Histiocytic lesion mimicking intrinsic brainstem neoplasm

Case report

KYLE D. WEaver, M.D., DIANE ARMAO, M.D., JOSEPH M. WILEY, M.D., AND MATTHEW G. EWEND, M.D.

Divisions of Neurosurgery, Neuropathology, and Pediatric Hematology/Oncology, University of North Carolina—Chapel Hill School of Medicine, Chapel Hill, North Carolina

Cerebral histiocytic lesions are a rare disease involving the monoclonal proliferation of a weakly phagocytic dendritic antigen–processing cell, usually of the Langerhans variety. These lesions occur primarily in children, usually in those between 1 and 15 years of age. At the time of discovery of the intracranial lesion, more than one third of patients have evidence of multisystemic disease, usually pulmonary, hepatic, or hematopoietic. The most common site of central nervous system (CNS) involvement is the hypothalamus, and patients frequently present with diabetes insipidus. Involvement of other locations such as the brainstem and cortex is uncommon and occurs later in the course of the disease, frequently with multiple intracerebral and bone lesions. We describe for the first time an isolated case of brainstem histiocytosis in a child with no other stigmata of this disease. The original radiographic diagnosis of intrinsic brainstem glioma had been adopted without confirmation on pathological studies, inappropiate therapy might have been initiated.

KEY WORDS • histiocytosis • dendritic cell • brainstem glioma • excisional biopsy • radiotherapy

This 10-year-old girl presented with a 1-month history of progressive bulbar palsy and a solitary enhancing mass originating within the floor of the fourth ventricle. Results of initial imaging studies and presentation were suggestive of neoplasia. Subtotal resection was performed and pathological examination revealed the mass to be a histiocytic lesion, with no evidence of a glioma. The patient had no other stigmata of histiocytosis and was treated with steroid medications, resulting in prolonged resolution of the lesion. This case demonstrates that for discrete brainstem lesions the differential diagnosis includes entities other than glioma for which treatment is available. Biopsy sampling should be considered when technically feasible.

Case Report

History and Examination. This otherwise healthy 10-year-old girl presented with a 3.5-week history of nausea, vomiting, and anorexia. Initially she was treated for gastrixis, dysphonia, and sialorrhea. Three days before presentation a right-sided facial palsy was noted and the patient complained of dizziness. On physical examination, she was found to be lethargic with right-sided sixth and peripheral seventh cranial nerve palsies. Her gag and cough reflexes were intact. She showed marked ataxia on finger-to-nose testing on the right side. Her muscle strength was full in all extremities.

Administration of intravenous dexamethasone was begun and the patient was electively intubated for airway protection because of concerns about progressive bulbar compromise.

Imaging Studies. Magnetic resonance (MR) imaging revealed a 1-cm-diameter expansile mass originating in the caudal pontine tegmentum at the pontomedullary junction. The mass was hypointense on T1-weighted MR images and moderate brainstem edema was demonstrated on T2-weighted images. Contrast enhancement was brisk and homogeneous, with no evidence of cystic or nodular architecture (Fig. 1 left and center). Although relatively discrete, the mass was intrinsinc to the brainstem and was not exophytic. No other intracranial or bone lesions were noted.

Operation. Based on the MR imaging findings, a tentative diagnosis of brainstem glioma was made. Because the lesion appeared discrete and it approached the fourth ventricular floor, surgical exploration was undertaken via a transvermian approach to the fourth ventricle. On entering the fourth ventricle, a bulge in the floor was noted in the area of the stria medullaris. The tumor itself was not visible on the floor of the fourth ventricle, which was opened lateral to the facial colliculus to reveal a grayish tumor that
was distinct from the surrounding brainstem. The tumor was easily debulked initially, but the tumor plane became less distinct as the dissection continued anteriorly and subtotal resection was performed.

**Histological Examination.** On microscopic evaluation we noted abundant macrophage- or histiocyte-like cells arranged in sheets and loosely aggregated clusters (Fig. 2). Infiltrating cells possessed deeply eosinophilic granular to slightly vacuolated cytoplasm, with crisp cell borders and eccentric nuclei, and a few multinucleated forms were present. The phagocytic nature of these cells was demonstrated by the occasional engulfment of red or white blood cells. This proliferation was flanked by moderate reactive astrocitosis. A sparse chronic inflammatory infiltrate was present; mitotic activity or necrosis was not visualized.

Immunohistochemical staining revealed strong positivity of infiltrating histiocytes for alpha-1 antichymotrypsin but not CD1a. Glial fibrillary acidic protein staining demonstrated positive reactivity of astrocytes, whereas histiocytes remained uniformly negative. The S-100 stains were positive for two populations of cells; reactive glial cells with multiple stellate processes and a more uniform population of rounded, plump cells that showed cellular phagocytosis. Leukocyte common antigen staining disclosed positivity of the chronic inflammatory infiltrate. Immunohistochemical stains for actin, desmin, and epithelial markers, including low- and high-molecular-weight cytokeratins, were nonreactive. There was no evidence of acute or chronic infection; no other inflammatory cells were detected and organisms were lacking.

**Postoperative Course.** Postoperatively, the patient made a good recovery. All cranial nerve palsies slowly resolved and she was able to tolerate a regular diet by the time of discharge. She was treated with a short course of dexamethasone, and follow-up MR imaging demonstrated progressive shrinkage and near-disappearance of the lesion. Because of her excellent neurological functioning and radiographic improvement, radiotherapy was deferred and MR surveillance of the lesion was initiated.

One year postsurgery, her neurological status remains stable, with no radiographic evidence of disease progression (Fig. 1 right). At 18 months of follow up we have not observed the development of further histiocytic lesions or encountered the appearance of a primary extracranial neoplasm.

**Discussion**

This is the first report of an isolated brainstem histiocytic lesion in a child. High-grade glioma is the most likely diagnosis in a child presenting with an enhancing brainstem lesion and bulbar palsies. However, several other potentially treatable diseases such as metastases, eosinophilic granuloma, tuberculosis, sarcoidosis, bacterial and fungal abscesses, and nonglial malignant tumors should be considered in the diagnosis. There is significant controversy regarding the appropriate surgical therapy for intrinsic brainstem gliomas, with attempted excision beyond biopsy sampling not recommended. The findings in this case present an interesting and somewhat confusing diagnostic dilemma. The presence of a large pontine lesion associated with rapidly progressive cranial nerve...
Isolated pediatric brainstem histiocytosis

deficits in a 10-year-old child indicates a primary CNS malignancy. In most situations the position of the tumor would preclude surgical removal and perhaps even biopsy sampling. In this case the the pathological findings for the lesion were clearly not those of a primary CNS malignancy and it was treated in a very different manner, with a successful outcome. This case demonstrates the importance of excisional biopsy studies in accessible pediatric brainstem lesions to avoid the initiation of potentially harmful therapy.

Although histiocytic diseases are uncommon, CNS complications are noted in 15% of children with this diagnosis. Of these, 15 to 50% develop diabetes insipidus secondary to hypothalamic involvement. Disease in the CNS usually occurs secondary to spread from contiguous osseous sources; isolated disease is uncommon. Isolated brainstem histiocytosis in a child such as in this case has never before been reported.

Histiocytic diseases are a loose group of poorly defined pathological conditions including eosinophilic granuloma, Hand-Schüller-Christian disease, and Letterer-Siwe disease. These were recognized to be different manifestations of a single disease process by Lichtenstein13 and grouped under the name “Hand-Schüller-Christian disease, and Letterer-Siwe disease.” Four classes were described: Class I (Langerhans cell histiocytosis); Class II (genetic and sporadic hemophagocytic lymphohistiocytosis); Class III (malignant disorders of histiocytes as acute monocytic leukemias and malignant histiocytosis); and Class IV (other histiocytic syndromes such as sinus histiocytosis with massive lymphadenopathy [Rosai-Dorfman disease], xanthogranuloma, and reticulohistiocytoma). The pathogenesis of the proliferative histiocytic diseases is poorly understood, with neoplastic, viral, and cytokine-mediated origins all receiving moderate support.

The diagnosis of subclasses of CNS histiocytic diseases, the most common being the Langerhans cell variety, rests on microscopic and immunohistochemical studies. The histological appearance is quite variable, but usually contains a polymorphic infiltrate of histiocytes and other cells of the lymphoreticular lineage. Giant cells may be found in a minority of specimens. Electron microscopy or immunohistochemical investigations are required to differentiate between the subclasses of the disease. Requirements for a diagnosis of Langerhans cell histiocytosis include demonstration of Birbeck granules on electron microscopy and immunopositivity for CD1a. Our patient’s tumor was CD1a-negative, and thus a specific diagnosis of Langerhans cell histiocytosis could not be given. However, the light microscopy and other immunohistological characteristics of the lesion are consistent with histiocytic disease.

The treatment of histiocytic syndromes depends largely on the location of the lesion and the severity of the symptoms. Therapy of CNS lesions is most frequently undertaken in the setting of progressive multisystemic disease. Very little experience has been gained in the therapy of isolated CNS disease. In patients with the Langerhans cell variety, multiple chemotherapeutic regimens, including vincristine, vinblastine, doxorubicin, cytosine arabinoside, etoposide, and prednisone have been used with varying success. Historically, radiation therapy has been used successfully in the management of cutaneous or bone lesions, but has been used infrequently since the discovery of the spontaneously regressive nature of these lesions. Emergency low-dose radiotherapy (600–1000 cGy) to sensitive regions (that is, optic apparatus, spinal cord) may be beneficial in patients with rapidly progressive neurological deficits.

In most studies of isolated CNS histiocytosis the number of patients is small, and therapeutic strategies have varied widely. A significant number of cases remain stable, both with and without resection. In patients in whom the diseases progresses, low-dose radiotherapy and specific chemotherapeutic agents preceded by corticosteroid therapy may slow or halt disease progression.

Histiocytosis in the CNS can mimic primary CNS neoplasms in many locations, including the brainstem. Frequently, the presence of systemic manifestations aids in the diagnosis of the intracranial lesion, and treatment of asymptomatic or minimally threatening lesions can be deferred. However, localized CNS histiocytic diseases may be difficult to differentiate from gliomas without histological analysis. Chemo- and radiotherapy protocols for CNS histiocytosis are significantly different from those for intrinsic neoplasms, and the lack of an adequate tissue diagnosis may result in the administration of unnecessarily, and possibly harmful, therapy. The diagnosis of brainstem gliomas on MR images is usually straightforward. However, the differential diagnosis of atypical lesions includes entities such as histiocytic disease, for which therapy is available. Thus, an important role remains for surgical biopsy and/or resection of brainstem lesions.

References

2. Berry DH, Becton DL: Natural history of histiocytosis-X. Hema-

4. Dunger DB, Broadbent V, Yeoman E, et al: The frequency and natural history of diabetes insipidus in children with Langer-
5. Egeler RM, D’Angio GJ: Langerhans cell histiocytosis. J Pedi-

atr 127:1–11, 1989
7. Epstein F, McCleary EL: Intrinsic brain-stem tumors of child-

8. Favara BE, Jaffe R: The histopathology of Langerhans cell his-


ment strategy for pediatric brainstem tumors. Med Pediatr On-
col 17:117–126, 1989

study of adult histiocytosis X involving the brain. J Neurol

Neurosurg Psychiatry 56:1008–1012, 1993

Manuscript received April 13, 1999.
Accepted in final form July 23, 1999.
Address reprint requests to: Matthew G. Ewend, M.D., Division of Neurosurgery, University of North Carolina–Chapel Hill, 148 Burnett-Womack/CB#7060, Chapel Hill, North Carolina 27599–7060.