Human & Veterinary Medicine
International Journal of the Bioflux Society HVM

OPEN ACCESS
Case Report

An unusual cause of longitudinally extensive transverse myelitis - case report

[1,2]Adina Stoian, [2,3]Rodica Bălaşa, [2,3]Laura Bărcuţean, [2,3]Anca Motataianu, [4]Simona Mocan, [2,3]Smaranda Maier, [2,3]Zoltan Bajko, [5]Simona Szasz

[1] Department of Patophysiology, University of Medicine and Pharmacy Târgu Mureş, Romania; [2] Mures County Clinical Emergency Hospital, Ist Neurology Clinic, Târgu Mureş, Romania; [3] Department of Neurology, University of Medicine and Pharmacy Târgu Mureş, Romania; [4] Department of Pathology, University of Medicine and Pharmacy Târgu Mureş, Romania; [5] Department of Reumatology, University of Medicine and Pharmacy Târgu Mureş, Romania.

Abstract. Longitudinal extensive transverse myelitis (LETM) is an inflammatory disorder of the spinal cord that extends over three or more vertebrae. The etiology is broad, including neuromyelitis optica, various infectious, autoimmune and inflammatory diseases. The clinical presentation implies usually severe paraparesis or tetraparesis, bladder and bowel dysfunction and sensory abnormalities. We present a case of a 56-year-old Caucasian woman, who presented suddenly progressive muscular weakness in the lower extremities accompanied by urinary retention and numbness in the superior thoracic region. The spinal cord MRI revealed a longitudinally extensive spinal cord lesion from D2 to D7 level. An extensive laboratory workup was performed for infectious, inflammatory and autoimmune disorders, revealing elevated antinuclear antibody and anti-Ro/SSA level. The Schirmer's test was positive, and the minor salivary gland biopsy revealed limfoplasmocitar inflammation. The diagnosis of primary Sjögren syndrome (SS) was established. The outcome was favorable on high dose of corticoteraphy and immunosupressive medication. It is important to include SS in the differential diagnosis of LETM even if the classical SICCA syndrome is not present.

Key Words: Longitudinally extensive transverse myelitis, primary Sjögren syndrome, SICCA syndrome

Corresponding Author: A. Stoian, email: cretadina@yahoo.com

Introduction

Sjögren syndrome (SS) is a chronic, autoimmune systemic disease defined by chronic lymphocyte and plasma cell infiltration of the exocrine glands. The exocrinopathy especially affects the salivary and lacrimal glands (Moutsopoulos 1994) leading to not only dysfunction with the loss of secretory function but also extraglandular impairment, which includes pulmonary, gastrointestinal, haematological and central and peripheral nervous system (i.e., spine, brainstem, optic nerves, cerebellum and cerebral hemispheres) diseases.

This disease can manifest itself as primary Sjögren syndrome (pSS) or in combination with other connective tissue disease, secondary Sjögren syndrome (sSS). The symptoms of keratoconjunctivitis sicca, secondary to the lacrimal gland impairment and xerostomia, are the result of salivary gland destruction and usually manifest themselves in a remarkable way; but pSS presents with a wide variety of clinical manifestations (e.g., arthralgia, generalised fatigue, Raynaud phenomenon, renal, pulmonary and neurological disease), a clinical polymorphism that leads to a delay in diagnosis (Tobón et al 2012).

The neurological symptoms can precede the sensation of the sicca symptoms (i.e., dry eyes and mouth) in 40–93% of cases (Tobón et al 2012; Lafitte et al 2001) and represent severe characteristics of the extraglandular manifestations of pSS (Berkowitz et al 2014). Peripheral nervous system (PNS) involvement was reported with a prevalence as high as 20%, and the central nervous system (CNS) involvement represents a rare complication found in 5.8% of the cases (but with a great impact). Mori et al. published that 93% of their patients had been diagnosed with pSS after the onset of neurological symptoms (Mori et al 2005).

The PNS involvement manifests with axonal polyneuropathy (both sensitive and sensory-motor), small fibre neuropathy and trigeminal neuropathy (Tobón et al 2012; Delalande et al, 2004). CNS manifestations are heterogeneous and are the results of a focal or diffuse process (Tobón et al 2012). Diffuse involvement can manifest as encephalopathy, cognitive deficits, dementia, psychiatric anomalies and aseptic meningoencephalitis, while focal involvement can manifest as spinal lesions or optic myelitis. Spinal lesions include acute and chronic progressive myelopathies, which, although appearing rare in pSS, are severe and potentially lethal (Tobón et al 2012; Moutaouakil et al 2005).

Acute transverse myelitis is an inflammatory process that affects the spine, which represents a medical emergency and sometimes might indicate a lesser-known initial manifestation of autoimmune diseases such as systemic lupus erythematosus (SLE) or SS. Transverse myelitis is generally monophasic, but some patients can present with recurrences. An association between transverse myelitis and anti-Ro antibodies has been described, which suggests that the spinal lesion mechanism is autoimmune in nature. Early detection and aggressive therapy

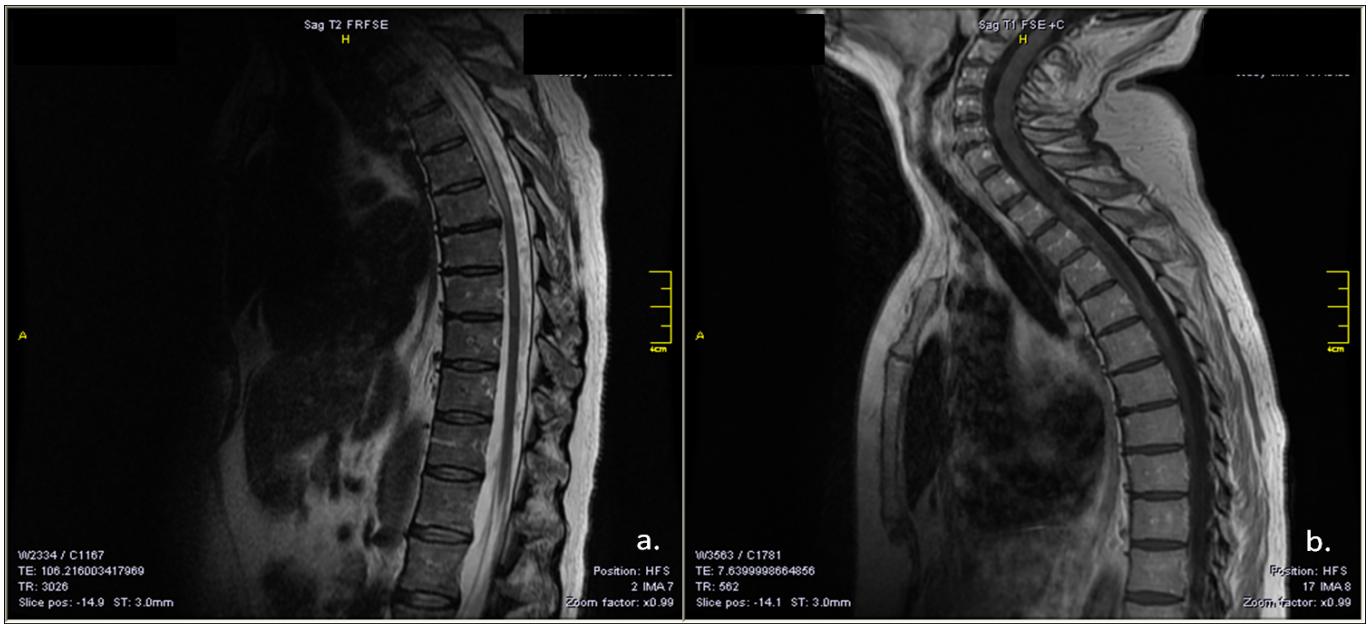

Figure 1. Spinal cord MRI a. Sagittal T2 sequences showing a hyperintense intramedullary lesion extending from D2 to D7 level; b. Post contrast sagittal T1 sequences showing mild peripheral gadolinium enhancement

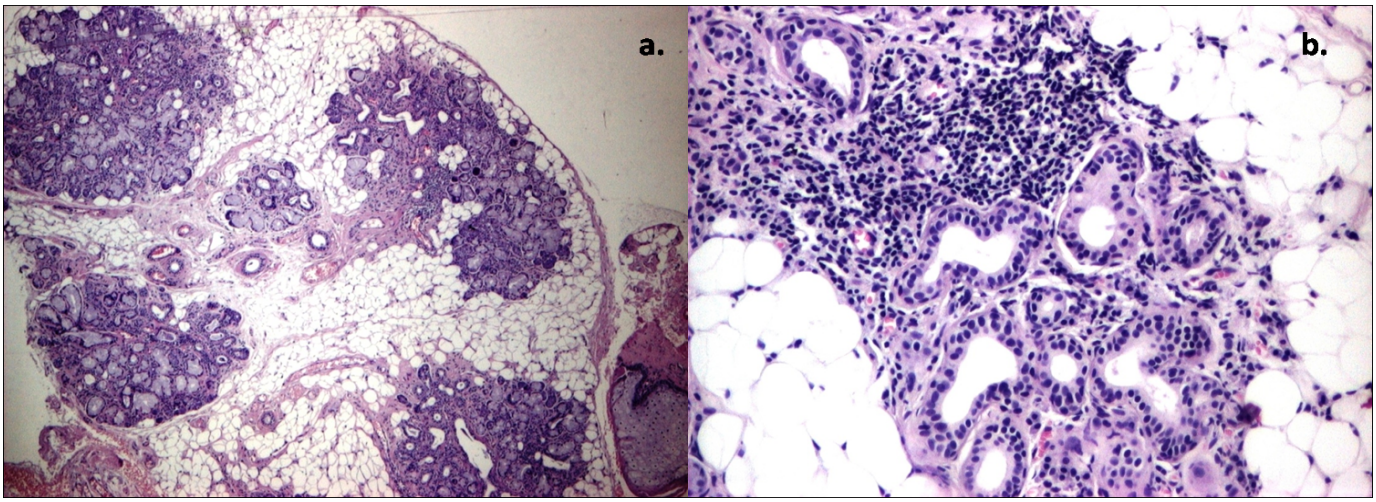

Figure 2. Histopathological examination. a. Minor salivary gland biopsy with adipous tissue replacement and fibrosis associated with an inflammatory infiltrate, with formations of small focus (Hematoxilline eosine staning, x2); b. One focus with lymphocytes and plasma cells, exceeding 50 cell per focus. (Hematoxiline eosine staning, x 20)

are mandatory in order to improve the prognosis (Melikyan et al 2012; Tristano 2006).

Case presentation

We present the case of a 56-year-old Caucasian woman who presented to our clinic in 2016 complaining of progressive muscular weakness in the lower limbs (symptoms that started two days prior to hospital admission) accompanied by urinary retention and numbness in the superior thoracic region.

Written informed consent was obtained from the patient. The ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments were respected.

Neurological exam on admission revealed decreased muscular strength in the lower limbs with flaccid paraparesis (0/5 in right inferior limb and 2/5 in left inferior limb), deep tendon reflexes abolished in the inferior limbs, bilateral Babinski sign, superficial thermo-algesic anaesthesia with a D2 level, apallesthesia of the lower limbs, abolished cutaneous abdominal reflexes and urinary retention.

Magnetic resonance imaging was performed and revealed a contrast-enhancing lesion that extended between D2 and D7 (with a cranial-caudal diameter of 94 mm) and peripheral contrast enhancement in the anterior columns from D2 to D4. The lesions appeared continuous towards the posterior columns with no indication of a primary neoplastic process (Figure 1).

The cerebrospinal fluid (CSF) exam performed at the prior admission showed no abnormalities. The laboratory results excluded organ failure and endocrinopathies. B12 and angiotensin convertase levels were normal. Neuromyelitis optica (NMO) antibodies (Aquaporin 4) were measured during hospitalisation and were within normal limits. A comprehensive infectious workup was done, including testing for varicella zoster virus (VZV), herpes simplex virus (HSV), hepatitis B and C, Lyme disease serology, syphilis, HIV, EBV and CMV. Tumour screening to

exclude paraneoplastic myelitis was done. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complements and immunofixation electrophoresis were normal. Anti-double stranded DNA (anti-dsDNA) antibodies, anti-neutrophil cytoplasmic antibody (ANCA) serology and antiphospholipid antibodies were negative. The antinuclear antibody (ANA) was positive with a high anti-Ro/SSA level of 55.2 U/ml (normal value < 7 U/ml).

Other investigations such as brain MRI, visual evoked potential, thoracic-abdominal-pelvic CT and nerve conduction studies were normal.

On a careful history examination, she mentioned sicca symptoms (a decrease in saliva production), which she did not find significant. Schirmer's test was positive, and minor salivary gland biopsy revealed limfoplasmocitar inflammation with a focus score of 3 (Figure 2).

After admission, corticosteroid treatment was initiated with methylprednisolone 500mg intravenous (IV) daily (until a total of 5 grams) with slight improvement of the motor deficits. She was discharged with flaccid paraparesis (1/5 right inferior limb and 3/5 left inferior limb). Immunoglobulins or plasmapheresis were not attempted due to improvement and favorable progression under corticosteroid treatment.

She began intensive physical therapy (PT) and after the diagnosis of SS was reached (in accordance to the criteria for SS as established by the American-European Consensus group (Massara et al 2010; Vitali et al 2002), she started cyclophosphamide treatment 700 mg/m2 IV monthly (for six cycles) and prednisone 20 mg daily. After four infusions of cyclophosphamide combined with prednisone and PT, the motor deficits regressed. After four months, the neurological exam revealed flaccid paraparesis 3/5 in the right inferior limb and 4/5 in the left inferior limb plus spontaneous urinary output with no need for urinary catheterisation. The maintenance therapy involved azathioprine 1.5 mg/kg per day in association with low doses of corticosteroids (prednisone 10 mg/day).

Discussion

Neurological symptoms appear in 20% of the patients with SS and CNS involvement appears in 2% of the cases (Mori et al 2005). CNS involvement is less frequent than PNS involvement but can manifest quite frequently at the onset of pSS (Morreale et al 2014) (preceding the SS diagnosis by approximately two years) due to the fact that mild sicca symptoms are easy to ignore. The neurologist must be advised of CNS manifestations of SS, including transverse myelitis, NMO and diffuse cerebral injuries (Berkowitz et al 2014). It is important to consider pSS in the differential diagnosis of a patient with recurrent CNS pathology (Massara et al 2010).

A study published by Massara et al. in 2010 showed that extraglandular manifestations such as arthritis have been less frequent in patients with pSS, which applies in our case. Our patient had no articular manifestations. Pulmonary involvement, duration of the disease and a low C4 level has correlated with CNS involvement in patients with SS. We found no pulmonary lesions in our case, although this seems to be the strongest risk factor for CNS complications (which underlines the importance of pulmonary follow-up in these patients) (Massara et al. in 2010).

The evolution of acute myelitis can be monophasic or recurrent, which is similar to multiple sclerosis (MS) and in some other autoimmune diseases (Sá 2009). Transverse myelitis that accompanies SS often extends to more than three levels in the spine and presents as extensive transverse myelitis (Berkowitz et al 2014). In a series of cases reported by Lafitte et al., myelopathies were described in 3 out of 11 patients with SS and CNS involvement (Lafitte et al 2001). Furthermore, the clinical picture was often characterised by transverse myelitis (Tobón et al 2012; Manabe et al 2000), which seemed to especially involve the cervical and/or thoracic levels (Berkowitz et al 2014). Our patient also presented with longitudinally extensive myelitis on five thoracic medullary levels (D2–D7).

The autoantibodies usually associated with SS are anti-SSA and anti-SSB. Anti-SSA antibodies appear in 33–74% of the patients and have been associated with more serious CNS involvement and small vessel vasculopathy (Massara et al 2010, Soliotis et al 2004). The anti-SSB antibodies appear in 23–52% of the patients, and ANA appears in 59–85% of the patients (Berkowitz et al 2014; Bournia et al 2012). In a recent review concerning the patients with transverse myelitis associated with SS, 85% of the patients presented with anti-SSA and/or anti-SSB antibodies. The presence of anti-SSA antibodies increased the risk of recurrence and extensive lesions of the CNS (Berkowitz et al 2014; Kahlenberg 2011).

NMO, or Devic's disease, is another demyelinating disease of the CNS and is characterised by longitudinally extensive transverse myelitis, optic neuropathy and the presence of anti-aquaporin-4 antibodies (NMO-IgG) (Wingerchuk et al 2007). NMO and SS transverse myelitis share common features. It has been disputed if they are associated or appear at the same time. James et al. performed a study on 109 patients with connective tissue diseases and noticed that 78% of the patients with NMO spectre diseases (e.g., recurrent optic neuritis and longitudinally extensive transverse myelitis) presented with anti-aquaporin-4 antibodies, but other patients with other neurological diseases did not present with anti-aquaporin-4 antibodies (Jarius et al 2011). Pittock et al. described that even though 16% of the patients with NMO presented with positive anti-SSA and/or anti-SSB antibodies, only five of these patients (3%) met the criteria for SLE and/or SS (Pittock et al 2016). Small salivary gland biopsy performed in patients with NMO or NMO spectre disease revealed lymphocyte inflammation similar to the medullary areas, suggesting a superposition between the mechanisms of NMO spectre disease and secondary longitudinal transverse myelitis in pSS (Kahlenberg 2011).

Our patient did not meet the clinical criteria for NMO, as she showed no signs of optic neuritis in the brain MRI. Additionally, the visual evoked potentials and NMO-IgG were normal.

Another disease that presents with demyelinating lesions and affects multiple spine levels is multiple sclerosis (MS). But in this case, they are limited to less than three segments and have radial orientation of the lesions (Berkowitz et al 2014). Our patient did not meet the clinical and imagistic criteria for MS.

Our patient met the criteria for SS, which highlights the necessity of rheumatologic screening in patients with transverse myelitis. In accordance with early observations (Massara et al 2010), the case we presented confirms that CNS involvement represents a diagnostic challenge for the clinician and that this

differential diagnosis must be considered especially in cases with recurrent neurological events.

Corticosteroid therapy is the first-line treatment for patients with SS associated myelitis. Cyclophosphamide in a monthly dose of 700 mg/m2 for 6 months can also be used in the patients, followed by azathioprine 1–2 mg/kg/day associated with prednisone. Like other alternative treatments, we have azathioprine, chlorambucil, cyclosporine, methotrexate and plasmapheresis for refractory cases that do not tolerate cyclophosphamide. Rituximab is indicated in NMO, and together with anti-CD20 antibodies seem to have a favourable effect on some systemic complications and in cases of pSS with refractory neuropathy (Berkowitz et al 2014; Kahlenberg 2011; Tobón et al 2012).

Conclusions

Transverse myelitis in SS is a rare complication, but it is noted in the general scientific literature. SS can affect any component of the nervous system (i.e., CNS and PNS), often preceding the diagnosis of pSS. SS and NMO-IgG testing is recommended in all the patients with longitudinally extensive transverse myelitis. The presence or absence of NMO-IgG provides additional prognostic information and is important for the therapeutic decision. The presence of NMO-IgG in patients with transverse myelitis and pSS increases the risk for recurrences, which is the reason why testing for it is indicated in order to obtain an optimal therapeutic decision.

The spinal MRI is essential for the diagnosis, and a multidisciplinary approach between the neurologist, rheumatologist, ophthalmologist and morphopathologist is mandatory in order to reach a final diagnosis and to optimise treatment.

Acknowledgement

This work was supported by the internal research grant of the University of Medicine and Pharmacy Târgu Mureş, 649/14.01.2016.

References

Berkowitz AL, Samuels MA. The neurology of Sjogren's syndrome and the rheumatology of peripheral neuropathy and myelitis. Pract Neurol 2014;14:14-22.

Bournia VK, Vlachoyiannopoulos PG. Subgroups of Sjögren syndrome patients according to serological profiles. J Autoimmun 2012;39:15-26.

Delalande S, de Seze J, Fauchais AL, et al. Neurologic manifestations in primary Sjögren syndrome: a study of 82 patients. Medicine (Baltimore) 2004;83:280-291.

Jarius S, Jacobi C, de Seze J, et al. Frequency and syndrome specificity of antibodies to aquaporin-4 in neurological patients with rheumatic disorders. Mult Scler. 2011;17:1067-1073.

Kahlenberg JM. Neuromyelitis optica spectrum disorder as an initial presentation of primary Sjögren's syndrome. Semin Arthritis Rheum. 2011;40:343-348.

Lafitte C, Amoura Z, Cacoub P, et al. Neurological complications of primary Sjögren's syndrome. J Neurol 2001;248:577-584.

Manabe Y, Sasaki C, Warita H, et al. Sjögren's syndrome with acute transverse myelopathy as the initial manifestation. J Neurol Sci 2000;176:158-161.

Massara A, Bonazza S, Castellino G, et al. Central nervous system involvement in Sjögren's syndrome: unusual, but not unremarkable--clinical, serological characteristics and outcomes in a large cohort of Italian patients. Rheumatology (Oxford) 2010;49:1540-1549.

Melikyan G, Abdelrahman MH, D'Suoza A, Akhtar N, Elzouki AN, Hammoudeh M. Transverse Myelitis Associated with Anti-Ro (SSA) Autoantibodies: A Record of Two Cases. Case Rep Rheumatol 2012;2012:515768.

Mori K, Iijima M, Koike H, et al. The wide spectrum of clinical manifestations in Sjögren's syndrome-associated neuropathy. Brain 2005;128:2518–2534.

Morreale M, Marchione P, Giacomini P, et al. Neurological involvement in primary Sjogren syndrome: a focus on central nervous system. PLoS One 2014;9(1):e84605.

Moutaouakil F, El Moutawakkil B, El Otmani H, Gam I, Rafai MA, Slassi I. Aseptic meningoencephalitis in primary Gougerot-Sjögren's syndrome. Rev Neurol 2005;161:1225-1227.

Moutsopoulos HM. Sjögren's syndrome: autoimmune epithelitis. Clin Immunol Immunopathol 1994;72:162-165.

Pittock SJ, Lucchinetti CF. Neuromyelitis optica and the evolving spectrum of autoimmune aquaporin-4 channelopathies: a decade later. Ann N Y Acad Sci 2016;1366:20-39.

Sá MJ. Acute transverse myelitis: a practical reappraisal. Autoimmun Rev 2009;9:128-131.

Soliotis FC, Mavragani CP, Moutsopoulos HM. Central nervous system involvement in Sjogren's syndrome. Ann Rheum Dis 2004;63:616-620.

Tobón GJ, Pers JO, Devauchelle-Pensec V, Youinou P. Neurological Disorders in Primary Sjögren's Syndrome. Autoimmune Dis 2012;2012:645967.

Tristano AG. A case of Sjögren's syndrome with acute transverse myelitis and polyneuropathy in a patient free of sicca symptoms. Clin Rheumatol 2006;25:113-114.

Vitali C, Bombardieri S, Jonsson R, et al. European Study Group on Classification Criteria for Sjogren's syndrome. Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group, Ann Rheum Dis 2002;61:554-558.

Wingerchuk DM, Lennon VA, Lucchinetti CF, Pittock SJ, Weinshenker BG. The spectrum of neuromyelitis optica. Lancet Neurol. 2007;6:805-815.

Authors

•Adina Stoian, Department of Pathophysiology, University of Medicine and Pharmacy, Gheorghe Marinescu 38, 540139, Târgu Mureş, Romania, EU, email: cretadina@yahoo.com

•Rodica Ioana Bălaşa, Department of Neurology, University of Medicine and Pharmacy, Gheorghe Marinescu 38, 540139, Târgu Mureş, Romania, EU, email: iipascu@redatronic.ro

•Laura Bărcuţean, Department of Neurology, University of Medicine and Pharmacy, Gheorghe Marinescu 38, 540139, Târgu Mureş, Romania, EU, email: laurabarcutean@gmail.com

•Anca Moţăţăianu, Department of Neurology, University of Medicine and Pharmacy, Gheorghe Marinescu 38, 540139, Târgu Mureş, Romania, EU, email: motataianuanca@gmail.com

•Simona Mocan, Department of Pathology, Emergency Clinical Hospital, Gheorghe Marinescu 50, 540136, Târgu Mureş, Romania, EU, email: slmocan@gmail.com

•Smaranda Maier, Department of Neurology, University of Medicine and Pharmacy, Gheorghe Marinescu 38, 540139, Târgu Mureş, Romania, EU, email: maier_smaranda@yahoo.com

•Zoltan Bajko, Department of Neurology, University of Medicine and Pharmacy, Gheorghe Marinescu 38, 540139 Tîrgu Mureş, Romania, EU, email: bzoltan2003@yahoo.com

•Szasz Simona, Department of Rheumatology, University of Medicine and Pharmacy, Gheorghe Marinescu 38, 540139 Tîrgu Mureş, Romania, EU, email: szasz_fc@yahoo.com

Citation	Stoian A, Bălaşa R, Bărcuţean L, Motataianu A, Mocan S, Maier S, Bajko S, Szasz S. An unusual cause of longitudinally extensive transverse myelitis - case report. HVM Bioflux 2017;9(4):161-165.
Editor	Ştefan C. Vesa
Received	19 December 2017
Accepted	27 December 2017
Published Online	27 December 2017
Funding	This work was supported by the internal research grant of the University of Medicine and Pharmacy Târgu Mureş, 649/14.01.2016.
Conflicts/ Competing Interests	None reported