CASE REPORT

Association of severe and therapy-refractory systemic lupus erythematosus and neuromyelitis optica: a management challenge

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SUMMARY

Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disorder. Neuromyelitis optica (NMO) is an infrequent neuroinflammatory disorder, whose association with SLE remains rare. The authors report the case of an 18-year-old woman, with SLE refractory to multiple immunosuppressive therapies and novel biological agents. Under immunosuppressive therapy, the patient presented with transverse myelitis with contiguous spinal cord lesions and urinary incontinence, having been diagnosed with seropositive NMO, which was also proven to be refractory to common treatments. Partial recovery of the neurological deficits occurred with plasmapheresis, although not averting the brain involvement by NMO that ensued. The patient was listed nationally for allogeneic bone marrow transplant, but, unfortunately, no match was found and the patient died of severe cerebral NMO flare with coma due to brain swelling and consequent respiratory failure. Although the association of SLE and NMO is very rare, early diagnosis is crucial to facilitate initiation of immunosuppressive therapy.

BACKGROUND

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder, which can affect multiple organs—including the central nervous system (CNS). About ¼ of all patients with SLE are diagnosed in childhood and the disease is characterised primarily by episodic recurrence. SLE reflects a state of chronic inflammation and the clinical picture is a reflection of the affected organs.¹ Although there is still much undiscovered ground, SLE appears to be secondary to the production of antibodies against the components of the cell nucleus and the most significant pathological findings are those of immune complex deposition (and the failure of their clearance) and vasculitis. Moreover, SLE is a multifactorial disease with unclear impact of environmental and genetic factors, which appear to be determinant in the diversity of disease expression. The disease is also clinically marked by the presence of ‘triggers’ which can precipitate the development of flares, leading to clinical deterioration.²

Devic’s disease—or neuromyelitis optica (NMO)—is a rare (1–2/100 000) demyelinating inflammatory neurological disease of the CNS, first described in 1894 by Eugène Devic. It is a heterogeneous disease which can occur in association

with other autoimmune diseases or isolated. It is characterised by sequential or continuous flares of transverse myelitis and optic neuritis, with contiguous spinal cord MRI lesions extending over three or more vertebral segments, and seropositivity for NMO-IgG (anti-aquaporin-4 (anti-AQP4)), a sensitive and specific marker for NMO. It is more prevalent in women, can occur at any age (most commonly 20–50 years old) and does not seem to have a geographic predominance.³ The possibility of antibody screening and increased awareness for the disease has greatly improved diagnostic accuracy and mortality rates in the last 10 years. The association of SLE and NMO is very rare (1 in 5 000 000) and its pathological features are yet to be determined.⁴

Usually, NMO presents acutely—in up to half of the patients preceded by a viral syndrome (characterised by, but not limited to, upper airway symptoms, malaise and headaches)—as an ascending myelitis associated with severe pain or paralysis as well as urinary incontinence. The year 2004 marks a very important step in NMO history with the discovery of NMO-IgG—an autoantibody that targets AQP4. AQP4 is a protein—part of the aquaporin family—which ensures water transport through integral membranes. It is expressed in the kidney and astrocytes (being upregulated by direct insult to the CNS), thus playing a determining role in the maintenance of the blood-brain-barrier homeostasis.⁵

The discovery of this biomarker represents the ability to distinguish the cause of neurological involvement in autoimmune diseases, as coexisting NMO rather than a vasculitic process (as seen in other autoimmune diseases such as myasthenia gravis, paraneoplastic myelopathy, among others) and thus increasing diagnostic accuracy, being present in up to 80% of all patients with NMO. AQP4 is an autoimmune target in NMO, in which specific antibodies aim for astrocytic AQP4, leading to complement activation and subsequent inflammation. It is our aim to highlight the importance of diagnostic suspicion in neurological involvement in patients with SLE, especially when faced with therapy refractory conditions.

CASE PRESENTATION

The authors report the case of an 18-year-old woman, with an 8-year-old history of SLE, presenting with multiorgan involvement

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Figure 1 MRI, sagittal short T1 inversion recovery. Diffusely heterogeneous spinal cord signal intensity, depicting high signal central lesions spanning the third and fourth cervical vertebral levels (arrow).

(rheumatological, neurological, haematological, cutaneous, pulmonary, serous and immunological)—scoring 8/11 American College of Rheumatology Criteria.⁶ The immunological profile was, as follows, positive for: antinuclear antibodies, anti-dsDNA antibodies, hypocomplementaemia (C3+C4), antihistone antibodies, anti-actin antibodies, Beta(2) GP1-dependent aCL (anticardiolipin) antibodies and anticardiolipin antibodies.

Figure 2 Non-contrast-enhanced CT depicting hypodense bulging lesions in the corpus callosum (short arrow) and bilaterally in the posterior limb of the internal capsule (long arrows).

Moreover, anti-SS-A/anti-SS-B were negative (10.0/0.6 U/mL respectively; normal ≤ 10 U/mL), as was anti-Jo-1 (0.7 U/mL; normal ≤ 10 U/mL). The patient also tested negative for the following antibodies: antimitochondria, anti-LKM (liver-kidney -microsomal antibody), anti-liver-cytosol-1, (anti-LC1), anti-SLA/LP (soluble liver antigen/liver-pancreas), antismooth muscle, ANCA (Anti-neutrophil cytoplasmic antibodies) and anti-PR3 (proteinase 3). CSF (cerebrospinal fluid) data on first presentation were as follows: glucose=0.53 g/L (normal range: 0.39–0.71 g/L), proteins=0.42 g/L (normal range: 0–0.45 g/L), erythrocytes=0 cell/uL (normal range: 0–10 cell/uL), leucocytes 32 cell/uL (normal range: 0–5 cell/uL); granulocytes=4 cell/uL, agranulocytes=28 cell/uL. CSF was also tested for *Cryptococcus*, *Mycobacterium tuberculosis*, Enterovirus, Polyomavirus, Epstein-Barr virus, Herpes 6 virus, Herpes simplex (1 and 2) virus and Varicella-zoster virus—all negative.

The SLE flares presented as severe and refractory to multiple immunosuppressive therapies, fulfilling five criteria of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index: seizures, cataracts, muscular atrophy, deforming arthritis and osteoporosis with fracture. Treatment strategy consisted of steroids (methylprednisolone bolus—1 g/day for 5 days—followed by prednisolone 1 mg/kg/day) in combination—successively—with: methotrexate titrated up to 20 mg weekly, intravenous immunoglobulin (IvIg) 0.4 g/kg/day (for 5 days, once a month), cyclophosphamide 750 mg/m² (every 2 weeks for 3 months), mycophenolate mofetil up to 2.5 g/day and rituximab 375 mg/m². Under immunosuppressive therapy, the patient presented with transverse myelitis and contiguous spinal cord lesions, exhibiting symptoms of paresis, peripheral neuropathy, persistent tonic muscular spasms and urinary retention. She was diagnosed with extensive and seropositive (anti-AQP4 antibody positive) NMO with brain involvement (see figures 1 and 2). Furthermore, the patient developed chronic right arm and bilateral lower limb paresis, as well as neurogenic bladder, requiring intermittent urinary catheterisation. This condition was also proven to be refractory to common treatments, with no response to high-dose corticosteroids, IvIg and cyclophosphamide. As second-line therapy steroids were associated with IvIg and plasmapheresis (five consecutive sessions in 5 days, followed by five more sessions every other day), followed by two additional courses of 5 daily plasmapheresis sessions. Tocilizumab was considered but not administered due to the recurrent severe infections in our patient.

OUTCOME AND FOLLOW-UP

Partial recovery of the neurological deficits occurred with plasmapheresis, although not averting the brain involvement by NMO. The condition progressed rapidly with multiple hospitalisations due to severe NMO flares, with paresis exacerbation, neuropathic pain and aggravated neurogenic bladder, leading to progressive quality of life deterioration (ie, loss of walking ability). At this moment, the patient was also under treatment with gabapentin, pregabalin and baclofen for symptom control. Most of the subsequent hospitalisations were complicated by hospital-acquired infections by multiresistant agents, demanding broad-spectrum antibiotics. Due to the insufficient response to the above-mentioned therapies and time-sensitive clinical deterioration, the patient was listed nationally for allogeneic bone marrow transplant (after immediate family proven not to be a match). Further immunosuppression was not feasible due to serious infectious complications but the disease was aggressively progressing through a hyperactive immune system—there was a need to modulate the immune system without further suppression. Although still controversial, bone marrow

transplantation was a last attempt to save the patient, focusing on the positive results obtained in patients with aggressive forms of the disease.⁷⁻⁹

Unfortunately, no match was found and the patient died of severe cerebral NMO flare with coma due to brain oedema and consequent respiratory failure.

DISCUSSION

Although the association of SLE and NMO is very rare, early diagnosis is crucial to facilitate prompt initiation of immunosuppressive therapy for attack prevention. A review of the available literature reveals scarce recommendations and the published clinical cases underline the importance of immediate treatment initiation. Immunosuppression should not be delayed.

Moreover, treatment failure should trigger timely evaluation for bone marrow transplant, while the patient still maintains an adequate physical condition. This is particularly important in the scenario of severe and debilitating NMO in patients under immunosuppression for another autoimmune disease.

Learning points

- The association of systemic lupus erythematosus and neuromyelitis optica is very rare.
- Early diagnosis is important for the prompt initiation of treatment.
- In the absence of treatment response, bone marrow transplant should be considered.

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