Sarcoidosis with an uncommon presentation: apropos of a case

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A 17-year-old male presenting with chronic renal failure whose supporting clinical manifestations of the disease had appeared independently over a four-year period is reported. The renal biopsy specimen of the patient revealed tubulointerstitial nephritis and membranous glomerulonephritis. He never had hilar adenopathy, but maculopapular rashes, erythema nodosum, arthritis, chronic lymphocytopenia, hepatomegaly, splenomegaly, and lymphadenomegaly had been observed at different periods over four years. The presence of non-caseating granulomatous lesions in the liver biopsy accompanying uveitis verified the diagnosis of sarcoidosis. Low dose steroid was applied to this hepatitis-C carrier, and uveitis was suppressed. No recurrence has been observed in two-year follow-up.

Key words: sarcoidosis, chronic renal failure.

Sarcoidosis is a chronic, multi-system granulomatous disorder of unknown etiology characterized by non-caseating granulomas. The most commonly affected organ is the lung, other organs include the lymph nodes, skin, eyes, parotid glands, bones, joints, liver and kidney. Patients mostly present with respiratory symptoms, or joint and skin manifestations. Renal involvement and presentation with renal failure are relatively rare in sarcoidosis[1,2]. We report a 17-year-old male with sarcoidosis presenting with end-stage renal disease in the absence of pulmonary involvement; his supporting clinical manifestations occurred intermittently over a four-year period.

Case Report

A 17-year-old male admitted to the hospital complaining of fever, chest pain, respiratory distress, and edema around his ankles and back of his feet. He was referred from another hospital following several hemodialysis treatments due to uremia during the preceding fortnight. His past medical history was only remarkable for his hearing loss that had appeared after receiving repeated high doses of antibiotics for chronic otitis media and for failure to learn to read and write in primary school. Physical examination revealed a cooperative male with a high blood pressure measuring 150/100 mmHg, weight and height parameters be low fifth percentiles, bilateral axillary lymphadenomegalies, the largest of which measured 1.5x1.5 cm, rales, cystolic cardiac murmurs, splenomegaly of 10 cm, and hepatomegaly of 8 cm. He had two BCG scars. His ophthalmologic examination was normal. His IQ was determined as 40 and was thought to be the result of his hearing impairment.

Remarkable laboratory findings included high levels of blood urea nitrogen (BUN: 84 mg/dl), serum creatinine (3.9 mg/dl) and liver function tests (SGOT: 426 IU/L, SGPT: 324 IU/L). Serum albumin and globulin levels were 2.8 g/dl and 4.9 g/dl, respectively. All hepatitis markers were negative. Chest X-ray showed hydrothorax and cardiomegaly. Echocardiography identified mitral valve insufficiency and mild tricuspid and pulmonary valve insufficiency. Abdominal ultrasonography revealed hepatosplenomegaly without any focal lesions, ascites, grade-II renal density rise and bilateral small kidneys.

The first liver biopsy was reported to be concordant with a deficiency in the venous draining of the liver. Renal biopsy specimen included 24 glomeruli, all of which showed mild

thickening of the glomerular basement membranes and severe mononuclear cell infiltration of interstitial space (Fig. 1). Interstitial fibrosis, focal tubular atrophy and fine granular IgG deposition at the glomerular basement membranes were demonstrated. At that time, interstitial mononuclear cell infiltration was thought to be the result of chronic antibiotic usage, so no specific therapy, including corticosteroids or other alkylating agents, was applied for the renal lesions since it was a chronic process and he had already had a severe systemic infection. He was accepted as having end-stage renal disease due to membranous glomerulonephritis and tubulointerstitial nephritis, and thus chronic hemodialysis treatment was instituted.

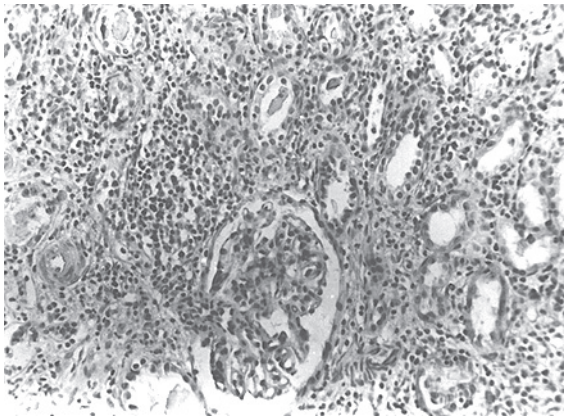

Fig. 1. Severe interstitial infiltration of mononuclear cells. Note mild thickening of glomerular basement membranes and mild increased cellularity of the glomerulus (original magnification x10, H&E).

During the two-year period, while receiving renal replacement treatment, he had maculopapular lesions at different times. The erythrocyte sedimentation rate (ESR) was approximately 120 mm/h, white blood cell counts were always beyond 4,000/mm^3, and he sometimes had to be treated as neutropenic sepsis. Bone marrow aspirations showed megaloblastic changes and no blastic involvement. Negative rheumatoid factor, antinuclear antibody and anti-smooth muscle antibody reactions with normal levels of complement 3 and components 4 were obtained when bilateral tenderness, warmth, swelling, erythema and decreased range of motion around his ankles developed.

Six months later a hyperemic, tender, warm nodule appeared at the left medial distal tibia, which was defined as erythema nodosum. After another six months, he had diffuse maculopapular lesions and fever. White blood cell count was 3,200/mm^3 on admission and decreased to 500/mm^3. Dermal biopsy of maculopapular lesions showed accumulation of IgM, C3 and mononuclear cells around capillary vessels. During that four-year period, PPD tests were applied several times and all were negative. Because of his persisting splenomegaly and hepatomegaly, Doppler ultrasonography was obtained. Diffuse homogeneous organomegaly and a lymph node with a diameter of 2 cm at portal hilus were reported. The liver biopsy revealed non-caseating granulomatous lesions (Fig. 2), and when the first biopsy was evaluated again retrospectively, a few granulomatous lesions were observed. The patient later complained of bilateral lacrimation, photophobia and pain. Uveitis was confirmed by ophthalmological examination. Simultaneous angiotensin converting enzyme (ACE) level was 81 mU/ml (normal: 8-51 mU/ml).

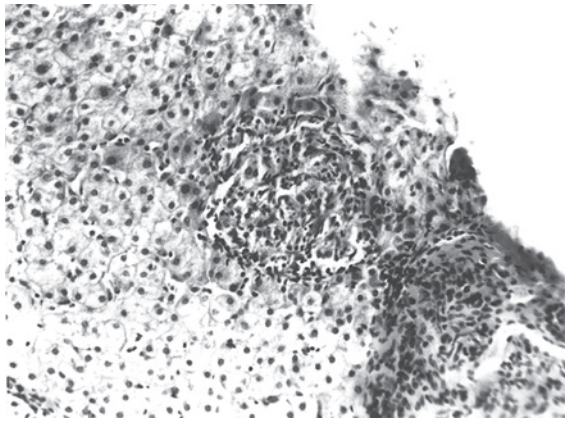

Fig. 2. Non-caseating granuloma adjacent to the portal tract (original magnification x10, H&E).

He was diagnosed as sarcoidosis and steroid therapy was planned. Although anti-HCV was positive, we instituted low-dose steroid therapy since HCV-RNA was negative. Therapy was continued for five months and uveitis regressed.

Discussion

Sarcoidosis is a systemic disorder ofunknown origin characterized by non-caseating epithelioid granulomas. Clinical manifestations

may be generalized or focused on one or more organs. Lungs, liver, spleen, brain, parotid gland, musculoskeletal system, skin, eyes and kidneys can be involved. There is no current diagnostic laboratory test, but anergy, increased ESR and ACE levels, hyperglobulinemia, hypercalcemia and hypercalciuria may support the diagnosis.

The organ most frequently affected is the lung. Granulomatous involvement of interstitial areas affecting alveoli, blood vessels and bronchioles leads to dyspnea, cough, chest pain and, rarely, hemoptysis. Another common manifestation of the disease is hilar or paratracheal (or both) adenopathy. A small percent age of patients (almost 10%) present with symptoms referable to organs other than lung[1].

There are two distinct forms of sacroidosis in children. Older children usually present with a multi-system disease similar to the adult manifestation, with frequent hilar lymphadenopathy and pulmonary infiltration. Early-onset childhood sacroidosis is a unique form of the disease characterized by the triad of arthritis, rash and uveitis and presenting in patients before for years of age[3]. Our case had neither an abnormal chest X-ray revealing interstitial lung disease or bilateral hilar or paratracheal lymphadenopathy, nor any respiratory distress during his course, but he did experience arthritis, rash and uveitis at different periods.

The patient presented with end-stage renal disease in the absence of hypercalcemia or nephrocalcinosis, which are common in sarcoidosis. Renal sacroidosis is reported to have three categories: 1) renal changes by abnormal calcium metabolism, 2) interstitial nephritis or granulomatous nephritis or granulomatous nephritis and 3) glomerulonephritis (mostly membranous)[4]. The biopsy specimen of the patient demonstrated tubulointerstitial nephritis and membranous glomerulonephritis, which are reported as the most frequent glomerular and interstitial lesions of adult sarcoidosis, but there is only one previously reported 13-year-old case of membranous glomerulonephritis in childhood[5,6,2]. Sarcoidosis-associated glomerulonephritis includes a variety of histological forms, the membranous form being dominant, and may appear before the symptoms related to the other organs, as observed in our patient[7]. Tubulointerstitial mononuclear cell infiltration was initially thought to be the result of chronic antibiotic management, but after the other clinical manifestations of sarcoidosis appeared and the patient was evaluated with the preceding hepatic biopsy specimen, its association with that systemic disease was clarified. When the patient is evaluated in the childhood group, we suggest that he is the first case having both membranous glomerulonephritis and tubulointerstitial nephritis in the absence of lung involvement associated with childhood sarcoidosis.

Ocular manifestations are present in most of the patients, causing blurred vision, photophobia and excessive lacrimation. Sarcoidosis classically presents as acute anterior uveitis; the other ocular lesions include posterior uveitis, conjunctival nodules, scleral plaques and lacrimal gland enlargement[1]. The diagnosis of uveitis is important and requires systemic corticosteroid or immunosuppressive treatment[8]. Our patient had bilateral uveitis, which together with renal failure should raise the possibility of sarcoidosis even with a normal chest radiograph and improvement with corticotherapy[9]. Cervical, axillary and inguinal lymphadenopathies, arthritis, maculopapular rashes, erythema nodosum, lymphocytopenia, and mild eosinophilia supported the diagnosis. Hyperglobulinemia, negative PPD tests in spite of his scars, increased ESR and elevated ACE levels were reported, but since all of these findings can be observed in patients with chronic renal failure, they were not indicative for diagnosis of sarcoidosis in our patient[10,11].

This biopsy-proven case is of interest for several reasons. He presented with renal failure, which is an infrequent involvement for sarcoidosis, and he had no lung involvement. While experiencing vague intermittent clinical manifestations over a four-year period the subsequent development of uveitis and demonstration of granulomatous lesions on liver biopsy verfied the diagnosis. When we evaluated the case retrospectively and observed the granulomatous lesions in the previous liver biopsy specimen, we realized that membranous glomerulonephritis and interstitial nephritis leading to chronic renal failure had been associated with sarcoidosis.

This case points out that sarcoidosis may present with manifestations related to organs other than lungs, and that despite a normal

chest radiograph, in the presence of suspected clinical and laboratory findings, a biopsy of the organ suspected to be involved may help to diagnose sarcoidosis.

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