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TWENTY YEARS OF UNDIAGNOSED EOSINOPHILIA: DIABETIC ATTRIBUTION BIAS DELAYING DIAGNOSIS OF ANCA-POSITIVE EGPA UNTIL END-STAGE ORGAN DAMAGE

Minha Aslam, Amira Bitar, Stephanie Ammari, Nawras Ibrahim

Department of Internal Medicine, HCA Houston Healthcare Clear Lake, Houston, USA
University of Houston College of Medicine, Houston, USA

Corresponding author's e-mail: nawras.ibrahim@hcahealthcare.com

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ABSTRACT

Introduction: Eosinophilic granulomatosis with polyangiitis (EGPA) has the longest diagnostic delay among anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides, with a reported median of 455 days. Cardiac disease, the leading cause of EGPA-related mortality, is largely preventable with early immunosuppression.

Case description: A 53-year-old Hispanic woman with type 2 diabetes, hypertension, and no documented asthma had 20 years of persistent peripheral eosinophilia (absolute eosinophil count 1–2.7 $\times 10^3/\mu l$) and active glomerulonephritic sediment. Eosinophilia was first documented at age 33 when no medical comorbidities existed, predating the diabetes diagnosis by years. Renal function declined from creatinine 0.6 mg/dl (2013) to end-stage renal disease requiring peritoneal dialysis (2024). Ejection fraction fell from 70% (2024) to 20–24% (2026), with left heart catheterization excluding ischemic aetiology. Peripheral neuropathy was attributed to diabetes without electrodiagnostic evaluation. Bone marrow biopsy excluded clonal eosinophilic disorders. ANCA testing, never previously ordered, revealed myeloperoxidase (MPO)-ANCA positivity (>8.0 units, reference 0–0.9) with ANCA IIF titre 1:160 in April 2026. The 2022 American College of Rheumatology / European Alliance of Associations for Rheumatology classification criteria score was ≥6 points without asthma or nasal polyps. Seven missed diagnostic opportunities were identified across multiple specialties and facilities over two decades.

Conclusion: This case illustrates how "diabetic attribution bias," care fragmentation, and socioeconomic barriers delayed EGPA diagnosis for 20 years despite persistent eosinophilia and progressive multi-organ damage. Systematic ANCA testing in patients with unexplained eosinophilia and organ involvement could prevent irreversible end-organ damage.

KEYWORDS

Eosinophilic granulomatosis with polyangiitis, ANCA-associated, diagnostic delay, eosinophilia, attribution bias

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LEARNING POINTS

- Persistent unexplained eosinophilia (absolute eosinophil count >1 $\times 10^3/\mu l$) with active glomerulonephritic sediment warrants (ANCA) testing regardless of asthma status, as myeloperoxidase (MPO)-ANCA–positive eosinophilic granulomatosis with polyangiitis (EGPA) may present without prominent asthma and with predominant vasculitic manifestations including glomerulonephritis and peripheral neuropathy.
- "Diabetic attribution bias": the reflexive attribution of organ damage to diabetes in patients with coexisting diabetes. can delay vasculitis diagnosis for years when renal decline and peripheral neuropathy are present alongside atypical features such as improving glycaemic control and active glomerulonephritic sediment.
- Corticosteroid exposure suppresses eosinophilia in peripheral blood within hours and in body fluids within days, masking the hallmark laboratory finding of EGPA; eosinophil counts and serosal fluid analyses should always be interpreted in the context of recent steroid use.

INTRODUCTION

Eosinophilic granulomatosis with polyangiitis (EGPA) is a systemic necrotizing vasculitis of small- and medium-sized vessels that evolves through prodromal allergic, eosinophilic, and vasculitic phases[1]. Approximately one-third of patients are anti-neutrophil cytoplasmic antibody (ANCA)-positive, predominantly with myeloperoxidase (MPO) specificity, and exhibit more pronounced vasculitic manifestations including glomerulonephritis and peripheral neuropathy, with less prominent asthma[1].

Diagnostic delay in EGPA is the longest among ANCA-associated vasculitides (AAV), with a median of 455 days[2]. Cardiac disease, the leading cause of EGPA-related mortality, is largely preventable with early immunosuppression[1]. Despite expert consensus recommending ANCA testing in unexplained eosinophilia with organ involvement[3], such testing frequently goes unordered.

No gold standard diagnostic test exists; the diagnosis is clinical. The 2022 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) classification criteria, designed for research, require a prior clinical diagnosis of small- or medium-vessel vasculitis and can be applied without biopsy when clinical and serologic data are concordant[4]. Separately, the 2021 ACR/Vasculitis Foundation guidelines support treatment initiation without biopsy in the setting of positive ANCA serology and compatible clinical features[5].

We present a patient with 20 years of documented eosinophilia diagnosed only after progression to end-stage renal disease (ESRD) and severe cardiomyopathy, illustrating diagnostic delay and a cognitive pattern we term "diabetic attribution bias".

CASE DESCRIPTION

A 53-year-old woman, a never-smoker, with type 2 diabetes, hypertension, and no documented asthma, sinusitis, or nasal polyps was admitted in April 2026 with shortness of breath and chest pain. Peripheral neuropathy had been attributed to diabetes without nerve conduction

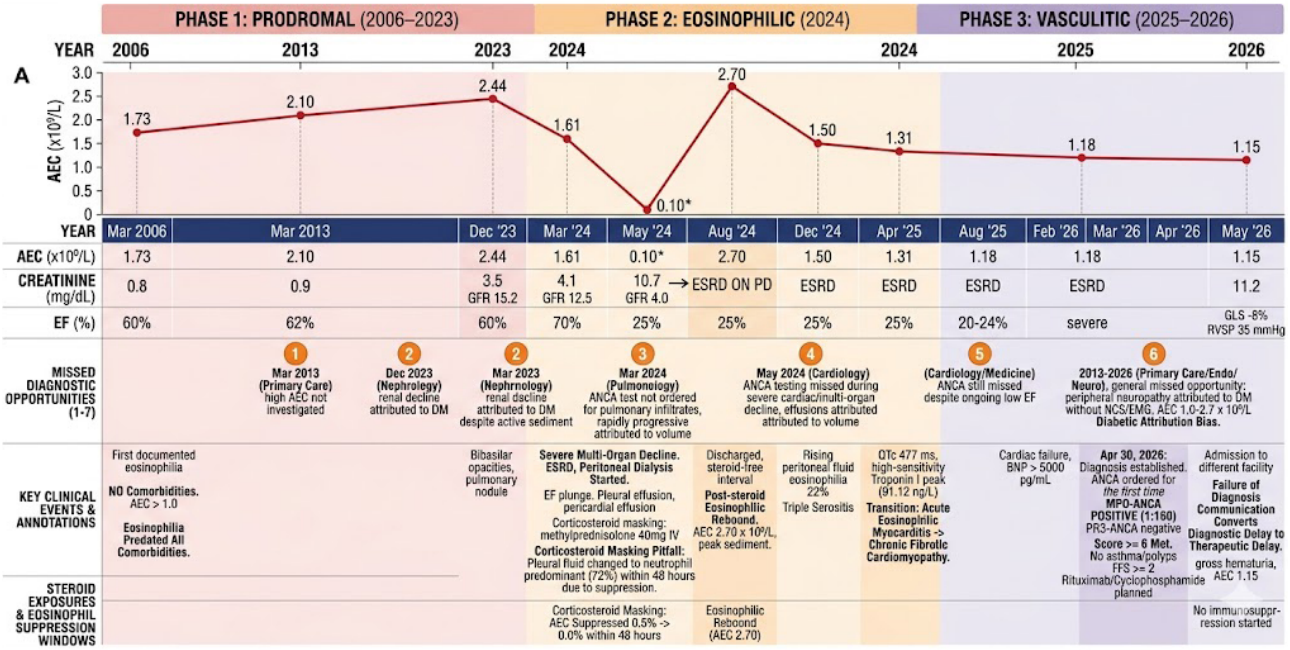


Figure 1. Timeline of disease phases missed opportunities, and organ damage accrual.

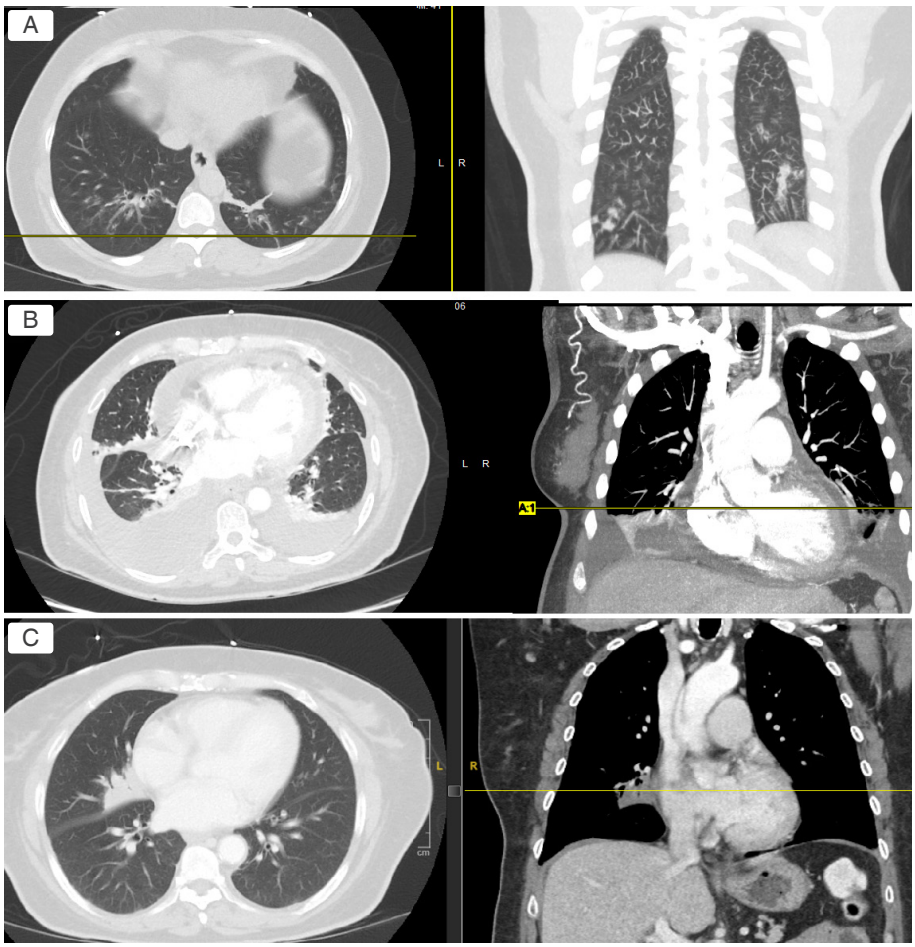


Figure 2. *Serial CT chest imaging demonstrating migratory pulmonary involvement across three disease phases. A) 2024 (eosinophilic phase onset): axial (left) and coronal (right) CT without contrast showing patchy bilateral lower lobe infiltrates with nodular components. No pleural or pericardial effusions. Normal cardiac silhouette.*

B) 2024 (eosinophilic phase, serosal transition): axial (left) and coronal (right) CTA showing interval development of large bilateral pleural effusions with compressive lower lobe atelectasis and a pericardial effusion over 11 weeks.

studies (NCS) or electromyography (EMG) *(Fig. 1)*.

Phase 1: prodromal phase (2006–2023)

The earliest documented eosinophilia dates to March 2006 (absolute eosinophil count [AEC] 1.73 $\times 10^3/\mu l$) *(Table 1)*. The patient had no documented comorbidities, establishing that eosinophilia predated all conditions later used to explain her organ damage. Socioeconomic barriers (limited English proficiency, no insurance, no primary care physician) were documented.

Eosinophilia persisted in March 2013 (AEC 2.1 $\times 10^3/\mu l$) with normal renal function (creatinine 0.6 mg/dl) and abnormal urine sediment (protein 2+, blood 3+, red blood cells [RBC] 3–5/HPF, white blood cells [WBC] 0–3/high-power field [HPF]), with proteinuria and haematuria suggesting early glomerular involvement. By December 2023, creatinine had risen to 3.5 mg/dl (glomerular filtration rate [GFR] 15.2) with persistent eosinophilia (AEC up to 2.44 $\times 10^3/\mu l$), nephrotic-range proteinuria (protein-to-creatinine ratio 10.1 g/g), and a glomerulonephritic sediment (>50 RBC/HPF). Nephrology attributed the decline to diabetic nephropathy despite these atypical features; ANCA testing was not performed *(Fig. 1)*.

Phase 2: eosinophilic phase (2024)

In March 2024, the patient was admitted with cough, dyspnoea, and wheezing. Computed tomography (CT) scan of the chest showed bilateral lower lobe infiltrates with nodular components *(Fig. 2A)*. Bone marrow biopsy showed a hypercellular marrow with a reactive eosinophilic process, excluding clonal eosinophilic neoplasms (e.g., FIP1L1-PDGFRA–associated disease). Echocardiography showed ejection fraction (EF) 55–60%; stress testing showed an EF of 70% *(Fig. 3)*.

By May 2024, the patient had progressed to ESRD requiring peritoneal dialysis (creatinine 10.7 mg/dl). C-reactive protein (CRP) was markedly elevated at 280 mg/l (reference <10 mg/l), consistent with severe systemic inflammation. CT angiography (CTA) demonstrated large bilateral pleural and pericardial effusions *(Fig. 2B)*. Methylprednisolone 40 mg intravenously (IV) every 12 hours suppressed peripheral eosinophils to undetectable levels within 48 hours. Thoracentesis yielded an exudative effusion with neutrophilic predominance (72% polymorphonuclear neutrophils); the exudative character was inconsistent with the clinical attribution to volume overload. The absence of eosinophils in the fluid likely reflected concurrent steroid-induced suppression. Antinuclear antibody (ANA) was negative. ANCA testing was not ordered.

After steroid discontinuation, eosinophilia rebounded to its highest level (AEC $2.7\times 10^3/\mu l$) by August 2024, with active glomerulonephritic sediment (protein 3+, blood 3+, >50 RBC/HPF, 10–20 WBC/HPF). The rising urinary WBC count: from 0–3/HPF (December 2023) to 10–20/HPF, suggested increasing glomerular inflammation.

Phase 3: vasculitic phase (2025–2026)

Progressive cardiac deterioration ensued. High-

Date	Event	Eosinophils (%)	AEC (×10³/µl)	Creatinine (mg/dl)	BNP (pg/ml)	hs-TnI (ng/l)	Hb A1c (%)	Urinalysis RBC/HPF
Mar 2006	First documented eosinophilia	13.5	1.73	-	-	-	-	-
Mar 2013	Earliest labs	12.8	2.10	0.6 (GFR >60)	-	-	-	3–5
Dec 2023	Abdominal pain	19.2	2.44	3.5 (GFR 15.2)	-	-	7.9	>50
Mar 2024	Pulmonary admit	13.8	1.61	4.1 (GFR 12.5)	-	-	-	>50
May 2024	ESRD / pleural effusion	0.5→0*	0.10→0*	10.7 (GFR 4.0)	351	17 (normal)	6	-
Aug 2024	Post-steroid rebound	21.1	2.7	ESRD	-	-	-	>50
Dec 2024	Peritoneal fluid 22% eos	15.2	1.5	ESRD	-	-	-	-
Apr 2025	Cardiac decompensation	13.3	1.31	ESRD	1,769	91.12 (HIGH)	-	-
Aug 2025	Chest pain / QTc 477 ms	14.3	1.44	ESRD	3,249	38.9	-	-
Feb 2026	Worsening cardiac	15.8	1.18	10.5	4,012	20–38	-	-
Mar 2026	Cardiac failure	10.4	0.89	13	>5,000	20–38	5.6	-
Apr 2026	ANCA result: MPO >8 U	10.1	0.75	11.2	-	-	-	>50 (4+)

Table 1. *Longitudinal laboratory data (2006–2026) demonstrating the three-phase evolution of EGPA.*
**Eosinophil counts obtained during methylprednisolone therapy.*
Abbreviations: EGPA, eosinophilic granulomatosis with polyangiitis; AEC, absolute eosinophil count; BNP, B-type natriuretic peptide; hs-TnI, high-sensitivity troponin I; HPF, high-power field; ESRD, end-stage renal disease; Dx, diagnosis. GFR, glomerular filtration rate; ANCA, anti-neutrophil cytoplasmic antibody; MPO, myeloperoxidase.

Criterion	Weight	Present in this patient	Evidence
Obstructive airway disease	+3	Not documented*	No spirometry performed
Nasal polyps	+3	No	No ENT disease documented
Mononeuritis multiplex / motor neuropathy	+1	Not scored	No NCS/EMG performed
AEC ≥1 ×10³/µl	+5	Yes	AEC up to 2.7 ×10³/µl
Extravascular eosinophilic-predominant inflammation	+2	Yes	Peritoneal fluid eosinophilia 22%
Positive ANCA	-	Yes (MPO >8.0 U)	Entry criterion met
Haematuria	−1	Yes	>50 RBC/HPF on multiple UAs
Total Score		≥6	Threshold met (≥6 classified as EGPA)

Table 2. *2022 ACR/EULAR classification criteria applied to this patient.*
Wheezing documented March 2024 but spirometry never performed.
Abbreviations: ACR/EULAR, American College of Rheumatology / European Alliance of Associations for Rheumatology; ENT, ear, nose and throat; NCS, nerve conduction studies; EMG, electromyography; AEC, absolute eosinophil count; MPO, myeloperoxidase; RBC, red blood cells; HPF, high-power field; EGPA, eosinophilic granulomatosis with polyangiitis.

sensitivity troponin I peaked at 91.12 ng/l (April 2025), then declined to 36.5–38.9 ng/l (August 2025), consistent with acute eosinophilic myocarditis transitioning to chronic fibrotic cardiomyopathy[6]. The EF fell from 55–60% at rest (March 2024) to 25% (April 2025). Left heart catheterization revealed only minimal coronary disease. An electrocardiogram (EKG) showed prolonged QTc (477 ms). B-type natriuretic peptide rose from 351 pg/ml (May 2024) to >5,000 pg/ml (March 2026). CT imaging demonstrated migratory pulmonary infiltrates *(Fig. 2C)*, with



| ***Figure 3.*** *Divergent renal and cardiac trajectories during 13 years of undiagnosed EGPA.*

right middle lobe consolidation replacing the prior bilateral lower lobe disease and complete resolution of pleural and pericardial effusions. Serial peritoneal fluid analyses showed rising eosinophilia from 8 to 22% over four steroid-free months, inconsistent with idiopathic peritoneal dialysis (PD)-associated eosinophilic peritonitis. Eosinophilic involvement of all three serous cavities (pleural, pericardial, peritoneal) was never linked to a unifying diagnosis.

On the April 2026 admission, urinalysis showed the most severe findings in the series (protein 4+, blood 4+, >50 RBC/HPF, 10–20 WBC/HPF), documenting progressive worsening across all three phases.

Echocardiography confirmed an EFof 20–24% with diffuse hypokinesis, elevated filling pressures (E/e' 24), and decreasing wall thickness (IVS 1.4 → 1.2 cm)

ANCA testing was first ordered on April 30, 2026; the first time in the patient's documented medical history[3]. Results showed ANCA IIF positivity at 1:160 with MPO-ANCA >8.0 units (reference 0.0–0.9). PR3-ANCA was negative. ANA was negative. Total IgE was 935 IU/ml. The clinical diagnosis of EGPA was established: MPO-ANCA positivity combined with glomerulonephritis, non-ischemic cardiomyopathy, migratory pulmonary infiltrates, eosinophilic serositis, and peripheral neuropathy. ACR/EULAR weighted scoring yielded ≥6 points *(Table 2)* (+5 for AEC ≥1 $\times 10^9$/l, +2 for extravascular eosinophilic-predominant inflammation [based on peritoneal fluid eosinophilia up to 22% during steroid-free intervals], –1 for haematuria), meeting the threshold without asthma or nasal polyps[4]; the +1 for mononeuritis multiplex was not scored as no NCS/EMG had been performed. Hypereosinophilic syndrome (HES) was excluded by MPO-ANCA >8× ULN (essentially absent in primary HES), bone marrow excluding clonal disorder, and active glomerulonephritic sediment characteristic of pauci-immune glomerulonephritis[1]. Drug-induced vasculitis (hydralazine) was excluded by negative ANA, single-specificity MPO-ANCA, and eosinophilia predating hydralazine by 20 years.

The revised (2011) Five-Factor Score (FFS) was 3 (cardiac involvement +1, renal insufficiency +1, absence of ear, nose and throat manifestations +1), indicating poor prognosis. Using the original (1996) FFS, a score ≥2 was associated with approximately 40% five-year mortality[5,7].

Remission induction with glucocorticoids plus cyclophosphamide or rituximab was planned per ACR/Vasculitis Foundation guidelines[5]. Anti-IL-5 agents (mepolizumab, benralizumab) may serve as adjunctive or maintenance therapy[5,8].

Approximately four weeks after ANCA results were reported, the patient was admitted to a different facility within the same hospital system for symptomatic anaemia (haemoglobin 7.2 g/dl) with persistent gross haematuria. Peripheral eosinophilia persisted at 14.1%. No immunosuppressive therapy had been initiated.

DISCUSSION

This case documents a 20-year prodromal-to-vasculitic phase transition *(Table 1)*, quantifying irreversible organ damage: creatinine 0.6 mg/dl and EF 60% to ESRD and EF 20–24% *(Fig. 3)*.

Notably, renal involvement is associated with shorter time to AAV diagnosis (HR 1.65, p = 0.004)[2], yet here it was present for over a decade without prompting ANCA testing, likely because diabetic attribution bias overrode the diagnostic signal renal disease typically provides.

We propose the term "diabetic attribution bias" to describe the reflexive attribution of organ damage to diabetes when clinical features are atypical. This operated at two levels. First, renal decline was attributed to diabetic nephropathy despite a glomerulonephritic sediment more consistent with pauci-immune glomerulonephritis; the progressive rise in urinary WBCs further supports active inflammatory glomerulonephritis rather than the relatively acellular sediment of diabetic nephropathy. The serial HbA1c trajectory (7.9% → 6.0% → 5.6%) likely reflects a reduced erythrocyte lifespan in ESRD; regardless, the sediment

pattern was inconsistent with diabetic glomerulosclerosis (*Fig. 3)*. Second, peripheral neuropathy was attributed to diabetes without NCS/EMG. Peripheral neuropathy, the most common non-pulmonary manifestation, affects 50–75% of EGPA patients[1,9].

MPO-ANCA positivity is an independent risk factor; sural nerve biopsy characteristically shows epineurial vascular destruction with asymmetric axonal loss distinct from diabetic neuropathy[9]. Had NCS/EMG been performed, an atypical pattern could have triggered earlier ANCA testing.

Corticosteroid masking was evident: peritoneal fluid showed 22% eosinophils during steroid-free intervals but none during steroid-exposed admissions, a recognized diagnostic pitfall[1].

While asthma is present in >90% of EGPA cases, ANCA-positive patients less commonly present with prominent asthma[1], and the 2022 ACR/EULAR criteria do not require it for classification[4]. However, spirometry was never performed, so absent versus undiagnosed asthma cannot be resolved.

Seven opportunities for earlier diagnosis were identified across five specialties over 20 years *(Fig. 1)*. Contributing factors included diabetic attribution bias, premature dismissal of vasculitis without ANCA testing; a pattern consistent with the finding by Bussmann et al. that prior pulmonology consultation paradoxically prolonged time to AAV diagnosis (HR 0.58, p = 0.003)[2], corticosteroid masking, misattribution of exudative effusions to volume overload, fragmented care, and socioeconomic barriers.

Limitations include the absence of renal biopsy (precluded by advanced chronic kidney disease), cardiac magnetic resonance imaging, NCS/EMG, sural nerve biopsy, and histologic evaluation of a gastroesophageal junction nodule (endoscopy aborted due to desaturation). The 7-year and 10-year gaps between early data points limit prodromal phase precision. Treatment response data are not yet available.

This case underscores the imperative for systematic ANCA testing in patients with unexplained eosinophilia and organ involvement, as recommended by the 2020 International Consensus on ANCA Testing and the 2024 European red flags consensus[3,10].

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