Case Report

Simultaneous relapse of Graves’ disease and minimal change glomerular disease

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Keywords: Graves’ disease; glomerular disease; minimal change

Introduction

Nearly 30% of patients with autoimmune thyroid disease have proteinuria [1]. Membranous glomerulonephritis is the most common finding when thyroid disease is associated with nephrotic range proteinuria. There are only three previous reports of autoimmune thyroid disease and minimal change glomerular disease (MCD). We report the case of a patient in whom Graves’ disease and MCD were diagnosed simultaneously and in whom relapse of the Graves’ disease was invariably accompanied by relapse of MCD.

Case

A 22-year-old Caucasian female initially visited her general practitioner (GP) in 1994 with a history of coryzal symptoms and a viral upper respiratory tract infection was diagnosed. She returned to her GP one month later complaining of ankle swelling and was found to have developed proteinuria and peripheral oedema. She had no significant past medical history but her father had sarcoidosis.

Initial assessment in hospital revealed severe oedema to the flanks, a serum albumin of 18 g/l, a 24 h urinary protein leak of 4.26 g/24 h and a serum creatinine concentration of 84 μmol/l (0.95 mg/dl). Light microscopy findings on a renal biopsy were normal and electron microscopy showed foot process fusion alone and was compatible with MCD. The patient was treated with oral prednisolone and anticoagulation until her nephrotic illness had abated. Her protein leak resolved (0.08 g/24 h) and serum albumin recovered (40 g/l) within 15 days of diagnosis.

At the first consultation, tachycardia (heart rate of 110 bpm), a fine tremor, a small goitre and mild exophthalmos were also found. A clinical diagnosis of hyperthyroidism was given and the patient was immediately started on propranolol. Subsequently her thyroid stimulating hormone (TSH) level was found to be <0.2 U/ml (normal range (NR), 0.5–4.7 U/ml) and free thyroxine (FT4) >83 μM (NR, 10–25 μM), free triiodothyronine (FT3) 38.1 μM (NR, 3–8.6 μM). Microsomal thyroid peroxidase and thyroid receptor autoantibodies were found to be strongly positive. A diagnosis of Graves’ disease was made, and she was commenced on carbimazole.

Her family history of sarcoidosis prompted a screen for this disease, but her serum calcium, angiotensin converting enzyme (ACE) and chest X-ray were normal, and she had no other symptoms.

The patient has been monitored regularly since her initial presentation during which time her renal function has remained stable (serum creatinine 60–80 μM). However, she has had a number of nephrotic relapses (Figure 1) and these have invariably been accompanied by clinical and biochemical hyperthyroidism.

Discussion

We have reported a patient with relapsing MCD in whom multiple nephrotic relapses coincided with relapses of Graves’ disease.

The only previous reported case of Graves’ disease and MCD occurred in a patient with sarcoidosis [2]. It is of interest that two cases of Hashimoto’s thyroiditis and minimal change have recently been described, one of whom also had sarcoidosis [3]. In this respect, our patient’s family history of sarcoidosis is intriguing. However, there was no evidence of sarcoidosis in the patient herself and it is unclear whether there is a true association between sarcoidosis and MCD [4].
A number of observations suggest a link between T-lymphocytes and MCD. An association between lymphoma, particularly the T-cell disease 'mycosis fungoides', and MCD is well recognized. Suppression of T-cell function during infection with the measles virus may coincide with MCD remission. MCD, almost by definition, responds completely to steroids and calcineurin blocking agents, which modulate T-cell function. A glomerular vascular permeability factor (VPF), isolated from T-cell hybridomas, has been implicated in the pathogenesis of MCD, and cytokine stimulation and inhibition of the release of VPF by T-lymphocytes has been described in in vitro studies. T-cell subset changes and high IL-2R expression on peripheral lymphocytes may indicate the presence of stimulated T-cell populations in MCD. There is a single report of reduction in VPF production in lymphocytes from patients with MCD after treatment with tacrolimus.

Thyroid stimulating antibodies are the hallmark of Graves' disease and the extracellular domain of the TSH receptor is the major autoantigen. Lymphocytes infiltrating the thyroid are the major source of these autoantibodies and production of these antibodies is T-cell dependent. The demonstration that the production of interferon γ by infiltrating T-cells provokes thyroid cells to express HLA class II molecules suggests that these cells may act as antigen presenting cells. Is it possible then that thyroid cells can also secrete cytokines that stimulate VPF secretion from lymphocytes?

MCD and Graves' disease are relatively common conditions, so why has this association not been reported more frequently? It is not clear whether the MCD relapses provoked the Graves' relapses or whether the converse was true. It seems unlikely that such multiple simultaneous relapses can be explained by chance alone. Renal handling of endocrine hormones may explain why the association is unusual. In a nephrotic illness urinary losses of thyroid-binding globulin (MW < 100 kDa) and T3 and T4 might be expected to ameliorate hyperthyroidism. However, plasma levels of T3/T4 and TSH are usually normal in nephrotic patients.

It is possible that the heavy proteinuria associated with MCD is associated with the loss of thyroid or immune regulatory factors, which could exacerbate underlying hyperthyroidism.

We speculate that dysregulation of the T-cell populations producing thyroid stimulating autoantibodies...
and VPF could explain the striking temporal association we have observed between relapses of Graves’ and MCD seen in this case.

References


Received for publication: 25.9.01
Accepted in revised form: 27.11.01