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# Rituximab for prevention of strokes in cerebral rheumatoid vasculitis

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Case report

# Rituximab for prevention of strokes in cerebral rheumatoid vasculitis

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ABSTRACT

Rheumatoid arthritis (RA) is an autoimmune disorder which manifests as inflammation of the synovial joints alongside extra-articular involvement. Uncommonly, patients may develop vasculitis of small and medium-sized blood vessels, formally diagnosed as systemic rheumatoid vasculitis (SRV). In particularly rare cases, patients may develop a subtype of SRV known as cerebral rheumatoid vasculitis (CRV) which manifests in patients as stroke. To date, no formal recommendations or guidelines have been established for treatment and prevention of CRV-induced stroke besides experiential therapy with various immunomodulators. Here, we describe the utility of Rituximab in addition to steroids for prevention of stroke in our patient with evidence of multiple CRV-induced strokes with excellent recovery of post-stroke symptoms and remission of new onset cerebral vasculitis processes.

## 1. Introduction

Rheumatoid arthritis (RA) is an autoimmune disorder which manifests as inflammation of the synovial joints alongside extra-articular involvement [1]. Presently, no pathognomonic laboratory test is available for diagnosis of RA, however the utility of anti-citrullinated protein antibodies (ACPA) is increasingly used in developing a diagnosis with concomitant clinical symptoms of arthritis, known as seropositive RA. Approximately 75–85% of patients with RA will test positive for rheumatoid factor (RF), ACPA, or both [1]. Diagnosis is presently in accordance with the 2010 American College of Rheumatology and the European League Against Rheumatism (ACR/EULAR) criteria which assesses for the number and site of involved joints, serological testing for RF and ACPA, presence of acute phase reactants, and symptom duration of at least 6 weeks [1]. Arthritis is most common in smaller joints of the hands but may present in the cervical spine as well.

Vasculitis of small and medium-sized blood vessels may manifest as a symptom of RA in rare instances of approximately 1–5%. In such cases, patients with rheumatoid vasculitis (RV) typically exhibit mononeuritis multiplex or asymmetric polyneuropathy secondary to a vasculitis process [2]. Moreover, patients with RA are at increased risk of venous thromboembolic diseases secondary to chronic inflammatory states [3]. Cerebral RV (CRV) is a particularly rare complication of RA for which no formal recommendations have been established for primary prevention and treatment.

Here, we present the case of a young female patient with a history of rheumatoid arthritis complicated by CRV managed successfully with dual steroid and rituximab therapy for primary CVA prevention.

## 2. Case report

Our patient was a 44-year-old African American female who presented to our clinic with clinical symptoms of rheumatoid arthritis complicated by medication non-adherence, an atypical presentation of disease course and recent onset of multiple strokes.

Patient began exhibiting pain in the metacarpophalangeal and proximal interphalangeal joints from the age of 30 without nodular formation. Initial laboratory testing demonstrated elevated CCP and RF as well as elevated inflammatory markers, ESR and CRP. Interestingly, radiographic evidence of RA in joints was absent with findings only of calcific/osseous density in the wrists suggestive of prior mechanical injury. CT spine was remarkable only for mild central disc protrusion at C3-C4 without radiculopathy. Patient scored a 6 according to the 2010 RA classification criteria, meeting the cut-off diagnosis of RA.

Patient had trialed various immune modulator therapies for RA with minimal efficacy or poor adherence tolerance, including methotrexate, etanercept, infliximab, tofacitinib, and adalimumab. Patient began a regimen with methotrexate 5 mg daily and leflunomide 10 mg daily for one year before onset of asymmetric right-sided moderate-severe sensorineural hearing loss, imbalance and incoordination. She had poor

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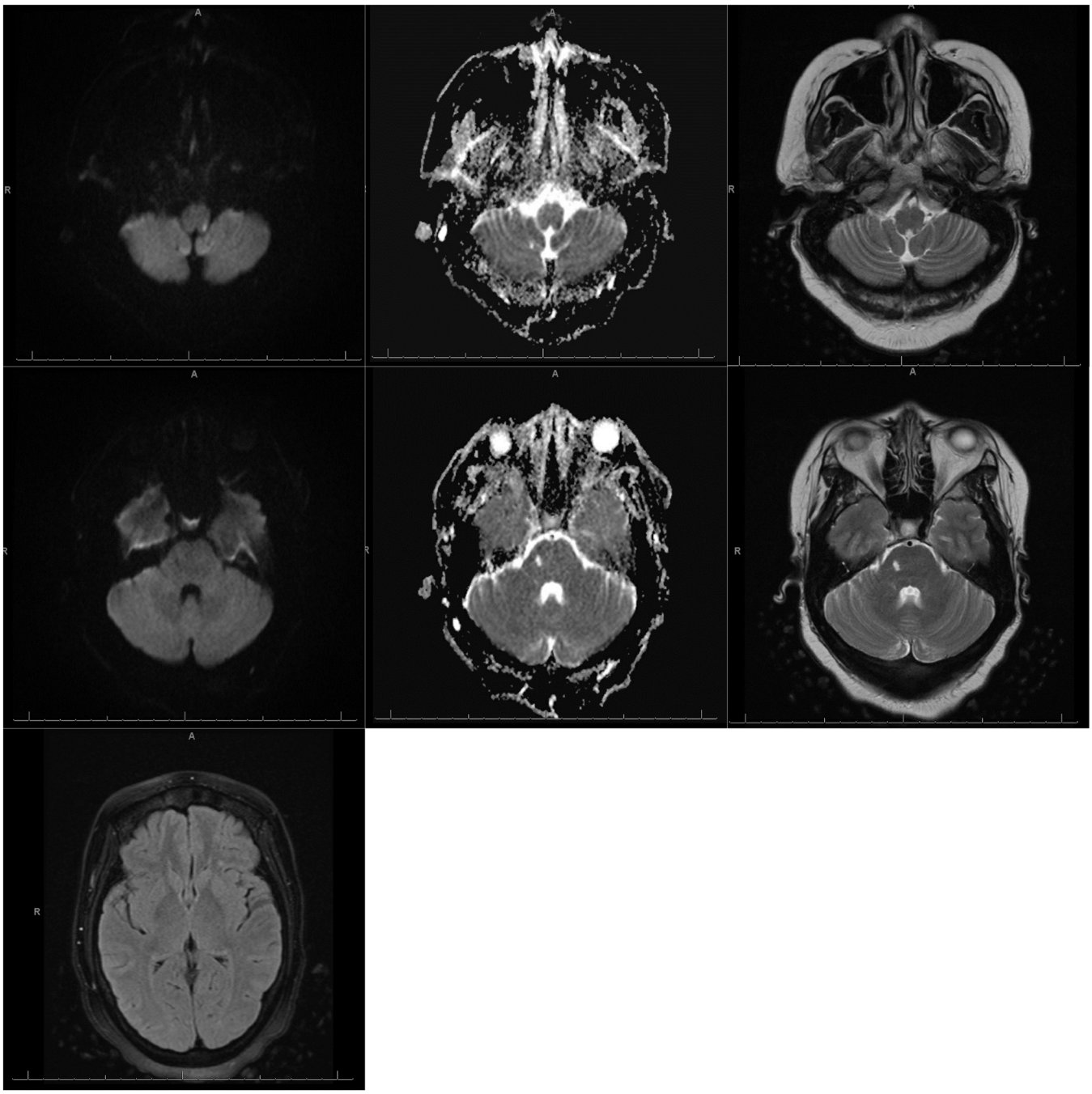

**Fig. 1.** MRI brain on initial presentation with lateral medullary syndrome. *Top Row; Left to Right:* DWI, ADC, and T2 demonstrating acute infarction of the left postero-lateral medulla. *Middle Row; Left to Right:* DWI, ADC, and T2 demonstrating chronic infarction of right lateral pontine. *Bottom Row:* Hyper-intense and non-specific foci in the right parietal and left frontal lobes on T2 FLAIR suggestive of subacute infarctions.

follow-up and presented 6 months later with similar symptoms and dizziness, left-leaning predominance, and feelings of disequilibrium in addition to subjective decreased sensation of the left side of the face and left upper and lower extremities. Her National Institutes of Health Stroke Scale (NIHSS) score was 3 on presentation. CT head without contrast demonstrated a chronic right middle cerebellar peduncle infarct. CT angiogram found no evidence of proximal large vessel occlusion. MRI brain demonstrated an acute infarct in the left inferior cerebellar peduncle and restiform body, with an old right pontine infarct (Fig. 1). MRA head with contrast demonstrated arterial stenosis involving the posterior cerebral arteries bilaterally and left proximal M2 branches of the MCA with linear enhancement of the walls of the superficial temporal arteries bilaterally. MRA neck further demonstrated findings of a hypoplastic left vertebral artery. Laboratory assessment including ANA, C-ANCA, ENA, anti-Smith, RNP, dsDNA, C3 and C4, and cardiolipin were unremarkable. Lumbar puncture was remarkable for elevated protein and WBC count. CT angiogram of the chest, abdomen and pelvis demonstrated no findings suggestive of vasculitis. Patient was initiated on rituximab monthly infusions, atorvastatin 80 mg daily, aspirin 81 mg daily, clopidogrel 75 mg daily, and prednisone 60 mg daily.

Patient presented 4 months later for a repeat CVA involving an acute infarction of the left basal ganglia and left temporal lobe. Repeat LP demonstrated significant reduction in the lymphocytic pleocytosis, and

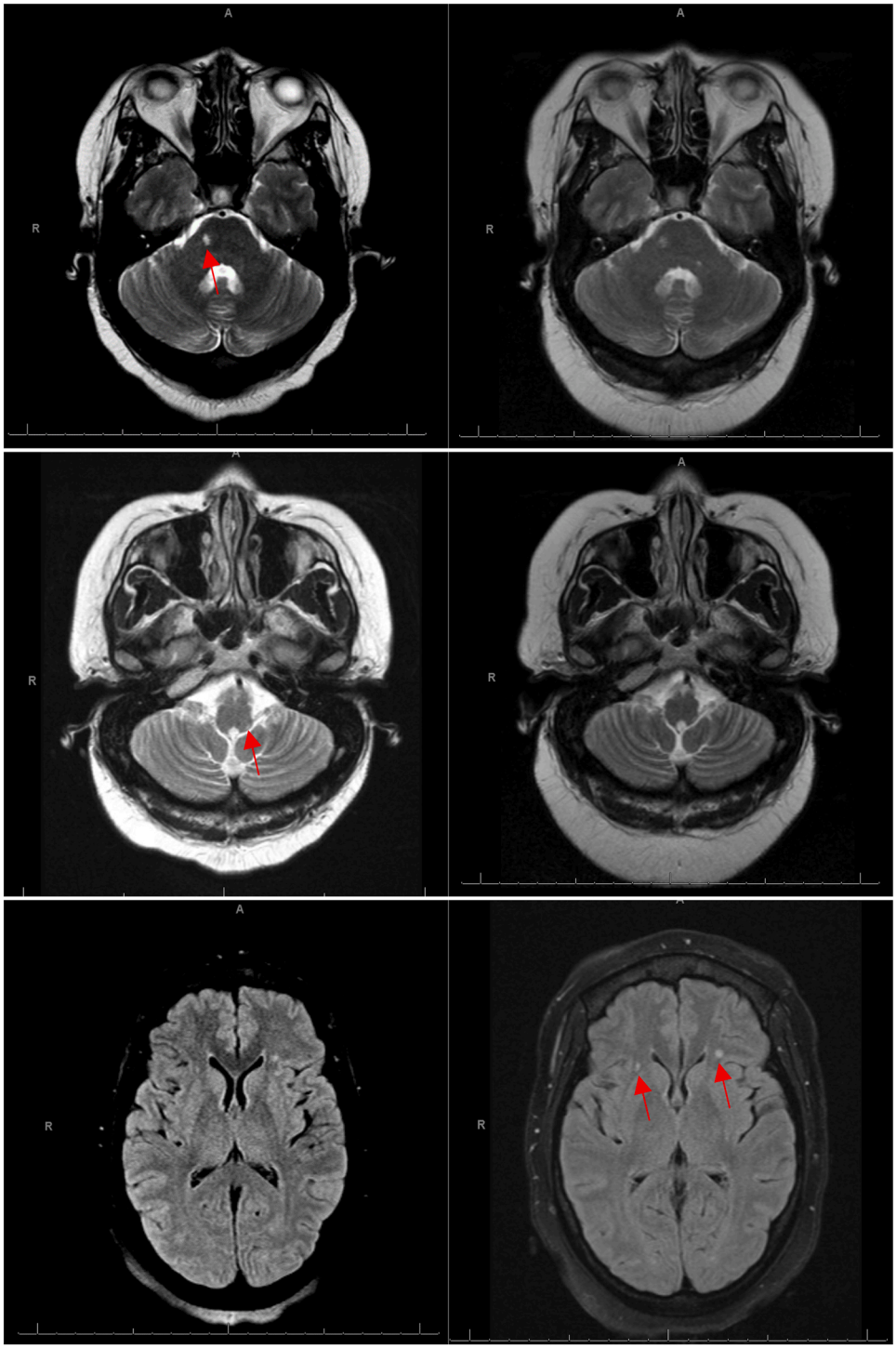

**Fig. 2.** Follow-up MRI brain at 4 and 7-month intervals. *Top; Left to Right:* Axial T2 sequence demonstrating minimal encephalomalacia interval changes at 4 and 7-months, respectively, from initial right pontine stroke. *Middle; Left to Right:* Axial T2 sequence demonstrating minimal encephalomalacia interval changes at 4 and 7-months, respectively, from initial left posterolateral medullary stroke. *Bottom; Left to Right:* Axial T2 FLAIR sequence demonstrating minimal evolution at 4 and 7-months, respectively, of initial incidental non-specific subacute infarctions of right parietal and left frontal lobes.

no evidence of neoplasia on cytology. Carotid duplex demonstrated no evidence of temporal arteritis or stenosis of CCA and ICA. Patient was instructed to continue medical regimen with rituximab infusions and prednisone 40 mg daily. Repeat MRI one month and three months post-CVA demonstrated partial normalization of most recent and prior CVA, improvement in intracranial vascular multifocal stenosis, mild chronic ischemic changes, and no evidence of new ischemic events (Fig. 2).

## 3. Conclusion

To date, only 27 known reported cases of CRV have been reported in literature with variability in patient presentation ranging from involvement of white matter cortical structures to subcortical involvement of the basal ganglia and brainstem [3]. In all cases, patient prognosis was poor with high mortality but significantly improved with the addition of an immunosuppressive therapy to a steroid regimen. Choice of immunosuppressive therapy included methotrexate, cyclophosphamide, or azathioprine, lending to the recommendation of dual therapy with steroid and immunosuppressive therapy for improved outcomes [3].

In our patient, given the relatively indolent course, a blind brain biopsy without leptomeningeal involvement was considered to be less

likely diagnostic, and would not change the clinical management with rituximab that the patient was already on. We agreed with the patient that we would proceed with a biopsy and consider cyclophosphamide, if she had further clinical events. Our patient did demonstrate evolution of her initial stroke on repeat MRI but in fact had excellent recovery of most clinical symptoms in both instances, including motor strength, sensation, and balance, with no change to her right-sided hearing deficits. Additionally, imaging studies since have demonstrated no new vasculitic involvement.

Currently, no consensus has been made on the appropriate therapeutic regimen for patients with rheumatoid cerebral vasculitis. Moreover, no randomized clinical trials exist comparing treatment options for CRV and systemic RV (SRV). The therapeutic regimen is often based on the severity and extent of the disease. In patients with CRV, steroid therapy alone has been associated with increased mortality rate while patients on combined therapy, such as steroids and cyclophosphamide, has shown improved outcomes [3]. In both CRV and severe SRV, therapeutic recommendations often include high-dose glucocorticoids in addition to either cyclophosphamide or a biological agent such as rituximab. There are currently no trials comparing outcomes and efficacy of cyclophosphamide to rituximab in patients with RV. Rituximab has been shown to be non-inferior to cyclophosphamide in severe anti-neutrophilic cytoplasmic antibody (ANCA)-associated vasculitis in one randomized clinical trial [4]. Moreover, a study by Puechal et al. has demonstrated the efficacy of rituximab for management of SRV with complete remission in 75% of the enrolled patients and a significant decrease in the required prednisone dosing [5]. On the basis of previous literature and this current report, rituximab may be considered for patients with CRV and a relatively indolent course as an efficacious option for prevention of vasculitis-mediated stroke.

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