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Case Report

Inflammatory myofibroblastic tumors of the central nervous system that express anaplastic lymphoma kinase have a high recurrence rate

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Abstract

Background: Inflammatory myofibroblastic tumors (IMTs) of the central nervous system (CNS) are rare entities with diverse histopathological features and varying propensities to recur.

Case Description: A 26 year-old male with an IMT of the CNS of the left tentorium had tumor progression 2 months after partial surgical resection. Histopathological studies confirmed expression of ALK. Macroscopic total resection was performed followed by radiotherapy. A recurrence occurred 20 months after the second surgery that necessitate reoperation. Including the present case, we identified 30 cases of IMT of the CNS corresponding to our search criteria in the literature. The extent of resection was reported in 26 of these cases. Gross total resection was done in 75% of ALK-positive and in 61% of ALK-negative cases. Recurrence rate after gross total resection for ALK-positive and ALK-negative cases was 33% and 9%, respectively. Every recurrence in ALK-positive patients occurred within 2 years after surgery.

Conclusion: IMT of the CNS are a heterogeneous group of tumors and the treatment of choice is complete surgical resection. Because of the high recurrence rate reported for IMT of the CNS expressing ALK, a closed follow-up is recommended. When faced with an early recurrence, a surgical resection followed by radiotherapy may be advised.

Key Words: Anaplastic lymphoma kinase, fibrohistiocytic, inflammatory myofibroblastic tumor, pseudotumor, plasma cell granuloma, recurrence

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INTRODUCTION

Inflammatory myofibroblastic tumor (IMT) is a rare neoplasm composed of myofibroblastic spindle cells, accompanied by an inflammatory infiltrate of plasma cells, lymphocytes, and eosinophils.[5] This tumor is usually found in the lung or abdomen of children and young adults.[8] Its occurrence in the central nervous system (CNS) is rare. Here, we report a case of IMT of the CNS expressing anaplastic lymphoma kinase (*ALK*) with an aggressive pattern of recurrence despite macroscopic total resection and radiotherapy. We performed a literature review to determine features of IMTs of the CNS that may be associated with tumor progression.

CASE REPORT

History and examination

A 26-year-old right-handed male presented with a 3-month history of mild headaches and blurred vision. He had a 10-year history of tobacco use. There were no other neurological symptoms. Neurological exam was normal except for right homonymous hemianopia. A contrast-enhanced computed tomography (CT) scan revealed an enhancing left temporal mass. Magnetic resonance imaging (MRI) showed a gadolinium enhancing extra-axial tumor, originating from the left tentorial incisure. The lesion had a supratentorial extension with significant mass effect and peri-lesional edema in the left temporal lobe [Figure 1]. Cerebral angiography demonstrated a poorly vascularized tumor. The preliminary diagnosis was that of a tentorial meningioma.

Operation

In order to prevent retraction of the temporal lobe and stretching the vein of Labbe, a supracerebellar transtentorial approach in the park-bench position was performed. Incision of the thickened posteromedial part of the left tentorium revealed a yellowish and fibrous tumor. The tumor was resected using standard microsurgical technique including intracapsular debulking and extracapsular dissection.

Postoperative course

No new neurological deficit was found after the surgery. Immediate postoperative CT showed a 2.0 × 1.5 × 1.0 cm tumor remnant involving the lateral border of the tentorium [Figure 2]. The patient was discharged without steroids 1 week after the operation.

Pathological findings

Histopathological examination showed a predominance of spindled myofibroblasts arranged into fascicles surrounded by a diffuse inflammatory infiltrate of lymphocytes and plasmocytes [Figure 3]. This confirmed the diagnosis of IMT. Mitotic activity was evident and the proliferative index was estimated to be 20%. *ALK* expression was strongly positive. Knowing that some of these lesions might recur after many years, we opted for a close follow up.

Second operation and outcome

The patient presented 2 months later with a new episode of headache and transient aphasia. A second MRI [Figure 4] showed significant local tumor progression. Gross total resection was achieved through a supratentorial approach for the lateral aspect of the tumor and through an infratentorial approach for its medial part. There was no neurological deterioration and a radiotherapy treatment of 60 Gy in 30 fractions was promptly started after discharge. MRI taken 3 [Figure 5], 6, and 10 months after the second surgery showed no residual lesion.

Third operation and outcome

Twenty months after his second surgery, the patient presented with aphasia, inappropriate laughter and increased aggressiveness. A head CT-scan with contrast showed a local recurrence with infra- and supratentorial extension [Figure 6a and b]. The previous craniotomy was enlarged and a mastoidectomy was done to expose the transverse, sigmoid, and superior petrosal sinuses. The tumor was dissected from the temporo-occipital and cerebellar parenchyma and excised. Medial transverse sinus tumoral infiltration was macroscopically totally removed. Immediate and 2 months postoperative CT-scan with contrast showed no residual tumor. Pathological findings did not differ from the first surgery.

MATERIALS AND METHODS

To establish prognostic factors for IMT of the CNS aggressiveness, we searched the PubMed database using "myofibroblastic," "pseudotumor," "central nervous system," "*ALK*," and "recurrence" as search terms. We restricted our analysis to include only papers that investigated *ALK* expression by immunohistochemistry or fluorescence *in situ* hybridization (FISH). We based our review on articles that presented IMTs of the CNS cases investigated for *ALK* expression, since previous reports of extra-CNS IMTs have suggested that this gene could lead to a more aggressive course.[3,6]

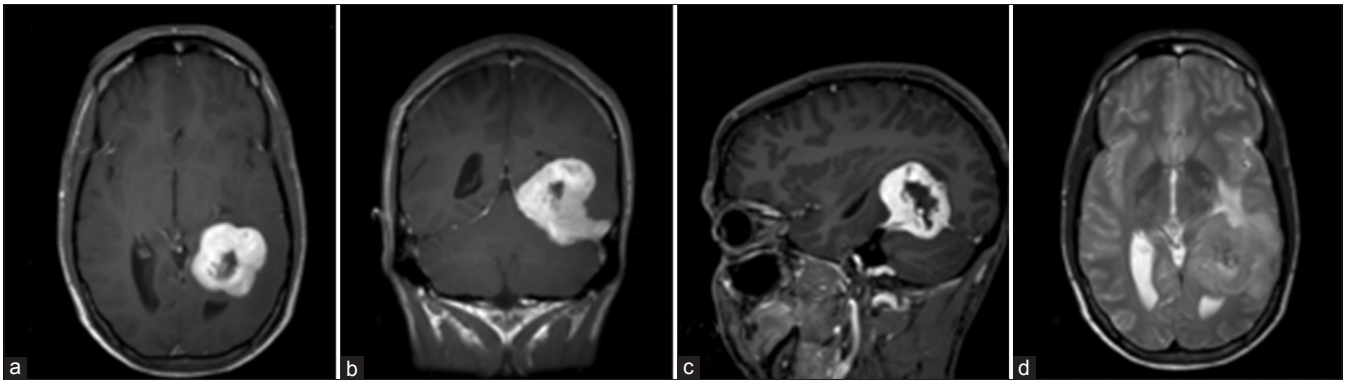

Figure 1: Preoperative axial (a), coronal (b) and sagittal (c) T1-weighted MRI studies showing a gadolinium enhancing extra-axial mass of the left tentorial incisure. Temporal lobe edema is seen on the axial T2-weighted MRI studies (d)

RESULTS

Including our patient, we identified 30 cases of IMTs of the CNS investigated for *ALK* expression and followed for recurrence.[2,4,8-11,13,14,17,18] Six of the 30 cases (20%) presented with recurrence during a mean follow-up of 5.5 years [Table 1]. The extent of resection was reported in 26 cases [Table 2]. Most cases received gross total resection and nine cases received subtotal resection. The recurrence rate after gross total resection for *ALK*-positive and *ALK*-negative cases was 33% and 9%, respectively. No tumor progression was reported in six of the seven *ALK*-negative cases that had subtotal resection, whereas tumor progression was seen in every ALK-positive case that received subtotal resection.

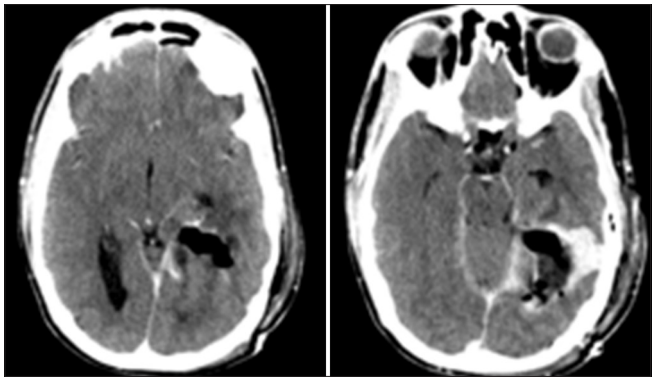

Figure 2: Postoperative axial CT-scan with contrast after a partial resection of the tumor through a supracerebellar-transtentorial approach

Eight of the 16 cases with the fibrohistiocytic (FHC) variant (50%) were positive for *ALK*, but none of the cell granuloma-like (PCG-like) type cases showed this feature. All *ALK*-positive cases reported had a nodular morphology. Most *ALK*-positive tumors were supratentorial dural-based lesions, but one case was in the third ventricle near the pineal region[2] and one case was intradural and extramedullar in the thoracic spine.[13] All first recurrence in *ALK*-positive patients was noted early during the first 2 years after surgery. Recurrence of *ALK*-negative cases, by contrast, appeared between 7 and 12 years after initial surgery and at a different brain region.[10]

DISCUSSION

IMT is a rare tumor that can exceptionally be found in the CNS. This tumor's rarity, its various histopathological characteristics and its variable aggressive course render it difficult to diagnose and treat. Characteristics of tumor aggressiveness have not been systematically evaluated for IMT of the CNS. We sought to assess and further identify possible prognostic factors for tumor progression and recurrence through an analysis of previously published cases of IMT of the CNS.

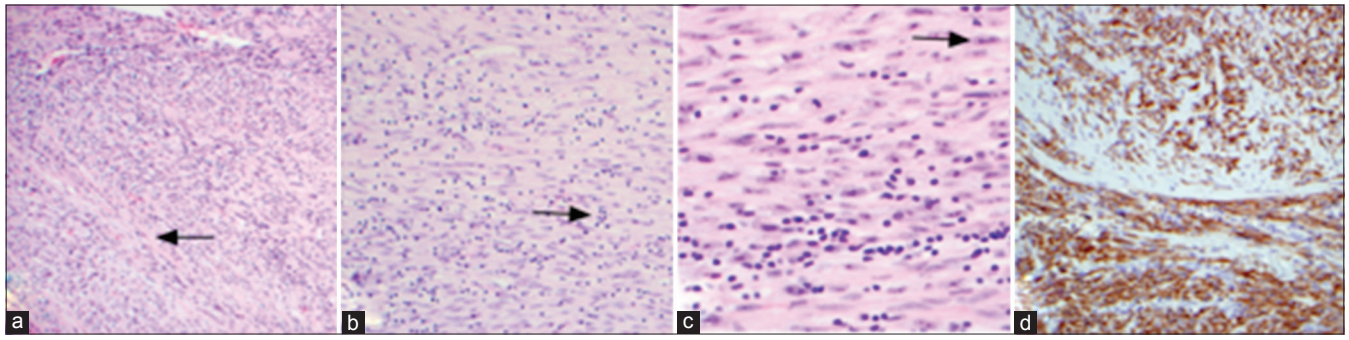

Figure 3: Histologic appearance of IMT of the CNS. (a) Fusiform cells organized in perpendicular oriented fascicules (arrow) (×100). (b) Diffuse lymphocytes and plasmocytes infiltrate (arrow) (×200). (c) Tumor cells have an oval shape nucleus, pale chromatin and a big purple nucleolus. Mitosis is seen (arrow) (×400). (d) ALK expression by tumor cells (×200)

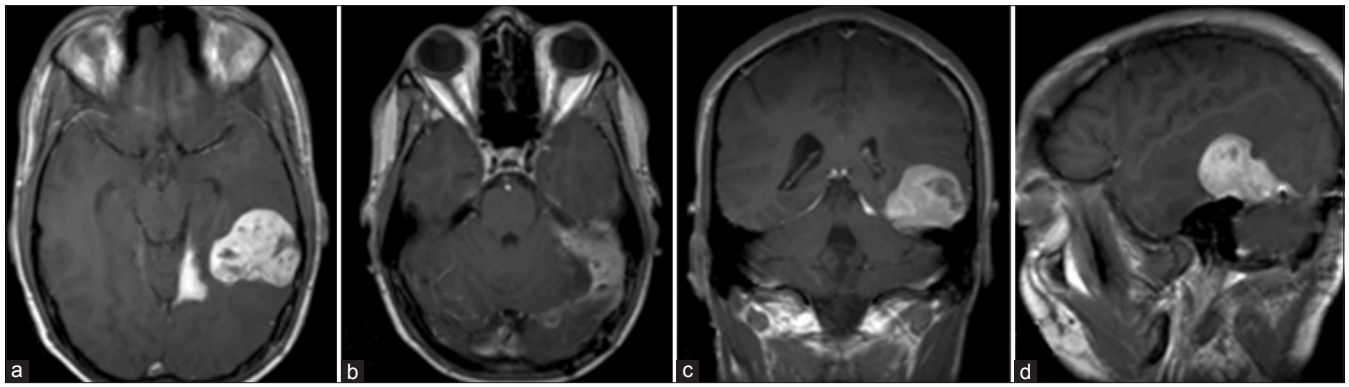

Figure 4: Axial (a and b), coronal (c) and sagittal (d) postgadolinium T1-weighted MRI studies showing tumor progression 2-months following surgery

Table 1: Characteristics of six patients with recurrent IMT of CNS investigated for ALK positivity

Authors and year	Age (years), sex	Morphology	Location	Histopathology	ALK	Extent of resection	Time to recurrence	Follow up (years)
Hausler *et al*. 2002	17, F	Nodular	Extra-axial, left frontal	FHC	+	Total for both surgeries	2 and 5 years after 1st surgery	5
Lacoste-Collin *et al*. 2003	22, M	Nodular	Indradural, extramedullary, partially intramedullary, thoracic spine (T9)	FHC	+	Sub-total	1 year after 1st surgery	2
Jeon *et al*. 2005	65, F	Nodular	Occipital area	FHC	–	Total	7 years after 1st surgery	7
	43, M	En plaque	Orbit, falx, superior sagittal sinus, tentorium and mastoid with brain invasion	PCG-like	–	Sub-total for both surgeries	12 and 15 years after 1st surgery	15
de Oliveira *et al*. 2009	7, M	Nodular	Right temporal fossa, associated with prior VP shunt installation	FHC	+	Total	2 years after 1st surgery	2
Present case	26, M	Nodular	Left tentorial incisura and posterior temporal lobe	FHC	+	Partial for 1st and total for 2nd surgery	2 months and 2 years after 1st surgery	2

CNS: Central nervous system, F: Female, FHC: Fibrohistiocytic variant, IMT: Inflammatory myofibroblastic tumor, M: Male, PCG-like: Plasma cell granuloma like type, VP: Ventriculoperitoneal

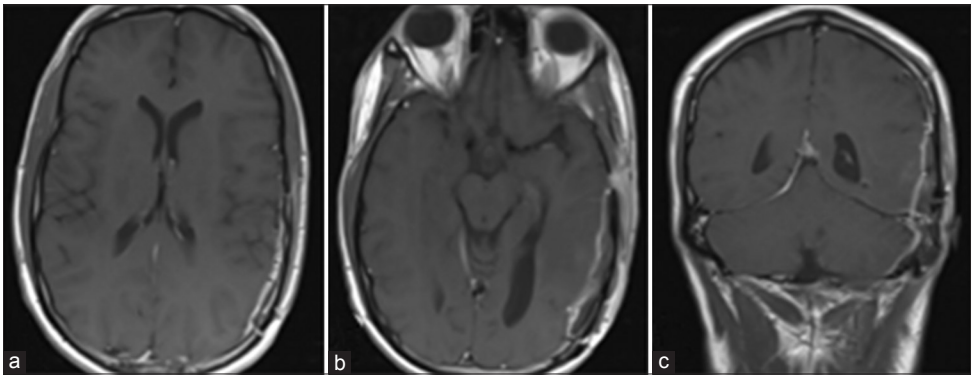

Figure 5: Axial (a and b) and coronal (c) post-gadolinium T1-weighted MRI studies performed 3 months after showing no recurrence after the second surgery and one cycle of radiotherapy

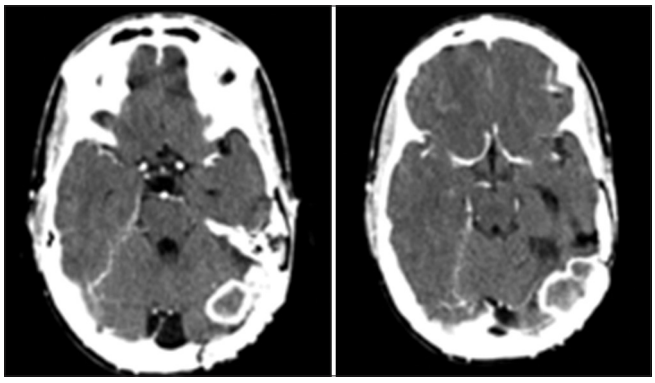

Figure 6: Axial head CT-scan with contrast showing tumor recurrence 20 months after the second surgery

Over the past 20 years, some 100 sporadic cases of IMTs of the CNS have been reported, sometimes with different nomenclature such as "inflammatory pseudotumor" (IP) or "plasma cell granuloma".[5,8] Theses lesions are predominantly extra-axial, occurring as dural-based nodular or en plaque-like lesions, and have a predilection to involve the mastoid and the orbit.[10] Most are meningeal lesions that can invade the brain tissue, whereas some are purely intraparenchymal or intraventricular.[8,14] Intradural spinal lesions have been described with or without intramedullary involvement.[10,13] Clinical manifestation with multiple synchronous lesions involving different levels of the neuraxis is another possibility.[1,9] Based on radiology, the differential diagnosis for intracranial IMTs includes meningioma, plasmacytoma, lymphoma, and idiopathic hypertrophic pachymeningitis.[12]

IMTs of the CNS can be classified into two histopathological types: A form rich in spindle myofibroblasts mixed with few inflammatory cells, also called the FHC variant, and the PCG-like type composed mainly of plasma cells and lymphocytic infiltration.[10,14,18] Recent case series proposed that the two types are different in terms of tumor aggressiveness.[10,14,18] The FHC variant often contains clonal

Table 2: Characteristics for 26 cases of IMT of the CNS investigated for ALK positivity and tumor progression

Variable	ALK positive	ALK negative
No. of cases	8	18
Mean age (years)	33.6±24.5	41.6±17.7
Sex (no. of patients)		
Male	3	11
Female	5	7
Morphology		
Nodular	8	13
En plaque	0	5
Histopathology		
FHC	8	8
PCG-like	0	10
Extent of resection		
Sub-total	2	7
Tumor progression rate	100%	14%
Total	6	11
Tumor progression rate	33%	9%

FHC: Fibrohistiocytic variant, PCG-like: Plasma cell granuloma like type, ALK: Anaplastic lymphoma kinase, IMT: Inflammatory myofibroblastic tumor, CNS: Central nervous system

rearrangements in chromosome band 2p23, that constitutively activate the *ALK* gene.[7] *ALK* is a tyrosine kinase receptor that is normally expressed in the developing CNS.[19] In IMTs located outside of the CNS, investigators have reported several fusion genes that render *ALK* oncogenic.[20] In addition, *ALK* rearrangements with specific fusion genes have been reported in other types of cancer such as anaplastic large cell lymphoma, nonsmall cell lung cancer and renal medullary carcinoma.[15] To our knowledge, no *ALK* fusion gene has yet been identified in IMTs of the CNS.

From this review, we conclude that IMT of the CNS that express *ALK* can have an aggressive course despite gross total resection. The ALK expression in IMT of the CNS is specific to the FHC variant. Compared with IMT of the CNS that do not express *ALK*, the reported recurrence rate of *ALK*-positive tumors tend to be higher. The *ALK*-positive recurrences also seem to occur earlier. Our results are similar to those found for IMTs located outside the CNS, which tend to be associated with an earlier age of presentation and a higher rate of recurrence.[3] This study was limited by its retrospective nature and by the small number of IMT of the CNS cases that were investigated for *ALK* expression in the literature. Further research with longer follow up is needed to clarify the natural history of this rare tumor.

CONCLUSION

Total resection of *ALK*-positive IMTs should be achieved as theses tumors recurred often rapidly. Confirmation of the FHC variant by histopathology warrants searching for *ALK* expression. Such findings may lead to considering adjuvant therapy such as radiotherapy or novel *ALK* inhibitors.[16]

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