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LETTER TO THE EDITOR

Rare association between neuromyelitis optica spectrum disorder, anti-synthetase syndrome, and systemic lupus erythematosus in an adult female

Mohamed Islam Kediha

Mustapha Bacha University Hospital, Department of Neurology, Algiers, Algeria

Dear Editor,

Neuromyelitis optica spectrum disorder (NMOSD) encompasses inflammatory demyelinating autoimmune disorders of the central nervous system (CNS) that preferentially involve the optic nerve and spinal cord. This phenotypic spectrum includes seropositive forms, associated with positive anti-aquaporin 4 (AQP4) antibodies (AB), and seronegative forms lacking these ABs (1). The association of NMOSD with other systemic autoimmune diseases has been documented, with over 20 conditions identified as contributing to recurrent neurological syndromes, including systemic lupus erythematosus (SLE), Sjögren syndrome, and thyroiditis. Although one case has reported an association with anti-synthetase syndrome (ASS) (2), no cases of coexisting NMOSD with both ASS and SLE have been reported to date.

We describe the case of a 57-year-old female patient of Algerian origin, admitted to the neurology department for diagnostic and therapeutic management of rapidly progressive muscle weakness in the lower limbs, occurring over 10 days prior to admission and resulting in cessation of walking. This clinical presentation was further complicated by sphincter dysfunction, including urinary retention, and a loss of perineal sensation. Her medical history included two early miscarriages (less than three months of gestation) in 1993 and 2001. She has been monitored for anemia of undetermined etiology since 2015. Since 2017, she has experienced localized pain in the small joints of her hands and feet. Additionally, she reported the onset of blurred vision in her right eye six months ago, which, according to her, appeared to be stationary. Examination of the cranial nerves revealed severe visual acuity loss, predominantly in the right eye. Fundus examination showed optic atrophy with peripapillary retinal atrophy in the right eye and a healthy papilla with peripapillary atrophy in the left eye. The remainder of the examination revealed a medullary syndrome below the D6 level, pyramidal syndrome with acute flaccid paraplegia, abolished osteotendinous reflexes, and an indifferent cutaneous-plantar reflex on both sides. Tactile and thermoalgesic hypoesthesia was observed in the lower limbs up to the D6 level. The Expanded Disability Status Scale (EDSS) score was 7. A somatic examination revealed pudgy fingers with digital sclerosis, keratotic and eczematous lesions on the lateral surfaces of the fingers, diffuse koilonychia (Fig. 1), onychogryphosis of the big toes, Raynaud's phenomenon with several megacapillaries on dermoscopy, and a stellate angioma on the face. Gynecological, senological, cardiovascular, and pleuropulmonary examinations were unremarkable, apart from exertional dyspnea.

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Correspondence: Mohamed Islam Kediha, Mustapha Bacha University Hospital, Department of Neurology, Algiers, Algeria
E-mail: ms.kediha@univ-alger.dz
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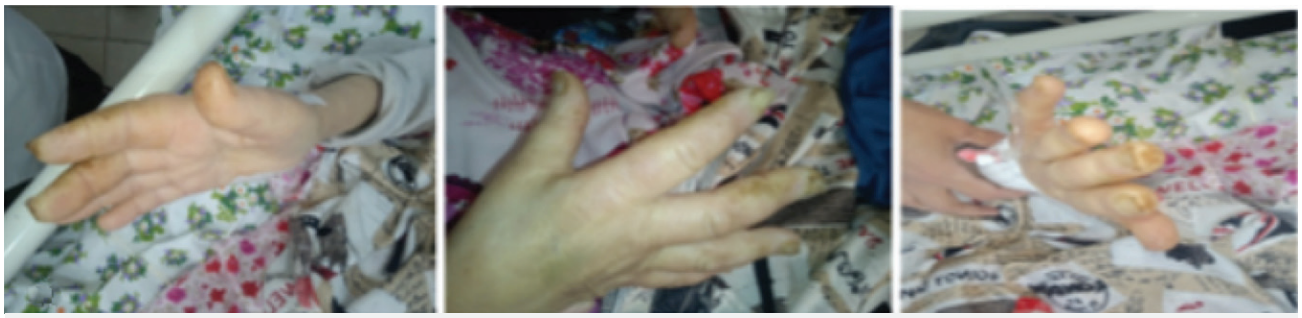

Figure 1. Mechanic's hands: keratotic lesions on the lateral surfaces of the hands and fingertips.

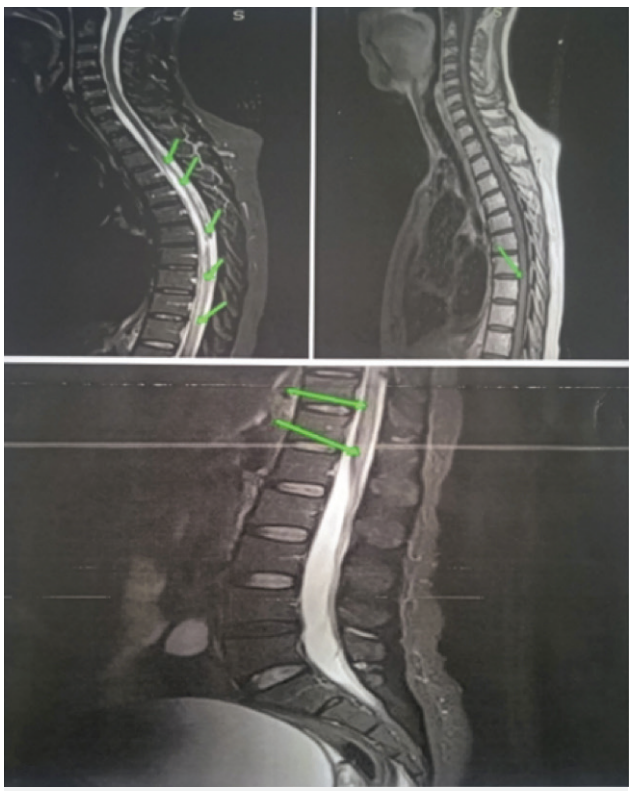

Figure 2. Spinal cord magnetic resonance imaging (MRI): extensive longitudinal myelitis spanning from T4 to T12.

Magnetic resonance imaging (MRI) of the spinal cord showed an enlarged dorsal cord with T2 hyperintensity extending from D4 to D12, with areas of enhancement following gadolinium injection (Fig. 2). Orbital and cerebral MRI revealed a few nonspecific white matter lesions. Cerebrospinal fluid analysis revealed a protein level of 0.66 g/L (normal range: 0.2–0.4 g/L), normal intracranial pressure, and normal glucose and iron levels. There was cellularity of 120 elements/L, predominantly monocytic (85%). The immunoglobulin G (IgG) index was normal (0.69), but oligoclonal IgG bands were detected. Cerebrospinal fluid (CSF) viral and bacterial polymerase chain reactions (PCRs) for Koch's bacillus, cytomegalovirus (CMV), Lyme disease, and herpes viruses were negative. Serologic tests for human immunodeficiency virus (HIV), syphilis, hepatitis B, and hepatitis C were also negative. C-reactive protein (CRP) was elevated (42.3), and muscle enzyme levels, specifically creatine phosphokinase (CPK) levels, were also elevated, measuring 1680 UI/L, which is eight times higher than the normal range (less than 190 UI/L). Renal function tests revealed an imbalance, with elevated urea and creatinine levels. Additionally, serum ferritin levels were high, and 24-hour proteinuria was measured at 1.53 g/24 hours, exceeding the standard value of less than 0.15 g/24 hours. The autoimmune workup revealed the following findings: a high titer of anti-nuclear ABs, a high titer of anti-Ro52 ABs, (also known as anti-tripartite motif-containing 21 [anti-TRIM21]), a low titer of anti-PL7 ABs, a high titer of anti-Smith/ribonucleoprotein (anti-SM/RNP) ABs, and strongly positive anti-aquaporin 4 (anti-AQP4) ABs at 1/40 (normal range: less than 1/10). Anti-myelin oligodendrocyte glycoprotein (anti-MOG) ABs were negative, as were antiphospholipid ABs (anticardiolipin and anti-B2 glycoprotein 1). The direct antiglobulin test (Coombs test) was positive. Onconeural antibodies were negative. Additional investigations included the following: Optical coherence tomography (OCT) revealed total atrophy in the right eye with thinning of the neurofilament layer to 21 microns, while the left eye was normal at 95 microns. Cardiac ultrasound showed pericardial detachment. Respiratory function tests using spirometry indicated a restrictive ventilatory disorder due to respiratory muscle damage. Electromyography demonstrated a clear myopathic pattern (Fig. 3). Thoracoabdominal-pelvic computed tomography (CT) revealed a pulmonary nodule in the upper lobe of the left lung, hepatomegaly, splenomegaly, and myositis ossificans in the muscle compartments extending from the thigh roots to

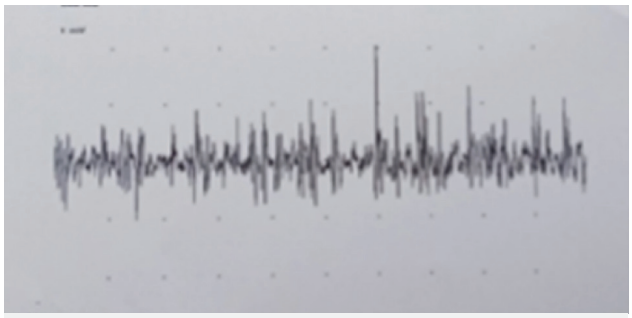

Figure 3. Myopathic changes observed in electromyography.

the pelvis. These findings showed a sequelae-like appearance, with hypertrophic muscles exhibiting heterogeneous density and numerous calcifications. A muscle biopsy was planned but not performed. All clinical and paraclinical data are summarized in the accompanying table. We recommended a corticosteroid bolus of 1.5 g per day for five days, administered under antibiotic coverage and with the dermatologists' approval due to the presence of a deep eschar on the buttock. The clinical evolution remained stationary. A course of intravenous immunoglobulin at a dose of 1 g/kg was offered but showed no improvement. Plasma exchange was not performed in her case due to the presence of a deep bedsore on her buttocks, which contraindicated this treatment. The patient was presented to the multidisciplinary consultation meeting for systemic diseases, where the decision was made to initiate treatment with rituximab. Unfortunately, the patient succumbed to her condition, with a deteriorating general state, anemia (hemoglobin at 6 g/dL), and an infectious syndrome. The final diagnosis was overlap syndrome, comprising seropositive neuromyelitis optica (NMO) associated with Sjögren's-syndrome-related antigen A (SSA) and SLE.

The diagnosis of NMOSD was established based on the presence of transverse longitudinal myelitis, severe optic neuritis, and a positive anti-AQP4 antibody assay, fulfilling Wingerchuck's diagnostic criteria (3). Anti-synthetase syndrome is a rare autoimmune disease characterized by a multisystemic disorder, primarily involving inflammatory myopathy, interstitial lung syndrome, Raynaud's phenomenon, "mechanic's hands," and polyarthritis (4). In our patient, all clinical and biological criteria were met, including elevated CPK, evidence of an inflammatory syndrome, myopathic tracing, and positive anti-Ro52/anti-TRIM21 ABs. Systemic lupus erythematosus, a systemic vasculitis, was also indicated by dermatological signs (pudgy fingers and sclerodactyly), cardiac involvement, a positive autoimmune work-up, renal involvement with significant protein leakage, anaemia, hepatomegaly, and splenomegaly. The association of NMOSD with other autoimmune diseases has been well documented (5). Reported associations include Sjögren's syndrome type A (anti-SSA ABs), Sjögren's syndrome type B (anti-SSB ABs), SLE, and autoimmune thyroiditis (anti-thyroglobulin antibodies and anti-SSA ABs), as well as autoimmune myasthenia gravis. To date, 22 cases of NMOSD associated with SLE have been reported (6). The initial symptoms of NMO are typically dominated by transverse myelitis, followed by optic neuropathy. Regarding ASS, only one case of ASS associated with NMO has been reported (2). In that case, myositic and arthritic symptoms, along with interstitial lung involvement, occurred initially, followed by NMO symptoms. This pattern was also observed in our patient. Anti-PL7 antibody positivity, polyarthritis, myositis, Raynaud's phenomenon, and dermatological lesions provide a comprehensive clinical picture supporting this diagnosis. With respect to anti-Ro antibodies, they have been associated with disease activity and severe disability in NMOSD (7). Given that our patient presented with a rare combination of three autoimmune diseases, and considering that ASS is mediated by cellular immunity (CD8 cells) while NMOSD involves a B-cell-mediated molecular pathway, we recommended the use of rituximab, particularly in light of its well-established efficacy in NMOSD (8). Unfortunately, the patient passed away before the proposed treatment protocol could be implemented.

This case is the first to report the association of NMOSD with two additional autoimmune diseases (ASS + SLE). The phenotypic severity of our patient's condition underscores the functional and vital prognostic risks associated with these overlapping diseases. It is imperative to expand the paraclinical workup to include evaluations for these conditions, even when anti-AQP4 antibodies are positive and the radiological findings (such as extensive myelitis) are suggestive, with a view toward the earliest possible therapeutic management.

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