Clinical case

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Primary brain CD30+ ALK1+ anaplastic large cell lymphoma ('ALKoma'): the first case with a combination of 'not common' variants

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Background: Primary central nervous system lymphomas (PCNSLs) are rare tumors, mostly represented by diffuse large B cells. PCNSLs with a T phenotype are less frequently reported; even rarer are anaplastic large cell lymphomas (ALCLs). PCNSL ALCLs are commonly represented, like their systemic counterpart, by a variably prevalent amount of large pleomorphic tumor cells ('hallmark cells'), and this feature enhances their recognition.

Patient and methods: We report the first case of primary brain CD30+ ALK-1+ ALCL with a T-cell phenotype, showing the combination of both the 'lymphohistiocytic' and the 'small cell' variants of the disease. A few elements consistent with 'hallmark cells' were recognizable. However, these cells were never prominent, increasing diagnostic difficulties. Immunohistochemistry results were critical for the correct interpretation. Our findings also differ from the majority of PCNSL ALCLs for the absence of tumor necrosis and the lack of prominent mitotic activity. The neuroimaging picture was not specific. A comparison with literature data concerning the clinical/instrumental features shows a very frequent meningeal involvement in PCNSL ALCLs, in contrast to the majority of PCNSLs.

Conclusion: The occurrence of such a rare form of ALCL may widen the spectrum of differential diagnoses in PCNSL and their recognition may allow a rapid diagnosis, thus encouraging adequate treatment, which should take into account the high rate of meningeal involvement observed in these cases.

Key words: ALK, anaplastic, brain, central nervous system, hallmark cell, lymphoma

Introduction

Primary central nervous system lymphoma (PCNSL) is a rare malignancy (0.5–1.5% of all brain neoplasms) [1], although its incidence is increasing, also in immunocompetent individuals [2]. The vast majority of PCNSLs are represented by large cell forms and display a B-cell phenotype. T-cell PCNSL is uncommon [3]; even rarer are anaplastic large cell lymphomas (ALCLs) [4].

In the present report, a case of PCNSL CD30+ ALK-1+ ALCL with a T-cell phenotype in a young immunocompetent adult is described. The morphological features of the lesion, consistent with an admixture of 'not-common' variants of the disease, as well as clinical, instrumental and therapeutic management characteristics, are analyzed and compared with literature data; in particular, the critical diagnostic role of immunohistochemistry is acknowledged. Finally, the impact of ALCL diagnosis on therapeutic management of PCNSL is discussed.

Case report

A 29-year-old man was admitted to hospital because of fever, headache and generalized seizures, arising a few days earlier. After a crisis of generalized seizures, a reduction of spontaneous speech was observed. The results of a general physical examination were normal. On neurological evaluation no defects in motor sensitivity were observed. A lumbar puncture showed clear colorless fluid, 5 lymphocytes/mm^3 and a protein content of 53 mg/dl (normal value 15–60 mg/dl). Neither malignant cells nor microorganisms were seen, and cultures were negative. An unenhanced computed tomography (CT) brain scan and magnetic resonance imaging (MRI) failed to

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show any abnormality. On a clinical basis, acute meningitis was diagnosed and the patient was discharged with antibiotics, obtaining remission of fever and headache.

Two weeks later the patient was re-admitted with further generalized seizures; after the crisis a motor/sensitive defect in the right hemibody was persistent for a few days**.** A brain CT scan showed the presence of a hypodense edematous cortical–subcortical fronto-temporal lesion. Enhanced MRI of the brain better defined the lesion, showing the presence of a cortical frontal enhancing nodule surrounded by edema; the lesion appeared hypointense on T2-weighted images and after injection of gadolinium it enhanced strongly and homogeneously; some pial and subarachnoid enhancement was also present close to the lesion. In consideration of the clinical and imaging evolution, the lesion was interpreted as a probable infective localization, and multiple combinations of antibiotics were therefore administered. A further brain MRI performed 2 weeks later showed progression of the lesion resulting in multiple, confluent enhancing nodules mostly cortical in location and dislocated around the left sylvian scissure (Figure 1A and B); pia and subarachnoid enhancement persisted although less evidently, whereas edema was increased together with the mass effect. With the suspicion of the presence of an underlying progressive lesion, an open brain biopsy was performed, which concluded that there was a picture consistent with reparative changes of a former abscess. Systemic steroid treatment was then added to ceftriaxone, producing cessation of fever and partial seizures.

Two months later, motor epilepsy involving the same areas re-occurred and the patient was referred to our institution. MRI at this time showed only a slight enlargement of the lesion with unchanged extension of surrounding edema. Eastern Cooperative Oncology Group performance status was 2, systemic symptoms were absent; the lactate dehydrogenase (LDH) serum level was elevated (ratio = 2.43).

A second open brain biopsy was therefore performed. At surgery, the pathological tissue showed hypervascularization and firm consistency. Cultural analysis made on a portion of the specimen showed no microorganisms. Histological examination revealed a population composed of medium-to-large lymphoid-looking cells; the latter showed slightly kidney-shaped nuclei devoid of prominent nucleoli and relatively abundant cytoplasm. A few of these cells were consistent with ‘hallmark cells’, but they were never prominent and homogeneously smaller than those encountered in the ‘common variant’ (Figure 2A). The neoplastic elements were immunoreactive for leukocyte common antigen, CD30 (Figure 2B), ALK-1 (Figure 2B, insert), epithelial membrane antigen, monoclonal CD3 and CD45RO but not for CD20, CD79a, S-100 protein, glial fibrillary acidic protein, myeloperoxidase, CD34 or CD68 (KP-1). Necrosis or prominent mitotic activity (i.e. more than 10 mitoses/mm^2) were absent; moreover, some

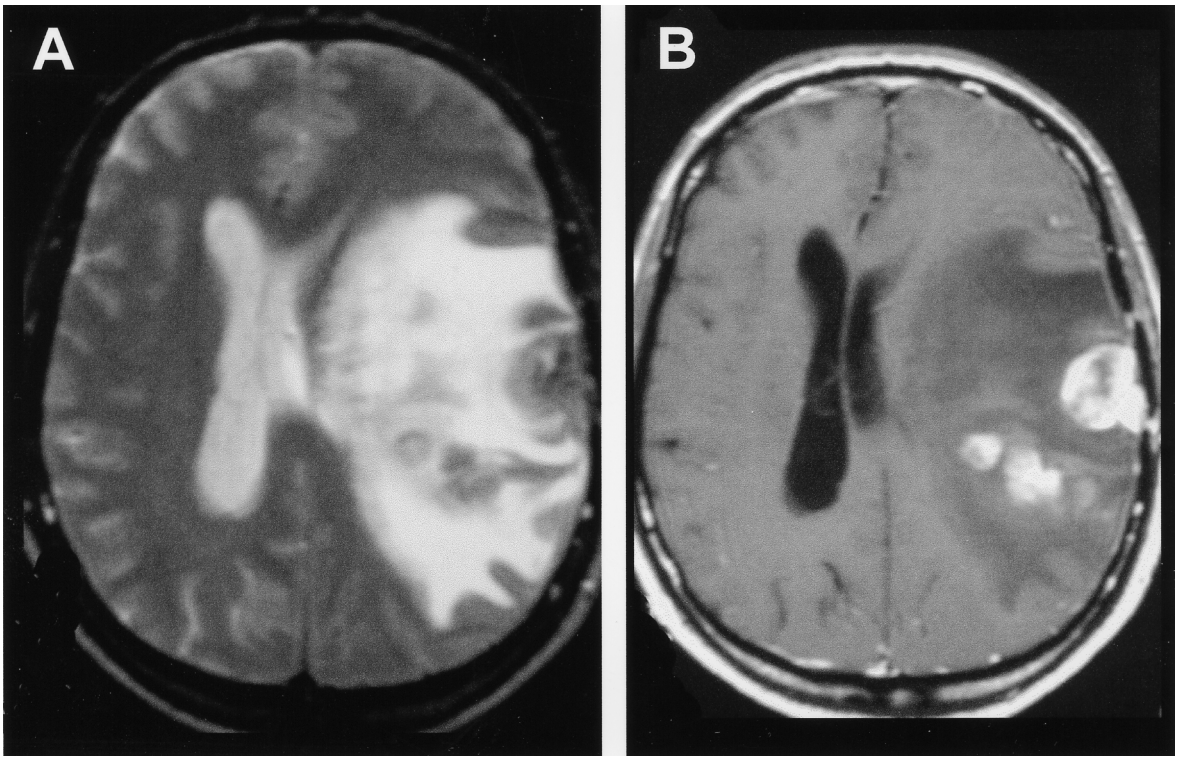

Figure 1. (**A**) MRI study. Axial spin-echo T2-weighted image (TR/TE 2200/75) demonstrates the presence of a fronto-temporal cortical–subcortical hypo-isointense lesion (arrow) with significant edema and a mass effect on median structures. (**B**) Contrast-enhanced spin-echo T1-weighted (TR/TE 500/15) axial image. Gadolinium injection better delineates the lesion, which enhances strongly, showing the presence of multiple nodules.

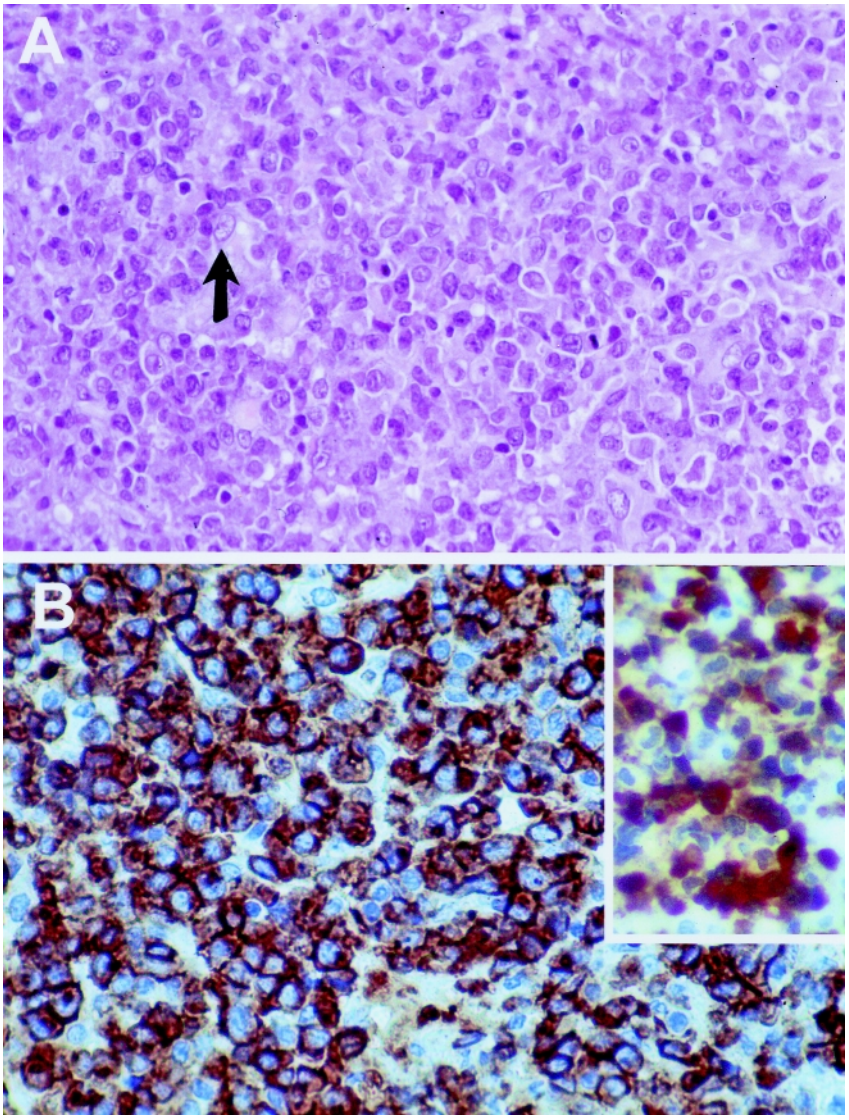

Figure 2. (**A**) The neoplastic population is composed of medium-to-large cells, without predominance of 'hallmark cells'. An arrow indicates a monocyte in order to compare the overall smaller size of lymphomatous cells (hematoxylin–eosin, ×400). (**B**) Lymphoma cells are strongly and diffusely reactive for CD30 molecule: insert (top right) shows intense nuclear reactivity for ALK-1 protein, ×400.

apoptotic figures were evident. In some areas, tumor cells were obscured by the preponderance of macrophages, and revealed a heavy inflammatory infiltrate, mainly represented by granulocytes and small lymphocytes. This aspect prompted us to re-evaluate critically the initial series of biopsies; the latter disclosed one small area with the same characteristics. A diagnosis of CD30+ ALK-1+ systemic ALCL was made [5]. Cerebrospinal fluid (CSF) cytological examination was repeatedly negative, as well as HIV serology. CSF protein level was increased (604 mg/dl).

The patient underwent an extensive staging including thoracic and abdominal CT scans, bilateral bone marrow biopsy and aspirate, CNS ^{18}F-labeled deoxyglucose positron emission tomography and eye slit-lamp examination, which ruled out any other site of disease. In particular, bone marrow involvement was ruled out either by morphology or immunocytochemistry for the CD30 molecule. Treatment consisted of four courses of a combination chemotherapy (MATILde regimen) with methotrexate (3.5 g/m^2, day 1), idarubicin (16 mg/m^2, day 1), cytarabine (2 g/m^2 × 2/day, day 2) and thiotepa (25 mg/m^2, day 3) followed by whole-brain radiotherapy. Whole-brain irradiation therapy was stopped at 36 Gy, including the first two cervical segments and the posterior two-thirds of the eyes, which were shielded after 30 Gy. Whole-brain radiation was followed by a tumor bed boost of 9 Gy. The patient is in complete remission after 13 months from the completion of the treatment and 19 months after the onset of symptoms.

Discussion

Our case of PCNSL ALCL shows peculiar morphological features in the brain. To the best of our knowledge, this is the first case of combination of 'not-common' variants of ALCL in the CNS. The neoplastic elements were predominantly medium-to-large sized, while only occasional cells consistent with 'hallmark cells' were seen (Figure 2A). In addition, lymphomatous cells were admixed to a significant amount of CD68+ macrophages, masking the diagnostic cells in some microscopic fields, and other inflammatory cells, like small lymphocytes, plasma cells and granulocytes. The above mentioned features are consistent with a mixture of both the 'small cell variant' and the 'lymphohistiocytic' variant of ALCL [5]. The potential confusion in the above-described picture is confirmed also by the difficulty of its recognition in the first series of biopsies evaluated, and the presence of the reactive cellular milieu may also raise differential diagnostic problems with non-neoplastic process, mainly represented by abscesses. Within such a background, CD30 immunostaining (Figure 2B) permitted a better estimation of the neoplastic infiltrate, while ALK-1 staining (Figure 2B, insert) appeared critical in reaching the correct diagnosis, since virtually all the tumor cells were reactive for this marker. High mitotic rate [1, 6–10], as well as necrosis [1, 7–11] is usually described, in contrast with the present and previous experience [12].

ALCL was defined as a new category in 1985 [13] and as a clinico-pathological entity by the Revised European–American Classification of Lymphoid Neoplasms (REAL) classification scheme [14], where only cases with T or null (i.e. non-B, non-T) phenotype were considered. ALCL with a B-cell phenotype was therefore included in the group of diffuse large B-cell lymphomas. The most common extranodal sites involved include skin (21%), bone (17%), soft tissues (17%), lung (11%) and liver (8%) [15]. ALCLs rarely arise in the CNS, particularly in the brain. When using REAL and WHO classification criteria, only eight cases in immunocompetent patients have been reported so far in the English language literature [1, 6–12]. In the seven cases with available detailed histological description [1, 7–12], the 'classic' variant was almost constantly reported with the exception of a case of lymphohistiocytic variant [11] (Table 1). We describe for the first time the coexistence of two rare variants, the 'lymphohistiocytic' and the 'small cell' one; this occurrence is *per se* quite rare, since it has been stated that more than one variant within an individual patient can be seen in approximately 10% of ALCLs [16]. Including our case, ALK-1 immunoreactivity has been reported in two instances [8]. In our experience, this marker was helpful in the differential diagnosis of T-cell PCNSL, actually being critical for the definition of that particular type of lymphoma defined as 'ALKoma' [16]. A comparison with the previously published results is difficult, since ALK-1 immunoreactivity was rarely tested [8, 11]. Our findings really question if some of the previously reported primary T-cell PCNSLs may actually be forms of CD30+ ALK-1+ ALCLs.

In our case, lymphoma consisted of a single lesion localized in the fronto-temporal region, while the parietal lobe is the most constant site in previously reported cases, although the majority of them showed more than one lobe involved. Notably, a single lesion composed the neoplasm; this feature accounts for half of the cases [6, 11, 12]. The relationship with meninges and subarachnoid spaces could raise differential diagnostic problems with either infective diseases or metastases (Table 2). Notably, although bona fide exquisitely intraparechimal, the vast majority of assessable PCNSL ALCLs showed meningeal involvement [5, 8, 9, 11], as confirmed also by CSF cytological examination in two of them [8, 9]. In our case the lesion was adhering to dura, while CSF cytology failed to show neoplastic cells. Interestingly enough, however, the frequent meningeal involvement in PCNSL ALCLs differs from the 16% of usual PCNSLs [17]; this feature suggests that these patients may benefit from the inclusion in their therapeutic scheme of strategies directed at meningeal prophylaxis, such as intrathecal chemotherapy or high-dose methotrexate-based chemotherapy. The increased CSF protein level, an

Table 1. Pathological features of primary central nervous system anaplastic large cell lymphomas

Reference	Lineage	ALK-1	Hallmark cells	Variant	Necrosis	Mitoses
Chuang et al. [11]	T	Not reactive	Yes	LH	Prominent	No
Abdulkader et al. [8]	T	Reactive	Yes	Common	Prominent	Prominent
Buxton et al. [6]	T	NR	NR	NR	NR	Prominent
Feldges et al. [12]	T	NR	Yes	Common	Absent	Few
Havlioglu et al. [9]	Null	NR	Yes	Common	Prominent	Prominent
Paulus et al. [7]	T	NR	Yes	Common	Prominent	Prominent
Goldbrunner et al. [1]	T	NR	Yes	Common	Prominent	Prominent
Goldbrunner et al. [1]	T	NR	Yes	Common	Absent	Prominent
Present case	T	Reactive	Few	LH + SC	Absent	Few

LH, lymphohistiocytic; NR, not reported; SC, small cell.

Table 2. Clinical-instrumental features of primary central nervous system anaplastic large cell lymphomas

	Reference								
	Chuang et al. [11]	Abdulkader et al. [8]	Buxton et al. [6]	Feldges et al. [12]	Havlioglu et al. [9]	Paulus et al. [7]	Goldbrunner et al. [1]	Goldbrunner et al. [1]	Present case
Sex/age (M, male; F, female/years)	F/46	M/13	F/10	M/20	F/4	M/63	M/63	M/49	M/29
No. of lesions	Single	Multiple	Single	Single	Multiple	Multiple	Multiple	Multiple	Single
Site	Occipital lobe, parietal lobe	Frontal lobe, parietal lobe	Parietal lobe	Parietal lobe	Multiple lobes	Frontal lobe, parietal lobe	Frontal lobe, parietal lobe	Multiple lobes	Frontal lobe, temporal lobe
Meningeal involvement	Adhesion to dura	Positive CSF cytology	Falcine enhancement	NR	Positive CSF cytology	NR	NR	No	Adhesion to dura
Perilesional edema	NR	NR	Yes	Yes	NR	No	Yes	Yes	Yes
Radiological enhancement	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes
Lactate dehydrogenase serum level	Normal	Normal	Normal	NR	NR	NR	NR	Normal	Increased
CSF protein level	NR	Increased	NR	NR	Increased	NR	NR	NR	Increased
Clinical suspicion	NR	Infection	Tumor	Infection	Infection	Metastasis	Metastasis/infection	NR	Tumor/infection
Surgical resection (biopsy)	Subtotal	Stereotactic	Total	Total	Subtotal	Subtotal	Subtotal	Subtotal	Subtotal
Time symptoms to diagnosis (weeks)	8	12	3	3	3	4	3	16	12
Time symptoms to therapy (weeks)	14	NR	4	6	NR	8	14	>16	20
Treatment	RT	CHT	CHT→RT	RT→CHT	CHT	RT	RT	RT→CHT	CHT→RT
Drugs (CHT)	–	MAEOCde	MAdaCOP	alexan→A	CHOP	–		M	MATILde
RT dose (WB, whole-brain; T, tumor bed; SC, spinal-cord)	WB 40Gy, T 20 Gy	–	WB 24 Gy, SC 12 Gy	WB 50 Gy	–	WB 27 Gy, incomplete	WB 27 Gy, incomplete	WB 50 Gy	WB 36 Gy, T 9 Gy
Objective response	Complete	Progression	Complete	Complete	Undefined	Progression	Progression	Complete	Complete
Time to relapse (months)	13+	<3	6+	24+	NR	<3	<3	<2 (?)	13+
Follow-up (months)	25	<3	6	24	NR	<3	<3	42	19
Status	Alive, NED	DOD	NR	Alive, NED	NR	DOD	DOD	Alive, ED (?)	Alive, NED

+, not relapsed; A, cytarabine; C, cyclophosphamide; CSF, cerebrospinal fluid; CHT, chemotherapy; da, daunorubicin; de, dexamethasone; DOD, died of disease; E, etoposide; ED, evident disease; H, adriamycin; M, methotrexate; MATILde, see text; NED, no evidence of disease; NR, not reported; O, vincristine; P, prednisone or prednisolone; RT, radiotherapy.

unfavorable predictor of survival [17], in our patient was in keeping with previous experience [8, 9], while a rather unique finding in our case was the elevation of serum LDH levels.

Since reported cases are so few and management heterogeneous, statements about treatment strategy and prognosis cannot be drawn with sufficient confidence. The overall therapeutic approach of PCNSL ALCL patients does not seem to differ greatly from the current therapy of PCNSLs.

The rapid recognition of PCNSL ALCL, even without the morphological features of the 'classic' variant, may therefore be helpful in permitting a more tailored therapeutic approach.

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