American Journal of Case Reports

ISSN 1507-6164
© Am J Case Rep, 2013; 14: 543-547
DOI: 10.12659/AJCR.889684

Received: 2013.08.17
Accepted: 2013.10.03
Published: 2013.12.16

Membranous glomerulonephritis associated with *Mycobacterium shimoidei* pulmonary infection

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Patient: Male, 83
Final Diagnosis: Membranous glomerulonephritis
Symptoms: Producting cough
Medication: —
Clinical Procedure: —
Specialty: Nephrology

Objective: Rare disease

Background: Membranous glomerulonephritis can occur secondarily from infectious diseases. There are no reports describing membranous glomerulonephritis caused by non-tuberculous mycobacterium infection. However, several cases with membranous glomerulonephritis due to *Mycobacterium tuberculosis* have been reported. *Mycobacterium shimoidei* is an uncommon pathogen, and less than 20 cases with this species have been reported. A therapeutic regimen for this infection has not been established yet.

Case Report: An 83-year-old Japanese man presented with productive cough for 6 months. Computed tomography scan showed multiple cavities in the bilateral pulmonary fields. Acid-fast bacilli were evident in his sputum by Ziehl-Neelsen staining (Gaffky 3). PCR amplifications for *Mycobacterium tuberculosis*, *Mycobacterium avium*, and *Mycobacterium intracellulare* were all negative. Finally, *Mycobacterium shimoidei* was identified by rpoB sequencing and 16S rRNA sequencing. Urine examination showed a sub-nephrotic range of proteinuria and histology of the kidney showed membranous glomerulonephritis. Antimycobacterial treatment with clarithromycin, rifampicin, and ethambutol dramatically improved not only the pulmonary disease, but also the proteinuria.

Conclusions: To the best of our knowledge, the presented case is the first report showing non-tuberculous mycobacterium-induced secondary membranous glomerulonephritis. A combination with clarithromycin, ethambutol, and rifampicin might be effective for treatment of *Mycobacterium shimoidei* infection.

Key words: non-tuberculous • mycobacterium • shimoidei • membranous glomerulonephritis • proteinuria

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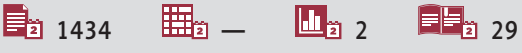

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Background

Mycobacterium shimoidei (M. shimoidei) was first described in 1975 [1] and gained species status in 1982 [2]. A total of 15 patients with this uncommon pathogen have been reported in various countries around the world [1,3–15]. The clinical symptoms of *M. shimoidei* pulmonary disease are nonspecific and similar to those of tuberculosis, including fever, cough, sputum, weight loss, fatigue, and hemoptysis [11]. Tuberculosis-like cavitation is the most common radiographic finding in *M. shimoidei* pulmonary disease [11]. A therapeutic regimen for this disease has not been established yet.

It is well-known that membranous glomerulonephritis (MGN) can occur secondarily from malignancy, drugs and toxic substances, collagen diseases such as systemic lupus erythematosus, and infectious diseases, including hepatitis B, quartan malaria, and schistosomiasis [16]. Several cases with MGN due to *M. tuberculosis* have also been reported without classical renal tuberculosis [17,18]. However, there are no reports describing MGN caused by non-tuberculous mycobacterium (NTM) infection.

Here, we describe a case of MGN associated with *Mycobacterium shimoidei* pulmonary infection. Antimycobacterial treatment with clarithromycin, rifampicin, and ethambutol dramatically improved not only the pulmonary disease, but also the proteinuria.

Case Report

An 83-year-old Japanese man had suffered from productive cough for 6 months and visited our hospital in March 2011. He had no fever. His sputum was yellowish. He had smoked 60 pack-years until 50 years of age. He had no past history of illness. He was a tobacco farmer and had also raised silkworms. On physical examination, there was no lymphadenopathy, no clubbing, and no edema. SpO_2 was 98% and blood pressure was 150/80 mmHg. His vesicular sound was slightly decreased throughout both lung fields and no crackle was auscultated. A chest X-ray and computed tomography (CT) scan showed emphysematous changes and multiple cavities in the bilateral pulmonary fields (Figure 1). Laboratory test results were as follows: WBC, 6500/μl; RBC, 3.29 million/μl; hemoglobin, 9.9 g/dl; MCV, 94.5 fl; MCH, 30.1 pg; total protein, 6.8 g/dl; albumin, 3.0 g/dl; total cholesterol, 167 mg/ml; BUN, 29.4 mg/ml; Cr, 1.57 mg/ml; and CRP, 1.34 mg/ml. Urine examination showed a sub-nephrotic range of proteinuria (3.1 g/gCr) and many hyaline casts (>50/total fields) in the urinary sediment. Pulmonary function tests showed low%VC (70.8%) and normal range of FEV1.0% (78.1%). Acid-fast bacilli were evident in his sputum by Ziehl-Neelsen staining (Gaffky 3). PCR amplifications for *Mycobacterium tuberculosis*, *Mycobacterium avium*, and *Mycobacterium intracellulare* were all negative. Numerous colonies of acid-fast bacilli appeared upon culture. DNA-DNA hybridization, which can detect 18 species of acid-fast bacilli using cultured colonies, failed to identify the species. The mycobacterial characteristics of a sputum sample obtained on another day were exactly the same as those of the first sample. Finally, *Mycobacterium shimoidei* was identified by rpoB sequencing and 16S rRNA sequencing [19], with 100% homology to the sequences.

Renal tissue samples obtained by renal biopsy mainly showed membranous glomerulonephritis (MGN), with partial

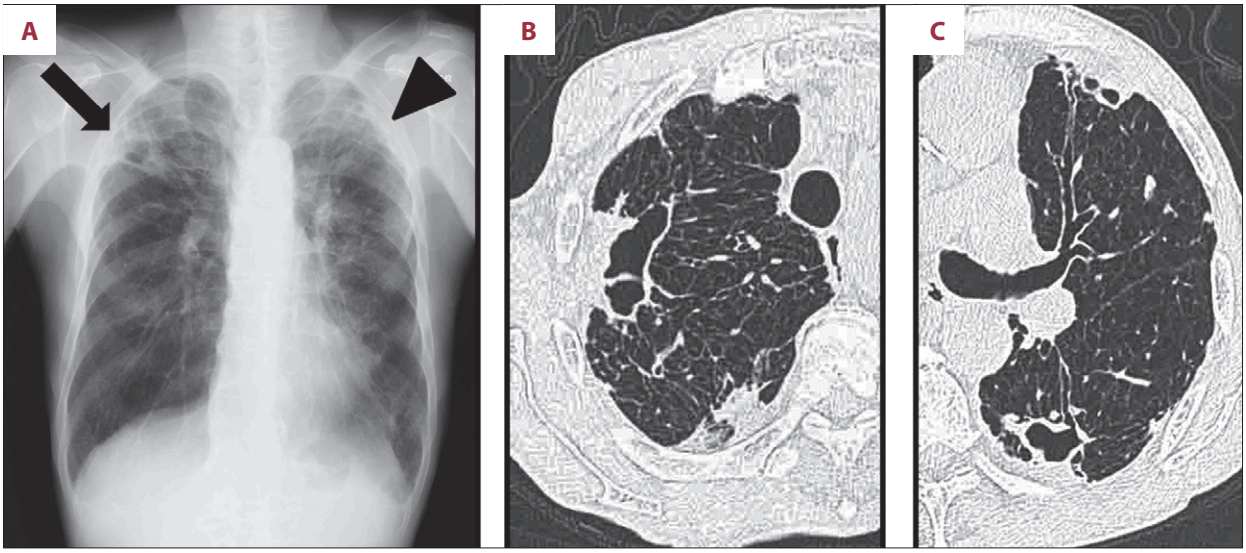

Figure 1. Chest X-ray and computed tomography. (**A**) Chest X-ray showing cavities (arrow), nodules, and pleural thickening (arrowhead) in the bilateral, predominantly upper, lung fields. (**B, C**) Computed tomography images showing multiple cavities, nodules, and bronchiectasia.

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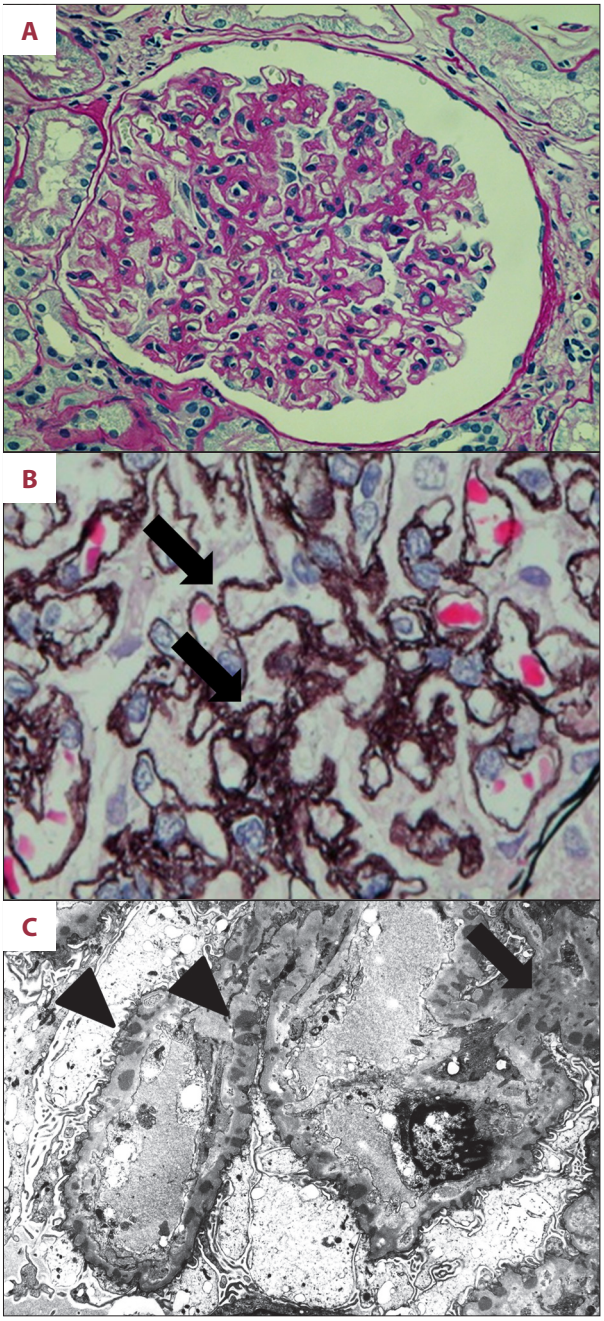

Figure 2. Histology of the kidney showing membranous glomerulonephritis. (**A**) Thickening of basement membranes, enlarged mesangial areas, and proliferated mesangial cells in part (PAS stain). (**B**) Spike lesions (arrows; PAM stain). (**C**) Electron microscopic observation showing electron-dense deposits in the subepithelium, basement membranes (arrowheads), and mesangial area (arrow).

hypertensive renal damage (Figure 2). In addition, the mesangial areas were slightly enlarged and mesangial cells had proliferated in part (Figure 2A). Electron-dense deposits were observed in the mesangial areas as well as the subepithelium and basement membranes (Figure 2C). Immunofluorescence analyses showed positive staining for IgG, IgA, and IgM in the basement membranes (data not shown). No granulomatous change was observed in the renal tissue samples. No acid-fast bacilli were detected by Ziehl-Neelsen staining.

Because the productive cough continued, *M. tuberculosis* was excluded, and a new lesion appeared on his chest X-ray, antimycobacterial treatment (clarithromycin, 400 mg/d; rifampicin, 300 mg/d; and ethambutol, 500 mg/d) was started before the identification of *M. shimoidei*. Candesartan (80 mg/d), an angiotensin II receptor blocker (ARB), was also started. After 1 month of treatment, the species was identified as *M. shimoidei* and the initial treatment was continued. The isolate was sensitive to ethambutol, streptomycin, kanamycin, enviomycin, ethionamide, and levofloxacin, and was resistant to isoniazid, rifampicin, cycloserine, and para-aminosalicylic acid, in *in vitro* drug sensitivity tests. At 2 months after starting the treatment, his sputum was clearly decreased. After 6 months of treatment, acid-fast bacilli were not detected by either Ziehl-Neelsen staining or 8-week culture, and the chest CT findings were also improved (data not shown). He continued antimycobacterial treatment for an additional 1 year (18 months in total) in accordance with the statement from the American Thoracic Society and the Infectious Diseases Society of America [20]. The amount of urine protein decreased gradually after initiation of the antimycobacterial treatment and ARB, and reached 0.6 g/gCr. The serum albumin level recovered to 3.6 g/dl at the end of the treatment.

Discussion

In the present case, several findings suggest that MGN was secondarily induced by an NTM, but not idiopathic MGN. First, the antimycobacterial treatment and ARB dramatically improved the proteinuria as well as the pulmonary disease. Second, the mesangial areas were slightly enlarged histologically. In addition, electron-dense deposits were observed in the mesangial areas as well as the subepithelium and basement membranes. Third, no other disease that could cause MGN was detected. Fourth, the CT findings showed a tuberculosis-like fibrocavitary pattern, but no nodular/bronchiectatic pattern, which might have the potential to induce glomerular diseases.

In several cases with MGN due to *M. tuberculosis*, urinary protein excretion caused by MGN was improved by treatment with antituberculosis agents with or without prednisolone (30 mg/d) [17,18]. Some patients with tuberculosis present glomerular diseases other than MGN, including IgA nephropathy, focal proliferative glomerulonephritis, and focal segmental glomerulosclerosis [21–24]. Regarding the mechanisms by which tuberculosis causes glomerular diseases, immune

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responses may be involved. *M. tuberculosis* was reported to induce both cellular and humoral immune responses when the bacilli invade the body [17]. *M. tuberculosis* infection can lead to disturbance of Th1/Th2 cells, which may give rise to nephritis [25]. Immune complexes were reported to be detectable at high levels in the active phase of disseminated tuberculosis, suggesting an association with humoral immunity [21]. Thus, MGN could be induced indirectly by pulmonary tuberculosis.

Candesartan has been reported to exert a protective effect on the kidney. In patients with non-nephrotic proteinuria (0.5–3.5 g/d), candesartan alone reduced proteinuria, by an average of 13% [26]. Therefore, candesartan may have contributed somewhat to the improvement in proteinuria in the present case. However, the proteinuria was dramatically improved in the present case (80% reduction), suggesting that the treatment for NTM had a greater effect on the proteinuria.

Regarding the pathology of MGN, enlargement of mesangial areas and proliferation of mesangial cells are sometimes observed in secondary MGN [27–29]. Moreover, mesangial electron-dense deposits are uncommon in idiopathic MGN, and a secondary form of MGN should be excluded when they are present [27–29]. In the present case, these pathologic findings were observed, and no causes of MGN were identified except for mycobacterium infection.

Taken together, these findings and therapeutic outcome clearly suggest that the MGN in the present case was associated with *M. shimoidei* infection.

The radiographic features of NTM pulmonary disease include 2 patterns: fibrocavitary disease similar to tuberculosis and nodular/bronchiectatic disease characterized by nodules and bronchiectasis [20]. It is noteworthy that a nodular/bronchiectatic pattern without cavitation has never been reported in *M. shimoidei* pulmonary disease. On the other hand, cavity formation was observed in 11 of 15 available cases [1,3–15]. Since cavitation is accompanied by destruction of the lung structure, immune responses may occur more strongly in fibrocavitary diseases compared with nodular/bronchiectatic diseases, which may lead to glomerular diseases.

Antibiotic sensitivity data were sparse or absent for some reported cases. However, all 11 tested cases were resistant to isoniazid, and 7 of 11 cases were resistant to rifampicin. On the other hand, 11 of 12 cases were sensitive to ethambutol. Although the number of cases tested was small, 3 of 3 were sensitive to rifabutin, 3 of 3 were sensitive to pyrazinamide, and 2 of 3 were sensitive to clarithromycin. All 4 cases, including the present case, improved when treated with clarithromycin, ethambutol, and rifampicin (or rifabutin) for 6 months [8,14,15]. Although a therapeutic regimen has not been established, these could be key drugs for the treatment of *M. shimoidei*. Compared with pulmonary tuberculosis, NTM is generally resistant to antimycobacterial treatment. This may also make it difficult to confirm that the glomerular disease is caused by NTM infection.

Conclusions

The present case is the first report showing NTM-induced secondary MGN. Tuberculosis-like symptoms and cavity formation on CT are typical clinical features of *M. shimoidei* pulmonary disease. A therapeutic regimen with clarithromycin, ethambutol, and rifampicin might be effective for *M. shimoidei* infection.

Acknowledgments

There were no sources of funding for this study. The authors thank Ms. Yuko Kazumi for the isolation of *M. shimoidei* by rpoB sequencing and 16S rRNA sequencing.

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