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Headache that Never Went Away

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Abstract

Central nervous system (CNS) vasculitis encompasses a broad range of diseases characterized by inflammation of blood vessels within the brain, spinal cord, and meninges. This review focuses on Primary Angiitis of the CNS (PACNS), a unique form affecting only the CNS without other organ involvement. PACNS primarily affects the small- and medium-sized arteries in the brain, leading to neurological symptoms. Early recognition and intervention are essential for optimal management. This case report of a 25-year-old male highlights the diagnostic challenges, where a multidisciplinary approach was necessary to diagnose PACNS, given initial negative results. The paper also explores the etiology and pathogenesis of PACNS and discusses the diagnostic criteria proposed by researchers. Medical professionals primarily base management strategies on induction and maintenance therapies, utilizing a combination of glucocorticoids and immunosuppressants as the standard treatment. However, the exact dosages and administration methods need further research due to the absence of randomized clinical trials. The review underscores the need for continued research to enhance diagnostic and treatment protocols, given the severity of PACNS.

Keywords

Primary Angitis of Central Nervous System

1. Introduction

Central nervous system (CNS) vasculitis encompasses a wide spectrum of diseases characterized by inflammation and destruction of blood vessels within the brain, spinal cord, and meninges. Among them, PACNS distinguishes itself as a distinct entity, exclusively affecting the CNS without involving blood vessels in other organs. In this review, we delve into the pathophysiology, clinical manife-

stations, and diagnostic challenges associated with PACNS, aiming to facilitate early diagnosis and optimal management.

PACNS predominantly affects the small- and medium-sized arteries of the brain parenchyma, spinal cord, and leptomeninges. The ensuing inflammation leads to various neurological symptoms and signs, reflecting CNS dysfunction. Timely recognition of these clinical presentations is crucial for initiating appropriate investigations and therapeutic interventions.

2. Case Report

A severe headache and left-sided weakness associated with numbness brought a 25-year-old male to Wexford General Hospital as his chief complaint. He reported experiencing a sudden, severe frontal headache that persisted despite taking over-the-counter analgesics. While driving to work on the day of admission, he experienced weakness in his left arm and leg, accompanied by numbness.

The patient's medical history included a recent root canal repair three weeks ago and a past medical history of frequent migraines. He had a high body mass index (BMI) and a history of heavy smoking. He denied regular alcohol consumption, illicit drug use, and had no significant family history. Notably, the patient had chosen not to be vaccinated.

Clinical examination revealed that the patient appeared in discomfort due to the headache. Neurological examination demonstrated left arm and leg weakness with a power grade of four out of five. Based on the National Institutes of Health Stroke Scale (NHSS) assessment, the patient scored a three.

Initial investigations, including a chest x-ray and electrocardiogram (ECG), showed clear lungs and a normal sinus rhythm without acute changes, respectively. The medical team admitted him to the hospital with a preliminary diagnosis of hemiplegic migraine for further neurological observation, and they prescribed analgesia.

As the patient's neurological symptoms persisted, the medical team ordered a CT brain scan and a lumbar puncture. The CT brain scan results showed no significant abnormalities. Initial laboratory tests, including full blood count (FBC), anemia screen, liver function, and inflammatory markers, all yielded normal results. The cerebrospinal fluid (CSF) analysis indicated a white blood cell count (WCC) of 92 with 100% lymphocytosis. On the following day, the patient's condition deteriorated, and he experienced seizure-like activity characterized by erratic movements of his hands and limbs. Additionally, his left-side weakness deteriorated to a power grade of zero out of five.

The on-call consultant received information about the new developments, and they requested a neurology consult. Considering the worsening condition and new seizure-like activity, the medical team performed urgent CT brain imaging with contrast. Repeat blood cultures, full blood tests, and investigations for vasculitis were also ordered.

The CT brain (Figure 1) with contrast revealed multifocal areas of reduced attenuation, most prominent in the right frontal and left parietal lobes, suggesting multifocal abscess formation.

To further investigate the possible underlying causes, specialists from St. Vincent's University Hospital (SVUH) and University Hospital Waterford (UHW) were consulted. The microbiology team in Waterford recommended starting intravenous Amoxicillin (2 g twice a day), Vancomycin (25 mg per kg once-a-day), and Metronidazole (500 mg three times a day) due to the possibility of an infectious etiology.

MRI brain imaging (Figure 2) revealed a focal area in the left occipital lobe and the head of the right caudate, ruling out herpes encephalitis and considering multifocal infarcts with a less likely possibility of evolving abscess formation.

Neurosurgery consultants from Beaumont Hospital concluded that the CT brain and MRI findings were more consistent with a possible vascular event, such as a watershed infarct. The patient was prescribed aspirin and evaluated for a stroke in young adults.

The stroke team requested consultations with hematologists and rheumatologists to explore inflammatory processes and potential infection causes. Tests for

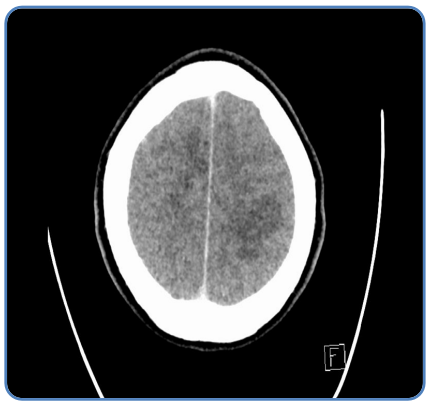

Figure 1. CT of brain.

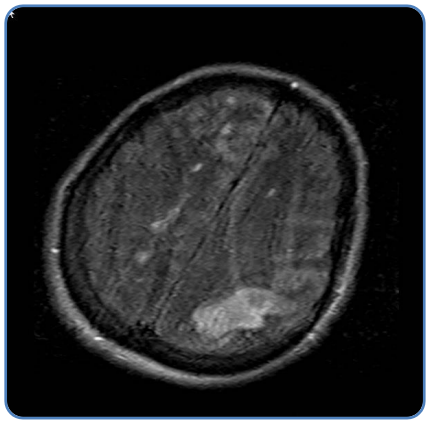

Figure 2. MRI brain imaging.

HbA1c, autoimmune screen, and vasculitis screening were ordered. An echocardiogram showed good left ventricular function with no vegetation, except for mild mitral regurgitation. Subsequently, a CT angiogram revealed multiple hypoattenuation foci, suggesting a possibility of vasculitis in the patient's age group.

Extensive Investigation Panel

Antibody Screen	**Result**
ANA	Negative
Anti-smooth muscle Ab	Negative
Anti-mitochondrial Ab	Negative
Anti Parietal Cell Ab	Negative
Immunoglobulin screen	**Result**
IgG	normal
IgM	normal
ACE	15
Paraneoplastic	**Result**
NMDA	Negative
CASPAR 2	Negative
LG1	Negative
Repeat LP	**Result**
No malignant cells seen	
CSF	viral PCR
CSF	cytology – cellular sample containing scattered mononuclear lymphocytes
AQP4 and MOG	Negative
Thyroid	**Result**
TSH.	– 10
T4	– 21
T3	– 3.6
TPO	Negative
Heamatology	**Result**
SPEP	– No abnormal bands
Lymphocyte subset	
T cells	67%
Helper	52%
Infection	**Result**
QUENTIFERON NEGATIVE	
Hep A IgM	Negative
Hep B sAg	Negative

Continued

Anti Hep B ab	Negative
Hep C	Negative
Lyme serology	Negative
Bartonella	Negative
IgG	Negative
IgS	Negative
HIV	Negative
CmV	Negative
EBV	Negative

Based on the evolving clinical picture and MRI findings, rheumatologists initiated high-dose oral steroids (methylprednisolone) and cyclophosphamide. Hematologists advised prescribing Apixaban.

The patient was accepted for admission to St. Vincent's University Hospital (SVUH) for further specialized care. However, due to the patient's unvaccinated status, they could not be transferred, and he was sent back to Wexford General Hospital for ongoing management. The patient's follow-up with rheumatology was planned to adjust steroid therapy and monitor his condition. Additionally, he was referred to the Royal Hospital of Donnybrook, but his unvaccinated status posed a challenge for transfer. Consequently, he remained under the care of Wexford General Hospital, awaiting further updates on his vaccination status.

3. Discussion

The presented case illustrates the diagnostic intricacies associated with PACNS. The patient's persistent headache and neurological deterioration, despite initial negative imaging and laboratory results, underscore the necessity for a multidisciplinary and sequential investigative approach. The patient's clinical picture evolved, culminating in a probable vascular event, navigating through a myriad of differentials including hemiplegic migraine, infectious etiologies, and ultimately PACNS. The diagnostic endeavor underscores the value of combining imaging modalities, laboratory analysis, and specialist consultations to traverse the convoluted path towards diagnosing PACNS.

Researchers have not yet identified the exact etiology and pathogenesis of PACNS. However, it's identified as a rare and severe form of vasculitis affecting the brain, spinal cord, and leptomeninges. The primary histopathologic patterns include granulomatous inflammation, lymphocytic cellular infiltrates, and acute necrotizing vasculitis [1]. Various types of immune cells infiltrate cerebral vessels, resulting in distinct histopathologic subtypes of the disease. Mandel-Brehm et al. found evidence of a deregulated alternative pathway of complement activation in CSF from biopsy-proven PACNS compared with a group of mimicking conditions [2]. A histopathologic study from Mihm et al. identified potential

pathogenic mechanisms, such as a deregulated alternative pathway of complement activation and the involvement of MRP8-positive intermediate/late-activated macrophages [3]. Moreover, a subtype of PACNS called ABRA is suspected to be a spontaneous form of autoimmune disease directed against amyloid β peptide (Aβ), characterized by an immune response causing leptomeningeal and parenchymal inflammation, clearance of parenchymal Aβ, and increased deposition of Aβ in cortical and leptomeningeal blood vessels. More research is needed to unravel and understand the pathological mechanisms of various PACNS subtypes to develop subtype-specific treatment options.

The diagnostic criteria for PACNS, as proposed by Calabrese and Mallek in 1988, includes an acquired, otherwise unexplained neurologic or psychiatric deficit; either classic angiographic or histopathologic features of angiitis within the CNS; and the exclusion of systemic vasculitis or any disorder that could cause or mimic the angiographic or pathologic features of the disease [4] [5].

Medical professionals use various methods to diagnose PACNS, including biopsy or angiogram, with newer criteria emphasizing cerebrospinal fluid (CSF) analysis. Amara *et al.* reported low agreement between biopsy histology and angiography [6], possibly due to sample artifacts from biopsies of unaffected tissue in the patchy disease pattern. Another explanation is that angiogram- and biopsy-confirmed cases may represent different PACNS subtypes (**Figure 1**). The key distinguishing factor is the vessel size associated with the vasculitis [7]. Increasing evidence suggests that angiogram-confirmed PACNS typically involves medium to large vessels, while biopsy-confirmed cases relate to small-vessel vasculitis [8]. Additional clinical and laboratory differences supporting this concept are summarized in **Figure 3** [1].

There are overlapping (para-)clinical attributes between biopsy- (blue bars) and angiogram-confirmed (red bars) cases of PACNS, and distinct characteristics. DSA = digital subtraction angiography; GD = gadolinium; MRA = magnetic resonance angiography; PACNS = primary angiitis of the CNS [1].

The management of PACNS mainly involves induction and maintenance therapies, although randomized trials for treatment are lacking. Treatment strategies are derived from the management of systemic vasculitides and observational studies. Induction therapy is typically composed of glucocorticoids and/or cyclophosphamide. High dose IV methylprednisolone is often the initial treatment followed by oral prednisone. The dosage of IV glucocorticoids was around 1 g/day for 3 - 5 days in the majority of studies [1]. The median initial oral dose of prednisone was 1 mg/kg/day in most studies [1]. There is some thought that the route of administration should be decided based on severity of the disease course. A minority of patients with PACNS received glucocorticoid therapy alone as induction treatment. In most patients, glucocorticoids were combined with another immunosuppressant, most prominently cyclophosphamide. With cyclophosphamide, IV pulses seem to be the preferred method of administration. It is usually administered in a median dose of 1 g given 2 - 12 times over 2 - 12 months [7]. Oral cyclophosphamide is given daily with studies showing varying

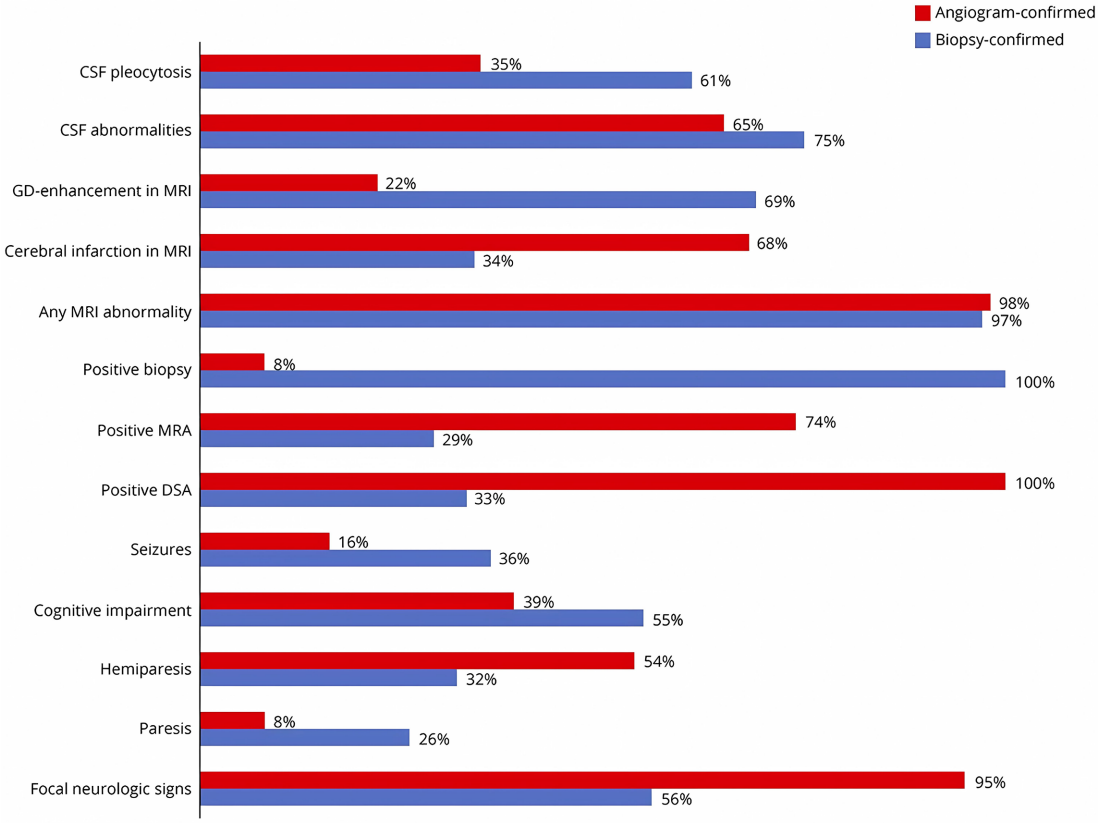

Figure 3. PACNS—a disease spectrum.

starting doses due to a lack of randomized clinical trials. Regimens include treatment with a median starting dose of 150 mg/day and a median treatment duration of 7 months, with a median starting dose of 100 mg/day and a median treatment duration of 10 months, or with 2 mg/kg/day and a treatment duration of 6 months [1]. Other induction treatments include cyclophosphamide alone or combinations of glucocorticoids with azathioprine, mycophenolate mofetil, rituximab, or methotrexate. IV immunoglobulins, infliximab, and plasma exchange were applied as well in single cases.

Maintenance therapy in PACNS commonly involves a combination of immunosuppressants with oral glucocorticoids being gradually tapered. Common immunosuppressant adjuncts to glucocorticoids for maintenance therapy include azathioprine at a dose of 1.5 or 2 mg/kg/day or 100 - 200 mg/day, mycophenolate mofetil at a dose of 2 - 3 g/day, and methotrexate at a dose of 0.3 - 0.5 mg/kg/wk or 7.5 - 20 mg/wk [1]. Some studies recorded the use of rituximab for induction and/or maintenance therapy. With rituximab, the treatment regimen for induction was two 1000 mg infusions separated by 2 weeks or weekly rituximab admission (375 mg/m^2) for 4 weeks and for maintenance therapy it was 1000 mg every 6 months [1]. Rituximab was especially useful in patients with disease resistant to the other immunosuppressants and led to improvement in neurologic symptoms and fewer relapses [1]. According to one study by de Boysson, maintenance therapy started at a median time of 4 (3 - 18) months af-

ter induction therapy was started and for a median duration of 24 (6 - 72) months [7].

To get a better understanding of the treatment of PACNS, it is important to understand the side effects, complications, and contra-indications. Common side effects of systemic glucocorticoids include an increased appetite, weight gain, neuropsychiatric side effects, gastrointestinal side effects, muscle weakness, delayed wound healing and lower resistance to infections (BNF 2). Prolonged courses of glucocorticoids can lead to serious complications. Adrenal atrophy develops with prolonged therapy and abrupt withdrawal can lead to acute adrenal insufficiency, hypotension, or death (BNF 2. As such, to compensate for diminished adrenal activity, any significant illness, trauma, or surgical procedure requires an increase in glucocorticoid dose temporarily (BNF 2. Prolonged courses of glucocorticoids increase susceptibility to infections and severity of infections, and infections may reach an advanced stage before being recognised due to atypical clinical presentations [9]. Systemic glucocorticoids should be prescribed with care in patients with a predisposition to neuropsychiatric side effects including those with a personal or family history of psychiatric disorders or who have previously suffered glucocorticoid-induced psychosis [9]. Live virus vaccines should be avoided in patients on glucocorticoid therapy, and glucocorticoid therapy is contra-indicated when the patient has a systemic infection [9].

The most common side effects of cyclophosphamide are alopecia, bone marrow disorders, decreased weight or appetite and gastrointestinal side effects [10] [11]. Leukocyte counts should be monitored with cyclophosphamide because of the potential of leukocytosis leading to increased risk of infections that may be more severe [10]. A rare but serious complication of cyclophosphamide use is haemorrhagic cystitis due to acrolein, a urinary metabolite of the medication. Increasing fluid intake for 24 - 48 hours after intravenous injection can prevent haemorrhagic cystitis [10]. Cyclophosphamide is also associated with an increased incidence of secondary malignancies [10]. Furthermore, cyclophosphamide may interfere with the normal menstrual cycle in women and may cause sperm abnormalities in men [10]. These effects are normally transient but, in some cases, cause persisting amenorrhea and infertility [11]. Cyclophosphamide should be avoided in pregnancy, as it is teratogenic, and patients with a history of hypersensitivity reactions to it or its metabolites [10] [11]. Breast-feeding should also be discontinued during the use of cyclophosphamide and for 36 hours after stopping treatment [10]. Caution should be exercised with cyclophosphamide use in a patient with hepatic impairment due to a risk of decreased cyclophosphamide activation and increased risk of veno-occlusive liver disease. As well, doses should be reduced in renal impairment [10].

The best functional outcomes were achieved in patients that were treated with a combination of glucocorticoids and another immunosuppressant as induction therapy, followed by maintenance therapy. In the analysis of patients with PACNS by de Boysson, 95% of patients achieved remission after induction

therapy with glucocorticoids frequently combined with cyclophosphamide [7]. Azathioprine was the most used immunosuppressant for maintenance therapy [1]. In relapsing patients, a reinduction was performed with the same drugs as applied as induction treatment.

In summary, the standard treatment for PACNS involves glucocorticoids combined with cyclophosphamide followed by maintenance therapy, but optimal dosages and administration routes remain uncertain due to the lack of randomized clinical trials. Overall, the disease represents a severe disorder with significant morbidity and mortality, requiring further research for improved diagnostic and treatment strategies. Most patients with PACNS achieve remission with glucocorticoids and immunosuppressants. Maintenance therapy, especially with immunosuppressants, appears beneficial in preventing relapses. However, gadolinium-enhanced lesions on MR imaging increased the risk of relapse [7].

4. Conclusions

This case report highlights the diagnostic challenges associated with PACNS, the diverse clinical presentations it can manifest, and the complexities of differentiating it from other conditions. Despite initial negative results, a multidisciplinary approach proved crucial in arriving at the correct diagnosis.

Furthermore, this review sheds light on the enigmatic etiology and pathogenesis of PACNS, emphasizing the need for further research to unravel its underlying mechanisms. Diagnostic criteria proposed by researchers, including the importance of cerebrospinal fluid analysis, offer valuable guidance for medical professionals in confirming PACNS.

The management of PACNS remains a challenge, with limited randomized clinical trials to guide treatment strategies. However, this review highlights that induction and maintenance therapies, often involving glucocorticoids and immunosuppressants, are commonly used in clinical practice. Optimal dosages and administration methods still require more investigation. Despite the severity of PACNS, a significant proportion of patients achieve remission with appropriate treatment.

Continued research efforts are essential to enhance diagnostic protocols and refine treatment strategies for PACNS. As our understanding of this complex condition evolves, there is hope for improved outcomes and quality of life for individuals affected by PACNS.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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