Primary Central Nervous System Anaplastic Large Cells Lymphoma in children: case presentation and systematic review of literature

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Abstract

Primary Central Nervous System Lymphoma is a rare extranodal non-Hodgkin lymphoma, primarily arising in brain and spinal cord tissue, leptomeninges and vitreoretinal eye. Pediatric PCNSLs are even rarer. We describe the case of a boy presenting with seizures and a suspected brain meningioma, but a final diagnosis of ALK+ Anaplastic Large Cell Lymphoma. We conducted a qualitative systematic review following the ENTREQ framework on pediatric cases of PCNSL, identifying only nine cases of brain ALCL. Our work describes the high frequency of misdiagnosis correlating with poor prognosis, and highlights the importance of a multidisciplinary approach considering ALCL among differential diagnosis.

Introduction

Primary Central Nervous System Lymphoma (PCNSL) is an extranodal non-Hodgkin lymphoma (NHL) originating in brain tissue, spinal cord, leptomeninges and vitreoretinal eye accounting for 3% to 5% of all brain tumors and less than 1% of all NHLs. The 95% of PCNSLs are B-cell lymphomas; T-cell lymphomas constitute the remaining 2-5%[1]. Pediatric PCNSLs are very rare (about 1%). Cerebral hemisphere, basal ganglia, corpus callosum, brainstem and cerebellum are the most common involved brain sites. Clinical manifestations include headache, aphasia, sensory and motor deficits, speech disorders, ataxia, seizures and short- term memory difficulties[2]. ALCL is a peripheral T-cell lymphoma, accounting for about 2-8% of all NHLs. Brain ALCL is a very rare subtype of PCNSL. Mean age at diagnosis is 21 years and leptomeningeal involvement occurs in 80% of cases as tan-white nodules on the dural surface[3]. ALCL can be classified into ALK+ and ALK- ALCL, according to the pattern of genetic abnormalities. ALK+ cases generally occur in younger patients and have a more favorable prognosis than ALK- cases, with two years survival rate of 71% and 22% respectively[3]. ALCLs are hypointense on MRI T1 and isointense to hyperintense on T2-weighted images, mainly occurring as single or multiple supratentorial lesions. The enhancement pattern doesn't clearly distinguish it from meningiomas, metastasis or gliomas[4].

Methods

A 9-year-old caucasian boy was admitted to our Oncology Department with a history of seizures, asthenia and dizziness from two weeks. No abdominal and lung involvement was detected on a total body CT scan. Brain MRI showed a wide right parieto-occipital edema and two isointense lesions on the right side of the cerebral falx, and in the upper surface of the ipsilateral tentorium (Fig. 1A-D). Radiological signs oriented for malignant meningiomas. Electroencephalogram showed slow cerebral electrical activity on the

right temporal-occipital regions. CSF and bone marrow cytopathological examinations detected no tumor infiltration. Thus, the multidisciplinary neuro-oncological pediatric board discussed the case and decided for surgical approach. A complete surgical excision of the falx-tentorial lesions was performed with the aid of neuronavigation system, fluorophores and intraoperative neurophysiological monitoring. Histologically, the tumor showed a diffuse proliferation of large cells, with markedly atypical nuclei and abundant eosinophilic cytoplasm (Fig. 2A). There were many neoplastic cells characterized by bean-shaped nuclei and an eosinophilic peri-nuclear area (Fig. 2B). The tumor cells extensively infiltrated the surrounding brain tissue and focally the meninges. Tumor cells were positive for CD30 (Fig. 2C), EMA (Fig. 2D) and ALK, also showing positivity for T-cell markers (CD3, CD4 and CD5). One week after surgery, the boy became febrile with no signs of infection. A^{18}F-FDG PET/CT scan showed a pathological uptake in supra- retro clavicular, mediastinal, ilar, peribronchial, paraesophageal, paraaortic and mesenteric fields, and multiple enlarged lymph nodes. T (2;5) (p23; q35) NPM-ALK RT-PCR was negative both in bone marrow and peripheral blood. Thus, we decided to treat the patient with 6 chemotherapy cycles (including corticosteroids, methotrexate, cytarabine, cyclophosphamide, daunomycin, ifosfamide, etoposide, vindesine, vincristine), plus CNS prophylaxis with intrathecal injections of methotrexate, cytarabine and prednisolone, according to the AIEOP LNH-97 protocol, high risk group. The disease MRI reassessment demonstrated no signs of residual disease. Chest and abdomen CT scan detected a lymph nodes shrinkage, and PET-CT scan showed no pathological enhancement. Complete disease remission was achieved at the end of chemotherapy, and no evidence of disease recurrence emerged at one-year follow-up.

We've conducted a systematic review following the ENTREQ framework. This methodology was chosen as it better describes qualitative research according to the guidelines for reporting systemic rewiews at: http://www.cochrane.de/de/LeitlinienForschungsberichte. A case-based literature search about pediatric cases of CNS ALCLs was performed. The main search was conducted through PubMed and MeSH Database and the terms used were "ALCL", "ALCL" AND "brain" OR "ALCL" AND "brain" AND "pediatrics", "ALCL" AND "CNS". Only full text, published between 2002 and 2022 in peer-reviewed journals, were included. A systematic approach to the collected data and a collegial discussion between the authors led to a final version of the manuscript.

Results and Discussion

We identified a total of 179 records, according to our selection criteria. Thirty-eight studies were duplicate and excluded. A total of 141 peer-reviewed papers were screened, based on this review's focus: ALCL in pediatric patients with CNS involvement. Thus, 132 not relevant papers were excluded.

Only 9 pediatric cases of primary CNS ALCL were reported in literature (TABLE 1)[4-12]. In five out of nine, the initial clinical suspicion concerned an infectious disease. In our case, the radiological features, symptoms and the absence of any nodal involvement, had supported the hypothesis of meningioma. Therefore, safe complete surgical removal was planned. However, general conditions can easily deteriorate and the disease can be so aggressive that multi-nodal involvement can be detected soon after surgery.

CNS ALK+ALCL (a T- cell lymphoma) is an exceptional subtype in pediatric patients. Metastasis, multiple organ failure, and intracranial hypertension are the most frequent causes of death. There is no standard treatment because of its rarity, and the role of neurosurgery varies in different case series. Surgical excision is usually performed in case of a single lesion in a safe site. However, the degree of surgical removal does not affect the prognosis. No standard medical treatment has been established. High dose methotrexate (3,5g/m^2) is an important induction chemotherapy, and the addition of high-dose cytarabine is advised in younger patients. Cyclophosphamide, doxorubicin, vincristine and prednisolone therapy is transiently efficient, but CNS ALCL becomes rapidly resistant because of the inadequate penetration of drugs through the BBB. There is no evidence regarding whether brentuximab vedotin can cross the BBB, whereas intrathecal methotrexate therapy is often added to intravenous chemotherapy, in order to treat and protect CNS from recurrence. The use of allogeneic hematopoietic stem cells transplantation as consolidation therapy, results in 5- years post-relapse survival over 50% with OS of 77%. Radiation therapy should be considered as a part of consolidation, but it is associated with an increase of neuro-cognitive deficits. ALK-inhibitors (alectinib and crizotinib)

have been evaluated in trials recruiting patients with refractory/relapsing ALCL ALK+ tumors. Crizotinib was approved by FDA in USA in January 2021, for treatment of pediatric patients one year of age, and young adults with relapsed or refractory ALCL. Some case series reported that mono-therapy with ALK inhibitors at relapse, guarantees 70-90% response rates with manageable acute toxicity[13-15]. Potential long-term effects, such as ocular and endocrine toxicity, need to be addressed. Clinicians are currently investigating the efficacy of the inclusion of ALK inhibitors in front-line therapy, in order to decrease acute chemotherapy toxicity and evaluating an ALK inhibitor with good CNS penetrance, and to decrease the risk of CNS recurrence. Symptoms at the onset are nonspecific for this condition. CNS ALCL is often misdiagnosed as infection, and treated accordingly.

Therefore, primary CNS lymphoma should always be considered in differential diagnosis, in order to manage correct multidisciplinary approach and, whenever possible, promptly start chemotherapy. Due to the aggressiveness of the disease, we decided to treat our patient with standard non-Hodgkin Lymphoma Protocol (LNH97) with adjunctive intrathecal chemotherapy. The boy is currently in complete remission 10 months from stop-therapy.

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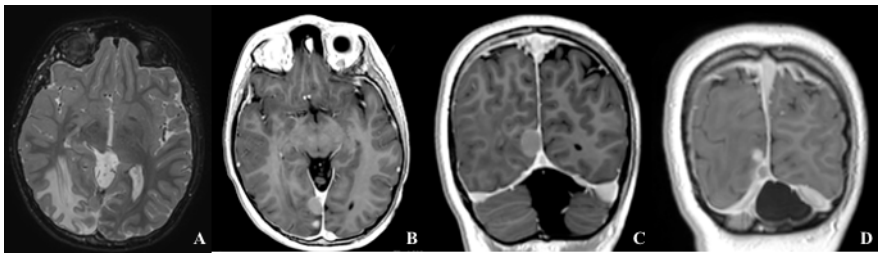
Legend list

TABLE 1 Features of pediatric primary central nervous system ALK+ALCL reported in the literature

FIGURE 1 A: MRI T2-weighted images, showing two isointense parasagittal lesions on the right falcotentorial corner, surrounding by wide edema. B (axial), C-D (coronal): T1-weighted images with homogeneous contrast enhancement after Gadolinium administration.

FIGURE 2 A: Diffuse infiltration of large atypical T-cells (H-E, 100x). B: Higher power detail, showing hallmark T-cells with large bean-shaped nuclei (H-E, 200x). C: Diffuse immunopositivity for CD30 (200x). D: Immunoreactivity for EMA (200x).



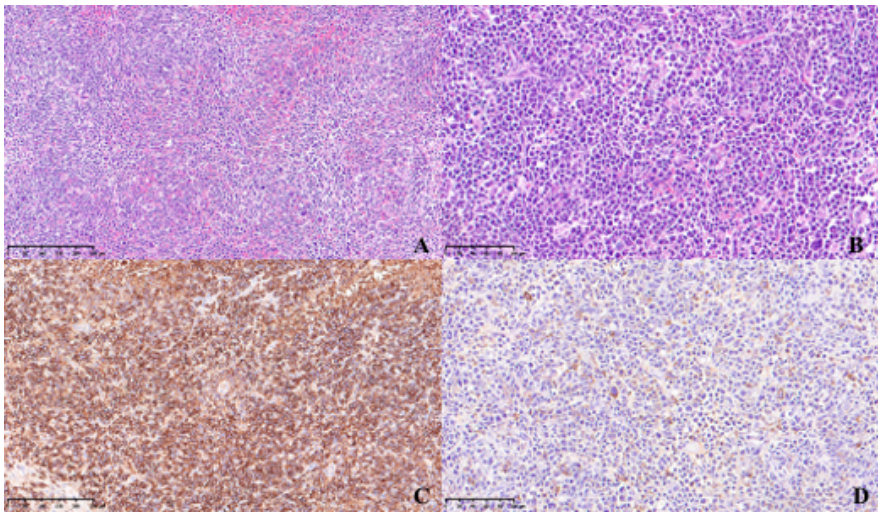


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TABLE 1.docx available at https://authorea.com/users/627444/articles/648385-primary-central-nervous-system-anaplastic-large-cells-lymphoma-in-children-case-presentation-and-systematic-review-of-literature