Bleeding Tendency Caused by the Deposit of Amyloid Substance in the Perivascular Region

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A 55-year-old woman, who had systemic amyloidosis associated with multiple myeloma, had sudden development of hematomas of her lip and upper eye lid. There was no evidence of deterioration of multiple myeloma, thrombocytopenia nor deficiency of coagulation factors. Biopsy specimen showed the deposit of amyloid substance in the dermis and perivascular region. The bleeding tendency in this patient with myeloma was likely due to the deposit of amyloid substance in the vascular wall; improvement was achieved with administration of hemostatic agents. (Internal Medicine 32: 879–881, 1993)

Key words: multiple myeloma, amyloidosis, hemostatic agent

Introduction

Amyloidosis is one of the common complications of multiple myeloma. Amyloid substance is classified into two types: amyloid L (AL) which mainly consists of light chains and amyloid A (AA) mainly consisting of protein A (1). Amyloidosis associated with multiple myeloma is mainly AL. The bleeding tendency in amyloidosis is usually due to a deficiency of factor X, intravascular coagulopathy, deposit of amyloid substance and so on (1, 2). We report here the bleeding tendency in a case of amyloidosis with multiple myeloma probably due to deposits of amyloid substance in the perivascular region; improvement was achieved with hemostatic agents.

Case Report

A 55-year-old house wife was admitted to our hospital because of hematomas on her lower lip and left upper eye lid on April 2, 1991. She had a past history of dysentery at age 7 years, an appendicitis at age 20 years and pulmonary tuberculosis at age 22 years. In July 1988, she found yellow papules on the back of her neck, and consulted her family physician. She received steroid ointment therapy, however there was no improvement. In November 1988, she noticed a bleeding tendency in her oral cavity and her fingers. She was admitted to the Department of Dermatology of our hospital in May 1989.

The skin biopsy revealed the presence of amyloidosis. Immunoelectrophoresis of urine showed an M component of

Bence Jones protein κ type. Myeloma cells occupied 31% of nucleated cells in the bone marrow. She was diagnosed as having multiple myeloma associated with amyloidosis and was discharged from the hospital on August 12, 1989, receiving periodical chemotherapy of vincristine and melphalan thereafter.

She showed a good response, and had been doing well until April 2, 1991, when hematomas suddenly emerged on her lower lip and upper eye lid with no apparent cause. She was admitted to our hospital on emergency. Physical findings on admission revealed that she had hematomas on her lip and eye lid, and she had yellow, glossy papules on her upper limb and trunk. There was no abnormal finding in her chest, abdomen nor nervous system. Slight leukocytopenia and anemia were observed, but no significant abnormal data were observed in prothrombin time (PT), activated partial thromboplastin time (APTT), α_2 -plasmin inhibitor (α_2 -PI), plasminogen activity, fibrin degradation product (FDP) and bleeding time (Table 1). After admission, we treated her bleeding tendency with carbazochrome sodium sulfate and tranexamic acid. There was no newly forming hematomas nor ecchymosis. The hematomas came off as clots after one week. In iliac bone marrow, the percentage of myeloma cells was 6.2% of nucleated cells, and the amount of M component determined by immunoelectrophoresis in her urine did not increase as compared with the previous data. As to her systemic amyloidosis, there was no evidence of cardiac amyloidosis by echogram nor thyroid dysfunction. Skin biopsy specimen showed deposit of amyloid in dermis (Fig. 1).

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Table 1. Laboratory Data on Admission (April 2, 1991)

Blood cell count		Biochemistry	
WBC	3.9×10 ³ /μl	Total protein	5.6 g/dl
band neutrophil	19%	Albumin	70.3%
segmented neutrophil	63%	α ₁ -globulin	3.6%
monocyte	4%	α ₂ -globulin	8.3%
lymphocyte	14%	β-globulin	8.5%
Hb	9.0 g/dl	γ-globulin	9.3%
Ht	26.1%	Total bilirubin	0.77 mg/dl
RBC	2.5×10 ⁶ /μl	γ-GTP	18 mU/ml
Platelet	9.4×10 ⁴ /μl	ALP	173 mU/ml
Coagulation		GOT	17 mU/ml
Prothrombin time	10.5 s	GPT	12 mU/ml
(control 12.1 s)		LDH	404 mU/ml
Activated partial thromboplastin time	39.1 s	CPK	68 mU/ml
(control 35.9 s)		Amylase	87 Somogyi
Fibrinogen	347mg/dl	BUN	18 mg/dl
Factor XIII activity	73%	Creatinine	0.7 mg/dl
Bleeding time	2 m in 30 s	Uric acid	5.0 mg/dl
FDP <10 μg/ml		Na	145 mEq/l
(D-dimer <200 ng/ml)		K	4.0 mEq/l
Plasminogen activity	80.7%	Cl	112 mEq/l
a ₂ -plasmin inhibitor activity	87.5%	Ca	9.2 mg/dl
		P	3.1 mg/dl
		CRP	0.117 mg/dl
Bone marrow		Immunoglobulin	
NCC	12.7×10 ⁴ /μl	IgG	734 mg/dl
Megakaryocyte	56/μl	IgA	42 mg/dl
Myeloid		IgM	29 mg/dl
Myeloblast	1.2%		
Promyelocyte	1.4%		
Myelocyte	18.8%		
Metamyelocyte	7.2%		
Band neutrophil	25.8%		
Segmented neutrophil	3.2%		
Eosinophil	2.4%		
Basophil	0.2%		
Monocyte	1.2%		
Plasma cell	6.2%		
Erythroid	18.8%		
Reticulum cell	1.4%

Fig. 1. The biopsy specimen of her skin. Arrows indicate the amyloid substance in the dermis (HE stain, ×200).

Fig. 2. The biopsy specimen of a polyp of the colon. Arrow indicates the vascular wall with amyloid substance (HE stain, ×200).

Colonoscopy revealed red mucosal lesions, compatible to colitis, and two polyps in the ascending colon. By histological examination, deposition of amyloid was detected in the perivascular region of the polyp with no malignant cells (Fig. 2). Since she did not have any further new bleeding event, she was discharged on May 5, 1991.

Discussion

Amyloidosis is one of the common complications of multiple myeloma. The diagnosis of amyloidosis depends on a histopathological finding of an appropriate specimen (1, 3). In some cases of amyloidosis with multiple myeloma, the amyloid substance has been deposited in the bone marrow (4), cardiac system (5, 6), or the intestinal wall (7). Although about 10% of the patients with multiple myeloma have amyloidosis (5), a more detailed study including biopsy of the tongue showed that 27% of the patients were complicated with amyloidosis (8). Initial symptoms and findings of amyloidosis with multiple myeloma are fatigue, body weight loss, pain, purpura, hepatomegaly and macroglossia (1). Colchicine and dimethyl sulfoxide are reported to be effective for amyloidosis (9, 10). In cases of amyloidosis, bleeding can occur from skin, oral cavity, gastrointestinal system and other organs (1, 2, 8). In multiple myeloma, the bleeding tendency is due to the deficiencies of factor VIII, IX, X and other vitamin K-dependent clotting factors, intravascular coagulopathy, or the deposit of amyloid substance which causes fragility of tissue (1, 2). And it has also been reported that an impairment in fibrinogen conversion to fibrin, and increased fibrinolytic activity are observed in cases of multiple myeloma (2). Clinically significant bleeding was described in approximately 40% of patients with amyloidosis (2). In one autopsy series, massive hemorrhage was determined to be the cause of death in 3% of patients with multiple myeloma (11). In the present case, however, the data of PT, APTT, FDP and bleeding time remained normal. Therefore the deficiency of the factors, intravascular coagulopathy, thrombocytopenia or

dysfunction of platelet were not likely responsible for this bleeding tendency. Further, there were no data suggestive of an increased fibrinolytic activity in the present case. The biopsy specimen from the polyp of the ascending colon showed a deposit of amyloid substance in perivascular region. Thus, the deposit to the vascular system might have caused the weakness of vascular walls, and subsequently the bleeding tendency. Therefore, in the case of bleeding tendency of amyloidosis or multiple myeloma, a deposit of amyloid substance in the vascular wall should be suspected, in addition to the defective coagulation factors.

As a therapy for the bleeding tendency of the present case, hemostatic agents were effective. Although an antifibrinolytic drug was thought not to be very effective because of the lack of data showing increased fibrinolytic activity, the two-drug combination therapy was effective. The effectiveness of these agents might also suggest that the bleeding tendency of the present case was due to the weakness of the vascular wall from the deposit of amyloid substance. These agents should be considered in cases of bleeding tendency which may be due to the deposit of amyloid substance.

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