MINIMAL-CHANGE NEPHROTIC SYNDROME ASSOCIATED WITH ISONIAZID IN ANTI-TUBERCULOSIS CHEMOPROPHYLAXIS FOR A PATIENT WITH RHEUMATOID ARTHRITIS

Shunsuke Mori¹, Yoshiro Matsushita² and Kenji Arizono²

Abstract

A 66-year-old woman with seropositive rheumatoid arthritis (RA) and latent tuberculosis infection developed minimal-change nephrotic syndrome following the initiation of anti-tuberculosis chemoprophylaxis with isoniazid. This is the first reported case of an isoniazid-induced nephrotic syndrome. Isoniazid as a single-drug intervention is widely accepted as a safe and effective means of anti-tuberculosis chemoprophylaxis, particularly for RA patients with latent tuberculosis infection; the present case, however, demonstrates that isoniazid has the potential to induce minimal-change nephrotic syndrome, even when used as a single-drug intervention.

Key words: anti-tuberculosis chemoprophylaxis, isoniazid, latent infection, minimal-change disease, nephrotic syndrome, rheumatoid arthritis


Introduction

Anti-tumor necrosis factor-α (TNFα) agents are recognized to drastically improve the course of rheumatoid arthritis (RA) refractory to existing disease-modifying anti-rheumatic drugs. However, significant concern has been expressed regarding the increased risk of reactivation of latent tuberculosis infection associated with all currently available anti-TNFα agents (1). Various recommendations for RA patients with latent tuberculosis infection have been proposed worldwide by scientific organizations and health authorities. Single-drug intervention with isoniazid is widely accepted as a treatment protocol for such patients (2-4). Here, we report a case of minimal-change nephrotic syndrome (MCNS) occurring 3 days after the initiation of anti-tuberculosis chemoprophylaxis with isoniazid in a patient with RA who was due to start anti-TNFα therapy. This is the first published report of an isoniazid-induced nephrotic syndrome.

Case Report

A 66-year-old woman with a 45-year history of seropositive RA visited our hospital for management of methotrexate (MTX)-resistant RA. The patient had been receiving oral MTX at 8 mg/week for 32 months, but even so her RA was not adequately controlled. The patient’s disease activity score for 28 joints was high, and her laboratory data showed high levels of serum C-reactive protein (4.17 mg/dL). The patient was eligible for anti-TNFα therapy according to the guidelines officially approved by the Japan College of Rheumatology. Eight years earlier, however, this patient had been given a diagnosis of active pulmonary tuberculosis caused by Mycobacterium tuberculosis. At that time, she had received anti-tuberculosis therapy consisting of isoniazid (400 mg/day), rifampicin (450 mg/day), ethambutol hydrochloride (750 mg/day), and pyrazinamide (2 g/day) for 2 months, followed by 4 months of continuation therapy consisting of the same drugs except for pyrazinamide. Subsequent to this anti-tuberculosis therapy, mycobacterial cultures of the pa-

¹Clinical Research Center for Rheumatic Disease and Department of Rheumatology, NHO Kumamoto Saishunsou National Hospital, Japan
²Division of Renal Disease, Kumamoto-Chuo Hospital, Japan

Received for publication August 8, 2010; Accepted for publication October 13, 2010
Correspondence to Dr. Shunsuke Mori, moris@saisyunsou1.hosp.go.jp
M. tuberculosis had tested negative for the patient’s sputum specimens and bronchoalveolar lavage fluids had tested negative for *M. tuberculosis* and polymerase chain reaction (PCR) tests on these samples also tested negative.

Prior to commencing anti-TNFα therapy, the patient underwent the Quantiferon-tuberculosis Gold (QFT-G) test, which returned a positive result. Cultures and PCR testing of sputum was negative for *M. tuberculosis*. Chest computed tomography revealed residual changes indicative of prior tuberculosis infection in the upper lobe of the right lung (Fig. 1). Since a latent *M. tuberculosis* infection was suspected, the patient was given anti-tuberculosis chemoprophylaxis consisting of isoniazid (300 mg/day). Immediately before the introduction of isoniazid, the patient had normal renal function (serum creatinine, 0.5 mg/dL; blood urea nitrogen (BUN), 18.3 mg/dL) and her serum total protein and albumin levels were 6.6 g/dL and 4.2 g/dL, respectively. Urinalysis by dipstick showed only trace levels of hematuria (1-5 red blood cells/high-power field). Serum total cholesterol was 290 mg/dL. The e-GFR was 86.3 mL/min/1.73 m². Three days later, she suddenly developed systemic edema and general fatigue. Five days after the start of isoniazid treatment, the patient’s urinalysis showed proteinuria (4+) and microscopic hematuria (1-5 red blood cells/high-power field). Serum creatinine and BUN levels were 1.1 and 44 mg/dL, respectively. Total cholesterol was 290 mg/dL. The e-GFR was decreased (38.8 mL/min/1.73 m²). Since a drug-induced adverse effect on the kidneys was suspected, isoniazid was discontinued, and the patient was admitted to the hospital. Three weeks after hospitalization, 24-hour urine protein levels had decreased but nephrotic-range proteinuria persisted (5.0 g/day). Renal function had improved (serum creatinine, 0.9 mg/dL; BUN, 20.5 mg/dL; e-GFR, 48.3 mL/min/1.73 m²). A percutaneous renal biopsy followed by light microscopy revealed minor glomerular abnormalities, and interstitial changes were not observed (Fig. 2A). Through staining with Congo red, amyloid deposits were observed in the biopsy sample, in vascular lesions but not in glomeruli (Fig. 2B and 2C). The congophilic deposits faded out after treatment with potassium permanganate; this result is characteristic of secondary amyloidosis. No positive findings for immunoglobulins or complement components were observed in the glomeruli examined by immunofluorescence microscopy. Electron microscopy revealed widespread effacement of podocyte foot processes and a normal texture and thickness of the glomerular basement membrane (Fig. 3). No immune-type electron-dense deposits were seen in the glomeruli. Non-branching extracellular fibrils characteristic of renal amyloidosis were not evident in the examined glomeruli. A diagnosis of isoniazid-induced MCNS was given, and oral administration of prednisolone (40 mg/day) was initiated. Ten days later, the proteinuria had completely disappeared and renal function tests showed normal results (serum creatinine, 0.7 mg/dL; BUN, 9.2 mg/dL; e-GFR, 63.6 mL/min/1.73 m²). The prednisolone was then tapered off to 5 mg/day. To control the RA disease activity, treatment with tacrolimus (1 mg/day) was started in combination with MTX (8 mg/week). At the time of submission, no recurrence of proteinuria had been observed. The patient’s clinical course is depicted in Fig. 4.

**Discussion**

Isoniazid intervention therapy is considered a safe and effective anti-tuberculosis chemoprophylaxis, particularly for patients undergoing anti-TNFα therapy (5). It is recognized that this drug can induce severe adverse effects such as hepatotoxicity (6); isoniazid-induced nephrotoxicity, however, has rarely been documented. Only one case of acute interstitial nephritis has been reported as part of a lupus-like hypersensitivity reaction to isoniazid (7). In that case, glomerular abnormalities were not observed. The clinical presentation of drug-induced glomerular diseases, such as MCNS, focal segmental glomerulosclerosis, and membranous glomerulonephritis, is the abrupt occurrence of nephrotic syndrome characterized by hypoalbuminemia and high-grade proteinuria. Several drugs have been reported to cause secondary nephrotic syndrome (8, 9). Nonsteroidal anti-inflammatory drugs (NSAIDs) are well known to cause both MCNS and membranous glomerulonephritis. It is worth mentioning, however, that our patient had been taking this type of drug for several decades without experiencing adverse effects, and had not taken any NSAIDs since arriving at our hospital. Antirheumatic drugs such as gold, penicillamine, and bucillamine, which are recognized as causative agents of membranous glomerulonephritis, had never been used for this patient. It seemed unlikely that the appearance of nephrotic syndrome in this case was due to renal amyloidosis secondary to RA, because Congo red staining-positive deposits were limited to vascular lesions under light microscopy and characteristic amyloid fibrils were not evident in glomeruli examined by electron microscopy.

MCNS is occasionally associated with atopic attacks and lymphoproliferative malignancies such as Hodgkin’s lym-
phoma and leukemias (10), but the present patient exhibited no clinical signs suggestive of these conditions. A possible relationship between tuberculosis infection and MCNS has been described in several reports (11-13). Tuberculosis is known to induce cell-mediated immunity and alter lymphocyte function, which may play a crucial role in the pathogenesis of MCNS. The present patient had suffered from active pulmonary tuberculosis 8 years previously, but had been cured upon the introduction of anti-tuberculosis therapy. At the time of MCNS development, her tuberculosis was inactive as shown by the negative results of mycobacterial cultures and PCR testing, and no recurrence was noted during hospitalization. In addition, the remission of MCNS was maintained despite persistent latency of M. tuberculosis. We therefore considered it unlikely that the quiescent tuberculosis infection triggered the onset of MCNS in this patient.

The vast majority of MCNS cases are idiopathic conditions (10). We cannot entirely exclude the possibility that incidental idiopathic MCNS, unrelated to isoniazid therapy, may have developed in the present patient, but we have noted the use of isoniazid immediately before the onset of nephrotic syndrome and the improvement upon its discontinuation. Such a temporal relationship strongly suggests that this was a case of isoniazid-induced MCNS. Furthermore, no relapses of nephrotic syndrome have been observed since isoniazid was suspended.

Anti-tuberculosis therapy using rifampicin occasionally causes interstitial nephritis, and glomerular abnormalities have been reported in a few such cases (14-16). Therefore, most physicians suspect that rifampicin is the offending agent in such cases.

**Figure 2.** Light micrographs of the renal biopsy specimen. (A) There is no obvious evidence of glomerular hypercellularity, mesangial matrix expansion, or thickening of the glomerular basement membranes. Amorphous material deposits were observed in the small artery wall (asterisk). (Periodic acid-Schiff stain, original magnification ×200). (B) No deposition of Congo red stain-positive materials is observed in the glomerulus (Congo red stain, original magnification ×200). (C) Deposits of Congo red stain-positive materials are visible in the wall of the small arteries (bar=100 μm).

**Figure 3.** Electron micrograph of the glomerulus. Diffuse effacement of foot processes of visceral endothelial cells (podocytes) is shown. Neither electron-dense deposits nor amyloid fibrils were evident (bar=5 μm).
agent when nephrotoxicity occurs during the management of tuberculosis infection with combination therapy consisting of isoniazid and rifampicin. The present case, however, supports the notion that isoniazid should also be considered as a possible agent of nephrotic syndrome.

Idiopathic MCNS is a condition characterized by widespread effacement of podocyte foot processes, though the relationship between this morphological change and increased glomerular permeability to proteins is unclear. Recent studies have indicated that podocyte foot process effacement is not a prerequisite for the development of proteinuria; rather, these two symptoms are independent sequelae of injury to the glomerular filtration barrier (17, 18). The pathogenic role of abnormally activated T lymphocytes and the cytokines they produce may be implicated in the occurrence of MCNS, since some of the T-cell-derived cytokines can alter the permeability of the glomerular filtration barrier. In addition, type 2 helper T-cell-dominant conditions are induced as a result of abnormal T-cell response, which may be involved in hypersensitivity reactions (19, 20). Whether the mechanism underlying drug-induced MCNS is similar to that underlying idiopathic MCNS remains unclear. NSAID-induced MCNS is believed to originate in a hypersensitivity reaction to the drug. The increased glomerular permeability is probably due to the production of cytokines as an immunological response (21). In lithium-induced MCNS, the drug may stimulate T-cell activation and cytokine production, which may increase glomerular permeability to protein (22). Pamidronate, which has also been reported as a causative drug of MCNS, may have direct toxic effects on podocytes with phenotypic alterations (23, 24). It is not clear whether isoniazid-induced MCNS is due to immunological mechanisms or to direct toxic effects on podocytes.

Most episodes of drug-induced renal impairment are reversible if they are recognized at an early stage and the offending drug is discontinued (25). Physicians need to be aware of the possibility that isoniazid, even in single use, can cause nephrotic syndrome in chemoprophylaxis for RA patients with latent tuberculosis infection.

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

References
2. Targeted tuberculin testing and treatment of latent tuberculosis infection. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. This is a Joint Statement of the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC). This statement was endorsed by the Council of the Infectious Diseases Society of America. (IDSA), September 1999, and the sections of this statement. Am J Respir Crit Care Med 161: S221-S247, 2000.


