Ankylosing spondylitis and monoclonal gammopathies

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Abstract

From 1960 to 1990, 557 patients with ankylosing spondylitis (428 men, 129 women) were diagnosed and indexed in the department of rheumatology. Monoclonal gammopathies were found in seven (five men, two women) patients (1·3%). With one exception, ankylosing spondylitis preceded monoclonal gammopathies by many years.

The distribution of the isotypes of the mIg found in these seven patients was striking when compared either with previous reports of an association between ankylosing spondylitis and monoclonal gammopathies or with local data on the epidemiology of monoclonal gammopathies: five patients with IgG, four of them of the λ (lambda) type, and two IgM, both of the κ (kappa) type were found; no patients with mIgA were recorded.

Two patients were HLA-B27 positive and had slight and transient monoclonal gammopathies, whereas three subjects were HLA-B27 negative and had important spikes, corresponding in two subjects to malignant diseases. This observation raises the question of whether the coexistence of HLA-B27 and ankylosing spondylitis might provide a protective action. Epidemiological studies are required to clarify such points.

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The association of ankylosing spondylitis and monoclonal gammopathies has been reported occasionally[1–11] but the frequency of occurrence of the combination has not been determined. This association may be truly exceptional or merely unrecognised. To investigate the relation between the two diseases, we compared the clinical and laboratory findings in patients with monoclonal gammopathies and ankylosing spondylitis diagnosed at the University Hospital in Angers.

Patients and methods

Subjects presenting with ankylosing spondylitis and monoclonal gammopathies were selected by comparing hospital records of patients with each disease.

From 1960 to 1990, 557 patients with ankylosing spondylitis (428 men and 129 women) were diagnosed according to the usual criteria[12] and indexed in the department of rheumatology. Three hundred and twenty three patients were admitted to this unit and serum protein electrophoresis was systematically performed.

The typing of monoclonal immunoglobulins was carried out by immunoelectrophoresis and, from 1985, by immunofixation when necessary. The measurement of IgG, IgA, and IgM was performed by radial immunodiffusion (Behring Laboratory) until 1981, then by immunonephelometry (Beckman analyser). The HLA phenotype was studied by microlymphocytotoxicity with special attention to HLA-B27.

Results

Monoclonal gammopathies were found in seven (five men and two women) of the 557 patients with ankylosing spondylitis. Table 1 summarises the clinical data and main biological features of these patients. For two patients monoclonal gammopathies were found when the patients were admitted to the department of rheumatology; conversely five patients with monoclonal gammopathies were found during admission to other units. The frequency of occurrence of monoclonal gammopathies was 0·62% (2/323) in patients with ankylosing spondylitis admitted to the rheumatology department and 1·26% (7/557) for the entire group.

In most patients ankylosing spondylitis preceded the monoclonal gammopathies by at least 20 years with one exception: ankylosing spondylitis and monoclonal gammopathies were simultaneously diagnosed in a 37 year old woman who was HLA-B27 negative.

The mIg were mIgG in five patients, four of the λ type and one κ. They were found in subjects aged 37, 57, 58, 72, and 78 years. In the other two subjects, the mIg were mIgM of the κ type, found in patients aged 71 and 79 years. Neither monoclonal IgA or light chain, nor biclonal gammopathy were found.

The mIg concentration was less than 5 g/l in four patients. Two of them were HLA-B27 positive and their mIgG was transient; it was discovered during infectious diseases (viral hepatitis and repeated respiratory tract infections respectively), and then disappeared into the associated polyclonal hypergammaglobulinaemia. The other two patients, who died before our study began, had not been phenotyped. No variations in the level of mIg were seen during their short follow up, thus we considered them as having monoclonal gammopathies of undefined significance.[13]

The spike was greater than 20 g/l in three patients, all of them HLA-B27 negative. One was still unchanged after a six year follow up. The second was initially discovered without any associated feature of malignancy; however, an

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Table 1 Clinical data and main biological features of the seven patients with ankylosing spondylitis and monoclonal

Patient No	Sex	Year of birth (death)	Age (years) at finding of		HLA-B27	Treatment for ankylosing spondylitis†	Monoclonal Ig	
			Ankylosing spondylitis*	Monoclonal gammopathies			Isotype	Amount (g/l)
1	M	1910 (1990)	60	79	–	NSAID	IgM κ	>20
2	M	1914 (1987)	45	71	?	NSAID, radiotherapy	IgM κ	<5
3	M	1916 (1990)	71 (old)	72	+	NSAID	IgG λ	<5
4	F	1947	37	37	–	NSAID	IgG λ	>20
5	M	1907 (1989)	78 (old)	78	?	NSAID	IgG λ	<5
6	F	1921	48 (32)	57	+	NSAID, gold, depomedrol	IgG κ	<5
7	M	1928	46 (20)	58	–	Salicylates	IgG λ → +BJ‡	20 → >40

*Age at onset of disease in parentheses ('old' means the age at which the disease started is unknown, but many years previously).
†NSAID=non-steroidal anti-inflammatory drugs.
‡BJ=Bence Jones protein.
§MGUS=monoclonal gammopathy of undefined significance; BMG=benign monoclonal gammopathy.

Table 2 Main data from previous reports of the association of ankylosing spondylitis and monoclonal gammopathies

Reference	Year	Sex	mIg	Diagnosis†	Comments
Ogryslo *et al*[8]	1959	M	IgG?		Cryoglobulinaemia
Rocheteau[9]	1960	M	?	Myeloma	Radiotherapy
Zeitoun-Moreau[11]	1963	M	IgG	MGUS†	Cryoglobulinaemia, tuberculosis
Coste *et al*[39]		M	IgA	MGUS	Cryoglobulinaemia
Benedek and Zawadski[1]	1966	M	BJ*		Amyloidosis, ulcerative colitis
Danon *et al*[3]	1967				Four of 104 MGUS (mIgG or mIgA)
Dryll *et al*[4]	1969	M	IgG λ	MGUS	Survey: 10 years, mIg decrease
		M	IgA λ	MGUS	3 years
		F	IgG κ	MGUS	2 years, mIg decrease
		F	IgG κ	MGUS	6 months
Verdier *et al*[10]	1974	M	IgG κ	Myeloma	Paget's disease
Blanc *et al*[2]	1979	M	IgA κ	Myeloma	
Gualandi *et al*[6]	1981	M	IgA κ	Myeloma	HLA-B27 negative; unreleased mIgA
Ghirlanda *et al*[5]	1984	M	IgA κ	MGUS	HLA-B27 positive
Naude *et al*[7]	1990	M	IgA κ	Myeloma	HLA-B27 positive; survey six years No evolution without treatment
		M	IgA κ	Myeloma	HLA-B27 positive; stable 54 months later
		M	IgG κ	Myeloma	HLA-B27 positive; stable 18 months later

*BJ=Bence Jones protein.
†MGUS=monoclonal gammopathy of undefined significance.

aggressive myeloma was diagnosed two years later. The last spike corresponded to a Waldenström macroglobulinaemia.

Discussion

Our method was not efficient enough for a true epidemiological evaluation of the frequency of monoclonal gammopathies in patients with ankylosing spondylitis as some patients with either diagnosis might have been seen in the hospital without being identified as having either of these two diseases. This work is to our knowledge, however, the first attempt to assess a relation between monoclonal gammopathies and ankylosing spondylitis. Previous studies devoted to the immunological status in ankylosing spondylitis generally found increases of Ig levels, especially IgA. Unfortunately, they did not report the qualitative examination of serum samples from patients.[14–21] Thus the only data available were either the cases occasionally recorded (summarised in table 2) or long term follow up of patients with ankylosing spondylitis.[22–24] One of these papers[22] only reported two myelomas in the group examined and another[24] reported six deaths due to myeloma out of 14 106 patients with ankylosing spondylitis who had been treated with x radiation.

As previously reported,[25] the west of France presents unusual characteristics with regard to the epidemiology of monoclonal gammopathies

gammopathies

Other Ig levels	*Bone marrow aspiration*	*Diagnosis, evolution, and other pathological conditions§*
Normal	Lymphocytes, 52%; plasma cells, 3%	Waldenström macroglobulinaemia; alcoholic cirrhosis leading to death; arteritis; bilateral hip arthroplasties
Normal	Normal	MGUS unchanged six months later; cardiopathy (acute pulmonary oedema leading to death, aortic stenosis, streptococcal endocarditis); chronic respiratory insufficiency; hypertension; maturity onset diabetis mellitus
High	Normal	BMG after infection (respiratory tract infection; disappearance); chronic obstructive lung disease, surinfections leading to death; cardiopathy (atrial fibrillation, left sided heart failure); maturity onset diabetis mellitus
Low IgA High IgM	Lymphocytes, 15%; plasma cells, 2%; no abnormality	MGUS during viral keratitis, unchanged six years later
Normal		MGUS during urinary tract infection, unchanged two years later; septic shock leading to death; atrioventricular block (pacemaker); hypertension
High		BMG after hepatitis, disappearance; chronic viral (non-B) hepatitis
Normal→ low	Plasma cells, 33%; atypical	MGUS leading to myeloma after two years; asthma

(essentially a high percentage of mIgM). Thus the 30 000 people studied by Saleun in the department of Finistere[26] are the most convenient control group. In this study, the frequency of monoclonal gammopathies was 1·35% for men and 0·86% for women. In comparison, our evaluation of the frequency of monoclonal gammopathies (1·26%) was similar when considering the entire group of patients with ankylosing spondylitis. It was only 0·62% among the patients studied during their admission to the rheumatology department, however, so that a lower frequency of monoclonal gammopathies in patients with ankylosing spondylitis cannot be definitely excluded.

In the Finisterian population, the frequency increased with age; myeloma and Waldenström macroglobulinaemia accounted for 12·6 and 9% of monoclonal gammopathies respectively. Our findings are consistent with these results.

The distribution of the isotypes of the mIg found in our seven patients was striking when compared either with previous reports of the association of ankylosing spondylitis and monoclonal gammopathies or with local data on the epidemiology of monoclonal gammopathies (table 3).[27] Whereas up to seven mIgA were previously recorded in 15 patients with an association of ankylosing spondylitis and monoclonal gammopathies, none was present in our patients. Our patients with ankylosing spondylitis actually had mIgG rather than mIgA. The higher occurrence of mIgG might, however, be a random finding due to the small number of subjects studied in this work.

Table 3 Isotypes of mIg in patients from Angers who had a monoclonal gammopathy associated or not associated with ankylosing spondylitis (AS) compared with patients from elsewhere (data from previous reports listed in table 2 and from references 25 and 27)

	Angers		*Elsewhere*	
	Without AS (%)	*No with AS (%)*	*No with AS (%)*	*Without AS (%)*
IgG	45	71 (5)	47 (7)	59
IgM	39	29 (2)	0	16
IgA	11	0	47 (7)	18
BJ*	4	0	7 (1)	6

*BJ = Bence Jones protein.

Interestingly, mIgM was discovered in two subjects, whereas none had been reported previously. This discrepancy is probably due to a bias as previous data were obtained from papers focusing on selected conditions such as mIgG or mIgA monoclonal gammopathies of undefined significance[3] or, from 1974, myeloma.

Another surprising feature was that four patients with mIg (all of them mIgG) were of the λ type, which is the opposite of what is seen in uncomplicated monoclonal gammopathies. This may be related to the amyloidosis sometimes found in patients with ankylosing spondylitis.[28 29] In immunoproliferative disorders, this anomaly is more often due to light chains of the λ type. The amyloid component observed in chronic inflammations such as ankylosing spondylitis, however, does not have the same biochemical structure.[30 31] Moreover none of our patients had symptoms suggestive of amyloidosis. The investigation for amyloidosis was negative in all but one of the previously reported subjects,[1 3–5] in whom the association of ankylosing spondylitis, ulcerative colitis, and Bence Jones protein made the real source of amyloidosis uncertain.[1]

In two of our seven patients mIgG disappeared within two years. This finding was unexpected as previous studies[32–35] had shown that less than 4% of monoclonal gammopathies were transient. This discrepancy is not due to methodological reasons. Conversely, it is noteworthy that at least four of our seven patients, including those with transient monoclonal gammopathies, had infectious diseases when their monoclonal gammopathies were discovered.

The two patients who had a slight and transient monoclonal gammopathy were HLA-B27 positive whereas the three subjects who were HLA-B27 negative had important spikes corresponding, in two subjects, to malignant diseases. Although inconsistent with reports on the relationships between monoclonal gammopathies and HLA alleles,[36–38] this observation raises the questions of the possible part played by the coexistence of HLA-B27 and ankylosing spondylitis. Among previously reported cases of monoclonal gammopathies associated with ankylosing spondylitis, the HLA phenotype was only available for five patients (table 2). Although three of these were HLA-B27 positive and had a slowly progressing myeloma, to date most patients who had benign monoclonal gammopathies or monoclonal gammopathies of undefined significance were HLA-B27 positive and most patients who were HLA-B27 negative had a malignant gammopathy. Patients with ankylosing spondylitis who

are HLA-B27 negative may therefore be at higher risk than those who are HLA-B27 positive with regard to monoclonal gammopathies. Alternatively, if the occurrence of monoclonal gammopathies was lower in patients with ankylosing spondylitis, the conjunction of ankylosing spondylitis and HLA-B27 might provide a protective action. Epidemiological studies are required to clarify such points.

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