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Case Report

MULTIPLE INTRACEREBRAL HEMORRHAGE AS A POSSIBLE PRESENTATION OF CHURG-STRAUSS SYNDROME: A RARE CASE REPORT

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ABSTRACT

Introduction: Churg-Strauss syndrome (CSS) is a rare small-to-medium vessel vasculitis, associated with asthma, eosinophilia, and systemic inflammation. While peripheral nerve involvement is common in CSS, central nervous system (CNS) involvement is rare, with cerebral infarction and encephalopathy being the most frequent. Here, we report a rare case of multiple intracerebral hemorrhage (ICH) thought to be associated with CSS.
Case Summary: A 26-year-old woman with a history of asthma and allergic rhinitis presented with an acute headache, worsening a day before admission, accompanied by nausea, vomiting, low-grade fever, and arthralgias. Further investigations revealed multiple cerebral hemorrhage with perifocal edema and partial sulcal enhancements bilaterally. Cerebrospinal fluid (CSF) analysis showed eosinophilic pleocytosis, with elevated Immunoglobulin E (IgE) in the blood test, suggesting cerebral vasculitis by CSS manifested in ICH. Treatment with corticosteroids and immunosuppressant was initiated, leading to a favorable outcome.
Discussion: CSS is a rare systemic disorder characterized by multi-organ vasculitic involvement, though rare, CNS involvement was reported in 6–10% and ICH in association of CSS is extremely rare. The exact mechanism of CSS related cerebral bleeding remains unclear, but may result from cerebral vasculitis during phases of disease activity (indicated by raised inflammatory markers or eosinophilia), as observed in our patient.
Conclusion: This case highlights that, although rare, ICH can be a manifestation of CSS-related vasculitis. Therefore, it should be considered as a differential diagnosis of ICH. In this patient, an immunosuppressive treatment using methylprednisolone and azathioprine led to a favorable outcome, emphasizing the importance of prompt intervention to minimize morbidity and mortality.

Keywords: central nervous system; churg-strauss syndrome; intracerebral hemorrhage; vasculitis

INTRODUCTION

Churg-Strauss syndrome (CSS), also known as eosinophilic granulomatosis with polyangiitis (EGPA), is a rare systemic necrotizing small-vessel vasculitis. It is associated with asthma, peripheral

and tissue eosinophilia, and is classified among the antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), however ANCA is only observed in about one-third of cases, indicating that its presence is not consistent across all cases.[1–4] CSS is found across a broad age range, from 7 to 74 years old, with mean age of disease onset approximately around 50 years. The estimated incidence ranges from 0.11 to 2.66 new cases per million individuals annually, with a reported prevalence of 10.7 to 14 cases per million adults. There is currently no clear evidence to suggest a sex predominance.[3,4]

CSS often follows a rapid progressive course. The prodromal phase, characterized primary by a variety of allergic manifestations (usually sings of asthma with frequent dry wheezing and shortness of breath), may persist for several months to two decades preceding before the systemic vasculitis becomes more evident. The respiratory system, particularly the lungs, is typically the first and most commonly involved.[5] Neurological involvement is also a known feature of CSS, occurring in approximately 55% of all cases, with the peripheral nervous system (PNS) the most commonly affected (55%), while the central nervous system (CNS) and cranial nerve involvement are relatively rare, reported in about 5% and 3% of all patients, respectively. Among CNS manifestations, cerebral infarction and subarachnoid hemorrhage (SAH) are the most frequently observed events associated with CSS, and hemorrhagic lesions in CSS is extremely rare.[4] According to the Global Burden of Disease (GBD) data in 2019, there are over 3.4 million new cases of intracerebral hemorrhage (ICH) each year, with 23% of all ICH occurring in individuals aged 15 to 49 years.[6] However, reports of ICH associated with cerebral vasculitis due to CSS are very limited.

In this case report, we present the clinical course of a 26-year-old female diagnosed with multiple ICH secondary to cerebral vasculitis due to CSS, who presented with a chief complaint of headache, and a history of bronchial asthma along with allergic rhinitis. The

pathophysiology of CNS involvement in CSS remains poorly understood, emphasizing the importance of documenting such atypical presentation.

CASE REPORT

A 26-year-old woman presented at our emergency department with a chief complaint of headache persisting for five days before admission. The pain was initially localized on the posterior side of the neck and subsequently radiated to her entire head. The pain was described as a constant, aching headache, that progressively worsened with a Visual Analog Scale (VAS) score of 7–8 out of 10 on the day prior to hospitalization. The patient reported that the headache did not improve despite taking over-the-counter medications (paracetamol and ibuprofen) at home. The patient also experienced nausea, vomiting, low-grade fever, diffuse arthralgias, and photophobia. There were no episodes of altered consciousness, seizure, blurred vision phonophobia, and limb weakness or numbness. The patient had a previous history of well-controlled bronchial asthma and allergic rhinitis, managed with inhaled bronchodilators and antihistamines. There was no history of sinus or ear infections, recent upper respiratory tract infections, dental cavities, or other long-term conditions. Additionally, the patient denied having recently travelled or exposed to any infectious diseases, including tuberculosis.

On physical examination, the patient was alert with Glasgow Coma Scale (GCS) score of E4M6V5, though psychomotor slowing was noted. Vital signs revealed a subfebrile temperature of 37.8^{o}C, regular heart rate of 99 beats per minute, blood pressure of 110/80 mmHg, and normal oxygen saturation (SpO2) 99% on room air. Electrocardiogram (ECG) revealed normal heart rate. The patient appeared cachectic, with a weight of 43 kg and height of 160 cm, resulting a Body Mass Index (BMI) score of 16.8 kg/m^2. General and neurological assessment were otherwise unremarkable.

Laboratory investigations revealed leukocytosis with white blood cell (WBC) score of 16.91 x 10^3/µL, differential count shift to the left with marked eosinophilia (12%), elevated C-Reactive Protein (CRP) of 7.07 mg/dL, increased immunoglobulin E (IgE) score of 102 IU/mL, mild hyponatremia (130 mmol/L), mild hypochloraemia (93 mmol/L), and protein electrophoresis showed an acute inflammatory pattern. Further immunological and serological laboratory investigations, including

ANA/ENA profile, HBsAg (qualitative), anti-HCV total, anti-dsDNA, rheumatoid factor, C3 complement, C4 complement, ANCA (IF), lupus anticoagulant showed no abnormalities. Cytological analysis of cerebrospinal fluid (CSF) demonstrated eosinophilic pleocytosis, with a total cell count 485, of which eosinophils accounted for 30% of the 100-cell leucocyte differential count. Further CSF analysis for PCR herpes simplex virus (HSV)-1 and 2, varicella zoster virus (VZV), and PCR *Mycobacterium tuberculosis* were all found to be negative. The coagulation indexes were all within normal range. Magnetic Resonance Imaging (MRI) head with contrast before the treatment started revealed multiple cerebral hemorrhage with perifocal edema and partial sulcal enhancements bilaterally, along with mucosal thickening within the bilateral maxillary and ethmoid sinuses (Figure 1). Chest x-ray revealed normal findings and cardiovascular monitoring during the hospitalization confirmed a condition of well-controlled arterial pressure, no pathological cardiac events were recorded.

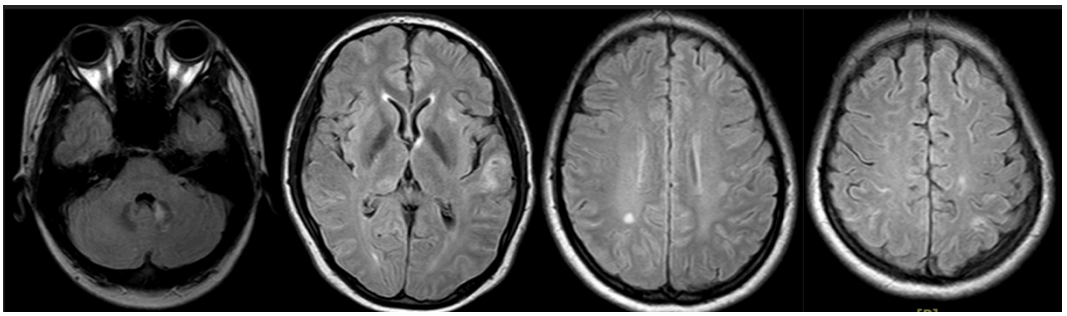

Figure 1. MRI head with contrast (FLAIR sequences) before the combined therapy was initiated. Multiple ICH and perifocal edema on the left side (periventricular IV), on the right side of cerebellum, and thalamus bilateral. Enhancement of the frontoparietotemporoocipital sulci bilaterally, partially seen with hemorrhagic components

The patient was diagnosed with multiple ICH due to CSS. High-dose intravenous corticosteroid therapy was initiated, with methylprednisolone 1,000 mg daily for five days, followed by tapered doses of oral corticosteroids. Subsequently, azathioprine (50 mg daily) and hydroxychloroquine (200 mg daily) were administered as an immunosuppressant and immunomodulatory agent, respectively. Serial contrast-enhanced brain MRI and follow up CSF analysis were performed to monitor the disease progression and treatment response. The follow up MRI revealed reduction in haemorrhage sizes

and resolution of the surrounding perifocal edema (Figure 2 and Figure 3). Correspondingly, CSF analysis demonstrated improving parameters, and the patient's clinical condition also showed marked improvement following the combined immunosuppressive and immunomodulatory therapy.

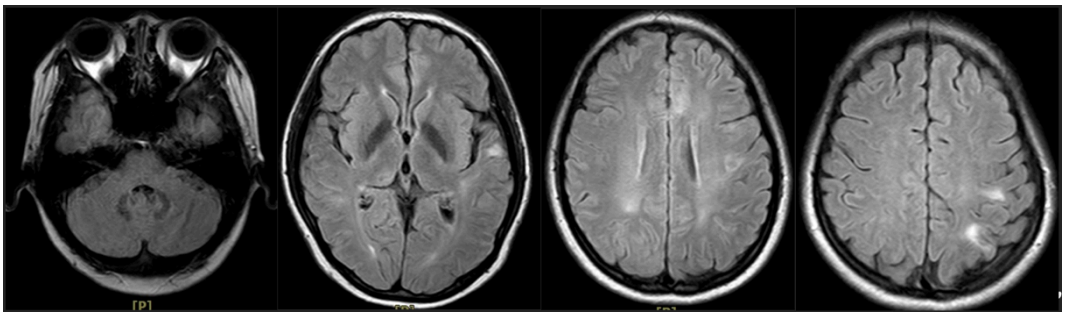

Figure 2. MRI head with contrast (FLAIR sequences) three weeks on immunosuppressive and immunomodulatory therapy. Chronic ICH are noted in bilateral thalamus, left cerebellum, bilateral parietal lobes (predominantly on the left side), and the left temporal lobe. No post-contrast enhancement. The appearance relatively unchanged since previous last examination. No perifocal edema is observed.

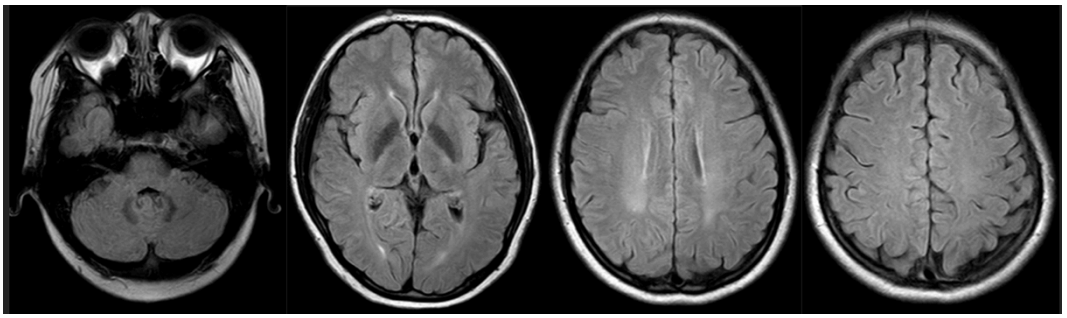

Figure 3. MRI head with contrast (FLAIR sequences) five months on immunosuppressive and immunomodulatory therapy. Mild chronic multiple ICH in the left cerebellum, bilateral thalamus, bilateral parietal lobes (predominantly on the left side), and left temporal lobe are no longer observed. No post-contrast enhancements. No perifocal edema.

DISCUSSION

CSS is a rare systemic disorder characterized by multi-organ vasculitic involvement, it is also regarded as an inflammatory-allergic lesion of small and medium vessels.(1) PNS involvement in CSS is relatively common, whereas CNS involvement is far less frequent. ICH associated with CSS is exceptionally rare, with only nine out of 39 cases reported from 1985 to 2024.[5] General symptoms often occur before the systemic manifestations become more evident. Patients typically present with constitutional signs such as fever, myalgias, arthralgias, and

significant weight loss with a mean weight loss 7.8 ± 4.7 kg. Asthma remains the hallmark feature of CSS, affecting 91% to100% of the patients, most often before systemic vasculitis occurs (mean interval: 9.3 ± 10.8 years).[2] Currently, there is no accepted diagnostic criteria for CSS, however there are a few diagnostic criteria that are used to diagnose this condition, such as Lanham criteria (Table 1) and American College of Rheumatology (ACR) criteria (Table 2).[7]

Table 1. The diagnostic criteria by Lanham *et al*.[7]

Criteria
Asthma
Peak peripheral blood eosinophil count >1.5 x 10^6/cc
Systemic vasculitis involving two or more extrapulmonary organs
All three criteria should be fulfilled for diagnosis of the disease

Table 2. The 1990 classification criteria of CSS by the American College of Rheumatology[7]. Patient had a total score of 4 out of 6 (underlined)

Criteria
Asthma
Eosinophilia >10%
Neuropathy, mono or poly
Pulmonary infiltrates, non-fixed
Paranasal sinus abnormalities
Extravascular eosinophils
For classification purpose, a patient shall be said to have the disease if at least 4 of these 6 criteria are positive

The ACR criteria (Table 2) remains the most widely used diagnostic criteria for CSS, with a sensitivity of 85% and specificity of 99.7%.[3] In our patient, four out of six criteria were met: history of asthma, eosinophilia >10%, paranasal sinus abnormalities, and the presence of extravascular eosinophils, findings that are consistent with a diagnosis of CSS. CSS can be classified into two subtypes: ANCA-positive and ANCA-negative. ANCA can be detected in 40% of patients with CSS. ANCA-positive patients are more likely to develop renal impairments, neuropathy, alveolar hemorrhage, and purulent vasculitis. In contrast, ANCA-negative patients more commonly exhibit cardiac, pulmonary, and gastrointestinal tract symptoms, and fever is more frequent. However, differentiating these two subtypes is impossible in many cases and there is no current evidence that these two subtypes may have a different outcome.[1,7,8] In our patient, serologic testing confirmed an ANCA-negative form of CSS. However,

only four out of seven reported incidences of CSS related cerebral hemorrhage from 1985 to 2008 were reported to have ANCA present, hence it can be inferred that ANCA detection is only partially helpful in identification of CSS associated cerebral bleeding.[9]

The clinical course of CSS is divided into three consecutive stages: prodromal stage, eosinophilic stage, and vasculitis. In prodromal stage, usually characterized by a variety of allergic manifestations, such as bronchial asthma, allergic rhinitis, and recurrent sinus infections. The eosinophilic stage is marked by the accumulation of eosinophils in various body tissues as the consequence of continuous hyperproduction of eosinophils (predominantly, the lungs, gastrointestinal tract, and the skin). The third phase is vasculitis, during which systemic necrotizing inflammation of small- and medium-sized vessels becomes apparent, often resulting in vascular complications. The risk of bleeding events is heightened in this phase due to vessel wall damage.[1,2] All three phases of the disease were apparent in our patient, in which our patient had gastrointestinal tract symptoms which were nausea and vomiting, prior history of allergic manifestations (bronchial asthma and allergic rhinitis), and an acute headache followed by a bleeding event (multiple ICH and perifocal edema on contrast-enhanced brain MRI). Hence, the diagnosis of CSS in our patient was made based on fulfilling the ACR criteria, consistent clinical symptoms, and laboratory findings.

The exact pathogenesis of CSS-related cerebral bleeding remains unclear. One proposed mechanism involves vascular injury and tissue damage caused by eosinophil-derived particulate matter and cytokines—eosinophil cationic protein and major basic protein (MBP)—as previously described in the eosinophilic stage of the disease. Additionally, immune dysregulation involving B and T lymphocytes interactions may also contribute to the disease progression. This supports the hypothesis that CSS symptoms may, in part, result from autoimmune mechanisms targeting various tissues[5] (Figure 4).

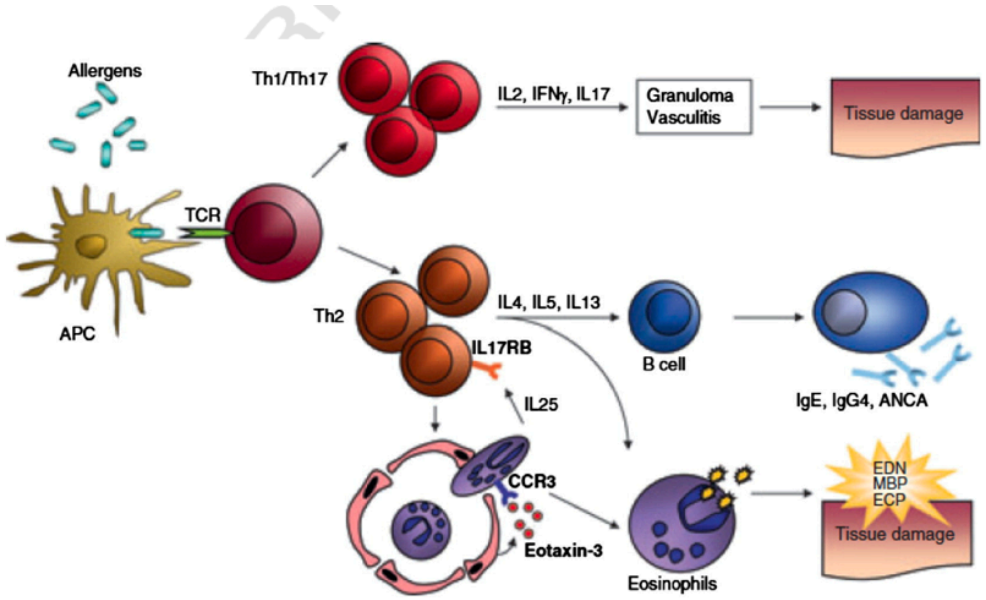

Figure 4. Pathogenesis of CSS[3]

Based on the reported cases of CSS complicated with cerebral hemorrhage by Pu Bai and Peitao Xie,[5] it was also found that the patients had a mean age of 34 years old and shared clinical features of sinus abnormalities, asthma, eosinophilia, and lung involvement. Based on the literature CSS-related ICH, revealed that ICH almost always preceded by prolonged asthma and atopic reactions—as seen in our case. The treatment includes a combination of glucocorticoid and immunosuppressant.

Corticosteroid therapy is viewed as the first line therapy for CSS, because it is sufficient to treat most CSS patients who do not have severe organ involvement (kidney damage, mononeuritis multiplex). The French Vasculitis Study Group has identified five prognostic factors, five-factor score (FFS) (Table 3), for patients with necrotizing vasculitis, including CSS.[7,8]

Table 3. The French Vasculitic Study Group, five prognostic factors (FFS)[7]. Patient FFS score = 0

Factor
Age >65 years
Presence of symptomatic cardiac insufficiency
Presence of severe gastrointestinal involvement (powel perforation, bleeding, and pancreatitis)
Presence of renal insufficiency (creatinine >150 µmol/L)
Absence of ear, nose, and throat symptoms

The patient's prognostic profile primarily determines the choice of initial therapy remains debated. In CSS patients without poor-prognosis factors (FFS = 0), clinical remission was achieved and maintained in 93% of patients with corticosteroid treatment alone, however 35% relapse, and eventually medium potent immunosuppressants such as azathioprine or methotrexate may also be used to limit relapses. In patients with poor prognosis (FFS $\geq$ 1), combining immunosuppressant with glucocorticoid is recommended. CSS is usually treated with prednisone 1–2 mg/kg per day for patients with mild disease and methylprednisolone 1,000 mg (15 mg/kg) for three days, then oral prednisone 1–2 mg/kg per day for patients with rapid disease progression and vital organ involvement.[5,8] Our patient had no poor prognosis factor (FFS = 0); however, our patient had a vital organ involvement (CNS involvement), hence she was treated with intravenous methylprednisolone 1,000 mg daily for five days, followed by tapered doses of oral corticosteroids, azathioprine 50 mg daily, and hydroxychloroquine 200 mg daily. Our patient demonstrated improved clinical, laboratory, and radiological findings after the treatment was initiated. This proves that prompt treatment is important as delayed diagnosis can lead to a fatal outcome. Adequate therapy ensures 5-year-surival rate for patients up to 75%.[8]

CONCLUSION

This case highlights that, although rare, ICH can be a presenting feature of CSS -associated vasculitis. Therefore, CSS should be considered as a differential diagnosis of unexplained ICH, particularly when accompanied with systemic features suggestive of CSS. A thorough evaluation of other systemic symptoms should be investigated after excluding other possible causes of ICH. Early diagnosis and prompt initiation of corticosteroids and immunosuppressive therapy are important to reduce both morbidity and mortality caused with this condition.

Given the potential risk of cerebral hemorrhage, particularly ICH in this case, intensive monitoring is warranted to

mitigate other additional risk factors—such as hypertension—that may predispose patients to further bleeding events. Diagnosis of CSS remains challenging and needs a comprehensive approach, integration of clinical signs, past history, laboratory findings, and additional methods of examinations. Ultimately, early recognition and appropriate treatment targeting both the inflammatory and autoimmune components of the disease using corticosteroids and immunosuppressive therapy, are essential to improving prognosis and induce remission of the disease.

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