High-titer Anti-aquaporin-4-IgG-associated Myelitis in Rhupus Syndrome

To the Editor:

Severe organ damage, especially central nervous system (CNS) involvement, has rarely been reported in patients with rhupus syndrome (RS). Two recent articles in *The Journal of Rheumatology*[1,2] have discussed this condition, which is a challenge in rheumatology.

A 51-year-old woman was referred to our center for longstanding polyarthralgia, fever, malaise, and malar rash associated with a history of neurological abnormalities.

In 1999 the patient felt a sudden pain in her back between the shoulder blades and then developed weakness of the upper extremities and paresthesias at the lower ones. No urinary symptoms were found. During the physical examination a decrease of arm strength was recorded, and a loss of sense of touch and of pain from the nipples through the feet. Scans of T2-weighted sequences of magnetic resonance imaging (MRI) of the spine showed a hyperintense lesion involving the medulla from level C5 to T7. An MRI scan of the brain was normal. Examination of the cerebrospinal fluid showed a high protein content and pleocytosis. Neither viruses nor bacteria nor oligoclonal IgG bands were found. A diagnosis of aseptic myelitis was made and she was treated with high doses of intravenous steroids. This treatment resulted in healing of a spinal cord lesion — an MRI of the spine done 6 months later showed that the length of the lesion had clearly decreased. In 2010, when she came to our center, a neurological examination showed hypopallesthesia from the T1 level. An MRI scan of the spine confirmed the well known T2-hyperintense medullary lesion from T1 to T5. Brain MRI and visual evoked potential were normal. High-titer anti-aquaporin-4-IgG (NMO-IgG) was also reported. However, the diagnosis of neuromyelitis optica (NMO) was not supported by clinical and electrophysiological investigations. About 2 months after admission to our center, she still had polyarthralgia, fever, malaise, and malar rash (Figure 1A), with photosensitivity and oral aphthosis. Her immunological profile was characterized by positivity for antinuclear antibody (1:160, granular pattern), anti-dsDNA, anticitrullinated protein antibodies (47.95 U/ml), and rheumatoid factor, along with an erosive radiograph-documented polyarthritis (Figure 1B). The clinical setting and the serological profile were consistent with a diagnosis of RS. She was treated with hydroxychloroquine, azathioprine (50 mg/day), and low-dose prednisone, and a year after the RS diagnosis, she was in good health, with maintenance therapy.

RS is a rare clinical condition characterized by overlapping clinical and immunologic features of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE)[3]. Whether RS is a clinically and immunologically distinctive entity[4], a coincidental concurrence[5], or a subgroup of patients with SLE[6] remains somewhat controversial.

Severe CNS involvement is rare in patients with RS[4]. We speculate whether our patient's previous episode of myelitis could represent an isolated coincidental neurological manifestation not related to RS or whether it could be interpreted as neuropsychiatric involvement secondary to the autoimmune disease. Moreover, isolated connective tissue disease-related nervous system impairment can mimic other neurologic disorders, resulting in misdiagnosis and unfavorable clinical outcome, mainly in rare conditions such as RS. Myelopathy is a rare but severe neurological manifestation of SLE. The etiology is not completely understood, but antiphospholipid antibodies (aPL) are presumed to be involved[7]. Nevertheless, besides aPL, cytokine- and autoantibody-mediated neuronal dysfunction have been suggested as underlying processes in neuropsychiatric SLE.

Idiopathic longitudinally extensive myelitis is an NMO spectrum disorder and patients with NMO often have an accompanying autoimmune disease, usually SLE. The autoantibody NMO-IgG is detectable in patients with NMO, but also in a high proportion of patients with an NMO spectrum disorder. A pathogenetic role for the NMO-IgG is well known[8] and the specificity of NMO-IgG for differentiating patients with NMO or NMO spectrum disorder from patients with multisystem autoimmune disorder associated with other neurological syndromes has been thoroughly assessed[9]. Hence NMO-IgG is not a nonspecific companion of SLE.

The presence of NMO-IgG in this clinical setting demonstrates that NMO can accompany RS, just as SLE can. Moreover, the evidence of autoantibodies against aquaporin-4 bears important diagnostic and prognostic implications and could also guide critical therapeutic decisions. In fact, early use of immunosuppressive therapy is thought to help patients with NMO[10]. Certainly, the complex autoimmune profile of our patient makes the interpretation and the clinical relevance of NMO-IgG positivity controversial.

Predominant RA manifestations in patients with RS are erosive arthropathy, with almost half the cases having rheumatoid nodules. At the

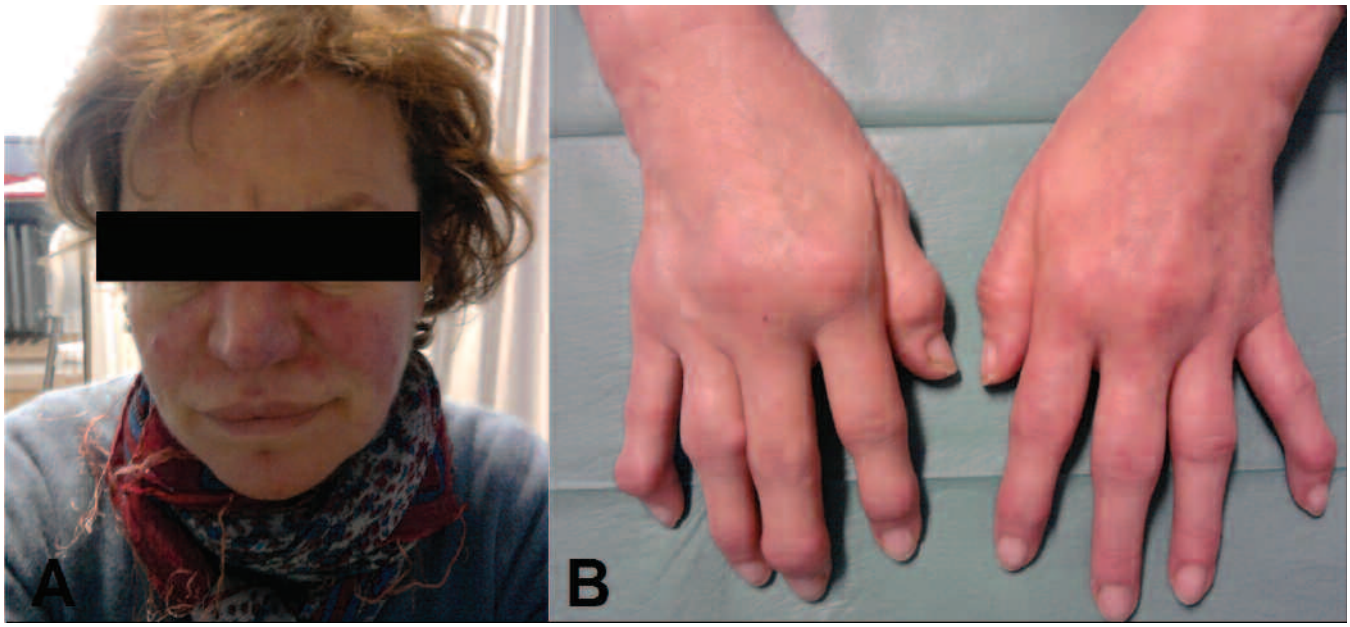

Figure 1. Clinical features of systemic lupus erythematosus (A, malar rash) and rheumatoid arthritis (B, radiograph-documented erosive polyarthritis), consistent with diagnosis of rhupus syndrome.

time of appearance of SLE manifestations, these are characterized by cutaneous and hematological alterations with mild renal damage[4]. Neurologic involvement in patients with RS is very uncommon. But a rapid diagnosis of this disorder is essential because connective tissue disease-related transverse myelopathy has a poor prognosis, and neurological recovery is more likely with prompt, aggressive treatment with high-dose corticosteroids and cytotoxic agents.

To date, the coexistence of RS associated with neuromyelitis has not been convincingly reported in English-language scientific literature. Our case documents the possible association between these rare conditions, in a complex autoimmune mosaic.

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