Case Report

Simultaneous presentation of Goodpasture’s disease and insulin-dependent diabetes mellitus

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Introduction

Goodpasture’s disease (GD) is characterized by the presence of circulating and deposited anti-glomerular basement membrane (anti-GBM) antibodies resulting in rapidly progressive glomerulonephritis and pulmonary haemorrhage. The autoantibodies interact with the non-collagenous domain of the α3 chain of type IV collagen (Goodpasture antigen) on the basement membrane of glomeruli. A variety of autoimmune conditions have been associated with GD including insulin dependent diabetes mellitus (IDDM) [1]. We document the presentation of GD simultaneously with the onset of IDDM, suggesting the possibility of a shared pathogenesis.

Case

A 39-year-old welder was admitted with a 5-day history of malaise, pyrexia, and diarrhoea and subsequent haemoptysis. He had been admitted 1 month earlier following a similar ‘flu-like’ illness. Associated features of hyperglycaemia and ketosis resulted in the diagnosis of IDDM. Anti-islet cell antibodies (in house assay, Immunology Department) were not detected. No infectious aetiology was established during either admission. Viral serology was negative.

On the second admission, the patient’s blood pressure was 160/80 mmHg, creatinine was 980 µmol/l, and urea was 32 mmol/l. His ESR was 156 and CRP 377. Urinalysis showed microscopic haematuria and proteinuria. Anti GBM antibodies (in house assay, Immunology Department) were strongly positive to a titre of 252 IU. Antineutrophil cytoplasmic antibodies (ANCA) (in house assay), rheumatoid factor, and cryoglobulins were negative. A renal biopsy demonstrated a florid crescentic glomerulonephritis with all glomeruli involved. Immunofluorescence showed strongly positive IgG and C3 linear staining and weakly positive linear IgA staining consistent with anti-GBM antibody disease. His renal function failed to improve and he remained dialysis dependent.

He was managed with intravenous methylprednisolone (1 g) daily for 3 days followed by oral prednisolone 40 mg daily, together with plasma exchange and azathioprine 200 mg daily, predominantly to control his respiratory manifestations. Over the next 8 months, his anti-GBM antibodies returned to baseline and he had no further relapses. He has subsequently undergone successful renal transplantation.

Discussion

Goodpasture’s disease (GD) is perhaps one of the best characterized autoimmune diseases in which pathogenic autoantibodies, recognizing a similar epitope on the α3 chain of type IV collagen, initiate injury on the glomerular basement membrane, Bowman’s capsule, or the distal tubules and alveoli basement membrane. However, clinically identical anti-GBM disease can also be associated with antibodies directed towards different molecular targets including α5 (IV) NC1 [2]. Certain anti-GBM antibodies may interact with other antigens. It has been shown that some patients have limited antibody reactivity with other structural antigens on collagen IV, including the 7S portion and other α isoforms [3]. It is possible therefore that this heterogeneity may contribute to the production of antibodies that cross-react with both glomerular and islet cell epitopes to provoke the simultaneous presentation of GD and IDDM observed in our case.

A number of autoantibodies may be associated with IDDM, including antialbumin, ssDNA, dsRNA, tubulin and thyroglobulin, and soluble immune complexes [4]. Up to 36% of diabetics have circulating antibodies that bind at diverse epitopes to the GBM [5] including...
reticulin FxIa, and the sulphatide antigen, GD has rarely complicated IDDM, possibly through increased subepithelial expression of collagen IV [1]. In this milieu, the production of pathogenic anti-GBM antibodies is conceivable. However, the simultaneous occurrence of GD with IDDM has never previously been described.

Recent reports suggest that genetic susceptibility to GD is strongly associated with the HLA DRB1 genes and more specifically the DRB1*1501/1502 locus [6]. Our patient was homozygous for the DRB1*1501 allele present in over 90% of patients with GD compared to 20% of the general population. It is thought that the same DRB1*15 alleles are usually protective against the development of IDDM [4]. The HLA-DR region is characteristically very tightly linked making crossover unlikely for this disease association.

There are also recent reports that suggest a possible role for viral agents in the pathogenesis of GD, with virus-like structures seen in electron microscopy and with a distinctive seasonal clustering in some cases [7]. It has long been felt that IDDM may have a viral aetiology (especially Coxsackie virus B4), and similar seasonal clustering is seen in IDDM [8]. Autoreactivity may be an indirect consequence of viral infection with resultant local infection, inflammation, and tissue damage leading to the release of sequestered antigen and the re-stimulation of resting autoreactive T cells (bystander T-cell activation). It is thought that IDDM could be induced in this manner [8]. Lung injury by anti-GBM antibodies is perceived to be dependent on local inflammation with the expression of adhesion molecules and cytokines, including TNFα and IL-1. An infecting virus may also initiate an immune response against self proteins by immunogenic similarities to foreign epitopes (molecular mimicry). Another possibility is the expression of a super-antigen in response to an infecting agent, with stimulation of large number of T-cells, irrespective of their antigen specificity, leading to a proliferation of autoreactive T-cells. Our patient described a ‘flu-like’ illness and diarrhoea preceding the onset of IDDM and again prior to his admission with GD. It is therefore possible that, in our case, an infectious agent led to a breakdown of immune tolerance in a genetically susceptible individual and that this resulted in the simultaneous production of both IDDM and GD.

References

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