Interaction between pathogens and acute glomerulonephritis in childhood: A case report and sonographic appearance

Stefania Lasorella¹, Alberto Verrotti¹, Maria Laura Iezzi¹

¹ Department of Pediatrics, San Salvatore Hospital, University of L’Aquila, L’Aquila, Italy

ABSTRACT

More than one trigger are known as responsible for acute glomerulonephritis in the pediatric age. The most common infective trigger is beta-hemolytic Streptococcus group A (GAS) but various infective agents, bacterial and viral, are capable of triggering the inflammatory process. We report a case of 5-year-old child who developed an acute glomerulonephritis related to a GAS and Mycoplasma pneumonia infection and Cytomegalovirus urine reactivation with ultrasound picture suggestive of important kidney involvement. The case support the hypothesis of a relationship between multiple infectious disease and immune-mediated and/or autoimmune mechanism whereas underling mechanism is still unclear and highlights the possible use of ultrasound as a tool to assess the severity of renal involvement.

Key Words: Glomerulonephritis; beta-hemolytic Streptococcus group A; Mycoplasma Pneumonia; Cytomegalovirus; ultrasound.

Introduction

Infectious diseases are an underestimated causative factor of renal and glomerular disorders in childhood. Although the pathogenesis of acute poststreptococcal glomerulonephritis is increasingly understood [1], the mechanisms of physiopathological relationship between other infection and renal involvement is not clear. Mycoplasma pneumonia is a common cause of respiratory disease children and is generally self-limiting, occasionally is associated with extrapulmonary conditions [2]. Glomerulonephritis after a Mycoplasma pneumonia infection has been reported only in few children [3-4], and a probable autoimmune and/or immunomediated mechanism has been proposed. We report a 5-year-old child affected by an acute streptococcal glomerulonephritis, recent Mycoplasma pneumonia infection and detect Cytomegalovirus (CMV) DNA in urine with particular ultrasound presentation.

Case report

M.S., a 5-year-old female child was admitted to our Pediatric Unit for a first episode of
persistent macrohematuria in 2 days in the absence of dysuria and pollakiuria. When she was admitted to our Unit, the mother referred that the child had fever with nonproductive cough from 3 days, treated with amoxicillin (50 mg/kg/day orally in 3 divided doses) for 5 days, with improvement of her symptoms. At clinical examination at admission, absence of periorbital and peripheral edema, no acute inflammation of upper respiratory tract. Her body temperature was 37°C and blood pressure 130/80 mmHg (> 95th percentile) so she started a low-sodium diet with restriction of oral liquids (600 ml/m²sc/day). Complete blood count was normal for age; C-reactive protein was increased (100 mg/L, normal range: < 10 mg/L); plasma C3 levels were reduced (68 mg/dl; normal range: 80 mg/dl) with normal C4 levels; Antistreptolysin O (ASLO) titer has an increased value 905 UA/L (normal range: 0-200); total IgG and IgM values were at the upper limits of the norm; serum rheumatoid factor, ANA, ANCAs were absent. Coagulation baseline study and protein electrophoresis showed normal values. Urinalysis revealed hematuria (1.0 mg/dl) and proteinuria (30 mg/dl), protein/creatinine ratio from a single urine sample was 0.88 mg (normal range: 0.2 mg) indicative of moderate proteinuria. The analysis of 24-hour urine collection showed renal function worsened (creatinine 0.34 gr/24h) with normal proteinuria (114 mg/L) and a conserved urine output (350 m/24). The urine culture was negative. Throat culture was positive for Streptococcus pyogenes (beta-hemolytic streptococcus group A, GAS) and diagnosis of acute streptococcal glomerulonephritis was made and benzylpenicillin was administered (intramuscular injection, 600,000 units/one somministration). Also, the serum titer of antibodies for Mycoplasma Pneumonia is suggestive of primary infection (positive IgM and IgG, 14 index [normal range: <10] and 30 AU/ml [normal range: <10] respectively) associated with reactivation of Cytomegalovirus (positive IgG with negative IgM). On the second day, for a persistent blood hypertension, she performed ECG and thorax posterior-anterior and lateral X-ray that were normal and also furosemide (1 mg/kg IV) was administered with improvement in the following days. Total abdominal ultrasound showed normal-sized kidneys (50th percentile). Left kidney show a moderately hyperechoic cortex (2nd degree according to the Classification of Hrikak), with evident hypoechoic renal pyramids and normal representation of renal pelvis. On the left, the cortex appears isoechoic with marked hypoechoic renal pyramids that seemed beyond the cortex with reduction of pielic echoes. The cortex was thickened in both kidneys, maximum detected value of 12.4 mm (normal range: 8-11 mm). Neither hydronephrosis nor nephrolithiasis was appreciated [Fig. 1A, B]. This ultrasound picture, in particular in the right kidney, seemed to be an important monocyte infiltration, associated with ischemic vascular alterations during a renal insult comparable to a renal toxicosis, while on the left the picture was compatible with acute glomerulonephritis. The complexity of the ultrasound picture suggests an "aggravating factor" virtually localized in the renal parenchyma. Further investigations detected positive CMV DNA in urine with high value (1120 cp/ml), negative in saliva. After 6 days pressure values were normal with normalization of gross hematuria whereby kidney biopsy has not been carried out. Furthermore, the ultrasound showed a marked improvement in renal involvement. In detail, microscopic hematuria is completely
resolved in 5 weeks. After 15 days throat culture was negative for GAS. The increase in IgG titers for Mycoplasma pneumonia supported the diagnosis of recent infection. At 1 month from admission, CMV DNA in the urine was negative. One month after initial diagnosis with continuous conservative treatment, serum C3 were normalized and the ultrasound findings were normal.

Discussion
Acute streptococcal glomerulonephritis is a non-suppurative inflammatory involvement of kidney, due to immunological basis. It is the classical example of acute nephritic syndrome that can be only manifested with a macroscopic hematuria. Various infective agents, bacterial and viral, are capable of triggering the inflammatory process, although classically the causative agent is beta-hemolytic streptococcus group A, in particular the so-called "nephritogenic" groups (numbers 1,3,4,12,25). Alterations leading to glomerular damage are multiple: deposition of antibodies in the epithelium of the basal membrane and in the mesangium, activation of the complement (which explains the reduction of C3), hemodynamic alterations, production of inflammatory cytokines and growth factors and all factors able to activate local cells and involve transformations to the extracellular matrix. Normally the clinical appearance includes macroscopic hematuria, periorbital and perioral edema, arterial hypertension (which resolves into 7-10 days) microhematuria also lasting 1 year. Despite being the most frequent trigger factor, streptococcus is not the only one. CMV and Mycoplasma pneumonia can play an important role [5,6]. CMV is a virus capable of establishing a latent renal infection, escaping systemic immune response. In rejected renal transplants, virus has multiple renal localizations: glomerular and tubular epithelial cells, mesangium and in the glomerular endothelium. Following local reactivation, CMV can cause an important monocyte infiltration, in particular composed of CD8+ lymphocytes. This localization could be responsible for viruria, without increase in antibody titres. In infected renal cells, CMV can increase expression of MCH II complexes; normally, non-immune cells do not express MCH II but it can be induced by release of interferon-gamma, produced during viral infection. This mechanism could explain the particularity ultrasound-related renal damage, more like a toxicosis than an acute glomerulonephritis. In our case, she also presented serology for primary Mycoplasma Pneumonia infection in the absence of pulmonary involvement or acute inflammation.
of the upper respiratory tract. Although rare, renal manifestations in the course of Mycoplasma infection in the pediatric population are known. The most frequent renal lesion is proliferative membranous glomerulonephritis, but cases of acute interstitial nephritis with or without a nephrotic syndrome and cases of isolated hematuria have also been reported [3,4]. Mycoplasmas are able to induce immunomodulatory effects similar to virus: stimulation of T and B lymphocyte proliferation, induction of cytolytic activity of macrophages and cytotoxic T cells, stimulation of cytokine production, the induction of MCH expression in macrophages and B cells and the production of chemotactic factors, Fc factors, Fc receptors, superantigens and immunoglobulin proteases [7,8]. This polymorphous immunological activity can contribute to persistence of glomerular disease. In the few cases described in the literature, there is persistence of IgG and IgM antibodies of Mycoplasma pneumonia and a reduction of C3 values [9,10].

The increased cortex echogenicity is an echographic characteristic common to multiple renal pathologies (acute glomerulonephritis, pyelonephritis and nephrotic syndrome). Jin Hee Lee et al., [11] have reported the association between renal sonography and prognosis in two pediatric patients and they highlighted how an extended and increased echogenicity of renal parenchyma could predict the severity and prognosis of the disease, so it is necessary more information from further studies to make a consensus about this association.

More than a trigger are able to cause an acute renal inflammation. Streptococcus and Mycoplasma produce indirectly a monocyte infiltration with endothelial and mesangial cells proliferation and capillary occlusion. Latent CMV renal infection, activated by pro-inflammatory environment, can stimulate virally infected cells to present the antigen o T lymphocytes or establishing an acute cytolytic infection. Although we have not performed kidney biopsy, it is the gold standard for diagnosis and it is required for definitive diagnosis when the clinical response is atypical, correlation studies between ultrasound and biopsy could highlight a strong useful link for therapeutic management and follow-up.

**Compliance with ethical statements**

**Conflicts of Interest:** None.

**Financial disclosure:** None.

**Consent:** All photos were taken with parental consent.

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