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Mike Fritz

University of Kentucky, Mark.Fritz@uky.edu

Daniel Tinker

Saint Louis University

Alex W. Wessel

Washington University in St. Louis

Gabriela M. Morris

Saint Louis University

Linda Goldenberg

Saint Louis University

See next page for additional authors

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Authors

Mike Fritz, Daniel Tinker, Alex W. Wessel, Gabriela M. Morris, Linda Goldenberg, Mark Fesler, Lokesh Rukmangadachar, and M. Yadira Hurley

SARS-CoV-2: A potential trigger of dermatoneuro syndrome in a patient with scleromyxedema



Mike Fritz, BS,^a Daniel Tinker, MD,^b Alex W. Wessel, BS,^c Gabriela M. Morris, MD,^b Linda Goldenberg, MSN, RN,^d Mark Fesler, MD,^d Lokesh Rukmangadachar, MD, MS,^e and M. Yadira Hurley, MD^b
Lexington, Kentucky and St. Louis, Missouri

Key words: COVID-19; dermatoneuro syndrome; epilepsy; IVIG; mucinosis; SARS-CoV-2; scleromyxedema.

INTRODUCTION

Scleromyxedema (SMX) is characterized by excessive mucin deposition in connective tissues and skin.¹ It shares clinical features with other mucinosises, including generalized myxedema, pretibial myxedema, reticular erythematous mucinosis, and scleredema.¹ However, diagnosis of SMX is distinguished by the following criteria: absence of thyroid disease, presence of monoclonal gammopathy (classically IgG λ), and cutaneous eruption of waxy papules and plaques, characterized histopathologically by increased dermal mucin, fibroblast proliferation, and fibrosis.² SMX also causes multi-system disease with approximately 20% fatality.³

Dermato-neuro syndrome (DNS), a potentially fatal complication of SMX, occurs in approximately 18% of the patients.⁴ It presents with fever and neurologic disturbances including confusion, dysarthria, seizures, and coma. The pathogenesis of DNS remains uncertain; however, reports speculate that elevated levels of vasoactive cytokines (eg, interleukin 6) during viral infection may contribute by compromising the blood-brain-barrier.^{5,6} Enhanced blood-brain-barrier permeability in the setting of monoclonal gammopathy may elevate IgG levels in the brain microvasculature, causing hyperviscosity, sludging, and neurologic abnormalities.⁷⁻⁹ Available literature indicates that reported cases of DNS are frequently preceded by a flu-like prodrome^{3,4,9-18} or other suspected upper respiratory tract infection.^{8,19} Notably, 2 case studies identified influenza A

Abbreviations used:

CSF: cerebrospinal fluid
DNS: dermatoneuro syndrome
IVIG: intravenous immunoglobulin
SMX: scleromyxedema

infection in association with DNS.^{6,10} Here, we describe a patient with SMX complicated by 2 episodes of DNS, each associated with different RNA virus infections: Influenza A or SARS-CoV-2.

CASE REPORT

A 48-year-old man with a history of hypertension initially presented with 3 months of skin tightening, difficulty clenching his fists or opening his mouth, and mild shortness of breath. Physical examination revealed numerous waxy, 2 to 3-mm papules on the upper arms, chest, post-auricular scalp, and eyebrows. Histologic examination of lesional skin biopsy material revealed increased stromal fibroblast proliferation and mucin deposition in the upper dermis (Fig 1), consistent with SMX. Thyroid function tests were normal, and serum protein electrophoresis with immunofixation revealed IgG λ paraproteinemia, leading to a diagnosis of SMX. Initial treatment included prednisone and intravenous immunoglobulin (IVIG) administered every 4 weeks at 1 g/kg of ideal body weight. Within 3 months, cutaneous disease improved, and the

From the University of Kentucky College of Medicine, Lexington^a; Washington University School of Medicine^c; Department of Dermatology^b, Division of Hematology, Oncology, & Cellular Therapy, Department of Internal Medicine^d, and Department of Neurology^e, Saint Louis University, St. Louis.

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Correspondence to: Mike Fritz, BS, University of Kentucky College of Medicine, MN Building Room 150, 800 Rose Street, Lexington, KY 40506. E-mail: mike.fritz@uky.edu.

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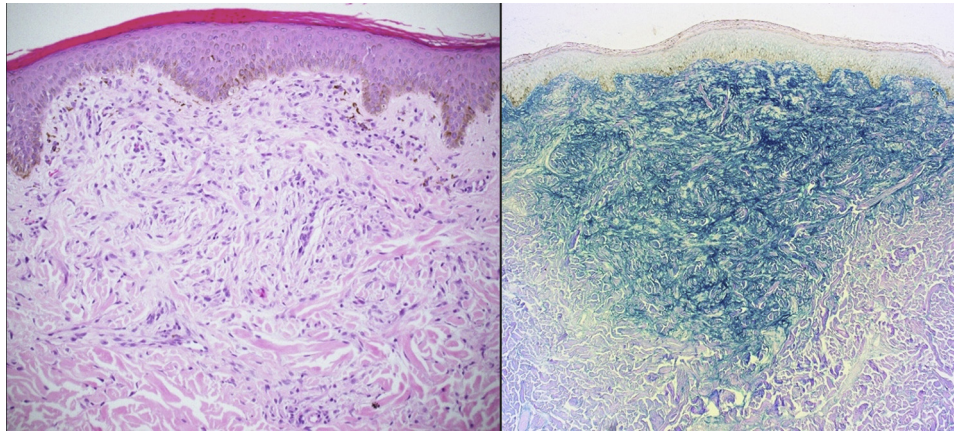


Fig 1. Histology of lesional skin biopsy material revealing stromal hypercellularity in the upper dermis (left; hematoxylin-eosin stain, original magnification $\times 60$) and increased interstitial mucin deposition (right; colloidal iron stain, original magnification $\times 60$).

patient continued IVIG maintenance therapy at varying frequencies based on severity of cutaneous disease.

Seven years after initial diagnosis, the patient developed several days of flu-like symptoms including fatigue, myalgia, sore throat, and cough. Chest X-ray revealed a small lung infiltrate, and the patient was treated empirically for community-acquired pneumonia with azithromycin. Days later, the patient presented with altered mental status, aphasia, and tonic-clonic movements in all extremities. After hospital admission, the patient developed fever and seizures confirmed to be status epilepticus on electroencephalography. The patient was transferred to the intensive care unit and intubated. Neurology consult noted left-sided motor weakness and right-sided gaze deviation. However, computed tomography and magnetic resonance imaging of the head were unremarkable. Analysis of cerebrospinal fluid (CSF) revealed mild pleocytosis (10 white blood cells/ μL ; reference range, 0-5 cells/mL), mildly elevated protein (47 mg/dL; reference range, 15-45 mg/dL), and an opening pressure of 29 cm H_2O . CSF testing was negative for bacteria by culture, herpes simplex virus 1 and 2, and varicella zoster virus. A nasal swab polymerase chain reaction test confirmed influenza A infection. Complete blood count, comprehensive metabolic panel, urinalysis, chest X-ray, and blood cultures/flow cytometry were unremarkable. Status epilepticus was controlled with intravenous antiepileptics, and the patient improved over a 3-day course of IVIG (3 g/kg of ideal body weight), methylprednisolone, and broad-spectrum antibiotics (despite negative cultures). After consulting neurology, the patient was diagnosed with DNS

given findings of fever, status epilepticus, and encephalopathy without identifiable cause in the setting of SMX. Over the next 4 years, no progression occurred on a strict every-4-week IVIG (1 g/kg) dosing schedule.

Three years after the initial episode of DNS, the patient presented with anosmia and malaise 2 days prior to scheduled IVIG treatment. Physical examination showed no progression of cutaneous disease (Figs 2 and 3). Polymerase chain reaction testing of a nasopharyngeal swab, however, confirmed SARS-CoV-2 infection, precluding treatment at his regular outpatient infusion center. Consequently, he was admitted to the hospital to receive his scheduled IVIG. During IVIG infusion, he developed altered mental status, tonic-clonic movements, and fever (up to 39.4 $^{\circ}\text{C}$). Electroencephalography revealed status epilepticus. He was transferred to the intensive care unit, intubated, and treated with intravenous antiepileptics and broad-spectrum antibiotics. CSF analysis revealed mild pleocytosis (7 white blood cells/ μL), mildly elevated protein (63 mg/dL), and an opening pressure of 24 cm H_2O . CSF testing was negative for gram stain, *Cryptococcus* antigen, and herpes simplex virus 1 and 2. Complete blood count, comprehensive metabolic panel, urinalysis, chest X-ray, blood cultures, and brain computed tomography/magnetic resonance imaging were unremarkable. Neurology was consulted and could not identify underlying cause of the precipitous neurologic decline; thus, recurrent DNS was considered as the potential diagnosis. The patient was treated with a 3-day course of intravenous methylprednisolone and IVIG (3 g/kg of ideal body weight).



Fig 2. Scleromyxedema presenting as numerous 2 to 4-mm waxy, perfollicular papules on the upper extremities (left, right), face, trunk, and thighs. Some of the papules were arranged in a linear configuration over the chest, a classic finding in scleromyxedema.



Fig 3. Scleromyxedema with numerous waxy 2 to 3-mm papules on the brows and forehead. Induration of the glabella, an early finding in progression to leonine facies, can also be appreciated.

DISCUSSION

We described 2 episodes of DNS in a patient with SMX who presented with classic findings (fever, confusion, and seizures) preceded by a flu-like prodrome, with confirmed viral infection (influenza A or SARS-CoV-2). Both episodes occurred despite regular IVIG therapy. Possibly, antecedent infections

that elicit hyperinflammatory states may increase the risk of developing DNS. Notably, recent infection or vaccination also is speculated to underlie increased risk of exacerbations in multiple sclerosis.²⁰ By limiting inflammation, low-dose glucocorticoids could potentially mitigate the risk of DNS in SMX. Indeed, some patients with SMX benefit from adjunct glucocorticoids when IVIG maintenance therapy fails to prevent progression of skin disease. Importantly, other causes of neurologic decline should be considered in the differential diagnosis for DNS, such as the possibility of occult central nervous system infection (despite equivocal CSF studies) or neurologic manifestations of SARS-CoV-2.

Evaluation for infection in DNS often focuses on ruling out neurotropic organisms (eg, herpes simplex virus), but fails to test for many respiratory tract or other systemic pathogens. To better understand the association of DNS with infection, modern techniques, such as BioFire, could be employed to evaluate large panels of viruses and bacteria in SMX patients acutely presenting with DNS.²¹ Cytokine profiling of the serum and CSF of DNS patients also may elucidate potential immune-mediated pathology.

Conflicts of interest

None disclosed.

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