Hepatopulmonary syndrome: an emerging complication in HIV-hepatitis C virus co-infected patients

Hepatopulmonary syndrome is defined as a triad of chronic liver diseases, hypoxemia < 70 mmHg and pulmonary vascular dilation [3]. The estimated prevalence of HPS in patients with chronic liver disease varies between 4 and 29% according to the heterogeneous criteria used for definition of the condition [3,4]. In a recent study among patients with hepatitis B or C infection, the reported prevalence was 1.1% [5]. Little data is available on HIV-infected patients as only two cases have previously been reported in the literature [6,7]. The mechanisms leading to pulmonary vasodilation are complex and multifactorial. There appears to be an imbalance between the vasodilating and vasoconstricting mediators (nitrogen monoxide and endothelin-1). Hypoxemia can be explained by anatomical shunting and a diffusion–perfusion abnormality [3,4,6].

HPS occurs mainly but not exclusively in cirrhotic patients with portal hypertension [3,4]. This increasingly frequent complication is characterized by a delayed diagnosis with a mean duration of respiratory symptoms of 4.8 years before diagnosis. The presence of hypoxemia associated with platypnea and orthodeoxia (decrease in PaO2 in the erect position) as in our observation is suggestive of clinically significant HPS [3,4,6,7]. When the diagnosis is suspected, analyses of arterial blood gases should be obtained in both erect and supine positions. Attention in daily practice should be drawn to the presence of basilar interstitial infiltrates on chest radiographs, mimicking interstitial lung diseases or opportunistic pulmonary infections. Moreover, a high-resolution computerized tomography scan of the chest is useful to rule out other causes of hypoxemia and confirm the vascular etiology (dilated lung vessels) of the opacities [8]. Contrast-enhanced echocardiography is the key diagnostic tool [3,4]. HPS represents a significant mortality risk factor (overall mortality of 41% at 3 years after onset of dyspnoea) among cirrhotic patients, even after transplantation [9]. The most relevant prognosis factor is severe hypoxemia, with a baseline PaO2 < 50 mmHg associated with high mortality [10]. Currently, there is no effective medical treatment (methylene blue, inhaled NO, garlic, norfloxacin) for HPS [4,6,9,11]. Orthotopic liver transplantation (OLT), an emerging practice in selected HIV/HCV co-infected patients, is the only efficient treatment since it can reverse oxygenation abnormalities [11–13]. No data is available yet in this group. Thus, HPS should be considered in every case of a HIV patient with associated liver disease, presenting with an unexplained dyspnoea and hypoxemia. Early detection of ‘subclinical HPS’ by systematic arterial...
blood gas measurements in HIV-associated liver disease improves the prognosis.

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Pulmonary pneumocystosis in a patient with greater than 500 CD4 cells/μl: a role for IL-2 therapy?

Pulmonary pneumocystosis (PCP) is the most frequent initial AIDS-defining disease [1]. Cellular and humoral immunity are both required to control Pneumocystis, the causative protozoan parasite [2]. Primary prophylaxis with cotrimoxazole (trimethoprim–sulfamethoxazole) is recommended for all HIV-infected patients with CD4 T-cell counts below 200 cells/μl (15% of total T cells) [3].

We report the case of a 41-year-old HIV-infected man who developed PCP despite a CD4 cell count of 500 cells/μl (23% of total T cells). PCP was his first AIDS-defining event. HIV infection had been diagnosed in 1991, and he had been taking antiretroviral drugs since 1992. The nadir CD4 cell count (122 cells/μl, 6% of total T cells) was reached in 1995.

In April 2001, after several lines of antiretroviral therapy, he was switched to a combination of zalcitabine, lopinavir and ritonavir, which, since June 2001, had maintained his CD4 cell count above 200 cells/μl and his HIV viral load below 50 copies/ml.

Between October 2002 and March 2003, as a participant in the ANRS 101 ‘Esprit’ trial, he received subcutaneous recombinant IL–2 that was given twice a day in seven 5-day cycles every 8 weeks, as previously reported [4].

Some months before PCP diagnosis, he had two episodes of acute lobular pneumonia, which was treated with amoxicillin–clavulanic acid, and then with ceftriaxone plus short-course steroid therapy (48 h) at a daily dose of 1 mg/kg.

On admission to our department in March 2005, 3 years after IL–2 therapy, he was febrile (39°C), polypnoeic (20 breaths per minute) and hypoxic (arterial oxygen tension 65 mmHg). He had a 3-day history of breathlessness and productive cough. Chest radiography was normal. Angio computed tomography was performed because of a shunt effect revealed by blood gas analysis (arterial carbon dioxide tension 32 mmHg). It did not show pulmonary embolism but revealed diffuse alveolo-interstitial ground-glass opacities. Bronchial fiberoscopy with bronchodialveolar lavage confirmed the diagnosis of PCP by yielding Pneumocystis jiroveci cysts. The patient said he was unaware of any contacts with PCP.

He started to improve after 48 h of curative treatment with cotrimoxazole and steroids (1 mg/kg). Cotrimoxazole was continued at a curative dose for 12 weeks and then replaced with a prophylactic dose; the steroid was gradually withdrawn over 3 weeks.

Most reported cases of PCP in HIV-seronegative adults involve individuals receiving chronic steroid therapy or immunosuppressive treatment for transplantation, haemopathies, solid tumours, or inflammatory disorders [5].
In the HIV-infected population, PCP rarely occurs at CD4 cell counts above 200 cells/μl; such cases are usually attributed to immunosuppressive treatments (steroids, chemotherapy, etc.) or to the interruption of cotrimoxazole prophylaxis.

Between April 1996 and June 2004, 2725 cases of primary PCP were recorded in the French hospital database on HIV infection. A total of 180 patients (6.6%) had CD4 cell counts above 200 cells/μl, of whom 21 had counts above 500 cells/μl. Only two patients, with CD4 cell counts between 200 and 350 cells/μl, had received IL-2 before PCP onset. PCP was the first AIDS-defining disease in only one of these two patients.

Studies of IL-2 therapy for HIV infection started approximately 15 years ago. IL-2 durably increases the CD4 cell count in patients on antiretroviral therapy, regardless of the baseline CD4 cell count; it is not associated with virological failure or with antiretroviral resistance [6–8]. IL-2 has not been shown to prevent AIDS-defining opportunistic infections, but two ongoing international trials (SILCAAT and ANRS 101 ‘Esprit’) are focusing on this issue.

We found no published cases of PCP occurring after IL-2 therapy in patients with more than 200 CD4 cells/μl. Our patient’s only known risk factor for PCP was HIV infection. This suggests that immunological recovery on IL-2 was insufficient to prevent P. jiroveci infection. The results of ongoing multicentre studies may confirm this possibility.

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No change to HIV-1 latency with valproate therapy

Integrated HIV-1 proviruses in resting CD4 T cells are believed to be a significant barrier to HIV eradication. The activation of latent HIV infection using a histone deacetylase inhibitor (sodium valproate) and the intensification of antiretroviral therapy (ART) with enfuvirtide accelerated HIV-1 clearance from CD4 memory T cells isolated from patients with HIV-1 infection [1], and was widely reported to be a potential milestone in the cure of this disease [2]. We report a case of a single patient, in whom long-term combination therapy with ART and sodium valproate did not significantly alter the rebound kinetics of viral replication after the cessation of ART.

A 54-year-old Armenian Iranian man was diagnosed with HIV-1 in 2001 when he presented with cerebral toxoplasmosis; his CD4 T-cell count was 44 cells/μl and viral load was 1 280 000 copies/ml. He was treated with ART (efavirenz, abacavir and lamivudine) for HIV-1 infection and sodium valproate for recurrent grand mal seizures since 2001. Since 2003 his plasma viral load has always been less than 75 copies/ml, using the branched DNA assay v3.0 (Chiron Corp., Emeryville, California, USA), and his CD4 T-cell count has ranged from 467 to 1 115 cells/μl. Sodium valproate levels have been in the therapeutic range (50–100 mg/l). After the publication of the recent Lancet report [1], the patient attended our clinic requesting help in establishing whether he was cured of HIV-1 infection.

Baseline blood samples for viral load, lymphocyte subsets, valproate levels, episomal complementary DNA circles [3], and CD8+CD38++ immune activation were taken (Table 1). Antiretroviral therapy was modified to prevent the risk of viral resistance, and 2 weeks later all ART was stopped. Serial measures of HIV-1 viral load, lymphocyte subsets and immune activation were performed. Within
3 weeks of stopping ART there was a rapid rebound of the HIV-1 viral load, with a concomitant marked increase in CD8+CD38++ immune activation and a fall in the CD4 T-cell count. Episomal cDNA circles were negative at day 0 and day 20. HAART was recommenced 28 days after the cessation of therapy with good effect. At the last follow-up 66 days after restarting HAART, the viral load was 1761 copies/ml and the CD4 T-cell count was 697 cells/ml.

The addition of long-term valproate therapy did not significantly increase the time to virological relapse after the stopping ART [4], nor did it alter the kinetics of viral relapse, with linear regression analysis demonstrating a viral rebound rate constant 0.34 per day, which falls within the range previously reported: 0.12–0.91 per day [4]. Our patient had well-controlled disease, with a viral load below the limit of detection for over 2 years. He had normal percentages of CD8 T cells expressing CD38, suggestive of a plasma viral load less than 7 copies/ml (unpublished observations). Our data suggest that sodium valproate had only a modest effect on the eradication of HIV-1 infection from latently infected CD4 T cells. The intensification of ART can decrease the t1/2 of latent HIV-1 cellular reservoirs [5]. We suggest that further controlled studies are needed to establish the relative contribution of the intensification of pre-existing ART and sodium valproate in the clearance of HIV-1 from CD4 memory T cells.

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**References**


### Hypertension in HIV patients

In their interesting article, Crane et al. [1] reported an increase in blood pressure among patients treated with HAART. Systolic blood pressure (SBP) during treatment with HAART, but not diastolic blood pressure, was significantly higher compared with SBP measured before initiating HAART. Among protease inhibitors (PI), lopinavir/ritonavir was associated with the greatest risk of mainly systolic elevations in blood pressure. In this work, the authors did not report specifically whether pulse pressure was different before and after therapy. Pulse pressure is considered a more sensitive measure of risk than other indexes of blood pressure [2]. Probably, many

### Table 1. Serial measurements of CD4 and CD8 T-cell counts, viral loads (branched DNA assay) and CD8 CD38 immune activation.

<table>
<thead>
<tr>
<th>Day</th>
<th>CD4 cells/µl (450–1660)</th>
<th>CD8 cells/µl (190–1210)</th>
<th>Viral load</th>
<th>%CD8+CD38++</th>
</tr>
</thead>
<tbody>
<tr>
<td>−14</td>
<td>773</td>
<td>991</td>
<td>&lt; 50</td>
<td>2.9</td>
</tr>
<tr>
<td>0</td>
<td>776</td>
<td>916</td>
<td>&lt; 50</td>
<td>2.3</td>
</tr>
<tr>
<td>2</td>
<td>761</td>
<td>949</td>
<td>&lt; 50</td>
<td>1.7</td>
</tr>
<tr>
<td>6</td>
<td>1212</td>
<td>1665</td>
<td>55</td>
<td>1.8</td>
</tr>
<tr>
<td>9</td>
<td>855</td>
<td>1148</td>
<td>&lt; 50</td>
<td>2.1</td>
</tr>
<tr>
<td>13</td>
<td>1115</td>
<td>1478</td>
<td>&lt; 50</td>
<td>2.2</td>
</tr>
<tr>
<td>16</td>
<td>627</td>
<td>768</td>
<td>&lt; 50</td>
<td>3.0</td>
</tr>
<tr>
<td>20</td>
<td>975</td>
<td>1047</td>
<td>3500</td>
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</tr>
<tr>
<td>23</td>
<td>631</td>
<td>663</td>
<td>66 000</td>
<td>10.5</td>
</tr>
<tr>
<td>28</td>
<td>322</td>
<td>1784</td>
<td>500 000</td>
<td>71.6</td>
</tr>
</tbody>
</table>

Day −14 was change of antiretroviral therapy and day 0 was cessation of all antiretroviral therapy.
of the patients reported had an increase in pulse pressure. The increase in SBP and pulse pressure is primarily caused by an increase in large-artery stiffness and an associated increase in wave reflection amplitude. There is increasing evidence that pulse pressure is an independent predictor of the risk of coronary heart disease compared with mean arterial pressure [3]. Recent data suggest that HIV-infected patients under HAART including a PI have higher values of aortic stiffness than a matched group of HIV-uninfected control subjects, and that pulse wave velocity increased with longer exposure to PI treatment [4]. With increased arterial stiffness, central SBP increases and diastolic blood pressure falls in the central arteries as a consequence of earlier wave reflection, which shifts the augmentation of blood pressure from diastole to systole. Augmentation of central pressure is a direct determinant of increased cardiac workload and of diminished myocardial perfusion, and has recently been implicated as a powerful risk factor for cardiovascular events independently of pulse pressure and other risk markers [5].

PI treatment might selectively contribute to increase aortic stiffness. The changes in arterial stiffness may partly mediate the association between the use of PI and cardiovascular risk in patients with HIV infection. Crane et al. [1] reported that increased body mass index was significantly associated with elevated blood pressure in their patients, but do not report whether their patients met the criteria for the metabolic syndrome. We suggest that the metabolic syndrome might represent a link between the use of HAART and arterial stiffness, reflected by a selective increase in SBP and pulse pressure. In our opinion, this would be valuable information, because the metabolic syndrome is both a side-effect of PI [6] and an important determinant of large-artery stiffness [7]. In other words, PI therapy may contribute to increase arterial stiffness and the risk of developing the metabolic syndrome and the associated cardiovascular risk.

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