Drug-Induced Sarcoid-Like Granulomatous Interstitial Nephritis in a Patient with JIA

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Abstract
We present the case of a 11-years-old girl who suffered from juvenile idiopathic arthritis since she was 18 months of old. She presented to our clinic with renal failure. Some notable findings were hypercalcemia, elevated angiotensin converting enzyme (ACE) level and granulomatous interstitial nephritis on kidney biopsy. She was diagnosed with sarcoid-like granulomatous interstitial nephritis due to long term drug usage.

Key words: Juvenile idiopathic arthritis, renal sarcoidosis, drug

Introduction
Juvenile idiopathic arthritis (JIA), consisting of heterogeneous clinical features, is the most common rheumatologic disease in children [1]. Onset of the disease is observed before the age of 16. 10% of patients suffer chronic anterior uveitis which is a major cause of visual loss [2-5]. Systemic onset juvenile idiopathic arthritis (SoJIA) is a subset of JIA, which is manifested by intermittent fever, rash, and arthritis. SoJIA may begin as early as the first or second year of life. Nonsteroidal antiinflammatory drugs (NSAIDs) alone are effective for most children with systemic onset juvenile idiopathic arthritis (JIA) [6]. Second line agents, such as glucocorticoids or methotrexate are used, if NSAIDs are ineffective. TNFa inhibitor therapy was recommended for patients who had received 3 months of methotrexate but still had moderate or high disease activity [7].

Granulomatous interstitial nephritis (GIN) has been shown to be related with administration of antibiotics, analgesics and diuretics, in patients with sarcoidosis, tuberculosis, or Wegener’s granulomatosis [8]. It is unclear whether the presence of granulomas in interstitial nephritis affects the prognosis of renal failure [9]. We report a case of interstitial granulomatous nephritis presenting with acute renal failure in an on treatment JRA patient.
Case Report
An 11-year-old girl who had been followed with SoJIA was admitted to our hospital due to vomiting, loss of appetite, and weakness. She was found to have severe renal failure with a serum creatinine level of 8.1 mg/dL and an estimated Glomerular Filtration Rate (eGFR) of 12 ml/min/1.73 m².

In the patient’s history, there was a hospitalization in 1999 when she was 18 months old. At the time she had high spiking fever, macular rash, and bilateral pain and swelling of toes for three weeks. Laboratory results were as follows: erythrocyte sedimentation rate (ESR): 95 mm/h, C-Reactive Protein: 2.6 mg/dl, rheumatoid factor: (-), ferritin: 223 mg/dl, Antinuclear antibody (ANA): 1/80, serum urea: 23 mg/dl, serum creatinine: 0.5 mg/dl, eGFR: 110 ml/min/1.73 m². She was diagnosed with SoJIA and treated with naproxen sodium (20mg/kg/day) and methylprednisolone (1mg/kg/day). Systemic symptoms (fever and rash) were relieved with steroid therapy but, during the following 4 years her arthritis returned every 4 to 5 months appearing in both ankles, fingers, wrists and toes. Methotrexate (mtx) (15mg/week, subcutan) and tolmetin (10mg/kg/day) were added to the treatment on the 3rd year of diagnosis owing to the recurrent attacks. However neither patient’s complaints of recurrent painful attacks nor high levels of acute phase reactants improved. Hence, hydroxychloroquine (5mg/kg/day) and sulphasalasine (50mg/kg/day) were added to the treatment in 2005. As there were not enough response to these conventional therapies, in 2006 etanercept (0.8mg/kg/week, sc) was started. After etanercept therapy, there was a significant improvement in her pain/attacks, without any intolerance. According to the medical records of the patient, from the onset of the disease to the admission to us, all renal function tests had been normal; the evaluated levels are shown in figure 1. At the time of admission (2010), the patient’s symptoms included pain in her ankles and knees, loss of appetite, and vomiting. Physical examination revealed normal blood pressure, no evidence of lymphadenopathy or lacrimal gland enlargement. Ophthalmic examination showed bilateral uveitis.

Laboratory tests showed an increased serum creatinine level of 8.15 mg/dL (reference range, 0.55-1.02 mg/dL), which had been 1.1 mg/dL 2 months before admission. Other results were as follows: serum urea: 322 mg/dL (reference range, 6-25 mg/dL); eGFR: 12mL/min/1.73 m²; ANA: positive at a titer of 1:320 (reference range,1:80); double stranded DNA and anti-glomerular basement membrane antibodies: negative; C3: within the reference range.

Figure 1. Diagram of relationship between drugs and her renal functions over time.
Figure 2. Renal biopsy showing a glomeruli and interstitial granulomatous inflammation with multinucleated giant cells A) Hema
toxilene eosin stain, original magnification, × 200, B) anti CD68 immunhistochmistry original magnification 100, C) anti CD10 immunohistochemistry; D) CD34 immunohistochemistry

Eosinophilia was detected in both urine and blood. Urine culture was negative. Low urine osmolarity and proteinuria (24mg/m2/hour) were also supporting renal failure. She had hypercalcemia, hypergammaglobulinemia and high levels of angiotensine –converting enzyme(ACE), 84 IU/L (8.3-21.4 IU/L). All viral serologic markers including hepatitis, rubella, Eestein-Barr, Cytomegalovirus and HIV were found negative. PPD and chest X-ray revealed that there was no tuberculosis infection; gastric washing and urine analysis for ARB were also negative. No bacterial or parasitic agents like toxoplasma, shistosoma, brucella, or salmonella, were detected. Renal ultrasonography showed bilateral normal sized kidneys with increased (grade 2) paranchymal echogenity.

At admission, renal function tests revealed a failure stage according to the pediatric RIFLE criteria [10]. Upon observation of these results we stopped all treatment that the patient had been receiving. This resulted in the renal function tests gradually returning to normal (figure 1). Her renal dysfunction was recovered according to pediatric RIFLE criteria. A left kidney needle biopsy was performed and examined with a light microscope. 20 glomeruli were evaluated; half of them were globally sclerozed and also granulomatous interstitial nephritis was found in the interstitium of the cortical and medul lary regions (Figure 2). Specific stainings of the biopsy mate rial showed no positivity for fungi or acid-fast bacilli (ARB), nor features of sarcoidosis, Wegener’s granulomatosis or other systemic diseases.

On the 5th month of follow up, the patient had a new attack with recurring pain of the wrists and ankles. Methotrexate (20mg/week, sc) and prednisolone (0.5 mg/kg/day) were restarted (figure 1). A year later, creatinine level was 1.45 mg/dl, serum urea nitrogen 66 mg/dl, and eGFR 37 ml/min/1.73 m2 under on going prednisone and mtx therapy.

Discussion

This reported case displays an unusual form of interstitial nephritis named granulomatous interstitial nephritis (GIN) which presented with acute renal failure. GIN is a very rare diagnosis, with an incidence of 0.5-0.9% [11,12]. GIN has been associated with adverse reactions to therapeutic agents, such as penicillin, methicillin, ampi−cillin, glafenin, spiramycin, NSAIDs, diuretics and diphenylhydantoin, infections (tuberculosis, leprosy, histoplasmosis, brucellosis, fungal, idiopathic), Wegener’s granulomatosis, crystal-induced nephropathy, paraproteinemia, TINU syndrome, sarcoidosis and Crohn’s disease [13-16].

Joss et al. [17] reviewed kidney biopsies of over a 15-year period, and identified a total of 18 GIN cases (less than 1% of the biopsies). Of these, 5 were due to sarcoidosis, 2 were associated with TINU syndrome, 2 were secondary to medication, and 9 were classified as idiopathic.

In our patient, deterioration of renal functional tests began during the JIA treatment. Shortly after the cessation of all drugs (including etanercept) and administration of prednisolone, creatinine and proteinuria levels decreased. Despite the re-administration of prednisolone and methotrexate, her renal functions were still normal after a year.

Sarcoidosis is a multisystem disease of unknown etiology which is characterised by a noncaseating granulomatous process. Parenchymal involvement by granulomatous lesions is most commonly seen in the lungs, whereas renal involvement is relatively rare [18].

Garland et al. [19] firstly documented renal parenchymal granulomatous lesions in sarcoidosis in 1933. In 1981, Muther et al [21] reported their experience with sarcoidosis and discussed 10 cases of ARF owing to GIN. In 1987, Ford et
al. [20] described the first association between granulomatous interstitial nephritis in a patient with sarcoidosis and the development of acute renal failure.

Renal involvement results in functional abnormalities associated with altered metabolism of calcium. Depending on coexistent deterioration of renal function, hypercalcemia can be observed if the capacity of the kidney to excrete calcium is compromised. However, this is less common and in most patients, hypercalciuria remains asymptomatic [18]. According to a number of retrospective studies, chronic renal failure develops in less than 1% of the cases although the prevalence of tubulo-interstitial nephritis ranges from 7% to 27% [22]. Two associated metabolic abnormalities of diagnostic and clinical importance are elevated levels of calcitriol (1,25-dihydroxy-vitamin D3) and angiotensin-converting enzyme (ACE) [23]. Taking into consideration the suboptimal sensitivity of the test, high serum ACE levels has a limited value as a marker in sarcoidosis [24]. O’Riodan E. et al. [11] found only one patient with elevated ACE levels among the 5 patients with isolated sarcoid GIN.

GIN in the absence of extrarenal sarcoidosis is very rare. Robson et al. [25] presented 7 cases of GIN in the absence of extrarenal sarcoidosis. Notable findings of this study were the predominance of men (71%), the mean age of 69, the observation of severe renal failure at the time of presentation (calculated creatinine clearance of 14 ml/min), the need for temporary haemodialysis at onset in one case, minimal proteinuria (mean 0.4 g/day), high ACE levels in 3 patients, and good response to corticosteroid treatment in 5 cases (prednisolone at between 20 and 60 mg/day). Two patients needed to begin periodic haemodialysis at 3 and 15 months after diagnosis.

We considered our patient’s isolated sarcoid GIN to be related to JIA treatment; this conclusion is supported by the hypercalcemia, hypercalciuria, hypergammaglobulinemia and high level of ACE.

There are reports about various biologic agents induced sarcoidosis in the literature. Fareesa et al [26] mentioned a case of interferon-induced cutaneous granulomatous reaction. They reported systemic sarcoidosis presenting as a cutaneous granulomatous reaction with nodules developing along the veins of drug usage [26]. Another study reported systemic sarcoidosis secondary to interferon treatment of chronic hepatitis C [27].

Most previously reported cases of sarcoid-like reactions after treatment with TNF blocking agents involved etanercept or infliximab [28-29]. The reported number of sarcoid-like granulomas secondary to anti-TNF therapy has been increasing [30]. It is unclear whether this phenomenon represents a class effect.

Tubulointerstitial nephritis with uveitis (TINU) syndrome was another possible differential diagnosis. Uveitis can occur several months before or after kidney involvement in this syndrome [30]. We ruled out TINU, with the presence of uveitis since the patient was 18 months old when diagnosed with JIA and developed GIN years later.

We cannot definitively exclude granulomatous interstitial nephritis caused by nonsteroidal anti-inflammatory drug use because granuloma formation has been described after use of these drugs [30].

Drugs used for JIA treatment have proven effects and very few adverse effects. The complications we observed have not been reported previously. Our case indicates the need for following the renal function tests closely and in the presence of any doubt, performing histologic renal examination without hesitation.

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