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Exceptional Cases

Remission of proteinuria with treatment of *Actinomyces* infection: eradicating a cause of secondary membranous glomerulopathy suppresses nephrotic syndrome

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Abstract

Eradication of a cause of secondary membranous glomerulopathy might suppress nephrotic syndrome. Here we report a patient with membranous nephropathy (MN), whose proteinuria entered complete remission after treating actinomycosis. A 45-year-old woman presented with nephrotic syndrome and was diagnosed as having MN. Her urine protein excretion was 5.3 g/day and the serum creatinine level was 70.7 μmol/L. When we searched for causes of secondary MN, pelvic actinomycosis was detected. After removing the pelvic abscess surgically, we administered amoxicillin for 6 months. Then, her proteinuria had decreased to <0.1 g/day, and since it entered remission, she has not relapsed.

Keywords: membranous nephropathy; nephrotic syndrome; pelvic actinomycosis; remission

Introduction

Membranous nephropathy (MN) is the most common glomerular disease causing nephrotic syndrome in adults. Histologically, MN is characterized by thickening of the glomerular capillary wall, which is caused by subepithelial deposits of immune complexes. When the same pathological lesions occur in autoimmune diseases, malignancies, hepatitis B virus (HBV) infection and with use of drugs, they are called secondary MN [1].

Here, we describe a patient with MN, whose nephrotic-range proteinuria entered complete remission after eradicating pelvic actinomycosis.

Case report

A 45-year-old woman was admitted with generalized oedema. Her medical history was unremarkable (i.e. no diabetes mellitus, hypertension or hepatitis). Three months before admission, she visited a local hospital for leg oedema and weight gain and was found to have proteinuria. At that hospital, a percutaneous renal biopsy was performed and pathological diagnosis of MN was made. After the renal biopsy, she was given only diuretics and was referred to our hospital with her renal specimen and radiological data for further evaluation and treatment.

On admission, she was fully conscious, with a blood pressure of 120/70 mmHg, a regular pulse of 76/min and a body temperature of 36.8°C. The physical examination revealed bilateral pretibial pitting oedema. Laboratory studies showed the following: white blood cell count, 7×10^9/L (segmented neutrophils 79.3%, eosinophils 1.9%, basophils 0.3%, monocytes 3.9%, lymphocytes 14.6%); red blood cell count, 3.5×10^{12}/L; haemoglobin, 85 g/L; platelet count, 334×10^9/L; total protein, 34 g/L; albumin, 15 g/L; blood urea nitrogen, 2.8 mmol/L; serum creatinine, 70.7 μmol/L; total cholesterol, 7.5 mmol/L; serum iron, 2.0 μmol/L; total iron-binding capacity, 34.7 μmol/L; serum ferritin, 22.5 pmol/L; and C-reactive protein (CRP), 0.15 mg/dL. The urinary protein excretion was 5.3 g/day, and the creatinine clearance was 73.3 mL/min/1.73 m^2. Hepatitis B antigen and hepatitis C virus antibody were negative.

The renal biopsy specimen was reviewed at our hospital, which revealed normocellular glomeruli with marked capillary wall thickening. Immunofluorescent microscopy disclosed granular deposits of IgG and C3 on the capillary wall. Electron microscopy revealed heavy subepithelial electron-dense deposits with near-total effacement of the foot processes of visceral epithelial cells (Figure 1).

Since all of the autoimmune markers examined at the previous hospital were negative, including immunoglobulins, complement, anti-neutrophil antibody, anti-DNA antibody and anti-GBM antibody, we searched for hidden internal malignancies. The chest X-ray and upper endoscopy were normal. The serum carcinoembryonic antigen (CEA) was 0.9 ng/mL and the CA-125 was 48.4 U/mL. Whole body positron emission tomography (PET) showed a suspicious

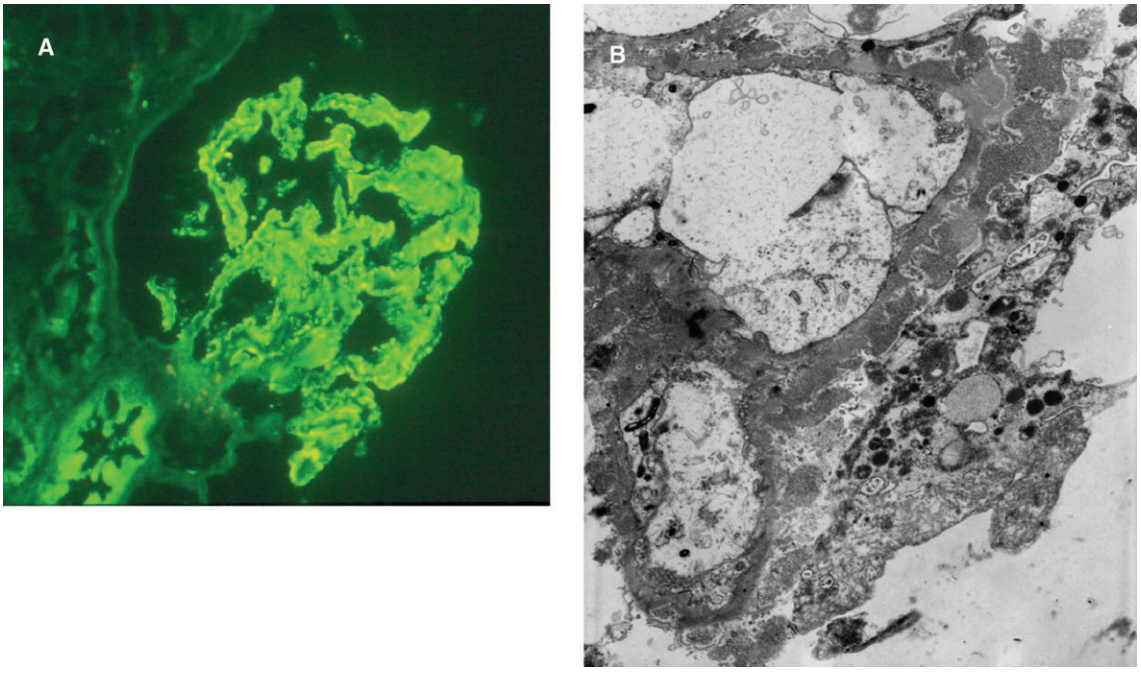

Fig. 1. Renal biopsy findings. (**A**) Immunofluorescence microscopy shows granular deposits of IgG on the capillary wall. (**B**) Electron microscopy shows heavy subepithelial electron-dense deposits with nearly total effacement of the foot processes of visceral epithelial cells (6000×).

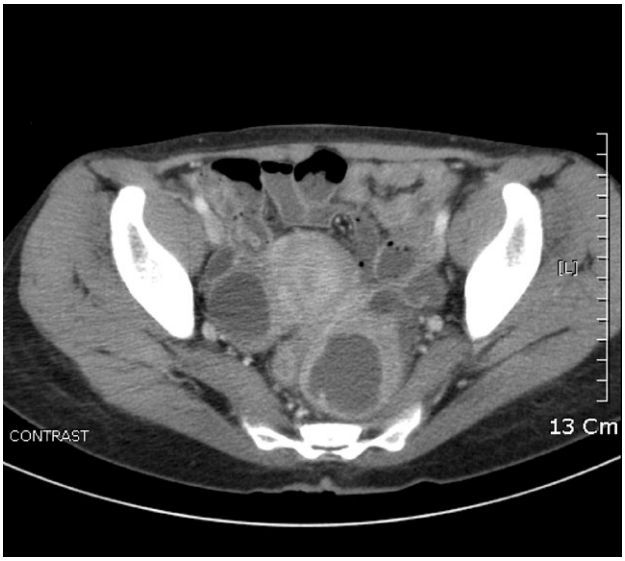

Fig. 2. Preoperative abdominal CT shows a multilocular cystic mass in the left adnexa and posterior cul-de-sac with a strongly enhancing thick wall peripherally.

accumulation of fluorodeoxyglucose (FDG) in the vicinity of the rectum, and abdominal computed tomography (CT) revealed a multilocular cystic mass in the left adnexa and posterior cul-de-sac with a strongly enhancing thick wall peripherally, suggesting a tubo-ovarian abscess or cystic malignancy (Figure 2). A gynaecologist removed the cystic mass at surgery and found that it was an abscess pocket. When the pathology examination diagnosed actinomycosis, we administered amoxicillin 375 mg three times daily. One month after beginning this therapy, her urinary protein excretion had decreased markedly to 2.06 g/day (Table 1) without any treatment for nephrotic syndrome. After treatment for 6 months, her proteinuria had decreased at <0.1 g/day (Table 1). Since then, she has not relapsed for 2 years.

Discussion

MN is frequently associated with viral hepatitis, although many other organisms have been reported to be associated with MN, including streptococcal infection, malaria, schistosomiasis, tuberculosis, leprosy, filariasis and syphilis [2–4]. *Actinomyces* are slowly growing fastidious, obligate anaerobic gram-positive bacilli [5] that are part of the normal flora in the human mouth and gastrointestinal (GI) tract, particularly the caecum and appendix. Pelvic actinomycosis is extremely rare. It arises primarily from the appendix and can result in an ascending infection forming tubo-ovarian abscesses [6]. Recently, numerous case series have reported actinomycotic pelvic abscesses in women using modern intrauterine devices (IUDs) [6], although our patient did not have an IUD.

MN is characterized by subepithelial deposits of immune complexes, and it is considered to be an immune complex-mediated disease, although the precise pathogenic mechanism of MN remains uncertain. The nephritogenic antigen and its antibody may form an immune complex in the blood stream or *in situ* in the subepithelial area, and this may subsequently form immune deposits [1]. Many animal studies have sought to define the nephritogenic antigen of MN. In Heymann nephritis (HN), the rat model of MN, circulating anti-megalin (gp-330) antibodies cross the glomerular basement membrane (GBM) and bind to megalin, forming

Table 1. Laboratory findings in the presented case

Variable	Baseline	1 month	3 month	6 month	12 month	24 month
Total protein (g/L)	34	59	58	62	69	72
Albumin (g/L)	15	34	35	40	43	45
Blood urea nitrogen (mmol/L)	2.8	4.1	3.5	5.1	5.7	4.2
Creatinine (μmol/L)	70.7	61.9	61.9	61.9	70.7	61.9
Total cholesterol (mmol/L)	7.5	4.3	4.0	4.0	3.8	4.4
Urinary protein (g/day)	5.3	2.06	1.15	0.10	0.05	0.04

Table 2. Detected antigens or antibodies other than hepatitis viruses that clearly induced MN

Authors	Diagnosis	Antigens or antibodies	Treatment
Muramoto *et al*. [18]	Oesophageal squamous cell carcinoma	Squamous cell carcinoma antigen (SCC)	Radiotherapy, endoscopic mucosal resection
Wadhwa *et al*. [19]	Adrenal ganglioneuroma	Circulating tumour antigen-specific antibody that cross-reacted with an antigen present on the podocyte membrane of the renal glomeruli	Surgery
Colletti *et al*. [20]	Autoimmune enteropathy	Circulating anti-epithelial cell antibodies	High-dose prednisone
Touchard *et al*. [21]	Chronic lymphocytic leukaemia	Monoclonal cryoglobulin, immunoglobulin	Chlorambucil, prednisone
Sobh *et al*. [22]	Schistosomiasis	Schistosomal-specific antigens (CAA and CCA) and antibodies	Oxamniquine, praziquantel

in situ immune complexes [7,8]. Studies in mice have shown that other podocyte-membrane proteins, such as neutral endopeptidase (NEP) and aminopeptidase A, may represent the target for immune complex formation [9].

However, megalin has not been found in human podocytes or detected in subepithelial immune deposits in patients with MN. Several potential antigens have been proposed in so-called secondary forms of MN (e.g. hepatitis B and C viruses), but no real proof exists that these antigens are pathogenic. In 2002, Debiec *et al*. identified a human counterpart to the HN antigen in a patient with neonatal MN. They reported that anti-NEP antibodies produced by a pregnant woman were transferred to her foetus, which developed a severe form of MN prenatally, and they postulated that alloimmunization against NEP was a novel pathomechanism of MN that might also account for some cases of MN after renal or bone marrow transplantation [10,11]. In addition, they found heavy deposits of the membrane attack complex (MAC) of complement C5b-9 on the outer aspect of the glomerular capillary walls in kidney biopsy specimens from the infant. A subsequent report by Pippin *et al*. also showed that C5b-9 could induce DNA damage in podocytes, either directly or via the production of reactive oxygen species [12]. Other studies reported that C5b-9 can also enhance the expression of matrix metalloproteinase-9 by podocytes and alter nephrin expression. In practise, the glomeruli of patients with MN showed a more granular pattern or a loss of staining for nephrin [13–15].

Therefore, the binding of nephritogenic anti-NEP antibodies and ensuing complement activation may play a key role in the development of human MN. Since several studies have failed to find NEP in the subepithelial immune deposits in adult patients with MN, the pathogenic antigen of MN is still under debate.

In contrast, several antigens have been found in secondary MN in humans, and these were strongly related to the clinical course of the disease. We reviewed the cases in which the proteinuria cleared completely after removing the cause of MN using the PubMed database in April 2009. The literature review produced 106 case reports using the search 'MN and remission'. Of these, 23 were idiopathic MN and two were glomerulonephritis other than MN. Of the remaining 81 MN cases, 21 were associated with malignancy, 13 were associated with viral hepatitis, 10 were post-bone marrow transplant MN, 7 were post-renal transplant MN, 4 were associated with infection and 26 had other causes, including drugs.

The disappearance of the proteinuria after removing the cause of MN suggests that nephritogenic antigens exist. Shin *et al*. reported a patient with MN secondary to fluconazole treatment who had recurrent episodes of nephrotic syndrome caused by readministering fluconazole [16]. Chuang *et al*. reported an adult patient with chronic hepatitis B who developed MN with nephrotic syndrome and who experienced complete remission after lamivudine monotherapy. Using electron microscopy, they found viral-like particles distributed within the GBM. In addition, active HBV infection during the course of disease progression and evidence of the reversibility of the renal disease concomitant with a decrease in viral load suggested a direct link between MN and HBV infection [17]. Muramoto *et al*. reported a case of MN associated with oesophageal squamous cell carcinoma, in which the patient's proteinuria disappeared soon after achieving a pathologic complete response (CR) of the carcinoma, and the level of proteinuria was correlated with his serum squamous cell carcinoma (SCC) antigen level [18]. Table 2 summarizes some of the reports in which antigens or antibodies responsible for the pathogenesis of

MN were found in the serum or renal biopsy specimens and the proteinuria disappeared after appropriate treatment [18–22].

To our knowledge, this is the first reported case of MN associated with actinomycosis. Unfortunately, we do not know whether the *Actinomyces* produced a nephritogenic antigen themselves or if they damaged part of the renal structure, producing the responsible antigen and activating complement.

Wen and Chen [23] reported an unusual case of MN that responded to high-dose trimethoprim–sulphamethoxazole (TMP-SMX) used to treat *Pneumocystis jiroveci* infection. Recently, Sugimoto *et al*. [24] reported that only the eradication of *Helicobacter pylori* infection successfully reduced the proteinuria in a patient with nephrotic syndrome caused by MN. Therefore, the amoxicillin given to our patient might have reduced the proteinuria, although no report of amoxicillin attenuating the proteinuria in patients with nephrotic or non-nephrotic proteinuria exists, regardless of the cause.

In summary, we present a case of MN associated with pelvic actinomycosis. This case suggests that in women with MN, actinomycotic pelvic infection should be considered in addition to other well-known causes of secondary MN.

Conflict of interest statement. None declared.

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