Isolated tumorous Langerhans cell histiocytosis of the brainstem: a diagnostic and therapeutic challenge

Case report

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Langerhans cell histiocytosis (LCH) of the CNS is a rare entity, known to involve primarily the hypothalamic-pituitary region, with the clinical hallmark of diabetes insipidus. There have been a few reports of CNS LCH involving the brainstem as intraparenchymal enhancing lesions, but this has never been the presenting complaint of LCH. The authors report on a 7-year-old boy who presented with right cerebellopontine syndrome, in whom a well-defined, solid, enhancing lesion in the brainstem was diagnosed. Clinicoradiological differential diagnosis included glioma and tuberculosis. Biopsy revealed atypical histiocytes positive for CD68, CD1a, and S100 protein; these are the diagnostic features of LCH on histopathological examination. The rapid growth of the lesion was controlled with a chemotherapeutic regimen of cladribine. (http://thejns.org/doi/abs/10.3171/2013.6.PEDS13132)

KEY WORDS • central nervous system • Langerhans cell histiocytosis • brainstem • treatment options • oncology

Langerhans cell histiocytosis is a rare disease of the monocyte-macrophage system and includes the subtypes Letterer-Siwe disease, Hand-Schuller-Christian disease, and eosinophilic granuloma. Cases of LCH most often present in childhood, with the clinical presentation ranging from a single bone involvement to widespread multiorgan involvement.1 Lytic craniofacial bone lesions and hypothalamic-pituitary region involvement, with the clinical presentation of diabetes insipidus, are the hallmarks of CNS LCH.3 Intracranial lesions have been observed during the course of disease in patients with proven LCH, and also as the first and presenting manifestations of LCH, albeit rarely.3,4 Different patterns of CNS involvement are described in the MRI-based classification system of CNS LCH.7 Enhancing parenchymal CNS lesions are very rare, and such lesions involving the brainstem have been described in few case reports.6,11 Such lesions cause considerable diagnostic problems because no morphological patterns characteristic of LCH have been identified to facilitate prompt diagnosis.9

We present a case of solitary CNS LCH lesion of the brainstem in a child, primarily presenting as right cerebellopontine syndrome. We describe the characteristic pattern of LCH on immunohistochemical investigation and document the rapidly growing nature of the LCH lesion in our patient, which eventually responded to chemotherapy.

Case Report

History and Examination. A 7-year-old boy presented with gradually worsening left facial paresis of 3 months’ duration, along with frequent headaches and vomiting. The mother reported that the child had frequent falls while walking. There was no history of seizures, respiratory complaints, jaundice, pathological fractures, or any other systemic illness. Neurological examination revealed right-sided abducence, facial, and vestibulocochlear nerve involvement. Bilateral pyramidal tracts were involved, with hypertension and exaggerated deep tendon reflexes in all 4 limbs. Right-sided cerebellar signs were positive and the patient had gait ataxia. Results of the rest of the systemic examination were unremarkable, and results of the baseline blood investigations were normal.

This article contains some figures that are displayed in color online but in black-and-white in the print edition.
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Radiological Findings. Admission MRI studies revealed a well-defined, rounded, “solid” lesion involving the middle cerebellar peduncle and dorsal aspect of the pons on the right side. The lesion was isointense on T1-weighted imaging, hypointense on T2-weighted imaging, intensely enhancing with contrast administration, and showing moderate perilesional edema (Fig. 1). Additional findings included thrombosis of the posterior superior sagittal sinus and transverse sinus. There was no abnormality noted in the hypothalamic pituitary region, with normal bright spot of the posterior pituitary seen on T1-weighted imaging. Based on the clinicoradiological correlation, our differential diagnosis included a brainstem glioma or an inflammatory lesion, typically tuberculosis.

Operative Findings and Postoperative Course. The patient underwent suboccipital craniectomy with subtotal excision of the tumor. Intraoperatively there was a firm, nonsuckable, and mildly vascular tumor that was firmly adherent to the surrounding brainstem. The lesion was not amenable to removal even with a Cavitron ultrasonic aspirator. Our impression was of a granulomatous lesion. Examination of a frozen section was inconclusive and histopathological findings favored an inflammatory lesion, for which the patient was started on a 4-drug antitubercular regimen. Postoperatively the patient did not have any additional deficits. However, he had an episode of generalized tonic-clonic seizure on postoperative Day 1. The patient deteriorated to a Glasgow Coma Scale score of E3/V(tracheostomy)/M5 status postictus and continued to be in the same status for the next month. The lack of improvement in his clinical status and the increase in size of the lesion on repeat imaging, in spite of the patient receiving antitubercular drugs, prompted us to bring him to the operating room for reexploration. He underwent reexploration via the suboccipital approach and intratumoral decompression of the lesion. The lesion was firmly adherent to the adjoining brainstem, which precluded its total excision.

Histopathological Findings. The biopsy sample obtained after the second surgery revealed sheets of atypical histiocytes. These cells were mildly pleomorphic with indented, bean-shaped nuclei and abundant cytoplasm. The background showed mixed inflammatory cell infiltrate composed of eosinophils, lymphocytes, and plasma cells. The tumor was invading adjacent brain parenchyma, with evidence of reactive gliosis. The histiocytes were positive for CD68, CD1a, and S100 protein, confirming a diagnosis of LCH (Fig. 2).

Treatment and Follow-Up. After the second procedure and successful histopathological diagnosis of the lesion, the patient was thoroughly investigated for evidence of LCH at non-CNS sites. Results of the skeleton survey, chest radiograph, liver function tests, and bone marrow examination were normal. Examination of CSF demonstrated a normal cytology and protein/sugar content. Thus, a diagnosis of isolated (single-system) CNS tumorous LCH was made and the patient was treated with chemotherapy. Cladribine (2-chlorodeoxyadenosine) was administered as 5 mg/m2/day in 250 ml/m2 normal saline, as a 2-hour intravenous infusion daily for 5 days per course.

A total of 6 courses were administered. The chemotherapy was well tolerated, with no episodes of febrile neutropenia. At 1-year follow-up, the patient has neurological sequelae. The CNS lesion has shown partial response (>60% regression) (Fig. 3).

Discussion

Central nervous system LCH lesions have been classified into tumorous/granulomatous lesions, nontumorous/nongranulomatous lesions, and brain atrophy.7 Solitary intraparenchymal CNS lesions without signs of systemic disease predominantly occur in the hypothalamic-hypophysial axis.2,3 The second most frequent presentation of CNS LCH is a combination of pathological changes in the cerebellum, basal ganglia, and/or pons, with a characteristic MRI pattern, which is termed “radiological neurodegeneration.”7

A tumorous lesion of the CNS is defined as a space-occupying lesion involving brain structures. These tumoralike lesions are contrast enhancing on MRI, which distinguishes them from the nonenhancing lesions without mass effect that are referred to as neurodegenerative-like pathological entities.3 Pathologically, tumorous lesions have been shown to be active LCH, whereas neurodegenerative lesions are thought to represent a cytotoxic/antigen activity reaction or the late effects of cytokine damage.7 A solitary tumorous CNS LCH lesion occurring outside the hypothalamic-pituitary region without extracranial involvement is rare.20 In a report on 69 children with LCH from our institution, none had CNS LCH.1

Fig. 1. Brain MRI studies showing the right-sided pontine lesion that is isointense on T1-weighted imaging (A), hypointense on T2-weighted imaging (B), and shows intense enhancement on contrast administration (C and D).
The review of literature on intracranial LCH by Bergmann et al. and Cagli et al. documents that the majority of patients were young males and that they presented with either acute headache or seizures.3,4 Our patient was a 7-year-old boy presenting with neurological symptoms of right cerebellopontine syndrome. On MRI, tumorous CNS LCH lesions manifest as enhancing masses, which are iso- or hypointense on T1-weighted imaging and hyperintense on T2-weighted imaging. Our case was unique in that the lesion was hypointense on T2-weighted imaging. This feature suggested an inflammatory pathology. Taking into consideration the age group, socioeconomic stratum, and radiological features of this patient, our differentials included brainstem glioma and tuberculoma. Our aim surgically was to decompress the lesion and establish a histopathological diagnosis, considering the critical location of the lesion and the fact that tuberculomas usually respond to drug therapy. Intraoperatively, the firmness of the tumor and its adherence to the surrounding brainstem was highly suggestive of an inflammatory pathology. We stopped after taking an adequate biopsy sample because we did not wish to give the patient postoperative deficits. In hindsight, the presence of ill-formed granulomas (sometimes seen in LCH pathology) and the fact that Langerhans cells may mimic epithelioid cells seen in tuberculosis could have led us to overlook the rare entity of CNS LCH. However, the lesson learned is that nuclear atypia in epithelioid cells should always be investigated further with immunohistochemical studies.

The clinical deterioration and increase in size of the lesion on repeat imaging, even though the patient was receiving antitubercular treatment, made us reconsider our diagnosis. This led to the second surgery, in which we performed intratumoral decompression of the lesion. The mainstay of therapy for intraparenchymal LCH has been, when possible, complete surgical excision. For incompletely excised lesions and local recurrence, postoperative radiotherapy has been used.10 Conventional radiotherapy poses many problems for the treatment of brainstem tumors; radionecrosis is one of the adverse effects. Gamma Knife surgery has been used as a treatment option for a case of brainstem LCH.4 The response rate to radiation therapy has been estimated at 50%–70%. According to the treatment protocol of the Third International Study for Langerhans Cell Histiocytosis, a 6-month course of chemotherapy is required for CNS LCH lesions.5 Cladribine (2-chlorodeoxyadenosine) is an active drug in patients with CNS LCH, and has shown very good response in tumorous lesions of the CNS due to LCH.6

The course of LCH is unpredictable, with a spectrum of spontaneous regression, chronic recurrences, or a rap-

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**Fig. 2.** Photomicrographs of tumor sections. A: Medium-power micrograph showing a polymorphic population of cells composed of pleomorphic tumor cells intermixed with lymphocytes, eosinophils, and occasional plasma cells. The larger pleomorphic cells range from round to oval to spindle shaped, and have large single to multiple vesicular nuclei with prominent nucleoli. H & E, original magnification ×450. B and C: High-power photomicrographs showing diffuse strong granular cytoplasmic positivity for CD1a (B) and CD68 (C) by the larger pleomorphic cells. Peroxidase antiperoxidase, original magnification ×450. D: High-power photomicrograph showing many of the larger pleomorphic cells, which have strong diffuse cytoplasmic positivity for S100. Peroxidase antiperoxidase, original magnification ×450. E: Medium-power photomicrograph showing a few scattered glial fibrillary acidic protein–positive cells among the other cells of the tumor indicating residual glial cells. Peroxidase antiperoxidase, original magnification ×300.

**Fig. 3.** Brain MRI studies obtained with contrast enhancement showing axial image with lesion at presentation (A), follow-up axial image at 2 months showing almost doubling of the lesion (B), and axial (C) and sagittal (D) cuts showing response of the lesion to chemotherapy at 1-year follow-up.
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idly fatal deterioration. After 2 decades of research in CNS LCH there are considerable gaps in understanding the disease process and its course. Limited follow-up with respect to CNS LCH lesions indicates that patients with extrahypothalamic LCH may have a better prognosis than those with hypothalamic LCH. The lesion in our patient doubled in size in 2 months, with associated clinical deterioration. However, after successful diagnosis and treatment with a chemotherapeutic regimen of cladribine, the lesion has shown good response at the 1-year follow-up (Fig. 3).

We present a rare case of LCH presenting as a solitary brainstem lesion. There have been reports of previously diagnosed patients with LCH harboring brainstem masses, but the patients did not present with these lesions. The diagnosis of LCH was never considered in our case until the second histopathological investigation revealed atypical histiocytes. This may have affected the management of our patient’s disease because we were not able to offer adjuvant therapy earlier.

**Conclusions**

We report a solitary CNS LCH of the brainstem, with classic immunohistochemical characteristics, presenting primarily as a cerebellopontine syndrome. The lesion showed rapid growth on follow-up imaging, but eventually responded to chemotherapy.

**Disclosure**

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Savardekar. Acquisition of data: Savardekar, Tripathi. Analysis and interpretation of data: Bansal, Vaiphei, Gupta. Drafting the article: Savardekar, Tripathi, Gupta. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Savardekar.

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