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## **Case report**

Fernando Morales-Ramírez,<sup>1</sup> Brenda Bertado-Cortés,<sup>2</sup> Raúl Carrera-Pineda.<sup>3</sup>

<sup>1</sup>Third year Neurology Resident at the Centro Médico Nacional Siglo XXI Specialties Hospital.
<sup>2</sup>Medical Assistant at the Neurology Service at the Centro Médico Nacional Siglo XXI Specialties Hospital.
<sup>3</sup>Head of the Neurology Service at the Centro Médico Nacional Siglo XXI Specialties Hospital.

#### Keywords

Vasculitis, central nervous system, rituximab.

#### Primary Angiitis of the Central Nervous System Successfully Treated with Rituximab: Case Report

Vasculitis Primaria del Sistema Nervioso Central Tratada Exitosamente con Rituximab: Reporte de Caso

# Abstract

**Background.** Primary Central Nervous System Vasculitis (VPSNC) is an heterogeneous and infrequent disease characterized for vasculitis limited to the brain and spinal cord. The diagnosis is oriented by angiography and confirmed by biopsy. The treatment of VPSNC is based on the combination of steroids and cyclophosphamide, but nevertheless, some patients are intolerant or do not have favorable response to this treatment. To our knowledge there is only two other reports (three patients total) of VPSNC treated with Rituximab.

**Case report.** We document the case of a female patient, 28 years old with diagnosis of VPSNC pseudotumoral variant, angiographically negative. In consideration of refractoriness of pseudotumoral variant with first-line treatment, we decided to administer treatment with Rituximab.

**Conclusions.** Rituximab can be considered in a future to be a fistline treatment for VPSNC.

#### Resumen

**Introducción.** La vasculitis primaria del sistema nervioso central (VPSNC) es una entidad heterogénea e infrecuente caracterizada por vasculitis limitada al cerebro y médula espinal. El diagnóstico es orientado por angiografía y establecido mediante biopsia. El tratamiento se basa en la combinación de esteroides y ciclofosfamida, sin embargo, algunos pacientes son intolerantes a este esquema de tratamiento o no obtienen respuesta favorable. En nuestro conocimiento sólo existen dos reportes (con tres pacientes en total) de VPSNC tratados con Rituximab.

**Reporte de caso.** Documentamos el caso de un paciente femenino de 28 años de edad en la que se establece diagnóstico de VPSNC variante pseudotumoral con angiografía normal. Ante los reportes de refractariedad en la variante pseudotumoral con el manejo de primera línea se decide manejo con Rituximab.

**Conclusiones.** El Rituximab puede ser considerado en un futuro como tratamiento de primera línea para VPSNC por su efectividad y seguridad.

#### Palabras clave

Vasculitis, sistema nervioso central, rituximab.

**Corresponding author:** Dr. Brenda Bertado Cortés Demyelinating disease clinic. Neurology Service Centro Médico Nacional Siglo XXI Specialties Hospital Avenida Cuauhtemoc 330, Colonia Doctores, Delegación Cuauhtemoc, C.P. 06720 Ciudad de México. Phone: 56 27 69 00 E-mail: bertadobrenda@hotmail.com

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Primary angiitis of the central nervous system (PACNS) is a rare disease of unknown cause, with exclusive involvement of the brain and spinal cord.<sup>1</sup> Its recognition dates back to the mid-1950s when Carvioto and Feigin described several cases of noninfectious granulomatous angiitis. The largest series of patients was published by Salvarani et al. and it included 163 patients.<sup>2-5</sup> The incidence is estimated at 2.4 cases per million inhabitants per year, it occurs in the same frequency in both sexes, and the average age of diagnosis is 50 years.<sup>6</sup> The pathogenesis is unknown. It has been proposed that infection with varicella-zoster virus has a leading role in the disease.<sup>7</sup> We do not know of any randomized trials for the medical management of central nervous system vasculitis, the current strategies are derived from those used in other vasculitis.<sup>8</sup> Corticosteroids alone or in combination with cyclophosphamide achieve a favorable response in most cases, however, some patients respond poorly to this scheme or are intolerant to the treatment.<sup>9</sup> We report a case of PACNS treated with rituximab in our hospital.

## Clinic case

Female patient, 28 years old, with a history of hypothyroidism, four years since diagnosis, in treatment with levothyroxine. She presented with right palpebral ptosis in 2010. In 2015 she had an episode of language arrest lasting three hours, spontaneously remitting. She later reported a left hemicranial headache, oppressive, of moderate intensity, for which she sought assessment by the neurology service at our hospital. Upon evaluation, a right palpebral ptosis and generalized hyperreflexia were found; otherwise, the neurological examination was normal. Magnetic resonance imaging of the brain was performed, the presence of three parenchymal lesions at the frontal lobe and left parietal lobes were observed. The lesions were isointense in T1 weight, hyperintense in T2, and upon administration of contrast medium presented irregular ring reinforcement. The spectroscopy of the larger lesion showed an increase in choline with a decrease in N-acetylaspartate (Figure 1 A, B, C). A diagnostic approach was performed that included the following tests: ANA, ANCA-c, ANCA-p, Anti-DS, Anti Smith, Anti-Ro, Anti-La, Anticardiolipin IgG, IgM, which were all negative. Cerebrospinal fluid clear and colorless, cells 4, glucose 50, proteins 37. Polymerase chain reaction in cerebrospinal fluid for tuberculosis negative. Brain angiography (Figure 2) and renal without alterations. It was decided to perform a biopsy where perivascular lymphocytic infiltration, gliosis, edema and multiple zones of ischemia with microinfarcts were found without observing acid-fast bacilli or neoplastic cells. Treatment was started with intravenous methylprednisolone and subsequent cycles of rituximab at a dose of 2 grams every six months for one year. No further clinical progression, resolution of the edema, decrease in the size of the lesions and lower gadolinium uptake were evidenced by magnetic resonance (Figure 1 D, E, F). Eighteen months after starting treatment there was no evidence of clinical or radiological progression (Figure 1G, H, I). Later, she underwent plication of aponeurosis of the eyelid with partial functional recovery of it.

Figure 1. 1 Magnetic resonance imaging of the brain in T2, FLAIR, and T1Gad weights (A, B, and C, respectively) show ring-enhancing lesions with significant perilesional edema. Eight weeks after treatment with rituximab (D, E, F) resolution of the edema is observed and, after administration of gadolinium, there are no abnormal enhancements. Eighteen months after starting treatment (G, H, I), no evidence of progression.





Figure 2. Normal cerebral angiography. Angiography can be negative in up to 50% of patients. A negative angiogram is associated with recurrence after treatment.

Figure 3. Hemotoxilin-Eosin preparation of a brain parenchyma sample obtained from the largest lesion. It is observed perivascular lymphocytic infiltrate



## Discussion

PACNS is an uncommon disease, of unknown cause, with exclusive involvement of the brain and spinal cord. Clinically, it has varied and unspecific manifestations, often insidious and progressive. The most common manifestation is headache, which is of nonspecific characteristics. Cognitive impairment is the second most common manifestation. Neurological focality is frequent, with or without evidence of cerebral infarction, while systemic symptoms such as fever or weight loss are uncommon, unlike in secondary vasculitis.<sup>2-5</sup> There are different clinicalradiological varieties of the disease, which differ in prognosis and treatment.<sup>2-5</sup> PACNS with normal angiography is characterized by affecting the smaller intracerebral arteries. These patients frequently present cognitive deterioration, hyperproteinorrachia (118 mg/dl), and meningeal enhancement or gadolinium-enhancing lesions in magnetic resonance. This form is associated with recurrence after treatment.<sup>10</sup>

Patients with leptomeningeal enhancement usually have a rapid response to treatment, although relapses are frequent.<sup>11</sup>

There is a rapidly progressive form of PACNS, which represents the most ominous form and frequently has a fatal outcome. It is characterized by multiple lesions visible on magnetic resonance, along with bilateral cerebral infarcts. The response to immunosuppressive treatment is poor.<sup>12</sup>

Spinal abnormalities occur in 5% of patients with PACNS, mainly affecting the thoracic spinal cord, presenting as partial or complete myelopathy.<sup>2-5</sup>

Four percent of patients present a single lesion with mass effect, named the pseudotumoral variant. In some cases, surgical resection of the lesion is curative, while in other cases it has been reported that aggressive immunosuppressive therapy has a favorable response, obviating the need for surgery.<sup>14</sup>

Intracranial hemorrhage occurs in 12% of patients, mainly as intraparenchymal hemorrhage, although cases of subarachnoid hemorrhage have been reported.<sup>15</sup>

The diagnosis of PACNS is based on three aspects: neurological deficit without explanation after comprehensive approach, vascular abnormalities in the central nervous system evidenced by angiography or histopathology, and exclusion of other causes.<sup>16</sup>

Magnetic resonance is the first study to be performed; its sensitivity is reported to be close to 100%. The findings are not specific and vary from cortical or subcortical infarcts, pachymeningeal and/or leptomeningeal enhancement, intracranial hemorrhage, pseudotumoral lesions, and hyperintense areas in T2/FLAIR.<sup>13</sup>

The typical images of cerebral angiography are alternating areas of narrowing and dilation of the cerebral arteries or occlusions affecting several brain vessels in the absence of abnormalities at the proximal level. When the affected vessels are less than 500 micrometers in diameter, the angiography is usually reported as normal.<sup>14</sup>

Cerebral and meningeal biopsies are the gold standard for the diagnosis of primary central nervous system vasculitis, since they confirm the diagnosis and discard its imitators. An optimal sample should include dura mater, leptomeningeal, cortex and white matter samples, and should preferably be taken from a site with radiological abnormality.<sup>2,7</sup> Biopsy is especially important in the differential diagnosis of pseudotumoral lesions.<sup>17</sup> Three histological patterns are known: granulomatous (56%), lymphocytic (28%), and necrotizing (14%).<sup>2</sup>

Several diagnostic criteria have been established. The most common are Birnbaum and Hellmann, based on clinical findings, angiography, and biopsy.<sup>2</sup> (Table 1) As mentioned before, there are no randomized trials for the treatment of PACNS and the strategies derive from those used in other vasculitis.<sup>8</sup> Corticosteroids alone or in combination with cyclophosphamide achieve a favorable response in the majority of cases, however, there are patients who respond poorly or are intolerant to this scheme so it is necessary to evaluate the efficacy of other immunomodulatory treatments.<sup>9</sup> Azathioprine, methotrexate, mycophenolate mofetil, infliximab, and etanercept have been used with variable results.<sup>8,18,19</sup>

In the related literature, there are only three reported cases of PACNS treated with rituximab, the first published by Salvarani et al in 2014, in which the patient presented intolerance to cyclophosphamide. The other two cases were published by Boyson and colleagues in 2015. One of them found refractoriness to the treatment with a combination of cyclophosphamide and steroids. The other had decided to use rituximab instead of cyclophosphamide due to a history of vesical polyps. In all three cases, a sustained improvement of 8-12 months post-treatment was reported.<sup>1,16</sup>

Our case was a woman in the third decade of life with pseudotumoral lesions in imaging studies. Biopsy was performed with data concordant with lymphocytic vasculitis. Secondary causes of vasculitis were ruled out and a brain angiography was performed without alterations. PACNS with pseudotumoral variant and a normal angiography was concluded; these variants are associated with refractoriness to the standard treatment. Considering the patient was of reproductive age, rituximab was preferred over cyclophosphamide because of its better safety profile and lesser effect on fertility. The clinical progression stopped after the treatment and improvement of the lesions was observed in magnetic resonance 18 months posttreatment.

Diagnostic criteria proposed by Calabrese and Mallek	History or clinical findings of an acquired neurological deficit that remains unexplained after an initial rigorous approach.
	Classical findings by angiography or histopathological characteristics of vasculitis within the central nervous system.
	No evidence of vasculitis or any other systemic condition where angiographic and/or pathological findings may be secondary.
	The diagnosis of primary central nervous system vasculitis is established if it meets all the aforementioned criteria.
Diagnostic criteria proposed by Brinbaum and Hellmann	Definitive: Confirmation of vasculitis by biopsy.
	Probable: In the absence of a biopsy, if there are highly compatible findings in angiography along with concordant abnormal findings in MRI of the brain and cerebrospinal fluid.

 Table 1. Diagnostic criteria for Primary Angiitis of the Central Nervous System.

Modified from Salvarani C, Brown RD, Hunder GG, 2012.

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## Conclusions

PACNS is an infrequent and poorly understood disorder of the CNS. The optimal treatment has not yet been defined. It is reported in the international literature that the combination of prednisone and cyclophosphamide is the treatment of choice; however, some patients have contraindications, intolerance to the adverse effects, or little response to this treatment scheme. In our experience, the use of rituximab showed regression of the brain lesions and stopped the clinical progression without the occurrence of adverse effects.

#### **Conflicts of interest**

The authors state that there are no relevant conflicts of interest in this study.

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