Development of Cervical Fat Pads Following Therapy with Human Immunodeficiency Virus Type 1 Protease Inhibitors

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Eight patients with infection due to human immunodeficiency virus type 1 developed fat pads at the bases of their necks a median of 22 weeks (range, 4–61 weeks) after initiation of protease inhibitor therapy. This finding was seen in association with the use of each of the available protease inhibitors. The patients had no other cushingoid features or histories of corticosteroid use, and all had normal 24-hour urine cortisol levels. The computed tomography scans of five patients showed large, nonencapsulated accumulations of subcutaneous adipose tissue. Histological examination of tissue from one patient confirmed a nonlipomatous subcutaneous fat deposition. Although the pathogenesis of this unique clinical finding is unclear, the temporal relationship between the use of protease inhibitors and the development of cervical fat pads is suggestive of a complication of therapy.

HIV-1 protease, an aspartyl protease, is an essential enzyme for the proteolytic cleavage of precursor proteins in the final step of viral maturation. Inhibition of this enzyme prevents the release of mature virions from infected host cells [1]. The use of protease inhibitor–based antiretroviral regimens has been shown to increase CD4+ T cell counts [2–7], reduce plasma HIV RNA levels [2–7], slow the progression of HIV-1 infection to AIDS [6, 8], and decrease mortality [6, 8]. Although mild adverse effects are commonly reported, protease inhibitors appear generally safe and well tolerated [1, 9]. However, follow-up periods in clinical trials thus far have been relatively short, and little is known about the long-term side effects of these drugs. For instance, increased experience with indinavir has led to reports of nephrolithiasis [10, 11], uveitis [12], hepatitis [13, 14], and hyperbilirubinemia [15]. Hyperlipidemia has been attributed to the use of ritonavir [16], and all the available protease inhibitors have been associated with the development of hyperglycemia [17].

We report the development of cervical fat pads in eight patients receiving protease inhibitor therapy.


Cases

Staff at the Immunodeficiency Clinic of the Ottawa General Hospital (Ottawa) follow up >800 HIV-positive patients, approximately one-half of whom are receiving at least one protease inhibitor. Between May 1996 and September 1997, eight patients presented with progressively enlarging soft tissue masses at the base of the neck (figure 1). Three patients complained of associated warmth, discomfort, and restriction of neck movement; the remainder were asymptomatic but expressed cosmetic concerns. All patients were receiving at least one of the protease inhibitors saquinavir, ritonavir, indinavir, or nelfinavir, and all but patient 8 (table 1) were also receiving reverse transcriptase inhibitors. None of the patients were taking exogenous corticosteroids, growth hormone, or megestrol acetate. Patient 1 was receiving intramuscular injections of depottestosterone and decadurabolin every 2 weeks, and patient 6 was receiving exogenous estrogen as hormonal replacement therapy.

The length of time between the initiation of protease inhibitor therapy and the onset of a clinically apparent neck mass varied from 4 weeks to 61 weeks (median length of time, 22 weeks). On physical examination, the soft tissue masses resembled the “buffalo hump” characteristic of hypercortisolism. Patients 3 and 7 also had supraclavicular fullness, and patient 3 had submandibular soft-tissue swelling. All patients were normotensive and had no postural changes in blood pressure. Of note, six patients gained weight following the initiation of protease inhibitor therapy (median weight gain, 3.5 kg; mean [±SD] weight gain, 3.14 ± 2.90 kg; n = 8). Truncal obesity was not evident in any patient, and cushingoid features were otherwise absent.

Laboratory investigations for all patients included levels of serum electrolytes, glucose, and triglycerides. A 24-hour urine cortisol measurement was done for all patients except patient 4. In each instance electrolyte levels and 24-hour urine cortisol levels were normal, making hypercortisolemia unlikely. Three patients (patients 4, 6, and 8) had mild hyperglycemia; one of these patients had a history of glucose intolerance. One patient receiving ritonavir (patient 6) and one patient receiving nelfi-
Figure 1. Dorsal cervical neck masses in two HIV-1-positive patients receiving protease inhibitor therapy. A, Patient 2; B, patient 6.

Patient 5 chose to discontinue all antiretroviral therapy because of progressive enlargement of his neck mass. Ten weeks after stopping therapy, there has been no objective evidence of regression of the mass. In the remaining patients there has been no further progression in the size of the cervical masses.

Discussion

The development of cervical fat pads in HIV-1-infected patients receiving antiretroviral therapy appears to be a novel observation. The temporal relationship between the use of protease inhibitors and the onset of this unusual finding in our patients is suggestive of a side effect of therapy. The development of the cervical neck masses appeared to be independent of the protease inhibitors used, the immunologic

Table 1. Demographic, clinical, and laboratory data obtained before the initiation of protease inhibitor therapy and at the onset of cervical fat pads in HIV-1-infected patients.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (y)/sex</th>
<th>Antiretroviral therapy</th>
<th>Time from initiation of PI therapy to onset of fat pad (w)</th>
<th>CD4 cell count (/μL)</th>
<th>Viral load (copies/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PI RTI</td>
<td>Before PI therapy*</td>
<td>At onset*</td>
<td>Before PI therapy</td>
</tr>
<tr>
<td>1</td>
<td>47/M</td>
<td>SQ d4T, 3TC</td>
<td>4</td>
<td>7 (2.7)</td>
<td>34 (17.0)</td>
</tr>
<tr>
<td>2</td>
<td>50/M</td>
<td>IND d4T, 3TC</td>
<td>17</td>
<td>149 (13.3)</td>
<td>265 (12.3)</td>
</tr>
<tr>
<td>3</td>
<td>43/M</td>
<td>NEL, SQ</td>
<td>48</td>
<td>138 (8.1)</td>
<td>204 (11.4)</td>
</tr>
<tr>
<td>4</td>
<td>33/M</td>
<td>IND d4T, 3TC</td>
<td>26</td>
<td>443 (20.5)</td>
<td>466 (28.9)</td>
</tr>
<tr>
<td>5</td>
<td>49/M</td>
<td>IND d4T, 3TC</td>
<td>19</td>
<td>5 (1.1)</td>
<td>30 (2.9)</td>
</tr>
<tr>
<td>6</td>
<td>42/F</td>
<td>RIT ZDV, 3TC</td>
<td>13</td>
<td>64 (14.8)</td>
<td>423 (12.0)</td>
</tr>
<tr>
<td>7</td>
<td>32/M</td>
<td>RIT, SQ</td>
<td>61</td>
<td>144 (10.7)</td>
<td>268 (14.0)</td>
</tr>
<tr>
<td>8</td>
<td>44/M</td>
<td>NEL, SQ</td>
<td>27</td>
<td>278 (14.0)</td>
<td>232 (13.0)</td>
</tr>
</tbody>
</table>

NOTE. ddI = didanosine; d4T = stavudine; IND = indinavir; NA = not available; NEL = nelfinavir; PI = protease inhibitor; RTI = reverse transcriptase inhibitor; SQ = saquinavir; 3TC = lamivudine; ZDV = zidovudine.

* Numbers in parentheses are percentages.

1 RTI therapy initiated ≤4 weeks before initiation of PI therapy.

1 Patient 2 was switched from saquinavir to indinavir after 4 weeks to increase the potency of his antiretroviral regimen.
Figure 2. Biopsy specimen from a dorsal cervical neck mass in an HIV-1-positive patient (patient 1, table 1) shows nonencapsulated mature adipose tissue (stain, hematoxylin-eosin; original magnification, ×200).

and virological responses to therapy, and the stage of HIV infection (table 1).

The pathophysiology of the unusual fat distribution in these patients is not known. Atypical fat accumulations at the base of the neck have not been previously described except in patients with Cushing’s syndrome. Metabolic changes such as hyperglycemia and hypertriglyceridemia in patients receiving HIV-1 protease inhibitor therapy are known to occur [16, 17]; however, such metabolic abnormalities were not consistently observed in our patients. A recent description of hepatic lipase suppression in association with ritonavir use [18] indicates that protease inhibitors cause metabolic changes that are as yet poorly understood. Development of breast hypertrophy, abdominal enlargement, and thinning of the buttocks and thighs in a patient treated with indinavir has recently been reported [19]; these findings suggest that protease inhibitors may influence body fat distribution or have a direct effect on adipose tissue independent of their effect on HIV-1 viral replication.

It is not yet known whether discontinuation of protease inhibitor therapy or substitution with another protease inhibitor drug would result in regression of a cervical fat pad. The only patient in this series in whom therapy was discontinued (patient 5) did not evidence regression of his neck mass. Until further information regarding the etiology and natural history of these lesions is available, it is difficult to offer recommendations with regard to antiretroviral therapy for patients who develop cervical neck masses while receiving protease inhibitors. Long-term clinical trials and postmarketing surveillance of these drugs should help define the frequency of occurrence and the optimal management of this unusual complication.

References