Wegener's granulomatosis in a 15-year-old boy

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Wegener's granulomatosis (WG) is an uncommon systemic vasculitis that is rarely encountered in children. A 15-year old boy presented with a one-month history of nasal obstruction, hemorrhagic rhinorrhea, malaise, fever, anorexia and weight loss, together with high values of inflammatory markers, microscopic hematuria and progressive decrease of renal functions. Renal biopsy revealed rapidly progressive crescentic glomerulonephritis with rare findings of interstitial and periglomerular granulomas. The diagnosis of WG was established and intravenous methylprednisolone and cyclophosphamide therapy followed by oral application of prednisone and azathioprine led to a complete clinical and laboratory remission of the disease. The second renal biopsy performed after 28 months of treatment did not show any activity of the process. Currently, the boy is without any clinical or laboratory signs of active disease. Since untreated WG has a fatal prognosis, early diagnosis and appropriately aggressive immunosuppressive therapy are necessary for a favorable outcome.

Key words: Wegener's granulomatosis, rapidly progressive crescentic glomerulonephritis.

Wegener's granulomatosis (WG) is an uncommon systemic vasculitis of unknown etiology that is rarely encountered in children[1,2]. The disease was first described by Friedrich Wegener in 1936 and usually begins as a localized granulomatous inflammation of upper and/or lower respiratory tract mucosa and may progress into generalized necrotizing granulomatous vasculitis and glomerulonehphritis with consecutive renal failure[1-3]. Untreated WG has a fatal prognosis. Early diagnosis and appropriately aggressive immunosuppressive therapy are crucial, as high remission rate is now possible[3].

Case Report

A 15-year-old boy presented with a one-month history of nasal obstruction, hemorrhagic rhinorrhea, malaise, fever, and anorexia and weight loss, together with microscopic hematuria. There were high values of inflammatory markers, in particular erythrocyte sedimentation rate (105/120) and C-reactive protein (95 mg/L; normal <20 mg/L). A drop in the patient's hemoglobin value occurred within the first week after admission from 98 g/L to 64 g/L (n: 130-180 g/L) together with a rise in blood urea nitrogen and serum creatinine from 7.7 mmol/L (n: 2.9-8.9 mmol/L) and 112 umol/L (n: 53-133 umol/L) to 17.2 mmol/L and 239 umol/L, respectively, with a concomitant decrease of the creatinine clearance from 1.154 to 0.569 ml/s/1.73 m^2 (n: 1.61 –2.42 ml/s/1.73 m^2). There was a slight positivity of perinuclear antineutrophil cytoplasmic antibodies (p-ANCA). The X-ray of the chest and biopsy of the nasal mucosa revealed no pathologic findings. Renal biopsy was performed two weeks after admission. The histologic evaluation of the renal tissue showed rapidly progressive crescentic glomerulonephritis with interstitial and periglomerular granulomas (Figs. 1-3). Therefore, the diagnosis of WG was established and high-dose intravenous methylprednisolone therapy (15 mg/kg/day for 3 consecutive days) was initiated, followed by oral application of prednisone (1 mg/kg/day) for the next 30 months. Cyclophosphamide (0.7 g/m^2 of body surface) was applied intravenously on day 4, followed by the cyclophosphamide pulses every three weeks for three months. Afterwards, the patient was treated with azathioprine for an additional 18 months. In the course of cyclophosphamide therapy he was given trimethoprim-sulfamethoxazole prophylaxis. The

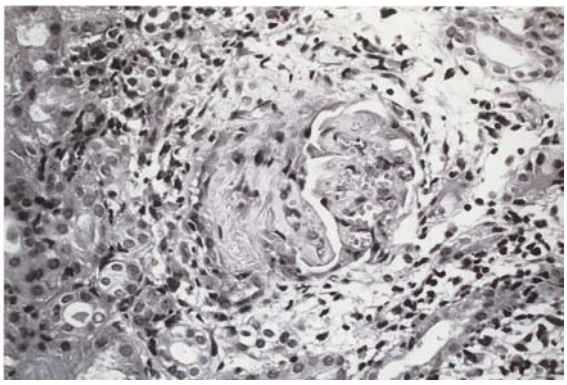

Fig. 1. Advanced stage of crescentic glomerulonephritis. Glomerulus showing a large fibrous crescent. Stained by hematoxylin-eosin (magnification x 400).

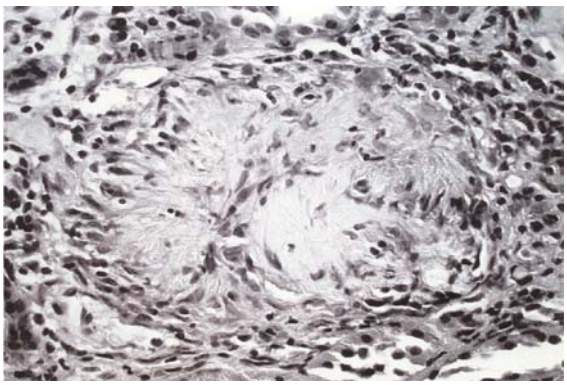

Fig. 2. First biopsy specimen: Granulomatous reaction around a sclerosed glomerulus. Stained by hematoxylin-eosin (magnification x 400).

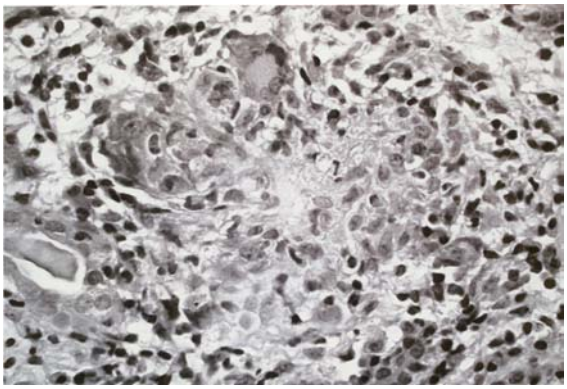

Fig. 3. First biopsy specimen: Granuloma with multinucleated giant cell affecting the interstitium of the kidney stained by hematoxylin-eosin (magnification x 400).

combined immunosuppressive therapy led to a complete clinical remission together with normalization of altered laboratory values within six weeks. The second renal biopsy, performed after 28 months of treatment, revealed collapse and segmental sclerosis of approximately one half of evaluated glomeruli, with no crescents and without any signs of activity of the process (Fig. 4). Currently, the boy is without any clinical or laboratory signs of active disease and has only mildly altered renal functions.

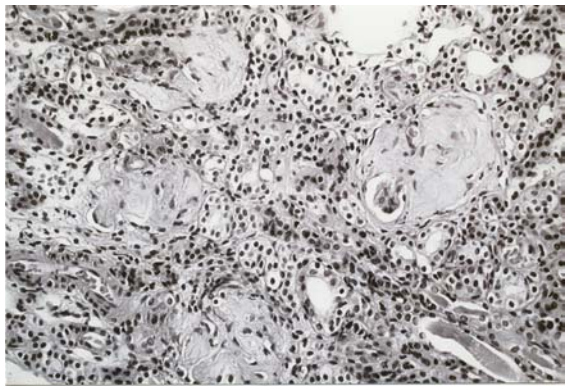

Fig. 4. Second biopsy specimen: Four sclerosed glomeruli. Stained by hematoxylin-eosin (magnification x 200).

Discussion

Wegener's granulomatosis is an uncommon autoimmune disease and is characterized by the presence of inflamed granular material in the nose and nasophrynx with granulomatous tissue containing epithelioid cells, Langhans' cells, and foreign body giant cells, together with overall vascular disruption, sheets of released red blood cells, and numerous leukocytes in varying degrees of cytoclasis. There are inflammatory perivascular exudates and fibrin depositions in small arteries, capillaries and venules of the lungs and skin. Focal and segmental glomerulonephritis of varying severity together with necrotizing vasculitis can be encountered in the kidneys[1-3]. Wegener's granulomatosis has a peak incidence in the fifth decade of life, but can occur at any age[2]. Any organ system can be affected by the pathologic process. The onset of WG can be slow or acute[1-5], and the full spectrum of the disease may take years to evolve. While Wegener's granulomatosis usually presents as a respiratory tract disease[6], there might be central nervous system affections, ocular manifestations and migratory polyarthritis[1,2].

Cutaneous manifestations might occur in 40% to 50% of patients with WG[7]. Patients complain of malaise, anorexia with weight loss and fever[1-4]. The kidneys are among the most frequently and severely affected organs in WG, with vasculitis and rapidly progressive glomerulonephritis leading to renal failure[1-3,5]. The detection of ANCA, in particular cytoplasmic-ANCA (c-ANCA), is considered helpful in establishing the diagnosis of WG[8]. However, screening for ANCA is usually but not invariably positive in children with WG[9]. According to the American College of Rheumatology criteria from 1990, the diagnosis of WG is established by the evaluation of the characteristic clinical and pathological findings: (i) abnormal urinary sediment (red cell casts or more than 5 red blood cells per high power field); (ii) abnormal findings on the chest radiograph (nodules, cavities, or fixed infiltrates); (iii) oral ulcers or nasal discharge; and (iv) granulomatous inflammation on biopsy. The presence of two or more of these four criteria is associated with a sensitivity of 88.2% and specificity of 92.0%[10]. Recently, the following diagnostic criteria were proposed for WG: (i) biopsy or surrogate parameter for granulomatous inflammation in the respiratory system; (ii) biopsy-verified necrotizing vasculitis in small-to-medium sized vessels or biopsy/ surrogate parameter for glomerulonephritis or positive PR3-ANCA test, and (iii) lack of eosinophilia in blood and biopsy samples[11]. The differential diagnosis of WG includes polyarteritis nodosa, Henoch-Schönlein purpura, Churg-Strauss syndrome and microscopic polyangiitis.

The prognosis of WG, once fatal, has significantly improved from the 18% five-month survival rate before the era of immunosuppressive agents to the current remission rate of over 75% with a regimen of cyclophosphamide and glucocorticoids[3]. The therapy is started with prednisone or methylprednisolone with concurrent administration of cyclophosphamide. Corticosteroids are gradually decreased after two to three months, until the patient is maintained solely on cyclophosphamide, which is given at least a full year after a clinical remission of the disease[1-3,5]. Azathioprine is less effective than cyclophosphamide, but may be used as an alternative or adjunct in those patients who cannot tolerate cyclophosphamide[1,2]. Long-term prophylactic administration of oral trimethoprim-sulfamethoxazole is highly effective for the upper respiratory tact lesions[2].

The history of fever, hemorrhagic rhinorrhea, malaise and weight loss together with the high values of inflammatory markers and impairment of the renal functions were all indicative of WG in our patient. This diagnosis was further confirmed by the histologic evaluation of the renal biopsy sample, with the rare finding of granulomas in the kidney tissue. Interstitial and periglomerular granulomas are considered as infrequent lesions[12]. The slight positivity of p-ANCA and the absence of c-ANCA in our patient did not rule out the diagnosis of WG, as screening for p-ANCA is not always positive in WG[9]. The appropriate immunosuppressive therapy induced remission within six weeks. However, a close follow-up of the boy is necessary, as relapses occur in almost 50% of patients with WG, usually due to infection.

In conclusion, WG, although very rare even in adulthood, should be considered in children. An interdisciplinary approach to the care of WG patients is necessary and results in an increased survival rate[13,14].

The prognosis of WG depends on early diagnosis and appropriately aggressive immunosuppressive therapy.

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