significance ($p=0.115$) (Fig. 4B). No statistical significance was found between patients with solitary mass and multiple tumors ($p=0.940$).

Discussion

ALK + ALCL frequently involves both lymph nodes and extranodal sites. The most commonly involved extranodal sites include the skin, bone, soft tissue, lungs, and liver(23–26). Involvement of the CNS is rare(2). Of all cases of ALCL, < 1% are primary in CNS(27). Our results revealed that primary CNS ALK + ALCL only accounted for 0.9% (3/337) of all primary CNS lymphomas during the study period in our cancer center. After an extensive search of the English literature, only 20 cases of primary CNS ALK + ALCL were identified. Hence, these data once again support that primary CNS ALK + ALCL is extremely rare. Interestingly, primary CNS ALK + ALCL mostly affected male patients with a male to female ratio of 6.7:1. The ages of patients ranged from 4 to 43 years, with a median age of 18 years. Accordingly, it seems that primary CNS ALK + ALCL tends to occur in young adults with a male preponderance.

Due to its rarity, the clinicopathologic features and the prognosis of primary CNS ALK + ALCL have not been well characterized. Up to date, no known risk factors have been identified. Patients mainly initially presented with headache, dizziness, vomiting, seizures, or a combination of these. They are often initially thought to have an infection rather than a neoplasm, especially for the cases with multiple lesions. When combined with the cases previously reported in the literature, we found that most (87%, 20/23) of cases had intracerebral mass(es), and among these cases, 25% (5/20) of cases were accompanied by involvement of spinal cord and (or) leptomeninges; rare cases (3/23,13%) were confined to the spinal cord and (or) leptomeninges. A single lesion was slightly more common than multiple lesions, which were observed in 56.5% and 43.5% of patients, respectively. Of note, the morphology and immunophenotype of primary CNS ALK + ALCL are similar to systemic ALCL. Most cases of this entity are of common type, but primary CNS ALK + ALCL of the lymphohistiocytic variant(27) and combined lymphohistiocytic and small-cell variants have also been reported(28).

The most majority of PCNSL is DLBCL and patients with CNS DLBCL have remarkably worse outcome than do patients with systemic DLBCL(2). Patients with systemic ALK + ALCL show favorable outcome. However, the outcome and the prognostic risk factors of primary CNS ALK + ALCL have not been well characterized. Only few cases have been reported, mainly as case reports rather than as study series. Recommendations regarding therapies are unavailable due to the small numbers of disparately treated cases. Most reports do describe therapy segments and outcomes, but consensus statements about the best therapeutic intervention are not available. Our results showed that the 2-year overall survival (OS) of patients with primary CNS ALK + ALCL was 69%. Of note, all 3 patients from our cancer center survived during the follow-up period with median follow-up interval of 52 months, and patient 2# survived for 98 months. Hence, patients with this disease have relatively favorable outcome. Accurate diagnosis, as well as timely and optimal treatment for patients with this disease is important. Interestingly, patients under 18-years old showed a trend toward inferior overall survival, which had not been reported previously. No statistical significance was found between patients' outcome and gender, number of lesions.

Conclusions

Primary CNS ALK + ALCL is an extremely rare disease, which only accounted for 0.9% (3/337) of all primary CNS lymphomas during the past 14 years in our cancer center. It tends to occur in young adults with a male preponderance. Patients with this disease have relatively favorable outcome than other types of primary CNS lymphomas. Accurate diagnosis, as well as timely and optimal treatment for patients with this disease is important.

Declarations

Compliance with Ethical Standards:

Funding

There is no financial support for this study.

Disclosure of potential conflicts of interest

The authors declare that they have no conflict of interest.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent

All patients provided written informed consent for the collection and publication of their medical information during the first visit to the hospital.

Authors' contributions

Xin Weng designed the study and wrote the manuscript. Jia Fu and Jianchang Fu contributed to the clinical and follow-up information collection, as well as data analysis. Qitao Huang, Xia Yang and Xia Liu performed immunohistochemical staining and in situ hybridization (ISH). Xinyou Zhang provided supervision. Yuhua Huang conceived the project and provided leadership.

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Tables

Table 1
Clinical Features of the Three Cases of Primary CNS ALK-positive ALCLs

Case #	Age (y)	Gender	Initial main symptoms	Clinical History (mo.)	Initial suspicion	Location	Lesion (s)	Tumor size (cm)	Surgical excision	WBRT	Chemotherapy regimens	Outcome (mo)
1	16	M	Headache, dizziness	6	Glioma	Right frontal lobe	Single	3.4×2.7	Yes	No	Crizotinib	Alive, 18
2	27	M	Headache, vomiting	2	Tumor	Right parieto-occipital lobe	Single	4.0×3.0	Yes	Yes	HD-MTX + Ara-c	Alive, 98
3	12	M	Headache, vomiting	4	Infection	Cerebellum	Multiple	NA	Yes	Yes	HD-MTX + VM-26 + HD-MTX + Ara-c	Alive, 52

M, male; mo, months; NA, not available; WBRT, whole brain radiotherapy; HD MTX, high-dose methotrexate; VM-26, teniposide; Ara-c, cytarabine.

Table 2
Immunophenotype of the Three Cases of Primary CNS ALK + ALCL

Case#	CD30	ALK	EMA	MUM1	CD43	CD2	CD3ε	CD5	CD7	CD20	PAX5	TIA-1	GranB	Ki-67	EBER
1	+	+	+	+	+	Partial+	–	–	Partial+	–	–	+	+	80%	–
2	+	+	NA	+	+	NA	Partial+	NA	NA	–	–	+	+	60%	–
3	+	+	+	+	NA	NA	–	NA	NA	–	–	+	+	80%	–

Table 3
Clinical Features of the 20 Cases of Primary CNS ALK + ALCL Reported in the Literatures

Case #	Author	Age	Gender	Location	Lesion(s)	Treatment	Follow up (mo.)	Outcome
L1	Qian Liu et al.(4)	12	M	R. occipital to falx cerebrum	S	No	1	Died
L2	David H.George et al.(5)	18	F	L. tempora, dura	S	CT + RT	62.4	Alive
L3	Havlioglu et al.(11)	4.5	F	Brainstem, spinal cord, meningeal	M	CT + RT	73.2	Alive
L4	Buxton et al.(7)	10	F	R. parietal, falx	S	CT + RT	6	Died
L5	Abdulkar et al.(6)	13	M	R.parietal, frontal, meningeal	S	CT	/	Died
L6	Karikari et al.(12)	4	M	Frontal, parietal, pineal region	M	CT + RT	/	Alive
L7	Merlin et al.(23)	13	M	Frontal, leptomeninges	S	CT + RT + ABMT	10	Died
L8	Furuya K et al.(22)	11	M	Parietal, leptomeninges	M	CT + RT	98	Alive
L9	Ponzoni et al.(18)	29	M	Frontal and temporal	M	CT + RT	19	Alive
L10	P B Cooper et al.(9)	39	M	R.occipitoparietal	S	/	9	Alive
L11	Mark G Carmichael (8)	38	M	R. parieto-occipital	S	CT + RT	6	Alive
L12	Sindu Vivekanandan et al. (21)	20	M	R. sylvian fissure	M	CT + RT	96	Alive
L13	Masashi Nomura et al.(15)	20	M	L. frontal lobe	S	CT	60	Alive
L14	Jae Sung Park et al.(17)	31	M	Leptomeninges	S	CT	6	Alive
L15	Kuntegowdenahalli et al. (13)	18	M	L. parieto-occipital	S	CT + RT	/	/
L16	Splavski et al.(20)	26	M	Frontal horn	S	CT + RT	24	Alive
L17	Xiaoqin Dong et al.(10)	34	M	Spinal cord	M	CT + RT	25	Died
L18	Madhu P Menon, et al.(14)	43	M	Dural, leptomeningeal and spinal	S	/	/	Died
L19	Mehmet Fevzi Ozkaynak (16)	9	M	Bilateral frontal lesions, meningeal	S	CT + RT + ASCT	26	Alive
L20	A Rupani et al.(19)	17	M	R. fronto-parietal	M	CT + RT	1	Died
M, male; F, female; mo., months; /, not available; R., right; L., left; CT, chemotherapy; RT, radiotherapy; ABMT, allogeneic bone marrow transplantation; ASCT, autologous peripheral blood hematopoietic stem cell transplantation.								

Table 4
Summary of the Brief Clinicopathologic Features of Primary CNS ALK + ALCL in Present Study and the Literature

Characteristics	Present study	Literature	Total
Total cases	3	20	23
Age Range	12–27	4–43	4–43
Median Age (year)	16	18	18
Male/female	3:0	17:3	20:3
Location			
Brain	3	12	15
Leptomeninges	0	1	1
Spinal cord	0	1	1
Brain, leptomeninges and (or) spinal cord	0	6	6
Solitary lesion/ multiple lesions	2/1	11/9	13/10
Follow up Rang (months)	18–98	1–98	1–98
Median follow-up (months)	52 (n = 3)	21.5 (n = 16)	24 (n = 19)
Outcome (died/alive)	0/3	7/12	7/15
2-years overall survival	100%	62%	69%

Table 5
Primary Antibodies and Conditions Used for Immunohistochemical Staining

Antigen	Clone	Dilution	Antigen Retrieval	Manufacturer
CD20	L26	1:200	EDTA, pH9.0	Ascend BIO, China
CD19	BT51E	1:200	EDTA, pH9.0	ZSGB BIO, China
PAX5	ZP007	1:50	EDTA, pH9.0	Ascend BIO, China
CD3	2GV6	RTU	EDTA, pH9.0	Roche, China
CD5	4C7	1:100	EDTA, pH9.0	Ascend BIO, China
CD2	AB75	1:30	EDTA, pH9.0	Gene, China
CD7	EP132	1:100	EDTA, pH9.0	Gene, China
CD4	UMAB64	1:100	EDTA, pH9.0	ZSGB BIO, China
CD8	SP16	1:75	EDTA, pH9.0	Gene, China
MUM1	EP190	RTU	EDTA, pH9.0	ZSGB BIO, China
CD56	123C3	1:600	EDTA, pH9.0	ZSGB BIO, China
TIA-1	2G910F5	1:75	EDTA, pH9.0	Gene, China
Granzyme B	GZB01	1:75	EDTA, pH9.0	Gene, China
Perforin	5B10	1:50	EDTA, pH9.0	Gene, China
ALK	ALK1	1:200	EDTA, pH9.0	Ascend BIO, China
CD30	JCM182	1:100	EDTA, pH9.0	Gene, China
Ki-67	MIB-1	RTU	EDTA, pH9.0	Dako, Denmark
RTU: Ready to use.				

Figures

Figure 1

Pretherapeutic and post-therapeutic magnetic resonance imaging (MRI) scans of the mass in right frontal lobe for Case#1.

Pretherapeutic MRI examination showed a mass in right frontal lobe with large area cerebral edema (A). MRI undertaken after surgical excision and Crizotinib treatment revealed no residual enhancement, which suggested complete remission (B).

Figure 2

Morphology of primary CNS ALK+ ALCL

Normal brain architecture was replaced by lymphoid cells (A). The tumors had a diffuse growth pattern, and some neoplastic cells often clustered around blood vessels (B). The lymphoma cells were of medium to large size with abundant cytoplasm and irregular nuclei. The nuclear chromatin was finely clumped or dispersed, with prominent nucleoli (C-D).

Figure 3

Immunophenotype of primary CNS ALK+ ALCL

The neoplastic cells were strongly positive for CD30 on the cell membrane and in the Golgi region(A). ALK-1 positivity was identified with staining in both cytoplasm and nucleus (B). The tumor was positive for MUM1(C) and TIA1(D). Two available cases were positive for EMA (E) and Ki-67 (F).

Figure 4

Overall survival (OS) analysis for primary CNS ALK+ ALCL

The 2-year overall survival (OS) of patients with primary CNS ALK+ ALCL was 69% (A). Patients under 18-years old had worse 2-year overall survival, but the difference did not reach statistical significance ($p = 0.115$) (B).