Neurología 36 (2021) 625—656

NEUROLOGÍA

www.elsevier.es/neurologia

LETTER TO THE EDITOR

Primary lymphomatoid granulomatosis of the central nervous system: a diagnostic challenge☆

Granulomatosis linfomatoide primaria del sistema nervioso central: un reto diagnóstico

Dear Editor:

Lymphomatoid granulomatosis is a B-cell lymphoproliferative disorder associated with Epstein-Barr virus (EBV) infection, and characterised by a reactive T-cell infiltrate with an angiocentric, angiodestructive growth pattern.[1—3] In exceptional cases, the condition may affect the central nervous system (CNS) exclusively.[3—5]

We present the case of a 56-year-old woman who consulted due to repeated episodes of transient dysarthria. She had history of arterial hypertension, dyslipidaemia, and chronic kidney disease. She had undergone kidney transplantation and had been receiving immunosuppressive therapy since 1981; at the time of consultation, she was receiving prednisone (5 mg/24 h), tacrolimus (2 mg/24 h), and mycophenolate mofetil (360 mg/12 h). An emergency CT scan revealed a hypodense lesion in the left frontal lobe. During hospitalisation, she presented episodes of anarthria and clonic movements affecting the perioral region, suggestive of opercular epilepsy, and started treatment with levetiracetam dosed at 500 mg/12 hours. Graft failure was also observed, and haemodialysis was restarted. A brain MRI scan (Fig. 1) revealed a corticosubcortical lesion in the left frontal lobe, vasogenic oedema, and ring contrast enhancement; differential diagnosis between infectious and neoplastic processes was considered. Empirical antibiotic therapy was started and immunosuppressive therapy suspended. Whole-body CT and PET/CT scans revealed no abnormalities. CSF biochemical analysis yielded normal results, with negative results for immunophenotyping, cytology, and microbiology studies (cryptococcal antigen screening; venereal disease research laboratory test; polymerase chain reaction assay for *Toxoplasma gondii*, *Listeria monocytogenes*, and John Cunningham virus; fungal and mycobacterial cultures). The patient remained asymptomatic after starting antiepileptic treatment. Radiological improvements were observed after 21 days of antibiotic therapy (Fig. 1). Two months later, she presented progressive speech impairment with naming difficulties, right facial paresis, and right faciobrachial clonic movements, which were controlled with levetiracetam (1000 mg/12 h) and lacosamide (50 mg/12 h). An MRI scan revealed increased lesion size and oedema extension. Results from a brain biopsy (Fig. 2) revealed grade 3 lymphomatoid granulomatosis. Additional whole-body CT and PET/CT scans were performed to detect any metastasis, yielding normal results. After a multidisciplinary assessment, radiation therapy and chemotherapy (R-CHOP, rituximab) were ruled out due to the patient's poor health status and history of chronic kidney disease. Treatment was started with ibrutinib (a Bruton's tyrosine kinase inhibitor) at 560 mg/day for compassionate use; tolerance was good. After 8 months of treatment, the patient presented a partial clinical improvement (mild anomia and facial paresis) and significant radiological improvement (Fig. 1).

Lymphomatoid granulomatosis is an extremely rare type of mature B-cell neoplasm.[1,2,5—7] It is most common in men aged 40-60 years.[1—5,7] The condition frequently affects immunosuppressed patients,[1,2,7] although cases have also been reported in immunocompetent individuals.[2,4,5] It is an atypical EBV-associated B-cell lymphoproliferative disorder[1,2,7,8] involved in the development of different types of lymphoproliferative neoplasms.[9] Although the exact pathophysiological relationship between EBV infection and lymphomatoid granulomatosis is not understood, immunosuppression-dependent EBV reactivation is believed to promote the expression of oncogenes, which in turn promote lymphoproliferation.[1,4] Lymphocytic aggregates appear around a necrotic central region, due to the angiocentric and angiodestructive behaviour of the disorder.[1,7,8] Lymphomatoid granulomatosis is classified into 3 grades, depending on the extension of necrosis (absent, patchy, or extensive) and the number of EBV-positive B cells (< 5, 5-20, or > 20 per high-power field).[1,3,7,8] Lymphomatoid granulomatosis grade 1 or 2, considered indolent processes, may improve with corticosteroid therapy.[2] The prognosis of lymphomatoid granulomatosis is poor; the condition is equivalent to diffuse large B-cell lymphoma, and requires aggressive treatment with chemotherapy and/or radiation therapy.[1—3] The lung is the most frequently affected organ (90%). Secondary dissemination to the CNS is not infrequent (25%-30%),[1,3] but primary, isolated CNS involvement is exceptional, with only 49 cases reported to date.[2—5] Cases not involving the lungs are atyp-

☆ Please cite this article as: Moreno-Estébanez A, González-Pinto T, Agirre-Beitia G, González LM. Granulomatosis linfomatoide primaria del sistema nervioso central: un reto diagnóstico. Neurología. 2021;36:625—628.

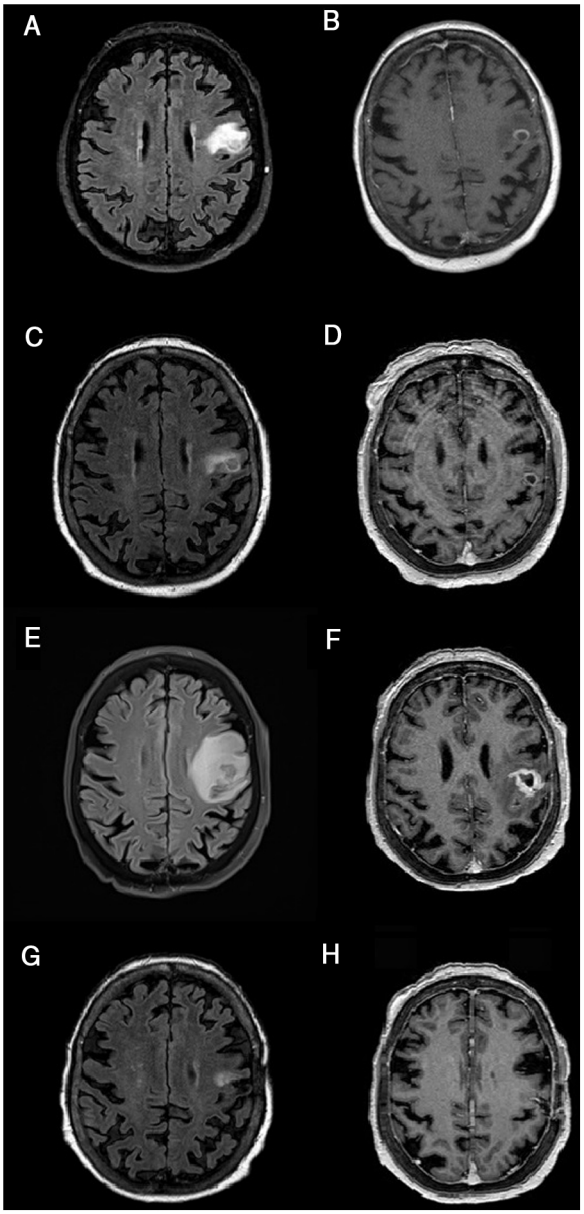

Figure 1 Brain MRI scan showing lesion progression. A-B) At admission. C-D) After 21 days of treatment. E-F) After 2 months of treatment. G-H) After 3 months of treatment. FLAIR (A, C, E, G) and gadolinium-enhanced T1-weighted sequences (B, D, F, H), axial plane. Images show the progression of a corticosubcortical lesion located in the left precentral gyrus/frontal operculum; the lesion is rounded and well defined, and appears iso- and hyperintense on FLAIR sequences (A, C, E, G) and hypointense on T1-weighted sequences (B, D, F, H), surrounded by vasogenic oedema and with contrast ring enhancement (B, D, F, H). Lesion size at admission was 15 × 12 mm (anteroposterior × lateromedial) (A). After a slight decrease in lesion size (12 × 7.5 mm) and significant improvements in the perilesional oedema (C), with contrast ring enhancement remaining nearly unchanged (D), remarkable increases were observed in lesion size (16 × 16 mm) and vasogenic oedema (E), as compared to the previous study (D). The lesion also changed in terms of morphology (more heterogeneous) (D), and displayed more extensive and irregular contrast uptake (F). Significant improvements were observed 3 months after onset of treatment with ibrutinib, with a decrease in lesion size and improvement in oedema (G); contrast uptake was barely perceptible (H). Changes were observed after craniotomy (biopsy) (G, H).

ical, and are therefore associated with greater diagnostic delays; this may have a negative impact on prognosis, since low-grade lymphomatoid granulomatosis can progress to more aggressive forms.[1,10] Neurologists should therefore be familiar with this entity. In patients with history of transplantation, lymphomatoid granulomatosis should be differentiated from post-transplant lymphoproliferative disorder; this B-cell proliferative disorder is also associated with EBV infection but does not present reactive T-cell infiltration or necrosis.[2,4,8,11,12] In immunocompetent individuals, lymphomatoid granulomatosis may be misdiagnosed as glioblastoma multiforme due to the presence of necrosis. Lymphomatoid granulomatosis associated with brainstem involvement may be indistinguishable from CLIP-

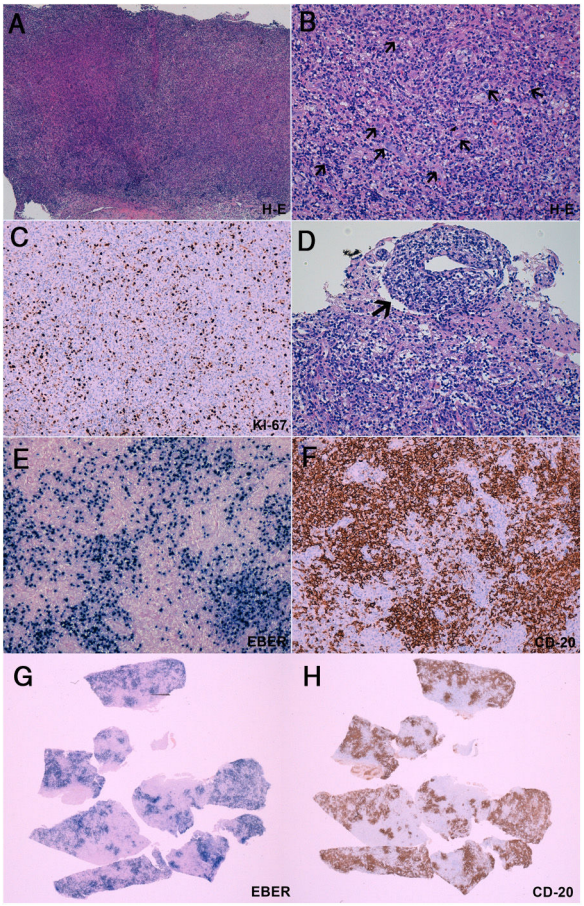

Figure 2 Brain biopsy. A-B) Haematoxylin-eosin staining showed intense polymorphous inflammatory infiltrate containing lymphocytes, plasma cells, and histiocytes, intermingled with large, atypical cells (B, arrows), some of which were close to blood vessels (B, arrowheads). C) The Ki67 proliferation index was > 40%. These cells tend to form aggregates of >50 cells (B) and present an angiocentric and angiodestructive growth pattern (D). Immunohistochemical studies (E, F, G, H) revealed that these atypical cells express CD20 (present in B-cells) and EBER (Epstein-Barr virus—encoded RNA, which indicates Epstein-Barr virus infection). A comparison of histology sections revealed a nearly complete overlap between EBER-expressing and CD20-expressing cells (G, H). All these findings are diagnostic of an EBV-associated B-cell lymphoproliferative disorder, compatible with lymphomatoid granulomatosis grade 3.

PERS syndrome.[13] These similarities between lymphomatoid granulomatosis and other diseases make diagnosis even more challenging. Furthermore, in our case, chronic kidney disease and limitations with drug transportation across the blood-brain barrier constituted a therapeutic challenge. Ibrutinib, a drug currently under study for the treatment of primary CNS lymphoma,[14] was administered for compassionate use due to its ability to cross the blood-brain barrier and its limited renal clearance.[15] This is the first reported case of primary lymphomatoid granulomatosis of the CNS treated with ibrutinib; the drug may constitute a treatment option for patients ineligible for R-CHOP.

Our case is interesting in that lymphomatoid granulomatosis exclusively involved the CNS and was treated with ibrutinib. Neurologists should be familiar with this entity in order to prevent diagnostic delays.

Disclosures

All authors made intellectual contributions to this study and approved the final version of the manuscript.

Confidentiality of patient data was preserved.

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgements

We would like to sincerely thank Dr Zaldumbide Dueñas (anatomical pathology department, Hospital Universitario de Cruces) for her constant collaboration with the neurology department, and particularly in this case for her insightful explanation of anatomical pathology images.

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https://doi.org/10.1016/j.nrleng.2020.09.001
2173-5808/

Adult rhombencephalosynapsis: an unusual presentation of an infrequent entity☆

Romboencefalosinapsis en el adulto: una presentación inusual de una entidad poco frecuente

Dear Editor:

Rhombencephalosynapsis (RES) is a rare posterior fossa malformation first described in 1914 by Obersteiner[1] in a post mortem study of a 28-year-old man. The term RES was coined by Gross[2] and Hoff in 1959. The entity is characterised by aplasia or hypoplasia of the cerebellar vermis, associated with midline fusion of the cerebellar hemispheres.[3,4] RES may be associated with other malformations of the central nervous system and other structures.[3,5] Diagnosis of this rare condition in adulthood is extremely infrequent, with very few cases reported to date.[6—9]

We present a case of late diagnosis of paucisymptomatic RES.

Our patient was a 43-year-old man, a former smoker with history of repeated syncope, with no known structural heart disease. He visited our hospital's emergency department due to paraesthesia in the face and the left crural region associated with headache in the context of a hypertensive crisis. The neurological examination revealed tactile hypoaesthesia and hypoalgesia in the aforementioned location, with no alterations in muscle strength, language comprehension and production, or cranial nerve function, and no limb dysmetria. The patient remained asymptomatic after blood pressure was controlled. CT, blood and urine analyses, and ECG yielded normal results, with no signs of haemodynamically significant stenosis in the duplex ultrasound of the supra-aortic trunks.

An MRI study revealed partial agenesis of the cerebellar vermis with partial posterior fusion of the cerebellar hemispheres (Fig. 1A and B), absence of the primary and prepyramidal fissures of the cerebellum (Fig. 1C), proximity of the dentate nuclei to the midline (Fig. 1D), left-sided incomplete hippocampal inversion associated with colpocephaly (Fig. 1E), and capillary telangiectasia in the right middle cerebellar peduncle (Fig. 1F).

A subsequent examination only revealed severe difficulty walking in tandem. In a targeted medical history interview, the patient reported a long history of gait instability, presenting only when performing certain activities.

Diagnosis of RES is based on brain MRI findings and correct interpretation of clinical signs and symptoms, particularly in more subtle cases with partial RES. The main radiological finding for diagnosis is aplasia or hypoplasia of the cerebellar vermis, associated with midline fusion of the cerebellar hemispheres.[3,4] Other diagnostic findings include hydrocephalus or ventriculomegaly (which may be associated with aqueductal stenosis),[9] corpus callosum abnormalities (hypoplasia), and absent septum pellucidum.[4] The literature also includes reports of other abnormalities associated with RES: fusion of the thalamus, tectum, and fornices; temporal lobe hypoplasia; incomplete hippocampal inversion[10]; and hypoplasia of the optic chiasm, olivary nuclei, and anterior comissure.[11—13] Other noteworthy neuroradiological findings include: 1) on sagittal images: absence of the primary fissure (Fig. 1C), abnormal (rounded) morphology of the fourth

☆ Please cite this article as: Sánchez-Villalobos JM, Torres-Perales AM, Serrano-Velasco L, Pérez-Vicente JA. Romboencefalosinapsis en el adulto: una presentación inusual de una entidad poco frecuente. Neurología. 2021;36:628—630.