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Chapter

Granulomatous Interstitial Nephritis in Children Resulting from Wegener’s Granulomatosis, Crohn’s Disease, or Sarcoidosis

Galina Makovetskaya, Lilia Mazur and Elena Balashova

Abstract

Granulomatous interstitial nephritis (GIN) is a rare type of kidney disease, the precise etiology of which is obscure, but is most commonly seen following drug therapy and infection. The main infections seen in the onset of this pathology, especially in immunocompromised patients, include mycobacteria and fungi. Granulomatous interstitial nephritis can be a manifestation of systemic diseases, such as Wegener’s granulomatosis, Crohn’s disease, or sarcoidosis. We present our experience with GIN diagnosis and management.

Keywords: granulomatous interstitial nephritis, chronic kidney disease, children, toxocariasis, chronic granulomatous disease

1. Introduction

Granulomatous inflammation is a chronic inflammatory reaction, the main feature of which is the cellular transformation of a monocyte into a macrophage—a multinucleate giant epithelioid cell. The most common cause of this transformation is incomplete phagocytosis.

Difficulties in the clinical diagnosis of granulomatous interstitial nephritis (GIN) relate to the lack of a reliable noninvasive diagnostic method. Granulomatous interstitial nephritis is a rare type of kidney disease with a frequency of no more than 1%, according to the data at hand [1]. The precise cause of GIN is not known; due to the rarity of the disease, researchers rely primarily on a series of cases, rather than on the results of multicenter studies. In addition, the etiological structure of GIN can vary in different countries: in more developed countries, GIN is more probably related to drugs and sarcoidosis, whereas in less developed regions, it is likely to be associated with infections [2]. However, the most common causes are drug therapy and infection, and drugs (NSAIDs, antimicrobials, anticonvulsants, diuretics, and allopurinol) [3–5] account for 9–45% [6, 7] up to 55–70% [1], according to different studies.

The main infectious factors in the onset of this pathology, especially in immunocompromised patients, include mycobacteria [7] and fungi [1, 7]. GIN can be associated with HIV infection [8] and the influenza A (H1N1) virus [9]. Patients
with GIN of infectious etiology were stated to have acute kidney damage at onset [6]. In some cases, the etiology of GIN cannot be pinpointed; thus, the disease is considered to be idiopathic [3, 10]. GIN resulting in nephrosclerosis and chronic pathology of the digestive organs, and atopic dermatitis associated with carriage of *Toxocara*, has been reported.

We had a patient born with a body weight of 2.0 kg after an uneventful first pregnancy whose infantile period was unremarkable. When the girl was 1.5 years old, she suffered a common form of atopic dermatitis with periodic exacerbations (treated with topical steroids during exacerbations). At the age of 3 years, she was seen by a gastroenterologist for chronic esophagitis and chronic duodenitis. ELISA revealed contamination with *Toxocara* and *Giardia lamblia*; therapy with albendazole was administrated on an outpatient basis. However, the carriage of *Toxocara* continued. A repeated course of treatment was conducted in adolescence, but the antibody titer remained. Further courses of therapy were canceled, and *Toxocara* IgG antibody carriage was diagnosed. When the patient was 15, follow-up examination at the gastroenterology department revealed hydronephrosis of the nonfunctioning right kidney. Previously, there were no complaints or clinical manifestations indicating the damage to the urinary organs; urinalysis was unremarkable; blood pressure was normal.

In the course of further examination, urography showed a nonfunctioning right kidney; the excretory function of the left kidney was maintained. Cystography did not reveal any reflux. The patient underwent right nephrectomy.

Findings of the histology exam revealed a kidney with enlarged pelvis cups and the presence of cavities filled with fluid in the medulla and partly in the cortical layer. The capsule of the kidney was thickened by sclerosis. Renal glomeruli demonstrated fibrosis of the capsule with thickening, focal sclerosis of individual glomeruli, and singular glomerular cysts. Multiple, large-sized granulomas with necrosis in the center, surrounded by epithelioid cells and lymphocytes, including Pirogov-Langhans giant cells and eosinophils, were found mainly in the cortical layer (Figures 1–4).

Smaller granulomas showed fibrosis without central necrosis. Hyaline-droplet dystrophy was noted in the convoluted tubules. Sclerosis was detected in the vessels, diffuse lymphocellular infiltration and foci of fibrosis were observed in the stroma.

Figure 1.
Medium-sized granuloma and peripheral lymphocytic infiltration. Renal glomeruli with edema of the mesangium are seen in the upper part.
Figure 2. A giant multinucleated cell in the center. To the left and to the right, there are renal glomeruli with edema, tubules with dystrophic changes, and the stroma replete with lymphoid infiltration.

Figure 3. The giant granuloma; two glomeruli with marked mesangial edema are on top. Renal tissue with pronounced lymphoid infiltration.

Figure 4. Granuloma with surrounding infiltration. A granuloma with a necrotic focus in the center. On the periphery, there is a proliferation of connective tissue fibers with mildly expressed lymphocytic infiltration (a marker of chronic inflammation).
2. Granulomatous nephritis resulted in nephrosclerosis

Granulomas had large central foci of necrosis with features of organization. There was no presence of microorganisms; the absence of microorganisms could be related to the remoteness of the process.

The detection of granulomatous nephritis during histological examination prompted an extended diagnostic screening in order to seek the etiology of the disease.

On examination, the patient’s condition was satisfactory. The patient complained of pain in the right leg with loss of sensitivity. The girl was asthenic; her height was 185 cm, weight 57 kg, and BMI 16.65. The subcutaneous fat layer was poorly developed. Her skin was dry overall with fading rashes of atopic dermatitis on the chest and extremities.

The findings of the ultrasound examination documented that the right kidney had been removed. The left kidney had compensatory enlargement. Cortical-medullary differentiation was preserved; there was a moderate amount of hyperechoic signals and a thin hyperechoic rim around the pyramids. Functional bend of the gallbladder was found. Structure of the pancreas was moderately inhomogeneous.

MRI of the lumbosacral part of the spinal column and cauda equina revealed scoliosis and degenerative-dystrophic changes in the intervertebral discs of the lumbosacral spine, sacralization of L5, spina bifida S1–S3, and no MRI signs of organic pathology of cauda equina.

During the observation period, CBC revealed moderate leukocytosis (up to $11.5 \times 10^9/l$), mild anemia (maximum hemoglobin reduction to 103 g/l), and an intermittent increase in ESR to 27–28 mm/hour.

Biochemical blood analysis showed no pathological changes, except for an increased level of CRP up to 7.44 mg/l. Protein, fat, mineral metabolism, as well as the level of enzymes were normal.

For this patient we ruled out autoimmune diseases (rheumatoid factor 1.4 IU/l, ASLO 141.5 IU/l, antibodies to DNA, and antibodies to extractable nuclear antigens were not detected), TORCH infections, viral hepatitis C, HIV infection, and tuberculosis.

We also excluded parasitic diseases such as echinococcosis, opisthorchiasis, trichinosis, and brucellosis.

Helminthic eggs were not found. Blood test for *Toxocara* antibodies was slightly positive 1:200.

Clinical urinalysis revealed traces of protein (daily protein excretion—negative), up to 10 leukocytes per hpf and up to 3–5 erythrocytes per hpf (in isolated tests).

Oxaluria was detected (excretion of 98.4 mg/day, daily diuresis of 2000 ml). Urate excretion was normal (2.14 mmol/day).

The glomerular filtration rate by the Schwartz formula was 102 ml/min.

Final diagnosis was single left kidney and loss of renal concentration ability. The condition after surgical treatment (right nephrectomy in January 2016, hydronephrosis stage 5 with absence of right kidney function, morphologically: granulomatous interstitial nephritis resulting in nephrosclerosis).

She had atopic dermatitis; chronic gastroduodenitis; erosive gastritis Hp (+/−); gastroesophageal reflux disease; biliary dysfunction reactive pancreatic changes; oxaluria; juvenile osteochondrosis; sacralization of L5; spina bifida S1–S3; neuritis of the sciatic nerve; juvenile kyphosis; thoracolumbar scoliosis, grade 2; body weight deficit, grade 1; mild myopia; chronic subcompensated tonsillitis; and carriage of *Toxocara* antibodies.

This clinical case was peculiar due to the comorbidity of the patient and the impossibility of accurate identification of the main etiologic agent of GIN.
Our patient was diagnosed with toxocariasis at the age of 3 years, when she received anthelmintic treatment; however, the results of immunological studies showed that *Toxocara* carriage continued. *Toxocara canis* is a large roundworm, the source of which is dogs or less commonly cats. Toxocariasis is characterized by a long-term recurrent course with damage to organs and systems based on immunopathic processes [11]. The clinical picture may include general symptoms of infectious toxic syndrome, subfebrile condition, cough, and enlargement of the liver and lymph nodes. Systemic forms of toxocariasis may damage the heart, the pancreas, and the central nervous system (resulting in epileptic seizures). From a pathomorphological point of view, toxocariasis causes disseminated eosinophilic granulomatosis [11]. There is no conclusive data connecting parasitosis with renal damage; but there are reported cases of experimental models [11] and individual case reports, mainly in the form of nephrotic syndrome [11–13].

For 1 and 1/2 years, the patient suffered from atopic dermatitis and periodic exacerbations. Nephrologists from St. Petersburg described the formation of granulomas from epithelioid histiocytes and giant cells in allergic types of acute interstitial nephritis; in addition to the aforementioned, tuberculosis, sarcoidosis, Wegener’s granulomatosis, and berylliosis were excluded in our patient [14]. An association between atopic diseases and idiopathic nephrotic syndrome and minimal change glomerulonephritis has also been described [15, 16]. Perhaps, the peculiarities of the individual response of the immune system contribute to an increased risk of atopy and immunopathic diseases of the kidneys. However, in the patient’s medical notes, there are no records of acute interstitial nephritis and any episode of renal failure in the past, and nephromegaly was discovered accidentally.

The pathology of the gastrointestinal tract, except for Crohn’s disease, can hardly be the cause of GIN.

Therefore, though it is difficult to identify the importance of comorbidity as the cause of GIN, we assumed that infection from *Toxocara* carriage is etiologically responsible for the development of GIN in our patient.

Granulomatous interstitial nephritis can be a manifestation of systemic diseases, such as Wegener’s granulomatosis, Crohn’s disease [17], and sarcoidosis. Usually, renal damage in sarcoidosis is associated with nephrocalcinosis, hypercalciuria, or urolithiasis [4]. The development of granulomatous inflammation of the kidneys is considered to be rare, with a frequency of 0.7–30% [18]. However, the proportion of sarcoidosis in the etiological structure of GIN can be from 9 to 29% [6]. In the study conducted by Oliveira et al., sarcoidosis with extrarenal damage was detected in 38% of patients, and 24% of patients had sarcoidosis with only renal damage [19]. In the literature, we found cases wherein the GIN preceded the diagnosis of sarcoidosis [1, 4]. Stehlé et al. reported that in 23% of cases, glomerulopathy supported the diagnosis of sarcoidosis, with an average delay of 8 years in diagnosing it [20]. According to Bagnasco, the results of a biopsy of a native kidney in 51 patients with sarcoidosis showed that GIN was the most common finding (19 cases, 37%) [18]. Similar data on the prevalence of GIN in sarcoidosis (approximately 30%) were obtained in a study conducted by Löffler et al. [21].

Due to the rarity of the disease, the degree of influence of GIN in sarcoidosis on the disease progression up to the terminal stage of CKD remains in question. There are no clinical recommendations for the therapy of renal sarcoidosis, though the use of glucocorticoids is considered the standard treatment.

We had another clinical case which was a type of granulomatous kidney disease associated with a rare form of primary immunodeficiency—chronic granulomatous disease (OMIM 233,670, 233,690, 233,700, 233,710, 306,400, 613,960). This disease is characterized by increased vulnerability to severe bacterial and fungal infections (most often *Staphylococcus aureus* and *Aspergillus* spp) and granuloma formation.
The cause of the disease is a mutation of one of five genes encoding phagocyte nicotinamide adenine dinucleotide phosphate (NADPH) oxidase subunits. The mutation of the CYBB gene (Xp21.1) is detected in most cases. The mechanism of granuloma formation is not clear, but in this disease abnormally long activation of neutrophils in inflammation foci is noted, which leads to chronic inflammation [22]. Most often, granulomatous damage involves the skin, lymph nodes, gastrointestinal tract, and liver [23]. Usually, the disease is diagnosed within the first 5 years of life; however, some cases presenting in adulthood have also been reported [23, 24]. This disease presented in a boy, who manifested all the typical symptoms. This 16-year-old boy was sick from birth. He was diagnosed with primary immunodeficiency and chronic granulomatous disease (missense mutation in exon 1 of the CYBB gene in the hemizygous state: c.1169 > T, CCC > CTC, p. Pro390Leu).

He had a positive family history. The patient’s mother suffered from pyelonephritis and arthritis. Her three brothers died in childhood: one of them died of systemic lupus erythematosus at the age of 9, the second from respiratory infection when he was 1.5 years old, and the third at 3 months (the cause unknown). Chronic granulomatous disease had not been diagnosed due to the lack of diagnostic methods at that time; however, the association of the disease with autoimmune disorders and severe life-threatening infections at an early age was characteristic of the disease [25–27]. At the age of 1 year, our patient had contact with a TBC patient; he was operated for tuberculoma when he was 6 years old.

Starting with the second year of life, the child suffered from recurrent bacterial infections in variable locations, which were typical of chronic granulomatous disease, paronychia, balanoposthitis, purulent otitis media, pneumonia, purulent lymphadenitis, furunculosis, abscesses of the anterior abdominal wall, and liver abscesses with inoculation of mainly catalase-positive microorganisms (characteristic of granulomatous disease) [28, 29]. The patient had no infections of fungal etiology.

When the patient was 5 years of age, a secondary immunodeficiency condition was suspected, but no further examinations were carried out. The diagnosis of primary immunodeficiency was made at the age of 14 years; the genetic test was carried out at the age of 17 years.

In addition to infectious complications, the patient also had inflammatory complications affecting the gastrointestinal tract in the form of chronic gastroduodenitis, although intestinal lesions are considered more frequent [30–32]. Renal damage in chronic granulomatous disease is frequent and is usually associated with obstruction and urinary tract infections [30, 31]. However, there are reported cases of glomerulonephritis associated with granulomatous disease [33].

Our patient had various types of urinary tract problems, namely, episodes of urinary tract infection since the age of 5 years; diagnosis of acute glomerulonephritis with nephritic syndrome when he was 11 years old; urolithiasis since the age of 14 years and secondary chronic granulomatous nephritis, hematuric form with preserved renal function; nephrobiopsy revealing IgA nephropathy; segmental and complete glomerulosclerosis; expressed tubular fibrosis; arteriosclerosis; and diffuse chronic tubulointerstitial nephritis. The patient has had stage 2 chronic kidney disease (GFR 44–61 ml/min) to date, with moderate positive dynamic and response to therapy with mycophenolate mofetil.

3. Conclusion

In conclusion, although GIN is rare, it is a disease most probably underestimated in frequency in pediatric practice; the variety of etiological causes of GIN, the absence of noninvasive diagnostic methods, as well as the possibility of
development of GIN in multiple pathologies and genetic syndromes render the task of diagnosis difficult for the physician. Moreover, the lack of clinical guidelines for diagnosis and management is another issue which generally complicates treatment and leads to a poor renal prognosis.

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