Acute Renal Failure due to Acute Tubular Necrosis caused by Direct Invasion of *Orientia tsutsugamushi*

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Abstract

We describe scrub typhus patient with acute renal failure, in which diagnosis was made based on serology as well as immunohistochemistry (IHC) and electron-microscopic examination (EM) of renal biopsy. Our case demonstrated by IHC and EM that renal failure is caused by acute tubular necrosis due to direct invasion of *Orientia tsutsugamushi*.

**Key words:** Renal failure, Scrub typhus, Electron microscopy, Immunohistochemistry.
Introduction

Scrub typhus is an acute febrile disease caused by *Orientia tsutsugamushi* (*O. tsutsugamushi*), a gram-negative intracellular bacterium. Patients with scrub typhus present with eschar at the site of mite bite, maculopapular rash, fever, myalgia, headache and anorexia (4). Because scrub typhus causes a systemic vasculitis, it can cause meningitis, interstitial pneumonia, acute pulmonary edema, hepatitis and acute renal failure in untreated cases (6, 7, 9). We encountered an idiopathic case of acute renal failure, in which *O. tsutsugamushi* directly invaded the kidney tubule on renal biopsy. This caused an acute tubular necrosis and resulted in acute renal failure. Here, we report our case with a review of literatures.

Case Report

A healthy-looking, 33-year-old male patient received a drug treatment for a 2-week history of cough and sputum. One day before admission to our hospital, he complained of abdominal pain and nausea after he played a football. He was suspected to have renal failure on examination at local clinic, and transferred to *Chosun University Hospital* in Gwang-ju, Korea. At the time of admission, his vital signs were blood pressure 120/80 mmHg, pulse rate 72 times/min, respiratory rate 20 breaths/min and temperature 37.2°C. On urinalysis, he had no gross hematuria with a urine output of 50 cc/h. His mental status was alert. There was
no skin rash or lymphadenopathy. The patient’s complete blood count showed WBC count 11,630/mm³, Hb 14.5 g/dL and platelet count 243,000/mm³. An arterial blood gas analysis (ABGA) showed pH 7.404, PaCO₂ 38.1 mmHg, PaO₂ 79.4 mmHg, HCO₃⁻ 23.3 mmol/L and O₂ saturation 95.8%. His serum biochemistry was [Na⁺] 135 mEq/L, [K⁺] 4.2 mEq/L, [Cl⁻] 120 mEq/L, BUN 39.3 mg/dL and creatinine 5.0 mg/dL. It also showed total protein 6.73 g/dL, albumin 3.78 g/dL, AST 30 IU/L, ALT 18 IU/L, CPK 446 U/L, LDH 565 U/L, myoglobin 168.4 ng/mL, FDP 1 mg/mL (0~5.0) and D-dimer 143.6 ng/mL (0~255). On urinalysis, hematuria (+3) and proteinuria (+4) were present. A microscopic urinalysis revealed 10-19 RBC/hpf, dysmorphic RBC 2%/hpf, 1-4 WBC/hpf and no cast/hpf. A 24-h urinalysis detected selective proteinuria – albumin 895 mg/day. Serologic tests were all negative for rheumatoid factor, antinuclear antibody, antineutrophil cytoplasmic antibody, cold agglutinin, VDRL, HIV, HBV and HCV antibody. ASO (antistreptolysin O) and complement level were all normal.

A small-scale, self-employed person, our patient presented with no typical symptoms of scrub typhus, including rash, fever and headache. He had a history of outdoor activity ten days before admission. He maintained a previous healthy life, but had a markedly increased level of creatinine. He therefore received a renal biopsy for further evaluation and to make a differential diagnosis from other diseases including rapidly-progressing glomerulonephritis (RPGN).

Our case underwent immunohistochemical staining (IHC) and immunofluorescent
staining, in which primary antibody was the ICR mice hyperimmune serum immunized with *O. tsutsugamushi* strain Boryong at dilution of 1:200. The antibody could detect other disparate strains of *O. tsutsugamushi* in addition to the strain Boryong in the IFA (data not shown). The IHC was performed using a streptavidin-biotin immunoperoxidase method, according to the supplier's protocol (LSAB Kit, DAKO, Carpinteria, California, USA) as described previously (2). The IHC, immunofluorescent staining and electron microscopy using a renal biopsy identified the presence of *Orientia tsutsugamushi* coccobacilli within the tubule. Based on these findings, a diagnosis of scrub typhus was established in our patient. He was immediately given doxycycline. Serological test was performed using the paired sera by IFA (2). At the time of admission, his IFA serologic profile showed an IgM titer of 1:10 and an IgG titer of 4,096. One week after he was given doxycycline, samples from the recovery phase had an Ig M titer of 1:1,280 and an Ig G titer of 1: 4,096. A follow-up antibody test was performed to examine the presence of concurrent diseases. This was all negative for endemic typhus, hemorrhagic fever with renal syndrome (HFRS), leptospirosis and measles. He was recovered without any notable complications following doxycycline treatment. He was discharged when his serum creatinine level returned to normal.

**Discussion**

Scrub typhus is an acute febrile disease, whose prognosis varies between patients, ranging from asymptomatic infection to death. A prompt recovery can be achieved by the early
diagnosis and treatment. It is noteworthy, however, that such complications as interstitial pneumonia, meningitis, disseminated intravascular coagulation (DIC) and hepatitis may occur (6, 7, 9). Hematuria and proteinuria may occur because of renal invasion in 10-20% of patients with scrub typhus. Acute renal failure is not a common entity, but it is known to be one of the serious complications seen in patients with scrub typhus, spotted fever or murine typhus (3, 5, 10). Fever, headache and rash are potential indicators for rickettsia disease, which are known to be a useful clue for the diagnosis of scrub typhus (1). However, our patient visited us with a chief complaint of prompt deterioration of renal function without the triad symptoms of scrub typhus, including typical skin lesions, fever and headache. To identify the cause of prompt deterioration of renal function, a renal biopsy with IHC, immunofluorescent staining, EM were performed. This established a diagnosis of scrub typhus. An early recovery was achieved following doxycycline treatment.

In our case, a renal biopsy showed that capillary loop or cellularity were all normal in the glomerulus. The renal tubules underwent multifocal tubular necroses and foci of some mononuclear cells infiltration were identified in the tubulointerstitium. Tubular epithelial cells underwent degenerative change and were detached from the basement membrane (Fig. 1). Epithelial casts were observed in some renal tubules. These histopathologic findings were suggestive of acute tubular necrosis with chronic tubulointerstitial nephritis.

Several hypotheses have been proposed to explain the mechanism by which *O. tsutsugamushi* infection causes acute renal failure. Firstly, it is assumed that the
pathophysiology of acute renal failure is associated with prerenal azotemia due to renal hypoperfusion in cases of shock or volume depletion. According to Dumler et al., prerenal azotemia is the main pathophysiology of renal failure, caused by the decreased effective renal blood flow due to the increased vascular permeability in patients with murine typhus accompanied by systemic vasculitis (1). Hypoalbuminemia is commonly noted in patients with rickettsia disease. This has been reported to be due to the leakage of plasma albumin into the perivascular space because of widespread vascular damage (1). In our case, however, there was no clear evidence of decreased blood pressure, or other signs and symptoms including diarrhea or vomiting, suggestive of volume depletion. Furthermore, our patient had a normal range of serum albumin level. This led to the speculation that acute renal failure did not occur due to prerenal azotemia in our patient. Secondly, DIC is considered as another pathophysiology of renal failure. To put this in another way, renal failure is caused by microangiopathy due to the thrombosis or coagulation in multiple organs of patients with DIC. In our case, however, there were no notable laboratory findings suggestive of DIC or histopathologic ones suspected to be thrombosis. Thirdly, acute tubular necrosis might cause renal failure because of the direct invasion of *O. tsutsugamushi* to renal parenchyma. Walker *et al.* reported that histopathologic findings were suggestive of multiple interstitial nephritis in patients with renal failure accompanied by murine typhus [7, 10]. Our patient also had acute tubular necrosis, in which numerous *O. tsutsugamushi coccobacilli* were deposited within the renal tubule on IHC, immunofluorescent staining and EM. Furthermore, his renal
function was promptly recovered following doxycycline treatment. These findings support the possibility that the direct invasion of *O. tsutsugamushi* to the renal tubule caused acute tubular necrosis and then resulted in acute renal failure. Neither acute glomerulonephritis, non-traumatic rhabdomyolysis with myoglobinuria or DIC have been documented so far to contribute to the development of the acute renal failure. Little is known about whether the development of renal failure is associated with DIC or acute glomerulonephritis. Further clinical studies are therefore warranted to examine the pathophysiology of acute renal failure in patients with scrub typhus.

In conclusion, our case highlights the following two points: First, to identify the cause of prompt deterioration of renal function, a renal biopsy with immunohistochemistry and electron-microscopic examination were performed. The adequate use of IHC or EM established an early diagnosis of scrub typhus prior to serologic follow-up. Second, our case demonstrated by IHC and EM for the first time that renal failure in patients with scrub typhus is caused by acute tubular necrosis due to the direct invasion of *Orientia tsutsugamushi*. 
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References


Figure Legends

Fig. 1. Histopathologic findings of kidney from the patient with Scrub typhus

Fig. 1a. Histopathologic findings of the kidney. H&E, X100

Acute tubular necrosis with chronic interstitial nephritis is illustrated. Many atrophic tubules and lumens containing desquamated epithelial casts (asterisks) are found.

Fig. 1b. Immunofluorescent staining findings of the kidney. X100

Positive immunofluorescent staining is highlighted in the tubular structures (arrows). Scattered positive signals are also identified in the vascular structures (asterisks).

Fig. 1c. Immunohistochemical staining findings of the kidney. X100

Positive IHC is highlighted in the tubular structures. Scattered positive signals are also identified in the vascular structures.

Fig. 1d. Ultramicroscopic findings of the renal tubular epithelial cells. Many *O. tsutsugamushi* (O) are seen in the cytoplasm. Many small vesicles (arrows) with an *O. tsutsugamushi* envelope appear around the degenerated *Orientia* (DO). Scale bar measures 2.0 µm.