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Short Communication

Neuromyelitis optica after splenectomy: A secondary autoimmune phenomenon

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ABSTRACT

We describe the case of a 53-year-old woman who undergoes total splenectomy and later presents with aquaporin-4 antibody positive neuromyelitis optica (NMO). The occurrence of NMO after acquired immunosuppression raises the possibility of NMO as a form of secondary autoimmunity.

1. Report of a case

A 53-year-old woman underwent total splenectomy with resection of a benign pancreatic mucinous cystadenoma. Five years later, she was diagnosed with NMO after presenting with binocular vision loss, right lower extremity numbness and left upper extremity pain. Aquaporin-4 antibodies were present in the serum and cerebrospinal fluid (CSF). Two oligoclonal bands were present in 80× concentrated CSF. Magnetic resonance imaging (MRI) of the orbit demonstrated left optic nerve enlargement, gadolinium contrast enhancement and short-TI inversion recovery (STIR) hyperintensity (Fig. 1). She was initially managed with 1g intravenous methylprednisolone daily for 5 days before 11 days of oral prednisone 60 mg daily and then 4 days of a tapering dose. She received 2 doses of 1000mg rituximab separated by 2 weeks once her antibody tests returned.

Approximately 4 months later, she experienced truncal and bilateral lower extremity paresthesias and numbness, and worsened left eye visual acuity. MRI of the spinal cord demonstrated a longitudinally extensive C6-7 to T6-7 STIR hyperintense and gadolinium enhancing lesion (Fig. 1). MRI of the orbit showed left optic nerve T2 hyperintensity and enhancement. Total white blood cell count was normal at 8.8 × 10^3/mL. Total lymphocyte count was normal at 2.33 × 10^3/mL (26.4% of white blood cells). CD19 + CD20 + cell count was < 1 cells/mm^3. CD3 + cell count was 1732 cells/mm^3 (normal 690-2540 cells/mm^3). She was managed with intravenous methylprednisolone, 5 sessions of plasma exchange, and a dose of intravenous rituximab. Azathioprine was started at 100mg orally daily, dosed at approximately 2mg/kg.

She continued to receive IV rituximab every 6 months and azathioprine daily for 4 years without further relapse. She developed frequent infections including shingles, pneumonia, and *Clostridium difficile* colitis. Her azathioprine was slowly tapered over 8 months, then discontinued. She continues on rituximab and has not had a further flare after 6 months on monotherapy. Her current Expanded Disability Status Scale (Kurtzke, 1983) score is 3.5.

2. Data availability statement

Anonymized data relating to this case will be made available by the authors upon request from a qualified physician or investigator. The patient provided her written consent to publish her case.

3. Discussion

We describe what we believe is a unique case in the literature of aquaporin-4 antibody seropositive NMO after total splenectomy. While we cannot rule out a coincidental association, this case potentially demonstrates NMO as a form of secondary autoimmunity and highlights possible treatment implications for patients with other preceding immunosuppressive conditions involving T-lymphocytes (Blanche et al., 2000; Bhigjee et al., 2017; Mathew et al., 2019). In particular, there is an emerging literature of patients with both Human Immunodeficiency Virus (HIV) infection and aquaporin-4 antibody seropositive NMO, questioning whether an important and previously unrecognized relationship exists between these two conditions (Bhigjee et al., 2017; Mathew et al., 2019).

The temporal profile of splenectomy followed by NMO in our patient fits with a pathogenic hypothesis. Splenectomy decreases suppressor T-lymphocyte activity (Melamed et al., 1982). Splenectomy is

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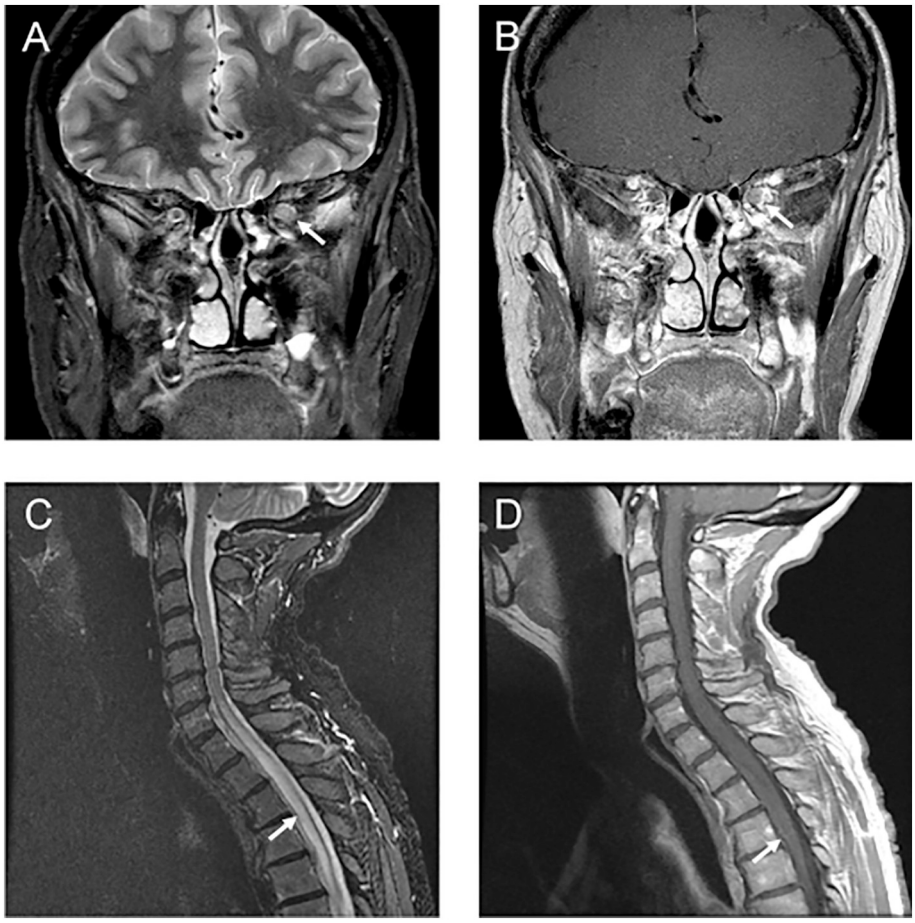

Fig.1. MRI images at initial presentations.
Coronal MRI images demonstrating STIR hyperintensity (A) and gadolinium contrast enhancement (B) of the left optic nerve. Sagittal MRI images demonstrating a longitudinal cervical and thoracic spinal cord lesion with STIR hyperintensity (C) and peripheral gadolinium contrast enhancement (D). Arrows indicate the respective finding in each image.

also associated with a 10.3-fold increase in systemic lupus erythematosus (Hsu et al., 2016). NMO is often part of a broader autoimmune picture with one-third of relapsing NMO patients having other autoimmune conditions (Wingerchuk et al., 1999). Even though NMO is commonly thought of as antibody- and complement-mediated, T-lymphocytes are implicated as the anti-aquaporin 4 immunoglobulin subclass (IgG1) is T-lymphocyte-dependent (Papadopoulos and Verkman, 2012).

The importance of T-lymphocytes also affects treatment decision-making. Our patient initially relapsed on rituximab that targets CD20 on B-lymphocytes. She had no further relapse on azathioprine that targets both B- and T-lymphocytes, even though it is considered less effective than rituximab at preventing relapses as monotherapy (Mealy et al., 2014). It remains unclear whether T-lymphocytes provide a sufficient role for the pathogenesis or whether they are additive to B-lymphocytes, and therefore whether our patient requires ongoing treatment targeting both. We reduced her immunosuppression due to opportunistic infections and chose to keep rituximab due to patient preference.

As secondary autoimmunity increases with the rising use of immunomodulatory therapies, increased clinical vigilance should be given for NMO in cases of prior acquired immunosuppression, even if the association is not intuitive. Further case reports will assist in clarifying whether splenectomy or other forms of acquired immunosuppression lead to aquaporin-4 antibody mediated disease and the treatment implications. We recognize that the most definitive evidence of immunodeficiency from splenectomy leading to NMO would be to test for aquaporin-4 antibodies pre-splenectomy and post-splenectomy; however, aquaporin-4 antibodies are reasonably only tested when there is a clinical suspicion of NMO. Pre-splenectomy aquaporin-4 antibody testing would have been highly unlikely without a clinically fitting syndrome. Therefore, we are unable to unequivocally prove that this association exists, but find its likelihood important to report given the increasing range of conditions that deplete or dysregulate the immune system and are hypothesized to precede NMO. Fortunately, our patient had a good outcome with combined rituximab and azathioprine immunosuppression.

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