IgA- λ /IgG- κ Biclonal Myeloma in which Two Clones Proliferated in Individual Sites

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Abstract

A 72-year-old man was admitted to our hospital because of lumbago and numbness of legs. Tumor invasion at the fourth lumbar vertebra was revealed. Immunohistochemistry using specific antibodies against each heavy and light chain of immunoglobulin revealed that the myeloma cells in bone marrow were all IgA- λ type whereas they were all positive for IgG- κ type in a tumor of the fourth lumbar vertebra. These data indicate that the patient had IgG- κ /IgA- λ biclonal myeloma. Different phenotypes of M-proteins and distinct proliferating sites for two clones suggest that they may have resulted from two independent transforming events.

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Key words: biclonal gammopathy, myeloma, biclonal

Introduction

Biclonal myeloma is known as a very rare type of myeloma and is characterized by the production of two distinct monoclonal proteins by two proliferating clones of myeloma cells (1–4). In most cases, two distinct myeloma globulins share the common light chain, suggesting that the transforming event may occur at the stage of class switch of immunoglobulin genes during the process for B cell maturation (5, 6). We report a case of biclonal myeloma in which the phenotypes of myeloma protein were completely unrelated.

Case Report

A 72-year-old male was admitted to the department of plastic surgery in our hospital because of lumbago and numbness of the legs on March 21, 1998. Lumbar roentgenogram findings showed an oppressive fracture of the fourth lumbar vertebra. Since abdominal computed tomography (CT) and magnetic resonance imaging (MRI) revealed tumor cell invasion

at this site, a biopsy was performed. Pathological findings suggested plasma cell infiltration. Then the patient was referred to our hematology division of internal medicine on April 10, 1998.

On physical examination, the patient's height was 154 cm, his body weight 52 kg. His blood pressure was 124/74 mmHg. He did not have macroglossia, superficial lymphadenopathy, hepatosplenomegaly, nor pitting edema on his legs. Knocking pain on the fourth lumbar vertebra, sensory disturbance and disappearance of tendon reflex on both legs were observed. No pathologic reflex was detected. He was not able to walk by himself at this time. The initial laboratory data are summarized in Table 1. Neither anemia nor renal dysfunction was detected. However, erythrocyte sedimentation rate, serum viscosity, and β_2 -microglobulin were increased. Serum-protein electrophoresis using nitrocellulose-acetate membrane showed asymmetric M-component on the γ -globulin fraction (Fig. 1A). Serum IgG and IgA levels were 3,010 mg/dl and 1,580 mg/dl, respectively, whereas IgM and IgD were under detectable levels. A bone-marrow aspirate from the iliac bone showed 27.0% plasma cells, most of which appeared abnormal (Fig. 2). These data indicated that the patient had a multiple myeloma.

Roentgenogram of the whole skeletal system showed no punched-out lesions. Bone scintigram using ^{99m}Tc -methylene diphosphonate revealed no hot spots except one at the fourth lumbar vertebra. Figure 3 shows the osteodestructive changes with tumor invasion at the fourth lumbar vertebra by abdominal CT and MRI. Cardioechogram, abdominal echogram, and funduscopy showed no particular findings. Immunoelectrophoretic analysis of the patient's serum using specific antibodies demonstrated the M-bows for each IgG and IgA (Fig. 1B). In addition, each arc detected by anti- κ antibody and anti- λ antibody, respectively, could be superimposed to IgG- and to IgA-derived M-bows. In addition, Bence-Jones κ -type protein was detected in the patient's concentrated urine (Fig. 1C). These data suggested that the patient had an IgG- κ /IgA- λ biclonal myeloma. To confirm this, we performed immunohistochemistry in a biopsy specimen of a lumbar tumor and a clot of bone-marrow aspirates. As shown in Fig. 4, the myeloma cells in a lumbar tumor were positive for anti-IgG and anti- κ antibodies, but negative for anti-IgA and anti- λ antibodies. In con-

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IgA-λ/IgG-κ Biclonal Myeloma

Table 1. Laboratory Data on Admisson

【Peripheral Blood】		【Biochemistry】		【Serological test】		【Bone Marrow Aspiration】	
White blood cell	4,700/μl	AST	20 U//	β ₂ -MG	2.32 mg//	NCC 42,000/μl	
Red blood cell	395×10 ⁴ /μl	ALT	21 U//	IgG	3,010 mg/dl	L/E 4.4	
Hemoglobin	12.4 g/dl	LDH	296 U//	IgA	1,580 mg/dl	myelogram	
Hematocrit	36.9%	ALP	158 U//	IgM	<29.8 mg/dl	blast	0.4%
Platelet	15.5×10 ⁴ /μl	γ-GTP	13 U//	IgD	<10.0 mg/dl	pro	0.8%
Hemogram		TTT	1.5 U	CRP	<0.3 mg/dl	myelo	8.0%
Neutro	46.1%	ZTT	39.9 U	serum electrophoresis		meta	9.6%
Eosino	4.7%	T. Chol	176 mg/dl	A/G	0.93	stab	10.4%
Baso	0.4%	TP	7.8 g/dl	Alb	48.3%	seg	25.2%
Mono	6.3%	Al	3.4 g/dl	α1	13.2%	baso	0.4%
Lymph	42.5%	T. Bil	0.42 mg/dl	α2	7.8%	mono	3.6%
Reticulo	11.3%	BUN	19.4 mg/dl	β	5.9%	lymph	12.4%
ESR	34 mm/h	UA	6.1 mg/dl	γ	34.8%	plasma	27.0%
【Coagulation Test】		Cr	0.71 mg/dl	M-protein	2.9 g/dl	erythroid	16.4%
PT-INR	0.96	Glu	92 mg/dl			chromosome 46, XY (18 cells)	
APTT	31.1 sec (control 30.1 sec)	TG	77 mg/dl				
fibrinogen	211 mg/dl	CPK	63 U//				
FDP	53.3 ng/ml	Fe	99 μg/dl	【Surface marker of bone marrow nuclear cells】			
blood viscosity	2.0	TIBC	256 μg/dl	(% of positive cells)			
【Urinalysis】		Ferritin	156.7 ng/ml	CD19	1.2%	CD40	67.4%
urine protein (-) sugar (-) blood (-)		Na	141 mEq/l	CD38	92.7%	CD44	81.5%
sedimentary urine normal		K	4.4 mEq/l	CD49d	94.3%	CD49e	2.7%
		Cl	108 mEq/l	CD54	27.3%	CD56	57.0%
		Ca	8.7 mEq/l	CD62L	1.8%	CD126	2.9%

Figure 1. IgG-κ and IgA-λ myeloma proteins detected by electrophoresis. A) Electrophoresis of serum protein showing M-component. B) Immunoelectrophoresis of serum showing M-bows detected by anti-IgG, anti-κ, anti-IgA, and anti-λ antibodies, respectively. C) Immunoelectrophoresis of urine. Bence-Jones κ-type protein was detected (×25 concentrated urine).

trast, the myeloma cells in bone marrow reacted with both anti-IgA and anti-Ig λ antibodies, but not with anti-IgG and anti-Ig κ antibodies. Southern blotting of the extracted DNA from the biopsy specimen of the lumbar tumor revealed rearrangements of JH and J κ genes (Fig. 5). However, no gene rearrangement was detected in the bone marrow specimen probably because of insufficient sample volume (Fig. 5).

After surgical laminectomy followed by spinal fusion at the fourth lumbar vertebra, the patient received two courses of VAD therapy which consisted of vincristine sulfate, doxorubicin hydrochloride, and dexamethasone (7). This led to the normalization of both serum IgG and IgA levels and improvement of osteodestruction. The patient has become able to walk by him-

self. A bone-marrow aspirate from the iliac bone showed 1.6% plasma cells. Thereafter, a combination of interferon- α plus monthly MP therapy (melpharan plus prednisolone) has been continued. A good clinical performance status has been maintained for over one year.

Discussion

Biclonal gammopathy is observed in 3 to 4% of paraproteinemia (1–4). Kyle et al reported that biclonal gammopathy is observed in 3.5% of 787 cases of monoclonal gammopathy of undetermined significance (MGUS) (1). In 57 cases of biclonal gammopathy, 9 cases (16%) were multiple myeloma (8). The frequency of combination of the two phenotypes has been reported to be 53% in IgG+IgA and 26% in IgG+IgM (1). However, they usually share the common light chain. In addition, great structural similarity or identity was reported when the amino acid sequences of light and heavy chain variable regions and light chain constant regions were compared. These lines of evidence suggest that the two clones originate from one common ancestor and that the “transformation event” may occur at the class switch of immunoglobulin genes during the process of B cell maturation (9, 10). In other cases, it has been reported that, double staining of immunoglobulin-producing cells has been observed when using anti-idiotypic antibodies. This suggests that a single population of cells may be producing two distinct M-components (5, 11). In the present case, not only heavy chains but also light chains were distinct between two clones such as IgG- κ and IgA- λ . In addition, they proliferated in different sites; bone marrow for the IgA- λ clone and the fourth lumbar vertebra for the IgG- κ clone. Furthermore,

Figure 2. Myeloma cells in bone marrow (May-Grünwald-Giemsa stain, $\times 1,000$).

Figure 3. Abdominal CT (left) and MRI (right) showing osteodestructive change and tumor invasion at the fourth lumbar vertebra.

L4 tumor

Bone marrow

Figure 4. Immunohistochemistry of the lumbar tumor and bone marrow. The myeloma cells in lumbar tumor were reactive to anti-IgG and anti- κ antibodies but negative for anti-IgA and anti- λ (L4 tumor, $\times 800$), whereas the cells in bone marrow were positive for anti-IgA and anti- λ antibodies but negative for anti-IgG and anti- κ antibodies (bone marrow, $\times 400$).

Figure 5. Southern blot analysis of DNA extracted from lumbar tumor and bone marrow. Restriction enzymes used for digestion: E+H; Eco RI + Hind III, B; Bam HI, H; Hind III, B+H; Bam HI+Hind III.

the serum levels for IgG and IgA respectively satisfied diagnostic criteria for multiple myeloma by Durie BGM & Salmon SE (IgG>2,000 mg/dl and IgA>1,000 mg/dl) and this patient was categorized as stage IIIa (12). This suggests that two clones of myeloma are unrelated and coincidentally evolved in this case. Some immunological or genetic background of the patient may lead to this kind of simultaneous transforming event in B cell lineage.

Median survival duration of biconal myeloma has been reported to be 25 months, which indicates a poor prognosis for this disease next compared to Bence-Jones and IgD type- myelomas (13). In the present case, the patient received VAD therapy (7) for reduction of total tumor mass followed by MP plus interferon as maintenance therapy. So far, the two clones seemed to respond equally to the treatment. However, it is still possible that the two clones will behave differently in response

to chemotherapy in this case.

Considering previous reports and our case together, biclonal myeloma appears to be categorized into at least two types: in one, the two clones originate from a common origin at class switch; in the other, the two clones evolve individually. Further careful clinical observation should clarify the disease entity of biclonal myelomas and indicate a strategy for the treatment of these patients.

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