Scleredema associated with immunoglobulin A-κ smoldering myeloma: a case report and review of the literature

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Abstract

Background: Scleredema is a rare sclerodermoid skin condition characterized by diffuse symmetrical thickening of the upper part of the body. Its association with monoclonal gammopathy and myeloma was recently described; very few cases have been reported to date.

Case presentation: A 66-year-old Sri Lankan woman who had been followed in a dermatology unit for 34 years with diffuse systemic sclerosis presented with an acute exacerbation of the skin disease. Absence of Raynaud’s phenomenon; sclerodactyly; characteristic lung, gastrointestinal, and cardiac involvement of systemic sclerosis; and repeatedly negative antinuclear antibodies test results led to reevaluation for the possibility of scleredema. Skin biopsies from four body sites showed normal epidermis and thickened reticular dermis with swollen collagen bundles separated from one another by clear spaces, resulting in fenestration. The skin appendages were not atrophied or bound down. Alcian blue staining showed interstitial mucin deposition. Serum protein electrophoresis demonstrated an abnormal monoclonal band in the β-region with a paraprotein level of 8.9 g/dl. Immunofixation showed an abnormal band in the γ-region consisting of immunoglobulin A and κ. Bone marrow biopsy revealed abnormal monoclonal plasma cells (15%) with multinuclearity. There was no evidence of end organ damage, and whole-body magnetic resonance imaging did not reveal any evidence of bone involvement. The patient’s diagnosis was revised as scleredema type 2 associated with IgA-κ, and she was referred to a hemato-oncologist for chemotherapy, which led to significant improvement in the skin condition.

Conclusions: Scleredema is a rare disorder that has an enigmatic, rare association with monoclonal gammopathy. Dermatologists should be aware of this rare but important association.

Keywords: Scleredema, Smoldering myeloma, Monoclonal gammopathy

Introduction

Scleredema is rare sclerodermoid skin disease characterized by symmetrical diffuse woody induration of the upper part of the body owing to thickened dermis and excessive dermal mucin deposition. Though the commonest association of it is diabetes mellitus (type 3) [1], scleredema has been reported to occur with a history of an antecedent infection (type 1) and many other systemic diseases. Of them, monoclonal gammopathy was a recently described unusual association (type 2) with unknown significance. A high degree of suspicion is needed to differentiate scleredema from scleroderma when scleredema has a chronic course with generalized involvement. Owing to the rarity of the disease and subtle differences in the skin manifestation, histopathological assessment with mucin staining is invaluable in doubtful instances.

We report a case of a patient with long-standing widespread scleredema associated with immunoglobulin A-κ smoldering myeloma, which was misdiagnosed as scleroderma for many years. Only a few case reports are available in the literature on scleredema associated with myeloma; to the best of our knowledge, this is the first patient to be...
reported with scleredema who was diagnosed with smoldering myeloma of IgA-κ. This case report highlights the importance of awareness of scleredema because it is rare and can be misdiagnosed and, if diagnosed, it can be treated. We also include a detailed literature review.

**Case presentation**

A 66-year-old Sri Lankan woman who had been followed in a dermatology unit for 34 years for diffuse systemic sclerosis presented to our institution with an acute exacerbation of the skin disease. She was treated with corticosteroids and cyclophosphamide pulses and subsequently with mycophenolate mofetil for the skin condition. She did not have any other past medical or family history of systemic diseases, chronic infections, malignancies, or genetic diseases. She was a housewife, was unemployed, and was not exposed to any indoor or outdoor toxins, chemicals, or radiation. She was a nonsmoker and nonalcoholic.

On examination, she had widespread thickening of the skin predominantly involving the trunk and proximal extremities (Fig. 1). She did not have sclerodactyly, but she had deformities in keeping with osteoarthritis (Fig. 2). She denied cold-induced episodic acral bluish discoloration suggestive of Raynaud’s phenomenon. She was not febrile, and the result of her general examination was normal without pallor, cyanosis, clubbing, lymphadenopathy, or bilateral ankle edema. Her respiratory and cardiovascular examination results were normal with a heart rate of 82 beats per minute and a blood pressure of 130/80 mmHg. The result of her neurological examination was normal with normal funduscopy without any cranial neuropathy or peripheral neuropathy. Repeated echocardiography did not reveal any evidence of pulmonary hypertension. Upper gastroduodenoscopy did not show reflux disease. Radiographically, there was no evidence of interstitial lung disease. The patient’s autoimmune antibody profile (antinuclear antibody, anti-double-stranded DNA, perinuclear antineutrophil

![Fig. 1](image1.png) Widespread thickening of the skin predominantly involving the trunk and proximal extremities

![Fig. 2](image2.png) The patient did not have sclerodactyly but had deformities in keeping with osteoarthritis

### Table 1: Full blood count, liver function test, and serum electrolyte results

| Investigation       | Value     | Normal range | Comment |
|---------------------|-----------|--------------|---------|
| WBC                 | 9.32 × 10³/μl | 4–10         | Normal  |
| Lymphocytes         | 2.17 × 10³/μl | 0.8–4        | Normal  |
| Serum creatinine    | 0.9 mg/dl  | 60–120       | Normal  |
| Serum potassium     | 3.4 mmol/L | 3.5–5.1      | Normal  |
| AST                 | 27 U/L    | 10–35        | Normal  |
| Albumin             | 38 g/L    | 35–45        | Normal  |
| Alkaline phosphatase| 104 U/L   | 100–360      | Normal  |
| Ionized calcium     | 1.21 mmol/L| 1.0–1.3      | Normal  |
| Amylase             | 68 U/L    | 22–80        | Normal  |
| Neutrophils         | 6.09 × 10³/μl| 2–7         | Normal  |
| Platelets           | 277 × 10³/μl| 150–450      | Normal  |
| Serum sodium        | 138 mmol/L| 135–148      | Normal  |
| ALT                 | 20 U/L    | 10–40        | Normal  |
| INR                 | 1.26      | Normal       |         |
| Serum magnesium     | 1.7 mg/dl | 1.7–2.7      | Normal  |
| Troponin I          | < 0.1 ng/ml| < 0.5        | Normal  |

Abbreviations: ALT Alanine aminotransferase, AST Aspartate aminotransferase, INR International normalized ratio, WBC White blood cells
cytoplasmic antibodies, cytoplasmic antineutrophil cytoplasmic antibodies, anti-Smith antibody, anti-RO and anti-L.A, antitopoisomerase antibody, anticentromere antibody, and complements) was persistently negative, and her full blood count, urine full report, and renal and liver function were normal (Table 1). Absence of Raynaud’s phenomenon; sclerodactyly; characteristic lung, gastrointestinal, and cardiac involvement of systemic sclerosis; and repeatedly negative antinuclear antibody test results lead us to reevaluate the patient for the possibility of sclerodema.

Skin biopsies from four body sites showed normal epidermis and thickened reticular dermis with swollen collagen bundles separated from one another by clear spaces, resulting in fenestration. The skin appendages were not atrophied or bound down. Alcian blue staining showed interstitial mucin deposition suggestive of sclerodema. Serum protein electrophoresis demonstrated an abnormal monoclonal band in the gamma region with a paraprotein level of 8.9 g/dl. Immunofixation showed an abnormal band in the gamma region consisting of IgA and κ. Bone marrow biopsy revealed abnormal monoclonal plasma cells (15%) with multinuclearity. There was no evidence of end organ damage with normal calcium, renal function, and full blood count, and whole-body magnetic resonance imaging did not reveal any evidence of bone involvement (Fig. 3). The patient’s diagnosis was revised as sclerodema type 2 associated with IgA-κ smoldering myeloma. She was commenced on intravenous immunoglobulin (IVIG) monthly (1 g/kg for 2 days per month), and a hemato-oncologist started
intravenous bortezomib cycles (1.7 g on day 1, day 8, day 22, and day 29). Currently, she was receiving 6 months of IVIG and four cycles of intravenous bortezomib, and significant improvement of the skin was observed.

**Discussion**

In this report, we present a case of a patient with widespread thickening of the skin predominantly involving the trunk and proximal extremities for more than 30 years who was misdiagnosed with systemic sclerosis. Absence of Raynaud’s phenomenon; sclerodactyly; characteristic lung, gastrointestinal, and cardiac involvement of systemic sclerosis; and repeatedly negative antinuclear antibody test results led to re-evaluation of the diagnosis. Later she was diagnosed with scleredema with smoldering myeloma, and she responded well to treatment.

In keeping with the literature, even though sclerodema with monoclonal gammopathy is reported, multiple myeloma (MM)-associated sclerodema is rare. In 1974, Korting et al. reported one patient with MM; in 1984, Venencie et al. reported one patient with smoldering myeloma; and in 1987, Ohta et al. reported one patient with MM [2–4]. After that, several case reports were reported (Table 2). Seven were male patients, six were female, and the majority were above the age of 50. Interestingly, one patient was in his 20s [5]. Only two patients were reported with smoldering myeloma (one with IgG-κ and the other with IgG-λ) and sclerodema [2, 6] in the literature, and all the others had MM (five with IgG-κ, four with IgA-κ, one with IgG-λ, and one with IgA-λ; two had IgG and the light chain was not mentioned). This shows that the number of patients with IgG and IgA were observed in almost equal numbers and that the majority of patients had κ-light chains compared with λ-light chains (10 patients with κ, 3 patients with lambda). Even in sclerodema associated with monoclonal gammopathy without MM, IgG-κ predominates (10 of 23 cases in one review) [7]. Our patient is the first to be reported with sclerodema who was diagnosed with smoldering myeloma of IgA-κ.

The diffuse woody induration described in almost all the cases in the literature involved the face, neck, back, shoulders, chest, and upper arm. Similar to our patient, all the patients had skin manifestations for a long time before the diagnosis of myeloma, except in one case where the skin changes appeared while the patient was receiving treatment for myeloma [8]. As in our patient, none of the patients in the literature had Raynaud’s phenomenon; sclerodactyly; or characteristic lung, gastrointestinal, or cardiac involvement of systemic sclerosis, which is important to differentiate from systemic sclerosis. One case report described a patient with MM and sclerodema who developed cardiomyopathy. Deposition of acid mucopolysaccharide in the heart is proposed as the mechanism for this sclerodema cardiomyopathy [9]. Acanthosis nigricans [10] and myelofibrosis [5] are also described in patients with sclerodema and MM.

The possible pathology of monoclonal gammopathy and sclerodema is still not clear. Kovary et al. suggested that paraproteins may function as antibodies directed against connective tissues, but monoclonal immunoglobulins were not detected in the skin by direct immunofluorescence microscopy [11]. This is in contrast to scleromyxedema (lichen myxedematosus), from which sclerodema can be distinguished clinically and histologically [11]. Ohta et al. showed that serum from patients with sclerodema stimulates collagen production in normal skin fibroblast cultures, collagen production in autologous cell cultures, and sulfate incorporation into fibroblasts [4]. They suggested that circulating serum factors in these patients, possibly related to the paraproteins, may stimulate the synthesis of extracellular macromolecules by dermal fibroblasts, leading to dermal fibrosis. On the basis of these studies, we can postulate that immunological factors may play a role in the pathogenesis of sclerodema.

Interestingly, all the patients in the literature showed improvement of the skin condition with therapy. Different chemotherapy regimens, including melphalan, cyclophosphamide, vincristine, and thalidomide combined with steroids, were used in these cases (Table 1). A bortezomib-based regimen has also shown a convincing response [12, 13]. In the two case reports with sclerodema associated with smoldering myeloma, we were unable to find any specific therapy given for the skin condition. However, IVIG has shown significant skin condition improvement in two patients with sclerodema [13]. Grudeva-Popova and Dobrev suggested that noninvasive skin elasticity measurements can be used to assess improvement after treatment [8].

**Conclusions**

We highlight that sclerodema should be considered in the differential diagnosis of patients with diffuse skin thickening without characteristic features of systemic sclerosis. In these patients, it is also important to investigate for monoclonal gammopathy and myeloma. Even if...
| Year | Age  | Sex | Clinical features | Myeloma | Bone marrow plasma cells | Myeloma investigations | Treatment | Prognosis | Reference |
|------|------|-----|-------------------|---------|--------------------------|------------------------|-----------|-----------|-----------|
| 1974 | 37 M | 2 years of disease | MM (IgG-κ) | | Urine Bence-Jones-positive | Chemotherapy | Good response | [3] |
| 1984 | 69 M | Rapid onset of skin involvement of face and chest; 7 years of little change; rapid progression to involvement of the shoulders, arms, back, abdomen, and thighs over 2 years | Smoldering myeloma (IgG-κ) | | | | From the sixth cycle, clear clinical evidence of softening of the skin and improved joint mobility | [4] |
| 1987 | 64 M | Symmetrical woody induration of face, neck, chest, shoulders, upper back, chest, abdomen, thigh over 2 years | MM (IgG-κ); IgG concentration of 4500 mg/dl | | Urine immunoelectrophoresis IgG-κ monoclonal proteinuria, anemia; skeletal survey normal | Prednisolone 80 mg/day and melphalan 14 mg/day, given for 4 days and repeated monthly | | |
| 1988 | 72 F | Symmetrical woody induration of face, neck, chest, shoulders, upper back, chest, abdomen, thigh over 2 years | MM (IgG-κ); IgG concentration of 2900 mg/dl | | | | | |
| 1988 | 76 F | Stiffening of the skin of upper trunk, arms, neck, face over 24 h with woody induration | MM (IgA-κ); IgA 814 mg/dl | 20% | Urine κ-light chains, multiple lytic lesions on skull x-ray | IV cyclophosphamide 750 mg over 3 days, prednisolone 30 mg daily for 3 days; six pulses; each pulse over interval of 3 weeks | Complete recovery of scleredema and remission of MM | [15] |
| 1988 | 62 F | Thickening of skin over 23 years with induration over face, neck, thorax, arms with loss of movements of the underlying joints | MM (IgG-κ); IgG 2500 mg/dl | 40% | anemia; urine Bence-Jones κ-light chains, cardiomyopathy | Pulse chemotherapy | Death with sepsis | [9] |
| 1992 | 46 M | Stiffening of face, neck, back, shoulders, chest, arms, hands, fingers with woody induration | Smoldering myeloma (IgG-κ) | 28% | | | | |
| 1995 | 74 M | Marked induration of the skin of neck, shoulders, upper chest, back, and upper arms over 15 years | MM IgA-κ; IgA 2530 mg/dl | 67% | Anemia, Bence-Jones protein (κ-light chain), osteolytic lesions | Chemotherapy with intravenous vincristine, cyclophosphamide, oral melphalan, prednisone 90 mg; six cycles at 3-weekly intervals | After the sixth chemotherapy cycle, myeloma was in remission; marked improvement of the skin | [7] |
| 1997 | 56 F | Scleredema over the last 6 years with acanthosis nigricans | MM IgA-κ | | | Melphalan and prednisolone | Recovery | [10] |
| 2000 | 63 F | Thickening of the skin on the face, neck, shoulders, arms, and upper torso while receiving treatment for MM | MM IgG-κ; IgG 9600 mg/dl | 80% | Urine IgG-κ light chain protein, anemia, lytic lesions in the skull | Melphalan 10 mg/day, cyclophosphamide 200 mg/day, prednisolone 60 mg/day given for 5 days, vincristine 2 mg given on the first day, six courses with a 3-week gap | Softening of the skin observed from sixth treatment cycle | [8] |
| Year | Age (years) | Sex | Clinical features | Myeloma | Bone marrow plasma cells | Myeloma investigations | Treatment | Prognosis | Reference |
|------|-------------|-----|-------------------|---------|-------------------------|-----------------------|-----------|-----------|-----------|
| 2001 | 70          | F   | over 12 months of period, she had developed a progressive induration and stiffness of the skin of her face, neck, shoulders, and upper aspect of her arms | MM, IgA-λ; IgA, 1830 mg/dl | 38% | Urine Bence-Jones protein | Oral melphalan, oral prednisone; six pulses, each pulse at an interval of 1 month | Clinical evidence of softening of the involved skin observed | [16] |
| 2008 | 28          | M   | Eight years of progressive diffuse cutaneous thickening of face, trunk, arms, and thighs | MM, IgA-κ | 55% | Anemia, myelofibrosis | Thalidomide, dexamethasone | Improvement in the texture of the skin | [5] |
| 2013 | 60          | M   | Symmetric, nonpitting swelling of the face, neck, trunk, and upper extremities | MM, IgG-κ | 10% | Multiple osteolytic lesions | IV cyclophosphamide, bortezomib, dexamethasone; six cycles and autologous stem cell transplant | Skin induration gradually decreased during treatment with complete recovery | [12] |
| 2015 | 62 (two patients) | Generalized symptomatic sclerodema | IgG MM | IV cyclophosphamide, bortezomib, dexamethasone, and IVIG | Significant improvement | [13] |

Abbreviations: IgG Immunoglobulin G, IV Intravenous, IVIG Intravenous immunoglobulin, MM Multiple myeloma, M male, F female
the initial screening result is negative, serum protein electrophoresis should be performed at regular intervals because paraproteinemia may appear later and, when present, may progress to myeloma. This case report and others in the literature show that this condition is treatable with significant improvement of the skin condition.

Abbreviations
ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; IgG: Immunoglobulin G; INR: International normalized ratio; IV: Intravenous; IVIG: Intravenous immunoglobulin; MM: Multiple myeloma; WBC: White blood cells

Acknowledgements
None to declare.

Funding
No source of funding.

Availability of data and materials
The datasets supporting the conclusions of this article are included within the article.

Authors’ contributions
BSDPK and HMMTBH did the literature survey and prepared the main manuscript. BSDPK, GHDCJ, BSD, DPL, TB, and CNG were involved in the diagnosis and management of the patient. SCS and SRC assisted in the histopathological diagnosis. SRC and CNG did the proofreading and correction of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors declare that they have no competing interests.

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Received: 23 October 2018 Accepted: 4 April 2019
Published online: 14 May 2019

References
1. Rongioletti F, Kaiser F, Cinotti E, Metze D, Battistella M, Calzavara-Pinton PG, Danevcka K, Girolomoni G, Andrej J, Perrot JL, et al. Scleredema: a multicentre study of characteristics, comorbidities, course and therapy in 44 patients. J Eur Acad Dermatol Venereol. 2015;29(12):2399–404.
2. Venencie PY, Powell FC, Su WP. Scleredema and monoclonal gammopathy: report of two cases. Acta Derm Venereol. 1984;64(6):554–6.
3. Korting GW, Gilfrich HJ, Meyer zum Büschenfelde KH. Scleredema adultorum and multiple myeloma [in German]. Arch Dermatol Forsch. 1974;248(4):379–85.
4. Ohta A, Uitto J, Olkainen Al, Palatii R, Mitrane M, Bancila EA, Seibold JR, Kim HC. Paraproteinemia in patients with scleredema: clinical findings and serum effects on skin fibroblasts in vitro. J Am Acad Dermatol. 1987;16(1 Pt 1):96–107.
5. Rao S, Kar R, Pati HP, Saxena R. Scleredema-associated IgA myeloma with myelofibrosis in a young adult: a case report. Turk J Haematol. 2008;25(4):195–7.
6. Schmidt KT, Gattuso P, Messmore H, Shrit MA, Massa M, Welykyj S. Scleredema and smoldering myeloma. J Am Acad Dermatol. 1992;26(2 Pt 2):319–21.
7. Pujol JA, Bueno M, Fuettes MA, Gimenez H, Carapeto FJ. Improvement of scleredema associated with IgA multiple myeloma after chemotherapy. Clin Exp Dermatol. 1995;20(2):149–52.
8. Grudevova-Popova J, Dobrev H. Biomechanical measurement of skin distensibility in scleredema of Buschke associated with multiple myeloma. Clin Exp Dermatol. 2000;25(3):247–9.
9. Rimon D, Lurie M, Storch S, Halon D, Eisenkraft S, Laor A, Cohen L. Cardiomyopathy and multiple myeloma: complications of scleredema adultorum. Arch Intern Med. 1988;148(3):551–3.
10. Valente L, Velho GC, Farinha F, Bemardo A, Ribeiro P, Massa A. Scleredema, acanthosis nigricans and IgA/K multiple myeloma (in French). Ann Dermatol Venereol. 1997;124(8):537–9.
11. Kovary PM, Valizadeh F, Macher E, Zauh H, Merk H, Goerz G. Monoclonal gammopathy in scleredema: observations in three cases. Arch Dermatol. 1981;117(9):536–9.
12. Szturz P, Adam Z, Vasku V, Fejt J, Krejci M, Pour L, Hajek R, Mayer J. Complete remission of multiple myeloma associated scleredema after bortezomib-based treatment. Leuk Lymphoma. 2013;54(6):1234–6.
13. Krejci M, Adam Z, Pour L, Michalkova E, Sandecka V, Szturz P, Kral Z, Mayer J. Scleredema associated with multiple myeloma or MGUS: treatment report of four cases [abstract]. Clin Lymphoma Myeloma Leukemia. 2015;15(Suppl 3):e207.
14. Hodak E, Tamir R, David M, Hart M, Sandbank M, Pick A. Scleredema adultorum associated with IGL-κ multiple myeloma – a case report and review of the literature. Clin Exp Dermatol. 1988;13(4):271–4.
15. Salisbury JA, Shallcross H, Leigh IM. Scleredema of Buschke associated with multiple myeloma. Clin Exp Dermatol. 1988;13(4):269–70.
16. Santos-Juanes J, Ossuna CG, Iglesias JR, De Quiros JF, del Rio JS. Treatment with chemotherapy of scleredema associated with IgA myeloma. Int J Dermatol. 2001;40(11):720–1.