A possible rare cause of renal failure in streptococcal infection

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Abstract
To the best of our knowledge, this is the first biopsy-proven case of streptococcal infection-associated acute interstitial nephritis (AIN) with existence of streptococcal pyrogenic exotoxin B (SPE B) by a controlled immunohistochemical method. Both the intact tubular epithelial cells and oedematous interstitium had strong positive signals, whereas only interstitial inflammation was dominant without tubular necrosis. Reflective of the nature of AIN is that the injury from the hypersensitivity reaction was specific for renal interstitium instead of tubules. SPE B is potentially allergenic and may confuse the clinicians due to its clinical mimicry of drug-induced AIN. Although very rare, AIN might be included into the differential diagnosis of patients with streptococcal sepsis and acute renal failure.

Keywords: interstitial nephritis; renal failure; Streptococcus

Introduction
Acute interstitial nephritis (AIN) was first described as a ‘cellular and fluid exudation in the interstitial tissue’ by Councilman in 1898. This venerable treatise illustrated the pathogenetic link between AIN and a septic state with beautifully hand-drawn images according to the kidneys of patients dying of scarlet fever and diphtheria [1]. Over 100 years have passed since Councilman recognized interstitial nephritis as a distinct disease entity, but no study to date has further demonstrated the pathogenesis by detection of streptococcal exotoxins in renal interstitium.

Streptococcal toxic shock syndrome is defined as an invasive Group A streptococcal (GAS) infection associated with shock, multiple organ failure, and erythematous rash with subsequent desquamation. Acute renal failure (ARF) is present in almost all patients within <72 h, and some of them require haemodialysis. However, the true aetiology of ARF has not been illustrated in detail and is mostly considered to be sepsis-related ischaemic acute tubular necrosis without kidney biopsy. Herein, we report an exceptional case of ARF fulfilling the diagnostic criteria of GAS toxic shock syndrome with biopsy-proven AIN.

Case report
A 22-year-old, previously healthy man experienced an episode of sore throat, diarrhoea and general myalgia for 1 week before admission. He sought medical help, and acetaminophen was initially prescribed. Antibiotic and non-steroidal anti-inflammatory drug (NSAID) exposure was denied. As the symptoms deteriorated, he was admitted due to high fever and chills. On the day of admission, his blood pressure was 80/38 mmHg, heart rate 144 beats per minute, respiratory rate 20 breaths per minute and temperature 38.5°C (101.3°F). Physical examination disclosed injected throat and erythematous rash over the trunk, but was otherwise unremarkable. Biochemical studies revealed the following: serum creatinine, 4.8 mg/dL (424.3 μmol/L); urea nitrogen 32 mg/dL (11.4 mmol/L); and serum sodium, 130 mEq/L (130 mmol/L). The haemoglobin level was 16.9 g/dL (169 g/L), platelet count 8.6 × 10⁹/μL (8.6 × 10⁹/L) and white blood cell count 19.3 × 10⁹/μL (19.3 × 10⁹/L). Urinalysis showed a 3+ positive for urine protein, 167 white
blood cells and 83 red blood cells per average high-power field. The blood culture grew Group A Streptococcus pyogenes, but the urine culture result disclosed an insignificant growth. As the generalized skin rash faded, desquamation occurred, especially on the palms and lip. The serologic tests were all within normal ranges such as antinuclear antibody, C3, C4, anti-neutrophil cytoplasmic antibodies, anti-human immunodeficiency virus antibody, markers for hepatitis B and C, and rapid plasma reagin for syphilis. Although the haemodynamic condition soon stabilized, his renal function and urine output still deteriorated. The patient underwent four sessions of haemodialysis from the fifth day of hospitalization because of lung oedema refractory to diuretic therapy. The peak serum creatinine was 16.6 mg/dL (1441.0 μmol/L). Under supportive medical care and infection control with ceftriaxone, his renal function recovered gradually. After 23 days of hospitalization, he was discharged in a dialysis-free status. During the 3-month follow-up period, his serum creatinine level declined to 1.47 mg/dL (130 mol/L).

Because of ARF with unclear aetiology, a kidney biopsy was performed on the 10th day of hospitalization. On light microscopic examination with haematoxylin and eosin stain, the routine and cryostat sections revealed eight and two viable glomeruli without obsolescence. All glomeruli

Fig. 1. Haematoxylin and eosin-stained section shows inflammatory cells infiltration and oedema in the interstitium of cortex. All glomeruli were intact without mesangial hypercellularity or matrix expansion. Neither tubular epithelial cell shedding nor interstitial fibrosis were seen (original magnification ×100).

Fig. 2. The oedematous interstitium is infiltrated by admixed inflammatory cells, including neutrophils, lymphocytes, plasma cells and especially eosinophils (black arrow). Scattered eosinophils corresponded to the typical presentation of hypersensitivity reaction in acute interstitial nephritis (haematoxylin and eosin, original magnification ×100).

Fig. 3. (A) The IHC study depicted diffuse strong positive signals of anti-SPE B monoclonal antibodies (obtained from Prof. Y-S Lin and Y-H Luo, Ph.D.) in tubular epithelial cytoplasm (red arrow) and renal interstitium of cortical tissue. The fixed cortical tissue was embedded in paraffin and sliced into 4-mm-thick sections. After the fixed tissue sections had been deparaffinized, they were incubated in the retrieval buffer (MARK2 buffer, Serotec Ltd, Oxford, UK) at 92°C for 10 min. The tissue sections were blocked using 10% BSA/PBS, and then using 1 mol/L of NH₄Cl to reduce autofluorescence before adding the primary antibody. Monoclonal anti-SPE B antibody (clone 9C, 10 μg/mL) was diluted (1:200) with antibody diluents (DAKO Corporation, Carpinteria, CA, USA), then applied to the sections and incubated at 4°C overnight. The sections were washed in 0.05% PBS–Tween-20 and then incubated with fluorescein isothiocyanate-conjugated goat anti-mouse IgG antibody (Jackson Immuno-Research Laboratories Inc., West Grove, PA, USA) at room temperature for 1 h. (B) The irrelevant monoclonal antibody of the same class (anti-cysteine protease antibodies) was omitted in sections as negative controls.
were undamaged with unchanged mesangial cellularity and matrix. The blood vessels were unremarkable. Neither tubular epithelial cell shedding nor interstitial fibrosis were seen. The interstitium was oedematous and infiltrated by admixed inflammatory cells (Figure 1), including lymphocytes, neutrophils, plasma cells, and especially eosinophils (Figure 2). The tissue submitted for direct immunofluorescence consisted of six glomeruli. The immunofluorescence staining revealed no significant deposition for immunoglobulin G, immunoglobulin A, immunoglobulin M, C3 and C1q. The immunohistochemical (IHC) study depicted diffusely strong positive signals of anti-streptococcal pyrogenic exotoxin B (SPE B) antibodies in tubular epithelial cells and tubulointerstitial compartments of the cortical tissue. Details of our IHC technique were described in Figure 3A. An anti-cysteine protease antibody was used as the negative control (Figure 3B). Conclusively, the final diagnosis was AIN with admixed eosinophils suspicious for being SPE B-induced.

Discussion

A myriad of case reports of infection-related AIN have been published, but so far, none of them could detect the pathogen or toxin in the kidney. GAS infection is also known to be a causative factor of AIN. GAS produces a large number of extracellular products including streptolysin S and O toxins, and pyrogenic exotoxins A, B and C, as well as streptokinase, DNase and protease. The pyrogenic exotoxins, previously known as erythrogenic toxins, cause a hypersensitivity reaction [2], including scarlet fever rash and probable AIN.

SPE B is a cysteine protease and functions as zymogen, which is initially expressed as a 40-kDa ProSPE B and subsequently converted to a 28-kDa active protease by its precursor to the active form, etc. In addition, antibody titres of SPE B were higher than other GAS antigens, including streptolysin O, DNase B, and hyaluronidase in acute post-streptococcal glomerulonephritis (APSGN) patient sera [3]. SPE B may play a role in AIN through its highly potent immunostimulatory effects making it an important virulence factor [4–7]. Nonetheless, the literature to date has not reported the pathogenesis between pyrogenic exotoxins and AIN. In this case, AIN associated with interstitial SPE B deposition was proved by controlled IHC study. Because necrotic debris and cast material will often stain non-specifically for any antibody applied to the tissue, we used an irrelevant monoclonal antibody of the same class (anti-cysteine protease antibodies) as the negative control in this case.

The diagnosis of SPE B-associated AIN was established for the following reasons: First, neither tubular necrosis nor glomerular abnormality were seen in renal biopsy specimen despite hypotension and streptococcal infection. Second, the patient presented sterile pyuria, erythematous rash and renal failure on admission before exposure to antibiotics and NSAIDs. Third, compared with the negative control, the strong positive staining of anti-SPE B antibodies in tubulointerstitial compartments suggested the association of SPE B and AIN. Last, but not least, both the intact tubular epithelial cells and oedematous interstitium had strong positive signals in IHC staining, whereas only interstitial inflammation was predominant without tubular epithelial cell shedding or necrosis. This reflects the nature of AIN in that the injury of the hypersensitivity reaction was specific for renal interstitium instead of tubules.

SPE B and its precursors had been detected in renal interstitium in previous studies [8,9]. SPE B may cause tubulointerstitial damage via T-cell proliferation and cytokine production [10]. In contrast to complement activation and leucocyte infiltration in the model of APSGN [3], the pathological changes in this case illustrated the typical pictures of AIN without significant glomerular reaction or tubular necrosis. Therefore, we speculate that the deposition of SPE B in the tubulointerstitial compartments induces an inflammatory response specific to renal interstitium. Although further immunologic and molecular studies are needed to confirm our speculation, the same causal agent and characteristics are difficult to reproduce again from the experimentally inoculated and infected host due to the idiosyncratic allergic response in AIN.

Streptococcal infection-associated ARF is most commonly considered to be sepsis-related ischaemic acute tubular necrosis or APSGN. Nonetheless, the therapeutic strategy of AIN was directed towards withdrawal of the offending medication and elimination of the infection, as well as supportive care [11]. We deem it a very important teaching point that early conclusive diagnosis and proper management contribute to better outcome.

In summary, this case alerts us that the possible rare cause of renal failure in streptococcal infection-related AIN may be neglected and underdiagnosed. For the cases of streptococcal infection-associated ARF, early renal biopsy with anti-SPE B stain is perhaps helpful for differential diagnosis. SPE B has a potential allergenic effect, and therefore, the clinician may confuse it with drug-induced AIN. Whether or not to discontinue the offending drugs is a rather important decision, especially in the case of crucial antibiotics. Although very rare, GAS-associated AIN might be included into the differential diagnosis for patients with GAS infection and ARF.

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Conflict of interest statement. None declared.

References

Focal segmental glomerulosclerosis as a complication of hepatitis B virus infection

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Abstract
Human hepatitis B virus (HBV) is well known as a cause of membranous nephropathy (MN). While the association of HBV infection with MN is strong, data regarding its association with other glomerular diseases are conflicting. Here, we report a case of focal segmental glomerulosclerosis (FSGS) with HBV infection. In this case, we have found HBV-DNA in urinary podocytes by real-time PCR methods. After the administration of anti-viral therapy, FSGS improved, paralleling the decreased level of HBV-DNA in podocytes. The refractory FSGS induced by HBV could be effectively treated with appropriate anti-viral agents.

Keywords: anti-viral therapy; focal segmental glomerulosclerosis; human hepatitis B virus

Introduction
A variety of extrahepatic manifestations, one of the commonest being hepatitis B virus (HBV)-associated nephropathy, may appear in persons chronically infected with HBV [1]. HBV is well known as a cause of membranous nephropathy (MN). Several morphological forms of renal disease including MN, membranoproliferative glomerulonephritis (MPGN), IgA nephropathy and rarely focal segmental glomerular sclerosis (FSGS) have been described in association with HBV infection. While the association of HBV infection with MN is strong, data regarding its association with other glomerular diseases are conflicting [1,2].

We report herein a case of FSGS with immunotolerated perinatal HBV infection. It was known that the key event in the pathogenesis of FSGS is podocyte injury [3]. In this case, we have found HBV-DNA in podocytes using real-time PCR methods. After the administration of anti-viral therapy, FSGS improved, paralleling the decreased level of HBV-DNA in podocytes.

Case report
A 33-year-old man was admitted to a hospital because of severe peripheral oedema. Laboratory data showed hypo-