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Glomerular involvement in patient with sickle cell disease☆

Afectación glomerular en paciente con enfermedad falciforme

Dear Editor,

Sickle cell nephropathy is one of the complications of sickle cell disease (SCD); this is due to the polymerization of deoxygenated hemoglobin S in the renal medulla, a place of special physiological conditions (hyperosmolarity, hypoxia and acidosis)[1,2] which contributes to the typical obstruction of vessels.[3]

Chronic renal failure and proteinuria are the risk factors associated with increased mortality in these patients.[4] Albuminuria is the initial marker of SCD associated glomerulopathy, the most frequent expression of which is focal and segmental glomerulosclerosis (FSG).[5,6] Renal biopsy is indicated if glomerulopathy is suspected.

We present the case of a 30-year-old white male, with a history of homozygous sickle cell disease that was treated with hydroxyurea and deferasirox, he develops 1–2 annual crises, with no renal repercussions until present. Smoker of 3 cigarettes per day.

The patient was sent for consultation in relation of proteinuria of 2.75 g in 24 h (albuminuria: 1.5 g/24 h). The urine density was 1006, pH: 5.5, proteinuria 100 mg/dl and a normal sediment. Renal function was normal (Cr: 0.7 mg/dl and MDRD > 60 ml/min); Hb: 10.8 g/dl; Hto: 30% (TSI: 80%, folic acid: 8.2 ng/ml; VitB: 570 pg/ml) and CRP: 6.6 mg/l. The expanded study with autoimmunity and hepatitis C and B viruses as well as HIV is negative. In abdominal ultrasound, the kidneys do not have morphological abnormality and the spleen was small with diffuse increase of echogenicity suggesting fibrosis after repeated infarctions.

Once proteinuria was confirmed, a renal biopsy was performed that showed glomerular hypertrophy without sclerosis, enlargement of the glomerular capillaries and the presence of sickle cells within the capillaries (Fig. 1). The tubules have cells with haemosiderin by Perls staining and occasional areas of atrophy associated with fibrosis seen with trichrome staining (Fig. 2A and B). Interstitial vessels do not reveal abnormalities and direct immunofluorescence shows absence of deposits.

The patient is diagnosed of sickle cell glomerulopathy. After one year with valsartan, 80 mg/day, proteinuria decreased to 1.6 g/24 h (albuminuria: 1.1 g/24 h) and the mean blood pressure was 111/63 mmHg by ABPM, values did not allow an increase in doses of ARA-II or double blockage of the renin–angiotensin system due to risk of symptomatic hypotension. At present, renal function is maintained normal

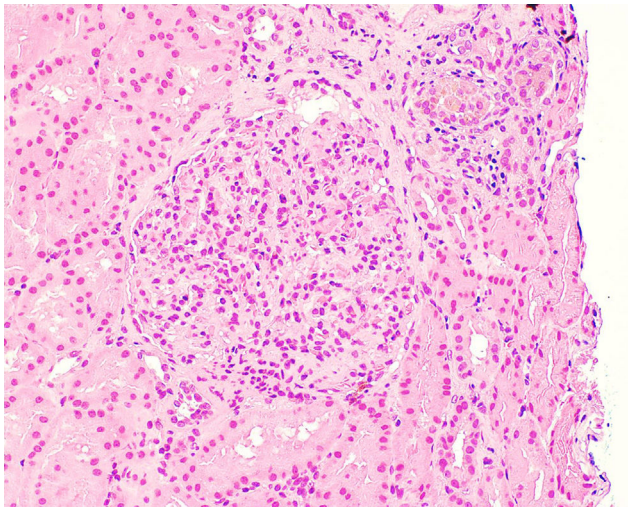

Fig. 1 – Hematoxylin–eosin. Glomerular hypertrophy.

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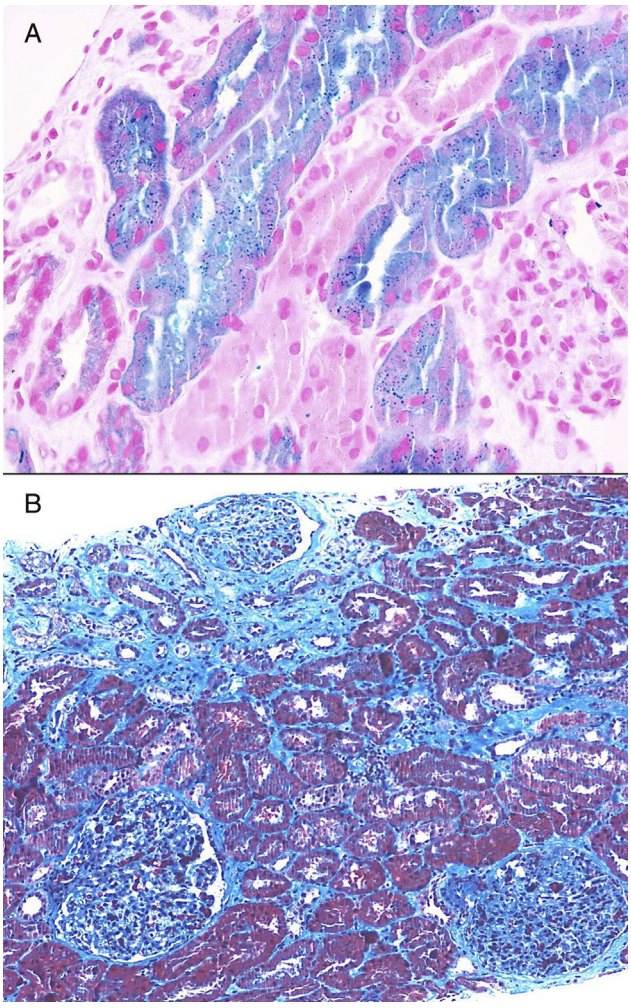

Fig. 2 – Perls and trichrome staining. Cells loaded with hemosiderin, areas of atrophy and fibrosis.

with Cr: 0.64 mg/dl (MDRD > 60 ml/min, CKD-EPI: 130 ml/min), serum phosphorus 5 mg/dl (tubular resorption phosphate: 0.9; tubular reabsorption of urate: 0.9) and urinary sediment continues to be normal.

Sickle cell disease is one of the most frequent hereditary hematological diseases, and it is classified as one of the hemoglobinopathies. This disease is caused by a point mutation that changes glutamine by valine in the globin gene on chromosome 11, it generates hemoglobin S (HbS), which polymerizes in long fibers when deoxygenated, this causes a decrease in erythrocyte deformability and produces cell membrane damage.[7] It includes the homozygous state (HbSS), which is the most severe form and it is most frequently in African, Mediterranean and Indian populations and the heterozygous forms HbSC and HbS-beta-thalassemia.[8]

Renal involvement of sickle cell disease has a great variability. Sickle cell nephropathy can range from difficulty of concentrating urine or hyposthenuria (in our case the urine density was 1006), to renal medullary carcinoma as the most extreme expression of severity.[9]

A supranormal proximal tubular function may be present (the patient has hyperphosphoremia and increased tubular phosphate reabsorption), microhematuria, microalbuminuria, proteinuria of glomerular origin (detected by Dipstick or more reliably by 24 h urine albuminuria), hypertension, acute renal failure and chronic renal failure.[8] Renal failure and glomerular proteinuria are risk factors associated with an increase in mortality in patients with sickle cell disease.[4,10] It is estimated an overall mortality of 16–18% attributed to renal disease.

In addition to the more frequent form of glomerulopathy (FSG), it may be manifested as membranoproliferative glomerulonephritis, thrombotic microangiopathy and sickle cell-specific glomerulopathy.[2,8] Biopsy is rarely used to establish the diagnosis; in early sickle cell nephropathy, glomerular hypertrophy is observed and is part of sickle cell disease description in 1960; the most frequent location of glomerular hypertrophy is at the juxtaglomerular level, in addition there is tubular hemosiderin deposits that play a relevant role in the progression of the nephropathy. Other microscopy findings include red blood cell sickling in vasa recta, capillary congestion, mesangial expansion and endothelial lesion expressed as expansion of the lamina rara interna. Renal biopsy is necessary in cases of significant proteinuria (>1 g/day) or rapid deterioration of renal function that suggests glomerulonephritis.

We conclude that the appearance of proteinuria in a patient with sickle cell disease should guide the existence of a sickle cell glomerulopathy where the glomerular hypertrophy is the consequence of an increased perfusion. Nephrotic range proteinuria is associated with progression of CKD; it is important to know the type of renal involvement given the high prevalence of glomerulopathy in adults with SCD, for which the renal biopsy can help to mark the evolution and prognosis.

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Immuno complex mediated acute glomerulonephritis in a patient with infectious mononucleosis☆

Glomerulonefritis aguda por inmunocomplejos en mononucleosis infecciosa

Dear Editor,

This case is a 44-year-old woman without previous medical history, who presented with fever of 38.7 °C of 2 weeks of evolution mainly in the afternoon, without evidence of source of infection, without chills or shaking. She was treated as a flu-like syndrome with NSAIDs and antipyretics. Subsequently, she developed a non-pruriginous generalized cutaneous exanthema, went to the emergency room and the blood tests revealed anemia (11.7 μg/dl hb) mild leukopenia with moderate lymphopenia (3640 μleuk/μl, 18% lymph), CRP 22 units and a moderate increase high serum transaminase levels. Renal function was normal (serum creatinine 0.73 mg/dl), physical exam anodyne except for a temperature of 37.7 °C and confluent exanthema including palms/plants that disappear with pressure. Normal chest X-ray. With the diagnosis of exanthematic febrile syndrome with hepatic and hematological alteration, she was admitted for study, and doxycycline was prescribed.

On subsequent days hepatosplenomegaly and pericardial effusion were detected, sedimentation rate was 110 and smears without cell atypias but a 11% of LUC cells were detected. Iron, folic acid, B12, IgA, IgG, C3-4, ANCA, ASLO, normal citrullic peptide. Proteinogram: polyclonal elevation of the gamma globiulins, elevated IgM, FR 300 IU/ml cryoglobulins were negative. ANA: 1/80, DNA, negative, ENA negative except 24 UI/ml U1-RNP. Serology: negative for HBV, HCV, HIV, Legionella, CMV, parvovirus B19, Leptospira, *C. burneti*, *R. coronii*, pneumococcus, negative blood cultures; EBV equivocal IgG/positive IgG.

He remained febrile, the fifth day of admission the fever increased with chills/shivering and respiratory insufficiency; the patient had atelectasis/bibasal condensation with symmetrical pleural effusion (Fig. 1A) and procalcitonin 4.39 μg/ml, and received broad spectrum antibiotic therapy.

Urine showed a proteinuria 1.8 g/day, sediment 40 H/C (28% dysmorphia), the serum cholesterol was normal, albumin 2.2 g/L; Minimal symmetrical pretibial edema, normal blood pressure and normal values of serum creatinine, as well as kidney morphology by ultrasound. He had no signs of systemic disease. Dermal biopsy confirms urticarial process (Fig. 1B). A renal biopsy reported a mesangial proliferative glomerulonephritis with immune deposits mainly IgM/C1q. PCR for EBV in blood was +, but in situ hybridization in the kidney being negative (Fig. 2). It is diagnosed of infectious mononucleosis (MI) with hematological, pleuropericardic, hepatic and renal involvement with mesangial proliferative glomerulonephritis by immunocomplexes. It evolves favorably, remaining asymptomatic and the PCR for EBV became negative. At the end of the year, remission persists, although anti-U1-RNP+ persists as well as generalized arthralgias treated with usual analgesia that had been present for years. He has not evidence of other autoantibody nor presented any other symptoms of systemic disease.

In adults the infectious mononucleosis (IM) is presented with atypical symptoms,[1] with absence of pharyngotonsillitis, lymphadenopathy and lymphocytosis/lymphocytic atypia. Pleural or pericardial effusions are exceptional that have been described in only isolated cases.[2] All this, together with the leucopenia-anemia, serositis and U1-RNP positivity, made us think of the coexistence of infection and autoimmunity.

The prevalence of renal involvement of IM is not well known, it usually goes unnoticed with urinary abnormalities that are asymptomatic (14–17%).[3] The published cases are isolated and are mainly tubulointerstitial involvement. There are few cases of various types glomerulopathies, mediated or

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