

# Sjögren's syndrome complicated with Fanconi syndrome and Hashimoto's thyroiditis: Case report and literature review

Mingmin Shi<sup>1</sup> and Lei Chen<sup>2</sup>

## Abstract

We report a unique case of Sjögren's syndrome complicated with Fanconi syndrome and Hashimoto's thyroiditis in a 53-year-old Chinese woman, initially found to have proteinuria, fatigue and multiple old costal fractures. Distal tubular dysfunction is the most common renal damage in Sjögren's syndrome, while Fanconi syndrome (which is caused by proximal tubular dysfunction) and Hypothyroidism are rare complications of Sjögren's syndrome.

## Keywords

Sjögren's syndrome, Fanconi syndrome, Hashimoto's thyroiditis

Date received: 28 February 2015; accepted: 3 June 2015

## Introduction

Sjögren's syndrome is a chronic inflammatory autoimmune disease, characterized by lymphocytic infiltration of exocrine glands, which is often underdiagnosed but affects between 1 and 3% of the general population.<sup>1</sup> The ratio of female to male patients with Sjögren's syndrome is about 9:1,<sup>2</sup> with peak incidence occurring in people between the ages of 50 and 80 years. Besides the most common involvement of salivary and lacrimal glands, Sjögren's syndrome can affect the skin, lungs, gastrointestinal tract, central and peripheral nervous systems, and the musculoskeletal apparatus. The incidence of osteomalacia in Sjögren's syndrome patients with renal tubular acidosis ranges between

25 and 45%.<sup>3</sup> We report a unique case of Sjögren's syndrome complicated with Fanconi syndrome, Hashimoto's thyroiditis and multiple old costal fractures in a 53-year-old Chinese woman.

<sup>1</sup>Department of Orthopaedics, 2nd Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China

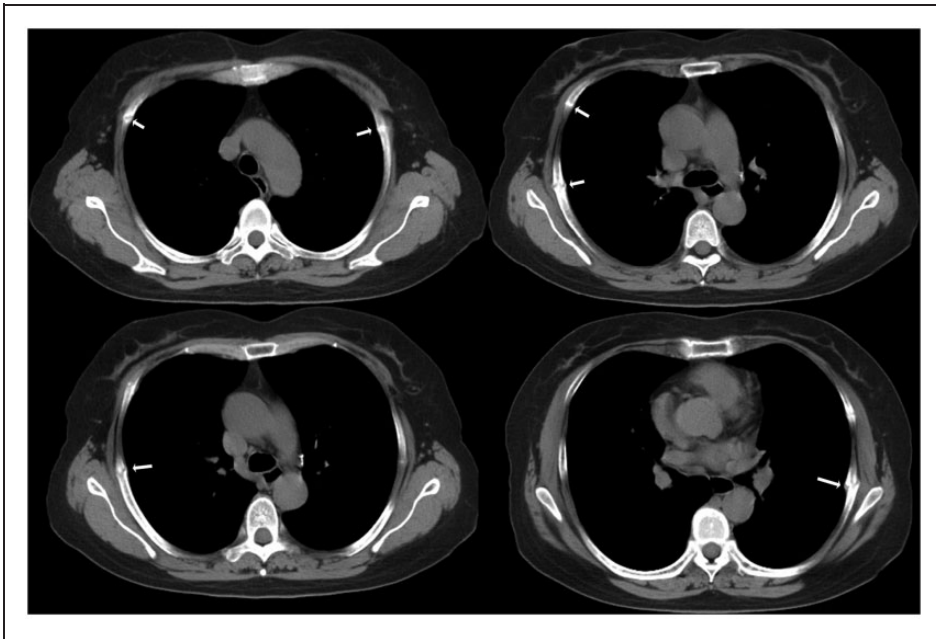
<sup>2</sup>Department of Endocrinology and Metabolism, Sir Run Run Shaw Hospital Affiliated with the School of Medicine, Zhejiang University, Hangzhou, China

### Corresponding author:

Lei Chen, Department of Endocrinology and Metabolism, Sir Run Run Shaw Hospital Affiliated with the School of Medicine, Zhejiang University, No. 3 Qingchun Road, Hangzhou 310009, China.

Email: chenlei@zju.edu.cn





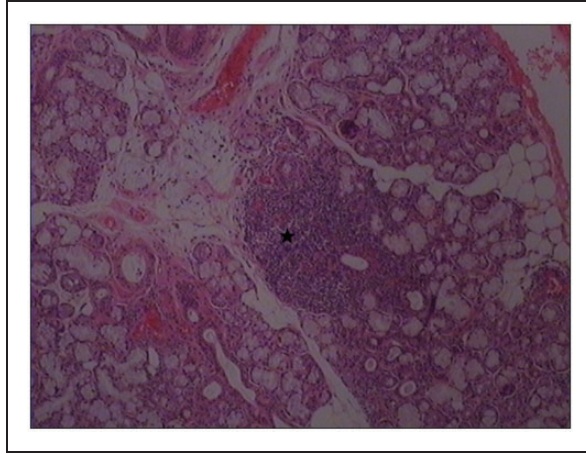
**Figure 1.** Computed tomography scan illustrating multiple old rib fractures (arrows) in a 53-year-old Chinese woman presenting with Sjögren's syndrome complicated with Fanconi syndrome and Hashimoto's thyroiditis.

## Case report

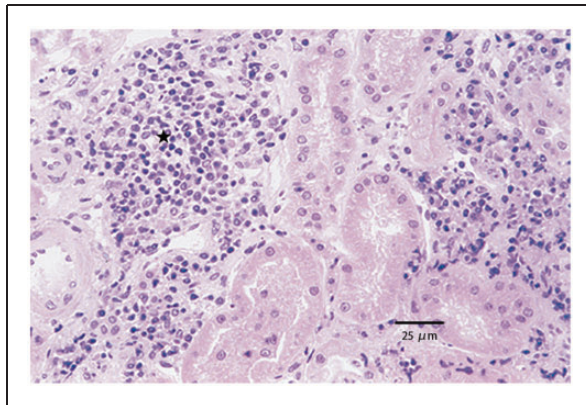
A 53-year-old female was admitted to Sir Run Run Shaw Hospital (Hangzhou, China) in March 2014, because of proteinuria and glycosuria, which she had for ~3 years and which had not been diagnosed in other hospitals. She also complained of dryness of her mouth and eyes, and had pain in her bilateral hypochondrium that later spread to her shoulders, elbows, knees and proximal metatarsophalangeal and metacarpophalangeal joints, and was reported to worsen in winter. The red rash on her face also worsened in winter.

Standard laboratory and clinical workup showed glycosuria (++++), proteinuria (+), hypothyroidism, substernal goitre, multiple old costal fractures and slightly dysfunctional salivary glands; 24-h urine protein quantitation was 2430.4 mg. The

anion gap was normal, serum pH was 7.34 and urinary pH was 5.5. Serum bicarbonate was 18.7 mmol/l, serum potassium was 3.07 mmol/l, serum calcium was 2.17 mmol/l and alkaline phosphatase was 74 U/l. Total thyroxine was decreased to 49.6 nmol/l, free thyroxine was decreased to 6.89 nmol/l, high sensitivity thyrotropin was increased to 5.51 nmol/l, thyroglobulin was decreased to 1.21 µg/l, antithyroglobulin antibody was increased to 774.60 IU/ml and antithyroperoxidase antibody was increased to 94.61 IU/ml. Computed tomography (CT) scanning revealed substernal goitre and multiple old costal fractures (Figure 1). A labial salivary gland biopsy (Figure 2) showed a focal lymph follicle in the sampled tissue. A kidney biopsy (Figure 3) was also performed. Periodic acid-Schiff and periodic acid-silver methenamine staining showed lymphocytic infiltration. Further examination of the kidneys showed one glomerulus out of 14 had become



**Figure 2.** Focal lymph follicle infiltration (star) revealed in a labial salivary gland biopsy (haematoxylin and eosin stain, 400 × magnification) in a sample taken from a 53-year-old Chinese woman presenting with Sjögren's syndrome complicated with Fanconi syndrome and Hashimoto's thyroiditis. The colour version of this figure is available at: <http://imr.sagepub.com>



**Figure 3.** Lymphocytic infiltration (star; 400 × magnification), in a kidney biopsy sample stained with periodic acid-Schiff (PAS) and periodic acid-silver methenamine (PASM), taken from a 53-year-old Chinese woman presenting with Sjögren's syndrome complicated with Fanconi syndrome and Hashimoto's thyroiditis. The colour version of this figure is available at: <http://imr.sagepub.com>

sclerotic, and slight mesangial proliferation of the glomeruli. There was calcified sediment and protein inside the tubule, which were red with Masson staining.

Sjögren's syndrome was diagnosed based on the patient's complaint of dry eyes and dry mouth, positive Schirmer and Saxon tests,

and the labial salivary gland biopsy result. Fanconi syndrome was confirmed by metabolic acidosis with hypokalaemia, hyperchloraemia and alkaluria, indicating proximal renal tubular acidosis. Hypothyroidism was confirmed by thyromegaly (grade 2), decreased thyroxine (T4) and

thyroglobulin, and elevated thyroid stimulating hormone. Since thyroglobulin antibodies and thyroid autoantibodies were significantly increased, we also considered the presence of an autoimmune thyroiditis, such as Hashimoto's thyroiditis. After standard treatment with methylprednisolone, potassium citrate, levothyroxine sodium and symptomatic therapy, the patient gained a normal serum pH, and normal levels of bicarbonate, potassium and thyroid hormones.

The patient reported here provided written informed consent for publication of her medical details and any accompanying images. The Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, China, does not require ethical approval for reporting individual cases.

## Discussion

To date and to our knowledge, there has been no previous report in the literature of a patient with concurrent Sjögren's syndrome, Fanconi syndrome and Hashimoto's thyroiditis. Reviewing the literature, we found that the complications mentioned in the introduction of this paper are common in worldwide reports of patients with concomitant Sjögren's syndrome and Fanconi syndrome.

Only eight case reports of nine patients with concurrent Sjögren's syndrome and Fanconi syndrome were found in a literature search, and are presented in Table 1.<sup>4-11</sup> Patients with both Sjögren's syndrome and Fanconi syndrome are more likely to develop the kidney problems seen in patients with Sjögren's syndrome only, rather than those seen in patients with Fanconi syndrome only. Kidney problems in patients with Fanconi syndrome are abnormalities of the proximal renal tubules leading to abnormal urinary or blood biochemistry. In addition, bone loss and proteinuria can be seen in patients with Fanconi syndrome, which may well explain the multiple old costal

fractures seen in our patient. Overload of light chains, seen as light chain proteinuria, and the inhibitory effect of light chains on the transport of amino acids, glucose, uric acid, phosphate, and on  $\text{Na}^+/\text{K}^+$  ATPase in the proximal tubules may activate cell stress and inflammatory responses in the proximal tubular epithelium.<sup>12,13</sup>

The reported cases, along with our case, are predominantly female (82%) and over 30 years of age; this profile is high risk group for autoimmune diseases.<sup>4-11</sup>

The present patient developed Hashimoto's thyroiditis in addition to Sjögren's syndrome and Fanconi syndrome. Plenty of epidemiological, clinical, immunological, histological and genetic evidence support an association between the two autoimmune diseases, Sjögren's syndrome and Hashimoto's thyroiditis. Fractures in patients with renal tubular acidosis result from osteomalacia, and rarely occur as the presenting symptom of Sjögren's syndrome, which is more commonly associated with proximal rather than distal renal tubular acidosis. There are several differential diagnoses. For example, myeloma can lead to proteinuria and multiple fractures. Serum electrophoresis can be helpful to differentiate between underlying diseases. In a study of 170 patients with Hashimoto's thyroiditis, 17% had Sjögren's syndrome.<sup>14</sup> In another retrospective study of patients with primary Sjögren's syndrome, the frequency of Hashimoto's thyroiditis was three to six times that of the general population.<sup>15</sup> One interpretation is that the thyroid and salivary glands share the same antigens, and the histopathological lesions reveal similar lymphocytic infiltration. Enzyme-linked immunosorbent assay analysis of serum samples from patients with Sjögren's syndrome and Hashimoto's thyroiditis found that the antihuman thyroglobulin in patients with both conditions overlapped one region of human thyroglobulin. This suggests that this region may be shared pathogenetically

**Table 1.** Case reports of Sjogren's syndrome (SS) complicated with Fanconi syndrome (FS).

First Author	Patient's sex	Patient's age	Diagnosis	Symptoms	Histology	Country	Year
Bridoux F <sup>7</sup>	Male	69	SS, FS, distal RTA	Renal failure with weight loss, xerostomia, xerophthalmia	Salivary gland biopsy: diffuse lymphocytic infiltrate	France	2004
Kong DH <sup>4</sup>	Female	33	SS, FS	Polyuria, polydipsia	Kidney biopsy: focal proximal tubulitis and diffuse interstitial nephritis with fibrosis	China	2005
Yang YS <sup>8</sup>	Female	60	SS, FS	Weakness, osteodynia, impaired mobility	Not mentioned	China	2007
Kobayashi T <sup>9</sup>	Female	49	SS, FS, distal RTA, monoclonal gammopathy	Multiple bone deformities, generalized muscle weakness	Salivary gland: mononuclear cells infiltration over periductal area	Japan	2006
Wang M <sup>5</sup>	Female	73	SS, FS, multiple fractures	Progressive fatigue; mild renal dysfunction; hypokalaemia	Kidney: diffuse tubulointerstitial nephritis; dense infiltrates of lymphocytes; immunoglobulin A and kappa light chain-positive plasma cells	China	2008
Nakamura H <sup>3</sup>	Female	66	SS, FS, organizing pneumonia	Osteodynia, impaired mobility	Salivary gland: acini atrophy and lymphocyte infiltration over periductal area	Japan	2009
Wang CC <sup>6</sup>	Male	39	SS, FS	Renal dysfunction, abnormal migrating lung shadow with a slight cough; xerophthalmia and xerostomia without fever	Labial salivary gland: foamy macrophages Lung: lymphocyte aggregation in air space	Taiwan	2010
Di Q <sup>10</sup>	Female	30	SS, FS, RTA, neurogenic bladder	Hypokalaemic paralysis	Kidney: diffuse tubulointerstitial nephritis	China	2010

RTA, renal tubular acidosis.

by patients with both Sjögren's syndrome and Hashimoto's thyroiditis.<sup>16</sup> Other possible explanations for the association between Sjögren's syndrome and Hashimoto's thyroiditis are a sharing of a common genetic predisposition<sup>17</sup> or environmental factors.<sup>18</sup> Patients with Sjögren's syndrome require periodic examination of their thyroid function so that routine treatment can be employed as soon as hypothyroidism becomes clinically relevant.

### Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

### Funding

This work received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

### References

- Bell M, Askari A, Bookman A, et al. Sjögren's syndrome: a critical review of clinical management. *J Rheumatol* 1999; 26: 2051–2061.
- Ren H, Wang WM, Chen XN, et al. Renal involvement and followup of 130 patients with primary Sjogren's syndrome. *J Rheumatol* 2008; 35: 278–284.
- Richards P, Chamberlain MJ and Wrong OM. Treatment of osteomalacia of renal tubular acidosis by sodium bicarbonate alone. *Lancet* 1972; 2: 994–997.
- Nakamura H, Kita J, Kawakami A, et al. Multiple bone fracture due to Fanconi's syndrome in primary Sjogren's syndrome complicated with organizing pneumonia. *Rheumatol Int* 2009; 30: 265–267.
- Kong DH, Gao Y and Qiu MC. Sjogren's syndrome, renal tubular acidosis and Fanconi syndrome—a case report. *Zhonghua Yi Xue Za Zhi* 2005; 85: 878.
- Wang M and Wang WZ. Sjogren's syndrome, Fanconi syndrome and multiple fracture: case report. *Sichuan Medicine Journal* 2008; 29: 1277–1278.
- Bridoux F, Kyndt X, Abou-Ayache R, et al. Proximal tubular dysfunction in primary Sjogren's syndrome: a clinicopathological study of 2 cases. *Clin Nephrol* 2004; 61: 434–439.
- Wang CC, Shiang JC, Huang WT, et al. Hypokalemic paralysis as primary presentation of Fanconi syndrome associated with Sjogren syndrome. *J Clin Rheumatol* 2010; 16: 178–180.
- Yang YS, Peng CH, Sia SK, et al. Acquired hypophosphatemia osteomalacia associated with Fanconi's syndrome in Sjogren's syndrome. *Rheumatol Int* 2007; 27: 593–597.
- Kobayashi T, Muto S, Nemoto J, et al. Fanconi's syndrome and distal (type 1) renal tubular acidosis in a patient with primary Sjogren's syndrome with monoclonal gammopathy of undetermined significance. *Clin Nephrol* 2006; 65: 427–432.
- Di Q and Qiu MC. Sjogren's syndrome, RTA, Fanconi syndrome and neurogenic bladder: case report. *Contemporary Medicine* 2010; 16: 63–65.
- Siamopoulos KC, Mavridis AK, Elisaf M, et al. Kidney involvement in primary Sjögren's syndrome. *Scand J Rheumatol Suppl* 1986; 61: 156–160.
- Sengul S, Li M and Batuman V. Myeloma kidney: toward its prevention-with new insights from in vitro and in vivo models of renal injury. *J Nephrol* 2009; 22: 17–28.
- Biró E, Szekanecz Z, Czirják L, et al. Association of systemic and thyroid autoimmune diseases. *Clin Rheumatol* 2006; 25: 240–245.
- Zehner M, Horvath IF, Szanto A, et al. Autoimmune thyroid diseases in a large group of Hungarian patients with primary Sjögren's syndrome. *Thyroid* 2009; 19: 39–45.
- Bouanani M, Bataille R, Piechaczyk M, et al. Autoimmunity to human thyroglobulin. Respective epitopic specificity patterns of anti-human thyroglobulin autoantibodies in patients with Sjögren's syndrome and

- patients with Hashimoto's thyroiditis. *Arthritis Rheum* 1991; 34: 1585–1593.
17. Foster H, Fay A, Kelly C, et al. Thyroid disease and other autoimmune phenomena in a family study of primary Sjogren's syndrome. *Br J Rheumatol* 1993; 32: 36–40.
  18. Jara LJ, Navarro C, Brito-Zerón Mdel P, et al. Thyroid disease in Sjogren's syndrome. *Clin Rheumatol* 2007; 26: 1601–1606.