



Membranous Nephropathy and Graves' Disease: A Case Report and Literature Review

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Abstract

Objective: To describe a possible association between Graves' disease and nephrotic syndrome secondary to membranous nephropathy and to review the literature related to renal diseases in patients with Graves' disease.

Methods: The clinical, laboratory, and renal biopsy findings in a patient with Graves' disease and membranous nephropathy are discussed.

Results: 50 Y, Male, non diabetic, non hypertensive, diagnosed to have Grave's disease treated with antithyroid drugs, radioactive iodine in recent past presented to us with edema since 2months, fever on/off since 2 months, and diarrhoea 20 days back. Investigations revealed nephrotic proteinuria, microscopic hematuria, normal serum creatinine, viral serology (HIV, HCV, HBsAg) were negative, ultrasound abdomen-showed normal sized kidneys, serum TSH was low (<0.05miu/ml), T3 was normal (1.74ng/ml), T4 was high (12.62mcg/dl), anti-microsomal (anti-thyroid-peroxidase) antibody was high (55 IU/ml), C3 was 74mg/dl, ANA, ANCA were negative, serum protein electrophoresis was normal. A renal biopsy showed membranous nephropathy (secondary). He was treated with steroids, diuretics, angiotensin converting enzyme inhibitors (ACEI), statins, and later, found to be in process of remission. But subsequently he lost for follow-up.

Conclusions: To the best of our knowledge, this is one of few reports of the occurrence of membranous nephropathy in a patient with Graves' disease in the absence of any other immunologic disorder known to be associated.

Keywords: Graves' disease; Membranous nephropathy; Nephrotic proteinuria

Introduction

There have been several cases of thyroid diseases associated with glomerular diseases [1-4]. Published studies, however, have described only a few cases of the association of Graves' disease with renal diseases. We describe a patient with Graves' disease who had nephrotic syndrome due to membranous nephropathy and discuss the potential pathogenic mechanisms involved in the renal lesions associated with autoimmune thyroid disease.

Case Report

50 Y, Male, non diabetic, non hypertensive presented to us in February 2011. He was diagnosed to have Grave's disease 1 1/2 years back, treated with antithyroid drugs, radioactive Iodine (¹³¹I). Retreated with radioactive iodine a week back. Now he presented with edema since 2 months, fever on/off since 2months, diarrhoea 20days back. There was no history of non steroidal anti-inflammatory drugs (NSAIDS) intake.

Physical examination revealed blood pressure of 130/88 mmHg, a pulse rate of 72 beats/min and regular cardiac rhythm. Pertinent findings on systemic examination were mild exophthalmos, lower extremity edema and clear lungs. The thyroid gland was not enlarged. No bruit was detected over the thyroid gland.

Investigations showed nephrotic proteinuria with 3600mg/day (reference range <150mg/day), microscopic hematuria 5-6 HPF (reference range 0-2 HPF), hemoglobin was 14.5g/dl (reference range 13.3-16g/dl), serum creatinine was 0.6mg/dl (reference range 0.6-1.2mg/dl), serum albumin was 2.3g/dl (reference range 3.5-5g/dl), serum cholesterol was 234mg/dl (reference range <200mg/dl), viral serology (HIV, HCV, HBsAg) were negative, ultrasound abdomen showed normal sized kidneys, serum TSH was low with <0.05μIU/

ml(reference range 0.34-4.25μIU/ml), T3 was normal with 1.74ng/ml (reference range 0.77-1.35ng/ml), T4 was high with 12.62 μg/dl (reference range 5.4-11.7μg/dl), anti-thyroid-peroxidase antibody was high with 55 IU/ml (reference range <35IU/ml), C3 was 74mg/dl (reference range 83-177mg/dl), antinuclear antibody(ANA) was negative, antineutrophil cytoplasmic antibody(ANCA) was negative.

On 9.2.11, a renal biopsy was done which showed MGN Membranous nephropathy (secondary) (Figures 1-3).

Light microscopy showed 32 Glomeruli, thickened basement membrane, focal and segmental proliferation of mesangial, endothelial cells in 1 glomerulus. Protein adsorption droplets seen in podocytes. Fuchsinophilic deposits seen along loops. Neither necrotizing lesion nor crescent is observed. Tubulointerstitium showed normal tubules, a focal lymphocytic aggregate in interstitium was seen. Neither fibrosis nor granuloma was seen. Blood vessels showed Mild media hyperplasia, no vasculitis. Immunofluorescence showed diffuse granular deposits with IgG(4+), C3(1+) along with capillary loops.

He was treated with oral prednisolone (1mg/kg/day), diuretics, and angiotensin converting enzyme inhibitors (ACEI), Statins. He was found to be in process of remission with urine proteinuria of 250mg/day at 3 weeks therapy, but subsequently lost for follow-up.

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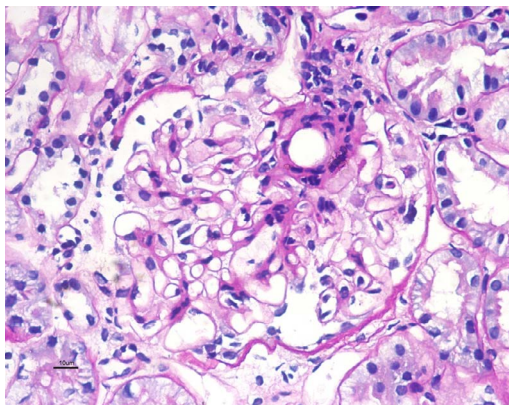


Figure 1: H&E stain shows diffuse thickening of the glomerular capillary basement membrane.

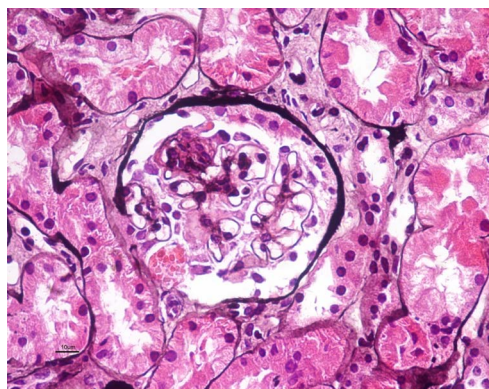


Figure 2: A silver methenamine stain complements other routine stains in highlighting capillary basement membrane thickening.

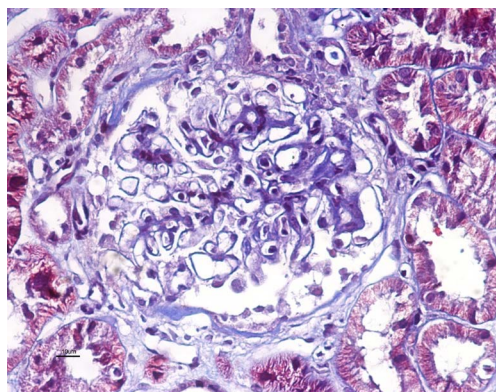


Figure 3: A periodic-acid-Schiff (PAS) stain highlights diffuse thickness of capillary basement membranes.

Discussion

Our case was a known Grave's disease treated with antithyroid drugs, and recently treated with radioactive iodine presented with nephrotic syndrome. There was no other obvious secondary cause for nephrotic syndrome as evidenced by history elicited and investigations. Both grave's disease and ^{131}I could have contributed to nephrotic syndrome (as supported by following literature review), though

electron microscopy could not be done in our case. Focal lymphocytic aggregate in interstitium could not explain nephrotic proteinuria. Immune mediated pathogenesis can explain the disease, as evidenced by remission process on steroid therapy, but could not be followed up, as patient was lost for follow-up.

Renal involvement in thyroid diseases is an unusual event. The most frequent thyroid condition associated to renal alterations is Graves' disease. The most frequently reported associated renal condition in these cases is membranous glomerulonephritis with nephrotic syndrome. However, there are sporadic cases of membranoproliferative glomerulonephritis (MPGN), minimal change disease (MCD) [1]. Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis has been reported in propylthiouracil-treated patients [2].

The coexistence of the two pathologies could be explained by a common autoimmune pathogenesis. Given the temporal coincidence of the diagnosis and the nephrotic flare after the iatrogenic hypothyroidism, the underlying thyroid disease could provoke a glomerular alteration [1]. Membranous glomerulonephritis has been reported in association with both antithyroglobulin and thyroid antimicrobial antibodies. The development of membranous glomerulonephritis may be associated with administration of ^{131}I [2]. These associations also apply in our case too.

^{131}I therapy of Graves' disease may result in the development of the nephrotic syndrome with membranous glomerulonephritis as a result of the release of antigens from the thyroid tissue being ablated. Proteinuria in association with Grave's disease may be caused also by antineutrophil cytoplasmic autoantibody-positive vasculitis, which has been reported with the use of both propylthiouracil and carbamazole [2]. Immune complex membranous glomerulonephritis is associated with autoimmune thyroid disease. Two mechanisms have been proposed for the deposition of immune complexes in membranous glomerulonephritis. Circulating immune complexes may be deposited in the glomerular membrane or antigen may be deposited followed by in situ immune complex formation [2,3].

Most patients are controlled with steroids or other immunosuppressive drugs, although therapy with iodine or radical thyroidectomy has been efficacious in those patients with repetitive flares [1].

Case report by Wirasat Hasnain, et al. of 60y, male with grave's disease with nephrotic syndrome was found to have minimal change disease on renal biopsy. Work-up for immunologic disorder, hepatitis was negative. Responded completely for steroids and near total thyroidectomy [4].

Limitations

Absence of electron microscopy findings, lack of longer follow-up.

Conclusions

To the best of our knowledge, this is one of few reports of the occurrence of membranous nephropathy disease in a patient with Graves' disease in the absence of any other immunologic disorder known to be associated.

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