Membranous nephropathy secondary to Graves' disease with deposits of thyroid peroxidase in an adult

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Abstract A 40-year-old woman was diagnosed with Graves' disease in 2001 and treated with thiamazole, but disease control was poor. She was referred to our hospital in 2011 for exacerbation of proteinuria, which had been present since 2006. Urinalysis showed a protein/creatinine ratio of 4.2 g/gCre and microhematuria, and a renal biopsy was performed. On electron microscopy, high electron density deposits were seen on the epithelial side of the glomerular basement membrane. IgG was also deposited along the glomerular loop wall, and membranous nephropathy was diagnosed. Immunostaining revealed thyroid peroxidase deposits but not thyroglobulin antigen deposits, suggesting that the membranous nephropathy was secondary to Graves' disease. The membranous nephropathy improved with ^{131}I treatment. To our knowledge, this is the first adult case of membranous nephropathy originating from Graves' disease in which deposits of thyroid peroxidase antigens have been detected.

Keywords Membranous glomerulonephritis · Graves' disease · Thyroid-peroxidase · Thyroglobulin

Introduction

Membranous nephropathy is characterized by the deposition of immune complex beneath the glomerular basement membrane epithelium with associated complement activation. Approximately 10–20 % of membranous nephropathy cases occur secondary to collagen disease, malignant tumors, drugs, infections, or other conditions [1, 2]. However, reports of membranous nephropathy as a complication of Graves' disease are sparse, and thyroglobulin antigen deposition has been detected in only several adult cases [3–6], and thyroid peroxidase (TPO) deposition in only a single pediatric case [7].

Case report

The patient was a 40-year-old woman. She developed severe dyspnea and was examined by a general practitioner who diagnosed Graves' disease in 2001. She was treated with thiamazole and propylthiouracil (PTU), but experienced repeated remissions and relapses. Urinalyses were normal until 2006, when proteinuria developed. In approximately 2010 her thyroid enlargement and tachycardia worsened, and she showed a poor response to medication. In 2011 she was referred to a thyroid specialist. On examination, she was found to have a high level of proteinuria, and 2 months later she was referred to our hospital for further workup. Laboratory data showed blood urea nitrogen 9.3 mg/dl, serum creatinine 0.5 mg/dl, total protein 5.0 g/dl, serum albumin 2.4 g/dl and total

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cholesterol 272 mg/dl. Urinalysis revealed a protein/creatinine ratio of 4.2 g/gCre and microhematuria (1–5 RBCs/high-power field). A renal biopsy was performed. On light microscopy, diffuse thickening of the glomerular loop wall

Fig. 1 Staining of a biopsy specimen of the kidney with periodic acid silver-methenamine, magnified 800 times. Portion of glomerulus shows spikes projecting from the epithelial side

was seen with periodic acid Schiff (PAS) staining, and spike formation was seen with periodic acid silver-methenamine (PAM) staining. Double contour was seen in some areas (Fig. 1). Mild enlargement of the mesangial region together with increased mesangial cells and matrix were seen. The fluorescent antibody technique revealed granular deposits of IgG (2+), IgA (1+), IgM (1+), C3 (1+), and fibrinogen (1+) along loop walls (Fig. 2a, b). Electron microscopy showed highly electron dense deposits on the epithelial side of the glomerular basement membrane and within the basement membrane (Fig. 3). Based on these findings, stage 2–3 membranous nephropathy was diagnosed. Her antinuclear antibody level was normal, and Graves' disease was present, with free thyroxine (fT3) 2.61 pg/ml (reference range: 1.71–3.71 pg/ml), free triiodothyronine (fT4) 0.65 ng/dl (reference range: 0.70–1.48 ng/dl), and thyroid-stimulating hormone (TSH) ≤ 0.01 μ IU/ml (reference range: 0.35–4.94 μ IU/ml). Observed levels of anti-thyroid peroxidase (TPO) antibodies (96.4 IU/ml; normal level <28.0 IU/ml) and anti-thyroglobulin antibodies (351.3 IU/ml; normal level <40.0 IU/ml) were elevated. Based on speculation that an

Fig. 2 Staining of a biopsy specimen of the kidney for IgG, C3, and thyroid peroxidase with the fluorescent antibody technique, magnified 400 times. Antibodies for IgG (a), C3 (b), and thyroid peroxidase (c) are deposited in a granular pattern along the glomerular loop wall

Fig. 3 Electron microscopy findings of the glomeruli, magnified 3,000 times. Highly electron dense deposits are seen on the epithelial side of the glomerular basement membrane and within the basement membrane

antigen–antibody complex associated with the thyroid gland was related to the membranous nephropathy, the sample was subjected to immunofluorescence staining of frozen sections for TPO and thyroglobulin. Serial sections were incubated with monoclonal antibody directed against human TPO (TPO47; BioCytex, Marseilles, France) and fluorescein isothiocyanate (FITC)-labeled primary antibody directed against human thyroglobulin (B34.1; Abcam, Cambridge, UK), washed, and then stained with FITC-labeled goat anti-mouse IgG for TPO. Sections from human thyroid gland were used as positive controls. The primary antibodies were omitted in the negative controls. Sections of renal biopsy tissue showing minor glomerular abnormalities were obtained by the same procedure to serve as histological negative controls.

On examination, TPO antigens were found to be deposited in granules along the loop walls (Fig. 2c). However, no thyroglobulin antigen deposition was seen. The membranous nephropathy was therefore considered to have occurred due to immune complexes associated with TPO.

In addition, ^{131}I treatment for Graves' disease was started after 1 month after renal biopsy. At 3 months of ^{131}I treatment, and without administration of angiotensin converting enzyme inhibitors or angiotensin receptor blockers, remission of Graves' disease was attained with fT3 2.57 g/m l, fT4 0.88 ng/dl, TSH 0.01 IU/ml, and a decrease in urinary protein to 1.24 g/gCre. Serum albumin and total cholesterol improved to 2.7 g/dl and 200 mg/dl, respectively.

Discussion

Very few reports of membranous nephropathy secondary to Graves' disease are available. Two mechanisms, not

mutually exclusive, have been thought to elicit thyroid disease-derived membranous nephropathy: adherence of immune complexes to glomeruli as a result of the antibody–antigen reaction of thyroglobulin and activation of the complement pathway [3, 4]; and release of thyroglobulin or other antigens from the thyroid gland that bind to glomeruli, thus forming immune complexes [5, 8]. Shima et al. [7] reported the first case of TPO antigen-positive membranous nephropathy in a child, and considered that the same mechanisms could also occur with TPO. The present case is the first report of TPO antigen-positive membranous nephropathy due to Graves' disease in an adult. To date, only thyroglobulin has been demonstrated to stain positively in membranous nephropathy due to Graves' disease [3–6], and our present case and that from Shima et al. are the only two that report staining for both the TPO antigen and the thyroglobulin antigen [7]. Interestingly, thyroglobulin and TPO antigen deposition in the kidneys has been previously reported in Hashimoto's disease; in these reports, deposits of both thyroglobulin and TPO antigens were seen with the fluorescent antibody technique [9, 10]. In contrast, both our group and Shima et al. [7] found only TPO antigen deposits, with no deposits of the thyroglobulin antigen in Graves' disease. The cause of this deposition of only the TPO antigen is unclear. Serum thyroglobulin levels were low in the report of Shima et al. [7] but high in our report, suggesting that the condition is not dependent on serum thyroglobulin levels. Further investigation with a greater number of patients is necessary.

The use of PTU in treatment has also been reported as a cause of membranous nephropathy originating from Graves' disease [9], and cannot be excluded as a cause in the present case. Thiamazole has been administered for the treatment of membranous nephropathy originating from Graves' disease, but thiamazole and PTU failed to control the hyperthyroidism in our present patient and she was treated with ^{131}I treatment instead. Membranous nephropathy has also been reported to result from ^{131}I treatment-induced antigen release from the damaged thyroid [5, 6], but this phenomenon was fortunately not seen in this case.

Conclusion

We describe the first adult case of membranous nephropathy originating from Graves' disease in which TPO antigen deposits were seen on immunostaining. When membranous nephropathy secondary to Graves' disease is suspected, immunostaining for not only thyroglobulin antigens but also TPO antigens may be necessary.

Conflict of interest The authors declare no conflicts of interest.

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