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Case report

Multiple bone fracture due to Fanconi's syndrome in primary Sjögren's syndrome complicated with organizing pneumonia

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Running title: Fanconi's syndrome and OP in SS

Abstract

A 66-year-old woman showing renal dysfunction with elevated serum alkaline phosphatase and anti-SS-A antibody was admitted. A labial salivary gland biopsy showing infiltration of mononuclear cells and positive anti-SS-A antibody with sicca symptoms led to a diagnosis of primary Sjögren's syndrome (SS). Fanconi's syndrome was diagnosed by renal tubular acidosis along with renal glucosuria or aminoaciduria and multiple bone fractures on bone scintigraphy. Typical bilateral pulmonary shadows were confirmed as organizing pneumonia (OP) determined by the analysis of bronchoalveolar lavage fluid and transbronchial lung biopsy. A rare complication of Fanconi's syndrome with OP in SS is described.

Key words: Sjögren's syndrome, multiple bone fractures, Fanconi's syndrome, renal tubular acidosis, organizing pneumonia

Introduction

Sjögren's syndrome (SS) is an autoimmune disorder characterized by the presence of autoantibodies and glandular or extraglandular manifestations (1). Tubulointerstitial nephritis in SS is often complicated with type 1 renal tubular acidosis (RTA 1) with hypokalemia (2), but complication of Fanconi's syndrome with proximal tubular dysfunction is reported with relatively low frequency (3). Previously, multiple non-union fractures due to osteomalacia in SS with Fanconi's syndrome were reported (4). Organizing pneumonia (OP) is one of the phenotypes in interstitial lung disease found in extraglandular manifestations of SS (5). Here, we report a rare case showing both multiple bone fractures due to osteomalacia of Fanconi's syndrome and OP in a patient with SS.

Case report

A 66-year-old woman was examined for an abnormal lung shadow in 2005 without a specific diagnosis. In September 2008, she was admitted to our hospital due to renal dysfunction and abnormal migrating lung shadow with a slight cough. On admission, the patient complained of xerophthalmia and xerostomia without fever, though she did not show mucocutaneous manifestations or

arthralgia. No crackle was detected in her lung by auscultation.

Laboratory findings showed a hemoglobin level of 10.5 g/dl, a total leukocyte count of $3,900/\text{mm}^3$ and a platelet count of $16.9 \times 10^4/\text{mm}^3$ with slight elevation of fibrinogen (384 mg/dl). Although aspartate aminotransferase (21 IU/l) was within the normal limit, elevation of creatinine (1.3 mg/dl) and alkaline phosphatase (629 IU/l) was found. The levels of potassium (3.0 mEq/l), inorganic phosphorus (1.9 mg/dl) and calcium (8.6 mg/dl) were decreased with elevation of chloride (120 mEq/l). The percentage of tubular reabsorption of phosphate decreased to 45% (normal: 81-90%). Although serum IgG and IgA were within normal limits, serum IgM was elevated to 439.0 mg/dl (normal range: 57-288 mg/dl). Anti-nuclear antibody and anti-SS-A antibody were positive without anti-double-stranded deoxyribonucleic acid antibody, anti-ribonucleoprotein antibody or anti-SS-B antibody. Glucosuria (2+) and proteinuria (1+) were repeatedly observed, despite normal HbA1c (4.8%) and normal sugar concentration. Urine β 2-microglobulin was remarkably elevated to 44,500 $\mu\text{g/l}$. Schirmer test (5/0 mm) and Saxon test (0.44 g/2 min.) were positive. A labial salivary gland biopsy was performed, resulting in a diagnosis of SS based on the criteria determined by the American-European Consensus Group

(6).

Computed tomography (CT) of the lungs showed multiple consolidations with a sub-pleural distribution in both lung fields (**Figure 1**). An elevated proportion of lymphocytes (42.9%) in bronchoalveolar lavage fluid (BALF) and foamy macrophages and lymphocytes aggregation in air space in transbronchial lung biopsy (TBLB) specimens were seen without malignancy or respiratory infection. The typical CT findings and the findings in BALF and TBLB specimens were consistent with OP. From the serum electrolyte level and results of blood gas analysis showing decreased pH (7.213) and base excess (-10.7 mmol/l) with renal glucosuria and aminoaciduria, RTA was suspected, although a renal biopsy was not performed because of the patient's low estimated glomerular filtration rate (34.04 ml/min).

The multiple hot spots on the patient's bilateral limbs and femoral necks were confirmed by bone scintigraphy (**Figure 2**) as bone fractures by CT or magnetic resonance imaging. These findings led to a diagnosis of Fanconi's syndrome with OP. Since the patient's bone mineral density was extremely low (52-62% when compared with age matching), we administered 50 mg of mizoribine with 2 g of potassium citrate/sodium citrate and 0.5 µg of vitamin D

daily instead of a steroid. With regard to publication, written informed consent to publish this data was obtained from the patient.

Discussion

Renal involvement is often observed as extraglandular manifestations in SS. Although the distal renal tubule is usually involved in SS as RTA 1 (2), involvement of the proximal renal tubule is relatively infrequent (7). Ren et al (3) recently reviewed renal involvement in 130 primary SS patients. In this report, 91 out of 95 (95.8%) SS patients demonstrated distal RTA. Ren et al also showed that 4 out of 130 (3.1%) SS patients showed Fanconi's syndrome, indicating that the prevalence of involvement of the proximal renal tubule is relatively low in SS patients. As Bridoux et al (7) previously described, not only distal but also proximal tubular dysfunction might occur as the pathological phenotype of Fanconi's syndrome in SS, although proximal tubular involvement has been only sporadically reported (8).

Fanconi's syndrome results from proximal tubular dysfunction and subsequent osteomalacia is induced (9). Yang et al (4) reported multiple non-union bone fractures in one SS patient with Fanconi's syndrome. The patient

also showed elevation of serum alkaline phosphate and serum chloride with reduction of serum potassium, which closely resembles our case. Usually, glucocorticoid is used to improve the extraglandular manifestations in SS. However, no steroid was used for treatment in the patient described by Yang et al, because serious osteomalacia could have exacerbated the fragile bone structure. Thus, mizoribine was selected for the patient, since the efficacy and safety of mizoribine for treatment of SS had been confirmed (10, 11).

In our case, Fanconi's syndrome was coupled with OP. OP, formerly called bronchiolitis obliterans with organizing pneumonia, is characterized by mixed alveolitis with increased lymphocytes, neutrophils and eosinophils in BALF (5). The analysis of BALF in our case showed elevation of lymphocytes, which is a shared characteristic of extraglandular manifestations such as tubulointerstitial nephritis or autoimmune pancreatitis in SS. Previously, Furukawa et al (12) reported that shared common epitopes in lacrimal glands, salivary glands and kidneys were recognized by the infiltrating T cells in an animal model of SS. These findings imply that different parenchymatous organs are damaged by common T lymphocytes that identify a specific antigen, in our case, the salivary glands, kidneys and lung.

In summary, this is a first report of Fanconi's syndrome complicated with OP in a patient with SS. The pathological characteristics might be a result of lymphocytic infiltration into parenchymal organs. To determine the clinicopathologic features of extraglandular manifestations such as RTA or OP, an accumulation of similar cases and reporting of detailed case analyses are required.

Abbreviations: CT: computed tomography, BALF: bronchoalveolar lavage fluid, OP: organizing pneumonia, SS: Sjögren's syndrome, RTA: renal tubular acidosis

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Figure legends

Figure 1

Computed tomography (CT) findings of organizing pneumonia on admission.

Multiple consolidations with sub-pleural distribution were detected in both lungs by CT scan. The lesions were accompanied by ground glass opacities.

Figure 2

Bone scintigraphy findings demonstrating multiple hot spots.

Multiple uptake of ^{99m}Tc was observed on the patient's bilateral limbs, neck and bilateral femoral necks.

Fig 1



Fig 2

