CASE REPORT

Reversible Cerebral Vasoconstriction Syndrome Following Blood Transfusion in the Setting of Possible Rheumatoid-associated Vasculitis: A Case Report and Review of Literature

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ABSTRACT

Reversible cerebral vasoconstriction syndrome (RCVS) is an uncommon cerebrovascular disease with a rare association with blood transfusions. Cerebral vasculitis and RCVS often share many common features and can be difficult to distinguish in a conclusive manner. We report a 45-year-old woman who presented with RCVS in the setting of clinical and angiographic evidence of rheumatoid-associated cerebral vasculitis, 2 weeks following a blood transfusion. This case describes a potentially novel overlap syndrome which shares the features of rheumatoid-associated cerebral vasculitis as well as RCVS following blood transfusion.

Key words: Blood transfusion, reversible cerebral vasoconstriction syndrome, rheumatoid arthritis, thunderclap headache

INTRODUCTION

Reversible cerebral vasoconstriction syndrome (RCVS) is an infrequent cerebrovascular disease characterized by severe thunderclap headaches associated with segmental and multifocal cerebral arterial vasoconstriction. The pathophysiology of RCVS is not well understood; however, several inciting factors have been identified in literature including migraines, the postpartum state, and exposure to vasoactive substances such as certain illicit drugs.[1] The occurrence of RCVS following blood transfusions has only been rarely reported in literature.[2] On the other hand, cerebral vasculitis related to autoimmune conditions such as rheumatoid arthritis can share many of the clinical and angiographic findings related to RCVS. The distinction between these entities is clinically important since vasculitis often responds to immune modulation while RCVS may respond to calcium channel blockade. It is unclear, whether the segmental and multifocal stenosis seen in RCVS cases is a distinct clinical entity that can solely be attributed to vasospasm or whether vessel wall inflammation as is the case with vasculitis is a part of the RCVS pathophysiologic mechanism. We report a case of RCVS in a patient with clinical and angiographic evidence of rheumatoid-associated vasculitis shortly after receiving a blood transfusion. This case suggests that RCVS and vasculitis may, in fact, represent an overlap syndrome and/or fall along a clinical continuum rather than being part of distinct clinical entities. To the best of our knowledge, these findings have never been reported in literature.

CASE REPORT

A 45-year-old woman presented with a new-onset severe thunderclap headache with associated dizziness, photophobia, phonophobia, tunnel vision, nausea, and dry heaves. The patient reported an approximately 5-year history

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of seropositive rheumatoid arthritis which was briefly treated with methotrexate around the time of diagnosis. She states that methotrexate was discontinued after several months of treatment based on her request. She also has a history of migraine headaches since she was 15 years old together with longstanding anemia and hypertension. Her neurological examination was normal upon admission. Two weeks prior, the patient had received a blood transfusion for hemoglobin of 4.4 g/dl. Her laboratories upon admission were significant for an elevated total complement level at >60 U/ml and a hemoglobin of 8.1 g/dl. Her antinuclear antibody screen, HIV 1/2 antibody, HIV-1 p24 antigen, rapid plasma reagin, serum protein electrophoresis, and urine drug screen were all unremarkable.

A computerized tomography angiogram (CTA) showed multifocal and segmental narrowing of the vasculature in addition to chronic complete occlusion of bilateral middle cerebral arteries at their origin with reconstitution of the left M1 segment through prominent collateral vessels and mild diffusely attenuated appearance of the vasculature. A cerebral angiogram showed chronic bilateral M1 segment occlusions with middle cerebral artery (MCA) territory perfused predominately through leptomeningeal collaterals from anterior and posterior cerebral arteries and multifocal areas of irregular narrowing involving the anterior, middle, and posterior cerebral arteries [Figure 1].

Magnetic resonance imaging (MRI) of the cervical spine showed degenerative changes without significant central canal stenosis or foraminal narrowing. An MRI of the brain with and without gadolinium showed three acute-early subacute lacunar infarcts involving the high posterior left parietal region scattered increased subarachnoid fluid attenuation inversion recovery hyperintensity and enhancement secondary to prominent leptomeningeal collaterals related to bilateral chronic M1 segment occlusions [Figure 2].

The patient was started on nimodipine, 60 mg orally every 8 h with complete resolution of her headaches within the first 1–2 weeks post-treatment. A follow-up transcranial Doppler ultrasound 3 weeks post-treatment revealed a patent basilar artery with improved velocity when compared to initial transcranial Doppler ultrasound done 3 days post-onset of symptoms as well as patent bilateral posterior cerebral arteries with normal velocities. Bilateral middle and anterior cerebral arteries were not identified presumably due to lack of flow. The patient was scheduled for a follow-up CTA of the head but missed her appointment. Unfortunately, the patient was subsequently lost to follow-up.

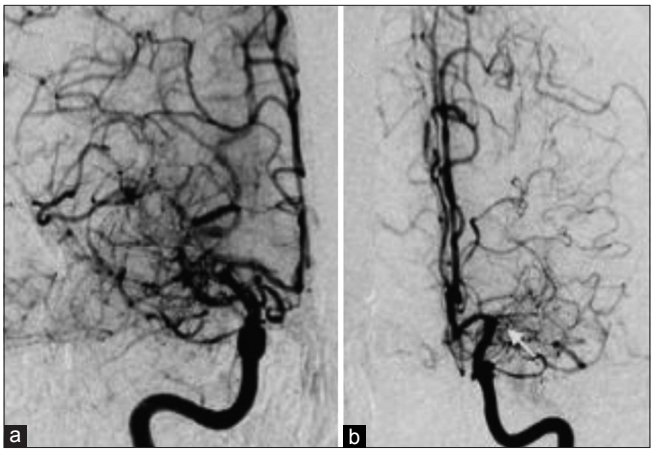

Figure 1: Digital subtraction angiography demonstrating chronic complete occlusion of bilateral middle cerebral arteries and prominent leptomeningeal collaterals. Note prominent leptomeningeal collaterals primarily from the anterior cerebral artery (a) and occlusion of the middle cerebral arteries (arrow, b)

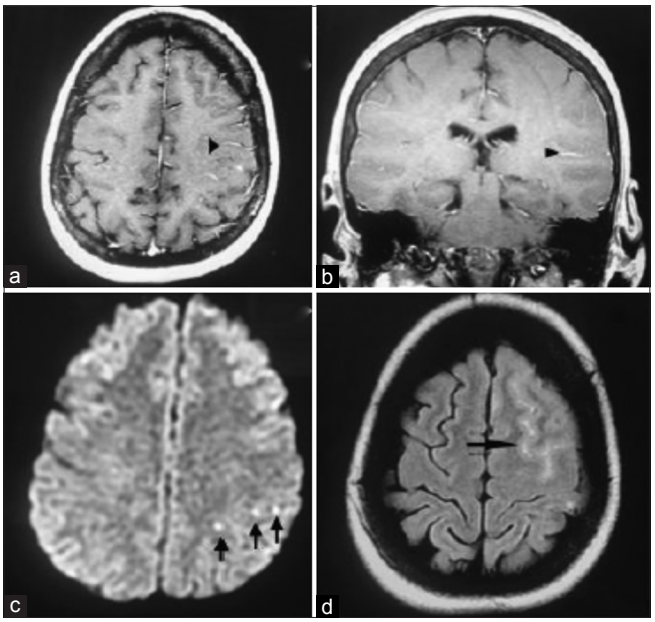

Figure 2: Magnetic resonance imaging of the brain demonstrating small infarctions and prominent leptomeningeal collaterals. Gadolinium-DTPA-enhanced T1 images (axial, a and coronal b) and axial fluid attenuation inversion recovery (large arrow in d) demonstrating pial enhancement (arrowheads in a and b) consistent with previously demonstrated leptomeningeal collaterals on angiography. The diffusion-weighted image in c (small arrows) demonstrates three small acute-early subacute infarcts in the right high parietal region

DISCUSSION

We report a case of RCVS following blood transfusion in a patient with long-standing seropositive rheumatoid arthritis and angiographic evidence of chronic bilateral MCA multifocal occlusions consistent with prior longstanding vasculitis. To the best of our knowledge, this association has never been described before, which in our view may shed important light on the pathomechanisms underlying both

RCVS and cerebral vasculitis. The relationship between vasculitis and RCVS has been the subject of ongoing debate;[3,4] in many cases, it is difficult to distinguish RCVS from cerebral vasculitis as both entities often share many of the clinical and angiographic features. For example, a study analyzing a French cohort found that patients with RCVS were predominantly female, with a history of migraines, more often exposed to vasoactive substances, postpartum, and with abnormal CT or MRI scans in only 31% of cases. On the other hand, primary angiitis of the central nervous system was associated with a much higher frequency of acute ischemic stroke and with an abnormal CT and MRI scan in all patients.[4] It is unclear what specific angiographic features definitively constitute vasculitis versus RCVS. Researchers have previously relied on lack of vessel enhancement as a feature supporting the diagnosis of RCVS and the presence of vessel enhancement as a reflection of vessel inflammation and, therefore, vasculitis.[5] However, other studies have shown that both acute and persistent wall inflammation can also be seen in half of RCVS patients and, therefore, cannot be relied on as a distinguishing feature.[6] To the best of our knowledge, a causative link between RCVS and rheumatoid arthritis has never been established. On the other hand, a recent study reported RCVS in a patient with lupus. This patient had clinical and radiological deterioration with high-dose steroids based on the assumption that clinical and radiographic findings were consistent with a lupus-associated vasculitis. Interestingly, this patient recovered after 2 weeks of nimodipine treatment similar to the patient reported in our study.[7] In our patient, the history of seropositive rheumatoid arthritis, the elevated total complement, and the presence of chronic proximal MCA occlusions support the presence of long-standing rheumatoid-associated vasculitis. On the other hand, the presence of acute-onset thunderclap headaches as well as satisfying the international classification of headache disorders, 3rd edition RCVS criteria as well as the complete clinical response to nimodipine would all support the presence of superimposed RCVS in our patient.

Recent blood transfusion before RCVS has been shown in some case reports.[8] In a case study of seven patients with RCVS following blood transfusions performed by Liang *et al*., six out of seven patients experienced various symptoms including blurred vision, dysarthria, hemiplegia, and generalized tonic-clonic seizures as well as thunderclap headaches.[2] It is important to quickly recognize the key characteristics and risk factors that differentiate RCVS from similar diseases due to the variation in treatments. For example, vasculitis is commonly treated with corticosteroids, a treatment that has been associated with worse outcomes if used in the setting of RCVS.[1] In our patient, cerebral angiography demonstrated chronic bilateral MCA occlusion as well as multifocal and segmental narrowing of the vasculature. The tapered and complete occlusion of the middle cerebral arteries, the rich leptomeningeal collaterals, and the shift in the watershed zone as well as lack of a large MCA stroke strongly suggested pre-existing chronic MCA occlusions. Based on the angiographic appearance, a diagnosis of vasculitis was entertained. However, our patient met all criteria for RCVS as outlined in the international classification of headache disorders, 3rd edition.[9] It is conceivable that further vasospasm related to RCVS resulted in the small areas of infarction noted in our patient and the development of thunderclap headaches.

The pathophysiology of RCVS is not well understood; however, given the reversibility of the cerebral vasoconstriction, it is considered a disease involving impaired control of cerebrovascular tone.[10] Whether blood transfusions result in a further impairment of cerebrovascular tone is unclear. A recent study suggested that RCVS may be linked to baroreflex failure in patients who have undergone resection for carotid body tumors.[11] Since the carotid sinus and carotid body are involved in blood pressure and oxygen sensing and resultant control of vascular tone, it is conceivable that the sudden changes in blood oxygen-carrying capacity following blood transfusions may result in further impairment of cerebrovascular tone mechanisms. Interestingly, dysregulation of vascular control mechanisms may even extend beyond the central nervous system in patients with a history of migraines. We have previously reported status migrainosus as a potential stressor for takotsubo cardiomyopathy, a condition which can be associated with vasoconstriction of the coronary microcirculation.[12] A study from the Cleveland Clinic by John *et al*. more recently suggested that RCVS may also result in coronary vasoconstriction, leading to cardiomyopathy.[13] The combination of an underlying vasculopathy presumably related to a rheumatoid associated vasculitis as well as the blood transfusion may have resulted in a "double hit," leading to RCVS in our patient.

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CONCLUSION

We present a case of reversible cerebral vasoconstriction syndrome in a patient with a possible rheumatoid-associated vasculitis following blood transfusion. This report presents evidence suggesting that RCVS and vasculitis are in fact an overlap syndrome rather than distinct clinical entities as has been previously thought. Further we show that blood transfusion is a potential precipitating factor for RCVS in this setting. Clinicians should be aware of this overlap syndrome given that successful choice of treatment can be highly dependent on understanding the patho-mechanisms of this disease.

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