NOTE

Dermatitis Herpetiformis Cured by Hormone Replacement for Panhypopituitarism

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Abstract. Dermatitis herpetiformis is an autoimmune skin disorder frequently associated with gastrointestinal diseases. We report a 53-year-old male with a four-year history of refractory dermatitis herpetiformis associated with hypopituitarism. Endocrine testing, ophthalmological examination and magnetic resonance imaging revealed hypopituitarism due to a non-functioning pituitary macroadenoma. Following transphenoidal removal of the pituitary tumor and appropriate hormone replacement, complete remission of the skin disorder was obtained. We discuss the permissive role of panhypopituitarism in the course of dermatitis herpetiformis.

Key words: Dermatitis herpetiformis, Panhypopituitarism, Hormone replacement

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DERMATITIS herpetiformis (DH) frequently occurs in association with various autoimmune diseases, of which gluten-sensitive enteropathy is the one most frequently associated [1, 2]. Among endocrine abnormalities, various thyroid and adrenal disorders have been reported to occur in association with DH [3, 4]. We report a patient with refractory DH who presented with panhypopituitarism due to a giant pituitary adenoma. The skin disorder disappeared completely following successful removal of the tumor and institution of glucocorticoid hormone replacement.

Case Report

A 53-year-old physiotherapist was admitted for

evaluation of loss of libido and erectile dysfunction. He had been completely well until 12 months ago, when he noticed progressive weakness, loss of body hair, and enlargement of his breasts. In addition, he noticed impaired vision bilaterally when playing tennis. Four years ago, DH had been diagnosed by skin biopsy. Histological examination and immunofluorescence-staining revealed subepidermal blistering, subepidermal microabscess formation composed of neutrophil and eosinophil granulocytes and papillary granular IgA-deposits, histopathological features characteristic of DH. While DH failed to respond to treatment with various skin ointments, the disease responded well to therapy with dapsone (100 mg/day). Hypothyroidism had been noted at another institution one year prior to admission, and prompted thyroid hormone replacement therapy with levothyroxine (100 µg/day). He did not take any other medication, had no previous history of endocrine and skin disorders. Family history was unremarkable.

Physical examination revealed a slender male with generalized muscle atrophy, decreased axillary and pubic hair, and bilateral gynecomastia.

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Heart rate was regular at 84/min and blood pressure was as low as 100/70 mm Hg with marked orthostasis. He was kept afebrile. Examination of the heart, lungs, and abdomen was normal. The thyroid gland was small, and testes were small and soft. Neurologic examination was normal except for marked bitemporal visual field defects on confrontational testing. Multiple, grouped blisters surrounded by urticarial plaques and excoriations were present on the extensor surfaces of elbows and on buttocks. Except for low serum sodium (127 mmol/L, normal 135–150 mmol/L) and high potassium (5.8 mmol/L, normal 3.5–5.0 mmol/L) blood chemistry was normal. Thyroid function tests revealed low serum TSH level (basal 0.2 mU/L, normal 0.4–4 mU/L; TRH-stimulated 0.4 mU/L, normal 3–18 mU/L) with a normal free T₃ and low normal free T₄ level (0.8 ng/dl; normal 0.8–1.8 ng/dl). Further endocrine testing revealed decreased serum levels of testosterone (0.5 nmol/L; normal 10.4–34.7 nmol/L), LH (basal 0.6 IU/L, normal 1.5–9.2 IU/L; LHRH-stimulated 1.4 IU/L, normal: 2–4 fold increase), adrenocorticotrophic hormone (basal 4.0 ng/L, normal 15–50 ng/L) and cortisol (a.m. basal 127 nmol/L, normal 250–1020 nmol/L; ACTH-stimulated 168 nmol/L, normal: increased by at least 280 nmol/L), and increased PRL level (basal 767 mU/L, normal <500 mU/L; TRH-stimulated 1478 mU/L, normal: 2–5 fold increase), suggesting secondary hyperprolactinemia due to stalk compression by the pituitary macroadenoma. Serum antibodies to the thyroid and the adrenal gland were negative. Formal visual field testing revealed extensive bitemporal hemianopsia. T₁-weighted magnetic resonance imaging (MRI) of the sella showed a hyperintense and inhomogenous mass 3 cm in diameter extending into the parasellar and suprasellar space (Fig. 1). Based on these clinical, endocrine, ophthalmologic and imaging studies, hypopituitarism due to a non-functioning pituitary macroadenoma was diagnosed, and hormone replacement with hydrocortisone (10–10–5 mg/day) was initiated. The hyperprolactinemia was interpreted as secondary due to compression of the stalk, since in the case of a PRL-producing macroadenoma much higher serum PRL levels would have been expected (>5000 mU/L). Subsequently, transsphenoidal pituitary exploration was performed and successful removal

of the tumor was achieved. Histopathology and immunohistochemistry revealed chromophobic anterior pituitary adenoma.

Postoperative hormone replacement included levothyroxine (150 µg/day p.o.), hydrocortisone (25 mg/day p.o.) and testosterone enantate (250 mg every 4 weeks, i.m.). Follow-up examination for three months revealed normal muscle mass and body hair, adequate orgasms, and recovery of visual fields. In addition, within three months after surgery and hormone replacement, complete disappearance of all skin lesions was noted, permitting discontinuation of dapsone treatment. Eighteen months after surgery, the patient was in excellent health and had resumed all his previous activities. No recurrence of DH occurred.

Discussion

DH may be associated with a variety of neoplasms [5–7]. Patients with this disorder should therefore undergo careful evaluation for an underlying malignancy. In contrast, endocrine

Fig. 1. T₁-weighted magnetic resonance image of the sella region demonstrates a 3 cm heterogenous, hyperintense mass that is located within the sella, extends into the parasellar and suprasellar regions, and compresses the optic chiasm (arrow).

tumors are rarely associated with DH [6, 8]. The complete remission of DH following removal of the pituitary adenoma and appropriate hormone replacement in this patient suggest that endocrinological and immunological sequelae of hypopituitarism may have played a role in the evolution of DH. Due to impairment of the hypothalamic-pituitary-adrenal axis, our patient presented clinical signs and symptoms of glucocorticoid deficiency. Gradual development of glucocorticoid deficiency over several years was paralleled by the appearance of DH which subsequently became chronic, severe and refractory to therapy. Several case reports have suggested a link between Addison's disease and DH [3, 9]. In a genetically predisposed individual, relative or absolute glucocorticoid deficiency may increase susceptibility to autoimmune or inflammatory disease [10]. This is further highlighted by the observation of Cushing's disease inducing remission of severe rheumatoid arthritis [11] and of surgical cure of Cushing's disease precipitating manifestation of autoimmune thyroid disease [12] and rheumatoid arthritis [13] in predisposed individuals. Conversely, replacement with glucocorticoid may restore an individual's capacity to suppress differentiation and activity of immune cells, to inhibit cytokines and other inflammatory mediators, and to induce resistance to the actions of cytokines [10]. Thus, in a patient with DH, correction of glucocorticoid deficiency may restore control over several important mechanisms involved in the pathogenesis including neutrophil and eosinophil recruitment, B cell activation, IgA synthesis and deposition, and complement activation [1, 2].

Various thyroid disorders have also been reported to occur in association with DH, including

frank hypothyroidism, subclinical hypothyroidism, Graves's disease, toxic multinodular goiter and follicular thyroid carcinoma [7, 8, 14, 15]. The presence of serum autoantibodies to the thyroid was detected in 38–48% patients with DH [8, 14], reflecting the patients' immunogenetic predisposition to organ-specific autoimmunity in this patient [2, 4, 14], but in the present case, correction of hypothyroidism prior to correction of hypocortisolism failed to improve DH, and may even have aggravated glucocorticoid deficiency.

Hyperprolactinemia and hypogonadism may have additionally influenced immune functions in the patient. Increased PRL levels may play a role in promoting or maintaining autoimmune diseases [10, 16]. Several studies conducted in animal and *in vitro* models suggest that PRL may be capable of aggravating autoimmune diseases [16, 17]. It is therefore possible that increased PRL levels may have stimulated the activity of important target cells involved in the pathogenesis of DH. Another factor of potential relevance in the course of DH in our patient is hypogonadism, which resulted in androgen deficiency and a decreased testosterone/estrogen ratio. Decreased serum levels of androgens have been reported in various autoimmune diseases including systemic lupus erythematosus, rheumatoid arthritis, insulin-dependent diabetes mellitus and myasthenia gravis [18, 19] and administration of testosterone led to complete remission of autoimmune activity in animal models of systemic lupus erythematosus and autoimmune thyroiditis [17]. An important lesson to be remembered is that DH may offer a valuable diagnostic clue to a more complicated, underlying disorder. Diagnosis and appropriate treatment of the latter can cure the former, and thus may serve to kill two birds with one stone.

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