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Letter to the Editor: New Observation

Breakthrough of Granulomatosis with Polyangiitis-Associated CNS Vasculitis Amidst Adequate B-cell Depletion

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Granulomatosis with polyangiitis (GPA) is a small-vessel vasculitis associated with anti-neutrophil cytoplasmic autoantibody (ANCA) that rarely presents with central nervous system (CNS) involvement.[1] Two main phenotypes have been described, classified according to their histological–radiological appearance: a granulomatous subtype, with pachymeningitis or focal granuloma invasion, and a vasculitic subtype, with diffuse leukoencephalopathy and inflammatory infiltration of the brain small vasculature. Although both clinical presentations include various focal and non-focal CNS deficits, headaches are most frequently associated with the granulomatous subtype, while cognitive dysfunction and motor impairment are mostly seen with the vasculitic subtype.[2] Similar to primary CNS angiitis, disease remission is typically achieved using high-dose corticosteroids and cyclophosphamide,[3] although recent evidence suggests an increasing role for B-cell depleting agents like rituximab.[4,5] Herein, we report the first case of GPA-associated CNS vasculitis in a patient adequately immunosuppressed on rituximab.

A 33-year-old woman was admitted in April 2020 to the Montreal Neurological Hospital following a 4-month history of cognitive decline and personality changes.

Her past medical history was consistent with anti-PR3-positive GPA. She had presented in 2018 with sinopulmonary involvement and saddle nose deformity, shortly followed by an ischemic stroke of the right precentral gyrus causing isolated left facial weakness. At that time, given the lack of traditional stroke risk factors, suspicion of GPA-associated CNS involvement was raised, but not further investigated. Treatment induction consisted in high-dose prednisone and rituximab. Maintenance therapy with low-dose prednisone and rituximab every 6 months allowed for disease remission. For 2 years, she remained highly functioning, with no evidence of cognitive impairment or recurrent focal neurological deficits. Latest rituximab infusion was 4 months before admission.

In January 2020, the patient started to exhibit personality changes and disorganization, followed by memory deficits, emotional lability, and executive dysfunction, which led to hospitalization in April 2020. No headaches nor focal neurological symptoms were elicited. Initial examination was remarkable for pseudobulbar affect, perseveration, and disinhibition, without new focal neurological deficits.

Brain magnetic resonance imaging (MRI) showed ill-defined, diffusely scattered hyperintense T2/FLAIR lesions of the white matter involving predominantly bilateral temporal and insular lobes, without pachymeningeal enhancement nor diffusion restriction (Figure 1A,B). General examination did not show evidence of systemic GPA relapse. Inflammatory markers were within normal limits and anti-PR3 titers were undetectable. CD19 and CD20 counts were undetectable, indicative of persistent B-cell depletion from rituximab. Cerebrospinal fluid (CSF) examination revealed mild increased protein of 0.57 mg/dl and 4 leukocytes/μL. CSF cytology showed reactive lymphocytes. Extensive serological and CSF infectious work-up, including CSF polyomavirus and enterovirus PCR, was negative. A whole-body positron emission tomography/computed tomography (PET/CT) was negative.

Two weeks into admission, the patient was treated with IV immunoglobulin (IVIg) 2 g/kg and IV methylprednisolone 1 g/day for 5 days for suspected autoimmune encephalitis, which did not result in any improvement. Paraneoplastic and autoimmune encephalitis panels were negative. One month following admission, a repeat brain MRI demonstrated progression in the confluence and extent of the white matter lesions involving the supra and infratentorial brain with frontotemporal predominance (Figure 1C,D,E). Cerebral angiogram showed no signs of vasculitis. A brain biopsy showed changes consistent with parenchymal inflammation, including perivascular histiocytic cuffing, small areas of infarctions suggestive of vascular inflammation, and the presence of a venous thrombus (Figure 2A), a histological feature observed in GPA vasculitides. No granulomas were seen. The presence of CD8-rich inflammatory infiltrates and the absence of CD163-positive microglial nodules (Figure 2B,C) argued against a viral etiology. Immunohistochemistry for polyomavirus was negative. In light of these results, patient was re-treated with another 5-

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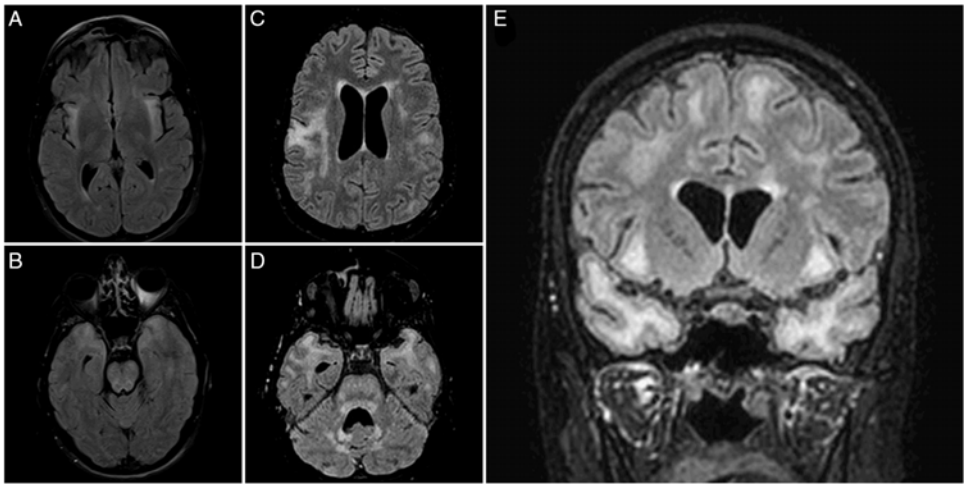

Figure 1: Magnetic resonance imaging. Initial axial (A, B) fluid-attenuated inversion recovery (FLAIR) MRI images show ill-defined, diffusely scattered symmetrical hyperintense signal abnormalities most prominent in the insulas and the antero-medial aspect of the temporal lobes bilaterally. Follow-up axial (C, D) and coronal (E) FLAIR MRI images show significant interval progression of the diffuse white matter hyperintense signal abnormalities involving the subcortical and periventricular white matter, insulas, anterior temporal lobes, brainstem, and cerebellar white matter.

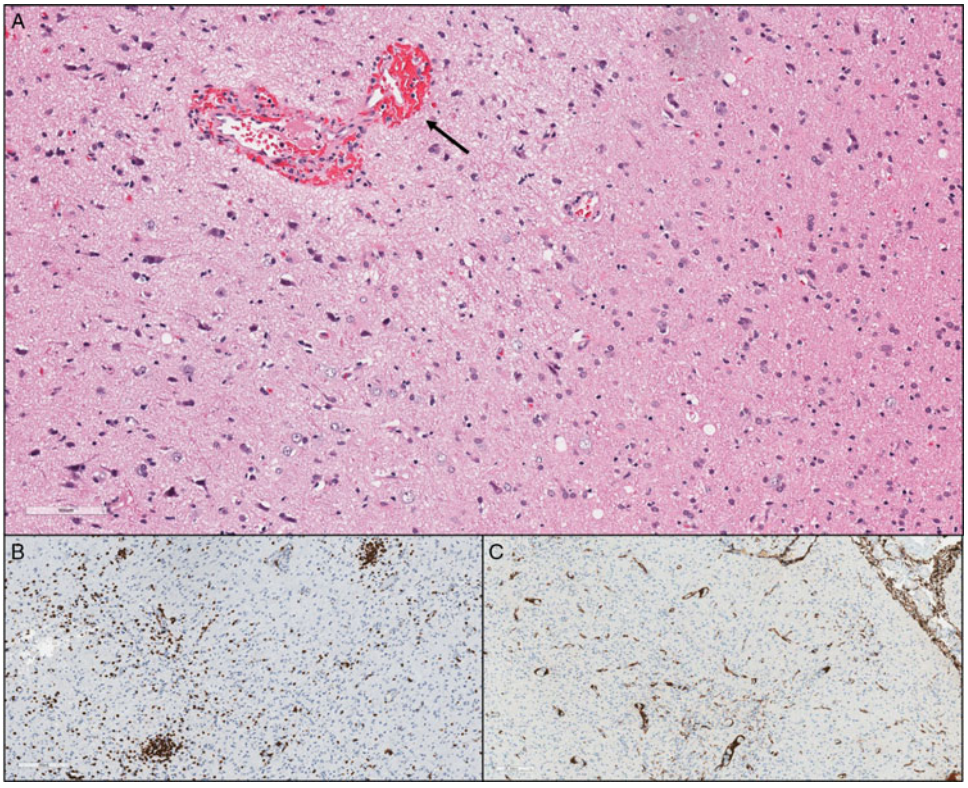

Figure 2: Histopathological findings. (A) Hematoxylin eosin/luxol fast blue stain (HE/LFB) stain (x200) shows the presence of a venous thrombus surrounded by reactive astrocytes. (B) IHC for CD8 (x100) shows diffuse infiltration of the parenchyma with small T cells and presence of nodules mimicking microglial nodules, but composed exclusively of CD8-positive and CD163-negative T cells. (C) Immunohistochemistry (IHC) for CD163 (x100) shows histiocytic inflammatory cells within the leptomeninges and around the blood vessels.

day course of IVIg and IV methylprednisolone as well as induction IV cyclophosphamide. Within 2 weeks, patient showed definite clinical improvement, but remained with behavioral and cognitive deficits on discharge to rehabilitation center. One month later, she experienced abrupt onset diplopia and ataxia. MRI showed a new left pontine stroke despite slight improvement in the white matter lesions. At follow-up 3 months later, she had shown continued clinical improvement, but remained with poor insight and mild cognitive dysfunction. She completed a 6-month course of cyclophosphamide and has since remained stable.

This case illustrates the complexity surrounding a diagnosis of CNS vasculitis, and the persistent relevance of tissue diagnosis in cases of uncertainty. Despite the absence of active extracranial disease and undetectable ANCA titers, a diagnosis of GPA-associated

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CNS vasculitis was deemed most likely given the suspicion of previous CNS involvement at the time of GPA diagnosis, histopathological changes suggestive of vasculitis, and clinical improvement with cyclophosphamide. The history of systemic vasculitis excluded the diagnosis of primary angiitis of the CNS. Our diagnostic impression is corroborated by a previous series of 35 GPA patients with CNS involvement in which 14% of cases had no extracranial manifestations and 11% had negative ANCA titers at the time of CNS disease diagnosis.[2] Interestingly, in the same case-series, CSF analysis was unremarkable in 37% of patients, as seen in our case.

This case is also an example of B-cell-depleting therapy failure, with subsequent improvement with comprehensive cellular immunosuppression. This suggests an independent role for T-cells in CNS inflammation associated with GPA, a disease in which antibody pathogenicity is robustly validated.[6] Previous reports of rituximab in GPA-related CNS disease have described its use almost exclusively as a rescue therapy in case of glucocorticoids and cyclophosphamide failure. Reported outcomes were favorable, with rare relapses occurring after a single cycle, in the context of rising ANCA and CD19 titers, that responded to a second rituximab cycle.[5,7] Reported cases were, however, depicting pituitary or pachymeningitic involvement, instances of the granulomatous subtype. To our knowledge, there is no previous report of GPA-associated CNS *vasculitis* successfully treated with rituximab. Our case supports the theory of a different pathophysiology between the two main CNS disease phenotypes,[8] with different clinical–biological characteristics,[2] which, one could infer, may require a distinct therapeutic strategy.

In conclusion, this report highlights the need for clinicians to remain vigilant for CNS vasculitic disease in patients known for GPA who present with rapid cognitive decline, even in the presence of quiescent systemic disease and adequate targeted immunomodulation. Furthermore, this case suggests that broadening immunosuppressive therapy could be key to limiting long-term neurological sequelae.

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Statement of Authorship. **Samantha Rivet**: Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. **David Pellerin**: Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. **Rami Massie**: Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. **Michael Stein**: Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. **Liam Durcan**: Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. Marie-**Christine Guiot**: Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. **Stuart Lubarsky**: Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

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