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Recurrent Hemoptysis In A Chronic Hemodialysis Patient With Indeterminate Nephropathy: The Role Of A Comprehensive Diagnostic Workup Including Anca Testing

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Abstract:

A 32-year-old woman on maintenance hemodialysis for five years (indeterminate nephropathy, bilateral small kidneys, anuria) presented with recurrent hemoptysis over a six-month period. In a tuberculosis-endemic region, an exhaustive infectious investigation was performed, including repeated sputum and gastric lavage polymerase chain reaction (PCR) and cultures (with 42-day mycobacterial culture), tuberculin skin testing, and bronchoscopy with bronchoalveolar lavage (BAL). BAL revealed abundant hemosiderin-laden macrophages, confirming alveolar hemorrhage. C-reactive protein (CRP) was elevated, but procalcitonin remained normal, arguing against bacterial infection. Echocardiography and abdominal ultrasound showed no abnormalities. Tumor markers were negative. After six months without a diagnosis, an autoimmune panel was obtained: anti-myeloperoxidase antibodies (anti-MPO, P-ANCA) were strongly positive by enzyme-linked immunosorbent assay (ELISA) (>120 IU/mL; normal <20 IU/mL); antinuclear antibodies (ANA) and anti-proteinase 3 antibodies (anti-PR3, C-ANCA) were negative. The patient was treated with prednisone 1 mg/kg/day and monthly intravenous cyclophosphamide 500 mg on non-dialysis days, with complete blood count monitoring. A rapid clinical and biological response occurred, with hemoptysis ceasing within two weeks and radiological resolution at three months. This case highlights that when an extensive infectious workup remains negative in a dialysis patient with hemoptysis, ANCA-associated pulmonary vasculitis should be suspected, especially when CRP is elevated without procalcitonin elevation and BALdemonstrateshemosiderin-ladenmacrophages.

Key words: ANCA-associated vasculitis; hemodialysis; hemoptysis; alveolar hemorrhage; tuberculosis; diagnostic delay

Introduction:

Chronic hemodialysis patients presenting with unexplained hemoptysis pose a significant diagnostic challenge. The differential diagnosis is broad and includes tuberculosis (particularly in endemic regions), pulmonary vasculitis, alveolar hemorrhage secondary to uremic platelet dysfunction, heart failure, and malignancy. When initial infectious evaluations are negative, a systematic and comprehensive approach is required.

In tuberculosis-endemic regions, pulmonary vasculitis is frequently misdiagnosed as tuberculosis, leading to diagnostic delays (1). This diagnostic challenge is well-recognized in the literature, with studies documenting that patients with systemic vasculitis may initially receive an incorrect diagnosis, with infection being the most common alternative (1). Furthermore, diagnostic delays in pulmonary tuberculosis itself remain a significant problem in endemic areas, with patient-related, health system-related, and disease-related factors all contributing to prolonged time to diagnosis (2).

We report a case in which a six-month diagnostic odyssey ultimately led to the identification of anti-MPO-positive pulmonary vasculitis, after all infectious, neoplastic, and structural causes had been rigorously excluded. This case underscores the importance of early ANCA testing in this clinical

context and illustrates how such testing can also provide a retrospective diagnosis of previously indeterminate nephropathy.

Case Presentation:

Background and Indeterminate Nephropathy:

A 32-year-old woman had been on maintenance hemodialysis for five years. Her original kidney disease remained indeterminate: she presented late with advanced chronic kidney disease, recurrent pulmonary edema, and bilateral small kidneys on ultrasound, which precluded safe renal biopsy. She had been anuric since the initiation of dialysis, with no residual urine output documented over the five-year period. She was hypertensive (controlled on a calcium channel blocker) and receiving vitamin D, calcium supplementation, and erythropoietin. No underlying autoimmune or infectious etiology had been identified at the time of dialysis initiation. She had no prior history of immunosuppressive therapy.

Onset of Hemoptysis:

Six months prior to diagnosis, she developed recurrent, mild-to-moderate hemoptysis, with episodes occurring every one to two weeks, sometimes with small clots. There was no associated fever, night sweats, weight loss, or extra-pulmonary symptoms (skin rash, arthralgia, sinusitis, or neurologic deficits). Her dialysis parameters were adequate (Kt/V >1.2), and ultrafiltration effectively controlled her volume status.

Extensive Infectious Workup:

Because the patient resided in a tuberculosis-endemic country, tuberculosis was the primary suspicion. In such settings, pulmonary vasculitis is frequently misdiagnosed as tuberculosis, leading to diagnostic delay (1). The following tests were performed over six months, all with negative results:

Investigation	Result
Sputum PCR for M. tuberculosis (3 samples)	Negative
Gastric lavage – PCR, smear, and culture	Negative
Mycobacterial culture (solid and liquid media, 42 days)	No growth
Tuberculin skin test (Mantoux)	0 mm (anergy)
Interferon-gamma release assay (IGRA)	Not available

Additional infectious etiologies were considered: CRP was persistently elevated (45–80 mg/L; normal <5 mg/L), but procalcitonin remained consistently normal (<0.1 ng/mL), arguing against typical bacterial infection. Fungal serologies (Aspergillus, Cryptococcus) and viral serologies (HIV, hepatitis B and C, EBV, CMV) were all negative.

Bronchoscopy and Bronchoalveolar Lavage:

- Flexible bronchoscopy was performed. Bronchoalveolar lavage (BAL) fluid analysis showed:
- Macroscopic appearance: Progressively bloodier returns, consistent with alveolar hemorrhage.
- Cytology: Numerous hemosiderin-laden macrophages (Perls' Prussian blue stain positive), confirming recurrent alveolar bleeding (3).
- Microbiology and virology: Negative for bacteria, fungi, mycobacteria (PCR and 42-day culture), CMV, HSV, and adenovirus.

Imaging:

High-resolution computed tomography (HRCT) of the chest revealed bilateral cavitating nodules, small pleural effusion, and ground-glass opacities. Echocardiography and abdominal ultrasound were normal. Tumor markers (CEA, CYFRA 21-1, NSE, CA 125) were negative.

Autoimmune and Immunological Workup:

After six months of exhaustive negative investigations, a systematic autoimmune panel was ordered:

Test	Result
Antinuclear antibodies (ANA)	Negative
Anti-dsDNA antibodies	Negative
Anti-MPO antibodies (P-ANCA by ELISA)	Strongly positive (>120 IU/mL; normal <20 IU/mL)
Anti-PR3 antibodies (C-ANCA by ELISA)	Negative
Anti-glomerular basement membrane (GBM) antibodies	Negative
Complement C3, C4	Normal
Cryoglobulins	Negative
Serum protein electrophoresis	Normal

The strong positivity for anti-MPO established the diagnosis of ANCA-associated pulmonary vasculitis (microscopic polyangiitis or granulomatosis with polyangiitis) (4, 5). ANCA testing by antigen-specific immunoassay provides a powerful diagnostic clue for systemic vasculitis (6). The detection and interpretation of ANCA have been standardized through international collaborative studies, which have established the clinical utility of both indirect immunofluorescence and antigen-specific immunoassays (6).

Retrospective Diagnosis of the Initial Nephropathy

The diagnosis of ANCA-associated vasculitis allowed a retrospective re-evaluation of the patient's long-standing indeterminate nephropathy. Many patients with ANCA-associated pauci-immune glomerulonephritis progress to end-stage renal disease without a prior renal biopsy, and the diagnosis is often missed or delayed (7). A study of patients with unexplained ESRD found that a significant proportion had serological evidence of prior ANCA-associated disease (7). Slowly progressive forms of renal-limited ANCA-associated vasculitis are poorly recognized and may present with indolent kidney disease that progresses to ESRD over many years (8).

In our patient, the unexplained ESRD with small kidneys and recurrent pulmonary edema prior to dialysis is highly suggestive of undiagnosed ANCA-associated glomerulonephritis that later manifested with pulmonary involvement. However, we acknowledge that other causes of chronic kidney disease with small kidneys (e.g., hypertensive nephrosclerosis) cannot be definitively excluded.

Treatment and Outcome:

Treatment was initiated with prednisone 1 mg/kg/day and monthly intravenous cyclophosphamide 500 mg (approximately 9 mg/kg based on the patient's weight of 55 kg) administered on non-dialysis days to avoid hemodialysis-induced drug clearance. Complete blood counts were monitored regularly. Hemoptysis resolved within two weeks. At three months, follow-up HRCT showed near-complete resolution of the cavitating nodules and ground-glass opacities. Anti-MPO antibody titers decreased by more than 80%. No severe neutropenia or infectious complications occurred.

Discussion:

This case illustrates several critical lessons for clinicians managing hemodialysis patients with unexplained hemoptysis, particularly in tuberculosis-endemic regions.

Diagnostic Delay Due to Tuberculosis Endemic Setting:

In tuberculosis-endemic countries, hemoptysis and cavitary lung lesions often trigger a reflexive, prolonged search for M. tuberculosis. Pulmonary vasculitis frequently goes undiagnosed due to lack of awareness and is commonly misdiagnosed as tuberculosis (1). Patients with systemic vasculitis may initially receive an incorrect diagnosis, with infection being the most common alternative(1) . This diagnostic challenge is compounded by the fact that pulmonary manifestations of ANCA-associated vasculitis, including cavitating nodules and alveolar hemorrhage, can closely mimic reactivation tuberculosis (4).

Furthermore, diagnostic delays in tuberculosis itself remain a significant problem in endemic areas. A systematic review and meta-analysis of diagnostic delay among pulmonary tuberculosis patients in East Africa found that the median total delay ranged from 30 to 90 days, with patient-related factors (lack of awareness, self-medication) and health system-related factors (misdiagnosis, referral delays) both contributing significantly(2) . In our patient, six months were spent on repeated negative infectious tests, leading to diagnostic exhaustion—a well-described phenomenon in regions where tuberculosis is highly prevalent.

Value of Bronchoscopy and Biomarkers:

This combination of elevated CRP with normal procalcitonin in a patient with alveolar hemorrhage (3), while normal procalcitonin despite elevated CRP argued strongly against bacterial infection. This combination of elevated CRP with normal procalcitonin in a patient with alveolar hemorrhage-should raise suspicion for non-infective inflammation, including vasculitis.

Bronchoalveolar lavage is a valuable diagnostic tool in this setting. The demonstration of hemosiderin-laden macrophages provides objective evidence of alveolar hemorrhage, which may be subtle or intermittent. The Prussian blue stain for hemosiderin is a simple, widely available test that can be performed on BAL fluid cytology specimens (3).

Pivotal Role of ANCA Testing:

ANCA testing provides a powerful and specific diagnostic clue for vasculitis (4, 6). The classification of ANCA-associated vasculitides has been refined over the past decades, with the Chapel Hill Consensus Conference providing standardized definitions (4). The detection of ANCA by both indirect immunofluorescence and antigen-specific immunoassays (anti-MPO and anti-PR3) is essential for accurate diagnosis and classification (6).

Even in tuberculosis-endemic areas, a positive anti-MPO antibody by ELISA is far more suggestive of ANCA-associated vasculitis than of tuberculosis, as false-positive ANCA in TB is rare with antigen-specific assays (5). In dialysis patients presenting with alveolar hemorrhage and a negative infectious workup, ANCA testing should be performed early, ideally at the time of initial presentation. The availability of standardized testing protocols, as established by the European Vasculitis Study Group (EUVAS), has improved the clinical utility of ANCA testing (6).

Retrospective Diagnosis of Indeterminate Nephropathy:

Perhaps the most important contribution of this case is the retrospective identification of the patient's initial nephropathy as probable ANCA-associated pauci-immune glomerulonephritis. It is increasingly recognized that slowly progressive forms of ANCA-associated vasculitis with renal involvement are frequently underdiagnosed and often lead to end-stage renal disease without an established etiology (7, 9).

A retrospective study of patients with unexplained ESRD found that a significant proportion had serological evidence of prior ANCA-associated disease (8) The clinical course of ANCA-associated vasculitis in patients with end-stage renal disease has been characterized in several studies, with some patients presenting with renal-limited disease that progresses slowly to ESRD before extra-renal manifestations appear (7, 9). Patients with ANCA-associated vasculitis who progress to ESRD may have a more indolent disease course and may be less likely to receive a definitive diagnosis before starting dialysis (7).

Our case supports this concept and emphasizes the importance of ANCA testing in any dialysis patient of unknown primary nephropathy who later develops unexplained pulmonary symptoms. The diagnosis of ANCA-associated vasculitis in a patient already on dialysis has important implications for management, as it may guide immunosuppressive therapy and influence decisions regarding kidney transplantation.

Limitations:

We acknowledge that histopathological confirmation (renal or lung biopsy) was not obtained, due to the patient's small kidney size and the risks of bleeding in a dialysis-dependent patient. The diagnosis therefore rests on a combination of strong serological positivity, typical imaging findings, BAL evidence of alveolar hemorrhage, and a dramatic clinical response to immunosuppression. While this is consistent with ANCA-associated vasculitis, tissue confirmation would have provided additional certainty.

Additionally, the retrospective nature of the diagnosis of the original nephropathy is a limitation. We cannot definitively prove that the patient's original kidney disease was ANCA-associated glomerulonephritis, as no renal biopsy or serum from the time of dialysis initiation was available for testing.

Conclusion

This case provides a practical algorithm for investigating recurrent hemoptysis in a chronic hemodialysis patient from a tuberculosis-endemic country:

- Rule out tuberculosis with extended cultures and molecular testing
- Perform BAL to confirm alveolar hemorrhage
- Check CRP and procalcitonin to differentiate infection from sterile inflammation
- Exclude structural and neoplastic causes
- When all are negative, perform ANCA testing (both IIF and antigen-specific ELISA)

Strongly positive anti-MPO antibodies point to pulmonary vasculitis. Furthermore, this diagnosis allowed the retrospective identification of the initial indeterminate nephropathy as probable ANCA-associated glomerulonephritis. Early ANCA testing may significantly shorten diagnostic delay and prevent unnecessary repetitive infectious workups.

Investigation	Result	Implication
Sputum/gastric PCR and 42-day culture	Negative	Tuberculosis excluded
BAL hemosiderin-laden macrophages	Positive	Alveolar hemorrhage confirmed
CRP / Procalcitonin	Elevated / Normal	Non-bacterial inflammation
Cardiac and abdominal ultrasound	Normal	No structural source
Tumor markers	Negative	Malignancy unlikely
Anti-MPO (P-ANCA by ELISA)	Strongly positive (>120 IU/mL)	ANCA-associated vasculitis

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