ANGERHANS cell histiocytosis (LCH) can involve virtually any site in the body and can occur as an isolated lesion or as widespread systemic disease.5,23 In acute disseminated LCH (also known as Letterer–Siwe disease), brain involvement often occurs, but most often it is detected only at autopsy in infants who have succumbed to disseminated disease.28 Involvement of the central nervous system (CNS) is relatively rare in unifocal eosinophilic granuloma,9,12,25 and Hand-Schüller-Christian (HSC) disease,6,11,15 and is usually localized in the hypothalamus and pituitary gland.1,15 Outside this region, cases of unifocal or multifocal LCH in the cerebellum,11 cerebrum,9,12,25 brainstem,36 optic chiasm,33 and spinal cord28 have been reported, but the involvement of choroid plexus in patients with HSC disease is exceedingly rare and has been reported in only two patients previously.21,37

We report a case of HSC disease with multiple LCH granulomas involving the choroid plexus of both lateral ventricles and the fourth ventricle.

Case Report

This 6-year-old boy presented with acute onset of headache, vomiting, right-sided Jacksonian seizure, and lethargy on July 10, 1994. He had been diagnosed with hemophilia B at the age of 5 months. At the age of 2 years and 6 months he was noted to have erythematous maculopapular rashes on the scalp, retroauricular region, and groin. Subsequently the rash progressed to involve the whole body, and progressive bilateral proptosis, polyuria, polydipsia, painful mass on the forehead, gum swelling, and otorrhea developed. When the patient was 3 years and 11 months old, the diagnosis of HSC disease was established on the basis of clinical manifestations and histopathological studies of his excised forehead mass. Skull x-ray films and abdominal ultrasonography at that time showed multiple lytic lesions and hepatomegaly, respectively. He showed complete response to vinblastine and prednisolone, but diabetes insipidus did not improve and required treatment with desmopressin acetate. He had remained in complete response to maintenance therapy with oral 6-mercaptopurine for 27 months until last admission.

Examination. The patient was 106 cm in height (below 3rd percentile) and his head circumference was 55 cm (50th–75th percentile). The scalp veins were prominent. Ophthalmological examination revealed bilateral proptosis and normal fundi. The patient was slightly lethargic.
and showed mild dysarthria. The remainder of the physical and neurological examination was unremarkable.

Skull x-ray films revealed bilateral bulgings and thinning of temporal squamae without any “punched-out” osteolytic lesions. A technetium-99m bone scan, chest x-ray film, and abdominal ultrasonogram were normal. A computerized tomography (CT) scan of the brain showed bilateral, nearly symmetrical sausage-shaped, isodense masses located in the choroid plexus of both lateral ventricles and extending to the foramina of Monro and trigona. The temporal horns of both lateral ventricles were found to be markedly dilated and entrapped due to obstruction of the trigone by intraventricular lesions. There were multiple small entrapped cerebrospinal fluid (CSF) spaces in both trigona. Edema was noted surrounding the trigona. The lesions showed intense, nearly homogeneous enhancement following injection of contrast material (Fig. 1).

**Laboratory Examination.** On admission, white blood cell count was 4550/mm³ with 84.4% neutrophils; platelet count was 614,000/mm³; and hemoglobin was 12.2 g%. The partial prothrombin time was 46.7 seconds (control 20–30 seconds), and the prothrombin time was 13 seconds (96% of normal). The coagulation factor IX activity was 45% of normal. Liver function test and electrocardiogram were normal.

**First Operation and Postoperative Course.** The patient was prepared for surgery with 4000 U of factor IX concentrate per day for 2 days. On July 27, 1994, a right temporoparietal craniotomy was performed with the patient under general anesthesia. The meninges appeared grossly normal. The temporal gyri were widened. Posterior and superior displacement of the sylvian fissure was found. The trigone of the lateral ventricle was entered through a vertical incision on the posterior middle temporal gyrus at a depth of approximately 1 cm and clear CSF flowed out. A large, very hard, moderately vascular, yellow–brown mass located along the choroidal fissure was noted. The normal choroid plexus could not be found. Separation of the mass from the ventricular wall was difficult due to severe adhesion to the ependymal wall; therefore the tumor was only partially excised.

The patient’s recovery was complete following operation. The normal prothrombin time was maintained by administration of factor IX concentrates. On the 8th postoperative day, sudden mild left hemiparesis and lethargy developed. A CT scan showed a small intracerebral hematoma in the right frontal lobe without midline shifting. The child was kept in intensive care and received high doses of steroids and coagulation factor IX. His neurological deficits improved gradually over the following several weeks. A follow-up CT scan showed disappearance of the hematoma, thin subdural fluid collection, and decrease in the size of the right temporal horn.

**Second Operation and Postoperative Course.** After discussion with a pediatric oncologist and radiation oncologist, we decided to decompress the tumor because it did not respond to chemotherapy and whole-brain irradiation (dose 1800 rads), and there was a possibility of shunt placement.
complications due to entrapped CSF spaces. On September 23, 1994, a left temporoparietal craniotomy was performed with the patient under general anesthesia. Fenestration of entrapped CSF spaces and partial removal of tumor were accomplished. The patient did not awaken after the operation, and a CT scan showed multiple intracerebral hemorrhage including the hypothalamus. He died on the 2nd postoperative day. An autopsy was not performed.

Pathological Examination. The surface of the specimen was irregular and varied from grayish-tan to brownish in color. The mass was firm in consistency. On sectioning, it was solid without evidence of necrosis or hemorrhage.

The major cellular components of the tumor were large oval round cells with either foamy or granular cytoplasm. They were scattered throughout the tissue along with eosinophilic and neutrophilic polymorphonuclear leukocytes. H & E, original magnification × 400. Large histiocytic cells staining positively with antibody to S-100 protein, a marker of pathological Langerhans cells. S-100 immunocytochemistry, original magnification × 400.

Discussion

At the meeting of the Histiocyte Society in 1985 it was recommended that LCH be used to replace the designations eosinophilic granuloma, HSC disease, Letterer-Siwe disease, and histiocytosis-X. These conditions are believed to represent different clinicoanatomical patterns of the same basic disorder, and although they differ with respect to the extent of organ involvement and the prognosis, they are unified by the presence in the lesions of large, histioyte-like cells that bear several similarities to Langerhans cells.5,16,23

Langerhans cells are known to be bone marrow–derived cutaneous dendritic histiocytes and bear Fe-imunoglobulin G and C3 receptors.14 They are not phagocytic,31 and contain unique Birbeck granules.2 Langerhans cells are the only extrathymic mononuclear cells to normally express the thymocyte differentiation antigen T6.22 Functionally, they present antigen to T lymphocytes in the induction phase of contact hypersensitivity reactions.34 It is clear that the proliferating histiocytes found in LCH are very similar, if not identical, to normal Langerhans cells.19 Nonetheless, several important questions remain regarding the relationship of the Langerhans cell to LCH. The etiology and pathogenesis of LCH remain unknown; however, there are indications that the disorder is associated with immunological aberrations.17

The writing group of the Histiocyte Society proposed strict diagnostic criteria of LCH.5 A higher level of diagnostic confidence (designated “diagnosis”) is justified when light microscopic findings are supplemented by the presence of two or more of the following features: 1) positive stain for adenosine triphosphatase; 2) S-100 protein; 3) α-1-d-mannosidase; or 4) characteristic finding of peanut lectin. “Definitive diagnosis” requires the identification of Birbeck granules in lesional cells by electron microscopy or demonstration of T6 antigenic determinants on the surface of lesional cells.

Because only 5% to 25% of patients with HSC disease exhibit classic triad,4,38 the term HSC disease is now more broadly used to include instances of more chronic evolution,29,30 occurring generally in children more than 3 years old. Clinical manifestations include multiple cranial lesions and sometimes involvement of other systems, or one of the other classic symptoms (exophthalmos or diabetes insipidus).

Although unifocal eosinophilic granuloma of the CNS unaccompanied by other systemic lesions is rare,6,12,25,35 CNS involvement as part of a systemic process is not uncommon (HSC disease, Letterer–Siwe disease).6,11,15,28 The intracerebral lesions are believed to be due to proliferation of the adventitial cells of blood vessels, creating at first perivascular histiocytic foci, which later coalesce to form a granulomatous mass15 and usually involve the hypothalamic–neurohypophyseal axis (that is, Gagel’s granuloma).16
Langerhans cell histiocytosis granuloma of choroid plexus

Recent case reviews suggest that the incidence of extrahypothalamic involvement is significantly higher than previously recognized. Extrahypothalamic forms of CNS involvement have been associated with a greater intensity and duration of disease activity, late occurrence in the disease course, and a poor prognosis. On review of the literature, we found three patients, including ours, with HSC disease in whom LCH granuloma developed in the choroid plexus. In 1967, Morello, et al. described a child with HSC disease who had bilateral LCH granulomas of the choroid plexus of lateral ventricles. Vaquero and coworkers also presented a case of LCH granuloma in the choroid plexus of the lateral ventricle in a patient with HSC disease. To our knowledge our case is the first reported case of LCH granuloma of the choroid plexus confirmed by electron microscopy and immunohistochemistry.

Langerhans cell histiocytosis granuloma of the choroid plexus must be distinguished from xanthogranuloma. The frequency of xanthogranuloma in the choroid plexus is 1.6% to 7%. These lesions tend to be more common in older than in younger patients and usually do not cause symptoms. Xanthogranuloma can be distinguished from LCH in that foamy cells show negative reactivity for S-100 and lack Birbeck granules on electron microscopic examination.

In reported cases of LCH granuloma in cerebral hemispheres, CT scans showed a low- to isodense mass with surrounding edema and homogeneous strong enhancement, and MR images showed low intensity or isointensity on T₁-weighted images, high intensity on T₂-weighted images, and homogeneous marked enhancement after the administration of Gd-DTPA. Thickening of the hypothalamus and/or the pituitary stalk in the absence of the posterior pituitary bright signal was seen in patients with LCH and overt diabetes insipidus. Findings on CT and MR studies in our case were consistent with the above-mentioned radiological findings.

The basic rule in treating LCH is that the aggressiveness of the treatment should be proportional to the aggressiveness of the disease in the individual patient. Although complete surgical excision of the intracranial lesion is the treatment of choice for unifocal intracerebral LCH, residual, recurrent, or systemic disease may respond to radiation or to chemotherapy. The response rate to either radiation or chemotherapy at various sites is approximately 50% to 70%, although some radioreistance may be encountered when the tumor is located in the cerebral parenchyma.

References


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Address reprint requests to: Eun-Young Kim, M.D., Department of Neurosurgery, Yonsei University College of Medicine, Severance Hospital, CPO 8044, Seoul, 120-752, Korea.