

Case Report

A novel case report of sickle cell disease-associated immunoglobulin A nephropathy: the diagnostic value of erythrocyte dysmorphism evaluation

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Abstract: Sickle cell disease is a severe disease with a genetic pattern; it may cause anemia, vaso-occlusive phenomena, and multiorgan injury. It may damage any renal compartment, thereby causing tubular abnormalities, papillary necrosis, or glomerulopathies such as focal and segmental glomerulosclerosis and membranoproliferative pattern. The clinical consequences are hematuria and proteinuria. Hematuria associated with SCD is characteristically isomorphic (non-glomerular). This case report describes a novel case of a patient with sickle cell disease who presented with proteinuria and microscopic dysmorphic (glomerular) hematuria. A renal biopsy revealed immunoglobulin A nephropathy. Despite the fact that immunoglobulin A nephropathy is the most commonly diagnosed glomerulonephritis worldwide, an association between this entity and sickle cell disease has not yet been reported, probably because all cases of hematuria in patients with sickle cell disease have been regarded as secondary to sickle cell disease. Thus, new approaches are necessary to differentiate these conditions, such as evaluation of urinary erythrocyte dysmorphism, even more so because these two entities have different therapeutic options, morbidity, and mortality rates.

Keywords: IgA nephropathy, glomerulonephritis, sickle cell disease, erythrocyte dysmorphism

Introduction

Sickle cell disease (SCD) is a hemoglobinopathy that results from globin gene mutations, which cause the production of abnormal hemoglobin tetramers. When globin is inherited in a recessive pattern, the individual becomes at risk of developing a severe disease characterized by serious anemia and multiorgan involvement, including the kidney [1].

In SCD patients, renal alterations begin in childhood and are characterized by hematuria, renal papillary necrosis, tubular abnormalities, and vaso-occlusive phenomena [2]. Consequently, glomerulopathies develop, such as focal segmental glomerulosclerosis and membranoproliferative-like glomerulopathy [3]. Hematuria associated with SCD is characteristically isomorphic (non-glomerular).

Immunoglobulin A (IgA) nephropathy (IgAN) is the most common primary glomerulopathy worldwide, affecting millions of people. Although it is a benign disease in most cases, it may progress to renal failure. IgAN has various clinical manifestations, but as observed in renal lesions of SCD, the most frequent symptoms are episodes of hematuria, which are frequently associated with proteinuria [4]. IgAN is the most common cause of dysmorphic (glomerular) hematuria.

This article presents the case of a patient who was diagnosed with SCD and developed IgAN, as confirmed by renal biopsy. Even though these entities are common, the scientific literature does not have any report of a simultaneous occurrence. In addition, evaluation of urinary erythrocyte dysmorphism is useful for differen-

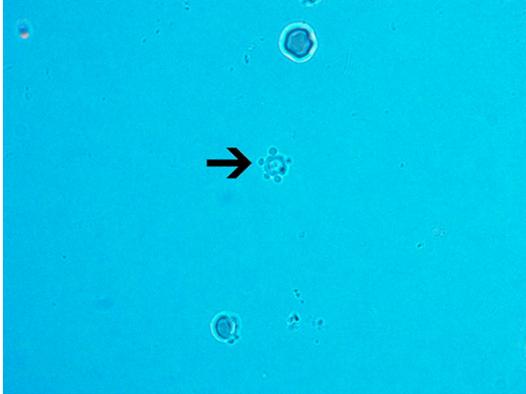


Figure 1. On light microscopy with lowering of the condenser lens, the patient's urinary analysis shows a typical acanthocyte (arrow) (1000 x). See reference 6 for a detail description of this method.

tial diagnosis of renal damage due to SCD and IgAN.

Case presentation

A 48-year-old black man was clinically followed-up for SCD (genotype SS), hypothyroidism and systemic arterial hypertension. He had no history of surgery, transfusion, smoking, alcoholism, drug abuse, or recent sickle cell crisis. His family history was significant for SCD in both parents. The main symptoms were edema of the lower extremities and foamy urine (16-month duration). Laboratory examination results indicated the following conditions: normocytic and normochromic anemia (hemoglobin = 8.0 g/dL, hematocrit = 25%, mean corpuscular volume = 89 μm^3 , and mean corpuscular hemoglobin = 28.6 pg/célula), leukocytosis (12.000 leukocytes), proteinuria (2300 mg in 24-hour samples), heme pigmentation and hematuria (15-20/hpf), and urinary erythrocyte dysmorphism > 60% with 12% of acanthocytes (**Figure 1**). In addition, the following values were obtained: urea, 78 mg/dL; creatinine, 2.4 mg/dL; sodium, 138 mEq/L; potassium, 5.4 mEq/L; aspartate aminotransferase, 31 U/L; gamma-glutamyltransferase, 53 U/L; serum proteins, 6.5 g/dL; serum albumin, 3.6 g/dL. The findings were positive for anti-nuclear antibody, perinuclear antineutrophil cytoplasmic antibodies (pANCA), antithyropoxidase, and antithyroglobulin. An ultrasound revealed the normal aspect (preserved length and echogenicity) of the kidneys.

A renal biopsy revealed global sclerosis in one of 9 glomeruli while the rest were hypertrophied with mesangial proliferation and matrix expansion (**Figure 2A**). There was a diffuse, and mild interstitial fibrosis and tubular atrophy. Immunofluorescence presented global and diffuse mesangial IgA deposits (**Figure 2B**). Electron microscopy revealed electron-dense deposits only in the paramesangial area. Therefore, the patient was diagnosed with IgAN and glomerular hypertrophy secondary to SCD. During follow-up, the patient was treated with clinical measures such as pressure-lowering medication and the use of an angiotensin-converting enzyme inhibitor to control proteinuria. Two years later, the patient's condition progressed to chronic kidney disease stage IV (serum creatinine level, 3.7 mg/dL), with decreased proteinuria of 1.1 g/24 h.

Discussion

Patients with SCD may present with diverse forms of nephropathy. Their clinical and laboratorial consequences involve deficiencies in urine concentration, hematuria, proteinuria, and even renal failure (in 40% of patients with an SS genotype). These alterations start in childhood, with hematuria as the most common symptom, which generally occurs because of vaso-occlusive phenomena and renal papillary necrosis. Other causes related to these processes are low medullary flow, hyposthenuria, ischemia, and microinfarcts [2]. Therefore, all these conditions are considered nonglomerular causes of hematuria.

The histopathological presentations of SCD include some kinds of lesions such as glomerular hypertrophy, focal and segmental glomerulosclerosis, interstitial fibrosis, and tubular hemosiderosis [5]. Its pathogenesis involves the events described earlier, and its morphological patterns are segmental and focal glomerulosclerosis along with membranoproliferative-like glomerulonephritis without immune complex deposition. It must be mentioned that sickle cell-related glomerulopathy disease may present with proteinuria, even within a nephrotic range [2]. Hematuria is frequently encountered in SCD, but recommendations for its evaluation and management have not been established thus far. Meanwhile, glomerular hematuria is rare in patients with sickle cell-

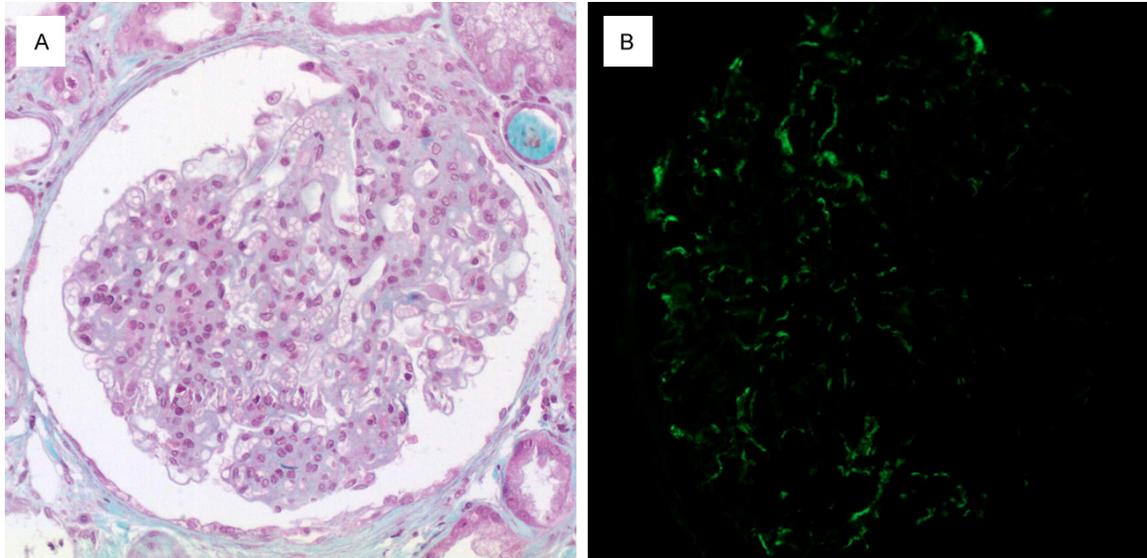


Figure 2. A. Glomerulus hypertrophied with moderate mesangial proliferation (Masson's trichrome, 400 x). B. Mesangial IgA deposits on immunofluorescence (400 x).

related glomerulopathy [3]. Hence, evaluation of urinary erythrocyte morphology could be an excellent tool to orientate the diagnosis toward a nonglomerular or glomerular hematuria. The method is simple and efficient, and can be performed under light microscopy [6].

Articles that detail the glomerulopathies related to SCD are scarce; therefore, the potential of aggression to the renal compartment can be underestimated. Nowadays, renal biopsy is considered only in patients with nephrotic syndrome or those with rapid evolution to renal failure [7]. Other glomerulopathies described in SCD is poststreptococcal glomerulonephritis, membranoproliferative-like glomerulopathy, minimal-change disease, and amyloidosis [8]. This case report describes a patient with SCD who presented with proteinuria and microscopic hematuria, and IgAN on renal biopsy. Despite the fact that IgAN is the most commonly diagnosed glomerulonephritis worldwide, no report of an association between this entity and SCD has been published to date, probably because all cases of hematuria in patients with SCD have been regarded as secondary to SCD.

Despite the diagnosis of IgAN, our patient presented with chronic kidney disease stage III on biopsy and a nonnephrotic proteinuria. For this reason, we preferred not to treat him with corticosteroids and used clinical control measures instead, such as angiotensin-converting enzy-

me inhibitors and pressure-lowering medications, according to the Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group [9].

In the present case, the laboratory examination results evidenced positivity for autoantibodies, namely anti-nuclear antibody and pANCA. Although the anti-nuclear antibody may be sensitive to autoimmune diseases, it is highly nonspecific and can occur in other chronic diseases [10], including SCD. In fact, in patients with SCD, the frequency of autoantibodies was reportedly relatively high [11]. In IgAN, pANCA was related to an increased risk of developing crescent glomerulonephritis and vasculitis [12].

Conclusion

The diagnosis of glomerulonephritis in patients with sickle cell anemia may be difficult owing mainly to the similar manifestations of these conditions. Hematuria is a common finding in SCD and the hallmark of IgAN; thus, new approaches are necessary to differentiate these conditions, such as evaluation of urinary erythrocyte dysmorphism, even more so because these two entities have different therapeutic options, morbidity, and mortality rates.

Disclosure of conflict of interest

None.

Sickle cell disease-associated immunoglobulin A nephropathy

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