

The Association between Multiple Myeloma and Ankylosing Spondylitis: A Report of Two Cases

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Multiple myeloma is a malignant disease of plasma cells, whereas ankylosing spondylitis is a chronic inflammatory disease of axial joints. The relationship between the two diseases is uncertain, but chronic inflammation could trigger multiple myeloma. The authors report the cases of two ankylosing spondylitis patients with a disease duration of more than 20 years, that subsequently developed IgA kappa and IgG lambda chain myeloma, respectively, and discuss the possible pathogenetic relationship between these diseases. (*Korean J Hematol* 2009;44:182-187.)

Key Words: Multiple myeloma, Monoclonal gammopathy of undetermined significance, Ankylosing spondylitis, Inflammation, Tumor

INTRODUCTION

Multiple myeloma (MM) is a B-cell malignancy that is clinically characterized by hypercalcemia, renal insufficiency, anemia, or osteolytic bone lesions.¹⁾ MM remains incurable using conventional treatments, and has a median survival of 3~5 years, although survival ranges from only a few months to more than 10 years.²⁾ The monoclonal proliferation of plasma cells in bone marrow is the hallmark of MM. Like other chronic hematologic malignancies, the vast majority of myeloma plasma cells appear mature and quiescent. Furthermore, myeloma cells are strongly dependent on their microenvironment, which produces cell communication signals, particularly myeloma growth factors. The typical clinically

asymptomatic precursor condition, monoclonal gammopathy of undetermined significance (MGUS), is believed to be the first pathogenetic step in the development of most, if not all cases of MM. However, the specific trigger that initiates progression from MGUS to MM has not been identified.³⁾

The causes of MM/MGUS are largely unknown; risk factors include various occupational and environmental exposures, one which is exposure to penetrating radiation.⁴⁾ Recently it was shown that broad categories of autoimmune, infectious, and inflammatory disorders are associated with significantly elevated risks of MM or MGUS.⁵⁾ Some of these disorders may be potential triggers of MM or MGUS development, while others may represent underlying conditions due to undetected MM or late stage MGUS. Inflammatory processes,

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in which the cytokine, chemokine, and cell adhesion molecule families participate, can lead to cancer development or tumor metastasis.⁶⁾ Ankylosing spondylitis (AS) is a form of chronic inflammation of the spine and the sacroiliac joints and causes pain and stiffness. Furthermore, over time, chronic spinal inflammation can lead to complete fusion of vertebrae, a process referred to as ankylosis, which leads to a loss of spinal mobility. The precise origin or site of inflammatory activity in AS remains obscure, inflammation obviously occurs along the axial skeleton and in peripheral joints and eye tissues, but this falls short explaining marked elevations in serum IgA, a class of immunoglobulin, within mucosal associated lymphoid tissues of the gastrointestinal tract. Moreover, elevated IgA levels are associated with active AS.⁷⁾ Furthermore, available evidence suggests that AS is an important etiological factor in MM.^{8,9)} Here, we report the cases of two patients with AS that developed IgA kappa and IgG lambda chain plasma

cell disorder, respectively, and discuss the possible pathogenetic relationship between these diseases.

CASE REPORT

1. Case 1

A 47-yr-old man presented with a 2-week history of painful swelling of his left mid clavicle. He had been suffered from back pain for 20 years, and 5 years previously, he had been diagnosed with advanced AS. He had been taking celecoxib (200 mg/day) and sulfasalazine (1 g/day) for symptomatic relief, but had not been prescribed TNF- α inhibitors. There was no evidence of a history of gastrointestinal infection, peripheral arthritis, psoriasis, or other infectious diseases.

On physical examination, his left mid-clavicle was tender and swollen and limitations of lumbar and cervical spine movements were marked. An incisional biopsy on his left mid-clavicle was performed, but pathology revealed only bone necrosis with small numbers of marrow cells. Laboratory

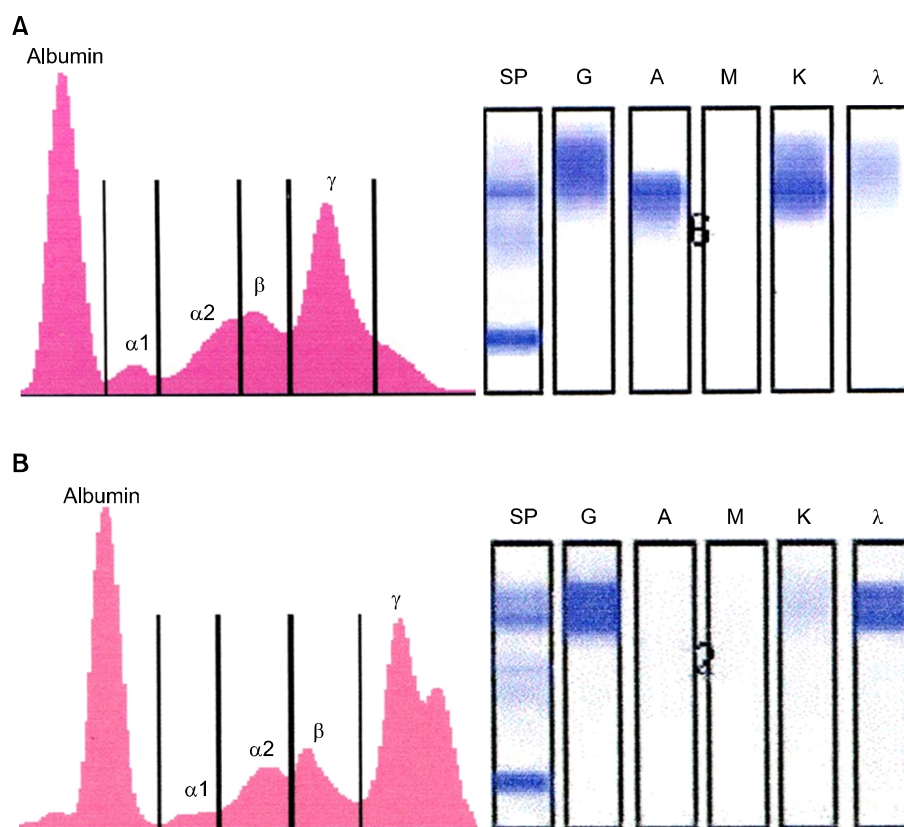


Fig. 1. (A) Serum protein electrophoresis (Left) showed a sharp peak in the gamma globulin region. The gamma globulin region composed 37.5% of total (8.92 g/dL). Immunofixation electrophoresis (IFE, Right) showed a monoclonal IgA, κ band. (B) Serum protein electrophoresis (Left) showed a prominent M-peak (39.9% of total protein, 8.78 g/dL), whereas immunofixation electrophoresis (IFE, Right) showed a monoclonal IgG, λ band.

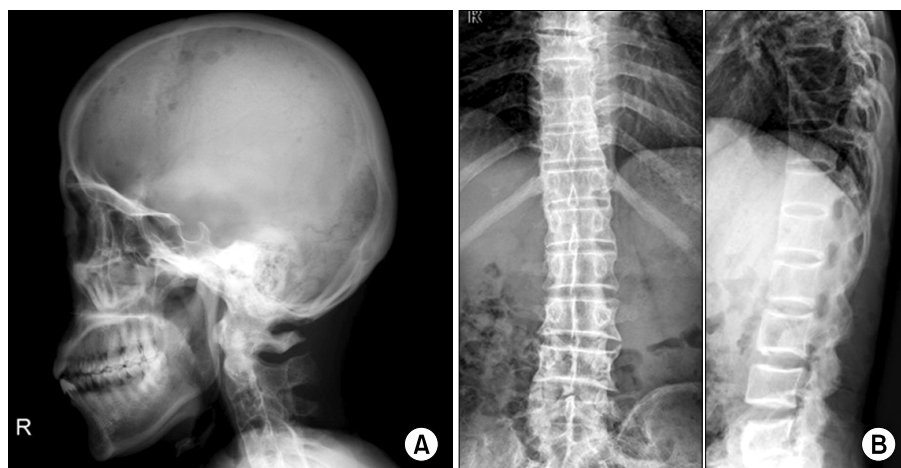


Fig. 2. (A) Skull radiograph showing multiple variably sized punched-out lesions in the fronto-parietal area. (B) D-L spine AP LAT radiograph showing extensive ankylosis and syndesmophytes in the thoracic and upper lumbar spine.

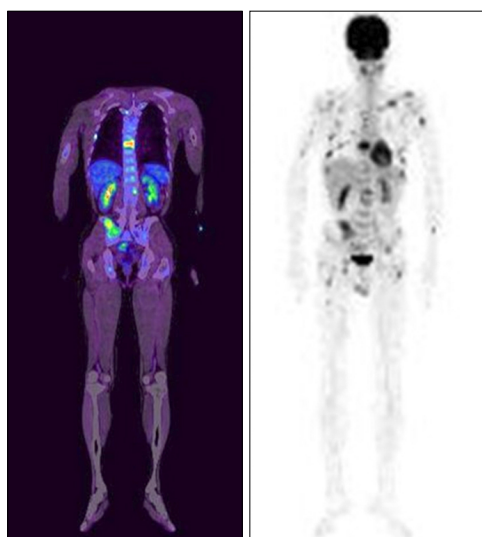


Fig. 3. PET scan showing multifocal increased uptakes in vertebrae, pelvic bones, clavicles, rib cages, and both humeri and femurs. No changes in uptake were observed after dexamethasone treatment.

examination revealed; hemoglobin 11.4 g/dL, white blood cell count $6.74 \times 10^9/L$, platelet count $276 \times 10^9/L$, ESR 120 mm/h, CRP 16.88 mg/L, serum total protein 8.92 g/dL, and serum albumin 3.97 g/dL. Electrolytes and renal function were normal. He was HLA-B27 positive, and his IgA was elevated at 1,173.4 mg/dL (70~400). However, IgG and IgM were normal at 1,083.5 mg/dL (700~1,600) and 44.7 mg/dL (40~230), respectively. Serum protein electrophoresis and immunofixation revealed a monoclonal IgA kappa band (Fig. 1A). Bence-Jones proteins in urine

were negative, and β_2 -microglobulin was 1.92 mg/L (1.0~2.4). A bone marrow examination revealed 3.4% plasma cells. Radiographs showed multiple variably sized nodular osteolytic lesions in the skull (Fig. 2A) and extensive ankylosis and syndesmophytes in the whole cervical, thoracic and upper lumbar spine, so called 'Bamboo spine' (Fig. 2B). A PET scan showed multifocal increased uptakes in vertebrae, pelvic bones, clavicles, rib cages, and in both humeri and femurs, suggesting tumor metastases (Fig. 3). A diagnosis of IgA-kappa multiple myeloma was made.

He was treated with in total 6 cycles of high dose dexamethasone (40 mg/day) for 4 days, which were administered every other week. However, although this resulted in a gradual decrease in monoclonal IgA protein, the multiple bone lesions were unaffected. He is currently being treated with bortezomib.

2. Case 2

A 58-yr-old man visited our clinic for a further workup of a reverse albumin/globulin (A/G) ratio protein abnormality. From his early 20's, he had presented with stiffness of the cervical and lumbar spine. He had been diagnosed as having AS some 25 years previously, but he was not being routinely followed or taking specific medication. There was no past history of gastrointestinal disturbance, pneumonia, or other infectious diseases.

On examination, he had typical features of AS with marked stiffness of the lumbar spine. Laboratory examination revealed hemoglobin 14.5 g/dL, white blood cell count $6.26 \times 10^9/L$, platelet count $265 \times 10^9/L$, ESR 10 mm/h, CRP 0.62 mg/L, serum total protein 8.78 g/dL, and albumin 3.58 g/dL with a reverse A/G ratio (0.69). Serum calcium was 9.1 mg/dL and creatinine 0.94 mg/dL. His HLA typing was not checked. IgG was elevated at 2,881.1 mg/dL (700~1,600). However, IgA and IgM were lower than normal at 27.1 mg/dL (70~400) and 46.9 mg/dL (40~230). Serum protein electrophoresis and immunofixation revealed a monoclonal IgG lambda band (Fig. 1B). β_2 -Microglobulin was 0.13 μ g/ml (1.0~2.4). A bone marrow examination revealed 9.3% plasma cells. Radiographs showed no

osteolytic lesion in his skull, but extensive ankylosis and syndesmophytes in the thoracic and lumbar spine with sacro-iliac joint fusion. He was diagnosed as having MGUS with underlying AS. He is currently only being followed-up.

DISCUSSION

We present two cases of AS that developed symptomatic IgA-kappa type MM and IgG-lambda type MGUS, respectively. These two patients had more than a 20-year history of symptomatic AS, and both were found to show a clear association between AS and MM, as has been previously reported.^{8,9)} Although the specific mechanism for this apparent association remains obscure, early age at AS diagnosis and a protracted latency from

Table 1. A summary of data from previous reports concerning the association between ankylosing spondylitis and plasma cell disorders

Reference	Year	Sex	Age at onset of Ankylosing spondylitis	Age at diagnosis of Monoclonal gammopathy	HLA-B27	Diagnosis	Monoclonal Immunoglobulin Isotype	Amount (g/L)	Bone marrow aspiration	ESR (mm/h)	CRP (mg/L)	Comments
This report	2009	M	27	47	+	Myeloma	IgA κ	11.7	Plasma cells, 3.4%	120	16.88	
This report	2009	M	23	58	N.A	MGUS	IgG λ	28.8	Plasma cells, 12.3%	10	0.62	
O'Neill et al (8)	1997	F	Many years ago	73	N.A	Myeloma	IgA λ	22	Plasma cells, 6% →14% (atypical)	98	N.A	
Lam et al (9)	1989	M	41	61	+	Myeloma	IgA κ	34.5	Plasma cells, 22%	162	N.A	
Renier et al (12)	1992	M	60	79	—	Waldenström's macroglobulinemia	IgM κ	>20	Plasma cells, 3%	N.A	N.A	
		M	45	71	N.A	MGUS	IgM κ	<5	Normal	N.A	N.A	
		M	Many years ago	72	+	BMG	IgG λ	<5	Normal	N.A	N.A	Post infection monoclonal gammopathy
		F	37	37	—	MGUS	IgG λ	>20	Plasma cells, 2%	N.A	N.A	
		M	Many years ago	78	N.A	MGUS	IgG λ	<5	N.A	N.A	N.A	
		F	32	57	+	BMG	IgG κ	<5	N.A	N.A	N.A	Monoclonal gammopathy after hepatitis
Blanc et al (13)	1979	M	33	49	—	MGUS	IgG λ	20	Plasma cells, 33% (atypical)	N.A	N.A	
		M	33	49	N.A	Myeloma	IgA κ	12.8	N.A	N.A	N.A	
Gualandi et al (14)	1981	M	N.A	N.A	—	Myeloma	IgA κ	5	N.A	N.A	N.A	

Abbreviations: MGUS, monoclonal gammopathy of undetermined significance; BMG, benign monoclonal gammopathy; N.A, not available.

diagnosis of AS to diagnosis of MM exclude the possibility that AS is an early manifestation of MM. Recently, a retrospective cohort study reported that the risks of MM and MGUS are significantly elevated in those with AS.⁵⁾

Chronic infection leading to unresolved inflammation, a known pathogenic mechanism of AS, is an important contributor to cellular transformation, tumorigenesis, and tumor progression in MM.¹⁰⁾ It has been suggested that elevated levels of IgA associated with AS occur as a result of microbial antigenic stimulation at mucosal surfaces, such as the gastrointestinal tract.⁷⁾ Protracted plasma cell stimulation and proliferation in our patients, as a result of a similar process, may have contributed to the developments of MM and MGUS, respectively.

In Korea, there was one report of ankylosing spondylitis following plasmacytoma. Unlike our patients, previous radiation therapy due to plasmacytoma might affect the pathogenesis.¹¹⁾ Table 1 depicts the main data from previous reports on associations between AS and monoclonal gammopathies. All previous reports, except one,¹²⁾ suggest that IgA myeloma and MGUS are associated with AS.^{8,9,13,14)} Our patients possessed IgA or IgG monoclonal proteins, respectively. The distribution of isotypes of monoclonal gammopathy in one report¹²⁾ differed strikingly from previous reports.^{8,9,13,14)} In this report,¹²⁾ 2 of 4 patients with IgG monoclonal gammopathy had transient monoclonal IgG during infectious disease (viral hepatitis and repeated respiratory tract infections, respectively).

Serum IgA levels are elevated in AS and this elevation is associated predominantly with the active phases of AS, as determined by ESR and CRP levels which correlate with clinical assessments of disease activity.⁷⁾ In our IgA positive symptomatic MM patient, both ESR and CRP levels were elevated, whereas in the IgG positive MGUS patient levels were normal. The mechanisms responsible for inflammation development and maintenance in different organs and joints in

AS, are the subjects of active research. Furthermore, individuals tend to have unique patterns of disease presentation and activity. The hallmarks of cancer-related inflammation include the presence of inflammatory cells and inflammatory mediators (for example, chemokines, cytokines and prostaglandin) in tumor tissues, tissue remodeling, and angiogenesis, which occur generally during chronic inflammatory response and tissue repair.¹⁵⁾ Case 1 with active disease showed a definite increase in serum surrogate markers of inflammation, while no such elevation was observed in case 2, which suggests that degree of inflammation is associated with the occurrence of malignant tumor-promoting effects. We presume that anti-inflammatory therapies, which have been found to be effective at reducing tumor incidence in epidemiological studies, could be utilized to complement the more conventional pharmacological treatments used to treat MM.

In summary, the concomitant occurrence of AS and MM suggests a pathogenic relationship. In AS, persistent reticuloendothelial stimulation, due to chronic subclinical infection, may lead to plasma cell activation and proliferation. Furthermore, the occurrence of either symptomatic MM or inactive MGUS is likely to be related with degree of inflammation in AS. Available evidence highlights the need to prospectively explore the pathologic mechanisms underlying the association between AS and MM/MGUS, and should encourage medical doctors to consider a diagnosis of MM/MGUS in patients presenting with AS.

요 약

형질세포의 악성신생물인 다발성골수종의 발병 원인에 대해서 아직 명확하게 알려진 바 없으나 대규모 연구결과 기존에 감염이나 자가면역질환에 이환된 환자에게 많이 발생하는 것으로 보고되었다. 저자들은 강직성척추염의 유병 기간이 20년 이상인 두 명의 환자에서 IgA κ 형의 다발성골수종과 IgG λ 형의 상세 불명 단클론감마병증이 각각 진단되어 가능성 있는 발병기전에 대하여 문헌고찰과 함께 보고하는 바이다.

강직성척추염은 척추관절의 만성염증이 동반되는 자가면역질환으로 다발성골수종의 발생 가능성이 높은 것으로 알려졌으며 두 질환 사이의 관련성은 아직 명확하지 않지만 장기간의 만성적인 염증이 다발성 골수종을 유발할 수 있을 것으로 추정된다.

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