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LETTER TO THE EDITOR

Neuromyelitis optica spectrum disorders associated with systemic sclerosis: a case report and literature review

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Introduction

Neuromyelitis optica (NMO) is an autoimmune demyelinating disease of the central nervous system (CNS) affecting predominantly the spinal cord, brainstem, and optic nerves [1]. NMOSD may be associated with a variety of immune-mediated disorders, such as systemic lupus erythematosus, Sjögren syndrome, and other organ-specific autoimmune diseases [2], though accurate information about their prevalence is not available [3]. Systemic sclerosis (SSc) is characterized by vascular alterations, activation of the immune system, and tissue fibrosis [4]. Only a few cases of coexisting systemic sclerosis (SSc) and NMOSD are described [1, 5–9].

We report a case of an NMOSD AQP4-IgG antibody-positive patient associated with SSc and a review of the available evidence of the relationship between these autoimmune diseases.

Case report

In January 2020, a Caucasian 60-year-old woman, with a history of Raynaud's phenomenon and arterial hypertension, subacutely presented progressive lower limbs weakness and paresthesias. Spinal magnetic resonance imaging (MRI) revealed a longitudinally extensive, from C5 to T5, T2-hyperintense spinal cord lesion, with more evident contrast enhancement from T3 to T4, and medullary swelling in the cervico-thoracic passage (Fig. 1), and brain MRI was unremarkable. Neurological examination showed severe paraparesis, lower limbs hyperreflexia, sustained right Achilles tendon clonus, bilateral positive Babinski sign, severe hypopallestesia, and urinary retention (EDSS 7.0). Cerebrospinal fluid (CSF) demonstrated 43 lymphomonocytoids/μL and moderate blood-CSF barrier dysfunction, with hyperproteinorrachia (110 mg/dL), intrathecal IgG synthesis, with CSF-restricted OCB (twenty-one abnormal fractions of immunoglobulins absent in serum).

Extensive laboratory evaluation, including thyroid function, vitamin B12 level, folic acid, angiotensin-converting enzyme, and homocysteine, was normal. Serologies and PCRs for common neurotropic viruses (HSV1, HSV2, CMV, EBV, HBV, HCV, VZV, HTLV ½, and HIV) were negative in blood and cerebrospinal fluid analysis (CSF).

Serum resulted highly positive for AQP4-IgG antibodies, and the titer was evaluated with a semiquantitative ratiometric method, as previously described [10], with an AQP4 quantitative ratio (AQP4qr) = 0.31. Systemic autoimmunity panel revealed anti-nuclear antibody (ANA) positivity with 1/320 titer in a centromeric pattern (ACA) and extractable nuclear antigen antibody (ENA) positivity for anti-centromeric protein-B (CENP-B) titer was 454.3 CU/mL.

During the hospitalization, the patient developed mild dysphagia for liquids. X-ray and high-resolution computer tomography of the chest revealed a non-specific fibrosing bilateral apical interstitial pneumonia associated with bolus stagnation. A diagnosis of SSc was made following the European League Against Rheumatism (EULAR) 2013 criteria [11]. Intravenous methylprednisolone (IVMP) treatment was started, 1000 mg for 7 days, with no recovery. The patient underwent the apheresis treatment with the immunoadsorption technique using tryptophan (TR350), 7 courses, which lead to almost no recovery.

In October 2020, spinal MRI showed a clear reduction of the lesion in the whole cervical-dorsal territory, despite a poor clinical treatment response. During the hospitalization, the patient developed a pressure sore in the coccygeal

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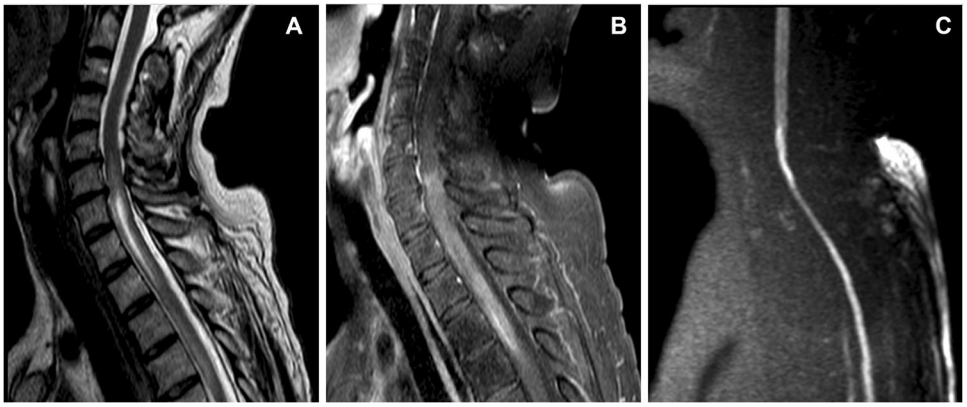

Fig. 1 Cervical and upper thoracic spinal MRI. **A** T2-weighted sequence showing hyperintense lesion from C5 to T5 level. **B** Post-contrast T1-weighted sequence showing more evident enhancement from T3 to T4 level. **C** Diffusion-weighted sequence

sacrum with two episodes of high fever and septic shock that prevented the use of immunosuppressive treatment.

Literature review

We reviewed all clinical series on patients with NMO and extracted information on co-existing SSc. A literature search was performed on the PubMed database from 2004 to 2020 to identify all English language publications (either their abstract or both abstract and the full text were in English) using the keywords "neuromyelitis optica" AND "systemic sclerosis" OR "Systemic Sclerosis" AND "anti-AQP4" OR "Transverse Myelitis." This yielded a total of 7 citations.

Result

In literature, only a few cases of coexisting NMO and SSc are reported (Table 1). We found that all patients documented are females, and the median age is 51 years (range 30–65 years). The systemic manifestations have preceded, even several years, the demyelinating disease in 4/6 patients (Raynaud's phenomenon 3/4, sclerodactyly 2/4, skin changes 3/4, arthralgias 1/4, and facial telangiectasia 1/4). In five out of six patients, as in our case, the AQP4-IgG antibodies were detected in serum and they fulfil the diagnostic criteria for NMOSD [12]. The main neurological involvement is characterized by LETM in 5/6 patients, in 1/6 associated with APS, and in 1/6 with recurrent optic neuritis. In three out of five patients, a partial or no recovery after steroid treatment, as in our patient, was reported; Hernandez et al. [13] described an improvement of symptoms without specifying whether partial or complete.

In the case described by Torabi et al. [9], the patient presented a conus medullaris lesion; the serostatus of this patient was not available, since it was published before the AQP-4 antibodies were identified [14]. All patients reported a good response to corticosteroid treatment in terms of clinical improvement, unlike our patient.

Discussion

NMO characterized by positivity for anti-AQP4 antibodies is an idiopathic demyelinating disease associated with various systemic and organ-specific autoimmune diseases. NMOSD patients have shown a general autoimmune tendency. Indeed, concomitant autoantibodies have been reported in 38 to 75% of NMO patients [3], but in a wide range of those patients, no clinical manifestations were reported [15, 16]. Most diseases associated with NMOSD are antibody mediated as the disease itself, but the pathogenesis of autoimmune diseases co-existing with NMOSD has not yet been completely recognized. In 2018, a review about the presence of rheumatologic disorders in NMOSD patients was published by Shahmohammadi and colleagues [17]. Sjogren syndrome (SS), myasthenia gravis (MG), and lupus erythematosus systemic (LES) were the most represented autoimmune disorders with 106, 48, and 19 cases reported, respectively. However, the growing ability to recognize NMOSD clinical and radiological features may lead to improving the prevalence data.

SSc is a complex disorder characterized by the involvement of small arteries, microvessels, and connective tissue [18]. Recently, it was observed how vascular dysfunction plays a central role in the pathogenesis of SSc [4]. Vasculopathy in these patients may lead to blood–brain barrier damage and facilitate the exposure of AQP4 channel protein in the process of antigen presentation and T-cell activation, triggering an autoimmune response. Indeed, in our patients as in 66% of patients reported in literature, signs and symptoms of SSc preceded the neurological manifestation even of several years.

Immunosuppressive treatments maintain a central role in the treatment of NMO and SSc [18]. Apheresis treatment should be considered as relapse therapy given the poor response to steroid treatment in more than half of the patients [19]. According to the European League Against Rheumatism (EULAR) recommendations, cyclophosphamide

Table 1 Demographic characteristics of the patients diagnosed with the coexistence of NMOSD and systemic sclerosis

	Sex	Ethnic origin	Age	Serostatus	Neurologic manifestation	Systemic manifestation	Comorbidities	Recovery to steroid treatment
Deeb et al. 2019	F	Hispanic	44	AQP4 positive	APS, LETM	Raynaud's phenomenon		Partial
Moriguci et al. 2015	F	N/A	51	AQP4 positive	ON, LETM	Raynaud's phenomenon, limbic skin sclerosis	Sjogren's syndrome	Partial
Hernández et al. 2012	F	African American	51	AQP4 positive	LETM	Sclerodactyly, esophageal spasm		Partial/complete*
Franciotta et al. 2011	F	N/A	62	AQP4 positive	LETM	Raynaud's phenomenon, sclerodactyly		Complete
Takahashi et al. 2009	F	N/A	65	AQP4 positive	LETM	Incomplete CREST syndrome (facial telangiectasia, sclerodactyly in bilateral fingers), Raynaud's phenomenon	Sjögren's disease Primary biliary cirrhosis	Complete
Torabi et al. 2004	F	African American	30	N/A	Conus medullaris lesion	Arthralgias, Raynaud's phenomenon, dysphagia, dyspnea		No recovery

M, male; *F*, female; *N/A*, not available; *APS*, area postrema syndrome; *LETM*, longitudinal extensive transverse myelitis; *ON*, optic neuritis; *CREST*, The acronym "CREST" refers to Calcinosis, Raynaud's phenomenon, Esophageal dysmotility, Sclerodactyly, and Telangiectasia.
*Authors did not specify the partial or complete recovery

remains the first choice for treatment of severe SSc with lung dysfunction, but also rituximab (RTX) and tocilizumab (TCZ) showed a clinical improvement in these patients with a good safety profile [18]. RTX and TCZ in NMO patients have shown acceptable tolerance, reduction of relapse frequency, and improvement of disability [20, 21]. Therefore, a strong collaboration between neurologists and rheumatologists to decide the therapeutic approach is crucial.

Accurate information about the prevalence of immune-mediated disorders in NMOSD patients is not available [3]. Large cohorts of NMOSD patients with a complete assessment of systemic autoimmunity are needed to evaluate the prevalence of autoimmune comorbidities and could help to compare demographic features, attack types, treatment response, and prognosis, between NMOSD patients with and without such comorbidities to select the best treatment option.

Declarations

Ethical approval The patient has consented to the submission of the case report to the journal and she signed an informed consent regarding publishing her clinical and MRI data.

Conflict of interest MT has served on Scientific Advisory Boards for Biogen, Novartis, Roche, Merck, and Genzyme; has received speaker honoraria from Biogen Idec, Merck, Roche, Teva, Sanofi-Genzyme, and Novartis; and has received research grants for her Institution from Biogen Idec, Merck, Roche, and Novartis. PI has served on scientific advisory boards for Biogen Idec and has received funding for travel and/or speaker honoraria from Sanofi-Aventis, Biogen Idec, Teva, and Novartis. DP received advisory board membership, speaker's honoraria, travel support, research grants, consulting fees, or clinical trial support from Almirall, Bayer Schering, Biogen, Celgene, Excemed, Genzyme, Merck, Mylan, Novartis, Sanofi, Roche, and Teva. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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