Clinical remission of IgA nephropathy in an HIV-positive patient after combined treatment with tonsillectomy and steroid pulse therapy

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Abstract Various renal diseases other than human immunodeficiency virus (HIV)-associated nephropathy, including IgA nephropathy (IgAN), have been recently reported to cause chronic kidney disease and end-stage renal disease in HIV-infected patients. The case of a 37-year-old HIV-infected male diagnosed as having IgAN with proteinuria and microscopic hematuria that was successfully treated with tonsillectomy and steroid pulse therapy in combination, resulting in disappearance of urinary abnormalities (clinical remission), is reported, the first such case in the literature. A renal biopsy revealed mesangial proliferation associated with mesangial deposition of IgA and C3, consistent with IgAN. Antiretroviral therapy and angiotensin receptor blocker therapy did not improve his proteinuria. Therefore, he underwent tonsillectomy and steroid pulse therapy, and clinical remission was successfully achieved with no opportunistic infections. Clinical remission has continued for more than 3 years even after discontinuation of steroid therapy. It appears that combined treatment with tonsillectomy and steroid pulse therapy can be a good choice in managing HIV-infected patients with IgAN as long as secondary infection is strictly and continuously monitored.

Keywords IgA nephropathy · HIV · Tonsillectomy and steroid pulse therapy

Introduction

IgA nephropathy (IgAN) is now generally known to be the most common form of primary chronic glomerulonephritis worldwide [1]. Various approaches to treatment have been attempted [1], but treatment of IgAN still remains controversial because the severity of IgAN varies greatly from asymptomatic microscopic hematuria to rapidly progressive renal failure. Recently, several reports have demonstrated the clinical effectiveness of treatment using a combination of tonsillectomy and steroid pulse therapy for normalizing urinary abnormalities (clinical remission) or preventing the progressive deterioration of renal function [2, 3].

The classic kidney disease of human immunodeficiency virus (HIV) infection, so-called HIV-associated nephropathy (HIVAN), is well known. HIVAN is often accompanied by heavy proteinuria and occurs almost exclusively in patients of African descent [4]. Untreated HIVAN progresses rapidly to end-stage renal disease (ESRD) [4]. Moreover, HIVAN is the third leading cause of ESRD in the US among African American males between the ages of 20 and 64 years [5]. There have been only a few detailed case reports of HIVAN patients in Japan and all the HIVAN patients in Japan were African ethnicity [6, 7]. In addition to HIVAN, a broad spectrum of other glomerular involvement has been described in HIV-positive patients in recent biopsy studies. This suggests that HIVAN is not the only glomerular lesion seen in HIV-infected patients, especially in the era of modern antiretroviral therapy (ART) [5, 8, 9]. Moreover, a number of patients with HIV infection reached ESRD not only due to HIVAN but also

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Fig. 1 **a** Light microscopy showing an increase in mesangial matrix and cellularity. (PAS stain, $\times 400$). **b** Immunofluorescence microscopy showing IgA deposition in the mesangial area. **c** Immunofluorescence microscopy showing C3 deposition in the mesangial area

due to other forms of glomerular diseases including IgAN [10].

The present report is the first of an HIV-infected patient with IgAN who achieved clinical remission after

combination therapy involving tonsillectomy and steroid pulse therapy.

Case report

A 37-year-old Japanese male was referred to our hospital in December 2008 because he was found to be infected with HIV. He had previously been tested for HIV in August 2008, with a negative result. After admission, he was started on ART consisting of zidovudine (AZT) 300 mg/day, ritonavir (RTV) 100 mg/day, and abacavir sulfate 600 mg + lamivudine 300 mg in combination (EZC), 1 tablet/day in February 2009. His baseline CD4 cell count and viral load were 222 cells/ μ L and 2×10^5 copies/mL, respectively. Proteinuria was 2.01 g/day, and there was no apparent reduction in proteinuria 3 months after starting ART. Therefore, he was referred to our unit for further examination.

At the time of admission for renal biopsy in June 2009, physical examination revealed blood pressure of 126/76 mmHg, temperature 37.0 °C, and pulse 68 beats/min. The patient had folliculitis on the skin. The rest of the physical examination was normal.

Laboratory studies on admission showed the following: CD4 cell count 661 cells/ μ L, viral load 9.2×10^2 copies/mL, serum creatinine 0.85 mg/dL, protein 6.5 g/dL, albumin 3.7 g/dL, and uric acid (UA) 8.1 mg/dL. The serum IgG level was 831.3 mg/dL, with IgA 542.3 mg/dL, C3 109.1 mg/dL, and C4 19.3 mg/dL. Serologic studies for antinuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies (ANCA), and hepatitis panel were negative. The urinalysis revealed microscopic hematuria with RBC 5–9/HPF (normal range 0–5/HPF) and granular casts 1+/HPF, without any RBC casts, and with proteinuria of 0.91 g/day.

A renal biopsy was performed. The renal tissue obtained consisted of eleven glomeruli, two of which were globally sclerotic. A mild increase in mesangial matrix and cellularity was found in the rest of the glomeruli (Fig. 1a). Immunofluorescence studies showed positive mesangial staining for IgA and C3 (Fig. 1b, c), as well as for IgM. On electron microscopy, numerous electron-dense deposits were found in paramesangial areas, compatible with IgAN. Treatment with candesartan was begun at a dose of 2 mg/day, and tight BP control ($<125/75$ mmHg) was achieved, but no marked decrease in proteinuria was found with ART and low-dose candesartan.

In August 2009, the patient underwent a tonsillectomy. From September 2009, steroid pulse therapy was performed as follows: high-dose methylprednisolone (0.5 g/day 3 times a week for three consecutive weeks), followed by oral prednisolone (PSL) at an initial dose of 30 mg on alternate days, with gradual tapering of the dose

Fig. 2 The patient's clinical course. Serial changes in urine protein, CD4 cell counts, and IgG before and after the combination of tonsillectomy and steroid pulse therapy (methylprednisolone 0.5 g/day 3 times a week for three consecutive weeks). AZT zidovudine, RTV ritonavir, EZC abacavir sulfate + lamivudine combination, PSL prednisolone

over the course of 1 year (Fig. 2). At the start of the steroid pulse therapy, his laboratory studies showed CD4 cell count 815 cells/μL, HIV-1-RNA <40+ copies/mL, and urine protein 1.64 g/day. Two months after the initiation of steroid therapy, his CD4 cell count decreased drastically from 815 to 125/μL, and IgG decreased from 752.7 to 253 mg/dL. Intravenous immunoglobulin (IVIg) therapy was administered three times to prevent opportunistic infection. In December 2009, his CD4 cell count and IgG increased to 974 and 396 mg/dL, respectively. His proteinuria gradually decreased over 7 months to 0.13 g/day, and microscopic hematuria finally disappeared over 14 months without any major adverse events related to steroid therapy. Disappearance of proteinuria and microscopic hematuria still continued beyond 3 years of follow-up after discontinuation of steroid therapy.

Discussion

To the best of our knowledge, this is the first case report to show the effectiveness of the combination of tonsillectomy and steroid pulse therapy in the management of an HIV-infected patient with IgAN. There have been a number of reports of IgAN occurring in HIV-infected patients [11–16]. Several reviews of renal biopsies from HIV-infected patients around the world reinforce the notion that glomerulonephritis other than HIVAN is a relatively frequent histologic diagnosis among patients of non-African ethnicity, and IgAN is one of the most common diagnoses among non-HIVAN glomerulonephritis [5, 8, 9, 17]. A

renal biopsy study of 73 HIV-infected patients from Italy and 88 patients from France showed 4 cases (5.5 and 4.5 %, respectively) of IgAN [8, 9].

Reports of therapy for IgAN in HIV-infected patients are very limited. There have been only a few case reports of adult IgAN patients with HIV infection, describing the clinical course and therapy [12–16]. Though various therapies from steroids to ART and angiotensin-converting enzyme inhibitors (ACE-Is) have been reported, these reports were from the era prior to the widespread use of highly effective ART.

Several recent studies have suggested that the role of ART in modifying the course of glomerulonephritis other than HIVAN, including IgAN, is unclear, and additional therapeutic strategies may be needed [10, 17]. Additional therapeutic strategies should include conservative medical therapy with ACE-Is or angiotensin receptor blockers (ARBs), and the use of immunosuppressive agents might be considered [17].

It has been reported that IgAN in the setting of HIV infection seems to be related to immune complexes containing IgA antibodies directed against HIV antigens [11]. Nevertheless, because of its high frequency in the general population, IgAN could simply represent a comorbidity in HIV patients, rather than having an etiological connection with HIV infection [8]. Therefore, it is justifiable to use the same therapies for IgAN in both non-HIV patients and in those with HIV-infection.

In 2001, Hotta et al. [2] proposed treatment using a combination of tonsillectomy and steroid pulse therapy as a new approach that can induce clinical remission in IgAN.

The combination of tonsillectomy and steroid pulse therapy has been recognized as an effective strategy for obtaining clinical remission and consequently arresting the progressive deterioration of renal function in patients with IgAN in Japan [2, 3, 18].

In the present patient, ART had an effect on improving his immunodeficient status, since his CD4 cell counts had increased. ART was confirmed to have no effect on the proteinuria for 6 months after the initiation of ART. In addition to ART, tight BP control was achieved by ARBs.

It is reasonable to have considered additional therapy to improve his proteinuria and hematuria as one would do in the general population. Finally, the patient was treated with a combination of tonsillectomy and steroid pulse therapy. Consequently, urinary abnormalities disappeared completely, and clinical remission was achieved.

It is important to note that the safety of steroid therapy remains controversial in the management of glomerulonephritis in HIV-infected patients. A number of retrospective, observational, or uncontrolled studies using steroid treatment have been conducted for selected patients with HIVAN [4, 19–21]. In the study by Eustace et al. [20], prednisone was not associated with an increased risk of infection, but steroid pulse therapy was not performed. A recent study suggested that short-term prednisone therapy given as part of initial therapy for HIV infection itself, especially when combined with ART and even in those with CD4 cell counts <200/μL, is relatively safe and does not predispose to severe infection [22].

In the present patient, baseline CD4 and IgG levels decreased rapidly after the start of steroid therapy. Then, intravenous immunoglobulin therapy was performed by HIV experts at our hospital to prevent opportunistic infections. This strongly suggests that CD4 cell count, HIV viral load, and the IgG level should be monitored periodically, and close collaboration with HIV experts is imperative, even if the patient's immune status seems stable before steroid therapy.

In Japan, the number of newly diagnosed patients with HIV has increased yearly. It is assumed that the number of HIV-infected patients with IgAN will increase in the near future. Based on the good clinical course in the present case, the combination of tonsillectomy and steroid pulse therapy may be an appropriate choice for the treatment of HIV-infected patients with IgAN. Additional clinical experience and research are needed to evaluate the pathogenesis and optimal treatment of IgAN in the setting of HIV infection.

Conflict of interest The authors have declared that no conflict of interest exists.

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