

Treatment of scleromyxedema with lenalidomide, bortezomib and dexamethasone: A case report and review of the literature

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Abstract

Scleromyxedema is a rare and progressive disease that currently has no standard treatment. Triplet therapy with lenalidomide, bortezomib, and dexamethasone can be an effective therapy for scleromyxedema, especially in patients with refractory or relapsed disease.

KEY WORDS

bortezomib, lenalidomide, paraproteinemia, plasma cells, scleromyxedema, treatment

1 | INTRODUCTION

Scleromyxedema currently has no standard treatment. Triplet combination chemotherapy, lenalidomide, bortezomib, and dexamethasone (RVD), is standard in plasma cell disorders, such as multiple myeloma. However, literature supporting its use in scleromyxedema is limited. We report a scleromyxedema patient who had complete clinical and very good hematologic response with RVD therapy.

Scleromyxedema is a rare disease that affects middle-aged adults (30–80 years) with similar incidence rates in males and females. The diagnostic criteria require a generalized papular and sclerodermoid eruption, histologic triad of mucin deposition and fibroblast proliferation, monoclonal gammopathy, and the absence of thyroid disease.¹ The most common monoclonal gammopathy is IgG with lambda light chains, observed in more than 80% of the patients.² Exact prevalence and incidence of scleromyxedema are unknown but as of 2009, 150 cases of patients have been reported.³

Scleromyxedema patients initially present with a gradual progression of a diffuse papular eruption over months, usually involving the hands and face.⁴ Advanced disease can be widespread, progressive, and unpredictable. Systemic symptoms associated with scleromyxedema are peripheral neuropathy, involvement of joints, lung involvement with dyspnea in

the form of restrictive or obstructive lung involvement, dysphagia,¹ and dermato-neuro syndrome. Dermato-neuro syndrome is a rare and sometimes fatal neurologic manifestation that can lead to fever, convulsions, and coma.⁵

Skin biopsy is the mainstay for diagnosis of scleromyxedema. Histologically, scleromyxedema is characterized by a triad of microscopic features—a diffuse deposit of mucin in the upper and mid-reticular dermis, an increase in collagen deposition and a marked proliferation of irregularly arranged fibroblasts.⁶ Evaluation for monoclonal gammopathy workup includes serum protein immunoelectrophoresis and immunofixation, urine protein immunoelectrophoresis and immunofixation, serum free light chain assay, and quantitation of immunoglobulins. Additional laboratories such as thyroid studies, rheumatologic studies, complete blood count, comprehensive metabolic panel, muscle enzymes, and urinalysis are routinely completed to evaluate for systemic disease, and to rule out thyroid dysfunction. Additional imaging and tests may be indicated for patients with extracutaneous symptoms depending on the specific organ involvement.

The course of scleromyxedema is unpredictable, especially due to the variable response to treatment and the high relapse rate after cessation of treatment. The overall survival rate at 3 years was reported to be 97% in a recent retrospective

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study,⁷ which is an improvement compared to 76.2% in a previous study.⁸

Treatment of scleromyxedema has been challenging due to the rarity and unclear pathogenesis of the disease. Currently, there are no randomized trials to compare different therapies. Treatments that have been frequently used to treat scleromyxedema include intravenous immunoglobulin (IVIG), steroids, thalidomide, autologous stem cell transplantation, and plasma cell-directed therapies. Treatment data have been largely limited to case reports and case series with variable success for initial and refractory disease. We report a case of scleromyxedema that responded to treatment with lenalidomide (R), bortezomib (V), and dexamethasone (D).

2 | CLINICAL CASE

A 73-year-old Caucasian man first developed redness on his bilateral volar forearms. He was prescribed topical steroid preparations for his skin lesions by a dermatologist which did not help. He subsequently developed concurrent bilateral upper extremity neuropathy and finger pad tenderness. He was evaluated by a neurologist for peripheral neuropathy; serum and urine protein electrophoresis were ordered. Laboratory evaluation revealed a small monoclonal protein spike measuring 0.3 g/dL with IgG lambda immunofixation. His skin findings progressed to woody firmness of the nose and extremities in conjunction with dome-shaped papules on the hands, digits, and upper back. Bone marrow biopsy was performed which revealed normal lineage hematopoiesis with no evidence of plasma cell dyscrasia. Flow cytometry revealed no clonal abnormality. His other workup included high normal hemoglobin likely secondary to testosterone supplementation, normal renal function, normal calcium, no evidence of bony lesions on skeletal survey, and free light chain ratio of 1.1. His thyroid function was normal and he was on exogenous levothyroxine. He had multiple dermatologic biopsies exhibiting classical features consistent with scleromyxedema including mucin production. He had trials of both methotrexate and systemic prednisone with little effect. His monoprotein cleared temporarily on laboratories drawn about one month prior to his initial hematology clinic visit, most likely due to methotrexate and/or prednisone exposure. At the time of presentation to the University of Arizona Cancer Center hematology clinic, he was only on single-agent prednisone. On the laboratories drawn on the day of his initial visit, his M protein was 0.3 g/dL. He also complained of mild dysphagia and abnormal bowel movements with bloating.

Initially, he was continued on Prednisone 40 mg daily, with a plan to start on IVIG 2 g/kg monthly. However, patient's health insurance did not provide coverage for the IVIG at the time. Due to this, the patient was instead started on

bortezomib 1.3 mg/m² once a week for one cycle (3 weeks). After the patient complained of worsening peripheral neuropathy of his hands after one cycle, bortezomib was held. Once insurance approval was obtained, the patient received a trial of IVIG but he reported worsening erythema in his extremities. He was then started on triple therapy with RVD Lite (lenalidomide 15 mg daily days 1-21, bortezomib 1.3 mg/m² weekly days 1, 8, 15, and 22 and dexamethasone 40 mg weekly on 35-day treatment cycle) with intent on treating the underlying clonal disease causing his cutaneous manifestations. Prednisone was tapered and switched to dexamethasone. After one cycle of RVD Lite, patient's cutaneous symptoms and dysphagia improved. His M protein remained detectable at 0.3 g/dL. For the second cycle of RVD Lite, lenalidomide was decreased to 10 mg due to complaint of fatigue. After 4 cycles of modified RVD Lite, bortezomib was stopped and only lenalidomide and dexamethasone were continued. Dexamethasone was decreased to 32 mg weekly due to concerns of chronic steroid use and feeling irritable on his off days and was eventually tapered off over 7 weeks. M protein of 0.1 g/dL reappeared at the subsequent laboratory after stopping dexamethasone. Patient was restarted back on Prednisone 5 mg daily after he complained of increased fatigue after stopping dexamethasone. His laboratory draws have fluctuated between M protein of 0.1 g/dL and no M protein despite being on the same regimen: Prednisone 5 mg daily and lenalidomide 10 mg daily days 1-21. Although his fatigue and neuropathic pain remains, his skin findings and dysphagia which resolved after starting RVD Lite has not returned.

3 | DISCUSSION

Effective treatment for scleromyxedema has been difficult to establish due to unclear pathogenesis of the disease. The role of paraproteins in the stimulation of fibroblasts and overproduction of mucin is not definitive. While serums from scleromyxedema patients have been shown to induce proliferation of fibroblasts *in vitro*,⁹ hyaluronic acid and prostaglandin E,¹⁰ the isolated paraproteins did not.⁹ These studies support case reports which have noted paraprotein levels do not correlate with disease outcomes, including our case. Our patient's M protein level fluctuated after tapering off dexamethasone even though he remained in clinical remission. A leading hypothesis is that circulating cytokines such as interleukin 1, tumor necrosis factor, and transforming growth factor-B play a central role in the pathogenesis of scleromyxedema. One recent study found scleromyxedema patients have abnormally high interleukin-4 secretion, a profibrotic cytokine.¹¹ Furthermore, the patients also had decreased levels of interferon-gamma cytokine, which are known to inhibit proliferation and

extracellular matrix production in fibroblasts.¹² The authors believe a chronic immune system activation against an unknown target antigen may be responsible for these changes.¹¹ However, a big limitation of this study is most of the patients were on therapy at the time of blood collection which may have altered relevant biological signals. There have also been two cases of scleromyxedema that developed after breast silicone implantation and injections of dermal fillers including hyaluronic acid, suggesting the disease can be triggered by adjuvants.^{13,14} Our patient may have improved with bortezomib and lenalidomide therapy as both are speculated to have immunomodulatory properties in addition to addressing plasma cell clones.^{15,16} There is a definite need for further studies with treatment-naïve patients to get a more accurate and clear pathophysiology behind scleromyxedema.

We reviewed published literature on treatment of scleromyxedema with an emphasis on plasma cell-directed therapies. In the past, melphalan was often considered first-line treatment for scleromyxedema but has since been discouraged due to high risk of death (over 30%) related to hematologic malignancies and septic complications.¹⁷ Recently, IVIG is recommended as a first-line treatment in scleromyxedema in multiple case reports due to its immunomodulatory potential and low incidence of severe side effects.^{7,18,19} It has been found to be effective for both cutaneous and extracutaneous symptoms. IVIG is hypothesized to have antifibrotic properties through modulation of cytokine production and it may have a role in blocking an unknown circulating factor.^{18,20} Frequent relapses after stopping treatment are common and long-term IVIG treatment with maintenance infusions is necessary to control the disease. However, as evident in our case, there may be delay in initiation of treatment with IVIG due to lengthy insurance approval process, high cost and, time-consuming administration. These treatment barriers are significant especially in the setting of requiring long-term maintenance to remain in remission.⁷

Other treatments which have reported success with scleromyxedema include thalidomide²¹⁻²⁴ and autologous stem cell transplantation (ASCT).²⁵ Thalidomide's mechanism of action in treatment of the disease is not clear but is thought to have antiangiogenic properties that block fibroblast growth.²⁰ Thalidomide is teratogenic and can cause peripheral neuropathy. It is also known to cause prothrombic activity.²⁶ Due to our patient's complaint of peripheral neuropathy on initial presentation to our clinic, we opted for lenalidomide which is a derivative of thalidomide with a more favorable toxicity profile. The first case of treating refractory scleromyxedema with ASCT was reported in 2001.²⁵ Since 2001, 17 patients have been treated with ASCT; 50% of the patients had complete remissions of all clinical symptoms, including serum paraprotein and 29% had partial remission.²⁷ Only 12% of

patients had persistent complete remission at a median follow-up of over 40 months. It is suggested that pre-induction of thalidomide and dexamethasone prior to ASCT may improve the long-term outcome.²⁷ We did not pursue ASCT for our patient due to his advanced age.

Prior to presentation to our hematology clinic, our patient was taking oral prednisone 40 mg. There are case reports (Table 1) of successful treatment of scleromyxedema with prednisone or dexamethasone alone.^{28,29} It is hypothesized dexamethasone pulse dose can rapidly suppress inflammatory conditions and it can target both the paraprotein production and hyperactive fibroblasts through its immunosuppressive and anti-fibroblast effects.^{30,31} Due to its relatively safe side effects profile compared to alkylating agents, corticosteroid therapy can be considered as a first-line option. However, the rate of treatment success with steroids alone is low. On review of 25 patients with scleromyxedema, two patients received steroids alone and had treatment failure.⁸ Similarly, a retrospective study of 33 scleromyxedema patients showed corticosteroids alone (0.75 mg/kg/day of equivalent prednisone) was successful in only 1 patient out of 3 total.⁷ This was similar to our patient as he had treatment failure with oral prednisone alone. Due to its ineffectiveness alone, glucocorticoids are more often used in conjunction with other treatment regimens such as melphalan, methotrexate, thalidomide, hydroxychloroquine, cyclophosphamide, and bortezomib.⁸

Prior literature has reported bortezomib and lenalidomide used in combination with dexamethasone or IVIG (Table 1) for treatment of scleromyxedema. Bortezomib was first used for refractory scleromyxedema as a maintenance therapy in 2008³² and has found success with dexamethasone in two cases.^{15,33} Possible mechanism of bortezomib is thought to be due to the direct apoptotic effects on the plasma cell clone but is speculated to also have an "immunosuppressive" effect.¹⁵ Lenalidomide was first used to treat refractory scleromyxedema in 2013. The pathophysiology of lenalidomide is thought to stimulate natural killer cell activity and increase IL-2 production which enhances T-cell activity. It is speculated IVIG and lenalidomide may have a synergistic effect as both have antifibrotic properties, present in mouse model.³⁴ Lenalidomide may sustain remission due to its immunomodulatory properties and its tolerability profile compared to thalidomide, especially for patients with neuropathy¹⁶ such as ours. A recent retrospective study recommended adding bortezomib and dexamethasone or lenalidomide and dexamethasone to IVIG for patients who have IVIG refractory disease.⁷ The same study reported the first known case of scleromyxedema patient treated with RVD therapy. The patient had IVIG refractory disease and had treatment failure with IVIG as well as a treatment regimen of bortezomib, cyclophosphamide, and dexamethasone. With RVD therapy, the patient had near complete clinical response and complete hematologic

TABLE 1 Bortezomib, lenalidomide, and dexamethasone use in scleromyxedema: A Literature Review

Author	Title	Outcome	Limitations
Horn, K, B. 2004 ²⁹	A complete and durable clinical response to high-dose dexamethasone in a patient with scleromyxedema	<ul style="list-style-type: none"> ■ A 63-year-old man with scleromyxedema limited to the skin and IgG lambda monoclonal protein received 3 consecutive weekly cycles each month of oral high-dose dexamethasone 40 mg once daily for four days (total: 160 mg/week) for four months. He remained on oral dexamethasone 40 mg once daily for maintenance for four days every month. ■ His cutaneous symptoms resolved and his IgG paraproteinemia disappeared for over one year, suggesting that dexamethasone therapy can target both paraproteinemia and SM. ■ Case report argues that corticosteroid can be a good, potential first-line therapy as it is well tolerated while alkylating agents with significant toxicities should be reserved for refractory scleromyxedema. 	<ul style="list-style-type: none"> ■ Small sample size ■ Due to the short follow-up time, it is uncertain how durable the therapy is ■ Article did not mention the side effects of long-term steroids ■ Did not address appropriate duration for maintenance dexamethasone
Kreuter, A. 2005 ²⁸	High-dose dexamethasone in scleromyxedema: report of 2 additional cases	<ul style="list-style-type: none"> ■ Case report of two women (48 and 55 years old) with scleromyxedema who have failed treatment with methotrexate and extracorporeal photopheresis. The same oral dexamethasone regimen reported by Horn was used. ■ While high-dose dexamethasone did improve their skin findings, IgG paraprotein did not disappear during therapy ■ Case report emphasizes that long-term follow-up is mandatory for recurrence of disease especially as underlying monoclonal gammopathy cannot be eliminated 	<ul style="list-style-type: none"> ■ Similar limitations as above
Ataerigin, S. 2008 ³²	Transient efficacy of double high-dose chemotherapy and autologous peripheral stem cell transplantation, immunoglobulin, thalidomide, and bortezomib in the treatment of scleromyxedema	<ul style="list-style-type: none"> ■ A 38-year-old man with IgG lambda monoclonal gammopathy and scleromyxedema whose papular mucinosis did not resolve despite treatment with oral cyclophosphamide, methylprednisolone, interferon-alpha, autologous stem cell transplantation (ASCT), immunoglobulin and thalidomide. A second ASCT was performed to consolidate the efficiency of the first transplant and only after the second transplant, patient's IgG level had returned to normal and papular lesions regressed. ■ Thalidomide (100 mg/day) and low-dose bortezomib 1.5 mg/day on days 1,4,8 and 11 every 3 weeks for 6 cycles was used as maintenance therapy ■ Patient had transient remission of paraproteinemia and skin lesions that lasted 30 months ■ Highlights need for durable and curative therapies 	<ul style="list-style-type: none"> ■ Uncertain of bortezomib's efficacy as a maintenance therapy as it was stopped at 6 cycles (3 weeks each) ■ Did not address tolerability or side effects of each treatment modality
Migkou, M. 2011 ¹⁵	Response to Bortezomib of a patient with scleromyxedema refractory to other therapies	<ul style="list-style-type: none"> ■ 70-year-old man with scleromyxedema and monoclonal IgG lambda gammopathy was initially treated with intravenous methotrexate, oral melphalan and low-dose methylprednisolone with no improvement of his skin lesions or reduction of his M protein. Lenalidomide/dexamethasone was trialed but symptoms worsened. ■ Skin lesions only resolved with 8 cycles of bortezomib and dexamethasone. There was also reduction of M protein levels but the hematologic response to bortezomib was modest. 	<ul style="list-style-type: none"> ■ Uncertain whether symptoms returned due to short follow-up time ■ Did not mention possible side effects of Bortezomib
Canueto, J. 2012 ³³	The combination of bortezomib and dexamethasone is an efficient therapy for relapsed/refractory scleromyxedema: a rare disease with new clinical insights	<ul style="list-style-type: none"> ■ 29-year-old woman with scleromyxedema who relapsed after melphalan and autologous peripheral blood stem cell transplantation achieve complete response with 7 courses of 21 day regimen of bortezomib (1.3 mg/m², days 1,4,8, and 11) and dexamethasone (20 mg/d, days 1,2,4,5,8,9,11 and 12). ■ Skin lesions responded before M component modifications, suggesting paraprotein is not the pathogenic substance 	<ul style="list-style-type: none"> ■ Small sample size ■ Short follow-up time (9 months)

(Continues)

TABLE 1 (Continued)

Author	Title	Outcome	Limitations
Brunet-Possenti, F. 2013 ¹⁶	Combination of intravenous immunoglobulins and lenalidomide in the treatment of scleromyxedema	<ul style="list-style-type: none"> ■ 44-year-old man with scleromyxedema and lambda light chain monoclonal gammopathy failed multiple treatments including hydroxychloroquine, corticosteroid therapy and thalidomide. ■ Improvement of skin changes after starting on lenalidomide (25 mg per day, 3 weeks a month). Monthly infusions of IVIG (2g/kg) was added and combined treatment led to complete regression of scleromyxedema. Paraproteinemia persisted. ■ Case report shows that lenalidomide can be used as a maintenance therapy and is better tolerated than thalidomide with less somnolence, constipation and neuropathy ■ Also shows that IVIG and lenalidomide may have a synergistic effect 	<ul style="list-style-type: none"> ■ Short follow-up time - around 24 hours after last IVIG administration
Mahévas, T. 2020 ⁷	Plasma cell-directed therapies in monoclonal gammopathy-associated scleromyxedema	<ul style="list-style-type: none"> ■ Multicenter French retrospective study of 33 scleromyxedema patients. Patients were defined to have severe scleromyxedema if there was neurological and cardiac involvement ■ Provided a treatment algorithm for scleromyxedema with IVIG (2 g/kg) every month as a first-line therapy due to high efficacy and good safety profile with maintenance for at least six months ■ Recommended plasma cell-directed therapies such as lenalidomide or bortezomib plus dexamethasone combined with IVIG for IVIG refractory or severe scleromyxedema ■ Reported first known case of successful treatment with RVD therapy ■ Found increased levels of TGFβ and collagen 1-a in skin samples - highlights need for prospective studies targeting fibrotic pathways or plasma cell clones to gain insights into pathophysiology of scleromyxedema and to guide therapeutic strategies ■ Argued that mortality rate of scleromyxedema patients have decreased and this may be due to increase use in IVIG therapies 	<ul style="list-style-type: none"> ■ Does not address difficulties with IVIG treatment although it is recommended as first-line treatment ■ Limited sample of patients for skin biopsy (n = 6)

response. The successful responses to RVD therapy of this patient and our patient are encouraging, especially in the treatment of severe, refractory disease.

4 | CONCLUSION

We have presented a case of successful treatment of scleromyxedema with RVD therapy. After 4 cycles of RVD Lite, our patient had complete clinical and very good hematologic response. Having a new treatment option for severe or refractory scleromyxedema is imperative as the course of the disease is unpredictable and progressive with high relapse rates. Review of literature and the case study show RVD may be an effective triplet therapy for the treatment of scleromyxedema. In contrast to glucocorticoids and IVIG, RVD therapy may represent a more potent therapeutic approach to address underlying plasma cell clone especially in patients with refractory or relapsed disease. Pathophysiology of scleromyxedema remains

poorly studied. Priority should be placed on recruiting treatment-naïve scleromyxedema patients for prospective studies. Patient's blood samples should be collected prior to treatment and be compared to blood samples collected after treatment with agents known to target fibrotic pathways or plasma cell clones. Additional research is needed to better understand the underlying pathophysiology and treatment of this rare disease.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

HW: analyzed the data, performed literature review, and drafted the manuscript. KG: conceived of the study, provided

data, supervised, reviewed, and edited the manuscript. All authors read and approved the final manuscript.

ETHICAL APPROVAL STATEMENT

This case report was conducted in accordance with the Declaration of Helsinki. The collection and evaluation of all protected patient health information was performed in a Health Insurance Portability and Accountability Act (HIPAA)—compliant manner. Informed consent was obtained for publication.

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