Myeloperoxidase-antineutrophil cytoplasmic antibody-positive crescentic glomerulonephritis associated with benzylthiouracil therapy: report of the first case

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Introduction

Grave’s disease is a common form of autoimmune thyroiditis which has been successfully treated with anti-thyroid drugs for more than half a century. However, these drugs may cause major complications including agranulocytosis, hepatotoxicity and immunological disturbances such as lupus erythematosus syndrome.

Anti myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA) mediated crescentic glomerulonephritis in association with anti-thyroid treatment was first described in 1994 [1]. In the literature, 22 cases have been reported to date. All were associated with propylthiouracil (PTU), except two [2–5]. One of the latter was associated with thiamazole (TMZ) [6] and the other with carbimazole (CMZ) therapy [7].

We report here the first case of an anti MPO-ANCA-positive crescentic glomerulonephritis in association with benzylthiouracil (BTU) treatment.

Case

In 1996, a previously healthy 22-year-old woman was admitted to our Endocrinology Division because of weight loss, thermophobia and neck swelling. Physical examination revealed an acquired exophthalmos with goitre, trembling of the upper extremities and tachycardia. Blood pressure was normal at 120/70 mmHg, sedimentation rate was 30 mm and serum creatinine of 46 µmol/l. There was no haematuria or proteinuria.

Free serum thyroxin (FT4) was 24 pmol/l (normal range 11–22 pmol/l) and thyroid-stimulating hormone (TSH) 0.03 µIU/l (normal range 0.2–6 µIU/l). Anti-thyroglobulin and anti-thyperoxidase antibody titres were, respectively, 328 IU/ml (normal <100 IU/ml) and 369 IU/ml (normal <70 IU/ml). Thyroid scintigraphy showed a homogeneous fixation. The diagnosis of Grave’s disease was made and anti-thyroid drug BTU started at 250 mg/day for 1 month. The dose was then slightly reduced to 50 mg/day. Symptoms improved and the patient has stayed euthyroid since.

She presented again in 1997 because of anorexia, nausea and vomiting of recent onset. She was still taking BTU at 50 mg/day. On admission, blood pressure was 110/70 mmHg and pulse rate was 70 beats/min and regular. An enlargement of the thyroid gland and exophthalmos were observed. There was no oedema and urinary output was within normal limits, 1–2 l/24 h.

Laboratory findings were: serum creatinine, 1040 µmol/l; proteinuria, 2.8 g/24 h; haematuria of 950 000 red blood cells/min; and erythrocyte sedimentation rate, 150 mm. Serum complement was normal: CH50, 444 IU/l (normal range 23–430 IU/l); C3, 0.96 g/l (normal range 0.7–1.5 g/l); and C4, 0.45 g/l (normal range 0.15–0.45 g/l). Anti MPO-ANCA was found with an ELISA test at three marks (Sanofi diagnostics Pasteur). Chest X-ray was normal. Ultrasound examination showed normal-sized kidneys. Renal biopsy revealed features of a fibrocellular, crescentic glomerulonephritis in three of six glomeruli. The other three glomeruli exhibited sclerotic changes. In addition, there...
were mild chronic tubulointerstitial alterations with focal interstitial fibrosis and tubular atrophy, but no arterial lesions. Immunohistochchemistry could not be performed because only medullary tissue was available. Although IgG and IgM complexes were detected in blood, this does not allow the conclusion that immune complex glomerulonephritis was present. The diagnosis of ANCA-positive crescentic glomerulonephritis was made, possibly in association with BTU therapy.

Since renal failure was severe, with a creatinine clearance at 8.5 ml/min and extensive renal fibrosis, and since there were no extrarenal manifestations we did not initiate steroid and/or immunosuppressive treatment and BTU treatment was continued at the same dose. Despite the relatively bad prognosis, partial recovery of renal function occurred, with the creatinine clearance returning to 44 ml/min (serum creatinine, 200 µmol/l) after 3 months, although proteinuria persisted at 2–3 g/24 h.

Discussion

This is the first report of an association of ANCA-positive crescentic glomerulonephritis with BTU treatment for Grave’s disease. An association between vasculitis, ANCA and anti-thyroid drugs was first reported by Dolman et al. [8] in six women who developed PTU-associated ANCA-positive vasculitis. Anti-MPO antibodies were present in two cases, associated with anti-proteinase 3 (PR3) antibody in one. The other four patients had anti-PR3, but no anti-MPO antibodies. A histopathological study was performed in three cases, showing cutaneous vasculitis in two cases and vasculitis of the nasal mucosa in the remaining one. None of the patients had renal failure or proteinuria, but three had microscopic haematuria. Symptoms improved with the discontinuation of PTU, leading the authors to incriminate PTU as the cause of these manifestations.

Vogt et al. [1] subsequently reported an association between Grave’s disease, PTU and MPO-ANCA-associated glomerulonephritis in two adolescents. They received PTU treatment for Grave’s disease and developed, respectively, 1 and 12 months later, a fever, arthralgias and acute renal failure due to pauci-immune necrotizing glomerulonephritis. After discontinuing PTU and starting corticosteroid and cyclophosphamide treatment, recovery of renal function was obtained in the first case but progression to end-stage renal failure could not be avoided in the second.

Since these first descriptions 22 cases have been reported subsequently, which were related to the intake of PTU in 20 cases, TMZ in one and CMZ in the remaining one. Our case is the first description of an association between BTU treatment and MPO-ANCA crescentic glomerulonephritis.

Of note, 16 of the above 22 cases were from Japan, may be because of the high prevalence of Grave’s disease in this country. The average time period of anti-thyroid drug use before the detection of renal changes was 36 months. ANCA was anti-MPO of perinuclear location in all cases where it was sought. In three cases, it was associated with anti-PR3 antibody. Anti-thyroid drugs were discontinued in 13 cases, whereas a switch to TMZ was done in two cases. Steroid and/or immunosuppressive treatment was given to 18 cases. An improvement of renal function was observed after discontinuation of anti-thyroid drugs in 10 cases, but despite continued administration in six cases. A negativation of ANCA was reported in eight of 12 cases.

Glomerular MPO reactivity was detected in patients with rapidly progressive glomerulonephritis, irrespective of the presence or absence of MPO-ANCA [9]. MPO activity was elevated and inversely correlated with the level of MPO-ANCA in the sera of such patients. It has been suggested that MPO plays an important role in the formation of glomerular injury in rapidly progressive glomerulonephritis.

An interaction between PTU and neutrophils may be the basis of ANCA production. MPO produced by neutrophils may metabolize the drug, leading to reactive intermediates which may be immunogenic for T cells and stimulate the immune system [10]. These metabolites also have cytotoxic activity, leading to cell death and abnormal degradation of self-material, as well as production of antibodies [11].

PTU and BTU derive from the same molecule where a benzyl group replaces a methyl group. It has been reported that the thiol group of the drugs is involved in the induction of the polyclonal autoimmune reaction. Although the two molecules have a thioamide group in common, this cannot explain why ANCA-associated vasculitis is more frequent in PTU than BTU treatment, which is widely used in our country.

In conclusion, despite this first description of ANCA-positive crescentic glomerulonephritis associated with BTU therapy, a causal relationship with this drug and the immunological and renal manifestations remains to be determined. The less frequent occurrence of this complication with BTU than with PTU needs to be explained as well. Finally, patients who receive anti-thyroid drugs should be regularly checked for proteinuria, haematuria and renal function.

Conflict of interest statement. None declared.

References

MPO-ANCA-positive crescentic glomerulonephritis


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