

# Mpo-Anca Positive Granulomatosis With Polyangiitis Mimicking Igg4-Related Orbital Disease: A Diagnostic Dilemma

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*Received: 20th Feb, 2026; Revised: 4th Mar, 2026; Accepted: 25th Mar, 2026; Available Online: 10th Apr, 2026*

## Abstract

**Background:** Orbital inflammatory diseases pose a diagnostic challenge due to overlapping features among igg4-related disease (igg4-rd), anca-associated vasculitis (aav), and infections such as tuberculosis. Lacrimal gland enlargement is classically associated with igg4-related ophthalmic disease (igg4-rod), but may rarely occur in granulomatosis with polyangiitis (gpa).

**Case Presentation:** We report a 47-year-old woman presenting with orbital pseudotumor, posterior scleritis, cranial neuropathy, pulmonary nodules, and mpo-anca positivity. Imaging demonstrated lacrimal gland enlargement and orbital inflammation. Histopathology revealed lymphoplasmacytic infiltration with fibrosis and vasculitis, along with igg4-positive plasma cells (10–15/hpf) but an igg4/igg ratio <40%. Tuberculosis screening tests were strongly positive, though microbiological confirmation was lacking.

**Results:** The presence of vasculitis on histopathology, mpo-anca positivity, ent involvement, and pulmonary nodules favored a diagnosis of anca-associated vasculitis over igg4-rd.

**Conclusion:** This case highlights the diagnostic challenge in differentiating mpo-positive gpa with orbital masses from igg4-rd. Integration of clinical, serological and histopathological data is crucial in distinguishing these two overlapping entities. Exclusion of infections prior to initiation of immunosuppression is essential, particularly in tuberculosis-endemic settings.

**Keywords:** Anca-Associated Vasculitis, Granulomatosis With Polyangiitis, Igg4-Related Disease, Orbital Pseudotumor, Dacryoadenitis, Mpo-Anca, Tuberculosis.

**How To Cite This Article:** Tejaswi Kl, Sankaralingam R, Prabhu Nr, Tiwari Vp, Sandhu A. Mpo-Anca Positive Granulomatosis With Polyangiitis Mimicking Igg4-Related Orbital Disease: A Diagnostic Dilemma. Int J Drug Deliv Technol. 2026;16(27s):284-289. Doi: 10.25258/ijddt.16.27s.34

## INTRODUCTION

Orbital inflammatory diseases encompass a heterogeneous group of conditions including infections, malignancies, and autoimmune disorders. Among systemic rheumatologic conditions, IgG4-related ophthalmic disease (IgG4-ROD) and granulomatosis with polyangiitis (GPA) are key differentials in patients presenting with orbital pseudotumor and lacrimal gland enlargement [1,2]. IgG4-RD is a fibroinflammatory condition characterized by tumefactive lesions, dense

lymphoplasmacytic infiltrates, storiform fibrosis, and increased IgG4-positive plasma cells [3]. Orbital involvement is common, with lacrimal gland enlargement reported in up to 60–80% of cases, typically bilateral and indolent [2].

GPA, a subtype of ANCA-associated vasculitis, is a necrotizing vasculitis affecting small- to medium-sized vessels and commonly involves the upper airway, lungs, kidneys, and orbit [4]. Orbital manifestations include pseudotumor, scleritis, optic neuropathy, and dacryoadenitis [5].

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Distinguishing between IgG4-ROD and GPA becomes particularly challenging when biopsy reveals plasma-cell-rich inflammation with IgG4 positivity. However, IgG4-positive plasma cells are not disease-specific and may occur in vasculitis and chronic inflammatory conditions [3,6]. Therefore, diagnosis requires integration of clinical, serological, radiological, and histopathological findings.

## CASE PRESENTATION

A 47-year-old woman with hypothyroidism presented with a progressive multisystem illness beginning in May 2022 with seropurulent right ear discharge followed by left lower motor neuron facial palsy. Nerve conduction studies revealed axonal involvement of the left facial nerve, while MRI brain was normal.

In February 2023, she developed progressive swelling of the left upper eyelid associated with diplopia and decreased vision. By April 2023, she was diagnosed with orbital pseudotumor and posterior scleritis.

Clinical examination of left eye revealed:

- Upper lid edema, Ptosis and non-axial proptosis
- Conjunctival chemosis
- Lacrimal gland enlargement
- Restricted extraocular movements
- Visual acuity reduced to 6/24
- Hyperaemic optic disc
- Persistent facial nerve palsy
- Granulations over right tympanic membrane

There was no lymphadenopathy or salivary gland enlargement.

## INVESTIGATIONS

### Imaging

- MRI orbit: Lacrimal gland enlargement, extraocular muscle enlargement, retrobulbar fat stranding, posterior Tenon's thickening
- CT thorax: Multiple pulmonary nodules, right middle lobe collapse, bronchiectasis

### Laboratory findings

- MPO-ANCA by ELISA: 66 IU/ml.
- ANCA by IF: p-ANCA positive in 1:10 dilution.
- Serum IgG4 levels – 1.65 g/L
- Mantoux test: 40 mm
- Quantiferon TB: Positive
- BAL AFB & GeneXpert: Negative

### Histopathology

Lacrimal gland biopsy showed:

- Lymphoplasmacytic infiltration
- Fibrosis
- Vasculitic changes

### Immunohistochemistry:

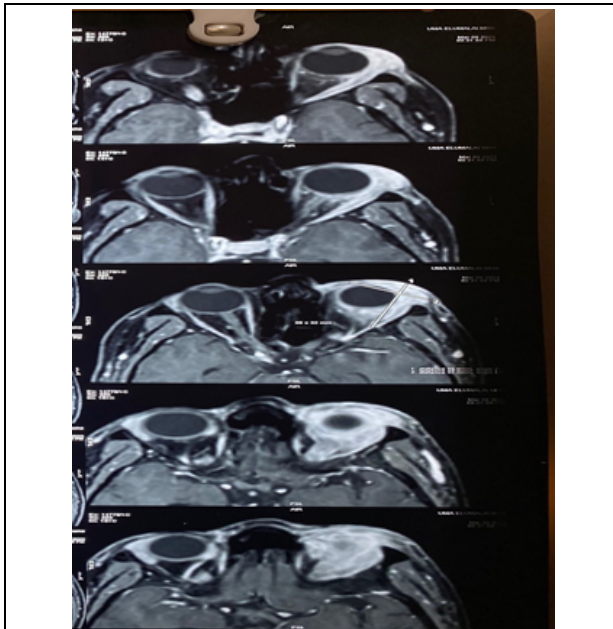
- IgG4-positive plasma cells: 10–15/HPF
- IgG4/IgG ratio: <40% (not diagnostic of IgG4-RD) [2,7]



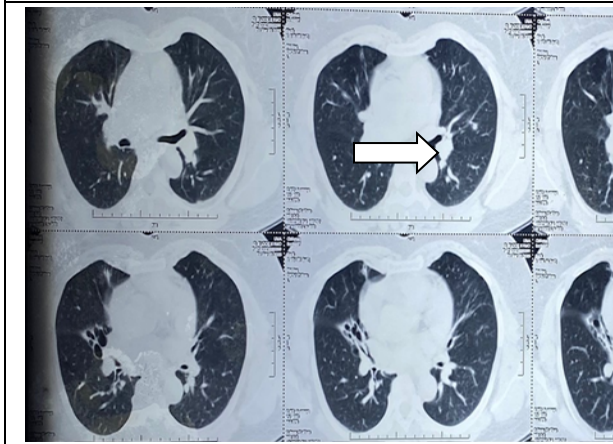
**Figure 1**

**Figure 1A:** Clinical presentation: Left eye- White arrow shows ptosis, Upper eyelid edema, Non-axial Proptosis. **Figure 1B** White arrow shows an enlarged lacrimal gland, Nasal and temporal conjunctival congestion.

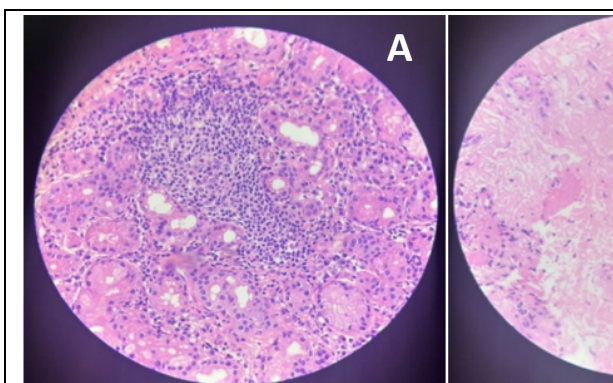
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**Figure 2:** MRI orbit White arrow shows Lacrimal gland enlargement-Both palpebral +orbital lobe. Yellow arrow shows Peri glandular and retrobulbar fat stranding



**Figure 3:** White arrow shows nodules in both lungs suggestive of granuloma.



**Figure 4**  
**Figure 4A:**Lymphoplasmacytic infiltration,  
**Figure 4B:** Fibrosis, **Figure 4C:** Vasculitis



**Figure 5**  
**Figure 5A:** Before **Figure 5B:** After treatment

**Table: Summary of Diagnostic Workup and Interpretation**

Domain	Investigation	Findings	Interpretation
Neurophysiology	Nerve conduction study	Axonal involvement of left facial nerve	Cranial neuropathy
Imaging - CNS	MRI brain	Normal	No central cause identified

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<b>Imaging – Orbit</b>	MRI orbit	Lacrimal gland enlargement, retrobulbar fat stranding, extraocular muscle enlargement, posterior Tenon’s thickening	Features suggest orbital inflammatory disease	<b>Immunohistochemistry</b>	gland biopsy	vasculitis	vasculitic process
	<b>Imaging – Thorax</b>	CT thorax	Multiple pulmonary nodules, right middle lobe collapse, bronchiectasis		Suggestive of granulomatous disease or vasculitis	IgG4 staining	IgG4 positive plasma cells 10–15 cells/HPF; IgG4/IgG plasma cell ratio < 40%
<b>Serology</b>	IgG4	Elevated	Not specific for IgG4-RD	<b>TB Screening</b>	Manoux test	40 mm induration	Strongly positive
	MPO-ANCA	Positive	Suggestive of ANCA-associated vasculitis (AAV)		Quantiferon-TB Gold	Positive	Latent or active tuberculosis is possible
<b>Microbiology</b>	BAL for AFB	Negative	No microbiological evidence of tuberculosis	<b>Histopat</b>	Lacrimal	Lymphoplasmacytic infiltrate, fibrosis, and	Suggestive of
	GeneXpert MTB/RIF	Negative	No active tuberculosis is detected		<b>Discussion</b>	This case highlights the significant diagnostic overlap between MPO-positive granulomatosis with polyangiitis (GPA) and IgG4-related orbital disease (IgG4-ROD), posing a considerable clinical	
	Ear swab culture	Growth of <i>Aspergillus fumigatus</i>	Likely secondary fungal infection			While dacryoadenitis and IgG4-positive plasma cell infiltration initially raised suspicion for IgG4-RD, a comprehensive clinico-pathologic synthesis confirmed ANCA-associated vasculitis (AAV). The diagnosis was substantiated by high-titer MPO-ANCA positivity and multisystemic involvement, including pulmonary nodules, ENT manifestations, and cranial neuropathy—features that diverge from the typical IgG4-RD phenotype. Most definitively, histopathological evidence of active vasculitis served as the pathognomonic discriminator, superseding the localized IgG4-positive inflammatory milieu.	

**DIAGNOSTIC INTERPRETATION**

While dacryoadenitis and IgG4-positive plasma cell infiltration initially raised suspicion for IgG4-RD, a comprehensive clinico-pathologic synthesis confirmed ANCA-associated vasculitis (AAV). The diagnosis was substantiated by high-titer MPO-ANCA positivity and multisystemic involvement, including pulmonary nodules, ENT manifestations, and cranial neuropathy—features that diverge from the typical IgG4-RD phenotype. Most definitively, histopathological evidence of active vasculitis served as the pathognomonic discriminator, superseding the localized IgG4-positive inflammatory milieu.

**TREATMENT AND OUTCOME**

The patient was managed with a combination of systemic and local therapies. Initial treatment included high-dose oral prednisolone at 1 mg/kg/day, along with topical ocular steroids and ciprofloxacin ear drops. In view of latent tuberculosis infection, empirical antitubercular therapy using the HRZE regimen was initiated. Given the presence of organ-threatening disease, remission induction was achieved with monthly pulses of intravenous cyclophosphamide at a dose of 15 mg/kg, administered with mesna for uroprotection. Following successful induction, the patient was transitioned to a gradual tapering of corticosteroids and started on maintenance immunosuppression with azathioprine. The patient showed a favorable clinical response, with complete resolution of orbital inflammation, significant improvement in visual acuity, and recovery of cranial neuropathy. Long-term follow-up demonstrated sustained remission for three years, with a Birmingham Vasculitis Activity Score (BVAS) of 0.

**DISCUSSION**

This case highlights the significant diagnostic overlap between MPO-positive granulomatosis with polyangiitis (GPA) and IgG4-related orbital disease (IgG4-ROD), posing a considerable clinical

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challenge, particularly when orbital manifestations predominate. IgG4-related orbital disease typically presents with bilateral lacrimal gland enlargement, reflecting its predilection for dacryoadenitis, along with an indolent and slowly progressive clinical course characterized by minimal pain or discomfort. Patients often exhibit painless swelling and mass-like lesions, which may initially be mistaken for benign inflammatory or lymphoproliferative conditions. Histopathologically, IgG4-ROD is defined by dense lymphoplasmacytic infiltration, storiform fibrosis, and obliterative phlebitis, with a hallmark increase in IgG4-positive plasma cells and an IgG4/IgG plasma cell ratio exceeding 40%, which serves as a key diagnostic criterion [2,3]. In contrast, granulomatosis with polyangiitis is a necrotizing vasculitis affecting small- to medium-sized vessels and demonstrates a more aggressive and potentially organ-threatening course. Orbital involvement in GPA occurs in up to 50% of cases and may manifest as orbital pseudotumor, scleritis, proptosis, or even optic neuropathy leading to visual compromise. Unlike IgG4-ROD, GPA frequently presents with significant pain, rapid progression, and systemic features, including involvement of the upper and lower respiratory tracts, such as chronic sinusitis, nasal crusting, epistaxis, pulmonary nodules, or cavitary lesions, thereby providing important diagnostic clues [4,5].

Serological evaluation plays a crucial role in differentiating these entities; although proteinase-3 (PR3)-ANCA is classically associated with GPA, myeloperoxidase (MPO)-ANCA positivity is increasingly recognized, especially among Asian populations, and may be associated with atypical or limited disease presentations, including predominant orbital involvement without overt systemic features [4,8]. This variability further complicates the diagnostic process, as MPO-ANCA-positive GPA may lack the classical manifestations typically expected in ANCA-associated vasculitis. Another important diagnostic pitfall is the presence of IgG4-positive plasma cells in tissue biopsies from patients with GPA and other inflammatory conditions. Elevated IgG4-positive cells are not exclusive to IgG4-RD and may also be observed in ANCA-associated vasculitis, sarcoidosis, and chronic infections, including fungal and bacterial etiologies. Consequently, reliance on IgG4 immunostaining alone can be misleading, and diagnosis must be based on a comprehensive assessment incorporating

clinical, radiological, serological, and histopathological findings [3,6].

In tuberculosis-endemic regions, such as India, an additional layer of complexity arises, as tuberculosis can closely mimic both GPA and IgG4-RD in its clinical and radiological presentation. Orbital tuberculosis, although rare, may present with mass lesions, granulomatous inflammation, and even systemic features that overlap with vasculitis. Furthermore, pulmonary tuberculosis may present with nodules or cavitations, which can be difficult to distinguish from GPA-related lung involvement. In such scenarios, empirical anti-tubercular therapy is often considered prior to initiating immunosuppressive treatment, particularly when diagnostic uncertainty persists, as the consequences of untreated tuberculosis in the setting of immunosuppression can be severe [9].

The distinction between ANCA-associated vasculitis, particularly GPA, and IgG4-related disease is therefore critical due to differences in management and prognosis. Key differentiating features include the presence of vasculitis, which is common in GPA but rare in IgG4-RD, as well as ANCA positivity, which supports a diagnosis of GPA but is typically absent in IgG4-RD. Pulmonary involvement, especially lung nodules and cavitations, along with ENT manifestations such as sinusitis and nasal involvement, are characteristic of GPA but uncommon in IgG4-RD. Conversely, IgG4-RD demonstrates prominent infiltration by IgG4-positive plasma cells and a higher IgG4/IgG ratio exceeding 40%, whereas in GPA, although IgG4-positive cells may be present, the ratio generally remains below 40%. Recognizing these distinguishing features is essential to avoid misdiagnosis and ensure appropriate therapy, as GPA requires prompt immunosuppressive treatment to prevent organ damage, while IgG4-RD often responds well to corticosteroids and may follow a more benign course if identified early.

### CONCLUSION

This case underscores the diagnostic complexity of orbital inflammatory disease with overlapping features of IgG4-RD and ANCA-associated vasculitis. Recognition that MPO-ANCA-positive GPA can present with lacrimal gland enlargement and IgG4-positive plasma cells is crucial to avoid misdiagnosis. Clinicopathological correlation remains essential, particularly in tuberculosis-endemic regions where infections may confound diagnosis. Early

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identification and appropriate immunosuppressive therapy are vital to prevent vision loss and systemic complications.

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