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Case Report

Primary CNS ALK-negative anaplastic large cell lymphoma: A case report and review of the literature ☆,☆☆

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ABSTRACT

Primary central nervous system (CNS) ALK-negative anaplastic large cell lymphoma (ALCL) is a rare and enigmatic disease, with limited data available in the literature. This case report adds to the existing body of knowledge by describing a unique case of a 68-year-old, immunocompetent male who presented with a single ring-enhancing lesion, which upon further analysis proved to be an ALK-negative ALCL that was primary to the CNS. A comprehensive review of the existing literature is provided, highlighting the genetic characteristics and diverse neuroimaging findings of this disease entity. This report adds valuable information to the understanding of this rare disorder, and highlights the need for further research in the field of primary CNS ALK-negative ALCL.

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Introduction

Anaplastic large cell lymphoma (ALCL) is a rare and aggressive type of non-Hodgkin lymphoma that can arise in various parts of the body, including the central nervous system (CNS). ALCLs

typically harbor demonstrable anaplastic lymphoma kinase (ALK) gene rearrangement with resultant ALK protein expression; ALK-negative ALCL is much less common. To date, only 16 reported cases of primary CNS ALK-negative ALCL appear in the literature, and its reported neuroimaging appearance can vary considerably. Herein we present a case of primary

Abbreviations: ALCL, Anaplastic large cell lymphoma; ALK, Anaplastic lymphoma kinase; CNS, Central nervous system, CD, Cluster of Differentiation; CT, Computed tomography; DUSP, Dual-specificity phosphatase; GFAP, Glial fibrillary acidic protein; IRF, Interferon regulatory factors; IV, Intravenous; MRI, Magnetic resonance imaging; OLIG, Oligodendrocyte transcription factor; PCNSL, Primary central nervous system lymphoma.

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CNS ALK-negative ALCL arising as a solitary ring-enhancing brain lesion in an immunocompetent adult. We review the relevant literature, with particular emphasis on neuroimaging findings in order to increase awareness of this rare tumor type and improve the diagnostic accuracy of physicians.

Clinical summary

A 68-year-old immunocompetent male with a history of diabetes, morbid obesity, coronary artery disease, hypertension, and atrial fibrillation presented with new-onset headache and tremor over several months. On examination, he was found to have a left homonymous hemianopsia. A magnetic resonance imaging (MRI) of the brain with and without contrast administration revealed a 4-cm ring-enhancing mass in the right occipital lobe. Further imaging with staging CT scans (thorax, abdomen and pelvis) and a bone marrow aspirate failed to identify a primary lesion or metastases elsewhere in the body. The tumor was subsequently completely resected 2 months later, and the pathology showed an ALK-negative ALCL. The patient was treated with high-dose methotrexate in combination with temozolomide. Supporting medications included dexamethasone and leucovorin. The patient received a total of eight cycles of chemotherapy, and the most recent brain MRI and lumbar puncture show no evidence of disease recurrence approximately 8 months postresection. Over the course of treatment, the patient experienced difficulty excreting methotrexate, resulting in persistently elevated levels after each cycle. Nevertheless, he responded well to treatment and remains in follow-up care.

Neuroradiology findings

Initial head CT without contrast, performed to rule out a right posterior cerebral artery stroke, showed a mass-like lesion within the right parietal occipital region with extensive surrounding edema in the parietal, temporal, and occipital regions. There was mass effect seen on the occipital horn of the right lateral ventricle but no midline shift. These findings were suggestive of a neoplasm until proven otherwise, and MRI was recommended for further evaluation (Fig. 1).

The same day, an MRI of the brain was performed with and without intravenous (IV) contrast material (Dotarem). Findings included a 4.2 × 3.2 × 3.2 cm, ring-enhancing mass seen within the right occipital lobe. There was surrounding edema, extending into the right parietal and temporal lobes causing mass effect on the occipital horn of the right lateral ventricle. There was no shift of the midline structures noted. There were scattered foci of increased T2 and FLAIR signal noted suggestive of chronic small vessel ischemic disease. There was a small cortical infarct seen in the right frontal lobe, which was chronic in nature. The differential diagnosis for the right occipital lobe mass was neoplasm (including glioblastoma, metastasis, and less likely lymphoma) and abscess. Therefore, neurosurgery was consulted for potential biopsy or resection.

Preoperative MRI of the brain with IV contrast (Gadavist), performed a month and a half later, redemonstrated rim-enhancing lesion with a lobulated margin, now measuring

Table 1 – The patient's immunophenotype of the lymphoma cells.

Positive staining	Negative staining
CD30	ALK
CD2	PLAP
CD4	SALL4
Granzyme B	OCT3/4
INI1 (retained)	CK7
ATRX (retained)	CK20
Ki67 (90%)	CAM5.2
P53 (25%)	CD56
	S100
	SOX-10
	MART-1
	HMB-45
	IDH1 R132H

5.0×3.0 cm with associated edema extending into the right temporal lobe.

Pathological findings

Histopathological examination of tissue from the right occipital lesion revealed a mitotically active lymphoid neoplasm containing abundant large atypical cells (Fig. 2), including those with horseshoe-shaped nuclei (Hallmark cells). These large lymphoid cells were immunopositive for stains targeting CD30, as well as CD2, CD4, and granzyme B. Immunostain targeting the ALK protein was entirely negative. CD56 immunostain was negative in the tumor cells. Furthermore, immunostains for OLIG2 and GFAP highlight the background reactive gliosis. CD5, CD45, and CD3 stains decorated the small mature-appearing lymphocytes with a few alternatively staining with CD20. The full immunophenotype of the lymphoma cells is outlined in Table 1.

Fluorescence in situ hybridization (FISH) for the detection of an ALK translocation status was negative. T-cell receptor gene polymerase chain reaction (PCR) documented a clonal T-cell receptor gamma chain gene rearrangement. Reference laboratory testing for *DUSP22-IRF4* rearrangement proved negative.

Discussion

The present case report describes the work-up and treatment of an immunocompetent 68-year-old male with primary CNS ALK-negative ALCL. His neuroimaging finding of a solitary ring-enhancing lesion had raised suspicion of high-grade glioma versus metastatic tumor or abscess, with primary CNS lymphoma being of much lower consideration. Following gross-total resection, he was treated with a combination of high-dose methotrexate and temozolomide chemotherapy and achieved a complete remission to date.

In general, primary CNS lymphomas are uncommon, making up only 2% of primary brain tumors. Furthermore, the vast majority of primary CNS lymphomas are of B-cell lineage,

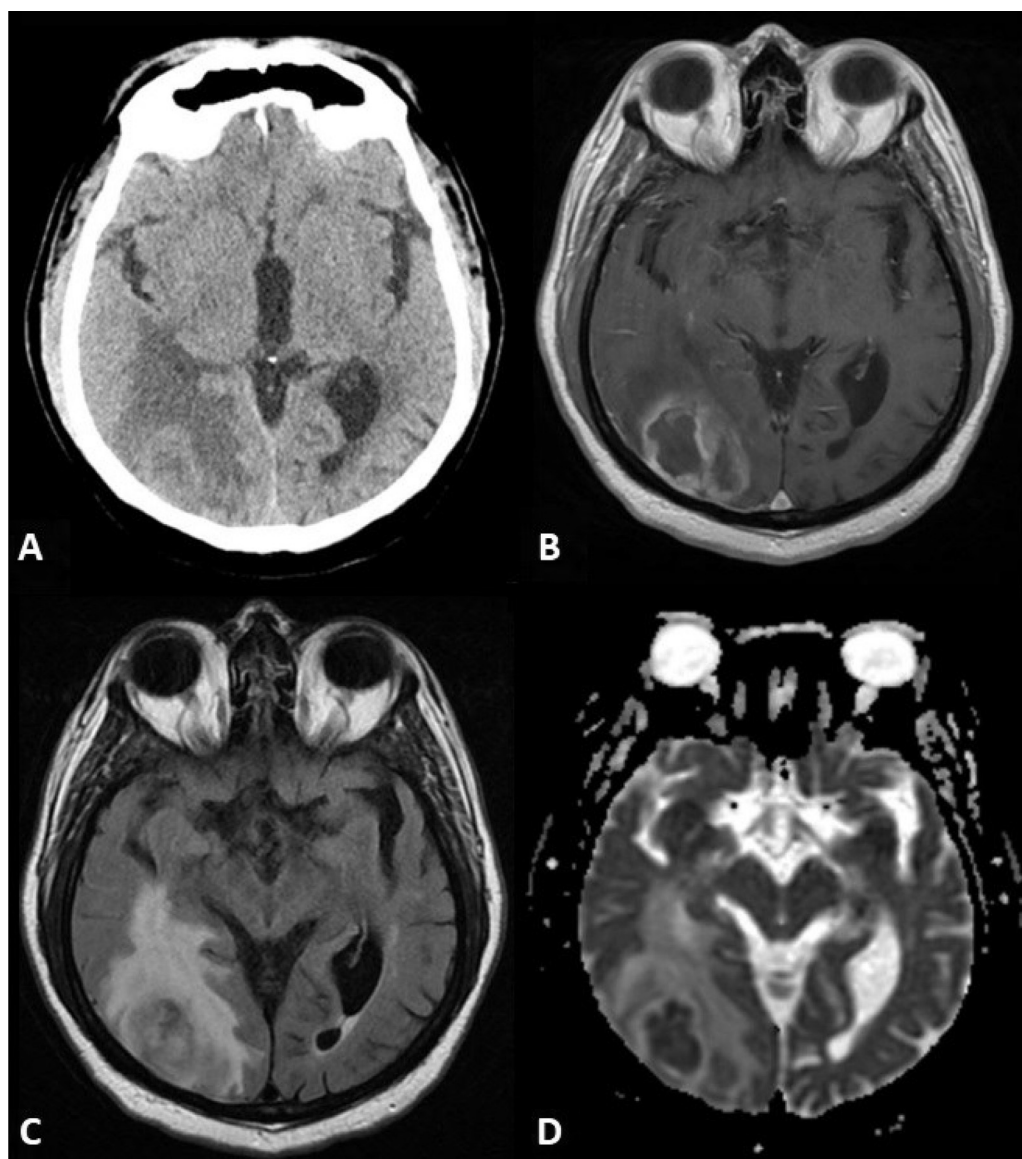


Fig. 1. (A-D) – Representative radiographic imaging. (A) Axial noncontrast CT shows a hyperdense ring lesion in the right occipital lobe surrounded by prominent edema. (B-D) Axial MRI images of the lesion. (B) Contrast-enhanced T1 weighted sequence shows a 4-cm ring-enhancing mass in the right occipital lobe. (C) FLAIR sequence displays prominent hyperintense edema surrounding the mass. (D) Apparent diffusion coefficient (ADC) map derived from diffusion weighted imaging displays hypointense signal in the central portion of the mass indicating low diffusivity, a finding that may correspond with necrotic material or purulence. The imaging-based differential diagnosis includes glioblastoma IDH-wild type, metastasis, abscess, and lymphoma. Ring enhancement in lymphoma typically occurs in immunocompromised patients.

mainly diffuse large B cell lymphoma. T-cell lymphomas, such as ALCL, account for only 2%-8.5% of primary CNS lymphomas [3,16]. Of primary CNS ALCL, ALK-positive tumors make up 70%-80% of cases [16]. Both ALK-positive and ALK-negative ALCL have a slight male predominance as well as similar CNS localization, occurring as single or multiple, usually supratentorial parenchymal lesions, sometimes with infratentorial involvement, and rarely involving the spinal cord [15]. Nevertheless, the epidemiology and prognosis of ALK-positive ALCL

differs from that of its ALK-negative counterpart. ALK-positive ALCL usually affects children and young adults with a median age of about 17-years-old and a long-term survival rate around 80%. In contradistinction, ALK-negative ALCL typically affects adults with a median age of 65-years-old and has a significantly worse long-term survival rate [2,15,16].

The genetics of ALK-negative ALCL are not well understood, but there are 2 recurrent and almost exclusive rearrangements that have been identified in this subtype. *DUSP22-*

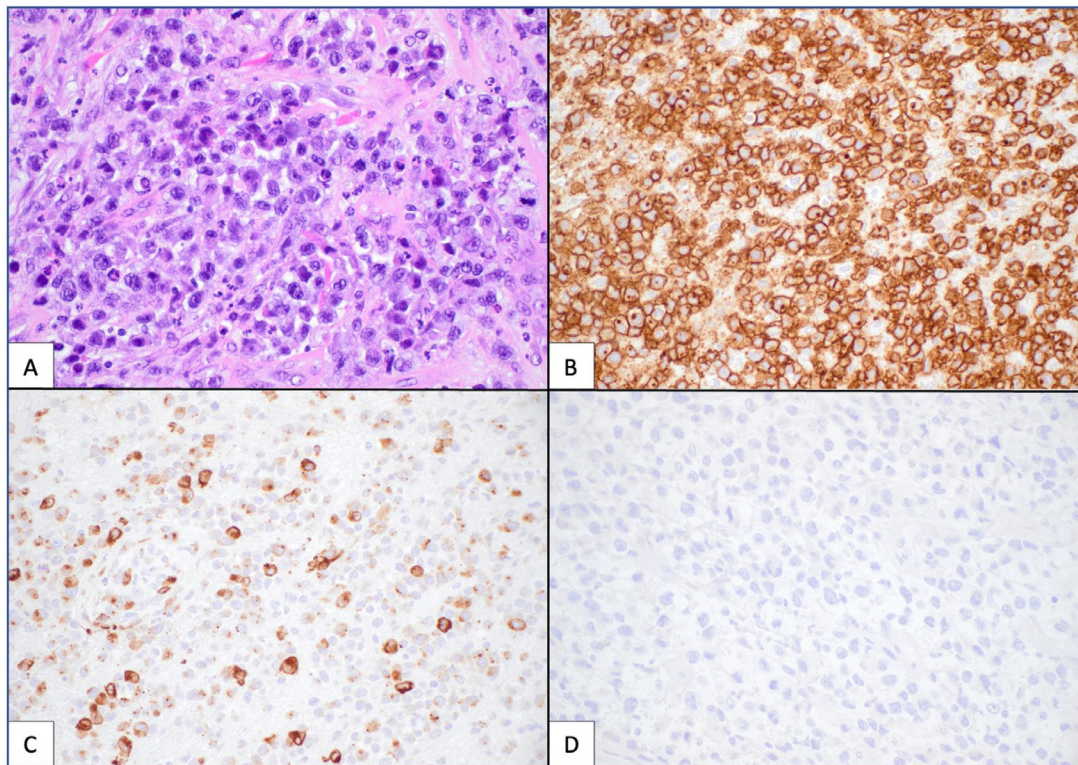


Fig. 2. (A–D) – Representative images of tumor histology. (A) Mitotically-active lymphoid proliferation with numerous large atypical lymphocytes including occasion horseshoe-shaped nuclei (hematoxylin and eosin). The large lymphocytes show diffuse positivity for CD30 (B) with a subpopulation positive for Granzyme B (C). (D) Stain targeting ALK protein is negative.

IRF4 and TP63 rearrangements have been documented; the former is more common and associated with a better prognosis, while TP63 rearrangements are much less frequent but portend heightened tumor aggressiveness [2,45,46]. However, a case reported by Magaki et al. [1] suggests that *DUSP22-IRF4* rearrangements may not always indicate a better prognosis, as their patient with a *DUSP22-IRF4* rearrangement was unable to undergo chemotherapy or radiation. The patient's lymphoma in the present case did not have a *DUSP22-IRF4* rearrangement, although his TP63 status is unknown. Further research with a larger number of patients is needed to draw more definitive conclusions about the correlation between *DUSP22-IRF4* rearrangements and prognosis in primary CNS ALK-negative ALCL.

In general, an intraparenchymal CNS lesion demonstrated on neuroimaging, particularly when found in an immunocompromised or elderly patient, raises the suspicion of Primary CNS lymphoma (PCNSL) and prompts a histologic diagnosis. PCNSL is typically not difficult to distinguish from secondary CNS lymphoma in that the latter is most commonly extra-axial (ie, leptomeningeal and/or dural-based) and PCNSL is most commonly intra-axial. PCNSL on conventional unenhanced CT shows iso- or hyperattenuated lesions, such as seen on our patient's initial imaging studies. Most of these lesions show some amount of contrast enhancement on CT and MRI. Using unenhanced T1-weighted MRI, these lesions are hypointense to gray matter. Lesional intensity varies on T2-

weighted MRI, though more than half are iso- to hypointense to gray matter [17].

PCNSL in immunocompetent patients can appear differently than those lesions arising in the immunocompromised. In the immunocompetent, PCNSL tends to appear as solid, often multifocal well-defined lesions with homogeneous contrast enhancement. PCNSL arising in the immunocompromised, especially those with human immunodeficiency virus (HIV) infection, frequently mimic toxoplasmosis, appearing as multiple nodular or ring-enhancing masses with edema and mass effect.

Although ALCLs are exceedingly rare among the primary CNS lymphomas, the handful of cases thus far reported in the literature do provide some insight into the spectrum of neuroradiologic findings which may be encountered. The neuroimaging of primary CNS ALK-positive ALCL [16–44] typically is that of a single, well-defined intraparenchymal brain mass characterized by homogeneous to heterogeneous enhancement and concomitant meningeal involvement. These findings are similar to those encountered with the more typical (diffuse large B cell) primary CNS lymphomas arising in the immunocompetent. On the other hand, case reports [1,3–14] (Table 2) of primary CNS ALK-negative ALCL have described lesions with more variable neuroimaging findings, including unifocality (47%), heterogeneous/amorphous enhancement (50%), and infrequent dural/leptomeningeal involvement (22%). Like most of the ALK-positive cases, ALK-

Table 2 – Overview of the reported cases of primary CNS ALK-negative ALCL in the literature, including our case.

Ref.	Patient age	Patient sex	Immune status	Tumor focality	Tumor location	Neuroimaging	Genetic testing
4	63	M	IC	Multifocal	Right fronto-parietal, dural involvement	3 well-delineated, heterogeneously enhancing lesions (MRI)	TCR beta chain PCR showing monoclonality
10	79	M	IC	Unifocal	Left parieto-occipital (dural involvement NR)	Heterogeneously enhancing lesion (MRI)	TCR C-beta-1 chain PCR showing monoclonality
3	19	M	IC	Multifocal	Left parieto-occipital, leptomeninges of cerebellum	Heterogeneously enhancing lesion (MRI)	NR
6	46	F	IC	Unifocal	Left parieto-occipital, dural involvement	Heterogeneous contrast uptake (CT)	TCR gamma chain PCR showing monoclonality
1	55	M	IC	Multifocal	Left cingulate, temporal, hippocampus, corpus callosum	Amorphous enhancement (MRI)	TCR PCR showing monoclonality; FISH DUSP22 showing an IRF4/DUSP22 rearrangement
7	82	F	NA	Unifocal	Tentorium cerebelli	Homogeneously enhancing lesion (MRI)	NR
9	46	M	ID	Unifocal	Right occipital (dural involvement NR)	Homogeneously enhancing lesion (MRI)	TCR gamma chain PCR showing monoclonality
11	65	M	IC	Unifocal	Floor of left middle cranial fossa, dural involvement	Homogeneously enhancing lesion (MRI)	NR
14	63	M	IC	Multifocal	Leptomeninges of spinal cord, brainstem, and cerebellum	Leptomeningeal enhancement (MRI)	NA
12	75	M	IC	Multifocal	White matter of bilateral cerebral hemispheres	Minimal enhancement (MRI)	NR
8	52	F	IC	Multifocal	Bilateral frontal (dural involvement NR)	Scattered ring-enhancing lesions (MRI)	NR
Current case	68	M	IC	Unifocal	Right occipital lobe	Ring-enhancing lesion	TCR gamma chain PCR showing monoclonality; FISH ALK rearrangement negative
5	66	F	ID	Unifocal	Right temporal	NR	NR
7	22	F	IC	Multifocal	Cerebellum, infratentorial	NR	NR
7	50	F	IC	Multifocal	Right parietal, supratentorial, dural involvement	NR	NR
13	61	F	NA	Multifocal	Diffuse, but not involving dura	NR	TCR gamma chain PCR showing monoclonality
13	62	F	ID	Unifocal	Right frontal	NR	NA

IC, immune competent; ID, immune deficient; NR, not reported; NA, not applicable; TCR, T-cell receptor; Ref., reference number.

negative case likewise show a predominance of supratentorial localization (70%). Other findings among these reported cases include a median age at diagnosis of 62 years (range: 19–82 years) and near equal male and female ratio. Furthermore, our case is the second example of primary CNS ALK-negative ALCL to present as a ring-enhancing lesion on MRI [8]. Both patients were immunocompetent; however, unlike the patient described by Tajima et al., our patient had only a solitary lesion.

In summary, we report a unique case of primary CNS ALK-negative ALCL arising in an immunocompetent adult as a solitary ring-enhancing lesion on neuroimaging studies. Our case, in combination with those from the handful of prior reported cases, calls attention to the neuroimaging diversity which may

be displayed by these rare tumors. Specifically, it emphasizes the need to consider primary CNS ALK-negative ALCL in the differential diagnosis of ring-enhancing lesions that may occur in immunocompetent adults.

Patient consent

I hereby confirm that the patient in this case report has provided informed consent for the publication of their medical information and related materials. The purpose, nature, and potential risks of the publication have been explained, and the patient has agreed to share their experiences with the medical community while ensuring their privacy and confidentiality.

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