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Unmasking DADA2: When ANCA Vasculitis Isn't What It Seems.

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INTRODUCTION

Deficiency of adenosine deaminase 2 (DADA2) is a recessively inherited, monogenic vasculitis syndrome, characterized by systemic vasculitis, early-onset stroke, bone marrow failure, and immunodeficiency, resulting from the biallelic mutations in the adenosine deaminase 2 (ADA2) gene on chromosome 22q11.1[1].

Myeloperoxidase (MPO)-specific antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (MPO-ANCA-associated vasculitis) is one of two major ANCA-associated vasculitis (AAV) variants predominantly affecting small blood vessels with kidney and lung as the most commonly affected organs[2].

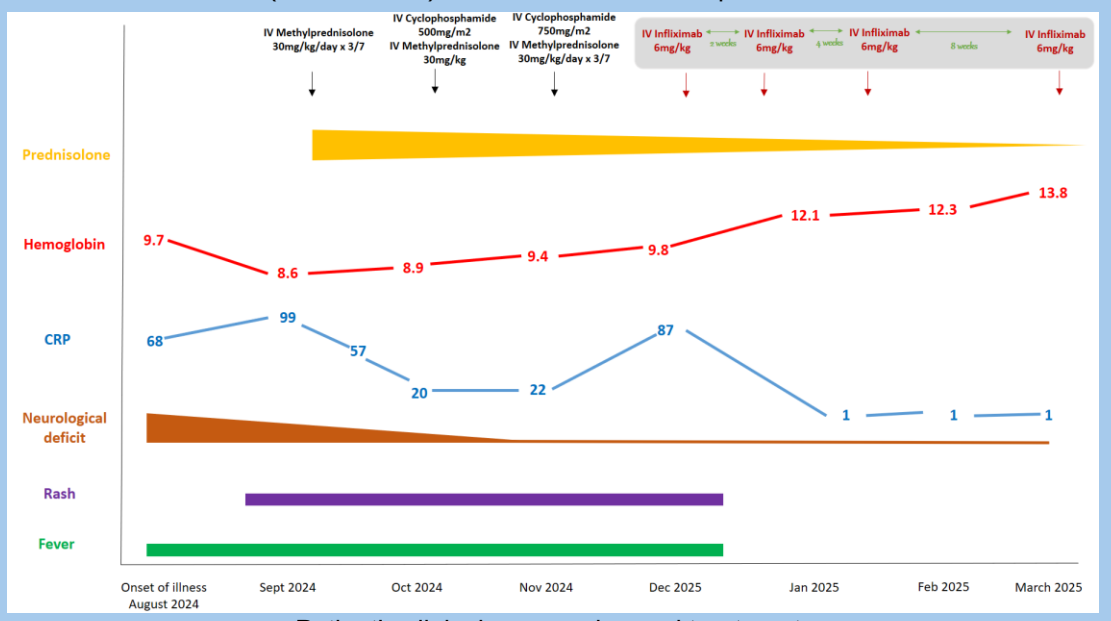
While ANCA positivity is not a hallmark of DADA2, there have been case reports describing patients with DADA2 who have MPO-ANCA positivity, leading to initial misdiagnosis as AAV[3,4].

CASE PRESENTATION

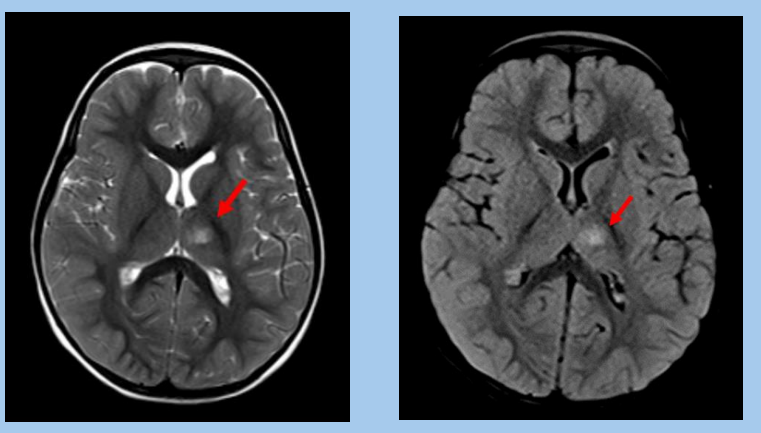
A 3-year-old girl, presented with fever, facial asymmetry, right sided body weakness and intermittent non pruritic rashes. Physical examination revealed a fully conscious, febrile child, with ptosis of the right eye, loss of nasolabial fold and drooping of her lips, hypertonia and reduced power of her right upper and lower limbs and macular rash over her thighs. Blood investigation showed anemia and raised inflammatory markers. CT Brain and MRI Brain showed left thalamic arterial infarct. Thrombophilia screening was negative while antinuclear antibodies (ANA) and anti-MPO were persistently positive.

In view of suspicion of small vessel vasculitis as the cause of her stroke with the persistent raised MPO-ANCA, she was initially treated for Microscopic Polyangiitis (MPA) with pulse intravenous Methylprednisolone and intravenous Cyclophosphamide. However, her clinical presentation was not typical for MPA as she presents with predominantly neurological manifestation with no renal or pulmonary involvement. Although she demonstrated significant recovery in her neurological function, she continued to have intermittent fevers, rash and raised CRP.

Whole exome sequencing revealed a homozygous pathogenic variant in ADA2 gene clinching the diagnosis of DADA2. She was treated with tumor necrosis factor inhibitor (TNF inhibitor). At two months follow up, she has no more fever and rash while her CRP level normalized.



Patient's clinical progression and treatment.



MRI images showing left thalamic infarct.

DISCUSSION

ANCA positivity in DADA2 may contribute to diagnostic confusion as DADA2 can mimic AAV both clinically and serologically.

Aspect	DADA2	MPA
Etiology	Genetic mutation in ADA2 gene leading to deficiency in ADA2 enzyme	Autoimmune disorder associated with ANCA antibodies
Age of onset	Typically in childhood	Can be present in children but is more common in adults
Clinical Manifestations	Recurrent strokes, systemic vasculitis, livedo racemosa, hepatospleenomegaly, bone marrow failure and immunodeficiency	Systemic vasculitis, glomerulonephritis, pulmonary haemorrhage, mononeuritis multiplex
ANCA positivity	Rare	Most patients are MPO-ANCA positive
Histopathology	Small and medium vessel vasculitis with fibrinoid necrosis.	Pauci-immune necrotising vasculitis affecting small vessels.
Treatment	TNF inhibitors, corticosteroids, hematopoietic stem cell transplantation	Corticosteroids, cyclophosphamide, rituximab

Differences between DADA2 and MPA[1,2, 5]

CONCLUSION

Early recognition of unusual clinical features of MPA prompted further diagnostic evaluation, including genetic testing, clinching a genetic diagnosis that redefined treatment strategy, resulting in improvements in the patient's condition.

REFERENCES

1. Isabelle Meyts, Ivona Aksentijevich, "Deficiency of Adenosine Deaminase 2 (DADA2): Updates on the Phenotype, Genetics, Pathogenesis, and Treatment", Journal of Clinical Immunology, July 2018.
2. Arnold S et al, "Myeloperoxidase-specific antineutrophil cytoplasmic antibody-associated vasculitis", The Lancet, May 2024.
3. Gibson KM et al. "Identification of Novel Adenosine Deaminase 2 Gene Variants and Varied Clinical Phenotype in Pediatric Vasculitis", Arthritis and Rheumatology October 2019, Vol 71.
4. Sharma A et al, "Deficiency of adenosine deaminase 2 (DADA2) in adults and children: experience from India", Arthritis and Rheumatology, February 2021.
5. Chasset F et al, "Clinical and pathological dermatological features of deficiency of adenosine deaminase 2: A multicenter, retrospective, observational study", Journal of the American Academy of Dermatology, December 2020.