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Case Report

Vasculitic Leukoencephalopathy Secondary to Epstein-Barr Virus: A Diagnostic Challenge Due to an Atypical Presentation — A Case Report

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Abstract

Vasculitis that clinically and pathologically affects the central nervous system (CNS) alone is defined as primary or isolated CNS vasculitis. Although rare, it is a diagnosis that should be considered by internists and neurologists in patients presenting with progressive neurological signs and symptoms of uncertain origin. There is no specific imaging or laboratory pattern that guides the diagnosis, and aside from biopsy, magnetic resonance imaging (MRI) is the only study that can substantially contribute to a definitive diagnosis. We report the case of a 20 -year -old man from Campeche diagnosed with small -vessel CNS vasculitis who initially presented with cognitive impairment. Polymerase chain reaction (PCR) testing of cerebrospinal fluid (CSF) was positive for Epstein -Barr virus. Two brain biopsies were performed, both revealing lymphocytic vasculitis with perivascular necrosis and foamy macrophages associated with secondary demyelination, Chronic vascular injury may manifest as cognitive decline; however, its occurrence as an initial presentation is extremely rare. This case represents a clear example of the diagnostic challenge posed by vasculitis, particularly when neurological manifestations are the sole clinical findings, and underscores the importance of biopsy in the diagnostic approach.

Keywords: *Vasculitis, infection, Epstein-Barr, Cognitive impairment, Central Nervous System*

Introduction

Central Nervous System vasculitis refers to a broad spectrum of diseases resulting from inflammation and destruction of the blood vessels of the spinal cord, brain, and meninges. It involves both venous and arterial sectors, affecting small- and medium-sized vessels, producing symptoms of central nervous system dysfunction without vasculitis in other organs. Its incidence is poorly known, and only a few retrospective studies estimate it at 2.4 cases per 1,000,000 inhabitants per year (1). There is a slight predominance in females, with a mean age at presentation of 50 years, although it can occur at any age (2).

Clinical manifestations are multiple and varied, with headache being the most frequent symptom (60%), typically with a subacute and insidious course, associated with cognitive decline, stroke involving multiple territories, and transient ischemic attack (TIA), observed in 30–50% of patients (3).

Cranial neuropathies, seizures, and coma are rare. Extranervous manifestations may include skin rash, weight loss, and fever. Symptoms usually progress over weeks or even months. These patients often present nonspecific cerebrospinal fluid (CSF) abnormalities, as well as alterations on electroencephalogram (EEG) (4). Imaging abnormalities detected on magnetic resonance imaging (MRI) are almost constant, although nonspecific for diagnosis. Diagnosis is established based on a compatible clinical presentation, combined with angiographic evidence showing a pattern suggestive of vasculitis, after other causes have been excluded (5).

It is essential to rule out differential diagnoses such as systemic vasculitides affecting the CNS, infections, cerebral embolism, and neoplastic processes, since treatment and prognosis differ in each of them. Treatment of this disease is based on the use of glucocorticoids (prednisone/methylprednisolone) in combination or not with immunosuppressive agents such as cyclophosphamide. Other therapeutic options have been used experimentally. Therefore, the objective of this case report is to present a case of vasculitis with an atypical clinical presentation, characterized by cognitive decline at onset, based on the clinical presentation and imaging findings consistent with vasculitis.

Timeline

A chronological summary of the case is presented to determine the progression from the initial appearance of localized induration in 2023 to the generalized symptoms that developed in the following months. The patient experienced paresthesias in the right side of the body without clinical improvement. After an absence of symptoms for 10 days, the symptoms relapsed, and mild to moderate bifrontal headache was added, without evidence of vasospasm for 24 hours. Two weeks later, the patient experienced an episode of urinary and fecal incontinence. The patient was admitted to the emergency department on September 15th, where a positive result for Epstein-Barr virus was obtained in the cerebrospinal fluid by polymerase chain reaction. A contrast-enhanced brain MRI was performed, which showed a diffuse hyperintense area in the white matter with frontoparietal and occipital extension in the left hemisphere and in the frontal region in the right. Two biopsies were performed, which showed evidence of vasculitis with secondary demyelination. as a multi-cell infiltrate, so methylprednisolone boluses of 1 g every day for 3 days were started, followed by 1 mg/kg of prednisone per day. Since a biopsy was already available, cyclophosphamide (15 mg/kg) was started. There was an improvement in cognitive impairment, with almost complete resolution of symptoms at the end of treatment and complete recovery sustained in follow-up appointments. **(Figure 1).**

Case Presentation

A 25-year-old man from Campeche, with no current chronic degenerative diseases, began his present illness on August 5, 2023, with paresthesias in the right hemibody. He consulted a general practitioner, who prescribed an unspecified medication without clinical improvement. Symptoms resolved for 10 days; however, he subsequently experienced a relapse, accompanied by mild-to-moderate bifrontal headache without signs of vasospasm, lasting 24 hours and improving with analgesics. He was unable to identify clear exacerbating factors, and there were no associated red flags at that time. Fifteen days later, he developed impairment of recent and work-related memory. At his job as a construction worker, he had difficulty remembering where he was supposed to work and how to prepare cement, prompting his family to restrict his work activities. Additionally, he exhibited decreased speech output and loss of interest in previously enjoyed activities, such as playing soccer.

Since September, he presented reduced sleep requirements with sleep-onset insomnia. Two weeks later, he experienced an episode of urinary and fecal incontinence while with his mother in a public area. That same night, he manifested impaired judgment with bizarre behavior (staring at lights and throwing stones at cars). Due to these events, he was brought to our facility for medical evaluation. He was admitted to the emergency department with a diagnosis of encephalopathy under investigation, and a consultation with our service was requested. A rapidly progressive cognitive impairment syndrome with right hemibody sensory exteroceptive deficit of undetermined etiology was established.

An immunological assessment was completed, including antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), and antiphospholipid antibodies (APL), all of which were negative, with normal complement levels. HIV testing was negative.

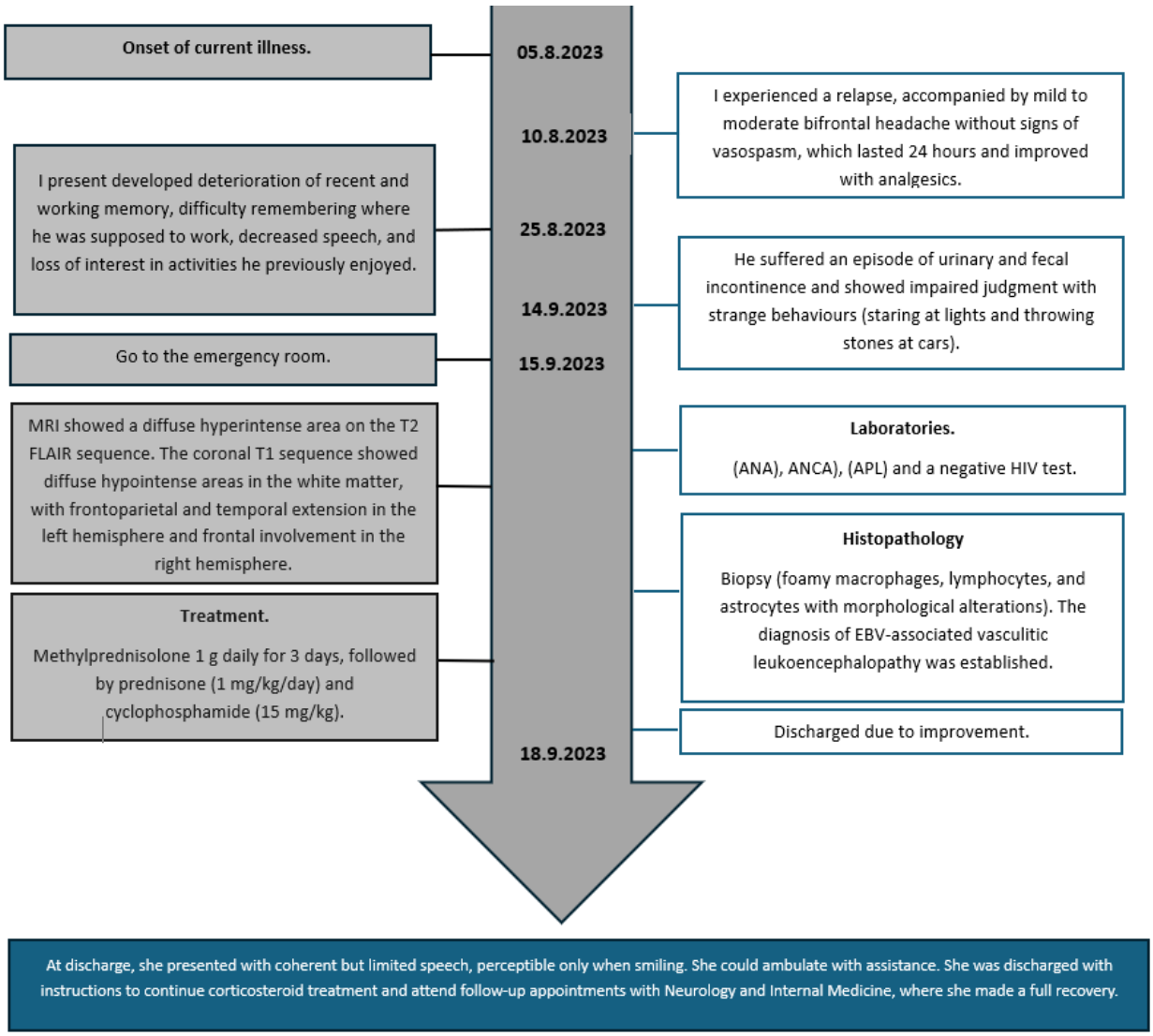

Figure 1.- Case report's timeline events and management: ANA: Antinuclear antibodies, ANCA: antineutrophil cytoplasmic APL: antibodies antiphospholipid, RMI: magnetic resonance imaging**.**

During hospitalization, extensive laboratory testing was performed to evaluate potential primary and secondary causes of demyelinating lesions. Cerebrospinal fluid, polymerase chain reaction testing was positive for Epstein–Barr virus. Contrast-enhanced brain magnetic resonance imaging, revealed a diffuse hyperintense area on axial T2 FLAIR involving the white matter with frontoparietal and occipital extension in the left hemisphere and frontal involvement in the right hemisphere (Figure 2A). Coronal T1 imaging showed diffuse hypointense areas in the white matter with frontoparietal and temporal extension in the left hemisphere and frontal involvement in the right hemisphere (Figure 2B).

Based on these findings, two biopsies were obtained, demonstrating features of vasculitis with secondary demyelination, as well as infiltration by multiple cell types (foamy macrophages, lymphocytes, and astrocytes with morphological alterations) (Figures 3A and 3B). A diagnosis of EBV-associated vasculitic leukoencephalopathy was established.

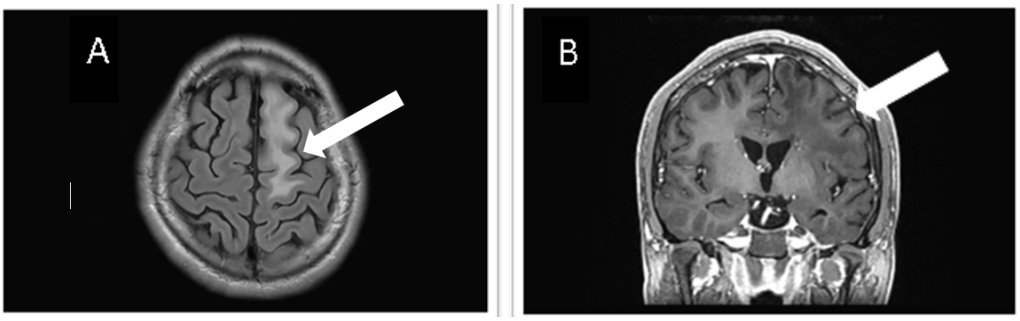

Figure 2. (A). Contrast-enhanced brain magnetic resonance imaging, axial T2 FLAIR sequence. A diffuse hyperintense area is observed in the white matter, with frontoparietotemporo-occipital extension in the left hemisphere and frontal involvement in the right hemisphere. **(B).** Contrast-enhanced brain magnetic resonance imaging, coronal T1 sequence. The arrow indicates a diffuse hypointense area in the white matter, with frontoparietotemporo-occipital extension in the left hemisphere and frontal involvement in the right hemisphere.

Treatment was initiated with methylprednisolone 1 g daily for 3 days, followed by prednisone at 1 mg/kg/day. Based on biopsy confirmation, cyclophosphamide (15 mg/kg) was started. During hospitalization, the patient experienced isolated headache episodes that were resolved with conventional analgesia. After initiation of therapy, he showed improvement in cognitive impairment. At discharge, he exhibited coherent but limited speech, right hemiparesis with improved strength compared to admission, and persistent right central facial paresis, noticeable only when smiling. He was able to ambulate with assistance. He was discharged with instructions to continue corticosteroid therapy and attend follow-up appointments with Neurology and Internal Medicine, where she made a full recovery.

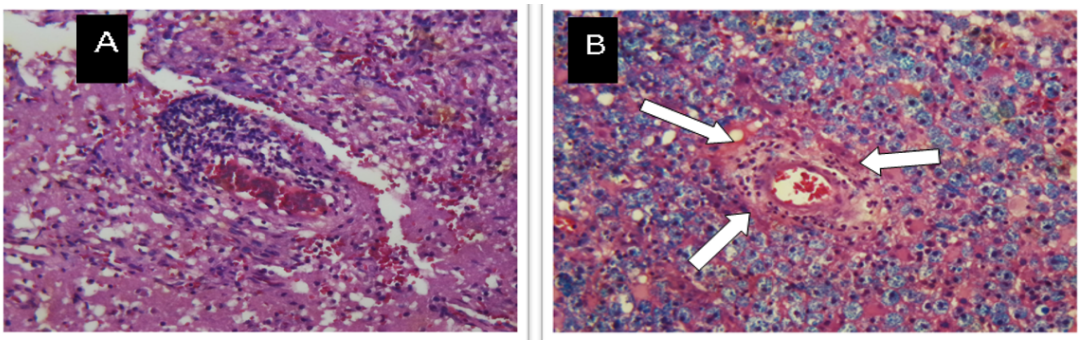

Figure 3. (A) White matter biopsy from the left frontal lobe stained with hematoxylin and eosin (100×). The arrows indicate the center of an arteriole with a lymphocytic infiltrate involving the entire infarcted area, accompanied by macrophages. **(B)** White matter biopsy from the left frontal lobe stained with hematoxylin, eosin, and Luxol fast blue (100×). The arrows indicate the center of the artery with the inflammatory infiltrate. Note the presence of macrophages (arrows) corresponding to the infarcted area.

Patient Perspective

The patient reports that the onset of symptoms was unexpected and progressive, causing significant concern due to the development of neurological manifestations that markedly affected his quality of life and daily functioning. Throughout the diagnostic process, he experienced uncertainty and anxiety related to the fluctuating nature of the symptoms and the difficulty in reaching a definitive diagnosis. Following confirmation of vasculitis secondary to Epstein–Barr virus infection and initiation of appropriate treatment, the patient perceived a gradual improvement in symptoms, which helped restore confidence in his recovery. At present, he emphasizes the importance of timely diagnosis, close medical follow-up, and clear communication with the healthcare team when facing a rare and potentially severe disease.

Discussion

This In the literature, primary central nervous system vasculitis is classified according to the size of the affected vessels, most commonly involving small vessels, in which magnetic resonance imaging findings are usually characteristic of vasculitis; however, brain biopsy is required to achieve a definitive diagnosis. Clinically, the presentation often spans weeks to months, with prodromal symptoms including headache, cognitive decline, personality changes, and/or constitutional symptoms, followed by the onset of acute neurological deficits. Due to the nonspecific nature of these manifestations, the diagnosis is usually not considered until sufficient clinical events prompt investigation for atypical pathological processes or neuroimaging findings suggestive of central nervous system vasculopathy. This is particularly relevant in our case, in which cognitive impairment was the initial symptom, a presentation that is extremely rare.

As previously described, the definitive diagnosis was obtained through brain biopsy, which demonstrated the characteristic histopathological features of this condition (6). There are no pathognomonic signs or symptoms, and therefore patients may present with a wide variety of clinical manifestations depending on the location of the affected blood vessels (7).

We believe that one factor contributing to the stagnation in diagnostic approaches and the lack of clear and robust diagnostic criteria is the fact that most reported cases of vasculitis lack histological studies, and, as mentioned earlier, our patient presented with cognitive impairment as an initial manifestation (8). Despite this, the most accepted approach is to consider a case "possible" when there is no histological confirmation, whereas a "definitive" case requires histopathological evidence.

Given the nature of this disease and its high morbidity and mortality, we advocate for biopsy and consider histopathological examination to be the only tool capable of establishing a definitive diagnosis (9). Moreover, in line with other authors, histopathological evaluation should be performed whenever possible, as it has been shown that there are more complications associated with immunosuppressive therapy than with the biopsy itself. It is crucial to adequately address differential diagnoses from the start in order to achieve a precise and reliable diagnosis and enable early initiation of appropriate treatment (10).

Despite the limitations inherent to small sample sizes and the limited capacity to draw broad conclusions, we emphasize the importance of clinical and histopathological diagnosis through biopsy in carefully selected patients, in order to reduce diagnostic delays and thereby enable early treatment, improve survival outcomes, and reduce functional disability.

Conclusions

In conclusion, the case presented is a clear example of the diagnostic challenges posed by vasculitis, particularly when only neurological manifestations are present, and highlights the importance of biopsy within the diagnostic approach.

Abbreviations

CNS: central nervous system.

MRI: magnetic resonance imaging.

PCR: Polymerase chain reaction.

CSF: testing of cerebrospinal fluid.

TIA: transient ischemic attack.
EEG: electroencephalogram.
ANA: antinuclear antibodies.
ANCA: antineutrophil cytoplasmic antibodies.
APL: antiphospholipid antibodies.

Author Contributions

CAEA: Conceptualization, Methodology, Investigation, Writing—original draft, Writing—review & editing, Supervision, Project administration. ECVM, CTHB: Investigation, Data curation, Writing—review & editing. DGE, ECVM: Investigation, Data curation.

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Conflicts of Interest

The authors declare no conflicts of interest.

Ethical Approval

Ethical approval was not required for this study, in accordance with the guidelines of the Medical Research Committee. This study complies with the Declaration of Helsinki (2013).

Consent to Participate

The consent to participate was waived because the data is anonymously reported.

Availability of Data and Materials

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

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