Isolated Granulomatous Renal Arteritis: A Variant Form of Giant Cell Arteritis with Few Macrophages

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Abstract

A 64-year-old woman with hypertension and hyperlipidemia was admitted to our hospital for the investigation and management of general fatigue, anorexia, a 5-kg weight loss, and a 4-week history of high-grade fever. She had no symptoms of headache, myalgia, or arthralgia, and the physical examination was unremarkable. The laboratory tests revealed renal dysfunction with urine abnormalities that had not been observed 1 year earlier. A renal biopsy showed granulomatous small arteritis without necrotic lesions or glomerular pathology. An immunohistochemical study of the infiltrating leukocytes showed a predominance of CD4⁺ T cells followed by CD8⁺ T cells, and only a few macrophages. The condition drastically improved after treatment with 30 mg/day of oral prednisolone. The granulomatous renal arteritis was considered a variant of giant cell arteritis, because it showed the peculiar finding of a few macrophages in the granulomatous lesions.

Key words: giant cell arteritis, granuloma, macrophage, T cell

(DOI: 10.2169/internalmedicine.49.2480)

Introduction

Giant cell arteritis (GCA) is a pathological entity characterized by chronic granulomatous inflammation of large- and medium-sized arteries. It affects predominantly temporal arteries (temporal arteritis), and the aorta and its major branches (1). Although the involvement of small arteries in the viscera such as kidneys has also been reported in disseminated GCA (2), isolated GCA of the kidney is extremely rare, and the characteristics of infiltrates into the small arteries of the kidney have never been examined. This report describes a case of biopsy-confirmed renal granulomatous arteritis of the small arteries without glomerular involvement, probably representing localized GCA. A detailed examination of leukocytes infiltrating the affected arteries revealed only a few macrophages in sharp contrast to GCA affecting large- and medium-sized arteries.

Case Report

A 64-year-old woman, with a medical history of hypertension and hyperlipidemia for several years, presented to her family physician with general fatigue, anorexia, body-weight loss of 5 kg, and high-grade fever in August 2007. She was treated with antibiotics based on a suspicion of bronchitis, as her serum creatinine level was 1.87 mg/dL and there were abnormalities in the urinary examination. The serum creatinine level 1 year earlier at the family clinic had been 0.5 mg/dL without urine abnormalities. Although antibiotic therapy was administered for 1 week, her clinical symptoms and renal function showed further deterioration, and she was admitted to our hospital in September 2007.

On admission, the patient did not complain of headache, myalgia, or arthralgia. The temporal arteries were non-tender bilaterally, and neurological abnormalities were absent. Body height and weight were 157 cm and 50 kg, respectively. Arterial blood pressure was 166/108 mmHg and her body temperature was 36.9°C. Physical examination showed...
no abnormalities in the heart, lung, or abdomen. Edema of the lower extremities was absent. Urinalysis showed mild proteinuria without hematuria. Urine β2 microglobulin had increased to 15,400 μg/L. A 24-hour urine collection showed creatinine clearance of 22.3 mL/min and proteinuria of 0.7 g/day. Serum complement levels were within normal limits. Hepatitis C virus serology and surface hepatitis B virus antigen were negative. The results of other laboratory tests included urea nitrogen, 24.7 mg/dL (8.82 mmol/L); serum creatinine, 2.53 mg/dL (224 μmol/L); uric acid, 5.6 mg/dL (0.33 mmol/L); total protein, 6.0 g/dL; serum albumin, 3.56 g/dL; total cholesterol, 235 mg/dL (6.08 mmol/L); white blood cell count, 7,570/μL (Neu 63.5%, Eos 0.0%, Bas 0.7%, Lym 31.5%, Mon 4.3%); red blood cell count, 3.04×10⁸/μL; hemoglobin, 9.6 g/dL; platelet count, 193×10⁵/μL; and erythrocyte sedimentation rate, 22 mm/1h and 53 mm/2h. The values of serum electrolytes, blood glucose, liver enzymes, and globulins were normal. Antinuclear antibody, proteinase 3 (PR3)- and myeloperoxidase (MPO)-antineutrophilic cytoplasmic antibodies (ANCA) were negative. The serum angiotensin-converting enzyme was 7.9 U/L (normal, 27-82 U/L). X-ray and computed tomography of the chest showed no signs of pneumonia or bilateral hilar lymphadenopathy (BHL). An ophthalmological examination revealed no particular abnormalities.

A renal biopsy was performed based on the above laboratory tests. The biopsy material contained 16 glomeruli, including 3 that showed global hyalinization. About half of the other glomeruli were hypertrophic and showed a mild increase in mesangial matrix without proliferative changes (Fig. 1A). The remaining glomeruli showed slight collapse. Other findings included atrophic renal tubules and expansion of the interstitium with marked infiltration of mononuclear leukocytes. However, no interstitial granulomas were noted. Granulomatous lesions were observed on and around the walls of small renal arteries (Fig. 1B). These granulomas consisted of clusters of spindle-shaped cells and were sometimes noted inside the arterial lumens. There were no necrotizing lesions. A immunofluorescence study in the glomeruli was negative for IgG, IgA, IgM, C3, and C1q. Immunoperoxidase staining demonstrated that the infiltrating leukocytes in the granuloma were mostly CD4+ T cells followed by CD8+ T cells (Fig. 2A and B). However, only a few CD68+ macrophages were observed (Fig. 2C). Also there were few S100+ cells, which are considered to be histiocytic cells (Fig. 2D).

Figure 1. Light microscopic findings. (A) There were no significant glomerular changes. However, noteworthy are the atrophic tubules, expansion of the interstitium, and mononuclear infiltration. (B) The small artery is obliterated by granuloma composed of spindle-shaped cells (arrowheads), and the latent lumen (arrow) is markedly narrowed. (A) Periodic acid Schiff stain. (B) Hematoxylin and Eosin staining. Original magnification: (A) ×100, (B) ×200.

Treatment with oral prednisolone at 30 mg/day resulted in a dramatic disappearance of the anorexia and general malaise within 1 week. In addition, her serum creatinine level had improved from 2.53 mg/dL to 1.90 mg/dL 2 weeks later, when the patient was discharged from hospital with 25 mg/day oral prednisolone.

Discussion

Based on the renal biopsy examination, the differential diagnoses included Wegener’s granulomatosis (WG), sarcoidosis, Churg-Strauss syndrome (CSS), and giant cell arteritis (GCA), all of which cause granulomatous arteritis. The patient did not show upper respiratory involvement, and PR3-ANCA was negative. The glomerular pathology was also incompatible with WG; crescentic and necrotizing glomerulonephritis are its characteristic feature. Sarcoidosis cases showing systemic vasculitis have been reported (3). However, such cases present with typical clinical manifestations such as uveitis, bilateral hilar lymphadenopathy, and lung infiltrates, none of which were observed in the present case. Granulomas in sarcoidosis are usually located in the media and adventitia. However, the granuloma seen in the present case grew bound by the lumen, and this feature is commonly observed in GCA granulomas in medium- or large-sized arteries (4). CSS was easily ruled out based on the lack of eosinophilic infiltrates into the granulomatous lesions, and by the absence of eosinophilia and asthma.
Figure 2. Immunoperoxidase staining for CD4, CD8, CD68, and S100 protein (serial sections). The predominant cells in the granulomatous lesion are CD4+ T cells (A), followed by CD8+ T cells (B). Only a few CD68+ macrophages and S100+ histiocytic cells are observed (C and D). Original magnification: ×200

These considerations along with the excellent response to a moderate dose of steroid led us to a diagnosis of GCA, despite the lack of giant cells. The absence of necrotic lesions, which are characteristic of WG, CSS, and polyarteritis nodosa (4), supported our diagnosis. Importantly, the absence of giant cells does not rule out GCA, because they are not necessarily present in GCA. Salvarani et al (5) reported the absence of giant cells in approximately half of their GCA cases.

To date, biopsy-proven isolated renal GCA has only been described in three cases. One case progressed to terminal renal failure despite therapy with high-dose corticosteroid and cyclophosphamide (6), whereas the remaining two cases showed a marked response to corticosteroid therapy (1, 7). The histopathological findings in the former showed necrotizing and extracapillary proliferative glomerulonephritis in addition to GCA. However, the findings of the latter showed no glomerular pathology, just like the present case. Therefore, isolated renal GCA without glomerular lesions may respond well to corticosteroid therapy.

The characteristics of cell infiltrates have not been studied in previous reports describing isolated renal GCA. GCA is an inflammatory vasculopathy affecting large- and medium-sized arteries. The classic histopathological picture of GCA is characterized by granulomatous inflammatory infiltrates with lymphocytes, macrophages, and in some cases, multinucleated giant cells. Inflammation tends to affect the arteries in segmental fashion, and the inflammatory process is usually most severe in the inner media adjacent to the disrupted internal elastic lamina (5). There is general agreement that GCA of medium- or large-sized arteries is a T-cell dependent disease, and that CD4+ T cells play a critical role in the vasculitic process. Activated CD4+ T cells in the adventitia produce interferon-γ (IFN-γ) and stimulate macrophages. In the media, the cellular infiltrate is organized in granulomas, forming a unique spatial relation between activated T cells and macrophages (4). In the present case, however, only a few macrophages were observed. Subtypes of GCA show different tissue-specific inflammatory response patterns, and a patient subset with low levels of IFN-γ production in the arterial wall has been reported (8). In such patients, the number of macrophages in the arterial wall may be low, because IFN-γ controls recruitment and differentiation of macrophages (4). Nevertheless, the finding that CD4+ T cells were predominant among the infiltrates was consistent with that observed in GCA in medium- and large-sized arteries. However, the number of macrophages was extremely low. These peculiar infiltrate findings led us to the conclusion that this case should be regarded as a variant form of GCA.

GCA in small-sized arteries is poorly understood and this is the first report that describes the characteristics of the disease infiltrates. Although the significance of the few macrophages in this case is not clear at this point, it may be char-
acteristic of GCA in small-sized arteries. Alternatively, macrophages may not play an important role in “isolated” granulomatous arteritis of the kidney or other organs, considering the fact that macrophage activation is responsible for systemic inflammatory syndrome in GCA and polymyalgia rheumatica (4).

References


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