Case report

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Fever, renal failure, and diffuse alveolar hemorrhage: Unraveling the ANCA vasculitis connection

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Abstract

***Background*: Microscopic polyangiitis (MPA), a small-vessel antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, may present insidiously with prolonged fever, renal dysfunction, and pulmonary infiltrates—often mimicking infections, especially in tropical settings.**

***Case presentation*: A 61-year-old man with longstanding type 2 diabetes, hypertension, and a previous cerebrovascular accident presented with a 3-month history of low-grade fever, exertional dyspnea, fatigue, and pedal edema. He initially received meropenem for pan-resistant Klebsiella urinary infection; later received Helicobacter pylori therapy for gastritis. However, he remained febrile with rising creatinine. On admission, he was tachypneic, hypoxemic, and oliguric, with bilateral lung infiltrates, microscopic hematuria, and anemia (hemoglobin 5.5 g/dl). Infectious workup—including tropical fevers and tuberculosis—were negative. Perinuclear ANCA (P-ANCA) titre >200 U/ml, computerized tomography (CT) lung findings consistent with diffuse alveolar hemorrhage (DAH), and bronchoalveolar lavage positive for hemosiderin-laden macrophages established the diagnosis of MPA. Due to poor renal reserve, the biopsy was deferred. Treatment included intravenous pulse methylprednisolone (1 g/day × 3), three cycles of plasma exchange, and supportive low-efficiency dialysis. He improved clinically, was weaned off oxygen, and transitioned to oral steroids.**

***Conclusion*: This case illustrates the diagnostic challenge of MPA presenting as prolonged pyrexia of unknown origin (PUO) with pulmonary-renal syndrome in a tropical context. After excluding infectious causes, early consideration of ANCA-associated vasculitis and prompt immunosuppressive therapy can be lifesaving.**

Keywords: Microscopic polyangiitis, ANCA, diffuse alveolar hemorrhage, rapidly progressive glomerulonephritis, pulmonary-renal syndrome, tropical, PUO.

Introduction

Microscopic polyangiitis (MPA) is a systemic necrotizing vasculitis that predominantly affects small-caliber vessels, including capillaries, venules, and arterioles, and is strongly associated with perinuclear antineutrophil cytoplasmic antibodies (p-ANCA), particularly directed against myeloperoxidase (MPO). (1) It is part of the broader group of ANCA-associated vasculitides (AAV), which also includes granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA). (2) Among these, MPA lacks granulomatous inflammation and upper airway involvement, distinguishing it from GPA.

The disease primarily manifests as rapidly progressive glomerulonephritis (RPGN) and pulmonary involvement, particularly diffuse alveolar hemorrhage (DAH), both of which may be life-threatening and demand prompt recognition and treatment. Constitutional symptoms such as fever, weight loss, malaise, and arthralgia often precede organ-specific signs, making early diagnosis challenging and frequently resulting in delayed treatment.

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In elderly individuals, especially those presenting with pyrexia of unknown origin (PUO), anemia, and progressive renal dysfunction, MPA should be considered as a potential etiology. (3) Positive p-ANCA serology with high MPO antibody titers, active urinary sediment, and radiologic evidence of pulmonary infiltrates are key diagnostic clues. A timely diagnosis and initiation of immunosuppressive therapy are crucial for improving outcomes and preventing irreversible organ damage.

In resource-constrained settings, where infectious etiologies like tuberculosis and leptospirosis are prevalent, the diagnosis of MPA is often delayed due to its overlapping clinical features with common tropical diseases. We report a case of a 61-year-old male who initially presented with PUO, progressive renal dysfunction, and later developed hemoptysis. Further evaluation confirmed a diagnosis of microscopic polyangiitis with pulmonary-renal syndrome. This case highlights the diagnostic complexity and the importance of early intervention in AAV.

Case presentation

A 61-year-old male with a history of diabetes mellitus (glycated haemoglobin: 6.3%), systemic hypertension, and an old cerebrovascular accident on single antiplatelet therapy, presented with low-grade fever, exertional breathlessness, pedal edema, and fatigue for three months. He was initially evaluated for PUO at another facility for two weeks, where a urine culture yielded pan-resistant Klebsiella pneumoniae, for which meropenem was administered. His creatinine rose from 1.5 to 2.8 mg/dl during hospitalization. Upper gastrointestinal (GI) endoscopy done in view of abdominal symptoms and anemia revealed a positive rapid urease test and chronic gastritis, and Helicobacter pylori eradication therapy was started. Despite antibiotic therapy for a urinary tract infection, he remained febrile, and renal function continued to decline.

He was referred to our tertiary centre for evaluation. The patient presented to our hospital with a history of unexplained fever for 3 months, breathlessness for 3 months, and worsening renal function. History was negative for night sweats, weight loss, diarrhoea, vomiting, recurrent sinonasal infections, intravenous (IV) drug abuse, high-risk behaviour, photosensitivity, rashes, or joint pains. There was no history of malignancy or autoimmune disorders in the family.

On admission, he was febrile (99.8 °F), tachypneic (respiration rate 35/min), tachycardic (pulse rate 120/min), and hypoxemic on room air (peripheral oxygen saturation [SpO2] 84%). He was admitted to the Critical Care Unit and was started on non-invasive ventilation.

On examination, jugular venous pressure (JVP) was elevated, and bilateral pitting pedal edema was present—no skin lesions. Lung examination revealed bilateral polyphonic wheeze and fine crepitations. Neurological exam showed right lower limb hypertonia and brisk deep tendon reflexes, consistent with a prior cerebrovascular event. Initial laboratory investigations are shown in **Table 1**.

In the background of a PUO, microscopic hematuria, worsening renal function, and pulmonary infiltrates, anemia in a tropical setting, differentials considered were leptospirosis, complicated urinary tract infection/pyelonephritis, tuberculosis, and GI malignancy. Evaluation was done for dengue IgM and IgG, scrub typhus IgM, and leptospira IgM, all of which were negative. Blood and urine cultures were sterile. Chest X-ray revealed heterogeneous opacities in the bilateral lung fields. A contrast-enhanced computerized tomography (CT) thorax showed bilateral pleural effusions, mild pericardial effusion, and bilateral patchy ground-glass opacities with interstitial thickening, predominantly in the lower lobes. This was initially suspected to represent endobronchial spread of infection. However, sputum acid-fast bacilli (AFB) and cartridge-based nucleic acid amplification test (CBNAAT) were negative, as were urine AFB and CBNAAT. The Mantoux test was also negative.

Figures 1A and **1B** show lower and upper thoracic cuts in the lung window, showing ground glass opacities, interstitial thickening, and tree-in-bud appearance.

Given the presence of anemia in a sixty-year-old male, upper GI endoscopy was performed and revealed antral gastritis; colonoscopy showed external hemorrhoids and no colonic malignancy.

At this juncture, the possibility of a vasculitic process was raised, given the rapidly progressive renal failure and pulmonary infiltrates. Complement levels (C3, C4) were normal, and antinuclear antibody (ANA) and anti-double-stranded deoxyribonucleic acid (anti-dsDNA) were negative, ruling out lupus. ANCA testing revealed strongly positive p-ANCA (titre>200) and negative cytoplasmic ANCA (c-ANCA). A nephrology consultation was sought for a renal biopsy. CT abdomen done to look for kidneys, showed a relatively small left kidney with focal cortical thinning; renal artery doppler was done, which showed no evidence of renal artery stenosis; the patient had orthopnea and could not lie flat, hence, biopsy was deferred.

A drop in hemoglobin in the setting of persistent hypoxia raised suspicion of diffuse alveolar hemor-

rhage (DAH). To rule out Goodpasture syndrome, an anti-glomerular basement membrane (anti-GBM) antibody test was performed, which was negative. Bronchoalveolar lavage from the right upper lobe posterior segment showed a hemorrhagic return. Cytology revealed hemosiderin-laden macrophages, with Perls' Prussian blue stain positive, confirming DAH.

Based on the constellation of rapidly progressive glomerulonephritis, diffuse alveolar hemorrhage, and a strongly positive p-ANCA, the patient was diagnosed with microscopic polyangiitis (MPA). A multidisciplinary team, including the treating physician, nephrology, rheumatology, and the intensive care unit, decided to initiate pulsing steroids. He was treated with intravenous high-dose methylprednisolone (1 g/day) for three days. The patient had persistent hypoxia, with a diagnosis of DAH; three cycles of plasma exchange (PLEX) were done. Slow low-efficiency dialysis (SLED) was done intermittently through the intensive care unit (ICU) stay. Patient required prolonged ICU care in view of PLEX and hemodialysis. Post steroids and plasma exchange, renal parameters improved. Ventilatory support was reduced to a venturi mask, and the patient was maintained on room air. The patient was then shifted to the ward. Creatinine at discharge was 2.4. On discharge, he was continued on oral prednisolone at 1 mg/kg body weight in divided doses and planned for maintenance immunosuppression with cyclophosphamide at follow-up. **Figure 2** shows the trend of creatinine.

Discussion

MPA is a rare, yet severe, small-vessel vasculitis that most commonly affects the kidneys and lungs. In critical care settings, it may present as a diagnostic enigma due to its insidious onset, constitutional symptoms, and overlap with infectious or autoimmune disorders. (1) Our patient's initial presentation suggested more common tropical or infective etiologies. In regions where infections such as tuberculosis, enteric fever, and leptospirosis are endemic, the possibility of vasculitis is often overlooked in the early stages, leading to potentially avoidable diagnostic delays. (2)

The renal manifestation of MPA, RPGN, typically involves bland urinary sediments, microscopic hematuria, non-nephrotic proteinuria, and a progressive decline in renal function. Our patient developed progressive azotemia and oliguria with microscopic hematuria. A renal biopsy, had it been feasible, would likely have revealed the hallmark lesion of necrotizing, crescentic, pauci-immune glomerulonephritis. However, due to reduced renal size, cortical thinning, and the patient's general condition, biopsy was contraindicated. In such situations, diagnosis often rests on a strong clinical index of suspicion, serological testing (especially ANCA), and radiological and bronchoalveolar lavage findings.

Pulmonary involvement in MPA may range from asymptomatic infiltrates to fulminant DAH. In our case, the patient developed bilateral infiltrates and hypoxemic respiratory failure, initially presumed to be pneumonia. The absence of response to antibiotics and the presence of falling hemoglobin, without overt hemoptysis, prompted further evaluation. Bronchoalveolar lavage, confirming hemosiderin-laden macrophages, established DAH. DAH is a serious complication and is frequently the cause of ICU admission in MPA patients. Importantly, hemoptysis may be absent in up to 30% of cases, underscoring the need for high clinical suspicion. (3)

The definitive diagnosis was supported by a markedly elevated p-ANCA (anti-MPO) level. Although ANCA positivity is not pathognomonic, in the right clinical context, it is highly suggestive. Anti-GBM disease (also known as Goodpasture syndrome) can sometimes occur alongside ANCA-associated small-vessel vasculitis. In fact, nearly 45% of patients with anti-GBM disease also test positive for ANCA, most often MPO-ANCA. Suppose a patient with a history of anti-GBM disease starts showing signs of a recurrence. In that case, it's important to check for ANCA—even if their previous tests were negative—since true relapses of anti-GBM disease are uncommon. Interestingly, patients who have both anti-GBM antibodies and ANCA tend to have worse kidney outcomes than those with ANCA vasculitis alone. However, their prognosis is still better than that of those with anti-GBM disease by itself.

Given the severity of both renal and pulmonary involvement, our patient met the criteria for generalized disease requiring prompt induction therapy.

The cornerstone of induction therapy in MPA remains high-dose corticosteroids combined with either cyclophosphamide or rituximab. (4) The addition of PLEX in cases of DAH or severe renal impairment has been debated. Still, findings from the PEXIVAS trial suggest a selective benefit (4)—particularly in patients with life-threatening manifestations such as severe DAH or need for dialysis. (5) In this case, we opted for pulse methylprednisolone (1 g IV daily × 3 days), followed by oral corticosteroids, alongside three cycles of plasma exchange. The clinical improvement in oxygenation and renal output following therapy further validated our approach.

An important consideration is the burden of diagnostic uncertainty and the risk of therapeutic delay

in real-world settings. Infections, particularly in tropical countries, often cloud the clinical picture, delaying immunosuppressive therapy. (3) In our patient, the delay was further compounded by the absence of a renal biopsy and initial improvement with supportive care. However, had immunosuppression been delayed further, irreversible renal damage or fatal pulmonary hemorrhage may have ensued.

A multidisciplinary approach, involving an interplay among internal medicine, nephrology, rheumatology, and critical care, was vital for establishing the diagnosis and guiding treatment. Multidisciplinary collaboration remains a cornerstone in the management of complex vasculitic syndromes like MPA. (6)

Conclusion

This case highlights the importance of maintaining a broad differential diagnosis in evaluating pyrexia of unknown origin, especially in an elderly patient with multiple comorbidities. In our setting, tropical infections such as leptospirosis, scrub typhus, and tuberculosis are common causes of PUO, and these were appropriately considered and ruled out. However, his progressive renal dysfunction, microscopic hematuria, and persistent pulmonary infiltrates made us consider other possibilities.

A key turning point in the case was the recognition of pulmonary-renal involvement, which led to evaluation for vasculitis. The positive p-ANCA with a high titre, along with the presence of hemosiderin-laden macrophages on bronchoalveolar lavage, confirming diffuse alveolar hemorrhage, strongly pointed toward microscopic polyangiitis (MPA). Although a renal biopsy would have helped confirm the diagnosis, it had to be deferred due to reduced kidney size and poor cortical thickness on imaging. Nevertheless, the clinical picture, serology, and imaging were consistent with a diagnosis of MPA.

Treatment was initiated promptly with intravenous high-dose steroids, followed by plasma exchange and supportive care, including dialysis. The patient required a prolonged ICU stay due to the severity of his illness, but his condition gradually improved. His oxygen requirements reduced, renal function stabilized, and he was eventually weaned off ventilatory support and shifted to the ward.

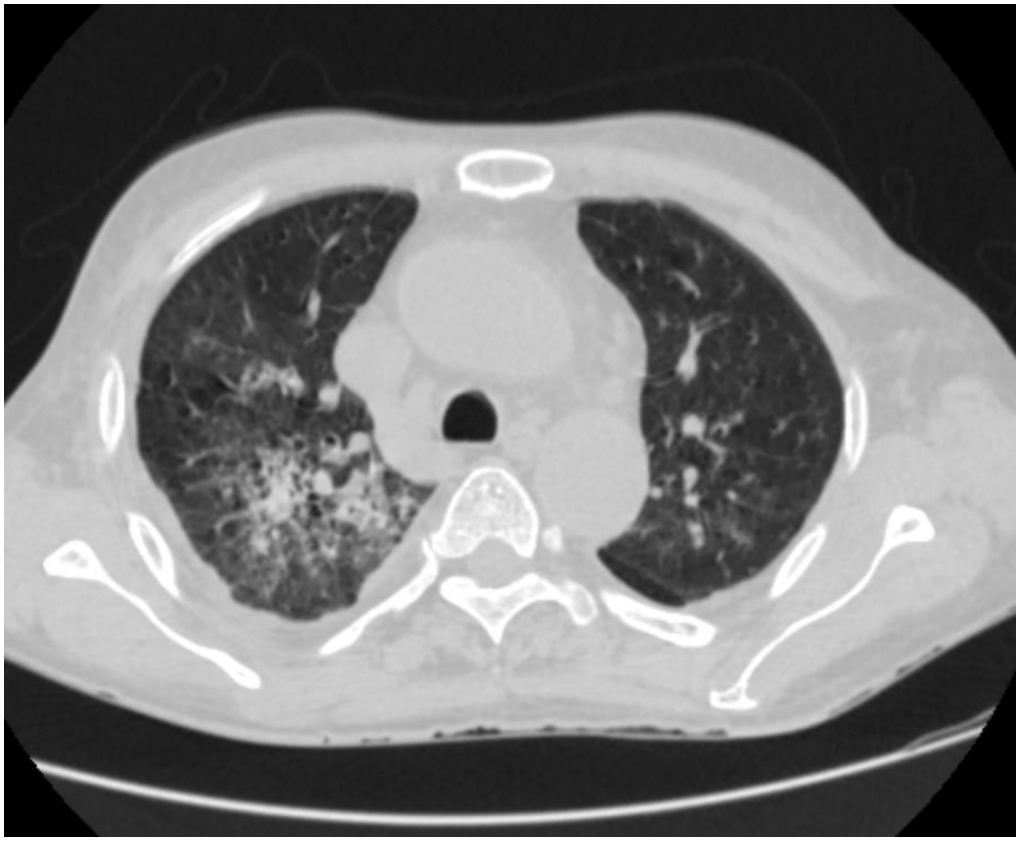
This case is a reminder that autoimmune conditions like ANCA-associated vasculitis can present subtly, mimicking infections or malignancy, especially in elderly patients. Early recognition and prompt immunosuppressive therapy can significantly alter the course of illness. It also emphasizes the value of multidisciplinary care in managing such complex presentations, involving intensivists, nephrologists, pulmonologists, and rheumatologists working together to achieve a good outcome.

Table 1. Basic relevant investigations

Relevant investigations	Patient's values	Reference values
BUN (mg/dl)	82	7–18
Creatinine (mg/dl)	7.5	0.6–1.3
Electrolytes - Sodium (mmol/l) - Potassium (mmol/l) - Bicarbonate (mmol/l)	 123 4.8 16	 134–144 3.5–5 21–29
Urine protein	1+	Nil
Urine RBC (/hpf)	6–8	Nil
Hemogram - Hemoglobin (g/dl) - Platelets (/mm^3) - WBC (/mm^3) - MCV (fl)	 5.5 6.82 x 10^5 22,160 78	 12–17 1.5–4.5 x 10^5 4000–11000 83–101
Liver function tests - Total bilirubin (mg/dl) - SGOT (U/l) - SGPT (U/l) - Albumin (g/dl)	 0.9 12 15 2.7	 0.1–1.2 0–35 0–41 3.2–4.8
ESR (mm/hr)	119	4–19
ECG	Normal sinus rhythm	-
Chest Roentgenogram	Heterogenous opacities in bilateral lung fields	-
Peripheral smear	Microcytic hypochromic anemia	-
Ferritin (ng/ml)	1191	300–400
Serum iron (mcg/dl)	12	60–180
TIBC (mcg/dl)	182	-
Stool occult blood	Negative	-

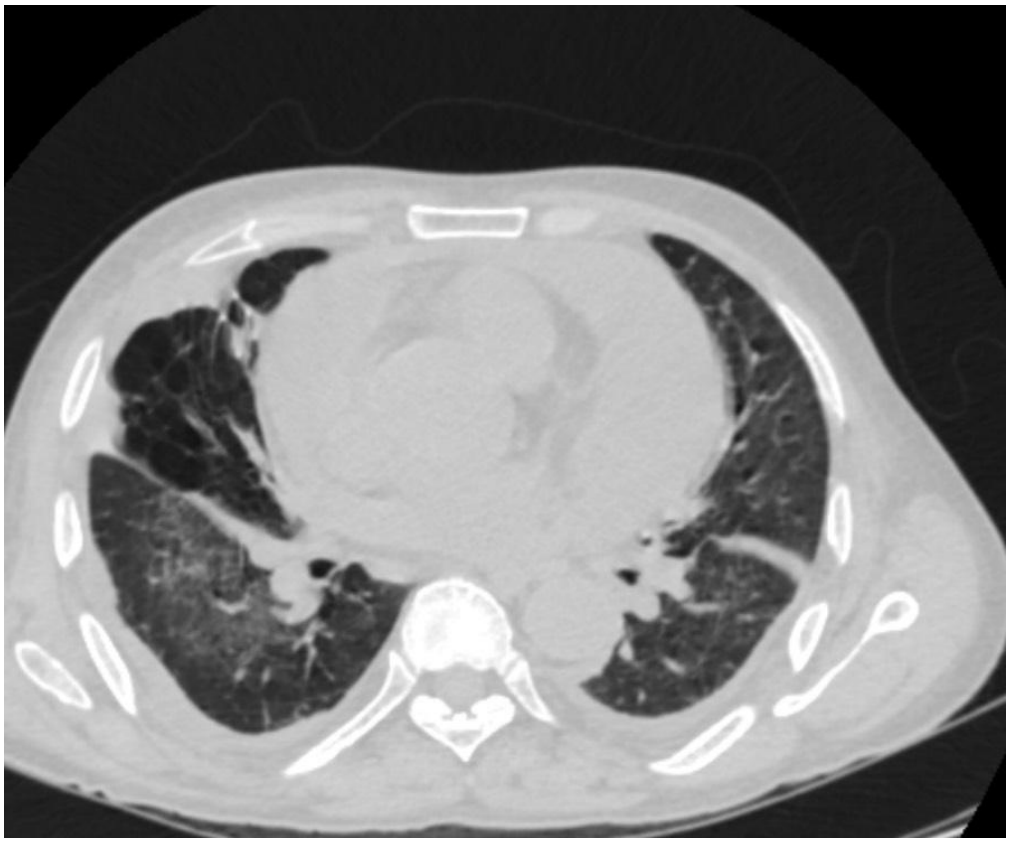
Legend: BUN=blood urea nitrogen; RBC=red blood cells; WBC=white blood cells; MCV=mean corpuscular volume; SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamic pyruvic transaminase; ESR=erythrocyte sedimentation rate; ECG=electrocardiogram; TIBC=total iron binding capacity.

Figure 1A. Lung window (upper thoracic cut)



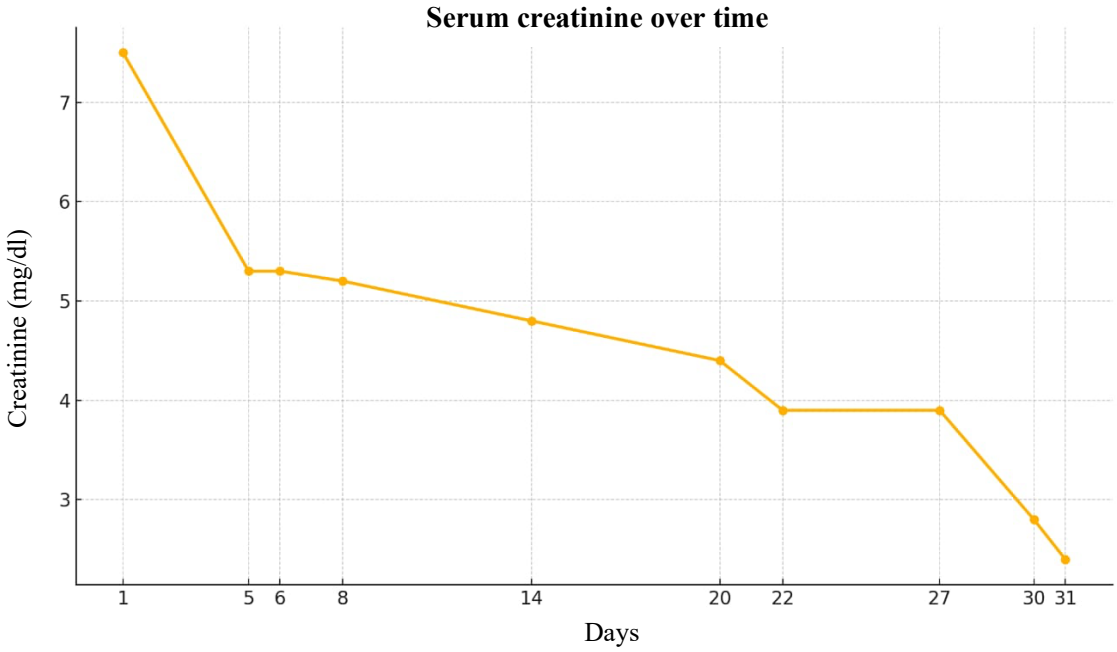
Legend: Dense consolidation with air bronchograms involving the posterior segment of the right upper lobe and part of the superior segment of the right lower lobe, peribronchial thickening and ground-glass opacities in the left upper lobe, and mild mediastinal lymphadenopathy.

Figure 1B. Lung window (lower thoracic cut)



Legend: Bilateral patchy ground-glass opacities with interstitial thickening, predominantly in the lower lobes, more on the right side. Classic of a tree-in-bud appearance, suggestive of endobronchial infection.

Figure 2. The trend in in-hospital creatinine



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