SHORT COMMUNICATION

Dermato-neuro Syndrome after COVID-19 Vaccination in a Patient with Scleromyxoedema Previously Controlled with Bortezomib and Intravenous Immunoglobulins

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Accepted Nov 17, 2022; Published Dec 13, 2022
Acta Derm Venereol 2022; 102: adv00836. DOI: 10.2340/actadv.v102.4430

Scleromyxoedema (SMX) is a rare, chronic and progressive connective tissue disorder of unknown origin, characterized by fibro-mucinous skin lesions associated with increased serum monoclonal immunoglobulin levels. It affects middle-aged adults (age range 30–80 years) with similar incidence rates in males and females. The diagnostic criteria for SMX include: a generalized papular and sclerodermoid cutaneous eruption; evidence of monoclonal gammopathy; a characteristic pathological triad associating dermal mucin accumulation, increased collagen deposition and fibroblast proliferation; absence of thyroid disease to exclude lichen myxoedematosus (1, 2). Apart from the skin, SMX can involve other organs, and may be associated with a variety of gastrointestinal, pulmonary, cardiac, renal and neurological complications. The latter include dermato-neuro syndrome (DNS), a rare, potentially fatal complication, presenting as fever, seizures and coma with flu-like prodromes (3). The pathogenesis of the disease remains obscure, although plasma cell-associated monoclonal gammopathy or dysregulated cytokine stimulation of glycosaminoglycans synthesis and fibroblast proliferation have been postulated (4).

SMX is notoriously difficult-to-treat. Intravenous immunoglobulins (IVIG) are considered the first-line choice of treatment. The next-line options for unresponsive patients are systemic glucocorticoids and thalidomide or lenalidomide as an add-on therapy. Alternative therapeutic options include melphalan, bortezomib plus dexamethasone, and autologous stem cell transplantation (4, 5).

We report here a patient who was successfully treated with bortezomib as additional therapy following clinical deterioration of her SMX previously controlled by IVIG plus oral prednisone. Despite regained remission of her skin manifestations she later developed DNS following SARS-CoV-2 vaccination and required treatment with plasmapheresis.

CASE REPORT

A 41-year-old woman with a 7-year history of SMX typically associated with light chain λ IgG monoclonal gammopathy presented with sudden deterioration of her skin lesions. The disease had so far been controlled by IVIG plus oral prednisone. The latter had been added after an early response to IVIG alone followed by relapse upon their discontinuation and partial tachyphylaxis upon their reintroduction.

Clinical examination revealed a severe generalized sclerodermoid eruption with typical SMX features (**Fig. 1**). The patient also referred numbness of the upper extremities suggestive of peripheral neuropathy.

Histology of lesional skin biopsies showed abundant interstitial mucin between collagen bundles in the dermis with proliferation of fibroblasts, dermal fibrosis and sclerosis, confirming the diagnosis of SMX. Complete blood count, kidney, liver, thyroid function tests and urinalysis were normal. A serum protein electrophoresis showed an IgG dosage of 3,369 mg/dl and a characteristic Mspike in the gamma region (0.8 g/l gammaglobulins). Serum immunofixation electrophoresis confirmed the presence of an IgG monoclonal light chain protein, while urine immunofixation electrophoresis was negative. No CRAB (C=calcium, R=renal failure, A=anemia, B=bone lesions) criteria of myeloma were found. After consultation with a neurologist and a haematologist, bortezomib with dexamethasone as add-on therapy was chosen, discarding thalidomide/lenalidomide due to their teratogenic and neuropathic effects. Bortezomib (Velcade©, Janssen-Cilag, Latina, Italy) 1.3 mg/m^2) plus dexamethasone (Soldesam© (Laboratorio Farmacologico Milanese, Caronno Pertusella, Italy) 40 mg/dose) were administered on days 1, 8, 15, and 22 per month for a total of 9 cycles. Parallel IVIG treatment was continued, while oral

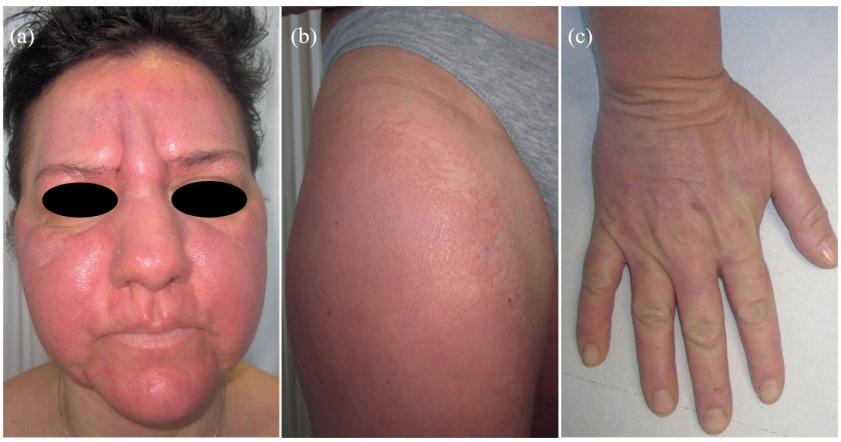

Fig. 1. Typical manifestations of severe scleromyxoedema in the current patient. (a) Erythema and firm oedema of the face with deep glabellar furrows resulting in characteristic facies leonine. (b) Diffuse erythema and induration of the thighs, resulting from the coalescence of innumerable firm waxy papules clearly visible at the edges of the affected areas. (c) Erythema and induration of the skin on the patient's hands resulting in the typical "doughnut sign", a central depression surrounded by an elevated rim on the extended interphalangeal joints. A written permission is given by the patient to publish these photos.

prednisone was gradually tapered off. The patient reported progressive "softening" of her skin and by the end of the 9 cycles her limbs/body lesions had resolved and her face had improved considerably apart from moderate facial erythema. After completing bortezomib, IVIG and dexamethasone (Venital© (Kedrion S.p.A., Lucca, Italy) 50 g/100 ml, 0.4 g/kg/day plus Soldesam© 4 mg/1 ml, every 3 weeks) were continued, with persistent remission of skin lesions. The monoclonal gammopathy remained stable over time.

Thirteen months after completing bortezomib, the patient received a second dose of the Pfizer- BioNTech COVID-19 vaccine (Pfizer-BioNTech, Germany) and 3 days later she developed malaise, vomiting and fever, quickly followed by altered mental status and aphasia. Within 1 week she developed seizures and coma, requiring admission to an intensive care unit where she was intubated. Electroencephalography revealed status epilepticus. Magnetic resonance imaging (MRI) of the brain and cerebrospinal fluid analysis were unremarkable, ruling out ischaemic stroke and infectious meningoencephalitis. Based on these findings probable autoimmune encephalitis was diagnosed.

During hospitalization, IVIG were initially maintained without any effect on the neurological manifestations. They were therefore discontinued, and 5 cycles of plasmapheresis were performed, leading to dramatic improvement. Valproic acid, lorazepam, and quietapine were also introduced. It is noteworthy that skin manifestations of SMX were always under control. The maintenance monthly regimen of IVIG and dexamethasone was restarted when the patient was discharged from hospital, 8 weeks later. To date, 2 years after starting bortezomib, her cutaneous manifestations are still under control.

DISCUSSION

To date, there is no well-defined treatment for SMX, and different therapies have been used with varying outcomes. According to expert opinion, IVIG should be the first-line systemic therapy. Most patients require maintenance therapy to remain in remission. Thalidomide and systemic glucocorticoids, alone or in association with IVIG, are appropriate second-line therapies. Severe refractory patients are candidates for stem cell transplantation, melphalan, or bortezomib with dexamethasone (2, 3). Bortezomib is a proteasome inhibitor which induces cell-cycle arrest and leads to enhanced apoptosis of monoclonal plasma cells. It is commonly used to treat relapsed/refractory multiple myeloma. Its use in SMX has been reported in 8 patients who differed in terms of clinical history, presentation and outcome, as well as treatment regimens (4–13).

The current case confirms that bortezomib combined with dexamethasone is an effective and well-tolerated add-on therapy for severe refractory SMX, and that it can reverse tachyphylaxis to IVIG, allowing it to subsequently maintain remission of skin symptoms.

After completing bortezomib, the current patient continued regular IVIG therapy and was in clinical skin remission when she developed DNS following SARS-CoV-2 vaccination. The close temporal relationship between the latter and the onset of the neurological symptoms in the absence of other demonstrable causes, in particular infections and ischaemia, strongly supports a pathogenic correlation. Plasmapheresis was necessary to reverse her neurological decline.

To our knowledge, this is the first reported case of DNS secondary to SARS-CoV-2 vaccination. Two patients with SMX who developed DNS following SARS-CoV-2 infection have been reported recently (3, 14). Both of these patients responded to plasmaphereses, while IVIG were ineffective. Fritz et al. (14) speculated that recent infections that elicit a hyper-inflammatory states may increase the risk of developing DNS, in the same way as recent infection or vaccination is suspected to favour exacerbations in multiple sclerosis (15). The current case supports their hypothesis. Furthermore, it confirms that plasmapheresis can be effective in patients non-responsive to IVIG treatment. We speculate whether plasmapheresis was successful in its own right or may have partly benefited from the treatments previously used to control the patient's cutaneous manifestations.

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