

The importance of immunoglobulin A nephropathy early diagnosis and management – case report

Georgiana Aurelia Nae¹, Mihai-Emil Gherghina¹, Ileana Peride¹, Mirela Tiglis²,
Tiberiu Paul Neagu³, Andrei Niculae¹

¹ Clinical Department No. 3, “Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania

² Clinical Department No. 14, “Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania

³ Clinical Department No. 11, “Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania

ABSTRACT

Immunoglobulin A (IgA) nephropathy is one of the most common glomerulonephritis. Its clinical manifestations vary from asymptomatic forms to cases with nephritic syndrome or nephrotic-range proteinuria. The prognosis depends on the level of proteinuria, decline of glomerular filtration rate and control of blood pressure. The pathognomonic histological changes are represented by the granular IgA deposits in the mesangium. The treatment consists of comprehensive support care and immunosuppressive therapy. We discuss the case of a 50-year-old man who presented microscopic hematuria, nephrotic-range proteinuria and decreased renal function, exacerbated in the last 6 months prior the admission. We performed a renal biopsy and granular deposits were present in the glomerular mesangium that were highly suggestive for IgA nephropathy. Immunosuppressive therapy was instituted immediately, but the decline of the renal function continued and renal replacement therapy was needed. Patients with poor prognosis have an unsatisfactory response to the immunosuppressants, especially those with a delayed diagnosis.

Keywords: IgA nephropathy, diagnosis, treatment, evolution

INTRODUCTION

Immunoglobulin A (IgA) nephropathy is the most common glomerular disease [1], with an estimated frequency of approximately 2.5 cases per year per 100,000 adults [2]. Even if it is characterized by predominant IgA deposition in the glomerular mesangium [3], there are other findings that contribute to the classification of IgA nephropathy (Table 1), which provides useful information regarding the risk of progression of the disease towards end-stage renal disease (ESRD) [4-7].

There are factors that might increase the risk of developing this condition, such as age, gender, race, genetic inheritance etc. In North America and Western Europe, IgA nephropathy is more common in male than female patients by a ratio of 2:1, and it is more observed in Caucasians and Asians than Afro-Americans. IgA nephropathy, usually develops be-

tween the 18-19 years and late 30s [1]. In some cases, IgA nephropathy could be diagnosed in specific families, highlighting the possibility of a genetic factor that can contribute to the onset of the disease [1]. Regardless the potential genetic involvement, more than 90% of all cases appear to be sporadic [3].

As far as signs and symptoms are concerned, they vary in frequency with age, and no clinical pattern is pathognomonic for IgA nephropathy. The disease is often characterized by nephritic syndrome that could develop into a nephrotic syndrome. Macrohematuria is very uncommon after 40 years old and it resolves spontaneously over a few days, and microhematuria with or without proteinuria (usually < 2 g/24 h) is noted [8].

Depending on the clinical and bioumoral features of the patients, according to the KDIGO (Kidney Disease Improving Global Outcomes) guidelines, the treatment could be stratified into [1,9]:

Corresponding author:

Mirela Tiglis

E-mail: mirelatiglis@gmail.com

Article History:

Received: 23 December 2021

Accepted: 29 December 2021

TABLE 1. The Oxford classification of IgA nephropathy [4,5,6]

Histopathological findings	Description	Score
Mesangial hypercellularity	> 4 mesangial cells are affected	M0 = < 50% of the glomeruli with mesangial hypercellularity M1 = > 50% of the glomeruli with mesangial hypercellularity
Endocapillary hypercellularity	increased number of cells spotted in the capillary loops (hypercellularity) inducing luminal narrowing	E0 = absent E1 = endocapillary hypercellularity in any glomeruli
Segmental glomerulosclerosis	partial adhesion / sclerosis of the glomerular tuft	S0 = absent S1 = segmental glomerulosclerosis in any glomeruli
Interstitial fibrosis and tubular atrophy	significant interstitial fibrosis and tubular atrophy	T0 = 0-25% T1 = 26-50% T2 = > 50%
Cellular or fibrocellular crescents	the presence of cellular or fibrocellular crescents	C0 = absent C1 = < 25% glomeruli are affected C2 = > 25 glomeruli are affected

- follow-up (at least annually) for a longer period of time (more than 10 years) for patients considered with a good prognosis: minor urinary abnormalities (i.e. isolated microhematuria, proteinuria < 0.5 g/dl), normal estimated glomerular filtration rate (eGFR) and normal blood pressure (BP).
- supportive conservative therapy for patients with an intermediate prognosis: significant proteinuria (> 0.5-1 g/dl), hypertension and mild decrease of eGFR (but above 50 ml/min/1.73 m²).
- immunosuppression is mandatory for patients with a poor prognosis correlated with a significant and rapid decrease of the renal function.

CASE PRESENTATION

A 50-year-old man, non-smoking patient, presented bilateral oedema of lower extremities. His personal medical history included hypertension diagnosed 16 years prior to the current presentation and treated inconsistently, mitral valve prolapse and chronic kidney disease (CKD) diagnosed two years before this episode (CKD G2 A2). The presence of oedema was observed 1 year before admission, but worsening in the last month. In the last 6 months, his medical records showed an important increase of serum creatinine values, an active urinary sediment with microscopic hematuria and dysmorphic erythrocytes, and proteinuria with an albumin-creatinine ratio over 300 mg/g. Immunologic tests were performed and all the results were negative. The patient had no significant family history and no recent upper respiratory infections.

The physical exam revealed an overweight patient with pitted peripheral edema, without pulmo-

nary crackles, BP = 140/70 mmHg, pulse = 95 beats per minute, regular tachycardia with a systolic murmur in all the sites of cardiac auscultation and radiated to the carotid arteries and without other abnormalities.

Serum analysis showed a moderate normocytic normochromic anemia (hemoglobin = 8.9 g/dl) with normal white blood cells and platelet count, a serum creatinine of 6.16 mg/dl, and a serum urea of 134 mg/dL. The coagulation profile was in normal range, as the hepatic function panel. Total serum proteins and serum albumin were low (4.8 g/dl, 2.5 g/dl respectively) and total cholesterol value was high (378 mg/dl). The erythrocyte sedimentation rate and C-reactive protein were increased (ESR = 70 mm/h, CRP = 22.2 mg/l). Complement and serum immunoglobulin levels were within normal range. The urinary analysis revealed proteinuria, microscopic hematuria with dysmorphic erythrocytes and frequent granular casts. The 24-hour protein excretion was 9248 mg, with a 6,910 mg albumin excretion, respectively. The abdominal ultrasound showed kidneys with lengths of 10.1-10.2 cm and a few parapelvic cysts, without other pathological findings.

Considering the evolution of serum creatinine concentration in the last 6 months prior admission, the presence of hematuria with dysmorphic erythrocytes, the amount of proteinuria, the nephrotic syndrome and the size of the patients' kidneys, a renal biopsy was performed. Immediately after, immunosuppressive treatment was started with methylprednisolone pulse therapy with 1 g/day, for 3 consecutive days, and then it continued with 0.5 mg/body weight/day prednisone for almost one month. Once immunosuppressive therapy was initiated the proteinuria diminished significantly (2,522 mg/24 hours), and we noted the disappearance of

the oedema. In contrast with this improvement, the renal function gradually deteriorated during the three weeks from the admission (serum creatinine reached 8.7 mg/dl). In addition, a cardiac ultrasound was performed, indicating the presence of pericarditis. After 3 weeks from the admission, the renal biopsy result was available highlighting: three glomeruli were examined with optic microscopy, all with sclerosis and segmental hyalinization. The arterioles had nodular and circumferential hyaline deposits and one was completely obstructed. The tubuli were atrophic and there was extensive fibrosis and interstitial inflammation. The immunofluorescence was intense positive for IgA granular deposits in the glomeruli and C3c in the vessels and moderate in the glomeruli. Electron microscopy was not performed. Even though the number of glomeruli in the sample was small, the immunofluorescence was highly suggestive of the diagnosis of IgA nephropathy (Figure 1).

Based on these medical findings (the renal biopsy results showing glomerulosclerosis, tubular atrophy and extensive interstitial fibrosis, the important deterioration of eGFR, the presence of pericarditis), urgent hemodialysis was initiated, and a central venous catheter was inserted for the vascular access. Concomitant the immunosuppressive drug dose tapering was initiated in order to safely withdraw the corticosteroid, as the renal biopsy findings emphasized irreversible lesions characteristics for advanced stages of CKD, and due to the significantly decrease of diuresis. Three days after the catheter insertion, the patient presented deep venous thrombosis, and consequently the catheter was changed and anticoagulant therapy was initiated. The culture of the catheter tip showed

an infection with *Pseudomonas aeruginosa*, and antibiotic treatment was started according to the antibiogram. The risk factors for this infection might have been the immunosuppressant therapy and the immunosuppressant state of the patient given by the chronic kidney disease. No further complications were noticed. Even if his past and during the admission medical records indicated a partial general improvement (i.e. proteinuria, oedema), once immunosuppressive treatment was initiated, because the diagnosis was not confirmed on time, the patient's renal function was irreversibly impaired, requiring chronic dialysis. The patient was discharged with the recommendations of continuing renal replacement therapy and gradually tapering the doses of the immunosuppressive drug until it could be safely withdrawn.

DISCUSSIONS

IgA nephropathy has a wide range of clinical manifestations from asymptomatic cases to rapidly progressive glomerulonephritis [10]. The patients with isolated microscopic hematuria and minimal proteinuria have a favorable prognosis [11], but once the disease progresses hypertension and increased proteinuria are noticed (levels over 3.5 g/24 hours could be observed in Ig A nephropathy patients, but nephrotic syndrome is rarely associated [12,13]). Furthermore, patients with proteinuria, hypertension and decreased eGFR at the moment of diagnosis, have a poor prognosis [14,15]. This serves as a reminder that long-term follow-up must be performed in all patients diagnosed with Ig A nephropathy [8,16].

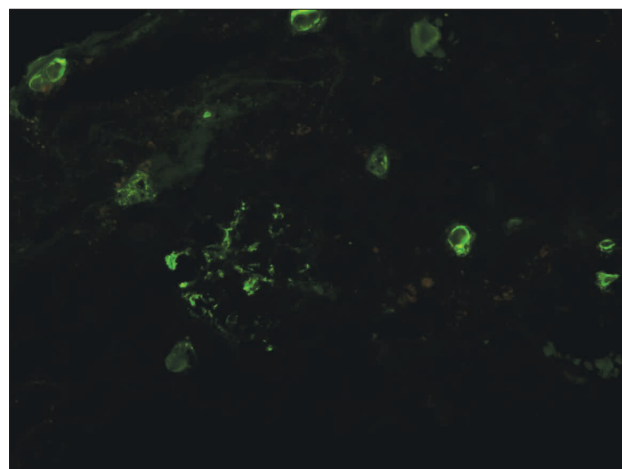
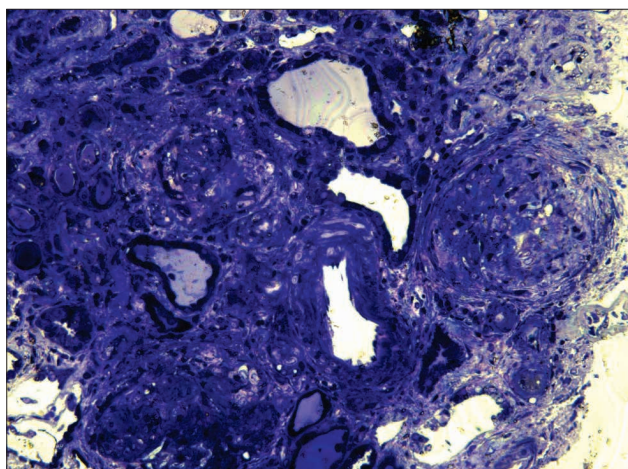


FIGURE 1. Biopsy findings – **A.** optic microscopy examination (3 glomeruli with sclerosis and segmental hyalinization; arterioles with nodular and circumferential hyaline deposits, one being completely obstructed; tubular atrophy; extensive fibrosis and interstitial inflammation); **B.** immunofluorescence examination (intense positive IgA granular deposits, but rare; IgG, IgM, C1q all negative; intense C3c in the vessels and moderate in the glomeruli; mild kappa granular deposits; moderate lambda granular deposits)

The treatment of IgA nephropathy depends on the prognosis of the patient [14]. As already emphasized, the cases with a good prognosis require only a long-term follow-up, and those considered with an intermediate prognosis could benefit from supportive care, such as the use of renin-angiotensin-aldosterone system inhibitors to control the blood pressure and reduce also the proteinuria, or supplementing the diet with omega-3 fatty acids [1,9]. Patients with important histological modifications, including the presence of crescents, and with a rapid loss of eGFR, require immunosuppression along with supportive care [1,9]. Usually, corticosteroids are used in all cases that need immunosuppression, proving their beneficial effects by significantly reducing proteinuria and slowing the progression of renal impairment [1,3,10]. The efficiency of other immunosuppressant agents (i.e. cyclophosphamide, mycophenolate mofetil, cyclo-

sporine and rituximab), as treatment options for IgA nephropathy, remains a matter of debate [17-19].

Our patient had a poor prognosis at the time of the admission and diagnosis, given the fact that he presented nephrotic syndrome, hypertension and eGFR under 15 mL/min/1.73 m². In addition, the confirmation of the diagnosis was too late established, highlighted by the renal biopsy results, and in consequence our patient required chronic renal replacement therapy.

CONCLUSIONS

This case illustrates the importance of an early diagnosis of IgA nephropathy, since the delaying of the diagnosis and adequate treatment can have important consequences on the preservation of the patient's renal function and over-all outcome.

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