Development of Acute Pericarditis Associated with New-onset Rheumatoid Arthritis in a Diabetic Patient with Renal Impairment: The Elusive Nature of Uremia

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Abstract

Uremic patients may have a variety of organ involvement, however, the precise causality may be impossible to determine in some cases because the symptoms of uremia are also associated with other diseases. With an emphasis on the elusive nature of uremia, we herein describe a 53-year-old man with preexisting renal impairment who developed acute pericarditis with deterioration of his renal function. Hemodialysis was immediately initiated on the presumption of uremia, however, articular symptoms emerged approximately a month later and led to a final diagnosis of rheumatoid arthritis, followed by successful withdrawal of hemodialysis.

Key words: rheumatoid arthritis, acute pericarditis, uremia, diabetic nephropathy

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Introduction

Uremia is a life-threatening condition that often requires emergency therapy, including dialysis. However, a precise diagnosis of uremia is a clinical challenge in some cases, in part because definite biomarkers for this condition have not yet been established. A recent review article (1) suggested that no single solute or group of solutes that contribute importantly to uremic illness can yet be named with confidence, despite a recent renewal of interest in uremic toxicity. Furthermore, clinical manifestations in uremia can also result from many other diseases. We herein describe a case of acute pericarditis, which may manifest in patients with uremia (2, 3), including those without dialysis (4). In our case, hemodialysis (HD) therapy was launched, in addition to pericardiocentesis, on the presumption of uremic pericarditis, however, the patient had a persistent and unexplained inflammatory condition that indicated an underlying disease. The delayed development of arthralgia finally led to a diag-

nosis of rheumatoid arthritis (RA), and HD was successfully discontinued. This case provides deeper insights into the elusive nature of uremia and the clinical management of extra-articular lesions of RA, which clinically account for only a small percentage of cases of acute pericarditis (2, 5).

Case Report

A 53-year-old man was referred to our hospital and immediately hospitalized in the cardiac care unit due to pericardial effusion accompanied by a fever of 38.0°C in early July 2014. His medical history was notable for diabetes mellitus and hypertension diagnosed 16 and 3 years earlier, respectively. He also had brain-stem infarction at 50 years of age, however, he had subsequently recovered with few sequelae. Renal impairment [serum creatinine (Cr) 4.40 mg/dL] with overt proteinuria (1.9 g/day) was consistent with diabetic nephropathy, and retinal lesions were present. The patient was transported to a local hospital by ambulance due to dyspnea and chest pain, which had started a couple of

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Figure 1. Representative imaging results. (A) At the time of hospitalization, severe heart enlargement (cardiothoracic ratio 65.8%) was observed on a chest X-ray. (B) Ultrasonography revealed a severely-compressed right ventricle in the apical four-chamber view. (C) Computed tomography (CT) showed a large amount of fluid in the pericardium (arrowheads) with a moderate amount of pleural effusion (arrows). (D) After pericardiocentesis, a marked reduction of the pericardial space was observed on CT, whereas fluid in the thorax remained. Abbreviations: RA: right atrium, RV: right ventricle, LA: left atrium, LV: left ventricle

weeks earlier and suddenly worsened. The findings on physical examinations were blood pressure 121/78 mmHg, heart rate 120 beats/min, and respiratory rate 26 breaths/min (orthopnea). A heart shadow was severely enlarged (Fig. 1A; cardiothoracic ratio 65.8%) and ultrasonography revealed a severely-compressed right ventricle due to a large amount of fluid in the pericardium (Fig. 1B). Computed tomography (CT) delineated a moderate amount of pleural effusion, in addition to pericardial effusion (Fig. 1C), whereas few chest abnormalities had been previously apparent in an examination in April 2014. Approximately 600 mL of wine-colored pericardial effusion was drained by needling under ultrasonic guidance. Laboratory tests showed cell count 16,700/mm³, protein 5.7 g/dL, glucose 0.11 g/dL, lactate dehydrogenase 1,591 mU/mL, and rheumatoid factor (RF) 128×.

Acute myocardial infarction was ruled out according to the lack of ventricular asynergy, elevation of serum cardiac enzymes (e.g. creatine phosphokinase 152 mU/mL), and abnormal ST segments in the electrocardiogram. Thus, the patient was diagnosed with acute pericarditis and the pericar-

dial space was significantly reduced following pericardiocentesis (Fig. 1D). Incidentally, friction rub was not heard in auscultation. Tumor lesions were not found on thoracoabdominal CT and malignant cells were cytologically negative in the pericardial effusion.

In light of the initial clinical presentations, two possible etiologies were considered. First, antimicrobial therapy was conducted for more than three weeks because of a high-grade fever and elevated inflammatory markers on the blood tests [white blood cell counts up to 22,000/μL; C-reactive protein (CRP) level up to 35.90 mg/dL], which strongly suggested an infectious disorder (Fig. 2). The patient received 500 mg of levofloxacin tentatively on the first day, followed by a 22-day course of intravenous infusion of 2.25 g of piperacillin/tazobactam thrice daily. Vancomycin was additionally administered using therapeutic drug monitoring. Despite partial declines in his fever and serum CRP level (down to 5.63 mg/dL; Fig. 2), no microbial species was detected in a cultivation test of the drained pericardial effusion and T-SPOT.TB[®] gave a negative test result.

Figure 2. Course during hospitalization. Abbreviations: TAZ/PIPC: piperacillin/tazobactam, VCM: vancomycin, PSL: prednisolone, Cr: creatinine, BT: body temperature. Symbols: black rhomboid: levofloxacin, gray rhomboids: cefazolin, triangles: hemodialysis therapy, closed circles: serum Cr, closed squares: urine volume, open circles: serum CRP, gray squares: BT

The second possibility was uremia, according to the deterioration of markers for renal impairment (e.g. blood urea nitrogen 75 mg/dL; serum Cr 6.33 mg/dL) with significant oliguria (urine output 155 mL/day; Fig. 2). An electrolyte imbalance (potassium 5.4 mmol/L) and metabolic acidosis (pH 7.338; carbon dioxide pressure 28.9 mmHg; bicarbonate 15.7 mmol/L; anion gap 20.3 mmol/L) were also noted. Therefore, thrice-weekly HD was initiated using central venous catheterization on the day after hospitalization. Serum Cr and inorganic phosphate levels elevated to 12.60 mg/dL (Fig. 2) and 9.5 mg/dL, respectively, shortly thereafter, even under dialysis therapy, in support of the conclusion of severely impaired renal function. A urinalysis showed characteristics of diabetic nephropathy: overt proteinuria (1.894 g/gCr) without significant hematuria and a variety of casts. Serum biomarkers for rapidly progressive glomerulonephritis, such as anti-neutrophil cytoplasmic antibodies (ANCA) directed against myeloperoxidase and proteinase 3, were not detected in chemiluminescent enzyme immunoassays. A urinary obstruction was not evident on CT. In contrast, marked elevation of serum anti-citrullinated peptide antibody (anti-CCP; 586 U/mL) and a positive result for serum RF (158×), in addition to pericardial RF (128×), were noted in tests for the differential diagnosis. However, the interpretation of these biomarkers remained a clinical puzzle during this period due to a crucial lack of articular symptoms, the major manifestation of RA.

After surgery for the creation of a forearm arteriovenous fistula (AVF), the patient was moved to the Division of

Nephrology in mid-August for expert management of maintenance HD. In the perioperative period, 1 g of cefazolin was injected for two days to prevent surgical infection. A recovery of the urine volume was followed by an improvement in the renal biomarkers (e.g. serum Cr 4.06 mg/dL) (Fig. 2). However, the patient's high-grade fever flared, indicating the possibility of subsequent infections, including those associated with the dialysis catheter. The catheter was removed with resumption of vancomycin infusion, also in consideration of the maturity of the previously created AVF, however, the fever with elevated inflammatory biomarkers did not completely resolve (Fig. 2). As such, discontinuation of dialysis therapy was thought to be difficult because HD had been started on the presumption of uremic pericarditis, according to the lack of an alternative etiological explanation. Of particular note, digital pain emerged shortly thereafter (Fig. 2). Moreover, burning arthralgia extended to the right wrist, left hip joint, and bilateral first toes. A diagnosis of RA was finally made with reference to the 2010-American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria (6) (total score estimated to be 7). Circulating markers associated with vasculitis and other connective-tissue diseases that potentially cause pericarditis (2), including anti-Sm antibody, anti-SS-A/Ro antibody, anti-SS-B/La, ANCA, anti-double stranded DNA antibody, and immune complex, were negative. Shortly after the initiation of steroid therapy with a low dose of prednisolone (PSL; 10 mg/day), the patient's articular symptoms and fever disappeared, as reflected in a

marked decrease of serum CRP (0.18 mg/dL). The altered clinical presentation also evoked a possible association of RA with the pericardial lesion, and therefore HD therapy was stopped.

The patient was discharged in early September and has been free from recurrence of pericarditis without HD reentry. The laboratory tests in December 2014 showed serum Cr 3.11 mg/dL and CRP 0.32 mg/dL, with the patient still receiving PSL at a dose of 10 mg/day.

Discussion

In the present case, a patient with renal impairment abruptly developed pericarditis, which was initially thought to be uremic or infectious, however, it was finally concluded to occur in association with RA. Acute pericarditis is an emergency disorder of diverse etiologies, including idiopathic, infection, vasculitis, connective-tissue diseases, metabolic disorders (including uremia), neoplastic disorders, and trauma (2, 7). Advances in diagnostic tests, such as pericardioscopy, immunohistochemistry, and polymerase chain reaction, have allowed a more comprehensive classification of the cause. However, the usefulness of these tests in routine clinical practice is uncertain and they are frequently not performed (2). A recent study of 500 cases showed that 83.2% of patients had a diagnosis of viral or idiopathic acute pericarditis (7), indicating the difficulty of the etiological diagnosis.

Connective tissue diseases such as RA, systemic lupus erythematosus, and scleroderma are an established cause of acute pericarditis (2). In a study of 114 patients with RA, Crilly et al. (8) found that 43% had at least one extra-articular feature, and pericarditis was observed in one patient (2%) in this population. In contrast, Koivuniemi et al. (5) found that pericarditis was detected in up to 27% of 369 autopsy cases of RA, whereas only 0.8% of these patients were diagnosed with myopericarditis while alive. These data imply that rheumatic pericarditis is not particularly rare, but that there are diagnostic limitations in clinical practice. In our case, the lack of articular manifestations hampered the diagnosis of RA, despite our etiological investigation. The anti-CCP test provides a powerful diagnostic clue for RA (6) with a high specificity of 96-98% (9), however, the detection of anti-CCP antibody may precede the clinical onset of RA by several years (10) and may also occur in diverse conditions (11). Thus, anti-CCP-positive cases without a definite diagnosis of RA are found and potentially raise a clinical dilemma.

Comorbidities were an additional obstacle to the etiological diagnosis of pericarditis in the present case. Infectious disorders (2) were initially regarded as a likely cause of pericarditis and might have partly contributed to the inflammatory condition through the clinical course. In fact, a partial improvement in the inflammatory markers occurred after the initiation of three-week antimicrobial therapy, followed by a reevaluation of these markers. This suggested that new

infections were present, including those associated with the dialysis catheter (Fig. 2). Nevertheless, it is less likely that pericarditis resulted mainly from infectious diseases for the following reasons. Ultimately, pyrexia with elevated CRP did not completely disappear, despite the long-term administration of antibiotics and removal of the catheter, and finally led to the emergence of articular lesions and positive circulating anti-CCP. In contrast, the clinical manifestations dissipated immediately after steroid therapy was started and did not reemerge, even in the absence of antimicrobial therapy. Pericarditis should have been aggravated under these conditions if the main cause was infection. The safety and efficacy of echocardiographically guided pericardiocentesis was shown by Cauduro et al. (12) in a case series of 16 patients with RA. In that study, the exudative had a mean protein concentration of 5 g/dL, and in some cases RF was positive in the pericardial effusion, in addition to the serum (12).

Deterioration of the renal impairment might be etiologically attributed to pericarditis, since the development of uremic manifestations is sometimes unpredictable. Wood and Mahnensmith suggested that in undialyzed cases of uremic pericarditis, blood urea nitrogen and serum Cr concentrations may not be significantly higher than those found in similarly uremic patients without pericarditis (3). In this regard, it is noteworthy that a marked improvement of the renal function, including the urine volume, was observed in our case following pericardiocentesis (Fig. 2). Saklayen et al. (13) highlighted the importance of an altered renal blood flow resulting from a reduced cardiac output in a report of two cases of acute renal failure associated with severe pericardial effusion and a review of similar previous cases (14, 15). In these cases, pericardiocentesis caused immediate massive diuresis with a quick recovery of the renal function to baseline, indicating that renal impairment may also result from pericarditis, although it is generally regarded to be causative (2). Similarly, our patient had a normalization of the urine volume followed by a decline of the serum Cr level to baseline within days. The time for renal recovery was somewhat longer than in the previous cases (13-15), presumably because of a preexisting renal disorder (diabetic nephropathy) and systemic inflammation due to RA.

In addition, pleural effusion was persistent, in contrast to the recovery of the renal function following a marked reduction of pericardial effusion by pericardiocentesis (Fig. 1D, 2). In retrospect, the discrepancy between the renal function and pleural effusion supports the presence of an underlying inflammatory disease as a potential cause of generalized serositis. Thus, our case suggests that patients with chronic renal failure, who are prone to uremic pericarditis, are affected by pericardial effusion, and this can potentially lead to an incorrect diagnosis. Therefore, the diagnosis of uremia should be performed carefully, even in cases with severely impaired renal function, and reconsideration after the diagnosis might be required.

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

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