CASE REPORT

A case of synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome complicated by IgA nephropathy with nephrotic syndrome

Katsuhiko Morimoto^{1,3} · Kimihiko Nakatani^{3,4} · Osamu Asai^{1,4} · Kuniko Mondori¹ · Kiyonori Tomiwa² · Takamitsu Mondori² · Yoshiyuki Nakagawa² · Masayuki Iwano^{3,5} · Hideo Shiiki¹

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Abstract A 62-year-old man visited our hospital with a mild sore throat, high-grade fever, and clavicular pain. Seven years earlier, he had been diagnosed with synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome. His clavicles were tender and remarkably swollen. Also noted was marked pitting edema in the lower extremities and pustulosis on the palms and soles of the feet. Laboratory studies on admission showed an elevated white cell count (23,400/ μ l) and serum C-reactive protein level (24.4 mg/dl). Urinalysis revealed proteinuria (2+) and occult blood (3+) with numerous dysmorphic red blood cells and hyalin casts. The patient was diagnosed with recurrence of his SAPHO syndrome and started on oral glucocorticoid therapy. By day 9 after admission, he had gained 16 kg in body weight, and his proteinuria (6.4 g/day) and serum creatinine level (2.3 mg/dl) were elevated. Renal biopsy revealed mesangial proliferative glomerulonephritis with deposition of IgA and C3 in the mesangial area and along the capillary walls. The patient was diagnosed with IgA nephropathy accompanied by nephrotic syndrome. With oral prednisolone therapy, his

fever, clavicular pain, and proteinuria were gradually relieved. The clinical course in this case suggests the onset of nephrotic syndrome with IgA nephropathy was associated with the recurrence of the patient's SAPHO. To our knowledge, this is the first reported case of SAPHO-associated IgA nephropathy.

Keywords IgA nephropathy · Nephrotic syndrome · SAPHO syndrome · Tonsillar infection

Introduction

Synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome is an autoimmune disease characterized by dermatological manifestations and osteoarthropathy frequently localized to the anterior chest wall [1]. It is predominantly manifests as aseptic inflammatory bone lesions and neutrophilic skin eruptions, including palmoplantar pustulosis, hidradenitis suppurativa, and acne conglobata and acne fulminans. Associated findings include osteosclerotic lesions, hyperostosis, and arthritis of the adjacent joints. There is also a predilection for skeletal involvement in the upper chest wall and sternum. On the other hand, reports of an association between SAPHO syndrome and renal disease have been rare. Herein, we provide the first report of a case of SAPHO syndrome complicated by IgA nephropathy leading to the development of nephrotic syndrome.

Case report

A 62-year-old Japanese man visited the orthopedic surgery of our hospital complaining of high-grade fever and precordial pain. Seven years earlier, he had been diagnosed at

✉ Kimihiko Nakatani
nkimihik@naramed-u.ac.jp

¹ Department of Internal Medicine, Uda Municipal Hospital, Uda, Japan

² Department of Orthopedics, Uda Municipal Hospital, Uda, Japan

³ First Department of Internal Medicine, Nara Medical University, 840 Shijo-cho, Kashihara, Nara 634-8522, Japan

⁴ Department of Nephrology, Kyoto Yamashiro General Medical Center, Kizugawa, Japan

⁵ Division of Nephrology and Clinical Laboratories, Faculty of Medical Science, University of Fukui, Yoshida, Japan

another hospital with SAPHO syndrome manifesting with synovitis, acne, pustulosis, hyperostosis, and osteitis. Thereafter, he frequently experienced clavicular pain but had not sought treatment until his visit to our hospital. Physical examination of the patient showed high-grade fever and flushed, feverish skin in the area around his clavicles, and laboratory studies showed the strong inflammatory reactions. Computed tomography revealed osteolysis of the sternoclavicular joints (Fig. 1a), and MR imaging showed numerous abscesses in the precordial subcutaneous tissue. The patient was diagnosed with purulent osteomyelitis and was incised to discharge pus; however, bacterial culture of the discharge was negative. Because the inflammatory reactions persisted, a suppurated-area curettage was performed, after which his symptoms subsided and the patient left the hospital.

Three months later, the patient developed a fever (38.6 °C) and clavicular pain with a moderate sore throat and was again admitted to our hospital. On admission, his height was 165.5 cm, weight 44 kg, body temperature 38.4 °C, blood pressure 138/82 mmHg, and pulse 82 beats/min. His clavicles were remarkably swollen and tender (Fig. 1b), and redness of the tonsils was noted. In addition, there was marked pitting edema in the lower extremities, and pustulosis had appeared on his palms and the soles of his feet (Fig. 1c). Laboratory studies (Table 1) revealed a white cell count of 23,400/ μ l, C-reactive protein (CRP) level of 24.4 mg/dl, serum total protein (TP) level of 8.3 mg/dl, serum albumin level of 2.8 mg/dl, serum alkaline phosphatase (ALP) level of 1288 IU/l, and serum creatinine (Cr) level of 0.8 mg/dl. Urinalysis revealed proteinuria (2+) and occult blood (3+) with numerous dysmorphic red blood cells and hyalin casts.

Fig. 1 Manifestation of musculoskeletal and cutaneous lesions. **a** Computed tomography revealed osteolysis of the sternoclavicular joints. **b** The skin around the clavicles was flushed and swollen. **c** Pustulosis was present on the soles of the feet

The patient was diagnosed with recurrence of osteomyelitis and promptly received treatments to drain pus and was administered antibiotics. The treatment provided some relief of the inflammatory reaction, but the discharge persisted, necessitating incision and drainage on several subsequent occasions. Bacterial cultures of the discharge were all negative. It was then that we suspected the patient's symptoms were caused by a recurrence of his SAPHO syndrome. On day 9 after admission, we stopped the antibiotic administration and started oral glucocorticoid (prednisolone 30 mg/day) therapy. At the start of oral glucocorticoid therapy, laboratory studies revealed massive proteinuria (5.2 g/gCr) and hypoalbuminemia (2.3 mg/dl). The patient's fever and clavicular pain gradually subsided, but the pitting edema in the lower extremities had advanced, and his body weight had increased by 16 kg in the 15 days since his admission. Urinary examination on day 18 revealed proteinuria of 6.4 g/day, and laboratory studies showed hypoalbuminemia (Alb 2.2 g/dl) and renal dysfunction (Cr 2.3 mg/dl). The patient was then diagnosed with nephrotic syndrome, and a renal biopsy was performed on day 21. The renal biopsy specimen (Fig. 2a, b)

Table 1 Laboratory data on admission

Urinalysis		Biochemistry	
Protein	2+	Total protein	8.3 g/dl
Occult blood	3+	Albumin	2.8 g/dl
Glucose	Negative	Amylase	38 IU/l
RBC	50–99/HPF	AST	54 IU/l
WBC	10–19/HPF	ALT	35 IU/l
Complete blood count		ALP	1288 IU/l
WBC	23,400/ μ l	γ -GTP	105 IU/l
RBC	427×10^4 / μ l	CK	37 IU/l
Hemoglobin	10.3 g/dl	LDH	150 IU/l
Platelets	42.9×10^4 / μ l	Cholinesterase	145 IU/l
Serology		Triglyceride	139 mg/dl
CRP	24.4 mg/dl	Total cholesterol	167 mg/dl
IgA	604 mg/dl	Glucose	99 mg/dl
IgG	2196 mg/dl	Uric acid	3.8 mg/dl
IgM	55 mg/dl	BUN	16 mg/dl
C3	90 mg/dl	Creatinine	0.8 mg/dl
C4	26 mg/dl	Sodium	129 mEq/l
CH50	42 U/ml	Potassium	6.8 mEq/l
RA	0 IU/ml	Chloride	96 mEq/l
ANA	Negative	Calcium	7.4 mg/dl
		Total bilirubin	0.6 mg/dl

WBC white blood cell, RBC red blood cell, CRP C-reactive protein, Ig immunoglobulin, CH50 total complement activity, RF rheumatoid factor, ANA antinuclear antibodies, AST aspartate aminotransferase, ALT alanine aminotransferase, ALP alkaline phosphatase, GTP guanosine triphosphate, CK creatine kinase, LDH lactate dehydrogenase, BUN blood urea nitrogen

contained 15 glomeruli: three were globally sclerotic, one was segmentally sclerotic, and the remaining ones showed mild mesangial proliferation. Some glomeruli showed segmental endocapillary proliferation. There were foci of tubular atrophy and fibrosis with moderate inflammatory-cell infiltration. Immunofluorescent examination (Fig. 2c, d) revealed deposition of IgA and C3 in the mesangial area and along the capillary walls. We therefore diagnosed IgA nephropathy accompanied by nephrotic syndrome. Since his symptoms of both SAPHO and nephrotic syndrome were gradually improving, we continued oral glucocorticoid therapy with the same dose. After the tapering of oral prednisolone dose, serum Cr declined to within the normal range by day 30, and proteinuria was less than 2 g/day on day 45, indicating that the nephrotic syndrome could be considered to be in incomplete remission. The patient was discharged from our hospital on day 61 (Fig. 3).

Discussion

We present here the first reported case of SAPHO complicated by IgA nephropathy with nephrotic syndrome. In 1987, Chamot et al. [1] coined the term SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis) syndrome in an effort to unify a group of clinical conditions previously thought of as separate entities [1–3]. SAPHO syndrome is a rare but possibly under-recognized, chronic, relapsing,

Fig. 3 Clinical course. PSL prednisolone, CRP C-reactive protein, SCr serum creatinine

inflammatory disorder of uncertain etiology that is characterized by distinct osteoarticular and cutaneous manifestations. Although the syndrome encompasses a broad spectrum of musculoskeletal and cutaneous manifestations, the great majority of reported cases typically manifest as sterile, noninfectious osteitis, and hyperostotic lesions, particularly involving the anterior chest wall (sternocostoclavicular hyperostosis), as well as palmoplantar pustulosis, severe acne (acne conglobata and acne fulminans) and/or hidradenitis suppurativa. Renal

Fig. 2 Renal histology and immunofluorescent examination. **a, b** Glomerulus showing mild mesangial proliferation and segmental endocapillary proliferation. Deposition of IgA (**c**) and C3 (**d**) in the mesangial area and along the capillary wall. **a** $\times 100$, **b–d** $\times 200$

manifestations are very rare, however. Although we're aware of two reports of SAPHO syndrome accompanied by renal injury—i.e., renal amyloidosis and crescentic glomerulonephritis [4]—we know of no cases accompanied by nephrotic syndrome.

The etiology of SAPHO syndrome remains unknown, but hereditary, bacterial, and immunological causes have been proposed. Infectious causes have long been suspected, though reports are conflicting. Some reports have implicated *Propionibacterium acnes*, which is a slow-growing anaerobic microorganism, usually found in acne lesions and considered to be a normal inhabitant of the skin [3, 5–10]. It has been hypothesized, for example, that in individuals with SAPHO syndrome sustained low-grade infection with *P. acnes*, which persist in osteitis lesions in a form incompatible with culturing, triggers a nonspecific activation/dysfunction of innate and T cell-mediated immune responses [7]. Another hypothesis is that immune complexes, including both fragments from microorganisms and immunoglobulins, deposited in a bone or joint produce sterile inflammation with inflammatory cytokine release and neutrophil activation [11].

IgA nephropathy (IgAN) is now recognized to be the most common form of primary glomerulonephritis occurring in developed countries, and it remains an important cause of nephrotic syndrome and end-stage renal disease [12, 13]. An important element in the pathogenesis of IgAN is the formation of IgA1 immune complexes. These antibodies often show reactivity against antigens from extrinsic microorganisms that represent subsequent hits, and they can arise following recurrent mucosal infections. Emerging evidence also indicates that B cells arising in response to mucosal infections, particularly tonsillitis, may produce the nephritogenic IgA1 molecule [14]. Tonsillar infection is also known to be involved with other diseases, including palmoplantar pustulosis, sternocostoclavicular hyperostosis, psoriasis vulgaris, nodular erythema, and rheumatoid arthritis [15], but overlap of these diseases with IgAN is rare. A search of the literature using the PubMed system turned up only six reported cases of IgAN complicated with skin or bone disease, excluding the present case (Table 2) [16–20]. As pointed out by the authors of those studies, palmoplantar pustulosis and sternocostoclavicular hyperostosis, as well as IgAN, are associated with tonsillar infections, and tonsillectomies are an effective treatment of those diseases [21–24]. That suggests activation/dysfunction of the immune response to tonsillar infection may be an important etiology for those ailments.

In our case, the relapse of SAPHO syndrome occurred following a tonsillar infection and led to the onset of nephrotic syndrome. Renal biopsy revealed IgAN to be the etiology of the nephrotic syndrome in this case. Moreover, with oral prednisolone therapy alone, the nephrotic

Table 2 Reported cases of IgAN complicated with skin and bone diseases

References	Age and sex	Kidney	Skin	Bone
Krothapalli et al. [16]	54 M	IgAN	PV	AS
Dan et al. [17]	36 M	IgAN	PV	PA
Numata et al. [18]	45 F	IgAN	PPP	SCCH
Imai et al. [19]	49 F	IgAN	PV	SCCH
Imai et al. [19]	58 F	IgAN	PV	SCCH
Noda et al. [20]	53 M	IgAN	PPP	SCCH

IgAN IgA nephropathy, *PV* psoriasis vulgaris, *PPP* palmoplantar pustulosis, *AS* ankylosing spondylitis, *PA* psoriatic arthritis, *SCCH* sternocostoclavicular hyperostosis

syndrome was relieved in parallel with reduction in the activity of the SAPHO. We therefore suggest that in this case tonsillar infection likely triggered the activation of an immune disorder that was pathogenic for both SAPHO syndrome and IgAN, leading to the recurrence of SAPHO and the development of nephrotic syndrome. Recently, several case reports have shown that tonsillectomy has resulted in improvement of SAPHO as well as IgAN [25–28]. Therefore, we offered him tonsillectomy to be a benefit surgical treatment, but he hardly rejected this offer.

In summary, this is the first known case of SAPHO syndrome accompanied by IgAN and concurrent nephrotic syndrome. This case is interesting when considering the pathogenesis of SAPHO syndrome and IgAN, which may share some common immune abnormalities.

Conflict of interest The authors declare that no conflict of interest exists.

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