□ CASE REPORT □

Complete Remission of Minimal Change Disease Following an Improvement of Lung *Mycobacterium avium* Infection

Aoi Yamashiro¹, Takahiro Uchida¹, Seigo Ito¹, Naoki Oshima¹,
Takashi Oda² and Hiroo Kumagai¹

Abstract

A 46-year-old woman suddenly developed peripheral edema. Her massive proteinuria, hypoproteinemia, and renal biopsy findings yielded the diagnosis of minimal change disease (MCD). In addition, lung *Mycobacterium avium* infection was diagnosed according to a positive culture of her bronchoalveolar lavage fluid. The lung lesion was improved by anti-nontuberculous mycobacteria therapy. Surprisingly, her proteinuria also gradually decreased and she attained complete remission of MCD without any immunosuppressive therapy. She has subsequently remained in complete remission. We herein report an interesting case of MCD with lung *Mycobacterium avium* infection, suggesting a causal relationship among infection, immune system abnormality, and MCD/nephrotic syndrome.

Key words: immune system abnormality, minimal change disease, *Mycobacterium avium*, nephrotic syndrome

(Intern Med 55: 2669-2672, 2016)

(DOI: 10.2169/internalmedicine.55.6885)

Introduction

Minimal change disease (MCD) is one of the major causes of nephrotic syndrome and is sometimes secondary to neoplastic diseases, pharmaceutical agents, or infections, such as syphilis and human immunodeficiency virus (1).

Nontuberculous mycobacteria (NTM) are ubiquitous microorganisms in the environment that inhabit the human body surface without causing any disease. However, recent studies have revealed that NTM caused infection in the lung, skin, or other organs of both immunocompromised hosts and healthy individuals (2).

Some NTM infections have also been reported to be associated with renal diseases such as membranous nephropathy (3) and rapidly progressive glomerulonephritis (4); however, to the best of our knowledge, there has been no report of MCD secondary to NTM infection.

We herein report a case of MCD with lung infection of *Mycobacterium avium* (*M. avium*), the most common NTM. In this case, complete remission of MCD was achieved fol-

lowing an improvement of the lung *M. avium* infection without any immunosuppressive therapy, including corticosteroids.

Case Report

A 46-year-old woman was referred to our Kidney Department after a nearby medical clinic noted proteinuria and hypoproteinemia. She felt peripheral edema, which had suddenly appeared. Although we did not have sufficient information regarding the diagnostic process, she had a past history of lung *M. tuberculosis* infection which was diagnosed and treated for 6 months at another medical institution at 36 years of age. In addition, at 45 years of age, she was suspected of having a NTM infection in her lung, which was pointed out at a medical checkup by a chest X-ray that showed thickening of the bronchial wall and small granular shadows in her right lung, and she had been carefully followed without any medication. She was a social drinker and never smoked.

A physical examination showed that she was 158.0 cm

¹Department of Nephrology and Endocrinology, National Defense Medical College, Japan and ²Department of Nephrology, Tokyo Medical University Hachioji Medical Center, Japan

Received for publication November 23, 2015; Accepted for publication February 1, 2016

Correspondence to Dr. Takahiro Uchida, DRI1905@ndmc.ac.jp

Figure 1. Histological features of the renal biopsy. a: Glomerular lesions such as proliferative changes or sclerotic changes were not observed in light microscopy sections (Periodic acid-Schiff stain), b: There was no remarkable change in the glomerular basement membrane (Periodic acid silver-methenamine stain), c: There was no interstitial fibrosis or tubular atrophy in the tubulointerstitial area, and neither inflammatory cell infiltration nor granuloma formation was found in the tubulointerstitial area (Periodic acid-Schiff stain), d: There was widespread effacement of podocyte foot processes on electron microscopy. No electron dense deposits were seen (Original magnification, a, b, 200 $\times$, c, 130 $\times$).

tall and weighed 60.0 kg. She had gained 4.0 kg after the appearance of peripheral edema. Her vital signs were stable with a temperature of 36.7°C, pulse of 68 beats/minute, and blood pressure of 130/82 mmHg.

Her urinary protein excretion was 8.83 grams per gram urinary creatinine. No hematuria was found in a urinary microscopic examination. Her white blood cell count was $5.7 \times 10^3/\mu\text{L}$; hemoglobin concentration, 10.0 g/dL; platelet count, $427 \times 10^3/\mu\text{L}$; serum creatinine, 0.74 mg/dL; urea nitrogen, 18 mg/dL; plasma total protein/albumin, 5.3/2.4 g/dL; total cholesterol, 278 mg/dL; immunoglobulin G, 847 mg/dL; and immunoglobulin A/M, 386/176 mg/dL. C-reactive protein was negative, and complement C3, C4, and CH50 levels were all within normal limits. Rheumatoid factor and antinuclear antibody were undetectable, and serologic tests for syphilis, human immunodeficiency virus, and hepatitis B and C yielded negative results.

According to these findings, the patient was diagnosed with nephrotic syndrome, and a renal biopsy was performed for a histological evaluation. Light microscopy sections with

34 glomeruli showed no remarkable glomerular changes. In addition, tubulointerstitial change was absent (Fig. 1a-c). Immunofluorescence staining showed no deposits of immunoglobulins or complement proteins. Electron microscopy revealed widespread effacement of podocyte foot processes (Fig. 1d). According to these findings, the patient was diagnosed with MCD.

Her chest X-ray showed a cavity in the right pulmonary apex (Fig. 2a). Bilateral costophrenic angles were blunted with pleural effusion. Thickening of the bronchial wall was also observed in the right middle and lower lung field. In addition, a computed tomography (CT) scan of the chest showed multiple small granular shadows, as well as thickening of the bronchial wall (Fig. 2b). There was no abnormality in her abdominal or pelvic CT scan. We therefore evaluated the etiology of the radiological abnormality of the lung. A tuberculin test was negative, and the cultures of both her bronchoalveolar lavage fluid and gastric juice were negative for *M. tuberculosis*. They were, however, positive for *M. avium*. We therefore considered that tuberculosis had been

Figure 2. Radiological findings and the therapeutic course. a: A chest X-ray on admission showed a cavity in the right pulmonary apex. Thickening of the bronchial wall was also observed in the right middle and lower lung field. Bilateral costophrenic angles were blunted with pleural effusion, b: A chest computed tomography scan on admission showed multiple small granular shadows as well as thickening of the bronchial wall. Pleural effusion was also observed, c: A chest X-ray two months after starting anti-nontuberculous mycobacteria (NTM) therapy showed that the cavity in the right pulmonary apex remained, d: A chest computed tomography scan approximately two months after starting anti-NTM therapy clearly showed the amelioration of multiple small granular shadows. Thickening of the bronchial wall was still observed, e: Her therapeutic course shows that her urinary protein gradually decreased after anti-NTM therapy was started, resulting in a prominent increase in serum albumin. Once complete remission of minimal change disease was achieved, there was no recurrence.

previously cured and she was now infected with *M. avium*.

Because immunosuppressive therapy can exacerbate an underlying infection, we avoided immunosuppressive therapy and started anti-NTM therapy (clarithromycin, 800 mg/d; rifampicin, 450 mg/d; and ethambutol, 750 mg/d). A chest X-ray two months after starting anti-NTM therapy showed that the cavity in the right pulmonary apex remained (Fig. 2c). Although thickening of the bronchial wall was observed as before, a chest CT scan approximately two months after starting anti-NTM therapy clearly showed the amelioration of the multiple small granular shadows, suggesting that the therapy was effective for the lung *M. avium* infection

(Fig. 2d). In addition, her urinary protein gradually decreased following anti-NTM therapy and the patient attained complete remission of MCD six months after starting anti-NTM therapy. She has subsequently remained in complete remission without any immunosuppressive therapy, including corticosteroids. Her therapeutic course is summarized in Fig. 2e.

Discussion

In the present case, the complete remission of MCD was achieved without immunosuppressive therapy, including cor-

ticosteroids. Although spontaneous remission was reported in some MCD cases (5, 6), proteinuria in the present case clearly decreased soon after starting anti-NTM therapy. Surprisingly, following the improvement of the lung lesion, proteinuria finally disappeared and the present case has remained in complete remission. We therefore speculate that there is a causal relationship between the patient's *M. avium* infection and MCD. Indeed, there have been some reports of renal diseases associated with NTM infection; Kanaji et al. (3) reported a case of membranous nephropathy associated with *M. shimoidei* infection, and Wen et al. (4) reported a case of rapidly progressive glomerulonephritis associated with *M. avium* infection. Both of these cases, similar to the present case, were effectively treated with anti-NTM therapy.

To the best of our knowledge, there has been no report of MCD secondary to NTM infection. Furthermore, the present case attained complete remission of MCD, whereas the previously reported cases of renal diseases associated with NTM infection did not. Although the renal prognosis of MCD is generally favorable, this case is interesting in that the patient achieved and has remained in complete remission with anti-NTM therapy alone.

It must be kept in mind that immunosuppressive therapy may have serious side effects. A previously reported case described a patient who presented with gastrointestinal hemorrhaging due to *M. avium* infection after receiving immunosuppressive therapy (7). Additionally, Brady et al. (8) reported a nephrotic syndrome patient who received immunosuppressive therapy and presented with erythema nodosum that was caused by *M. chelonae*. The patient in the present case was infected with *M. avium*. In addition, although we did not have sufficient information regarding the diagnostic process, she also may have had a past history of lung *M. tuberculosis* infection. We therefore believe that the present case suggests that the complete remission of MCD in patients having infections can be achieved without any immunosuppressive therapy, if such infections are treated appropriately.

The pathogenesis of MCD has not been clearly demonstrated, however, immune system abnormality, especially an imbalance in Th1 and Th2 cytokines, is considered to be important in the disease onset and progression (9). Th1 cells are typically activated when infectious pathogens invade the human body. However, some reports have demonstrated that some chronic infections primarily induce Th2 responses, and *M. species*, including *M. tuberculosis* and NTM, are considered to be pathogens that induce Th2 responses (10).

A predominant Th2 cell activation is suggested in the pathogenesis of MCD (11) and membranous nephropathy (12), and there are some reported cases of *M. species* infection associated with these renal diseases. An MCD case associated with *M. tuberculosis* has been previously re-

ported (13), and there are also reported cases of membranous nephropathy associated with NTM (3) and *M. tuberculosis* (14). Therefore, although we did not examine the present patient's immune response, such as Th1 or Th2 cytokines, it may be possible that her preceding lung *M. avium* infection induced a systemic Th2 response, thereby causing MCD.

In summary, we reported for the first time an interesting case of MCD with lung *M. avium* infection, suggesting a potential causal relationship among infection, immune system abnormality, and MCD/nephrotic syndrome.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

We thank our colleague Ms. Toshie Fujiwara for expert secretarial assistance.

References

- Glasscock RJ. Secondary minimal change disease. *Nephrol Dial Transplant* **18**: vi52-vi58, 2003.
- Henry MT, Inamdar L, O'Riordain D, Schweiger M, Watson JP. Nontuberculous mycobacteria in non-HIV patients: epidemiology, treatment and response. *Eur Respir J* **23**: 741-746, 2004.
- Kanaji N, Kushida Y, Bandoh S, et al. Membranous glomerulonephritis associated with *Mycobacterium shimoidei* pulmonary infection. *Am J Case Rep* **14**: 543-547, 2013.
- Wen YK, Chen ML. Crescentic glomerulonephritis associated with non-tuberculous mycobacteria infection. *Ren Fail* **30**: 339-341, 2008.
- Tse KC, Lam MF, Yip PS, et al. Idiopathic minimal change nephrotic syndrome in older adults: steroid responsiveness and pattern of relapses. *Nephrol Dial Transplant* **18**: 1316-1320, 2003.
- Meisels IS. Spontaneous remission in frequently relapsing minimal-change disease. *Clin Nephrol* **63**: 170, 2005.
- Nguyen HN, Frank D, Handt S, et al. Severe gastrointestinal hemorrhage due to *Mycobacterium avium* complex in a patient receiving immunosuppressive therapy. *Am J Gastroenterol* **94**: 232-235, 1999.
- Brady RC, Strife CF, Sheth AP, Passo M, Schleiss MR. An adolescent with nephrotic syndrome and multiple leg nodules. *Pediatr Infect Dis J* **17**: 1057-1058, 1061-1063, 1998.
- Grimbert P, Audard V, Remy P, Lang P, Sahali D. Recent approaches to the pathogenesis of minimal-change nephrotic syndrome. *Nephrol Dial Transplant* **18**: 245-248, 2003.
- Rook GA, Hernandez-Pando R. T cell helper types and endocrines in the regulation of tissue-damaging mechanisms in tuberculosis. *Immunobiology* **191**: 478-492, 1994.
- Komatsuda A, Wakui H, Iwamoto K, et al. GATA-3 is upregulated in peripheral blood mononuclear cells from patients with minimal change nephrotic syndrome. *Clin Nephrol* **71**: 608-616, 2009.
- Ifuku M, Miyake K, Watanebe M, et al. Various roles of Th cytokine mRNA expression in different forms of glomerulonephritis. *Am J Nephrol* **38**: 115-123, 2013.
- Jones JM. Tuberculosis and minimal change nephropathy. *Scott Med J* **29**: 114-116, 1984.
- Ram R, Swarnalatha G, Desai M, et al. Membranous nephropathy and granulomatous interstitial nephritis due to tuberculosis. *Clin Nephrol* **76**: 487-491, 2011.

The Internal Medicine is an Open Access article distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).