Introduction

Neuromyelitis optica (NMO, Devic’s syndrome) is an autoimmune, relapsing central nervous system (CNS) demyelinating disease with a predilection for spinal cord and optic nerve involvement. The diagnostic criteria include optic neuritis, longitudinal myelitis and at least two of three supporting criteria: myelitis with involvement of at least three contiguous vertebrae, brain magnetic resonance imaging (MRI) that is normal or inconsistent with multiple sclerosis, and seropositivity for aquaporin-4 (NMO IgG) antibodies [1]. Of these, longitudinal myelitis with NMO IgG seropositivity alone is associated with a 50% risk of relapse or progression to full-blown NMO within a year [2]. Recognition of the prognostic implications of seropositivity has prompted the designation of the more inclusive NMO spectrum disorders (NMOSDs), which include NMO only and other variants [1].

Case Report

A 60-year-old Chinese female with a history of HER+ ductal carcinoma in situ status post lumpectomy and radiation therapy 3 years prior presented with several days of diarrhea and intermittent paraesthesias evolving into lower extremity paralysis and fecal and urinary incontinence on the day of admission. This constellation of symptoms had been preceded by a 3-month history of new cutaneous lesions, weight loss, painful edema of bilateral hands, nonproductive cough and multi-joint arthralgias. The patient denied sicca symptoms. There was no personal or family history of autoimmune disease.

Skin examination was notable for a linear, violaceous plaque on the left forehead (fig. 1) and violaceous papules on the left preauricular cheek. The hands were notable for mottled violaceous erythema and...
fissuring of the palmar and lateral aspects of the distal fingers extending just beyond the distal interphalangeal joint. Synovitis was detected in multiple joints.

Thoracic MRI revealed a longitudinally extensive, contrast-enhancing lesion extending from T1 to T12, consistent with longitudinal myelitis (fig. 2). Cerebrospinal fluid studies revealed marked inflammation, with a neutrophil-predominant pleocytosis (374 WBC/mm³, 97% neutrophils) and protein elevated to 194 mg/dl (albumin 115 mg/dl). The cerebrospinal fluid glucose and IgG indexes were within normal limits, oligoclonal bands were absent and cytologic analysis was inconsistent with malignancy. The NMO IgG was found to be positive at >160 U/ml, consistent with a diagnosis of NMOSD as the cause. Work-up for infectious etiologies was negative. Computed tomography of the chest revealed findings consistent with radiation pneumonitis.

Complete blood count was notable for lymphopenia to 0.82 cells/μl. Acute phase reactants were mildly elevated, with an erythrocyte sedimentation rate of 52 mm/h and C-reactive protein of 1.7 mg/dl. Creatine kinase was normal. A comprehensive myositis panel was performed, revealing a weakly positive U3-RNP. Of the extractable nuclear antigen panel, only anti-Ro/SSA (1:156 units) was positive (ANA false-negative). Anti-CCP was moderately elevated at 40 U. RF, dsDNA and anticyclic citrullinated peptide IgG and IgM were all negative, and C3 and C4 levels were within normal limits. Punch biopsy of the lesion on the preauricular cheek demonstrated a subtle vacuolar interface reaction with postinflammatory pigment alteration, consistent with a waning lesion of connective tissue disease.

The patient received a 5-day course of intravenous methylprednisone 1 g q.d., followed by five courses of plasmapheresis and two doses of rituximab. For long-term immunosuppression, she was transitioned to a regimen of Plaquinil 200 mg q.d., dapsone 200 mg q.d. and methotrexate, which was gradually increased to a weekly dose of 20 mg.

Prednisone was tapered slowly due to development of new cutaneous lesions with decreased doses. One month after presentation, the patient presented with nasal bridge erythema. Several weeks later, she developed violaceous lesions over the distal interphalangeal and metacarpophalangeal joints that were morphologically consistent with Gottron’s papules. Despite the nonspecific histopathology and antibody profile, this constellation of lesions met the criteria for ADM, which along with the patient’s other clinical features was consistent with an overlap syndrome with features of ADM, RA and LE. A diagnosis of mixed connective tissue disease was considered given the arthritis and weakly positive U3-RNP, but ultimately discarded given that the more specific U1-RNP was negative and the clinical presentation was overall not consistent with this diagnosis (no Raynaud’s phenomenon, sclerodactyly, pulmonary hypertension, interstitial lung disease or myositis). While U3-RNP is often suggestive of systemic sclerosis, the overall clinical picture was not consistent with this diagnosis.

An exhaustive malignancy work-up, including breast MRI, Pap smear, full body computed tomography and ultrasound of the genitourinary system, was unremarkable.

One year post discharge, the patient was ambulating with assistance. Her cutaneous lesions continued to improve with use of clobetasol and photoprotection and there were no new areas of involvement.

**Discussion**

We present the case of a patient with cutaneous stigmata suggestive of an overlap syndrome with features of ADM, RA and LE in the setting of NMOSD. We reviewed 423 published cases of NMO and identified 10 reports of cutaneous findings (see online supplementary table 1, www.karger.com/doi/10.1159/000369616). Six of these reports detail cutaneous manifestations in the joint presentation of NMO and autoimmune disease, several of which were also seen in our case. Raynaud’s phenomenon was the most common cutaneous manifestation in this small sample of patients. As in our case, seropositivity for anti-SSA is reported in several other cases of systemic LE with NMO, but it is notable that in all of the previously reported cases, clinical features suggestive of an additional overlapping connective tissue syndrome were not present. The relationship between NMOSD and other autoimmune diseases, including RA, ulcerative colitis and polymyositis, is less established [5]. While the pathogenic mechanisms for this overlap have not been fully elucidated, the existing evidence suggests that NMO is a distinct...
clinical entity, with co-occurrence reflecting a predisposition for general autoimmunity [5, 6].

Another class of reports describes patients with presumed neuropathically mediated pathology, leading to full body xerosis, anhidrosis and pruritus, or often with secondary eczematous changes. While a mechanism of cutaneous pathogenesis has not been proposed in these cases, it is interesting to note that various aquaporins are expressed in mammalian skin and have been implicated in skin hydration, wound healing and cutaneous tumorigenesis, as well as in the pathophysiology of atopic eczema [7].

A third possible class may relate to preceding viral exanthems – we uncovered one case of a nonspecific ‘erythematous rash’ in the setting of Rotavirus-positive gastroenteritis preceding NMO [8]. While the paucity of cutaneous reports may reflect the rarity of cutaneous involvement in the presentation of NMOSD, it is also possible that these details are under-detected by non-dermatologist clinicians or omitted from reports – the latter is especially likely given the established relationship between NMOSD and autoimmunity and viral pathogens, both of which often feature cutaneous involvement.

The patient’s history of malignancy is noteworthy in light of the well-established association between the inflammatory myopathies and malignancy. Associations between NMO and malignancy have also been reported [9, 10]. Given the near ubiquitous distribution of aquaporin-4, it is possible that aquaporin-4 IgG is produced in the course of an immune response to a variety of solid tumors. Outside of the CNS, aquaporin-4 is expressed in the glamdular epithelium of the breast and salivary glands, in tracheal and bronchial epithelium of the lungs, in parietal cells of the stomach, in epithelium of the colon, in skeletal muscles and in the basolateral membranes of the distal collecting tubules of the kidneys [9]. NMO IgG has been identified in tissue microarrays of breast and lung carcinomas as well as other malignancies. In a cohort of patients with NMO IgG seropositivity, 27% with clinical evidence of CNS demyelination had a concomitant malignancy. Interestingly, NMO IgG seropositivity was also identified in the absence of clinical evidence of a CNS demyelinating process in one patient with breast and another with lung carcinoma from this cohort. Although it is reassuring that 1 year has passed since the patient’s cutaneous lesions emerged and her malignancy work-up has remained negative, our case begs the question of whether a primary malignancy or incipient recurrence could have been a common trigger for these diverse autoimmune phenomena, possibly via crossover attack of UV-exposed skin by tumor and myositis autoantigen-specific T and B cells, as proposed in the ‘crossover model’ [9, 11–14].

This case has important diagnostic and therapeutic implications for practicing dermatologists. NMOSD should be on the differential for any patient with cutaneous stigmata concerning for connective tissue disease and nonspecific gastrointestinal or sensory disturbances – prompt identification of NMO with antibody testing and rapid initiation of rescue immunosuppressive therapy is critical to minimize permanent tissue damage and residual neurologic disability. Attention to this entity to ensure differentiation from the multifaceted neuromuscular manifestations of autoimmune disease (e.g., dermatomyositis, lupus myelitis, Sjögren’s syndrome-related myelopathy) is also important, since NMO requires maintenance therapy to prevent the higher rate of relapses (approximately 60% in 1 year) and accumulation of neurologic disability [4]. Finally, further elucidating the various cutaneous phenotypes that may accompany NMO via more accurate reporting of and attention to these manifestations by dermatologists will allow earlier recognition of this devastating neurologic syndrome and may optimize treatment by enabling identification of subtypes of patients for which certain treatment regimens may be more efficacious.

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Disclosure Statement

The authors have no relevant conflicts of interest to report.


