Rapid response of plasmacytomas to lenalidomide plus low-dose dexamethasone therapy in a patient with relapsed multiple myeloma

To the editor: Plasmacytomas have sometimes been seen at the time of diagnosis or during the course of multiple myeloma (MM) [1,2]. Although the development of multiple plasmacytomas is considered to be associated with aggressive disease and poor prognosis of MM [2], a strategy for MM with multiple plasmacytomas has not been established. Herein, we present a relapsed MM patient who achieved a rapid response of plasmacytomas to lenalidomide plus low-dose dexamethasone (Rd) therapy. A 57-year-old Japanese woman was diagnosed immunoglobulin G lambda-type MM in July 2003. Abnormal cytogenetics including 13q-/-13 were not detected in metaphases. She achieved a complete response with three courses of ranimustine, vincristine, melphalan, and dexamethasone (ROAD) therapy and five courses of bortezomib-based therapy, at diagnosis and at first relapse in 2009, respectively. In December 2010, 7 months after the last chemotherapy, she complained of painless tumors of the head, numbness of the left leg and lumbago. Her serum β2-microglobulin was elevated (5.0 mg/l) and IgA and IgM were suppressed (67 and 33 mg/dl, respectively) while her IgG was normal (1,040 mg/dl). Her hemoglobin and serum albumin were 10.9 and 3.4 g/dl, respectively. Computed tomographic (CT) scan showed three skull tumors (5.0 cm × 3.5 cm, 2.5 cm × 0.5 cm, and 1.5 cm × 0.5 cm, Fig. 1A). ^{18}FDG-PET/CT scan showed systemic multiple positive lesions, including three skull tumors and systemic bone and bone marrow. She was therefore diagnosed with second relapse of MM with multiple plasmacytomas. Although bortezomib-based multidrug combination therapies are recommended for MM with multiple plasmacytomas [3], we decided on Rd therapy with 40% dose reduction of lenalidomide because she had a history of discontinuation of chemotherapy due to severe adverse events. Lenalidomide (15 mg) and dexamethasone (10 mg) were administered orally on days 1–21 and on days 1, 8, 15, and 22 of each 28-day cycle, respectively. A CT scan on day 20 of the first course of Rd therapy revealed complete disappearance of plasmacytomas of the skull (Fig. 1B). Numbness of the left leg and lumbago also disappeared after the first course of Rd therapy. To date (June 2011), six courses of Rd therapy have been administered without ≧Grade 3 adverse events and she has been symptom free. Although thalidomide has been considered ineffective for plasmacytomas [2,4] and lenalidomide is an analog of thalidomide, some reports have mentioned the efficacy of lenalidomide for MM with multiple plasmacytomas [5–9]. Antiangiogenic efficacy of lenalidomide is stronger than that of thalidomide [10], which may be one of the reasons for the clinical efficacy of lenalidomide for plasmacytomas because plasmacytomas have increased angiogenic activity [11]. Furthermore, a rapid response for plasmacytomas and rapid disappearance of symptoms associated with MM suggest that lenalidomide may have direct antiproliferation mechanisms for myeloma cells. In conclusion, this case report indicates that lenalidomide may be a promising agent and Rd therapy may be one of the options for MM with multiple plasmacytomas. Prospective trials should be conducted to confirm the efficacy of lenalidomide-based therapy for MM with multiple plasmacytomas.

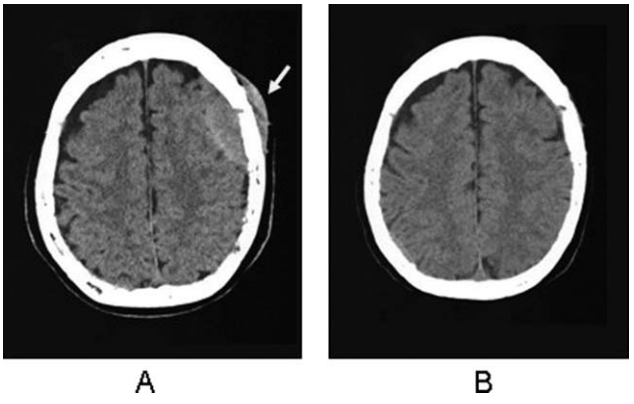

Figure 1. CT scan before (A) and on day 20 of the first course of lenalidomide plus low-dose dexamethasone (Rd) therapy (B). Arrow indicates plasmacytoma at the parietal bone. Plasmacytoma disappeared completely during the first course of Rd therapy.

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Scleromyxedema and dermato–neuro syndrome in a patient with multiple myeloma effectively treated with dexamethasone and bortezomib

To the editor: Scleromyxedema is a rare systemic mucinosis most frequently associated with an underlying IgG lambda gammopathy. Patients with scleromyxedema commonly have associated neurologic symptoms [1]. However, dermato–neuro syndrome, defined as scleromyxedema with concomitant fever, convulsions, and coma, is a rare manifestation of the disease with 11 cases described in the literature to date [2–12]. Effective treatment of dermato–neuro syndrome with intravenous steroids, plasmapheresis, and intravenous immunoglobulin (IVIG) has been described previously [2–12]. We describe a case of scleromyxedema and dermato–neuro syndrome with concomitant multiple myeloma effectively treated with a combination of bortezomib and dexamethasone. Combination therapy with bortezomib and dexamethasone resulted in complete resolution of the patient's cutaneous and neurologic signs and symptoms, as well as a complete serologic response, with normal serum protein electrophoresis (SPEP) and urine protein electrophoresis (UPEP), negative immunofixation of both serum and urine, and a normal serum-free light chain analysis. We propose that dexamethasone in combination with bortezomib may be an additional therapeutic option for patients with scleromyxedema and dermato–neuro syndrome.

A 56-year-old man presented to the clinic for evaluation of lethargy, mental slowing, paraphasias, dysarthria, dysphagia, tremors, a tonic–clonic seizure,

and sheets of 1–2 mm waxy, firm, flesh colored papules in the setting of newly diagnosed IgG lambda multiple myeloma.

The patient reported that ~1 year before presentation he had noted skin thickening over his dorsal fingers, knees, and elbows, as well as nodularity of his ears. His symptoms progressed to include fatigue, word-finding difficulties, incoordination, and severe dysphagia resulting in a 30 pound weight loss. His alcohol consumption was limited to two to three drinks per week. He presented to his primary care doctor 3 months before presentation at our facility after developing tremors. He was found to have an elevated serum total protein level. SPEP revealed an M spike quantitated at 2.1 g/dL and identified on immunofixation as IgG lambda. A 24-hr urine collection contained 710 mg of protein, with electrophoresis revealing a faint band in the gamma region, identified on immunofixation as free lambda light chain. Serum-free light chain analysis was also abnormal, with kappa light chains 6.8 mg/L, lambda light chains elevated at 41 mg/L, and kappa:lambda ratio low at 0.17. A bone marrow biopsy demonstrated a hypercellular marrow with 30% plasma cells that were lambda light chain restricted by immunohistochemistry, consistent with IgG lambda-secreting multiple myeloma. Laboratory investigation revealed a normal thyroid stimulating hormone (TSH), complete blood count, serum creatinine, calcium, and albumin. A skeletal survey showed no evidence of lytic bone lesions. After 1 week of lenalidomide and dexamethasone his IgG decreased to 2,590 (from 4,270) and M-spike decreased to 1.6 (from 2.1). One month before presentation at our facility and 1 week into lenalidomide and dexamethasone treatment, the patient presenting to a local ER with fever, increased fatigue and weakness, confusion, dysarthria, and worsening dysphagia. Upon presentation to the ER, he had a tonic–clonic seizure and required endotracheal intubation. Lumbar puncture revealed elevated protein levels but normal cell counts and glucose. electroencephalography (EEG) was consistent with encephalopathy without a seizure focus. His condition slowly improved with supportive care and broad spectrum antibiotic coverage. Therapy with lenalidomide and dexamethasone was stopped. He continued to have severe dysphagia, and a percutaneous endoscopic gastrostomy (PEG) tube was placed for enteral nutrition. Dermatologic evaluation revealed physical findings consistent with scleromyxedema. A skin biopsy revealed increased fibroblasts and widening of collagen bundles because of interstitial mucin deposition, consistent with scleromyxedema (Fig. 1).

His care was then transferred to our facility. On presentation he was thin and chronically ill appearing. He displayed obvious mental slowing with word-finding difficulties and dysarthria. His gait was ataxic, and he had difficulty with fine motor skills. His muscle strength was impaired in all four extremities, and reflexes were 2/5 throughout.

Skin exam revealed innumerable 1–2 mm waxy, firm, flesh colored papules over the extensor surfaces of his knees and elbows, posterior helixes and helical rims, lower abdomen, and glabellar region with early signs of leonine facies, and the characteristic "donut sign" (infiltration of over the dorsal finger joints; Figs. 2–4). An esophagram revealed esophageal aperistalsis. Repeat laboratory evaluation revealed albumin of 1.9 mg/dL, M-spike of 2.3 and IgG of 3,700 and normal serum viscosity of 1.38 cP.

He was treated with a combination of bortezomib and dexamethasone for 8 months, followed by an additional 4 months of bortezomib monotherapy. He had one additional episode of fever and seizure 1 month into therapy, but has since been seizure free. His skin lesions have resolved (Figs. 5 and 6). After 8 months of treatment, he achieved a complete serologic response, with normal SPEP and UPEP, negative immunofixation of both serum and urine, and a normal serum-free light chain analysis. His esophageal aperistalsis resolved, resulting in removal of the PEG tube. His mentation returned to his baseline. His gait, fine motor skills, muscle strength, and reflexes normalized as well. He remains well 12 months into therapy.

Scleromyxedema is a rare systemic mucinosis that is most commonly seen in middle-aged patients with an underlying IgG lambda gammopathy. It is estimated that less than 10% of patients with scleromyxedema will progress to overt multiple myeloma [13,14]. The remaining 90% of patients develop progressive infiltration of their internal organs associated with significant morbidity and mortality [4,12,14].

The pathogenesis of scleromyxedema remains elusive. The majority of patients with scleromyxedema have a concomitant monoclonal gammopathy of unknown significance. The serum of these patients has been shown to induce fibroblast proliferation in vitro, as well as increase fibroblast production of hyaluronic acid and prostaglandin E; however, the purified immunoglobulin alone does not induce these effects in vitro [14,15]. The level of paraproteinemia does not correlate with skin or systemic findings [14,15]. It has been suggested that the paraproteinemia may be a response to an unknown inciting factor and not the cause of disease manifestations.

Scleromyxedema typically presents with symmetric sheets of linearly arranged 2–3 mm waxy, firm, flesh colored papules most commonly involving the face, neck, forearms, and dorsal hands [14]. Infiltration of the face may result in leonine facies and a decreased oral aperture. Thickening of the skin on the hands and extremities results in decreased range of motion. Involved areas may also develop alopecia.

Characteristic histological findings are an increase in fibroblasts, stromal cells, and thickened collagen with variable amounts of mucin deposition in the upper and mid-reticular dermis [16]. Diagnosis requires the combination of the characteristic generalized papular sclerodermoid eruption, histological findings of increased fibroblasts and mucin, presence of a monoclonal gammopathy, and the absence of thyroid disease [16,17].

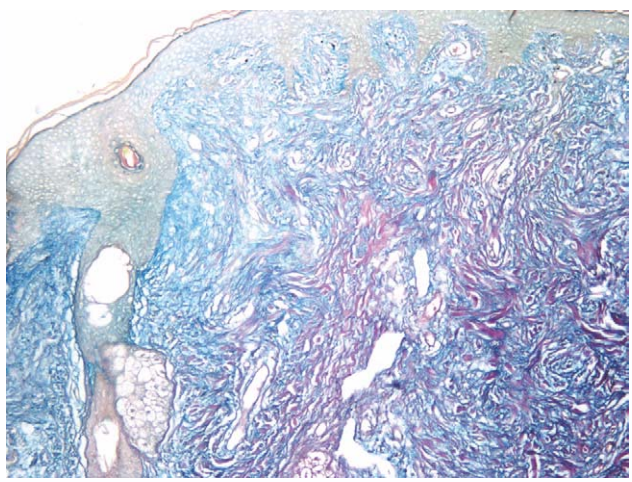

Figure 1. 20× colloidal iron stain revealing increased fibroblasts and widening of collagen bundles due to interstitial mucin deposition, consistent with scleromyxedema. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

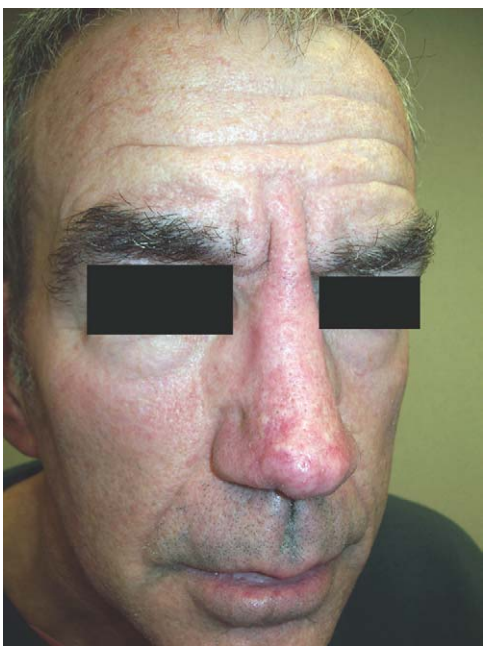

Figure 2. Sheets of 1–2 mm flesh colored papules infiltrating forehead, glabella, upper cutaneous lip and nose resulting in leonine facies. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

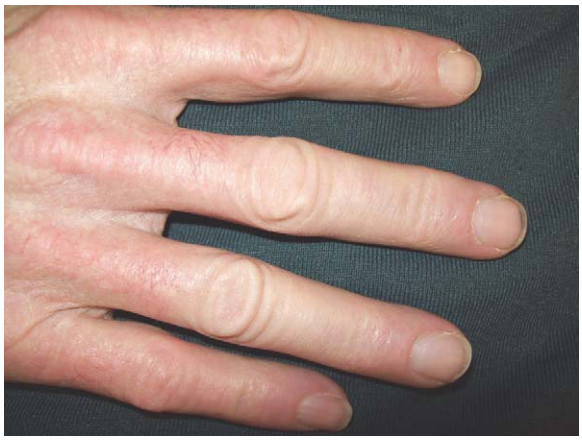

Figure 3. Sheets of 1–2 mm flesh colored papules over the dorsal aspects of the fingers with infiltration of the dorsal hand joints, resulting in the characteristic "donut sign." [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

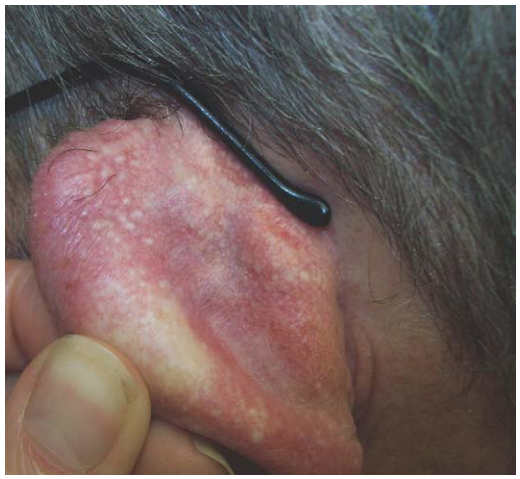

Figure 4. Flesh colored papules over the pinna. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Scleromyxedema is associated with a myriad of systemic manifestations including dysphagia, dysarthria, dyspnea, weakness, peripheral neuropathy, carpal tunnel syndrome, arthritis, myalgias, myositis, myocardial infarction, restrictive lung disease, cerebral vascular accidents, memory loss, gait problems, fevers, encephalopathy, seizures, and coma [1,9,10,14,15]. Esophageal dysmotility is the most common extracutaneous manifestation [14]. Scleromyxedema has also been reported to present with a "dermato–neuro syndrome" characterized by fevers, seizures, and coma [10]. To date, 11 such patients have been described in the literature [1–12].

Scleromyxedema is a chronic, progressive disease that is associated with high morbidity and mortality. A number of therapies have been reported to be varyingly successful in case reports and case series including high dose systemic corticosteroids, psoralen with ultraviolet A (UVA), electron beam radiation, retinoids, plasmapharesis, IVIG, extracorporeal photochemotherapy, dermabrasion, mephalan, cyclosporine, cyclophosphamide, methotrexate, chlorambucil, α-interferon, autologous stem cell transplant (ASCT) after conditioning with melphalan and thalidomide, ASCT after conditioning with carmustine, etoposide, cytarabine, and melphalan (BEAM), and thalidomide [14,15,18]. Treatments with thalidomide and IVIG, sometimes in combination, have been reported most frequently [15,19]. Patients with dermato–neuro syndrome have been reported to respond well to systemic steroids, plasmapheresis and IVIG [2–12].

The recent introduction of highly effective novel antiplasma cell therapeutic agents, such as bortezomib, thalidomide, and lenalidomide, provides a much higher likelihood of achieving complete paraprotein responses, especially when combined with the use of high-dose chemotherapy and autologous stem cell transplant. The favorable toxicity profile of these agents makes them reasonable treatment considerations for patients with scleromyxedema, even without classic manifestations of symptomatic multiple myeloma. To date, therapy with bortezomib in combination with dexamethasone has not been reported to result in significant skin and systemic improvement of scleromyxedema.

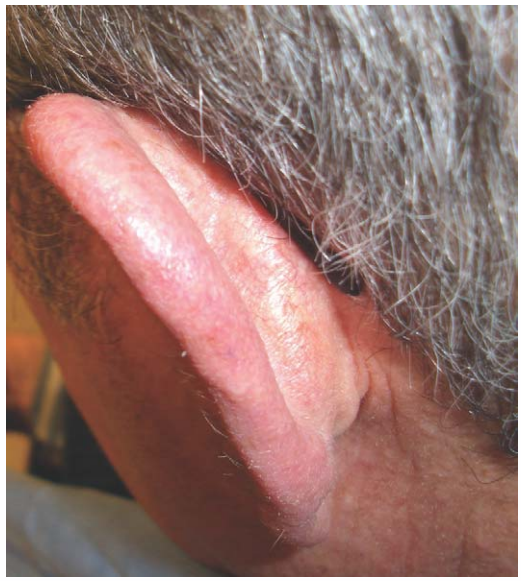

Figure 5. Resolution of flesh colored papules on the pinna after treatment with dexamethasone and bortezomib. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

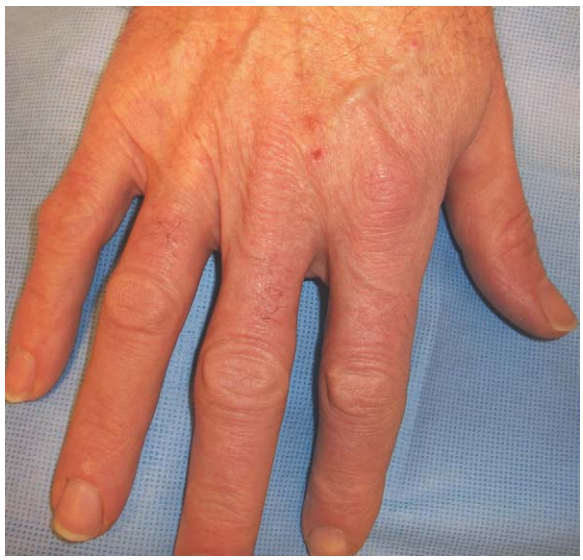

Figure 6. Resolution of flesh colored papules over the dorsal fingers with decrease in dorsal hand joint infiltration. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Our patient presented with typical findings of scleromyxedema, including characteristic skin findings, esophageal dysmotility, and neurologic dysfunction. His symptoms progressed over a year before a diagnostic skin biopsy and appropriate therapy were initiated. Although the percentage of plasma cells in his bone marrow defines a diagnosis of multiple myeloma, he had none of the classic manifestations of active multiple myeloma (such as hypercalcemia, renal insufficiency, anemia, or bone lesions), so that apart from the diagnosis of scleromyxedema, his disease was best characterized as smoldering multiple myeloma. His treatment with the proteasome inhibitor bortezomib and relatively low doses of corticosteroids resulted in a complete paraprotein response, accompanied by a dramatic reduction in all

the manifestations of his disease. As proteasome inhibition is not known to directly affect fibroblast physiology, it seems reasonable to assume that in his case it was the antiplasma cell activity of the treatment that led to his symptomatic improvement. It is possible that fibroblast stimulation in his case was directly due to his paraprotein, to the presence of monoclonal serum-free light chains, or to some other factor secreted by his malignant plasma cells.

In conclusion, we present a patient with scleromyxedema and a dermato–neuro syndrome associated with an otherwise asymptomatic IgG lambda multiple myeloma. Treatment with bortezomib and dexamethasone resulted in a complete paraprotein response, accompanied by a dramatic improvement in his skin and resolution of neurologic symptoms. Early recognition of this rare syndrome and treatment with effective antiplasma cell therapy has the potential to reduce its morbidity and mortality.

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