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Case report

Atypical Uremic Hemolytic Anemia – Case Report

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Abstract

Atypical Hemolytic Uremic Syndrome (AHUS) is a syndrome of rare incidence, approximately 0.5 per million per year, of genetic characteristic, being inherited or acquired. Mutations occur in the proteins that regulate the complement system, predominantly factor H. The reported case is a female patient, without comorbidities and without family history of autoimmune disease. At the age of 16, she started with the flu (fever, oropharyngeal pain, runny nose) and was submitted to NSAIDs and Amoxicillin to control the condition, with a significant evolution of symptoms. After seven days of remission of the flu, she presented generalized malaise, nausea and vomiting, and it was necessary to go to the emergency room. Hemodialysis was initially indicated, which is why the patient underwent two hemodialysis sessions in this hospital and, subsequently, three days after her admission, she was transferred to Hospital Beneficência Portuguesa de São Paulo (05/09/2019). There are no reports by the patient of weight loss, adenomegaly, neurological symptoms and/or bleeding. In the absence of the result of the ADAMS 13 test, it was decided to request the medication Eculizumab, which was released with 13 days of hospitalization by the health plan. About Eculizumab: medication of choice for the treatment of aHUS. Eculizumab is a humanized anti-C5 monoclonal antibody (Eculizumab), terminal complement inhibitor. This antibody binds specifically and with high activity to the human complement protein C5, inhibiting its cleavage into C5a and C5b and preventing the generation of the terminal complement membrane attack complex (C5b-9).

Keyword: Atypical Hemolytic Uremic Syndrome, Eculizumab, Human complement C5, Hemolysis

Abbreviations

aHUS: Atypical Hemolytic Uremic Syndrome
CFH: Complement Factor H
Cr: Creatinine
Hb: Hemoglobin
LDH: Lactic Dehydrogenase
TMA: Thrombotic Microangiopathy
TTP: Thrombotic Thrombocytopenic Purpura

1. Introduction

The atypical Hemolytic-Uremic Syndrome (aHUS) is a thrombotic microangiopathy (TMA) mediated by complement caused by the dysregulated activity of the alternative pathway, its clinic encompasses non-immune hemolytic anemia, thrombocytopenia and acute kidney injury. AHUS is a syndrome of rare incidence, approximately 0.5 per million per year, of genetic characteristic, being inherited or acquired. Mutations occur in the proteins that regulate the complement system, predominantly factor H (Table 1).

Some retrospective studies have evaluated the discontinuation of Eculizumab therapy in patients with aHUS, but there are still no conclusive results. Pathogenic variants in complement genes have been associated with a higher rate of aHUS relapse. We do not yet have studies to determine when we will discontinue the medication or not.

Case

Female patient, without comorbidities and without family history of autoimmune disease. At the age of 16, she started with the flu (fever, oropharyngeal pain, runny nose) and was submitted to NSAIDs and Amoxicillin to control the condition, with a significant evolution of symptoms. After seven

days of remission of the flu, she presented generalized malaise, nausea and vomiting, and it was necessary to go to the emergency room of her hometown (Lorena-SP-Brazil).

In her admission exams, the patient presented Hemoglobin (Hb): 8.5 g/dL, acute kidney injury, Creatinine (Cr) 4.0 mg/dL, Urea 210 mg/dL, Thrombocytopenia 74,000 mm^3, Lactic Dehydrogenase 2887 U/L, Total Bilirubin 2.3 mg/dL at the expense of Indirect. Hemodialysis was initially indicated, which is why the patient underwent two hemodialysis sessions in this hospital and, subsequently, three days after her admission, she was transferred to Hospital Beneficência Portuguesa de São Paulo (05/09/2019). There are no reports by the patient of weight loss, adenomegaly, neurological symptoms and/or bleeding.

Considering the clinical and laboratory tests of the patient, the hypothesis of TMA to be clarified (aHUS or Thrombotic Thrombocytopenic Purpura - TTP) was suggested. The admission exams were: Hb 9.1 g/dL, Platelets 74,000 mm^3, Cr 3.4 mg/dL, Lactic Dehydrogenase (LDH): 2887 U/L, Haptoglobin consumed, Reticulocytes 384,000 and Complement C3-C4 – CH50 normal.

After admission and examinations with high suspicion of TMA, the patient was referred to the Intensive Care Unit to be submitted to plasmapheresis, with a request for collection of the ADAMTS 13 test (Von Willebrand factor rupture protease activity), which is essential for the differential diagnosis between aHUS and TTP.

Once clinical and laboratory tests compatible with TMA are established, the company Alexion provides a program called Complementare, which offers test collection for diagnosis of the disease. The result was available in 10 days after collection, finding research of ADAMTS 13 (09/11/2019): 0.88 IU/mL (RV = 0.40-1.30).

From the time she was admitted to the hospital until the definitive diagnosis of the patient, 12 sessions of plasmapheresis were necessary, however, despite not presenting improvement in the hemolysis aspect, there was no need for new hemodialysis sessions. On the other hand, there was a delay in performing renal biopsy due to thrombocytopenia, which was only performed eight days after hospitalization.

After discussions with the Nephrology and Hematology teams, it was concluded that the clinical behavior, the lack of success with plasmapheresis and the tests compatible with hemolysis indicated the diagnosis of aHUS. Therefore, even in the absence of the result of the ADAMS 13 test, it was decided to request the medication Eculizumab, which was released with 13 days of hospitalization by the health plan [01-04].

About Eculizumab: medication of choice for the treatment of aHUS. Eculizumab is a humanized anti-C5 monoclonal antibody (Eculizumab), terminal complement inhibitor. This antibody binds specifically and with high activity to the human complement protein C5, inhibiting its cleavage into C5a and C5b and preventing the generation of the terminal complement membrane attack complex (C5b-9). Eculizumab preserves the initial components of complement activation that are essential for the opsonization of microorganisms and the removal of immune complexes. In patients with aHUS, uncontrolled terminal complement activation and consequent complement-mediated TMA are blocked in Eculizumab treatment.

The receipt of the medication requires some preparations, such as immunization and prophylaxis with antibiotics.

The following procedures were performed:

- Performed prophylaxis with Ceftriaxone during the beginning of treatment and maintenance of azithromycin 500 mg three times a week to the present day. Vaccinated in the hospital itself against Meningo ACWY conjugate, two doses, with an interval of two months between them and repeating every five years.
- Vaccination against Meningo B, two doses, thirty days apart.
- Administered the first dose of Eculizumab two days after release from the health plan (09/20/2019), 900 mg every seven days for four weeks, 1200 mg after seven days and maintenance every fifteen days with a dose of 1200 mg.
- After initiation of Eculizumab patient showed significant improvement of hemolytic anemia, as well as improvement of proteinuria and renal function.
- She was discharged on 10/18/2019 with the following tests: Hb 10.5 g/dL, Platelets 218,000 mm3, Cr 0.8 mg/dL, Reticulocytes 80,000, Haptoglobin still consumed <6, LDH 426 U/L, 24-hour urine proteinuria 500 mg.
- The maintenance of the medication Eculizumab was scheduled every fifteen days, patient made use of the medication in the period from 09/20/2019 to September 2022, however, the patient decided to cease use on her own.
- In December 2022 (three months after discontinuation of the medication), the patient reported an episode of urinary tract infection and, therefore, underwent treatment with the antibiotic ciprofloxacin. Subsequently, she started to have an upper airway infection, finding Covid-19 positive.
- She was re-admitted to the BP Hospital on 12/29/2022 due to worsening of renal function and anemia and was again found to have TMA.
- Because the patient had ceased her treatment, some medications were retained in the hospital, due to the severity of the condition Eculizumab was started, even with positive Covid-19, since the clinic was not prominent.
- In this second admission, she presented initial tests: Hb 9.4 g/dL, Platelets 94,000 mm3, Cr 2.0 mg/dL and, the next day, presented significant laboratory worsening Hb 8.3 g/dL, platelets 90,000 mm3, Cr 3.0 mg/dL, reticulo-

cytes 50,000, proteinuria in 24 hours 4 grams.

- She received the first dose of Eculizumab on 01/07/2023, 1200 mg and after fourteen days received the second dose of 1200 mg, showing significant improvement of hemolysis and renal function with a dose of Eculizumab, being discharged from hospital (14/01/2023) with 24-hour proteinuria of 1 gram and renal function in improvement Cr 1.7 mg/dL.
- On 01/12/2023, after platelet improvement, a renal biopsy was performed again to assess the degree of TMA, however, the biopsy found only segmental and focal glomerulosclerosis without any sign of TMA and disease activity.
- This point caused doubts as to the etiology of the biopsy finding, that is, whether focal segmental glomerulosclerosis would be secondary to the chronicity of chronic kidney disease or new immunological disease emerging.
- Due to the significant improvement of the disease, exams and clinic, the patient was discharged from the hospital on 01/14/2023, maintaining Eculizumab until the present day and outpatient follow-up. Discharge tests: Cr 1.7 mg/dL, platelets 260,000 m3, Hb 9.9 g/dL.

In May 2023, after the second hospitalization, a genetic test was performed to know which gene was compromised and a pathogenic variant in heterozygosis in the CFH gene was detected. Genetic or acquired abnormalities in the complement system have been documented in 60% of patients with aHUS. Complement Factor H (CFH) is the most important plasma regulator of the alternative pathway. CFH mutations are the most common genetic abnormality in aHUS, prevalence of 20 to 30 %.

Some mutations are associated with a quantitative deficit of **CFH**, while most are associated with normal levels of **CFH** and result in mutant protein that is unable to bind to and regulate complement on the cell surface. First hospitalization information (Table 2), First dose of the drug until discharge (Table 3), Second hospitalization table (Table 4).

Table 1. Genes abnormalities.

GENE	ABNORMALITIES	MAIN EFFECT	FREQUENCY IN aHUS
CFH	Heterozygous and (rarely) homozygous mutations mainly in the last 2 exons	Impaired cell-surface complement regulation	25%-30%
CFH/CFHRs	Nonallelic homologous recombinations	Impaired cell-surface complement regulation	3%-5%
CFHR1	Deletion and formation of anti-CFH antibodies	Impaired cell-surface complement regulation	5%-10%
CD46	Heterozygous and (rarely) homozygous mutations	Reduced surface expression	8%-10%
CFI	Heterozygous mutations	Low cofactor activity	4%-8%
C3	Heterozygous mutations	Resistance to C3b inactivation, C3 convertase stabilization	4%-8%
CFB	Heterozygous mutations	C3 convertase stabilization	1%-4%
THBD	Heterozygous mutations	Reduced TFI activation, reduced C3b inactivation	3%-4%
DGKE	Homozygous or compound heterozygous mutations	Protein truncation, proinflammatory and prothromboltic endothelial phenotype, increased netdothelial apoptosis	2%-27% of infantile cases

aHUS: Atypical Hemolytic Uremic Syndrome, **CD46:** Encode MCP, **CFB:** Complement Factor B, **CFH:** Complement Factor H, **CFHRs:** Related Complement Factor H, **CFI:** Complement Factor I, **DGKE:** Diacylglycerol Kinase, **MCP:** Membrane Cofactor Protein, **TFI:** Thrombinactivable Fibrinolysis Inhibitor, **THBD:** Thrombomodulin.

Table 2. Table examinations from admission to the first dose of medication.

Date	09/05/22	09/06/22	09/08/22	09/10/22	09/11/22	09/12/22	09/14/22	09/16/22	09/17/22	09/18/22	09/19/22
Hemoglobin	9,1	7,5	6,1	8,2	9,0	8,2	7,5	7,4	6,8	6,0	7,4
Platelets	74.000	59.000	45.000	69.000	82.000	122.000	122.000	131.000	133.000	100.000	105.000
Creatinine	3,4	3,6	4,36	4,31	3,9	3,77	3,4	2,6	2,7	2,86	2,9
Lactic Dehydrogenase	2887	1285	642		837		540	641	759	707	871
BT	2.23 at the expense of indirect		1.33	1.03	1.2		0.44	0.3	0.36	0.27	0.5
Haptoglobin	>6		<6			<6		<6	<6		
Coobs right	Negative										
Reticulocytes	384.000		281.000		145.000			101.000	126.000	126.000	134.000
Add-ons	Normal										
C3, C4, CH50											

Table 3. Tests performed from the first dose of Eculizumab to discharge.

Date	09/20/22	09/22/22	09/24/22	09/26/22	09/27/22	09/28/22	10/01/22	10/03/22	10/10/22	10/18/22
Hemoglobin	8,3	8,7	8,3	7,9		7,7	7,9	7,5	9,8	10,5
Platelets	105.300	114.000	121.000	138.000		165.000	236.000	305.000	409.000	218.000
Creatinine	3,03	2,3	2,3	2,07		1,6	1,4	1,39	0,98	0,8
Lactic dehydrogenase	590	867	906	885		852	853	704	472	426
Reticulocytes	107.500	98.000	107.000	89.000		71.000	70.000	79.000	80.000	80.000
BT	0,67	0,6		0,49		0,33			0,19	
Haptoglobin		<0,6		<6					<6	<6
24-hour proteinuria		8,92 g						8,6g		
Dose of Eculizumab	1st dose				2nd dose					

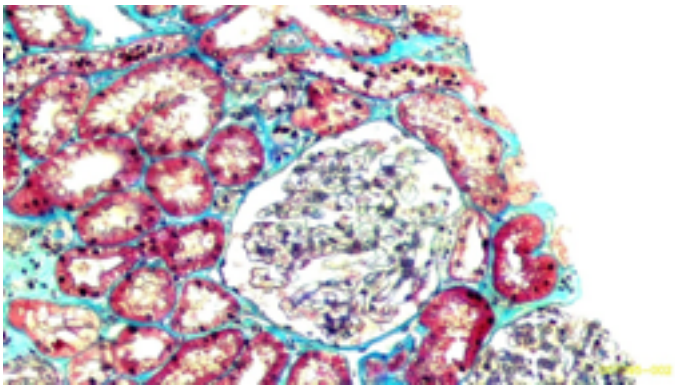
Table 4. Examinations according to the second hospitalization.

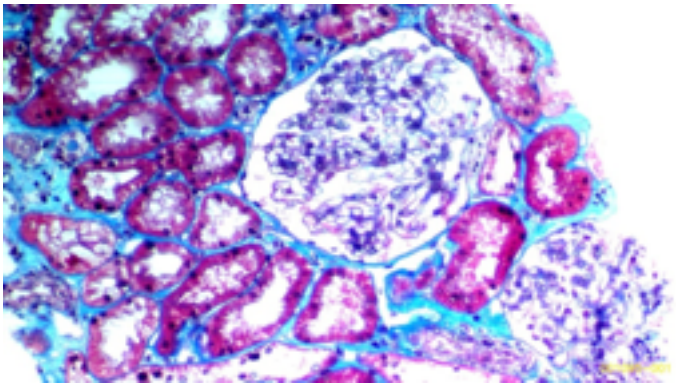
Date	12/29/22	12/31/22	01/02/23	01/04/23	01/06/23	01/08/23	01/12/23	01/14/23
Hemoglobin	9,4	8,3	6,5	8,5	8,5	9,2	9,4	9,9
Platelets	94.000	90.000	113.000	182.000	243.000	293.000	250.000	260.000
Creatinine	2,0	3,0	3,12	2,92	2,54	1,9	1,7	1,7
Coombs Direct		Negative	-	-			--	
Haptoglobin		<3	<3		<3	<3	<3	
Reticulocytes		50.000	54.000				54.000	
24-hour proteinuria								
Urine		4.39 g in 24-hour volume						
Lactic Dehydrogenase	500	508	42	397	396	250	293	
TGO and TGP		Normal	Normal	Normal	Normal	Normal	Normal	

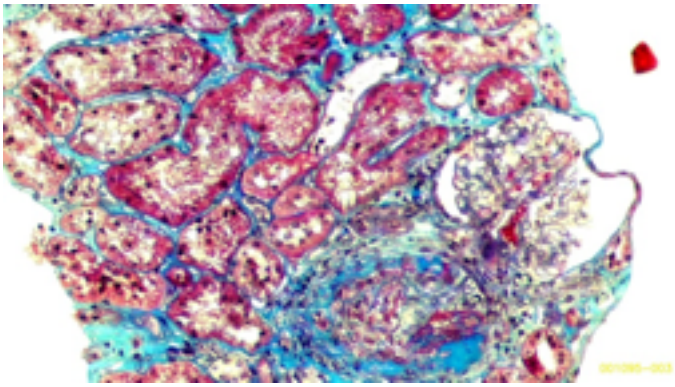
First diagnosis: focal segmental glomerulosclerosis, nos variant.

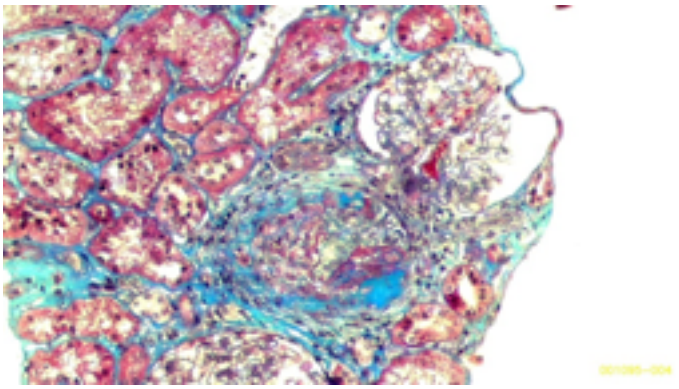
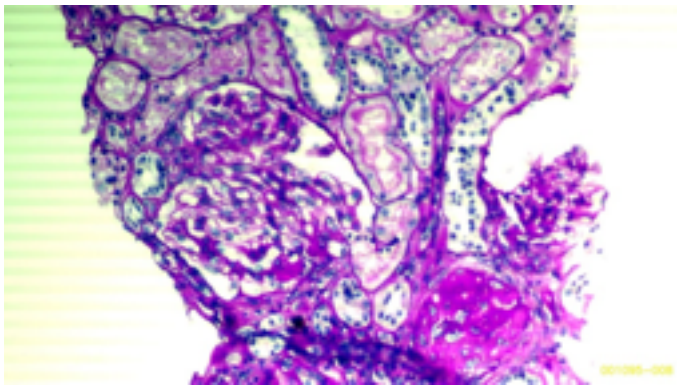
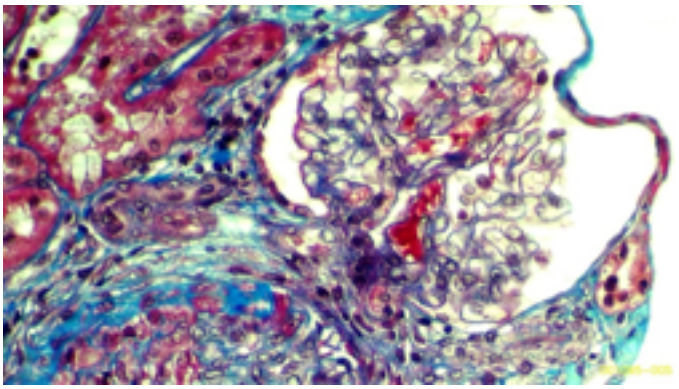
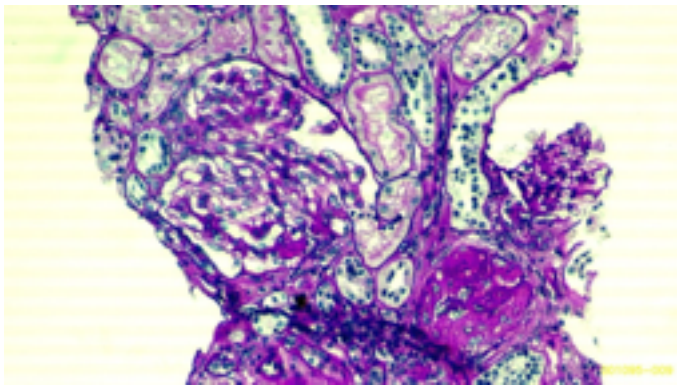
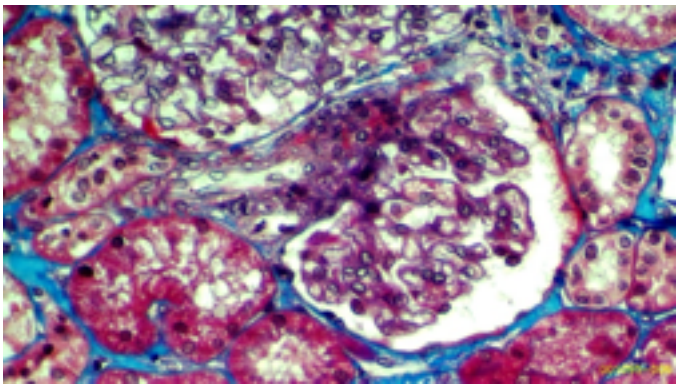
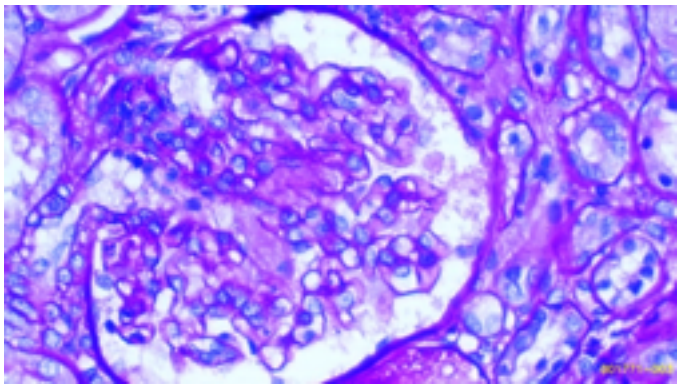
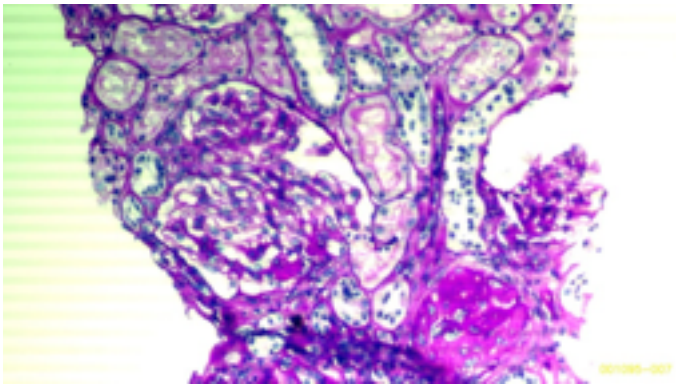
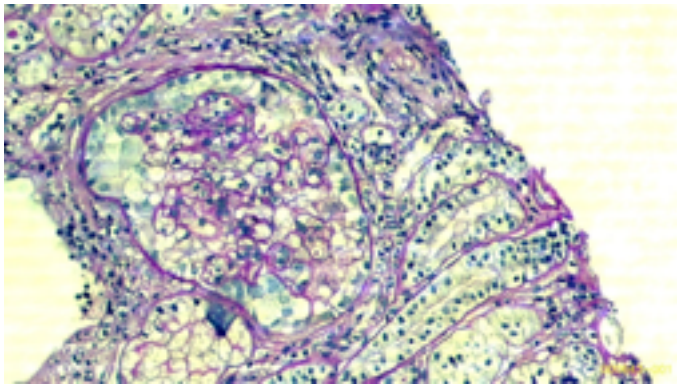
Second diagnosis: We observed, at immunofluorescence, granular deposits, arranged in such a way as to form coarse clusters always limited to segments of the capillary bundles that fixed the specific antisera for IgM (+++/+++), Lambda (+++/+++), Factor C3(+++/+++) of the complement and Fibrin (+/+++).

Macroscopic examination: Filiform fragments of firm, brownish tissue, the largest 2.0 cm long. All the material was submitted to histological examination (Figures 1-14).







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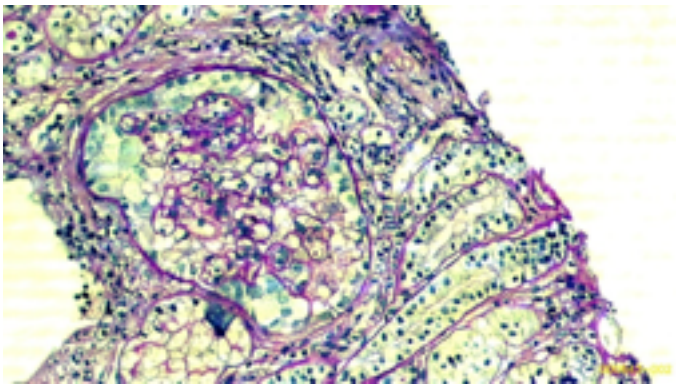

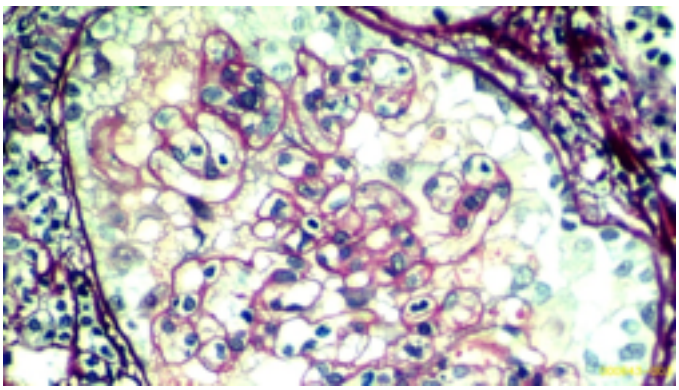

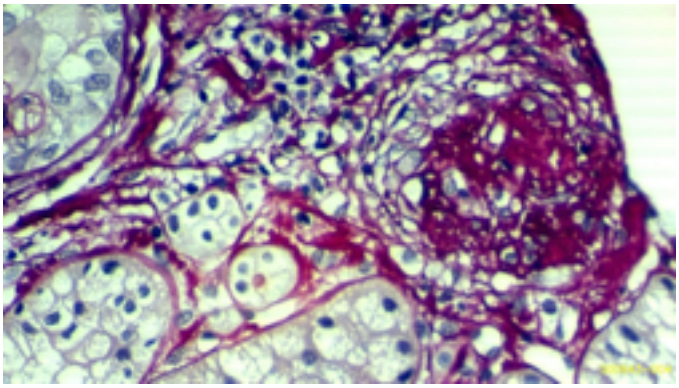

Microscopic examination: The preparations stained by hematoxylin-eosin, Masson's trichrome, picrosirius, PAS, argentic impregnation show renal tissue represented by subcapsular and deep cortical plus medullary enclosing 16 glomeruli, 3 transformed into solid hyaline spherules, and the others voluminous, exhibiting mild to moderate mesangial expansion always of axial disposition. In three of these corpuscles, partial retraction of the glomerular loops is observed. The lesions are segmental, fibro hyaline in nature and promote adhesions with the parietal lining of the Bowman's capsule. The podocytes are hypertrophic presenting abundant clear cytoplasm, finely granulous. The interstitium has small areas of fibrosis that surround the sclerotic corpuscles described above. In the remainder, tubules and interstitium are conserved. The tubulointerstitial involvement extends to less than 10% of the sample. In the biopsy, there are four interlobular arteries and arterioles. All these vessels are preserved.

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Conflicts of interest

No conflict of interest.

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