humanised antibody, enables reactivation of T cells, which are then able to target cancer cells. However, it also promotes increased autoimmune responses. In the case of PRES, this immune cascade would cause endothelial damage with definitive disruption of vascular integrity, resulting in cerebral oedema.[4,5]

The only patient reported to date with PRES associated with pembrolizumab had been treated with ipilimumab in the preceding months; several cases have been reported in association with this drug.[5] While cases of PRES have been reported in association with platins and pemetrexed, onset usually occurs after a longer interval following the last administration of the drug.[6] There is more evidence of a link between PRES and monotherapy with ICIs, after a single dose, with onset generally occurring in the weeks following treatment,[7] although we cannot rule out a potential cumulative effect involving the other 2 chemotherapeutic drugs in our patient.

Due to the death of the patient, it was not possible to perform a follow-up neuroimaging study to observe the degree of resolution. However, given the association with combination therapy with pembrolizumab in our patient, which was started 3 weeks earlier, the case has been notified for pharmacovigilance purposes.

We consider it important to report this case of a rarer neurological adverse event associated with immunotherapy; such events may become more frequent if these drugs are used in combination with other chemotherapeutic agents. Given their increasingly widespread use to treat different types of cancer, it is essential to raise awareness of these adverse reactions among both oncologists and neurologists.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Association between cerebral folate deficiency and hereditary spastic paraplegia☆

Asociación de deficiencia cerebral de folato y paraplejía espástica hereditaria

Dear Editor:

Cerebral folate deficiency (CFD) is a neurological syndrome associated with low concentrations of 5-methyltetrahydrofolate in the cerebrospinal fluid (CSF) despite normal serum folate levels.[1] It may present at any age, from the prenatal period to adulthood, and is associated with a wide range of phenotypes.[2] The generation of autoantibodies against folate receptors,[3] pathogenic variants of the folate receptor alpha (*FOLR1*) gene, and mitochondrial dysfunction have been reported as causes of CFD.[2,4] However, other mechanisms may also be involved, since the condition has been reported in patients with a wide range of neurological and psychiatric disorders.[5,6]

We present the case of a patient with CFD who was subsequently diagnosed with hereditary spastic paraplegia.

Our patient was a 26-year-old man who, at the age of 10 years, presented progressive cognitive and behavioural alterations, difficulty walking, and generalised tremor starting in the left arm.

When he was first examined, at 16 years of age, he presented multiple neurological symptoms, including cognitive impairment, intrusive saccades, movement disorder

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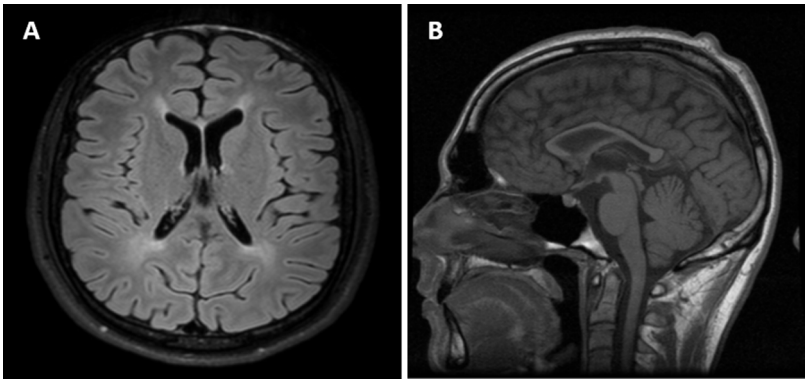

Figure 1 Magnetic resonance imaging study. A) Axial T2-FLAIR sequence showing periventricular white matter hyperintensity. B) T1-weighted sequence showing global atrophy, with marked atrophy of the corpus callosum.

(multifocal dystonia, generalised tremor, and bradykinesia), pyramidal syndrome, and gait ataxia with pes cavus.

The neuropsychological examination revealed frontostriatal dysfunction, and electroencephalography (EEG) detected slow background activity (6 Hz). Brain MRI revealed a hyperintensity in the periventricular white matter and global atrophy, with marked atrophy of the corpus callosum (Fig. 1).

Extrapyramidal symptoms improved considerably with levodopa.

We subsequently identified CFD (CSF folate level < 20 nmol/L; normal range, 50-78), with normal levels of neurotransmitters, pterins, and amino acids. Serum folate levels were within the normal range. We ruled out the presence of variants in genes *FOLR1* and *POLG*, and in the mitochondrial DNA. Analysis of autoantibodies against folate receptors in the serum revealed elevated titres of blocking antibodies (4.77 pmol of folate receptor blocked per mL serum).

Folinic acid supplementation (30 mg/day) normalised CSF folate levels and significantly improved cognitive function, extrapyramidal symptoms, and oculomotor and EEG alterations, but had no effect on pyramidal signs.

At age 18, spastic paraparesis was evident. The patient is now unable to stand or walk unassisted. Other neurological signs, such as parkinsonism and cognitive dysfunction, resolved nearly completely despite progressive decreases in the dosage of levodopa and anticholinergic medications. A brain and spinal cord MRI study ruled out new structural lesions, and CSF 5-methyltetrahydrofolate levels remained normal. The patient underwent 3 electrophysiological studies, at ages 19 and 24, which ruled out polyneuropathy and myopathy.

More recently, clinical exome sequencing identified 2 variants in the *ZFYVE26* gene, c.1675 T > C (p.[Cys559Arg]) and c.3394C > T (p.[Gln1132*]), and *BSCL2* gene variant c.1220C > T (p.[Pro407Leu]). *ZFYVE26* gene variant c.3394C > T (p.[Gln1132*]), not previously reported, results in a truncated protein and has therefore been classified as pathogenic. The other *ZFYVE26* variant is also a novel mutation, although its clinical significance is unknown; the same is true of the variant identified in *BSCL2*. Our patient's parents, who were asymptomatic, also underwent genetic studies: the 2 *ZFYVE26* variants were found in different alleles, and the *BSCL2* gene variant was also detected in the father. The patient continued to receive folinic acid supplementation.

It has been hypothesised that the different phenotypes of CFD are determined by the age at which folate transport to the CNS is impaired.[2] Initially localised and subsequently generalised dystonia, bradykinesia, and pyramidal syndrome have been described in patients with CFD presenting from adolescence to adulthood.[2] Other characteristics include cognitive impairment and gait ataxia.[2] This seems to be consistent with our patient's symptoms.

Presence of elevated folate receptor autoantibody titres supports the association between CFD and our patient's symptoms. Blocking antibodies have been detected in several conditions, including autism, schizophrenia, Rett syndrome, and Alpers disease.[6,7]

Progression of pyramidal syndrome justified clinical exome sequencing, identifying variants in genes *ZFYVE26* and *BSCL2*, which are associated with autosomal recessive spastic paraplegia type 15 (SPG15) and autosomal dominant spastic paraplegia type 17 (SPG17), respectively. Our patient's clinical phenotype resembles that of SPG15: cognitive impairment, behavioural alterations, pes cavus, ataxia, cerebral white matter hyperintensities on MRI, corpus callosum atrophy, and age of onset between 5 and 19 years.[8] Although the *BSCL2* variant was found in the father, who was asymptomatic, and this gene is associated with phenotypic variability and incomplete penetrance,[9] our patient's symptoms were not compatible with SPG17, and the variant is of uncertain significance.

As with other disorders, CFD may be associated with SPG15 and is probably responsible for some of our patient's symptoms, considering the positive response to folinic acid supplementation, particularly in extrapyramidal symptoms. To our knowledge, this association has not previously been described, either at the clinical or the molecular level. We wonder whether some traits linked to SPG15 in previous reports (eg, parkinsonism[10]) may be associated with CFD. Our case suggests a possible association between these 2 entities, and underscores the need to consider CFD in patients with these disorders.

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Cavernous sinus syndrome secondary to invasive aspergilosis with carotid involvement in a HIV pacient☆

Síndrome de seno cavernoso secundario a aspergilosis invasiva con afectación carotídea en paciente VIH

Dear Editor,

Cavernous sinus syndrome (CSS) is defined by involvement of 2 or more of the third, fourth, fifth, and sixth cranial nerves secondary to inflammation or a space-occupying lesion in the cavernous sinus.[1] The typical clinical presentation includes periorbital pain, ptosis, headache, diplopia, ophthalmoplegia, and visual alterations.[2–4] The most frequent causes include tumours (nasopharyngeal carcinoma, meningioma, lymphoma, and metastases), vascular disease (aneurysms, fistulas, and thrombosis), and inflammatory disease (Tolosa-Hunt syndrome, IgG4-related disease, sarcoidosis, vasculitis). Although less frequent, risk populations especially present infectious diseases (tuberculosis, *Haemophilus influenzae* septic thrombophlebitis, neurosyphilis, or mucormycosis in diabetic patients). Exceptionally, CSS may be associated with invasive aspergillosis, as in the case we present.

We present the case of a 49-year-old man with history of chronic obstructive pulmonary disease and category C3 HIV infection (CD4 count of 140 cells/mm^3), diagnosed 3 months prior to admission. He was receiving regular treatment with bictegravir, emtricitabine, and tenofovir alafenamide. The patient reported right frontoparietal headache of 6 months' progression, which led to several visits to the emergency department, where a head computed tomography (CT) scan was performed, revealing no alterations. He progressively developed diplopia and

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