Nephrotic Syndrome Due to Immunoglobulin M Mesangial Glomerulonephritis Preceding Juvenile Idiopathic Arthritis

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The association between nephrotic syndrome and juvenile idiopathic arthritis have rarely been described in pediatric patients. We report a child with steroid-responsive nephrotic syndrome, with frequent relapses, who presented with a new relapse of nephrotic syndrome associated with arthritis and uveitis at 21 months in remission after treatment with chlorambucil. Juvenile idiopathic arthritis was diagnosed and kidney biopsy examination showed mesangial glomerulonephritis with immunoglobulin M deposits. To our knowledge, only 2 cases of nephrotic syndrome preceding juvenile idiopathic arthritis have been reported, one without histopathology assessment and the other with minimal change disease. Although mesangial glomerulonephritis with nephrotic syndrome and juvenile idiopathic arthritis could have been coincidental, the immune pathogenic mechanism accepted for both diseases suggests they could be related.

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INTRODUCTION

Juvenile idiopathic arthritis (JIA) is one of the most common rheumatic diseases in childhood.[1] Juvenile idiopathic arthritis is a complex disease that can affect multiple organ systems, although renal involvement is well recorded in adults, it is an unusual finding in children.[1,2] Renal injury may be attributed to the disease itself, as well as caused by drugs, either nonsteroidal anti-inflammatory or antirheumatic drugs (gold salts, penicillamine, cyclosporine A, and methotrexate).[2-6] Since it is often clinically difficult to define the cause of the renal injury, kidney biopsy is necessary to determine precisely the renal lesion.[7] Pathologic examination of kidney biopsy shows, in order of frequency, mesangial glomerulonephritis (GN), renal amyloidosis, membranous nephropathy, focal proliferative nephritis, minimal change glomerulonephritis, and chronic or acute interstitial nephritis.[2,7] Exceptionally, rapidly progressive crescentic glomerulonephritis has also been reported.[8]

In children, renal compromise associated to JIA is rarely observed.[1] Renal involvement is quite variable and histopathological findings include membranous nephropathy, mesangial GN, focal segmental glomeruloesclerosis, renal amyloidosis, and crescentic glomerulonephritis.[1] Clinically, some patients may develop nephrotic syndrome (NS),[1,4-6] but only 2 cases of NS preceding JIA were reported.[9,10] Here, we report a child with NS showing mesangial GN with immunoglobulin (Ig) M deposits in the kidney specimen preceding the onset of JIA, 46 months earlier.

CASE REPORT

A 33-month-old boy was referred to our Nephrology Unit because of generalized edema. At the time of consultation, his body weight was 13.8 kg (25th to 50th centile), his height was 89 cm (10th

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centile) and he had normal development. Physical examination revealed a good general condition, in spite of the presence of ascites and facial and peripheral edema. His body temperature was 36.3°C, his pulse rate was 94/min, and his blood pressure was 100/60 mm Hg. Urinalysis revealed proteinuria of 140 mg/kg/d without hematuria and blood laboratory results showed the following: haemoglobin, 12.8g/ dL; leukocyte count, 12.7 × 10^3/L; platelet count, 210 × 10^3/L; total protein, 5.5 g/L; albumin, 2.46 g/L; α-1 globulin, 0.42 g/L; α-2 globulin, 1.21 g/L; β globulin, 0.78 g/L; γ globulin, 0.63 g/L; cholesterol, 283 mg/dL; urea, 26 mg/dL; creatinine, 0.31 mg/dL; complement C3, 100 mg/dL (reference range, 90 mg/dL to 120 mg/dL); and complement C3, 20 mg/dL (reference range, 10 mg/dL to 40 mg/dL). Serological markers for hepatitis A, B and C viruses; cytomegalovirus; toxoplasmosis; herpes simplex; and Epstein-Barr virus were negative. Tests results for syphilis and Chagas disease were negative, too.

Ultrasonography revealed bilateral normal-sized kidneys (right kidney presented a longitudinal diameter of 64 mm and the left of 67 mm) without ultrasonographic abnormalities. A diagnosis of NS was made and prednisone, 60 mg/m^2/d, was started for 6 weeks, followed by 40 mg/m^2/d of predsisone given on alternate days for another 6 weeks. The patient achieved remission quickly, but during the follow-up, he experienced frequent relapses triggered by upper respiratory tract infections; therefore, chlorambucil was administered at a dose of 2 mg/d for 3 months, achieving a sustained remission.

At the age of 5.5, the patients experienced a new relapse of NS associated with painful swelling of the right knee. Arthrocentesis ruled out infectious disease, and thus steroids were indicated. The mono-articular involvement progressed, affecting the right elbow and ankle, and shortly afterwards, uveitis developed. At this time, his weight was 19 kg (25th to 50th centile) and his height was 108 cm (10th to 25th centile). Blood laboratory parameters revealed the following: hemoglobin, 12.6 g/L; leukocyte count, 13.7 × 10^3/L; platelet count, 322 × 10^3/L; total protein, 5.1 g/L; albumin, 2.1 g/L; α-1 globulin, 0.44 g/L; α-2 globulin, 1.3 g/L; β globulin, 0.75 g/L; γ globulin, 0.58 g/L; cholesterol, 275 mg/dL; urea, 32 mg/dL; and creatinine, 0.43 mg/dL; while urinalysis showed massive proteinuria (52 mg/kg/d) without hematuria. Additionally, he presented an erythrocyte sedimentation rate of 42 mm/h, positive anti-nuclear antibodies (1/160 with homogeneous pattern), normal levels of complements C3 and C4, and negative results for anti-DNA antibody and rheumatoid factor. Serological markers for viral infections persisted negative. Based on these findings, JIA was diagnosed according to the International League of Associations for Rheumatology's criteria.[11]

The patient received methotrexate, 20 mg/m^2, once a week, plus prednisone, 30 mg/d, attaining remission of articular and renal involvement; however, bilateral uveitis persisted. Infliximab was added to methotrexate at a dose of 6 mg/kg/d every 6 weeks, but because of progression of the ocular damage, anterior vitrectomy was performed and instead of infliximab, adalimumab was administered at a dose of 20 mg/kg, every 14 days, for 2 years. At the time of simultaneous renal and articular involvement, a renal biopsy was performed, showing 20 glomeruli with slight increase of mesangial matrix and cellularity and segmental capillary collapse in 2 glomeruli without sclerosis or fibrous capsular adhesions. In 4 glomeruli, nonspecific loose adhesions were recognized. In the tubulointerstitial compartment, there were no areas of tubular atrophy, inflammatory interstitial infiltrates, fibrosis. No hyalinosis or intracapillary foam cells were observed either (Figure 1). Additionally, amyloidosis was ruled out. Mesangial immunofluorescence showed global

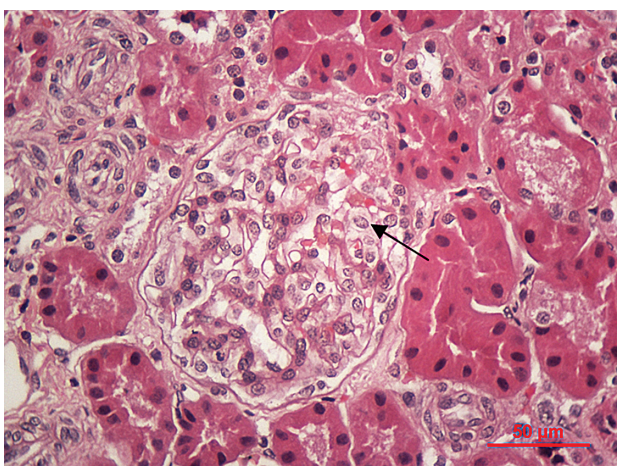

Figure 1. A glomerulus showing mild expansion of mesangial matrix and cellularity. The arrow shows capillaries that are patent throughout coexisting swelling and hypertrophy of podocytes (hematoxylin-eosin, × 400).

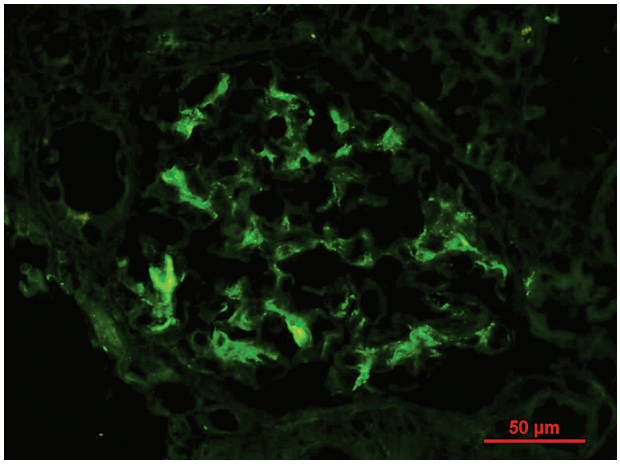

Figure 2. Global and diffuse granular pattern of deposits of IgM, even in glomeruli that appear normal in light microscopy (immunofluorescence, × 400).

diffuse granular deposits of IgM (++) and minimum IgA (+). The specimen was negative for IgG and complements C3 and C1q (Figure 2). Based on these findings, a diagnosis of IgM mesangial GN was established. On last follow-up visit, 5 years after JIA diagnosis, the patient showed no signs of renal compromise.

DISCUSSION

Renal involvement associated with JIA is rarely observed in children; however, various types of nephropathies have been described as glomerulonephritis (mesangial, membranous, focal proliferative, and minimal change lesions), amyloidosis, or acute or chronic interstitial nephritis.[9]

Nephrotic syndrome associated with JIA is extremely uncommon and is mostly associated with amyloidosis and infrequently with mesangial GN or minimal change disease.[1,9] In adult patients, amyloidosis increases morbidity and is the main cause of end-stage renal disease associated with arthritis rheumathoid.[7] Amyloidosis in children is usually associated with chronic disease activity and with a predilection for systemic onset of the disease.[1] It has been communicated as the most characteristic renal lesion related to JIA in children. Despite this, in a large study including 215 patients with various subtypes of JIA followed up for a median of 16.5 years, only 3 patients (1.4%) developed amyloidosis, and 2 of these three had the extended type of oligoarthritis.[12] In our patient, deposits of amyloid were not found.

A patient with frequently relapsing steroid-sensitive NS without hematuria, hypertension, or renal insufficiency makes presumptive diagnosis of primary NS with minimal changes, as we suspected in our patient. However, when he developed JIA, renal biopsy showed mesangial GN with IgM deposits. In adults with rheumatoid arthritis, mesangial GN is the most frequent histological lesion (35% to 60% of biopsies from patients with urinary abnormalities and/or kidney impairment). In contrast, this histopathological pattern has been described in only 1 child with JIA.[7,9]

Although mesangial GN and JIA could have been coincidental, the immune pathogenic mechanism accepted for both diseases suggests that they could be related. Thus, dysregulation of B cells with autoreactive antibodies production or of T cells triggered by viral infections,[13] monocyte-macrophage system dysfunction,[14] and abnormal expression of proinflammatory cytokines, such as interleukin-1, interleukin-6, and particularly, tumor necrosis factor-α,[15,16] have been postulated as involved in the pathogenesis of both diseases. The presence of IgM deposits also suggests an immune pathogenesis, whereas some authors consider mesangial GN with IgM deposits as a specific entity.[17,18] Others believe that the IgM deposits occurs by trapping due to altered mesangial function.[19] In JIA, it is unknown whether NS is an extra-articular manifestation of the disease or the immune mechanism involved in the pathogenesis of JIA may progress to NS in some cases. Supporting that mesangial GN probably represents an extra-articular manifestation of the basic rheumatoid disease, Korpela and colleagues found a striking association of the IgM rheumatoid factor with mesangial GN, suggesting that a functional response by the renal mesangium to remove IgM rheumatoid factor-IgG complexes could lead to these mesangial lesions.[20] However, results for IgM rheumatoid factor was not a universal finding in their series, as also occurred in our patient.

Renal involvement usually occurs several years after the diagnosis of rheumatorid arthritis, and secondary NS associated with chronic arthritis is usually steroid resistant and difficult to treat.[5] Interestingly, our patient presented with renal manifestations before the onset of features of JIA. Only 2 cases of NS preceding JIA were reported. Kari and colleagues communicated a 2.5-year-old

girl with frequently relapsing steroid-sensitive NS which preceded the development of JIA 4 years earlier. However, renal biopsy was not performed in this girl.[9] Ito and colleagues reported a boy who developed JIA after 7 years of the onset of the NS with minimal changes in the renal tissue.[10]

In conclusion, to our knowledge, this is the first reported case of a child with IgM mesangial GN revealed by steroid-sensitive NS who subsequently developed JIA.

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CONFLICT OF INTEREST

None declared.

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