A Case of Histiocytosis X associated with Panhypopituitarism and Hyperimmunoglobulinemia G and E

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Synopsis

A 43 year old man with diabetes insipidus who showed panhypopituitarism and marked hypergammaglobulinemia due to histiocytosis X is reported. His low basal plasma adrenocorticotropin (ACTH) and growth hormone (GH) failed to respond to insulin-induced hypoglycemia. His basal serum thyroid hormone level was below normal and normal basal plasma thyrotropin (TSH) showed a delayed response with normal peak value to TSH-releasing hormone (TRH). Normal basal plasma pituitary gonadotropin also showed a delayed response with normal peak value to luteinizing hormone-releasing hormone (LH-RH). Suppression of plasma prolactin (PRL) by levodopa (l-dopa) was impaired and elevation of basal plasma PRL was noted at the second admission. These results, combined with diabetes insipidus, suggested that the panhypopituitarism in these patients was hypothalamic in origin.

The polyclonal hypergammaglobulinemia was characterized by elevated serum IgG and IgE levels which returned to normal after corticosteroid treatment with concomitant clinical improvement. Elevated serum IgE levels, tissue and peripheral eosinophilia, and the effectiveness of corticosteroid therapy support the hypothesis that some allergic mechanism may be involved in the pathogenesis of this disease.

Diabetes insipidus is the most common endocrine manifestation of histiocytosis X. Various types of anterior pituitary insufficiency have occasionally been documented (Ezrin *et al.*, 1963; Braunstein and Kohler, 1972; Kaufman *et al.*, 1976), but are less common in Japan. Recently, further endocrine studies suggest that the histiocytic lesion resides mainly at the hypothalamic level (Gates *et al.*, 1973; Hirata *et al.*, 1975; Rothman *et al.*, 1978), which have been substantiated in postmortem studies (Bernard and Aguilar, 1969; Gates *et al.*, 1973). The present case exhibited panhypopituitarism. From hypothalamic-pituitary function studies, the site of lesion will be discussed in this paper.

Although several immunological abnormalities have been documented in histiocytosis X (Avioli *et al.*, 1963; Cederbaum *et al.*, 1972; Kikkawa and Inena, 1973; Leikin *et al.*, 1973), descriptions of serum IgE levels are rare (Hiwada, 1976). The present case presents not only marked hyperimmunoglobulinemia G but also elevated serum IgE levels with eosinophilia.

Methods

Assay methods

Serum triiodothyronine (T_3), thyroxine (T_4), TSH and testosterone were measured with radioimmunoassay kits from Eiken Immunochemical Laboratory. Plasma luteinizing hormone (LH), follicle-stimulating hormone (FSH) and resin T_3 uptake (RT_3U) were measured with radioimmunoassay kits from Daiichi

RI Laboratory. Plasma ACTH was measured with radioimmunoassay kits from Kaken Chemical Co., Inc. Plasma GH was assayed by the double-antibody radioimmunoassay technique using human GH NIAMDD HS2160E as a standard.

Test procedures

The insulin tolerance test was performed by administering 0.1 U/Kg body weight of regular insulin intravenously. TRH and LH-RH tests were performed by administering 500 μ g of TRH mixed with 100 μ g of LH-RH intravenously. L-dopa stimulation or suppression tests were performed by administering 500 μ g of L-dopa orally. The metochlopramide stimulation test of PRL was performed by administering 10 mg of the drug orally.

Case Report

A 43 years old Japanese man was admitted to our hospital on September 12, 1977, complaining of general weakness of 6 months' duration. He had noticed bilateral exophthalmos for the past 5 years. One year before admission, he noticed an abrupt onset of polyuria and polydipsia, and impotency simultaneously. His case was diagnosed as diabetes insipidus and had been treated with chlorpropamide, clofibrate and hydrochlorthiazide in another hospital. On admission, he was afebrile, but slightly anemic. Bilateral exophthalmos, periocular edema and ptosis were

noted. Fundus examination revealed retinal folding in the left eye. Visual fields were intact. Studies of the cardiovascular system and the lung were unremarkable. The thyroid gland was not enlarged. No lymphadenopathy or hepatosplenomegaly was present. Axillary hair was absent and pubic hair was sparse. Atrophy of the testis and penis were noted. The skin was dry and coarse. Pretibial edema was absent. No xanthomatous lesions were noted. Neurological examination was unremarkable.

Laboratory investigations (Table 1) revealed a high erythrocyte sedimentation rate (ESR) (68 mm/hr) and positive CRP reaction. The complete blood count showed moderate, normochromic normocytic anemia (hemoglobin-11.2 g/dl, hematocrit-33.4%) and a normal white cell count with eosinophilia (1176/mm³). The urine was normal. Blood chemistries showed somewhat increased serum GOT, LDH and CPK. Serum total protein was in the range of 6.5-9.0 g/dl. Serum electrophoresis and immunoelectrophoresis showed polyclonal hypergammaglobulinemia (2.15-3.87 g/dl). Serum immunoglobulin determinations revealed IgG in the range of 4,540-5,040 mg/dl (normal: 800-1,800 mg/dl) and IgE in the range of 1,150-1,200 IU/ml (normal: 36-340 IU/ml), but IgM and IgA levels

Table 1. Laboratory data before and after therapy.

Date	Eosinophil $\times 10^2/\text{mm}^3$	γ -globulin g/dl	IgG mg/dl	IgE IU/ml	ESR mm/hr	Therapy mg/day
09-12-77	11.76	2.15	—	—	68	—
10-03-77	22.04	—	4540	1200	105	10*
11-22-77	7.04	3.16	5040	1150	104	10*
12-01-77	—	—	—	—	—	15**
12-06-77	2.36	3.87	—	—	42	15**
12-20-77	—	2.10	3700	1150	8	30**
01-17-78	1.19	1.18	—	—	6	30**
02-23-78	—	0.91	1840	820	3	30**
06-09-78	1.63	0.62	—	—	—	25**
Normal range	0.5-3.5	0.81-1.75	800-1800	36-340	<15	

* Hydrocortisone.

** Prednisolone.

were below normal. Serum total complement was decreased. The intermediate-strength PPD and Candida skin tests were positive.

Basal plasma cortisol (F) level was 2.6 $\mu\text{g/dl}$ (normal: 4.5–24 $\mu\text{g/dl}$) and basal plasma ACTH level was in the range of 18–25 pg/ml (normal: 20–100 pg/ml). They did not increase after insulin-induced hypoglycemia. Basal plasma GH level was in the range of 0.6–2.8 ng/ml (normal: less than 5 ng/ml), but showed no response to insulin-induced hypoglycemia and low response to 1-dopa. Serum T_4 was 4.4 $\mu\text{g/dl}$ (normal: 4.6–11.0 $\mu\text{g/dl}$), T_3 was 86 ng/dl (normal: 95–200 ng/dl) and RT_3U was 24.4 % (normal: 25–35%). Basal plasma TSH level was in the range of 2.5–3.2 $\mu\text{U/ml}$ (normal: less than 4 $\mu\text{U/ml}$) and its response to TRH was normal but delayed. Serum testosterone level was 56 ng/dl (normal: 275–1,100 ng/dl). Basal plasma LH and FSH were 12.7 mIU/ml (normal: 1–36 mIU/ml) and 10.6 mIU/ml (normal: 1–22 mIU/ml). The LH response to LH-RH was delayed. The FSH response to the same hormone was normal. Basal plasma PRL levels were 6.1–16.9 ng/ml (normal: 2–20 ng/ml) and responses to TRH or meto-

chlupramide were normal, but suppression by 1-dopa was impaired (Table 2).

The spinal tap showed no abnormalities in cerebrospinal fluid. The bone marrow aspirate from the sternum revealed normocellularity with a myeloid/erythroid ratio of 2.64:1 and no atypical cell. About 11% of the cells were eosinophils. Chest X-ray revealed no abnormalities. Bone survey revealed two soybean size, clearly defined lytic lesions in the parietal portion of the skull, but sella turcica was normal.

A diagnosis of Hand-Schueller-Christian disease was made clinically and his diabetes insipidus was controlled by a nasal flushing of 0.2 ml of desamino-(D-arg⁸)-vasopressindiacetate (DDAVP) per day without any side effects. After initiation of treatment with oral hydrocortisone (10 mg/day), his general weakness rapidly improved. He was discharged on October 4, 1977 under his own discretion.

He was doing well until November, 1977, when he noticed the swelling of the bilateral submaxillary glands with tenderness. He was readmitted on November 16, 1977 for a further evaluation. Biopsy of the left submaxillary gland revealed findings compatible with eosinophilic granuloma.

Table 2. Hypothalamic-pituitary function tests.

Time (min)	0	15	30	60	90	120	150	180
Insulin								
Glucose (mg/dl)	75	—	42	41	54	61	—	—
Cortisol ($\mu\text{g/dl}$)	2.6	—	3.2	3.3	3.2	4.7	—	—
ACTH (pg/ml)	25	—	24	22	29	24	—	—
GH (ng/ml)	0.6	—	0.6	0.6	0.6	0.6	—	—
1-DOPA								
GH (ng/ml)	2.8	—	2.8	3.3	5.6	3.2	—	—
PRL (ng/ml)	12.4	—	20.0	10.7	10.4	19.3	—	—
LH-RH								
LH (mIU/ml)	12.7	16.7	18.9	18.0	19.6	—	—	—
FSH (mIU/ml)	10.6	17.0	22.6	13.1	17.2	—	—	—
TRH								
TSH ($\mu\text{U/ml}$)	2.5	10.5	18.0	21.5	26.5	—	—	—
PRL (ng/ml)	16.9	27.1	38.6	32.8	18.3	—	—	—
Metochlopramide								
PRL (ng/ml)	6.1	—	10.7	21.4	12.0	22.5	33.0	13.1

Basal blood hormone levels were determined again and an elevated basal plasma PRL level (34.4 ng/ml) was documented. Computed tomography of the head revealed an abnormal high density at the suprasellar cistern and along the bilateral optic nerves. Although a pneumoencephalogram revealed moderately enlarged lateral ventricles, a suprasellar tumor was not recognized.

A regimen of prednisolone (15 mg/day) and thyroid replacement (levothyroxine sodium 100 µg/day) was started. Within two weeks, the swelling of the right submaxillary gland and exophthalmos were improved remarkably. His abnormal laboratory data such as accentuation of ESR, positive CRP reaction, peripheral eosinophilia and hyperimmunoglobulinemia also returned to normal subsequently (Table 1). Computed tomography, reexamined on February, 1978, showed disappearance of the abnormal high density along the optic nerves. He was discharged on February 28, 1978 and is now undergoing the tapering administration of prednisolone without recurrence of symptoms.

Discussion

The patient described here had the classical triad of Hand-Schueller-Christian disease and may be also diagnosed as histiocytosis X according to Lichtenstein (1953) or as multifocal eosinophilic granuloma according to Lieberman *et al.* (1969). But at present proper classification of these abnormal proliferations of histiocytes remains unsolved.

Diabetes insipidus is common in histiocytosis X. Moreover, there have been several reports of anterior pituitary dysfunction, especially growth hormone deficiency (Ezrin *et al.*, 1963; Braunstein and Kohler, 1972; Kaufman *et al.*, 1976). On the other hand, postmortum studies demonstrat-

ed that histiocytic involvement of the central nervous system is usually confined to the hypothalamus, pituitary stalk and/or posterior pituitary gland and that the anterior pituitary gland is spared (Bernard and Aguilar, 1969; Gates *et al.*, 1973). It may be therefore reasonable to regard the hypopituitarism in this disease as a hypothalamic one. Clinical manifestations and baseline laboratory data in our patient were consistent with panhypopituitarism. It is, however, not necessarily easy to distinguish a hypothalamic lesion from a pituitary lesion by endocrine studies.

Insulin-induced hypoglycemia is thought to act through hypothalamus. However, subnormal response of ACTH or GH, as was documented in our patient, can not differentiate the site of lesion.

As for the response of TSH to TRH, it has been generally thought that reduced or absent responses indicate a primary pituitary disorder (Haigler *et al.*, 1971) and normal (Pittman *et al.*, 1971; Woolf and Schalch, 1973; Lovinger *et al.*, 1975) or delayed, prolonged and/or exaggerated (Costum *et al.*, 1971; Faglia *et al.*, 1973; Strauss *et al.*, 1974) responses indicate hypothalamic disorder. In our patient, basal plasma TSH levels were normal and showed normal but delayed responses to TRH. Therefore, hypothyroidism in our patient is supposed to result from TRH deficiency, although Patel and Burger (1973) have reported that, irrespective of the site of lesion, the TSH reserve is normal in most patients with hypothalamo-pituitary disorders.

Low or no response of LH to a single dose of LH-RH does not necessarily indicate primary pituitary disorder, because the pituitary gonadotroph requires adequate amounts of LH-RH for production and secretion of pituitary gonadotropin (Lovinger *et al.*, 1975). Hashimoto *et al.* (1975) proposed the usefulness of consecutive administration of LH-RH in evaluating the site

of the lesion. Rothman *et al.* (1978), using this method, demonstrated hypothalamic hypogonadism in a case of Hand-Schueller-Christian disease. In our patient, normal basal plasma LH and FSH levels, and normal, but delayed, response of them to LH-RH were documented, which indicated a hypothalamic origin for hypogonadism (Hashimoto *et al.*, 1972; Strauss *et al.*, 1974; Hirata *et al.*, 1975).

Our patient showed normal basal plasma PRL levels upon first admission, but suppression by l-dopa was poor. Moreover, an elevation in basal plasma PRL level was noted on the second admission. It has been reported that hypothalamic lesions produce hyperprolactinemia through prolactin-inhibitory factor (PIF) deficiency (Meites *et al.*, 1972) and l-dopa suppresses the release of PRL through the hypothalamus (Kamberi *et al.*, 1970). PIF deficiency secondary to hypothalamic disorder may therefore be present in our patient (Gates *et al.*, 1973; Hirata *et al.*, 1975).

The responses of TSH, PRL, LH and FSH to their hypothalamic releasing hormones, as described above, were normal, which indicated that sufficient amounts of potentially functioning pituitary trophes be might reserved, although histological infiltration of histiocytes into the anterior pituitary gland could not be ruled out. In conclusion, all results of the hypothalamic-pituitary function studies, in combination with the presence of diabetes insipidus, suggest that panhypopituitarism in our patient may have resulted from the hypothalamic lesion of histiocytosis X.

Immunological abnormalities in histiocytosis X have been described mainly in accounts of Letterer-Siwe disease. From its occasional association with thymic dysplasia or combined immunodeficiency (Cederbaum *et al.*, 1972), and its familial occurrence in relation to consanguineous marriage (Freundlich *et al.*, 1972), it has been suggested that the cause of this dis-

ease may have a genetic basis (Cederbaum *et al.*, 1972; Freundlich *et al.*, 1972).

Although immunological abnormalities of the other two subclassifications of histiocytosis X have not been well described, several cases associated with hypergammaglobulinemia appear in the literatures (Avioli *et al.*, 1963; Kikkawa and Inena, 1973; Leikin *et al.*, 1973). Leikin *et al.* (1973) reported on several patients who exhibited hyperimmunoglobulinemia with intact cellular immunity. Because of improvement following chemotherapy, he regarded the hyperimmunoglobulinemia as secondary to complicated infection or to stimulation of the B-cell system by histiocytic involvement of itself rather than as a basic abnormality of the disease. Our patient exhibited remarkably high serum IgG levels which subsequently returned to normal while undergoing prednisolone treatment. As there was no evidence of infection, elevated IgG levels were felt to reflect the activity of histiocytosis X.

The elevated serum IgE levels observed in our patient have a pathophysiological meaning somewhat different from those of IgG. They are characteristic of eosinophilic granuloma of soft tissue, so-called Kimura's disease, which is now believed to be caused by atopic allergy to *Candida albicans* (Takenaka *et al.*, 1976). Although elevated IgE levels have been described in some immunologic deficiency diseases (Waldman *et al.*, 1972), our patient clearly differs from such cases. Hiwada (1976) reported decreased IgE levels in two cases of eosinophilic granuloma of the lung. No other discussion of serum IgE levels in histiocytosis X has been found in the literature. Tissue and peripheral eosinophilia, elevated serum IgE levels, and the remarkable effectiveness of corticosteroid in our patient support the hypothesis that some allergic mechanism may be partly involved in the pathogenesis of this disease (Bickers *et al.*, 1962). Further immunological studies in

such patients seem to be necessary.

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