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CASE REPORT

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Sjögren syndrome associated with multiple myeloma of the IgA κ-type

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Abstract We report a case of a 62-year-old female patient with Sjögren syndrome (SS) who developed multiple myeloma (MM) of the IgA κ-type. In 1986, the patient was admitted to our hospital with a facial rash, keratoconjunctivitis sicca, and xerostomia. She was diagnosed as having discoid lupus erythematosus (DLE) and SS. She was treated with bromhexine hydrochloride for SS and with topical fluorinated steroid for DLE. In 1992, she developed compression fractures of the lumbar vertebrae and was readmitted to our hospital. DLE was not recognized. Laboratory findings revealed IgA 2046 mg/dl, IgG 529 mg/dl, and IgM 21 mg/dl. Anti-SS-A antibody was 1:32 and anti-SS-B antibody was 1:2. M protein of IgA κ was demonstrated by immunoelectrophoresis. Aspiration biopsy of the bone marrow revealed 20.2% plasma cells. A bone scintigram demonstrated many hot spots at the cervical and lumbar vertebrae. She was diagnosed as having SS and MM of the IgA κ-type. After chemotherapy for MM, the percentage of plasma cells in the bone marrow and the concentration of serum IgA decreased to 6.2% and 532 mg/dl, respectively. SS is frequently associated with benign monoclonal gammopathy or lymphoproliferative disorders, especially Waldenström's macroglobulinemia or malignant lymphoma. Although benign monoclonal gammopathy has frequently been observed in patients with SS, SS associated with MM is extremely rare.

Key words Sjögren syndrome · Multiple myeloma · Lymphoma · Gammopathy macroglobulinemia

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Introduction

Sjögren syndrome (SS) is an autoimmune disease characterized by diminished lacrimal and salivary gland secretion resulting in keratoconjunctivitis sicca and xerostomia.[1] In the past few decades, an increasing incidence of benign monoclonal gammopathy, malignant lymphoma (especially B cell lymphoma), and Waldenström's macroglobulinemia has been reported in patients with SS.[2,3] Although benign monoclonal gammopathy is frequently associated with SS, multiple myeloma (MM) in SS patients has rarely been reported.[4,5] We describe a case of SS associated with MM of the IgA κ-type.

Case report

A 62-year-old woman was referred to our hospital in 1986 for a facial rash and dryness of the mouth and eyes. She did not have a previous history of any known diseases. A lupus band test for facial eruption was positive. A Schirmer-I test revealed right 4 mm/5 min and left 8 mm/5 min. A Rose-bengal staining test was bilaterally positive. The amount of saliva produced by stimulating the salivary glands with chewing gum was 3.0 ml/10 min. A lip biopsy revealed atrophy of the small salivary glands with infiltration of lymphocytes of greater than 50 cells (focus score 3). Infiltration of plasma cells around the salivary glands was not found. As a result of these examinations, she was diagnosed as having keratoconjunctivitis sicca and xerostomia. The serum IgA concentration was elevated to 969 mg/dl (normal range 90–400 mg/dl). M protein due to the monoclonal IgA κ chain was recognized by immunoelectrophoresis. The patient was diagnosed as having discoid lupus erythematosus (DLE) and SS. She was treated with topical fluorinated steroid for DLE and bromhexine hydrochloride (12 mg/day) for SS. Although she was suspected to have MM of IgA type since her concentrations of IgG 843 mg/dl (normal range 800–1800 mg/dl) and IgM 54 mg/dl (normal range 60–250 mg/dl)

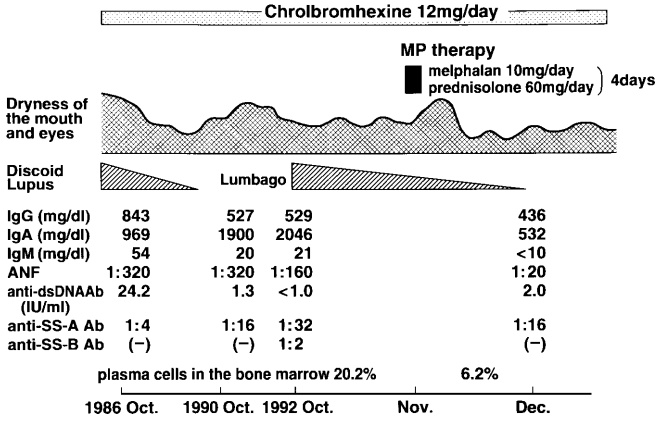

Fig. 1. Clinical course: summary of clinical symptoms and signs, treatment, and laboratory findings

Table 1. Laboratory data (October 2, 1992)

WBC	6200/μl	CRP	<0.3 mg/dl
Band + Seg	66.0%	ANA	1:320
Lymph	26.4%	(homogeneous, speckled)	
Mono	5.3%	Anti-DNA Ab	<1.0 IU/ml
Eosino	1.4%	Anti-SS-A Ab	1:32
Baso	0.9%	Anti-SS-B Ab	1:2
RBC	318 × 10^4/μl	Microsome test	<1:10^2
Hb	10.2 g/dl	Thyroid test	<1:10^2
Ht	31.3%	RAPA	<1:320
Plt	20.1 × 10^4/μl	CH50	37.3 U/ml
Ret	14‰	β-2-microglobulin	1.8 mg/dl
ESR	63 mm/h	IgG	529 mg/dl
		IgA	2046 mg/dl
TP	7.7 g/dl	IgM	21 mg/dl
Alb	4.2 g/dl		
GOT	25 IU/l	Urinalysis	
GPT	55 IU/l	Sugar	Negative
LDH	355 IU/l	Protein	Negative
γ-GTP	34 U/l	Sediment	Negative
ALP	263 IU/l	BJP in urine	Negative
LAP	195 GRU		
T-Bil	0.44 mg/dl	Schirmer test	Right 4 mm
D-Bil	0.10 mg/dl		Left 8 mm
CPK	93 IU/dl	Rose-bengal test	Positive
Fe	81 μl/dl	Gum test	3.0 ml
TIBC	300 μl/dl		

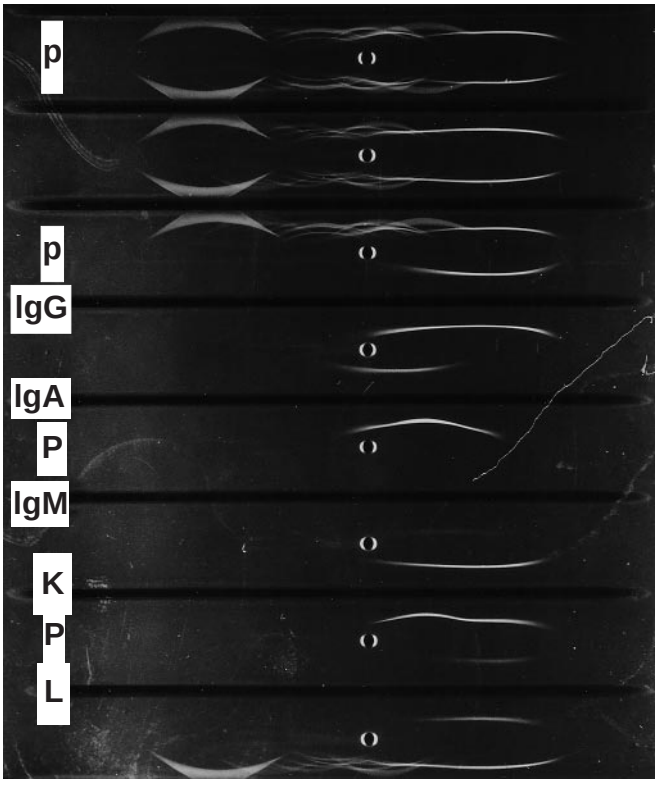

Fig. 2. The elevated levels of serum IgA and κ chain determined by immunoelectrophoresis. *P*, patient's serum; *K*, anti-κ serum; *L*, anti-λ serum

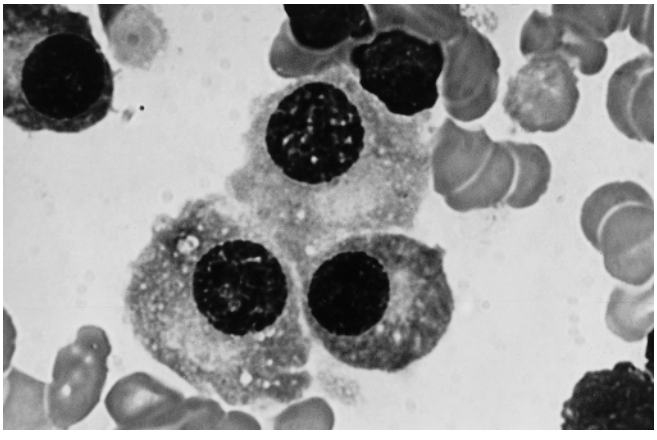

Fig. 3. Plasma cells detected by aspiration biopsy at the sternum

were low, she refused further examination, which prevented us from confirming the diagnosis (Fig. 1).

On October 2, 1992, the patient was admitted to our hospital with severe low back pain. Her body weight had decreased by 18 kg within a 1-year period. Physical examination revealed a body weight of 40.0 kg, height 152.5 cm, and body temperature 36.6°C. These was no discoid rash on her face. The low back pain was localized to the L3–L5 vertebral area. Laboratory examination revealed WBC 6200/μl, RBC 318 × 10^4/μl, Hb 10.2 g/dl, platelet 20.1 × 10^4/μl, IgG 529 mg/dl, IgA 2046 mg/dl, and IgM 21 mg/dl (Table 1). Monoclonal IgA gammopathy and M protein of IgA κ was again recognized by immunoelectrophoresis (Fig. 2). Antinuclear factor was 1:320 (homogeneous and speckled pattern) and anti-dsDNA antibody was negative. Anti-SS-A and anti-SS-B antibodies, which were determined by the double immunodiffusion method, were 1:32 and 1:2, respectively. Rheumatoid factor was 1:320. Bence–Jones protein was not detected in her urine. There were 20.2% plasma cells in a slightly hypoplastic marrow as detected by aspiration biopsy of the sternum (Fig. 3). No abnormal myeloblasts were found. Many hot spots were detected in the cervical and lumbar vertebral regions by technetium 99m bone scan and gallium 67 scintigram (Fig. 4). Accumulation of gallium 67 in the lymph nodes was not found. Based on these findings, we determined that our patient had

MM of the IgA κ-type associated with SS. She was treated with 10 mg/day melpharan and 60 mg/day prednisolone for 4 days. After treatment, the percentage of plasma cells in the bone marrow decreased to 6.2%, the concentration of IgA decreased to 532 mg/dl, and serum M protein was not found. The lumbar pain disappeared and she was discharged on December 13, 1992 (see Fig. 1).

Discussion

SS is usually associated with polyclonal B cell activation, which is expressed by hypergammaglobulinemia and the production of organ- and/or nonorgan-specific autoantibodies.[1] Furthermore, an increased risk of developing a B-cell neoplasm is known to be a unique feature of SS. In fact, the risk of developing non-Hodgkin's lymphoma, mainly B cell lymphoma, was found to be 43.8-fold higher than in controls.[2,3] The high incidence of benign monoclonal gammopathy in the serum or urine has also been reported in patients with SS.[4,6] In Caucasians, IgM or a free light chain, especially λ-type, is the most predominant monoclonal protein found in patients with SS. In contrast, over 50% of the monoclonal proteins are members of the IgA or IgG class in Japanese patients with SS.[7]

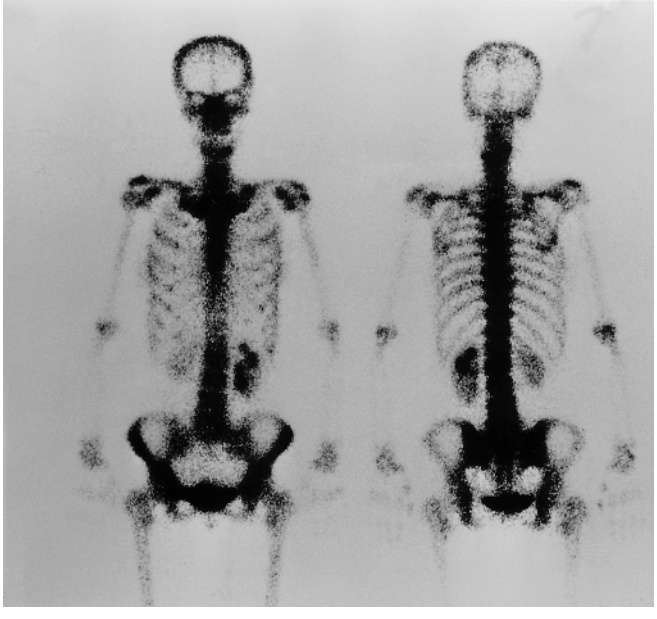

Fig. 4. Image of the technetium 99m bone scan. Many hot spots were seen at the cervical and lumber vertebrae

Lymphoproliferative malignancies occasionally arise in patients with a long history of benign monoclonal gammopathy. Keyle[8] reported that among 241 patients with benign monoclonal gammopathy who had been followed for more than 10 years at the Mayo Clinic, 46 (19.1%) developed MM, Waldenström's macroglobulinemia, primary amyloidosis, or related diseases. Thirty-two (70%) of the 46 patients had MM. Thus, MM is the most prevalent disease in patients with malignant lymphoproliferative disorders which arise from benign monoclonal gammopathy. However, there were only four English reports describing patients with SS who developed MM[5,9–11] (Table 2). There were also a few SS cases associated with plasmacytoma.[12] Therefore, it can be seen that MM is extremely rare among patients with SS.[5]

In our case, M protein due to monoclonal IgA κ chain and the suppression of both serum IgG and IgM levels suggested that our patient had MM. It is of interest that the titers of anti-SS-A and anti-SS-B antibodies gradually increased during the clinical course of this patient at the same time as the increase in IgA level and the decrease in IgG and IgM levels were found (see Fig. 1). Although the association of MM with SS is rare, we suspected that unknown immunological mechanisms especially related to our SS patient induced MM in this case.

The patient initially had a facial rash which was histopathologically diagnosed as DLE. DLE is rarely associated with SS. Only one case has previously been reported,[13] and anti-SS-A antibody has been determined at low frequency and with low titer in DLE patients.[14] Since this patient's facial rash disappeared only after the topical fluorinated steroid treatment, we do not know the clinical implications of DLE in this case.

It is not known why patients with SS rarely develop MM. It is possible that the Th 2-type of T lymphocytes induce the development of a plasmacytoma, or that the CD40L on T cells induces class-switching from IgM to IgG or A.[15,16] Hilbelt et al.[17] found that an oncogene-containing retrovirus induced the development of immunoglobulin-secreting plasmacytomas in BALB/c mice, while in nude mice, the retrovirus yielded non-immunoglobulin-secreting B-cell lymphomas. The reconstitution of T cells in the nude mice prior to tumor induction resulted in a shift from B-cell

Table 2. Sjogren syndrome associated with multiple myeloma

Case	Age	Sex	Type	Concentration of immunoglobulin	Associated disease	Reference
1	71	Female	λ chain	ND	IP	8
2	49	Female	IgG λ	IgG 3.39 g/dl	None	5
3	55	Female	BJP λ	ND	PBC	9
4	65	Female	IgG	IgG 3.8 g/dl	None	10
5	62	Female	IgA κ	IgA 2.05 g/dl	DLE	Present case

ND, not described; DLE, discoid lupus erythematosus; PBC, primary billiary cirrhosis; IP, interstitial pneumonia

lymphomas to immunoglobulin-secreting plasmacytomas. In patients with SS, decreased levels of peripheral blood T cells in response to activation signals or accelerated apoptosis of circulating T cells have been reported.[18–20] Therefore, the impairment or deviation of T cell function in SS may explain the evidence that B-cell lymphoma, but not MM, is more frequently associated with SS.

The association of MM with rheumatoid arthritis (RA) is common, whereas that with other rheumatic diseases such as SS or SLE is extremely rare.[5] Further studies into this aspect of immunology and oncology should be carried out to try to explain the reason for the rarity of MM in patients with SS.

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