



Recurrence of Anaplastic Large Cell Lymphoma in the Frontal Lobe After Eleven Years of the Initial Diagnosis: Histopathological Findings and Prognosis

Recorrência de linfoma anaplásico de grandes células no lobo frontal onze anos após o diagnóstico inicial: Achados histopatológicos e prognóstico

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Abstract Keywords

- ▶ anaplastic large cell lymphoma
- ▶ central nervous system
- ▶ pathology
- ▶ immuno-histochemistry
- ▶ prognosis

Anaplastic large cell lymphoma (ALCL) is a rare, high-grade, T-cell neoplasm classified into cutaneous primary, systemic primary ALK-positive (ALK⁺), systemic primary ALK-negative, or breast-implant associated. Secondary involvement of the central nervous system (CNS) by systemic primary ALK⁺ ALCL is a rare occurrence. We present a case of CNS involvement by ALK⁺ ALCL eleven years after diagnosis of the primary tumor in the thoracic vertebra. The anatomopathological examination confirmed the diagnosis of ALK⁺ ALCL. A brief review of the treatment and the clinical and pathological aspects is presented.

Resumo

Palavras-chave

- ▶ linfoma anaplásico de grandes células
- ▶ sistema nervoso central
- ▶ patologia
- ▶ imuno-histoquímica
- ▶ prognóstico

O linfoma anaplásico de grandes células (LAGC) corresponde a uma neoplasia de alto grau rara, com imunofenótipo T, que podendo ser dividido em primário cutâneo, primário sistêmico ALK positivo (ALK⁺), primário sistêmico ALK negativo, e associado a próteses mamárias. Acometimento secundário do sistema nervoso central (SNC) por LAGC primário sistêmico ALK⁺ é uma rara entidade. Os autores apresentam um caso de acometimento do SNC por LAGC ALK⁺ onze anos após o diagnóstico do tumor primário em vértebra torácica. O exame anatomopatológico confirmou o diagnóstico de LAGC ALK⁺. Fez-se também uma breve revisão de aspectos clínicos e patológicos e tratamento.

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Introduction

ALK-positive anaplastic large cell lymphoma (ALK⁺ ALCL) is a single entity defined by the World Health Organization (WHO) as a T-cell lymphoma composed of generally large, pleomorphic lymphoid cells with abundant cytoplasm, chromosomal translocation involving the *ALK* gene, and ALK and CD30 expression on surface membranes. Upon microscopic examination, the most common pattern is large cells with eccentric, horseshoe-shaped nuclei. However, there is great morphological variation, with reports of the following patterns: small cells, lymphohistiocytic, Hodgkin-like, multinucleated giant cells, and fusocellular. Anaplastic large cell lymphoma accounts for about 3% of non-Hodgkin lymphomas in adults, and for 10% to 20% of lymphomas in children.¹ The clinical presentation is generally characterized by advanced stages (III or IV) and associated with B symptoms. Lymph node and extranodal involvement are common, including sites such as the skin, bones, soft tissues, lungs, and liver. Involvement of the bone marrow occurs in about 30% of the cases analyzed by immunohistochemistry.² Primary involvement of visceral and central nervous systems (CNS) is rare, and CNS metastasis is even rarer.

We herein report a case of ALK⁺ ALCL involving the thoracic vertebra in a pediatric patient, with subsequent emergence of the same pathology in the right frontal lobe after eleven years of remission.

Case Report

An 18-year-old patient presented to the hospital with nausea and vomiting followed by five generalized tonic-clonic seizures lasting 30 minutes, associated with salivation, tongue biting, and urinary incontinence, without recovery between the seizures. The patient was medicated with five ampoules of phenytoin and transferred to the reference hospital, with no further abnormalities on the neurological examination. A review of the medical records revealed a history of anaplastic lymphoma of the twelfth thoracic vertebra treated with chemotherapy. Eleven months of clinical follow-up showed no disease recurrence or involvement of the bone marrow, liver, spleen, tonsils, skin, or CNS. The patient underwent regular follow-up with the neurosurgery team for progressive vertebral collapse. Brain computed tomography (CT) scans of the last 8 years revealed the presence of an extensive area of encephalomalacia in the right frontal lobe, without significant changes between evaluations. During the current hospitalization, a magnetic resonance imaging (MRI) scan of the CNS (►Figs. 1 and 2) was requested, which identified an expansive fronto-basal lesion on the right side, with marked low signal on fluid-attenuated inversion recovery (FLAIR) sequences and T1, hyperintense on FLAIR in the periphery, and a solid portion of blood-brain barrier breakdown near the lower anterior brain portion. The lesion measured about 4.8 × 3.3 cm in its largest diameters, and the solid portion with contrast enhancement measured about 1.3 cm in the largest diameter, which was suggestive of primary glial neoplasm. The patient underwent surgical intervention, with resection of the mural nodule, drainage of the cystic area via

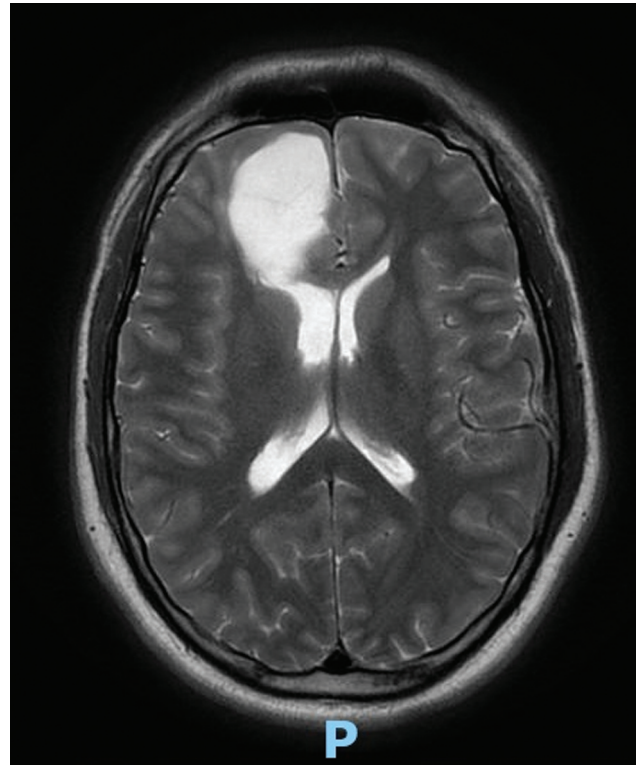


Fig. 1 Axial magnetic resonance imaging (MRI) scan showing an expansive fronto-basal tumor.

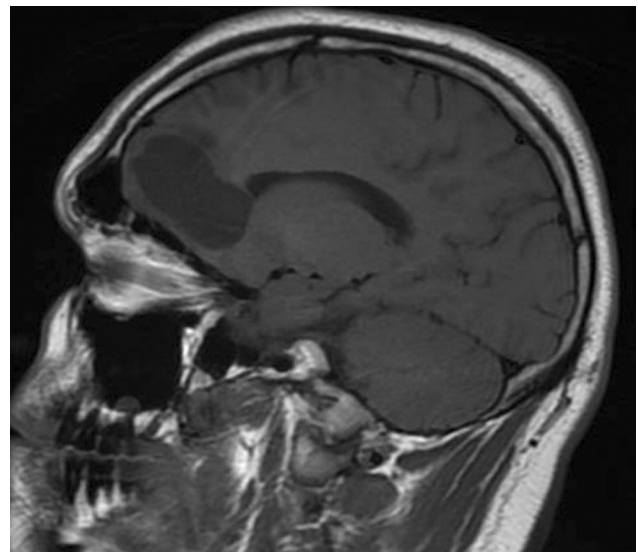


Fig. 2 Sagittal MRI scan showing an expansive fronto-basal tumor.

opening of the nodule/ventricle wall, and successful resolution of cerebrospinal fluid fistula, being discharged with outpatient follow-up. The anatomopathological examination revealed a poorly-differentiated malignant neoplasm compromising the CNS parenchyma, consisting of medium-sized round cells arranged in solid groups (►Figs. 3 and 4) or in a perivascular pattern, with moderate mitotic index and areas of necrosis. The immunohistochemical examination showed that the neoplasm was positive for cluster determinant 2 (CD2), cluster

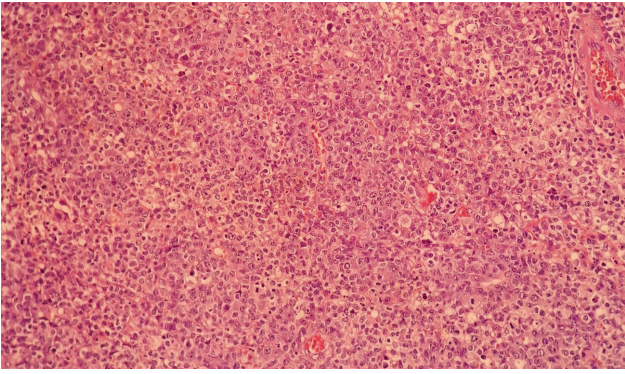


Fig. 3 A poorly-differentiated malignant neoplasm compromising the CNS parenchyma; hematoxylin-eosin, magnification: 200x.

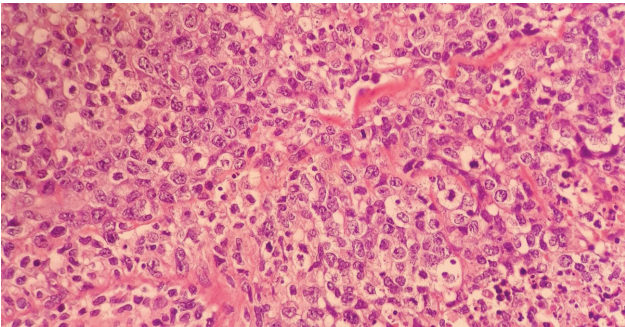


Fig. 4 A poorly-differentiated malignant neoplasm consisting of intermediate-sized round cells arranged in solid groups; hematoxylin-eosin, magnification: 400x.

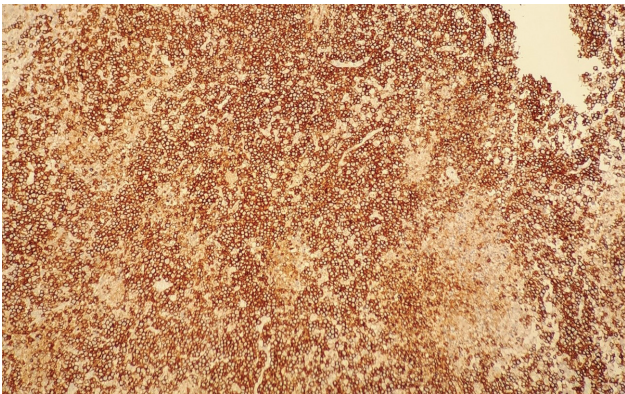


Fig. 5 Anaplastic large cell lymphoma showing positive immunorepression for CD30; Ventana System, 40x.

determinant 3 (CD3), cluster determinant 5 (CD5), cluster determinant 30 (CD30) (► **Fig. 5**), anaplastic lymphoma kinase (ALK) (► **Fig. 6**), epithelial membrane antigen (EMA), perforin, and granzyme B, enabling the diagnosis of ALK⁺ ALCL involving the cerebral parenchyma. The proliferative index of the neoplasm was of about 90%, as estimated by Ki-67 expression (► **Fig. 7**). The patient was referred to chemotherapy.

Discussion

Involvement of the brain parenchyma in cases of ALK⁺ ALCL is a rare event, with few reports of primary involvement³⁻⁷ and even

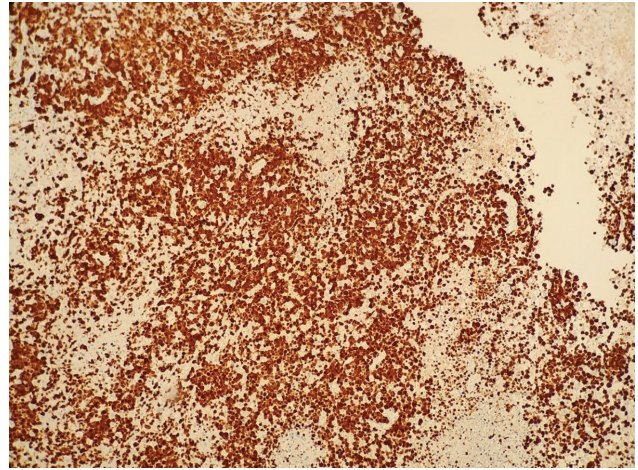


Fig. 6 Anaplastic large cell lymphoma showing positive immunorepression for ALK; Ventana System (Ventana Medical Systems, Tucson, AZ, United States), magnification: 40x.

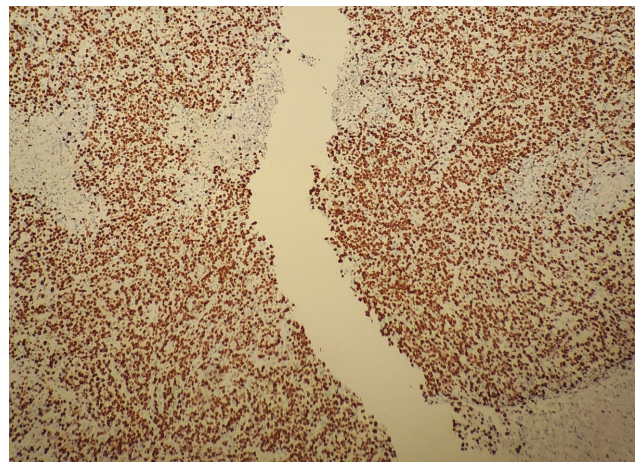


Fig. 7 Anaplastic large cell lymphoma showing a high proliferative index (of about 90%, estimated by Ki-67 expression); Ventana System, magnification: 40x.

fewer of secondary involvement.⁸⁻¹⁰ One study¹¹ analyzed the ALCL99 database, which comprises data on 618 patients with confirmed CNS biopsy between 1999 and 2017, involving 175 centers across 11 European countries and Japan. Central nervous system relapse was observed in 26 patients, 5 of whom had CNS disease at diagnosis. There was a mean interval of 8 months between the initial diagnosis and CNS relapse, with only 3 patients presenting relapse after 5 years; the latest relapse occurred 130.7 months after the initial diagnosis. We herein report the case of a patient who presented relapse in brain parenchyma 134 months after the initial diagnosis, becoming the latest case of relapse of ALK⁺ ALCL described in the literature.

The low incidence of CNS relapses can be explained by the effectiveness of the initial treatment and by the neoplasm's low tropism for the CNS. Central nervous system relapse is more common in patients who had the disease in this topography at the initial diagnosis, as well as in the case of bone marrow involvement or presence of peripheral blasts.¹¹ Patients with these risk factors could benefit from a more aggressive CNS prophylaxis.¹¹

As reported, however, our patient did not have the indicated risk factors and had undergone a long asymptomatic period, raising the hypothesis of primary ALCL of the CNS or presence of viable neoplastic cells in the encephalomalacic area identified in CT scans in the initial years of follow-up, which were located at the same topographic site of the current neoplasm.

There is little agreement on the most appropriate therapeutic approach for CNS relapses. The most common treatment options include high-dose chemotherapy, autologous stem-cell transplantation, radiotherapy, and, recently, brentuximab vedotin (anti-CD30 drug).^{12,13} ALK-inhibiting drugs, such as crizotinib, ceritinib, and alectinib, were shown to promote long-lasting responses in patients with refractory and/or relapsed ALK⁺ ALCL. A clinical trial¹⁴ used alectinib to treat ten patients, including children and older adults, with refractory/relapsed ALK⁺ ALCL; positive response was observed in eight out of the ten patients, and complete response, in six. Based on these results, in February 2020, Japan approved the use of this drug for refractory/relapsed ALK⁺ ALCL. Most clinical trials, however, exclude patients with CNS disease, explaining the lack of data on treatment efficacy in such cases. Vinblastine demonstrated good efficacy in relapsed ALCL, but there are few reports of the drug's efficacy when the tumor is located in the CNS, given the poor penetration of the blood-brain barrier. In fact, some patients had isolated CNS relapse despite their excellent systemic response.^{15,16}

New data on CNS penetration of second- and third-generation ALK inhibitors are emerging from studies on adults with ALK⁺ non-small cell lung carcinoma. Reports^{17,18} suggest that alectinib is superior to other ALK inhibitors with regard to CNS penetration (the penetration rates of crizotinib and alectinib were of 0.26% and 86% respectively¹⁹). Ceritinib, another ALK inhibitor, showed a rate of response of 75% in ALCL patients.²⁰ According to the International ALCL99 trial,¹¹ the 3-year survival rate of patients with CNS relapse is of 48.7%, suggesting that the goal of novel treatments should be to achieve complete cure.

In summary, we conclude that isolated CNS recurrence can arise even after more than a decade of the diagnosis and clinical remission of systemic ALK⁺ ALCL without primary CNS involvement. The need for prolonged follow-up becomes evident. Promising medications have emerged, and others are still in development; however, given the current heterogeneity in therapeutic approaches to the CNS relapse of ALCL, it is essential that new studies and strategies be developed.

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Conflict of Interests

The authors have no conflict of interests to declare.

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