Coexistence of scleroderma with multiple myeloma: a rare association

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Abstract

Introduction: Coexistence of scleroderma with multiple myeloma is an unusual finding with unclear significance. Only 15 cases of MM with scleroderma have been reported until now.

Case presentation : We report a case of a 58-year-old female with 10-year history sceroderma, complaining from pallor and fatigue. The initial workup showed a normocytic anemia with elevated ESR and

total proteins. On fruther investigation the gamma globulines were also high and the bone marrow biopsy showed interstitial and focal increase in plasma cells without bone marrow fibrosis. Skeletal survey showed osteopenia, but no osteolytic lesion or fracture. The patient was diagnosed as scleroderma with coexistence of immunoglobulin G (IgG) , kappa ($\varkappa$) MM.

Conclusion: In view of the possible coexistence of scleroderma with MM, it is suggested that all patients with scleroderma should be screened for monoclonal gammopathy and MM regarding their age. future studies should be directed to determine the exact mechanism of these two conditions association and the effect of MM treatment on SSc improvement.

Keywords : Systemic Sclerosis (SSc),Multiple Myeloma (MM), Osteolytic lesion, Immunoglobulin G, $\varkappa$ MM

Background

Scleroderma(SSc) is a rare connective tissue disorder of unknown etiology characterized by thickness of the skin. The disease usually affects patients between the ages of 30–50 (1). Scleroderma is reported to be associated with Sjogren syndrome, rheumatoid arthritis and systemic lupus erythematosus. It is also associated with solid tumors such as lung, breast, stomach and rectum .however, the association with multiple myeloma (MM) has seldomly been reported (2). To the best of our knowledge, only 14 cases of sceleroderma associated with MM have been reported in the literature. Inflammation and deregulation of immune system in this autoimmune disorder may cause clonal expansions of plasma cells but such aberrations still remain under investigation(2,3).

We report a case of a 58-year-old woman who presented with Systemic sclerosis associated with multiple myeloma.

Case presentation

A 58-year-old female presented with pallor and fatigue for the last month. She was diagnosed with sceroderma 10 years ago according to the American College of Rheumatology criteria for SSc(4),and was treated with methotrexate7.5mg/week for 5 years without adherence. Her past medical history was significant for breast cancer 15 years ago that was treated with surgery, chemotherapy, radiation and hormonal therapy for 5 years, with total remission.

On physical examination patient had thickened tight skin all over the extremities (Figure 1), and telangiectasia on her face and hands(Figure2,3).

Laboratory tests showed Haemoglobin 7.8 g/mL, total leucocyte count 5.7×10^9/L and platelet count 258×10^9/L. The erythrocyte sedimentation rate was 122 in the 1st hour and the C-reactive protein was 7.8mg/dl. Blood glucose, serum creatinine and electrolytes (including calcium) were within the reference ranges. Serology immune profile showed positive antinuclear antibodies (ANA) and SCL70 . The 25-Hydoxy vitamin D was low (<5 ng/mL; normal 9–37.6 ng/mL)and the parathyroid hormone level was normal (21.15 pg/mL; normal 15–65 pg/mL). On serum protein electrophoresis, a dense monoclonal band of 3.03 g/dL .No monoclonal proteins were detected in urine.

Immunoglobulin subtype evaluation showed significant high levels of IgG and Kappa light chain as demonstrated in (table 1)

Immunoglobuline	**Results**	**Reference range**
Immunoglobuline G (IgG)	3399	600-1600
Immunoglobuline A (IgA)	623.2	70-400
Kappa chain	764.14	174-370
Lambda chain	296.61	90-210

Table 1 : demonstrates Immunoglobulin subtype evaluation

Considering the patient's past history of breast cancer a PET Scan was performed to look for recurrence , the patient was injected by 11 microkuri of FDG18, and scanned after 1 hour in 3 dimension directions, the PET scan normal

A bone marrow biopsy showed interstitial and focal increase in plasma cells (15%) without bone marrow fibrosis in CD 138 staining.

On skeletal survey, there was diffuse osteopenia with osteoporotic changes in all the vertebrae without osteolytic fractures. The patient was diagnosed to have scleroderma coexisting with MM, and was treated with thalidomide (100 mg/day) and dexamethasone (20 mg/day weekly).The patient showed an improvement in skin thickening and increased range of movements after 6 months of therapy.

Discussion

Scleroderma is an autoimmune connective tissue disease, usually affects people of 30–50 years age group, with a female predominance (1).Patients with scleroderma can have specific antibodies such as antinuclear antibody, anticentromere or antitopoisomerase in their blood which suggest autoimmunity.

Our patient is 58-year-old female with systemic sclerosis and positive ANA and ScL 70.

Scleroderma is a disease with unknown etiology(1), but there may be a history of a preceding infection in most cases(2); however, associations have also been reported with diabetes, systemic lupus erythematosus, rheumatoid arthritis, Sjogren syndrome, monoclonal gammopathy, and MM(2,3).

There is possibility that inflammation , molecular deregulation events, and the circulating factors inducing immunostimulation of B cells in autoimmune disorders precede clonal proliferation of plasma cells and lead to the emergence of MM. The second possibility of developing MM may be related to the use of immunosuppressive drugs. In addition, a common genetic susceptibility for developing both an autoimmune disease and MM might also exist (2,3).

In our case the treatment of methotrexate could be a possible cause for MM development.

In literature cases of scleroderma associated with monoclonal gammopathy of undetermined significance have been reported. However, association of scleroderma with MM is rare (Table 2). Patients' age ranged from 37 to 76 years, with variable duration of developing MM after the diagnosis of scleroderma. This duration ranges from 1 month to 40 years. Our patient was diagnosed with MM after a period of 10 years of SSc diagnosis.

Table 2: Cases of systemic sclerosis with multiple myeloma

Cases	**Age/sex**	**Monoclonal protein**	**Duration (years)**	**Therapy**
Korting *et al* [5]	37/F	IgG ϰ	2	Improvement after myeloma
Doyle *et al* [6]	58/F 62/F	NA	4 40	NA
Ohta *et al* [7]	64/M	IgG ϰ	11	Improvement after myeloma
Hodak *et al* [8]	74/F	IgG ϰ	4	Improved after 1.5 years of
Rimon *et al* [9]	62/F	IgG λ	22	NA
Salisbury *et al*[10]	76/F	IgA ϰ	0.1	Improvement after 9 month
Nakanishi *et al* [11]	50/M	IgG ϰ	3	NA
Schmidt *et al* [12]	46/M	IgG λ	22	NA
Pujol *et al* [13]	74/M	IgA ϰ	15	Improvement after myeloma
Valente *et al* [14]	56/F	IgA ϰ	6	Improvement after melphala
Bachleitner-Hoffman *et al* [15]	73/F	IgG	24	Improvement after vincristi
Colovic *et al* [16]	55/F	IgG λ	20	Improvement after 6 cycles
Smeeta Gajendra ***etal*** [2]	24/M	IgA ϰ	8	Improvement after 9 month

In our case, diffuse osteopenia with osteolysis of phalanges on both sides and osteoporotic change in vertebrae was observed but no osteolytic lesions were seen in axial skeleton, unlike in MM, which is characterized by the presence of osteolytic lesions of the axial skeleton(2,3).

Plasma cells express osteoprotegrin (OPG) which blocks the interaction between RANKL and RANK receptor on osteoclast surface leading to impaired osteoclast resorption and preservation of bone structure(2). Unfortunately, OPG levels could not be investigated in our patient.

SSc treatment includes non-steroidal anti-inflammatory drugs, corticosteroids and immunosuppressants such as methotrexate, azathioprine, mofetil mycophenolate, and cyclophosphamide. Nintedanib, an antifibrotic agent, tocilizumab, an anti-interleukin-6 receptor antibody, and rituximab, an anti-CD20 antibody were approved for interstitial lung disease related to SSc and had showed improvement in both modified Rodnan skin score(17).

Thalidomide is used for the treatment of MM, as it acts as an anti-proliferative, antiangiogenic and inhibits myeloma tumor growth (15-17). The previously reported cases showed that systemic sclerosis symptoms were improved greatly by the treatment used for MM (when the two conditions were associated) (18).

In our case the patient showed a substantial improvement of her symptoms after 6 months of MM treatment

Conclusion

In view of the possible coexistence of scleroderma with MM, it is suggested that all patients with scleroderma should be screened for monoclonal gammopathy and MM regarding their age. Also, future studies should be directed to determine the exact mechanism of these two conditions association and the effect of MM treatment on SSc improvement.

Highlights

-Coexistence of SSc with MM is an unusual finding with unclear significance

-It is suggested that all patients with scleroderma should be screened for monoclonal gammapathy and MM regardless their age.

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