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CASE REPORT

Neurologic involvement in an overlapping systemic pathology

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Abstract

Background. Overlap syndromes are complex conditions, comprising elements of more than one distinct autoimmune disease, as well as multiorgan involvement.

Methods. We present the case of a 48-year-old female patient with systemic lupus erythematosus (SLE)/systemic sclerosis (SSc)/Sjögren syndrome (SS) overlap and a myriad of neurological manifestations, including bilateral trigeminal neuralgia, bilateral facial nerve palsy, mononeuritis multiplex and migraines cephalalgia.

Results. Physical examination revealed bilateral involuntary spasms of the lower face, bilateral facial motor deficit, a mild motor deficit of the lower limbs (4/5), tactile hypoesthesia on the left thigh, a diminished right patellar reflex and a positive bilateral Hoffman sign. This neurological symptomatology was present during an apparent inactive state of the rheumatologic condition, with no signs of active arthritis, and the following laboratory results: a mild normocytic normochromic anemia, mild leukopenia, a mildly decreased C3 and a mildly elevated ESR. Cerebral MRI revealed T2/FLAIR-hyperintense subcortical white matter lesions, suggestive of demyelination, without meeting the multiple sclerosis (MS) pattern.

Conclusion. The main clinical question arising from this case resides in the nature of the neurological involvement, in relation to the overlap syndrome.

Key words: overlap syndrome, neurologic involvement, MRI.

Introduction

Systemic lupus erythematosus (SLE)/systemic sclerosis (SSc)/Sjögren syndrome (SS) overlap represents a challenging rheumatologic entity, ambiguity regarding its definition and nomenclature persisting up to present time. The complexity of this disease extends beyond its musculoskeletal manifestations, to specific organ involvement, making it a multidisciplinary conundrum [1,2].

Case report

We describe the case of a 48-year-old female patient, with a known history of SLE/SSc/SS overlap, degenerative rheumatic disease (thoracolumbar spondylosis, bilateral coxarthrosis), mononeuritis multiplex, bilateral trigeminal neuralgia of the maxillary and mandibular branches and uterine leiomyomata. The patient presented to our department for mixed type arthralgia of the I-V metatarsophalangeal (MTP) joints, I right interphalangeal (IP) joint, II-V proximal and distal interphalangeal (PIP, DIP) joints of the right foot, radiating in the right calf. She also described exertional dyspnea at 100 m, orthopnea, exertional and resting anterior chest pain and polymenorrhea.

The patient's rheumatologic history began in 2013, following an intense psychoemotional stress, with mixed polyarticular arthralgia, bilateral hand edema and sclerodactyly. At that time, the patient was diagnosed with mixed connective tissue disease (MCTD), as the anti-U1RNP antibodies were mildly positive. The diagnosis was changed to SLE/SSc/SS overlap in 2016, considering the negative anti-U1RNP antibodies on repeated measurements, as well as the following constellation of clinical signs/symptoms and immunological markers: malar rash, photosensitivity, polyarthralgia, hypocomplementemia, positive lupus anticoagulant, sclerodactyly of the upper extremities, xerophthalmia, xerostomia and anti-Ro antibodies, a subsequent minor salivary gland biopsy confirming the Sjögren syndrome diagnosis. Treatment was initiated with hydroxychloroquine tablets 200 mg x 2/day.

The distinctive aspect of this case is the patient's neurological history, which was summarized in Table 1:

Table 1 – *The patient's neurological history*

Year	Neurological manifestation
1993	**Left facial motor deficit:** asymmetrical smile, difficulty in closing the left eye and raising the left eyebrow; the day before the onset: visual disturbance ("cloudy vision"), aggravated by bending forward and subsided in several days; sudden onset; associated with bilateral trigeminal neuralgia, persistent up to present time; associated with bilateral involuntary muscle spasms in the lower face, persistent up to present time; improvement in 2 months and apparent remission in 6 months, under prednisone treatment.
1996	**Right facial motor deficit:** clinically similar to the previous episode; sudden onset; improvement in 1 month, under prednisone treatment.
1999	**Left facial motor deficit:** clinically similar to the previous episodes; sudden onset; improvement in 1 month, under prednisone treatment.
2003	**Thoracoabdominal pain (T1 level) radiating to the lower limbs, associated with right crural paresis:** sudden onset; improvement in 2 months, after undocumented medical treatment.
2004	**Pulsatile occipital cephalalgia:** several episodes lasting minutes; followed by abnormal hand posture (positive Trousseau sign); followed by abnormal mouth posture ("jaw clenching"). **Tetraparesis:** 1 episode lasting several hours; associated with retrosternal pressure sensation; associated with generalized weakness (without losing postural tone).
2016	**Mononeuritis multiplex**: diagnosis was established during the workup for the overlap syndrome, considering the patient's mild motor deficit of the lower limbs and the tactile hypoesthesia of the left thigh.
2020	**Pulsatile frontal cephalalgia, diagnosed as migraine without aura:** 10/10 pain intensity; associated with nausea, vomiting and photophobia; episodes lasting 1-2 days without treatment; clinical improvement after self-administering metamizole or ibuprofen; prophylactic treatment with amitriptyline 25 mg 1 tb/day; 10 episodes/month.

On current admission, physical examination revealed bilateral acrocyanosis of the I-V toes and pain on palpation of the first right MTP joint, without signs of active inflammation. The neurological examination showed bilateral involuntary spasms of the lower face, including the platysma muscles, that stopped when the patient closed her eyes. We noticed bilateral facial nerve palsy, more significant on the left side: the patient could raise her left eyebrow less than the right one, could close her eyes completely, but weakly, could not puff out her cheeks or protrude her lips. Other notable changes were a mild motor deficit of the lower limbs (4/5), tactile hypoesthesia on the left thigh, a diminished right patellar reflex and a positive bilateral Hoffman sign.

The laboratory tests showed mild normocytic normochromic anemia, mild leukopenia, a mildly decreased C3, a mildly elevated ESR and hypovitaminosis-D, with normal CRP, fibrinogen, anti-dsDNA and antiphospholipid antibodies levels. We performed a right foot radiograph, which revealed osteoarthritic changes.

Considering this complex neurologic picture, neurology consultation was requested. Besides performing the thorough neurologic examination previously described, the neurologist analyzed the patient's previous MRIs: one cerebrospinal MRI with contrast (2022) and one cerebral MRI without contrast (2023). These investigations revealed several T2/FLAIR-hyperintense oval/round-shaped millimetric lesions, with a tendency for confluence, in the deep bilateral frontal white matter. The lesions had no contrast uptake and no restricted diffusion pattern. Furthermore, a possible T2/STIR-hyperintense lesion was observed in the cervical spinal cord, without contrast uptake. These findings were interpreted as demyelinating lesions but did not resemble a multiple sclerosis (MS) pattern. The neurologist considered a possible inflammatory involvement of the central nervous system (CNS), with regard to the rheumatologic disease, and requested the patient's admission to the Neurology department for further evaluation. Additionally, we requested a cardiology consultation, during which the cardiologist established the diagnosis of chronic coronary syndrome and initiated treatment.

Taking into account the clinical and immunological picture, as well as the radiologic findings, we made a diagnosis of osteoarthritis of the small joints of the right foot and decided not to escalate the immunosuppressive therapy, since there was no reason to appreciate the autoimmune disease as active.

The patient was discharged and was admitted a month later to the Neurology department. A non-contrast cerebral and cervical spine MRI in CISS sequence was done, showing similar lesions to the previous MRIs: multiple FLAIR-hyperintense round-shaped millimetric (<5mm) lesions in the subcortical, supratentorial white matter, with no specific pattern, not meeting the imaging criteria for a demyelinating disease like MS. Considering the cervical spinal cord, the only identified changes were disc protrusions at the C4-C6 levels, with associated disc-radicular conflicts.

Laboratory tests revealed increased levels of serum Borrelia burgdorferi IgM. However, there were no Borrelia IgM or IgG detected in the CSF, with normal Borrelia IgM and IgG CSF indexes, indicating no cerebral antibody production. Additionally, there were increased levels of total IgM in serum and CSF and increased protein levels in the CSF. The IgM, IgG and IgA CSF indexes were normal and the Reiber diagram identified no alteration of the blood-brain barrier (BBB), indicating no intrathecal synthesis of immunoglobulins. There were no oligoclonal bands detected in the CSF. The angiotensin-converting enzyme levels were normal in serum and CSF, dismissing sarcoidosis. During this admission there were no tests done to exclude potential infectious causes of the facial paresis, like tuberculosis

and Epstein-Barr virus, due to the low probability in this particular clinical constellation.

Finally, the neurologist concluded that there are no arguments towards an inflammatory CNS disease, considering the bilateral facial nerve palsy a Bell's palsy.

Discussion

This case is special because there is no objectifiable inflammatory cause of the neurological symptomatology, in a patient with complex neurological manifestations and a known autoimmune disease, inactive at the moment of the evaluation. However, the question remains, as the patient was not in an active state of the rheumatologic disease and did not have any acute neurological manifestations at the time these investigations were made. The inflammatory CNS disease hypothesis persists, until proven wrong by supplementary investigations done during an acute flare of the overlap syndrome or during an acute symptomatic neurological episode. The absence of medical records from the first neurological episodes described by our patient is a limitation of our study, as we can only rely on the patient's memory.

To the best of our knowledge, this is the first case report to describe such a complex neurological picture in a patient with SLE/SSc/SS overlap. However, as the controversy between overlap syndromes and MCTD persists, we can contemplate the scientific literature on the MCTD associated neurological manifestations. Trigeminal neuralgia is the most common neurological manifestation associated with MCTD, occasionally described as an initial presenting symptom [1–10] and occasionally responsive to corticosteroids [1,3], similar to our patient's earliest complaints. Cephalalgia, with or without migraine characteristics, can also be associated with MCTD [1,2,5,9,10]. Other neurological manifestations reported in association with MCTD are mononeuritis multiplex [1] and peripheral neuropathies [1,7,10].

From a different perspective, we can consider the overlap syndrome a combination of individual conditions, instead of a distinct entity, and integrate the neurological manifestations of each individual disease in the big picture. Neurological symptomatology is frequently described in SLE, although a clear causal relationship can be difficult to confirm in these complex patients [11,12]. Cephalalgia, including the migraines type, is one of the most commonly reported manifestations [11,12]. Mononeuritis multiplex, peripheral neuropathy and cranial neuropathy can also be observed, including trigeminal neuralgia that precedes the SLE diagnosis, similar to our case [11,12]. SSc associated neurological manifestations comprise cephalalgia, trigeminal neuropathy and peripheral sensorimotor polyneuropathy [13]. Considering the SS, a thorough literature research mostly revealed data about the primary condition, without specific acknowledgements for secondary or overlapping SS. In primary SS, neurological manifestations include cephalalgia, mononeuritis multiplex, sensorimotor axonal polyneuropathy, and cranial neuropathies, especially trigeminal [1,2,14]. A notable feature of primary SS is the presence of T2-hyperintense white matter lesions on cerebral MRI investigations, in the absence of a clear connection with the patient's clinical presentation, comparable to our case [1,2,15].

Conclusion

This case is challenging not only for the inflammatory or non-inflammatory etiology of the patient's neurological manifestations, but also for defining the patient's rheumatologic disease, in a controversial time regarding overlap syndromes and MCTD. Additionally, this case highlights the importance of a multidisciplinary approach of connective tissue disease patients, each specific organ manifestation being a piece of the puzzle and gradually leading us to the diagnosis.

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