https://doi.org/10.22491/2357-9730.133555

Case Report

Multiple sclerosis following splenectomy for idiopathic thrombocytopenic purpura: case report and review of published cases

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ABSTRACT

Introduction: Multiple sclerosis may rarely present alongside idiopathic thrombocytopenic purpura and scarcely ever following splenectomy for hematologic disease.

Methods and Results: We report the case of a 51-year-old woman presenting with subacute onset of mild ataxia, dysarthria and lower limb dysesthesia in close temporal relationship with splenectomy performed as a treatment for steroid-dependent idiopathic thrombocytopenic purpura. MRI showed hyperintense T2/FLAIR multifocal white-matter lesions and there were highly positive cerebrospinal-fluid oligoclonal bands, picturing her first clinical episode of multiple sclerosis. She was treated with intravenous methylprednisolone, with significant improvement, and then started on multiple sclerosis disease-modifying therapy.

Conclusion: This report suggests the possible role of splenectomy as an environmental trigger for clinical multiple sclerosis in genetically predisposed individuals, as well as for those with radiologically isolated syndromes.

Keywords: *Case Report; Demyelinating Disorders; Idiopathic Thrombocytopenic Purpura; Multiple Sclerosis; Splenectomy*

Clin Biomed Res. 2024;44:1-5

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INTRODUCTION

The association between multiple sclerosis (MS) and idiopathic thrombocytopenic purpura (ITP) is not clear, although they share similar immunopathological mechanisms[1]. A few cases of patients presenting with MS alongside ITP were reported[2-4], with varying temporal relationships between both events. Curiously, in a single report, MS presented after splenectomy[3]. Although this procedure may interfere with the immune system, its relation with emergence of MS activity is unknown.

We hereby describe a case of first clinical activity of MS soon after splenectomy performed as treatment for steroid-dependent ITP.

CASE REPORT

A 51-year-old woman, otherwise healthy, was diagnosed with ITP at the age of 49 based on persistent thrombocytopenia, a normocellular bone marrow biopsy and exclusion of alternative etiologies. Corticosteroid therapy was an effective treatment for 2 years, when she became steroid-dependent and required associated treatments. Danazol, dapsone, azathioprine and eltrombopag (a thrombopoietic growth factor) were tried, achieving no satisfactory disease control or corticosteroid-sparing effect. Therefore, splenectomy was elicited as a therapeutic alternative. She underwent surgery without periprocedural complications.

Ten days after the splenectomy, she began to notice right upper limb incoordination and dysarthria of subacute onset. In the following days, she developed left lower limb dysesthesia and imbalance. There was no previous history of neurological symptoms, substance abuse or use of other medications. Her last vaccination was SARS-Cov2 Pfizer-BioNTech in March 2022. Although medically recommended, she refused to be vaccinated against *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, and *Neisseria meningitidis* before splenectomy. On neurological examinations, she was awake and alert and had no abnormalities in higher brain functions. There was no cranial nerve involvement. Pupils were isochoric and the light reflex was intact. Muscles were not atrophic and did not demonstrate any weakness. There was mild gait ataxia and dysarthria, nystagmus at extreme upper gaze and mild dysmetria in the right upper limb. Also, in the left lower limb, there was normal strength and tonus, but slightly increased reflexes, as well as thermalgesic hypoesthesia. 3 Tesla MRI revealed several hyperintense T2/FLAIR weighted and hypointense T1 weighted lesions without contrast enhancement (Figure 1) with a predominantly ovoid aspect in periventricular and subcortical white matter. Spinal cord MRI showed a T2-weighted hyperintense lesion at T9 with gadolinium enhancement (Figure 1). Cerebrospinal fluid analysis was otherwise normal except for the presence of oligoclonal bands. Serum laboratory tests including testing for syphilis, hepatitis B and C, HIV, serum B12 levels, liver and thyroid function, coagulogram, search for hemolysis (including direct antiglobulin (coombs) test), immunoglobulin A, M and G levels, protein electrophoresis, complement levels, antinuclear antibodies (ANA), rheumatoid factor, anti-double-stranded DNA, anti-neutrophil cytoplasmic antibodies (ANCA), antibodies against extractable nuclear antigens (ENA), lupus anticoagulant and anticardiolipin antibody were all normal. The diagnosis of MS was established according to 2017 revised McDonald criteria[5].

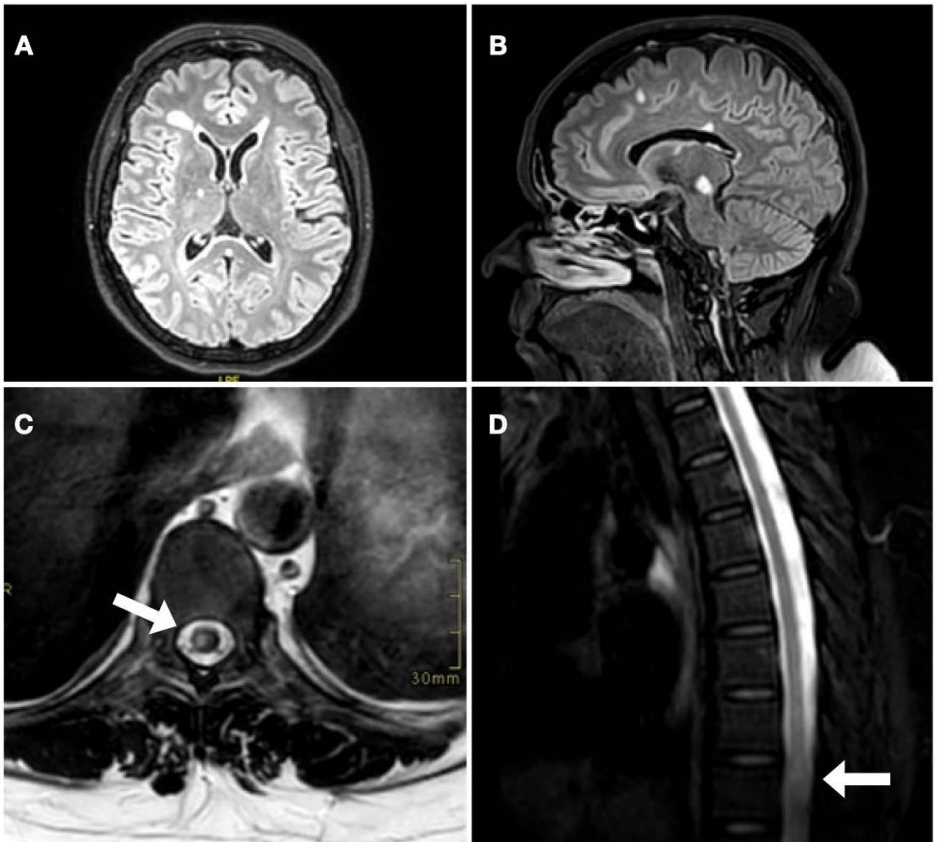

Figure 1: Central nervous system MRI (3 Tesla). Axial (a) and sagittal (b) FLAIR-weighted hyperintense ovoid white-matter demyelinating lesions typical of MS; Axial T1-weighted gadolinium-enhanced lesion (c) in the right half of the spinal cord at T9 (white arrow) associated with a mild focal volumetric increase, with the corresponding sagittal view (d) (white arrow).
MRI: magnetic resonance imaging; FLAIR: fluid-attenuated inversion recovery; MS: multiple sclerosis.

Follow-up exams showed postoperative thrombocytosis (Figure 2). Eltrombopag was readily suspended, with subsequent normalization of platelet counts. She underwent intravenous methylprednisolone (MTP) 1000 mg/day for 5 days, with significant neurological improvement, although mild ataxia persisted. Finally, she was discharged for outpatient follow-up, early initiation of disease-modifying therapy and rehabilitation.

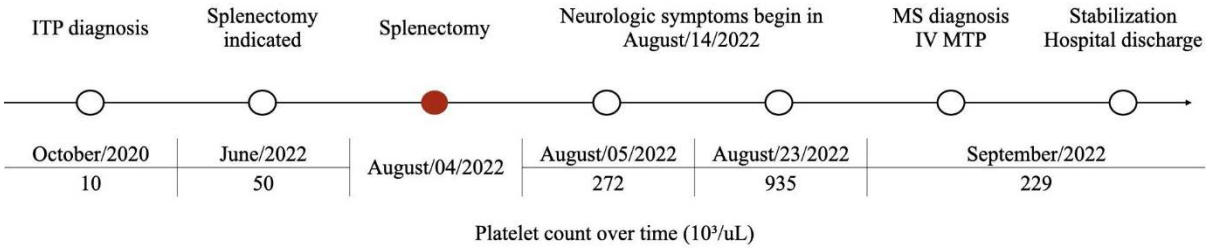

Figure 2: Timeline of main events. Neurologic symptoms begin alongside with a significant increase in platelet counts soon after splenectomy, followed by subsequent normalization after Eltrombopag suspension.
ITP: idiopathic thrombocytopenic purpura; MS: multiple sclerosis; IV: intravenous; MTP: methylprednisolone.

DISCUSSION

MS presenting soon after splenectomy for ITP was only once described after one year from the procedure[3]. We speculate both events could be associated, suggesting a possible triggering effect of splenectomy in MS.

Epidemiological associations between MS and ITP must be cautiously interpreted, since various MS disease-modifying drugs such as interferon[6,7], fingolimod[6], natalizumab[8] and alemtuzumab[9-11] may induce thrombocytopenia, acting as a confounder. One population-based Danish study found a four-fold higher incidence of essential thrombocytopenia in MS patients than expected for the general population, although the sample was too small to draw generalized conclusions[12]. Other observational studies found no significant association between MS and ITP[13,14]. One of them reported a comparison to the matched population focusing on the occurrence of purpura preceding MS diagnosis and did not find any difference[14]. Therefore, assigning MS activity and diagnosis to coexistence of previous autoimmune disease (ITP) in our case report would not be strongly supported by previous observational evidence. Few case reports describe the occurrence of MS alongside non-pharmacologically induced ITP or splenectomy (Table 1), all in women, two of them with ITP preceding MS, two with ITP following MS and one with both diagnoses simultaneously. Unfortunately, data about splenectomy and its temporal relation with MS diagnosis was missing in most cases.

Table 1: Case reports relating MS to ITP and/or splenectomy (excluding cases with possible pharmacologically-induced thrombocytopenia).

Patient	Author	Gender	ITP onset (age)	MS onset (age)	First MS presentation	Splenectomy / Time to clinical MS	Follow-up
1	Matsui et al.[3]	Female	21	27	Spinal cord syndrome	Yes / 1 year	Steroid-responsive optic neuritis at age of 29
2	Granier et al.[4]	Female	40	40	Spinal cord syndrome	No	Paresthesias in extremities and vertigo/nystagmus at age of 41; Stabilized with interferon beta-1b
3	Sahraian and Eshaghi[2]	Female	16	6	Internuclear ophthalmoplegia	Unknown	RRMS, treated with azathioprine
4	Sahraian and Eshaghi[2]	Female	23	36	Walking difficulties	Unknown	SPMS, treated with oral prednisolone
5	Sahraian and Eshaghi[2]	Female	31	27	Tongue paresthesia	Unknown	RRMS, treated with interferon beta-1a

ITP: idiopathic thrombocytopenic purpura; MS: multiple sclerosis; MRI: magnetic resonance imaging; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis.

Multiple sclerosis activity emerges from a disruption in the balance between peripheral immune cell subsets, mainly T cells, B cells, and myeloid cells[1]. Spleen plays a key role in the interface between innate and adaptive immune response, regulating the interaction between serum antigens and these immune cells. It is plausible to infer that immunological rearrangements may occur following splenectomy, potentially favoring the development of autoimmune disorders. This is consistent with a previous report[3]. In the absence of evidence linking the risk of MS activity with general surgical stress, the possible association with splenectomy itself becomes more prominent.

Also, platelets seem to play a role in the regulation of pathogenic CD4 T cells functions during initiation and progression of autoimmune neuroinflammation[15]. Our patient had persistent thrombocytopenia before splenectomy, evolving to a brief postoperative period of marked thrombocytosis (Figure 2). Eltrombopag, a thrombopoietin receptor agonist, has no direct known effects in the immune system, nor reported association with demyelinating diseases. Splenectomy, indeed, by removing the main platelet-depleting factor and allowing a substantial increase in platelet count in a patient exposed to chronic thrombocytopenia, may have contributed to immune unbalance and neuroinflammation through systemic platelet activation.

Since this patient never had a previous neuroimaging, we could not say accurately for how long she had demyelinating lesions. Considering the MRI images, still, which suggest most of them to be older, she would possibly have met criteria for radiologically isolated syndrome (RIS)[5]. Assuming this, splenectomy may have contributed to clinical conversion from RIS into clinical MS. To date, there is no such report in patients submitted to splenectomy nor with comorbid hematologic disease.

This study has a major hypothesis-generating role, although its intrinsic limitations as a case report do not allow generalizable conclusions. Naturally, clinical MS and splenectomy could have been coincidentally related due to chance, although this idea is weakened by their strict temporal relationship and physiopathological plausibility. Well-designed population-based studies are compelling to accurately assess this hypothesis.

CONCLUSION

This report suggests a possible role of splenectomy as an environmental trigger for MS activity in genetically predisposed and susceptible individuals, in addition to those with RIS. The risk of developing subsequent clinically active MS and other autoimmune diseases after splenectomy deserves attention, in addition to the usual concerns with infections and thrombotic complications. A careful assessment of the individual risk of MS in patients who are candidates for splenectomy may be considered.

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Received: Jun 29, 2023
Accepted: Mar 25, 2024