Histiocytosis X in the Optic Chiasm of an Adult with Hypopituitarism*

Case Report

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HISTIOCYTOSIS X (nonlipid eosinophilic granuloma, lipoid granulomatosis, xanthomatosis, reticuloendotheliosis, reticulosis, Hand-Schüller-Christian disease) is a well-known cause of cranial lesions, exophthalmos, visual loss, diabetes insipidus, and other hypothalamic-pituitary disturbances in children. Visceral and osseous involvement has been reported occasionally in adults with a seeming propensity for the pituitary-hypothalamic region. But an apparently isolated histiocytic granuloma mimicking a suprasellar tumor in an adult is extremely rare. We wish to report such an occurrence and to demonstrate the ultrastructure of the lesion which originated in the optic chiasm.

Case Report

The patient, a 34-year-old man, was admitted to St. Louis University Hospital on February 6, 1967, with a complaint of pain and dim vision in the left eye for 4 weeks. He had been struck over his left eye in an auto accident 1½ years earlier.

He had served in the army from age 19 to 21 and noted nothing abnormal until the age of 25 when he began to gain weight and lose libido. In the next 9 years, he went from 200 to 340 pounds. He shaved less frequently, and began to drink and urinate much more. He continued work as a metal inspector until his admission.

Examination. Vital signs were normal, height 73 inches, weight 335 lbs. The patient had a moon face, dry cracking skin, scanty body hair, female escutcheon, small soft testes, and extreme obesity of the trunk and extremities with no cutaneous striae. There was also bitemporal hemianopsia, extremely poor visual acuity on the left, and marked bilateral optic atrophy (Fig. 1). The patient's reflexes were not characteristic of hypothyroidism. The left eye was tender but not exophthalmic or inflamed.

X-rays of the skull, chest, and optic foramina were normal, with no areas of rarefaction of bone or changes in the sella turcica.

Laboratory examination showed a hematoctrit of 37%, a normal white blood cell count, and nonreactive tests for syphilis; the urinalysis was normal.

The generalized obesity was interpreted as due to an increased appetite and large consumption of food over many years. No signs of diabetes mellitus were present. An oral glucose tolerance test performed with 100 gm of glucose revealed a minimal elevation in blood sugar. During his hospital course the average daily output of urine was between 6 and 10 liters. The maximal specific gravity observed after 12 hours of water deprivation was 1.005. The intramuscular administration of 1.25 units of Pitressin tannate decreased urine output to 3.6 liters per day, and the specific gravity rose to 1.015. This confirmed the presence of diabetes insipidus. A fasting plasma growth hormone

![LEFT EYE (1/20) RIGHT EYE (20/40)]

Fig. 1. Visual fields at the time of admission. Visual acuities are indicated in parentheses.

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was 10.5 μg/ml. Hypoglycemia induced by intravenous administration of 8 units of insulin produced no elevation in growth hormone levels. Serum calcium was 4.6 mEq/liter, phosphorus 2.7 mEq/liter, alkaline phosphatase 1.6 S.U., and urinary hydroxyproline 38 mg/24 hrs. These data indicate an impairment of growth hormone secretion.

Clinical and laboratory evaluation of thyroid function revealed a mild secondary hypothyroidism. The protein-bound iodine was 3.3 μg%; the TBI 0.74, the radioactive iodine uptake at 6 hrs, 5%; at 24 hrs, 15%; and cholesterol 233 mg%. There was a 25% response of radioactive iodine uptake following administration of 10 units of thyroid-stimulating hormone per day, for 4 days. Adrenal function studies revealed 17 ketosteroids 10.5 mg/24 hrs, 17-OHcorticoids 4.2 mg/24 hrs, normal serum electrolytes: sodium 150 mEq/liter, potassium 4.1 mEq/Cl₂ 110 mEq/liter. Adrenal stimulation with 80 units of ACTHAR-Gel per day for 3 days increased the urinary output of 17-OHcorticoids fourfold. Oral administration of Metoprine (750 mg per 6 hrs) was not followed by an elevation of 17-OHcorticoids. These studies indicate a mild adrenal insufficiency due to impaired adrenocorticotrophin secretion. Hypogonadism was manifested by definitive changes in secondary sexual characteristics as well as functional impairment. Low urinary follicle-stimulating hormone (below 6 units) suggests that this hypogonadism was of secondary origin. Absence of gynecomastia or galactorrhea pointed out no impairment of prolactin secretion.

The endocrine-metabolic picture indicated incomplete panhypopituitarism and diabetes insipidus.

Operation. On February 24, a right frontal craniotomy was done for exploration of the chiasm. The right optic nerve had a brownish hue and was followed to its commissure. The left optic nerve was replaced by a tuberous, shaggy, brown mass which was incised, and biopsied.

The visible tumor appeared to be confined to the left optic nerve and chiasm; the right optic nerve appeared normal. The most likely gross diagnosis was optic glioma.

Postoperative Course. The patient had no light perception in the left eye. Vision in the right eye was unchanged. Pitressin was required for 2 weeks. He was maintained on cortisone acetate 25 mg per day, sodium levothyroxine 0.3 mg per day, and fluoxymesterone 10 mg per day. He received a 2700 r midline dose of radiation therapy over a 3-week period and is presently at work.

Histological Examination. There were numerous granulomas scattered in a matrix composed of many fine astrocytic fibers, a few large-bodied astrocytes, and moderate numbers of myelinated axons (in paraffin sections of the surgical specimen stained with hematoxylin and eosin). The cells within the granulomas were for the most part loosely arranged, small to medium in size, and polygonal or stellate in outline. Cytoplasmic vacuoles were absent. In the peripheral and central portions of several of the granulomas, large numbers of eosinophils were present. Nearby blood vessels were cuffed by mononuclear cells, mainly lymphocytes (Fig. 2).

Electronmicroscopic Examination. These elements were shown by electronmicroscopy in greater detail. After careful searching, a few histiocytes were found with characteris-

![Fig. 2. Photomicrograph of optic nerve showing two granulomas and an adjacent blood vessel cuffed by mononuclear cells. At the periphery of the larger granuloma there are moderate numbers of eosinophils and fibrous astrocytes. H. & T., ×100.](image-url)
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tic rod-shaped bodies in their cytoplasm (Fig. 3). These measured approximately 50 \( \times \) 200 \( \mu \) and had a double, beaded, outer membrane with a dense linear core (Fig. 4 left). These bodies are similar to those seen in granulomas of histiocytosis X from lung and bone by several French workers,\(^1,2,6,13\) from cutaneous lesions of Letterer-Siwe disease, and in a cranial lesion of a child with Hand-Schüller-Christian disease whom we have examined (Fig. 4 right). Identical structures have been seen in normal Langerhans cells in the epidermis of man and other mammals,\(^3,4,14\) the granules of Langerhans cells are shown in Fig. 5. Some of these granules have the shape of tennis rackets when cut in the proper plane, both in histiocytsis and in Langerhans cells, and there is some evidence that the handles are disc-shaped rather than rod-shaped. The composition and function of these structures are unknown. They have not been described in other cells. There is no known relationship between Langerhans cells and histiocytes. These characteristic granules have not been reported in normal histiocytes, but they could have been overlooked. Efforts by many workers to demonstrate reproductive or infectious properties of the contents of histiocytes within this type of granuloma have so far been negative.

**Discussion**

Histiocytosis X has been defined as: “a non-neoplastic, proliferative disorder of histiocytes, of unknown etiology, pathogenetically akin to an inflammatory reaction with multiple clinical manifestations mirroring the widespread distribution of the histiocytic system in the body.” Many terms and eponyms have been used to describe clinical syndromes which are now included under this category: Letterer-Siwe disease, Hand-Schüller-Christian disease, Schüller-Christian disease, eosinophilic granuloma of bone, xanthomatosis, lipid granulomatosis, aleu-

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Fig. 3. Electronmicrograph of a histiocyte within the left optic nerve. Myelinated nerve fibers and fibrous astrocytic processes are seen surrounding this cell. The histiocyte has a large irregular nucleus. Its cytoplasm is abundant with much endoplasmic reticulum, many ribonucleoprotein particles, and several mitochondria. Occasionally, large lipoid inclusions are found within the cytoplasm. At least one rod-shaped structure is present (arrow). \( \times 16,000. \)
Fig. 4. Left: Electronmicrograph showing the rod-shaped structure of Fig. 3 at greater magnification. A double outer membrane is present with an inner ribbon or core of material occupying the center of the seemingly tubular structures. $\times 77,000$. Right: Electronmicrograph from a biopsy of a lesion in the occipital bone of a 2-year old boy with multiple osteolytic lesions of the skull, and hypothalamic-pituitary insufficiency. The pathological diagnosis is classical Hand-Schüller-Christian disease. The histiocyte, or reticular cell, shown here contains a rod-shaped structure identical to those seen in our patient. Many such structures were found in this biopsy. $\times 92,000$.

Fig. 5. Photomicrograph of the cytoplasm of a Langerhans cell in the epidermis of a white rat. The rod-shaped granules have the same morphology as the structures within histiocytes of histiocytosis X. This micrograph illustrates the periodicity of the central core, which is also seen within the granules of some histiocytes. Similar structures occur in human Langerhans cells. $\times 72,000$. 
kemic reticulosis, and reticuloendotheliosis. Many pathologists believe all these conditions are related\(^8\) in certain respects, but others think some of them are distinct entities. It may be found that several etiological factors can cause histiocytic granulomas of varying severity in different age groups.

Histiocytosis X is an unusual cause of diabetes insipidus, hypopituitarism, or visual impairment in adults. Cavanagh and Russell\(^5\) reviewed the literature in 1954 and found seven patients over age 20 with lesions in or near the posterior pituitary. They reported two more such patients. All nine had xanthomatous lesions in bone, lung, and/or skin. Several had diabetes insipidus for a long time (up to 10 years) before the diagnosis of histiocytosis was made. Muller and Orthner\(^11\) found 17 cases of intracerebral “lipoid granulomatosis” in the literature before 1965, and reported two additional cases. One patient had the onset of diabetes insipidus 24 years before her death at age 53. At necropsy she was found to have multiple lesions in cerebrum, cerebellum, hypothalamus, and pituitary. Minute cerebral lesions may be overlooked in some widespread cases of histiocytosis.\(^12\)

In a series of 117 patients of all ages with all forms of histiocytosis X collected at the Mayo clinic\(^1\) from 1907–1962, 39 had only osseous involvement “eosinophilic granuloma,” five had only non-osseous involvement, and the remaining 73 had both osseous and non-osseous disease; 58 of these 73 were below age 15 years, leaving 15 adults with multiple histiocytic lesions. Seven of the 15 had diabetes insipidus, beginning at ages 21 to 49 years. None had exophthalmos. No mention was made of other neurological parameters. All but one of the adults were alive at the time of the survey.

A patient with a lesion very similar to the one in our patient was reported by Ezrin, et al., in 1963.\(^8\) This man developed diabetes insipidus at age 43. At age 47, an intradural, extramedullary non-specific granuloma was removed from the thoracic spinal cord. He developed panhypopituitarism and blindness over the next few years and died of myocardial infarction at age 55. Postmortem examination revealed a 3 cm mass in the interpeduncular fossa, pressing downward upon the optic nerves, replacing the infundibulum and invading the hypothalamus. He also had histiocytic granulomatous lesions of the heart, lungs, kidneys, and spinal cord. Miller and Ramsden\(^10\) reported a similar case in 1965.

No reason for the apparent propensity of histiocytosis for the pituitary-hypothalamic area is known. Paradoxically, the isolated lesions confined to bone (eosinophilic granuloma) almost never involve the sella turcica or sphenoid bone.

The treatment of histiocytosis X in adults is difficult to evaluate because of its very long natural course. Moderate doses of irradiation have seemed to arrest progression of osseous lesions. Children with extensive visceral involvement have been found to respond favorably to vinblastine in several instances,\(^8\) but longer follow-up is necessary to fully evaluate the efficacy of this drug in histiocytosis X.

We cannot be sure that our patient has only one lesion at present. As noted above some patients have had similar symptoms for many years and then have been found to have multiple, progressive lesions. This may occur in our case; therefore, careful follow-up is planned.

**Summary**

A 34-year-old man with a history of hypopituitarism for 9 years and sudden visual loss was found to have a histiocytic granuloma of the optic chiasm, with no other apparent visceral or osseous lesions. Electron-microscopy helped confirm the diagnosis by revealing characteristic cytoplasmic inclusions in the histiocytes. Their significance is unknown. Histiocytosis X should be considered in the differential diagnosis of lesions in the region of the hypothalamus, optic chiasm, and pituitary in adults as well as in children, although it rarely occurs in these sites as an isolated lesion.

**References**

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