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Primary Central Nervous System ALK-Negative Anaplastic Large Cell Lymphoma: A Case Report and Literature Review

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Abstract Primary central nervous system (CNS) lymphoma represents approximately 4% of CNS tumors, among which majority are originated from B-cells and only 2% from T-cells. Anaplastic large cell lymphoma (ALCL), a subtype of T-cell lymphoma, is classified into anaplastic lymphoma kinase (ALK)-positive and -negative subtypes. While the former accounts for 70-80% of cases, ALK-negative ALCL represents only a minority of cases. Here we present a case of primary CNS ALK-negative ALCL in a 73-year-old black male. He initially presented with significant fatigue and was treated for malaria with minimal improvement. He was subsequently found to have leukocytosis and developed left-sided weakness and facial droop. MRI showed a large temporoparietal intra-axial mass with vasogenic edema and mass effect. Initial brain biopsy was non-diagnostic. He was placed on steroids and pursued further workup in our institution. Upon tapering steroid, he developed left leg weakness. Repeat MRI revealed multiple intracranial lesions with one showing progression after steroid tapering. Repeat biopsy was performed and a diagnosis of primary CNS ALK-negative ALCL was rendered 47 days after the initial nondiagnostic biopsy. Literature review showed 39 reported cases of primary CNS ALCL, among which only 11 cases were ALK-negative. We present this case to demonstrate; a. the non- specific clinical presentation poses a diagnostic challenge. b. multiple intracranial lesions, along with waxing and waning clinical course with steroid administration, could be a sign of CNS lymphoma and c. biopsy prior to start of steroids is preferred for diagnosis.

Keywords: *ALK-Negative Anaplastic Large Cell Lymphoma*

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1. Introduction

Primary central nervous system (CNS) lymphoma refers to a lymphoma in the eye, brain, and spinal cord with no evidence of systemic disease. Among CNS tumors, primary CNS lymphoma represents approximately 4% of central nervous system tumors [1]. While majority of primary CNS lymphomas are B-cell lymphomas and approximately 95% are diffuse large B cell lymphoma [2,3,4], only approximately 2% of primary CNS lymphomas are T-cell lymphomas [5].

Anaplastic large cell lymphoma (ALCL), a subtype of T-cell lymphoma, is characterized by the CD30 positive large lymphocytes. This was initially introduced by using CD30 (Ki-1 clone) antibody to strongly highlight all or nearly all neoplastic cells in ALCL. Over 50% of CD30 positive lymphomas were also immunoreactive to T cell-associated antigen in the absence of B cell antigen [6]. Based on the expression of anaplastic lymphoma kinase (ALK), ALCL is further subclassified into ALK-positive and ALK-negative subtypes. ALK-positive ALCL represents approximately 70-80% of cases and is well characterized by translocation of t (2; 5) (p23; q35) resulting in a fusion of nucleolar phosphoprotein 1 gene and the ALK tyrosine kinase gene [7] and is often associated with better prognosis. However, multiple layers of facts make primary CNS ALK-negative ALCL an extremely rare entity [8]. It has been reported that DUSP22 rearrangements were associated with favorable outcomes TP63 rearrangements encoding p63 fusion proteins were associated with aggressive clinical behavior and poor outcomes [9,10]. Here we present a case of primary CNS ALK-negative ALCL.

2. Case Report

A 73-year-old African man with past medical history of prostate cancer status post radical prostatectomy in 2013, presented with significant fatigue in January 2021. Further infectious workup was negative including COVID-19 but his clinical presentation was consistent with active malaria infection. He was treated for malaria twice with minimal relief of symptoms and was hospitalized during the second treatment where he was found to have leukocytosis. He also developed left-sided weakness with facial drop and MRI demonstrated a large, temporoparietal intra-axial mass with vasogenic edema, mass effect, and midline shift with patchy contrast enhancement. Imaging studies including the thyroid, abdomen and pelvic did not reveal any primary site for malignancy. Initial stereotactic brain biopsy was nondiagnostic. He was placed on steroids and pursued further workup of right intracranial lesion at our institution. An outside MRI was reviewed at our institution demonstrating large area of ill-defined hyperintensity in the right cerebral hemisphere involving subcortical white matter on the right basal ganglia with increased mass effect. He was started dexamethasone taper, and repeat MRI showed the amount of enhancement is decreased compared to the previous MRI. PET scan was negative for disease outside the brain. Infectious disease studies including SARS-CoV-2, *nocardia*, Epstein-Barr virus (EBV), syphilis, *cryptococcus*, mycobacteria, and toxoplasma gondii were negative. He later developed left leg weakness and repeat MRI showed newly developed increased size of multiple enhancing nodules in the right periventricular region (Figure 1A) with the largest lesion measuring 15 mm in diameter and additional new punctate enhancing lesion in the left periventricular white matter. He was referred for repeat brain biopsy. This second brain biopsy demonstrated anaplastic large cell lymphoma, ALK-negative. Due to lack of evidence for a systemic disease and multiple socio-economic factors such as age, insurance coverage, immigration status, and available treatment options, whole-body irradiation followed by brentuximab vedotin, cyclophosphamide, hydroxydaunorubicin (doxorubicin), and prednisone was considered. He completed whole-body irradiation. On the most recent follow-up, the patient reported that he felt stronger after radiation but more recently weaker using a wheelchair with one episode of dizziness, with no residual toxicities noted. Review of MRI and laboratory findings did not reveal evidence of lymphoma (Figure 1B); therefore, patient was placed on surveillance. The patient has been doing relatively well, now at approximately 7 months post-diagnosis and 6 months post-irradiation.

Microscopic evaluation of the resected brain lesion as demonstrated in Figure 2 shows fragments of brain tissue with multifocal and perivascular infiltrates of malignant cells which are medium to large-sized with some containing multilobate/multiple nuclei. The tumor cells are positive for CD30 (strong and diffuse with membranous and Golgi staining patterns), CD2, CD4, CD25, MUM1, TIA1 (subset) and granzyme B (subset); negative for CD45, CD43, B-cell markers (CD19, CD20, PAX5, and CD79a), CD3, CD5, CD7, CD8, CD10, CD56, perforin, EMA, CD138, and CD68. ALK is negative. EBV is negative. Cytokeratin marker AE1/3, melanoma markers including Melan-A and S100 are negative. The Ki67 proliferation index is up to 80%. FISH studies of DUSP22 or TP63 gene rearrangement are negative.

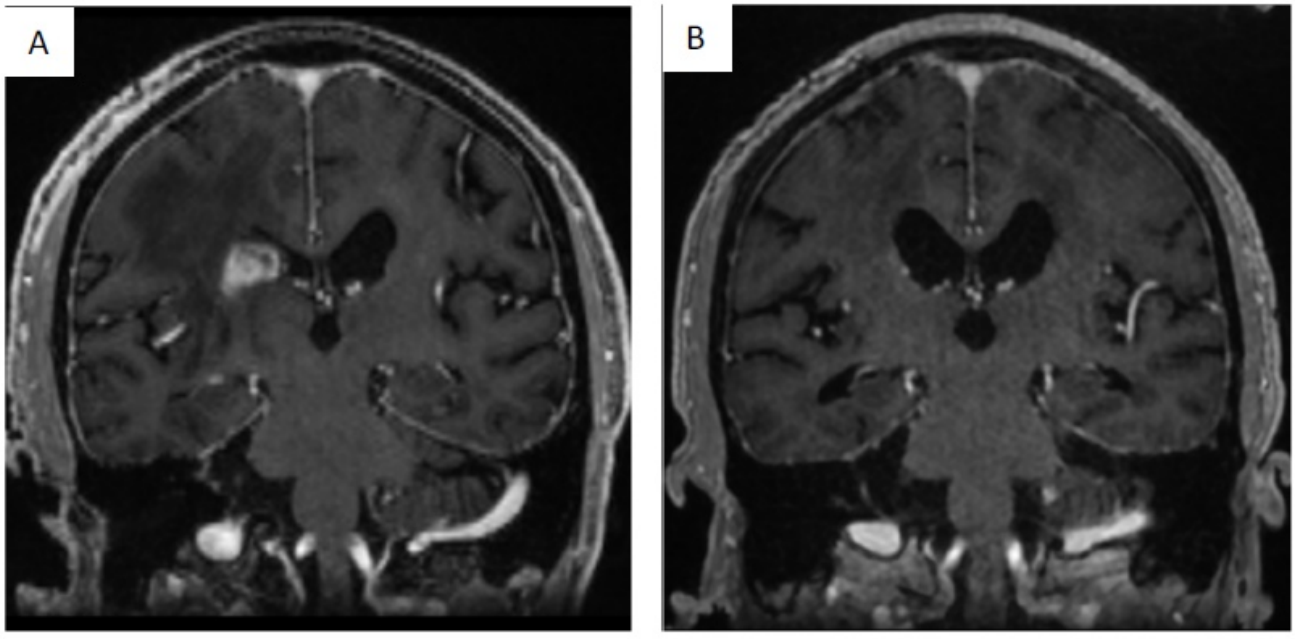

Figure 1. MRI Images of primary CNS ALK-negative anaplastic large cell lymphoma. A. Repeat MRI after steroid tapering shows multifocal contrast enhancing lesions involving the right periventricular region. B. Repeat MRI two month after radiation shows no evidence of residual/recurrent contrast enhancing lesions

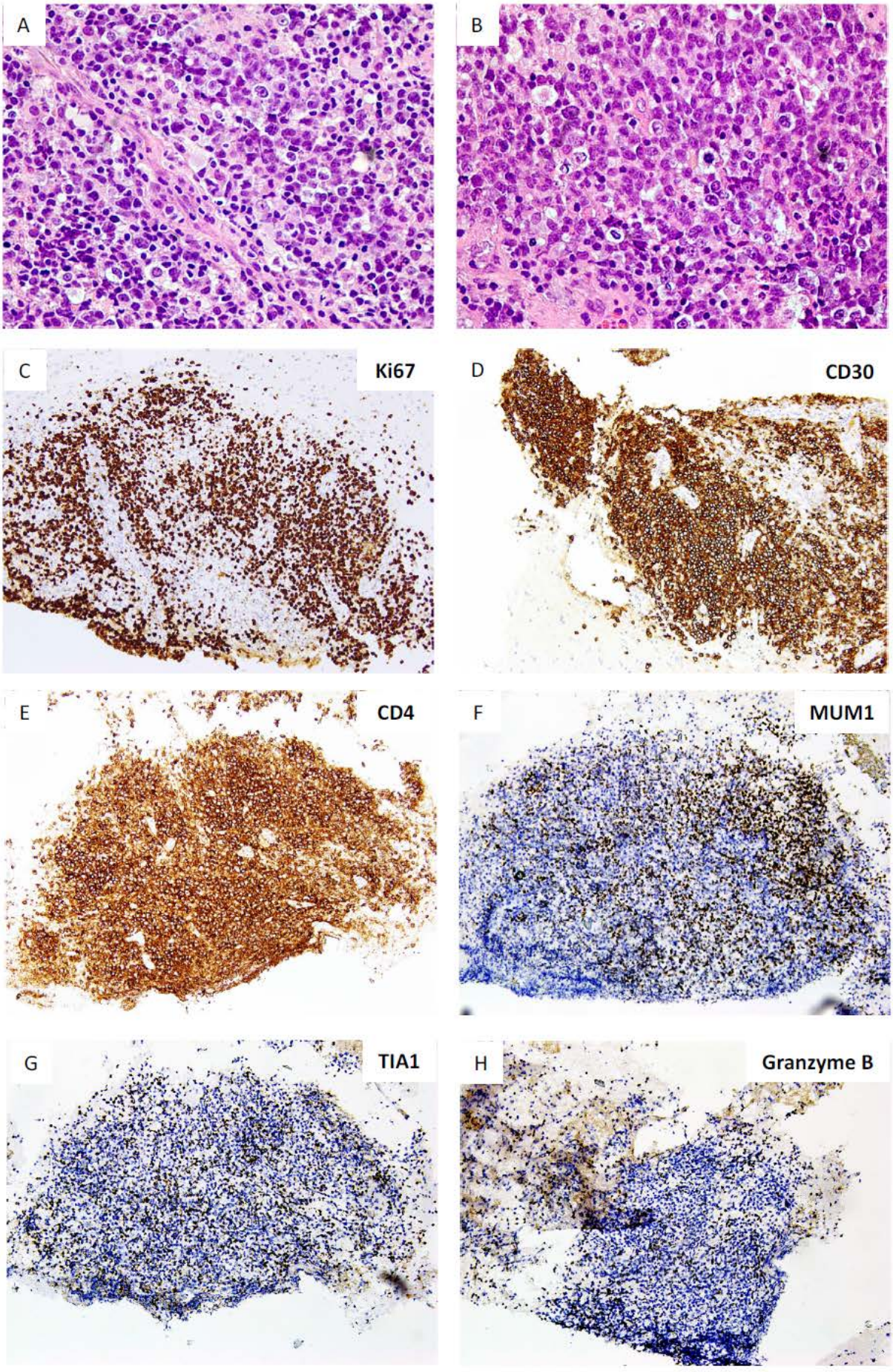

Figure 2. A-H

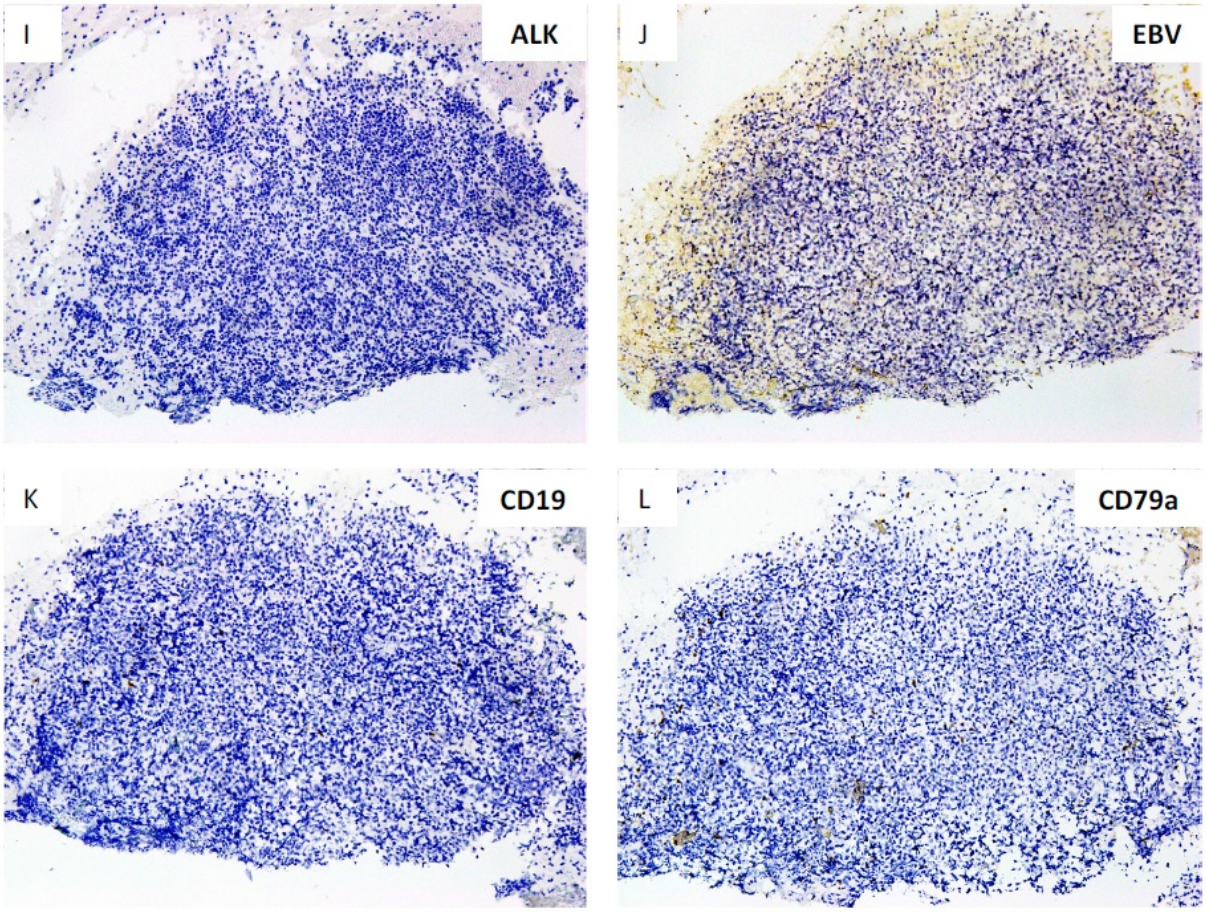

Figure 2. Images of primary CNS ALK-negative anaplastic large cell lymphoma. Brain lesion resection shows fragments of brain tissue with multifocal and perivascular infiltrates of medium to large-sized malignant cells, some with multilobate/multiple nuclei (A and B). They are mitotically active highlighted by Ki67(C), positive for CD30 (D), CD4 (E), MUM1 (F), TIA1 (G), and Granzyme B (H), and negative for ALK (I), EBV (J), CD19 (K), and CD79a (L). TIA1: T-cell intranuclear antigen 1

3. Discussion

Primary CNS ALCL is a rare entity, literature review showed only 39 reported cases in the current literature [11-46] (Table 1) with 28 cases ALK-positive ALCL, and 11 cases ALK-negative ALCL. These patients' age ranged from 22 to 82 with median of 63-year-old. Based on the reported 11 cases, CNS ALK-negative ALCL exhibited a male propensity (8/11, 72.7%); usually multifocal (6/11, 54.5%); and displayed a diverse prognosis with 8 patients passed away after 11 days to 8-month of follow-up, and 3 cases with no evidence of residual disease after 2 courses of chemotherapy, at 18- and 25-month follow-up.

Here we presented the 12th CNS ALK-negative ALCL case from a 73-year-old male patient from Africa. Rendering such a diagnosis is challenging and it took 47 days from the initial nondiagnostic brain biopsy to the repeat brain biopsy in the US, not to mention if the time required for diagnosis were calculated from the onset of early symptoms presented months earlier. The reported time required to make the diagnosis of this rare entity is an average of approximately 40 days [46]. One reason for such a challenging diagnosis may be due to the nonspecific symptoms like fatigue that our patient presented with initially, followed by left-sided weakness and facial drop. The nonspecific presentation is in line with the reported clinical symptoms from patients with final diagnosis of CNS ALK-negative ALCL including headache, blurry vision, hemiparesis, ataxia, leg weakness, memory loss, and dementia-like symptoms [11-46].

Chart review of this current case revealed that patient was started on steroids and the initial brain biopsy was nondiagnostic. He was referred to our institution for further workup. His steroids were tapered after which he developed left leg weakness and repeat MRI showed progression of one of the intracranial lesions. A repeat brain biopsy was performed and a diagnosis of ALK-negative ALCL was confirmed. The similar clinical temporal course was also reported by Lannon et al [46]. In that report, patient was discontinued on steroids and developed new onset of tingling in both hands and feet and the return of multiple intracranial abnormalities. After re-administration of steroids, MRI showed near-complete resolution of intracranial enhancement. However, patient's clinical symptoms aggravated, and MRI showed spinal disease with significant mass effect after two weeks of discontinuation of steroids. Then the patient underwent surgery of laminectomy and resection of the lesion from which a diagnosis was reached.

In terms of the location of the intracranial lesions, this current patient was initially found to have lesions located at temporoparietal and frontal regions. This is in accordance with previously reported parietal/frontal/occipital (6/11, 54.5%) lobes of the cerebrum [15,37,39-46]. Our current case did not show meningeal involvement, which may add inflammatory processes such as meningitis or sarcoidosis,

meningioma into the differential diagnoses. It has been reported that two cases with CNS ALK-negative ALCL had dura involvement [15] and majority of cases with CNS ALK- positive ALCL had meningeal involvement and some were treated with antibiotic and anti-tuberculosis regiments [12,13,14,16,19,21,22,28,30,31,36]. And the current patient was treated with anti- malaria therapy initially in Africa.

Table 1.

Cases	Age/sex	ALK	Location	No.of lesions	Clinical data	Primary diagnosis	Ref.
1	4/F	Pos	Brain stem and spinal cord	M	Nausea, vomiting, headache, and neck stiffness	Mycobacterial	[13]
2	10/F	Pos	Parietal	S	Sensory change	Data not available	[11]
3	13/M	Pos	Frontal and parietal	M	Vomiting and headache	Mycobacterial	[16]
4	29/M	Pos	Frontal and temporal	M	Fever, seizures and headache	Meningitis	[14]
5	17/M	Pos	Parietal	S	Data not available	Data not available	[15]
6	18/F	Pos	Temporal	M	Data not available	Data not available	[15]
7	17/M	Pos	Frontal and parietal	M	Seizure, headache and hemiparesis	Mycobacterial	[12]
8	39/M	Pos	Parietal and occipital	S	Seizures	Headaches	[17]
9	38/M	Pos	Parietal and occipital	S	Ataxia, visual defect, seizures and hemiparesis	PCNSL or glioblastoma	[20]
10	4/M	Pos	Fronal, parietal and pineal	M	Altered mental status and seizures	Meningitis	[19]
11	13/M	Pos	Frontal	S	Nausea and headache	Meningitis	[23]
12	9/M	Pos	Frontal	M	Altered mental status	Meningitis	[21]
13	1/M	Pos	Dura	S	Motor function loss and lethargy	ALCL	[24]
14	20/M	Pos	Sylvian fissue	S	Seizures	ALCL	[18]
15	30/M	Pos	Parietal and occipital	S	Headache	PCNSL or meningioma	[26]
16	20/M	Pos	Frontal	S	Seizures	High grade glioma	[25]
17	31/M	Pos	Leptomeningeal	S	Headache and altered mental status	Meningitis	[22]
18	10/M	Pos	Frontal	S	Hemiparesis and aphasia	Meningitis	[28]
19	11/M	Pos	Parietal	S	Nausea and headache	Meningitis	[30]
20	19/M	Pos	Cerebellum	S	Vomiting and headache	Tumor	[29]
21	18/M	Pos	Parietal and occipital	S	Headache, fever and seizures	Tumor	[33]
22	34/M	Pos	Spinal cord	M	Vomiting, headache and diplopia	Mycobacterial	[31]
23	26/M	Pos	Intravewntricular	S	Ptosis and diplopia	Tumor	[34]
24	21/M	Pos	Frontal and parietal	S	Fever, headache and seizures	Tumor	[27]
25	8/M	Pos	Parietal	S	Fever, vomiting, dizziness, cognitive impairment and convulsions	Viral encephalitis	[36]
26	26/M	Pos	Occipital	S	Blurry vision and headache	Meningioma	[35]
27	12/M	Pos	Parietal	S	Seizures and headache	PCNSL or meningioma	[32]
28	12/M	Pos	Occipital	M	Vomiting and headache	Tumor	[38]
29	63/M	Neg	Frontal and parietal	M	Data not available	Tumor	[40]
30	46/F	Neg	Parietal and occipital	S	Blurry vision, hemiparesis and headache	Tumor	[39]
31	22/F	Neg	Temporal and cerebellum	M	Data not available	Data not available	[15]
32	50/M	Neg	Parietal	M	Data not available	Data not available	[15]
33	82/M	Neg	Posterior fossa	S	Data not available	Data not available	[42]
34	52/F	Neg	Frontal	M	Hemiparesis	leukoenchephalopathy	[41]
35	46/M	Neg	Occipital	S	Ataxia	Tumor	[45]
36	79/M	Neg	Parietal and occipital	S	Symtoms of dementia	Tumor	[37]
37	65/M	Neg	Temporal	S	Blurry vision and headache	Meningioma	[44]
38	75/M	Neg	Hemispheres	M	Dementia	Tumor	[43]
39	63/M	Neg	Intraspinal and intracranial	M	Leg weakness	Lymphoma or sarcoidosis	[46]
New case	73/M	Neg	Frontal, parietal and temporal	M	Fatigue, weakness and facial drop	Malaria	

Pos: positive; Neg: negative; M: multiple; S: single; Ref: references; PCNSL: primary central nervous system lymphoma; ALCL: anaplastic large cell lymphoma

While the correlation of EBV with B-cell lymphoma has been documented, the convincing evidence of correlation between infection of EBV or human T-cell leukemia virus and the development of ALCL is lacking and pathogenesis of ALCL is not fully elucidated. The fusion of ALK, initially identified in 1994, with nucleolar phosphoprotein 1 gene in the t (2;5) (p23; q35) is associated with majority of ALK-positive ALCL [7]. This fusion results in activation of diverse pathogenic signaling pathways including RAS-extracellular signal regulated kinase pathway, Janus kinase 3-STAT3 intracellular pathway, and phosphoinositide 3-kinase-Akt pathway to facilitate cell survival, proliferation, cell cycle progression, and tumorigenesis [47]. However, on the other hand, the molecular basis of ALK-negative ALCL has been unclear. Studies have demonstrated that rearrangement phosphatase gene DUSP22 due to t (6;7) (p25.3; q32.3) resulting in down-regulation of DUSP22, the function of which in ALK-negative ALCL is poorly understood, and it has been proposed that it is worthwhile to investigate if DUSP22 serves as a putative tumor suppressor [48]. In addition, rearrangement of TP63 leads to inhibition of the p53 pathway and tumorigenesis [10]. And the rearrangement of DUSP22 and TP63 are mutually exclusive and are absent in ALK-positive ALCL with DUSP22 having as favorable outcome as ALK-positive ALCL, and TP63 rearrangement having inferior outcomes. Similarly, DUSP22 has been reported to be associated with better outcome of ALK-negative ALCL. But TP63 rearrangements has been reported to be associated with worse outcome of ALK-negative ALCL [9]. Furthermore, constitutive activation of Janus kinase 3-STAT3 pathway is also implicated in the oncogenesis of ALK-negative ALCL [49]. These rearrangements suggest that ALK-negative ALCL is a heterogeneous disease genetically and shows wide range of outcome clinically and may be utilized as predicative biomarkers to guide management decision making [50]. Rearrangement of DUSP22 and rearrangement of TP63 were performed for this case and were both negative. The patient is relatively doing well at 6 months post-diagnosis.

4. Conclusion

The current case, to our best knowledge, is the 12th case diagnosed with this rare entity of primary CNS ALK-negative ALCL. There are only 39 cases of primary CNS ALCL in the literatures with 28 cases of ALK-positive ALCL and 11 cases of ALK-negative ALCL. This case is in line with the previous reports in several aspects including the age, gender, location, focality, the time required to render the final diagnosis, and the effect of steroids on the lesions posing diagnostic challenges. It is suggested that when encountering patients with multiple intracranial lesions, waxing and waning clinical course after steroids administration and cessation, ALCL needs to be considered in the differential diagnosis. If clinically appropriate, biopsy/prior to steroids treatment is recommended to make earlier diagnosis.

Abbreviations

CNS: Central nervous system
ALK: Anaplastic lymphoma kinase
ALCL: Anaplastic large cell lymphoma
COVID-19: Coronavirus disease 2019
TIA1: T-cell intranuclear antigen 1
MUM1: Multiple myeloma oncogene 1
EMA: Epithelial membrane antigen

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