International Journal of Medical Science and Clinical Research Studies

ISSN(print): 2767-8326, ISSN(online): 2767-8342

Volume 03 Issue 11 November 2023

Page No: 2894-2899

DOI: https://doi.org/10.47191/ijmscrs/v3-i11-66, Impact Factor: 6.597

IgA Nephropathy Associated with ANCA Vasculitis: Case Report and Literature Review

Elizabeth Torres Ruiz[1], Andrea Carolina Torres Ruiz[2], Rodolfo Martín Ruiz Ravelo[1], Norma Cecilia Ruiz Cruz[3], José de Jesús Fernández Rivera[1], Perla Karina Hernández de Lira[1]

[1] Mexican Social Security Institute – General Hospital of Zone No. 33. Department of Internal Medicine. Monterrey, Nuevo León, México

[2] Mexican Social Security Institute – General Hospital of Zone No. 50. Department of Surgery. San Luis Potosí, San Luis Potosí, México

[3] Mexican Social Security Institute – General Hospital of Zone No. 33. Department of Nephrology. Monterrey, Nuevo León, México

ABSTRACT

IgA nephropathy is the most common primary glomerulonephritis, it's association with Antineutrophil cytoplasmic antibody (ANCA) vasculitis constitutes a rare way of presentation that is scarcely described in the literature and diagnosed in only 1-2% of the population. The typical clinical presentation is an episode of systemic arterial hypertension with macroscopic hematuria, non-nephrotic proteinuria, acute kidney injury and in the worst-cases if the disturb persists end-stage chronic kidney disease. The definitive diagnosis is made through a biopsy, which shows the main characteristics of this nephropathy, which consists in crescent-shaped glomeruli formation, fibrinoid necrosis, mesangial deposits of IgA, as well as positive ANCA antibodies. Treatment consists in systemic corticosteroids and immunosuppressants to prevent progression to end-stage renal disease. We present a case of a 55-year-old female patient with a history of upper respiratory tract infection 2 weeks prior to the development of macroscopic hematuria, foamy urine, non-nephrotic proteinuria, and persistent acute kidney injury in whom IgA nephropathy was determined, which had a successfully response to treatment with high doses of corticosteroids and systemic immunosuppressants.

KEYWORDS: Immunoglobulin A nephropathy, Glomerulonephritis, Antineutrophil cytoplasmic autoantibodies, Acute kidney injury, End-stage chronic kidney disease.

ARTICLE DETAILS

Published On:
27 November 2023

Available on:
https://ijmscr.org/

INTRODUCTION

IgA nephropathy (IgAN) is the most common primary glomerulonephritis, its characterized by episodes of macroscopic hematuria, proteinuria and systemic arterial hypertension; generally preceded by an upper airway infection [1,2].

The current theory is that after an infection, there are an overstimulation of B-cell populations with secondary production of IgA which is deposited in the renal mesangium, and finally a localized inflammatory response [1,2].

The coexistence of IgAN and ANCA-associated vasculitis is uncommon, it has been reported in 1.4% of patients with a previous diagnosis of IgAN, the exact mechanism of its association is unknown. However, like in IgAN patients without ANCA vasculitis associated, patients usually presents with nephritic syndrome and sometimes even with proteinuria in nephrotic ranges [3,4].

In cases where a positive ANCA are present in a rapidly progressive IgAN, is vital to identify if it could be a superimposition of ANCA-associated vasculitis on pre-existing IgAN or an increase in ANCA levels due to the proinflammatory state generated by the glomerular lesions induced by IgA deposits [5,6].

The definitive diagnosis is by histopathology in where mesangial IgA deposits in crescents form are observed as well as IgG and C3 deposits of variable form, which are the typical findings in immunofluorescence of IgAN in renal biopsy [1]. Optical microscopy shows diffuse mesangial proliferation and matrix expansion with segmental

glomerulosclerosis, tubulointerstitial fibrosis and tubular atrophy in the most advanced stages [3]. Nevertheless, there are some limitations in the diagnosis mainly due to the lack of knowledge of the pathology and the rarity of the association of IgAN with ANCA vasculitis, that prevents the timely diagnosis and treatment and an effective treatment, however it is important to note that if biopsy reports predominant IgA deposits with diffuse active extra capillary proliferation with fibrinoid necrosis, it´s highly suggested of small vessel vasculitis [1,3].

As other autoimmune diseases, the primary management includes the early initiation with systemic corticosteroids and immunosuppressants to induce the remission of acute disease activity and then continue with maintenance therapy to prevent the risk and recurrence of associated complications [3,7].

CASE REPORT

We present a case of a 55-year-old female patient with a genetic load for type 2 diabetes mellitus and lung cancer, history of systemic arterial hypertension under treatment with angiotensin-converting enzyme inhibitor, and a baseline creatinine level of 0.82mg/dl for the last 3 months.

She started her current condition with bad general state, fever, rhinorrhea, odynophagia, and nausea. After a week she had gross hematuria, hence the reason she seeks for medical evaluation, the following initial laboratory studies were performed: Leukocytes 5. 2 K/ul, hemoglobin 10.6 gr/dl, hematocrit 30.4%, platelets 235 K/ul, cholesterol 173mg/dl, triglycerides 135 mg/dl, albumin 3.5 g/dL, urea 80.6 mg/dl, BUN 37 mg/dl, creatinine 2.0 mg/dl, CRP 8.1mg/dl. Due to the elevated creatinine, initial supportive treatment was initiate and bilateral renal ultrasound was requested without showing structural renal damage (Fig 1).

Despite the initial treatment she persisted with creatinine elevation of 3.2mg/dL, urea 102 mg/dL, BUN 49 mg/dL, so diagnosis protocol was initiated with general urine test and quantification of proteins in 24 hr urine, findi

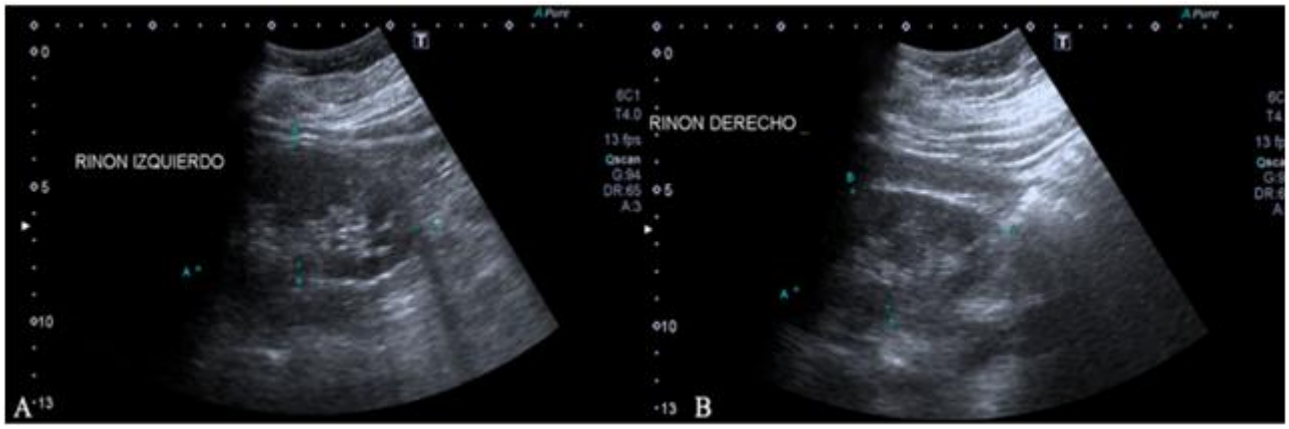

Figure 1. Renal ultrasonography, both kidneys with preserved morphology and echogenicity, without evidence of lesions are observed.

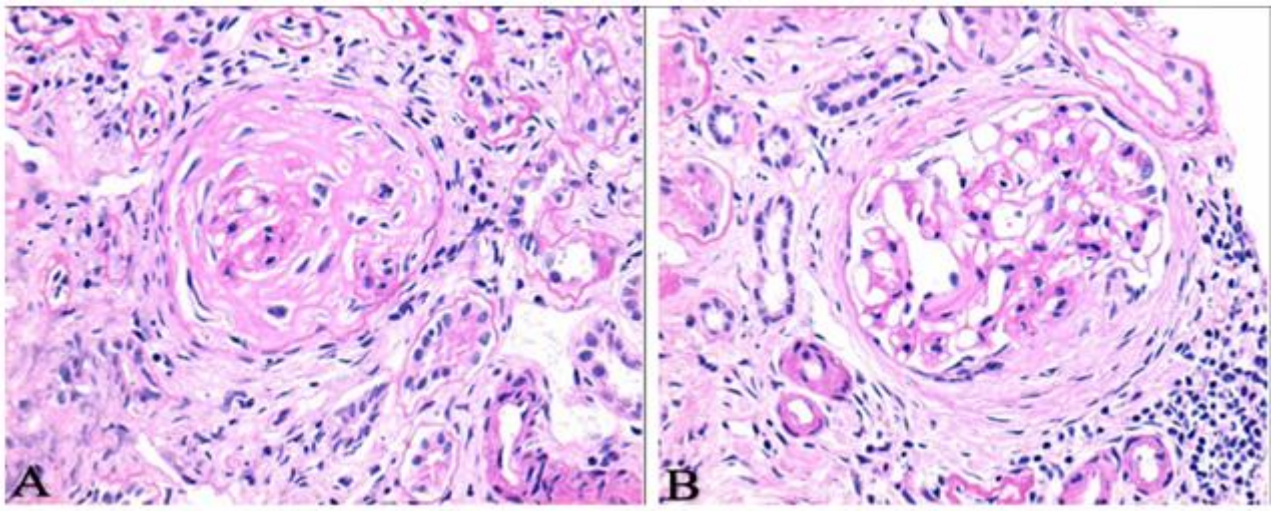

Figure 2. A) PAS stain (Periodic acid-Schiff) with some sclerosed glomerulus in approximately 35.29%, segmental sclerosing lesions (S1), and capillary synechiae in Bowman's capsule. B) PAS stain. A segmental proliferation of the mesangial matrix (M1) is observed. The glomerular basement membranes are folded and scarred, without spicules, and areas of hypercellularity/endocapillary proliferation (E1).

general urine test with urinary sediment, urinary density of 1.025, proteins +++, hemoglobin +++, dysmorphic erythrocytes, proteinuria in sub nephrotic ranges of 2.16 g/day, volume of 2160 ml/day, so a nephritic syndrome diagnosis was established and due to the history of recent viral infection the autoimmune etiology was suspected. Immunological markers were requested, being positive ANCA-p antibodies with a dilution of 1: 320, so ANCA vasculitis with renal manifestation was initially suspected and management was started with methylprednisolone 1 gr every 24 hours for 3 days with partial response. A renal biopsy was performed with suggestive evidence of glomerulosclerosis, endocapillary proliferation, tubular atrophy and active tubulointerstitial nephritis with some inflammatory infiltrate (Figs 2 and 3).

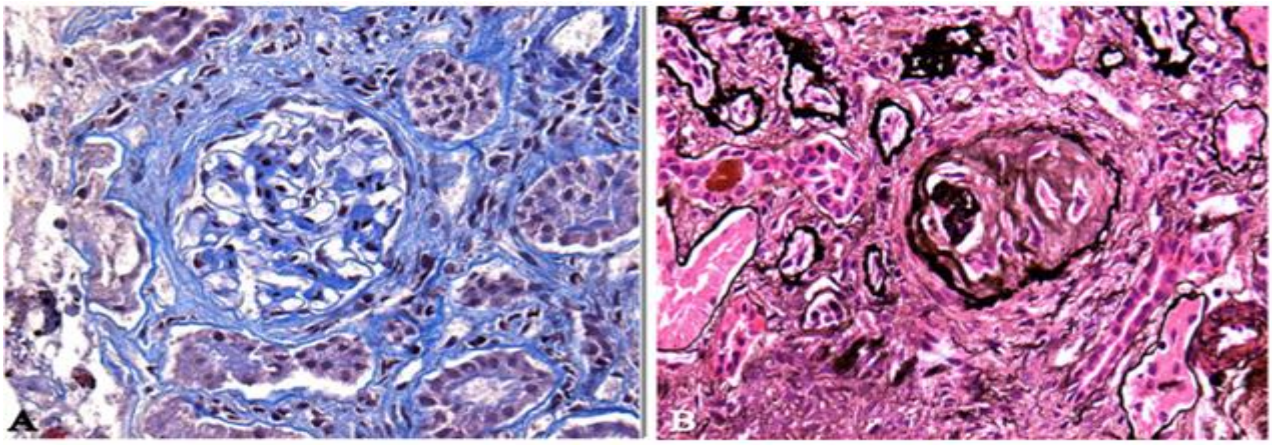

Figure 3. A) Masson's trichrome stain. Active extracapillary proliferative lesions (cellular crescents) (C2), with areas of glomerular fibrinoid necrosis are observed.

B) Jones methenamine silver stain. The interstitium with areas of fibrosis with associated tubular atrophy affecting approximately 30-35% of the cortical surface is observed (grade II) (T1). There are areas of interstitial inflammatory infiltrate made up of lymphocytes, plasma cells, neutrophils and eosinophils with extension towards the tubular walls. Inside the tubular lumens there is cellular debris and cylinders of blood remains. The preglomerular arteriolar vessels, interstitial vessels, and small-caliber arteries have moderate wall thickening due to hypertrophy and sclerosis.

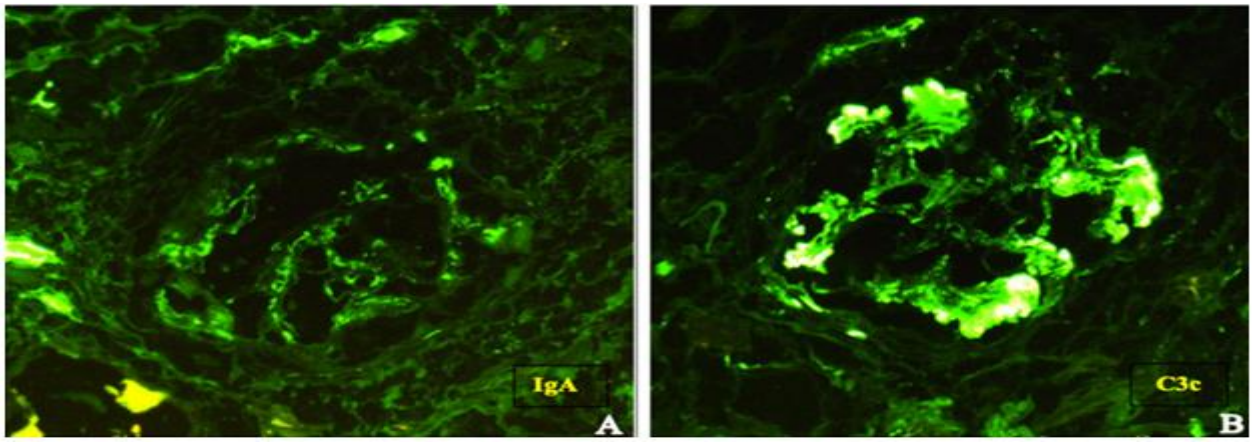

Figure 4. Direct immunofluorescence. A) 60% of the total glomeruli in the sample are observed with global sclerosis and the remaining 40% with segmental sclerosis with IgA deposits with a granular, global, and diffuse pattern at the mesangial level. B) Positive catchment for C3c immuno reactant, with granular, focal, and segmental mesangial pattern.

Given such histopathological findings, IgA nephropathy was suspected so immunofluorescence was performed, IgA and C3c deposits with mesangial granular pattern were observed, confirming the diagnostic suspicion of IgAN associated with positive ANCA vasculitis (Oxford M1, E1, S1, S1, T1, C2) (Figure 4).

We continued treatment with corticosteroids, but adding cyclophosphamide at dose of 500 mg every 4 weeks for 6 doses, showing a favorable response to treatment with a decrease in creatinine of 1.4 mg/dl and urea 42mg/dl, being discharged.

Four-month follow-up she remains asymptomatic with sustained improvement of her renal function (creatinine of 1 mg/dl) and continues with maintenance treatment with oral steroids, antiproteinuric drugs and immunosuppressants.

DISCUSSION

IgA nephropathy is one of the most common primary glomerulopathies, represents 40% of all primary

glomerulopathies diagnosed by renal biopsy in Asia (45% in China), and it's generally associated with acute kidney injury. However, up to 30-40% of patients with IgAN eventually develop end-stage renal disease [1,2].

The most accepted physiopathology theory is the repeated exposure to risk environmental factors (viruses, bacteria, etc.) which causes an excessive stimulation of B-lymphocyte populations in the tonsils, bone marrow and intestinal lymphoid tissue, leading an overproduction of IgA1, abnormal autoantibody synthesis and the formation of immune complexes that are deposited in the glomerular mesangium and occasionally in the capillary loops, causing local inflammation, proteinuria and hematuria [1,3].

The typical presentation of IgAN consists in episodes characterized by macroscopic hematuria, arterial hypertension and proteinuria with decrease in renal function [1,2]. Generally, when IgAN is diagnosed and treated early, the acute kidney injury is completely reversible, but IgAN tends to progress to end-stage renal disease in 30-50% of patients after 25 years due to the continuous deposition of antibodies in the glomerular mesangium. The presence of hypertension is a strongly factor associated with poor prognosis, while proteinuria absence or minimal proteinuria of >500 mg/day indicates better prognosis with lower rates of renal disease progression [1,3].

In rare occasions exist certain vascular involvement in IgAN in addition to mesangial IgA deposition and therefore would make us suspect a picture with associated antibody deposition; like an ANCA vasculitis, as evidenced in this case.ANCA associated vasculitis is a group of necrotizing vasculitis characterized by the involvement of small vessels such as capillaries, venules, arterioles, with little or not immune deposition in the vascular wall and the presence of autoantibodies directed against neutrophil proteins, leukocyte proteinase 3 (PR3-ANCA) or against myeloperoxidase (MPO-ANCA) [4,7]. The well-known disorders associated with small vessel vasculitis include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA) [3].

Renal involvement is common in ANCA-associated vasculitis (AAV) and is associated with significant morbidity and mortality [3,4]. In one study, Xie et al, identified ANCA in only 1.4% of 2390 patients with biopsy-proven IgA nephropathy, however its association is unknown, and the pathogenesis remains unclear. According to available reports, ANCA-positive patients with IgA nephropathy progress more rapidly to deterioration of renal function, has glomerular crescentic lesions and a greater degree of tubular atrophy compared to ANCA-negative patients [4].

The AAV diagnosis process depends on the recognition of a clinical phenotype and assess the extent of the disease whit some laboratory tests which may help to clarify the type of vasculitis and degree of organ involvement, so it should be requested complete blood count, serum creatinine, liver function tests, erythrocyte sedimentation rate, C-reactive protein, general urine test and urinary sediment, with additional tests as appropriate, such as chest X-ray or high-resolution computed tomography in case of respiratory symptoms or hemoptysis [4,7].

Like non-ANCA-positive IgAN, most patients debut between the second and third decade of life with macroscopic hematuria, which is usually asymptomatic or isolated, associated or not with proteinuria, and in some cases, about 5% with nephrotic syndrome [8].

It's recommended for cases that manifests with progressive renal function deterioration, persistent hematuria and/or proteinuria >500mg/day a renal biopsy, because there are no specific laboratory findings that can make reliably diagnose such nephropathy. The main histopathological findings are: microscopic IgA deposits mainly in the glomerular mesangium and sometimes infiltration in the capillary loops causing extracapillary proliferation, with or without capillary necrosis [2,9].

The dominant or codominant mesangial deposits of IgA, with IgG, C3, kappa and lambda in a variable form, cause the typical findings of crescents in the immunofluorescence renal biopsy [7,9,10]. When endovascular proliferation is present, its association with ANCA vasculitis should be considered, due this is its main histologic feature.

The Oxford classification for IgAN (Table 1) allows staging of the nephropathy, including mesangial hypercell-

Table 1. Updated Oxford classification of IgA nephropathy [5].

Histological Feature	Definition	Score
Mesangial hypercellularity	Percentage of glomeruli with > 3 mesangial cells per mesangial area	M0:≤50% M1: > 50%
Endocapillary hypercellularity	Increased number of cells within glomerular capillary lumina causing narrowing of the lumina	E0: Absent E1: Present
Segmental glomerulosclerosis	Any amount of the glomerular tuft involved in sclerosis, but not involving the whole tuft, or the presence of an adhesion	S0: Absent S1: Present
Tubular atrophy / Interstitial fibrosis	Percentage of cortical area involved by tubular atrophy or interstitial fibrosis,	T0: 0–25% of cortical area T1: 26–50% of cortical area

	whichever is greater	T2: > 50% of cortical area
Cellular or fibrocellular crescent	Percentage of glomeruli with cellular or fibrocellular crescent	C0: Absent C1: < 25% of glomeruli C2: ≥ 25% of glomeruli

ularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S), and tubular atrophy with interstitial fibrosis (T). The absence/presence of >50% of glomeruli showing mesangial hypercellularity is termed M0/M1, respectively; E1 indicates any endocapillary hypercellularity; S1 denotes any segmental glomerulosclerosis; and T0, T1, and T2 reflect fibrosis affecting 1 to 25%, 26 to 50%, or >50% of the cortical area [5,9].Histological evidence has shown that the presence of crescents and fibrinoid necrosis in biopsies of IgAN associated to ANCA-positive could be considered predictors of severity of renal progression and response to aggressive steroid therapy [6].As part of the treatment, current guidelines recommend the addition of renin-angiotensin-aldosterone system (RAAS) blockers to reduce proteinuria and if there is persistent proteinuria (>1 g/day for >4 to 6 months) with hematuria despite established treatment, oral corticosteroids should be administered to prevent progression to chronic kidney disease [8,11,12]. It's recommended start with high doses of corticosteroids, based on methylprednisolone pulses and early initiation of cyclophosphamide and/or rituximab, since it was is associated with a higher rate of preservation of renal function and a lower risk to develop end-stage renal disease [11,13].

In patients who don't respond to corticosteroids and immunosuppressants, in some cases has response to plasma exchange, intravenous immunoglobulins and biologic therapy with alemtuzumab and/or mizoribine so this therapies should be considered in the management of refractory IgAN-ANCA [13].

As part of follow-up, the European Vasculitis Society/European League Against Rheumatism (EUVAS/EULAR) recommends that the definition of remission should be the undetectable disease activity using the Birmingham Vasculitis Activity Score (BVAS) (Table 2), this score predicts response to treatment in patients with IgAN-ANCA. [6,10,14].

The disease prognosis depends on an early treatment.

Table 2. Birmingham Vasculitis Activity Score (BVAS) [15].

Patient ID:	**Date of birth:**	**Total score:**
Assessor:	**Date of assessment:**	

Tick an item only if attributable to active vasculitis. If there are no abnormalities in a section, please tick 'None' for that organ-system.

If all abnormalities are due to persistent disease (active vasculitis which is not new/worse in the prior 4 weeks), tick the **PERSISTENT** box at the bottom right corner

Is this the patient's first assessment? Yes ○ No ○

	None	Active disease
1. General	○	
Myalgia		○
Arthralgia / arthritis		○
Fever ≥38° C		○
Weight loss >? kg		○
2. Cutaneous	○	
Infarct		○
Purpura		○
Ulcer		○
Gangrene		○
Other skin vasculitis		○
3. Mucous membranes / eyes	○	
Mouth ulcers		○
Genital ulcers		○
Adnexal inflammation		○
Significant proptosis		○
Scleritis / Episcleritis		○
Conjunctivitis / Episcleritis / Keratitis		○
Blurred vision		○
Sudden visual loss		○
Uveitis		○
Retinal changes (vasculitis / thrombosis / exudate / haemorrhage)		○
4. Renal	○	
Bloody nasal discharge / crusts / ulcers / granulomata		○
Paranasal sinus Involvement		○
Subglottic stenosis		○
Conductive hearing loss		○
Sensorineural hearing loss		○
5. Chest	○	
Wheeze		○
Nodules or cavities		○
Pleural effusion / pleurisy		○
Infiltrate		○
Endobronchial involvement		○
Massive haemoptysis / alveolar haemorrhage		○
Respiratory failure		○

	None	Active disease
6. Cardiovascular	○	
Loss of pulses		○
Valvular heart disease		○
Pericarditis		○
Ischaemic cardiac pain		○
Cardiomyopathy		○
Congestive cardiac failure		○
7. Abdominal	○	
Peritonitis		○
Bloody diarrhoea		○
Ischaemic abdominal pain		○
8. Renal	○	
Hypertension		○
Proteinuria >1+		○
Haematuria ≥10 RBCs/hpf		○
Serum creatinine 125-249 µmol/L*		○
Serum creatinine 250-499 µmol/L*		○
Serum creatinine ≥500 µmol/L*		○
Rise in serum creatinine >30% or fall in creatinine clearence >25%		○
*Can only be scored on the first assessment		
9. Nervous system	○	
Headache		○
Meningitis		○
Organic confusion		○
Seizures (not hypertensive)		○
Cerebrovascular accident		○
Spinal cord lesion		○
Cranial nerve palsy		○
Sensory peripheral neuropathy		○
Mononeuritis multiplex		○
10. Other	○	
a.		○
b.		○
c.		○
d.		○
PERSISTENT DISEASE ONLY: (Tick here if all the abnormalities are due to persistent disease)		☐

If treatment delayed, there is rapidly progressive deterioration with irreversible complications in the short term; however, when immunosuppressive treatment is timely, it is associated with low relapse rates.

CONCLUSION

Although the coexistence of IgAN with vasculitis associated with positive ANCA is extremely rare and low studied, it should not be ruled out easily. Diagnostic approach should be carried out in a timely and early form to provide an intensive treatment to preserve kidney function, since it is It has been shown that they have worse prognoses with a higher degree of severity that IgAN without positive ANCA. We recommend to be attentive to the variable forms of presentation of this entity and carry out the study protocol early to avoid unfavorable complications.

CONFLICT OF INTERESTS

The authors have declared no conflicts of interests.

REFERENCES

I. Rojas-Rivera J, Fernández-Juárez G, Praga M. Rapidly progressive IgA nephropathy: a form of vasculitis or a complement-mediated disease? Clin Kidney J. 2015 Oct;8(5):477-81. doi: 10.1093/ckj/sfv095.

II. Wang X, Guo Z, Huang B, Xie M, Ren J, Zhu Y, Guo H, Wang Y, Yu D, Zhang J, Zhang L. IgA nephropathy with acute kidney disease: Characteristics, prognosis, and causes. Eur J Intern Med. 2022 Nov; 105:46-53. doi: 10.1016/j.ejim.2022.05.021.

III. Chebotareva N, Kamyshova E, Bulanov N, Lysenko L, Moiseev S, Antineutrophil cytoplasmic autoantibody (ANCA) positive immunoglobulin A (IgA) nephropathy: Case reports and review of literature. The Egyptian Rheumatologist. 2020 Jun; 42:251-254. doi 10.1016/j.ejr.2020.06.002.

IV. Yaseen K, Mandell BF. ANCA associated vasculitis (AAV): a review for internists. Postgrad Med. 2023 Jan;135(sup1):313.doi:10.1080/00325481.2022.2102368.

V. Rajasekaran A, Julian BA, Rizk DV. IgA Nephropathy: An Interesting Autoimmune Kidney Disease. Am J Med Sci. 2021 Feb;361(2):176-194. doi: 10.1016/j.amjms.2020.10.003.

VI. Ștefan G, Terinte-Balcan G, Stancu S, Zugravu A, Gherghiceanu M, Mircescu G. IgA nephropathy with serum ANCA positivity: case series and literature review. Rheumatol Int. 2021 Jul;41(7):1347-1355. doi: 10.1007/s00296-021-04888-2.

VII. Yang YZ, Shi SF, Chen YQ, Chen M, Yang YH, Xie XF, Zou R, Lv JC, Liu LJ, Zhang H. Clinical features of IgA nephropathy with serum ANCA positivity: a retrospective case-control study. Clin Kidney J. 2015 Oct;8(5):482-8. doi: 10.1093/ckj/sfv078.

VIII. Hilhorst M, van Paassen P, Tervaert JW; Limburg Renal Registry. Proteinase 3-ANCA Vasculitis versus Myeloperoxidase-ANCA Vasculitis. J Am Soc Nephrol. 2015 Oct;26(10):2314-27. doi: 10.1681/ASN.2014090903.

IX. Rodrigues JC, Haas M, Reich HN. IgA Nephropathy. Clin J Am Soc Nephrol. 2017 Apr 3;12(4):677-686. doi: 10.2215/CJN.07420716.

X. Yates M, Watts R. ANCA-associated vasculitis. Clin Med (Lond). 2017 Feb;17(1):60-64. doi: 10.7861/clinmedicine.17-1-60.

XI. Yasukawa M, Kitagawa S, Togashi R, Asakawa S, Nagura M, Arai S, Yamazaki O, Tamura Y, Kondo F, Ohashi R, Uchida S, Shibata S, Fujigaki Y. A Patient with MPO-ANCA-positive IgA Nephropathy Diagnosed with the Clinical Onset of Macrohematuria. Intern Med. 2019 Jul 15;58(14):2051-2056. doi: 10.2169/internalmedicine.2475-18.

XII. Tota M, Donizy P, Byrska M, Krajewska M, Kusztal M. An unsuspected histopathological finding - concomitant IgA nephropathy in a patient with ANCA-associated vasculitis: a case report and literature review. Front Immunol. 2023 Aug 15;14:1227878. doi: 10.3389/fimmu.2023.1227878.

XIII. Agraz I, Castañeda Z, Sanz-Martínez MT, Gabaldón A, Bermejo S, Viñas Gimenez L, Bury R, Bolufer M, López-Martínez M, Ramos N, Bestard O, Soler MJ. The Presence of ANCA in IgA Crescentic Nephropathy Does Not Lead to Worse Prognosis with Intensive Rescue Treatment. J Clin Med. 2022 Nov 30;11(23):7122. doi: 10.3390/jcm11237122.

XIV. Xie L, He J, Liu X, Tang S, Wang W, Li F, Zhang Y, Zhang J, Huang Y, Zhao J, Li Y, Zhang J. Clinical value of systemic symptoms in IgA nephropathy with ANCA positivity. Clin Rheumatol. 2018 Jul;37(7):1953-1961. doi: 10.1007/s10067-017-3931-z.

XV. Mukhtyar C, Lee R, Brown D, Carruthers D, Dasgupta B, Dubey S, Flossmann O, Hall C, Hollywood J, Jayne D, Jones R, Lanyon P, Muir A, Scott D, Young L, Luqmani RA. Modification and validation of the Birmingham Vasculitis Activity Score (version 3). Ann Rheum Dis. 2009 Dec;68(12):1827-32. doi: 10.1136/ard.2008.101279.