

# IgA Nephropathy: Sometimes a difficult diagnosis – A case of secondary hypertension

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### Abstract

IgA nephropathy or Berger disease is the most frequent etiology of idiopathic glomerulonephritis in the world, although of unclear etiology and target of active investigation. It can present itself in many different ways and it is easily mistaken by other conditions as happened in the clinical case we are referring to.

Usually there is a macroscopic recurring hematuria following an upper airways infection. Most patients are diagnosed when investigating an asymptomatic microscopic mild hematuria/

proteinuria.

It is a clinical condition representing a secondary arterial hypertension mainly etiology in younger age groups.

Around 50% evolve towards progressive terminal kidney failure relying on hemodialysis.

An early diagnosis is essential to improve the prognosis.

Key words: IgA nephropathy, Berger disease, arterial hypertension, deposits of IgA, renal transplant.

### Introduction

The current clinical case refers to a chronic renal failure progressing for 4 years featured by a microscopic hematuria condition, alternating with conditions of macroscopic hematuria, hypertension, peripheral edema, anemia and renal insufficiency needing hemodialysis and referral to transplant.

It is therefore of relevant interest to approach the question of possible change on the natural course of glomerulopathies affecting younger patients, making the differential diagnosis more difficult and featured by a not specific presentation.

### Clinical case

A male patient, 25 years old, Caucasian, born and residing in Lisbon, an indoor football coach: he has been followed up as an Urology outpatient since 2003, after two consecutive hospital admissions with a 3 months gap, due to fever, macroscopic hematuria and lumbar

pain, in a context of urinary infection with a renal commitment. Since then he has been asymptomatic and under clinical monitoring with 24 hours urinalysis, prostate ultrasound, abdominal CAT Scan and renal scintigraphy. In the routine analysis made on the 2<sup>nd</sup> February 2006 it was verified the presence of macroscopic hematuria. In March 2007, it started a progressive tiredness for all daily activities. On the 10<sup>th</sup> April 2007, he realized a facial and periorbital edema with remission at the end of the day. Three days afterwards he visited Odivelas Health Centre due to pulsatile occipito-frontal headaches and vomiting, without other complaints. Observation showed a blood pressure of 230/130 mmHg, reason why the treatment with furosemide and nifedipine was started and the patient referred to the Central Emergency Service of Santa Maria Hospital (HSM).

At arrival the patient was already asymptomatic. Blood pressure of 188/109 mmHg, 95 bpm heart rate, and tympanic temperature of 36.7°C [98.6F]. His skin was pale, mucosa slightly pale and dehydrated, mild periorbital and maleolar bilateral edema. Analyses showed creatinine serum levels of 9.2 mg/dL (0.7-1.2 mg/dL) and urea of 202 mg/dL (10-50 mg/dL), creatinine clearance was obtained through Cockcroft-Gault equation and it was 12.15 ml/min/1.73 m<sup>2</sup>. Serum levels of calcium were 6.3 mg/dL and phosphorus of 5.7 mg/dL. Normocytic normochromic anemia with Hb 8.3 g/dL, 49 g/L (66-87 g/L) total protein and albumin of 31 g/L (34-48 g/L), LDH 522 U/L (240-

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480 U/L), without raising inflammatory endpoints were present. The urine short test showed 0.5 g/dL proteinuria, 250 cel/uL red blood cells and all other values within a normal range. Renal ultrasound showed a mild kidney decrease in size (10 cm [3.9 inch] bipolar Ø); reduced differentiation on diffuse cortical hypercogenicity with regular borders; parenchyma thickening still within normal limits.

Treatment with furosemide, captopril, nifedipine and paracetamol was initiated and the patient was admitted into the Medicine I C Service to clarifying and monitoring his condition.

It was a serious hypertensive patient, probably secondary to a chronic kidney disease, evolving for about 4 years, in stage V (compatible clinical history, renal function values, ultrasound showing slight decrease on kidneys size and anemia), with mild proteinuria and abundant hematuria.

The values of the general analytical study, immunology, iron and urine are shown in *Tables I, II, III e IV*, respectively. Bilateral papillary stasis, mainly on the right side, without hemorrhage in the funduscopy was seen. Thorax X-ray (PA), electrocardiogram, ultrasound and cranioencephalic CAT scan did not show any relevant alteration.

There was a gradual decrease on the blood pressure having reached control values. Renal function endpoints were kept high with urea ranging between 180-200 mg/dL and serum creatinine between 8.8-9.5 mg/dL. Before the low hemoglobin levels, darbepoietin 100 mg subcutaneously/week was initiated and a transfusion of red cells concentrate 1U was made with a subsequent increase on hemoglobin value from 7,5 g/dL to 8,7 g/dL and later to 10 g/dL. Between the 16 and 21<sup>st</sup> April, he underwent 5 hemodialysis sessions based in clinical and laboratorial endpoints. A renal biopsy was made enabling the IgA nephropathy diagnosis.

The patient was discharged on the 23<sup>rd</sup> April, with a clinical condition improved and medicated with darbepoietin, nifedipin CR 60 mg and atenolol 50 mg. He was referred to the renal transplant unit for outpatients and to Loures Hemodialysis Centre (3 sessions/week) awaiting transplant.

## Discussion and Conclusion

Chronic kidney disease (CKD) definition requires that the pathophysiology process lasts for over 3 months<sup>1</sup> and, in the current clinical case, several aspects indi-

**TABLE I**  
Estudo analítico geral

Endpoint	Patient	Reference
Reb blood cells	2.710	4.5-5.9 x 10 <sup>12</sup> /L
Hemoglobin	7.5	13-17.5 g/dL
MCV	82.5	80-97 fl
MCH	28	27-33 pg
Leukocytes	8.850	4.0-11.0 x 10 <sup>9</sup> /L
Neutrphyles	79.7	45-75%
Platelet count	124	150-450 x 10 <sup>9</sup> /L
ESR	24	< 30 mm
CRP	0.28	<0,5 mg/dL
Urea	178	10-50 mg/dL
Creatinine	8.8	0.7-1.2 mg/dL
Na+	140	135-140 mmol/L
K+	5.4	3,5-5,0 mmol/L
Osmolality	306	275-295 mOsmol/kg
LDH	567	240-480 U/L
Total proteins	49	60-80 g/L
Albumin	31	35-50 g/L
Calcium	6,3	8.6-10.2 mg/dL
Phosphorus	5,7	2.7-4.5 mg/dL
PTH	161	14-72 pg/mL

cate its presence, namely macroscopic hematuria and renal dysfunction<sup>1,2</sup> (serum creatinine and urea increase) which have been reported since 2003, in the first admission. The circumstance of only in the last admission being reported a non-nephrotic proteinuria, hypertension, facial and periorbital edema, hydroelectrolytic disorders (hyperkalemia, hyperphosphatemia, hypokalcemia with secondary hyperparathyroidism) and yet the fact that no hematologic changes were noted (normocytic-normochromic anemia which might be associated to an erythropoietin deficit) and the presence of small kidneys in the renal ultrasound does not question the diagnosis reliability.

GFR or creatinine clearance estimates are usually used to establish CKD stages through Cockcroft-Gault equation including creatinine serum concentration,

**TABLE II**  
Immunology study

Auto-Immunity		Immunochemistry			
		Serum		Urine	
ANA	Negative	Imunocomplexes	0,5 U/mL	P. Bence-Jones	Negative
AMA	Negative	IgA	4,05 g/L	IgG	0.223 g/L
ASMA	Negative	IgG	7.60 g/L	K	0.073 g/L
Anti-LKM Ab	Negative	IgM	0.68 g/L	L	0.053 g/L
Anti-dsDNA Ab	<20 U/mL (<20)	K	2.19 g/L		
Antihistone Ab	<40 U/mL (<40)	L	1.55 g/L		

age, weight and the index related with the patient's gender.<sup>1,2</sup> GFR/creatinine clearance value of 12.15 mL/min/1.73 m<sup>2</sup>, seen in the 24 hours urinalysis, placing the patient in stage V of the disease featured by Chronic Kidney Failure (CKF) recommended for hemodialysis or transplant. Globally, CKD two main causes are cardiovascular hypertensive disease and diabetes.<sup>1,2</sup> Hypertensive nephrosclerosis results from hypertension on the kidney parenchyma. The clinical condition usually includes other target organs lesions, as left ventricular hypertrophy and hypertensive retinopathy. Proteinuria is mild to moderate and the sediment is inactive.<sup>3</sup> Usually there is a long standing hypertension and there is no evidence of another cause to kidney injury (nephrotoxicity, primary or congenital kidney disease, or any other systemic disease likely to be followed by kidney injury). The most common histological findings in this pathology are: intima fibrosis and arteries and arterioles medium layer hypertrophy and arteriolar hyalinisation with ischaemic collapse of capillary loops and peri- or intracapsular fibrosis.<sup>3</sup> Diabetic nephropathy usually has a reported history of diabetes (the disease evolving often over a period of 15-20 years), proteinuria, retinopathy, nephrotic syndrome and no hematuria.<sup>4</sup> There is no history of diabetes, and there is only a reference to hypertension and bilateral papillary stasis in the last admission.

The clinical condition made by macroscopic hematuria with recurrent episodes, proteinuria, edema, CKF is a strong indicator of glomerular disease being present, and among the main causes of glomerulopathy, the one standing out is IgA nephropathy or

Berger disease.<sup>1,5,6,7</sup> It is predominant in the second and third decades of life, in male Caucasians and Asians, in a gender ratio of 2:1.<sup>6,7</sup> The etiology is unknown, but it can be linked to infections and/or family history.<sup>7,8</sup> The disease diagnosis is based in the clinical suspicion that can only be verified through

kidney biopsy.<sup>8</sup> Immunofluorescence microscopy (Fig. 1) shows a proeminence of IgA globular deposits (IgA subclass) in the mesangium, under optical microscopy (Fig. 2) a mesangial diffuse proliferation and matrix expansion and presence of crescents in most advanced cases. Some electron dense deposits can still be viewed under electronic microscopy (Fig. 3).<sup>7,8</sup> However, IgA mesangial deposits may be present in other pathologies<sup>7,8</sup> which, almost always, progress without symptoms, namely cirrhosis, celiac disease and HIV infections or other glomerular diseases, including minimal lesion glomerulonephritis, Wegener granulomatosis and Henoch-Schönlein purpura. Kidney biopsy is crucial to verify the diagnosis.<sup>8</sup> Minimal lesion glomerulonephritis is more frequent in the female gender and has a benign evolution. Clinically, it presents itself with nephrotic syndrome (proteinuria>3-3.5g/dia, hypoalbuminemia, edema,

**TABLE III**  
Iron study

Endpoints	Patient	Reference
Serum Iron	50	65-180 ug/dL
Ferritine	340.8	23.9-336 ng/mL
TIBC	227	250-425 ug/dL
Transferrin saturation	22	26-42%
B12 Vitamin	391	180-914 pg/mL
Folate	1.9	2-20 ng/mL

**TABLE IV**  
Urine study

Summary of Urinalysis		24 hour Urinalysis	
Endpoints	Patient	Endpoints	Patient
Color	Pale yellow	Creatinine	452.4 mg/L
Density	1,010	Ionogram	Normal
pH	7,0	Urea	4.8 g/L
Protein	1,50 g/L	Glucose	0.3 g/L
Hemoglobin	150 uL	Calcium	2 mg/dL
Leukocytes	0	Phosphorous	10.5 mg/dL
Nitrites	0	Magnesium	<1.67 mg/dL
Glucose	0	Protein	1690.0 mg/L
Ketone bodies	0	Albumin	1445.4 mg/L
Urobilinogen	0	Creatinine Clearance	12.15 ml/min/1.73 m <sup>2</sup>
Bilirubin	0		
Reb blood cells	2396,2/uL	Urine culture	
Hyaline bodies	11,6/uL	Negative	
Granular bodies	10,6/uL		

hyperlipidemia, lipiduria, hypercoagulability), GFR decreasing and seldom progressing to CKD. This disease electronic microscopy is different from IgA nephropathy as podocytes fade away.<sup>8</sup> Wegener granulomatosis presents an insidious latent inflammation or kidney failure progressing rapidly. About 80% have

**TABLE V**  
Factors contributing for a worst prognosis\*

Clinical factors	Histological Factors
Persistent proteinuria > 1g/day	Glomerulosclerosis
Serum creatinine > 2 mg/dL	Tubular atrophy and interstitial fibrosis
Asymptomatic persistent microscopic hematuria	Immune deposits in Henle loop and mesangial capillaries
Hypertension associated to arteriosclerosis and tubulointerstitial changes	Vascular disease
Severe kidney dysfunction with GFR decrease higher than 1 to 3 mL per year	Glomerular scar
	Crescent formation

\*Treatment and prognosis of IgA Nephropathy April 2007<sup>11</sup>

cytoplasmatic ANCA on presentation. Kidney biopsy shows focal segment necrotizing pauci-immune glomerulonephritis with crescents formation.<sup>8,9</sup> In spite of being histologically indistinguishable from IgA nephropathy, Henoch-Schönlein purpura can be distinguished from the former for being a systemic disease, with an incidence peak on the second decade of life, a sudden onset of the clinical condition, often self-limited, made by a lower limb petechiae exanthem, arthropathy and abdominal pain associated to glomerulonephritis.<sup>8,10</sup> Before such clinical data, the patient underwent a kidney biopsy which confirmed IgA nephropathy to be present.

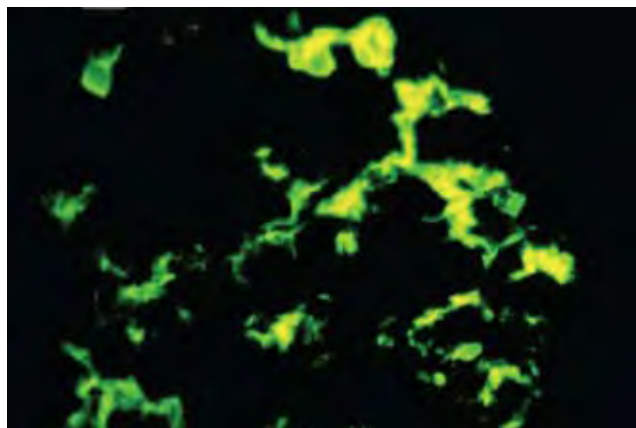
Thin basement membrane glomerulonephritis is also a differential diagnosis to be taken into account, as it evolves with a clinical setting similar to Berger's disease, however, usually there is a family history of kidney disease.

Alport's syndrome is predominant in the male gender, and one of the diagnosis criterion is recurrent hematuria progressing to kidney failure at a young age, however it presents itself concomitantly with progressive bilateral neurosensorial deafness and some eye complaints, with a family history.

Forty years after being described, IgA nephropathy, in spite of being the most frequent primary glomerulonephritis, keeps being an enigma in terms of diagnosis and therapy. Although it has a relatively benign prognosis, in a considerable percentage of cases there is progress to terminal kidney disease, 15-25% after progressing for 10 years, matching a rate of 1 to 2% per year (Table V).<sup>7,8,11</sup> This aspect becomes relevant if we consider that this disease incidence peak occurs between the second and third decades of life.

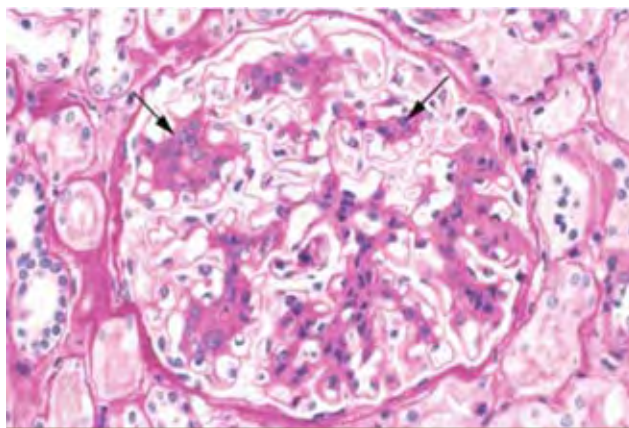
As previously seen, there is no consensus on how to approach patients with isolated hematuria. Kidney biopsy is the definitive diagnosis approach, in most renal diseases and it is crucial to approach patients with morbid conditions potentially reversible with therapy.<sup>1,7,8,11</sup> In general in the USA, kidney biopsy is considered only when the patient shows evidence of a serious illness or progression,<sup>11</sup> although sometimes it might be too late to prevent the disease to progress,





Immunofluorescence microscopy of an IgA nephropathy patient renal biopsy – IgA globular prominent deposits, mainly in the mesangium, present in IgA nephropathy or Henoch-Schönlein purpura.

FIG. 1

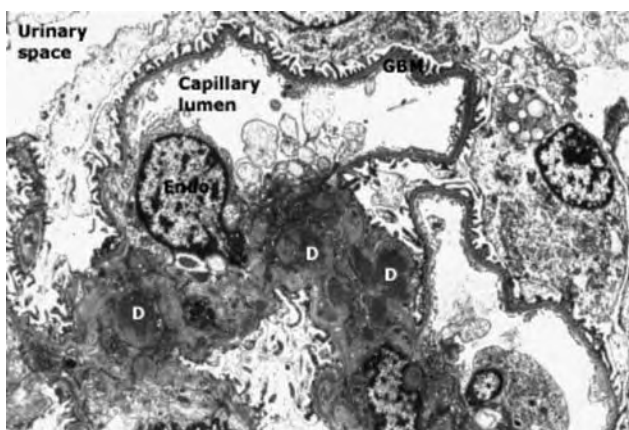


Optical microscopy of an IgA nephropathy patient renal biopsy – Mesangial glomerulonephritis with segmented areas and an increase in the mesangial matrix and cellularity.

FIG. 2

and all remaining cases are monitored at annual/biannual periods, depending on each centre. In Japan, the intervention incides more in primary prevention, with urinalysis being made to populations without a clinical evidence of the disease, namely students and workers.<sup>8,11</sup> The lack of agreement on whether to perform a kidney biopsy before the slightest clinical and laboratory suspicion of the disease is a dilemma to be solved by the clinical *praxis* of each country and it will depend largely on the technique cost/benefit, not overlooking the fact that kidney biopsy has some important contraindication namely in patients with smaller kidneys, badly controlled hypertension, urinary tract infection or bleeding diathesis.<sup>1,5</sup>

IgA nephropathy ideal therapy is unknown. The option has been to implement general nephroprotective action (diet restrictions, blood pressure controlled with ACE inhibitors and or ARA II, dyslipidemia treatment with statins and/or polynsaturated) and, in the most serious cases, introducing corticoids and/or immunosuppressors, to delay the disease progression.<sup>7,11</sup> In the current clinical case, the chosen therapeutic scheme to control the blood pressure was a calcium channel antagonist (nifedipine) associated to a beta-blocker, instead of using an ACE inhibitor/ARA II. This decision was taken considering the fact the patient was in serious Chronic Kidney Failure and the possibility of ACE inhibitors/ARA might increase renal dysfunction, decreasing GFR with an increase



Electron microscopy of an IgA nephropathy patient renal biopsy – Electrodense deposits limited to the mesangium (D). GBM normal, without deposits in the glomerular capillaries walls.

FIG. 3

on serum creatinine and urea values and a proteinuria increase. On the other hand, calcium channel antagonists, have the advantage of being good medicines to treat chronic hypertension, without the risk of adverse events if kidney failure is present.<sup>12</sup>

The patient is undergoing hemodialysis without much hope of kidney function recovery to pre-dialysis levels. Therefore, it is anticipated the need for kidney transplant.

According to the National Registry of Kidney

Transplant between 1980-2006,<sup>13</sup> the awaiting time for kidney transplant in Portugal has increased in the last 6 years and at present it is around 4 years. The post-transplant prognosis is favorable with a survival rate in patient vs graft at 5 years of 90.6 vs 76.5 and at 10 years of 81.2 vs 60.5. Decreases in acute rejection in the 1<sup>st</sup> year, and the main causes of graft loss are chronic rejection, kidney failure and disease recurrence. Mortality is related with infection, cardiovascular disease or neoplasia.<sup>13</sup> ■

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