Infective Endocarditis Developing as Uremia

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Abstract

A 49-year-old man presented with fever and uremic symptoms such as general malaise, leg edema and decreased urine output. He was diagnosed as having infective endocarditis (IE) accompanied by renal failure. Although he had been receiving hemodialysis for a long time, renal function dramatically improved after heart valve replacement. This case suggests that uremia can develop as an initial manifestation of IE and removal of an infected heart valve can improve renal function despite persistent renal failure. From the perspective of recovery of renal function, early surgery should be considered in patients with renal failure following IE.

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Introduction

The existence of renal dysfunction in some patients with infective endocarditis (IE) is well known, and the main mechanism is widely accepted to be immune complex-mediated glomerulonephritis, although renal embolization, abscess, and therapy-related or therapy-induced interstitial nephritis have also been reported as causes of renal dysfunction complicating IE (1, 2). Immune complex-mediated glomerulonephritis was reported to occur in 14 percent of patients with IE (2), however, its manifestations are usually limited to hematuria, proteinuria, and a slightly increasing serum creatinine level. Renal failure is a rare complication of IE and receives little attention, although congestive heart failure, neurological event, systemic emboli, splenic abscess, and peripheral manifestations are regarded as common complications of IE (3, 4).

Here, we report a case of IE whose initial symptom was uremia and review the related literature.

Case Report

A previously healthy 49-year-old man began to feel chilly and had general malaise two weeks before admission. Thereafter, he became slightly febrile. He gradually lost appetite and noted a decreased urine output and swelling of the lower legs, therefore he visited our hospital. There was no precipitating event to cause bacteremia.

On physical examination, his pulse rate was 94 beats/min, blood pressure 128/67 mmHg, and temperature 37.3°C. A grade 3/6 blowing early diastolic murmur and a grade 2/6 midsystolic murmur were heard best at the left third and the right second intercostal space, respectively. Third heart sound was not audible. Marked edema was noted in the lower legs. Other physical findings were unremarkable.

Urinalysis demonstrated marked proteinuria and hematuria, and the sediment contained more than 200 red blood cells and 5 to 10 white blood cells per high-power field. The blood urea nitrogen was 131.6 mg/dl, serum creatinine 10.5 mg/dl, and C-reactive protein (CRP) 3.2 mg/dl. The white blood cell count was 5,800 per cubic millimeter with a slight left shift. Serum levels of circulating immune complexes and complement were both within normal limits. On a chest X-ray film and an electrocardiogram, there were no abnormal findings. Two-dimensional echocardiography demonstrated a bicuspid aortic valve with severe thickening (Fig. 1A). A mobile mass attached to the aortic valve leaflet was consistent with vegetation. Doppler echocardiography showed moderate aortic regurgitation and mild aortic stenosis (Fig. 1B). Ultrasonography of the abdomen showed enlarged bilateral kidneys with hyperechoic parenchyma.

Nine months before admission, he was slightly injured in a motorcycle accident and he visited our hospital. The blood urea nitrogen and serum creatinine at that time were 10.3 mg/dl and 1.0 mg/dl, respectively. CRP level was also normal.
The clinical course in this case is shown in Fig. 2. Hemodialysis was performed three or four times a week since admission. Antimicrobial therapy with cefazolin was initiated after the first three blood cultures had been obtained. However, low-grade fever persisted and CRP level showed no tendency to decrease even at the end of the second week of therapy. Furthermore, the results of the blood cultures obtained on admission were all negative. Consequently we stopped the antimicrobial therapy, then two weeks later, we conducted further microbiological examinations. They were as follows: four additional blood cultures incubated for up to four weeks, urinary antigen test for Legionella, serum antibody tests for Coxiella burnetii (Q fever), Chlamydia, serum antigen test for Candida. However, all test results were negative or within normal limits. To rule out the possibility of marantic endocarditis, which is occasionally associated with malignant diseases, he underwent upper gastrointestinal tract endoscopy, computed tomography of both the chest and abdomen, and gallium scintigraphy (67Ga), but there were no remarkable findings in these examinations. Although the causative microorganism was not identified after all, the diagnosis of infective endocarditis was made based on the modified Duke criteria.

After the examinations described above, antimicrobial therapy with imipenem-cilastatin was started with the intention of providing broader coverage. However, because of its hepatotoxicity, it was replaced with meropenem. His fever responded and the CRP level gradually decreased with meropenem. However, anuria and renal function remained unchanged and the CRP level did not reach normal values even after five weeks of treatment with meropenem, so we began to administer ceftriaxone in consideration of the so-called HACEK group (Haemophilus parainfluenzae, Haemophilus aphrophilus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, and Kingella kingae). Since the CRP level increased immediately after shifting from meropenem to ceftriaxone, we stopped ceftriaxone and started meropenem again.

During the third month of hospitalization, aortic regurgitation and consequent impairment of cardiac function gradually developed and became uncontrollable. Therefore, he underwent aortic valve replacement. On repeated echocardiograms between admission and surgery the vegetation was unchanged. Native aortic valve was replaced with a 21-mm bi-leaflet mechanical prosthetic valve (St. Jude Medical, Inc., St. Paul, MN, USA). Histological examination of the removed valve demonstrated fibrous thickening of the aortic valve with marked calcification and infiltration of inflammatory cells (Fig. 1C), although cultures of the resected valve did not show the growth of any microorganism.

After surgery, renal function dramatically improved and urine output markedly increased. Serum creatinine level dropped immediately and stabilized between 2.0 and 3.0 mg/dl, and postoperative urine output was about 800 ml/day on average. Postoperative urinalysis also demonstrated improvement of hematuria; the sediment showed 40 to 60 red blood cells per high-power field. Therefore, it seemed possible for him to discontinue hemodialysis. However, he did not comply with the restriction of water intake and was drinking more than 2,000 ml of water daily. Thus, he could not be weaned from hemodialysis and hemodialysis was continued to prevent volume overload. CRP level also decreased postoperatively and has remained within the normal range since six weeks after surgery. He received 10 weeks of postoperative antimicrobial therapy with meropenem. He was discharged three months postoperatively and remains well on hemodialysis two years later.

An ultrasound-guided needle biopsy of the kidney, which
was performed one month after admission, demonstrated diffuse proliferation of both capillary and mesangial cells, and infiltration of leukocytes (Fig. 3A). Crescents were found in more than one-third of obtained glomeruli, many of which showed severely collapsed tufts (Fig. 3B). Immunofluorescence methods disclosed global granular deposits of IgM, C1q and C3 along the glomerular capillary walls and in the mesangial regions (Fig. 3C). Such findings were consistent with immune complex-mediated glomerulonephritis in patients with IE. In addition, the tubules and interstitium were also severely affected. Numerous casts were seen obstructing the tubular lumens, and the tubular epithelial cells surrounding the cast were atrophic. The influx of inflammatory cells was also noted in the tubules and adjacent interstitial tissue. Arteriolar changes were absent.

Discussion

This case indicates that renal failure can develop as an initial presentation of IE. In the pre-antibiotic era, renal failure was clinically present in 25 to 35 percent of patients IE and some form of nephritis was shown in 80 percent at autopsy, however, the introduction of antibiotic therapy has greatly reduced the renal complications of IE, particularly renal failure (1, 5, 6). Renal dysfunction is still thought to be one of the complications of IE, but renal failure necessitating hemodialysis is not generally recognized as a complication of IE. That is why we could not imagine at first that such a severe renal failure was a complication of IE, even though the heart murmur, vegetation on the aortic valve, and low-grade fever were suggestive of IE.

We could not find any causes of renal failure other than IE, and concluded that renal failure in this case was due to IE. But someone might think that the main cause of renal failure in this case was prerenal failure which resulted from heart failure due to aortic regurgitation, and that aortic valve replacement improved heart failure and consequently increased renal perfusion. Of course, we cannot deny an effect of aortic regurgitation on renal function, however, the fact that severe renal failure first developed even in the absence of heart failure seems contradictory to prerenal failure due to heart failure.

The main mechanism of renal dysfunction in patients with IE is reported to be immune complex-mediated glomerulonephritis (1, 2). It is categorized as postinfectious glomerulonephritis (7, 8), and regarded as analogous to glomerulonephritis associated with deep-seated visceral abscesses (8, 9) or infected ventricular shunts placed for hydrocephalus (shunt nephritis) (8, 10). These forms of glomerulonephritis have been thought to result from an immunologic reaction based on immunofluorescence and electron microscopic findings that indicated antigen-antibody immune complexes.
deposited in the renal glomeruli, as seen in the present case. Bacterial antigen-antibody immune complexes play a major role in the pathogenesis of glomerular injury (8).

Renal failure of mild to moderate severity due to such infection-associated glomerulonephritis is usually resolved with successful antibiotic therapy (1, 2, 8). However, irreversible renal failure can occur if diagnosis and antibiotic therapy are delayed or antibiotic therapy is ineffective, because the severity of glomerulonephritis is related to the duration of infection (1). In the present case, renal function dramatically recovered even after a three-month period of severe renal failure, although fatal outcome is usually expected in patients with IE who present with uremia from the beginning of the course (1). In this case, we speculate that in addition to antibiotics, the removal of the heart valve led to complete eradication of the infection and consequent remission of glomerulonephritis. Thus, the importance of eradication of infection should also be stressed from the perspective of recovery of renal function in IE. We recommend that early surgery should be considered in a setting of advanced renal failure following IE in order to preserve and improve renal function.

Unfortunately, the causative microorganism was not identified in this case, however, *Staphylococcus aureus* has been reported to be the most likely pathogen to cause renal failure in IE (2). Therefore, we first chose cefazolin on the presumption that the causative microorganism would be *Staphylococcus aureus*. It is likely that 95 to 100 percent of all blood cultures obtained will be positive in patients who have not received prior antibiotics and who ultimately demonstrate culture-positive IE (3). Only five to seven percent of patients who have been given a diagnosis of IE according to strict criteria and who have not recently received antibiotics will demonstrate sterile blood cultures. The most common causative organisms in such culture-negative patients are as follows: *Abiotrophia* species, *Bartonella* species, *Coxiella burnetii* (*Q fever*), HACEK organisms, *Chlamydia* species, *Tropheryma whippelii*, *Legionella* species, *Brucella* species, Fungi. (4). Three cases of necrotizing glomerulonephritis associated with culture-negative endocarditis caused by
Bartonella henselae were recently reported (11). In the present case, the response to antibiotics was highly suggestive of infectious disease and we finally made a diagnosis of IE according to modified Duke criteria (12), however, we regret not having plated the subcultures on more enriched media and not having used the polymerase chain reaction method.

References