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Regression of HIV-associated pulmonary arterial hypertension and long-term survival during antiretroviral therapy

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Summary

In a 37-year-old patient HIV infection was diagnosed in June 1986. Eight years later the patient complained of increasing shortness of breath and occasional syncopes on exertion. He developed peripheral oedema and ascites. Echocardiography revealed severe pulmonary hypertension. Right ventricular systolic pressure (RVSP) was 77 mm Hg. There was no evidence of left ventricular dysfunction, valvular heart disease, thromboembolic disease or obstructive or restrictive lung disease, nor were there other known causes or risk factors of pulmonary hypertension. HIV-associated pulmonary arterial hypertension was diagnosed. Oral anticoagulation and zidovudine were begun, but RVSP rose to 96 mm Hg. After the introduction of lamivudine, and later stavudine and nelfinavir, HIV-RNA copies decreased from 133 400 to below 50 copies per mL. Six years after the diagnosis of HIV-associated pulmonary arterial hypertension RVSP had continually fallen to 49 mm Hg and the grossly enlarged right heart dimensions had nearly normalised without vasodilator treatment. The patient remains in excellent health and his sole complaint is of mild dyspnoea on exertion.

Key words: pulmonary arterial hypertension; antiretroviral therapy; HIV infection

Introduction

Pulmonary arterial hypertension (PAH) is now a well-known complication of HIV infection [1]. Its clinical and pathological features resemble those of primary pulmonary hypertension (PPH). The incidence of HIV-associated PAH is about 0.5% [1, 2]. Thus, in comparison with the incidence of PPH in the normal population (1–2 per million), HIV-infected subjects have a 2500-fold risk of PAH [1–3]. More than 60% of the cases are males, and the mean age at the time of diagnosis is 33 years [4, 5]. Half of the patients have acquired the HIV infection through intravenous drug use, 30% through sexual contacts and 20% from blood products. The mean CD4 count is 300 cell per µL with a range from 0–900 [1, 4, 5]. Thus, PAH affects all stages of HIV infection, and only one third of the cases have AIDS. Patients with HIV-associated PAH have significantly decreased survival in comparison with a matched population of HIV-infected patients without PAH [2]. Median survival is about one year [2, 5], and most patients die within three years [5]. Treatment consists of anticoagulation and vasodilators. The latter elicit some haemodynamic response in about half of patients [6]. The pathogenesis of HIV-associated PAH is still unknown. While it has never been convincingly shown that the virus itself has a direct impact on the pulmonary vasculature, we have been able to demonstrate that the course of pulmonary hypertension tended to improve in our patients treated with zidovudine or didanosine [2]. On the other hand, an accelerated course of the disease has been reported in two patients given highly active antiretroviral treatment [7].

Case report

In a 37-year-old intravenous drug user HIV infection was diagnosed in June 1986. After entering a methadone programme he regularly consumed intravenous cocaine until mid-1995. For the next two years he consumed cocaine fewer than 6 times a year, and since summer 1997 he has been totally abstinent. In December 1991 echocar-

diography for suspected right-heart endocarditis was completely normal. Right ventricular systolic pressure (RVSP) was 27 mm Hg (normal ≤30 mm Hg) over right atrial pressure (RAP). Blood cultures were negative. The CD4 count was 840 cells per µL (figure 1). At that time the patient exhibited no cardiopulmonary symptoms or signs.

In September 1994 he complained of increasing shortness of breath and occasional syncope on exertion. He developed peripheral oedema and ascites. A further echocardiogram revealed severe pulmonary hypertension. RVSP was 77 mm Hg over RAP (figure 1). There was no evidence of left ventricular dysfunction, valvular heart disease, thromboembolic disease or obstructive or restrictive lung disease, nor were there other known causes or risk factors of pulmonary hypertension [8]. HIV-associated pulmonary arterial hypertension was diagnosed and oral anticoagulation and antiretroviral treatment with zidovudine 250 mg twice daily was begun. The CD4 count increased from 430 to 550 cells per µL, but severe exertional dyspnoea persisted. One year later an echocardiogram showed even higher RVSP of 96 mmHg over RAP. Right atrial and ventricular dimensions were grossly enlarged: the short right ventricular axis was 5.8 cm (normal ≤4.0 cm), and the long and short right atrial axes were 6.8 cm (normal ≤5.0 cm) and 6.3 cm (normal ≤4.1 cm) respectively (figure 1).

Six months later RVSP was still 90 mm Hg over RAP. At that time CD4 counts had decreased to 290 cells per µL, and the viral load, measured for the first time, was 133 400 HIV-RNA copies per mL. Lamivudine 150 mg twice daily was added, and the viral load decreased to 1580 copies per mL. Surprisingly, a further echocardiogram showed decreased RVSP of 54 mm Hg over RAP and near-normalisation of the right atrial and ventricular diameters without vasodilator treatment. Ascites and peripheral oedema had disappeared, and the patient complained only of mild dyspnoea on exertion (NYHA class II–III). One year later, RVSP had again risen, to 71 mm Hg over RAP, as had viral load (6860 copies per mL). After replacement of zidovudine by stavudine 40 mg twice daily, and introduction of nelfinavir 1250 mg twice daily, the viral load had fallen below the detection limit 6 months later. Concurrently, RVSP had again decreased to 63 mm Hg over RAP.

After another rise in RVSP to 74 mm Hg over RAP and transient reappearance of syncopes, ascites and peripheral oedema, there was a steady echocardiographic and clinical improvement. In January 2001 RVSP was only 49 mm Hg over RAP. Only the short right atrial axis was slightly enlarged (5.3 cm), while the other right heart dimensions had normalised. The patient remains in excellent health and his only complaint is of mild dyspnoea on exertion (NYHA class II) 6 years after the diagnosis of HIV-associated pulmonary arterial hypertension.

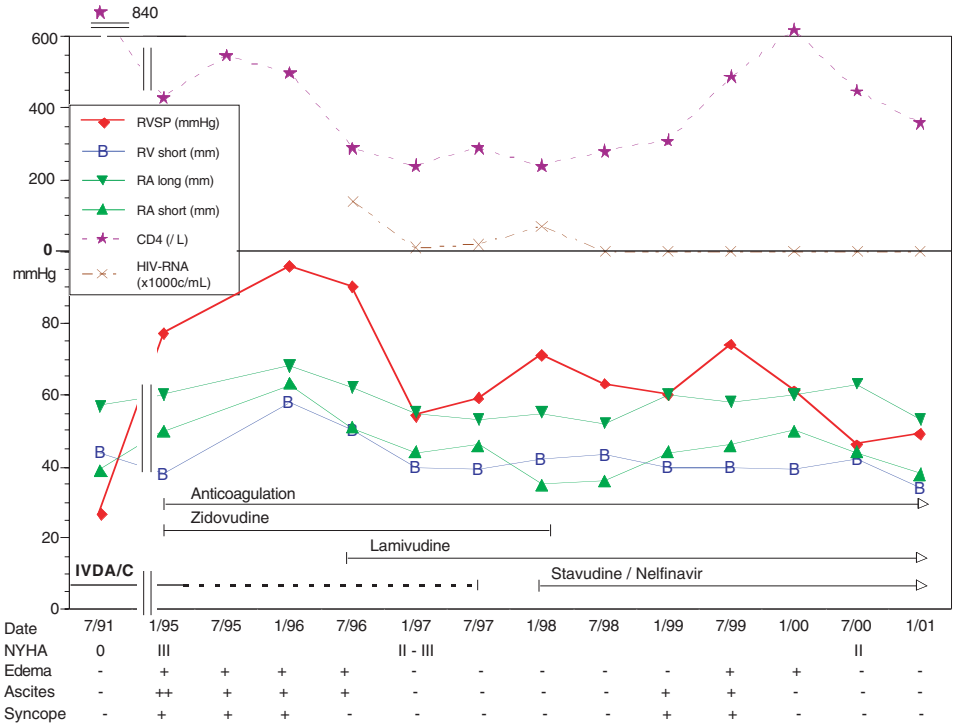

Figure 1

HIV-associated pulmonary arterial hypertension: clinical course during antiretroviral therapy. RVSP = right ventricular systolic pressure over right atrial pressure; RV = right ventricular axis; RA = right atrial axis; IVDA/C = intravenous cocaine abuse.

Discussion

The clinical course of this patient with HIV-associated pulmonary arterial hypertension suggests a favourable effect of antiretroviral combination therapy on the evolution of this disease, particularly after successful suppression of HIV viral load. The potential relationship between HIV RNA load and pulmonary hypertension is further suggested by the second improvement in the patient's RVSP after the introduction of stavudine and nelfinavir. The six years-plus survival in this case is exceptional in that most patients with HIV-associated PAH die within three years of diagnosis [2, 5]. Even more unusual is the spontaneous regression of pulmonary hypertension without vasodilator treatment. To date this has been described in only two cases in the literature. In both

of them pulmonary hypertension developed during infancy and haemodynamic improvement occurred in early adulthood [9, 10].

Although the patient's cocaine use may to some extent have contributed to the course of PAH, the second WHO conference did not regard cocaine as a very probable risk factor for PAH [11]. The occurrence of PPH in HIV-negative cocaine users is highly unusual: there are only nine reported cases in the literature, in which pulmonary hypertension was usually mild (RVSP 30–44 mm Hg over RAP) [12] and transient [13]. Thus, in accordance with our findings in a recently published cohort study [2], the favourable clinical course of HIV-associated PPH suggests an important role for antiretroviral combination therapy in this disorder. Even if the aetiology of HIV-associated PAH is still unknown, HIV infection probably acts as a trigger mechanism for the rise in pulmonary vascular resistance and the treatment-induced decrease in the HIV viral load may well exercise a beneficial effect on this postulated interaction.

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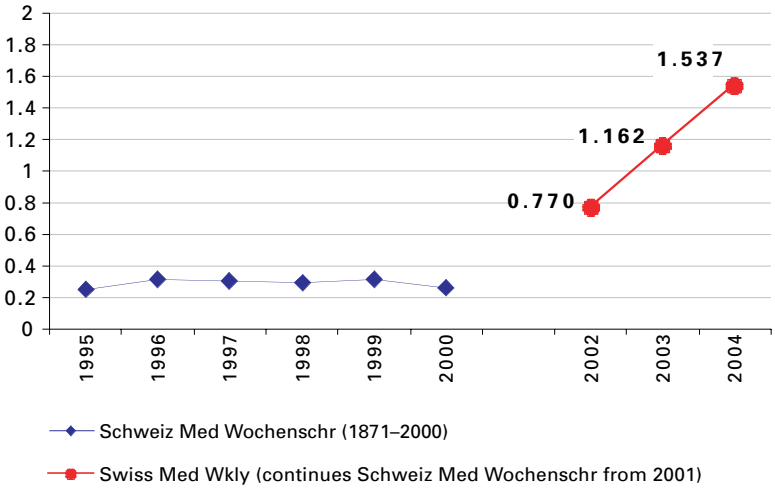

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