Isolated histiocytosis X of the hypothalamus

Case report

PHILLIP A. TIBBS, M.D., VENKATA CHALLA, M.D., AND RICHARD H. MORTARA, M.D.

Department of Surgery, Division of Neurosurgery and Department of Pathology, University of Kentucky Medical Center, and Saint Joseph's Hospital, Lexington, Kentucky

Failure to consider histiocytosis X in the differential diagnosis of hypothalamic masses may lead to inappropriate empirical radiotherapy. This report concerns a case of histiocytosis X of the hypothalamus, unassociated with systemic histiocytic lesions, in which early biopsy allowed specific therapy with subsequent total regression of the lesion.

KEY WORDS ▪ hypothalamus ▪ hypothalamic tumor ▪ histiocytosis X ▪ diabetes insipidus ▪ eosinophilic granuloma

CENTRAL nervous system involvement is not uncommon in cases of disseminated histiocytosis X, but presentation of this disorder as an isolated hypothalamic mass lesion is rare. Failure to make a definitive histological diagnosis wastes an equally rare opportunity to eradicate the granulomatous mass without the risks of empirical high-dose irradiation to the hypothalamus. This report describes a case of primary hypothalamic histiocytosis X in which early diagnosis by biopsy of the hypothalamic lesion led to the choice of low-dose irradiation and long-term prednisone therapy. There was total remission of intracranial disease during a 3-year follow-up period.

Case Report

This 10-year-old boy presented with a 6-month history of malaise, nausea, vomiting, and visual loss. Just before admission he had developed frontal headaches, and his schoolwork had deteriorated.

Examination. He was a somnolent, well developed boy with a temperature of 100.4° F. Funduscopic examination was normal. Visual field testing revealed an altitudinal defect on the right. Mild right facial weakness and hemiparesis were present. Deep tendon reflexes were brisk but symmetrical. No signs of cerebellar dysfunction were noted.

Urine output ranged from 4 to 6 liters/day with a maximum specific gravity of 1.002; urine specific gravity did not rise with water deprivation. Serum and urine osmolalities were 281 and 86 mOsm/ml, respectively. Serum electrolytes were normal. Other endocrine studies were compatible with moderate panhypopituitarism with low values recorded for thyroid-stimulating hormone, human growth hormone, 4 p.m. cortisol, and
thyroxine. Chest film, skull series, tomography of the sella turcica, and radionuclide brain scan were normal. Generalized delta grade II was present on the electroencephalogram. Cerebral angiography suggested moderate ventricular dilatation. Pneumoencephalogram revealed a mass displacing the anterior wall of the third ventricle superiorly and posteriorly (Fig. 1).

**Operation.** Biopsy of the anterior hypothalamic mass was performed through a right frontal craniotomy. The optic nerves appeared uninvolved but an abnormal dark gray mass was adherent to the lamina terminalis, appeared to infiltrate the hypothalamus bilaterally, and encroached upon the posterior margin of the optic chiasm.

**Histopathological Examination.** Microscopically, the fragments of tissue were composed of diffuse proliferation of mononuclear cells with pale cytoplasm and oval or elongated vesicular nuclei containing small nucleoli. Admixed with these cells were vacuolated histiocytes, small lymphocytes, and plasma cells (Fig. 2). Eosinophils were found occasionally. Multinucleated giant cells were not present. Stains for bacteria, acid fast bacilli, and fungi were negative. In view of the infrequency of eosinophils and the presence of vacuolated histiocytes, the lesion was thought not to represent either eosinophilic granuloma or nonlipid reticuloendotheliosis (Letterer-Siwe syndrome). Four independent pathologists concluded that the lesion represented histiocytosis X.

**Postoperative Course.** The patient’s neurological examination was unchanged after surgery. Diabetes insipidus was managed with lysine vasopressin insufflation, and prednisone therapy was begun. Repeat chest film, bone survey, and bone scan were normal. Bone-marrow aspiration was normal except for slight normoblastic hyperplasia and eosinophilia. One month after operation he developed hepatomegaly and abdominal distention. Liver biopsy showed fatty infiltration with no histological characteristics of histiocytosis X. The patient remained on prednisone and received 1500 rads of radiotherapy to the hypothalamic area. When computerized tomography scan (CT) became available in the postoperative period, sequential scans of the head demonstrated reduction, then disappearance of the mass (Fig. 3). Because of the excellent response to low-dose radiotherapy and prednisone chemotherapy, treatment with alkylating or cytotoxic agents was deferred. Oral prednisone was continued for 6 months. Although continuing vasopressin therapy has been required, there has been no evidence of recurrent hypothalamic lesion over a 3-year follow-up period. At the present time the patient is alert, oriented, and attends school but has a bitemporal hemianopsia.

**Discussion**

Histiocytosis X is a non-neoplastic disorder of unknown etiology characterized by masses of proliferating histiocytes, plasma cells, and eosinophilic inflammatory cells forming granulomata within the reticuloendothelial elements of any organ system in the body.\(^1,13\) The three clinical syndromes of this condition, eosinophilic granuloma of bone, Hand-Schüller-Christian disease (chronic disseminated form), and Letterer-Siwe disease (rapidly progressive non-lipoid systemic histiocytosis), were unified in 1953 by Lichtenein into a single nosological entity.\(^10\)

Cerebral involvement as a complication of systemic histiocytosis X is not uncommon. It occurs more often in males than females and in children than adults, but has been reported in all age groups in both sexes.\(^5,9,17\) There is a predilection for the hypothalamic area, although cases have been reported in the cere-
<table>
<thead>
<tr>
<th>Case No.</th>
<th>Authors, Year</th>
<th>Age, Sex</th>
<th>Chief Complaint</th>
<th>Endocrine Status</th>
<th>Contrast Studies</th>
<th>Diagnosed By</th>
<th>Therapy</th>
<th>Gross Pathology</th>
<th>Microscopic Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cureton, 1949</td>
<td>17, M</td>
<td>polydipsia, headaches</td>
<td>DI, 1 year, cachexia</td>
<td>PEG normal</td>
<td>autopsy</td>
<td>none</td>
<td>&quot;xanthomatous&quot; tumor in hypothalamus &amp; thalamus</td>
<td>foamy cells, eosinophils</td>
</tr>
<tr>
<td>2</td>
<td>Weitzman &amp; Friedman, 1960</td>
<td>27, F</td>
<td>confusion, somnolence, hyperosmolarity, amenorrhea</td>
<td>angiography: hydrocephalus; ventriculogram: anterior 3rd mass</td>
<td>autopsy (explored with no biopsy)</td>
<td>none</td>
<td>mass in tuber cinereum</td>
<td>histiocytic granuloma</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Kepes &amp; Kepes, 1969</td>
<td>63, F</td>
<td>weakness, nausea</td>
<td>normal</td>
<td>angiography: hydrocephalus</td>
<td>autopsy</td>
<td>none</td>
<td>rubbery lesion of anterior hypothalamus</td>
<td>histiocytosis, lymphocytes, plasma cells, eosinophils</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>19, F</td>
<td>headache, vertigo, fever,</td>
<td>DI, 2 years, obesity, amenorrhea</td>
<td>ventriculogram: &quot;inoperable&quot; hypothalamic mass</td>
<td>autopsy</td>
<td>none</td>
<td>mass in tuber cinereum</td>
<td>lipid-laden histiocytic granuloma</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>20, M</td>
<td>visual loss, nausea</td>
<td>DI, 3 years</td>
<td>enlarged optic foramen</td>
<td>hypothalamic biopsy</td>
<td>radiation</td>
<td>mass in Lt optic nerve &amp; hypothalamus</td>
<td>&quot;non-lipoid&quot; histiocytosis</td>
</tr>
<tr>
<td>6</td>
<td>Bernard &amp; Aguilar, 1969</td>
<td>20, M</td>
<td>headache, polyuria, somnolence</td>
<td>DI, 7 years, obesity, panhypopituitarism</td>
<td>PEG: anterior hypothalamic mass</td>
<td>autopsy</td>
<td>none</td>
<td>lesion through-out hypothalamus</td>
<td>foamy histiocytes, eosinophils, lymphocytes</td>
</tr>
<tr>
<td>7</td>
<td>Pressman, et al., 1975</td>
<td>21, F</td>
<td>fatigue, confusion, panhypopituitarism</td>
<td>PEG: hypothalamic mass</td>
<td>delayed biopsy of hypothalamus &amp; mandible</td>
<td>anti-tubercular drugs</td>
<td>not reported</td>
<td>hypothalamic biopsy insufficient; mandible: histiocytosis X</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>18, F</td>
<td></td>
<td>lethargy, fever, amenorrhea, polydipsia, polyuria</td>
<td>angiography &amp; PEG: &quot;glioma&quot;</td>
<td>delayed biopsy of lymph node</td>
<td>5000 rads</td>
<td>not reported</td>
<td>histiocytosis X</td>
<td></td>
</tr>
</tbody>
</table>

*DI = diabetes insipidus; PEG = pneumoencephalogram.
Diabetes insipidus was part of the original clinical triad of exophthalmos, diabetes insipidus, and bone defects of the skull described by Hand in 1893, and occurs in one-third to one-half of cases of histiocytosis X, often as an early or presenting sign. Other endocrine abnormalities, especially growth hormone deficiency, may coexist.

When a histiocytic granuloma arises in the hypothalamus in the absence of cutaneous, visceral, or skeletal forms of the disease, accurate diagnosis is difficult both clinically and pathologically. Fortunately, this circumstance is exceptional and well documented cases of isolated hypothalamic histiocytosis X are rare. Table 1 summarizes the clinical data in the eight cases of isolated histiocytosis X of the hypothalamus reported up to the present time. Cavanagh and Russell, Ezrin, et al.,7 Beard, et al., and Müller and Orthner reported cases with histiocytic xanthomatous granulomas in the hypothalamus, but their patients also had
Histiocytosis X of hypothalamus

FIG. 3. Left: Computerized tomography (CT) scan performed postoperatively but before radiotherapy revealing extensive involvement of hypothalamus and adjacent brain. Right: One year after completion of radiotherapy, CT scan indicates total regression of the lesion. Subsequent CT scans were also negative. All scans were contrast-enhanced.

multifocal intracerebral or extracerebral disease. The terms "Ayala's disease" and "Gagel granuloma" have also been used to describe this entity.9,12

Most examples of histiocytosis X presenting as a hypothalamic mass have been diagnosed at autopsy; in others, diagnosis was delayed until extracerebral disease appeared (Table 1). The present case emphasizes that good quality long-term survival is possible, even with a large histiocytic hypothalamic mass, if histopathological identification of the disease process is made early. Low doses of irradiation (300 to 1500 rads) are very effective in eradicating circumscribed skeletal or soft tissue lesions.1,11 Chemotherapy with prednisone, leukoblastine, or cyclophosphamide is adjunctive and of greatest benefit in disseminated forms of the disease, with 80% to 90% of patients responding.1,11,16 Empirical high-dose irradiation of histologically unidentified hypothalamic lesions in adults or children may therefore be suboptimal therapy.

Relating the present case to previous examples of primary hypothalamic histiocytosis X reported in the literature, several points in evaluation of an unidentified hypothalamic lesion should be confirmed with contrast studies, particularly the CT scan and pneumoencephalogram. Secondly, histiocytosis X should be included in the differential diagnosis of hypothalamic masses in both children and adults. A search for unrecognized extracerebral lesions accessible to biopsy should be conducted with a bone survey, bone scan, and bone-marrow biopsy. Liver biopsy should be performed if hepatomegaly is present. If no extracerebral lesions are found, hypothalamic biopsy is indicated to allow treatment based on early histopathological diagnosis.

References

4. Braunstein GD, Kohler PO: Pituitary function
P. A. Tibbs, V. Challa and R. H. Mortara


Address reprint requests to: Phillip A. Tibbs, M.D., Neurosurgery MS-107, University of Kentucky Medical Center, 800 Rose Street, Lexington, Kentucky 40506.