

## Bullous Pemphigoid and Graves' Disease: An Association Between Skin and Thyroid Autoimmunity

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Sir,

Autoimmune diseases may affect multiple organs beyond skin. Autoimmune bullous diseases, in particular, may be associated with endocrinological diseases including polyendocrine or autoimmune polyglandular syndromes (APS). Herpes gestationis, for example, has been repeatedly reported in combination with hyperthyroidism in the form of Graves' disease (GD) (1–4), but bullous pemphigoid (BP) has only once been reported in association with GD (5). Here we describe the second case of BP and GD.

### CASE REPORT

A 71-year-old Caucasian woman was seen in 2001 at the Dermatology Clinic, University of Genoa, because of a diffuse bullous disease. Her sister was affected by an undefined autoimmune thyroid disease and her mother had type 2 diabetes mellitus. At 39 years of age she had developed essential hypertension and thereafter type 2 diabetes mellitus. At the age of 62, lichen planus was diagnosed and at 70 a thyroid enlargement was associated with Graves' ophthalmopathy (GO) complicated by strabismus. Hyperthyroidism was diagnosed by increased serum levels of free triiodothyronine (11.34 pg/ml; normal 1.8–4.6) and free thyroxine (3.3 ng/ml; normal 0.9–1.7), while levels of thyrotropin stimulating hormone (TSH) were suppressed (0.005 UI/ml; normal 0.27–4.2). In addition, autoantibodies directed against thyroperoxidase (110 U/ml; normal <15), thyroglobulin (85 U/ml, normal <15), TSH receptor (54.1  $\mu$ U/ml; normal 0–9) and ANA (antinuclear autoantibodies) were all increased in serum. Thyroid ultrasonography and <sup>99m</sup>Tc-scan confirmed the diagnosis of GD with diffuse homogeneous goitre. Hyperthyroidism was initially treated with methimazole, 10 mg/day orally.

Two months later, large blisters developed on her legs, arms and trunk. Laboratory tests showed hypereosinophilia and increased total IgE levels. Histopathology showed a subepidermal bulla containing neutrophils and eosinophils. Direct immunofluorescence disclosed linear deposition of IgG and C3 at the dermal-epidermal junction.

Indirect immunofluorescence on monkey oesophagus demonstrated the presence of IgG directed to the basal membrane zone. Immunoblot assay with an epidermal extract and ELISA both revealed the presence of IgG antibodies directed to BPAg2 of 180 KDa. Immunological work-up was negative for anti-parietal cell antibodies, anti-endomysium antibodies (these are specific antibodies for coeliac disease and Dühring disease) and anti-adrenal cortex antibodies. HLA and DR antigen screening revealed HLA DRB1\*01,\*08, B3\*, DRQ4. Paraneoplastic screening was negative.

She began oral treatment with prednisone (25 mg/day the first month, then 50 mg daily), and cyclophosphamide (100 mg orally per day). Cyclophosphamide doses were decreased to 50 mg/day and stopped after 2 months. Afterwards, the skin

lesions were controlled with 25 mg/day of prednisone, then the dose was tapered and a dose of 5 mg/day of prednisone was still able to control the disease.

New blisters appeared and her hyperthyroidism worsened in February 2002, so propylthiouracil 50 mg daily was given instead of methimazole.

Because of the unsatisfactory control of the hyperthyroidism and to avoid further intake of thionamide, radioactive iodine therapy was administered in November 2002. In July 2003, the patient became hypothyroid and she is on thyroxine replacement therapy to date.

After radioactive iodine, a transient increase in serum thyroglobulin antibody titres was observed (from 104 to 187.7 U/l), followed by a clinical increased activity in her BP.

At present, after a 24-month course of therapy, the BP is partially controlled by systemic prednisone (10 mg daily), dapsone 50 mg daily and topical application of betamethasone dipropionate.

### DISCUSSION

Autoimmune thyroid diseases comprise a spectrum of inter-related clinical conditions, such as, chronic lymphocytic thyroiditis (or Hashimoto's thyroiditis), idiopathic myxoedema due to atrophic thyroiditis, symptomless autoimmune or post-partum thyroiditis, and GD. They are often associated with other autoimmune conditions. In particular, GD has been reported as associated with herpes gestationis in 11 cases (1–4), but only once with BP (5).

GD is an autoimmune disease marked by hyperthyroidism and circulating autoantibodies that belong to the IgG1 subclass. They are directed at four distinctive thyroid antigens, namely thyroglobulin, thyroperoxidase, sodium-iodide symporter and the TSH receptor, which is the primary autoantigen. Autoantibodies against the TSH receptor continuously stimulate the thyroid and, as a consequence, pituitary TSH secretion is suppressed and thyroid hormone and thyroglobulin are over-released. Iodine uptake, protein synthesis and growth in the thyroid gland are also overstimulated.

In contrast humoral autoimmunity plays the main role in BP with antibodies binding to BPAg2 antigen and promotes a cascade of inflammatory events, with complement activation and polymorphonuclear cell infiltration leading to subepidermal clefting.

Genetic factors may also be important, as patients with GD are known to express HLA-B8 more frequently than control subjects (6) and the risk of developing GD is increased in subjects with the haplotypes HLA-DR3 or -DQA1\*0501 and HLA-DR4 (7–9). In contrast, BP patients usually show HLA-DQB1, an HLA possibly

associated with multiple diseases of the APS group (10). Our patient had HLA DRB1\*01,\*08, B3\*, DRQ4, where the presence of HLA-B8 is associated with GD.

GD has been classified as a member of APS that encompass a clustering of clinical conditions simultaneously involving multiple endocrine glands, sometimes associated with non-endocrine diseases. They have recently been classified into four main types (11). In type 3, GD is combined either with other endocrine diseases excluding Addison's disease and hypoparathyroidism (type 3A), with non-endocrine organ-specific autoimmunity (types 3B–C), or with rheumatic diseases affecting connective tissue (type 3D). We propose to include a BP/GD association into the APS type 3, subgroup 3C, although the same group is heterogeneous, as it also includes diseases like vitiligo and alopecia, in which the role of autoantibodies is far from being proven.

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