OPEN ACCESS Freely available online

Rheumatology: Current Research

Case Report

ANCA Associated Cerebral Vasculitis: A Rarest Presentation

Richmond Ronald Gomes*

Department of Medicine, Ad-din Women's Medical College and Hospital, Dhaka, Bangladesh

ABSTRACT

Anti-Neutrophil Cytoplasmic Antibody (ANCA) associated vasculitis (AAV) is a systemic necrotizing inflammation of the small vessels that commonly involves kidney, lung, upper respiratory tract, skin, gastrointestinal and occasionally peripheral nervous system. Central Nervous System (CNS) is less commonly affected(less than 10% of patients) and is generally part of a multi-organ scenario. Angiography (CT angiography, MRA, or digital subtraction angiography) should be performed but can be normal in half of the patients given the involvement of small-sized vessels, which are beyond the detection capacity of the procedure. Biopsy is rarely performed in clinical practice but can help diagnosis. A complete workup including infective and autoimmune serologies as well as cerebrospinal fluid analysis is required, especially in patients with isolated or inaugural CNS manifestations. Finally, in absence of biopsy and/or demonstration of CNS vascular involvement, diagnosis is often probabilistic and relies on the systemic context and the ANCA positivity. Treatment of AAV-related CNS involvement requires combination of high-dose glucocorticoids and an immunosuppressant, mainly cyclophosphamide. Rituximab may be another option in patients with a contraindication for cyclophosphamide.

Keywords: ANCA; Vasculitis; CNS; Immunosuppressant; Glucocorticoid; Cyclophosphamide

INTRODUCTION

Central Nervous System (CNS) vasculitis, with its myriad and evolving presentations, always poses a great diagnostic challenge for neurologists. It occurs either as part of a systemic vasculitis, or a primary disorder restricted to the CNS [1]. Antineutrophil Cytoplasmic Antibody (ANCA) associated vasculitis (AAV) is a collection of relatively rare autoimmune diseases of unknown cause, characterized by inflammatory cell infiltration causing necrosis of small vessels, with few or no immune deposits [2,3]. Serologically, it is associated with a specific ANCA for myeloperoxidase (MPO-ANCA/P-ANCA) or proteinase 3 (PR3-ANCA/C-ANCA). In the clinical practice, AAV mainly includes Granulomatosis with Polyangiitis (GPA), Microscopic Polyangiitis (MPA) and Eosinophilic Granulomatosis with Polyangiitis (EGPA) or renal limited vasculitis [1]. AAV is rare with incidence ranging from 15 to 25/1 million in the general population [4]. AAV have a peak incidence at 65-75 years old, but may occur at any age, with a slight male predominance. Approximately one fourth to one half of patients with AAV will experience a relapse within several years. Clinical presentation comprises a wide spectrum of manifestations from the common nephrological, respiratory, dermatological, gastrointestinal symptoms to infrequent neurological and cardiac complications. Neurologic involvement is not uncommon in AAV throughout the disease course. CNS is affected in <15% of patients with AAV 5 but accounts for much of the morbidity in those patients [5-7]. However, the heterogeneous CNS symptoms in AAV may hinder early diagnosis among neurologists, causing treatment delays and disease progression, leading to relapses, or even death. Clinical presentation may be characterized by headache, focal neurologic deficits, seizures, ischemic stroke or subarachnoid hemorrhage [8-12]. Diagnosis is usually based on clinical CNS manifestations and multiple ischemic (sometimes hemorrhagic) MR lesions mainly affecting the white matter.

CASE REPRESENTATION

A 42-years old, normotensive, non-asthmatic lady, known to have poorly controlled diabetes mellitus (on insulin) for 20 years presented to us with intermittent headache, vertigo, blurring of vision for 3 months and unsteadiness of gait for last 1 month.

Correspondence to: Richmond Ronald Gomes, Department of Medicine, Ad-din Women's Medical College and Hospital, Dhaka, Bangladesh, Tel: 8801819289499; E-mail: rrichi.dmc.k56@gmail.com

Received: October 05, 2021; **Accepted**: October 19, 2021; **Published**: October 26, 2021

Citation: Gomes RR (2021) ANCA Associated Cerebral Vasculitis: A Rarest Presentation. Rheumatology (Sunnyvale). S18.004.

She denied any limb weakness, vomiting, altered sensorium, fever, seizure, speech swallowing or memory disturbances. She also reported short-term use of medications for suspected vascular headache with different NSAID's, amitriptyline and propanolol but there was no history of taking any oral contraceptive of late. There was also no H/O cough, runny nose, nasal block, joint pain, skin rash, photosensitivity, oral or genital ulcer, hematuria, hemoptysis, epistaxis. She is a mother of two healthy children with no history of any abortion. Her family history was insignificant for any auto immune disease. On physical examination, she was hemodynamically stable with no skin rash or joint swelling. Neurological examination was suggestive of right sided cerebellar lesion as evidenced by presence of impaired finger nose test, heel shin test, and dysdiadochokinesis on right and horizontal nystagmus with fast phase towards the right. There was a bilateral retinal hemorrhage on fundoscopy without any papilloedema (Figure 1). Rest of the physical examination was normal.

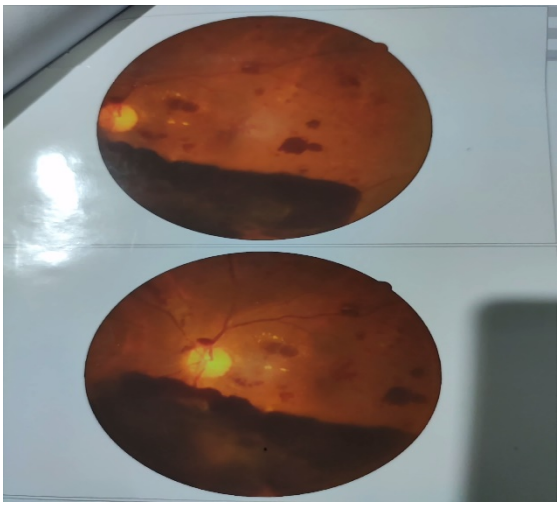

Figure 1: Fundoscopy revealed multiple retibal hemorrhage without papilloedema.

On investigation, complete blood count: mild normocytic normochromic anemia with Hb-10.93 gm% (MCV 83, MCH-27), ESR 60 mm in 1st hour, TC-10000/cmm (N-38%, L-54%), TPC-160000/cmm, CRP-58.5 mg/dl, PBF-normocytic normochromic anemia. Random blood sugar was high 21 mmol/L with HbA1c-11.8%. Urine R/E revealed; no proteinuria, RBC-2-3/HPF, but there were no granular, RBC or tubular cast. Serum ferritin was raised 535 ng/L. Serum albumin, SGPT, renal function tests (blood urea, serum creatinine, serum electrolyte), CPK, DCT, LDH, Blood C/S, Urine C/S all were noncontributory. CXR P/A, x-ray PNS, Echocardiography, X-ray of hands, USG of W/A revealed no abnormalities. Serological investigations for HBV and HCV were negative, VDRL non-reactive. On immunological test, ANA, Anti ds DNA, RA factor, Anti CCP, ENA profile, p-ANCA all came negative. Complement levels were normal. But c-ANCA came positive (10.5 U/ml, Normal <3 U/ml). MRI brain revealed white matter changes in subcortical region and over right cerebellar hemisphere (Figures 2 and 3).

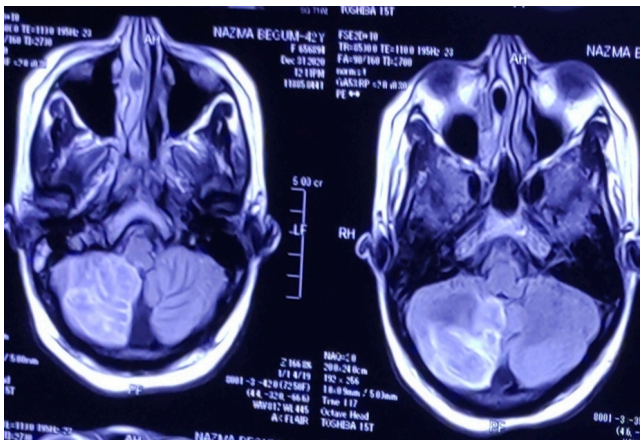

Figure 2: MRI of brain FLAIR sequence sho wing lesion in subcortical region of cerebrum.

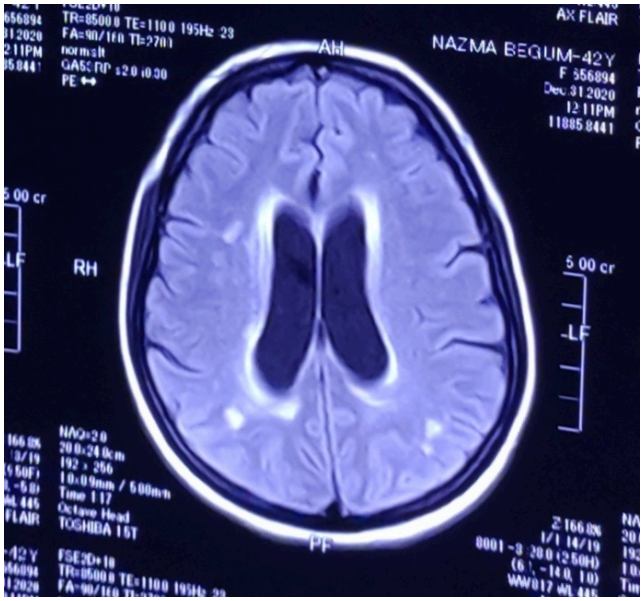

Figure 3: MRI of brain FLAIR sequence showing lesion in right cerebellar hemisphere.

So final diagnosis of ANCA associated CNS vasculitis was made and she was started induction therapy with high dose oral corticosteroid (1 mg/kg/day) and oral Cyclophosphamide (CYC) (2 mg/kg/day). Blood sugar was appropriately controlled, bisphosphonates was also given. Argon laser therapy was performed to both eyes. On follow up after 4 weeks, her condition was improving. Tapering of steroid was initiated. There is a plan to continue induction therapy with tapering glucocorticoid and oral CYC for 3 months in total followed by maintenance therapy with azathioprine.

RESULTS AND DISCUSSION

In general, extra-axial lesions involving the dura or pituitary gland are mainly attributed to granulomatous inflammation, while parenchyma pathologies are mediated by vasculitis and breakdown of blood brain barrier [13-18]. However, it remains unclear whether pathogenic ANCAs are produced intrathecally or from the systemic circulation and how the two ANCA serotypes contribute to different CNS manifestations.

Cranial nerves are rarely involved in MPA and EGPA (<5% of patients), however more frequently in GPA (up to 15% of patients) [15,18]. Optic and olfactory nerves are affected by spreading granulomas and peripheral cranial nerves (III-XII) can be involved because of pachymeningitis or other inflammatory process [19-23]. Clinical presentation involves visual impairment, olfactory impairment, facial nerve palsy, dysphagia and sensory disorders. Diagnosis is made upon neurological investigation and imaging studies (MRI).

This neutrophil-activation process is further augmented by the complement system, especially the alternative pathway, with C5a playing a key role in-between [24-30]. By contrast, the pathogenesis of extravascular granulomatosis is less well-understood. Current thinking holds that the chronic inflammation is initiated by the acute neutrophil-mediated necrosis [31]. Subsequently, defects in the cell death machinery and aberrant reaction of monocytes and macrophages contribute to the chronic inflammation and granulomatosis formation in AAV.

Neurological involvement is in majority of cases a part of generalized systemic disease, and as such should be treated. There is no specific treatment directed solely toward the neurological symptoms. The key issue is initiating AAV treatment as early in the disease course as it is possible [31-33]. Maintenance therapy is based on low-dose corticosteroids, Azathioprine (AZA) or Methotrexate (MTX) [34-36]. Recent studies proved efficacy of rituximab (RTX, monoclonal anti-CD20 antibody) in induction as well as maintenance therapy and according to the latest British AAV treatment guidelines it can be used interchangeably with CYC [37-39]. There are also encouraging reports about beneficial effects of intravenous immunoglobulins, especially for EGPA patients with residual neurological manifestations [40]. Therefore interdisciplinary approach is essential throughout whole patient care process and requires cooperation of the internists and neurologists. As there is no definite treatment for AAV, and the best thing we can achieve is remission, early treatment initiation or escalation in case of is lapse, can prevent from long-term, chronic organ damage, including neurological deficits. Although it is clear there are different phenotypes of the AAV, treatment regimens are now universal. Considering increasing research on systemic vasculitis, future will bring more therapeutic options for particular manifestations. Hopefully we will also be able to reduce complications of corticosteroids and highly potent immunosuppressant treatment.

CONCLUSION

AAV is a pauci-immune small-vessel vasculitis characterized by neutrophil-mediated vasculitis and granulomatosis. Hypertrophic pachymeningitis is the most frequent CNS presentation. Cerebrovascular events, hypophysitis, Posterior Reversible Encephalopathy Syndrome (PRES) or isolated mass lesions may occur as well. Spinal cord is rarely involved. Early recognition of AAV as the underlying cause for various CNS disorders is important for neurologists. Positive ANCA testing is highly suggestive of the diagnosis. Pathological evidence is the gold standard but not necessary. Once diagnosed, prompt initiation of induction therapy, including steroid and other immunosuppressants, can greatly mitigate the disease progression. Future studies are needed to better delineate the clinical spectrum of CNS involvement in AAV.

ACHNOWLEDGEMENT

Conflict of interest

None declared

REFERENCES

1. Jeanette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. Nomenclature of Vasculitides. International Chapel Hill Consensus Conference. Arthritis Rheum. 2013;65:1-11.
2. Jennette JC, Nachman PH. ANCA Glomerulonephritis and vasculitis. Clin J Am Soc Nephrol 2017;12(10):1680-1691.
3. Yates M, Watts R. ANCA-associated vasculitis. Clin Med. 2017;17(1): 60-64.
4. Watts RA, Mahr A, Mohammad AJ, Gatenby P, Basu N, Flores-Suárez LF. Classification, epidemiology and clinical subgrouping of Antineutrophil Cytoplasmic Antibody (ANCA)-associated vasculitis. Nephrol Dial Transplant. 2015;30(1):i14-i22.
5. Graf J. Central nervous system disease in antineutrophil cytoplasmic antibodies-associated vasculitis. Rheum Dis Clin North Am. 2017;43(4):573-578.
6. Sada K, Yamamura M, Harigai M, Fujii T, Dobashi H, Takasaki Y, et al. Classification and characteristics of Japanese patients with antineutrophil cytoplasmic antibody-associated vasculitis in a nationwide prospective, inception cohort study. Arthritis Res Ther. 2014;16(2):1-10.
7. Zhang W, Zhou G, Shi Q, Zhang X, Zeng XF, Zhang FC. Clinical analysis of nervous system involvement in ANCA-associated systemic vasculitides. Clin Exp Rheumatol. 2009;27(52):S65-S69.
8. Kallenberg CG. Key advances in the clinical approach to ANCA-associated vasculitis. Nat Rev Rheumatol. 2014;10:484-493.
9. Lyons PA, Rayner TF, Trivedi S, Holle JU, Watts RA, Jayne DR, et al. Genetically distinct subsets within ANCA-associated vasculitis. N Engl J Med. 2012;367(3):214-423.
10. Wójcik K, Wawrzycka-Adamczyk K, Włudarczyk A, Sznajd J, Zdrojewski Z, Masiak A, et al. Clinical characteristics of polish patients with ANCA-associated vasculitides-retrospective analysis of POLVAS registry. Clin Rheumatol. 2019;38(9):2553-2563.
11. Sznajd J, Mukhtyar C. How to treat ANCA-associated vasculitis: Practical messages from 2016 EULAR/ERAEDTA recommendations. Pol Arch Med Wewn. 2016;126(10):781-788.
12. Ghinoi A, Zuccoli G, Pipitone N, Salvarani C. Anti-Neutrophil Cytoplasmic Antibody (ANCA)-associated vasculitis involving the central nervous system: case report and review of the literature. Clin Exp Rheumatol. 2010;28(5):759-766.
13. Nishino H, Rubino FA, Deremee RA, Swanson JW, Parisi JE. Neurological involvement in Wegener's granulomatosis: an analysis of 324 consecutive patients at the Mayo Clinic. Ann Neurol. 1993;33(1): 4-9.
14. Seror R, Mahr A, Ramanoelina J, Pagnoux C, Cohen P, Guillevin L. Central nervous system involvement in Wegener granulomatosis. Medicine. 2006;85(1):54-65.
15. Holle JU, Gross WL. Neurological involvement in Wegener's granulomatosis. Curr Opin Rheumatol. 2011;23(1):7-11.

16. Drachman DA. Neurological complications of Wegener's granulomatosis. Arch Neurol. 1963;8(2):145-155.
17. Yokoseki A, Saji E, Arakawa M, Kosaka T, Hokari M, Toyoshima Y, et al. Hypertrophic pachymeningitis: Significance of myeloperoxidase anti-neutrophil cytoplasmic antibody. Brain. 2014;137(2):520-536.
18. Gwathmey KG, Burns TM, Collins MP, Dyck PJ. Vasculitic neuropathies. Lancet Neurol. 2014;13(1):67-82.
19. De Parisot A, Puechal X, Langrand C, Raverot G, Gil H, Perard L, et al. Pituitary involvement in granulomatosis with polyangiitis: Report of 9 patients and review of the literature. Medicine. 2015;94(16):e748.
20. Li S, Tang H, Rong X, Huang X, Li Q. Pachymeningitis as a manifestation of ANCA-associated vasculitis: A care report and literature review. Int J Clin Exp Med. 2015;8(4):6352-6359.
21. Robson J, Doll H, Suppiah R, Flossmann O, Harper L, Höglund P, et al. Damage in the anca-associated vasculitides: long-term data from the European vasculitis study group (EUVAS) therapeutic trials. Ann Rheum Dis. 2015;74(1):177-184.
22. Jennette JC, Falk RJ. Pathogenesis of antineutrophil cytoplasmic autoantibody-mediated disease. Nat Rev Rheumatol. 2014;10(1): 463-473.
23. Dumoitier N, Terrier B, London J, Lofek S, Mouthon L. Implication of B lymphocytes in the pathogenesis of ANCA-associated vasculitides. Autoimmun Rev. 2015;14(1):996-1004.
24. Feng B, Tang Y, Chen B, Xu C, Wang Y, Dai Y, et al. Transient increase of interleukin-1beta after prolonged febrile seizures promotes adult epileptogenesis through long-lasting upregulating endocannabinoid signaling. Sci Rep. 2016;6(1):21931.
25. Zhao J, Wang Y, Xu C, Liu K, Wang Y, Chen L, et al. Therapeutic potential of an anti-high mobility group box-1 monoclonal antibody in epilepsy. Brain Behav Immun. 2017;64:308-19.
26. Crisp SJ, Kullmann DM, Vincent A. Autoimmune synaptopathies. Nat Rev Neurosci. 2016;17(2):103-117.
27. Berlit P. Diagnosis and treatment of cerebral vasculitis. Ther Adv Neurol Disord. 2010;3(1):29-42.
28. Morgan MD, Day CJ, Piper KP, Khan N, Harper L, Moss PA, et al. Patients with Wegener's granulomatosis demonstrate a relative deficiency and functional impairment of T-regulatory cells. Immunology. 2010;130:64-73.
29. Chen M, Jayne DRW, Zhao MH. Complement in ANCA-associated vasculitis: Mechanisms and implications for management. Nat Rev Nephrol. 2017;13(6):359-367.
30. Soderberg D, Segelmark M. Neutrophil extracellular traps in ANCA-associated Vasculitis. Front Immunol. 2016;7:256.
31. Petersen HJ, Smith AM. The role of the innate immune system in granulomatous disorders. Front Immunol. 2013;4(1):120.
32. Nowack R, Wachtler P, Kunz J, Rasmussen N. Cranial nerve palsy in Wegener's granulomatosis-lessons from clinical cases. J Neurol. 2009;256(3):299-304.
33. Sokołowska B, Szczeklik W, Mastalerz L, Kuczia P, Wodkowski M, Stodółkiewicz E, et al. Effect of delayed diagnosis on disease course and management of Churg-Strauss syndrome: A retrospective study. Clin Rheumatol. 2013;32(3):349-354.
34. Luqmani RA. State of the art in the treatment of systemic vasculitides. Front Immunol. 2014;5:471.
35. De Joode AA, Sanders JS, Smid WM, Stegeman CA. Plasmapheresis rescue therapy in progressive systemic ANCA-associated vasculitis: Single-center results of stepwise escalation of immunosuppression. J Clin Apher. 2014;29(5):266-272.
36. Martin K, Bentaberry F, Dumoulin C, Miremont-Salamé G, Haramburu F, Dehais J, et al. Peripheral neuropathy associated with leflunomide: Is there a risk patient profile? Pharmacoepidemiol Drug Saf. 2007;16(1):74-78.
37. Ntatsaki E, Carruthers D, Chakravarty K, D'Cruz D, Harper L, Jayne D, et al. BSR and BHPR guideline for the management of adults with ANCA-associated vasculitis. Rheumatology. 2014;53(12):2306-2309.
38. Saech J, Owczarzyk K, Rösgen S, Petereit H, Hallek M, Rubbert-Roth A. Successful use of rituximab in a patient with Churg-Strauss syndrome an refractory central nervous system involvement. Ann Rheum Dis. 2010;69(6):1254-1255.
39. Sharma A, Kumar S, Wanchu A, Lal V, Singh R, Gupta V, et al. Successful treatment of hypertrophic pachymeningitis in refractory Wegener's granulomatosis with rituximab. Clin Rheumatol. 2010;29(1):107-110.
40. Koike H, Akiyama K, Saito T, Sobue G. Research Group for IfECSSiJ. Intravenous immunoglobulin for chronic residual peripheral neuropathy in eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome): A multicenter, double-blind trial. J Neurol. 2015;262(3):752-759.