Indinavir-Associated Interstitial Nephritis and Urothelial Inflammation: Clinical and Cytologic Findings

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The objective of the present study was to characterize the genitourinary syndromes that accompany indinavir-associated pyuria. Of 23 indinavir-treated patients with persistent pyuria, 4 had isolated interstitial nephritis, 10 had both interstitial nephritis and urothelial inflammation, 7 had isolated urothelial inflammation, and 2 had pyuria with nonspecific urinary tract inflammation. A total of 21 patients had multinucleated histiocytes identified by cytologic testing of urine specimens. Urine abnormalities resolved in all 20 patients who stopped receiving indinavir therapy. Pyuria continued in the 3 patients who continued receiving indinavir. Six patients had elevated serum creatinine levels, which returned to baseline levels when indinavir was discontinued. In conclusion, indinavir-associated pyuria was frequently associated with evidence of interstitial nephritis and/or urothelial inflammation, multinucleated histiocytes were commonly present in urine specimens, and cessation of indinavir therapy was associated with prompt resolution of urine abnormalities.

Several renal syndromes have been associated with the use of indinavir since its introduction for use in therapy for HIV type 1 (HIV-1) infection [1]. Nephrolithiasis affects ~4% of patients who receive indinavir and may induce obstructive uropathy and acute renal failure [2–7]. Indinavir is also associated with asymptomatic crystalluria in up to 67% of patients. Asymptomatic crystalluria may be continuous in some patients, but it is more typically intermittent [8–10]. Crystal formation within the urinary tract is also associated with flank pain and parenchymal defects visible on CT scans; these defects typically resolve within a few weeks after fluid intake is increased, with or without cessation of therapy. Some patients with this clinical syndrome have had reversible renal dysfunction. Indinavir therapy has recently been associated with altered cytologic appearance of urinary transitional cells, including hyperchromatism and nuclear polymorphism [11]. Unlike indinavir, other protease inhibitors have rarely been associated with renal complications [12, 13].

Indinavir therapy has also been associated with pyuria, which sometimes involves acute to subacute renal dysfunction in the absence of evidence of urinary obstruction caused by calculus or crystalline material [14, 15]. In some cases, pyuria has been associated with symptoms of allergic interstitial nephritis, including fever, abdominal pain or flank pain, eosinophilia, and eosinophiluria. Other patients have lacked these symptoms and signs and have presented with pyuria or elevated serum creatinine levels. The findings of examinations of renal biopsy specimens have been reported for 11 patients and have generally revealed interstitial...
edema with indinavir crystals and inflammatory cells, including foreign-body giant cells (multinucleated histiocytes) [16–22]. Some patients have presented with renal atrophy, possibly caused by chronic interstitial nephritis [23, 24]. Boubaker et al. [25] found that 20 patients (19%) who received indinavir developed elevated serum creatinine levels; 18 of these 20 patients had abnormal findings in urine, including pyuria. Similarly, Sarcletti et al. [20] reported that 18% of patients who received indinavir developed elevated serum creatinine levels, frequently in association with pyuria. Recently, Gagnon et al. [26] described 5 patients who had persistent pyuria while receiving indinavir, 3 of whom had elevated creatinine levels. Thus, pyuria and interstitial nephritis are common complications of indinavir therapy.

In this article, we describe 23 patients receiving indinavir who developed persistent pyuria and who were observed for periods of up to 4 years after the identification of pyuria. All patients lacked flank pain or dysuria. We defined the 2 clinical syndromes as follows: “interstitial nephritis” was diagnosed in patients with elevated serum creatinine levels or cellular casts in urine, and “urothelial inflammation” was diagnosed in patients with transitional cell clusters in urine. We found that both syndromes are common in patients with indinavir-associated pyuria.

MATERIALS AND METHODS

Case and syndrome definitions. The study population included patients with HIV-1 infection who presented at the Warren Grant Magnuson Clinical Center of the National Institutes of Health (NIH; Bethesda, MD). All patients participated in protocols that were approved by the appropriate institutional review boards; informed consent for the studies described in this article was obtained from all human subjects, following protocols that were approved by the appropriate institutional review boards, following protocols that were approved by the appropriate institutional review boards, following protocols that were approved by the appropriate institutional review boards, following protocols that were approved by the appropriate institutional review boards, following protocols that were approved by the appropriate institutional review boards.

Subjects’ records were reviewed to determine the date that indinavir therapy was started, the results of prior urinalyses, and serum creatinine levels. Patients with indinavir-associated pyuria were prospectively observed while they were receiving indinavir. Patients who discontinued use of indinavir were observed for ≥12 months, with the exception of 2 patients, one of whom was observed for 5 months and the other for 8 months; pyuria resolved in both of these patients. “Resolution of pyuria” was defined as the absence of pyuria for a period of 12 months, either after stopping or continuing receipt of indinavir therapy.

We defined 2 clinical-pathologic syndromes that occurred in patients with indinavir-associated pyuria. First, we defined interstitial nephritis as the presence of either an elevated serum creatinine level without other apparent cause (such as hemodynamic effect associated with medication) or as urinary cellular casts, composed of RBCs, WBCs, or tubular epithelial cells (figure 1A). Second, urothelial inflammation was diagnosed if any urine cytologic examination revealed transitional epithelial cell clusters (figure 1B). Patients were classified as having interstitial nephritis, urothelial inflammation, both syndromes, or neither syndrome.

Laboratory assessment. Baseline laboratory values were those obtained at the time indinavir therapy was initiated or, if such values were not available, those obtained at the earliest time at which data were available before the onset of pyuria. Eosinophilia was defined as a ≥3-fold increase over the baseline value. The total eosinophil count was obtained from a complete blood count determined by means of an automated leukocyte differential (Cell-Dyn 4000; Abbott Laboratories). Serum creatinine levels were measured with a Hitachi 917 (Hitachi/Roche Diagnostics; normal values, 0.9–1.4 mg/dL, for men, and 0.7–1.3 mg/dL, for women). An elevated serum creatinine level was defined as an elevation of ≥0.3 mg/dL over the baseline value sustained for ≥2 measurements on different days. Urinalysis was performed by use of an IRIS workstation (Yellow IRIS Model 500; International Remote Imaging Systems), which uses a flow cell to count leukocytes and reports these values as cells per high-power field. If IRIS analysis did not reveal any indinavir crystals and the patient was receiving indinavir, a 6-ml aliquot of urine was centrifuged at 400g for 5 min [9]. The sediment was resuspended in 1 mL of urine and was examined under low-power (×100) magnification. Indinavir crystals were identified by the characteristic shapes, including “needles,” “plates” with irregular edges, and “fan,” “bow tie,” and “star burst” forms, as described elsewhere [10]. Blood and urine tests were performed at various intervals, as determined by protocol specifications or clinical indications; in general, they were performed every 2–4 months. For patients with abnormal values, such as those indicative of pyuria or elevated serum creatinine levels, determinations were made more frequently.

Cytologic examination was performed with voided urine samples, including (+ SD) 2.2 ± 1.5 samples (range, 1–7) obtained from patients receiving indinavir and 1.2 ± 0.8 samples (range, 0–3) obtained from patients who had discontinued use of indinavir. Urine samples were fixed in alcohol, centri-
Figure 1. Urine sediment findings. The presence of cellular casts—which were, in this case, composed of leukocytes—was taken as evidence of interstitial nephritis (Wright stain; original magnification, ×120; A). Transitional cell clusters (umbrella cells) were taken as evidence of urothelial inflammation. Transitional cell clusters are distinguished from multinucleated histiocytes by the presence of individual cells within the clusters; nuclei are present at different planes of focus, which indicates that the nuclei are located within individual cells (Papanicolau stain; original magnification, ×150; B). Indinavir crystals appeared both isolated and associated with adherent mononuclear cells (crossed-polarization optics; original magnification, ×80; C). Occasionally, leukocytes were observed to have partially ingested indinavir crystals (crossed-polarization optics [original magnification, ×120; D] and Papanicolau stain [original magnification, ×120; E]). Multinucleated histiocytes (arrowheads) were characterized by a single giant cell that contained tightly clustered nuclei that were located at a similar plane of focus (Wright stain; original magnification, ×150; F). A multinucleated giant cell (arrowhead) stained with antibody to CD68 (immunoperoxidase technique that used a brown diaminobenzidine product, hematoxylin counterstain; original magnification, ×160; G). As expected, multinucleated giant cells (arrowhead) did not stain for cytokeratin, whereas transitional cells did stain for cytokeratin (immunoperoxidase technique that used a brown diaminobenzidine product, hematoxylin counterstain; original magnification, ×160; H).
fuged onto slides, and stained with Papanicolaou and/or Wright stain for the identification of tubular epithelial cells, transitional epithelial cells, neoplastic cells, neutrophils, eosinophils, and multinucleated histiocytes. Immunoperoxidase staining for CD68 (by use of monoclonal antibody KP1; Dako), a marker of mature macrophages, and cytokeratin (by use of monoclonal antibodies AE1 and AE3; Boehringer Mannheim), a marker for tubular epithelial and transitional epithelial cells, was performed when a sufficient sample was available. Cellular casts (composed of erythrocytes, leukocytes, or unidentified cells), transitional cell clusters, and urinary eosinophils were identified on the basis of urine cytologic criteria.

**Statistics.** Data are presented as mean values ± SDs. Frequency differences were compared by use of Fisher’s exact test with Instat software (Graphpad).

**RESULTS**

A total of 671 patients received indinavir at the NIH during the period from January 1995 through December 1998. We identified 23 patients (3.4%) who had conditions that met our case definition for indinavir-associated pyuria. These patients included 18 men and 5 women, aged 41 ± 9 years (table 1). Pyuria first developed after 16 ± 9 months of receipt of indinavir therapy (range, 0.25–32 months). Pyuria lasted for 14 ± 12 months, although, in some patients, it was only intermittent. Typical indinavir crystals were present on ≥1 occasion in 22 patients (92%); they were absent only in patient 10. Leukocytes were frequently found in association with these crystals (figure 1C–E). No patient underwent urologic cystoscopy during the course of the present study, and no patient had urinary cell findings that suggested malignancy. Renal ultrasonography was performed for 10 patients; 1 calculus was identified in a patient who did not have urinary tract symptoms.

Of the 23 patients with indinavir-associated pyuria, 14 (61%) had conditions that met our case definition for interstitial nephritis and 17 (74%) had conditions that met our case definition for urothelial inflammation. Four patients had isolated nephritis, 10 had both interstitial nephritis and urothelial inflammation, and 7 had isolated urothelial inflammation. Two patients did not meet the criteria for either syndrome.

Increased serum creatinine levels developed in 6 patients, with a median increase of 0.6 mg/dL (table 1). Of these 6 patients, 1 had isolated interstitial nephritis and 5 had both interstitial nephritis and urothelial inflammation. For all 6 patients, indinavir was discontinued and serum creatinine levels returned to the baseline value after a median duration of 4 weeks. Eosinophilia was present in 2 patients who had evidence of both nephritis and urothelial inflammation (peak eosinophil count for patient 5, 720 cells/µL; peak eosinophil count for patient 12, 1320 cells/µL). Eosinophilia was present in 14 patients (61%), although eosinophilia was absent in 1 patient (patient 12) with peripheral eosinophilia. Eosinophilia was present in 3 of 4 patients with isolated interstitial nephritis, 7 of 10 patients with nephritis and urothelial inflammation, 4 of 7 patients with isolated urothelial inflammation, and 0 of 2 patients with neither syndrome.

Multinucleated histiocytes (also known as “giant cells”; figure 1F) were present in 21 patients (91%), and they were absent in 2 patients who had isolated urothelial inflammation (patients 20 and 21). In 11 cases, sufficient urinary cells were available for immunostaining to detect CD68, a marker for the macrophage lineage. In 9 cases, these multinucleated histiocytes were shown to express CD68 (figure 1G). In 2 cases, the results of staining with antibodies to CD68 were negative, leaving the identity of these cells as multinucleated histiocytes unconfirmed. In contrast, transitional epithelial cell clusters uniformly revealed cytokeratin on immunoperoxidase staining (figure 1H). There was no difference (P = .10, by Fisher’s exact test) in the presence of multinucleated histiocytes between patients with nephritis (with or without urothelial inflammation; 14 of 14 patients), and those with only urothelial inflammation (5 of 7). Thus, the presence of multinucleated histiocytes did not help localize the site of inflammation and cannot be specifically shown by these data to be a marker for nephritis.

To measure the prevalence of multinucleated histiocytes in the general medical population, we reviewed our institution’s reported cytologic data from 306 voided urine samples obtained from patients without HIV infection during a 12-month period. None of these urine samples contained multinucleated histiocytes. We also reviewed the results of 19 cytologic examinations of urine samples obtained from 16 HIV-infected patients who were not receiving indinavir; 1 of these samples had multinucleated histiocytes. This patient had received indinavir >18 months prior to the finding of multinucleated giant cells. He has continued to have unexplained persistent pyuria, although multinucleated histiocytes have not been seen on 4 subsequent cytologic examinations of urine samples. The difference in the detection of multinucleated histiocytes in indinavir-treated patients with pyuria compared with patients who were not receiving indinavir was highly significant (P < .0001, by Fisher’s exact test).

After 20 patients stopped receiving indinavir therapy, urinary abnormalities resolved. In most patients, this happened within 1 month; in all patients, this happened within 4 months. Three patients (patients 14, 20, and 21) continued to receive indinavir for 18, 28, and 39 months, respectively, after the appearance of indinavir-associated pyuria. All 3 patients still have pyuria.
Table 1. Characteristics and laboratory findings for 23 HIV type 1–infected patients with indinavir-associated pyuria who attended the Warren Grant Magnuson Clinical Center of the National Institutes of Health.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th>Age in years, sex</th>
<th>Duration of indinavir therapy at onset of pyuria, months</th>
<th>Peak leukocyte level in urine, cells/hpf</th>
<th>Eosinophiluria</th>
<th>Serum creatinine level, mg/dL</th>
<th>Cellular casts</th>
<th>Transitional cell clusters</th>
<th>Duration of pyuria, months</th>
<th>Indinavir therapy status</th>
<th>Outcome (serum creatinine level, mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IN</td>
<td>51, M</td>
<td>11</td>
<td>21–40</td>
<td>–</td>
<td>1.0, 1.6</td>
<td>WBC</td>
<td>–</td>
<td>27</td>
<td>Stopped</td>
<td>Pyuria resolved (1.1)</td>
</tr>
<tr>
<td>2</td>
<td>IN</td>
<td>44, M</td>
<td>23</td>
<td>21–40</td>
<td>+</td>
<td>–</td>
<td>WBC</td>
<td>–</td>
<td>25</td>
<td>Stopped</td>
<td>Pyuria resolved</td>
</tr>
<tr>
<td>3</td>
<td>IN</td>
<td>44, M</td>
<td>22</td>
<td>21–40</td>
<td>+</td>
<td>–</td>
<td>Mixed</td>
<td>–</td>
<td>7</td>
<td>Stopped</td>
<td>Pyuria resolved</td>
</tr>
<tr>
<td>4</td>
<td>IN</td>
<td>40, M</td>
<td>16</td>
<td>11–20</td>
<td>+</td>
<td>–</td>
<td>Mixed</td>
<td>–</td>
<td>12</td>
<td>Stopped</td>
<td>Pyuria resolved</td>
</tr>
<tr>
<td>5</td>
<td>Both</td>
<td>45, M</td>
<td>21</td>
<td>&gt;40</td>
<td>+</td>
<td>1.0, 1.8</td>
<td>RBC</td>
<td>+</td>
<td>10</td>
<td>Stopped</td>
<td>Pyuria and eosinophilia resolved (0.8)</td>
</tr>
<tr>
<td>6</td>
<td>Both</td>
<td>18, M</td>
<td>26</td>
<td>11–20</td>
<td>+</td>
<td>0.6, 1.1</td>
<td>–</td>
<td>+</td>
<td>6</td>
<td>Stopped</td>
<td>Pyuria resolved (0.7)</td>
</tr>
<tr>
<td>7</td>
<td>Both</td>
<td>40, M</td>
<td>16</td>
<td>11–20</td>
<td>+</td>
<td>0.6, 1.0</td>
<td>–</td>
<td>+</td>
<td>6</td>
<td>Stopped</td>
<td>Pyuria resolved (0.7)</td>
</tr>
<tr>
<td>8</td>
<td>Both</td>
<td>45, M</td>
<td>29</td>
<td>11–20</td>
<td>–</td>
<td>0.7, 1.5</td>
<td>–</td>
<td>+</td>
<td>2</td>
<td>Stopped</td>
<td>Pyuria resolved (0.8)</td>
</tr>
<tr>
<td>9</td>
<td>Both</td>
<td>54, M</td>
<td>32</td>
<td>21–40</td>
<td>+</td>
<td>0.8, 1.3</td>
<td>RBC</td>
<td>+</td>
<td>8</td>
<td>Stopped</td>
<td>Pyuria resolved (0.9)</td>
</tr>
<tr>
<td>10</td>
<td>Both</td>
<td>56, F</td>
<td>15</td>
<td>&gt;40</td>
<td>+</td>
<td>–</td>
<td>WBC</td>
<td>+</td>
<td>48</td>
<td>Stopped</td>
<td>Pyuria resolved</td>
</tr>
<tr>
<td>11</td>
<td>Both</td>
<td>50, M</td>
<td>ND</td>
<td>&gt;40</td>
<td>+</td>
<td>–</td>
<td>Mixed</td>
<td>+</td>
<td>7</td>
<td>Stopped</td>
<td>Pyuria resolved</td>
</tr>
<tr>
<td>12</td>
<td>Both</td>
<td>45, F</td>
<td>10</td>
<td>21–40</td>
<td>–</td>
<td>–</td>
<td>Mixed</td>
<td>+</td>
<td>2</td>
<td>Stopped</td>
<td>Pyuria and eosinophilia resolved</td>
</tr>
<tr>
<td>13</td>
<td>Both</td>
<td>47, M</td>
<td>23</td>
<td>&gt;40</td>
<td>–</td>
<td>–</td>
<td>Mixed</td>
<td>+</td>
<td>5</td>
<td>Stopped</td>
<td>Pyuria resolved</td>
</tr>
<tr>
<td>14</td>
<td>Both</td>
<td>38, M</td>
<td>21</td>
<td>&gt;40</td>
<td>+</td>
<td>–</td>
<td>WBC</td>
<td>+</td>
<td>18</td>
<td>Continued Pyuria intermittent</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>UI</td>
<td>35, M</td>
<td>7</td>
<td>&gt;40</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>7</td>
<td>Stopped</td>
<td>Pyuria resolved</td>
</tr>
<tr>
<td>16</td>
<td>UI</td>
<td>39, F</td>
<td>25</td>
<td>21–40</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>2</td>
<td>Stopped</td>
<td>Pyuria resolved</td>
</tr>
<tr>
<td>17</td>
<td>UI</td>
<td>32, M</td>
<td>5</td>
<td>21–40</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>5</td>
<td>Stopped</td>
<td>Pyuria resolved</td>
</tr>
<tr>
<td>18</td>
<td>UI</td>
<td>38, M</td>
<td>4</td>
<td>&gt;40</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>3</td>
<td>Stopped</td>
<td>Pyuria resolved</td>
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<tr>
<td>19</td>
<td>UI</td>
<td>46, M</td>
<td>19</td>
<td>6–10</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>16</td>
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</tr>
<tr>
<td>20</td>
<td>UI</td>
<td>38, M</td>
<td>17</td>
<td>&gt;40</td>
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<td>–</td>
<td>+</td>
<td>28</td>
<td>Continued Pyuria continued</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>UI</td>
<td>34, M</td>
<td>4</td>
<td>21–40</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
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<td>&gt;40</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>18</td>
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<td>Pyuria resolved</td>
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<tr>
<td>23</td>
<td>Neither</td>
<td>29, F</td>
<td>2</td>
<td>&gt;40</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>11</td>
<td>Stopped</td>
<td>Pyuria resolved</td>
</tr>
</tbody>
</table>

**NOTE.** Diagnoses of interstitial nephritis (IN), urothelial inflammation (UI), both syndromes, and neither syndrome were made in accordance with the criteria described in the Results section. Peak urine leukocyte level was determined by urinalysis, and the presence of eosinophiluria, cellular casts, and transitional cell clusters were detected by cytologic examination of urine specimens. hpf, High-powered field; ND, not determined; +, present; –, not present.
DISCUSSION

In the present study, we have defined 2 overlapping syndromes associated with persistent indinavir-associated pyuria. Interstitial nephritis was present in 14 (61%) of 23 patients who had indinavir-associated pyuria, as evidenced by elevated serum creatinine levels and/or the presence of cellular casts in urine. Elevated serum creatinine levels developed in 6 patients, but we did not observe acute renal failure. Indinavir therapy was discontinued for all 6 patients, and the creatinine levels returned to baseline values. Pyuria did not resolve spontaneously in any patient, but it resolved within 4 months in all 20 patients who discontinued indinavir therapy. Elsewhere, reported findings of renal biopsy examinations for patients with indinavir-associated interstitial nephritis have described tubular casts composed of indinavir crystals and a mononuclear cell infiltrate in the interstitium, including foreign-body giant cells in some instances [17, 18, 21].

Indinavir-associated pyuria was associated with urothelial inflammation, as evidenced by clusters of transitional epithelial cells in 17 (74%) of 23 patients. The presence of transitional cell clusters in voided urine is an abnormal finding and may be seen in patients with cystitis, urinary calculi, and transitional cell carcinoma and in patients who have undergone urologic cystoscopy [27]. We believe that indinavir crystalluria acts as an irritant to the transitional cell urothelium of the lower urinary tract in some patients and initiates inflammation. The location of urothelial inflammation in these patients has not been fully defined but could conceivably be located in the renal calyces, renal pelvis, ureter, bladder, or urethra.

We recognize several limitations in the studies that we have performed. First, the number of urinary cytologic test results available for examination while patients received indinavir ranged from 1 to 7. It is possible that repeated urine examinations for all patients would have increased the number of patients who met the diagnostic categories for interstitial nephritis or urothelial inflammation. Second, the diagnosis of interstitial nephritis can be conclusively made only by examination of renal biopsy specimens, which was not performed for any patients in the present study. Nevertheless, the definition of interstitial nephritis included 2 widely used criteria: presence of an elevated serum creatinine level without other apparent cause and the presence of cellular casts [28].

We observed multinucleated histiocytes in 21 (91%) of 23 patients. Multinucleated histiocytes are an unusual finding in urine samples; they may be associated with multiple myeloma, chronic prostatitis, and xanthogranulomatous pyelonephritis [29]. Chronic inflammation of the bladder wall, such as that induced by local BCG therapy of bladder carcinoma, has been associated with increased numbers of tissue macrophages, some of which appeared as multinucleated histiocytes in tissue specimens [30]. In the present study, the urinary indinavir crystals were occasionally associated with macrophages and multinucleated histiocytes, which suggests phagocytosis by the cells. We did not detect multinucleated histiocytes in urine samples obtained from patients without HIV-1 infection. We did detect multinucleated histiocytes in 1 HIV-infected patient who was not taking indinavir at the time of sample collection. This suggests the possibility that other factors may occasionally cause multinucleated histiocytes to appear in the urine specimens of HIV-infected patients. Nevertheless, the presence of multinucleated histiocytes in the urine sample obtained from a patient receiving indinavir strongly suggests indinavir-associated genitourinary inflammation. The presence of multinucleated histiocytes, however, does not appear to predict the localization of the inflammation to a particular site within the urinary tract.

Eosinophilia was present in 2 patients, one of whom had interstitial nephritis and the other of whom had nephritis and urothelial inflammation. Eosinophiluria was relatively common and did not aid in the localization of inflammation.

The proper management of indinavir-associated pyuria remains to be determined. An appropriate evaluation for possible infectious etiologies should be performed. If pyuria cannot be attributed to an infectious agent, then consideration should be given to replacing indinavir with another antiretroviral agent. When there is evidence for interstitial nephritis—an elevated creatinine level, in particular—it is particularly desirable to stop receipt of indinavir. If the decision is made to continue therapy with indinavir, it is important to observe renal function with frequent assessment of the serum creatinine level. In addition, periodic ultrasonography may detect evidence of renal damage, including increased parenchymal echogenicity and renal atrophy [24]. When there is a persistently elevated serum creatinine level or evidence of structural damage to the kidney, indinavir use should be stopped. After the discontinuation of indinavir use, the patient’s renal function will likely return to normal. In selected cases, renal biopsy may help differentiate interstitial nephritis from urothelial inflammation of the lower urinary tract (i.e., renal pelvis, ureter, bladder, and urethra). A patient without evidence of nephritis may continue to receive indinavir, although the reported presence of premalignant urothelial cells in patients receiving indinavir suggests the need for caution and regular cytologic examination of urine specimens [11]. Given the number of protease inhibitors available and the need for long-term antiretroviral therapy for HIV-infected patients, discontinuation of indinavir is probably the optimal choice. Once indinavir use has been discontinued, pyuria should resolve within 4 months. Persistence of pyuria for >4 months would then suggest another etiology and the need for further evaluation, including possibly renal biopsy and urologic investigation.

In conclusion, indinavir-associated pyuria is commonly associated with evidence of interstitial nephritis and/or urothelial inflammation. Pyuria resolves promptly upon cessation of in-
indinavir therapy and does not resolve when therapy is continued. The presence of multinucleated histiocytes is an unusual finding of urinary cytologic testing and, for patients receiving indinavir, suggests nephritis or urothelial inflammation associated with indinavir use. It is increasingly apparent that indinavir is responsible for a range of clinical syndromes that are a consequence of indinavir crystals aggregating within or irritating the urinary tract, from the renal collecting tubule and the adjacent interstitium (interstitial nephritis), to the renal calyces and pelvis (manifesting as renal stone or sludging of indinavir crystals), to the bladder and/or urethra (cystitis and/or urethritis). Furthermore, patients may remain asymptomatic, despite ongoing tissue injury.

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**References**