CLINICAL BRIEF

Connective Tissue Disease Manifested as Multiple Myeloma

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FOR MOST PATIENTS with multiple myeloma, the diagnosis is obvious when based on a combination of bone marrow plasmacytosis, bone destruction, and large amounts of monoclonal globulin production associated with bone pain or anemia. With the increasing availability of chemical profile scans that reveal hyperglobulinemia, more patients with abnormal protein patterns have been recognized. In this report, we describe five middle-aged women referred with the suspected diagnosis of multiple myeloma based on a marked γ-globulin elevation. All were subsequently found to have connective tissue disorders, most commonly Sjögren's syndrome.

CLINICAL STUDIES

Among 210 patients referred between 1977 and 1982 with previously untreated multiple myeloma, there were five who had a markedly elevated serum γ-globulin level but no evidence of myeloma. These five patients, all women, ranged in age from 28 to 69 years, with a median age of 50 years. None had symptoms of severe anemia or other complications of multiple myeloma, but mild symptoms of arthralgia and/or keratoconjunctiva sicca were noted. The Table summarizes the salient biochemical findings. All were mildly anemic with hemoglobin values ranging from 9.3 to 11.9 gm/dl and with mild bone marrow plasmacytosis of 10% to 20%. Serum protein electrophoresis showed such markedly elevated globulins that a monoclonal component was suspected (Figure). Immunoelectrophoresis failed to identify a monoclonal globulin but direct quantitations confirmed markedly elevated IgG levels to about four times the normal value, with less markedly elevated IgA and IgM levels. (Normal IgA and IgM immunoglobulins are markedly depressed in 70% of our untreated patients with overt multiple myeloma.) Studies for rheumatoid factor were positive in two patients, nonreactive in two, and not done in one patient (Table); antinuclear antibody tests were positive in four patients (homogeneous in three, speckled in one) and not done in the remaining patient. Two patients had proteinuria (300 and 1,000 mg/day), with various γ-globulins of low molecular weight constituting the principal abnormality.

Sjögren's syndrome was diagnosed in four of the five patients on the basis of xerostomia and keratoconjunctiva sicca. Two patients had primary Sjögren's syndrome; the other two patients had Sjögren's syndrome associated with secondary scleroderma or hyperglobuli-

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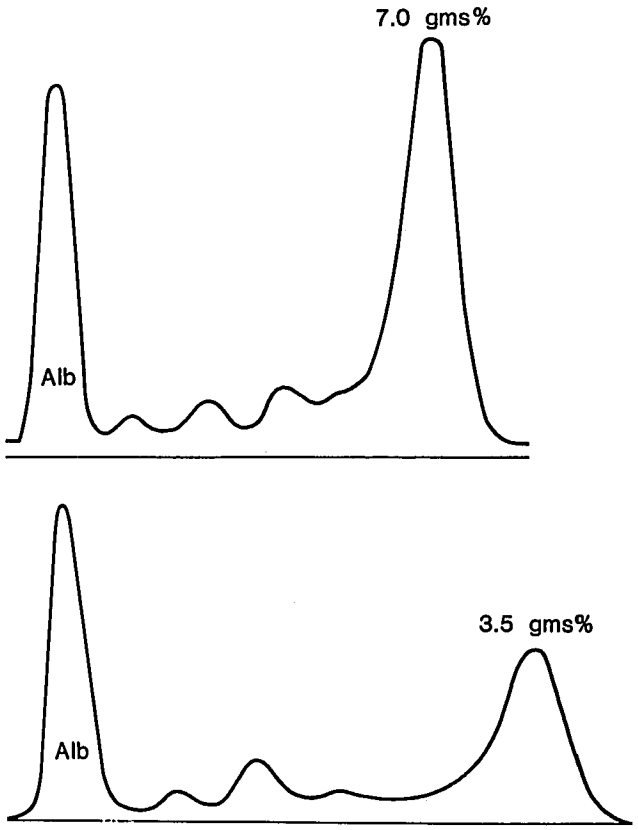
TABLE. Summary of Laboratory Findings

Test	*Median Value*	*Range*
Hemoglobin (gm/dl)	10.9	9.3-11.9
γ-globulins (gm/dl)	4.8	3.5-11.9
Immunoglobulins (mg/dl)		
IgG	5,020	3,530-9,370
IgA	360	150-800
IgM	140	100-180
ANA titer*	1:240	1:80-1:640

*Positive in 4 patients.



Serum electrophoresis with markedly elevated γ-globulins in two patients referred with myeloma, but with evidence of Sjögren's syndrome.

nemic purpura. The remaining patient had rheumatoid arthritis. All five patients have been in stable health for more than 24 to 65 months (median 47 + months), maintained with symptomatic therapy.

In addition to the patients described, six additional adults with marked γ-globulin elevations to more than 3.5 gm/dl were identified during the same period (1977 to 1982). None had been referred with possible myeloma. Of these, three were women and the median age was 47 (range 34 to 65). In this group, the median γ-globulin was 4.3 gm/dl (range 3.8 to 5.1). All were overtly ill with chronic septic processes (eg, miliary tuberculosis) or chronic active hepatitis with jaundice, associated with an underlying malignancy. No findings suggested a collagen disease.

DISCUSSION

Most patients referred with a diagnosis of multiple myeloma present evidence of a monoclonal gammopathy, bone marrow plasmacytosis, and varying degrees of bone destruction. Some patients with myeloma may be asymptomatic, and the diagnosis is confirmed only after the coincidental detection of a large monoclonal peak on serum electrophoresis.[1] Other patients with myeloma may have the typical clinical features, but lack the abnormal protein on serum or urine electrophoresis (ie, nonsecretory myeloma). It is critical to recognize that large amounts of γ-globulin production may be unrelated to myeloma, but represent an inflammatory reaction to chronic infection, chronic disease, or other disorders.[2]

In our report, five female patients with connective tissue disorders had serum electrophoretic patterns resembling that of multiple myeloma. In all, the degree of γ-globulin elevation was marked with a disproportionate increase of IgG immunoglobulins. However, IgA and IgM immunoglobulin levels were also elevated, in contrast to the marked depression usually present in multiple myeloma. While a reactive globulin stimulation in connective tissue disease has been recognized for many years,[2,3] few series have included patients with the degree of elevation found in our series. Thus, none of 72 patients with rheumatoid arthritis described by Claman and Merrill[4] showed such an increased IgG level. About 12% of the 62 patients with Sjögren's syndrome described by Bloch et al[5] had a γ-globulin value of more than 3.5 gm/dl. Patients with Sjögren's syndrome and a monoclonal gammopathy of the IgM type have also been described, with a clinical pattern similar to that of a macroglobulinemic lymphoma.[6,7]

Our patients represented an extreme in the spectrum of Sjögren's syndrome, with markedly elevated IgG immunoglobulins resembling the pattern found in myeloma. Of interest was the mild degree of bone marrow plasmacytosis, suggesting that extramedullary sites were a more prominent source of γ-globulin production in these patients than in patients with multiple myeloma. Despite the many more reactive plasma cells producing IgG immunoglobulins in Sjögren's syndrome, no patients have yet been described with Sjögren's syndrome that evolved into overt multiple myeloma. Yet, a benign monoclonal gammopathy of IgG or IgA type has been described in patients with similar connective tissue disorders,[8] and one report suggested a higher frequency of monoclonal IgG peaks in patients with rheumatoid arthritis than in normal persons of comparable age.[9]

We stress the caution required before attributing a marked globulin elevation to multiple myeloma, and the possibility that Sjögren's syndrome may account for this abnormality. This conclusion seems especially likely in middle-aged women without overt evidence of sepsis or liver disease and with very high levels of IgG immunoglobulins. In-depth probing may unmask mild symptoms of sicca and/or arthralgia, indicating the need for further specific studies to confirm the diagnosis of Sjögren's syndrome or other connective tissue diseases.[3,10]

SUMMARY

A diagnosis of Sjögren's syndrome or rheumatoid arthritis was made in five women in whom multiple myeloma was first suspected. All had mild symptoms of sicca or arthritis, positive tests for rheumatoid factor or antinuclear antibody, and markedly increased IgG immunoglobulins. A connective tissue disorder may produce the characteristic electrophoretic pattern of multiple myeloma.

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