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CASE REPORT

Simultaneous Complication of Multiple Myeloma with Sjögren Syndrome

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SUMMARY We report a 72-year-old female case of IgG-kappa type multiple myeloma (MM) simultaneously complicated with Sjögren syndrome (SS). She also presented marked hyperamylasemia of salivary-type isozyme. Although she had received sequential chemotherapy completed with high-dose therapy with autologous hematopoietic stem cell transplantation, she died of relapse fifteen months after the initial diagnosis. Various autoantibodies indicated that her sicca symptoms were due to true SS and not caused by MM cell infiltration to exocrine glands. MM cells appeared to produce amylase that fluctuated correspondingly to the disease status of MM. To our knowledge, this is the first English report of simultaneous complication of SS and MM referring to hyperamylasemia. Accumulation of this rare clinical manifestation is important to elucidate the pathogenesis of MM under condition of immunological disorder caused by SS.

Sjögren syndrome (SS) is an autoimmune disease characterized by chronic inflammation of exocrine glands, causing xerostomia and keratoconjunctivitis sicca. Lymphocytes and plasma cells are seen to infiltrate to salivary and lacrymal glands histologically. Although the development of B cell malignancies, *i.e.* malignant lymphoma, is relatively frequent in patients with SS,[1] complication of multiple myeloma (MM) is very rare.[2-9] Among these cases, simultaneous presentation of SS and MM has seldom been documented in English literatures. Only one case with primary biliary cirrhosis who concurrently presented SS and MM was reported.[5]

Patients with SS often show salivary-type hyperamylasemia usually considered to represent the glandular destruction. On the other hand, MM also occasionally presents hyperamylasemia,[10-12] whose isozyme reported to date is salivary-type with no exceptions. Immunostaining and cell culture method confirmed that MM cells produce and secrete amylase.[10,11] We report a case with simultaneous SS and MM incidentally diagnosed with hyperamylasemia, whose amylase value correlated with the disease status of MM.

CASE REPORT

A 72-year-old woman was introduced to our department to examine hyperamylasemia detected by routine medical check-up. She had experienced lumbago and xerostomia for two months. Physical examination showed no abnormality. Laboratory data

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demonstrated normocytic anemia, elevation of serum and urine amylase and hyperproteinemia (Table 1). Greater part of serum amylase was salivary-type isozyme. Neither of abdominal ultrasonography and computed tomography revealed significant pancreatic abnormality. Ophthalmological and otolaryngological examinations defined decrease of lacrymal and salivary secretion. Unfortunately, we could not obtain her consent for biopsy of these glands. SS was diagnosed from above findings and positivity of ss-A antibody, anti-DNA antibody and rheumatoid factor.

Hyperproteinemia was solely caused by increased IgG. Immunoelectrophoresis of her serum and urine detected monoclonal kappa-type IgG and kappa-type Bence-Jones protein, respectively. Atypical plasma cells that were positive for CD38 and CD56 occupied 37.2% of bone marrow nucleated cells. Multiple punched-out lesions of her cranial bone and compression fracture of her lumbar spines were depicted on X-rays examinations, while the latter appeared to cause her lumbago. Stage III MM was diagnosed.

She received two courses of induction chemotherapy consisting of intravenous vincristine, doxorubicine and dexamethasone for 4 days. Her lumbago and sicca symptoms were gradually relieved. Peripheral blood stem cells mobilized by high-dose cyclophosphamide were harvested. After additional two courses of therapy similar to the induction, stem cells were infused to support hematopoiesis after myeloablative dose of melphalan. After

Table 1 Laboratory data on admission of the patient

Complete blood cell count		**Blood chemistry**	
WBC	7,540 /mm^3	**T-protein**	11.4 g/dl
RBC	281 x 10^4/mm^3	**AST**	24 IU/l
Hemoglobin	9.0 g/dl	**ALT**	16 IU/l
Hematocrit	28.2%	**LDH**	200 IU/l
Platelets	2.6 x 10^5/mm^3	**ALP**	254 IU/l
		LAP	38 IU/l
		γ-GTP	15 IU/l
		T-bilirubin	0.3 mg/dl
Amylase		**BUN**	15.9 mg/dl
Serum	16,440 IU/l	**Cr**	0.6 mg/dl
Urine	56,620 IU/l	**Na**	131 mEq/l
s-type	98.4%	**K**	3.8 mEq/l
p-type	1.6%	**Cl**	104 mEq/l
		β2-MG	3.5 mg/l
Serology		**Bone marrow**	
CRP	0.15 mg/dl	**Plasma cells**	37.2%
IgA	40 mg/dl	**Surface markers**	CD38, CD56
IgG	7,011 mg/dl	**Karyotype**	46, XX
IgM	120 mg/dl		
kappa/lambda	9.5/0.5		
BJP	+		
ANA	< x40		
Anti-DNA	10.3 IU/ml		
Anti-ss-A	92.9 U/ml		
Anti-ss-B	5.3 U/ml		
RF	15 U/ml		

these sequential therapies, IgG and amylase values normalized (Fig. 1). Bone marrow plasma cells decreased to 10% of nucleated cells, considered as a partial response. Although she was uneventful for following 8 months, she was transferred to our hospital because of sudden fever elevation of 39°C. Rapidly progressive anemia (hemoglobin, 3.6 g/dl), thrombocytopenia (0.9 x 10^4/mm^3) and marked elevation of serum amylase (151,000 IU/l) and IgG (10,503 mg/dl) were seen. Sicca symptoms were also prominent. Plasma cells were detected at 17% of peripheral leukocytes. Despite of dexamethasone under the diagnosis of relapse, she died on the 10th hospital day, 15 months after the initial diagnosis.

DISCUSSION

Complication of SS and MM includes two groups: one is true complication[2,4,5,8,9] and the other MM cell infiltration to salivary or lachrymal glands, resulting in SS features.[3,6,7] Although pathological evidence was not obtained in our patient, various autoantibodies characteristic to SS indicate true complication. In most cases of true complication, MM has reported to occur after years of history of SS.[2,4,8,9] In our patient, it is possible that SS had existed latently till MM complicated. However, it is more likely that MM developed concurrently with SS since she had been asymptomatic till lumbago and xerostomia appeared. Wang *et al.*[13] additionally identified autoimmune activity of M-proteins produced by plasma cell neoplasms, indicating that plasma cell tumor is also potentially causative of autoimmune disease. It is thus alternatively possible that latent MM has caused SS, when both became symptomatic. Besides the initial presentation, her sicca symptoms improved with remission of MM and exacerbated at relapse. The relationship between disease activity of SS and MM should be investigated. Hematologists who note sicca symptoms in MM patients should examine specific autoantibodies to reveal actual frequency of this complication.

Various autoimmune diseases are known to complicate lymphoid malignancies that mainly consist of B-cell malignant lymphoma.[14] Autoimmune reaction that chronically stimulates B lymphocytes is considered as the crucial mechanism of this lymphomagenesis. Since plasma cells in SS patients are also exposed to similar immunological stimulation, monoclonal proliferation might emerge among these cells. The fact that SS frequently complicates monoclonal gammopathy of undetermined significance (MGUS),[15] a kind of plasma cell dyscrasia, appears

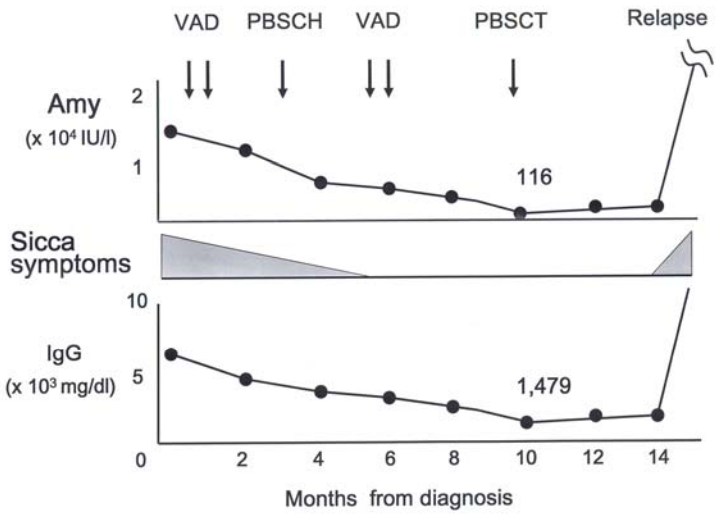

Fig. 1 Clinical course of the patient. IgG and amylase level decreased to normal range after sequential chemotherapy and re-elevated at relapse. VAD: Chemotherapy with vincristine, adriamycin and dexamethasone. PBSCH: Harvest of peripheral blood stem cell (PBSC) mobilized by high-dose cyclophosphamide. PBSCT: PBSC transplantation after myeloablative therapy with melphalan.

to be consistent with this hypothesis. However, it is of great interest that MGUS occurred in SS seldom progresses into MM. The frequency of MM from MGUS is much lower in SS patients than in non-SS population.[9] How the progression of MGUS to MM is suppressed in SS patients should be examined to help to elucidate the pathogenesis of MM.

As our patient showed extremely high amylase concentration, production of salivary-type amylase by MM cells has been demonstrated.[10-12] After induction chemotherapy, her serum IgG and amylase decreased and markedly elevated at the relapse. This finding suggests that MM cells directly produced salivary-type amylase and that salivary gland destruction by SS activity is not mainly responsible for her hyperamylasemia. Although precise mechanism of hyperamylasemia in MM is not well understood, amylase gene, located at chromosome 1p21, was activated by chromosomal translocations in a part of patients.[16] MM cells of our patient, however, showed no 1p21 rearrangement. While increase of amylase mRNA without alteration of genomic structures in plasmacytoma cell lines was also detected,[17] various mechanisms of amylase production by MM cells must exist. Hyperamylasemia has been preferentially seen in MM patients of women, non-IgM type and lambda light chain and recognized as a poor prognostic factor.[12] Our patient also demonstrated these factors except lambda chain and relapsed in a short interval after high-dose therapy. This is the first description of MM with hyperamylasemia simultaneously complicated with SS to our knowledge. Accumulation of the clinical data of this rare manifestation is important for further investigation of the significance of hyperamylasemia in MM, especially SS complication.

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