

Zitlali Guadalupe Paulín Zepeda , Louis Fernando Robles Fernandes , Vianey Guadalupe Tellez Bolaños , José Carlos Ortiz Díaz , María Inés Gil Arredondo
Centro Médico Nacional Siglo XXI, Mexican Institute of Social Security, Mexico City, Mexico

Rapidly progressive glomerulonephritis and ANCA-negative pauci-immune vasculitis: an unusual presentation. A case report

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Abstract. Rapidly progressive glomerulonephritis corresponds to a clinical scenario of glomerular damage involving rapid deterioration of renal function with multiple etiologies. Within these, 85 % of cases are associated with pauci-immune vasculitis with antineutrophil cytoplasmic antibodies (ANCA). However, a remaining subgroup may present ANCA-negative results. The clinical presentation often involves a decline in the glomerular filtration rate, sometimes requiring renal replacement therapy, as well as extrarenal manifestations such as diffuse alveolar hemorrhage. Confirmatory diagnosis is achieved through renal biopsy, negative serology for ANCA, and exclusion of other etiologies. According to international clinical practice guidelines, the recommended treatment for both entities is the same, with the addition of renal replacement therapy if necessary. However, the prognosis tends to be unfavorable with little to no recovery of renal function. This case presents a female patient in the early decades of life with ANCA-negative, rapidly progressive, pauci-immune glomerulonephritis.

Keywords: rapidly progressive glomerulonephritis; pauci-immune vasculitis; ANCA-negative results

Introduction

Crescentic or rapidly progressive glomerulonephritis (RPGN) represents a severe form of glomerular damage characterized by disruption of the glomerular basement membrane, resulting in extracapillary proliferation that may or may not be accompanied by fibrinoid necrosis. By affecting the integrity of the glomerular capillaries, it allows the interaction between inflammatory mediators and leukocytes, leading to the maturation and activation of macrophages, as well as proliferation of parietal epithelial cells that culminate in the formation of crescents. Clinically, this results in rapid loss of renal function manifested as oligoanuria, non-nephrotic range proteinuria, and dysmorphic hematuria [1, 2].

The causes of RPGN are divided into three types: type I attributed to anti-glomerular basement membrane antibodies, type II caused by immune complexes, and finally, type III attributed to pauci-immune etiology. 85 % of cases have positive ANCA, while the remaining 5–10 % are ANCA-negative [3]. Thus, ANCA-negative pauci-immune vasculitis represents an unusual and infrequent presenta-

tion of RPGN with few cases describes in international literature and no cases reported in Mexico. This case presents a patient with a debut of RPGN, with suggestive clinical manifestations of vasculitis, with negative ANCA serology, confirmed by histological findings as pauci-immune glomerulonephritis.

Case description

Female of 18 years of age, with a history of diffuse sclerosing papillary thyroid cancer diagnosed 2 years ago, treated with total thyroidectomy 2 years ago + 200 mCi radioiodine, currently in remission and on hormonal replacement therapy with levothyroxine 100 µg every 24 hours. She presents with non-productive cough, dyspnea, paresthesia, weight loss of approximately 5 kilograms, and muscle spasms beginning 2 weeks before her admission. A week later, she develops a fever of 38 °C, somnolence, lethargy, decreased urine volume, and gross hematuria. She goes to the emergency room where she is neurologically assessed with a Glasgow Coma Scale score of 12 points (O2, M6, V4), high blood pressure 155/95 mmHg, heart rate of 110 bpm,

bilateral crepitant rales, oxygen saturation of 91 % by pulse oximetry, respiratory rate of 22 rpm, non-specific abdomen, and intact extremities, with decreased strength of 3/5 on the Daniels scale. A urinary catheter is inserted, and a urine output of 10 ml with dark color is obtained within 2 hours. The following urgent laboratory tests and imaging studies are requested:

- complete blood count: Hb 8.1 g/dl, WBC 17,140 cells/mm³, platelets 172,000/μl;
- renal function tests: creatinine 13.98 mg/dl (estimated glomerular filtration rate by CKD-EPI 2021 at 4 ml/min/1.73 m²), urea 323 mg/dl, BUN 110 mg/dl, sodium 147 mEq/l, potassium 6.2 mEq/l, chloride 105 mEq/l, bicarbonate 15 mmol/l;
- urinalysis: specific gravity 1.015, pH 9, leukocyte esterase 100 Leu/μL, negative nitrites, protein 75 mg/dl, leukocyte sediment 10–12 per field, > 100 red blood cells per field;
- rapid antigen test for SARS-CoV-2: negative;
- chest CT scan shows multiple bilateral bronchiectasis with apical predominance and areas of ground-glass opacities compatible with community-acquired pneumonia;
- C-ANCA PR3 negative, P-ANCA MPO negative;
- ANA 1 : 160 granular pattern, negative anti-dsDNA, negative anti-Ro and anti-La, negative anti-Sm, negative anticardiolipin IgG and IgM;
- normal levels of C3 and C4, negative cryoglobulins, C-reactive protein 2.8 mg/dl;
- normal levels of IgA, IgE, and IgM, decreased IgG.

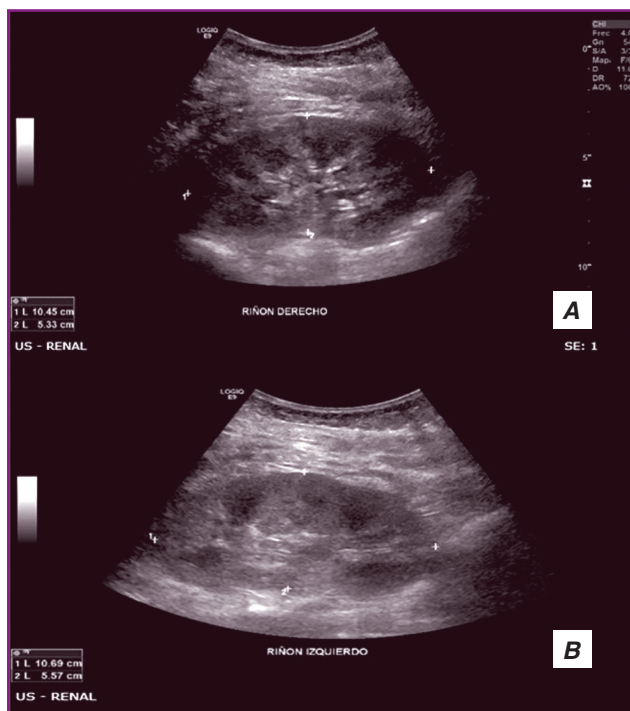


Figure 1. Bilateral renal ultrasound. A — right kidney, B — left kidney. Both kidneys have a normal morphology, position, and echogenicity. The cortex-medulla relationship is preserved. The dimensions of the left kidney are 10.6 × 9.5 × 4 cm, and the dimensions of the right kidney are 10.4 × 5.3 × 4 cm. There is no dilation in the renal pelvis or calyces, and no renal calculi are observed

Due to anuria and biochemical findings indicating the need for urgent dialysis, a vascular access is established, and 3 hemodialysis sessions are performed. A baseline serum creatinine of 0.63 mg/dl prior to the current illness is documented. Renal ultrasound shows preserved size and morphology (Fig. 1). After resolving the need for dialysis, a renal biopsy is performed considering RPGN with differential diagnoses of IgA nephropathy versus pulmonary — renal syndrome. Initial immunosuppressive management is initiated with boluses of methylprednisolone 500 mg for 3 days.

The final histopathological diagnosis reveals segmental necrotizing vasculitis with extracapillary proliferative glomerulonephritis (Fig. 2). Immunofluorescence testing is performed with negative results for IgG, IgM, IgA, C1q, C3, albumin, kappa, and lambda. Only fibrinogen shows a weak positive result (+1) in the crescents.

Given the histopathological findings consistent with ANCA-negative pauci-immune vasculitis, further studies are conducted to intentionally rule out a paraneoplastic origin due to the history of papillary thyroid cancer, confirming complete remission of the oncological disease. Additionally, an infectious origin is ruled out through urine culture, peripheral and central blood cultures, and chest tomography showing resolution of pneumonia but suggestive findings of incipient alveolar hemorrhage.

Due to the severity of the clinical condition, progressive deterioration of renal function with serum creatinine at onset > 4 mg/dl, and the development of incipient alveolar hemorrhage as evidenced in imaging studies, it is decided to initiate dual therapy with cyclophosphamide and rituximab reaching an accumulative dosage of 3 and 2 g, respectively. Close monitoring of renal function and scheduled hemodialysis sessions are implemented. In the subsequent months after hospital discharge, a serum creatinine curve showed a decreasing trend, allowing for a gradual reduction in the dose of renal replacement therapy (Fig. 3). After 4 months of initiation of immunosuppressive treatment, the serum creatinine level reaches 2.52 mg/dl, corresponding to an estimated glomerular filtration rate by CKD-EPI 2021 of 27 ml/min/1.73 m², classified as stage KDIGO G4. As a result, it is decided to discontinue renal replacement therapy and continue with medical surveillance only.

Discussion

RPGN is a glomerular syndrome characterized by rapid and persistent deterioration of renal function, subnephrotic range proteinuria, hematuria, and hypertension [11]. This syndrome is considered a hallmark of pauci-immune vasculitis, of which those with positive ANCA have an incidence of 20 cases per million. However, there is a subgroup where ANCA negativity is present in 10 % of cases, representing an incidence of 2 cases per 1 million [4, 5].

ANCA-negative vasculitis is primarily limited to the kidneys, with fewer systemic implications such as fever, arthralgia, or weight loss [13]. It usually occurs in younger patients, and histopathologically, glomerular lesions are particularly more severe compared to those with positive ANCA [2].

In a large cohort of 213 patients with RPGN studied by the Chapel Hill group in the United States, the probability of ANCA negativity was approximately 10–20 and 20–30 % when the intensity of immunoglobulin staining was 0 and 1+, respectively, on a scale of 0 to 4+. Therefore, around

10–30 % of patients with pauci-immune RPGN do not have ANCA [2, 6].

Renal biopsy is necessary for the differential diagnosis of pathologies presenting as a rapidly progressive syndrome. In our case, a young female patient presented with systemic manifestations and gradual deterioration of renal function requiring renal replacement therapy. In addition to negative antineutrophil cytoplasmic antibodies, other causes of RPGN, such as systemic lupus erythematosus and IgA nephropathy, were ruled out based on the clinical context, age group, and gender of the patient. IgA nephropathy can present as a rapidly progressive syndrome in 5–10 % of cases [5, 6].

The pathological anatomy of ANCA-negative pauci-immune vasculitis often shows segmental fibrinoid necrosis with leukocytic and leukocytoclastic infiltration on light microscopy [12]. Fibrinoid necrosis leads to sclerosing lesions that can be associated with thrombosis, and the presence of crescents is a pathognomonic feature. Depending on the evolving stage, crescents can be classified as cellular, fibrocellular, or fibrous [1]. Immunofluorescence typically shows weak or absent deposits of immunoglobulins and/or C3 [7], leading to the term pauci-immune when staining is $\leq 2+$ for any immunoreactant [8].

Although no specific studies have focused on the treatment of ANCA-negative vasculitis, current international clinical practice guidelines recommend similar treatment to patients with ANCA-positive vasculitis, with comparable outcomes in both cases. The treatment depends on the severity of the clinical presentation and ranges from mild cases treated with mycophenolate mofetil to a combination of renal replacement therapy and immunosuppressive therapies in cases of greater severity [9, 14]. Currently, the first-line treatment remains the therapy with cyclophosphamide as well as corticosteroid therapy for inducing remission, although in select cases, the use of biological therapy with rituximab can also be considered [10, 14]. In this case, it was decided to initiate an immunosuppressive regimen with steroid pulses, rituximab, and cyclophosphamide. The patient received 3 pulses of methylprednisolone, a cumulative dose of 3 g of cyclophosphamide, and 2 g of rituximab, respectively. The decision for induction therapy should not be solely based on biopsy findings; renal function recovery can be achieved even with unfavorable histopathology [9]. In our patient's case, she had 50% interstitial fibrosis and 79% crescent formation in the biopsy sample. Renal function was closely monitored, and significant improvement was observed after 4 months of treatment, allowing the discontinuation of renal replacement therapy as the estimated glomerular filtration rate remained at 27 ml/min/1.73 m².

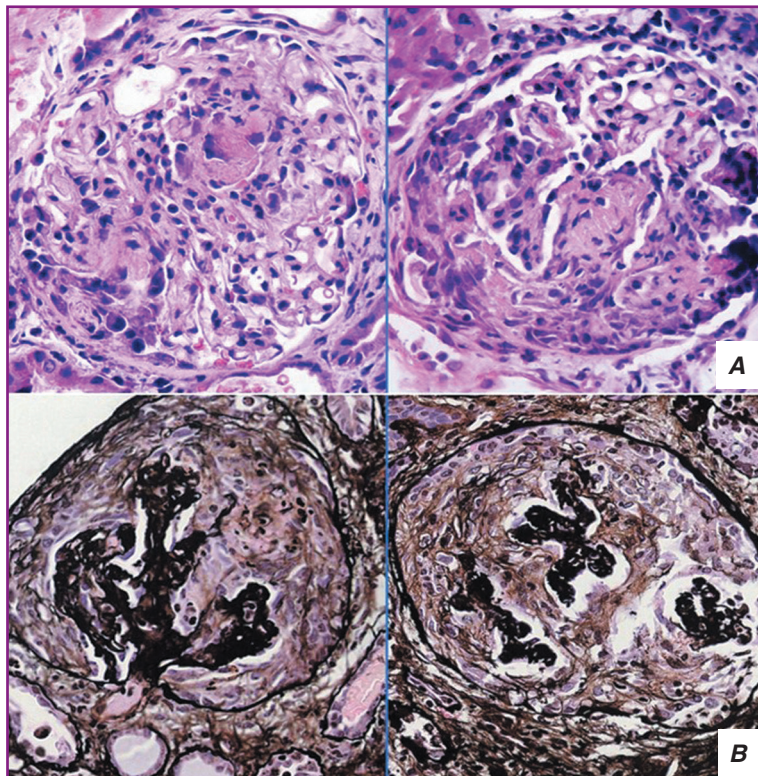


Figure 2. Renal cortex biopsy with a total of 61 glomeruli.

A — hematoxylin and eosin staining showing arteries and arterioles without significant histological alterations, tubular atrophy/interstitial fibrosis in 50 %, 40 % interstitial inflammation, focal interstitial hemorrhage, 21 % of glomeruli with focal sclerosis, 79 % with crescent formation, 26 % with fibrinoid necrosis, and 45 % with neutrophil infiltration. B — Jones staining revealing evidence of fibrous crescents in 14 %, fibrocellular crescents in 45 %, and cellular crescents in 39 %

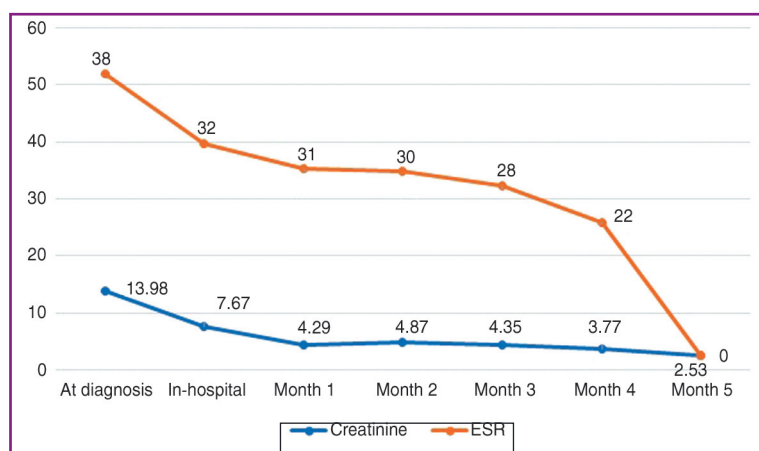


Figure 3. Follow-up of serum creatinine and erythrocyte sedimentation rate as an inflammation marker from diagnosis until the end of treatment, which concluded with successful withdrawal of renal replacement therapy

Currently, the patient maintains stable renal function, strict management of factors contributing to renal progression, and no clinical or biochemical signs of disease relapse.

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Information about authors

Zitlali Guadalupe Paulin Zepeda, Nephrology Resident Physician at Centro Médico Nacional Siglo XXI, Mexican Institute of Social Security, Mexico City, Mexico; e-mail: zitlali.paulin@gmail.com; <https://orcid.org/0009-0001-3833-9187>

Louis Fernando Robles Fernandes, Internal Medicine Resident Physician at Centro Médico Nacional Siglo XXI, Mexican Institute of Social Security, Mexico City, Mexico; e-mail: louis.roblesmi@gmail.com; <https://orcid.org/0000-0002-0387-8797>

Vianey Guadalupe Tellez Bolaños, Internal Medicine Resident Physician at Centro Médico Nacional Siglo XXI, Mexican Institute of Social Security, Mexico City, Mexico; e-mail: vianey_tellez@hotmail.com; <https://orcid.org/0000-0003-4613-3805>

José Carlos Ortiz Díaz, Nephrology Resident Physician at Centro Médico Nacional Siglo XXI, Mexican Institute of Social Security, Mexico City, Mexico; e-mail: ortizdiaz.josecarlos@gmail.com; <https://orcid.org/0009-0002-8655-9392>

María Inés Gil Arredondo, Nephrologist Physician Affiliated with the Nephrology Department at Centro Medico Nacional Siglo XXI, Mexican Institute of Social Security, Mexico City, Mexico; e-mail: drainsgil@gmail.com

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Zitlali Guadalupe Paulin Zepeda, Louis Fernando Robles Fernandes, Vianey Guadalupe Tellez Bolaños, José Carlos Ortiz Díaz, María Inés Gil Arredondo

Centro Médico Nacional Siglo XXI, Mexican Institute of Social Security, Mexico City, Mexico

Швидкопрогресуючий гломерулонефрит і АНЦА-негативний раусі-імунний васкуліт: незвичайні прояви. Клінічний випадок

Резюме. Швидкопрогресуючий гломерулонефрит відповідає клінічному сценарію ураження клубочків, що включає швидке погіршення функції нирок різноманітної етіології. Серед цих випадків 85 % пов'язані з раусі-імунним васкулітом з антинейтрофільними цитоплазматичними антитілами (АНЦА). Однак решта підгрупи може мати негативні за АНЦА результати. Клінічні прояви часто включають зниження швидкості клубочкової фільтрації, що іноді вимагає замісної ниркової терапії, а також екстрауренальні симптоми, такі як дифузна альвеолярна кровотеча. Діагноз підтверджують за допомогою біопсії нирки,

негативного серологічного тесту на АНЦА та виключення іншої етіології. Згідно з міжнародними рекомендаціями з клінічної практики, рекомендоване лікування для обох захворювань є однаковим із додаванням замісної ниркової терапії, якщо необхідно. Проте прогноз, як правило, несприятливий із незначним відновленням функції нирок або без нього. Описано випадок АНЦА-негативного швидкопрогресуючого раусі-імунного гломерулонефриту в пацієнтки перших десятиліть життя.

Ключові слова: швидкопрогресуючий гломерулонефрит; раусі-імунний васкуліт; АНЦА-негативні результати