Diabetic with Nephrotic Syndrome: A Case of "Masked" Membranous Nephropathy – A Case Report

Abstract

Distinguishing nondiabetic renal disease (NDKD) from diabetic nephropathy (DN) is of paramount importance in choosing treatment modalities and determining renal prognosis. Nearly 40% of the patients with diabetes are likely to have NDKD. We report a case of a patient with diabetes with a massive nephrotic range of proteinuria that was labeled as DN based on LM and IF, but paraffin IF confirmed the presence of masked MN.

Keywords: *Diabetes, nondiabetic kidney disease, membranous nephropathy*

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Introduction

Distinguishing nondiabetic kidney disease (NDKD) from diabetic nephropathy (DN) is of paramount importance in choosing treatment modalities and determining renal prognosis. Nearly 40% of the patients with diabetes are likely to have NDKD.[1] In Asia, Africa, and Europe, the most common isolated NDKD pathological type is membranous nephropathy (MN) (up to 34%), while focal segmental glomerulosclerosis is reported to be the primary pathological type in America (22%) and Oceania (64%).[2] Hence, the value of renal biopsy cannot be overemphasized, especially in cases of atypical presentations.

Ig deposits identified on renal biopsy samples by subjecting the paraffin block for IF that shows negative staining by routine IF on frozen tissue have become known as "masked" deposits. Membranous-like glomerulopathy with masked IgG deposits (MGMID) is a recently recognized pattern of immune complex deposition characterized by masked deposits that show IgG-κ restriction and are subepithelial by EM.[3]

We report a case of a patient with diabetes with a massive proteinuria that was labeled as DN based on LM and IF, but paraffin IF confirmed the presence of masked MN.

Case Report

A 63-year-old male was admitted for the evaluation of nephrotic syndrome. He had been a patient of type 2 diabetes for the past 10 years, and hypertension 4 before. He complained of gradually increasing anasarca and developed breathlessness for a week. He was evaluated elsewhere and found to have albuminuria (3+) 24-h urine protein uria of 14 g, serum creatinine 1.2 mg/dl, and serum albumin 2.6 g/dl. The fundus examination did not reveal any evidence of diabetic retinopathy. His further investigations revealed normal complement levels with negative Anti-Nuclear Antibodies, Anti Cytoplasmic antibodies and Anti-Phospholipase A2 Receptor (Anti-PLA2R) Antibody ANA and ANCA. Serum protein electrophoresis did not show an "M "spike. Free kappa/lambda ratio was 1.25 (kappa- 55.93 mg/l and lambda 44.65 mg/l). A percutaneous renal biopsy was done.

LM [Figure 1a] showed eight glomeruli, of which two were globally sclerosed. Viable glomeruli showed mesangial widening with mild glomerular basement membrane (GBM) thickening and no increase in cellularity, segmental sclerosis, and crescents. KW nodules were not seen. Circumferential arteriolar hyalinosis was seen with 20% of IFTA. IF did not show any immune deposits. He was diagnosed

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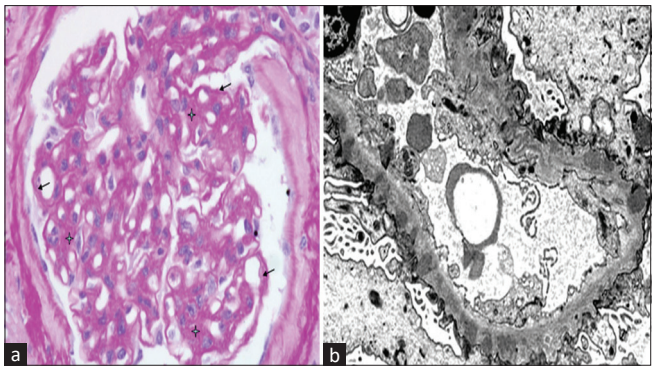

Figure 1: (a) PAS stain showing glomeruli with normal cellularity and thickened GBM with mesangial expansion and no sclerosis and crescents. (b). Electron microscopy shows subepithelial deposits in the glomeruli lacking substructure

to have Class 2 DN. EM [Figure 1b] revealed subepithelial electron-dense deposits with no definite substructure and a thickened GBM with diffuse effacement of visceral epithelial cell foot process, consistent with stage 2 MN. Paraffin block was subjected to tissue pronase digestion, which revealed IgG and kappa deposits [Figure 2]. The tissue for PLA2R was negative. Other antigens could not be tested as tissue was exhausted. IgG subclass staining could not be done. A diagnosis of MN with masked IgG-κ deposits was made, and he was started on rituximab 500 mg intravenous infusions once weekly for 4 weeks with low-dose steroid. His 24-h urine protein decreased to 2.8 g after 2 months of immunosuppressive therapy.

Discussion

Routine direct IF on fresh unfixed tissue is the gold standard for the detection and characterization of immune deposits. "Masked deposits" refer to Igs that are not detected on routine IF staining but can be detected when IF is repeated on formalin-fixed, paraffin-embedded tissue. The first description of masked deposits revealed by this technique was given by Nasr *et al*.[4] Larsen *et al*.[3] reported 14 cases that were characterized by numerous large subepithelial deposits visualized by EM and C3-predominant staining and negative immunoglobulin staining on routine IF. Repeat IF after digestion of the formalin-fixed, paraffin-embedded tissue with pronase elicited strong IgG-κ staining restricted within the deposits.

Masked MN has been reported predominantly in young patients with a mean age of 26 years. Our patient is an elderly man with diabetes. Thickened GBM is an invariable feature in DN. The diagnosis could not have been suspected if EM was not performed. As the EM findings were suggestive of subepithelial electron-dense deposits, we resorted to doing pronase digestion of the paraffin block to confirm the diagnosis of masked MN.

Pronase digestion of the paraffin block for IF is most commonly implemented as a salvage technique when no glomeruli are available in the tissue submitted for

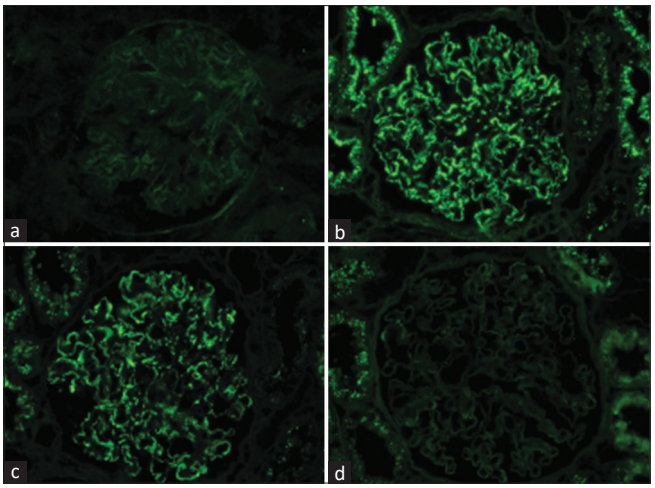

Figure 2: IF findings from membranous-like glomerulopathy with masked IgG-κ deposit. Glomeruli stain negative for IgG by routine IF on fresh tissue (a) and positive on paraffin-embedded tissue after pronase digestion (b). Glomeruli show staining for kappa (c) and not lambda (d) on the pronase-digested tissue. IF = immunofluorescence

routine IF. The reason why some deposits stain by paraffin-embedded tissue IF and not by routine IF is largely unknown. This could be due to the loss of Igs during the washing steps of IF, whereas they are retained in the tissue during formalin-induced protein crosslinking in paraffin-embedded tissue. Serum amyloid P (SAP) stain can also be used to confirm MGMID. Larsen *et al*.[5] compared the mass spectrometry profile of laser capture microdissected glomeruli from nine MGMID renal biopsies, with eight biopsies showing other patterns of membranous glomerulopathy. Immunostaining showed SAP co-localized with IgG in all the glomeruli of MGMID, but not with PLA2R- or THSD7A-associated membranous glomerulopathy.[5]

Our case illustrates not only the importance of performing a renal biopsy in diabetes with severe nephrotic syndrome, but also subjecting the tissue to EM as well as pronase digestion of paraffin-embedded tissue when there is discordance between the findings on LM, EM, and IF.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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