Pathology – Research and Practice 212 (2016) 650–653

Contents lists available at ScienceDirect

Pathology – Research and Practice

journal homepage: www.elsevier.com/locate/prp

Case report

Membranous nephropathy with crescents associated with levamisole-induced MPO-ANCA vasculitis

Irfan Moinuddin[a,*], Machaiah Madhrira[a], Erika Bracamonte[b], Bijin Thajudeen[a], Amy Sussman[a]

[a] Division of Nephrology, University of Arizona Medical Center, Tucson, AZ, United States
[b] Department of Pathology, University of Arizona Medical Center, Tucson, AZ, United States

ARTICLE INFO

Article history:
Received 12 December 2015
Received in revised form 16 February 2016
Accepted 18 March 2016

Keywords:
Levamisole
Crescentic
Membranous
Pauciimmune
Vasculitis
Glomerulonephritis

ABSTRACT

ANCA-associated vasculitis (AAV) is the most common cause of crescentic rapidly progressive glomerulonephritis (GN). Levamisole used as an adulterant in cocaine is increasingly recognized as a cause of AAV. We report the case of a 50 year old woman with atypical anti-MPO AAV associated with cocaine use and exposure to levamisole. In addition to the clinical and pathologic findings of crescentic GN, the patient also had biopsy evidence of secondary membranous nephropathy (MN). Although AAV and MN have been reported previously in the same patient and both have been induced by drug exposures, this is the first report of MN in a patient with AAV likely induced by levamisole. We suggest that MPO can cause both pauci-immune vasculitis and secondary membranous nephropathy in some cases, as in cases of levamisole-adulterated cocaine use.

1. Introduction

The first description of membranous nephropathy (MN) and concurrent crescentic glomerulonephritis (GN) dates back to 1975. There have been reports of MN with coexistent crescentic GN due to antinuclear antibody (ANA), anti-GBM (glomerular basement membrane) antibodies, and IgA Nephropathy. There have also been many reported cases of MN co-existing with crescentic GN, usually due to ANCA-associated vasculitis (AAV), including granulomatosis with polyangitis (formerly Wegener's), microscopic polyangitis and Eosinophilic Granulomatosis with Polyangitis (Churg-Strauss syndrome).

Recently, levamisole, used as an adulterant in cocaine, has been recognized as an important inducer of anti-MPO vasculitis [1]. Levamisole has been identified as a likely etiologic agent in one patient with anti-MPO vasculitis associated with nephrotic syndrome; however, the kidney was not biopsied in that case [2]. To our knowledge, this report describes the first case of levamisole-induced MPO-ANCA vasculitis with crescentic GN and accompanying MN.

2. Clinical summary

A 50 year old female with past medical history of asthma, hypertension, and rheumatoid arthritis presented for evaluation of rash and renal failure in the setting of cocaine use. A toxicology screen was positive for cocaine and opiates. On physical examination, the patient was afebrile. Skin exam revealed a purpuric and violaceous, non-blanching rash in a retiform pattern with areas of necrosis and infected ulcers located on the helix and earlobes and also on the upper and lower extremities. The patient denied photosensitivity, neurological complaints, symptoms of serositis, oral ulcers, temperature sensitivity, Raynaud's phenomenon, sore throat or dyspnea.

Urine analysis showed dysmorphic red blood cells, and 24 h protein excretion was quantified at 1600 mg. The serum creatinine (Cr) peaked at 194.5 mcmol/L. Both C3 and C4 were low at 0.61 g/L (normal 0.88–2.06 g/L) and 0.09 g/L (normal 0.13–0.75 g/L) respectively. Serologies for Hepatitis B and C were negative. Age-appropriate cancer screening, including colonoscopy, mammogram, pap smear and chest xray were all negative. Patient denied NSAID use. Syphilis was ruled out with a negative rapid plasma reagin. P-ANCA was positive and anti-MPO antibodies were quantified at 134 AU/mL (positive: 26 AU/mL or greater). Further serologic studies were neg-

* Corresponding author at: University of Arizona Medical Center, 1501 N. Campbell Ave, Room 6325, Tucson, AZ 85724, United States.
E-mail addresses: irfanmoinuddin@yahoo.com, irfanmoinuddin@deptofmed.arizona.edu (I. Moinuddin), mmadhrira@swkidney.com (M. Madhrira), erikab@pathology.arizona.edu (E. Bracamonte), bijint@deptofmed.arizona.edu (B. Thajudeen), asussman@deptofmed.arizona.edu (A. Sussman).

http://dx.doi.org/10.1016/j.prp.2016.03.008
0344-0338/

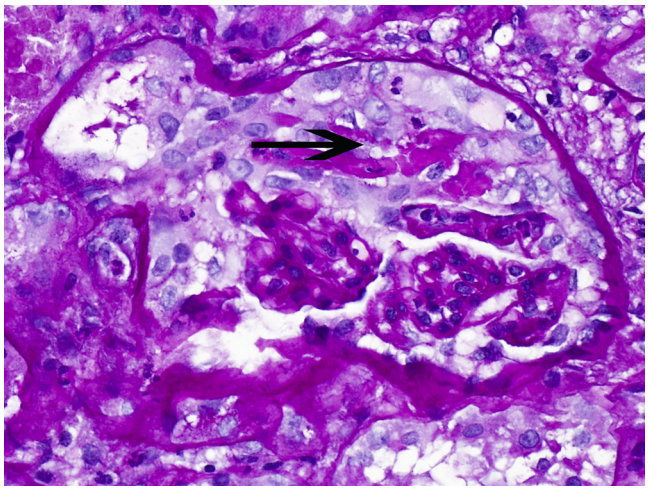

Fig. 1. Glomerulus with fibrin within the urinary space and associated cellular crescent (arrow). PAS 400× magnification.

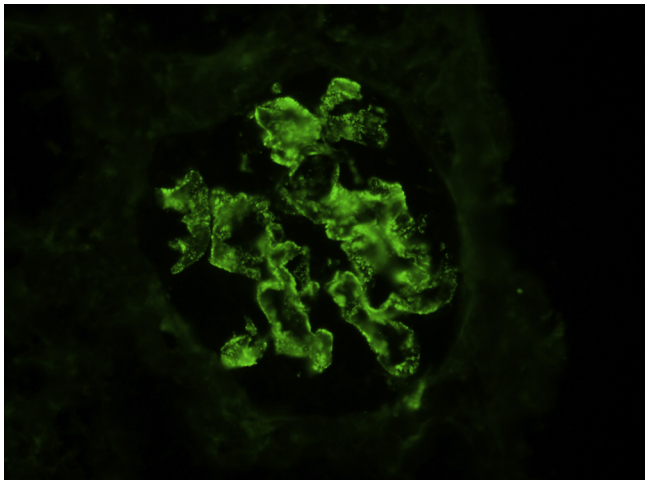

Fig. 2. Immunofluorescence for IgG shows fine granular staining of glomerular capillary loops. IgG 400× magnification.

ative for ANA, dsDNA, HIV, CMV, and EBV. Serology for IgG4-specific and total IgG anti-phospholipase A2 receptor (PLA2R) antibodies was negative. A kidney biopsy was pursued as there was high suspicion of glomerulonephritis.

3. Pathological findings

Kidney biopsy revealed one core of renal cortex with 9–11 glomeruli per level section, of which 0–1 per level section were globally sclerosed. Two glomeruli had segmental sclerosis and one glomeruli contained a small cellular crescent. Biopsy showed features of crescentic vasculitis in addition to membranous nephropathy (Fig. 1). Light microscopy showed mild thickening of basement membranes with spike formation. Capillary loops cut en face showed a moth-eaten appearance by silver stain. Occasional glomeruli also showed segmental endocapillary proliferation. In addition, focal segmental necrotizing lesions with early crescent formation were seen. Immunofluorescence staining revealed a uniform, fine granular capillary loop staining for IgG (2+), IgM (1–2+), C3 (2–3+), C1q (trace),kappa (1+), and lambda (trace to 1+) in a subepithelial pattern characteristic of MN (Fig. 2). Staining for IgA was negative.

Immunofluorescence staining of the renal biopsy for PLA2R was performed (Nephropath laboratory, Little Rock, AK) to help distinguish between primary versus secondary membranous glomerulopathy. Glomerular PLA2R staining was not enhanced in this case. Positive membranous glomerulopathy cases will show a pattern of staining identical to the IgG. The positive control was a confirmed primary membranous case. A negative control consisted of the secondary antibody only.

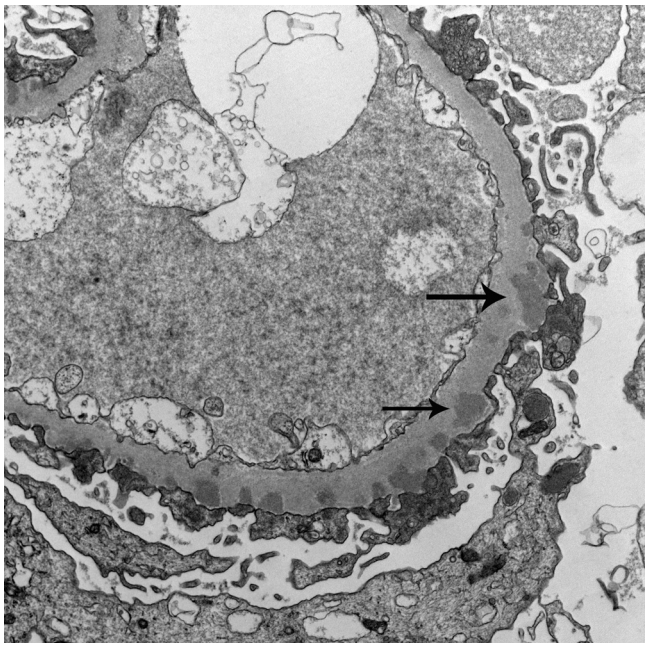

Fig. 3. Numerous small subepithelial immune deposits (arrows) are present along the glomerular basement membrane, with coarsening and effacement of podocyte foot processes. 8200× magnification.

Immunohistochemical staining for MPO and IgG4 was also performed (ARUP laboratory, Salt Lake, UT) and both stains were negative within the glomeruli. Staining for MPO was performed to help determine whether MPO could be detected in the subepithelial immune complexes as a planted antigen. MPO staining uses a rabbit anti-human polyclonal antibody to myeloperoxidase. Spleen tissue constituted positive control. There was no negative control. IgG4 staining was also done by ARUP. A mouse monoclonal antibody against human IgG4 designed to bind to the Fc portion of IgG4 molecules was used for IHC. The positive control was a mixed inflammatory infiltrate with some IgG4 staining cells. There was no negative control.

Anti-PLA2R antibody quantification by ELISA was done by Lawrence H. Beck's laboratory at Boston University School of Medicine. Both IgG4-specific anti-PLA2R as well as total IgG anti-PLA2R were quantified.

Electron microscopy revealed the glomerular capillary loops to be markedly irregular and frequently thickened, due to the presence of numerous subepithelial and intramembranous electron dense immune deposits (Fig. 3). The deposits were associated with remodeling of the GBM, including the formation of epimembranous "spikes" of new basement membrane material between the deposits. Mesangial areas contained increased matrix and cellularity as well as scattered immune deposits (Fig. 4). There was extensive effacement of epithelial cell foot processes with associated microvillous transformation. No significant subendothelial deposits were seen.

4. Discussion

The patient was treated with intravenous methylprednisolone and transitioned to oral prednisone. She was also started on oral