The results suggest using TBW to predict steady-state and post-steady-state blood CsA concentrations and LBW to predict pre-steady-state blood CsA concentrations. The results indirectly support the concept that CsA distribution obeys physicochemical principles. The estimation of pharmacokinetic parameters using TBW might lead to favorable TBW predictions. The facts that at pre-steady-state CsA might not fully distribute into fatty tissues and CsA concentration might not be dominated by CsA metabolism might lead to favorable LBW predictions.

The time of the continuous intravenous infusion was not identical in each patient, because several patients felt uncomfortable during infusion. Although the ages were not comparable between females and males, we did not consider this problematic because we were mainly concerned with inter-method comparisons at each age group. However, we hope to find patients at different ages in future studies, so we can analyze the integrity of CsA metabolism, which decreases with age, better. We also hope to find seriously obese female patients in future studies.

Acknowledgments

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Key words

Cyclosporine, dosing body weight, hematologic patient with multidrug resistance, inter-method comparison, lean body weight, obesity, prediction, total body weight.

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References

Indolent lymphoproliferative disease of large granular lymphocytes after lung transplantation

Sir,

Sequential assessment of peripheral blood lymphocyte subsets, useful for following post-transplantation immune reconstitution and detecting infectious or rejection episodes, also allows identification of lymphoproliferative disorders or unusual patterns in some patients. We report the case of a lung transplant recipient who has had, for over 7 years, a persistent immunophenotypic pattern reminiscent of that reported in LGL leukemia and lymphoproliferative diseases of granular lymphocytes (LDGL).

DR, 55 years old, suffered from chronic respiratory insufficiency due to panacinar emphysema with α1-antitrypsin deficiency, which led to a single lung transplant in February 1991. Post-transplant induction immunosuppression was achieved by anti-lymphocyte globulins (ALG; Thymoglobulin, Merieux, Lyon, France), followed by a maintenance regimen of cyclosporine, azathioprine and corticosteroids.

Three episodes of grade I acute rejection were treated by reinforced corticosteroids. Two episodes of bronchiolitis obliterans were controlled by reinforced immunosuppression including ALG treatment in the second instance. Pulmonary function tests have remained stable since.

Herpetic bronchitis was treated by acyclovir. CMV seroconversion, observed concomitantly to the detection of CMV cellular inclusions in a transbronchial biopsy, was treated by ganciclovir. Later, a CMV and Pneumocystis carinii lung infection developed which prompted treatment with ganciclovir and sulfamethoxazole-trimethoprim. Antibiotic therapy was necessary to clear several infectious episodes due to Haemophilus influenzae, Aspergillus fumigatus and Pseudomonas aeruginosa. Two epidermoid carcinomas developed in 1996 and in 1998; they were resolved after surgery and chemotherapy.

Sequential immunophenotyping of PBL subsets was performed in the same Immunology laboratory at regular intervals over 7 years (Figure 1) by flow cytometry (Coulter Corporation, Hialeah, FL, USA; reagents from Coulter Corporation and Immunotech, Marseille, France). Post-transplantation and during immunosuppressive treatment, there was a progressive restoration of the different subsets which had collapsed after ALG treatment. From September 1992 on, however, the level of T-cell subsets decreased severely to around 10%, i.e. absolute numbers of 0.11±0.05×10⁹/L, associated with persistently high levels of CD57⁺ cells (mean overall level out of ALG treatment 60.5±19%, 0.86±0.39×10⁹/L). White blood cell and lymphocyte counts remained within normal ranges, there being steady levels of around 4×10⁹/L polymorphonuclear cells. Cytologic examination consistently showed over 60% of typical large granular lymphocytes.

Extensive immunophenotypic studies demonstrated that the predominant population of CD57⁺ lymphocytes expressed surface CD7, CD2 and cytoplasmic CD3, but lacked CD5, CD3, CD4, CD8 and the T-cell receptor. CD16 and CD54 were always present but CD56 expression was only observed occasional-
ly. CD158a and b were not expressed by these cells. Natural killer activity was normal.

This case report describes an unusual context for the development of persistent NK lymphocytosis, i.e. more than one year post-transplantation, after infectious episodes not usual in transplantation. This patient differs from the 26 CD8+/CD4+/NKa cells cases reported by Scott et al., since nearly all lymphocytes were LGL, yet the absolute counts were lower than 4.5 × 10³/L. NK-LGL leukemia can also be ruled out in the absence of neutropenia, visceral involvement or coagulopathy. The long term and indolent character of this immunohematologic rarity is more reminiscent of the chronic NK cell lymphocytoses described after infectious episodes by several authors, and given diagnosis criteria by Semenzato et al. According to the latter, the patient described here appears to be another case of the very rare post infectious low count CD3+ LGL, only observed in 2 out of 195 patients by those authors. The indolent evolution of this patient’s disease could be related to the immunosuppression he receives as rejection prevention, which matches attempted therapeutic approaches in NK lymphocytosis.

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Key words
Lung transplantation, lymphoproliferative diseases

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References

Colorectal cancer and HFE gene mutations

Sir,

Hereditary hemochromatosis (HH) is characterized by an increased absorption of iron resulting in excess deposition of this metal in parenchymal cells of the liver, heart, and certain endocrine organs. Patients with HH have an increased risk, in relation to their increased iron stores, of suffering liver and esophageal cancer and skin melanoma. The relative risk of subjects with moderately high levels of serum transferrin saturation and high serum ferritin (laboratory abnormalities similar to those found in HH heterozygotes) suffering from colorectal cancer is three times higher than in the normal population.

Whether HH heterozygotes have a higher incidence of colorectal cancer is not known, although a slightly higher RR (1.28) in these subjects was found in one study.

In 1996 Feder et al. identified a gene strongly linked to HH, which is now known as HFE. A change in a single base pair of this gene (G282Y) is clearly associated with HH, and subjects who share a normal haplotype with G282Y are considered heterozygotes for the disease. The relationship between a second genomic change (H63D) and HH is currently unclear. We investigated both substitutions in 116 patients with colorectal cancer and in 108 healthy subjects in order to compare the frequencies of the substitutions and determine whether there is higher than expected proportion of HH heterozygotes in patients with colorectal cancer.

A total of 116 DNA samples which had been stored at 4°C were thawed from a colorectal cancer DNA bank. DNA samples from 108 healthy blood donors were used as normal controls. The distribution of sexes was similar in both groups (54.3% males in the cancer group, 57.4% males in the control group), but that of age was heterogeneous (mean age 66.9 years in cases vs 40 in controls, p <0.05). G282Y and H63D mutations were screened for by using enzymatic digestion of PCR products encompassing the mutation sites as described elsewhere. The frequencies of mutations in

Table 1. Genotype frequencies of mutations in the HFE gene in patients with colorectal cancer and healthy controls.

<table>
<thead>
<tr>
<th>Genotypes</th>
<th>Cases n=116</th>
<th>Controls n=108</th>
</tr>
</thead>
<tbody>
<tr>
<td>HH/CC</td>
<td>68</td>
<td>70</td>
</tr>
<tr>
<td>HH/CY</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>HD/CC</td>
<td>36</td>
<td>28</td>
</tr>
<tr>
<td>DD/CC</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>HD/CY</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>C282Y*</td>
<td>2.6 (1.5-5)</td>
<td>3.7 (1.6-7.2)</td>
</tr>
<tr>
<td>H63D*</td>
<td>21.1 (16.1-26.9)</td>
<td>15.7 (11.2-21.3)</td>
</tr>
</tbody>
</table>

*Allelic frequencies (%; 95% CI). Genotypes are given for aminoacid 63 (H63D)/aminoacid 282 (C282Y) of protein. CC/HH corresponds to the wild type.