EJR European Journal of Rheumatology

DOI: 10.5152/eurjrheum.2021.20071

Case-based Review

Central nervous system vasculitis in a patient with axial spondyloarthritis treated with infliximab: A case report and literature review

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Abstract

Central nervous system (CNS) vasculitis is a rare form of vasculitis involving the blood vessels of the brain. It may be primary when it is confined to the CNS or secondary in the context of systemic inflammatory conditions such as systemic lupus erythematosus, rheumatoid arthritis, or infections. However, there is no known association with axial spondyloarthritis. Herein, we present the case of a 37-year-old man, with axial spondyloarthritis treated with infliximab for 9 years, who presented with persistent fevers, elevated inflammation markers, lateral medullary syndrome, and right-sided hemiparesis. Magnetic resonance imaging of the brain demonstrated multiple cerebral infarcts. Examination of cerebrospinal fluid showed mild lymphocytic pleocytosis and protein elevation. Digital subtraction angiography and transcranial ultrasonography of the cerebral blood vessels revealed luminal narrowing of the basilar and the left posterior cerebral artery. The diagnosis of CNS vasculitis was made and intravenous methylprednisolone and cyclophosphamide pulses were administered, leading to fever remission with gradual improvement and resolution of the neurological manifestations.

Keywords: Spondyloarthritis, central nervous system vasculitis, lateral medullary syndrome

Introduction

Central nervous system (CNS) vasculitis is a rare form of vasculitis which affects the blood vessels of the brain. It usually involves small and medium-sized vessels and it may be primary when it is restricted to the CNS or secondary related to systemic inflammatory diseases or infections. Systemic inflammatory conditions associated with CNS vasculitis include systemic vasculitides, systemic lupus erythematosus, and sarcoidosis. Rheumatoid arthritis may also be complicated with vasculitis affecting the CNS. Treatment of CNS vasculitis secondary to systemic inflammatory diseases involves aggressive immunosuppression with combination of steroids and cyclophophamide or rituximab.[1]

We present the case of a patient with axial spondyloarthritis (SpA) treated by infliximab for 9 years who presented CNS vasculitis. While CNS vasculitis has been associated with systemic inflammatory diseases,[1] there is no known association so far with spondyloarthritis.

Case Presentation

A 37-year-old man presented with 10 days of malaise associated with a fever of 38.9°C. He had a past medical history of axial spondyloarthritis for 10 years, which had initially been presented with fatigue, morning stiffness, inflammatory low back pain, neck pain, restriction of movement of the cervical spine, and diffuse arthralgias and myalgias. Imaging of the cervical spine had shown osteophytes and that of sacroiliac joints revealed erosions and sclerosis. The axial spondyloarthritis had been treated with infliximab for 9 years. The patient had a positive tuberculin skin test, with normal chest x-ray, and had received prophylactic treatment with isoniazid for 9 months before initiation of treatment with infliximab. At the time of presentation of malaise and fever, axial spondyloarthritis was in remission. Last infusion of infliximab was administered 1 month before presentation. Physical examination of the patient was unrevealing.

Initial laboratory tests showed a C-reactive protein (CRP) of 8.4mg/L (0-7mg/L) and an erythrocyte sedimentation rate of 52 mm. Blood and urine cultures were negative. An extensive workup with imaging studies, including chest x-ray, abdominal ultrasound, brain, chest, and abdominal computed tomography (CT) scan, did not reveal any focus of infection or malignancy. Transthoracic and transesophageal echocardiography

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Cite this article as: Panagopoulos P, Katsifis G. Central nervous system vasculitis in a patient with axial spondyloarthritis treated with infliximab: A case report and literature review. *Eur J Rheumatol.* 2021;8(4):228-231.

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Submitted: May 15, 2020
Accepted: December 10, 2020
Available Online Date: September 16, 2021

were negative for endocarditis. Serology tests for Epstein-Barr virus, cytomegalovirus, hepatitis A virus, hepatitis B virus, hepatitis C virus, and human immunodeficiency virus were also negative, as well as serology for Brucella, Salmonella, Bartonella, Borrelia burgdorferi, Rickettsia, Toxoplasma, and Leishmania. Microscopic examination of blood smear and bone marrow aspirate yielded no pathologic results. Immunological workup was negative for antinuclear antibodies (ANA), antidouble stranded deoxyribonucleic acid (antidsDNA) antibodies, rheumatoid factor (RF), antimitochondrial antibodies, antismooth muscle antibodies, and perinuclear and cytoplasmic antineutrophil cytoplasmic antibodies (p-ANCA, c-ANCA). Endoscopic evaluation of the gastrointestinal tract was also negative.

Interferon-gamma release assay for tuberculosis infection was positive. Sputum, bone marrow, and gastric lavage specimens were collected, but acid-fast bacilli microscopy, nucleic acid amplification tests, and mycobacterial cultures were negative for *M. tuberculosis* or nontuberculous mycobacteria. Because of the concern of tuberculosis, empiric therapy with isoniazid, rifampin, pyrazinamide, and ethambutol was initiated. Despite treatment, fevers and the elevated inflammatory markers persisted.

Since extensive laboratory workup and imaging studies ruled out infectious and neoplastic causes of the prolonged fever, a systemic inflammatory condition was suspected. A decision was made to start an empiric trial of methylprednisolone 24 mg daily. The fever and the inflammatory markers remitted and the patient was discharged.

Main Points

- Vasculitis is not a common manifestation of spondyloarthritis, but there are case reports of patients with spondyloarthritis who developed different forms of vasculitis, mainly involving large vessels.
- Central nervous system (CNS) vasculitis may be primary or secondary to various systemic inflammatory and autoimmune disorders. However, there is no known association of spondyloarthritis with CNS vasculitis.
- We present a case of a 37-year-old man, with axial spondyloarthritis treated with infliximab, who developed CNS vasculitis and treated successfully with methylprednisolone and cyclophosphamide pulses.

Fifteen days after discharge, the patient presented with weakness of the right upper and lower limb, dysarthria, hoarseness, ptosis of the left upper eyelid, numbness of right upper and lower limb, vertigo, and difficulty in maintaining balance and walking. Physical examination revealed right-sided hemiparesis, hypesthesia of right upper and lower limb, dysmetria of left upper limb, nystagmus, and inability to swallow solid or liquid food. A brain CT scan was negative for intracranial hemorrhage. Based on the high likelihood of an ischemic stroke, intravenous thrombolytic therapy was administered and then oral antiplatelet therapy with aspirin and anticoagulation with low-molecular-weight heparin were initiated. The next day after fibrinolysis, magnetic resonance imaging (MRI) of the brain demonstrated lesions with high signal intensity on diffusion-weighted imaging in the left lateral part of the medulla oblongata in the brainstem and in the posterior limb of the left internal capsule, findings compatible with ischemic strokes (Figure 1). During the hospitalization course fevers and elevated CRP, persisted and the neurological manifestations gradually deteriorated. Repeated cultures and chest and abdominal CT scans were unrevealing. A second MRI of the brain showed multiple, new infarcts in the genu of the internal capsule bilaterally, in front of the right caudate nucleus and periventricularly, laterally to the left lateral ventricle (Figure 2), while magnetic resonance angiography did not yield any abnormal findings. Investigations for a source of embolization with electrocardiography, continuous cardiac monitoring, echocardiography and ultrasonography of carotids were negative. Screening for antiphospholipid syndrome (lupus anticoagulant, anticardiolipine antibodies, antibodies against β2-glycoprotein 1) was also negative. CNS vasculitis was thus suspected as a cause for the multiple cerebral infarcts. Examination of the cerebrospinal fluid (CSF) demonstrated mild lymphocytic pleocytosis (65 white blood cells per μL, 75% lymphocytes) and mild protein elevation of 80 mg/dL, (15-50mg/dl), while CSF culture was negative. Intra-arterial digital subtraction angiography (ie, DSA) and transcranial color Doppler ultrasonography of the cerebral blood vessels demonstrated luminal narrowing of the basilar and the left posterior cerebral artery.

The multiple cerebral infarcts, CSF, and cerebral angiography findings and elevated inflammatory markers led to the diagnosis of CNS vasculitis.

Ultrasonography of the temporal, axillary, and carotid arteries was negative for vasculitic findings and chest and abdominal CT scan had not demonstrated signs of large vessel inflammation. Repeated immunological investigations for ANA, RF, p-ANCA, c-ANCA, and cryoglobulins were also negative.

High-dose intravenous methylprednisolone pulses of 500 mg were administered for five consecutive days followed with oral methylprednisolone 32 mg/day. In addition, cyclophosphamide pulses of 1 g every 4 weeks were initiated. The treatment led to the immediate remission of fever and gradual improvement of the neurologic manifestations and inflammation markers. Subsequent physical and speech-language therapy helped to the gradual improvement and restoration of muscle strength, speech and swallowing. After one month, the patient was once again able to walk and eat and after three months he had fully recovered his strength. A brain MRI two months after discharge demonstrated significant improvement, with complete resolution of the infarcts in the medulla oblongata, the genu of the internal capsule bilaterally and periventricularly (Figure 3).

Discussion

In this article, we present a patient case with axial spondyloarthritis on infliximab who

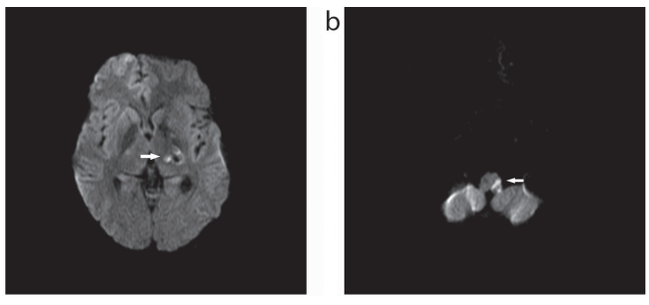

Figure 1. a,b. (a) Axial diffusion-weighted MRI scan on the second admission of the patient showing lesion with high signal intensity in the posterior limb of the left internal capsule (arrow), (b) A second lesion is depicted in the left lateral part of the medulla oblongata in the brainstem (arrow).

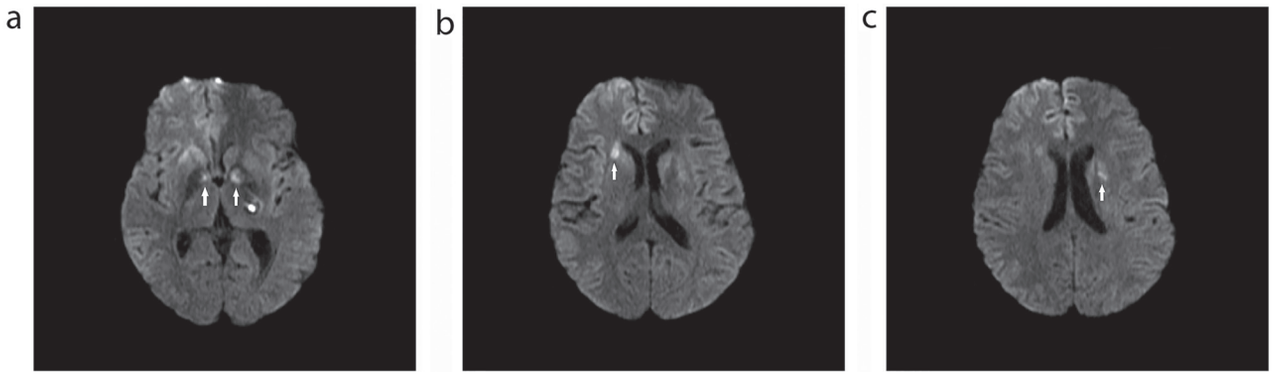

Figure 2. a-c. (a) Axial diffusion-weighted MRI scan 2 weeks after second admission, showing two new lesions with high signal intensity in the genu of the internal capsule bilaterally (arrows), (b) A third lesion is depicted in front of the right caudate nucleus (arrow), (c) Another new lesion is depicted periventricularly, laterally to the left lateral ventricle (arrow).

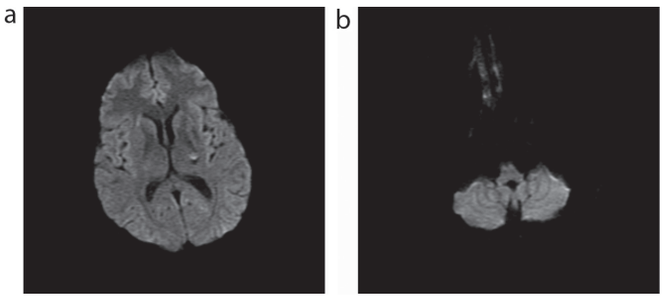

Figure 3. a,b. (a) Axial diffusion-weighted MRI scan 2 months after second discharge, showing resolution of the lesions periventricularly, while a small lesion with high signal intensity remains in the posterior limb of the left internal capsule, (b) The lesion in the medulla oblongata in the brainstem has resolved completely.

developed CNS vasculitis. Autoimmune diseases associated with CNS vasculitis include systemic vasculitides—such as granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, polyarteritis nodosa, and Behçet's disease—systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis, inflammatory bowel diseases, and sarcoidosis.[1] Reviewing the literature, we did not find any prior report of an association between spondyloarthritis and CNS vasculitis of small and medium vessels. There are only a few cases of spondyloarthritis patients and large vessel vasculitis.[2-5] In addition, there are case reports of spondyloarthritis patients who developed small vessel vasculitis without CNS involvement. John et al.[6] reported a 26-year-old man with HLA-B27-positive axial spondyloarthritis who developed IgA vasculitis, while Urrea-Pineda et al.[7] described a 47-year-old man with psoriatic arthritis who presented cryoglobulinemic vasculitis.

Central nervous system vasculitis has been reported mostly in seropositive rheumatoid arthritis patients with long-standing disease, rheumatoid nodules, and extra-articular manifestations.[8,9]

On the other hand, presentation of vasculitis in patients treated with tumor necrosis factor alpha (TNF-α) inhibitors has been described. In these patients, skin was the organ affected most frequently, with purpura being the most common manifestation, while CNS involvement was rare. Mean duration of TNF inhibitor (TNFi) treatment before vasculitis presentation was 9-34 months.[10-12] Ramos-Casals et al.[10] studied the Spanish registry of patients with systemic autoimmune diseases treated by biologic agents, reviewed the literature and described 133 patients who developed skin vasculitis and 49 of them had positive autoantibodies—ANA, ANCA, cryoglobulins, antidsDNA, and antiphospholipid antibodies. CNS was affected in five patients, but the nature of CNS involvement was not analyzed.[10]

Our patient was on infliximab for 9 years before the presentation of CNS vasculitis. Thus, it seems unlikely that infliximab treatment was responsible for the appearance of CNS vasculitis, since TNFi associated vasculitis tends to develop during the first years of treatment, while CNS involvement is rare. In addition, no definitive association of small and medium vessel CNS vasculitis with spondyloarthritis is reported. Our patient developed small and medium vessel vasculitis with multiple small infarcts and luminal narrowing of the basilar and the left posterior cerebral artery, while the axial spondyloarthritis was in remission. Thus, we believe that the coexistence of spondyloarthritis and vasculitis in our patient may be coincidental. We stopped infliximab and initiated treatment with high-dose methylprednisolone pulses and cyclophosphamide. Treatment resulted in CNS vasculitis remission, fever resolution, and improvement of neurological manifestations.

Informed Consent: Informed consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - P.P., G.K.; Design - P.P., G.K.; Supervision - P.P., G.K.; Materials - P.P., G.K.; Data Collection and/or Processing - P.P., G.K.; Analysis and/or Interpretation - P.P., G.K.; Literature Search - P.P.; Writing Manuscript - P.P., G.K.; Critical Review - G.K.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Dutra LA, de Souza AW, Grinberg-Dias G, Barsottini OG, Appenzeller S. Central nervous system vasculitis in adults: An update. *Autoimmun Rev*. 2017;16:123-131. [Crossref]
2. Corli J, Lemeunier L, Le Gouellec N, Flipo RM. Giant cell arteritis occurring during psoriatic arthritis treated by adalimumab. *Joint Bone Spine*. 2015;82:291-292. [Crossref]
3. Garcia-Cezon de la Cruz MDP, Almodovar R, Garcia Perez J, Dhimes PF, Zarco P. Aortitis due to giant cell arteritis and psoriatic arthritis: An uncommon association. *Reumatol Clin*. 2017;13:230-232. [Crossref]

4. Rotar Z, Tomsic M, Hocevar A. Secukinumab for the maintenance of glucocorticoid-free remission in a patient with giant cell arteritis and psoriatic arthritis. *Rheumatology (Oxford)*. 2018;57:934-936. [Crossref]
5. Riviere E, Arnaud L, Ebbo M, et al. Takayasu arteritis and spondyloarthritis: Coincidence or association? A study of 14 cases. *J Rheumatol*. 2017;44:1011-1017. [Crossref]
6. John KJ, Sadiq M, Thomas M, Turaka VP. Henoch-Schonlein purpura associated with HLA-B27 positive axial spondyloarthritis in a young man. *BMJ Case Rep*. 2019;12:E228881. [Crossref]
7. Urrea-Pineda LY, Gómez-Jimenez S, Jaramillo-Arroyave D, et al. Cryoglobulinemic vasculitis and psoriatic arthritis: Case report of an unusual association. *Reumatol Clin (Engl Ed)*. 2020;16:242-244.
8. Caballol Pons N, Montalà N, Valverde J, Brell M, Ferrer I, Martínez-Yélamos S. Isolated cerebral vasculitis associated with rheumatoid arthritis. *Joint Bone Spine*. 2010;77:361-363. [Crossref]
9. Joaquim AF, Appenzeller S. Neuropsychiatric manifestations in rheumatoid arthritis. *Autoimmun Rev*. 2015;14:1116-1122. [Crossref]
10. Ramos-Casals M, Brito-Zeron P, Munoz S, et al. Autoimmune diseases induced by TNF-targeted therapies: Analysis of 233 cases. *Medicine (Baltimore)*. 2007;86:242-251. [Crossref]
11. Saint Marcoux B, De Bandt M. Vasculitides induced by TNFalpha antagonists: A study in 39 patients in France. *Joint Bone Spine*. 2006;73:710-713. [Crossref]
12. Sokumbi O, Wetter DA, Makol A, Warrington KJ. Vasculitis associated with tumor necrosis factor-alpha inhibitors. *Mayo Clin Proc*. 2012;87:739-745. [Crossref]