Case Report

AN UNUSUAL PRESENTATION OF ANTI-GLOMERULAR BASEMENT MEMBRANE (GBM) DISEASE WITH SEVERE ANEMIA

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ABSTRACT

Background: Anti–glomerular basement membrane (anti-GBM) disease is a rare autoimmune small-vessel vasculitis classically characterized by rapidly progressive glomerulonephritis and pulmonary hemorrhage. Anemia is frequently observed but is usually mild to moderate and secondary to inflammation or bleeding. Severe anemia as the initial and predominant manifestation is distinctly uncommon and may lead to diagnostic delay.

Case presentation: We report the case of a 21-year-old woman who presented with a three-month history of profound, transfusion-dependent normocytic anemia associated with fever, asthenia, and mild respiratory symptoms, in the absence of initial renal impairment. Extensive hematological, infectious, and autoimmune investigations were unremarkable. Renal function was preserved and urinalysis was not performed at presentation. Several weeks later, the patient developed rapidly progressive acute kidney injury and hemoptysis. Imaging revealed diffuse alveolar hemorrhage, and serological testing demonstrated circulating anti-GBM antibodies. Renal biopsy confirmed crescentic glomerulonephritis with linear IgG deposition along the glomerular basement membrane. Immunosuppressive therapy with high-dose corticosteroids, cyclophosphamide, and plasmapheresis was promptly initiated. After treatment, the patient showed progressive clinical improvement, with a gradual increase and subsequent stabilization of hemoglobin levels and complete resolution of pulmonary manifestations. Despite only partial renal recovery, she required temporary hemodialysis and ultimately underwent successful living-donor kidney transplantation following sustained anti-GBM antibody negativity.

Conclusion: This case highlights severe anemia as an unusual presenting feature of anti-GBM disease and emphasizes the importance of considering small-vessel vasculitis in the differential diagnosis of unexplained anemia. Early urinalysis and immunological testing are crucial to avoid diagnostic delay and to enable timely initiation of life-saving therapy.

Një paraqitje e pazakontë e sëmundjes anti–membranë bazale glomerulare (GBM) me anemi të rëndë

Key words: anemia, anti-glomerular basement membrane disease, small vessel vasculitis, rapidly progressive glomerulonephritis, pulmonary hemorrhage

NJË PARAQITJE E PAZAKONTË E SËMUNDJES ANTI–MEMBRANË BAZALE GLOMERULARE ME ANEMI TË RËNDË

ABSTRAKT

Hyrje Sëmundja anti–membranë bazale glomerulare (anti-GBM) është një vaskulit autoimun i rrallë i enëve të vogla te gjakut, i karakterizuar në mënyrë klasike nga glomerulonefriti me progresion të shpejtë dhe hemorragjia pulmonare. Anemia vërehet shpesh, por zakonisht është e lehtë deri e moderuar dhe dytësore ndaj inflamacionit ose gjakderdhjes. Paraqitja me anemi të rëndë si manifestimi fillestar dhe dominues është dukshëm e rrallë dhe mund të çojë në vonesë diagnostike.

Paraqitja e rastit: Raportojmë rastin e një paciente 21-vjeçare që u paraqit me histori tre mujore të anemisë së rëndë normocitare normokromike, të varur nga transfuzionet, e shoqëruar me temperatur, asteni dhe simptoma respiratore të lehta, në mungesë të dëmtimit fillestar të funksionit renal. Ekzaminimet e gjera hematologjike, infektive dhe autoimune rezultuan pa gjetje patologjike. Funksioni renal ishte i ruajtur por analiza e urinës nuk u krye në momentin e paraqitjes. Pas disa javësh, pacientja zhvilloi dëmtim akut renal me progresion të shpejtë dhe hemoptizi. Ekzaminimet imazherike evidentuan hemorragji alveolare difuze, ndërsa testimi serologjik tregoi praninë e antitrupave qarkullues anti-GBM. Biopsia renale konfirmoi glomerulonefrit me kreshente dhe depozitim linear të IgG përgjatë membranës bazale glomerulare. U fillua menjëherë terapi imunosupresive me kortikosteroide me dozë të lartë, ciklofosfamid dhe plazmaferezë. Pas trajtimit, pacientja shfaqi përmirësim klinik progresiv, me rritje graduale deri ne stabilizim të niveleve të hemoglobinës, si dhe resolvim të plotë të manifestimeve pulmonare. Nga pikepamja renale pacientja ju nenshtrua trajtimit dialitik te perkoheshem i cili u pasua nga nje rekuperim i pjeseshem i funskion renal dhe mbas 1,5 vitesh iu nënshtrua me sukses transplantitt renal nga dhurues i gjallë pas negativizimit të qëndrueshëm të antitrupave anti-GBM.

Konkluzioni: Ky rast thekson aneminë e rëndë si një paraqitje të pazakontë të sëmundjes anti-GBM dhe nënvizon rëndësinë e përfshirjes së vaskuliteve të enëve të vogla në diagnozën diferenciale të anemive të pashpjeguara. Kryerja e hershme e analizës së urinës dhe testimi imunologjik janë thelbësore për të shmangur vonesën diagnostike dhe për të mundësuar fillimin në kohë të terapisë shpëtuese për jetën.

Fjalët kyçe: anemi, sëmundja anti–membranë bazale glomerulare, vaskulit i enëve të vogla,

glomerulonefrit me progresion të shpejtë, hemorragji pulmonare

INTRODUCTION

Anti–glomerular basement membrane (anti-GBM) disease, previously known as Goodpasture syndrome, is a rare but potentially life-threatening autoimmune vasculitis characterized by renal and pulmonary involvement. The disease is mediated by circulating anti-GBM antibodies directed against the non-collagenous (NC1) domain of the α3 chain of type IV collagen, a crucial component of the glomerular and alveolar basement membranes. Anti-GBM disease has an estimated prevalence of 1–2 cases per million population and presents a bimodal age distribution, with incidence peaks in the third and sixth decades of life. Although no well-defined risk factors have been identified, environmental and host-related factors such as smoking, inhalation of hydrocarbons, and a personal or family history of autoimmune disease have been implicated as potential triggers.

Clinically, patients may present with constitutional symptoms, including fever, malaise, weight loss, and arthralgia. Renal involvement, which occurs in more than 90% of cases, typically manifests as rapidly progressive crescentic glomerulonephritis, characterized by acute deterioration of renal function and nephritic urinary sediment. Pulmonary involvement is observed in approximately 30–60% of patients and is most commonly due to alveolar hemorrhage, presenting with hemoptysis, although in some cases it may manifest abruptly as life-threatening diffuse alveolar hemorrhage.
Mild anemia is a usual finding in anti-GBM disease, as in other small vessel vasculitis, and is usually attributed to systemic inflammation, pulmonary hemorrhage, and macrohematuria. However, severe anemia as the initial and predominant clinical manifestation is distinctly uncommon and may result in significant diagnostic delay.

Here, we report the case of a young female patient who presented with a three-month history of profound anemia, in whom the classical renal and pulmonary features of anti-GBM disease became evident only later in the disease course. This case highlights the importance of considering small vessel vasculitis, such as anti-GBM disease, in the differential diagnosis of unexplained severe anemia and underscores the value of early urinalysis and immunological testing to enable timely diagnosis and prompt initiation of immunosuppressive therapy.

CASE PRESENTATION

We present the case of a 21-year-old caucasian woman with no relevant past medical history and no family history of renal or autoimmune disease. She had been an active smoker during the previous year. Since October 2023, she developed recurrent episodes of hyperpyrexia (up to 39°C), alternating with subfebrile temperatures (37.2–37.3°C), associated with progressive and severe asthenia, pallor, dry cough, and profuse sweating. After approximately two months of persistent symptoms, laboratory investigations performed in January 2024 revealed severe normocytic normochromic anemia (Hemoglobin 3.9 g/dL), prompting urgent referral to the Hematology Unit.

Initial diagnostic workup An extensive diagnostic evaluation was performed, including protein and hemoglobin electrophoresis, immunoelectrophoresis, reticulocyte count, complement levels (C3, C4), autoimmune screening (ANA, ANCA including MPO-ANCA and PR3-ANCA, rheumatoid factor, AMA, anti-CCP, anti–double-stranded DNA antibodies), tumor markers (CEA, CA 19-9, CA 15-3, alpha-fetoprotein), and serological testing for hepatitis B and C viruses, HIV-1/2, cytomegalovirus, and Toxoplasma gondii. All investigations were unremarkable. Bone marrow aspiration and immunophenotyping excluded hematological malignancy or bone marrow failure syndromes.

Transthoracic echocardiography and cardiologic evaluation resulted in normal. Upper gastrointestinal endoscopy excluded gastrointestinal bleeding, showing only hyperemic duodenal bulb mucosa and a hiatal hernia.
At that time, renal function was preserved (serum creatinine 0.6 mg/dL, urea 26.2 mg/dL), and renal ultrasonography revealed kidneys of normal size and echogenicity with no evidence of obstruction or chronic parenchymal disease. Unfortunately, urinalysis was not performed at presentations.
Since no clear etiology of such severe anemia was found, the patient proceeded with follow-up and was treated with subsequent red blood cell transfusions, remaining transfusion-dependent for several weeks.

DIAGNOSIS

In March 2024, during a follow-up hematology consultation, a rapid deterioration of renal function was detected in a few days (Creatinine 0.6→ 5.08 mg/dL; Urea 26,2→ 118 mg/dL) associated with worsening of pulmonary symptoms with hemoptysis leading to urgent admission to our Nephrology Unit.
On admission, clinical and laboratory findings were consistent with a reno-pulmonary syndrome, characterized by rapidly progressive acute kidney injury with macroscopic hematuria, active nephritic urinary sediment, subnephrotic-range proteinuria, and pulmonary hemorrhage confirmed at chest contrast-enhanced computed tomography (CT) which showed bilateral pulmonary parenchymal opacities with a diffuse ground-glass pattern, more pronounced in the right lung, consistent with diffuse alveolar hemorrhage.
Based on the clinical presentation, anti–glomerular basement membrane (anti-GBM) disease was strongly suspected. Urgent serological testing confirmed the presence of circulating anti-GBM antibodies, subsequently corroborated by immunoblot analysis. The diagnosis was confirmed by renal biopsy, which showed on light microscopy revealed crescentic glomerulonephritis with fibrocellular crescents involving most sampled glomeruli and disruption of Bowman's capsule, without significant interstitial fibrosis or tubular atrophy. Immunofluorescence microscopy demonstrated strong, diffuse linear IgG deposition along the glomerular basement membranes in all evaluable glomeruli, with a corresponding linear pattern for both kappa and lambda light chains. IgA, IgM, C3, and C1q staining were negative. These findings were diagnostic of anti-GBM disease and concordant with the serological results.

Treatment and follow-up

Given the fulminant presentation and high mortality associated with anti-GBM disease, immunosuppressive therapy was initiated immediately. The patient received high-dose intravenous methylprednisolone (1g daily for three consecutive days), followed by oral prednisone at 1 mg/kg/day associated with intravenous cyclophosphamide (500 mg ev every two weeks) and therapeutic plasmapheresis.
During hospitalization, clinical conditions improved with a slow but progressive increase in hemoglobin levels; pulmonary manifestations progressively resolved, as corroborated by radiologic improvement. Unfortunately, despite preserved residual diuresis, renal function initially continued to deteriorate, necessitating the initiation of renal replacement therapy. The patient underwent twice-weekly maintenance hemodialysis from April to August 2024. Subsequently, a gradual but partial recovery of renal function was observed, allowing discontinuation of dialysis. At follow-up, the patient has remained dialysis-free for approximately 18 months, with stable chronic kidney disease stage 4 under conservative management. During this period, circulating anti-GBM antibodies remained persistently negative, and no recurrence of pulmonary hemorrhage was documented.
Following immunosuppressive treatment, hemoglobin levels stabilized and remained within the therapeutic target range under erythropoietin support.

DISCUSSION

Anti–glomerular basement membrane (anti-GBM) disease is a rare autoimmune vasculitis characterized by rapidly progressive glomerulonephritis and, in a subset of patients, pulmonary hemorrhage. Despite its well-described clinical triad, the initial presentation may be heterogeneous, leading to diagnostic delay and adverse renal outcomes. This case illustrates an uncommon presentation of anti-GBM disease, in which severe anemia represented the predominant and earliest clinical manifestation, preceding overt renal and pulmonary involvement by several months.

Anemia is frequently observed in anti-GBM disease and is typically multifactorial, resulting from systemic inflammation, urinary blood loss, and overt or occult alveolar hemorrhage. However, profound anemia as the initial and isolated manifestation is distinctly uncommon. In the present case, the patient experienced a three-month history of transfusion-dependent anemia before the development of rapidly progressive renal failure and clinically manifested alveolar hemorrhage. During this early phase, renal function was preserve contributing to a delay in recognizing the underlying process.

Pulmonary involvement in anti-GBM disease may be clinically overt or subclinical. Occult alveolar hemorrhage can lead to significant iron loss and anemia even in the absence of massive hemoptysis or acute respiratory failure. In our patient, early respiratory symptoms were present but nonspecific, and imaging initially suggested an interstitial pattern, underscoring how pulmonary hemorrhage may be misinterpreted as infectious or inflammatory lung disease.

Renal involvement ultimately followed a fulminant course, with rapid progression from normal renal function to dialysis-dependent kidney failure. Early initiation of immunosuppressive therapy, including high-dose corticosteroids, cyclophosphamide, and plasmapheresis, is the cornerstone of anti-GBM disease management and is associated with

improved patient survival. In this case, despite prompt treatment after diagnosis, the patient required maintenance hemodialysis, although a partial and transient recovery of renal function allowed discontinuation of renal replacement therapy for approximately 18 months. This fluctuating course reflects the severe initial glomerular injury demonstrated by crescentic glomerulonephritis on renal biopsy.

This case emphasizes several important clinical lessons. First, small vessel vasculitis, such as anti-GBM disease, should be considered in the differential diagnosis of unexplained severe anemia, especially when accompanied by systemic symptoms. Second, early urinalysis and immunological testing are essential to avoid diagnostic delay. Finally, although renal prognosis remains poor in advanced disease, timely diagnosis and appropriate long-term management can allow stabilization and recovery of extra-renal manifestations.

CONCLUSIONS

Severe unexplained anemia may represent an early manifestation of small vessel vasculitis, such as anti-GBM disease, and should prompt diagnostic evaluation particularly in the presence of systemic symptoms.
Immunosuppressive therapy can lead to rapid and sustained correction of anemia, highlighting hemoglobin as a potential marker of disease activity. Early urinalysis and immunological testing are essential to avoid diagnostic delay and improve outcomes.

Conflicts of interest: The authors declare that they have no conflicts of interest.

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