

## Systemic lupus erythematosus and multiple myeloma: an uncommon association. Two cases and literature review

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### ABSTRACT

*The association of systemic lupus erythematosus and multiple myeloma is uncommon. We report two cases of systemic lupus erythematosus associated to multiple myeloma. The cases are discussed in the light of a review of the literature.*

*The clinical, laboratory and radiographic findings of the patients, as well as the subsequent therapeutic approach are discussed. A systematic review of all the other cases of this association is performed.*

*We report two female patients of 50 and 35 years old who developed a multiple myeloma seven and three years respectively after the diagnosis of systemic lupus erythematosus. In the second case, systemic lupus erythematosus was associated to monoclonal gammopathy. One patient died after three months and one patient is still in remission after three years of the diagnosis of multiple myeloma.*

*The coexistence of systemic lupus erythematosus and multiple myeloma is very rare and the possible pathogenetic mechanisms underlying this association remain unclear.*

### Introduction

The association between systemic lupus erythematosus (SLE) and malignancy especially lymphoproliferative syndromes is often reported in the literature (1-4). The risk of non-Hodgkin lymphoma (NHL) was found to be increased 3 to 4 fold compared with the general population (4). Monoclonal gammopathy is often detected in SLE patients (5-6), but the coexistence of multiple myeloma (MM) is rarely reported. We report two unusual cases in which MM occurred three and seven years respectively after the onset of SLE.

### Case reports

#### Case one

A 50-year-old female patient was admitted in July 1992 for fever and chest pain with dyspnea. No family history of SLE or MM was reported. She had mild alopecia and pleuro-pericarditis. Renal function tests and serum electrolytes were normal. There was no

proteinuria. Antinuclear antibodies were elevated (1/640), anti-DNA antibodies were positive (ELISA: 16U/ml, range <7 U/ml). The diagnosis of an incomplete SLE was made, and she was treated with steroids (prednisone 60 mg daily). Remission of the disease was achieved after two months and the doses of corticosteroids were progressively reduced to 10 mg daily. Between 1992 and 1999, SLE was quiescent. In December 1999, she developed a functional disability and tumefaction of the right arm. Radiology showed multiple osseous lyses in right humerus, cranium, and iliac bone. Serum calcium was 2.9 mmol/l (range 2-2.6 mmol/l). C3 and C4 activity, hepatic and renal tests and complete blood count were normal. Anti-DNA antibodies were still positive, within the same level. Electrophoresis, which was normal previously, showed a monoclonal component. Immunofixation showed the presence of IgA- $\lambda$  type monoclonal component in the serum (29 g/l, normal range 0.9-5.6 g/l). The Bence-Jones protein was not detected in urine and cryoglobulins were absent in the patient's serum. The aspirated bone marrow revealed 40% abnormal plasma cells confirming the diagnosis of MM. The patient was initially treated with 3 courses of Alexanian (melphalan+prednisone) regimen without improvement, substituted by a VAD scheme. After the third course of VAD regimen, she developed septic shock from pulmonary origin and died after one week.

#### Case two

A 35-year-old woman was admitted in 1998 because of intermittent arthralgias and fever. Her father was diabetic and there was no history of familial SLE or MM. She was diagnosed as having SLE because of photosensitivity, malar rash, non-erosive polyarthritis and positive antinuclear antibodies. The anti-phospholipids and anti-DNA antibodies were negative. Electrophoresis showed a hypergammaglobulinemia and serum immunoelectrophoresis found an IgG- $\lambda$  monoclonal gammopathy (21 g/l, range 7.2-18 g/l), without cryoglobulins, and normal bone marrow aspiration. Proteinuria was negative. She was treated

Competing interests: none declared.

**Table I.** Review of the cases of the association SLE and MM.

Authors (ref.)	Age of SLE	Age of MM	Diagnostic delay	Type of MG	MM treatment	SLE treatment	Evolution
Canoso (8)	21	42	MM 21 years after SLE	-	-	CS	stable
Jordan (9)	35	52	MM 17 years after SLE	IgG $\kappa$	L-phentlalanine mustard + CS	CS	favourable
Pehamberger (10)	44	44	simultaneous	IgG	Cyclophosphamide Methylprednisolone		not specified
Braunstein (11)	-	-	-	-	-	-	-
Powell (12)	59	63	MM 4 years after SLE	Indeterminate	not precise	-	death
	47	73	MM 26 years after SLE	IgA $\kappa$	not precise	-	death
	68	68	simultaneous	IgG $\lambda$ (smouldering)	-	-	stable
	68	62	SLE 4 years after MM	IgG $\lambda$ (smouldering)	-	-	stable
Butler (13)	55	59	MM 4 years after lupus	IgG $\kappa$	no treatment	CS + azathioprine	dead 3 months after MM
Solary (14)	80	78	SLE 2 years after MM	IgG $\kappa$	Melphalan + CS	CS	Death : pulmonary embolism
Sendagorta (15)	43	43	simultaneous	IgG $\kappa$	-	-	SLE flares
Umemura (16)	-	-	-	-	-	-	-
Case report (17)	61	69	MM 8 years after SLE	IgG $\kappa$	Melphalan + CS	CS	favourable
Alfetra (18)	36	50	MM 14 years after SLE	IgA $\kappa$	Melphalan + CS + $\alpha$ 2b interferon	CS cyclophosphamide	SLE flares
Bjornadal (19)	-	-	-	-	-	-	-
Vaiopoulos (20)	76	76	simultaneous	IgG $\kappa$	Melphalan + CS	Chloroquine + CS	favourable
Urbanka-Rys (21)	38	45	MM 7 years after lupus	IgG $\kappa$	VAD CHOP	CS + azathioprine cyclophosphamide	favourable

SLE: systemic lupus erythematosus; MM: multiple myeloma; MG: monoclonal gammopathy; CS: corticosteroids; Ig: immunoglobulin

with steroids (prednisone 40 mg daily progressively reduced to 10 mg daily) and chloroquine (200 mg daily). Clinical remission was achieved after one month. Two recurrences were diagnosed between 1998 and 2001 and were easily treated with the higher doses of corticosteroids. During this period, the amount of monoclonal gammopathy was stable. In July 2001, she presented an unusual asthenia, progressive fatigue with slimming. Clinical examination was normal. Hemoglobin was 100 g/L. Hepatic, renal function tests and serum calcium were normal. The level of IgG- $\lambda$  paraprotein increased to 39 g/L. Urinalysis showed free  $\lambda$  chains Bence-Jones proteinuria (2.8 g/day). There were no osteolytic lesions. Bone-marrow aspirates revealed 30% abnormal plasma cells infiltration which confirmed the diagnosis of MM. No test of clonality in the bone marrow was performed at that time. Chemotherapy

was instituted (melphalan 10 mg daily and prednisone 50 mg daily, 4 days a month). After the completion of twelve courses, complete response of MM was obtained. Serum and urine immunoelectrophoresis were persistently negative and the bone marrow shows no infiltration with myeloma cells. At present, 6 years after the diagnosis of MM, she is still in clinical remission.

### Discussion

In this report, we describe two cases of women who, at the age of 50 and 35 years, developed a MM; respectively seven and three years after SLE. In the second case, SLE was first associated to monoclonal gammopathy and evolved into MM. The prevalence of monoclonal gammopathy of undetermined significance (MGUS) in SLE patients varies from 2.2% to 3.3% and the outcome of these patients seems not to differ from the other SLE patients (5-7).

In a recent report, Ali *et al.* (7) report a higher incidence of MGUS in a cohort of 1083 SLE patients (5.4%) than in the general population. IgG type of the monoclonal band was the most frequent, and malignancies were not more frequently found in SLE patients with monoclonal gammopathy (7). Despite the frequency of MGUS in SLE, the association with MM is uncommon and has been described sporadically in the literature. Those different cases are summarized in Table I (8-21).

SLE symptoms may precede, appear concomitantly or develop after the diagnosis of the MM. In our patients and in the most reported cases, MM was diagnosed after the onset of SLE. Pehamberger, Sendagorta and Vaiopoulos each described one case of simultaneous occurrence of both diseases (10, 15, 20), and Alfetra reported a case of SLE in a patient with a previous history of MM (18). There were no specific

clinical or biological presentations of those lupus cases. Two additional cases of extramedullary plasmacytoma have been reported in association with SLE (22-23).

The possible pathogenetic mechanisms underlying the association of SLE and MM are not elucidated. The implication of genetic factors has been hypothesized, a case-control study revealed an excess of rheumatoid arthritis and SLE in first-degree relatives of MM cases when compared with controls (24). In another study, Landgren *et al.* reported a significant elevation of the risk of MM (OR: 2.66, 95% CI 1.12-6.32) in subjects with familial history of SLE (25).

The risk of NHL in patients with SLE is found to be increased 2.5- to 5-fold compared with the risk in the general population. NHL, Hodgkin's disease, and leukemia account for nearly 70% of all the cancers found in SLE (26). The mechanisms underlying the increased risk of those hematological malignancies are not known. Numerous pathogenetic mechanisms have been suggested but remain largely speculative. The role of cytotoxic drugs used in SLE is still unclear in the development of malignancy (4). The majority of myeloma associated with SLE, including the 2 cases reported here, develops in patients who had not been treated with immunosuppressive therapy. The immune dysfunction observed in SLE had been emphasized. It has been suggested that suppressor-T-cell dysfunction and defective NK cell function may lead to abnormal B-cell proliferation in response to various auto antigens. T and B-lymphoid cells hyperactivity in SLE and the persistent stimulation of B-cell may favor the emergence of abnormal or malignant clone of plasma cells (26-27). Spontaneous lupus-like syndromes in mice are associated with a high incidence of plasma cell dyscrasias (28), but this appears to contrast with the rarity of the association of MM in human SLE.

The treatment of the association SLE-MM is not codified. Many authors treated the MM initially with classical cytotoxic drugs (prednisone-melphalan) mostly with success. Alpha-2b

interferon may be effective in prolonging the response phase of patients with MM previously treated by chemotherapy (29). Although inadvisable in patients with autoimmune disease, interferon treatment has been proposed by Afeltra as a therapeutic option in the plasma cell neoplasia (18). Thalidomide has been used in coetaneous lupus and in refractory myeloma (30-31) and may be a good alternative. In the second patient, we observed an uncommon long-term remission after treatment with melphalan and prednisone reported in less than 5% of MM (32).

### Conclusion

The link between malignancy, especially hematological neoplasia, and autoimmunity is discussed. Although, the coexistence of SLE and MM is very rare, the detection of monoclonal gammopathy in SLE patients is not rare and must be investigated for the detection of underlying myeloma.

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