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Meningoencephalitis caused by *Cryptococcus neoformans* and varicella[16_TD$DIFF]-zoster virus in a patient with systemic lupus erythematosus☆

Meningoencefalitis por *Cryptococcus neoformans* y virus varicela-zoster en paciente con lupus eritematoso sistémico

Dear Editor:

Infectious processes are one of the most frequent causes of morbidity and mortality in patients with systemic lupus erythematosus (SLE). This is due both to the immunological dysfunction caused by the disease itself and the immunosuppressive treatment[18_TD$DIFF].[1] Most of these infections are of bacterial origin[19_TD$DIFF],[2] although infection with parvovirus or viruses from the herpesvirus family, including varicella-zoster virus (VZV), is not infrequent[20_TD$DIFF].[3] In turn, case series of systemic infections with such fungi as *Cryptococcus neoformans* have also been reported[21_TD$DIFF].[4]

Most cases of *C. neoformans* meningoencephalitis occur in patients with AIDS with CD4 counts below 100 [22_TD$DIFF]cells/μL,[5] but it also manifests in seronegative patients, especially those who are immunocompromised for other reasons, including patients with SLE[23_TD$DIFF].[6,7] Cases of meningoencephalitis due to VZV infection in patients with SLE are scarce in the literature[24_TD$DIFF].[8]

The aim of this article is to report the first case in the literature of central nervous system co-infection with *C. neoformans* and VZV in a patient with SLE and treated with mycophenolate mofetil (MMF) and corticosteroids.

Our patient was an 18-year-old woman with SLE with haematological (autoimmune haemolytic anaemia treated with decreasing doses of prednisone from the previous year) and pulmonary involvement (bronchiectasis and recurring infections treated with antibiotics and cycles of prophylactic azithromycin), as well as positive antiphospholipid antibodies, treated with prednisone (5 [25_TD$DIFF]mg/24 h), MMF (1 g/12 h), and hydroxychloroquine.

The patient initially presented persistent severe headache and vomiting after manifesting symptoms compatible with respiratory infection in the previous week, which were treated with antibiotics. An eczema-like lesion without vesicles was observed on the outer ear. Several days later, she manifested behavioural alterations and irritability, as well as decreased level of consciousness, and finally an episode compatible with seizure. The patient did not present fever during the episodes.

An emergency head CT scan revealed a slight left occipital cortical hypodensity. She subsequently underwent a lumbar puncture, obtaining clear cerebrospinal fluid (CSF), which revealed slight, predominantly mononuclear pleocytosis (100 cells) and high protein levels. Opening pressure was not measured at that time.

Due to the possibility of autoimmune encephalitis, the patient received a megadose of methylprednisolone. She was also treated with aciclovir and antibiotics (as we could not rule out meningoencephalitis that resolved due to the recent antibiotic treatment), and MMF was suspended due to the possibility of posterior reversible encephalopathy syndrome.

We requested a CSF microbiological study, including Gram and India ink staining, bacterial and fungal cultures, and a PCR assay panel (FilmArray®). The PCR assay detected *Cryptococcus*[26_TD$DIFF] and VZV, and India ink staining showed presence of fungi. The culture was also positive for *C. neoformans*. We started treatment with amphotericin B and flucytosine and suspended antibiotic treatment and high-dose corticosteroids, but maintained aciclovir.

A brain MRI scan confirmed that the hypodensity observed in the head CT scan corresponded to vasogenic oedema, which is compatible with an encephalitis-like inflammatory process in this clinical context. We also observed diffuse leptomeningeal enhancement [27_TD$DIFF]and 2 dilated Virchow-Robin spaces with minimal contrast enhancement (Fig. 1). Dilated Virchow[15_TD$DIFF]-Robin spaces in the basal ganglia constitute one characteristic of brain cryptococcosis, and may merge and form what are known as gelatinous pseudocysts.

In the subsequent hours, the patient developed vesicles in the eczema previously observed on the outer ear. Reduced level of consciousness and intense headache persisted, in association with bilateral limitation of gaze abduction. Due to these symptoms, we suspected intracranial hyperten-

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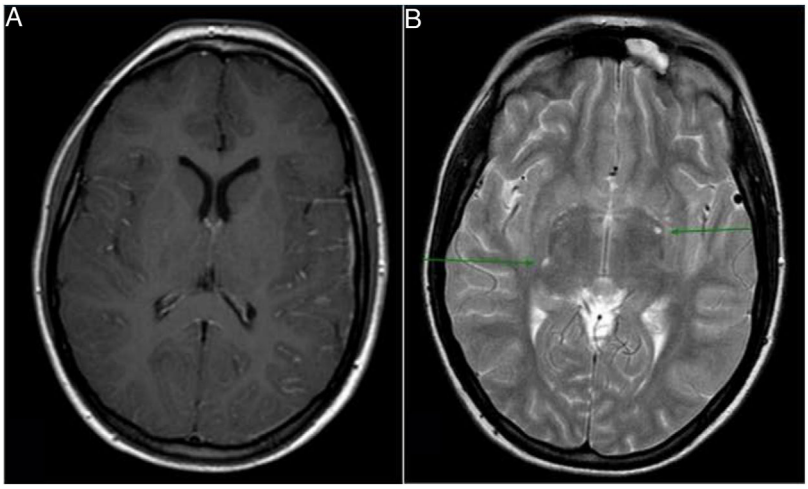

Figure 1 (A) Axial T1-weighted sequence with contrast administration showing leptomeningeal enhancement. (B) Axial T2-weighted sequence showing dilated Virchow[15_TD$DIFF]-Robin spaces (arrows).

sion, which is also characteristic of cryptococcal meningitis. CSF pressure was measured, revealing an opening pressure of 60 cm H_2O. In the absence of an intracranial space-occupying lesion, an external lumbar drain was placed, and achieved a significant improvement. Aciclovir was suspended after 2 weeks, and amphotericin B and flucytosine after 3 weeks[28_TD$DIFF]; after 4 weeks, oral fluconazole was started and the external lumbar drain was removed. The patient's condition progressed favourably, with eventual full resolution.

Discussion

Ours is the first case in the literature of central nervous system co-infection with VZV and *C. neoformans*. The literature does include reports of cryptococcal meningitis[9] following cutaneous herpes zoster, and vice versa[29_TD$DIFF][14_TD$DIFF],[10] in HIV-positive patients, with no presence of VZV in the CSF.

Several factors may have contributed to co-infection, including immunosuppressive treatment with corticosteroids and MMF, as well as the presence of SLE, an autoimmune disease.

This case highlights the importance of considering the possibility of infection with atypical pathogens, even simultaneously, as cause of encephalitis in patients with autoimmune diseases, especially those receiving immunosuppressive treatment. Therefore, we recommend performing an extensive microbiological study including bacterial cultures as well as fungal and viral studies.

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A novel *TTN* variant in a patient with distal myopathy of lower limbs and dilated cardiomyopathy☆

Una nueva variante en el gen de la titina en un paciente con miopatía distal de miembros inferiores y miocardiopatía dilatada

Dear Editor:

Titin is a sarcomeric protein expressed in the cardiac and skeletal muscles. It is encoded by a single gene, *TTN*, located on the long arm of chromosome 2.[1] *TTN* gene mutations have been associated with a wide range of cardiomyopathies and skeletal muscle disorders (late-onset tibial muscular dystrophy, early-onset recessive distal titinopathy, autosomal recessive limb-girdle muscular dystrophy-10, etc).[2] Tibial muscular dystrophy (TMD), also known as Udd distal myopathy (late-onset, type 2a), is characterised by late onset (between the ages of 35 and 55 years) and slow progression, and usually only affects the muscles of the anterior compartment of the lower limbs.[3] These patients present normal or slightly elevated serum creatine kinase levels, with EMG results suggestive of myopathy.[3,4] Muscle biopsy results reveal variability in fibre size, central nuclei, necrosis, fibroadipose tissue, and rimmed vacuoles.[5] Muscle MRI reveals selective fat replacement in the muscles of the anterior compartments of the lower limbs.

We present the case of a 37-year-old man with lower limb weakness and muscle atrophy affecting the peroneal and tibialis anterior muscles and the extensor muscles of the toes. He had no history of diabetes mellitus, cancer, or connective tissue disorders. A cardiac comorbidity was also detected, and the patient was diagnosed with dilated non-ischaemic cardiomyopathy. His parents were non-consanguineous, and he had family history of muscle disease of unknown origin in a maternal uncle, who presented weakness and muscle atrophy in the lower limbs. To date, his parents have not consulted due to neurological or cardiac symptoms.

The neurological examination revealed atrophy and weakness in the muscles of the anterior compartment of the lower limbs, with asymmetric weakness of ankle dorsiflexion (right, 1/5; left, 3/5). He was unable to toe walk as a result of the poor dorsiflexion.

A blood analysis including muscle enzymes and a mitochondrial respiratory chain enzyme assay yielded normal results. Electroneurography showed no alterations, and the EMG study revealed low-amplitude polyphasic motor unit potentials with early recruitment of the tibialis anterior muscles; these findings are compatible with a chronic myopathic process. A biopsy study of the quadriceps revealed myopathic alterations with nuclear centralisation and vacuolar degeneration, with no ragged red fibres and normal COX staining.

An MRI scan of the muscles of the lower limbs (Fig. 1) revealed atrophy with fat replacement in the extensor muscles (tibialis anterior, extensor digitorum longus, and extensor hallucis longus, predominantly on the right side). A cardiac MRI scan revealed biventricular dilatation with moderate systolic dysfunction affecting both ventricles, and dilatation of both atria; these findings are compatible with non-ischaemic cardiomyopathy.

Massive sequencing of 8 genes associated with muscular dystrophies (*ANO5*, *DMD*, *DYSF*, *EMD*, *FHL1*, *LMNA*, *SYNE1*, and *SYNE2*) detected no pathogenic mutations. A subsequent sequencing study of 22 genes, including *TTN*, revealed loss of heterozygosity, affecting at least exons 32 to 364 of the gene. The study detected the c.86581T>A (p.Trp28861Arg) *TTN* variant in homozygosis. Cosegregation analysis detected the same variant in heterozygosis in both parents.

TTN mutations have been associated with various muscle diseases, cardiomyopathies, or a combination of both. The first mutation (an 11-bp insertion/deletion) was reported in 2002, and was called FINmaj.[6] A dominant missense mutation in exon 364 (c.107840T>A p.Ile35947Asn) was subsequently detected in a Belgian family.[5] In 2008, Hackman et al.[4] described 3 novel mutations in 2 Spanish families and 2 French families (2 deletions, g.292998delT and g.293376delA) and a nonsense mutation (g.293379C>T [p.Q33396X]). A more recent study describes the phenotype of an Italian family with TMD and a new heterozygous mutation, g.293326A>C, which predicts the amino acid substitution p.His33378Pro.[7] Algahtani et al.[8] report the heterozygous nonsense mutation c.85652C>G (p.Pro28551Arg) in a Saudi patient with bilateral facial weakness.

We describe a novel variant of *TTN* in homozygosis in a Spanish patient with TMD and cardiomyopathy. The patient

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