mining subcellular localization of HCV-genomic RNA in lymphocytes. The aim of our study was merely to determine whether the cervical smear cells obtained from HCV-seropositive women were infected with HCV genomic RNA. We will include the subcellular staining of HCV-infected cells in our continuing study.

FISH was performed in accordance with the protocol by Pinkel et al. [3]. The sequence of the 5′-fluorescein labeled oligonucleotide probe used in our study is an HCV-specific primer that has been published [4]. HCV contains a positive-stranded RNA genome of ~9401 nucleotides, consisting of a single, uninterrupted, long open-reading frame that encodes a polyprotein of 3010–3011 amino acids. The gene sequence of the nucleocapsid protein is the region of highest stability (97%–100%) in the HCV genome; this suggests that the oligonucleotide probe is the genomic sequence of the nucleocapsid protein. If so, then the FISH signal is due to the presence of viral genomic RNA.

As for the presentation, in table 2 of our article [2], of hemoglobin amounts for the cervical smear samples, the cervical specimens were washed before RT-PCR. Thus, the last wash samples analyzed by PCR were negative for HCV.

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References


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A Cautionary Tale: Fatal Lactic Acidosis Complicating Nucleoside Analogue and Metformin Therapy

Sir—Lactic acidosis with hepatic steatosis is a rare complication of nucleoside analogue reverse-transcriptase inhibitor (NRTI) therapy in HIV-infected patients [1]. Metformin therapy has recently been used to improve the cardiovascular risk profile of patients with HIV infection and lipodystrophy [2]. Lactic acidosis associated with metformin therapy is also rare, and most patients with metformin-associated lactic acidosis have underlying renal, cardiac, or hepatic disease [3]. We report a case of fatal lactic acidosis occurring in an HIV-infected man receiving NRTI and metformin therapy.

A 52-year-old man with advanced HIV infection (CD4 count, 10 × 10⁶ cells/L; HIV-1 load, 295,000 RNA copies/ml; the virus strain was determined to have resistance to all antiretroviral classes by genotype analysis) and previous esophageal candidiasis, Kaposi sarcoma, and cytomegalovirus retinitis, presented 2 months prior to hospitalization with a 2-month history of intermittent nausea, vomiting, abdominal pain, and 10-kg weight loss. His medications were didanosine (300 mg once daily), stavudine (30 mg twice daily), tenofovir (300 mg daily), cotrimoxazole (160/800 mg daily), clarithromycin (500 mg twice daily), and ganciclovir (1 g three times daily). Laboratory investigation revealed elevated levels of carbon dioxide, 20.1 mm Hg. The patient’s venous lactic acid level was 14.6 mmol/L. In addition, he had elevated levels of potassium (7.5 mmol/L) and creatinine (0.2 mmol/L) (see table 1), but amylase and glucose levels were within normal limits.

Antiretroviral therapy and metformin therapy were ceased. Repeated doses of dextrose (50 mL of 50% dextrose), insulin (10 U of Actrapid insulin), calcium gluconate (10 mL of 10% calcium gluconate), and bicarbonate (100 mL of 8.4% bicarbonate) were administered intravenously, together with doses of oral resonium (30 g). Thiamine (20 mg), riboflavin (10 mg), pyridoxine (5 mg), nicotinamide (100 mg), and vitamin C (100 mg) were administered intravenously on 2 separate occasions. Thirty hours after hospitalization, the patient developed cardiac failure and electromechanical dissociation and died.

A possible explanation for the fatal outcome in this case is the combination of NRTI-induced mitochondrial toxicity and rapid recompensation due to the admin-
istration of metformin. It has been suggested that NRTI-associated hepatic steatosis is a manifestation of mitochondrial toxicity that decreases hepatic lactate clearance [4]. In most cases, the reduction in clearance of lactate is compensated for with normal or small elevations of serum lactate levels. In this case, rapid clinical decompensation with lactic acidosis occurred following administration of metformin. Underlying metabolic acidosis and hepatic dysfunction are known to create a predisposition to metformin-induced lactic acidosis [5]. Specific management strategies for NRTI-associated lactic acidosis have not been well defined. Cofactor administration has been described in case reports [6, 7]; however, analysis of efficacy is retrospective and is complicated by the heterogeneity of regimens used [8]. Standardized dosing protocols are lacking [9]. Although clearance of metformin and lactate by hemodialysis is recommended in metformin-associated lactic acidosis [10], a beneficial role for hemodialysis in treating NRTI-associated lactic acidosis is suggested by case reports only [11, 12]. In this instance, the patient requested conservative management, which precluded consideration of hemodialysis or hemofiltration. To our knowledge, there have been no previous reports of lactic acidosis in HIV-infected patients receiving metformin therapy. A recent small prospective study of metformin use among HIV-infected patients also taking NRTIs showed reduction in hyperinsulinemia and body mass index, without evidence of hyperlactatemia during 6 months of follow-up [2]. This case report highlights the need to carefully consider the potential risk of metformin use by patients with any evidence of NRTI-associated mitochondrial toxicity.

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References


Table 1: Laboratory test results for an HIV-infected patient with fatal lactic acidosis complicating nucleoside analogue and metformin therapy.

<table>
<thead>
<tr>
<th>Laboratory value</th>
<th>Normal range</th>
<th>Oct 2001</th>
<th>Dec 2001</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 cell count, cells × 10⁶/L</td>
<td>—</td>
<td>—</td>
<td>10</td>
</tr>
<tr>
<td>HIV-1 virus load, RNA copies/mL</td>
<td>—</td>
<td>—</td>
<td>295,000</td>
</tr>
<tr>
<td>Lactic acid, mmol/L</td>
<td>0.2–1.8</td>
<td>1.8</td>
<td>14.6</td>
</tr>
<tr>
<td>Alkaline phosphatase, IU/L</td>
<td>0–120</td>
<td>95</td>
<td>415</td>
</tr>
<tr>
<td>γ-glutamyl transferase, IU/L</td>
<td>&lt;50</td>
<td>216</td>
<td>563</td>
</tr>
<tr>
<td>Alanine aminotransferase, IU/L</td>
<td>&lt;55</td>
<td>285</td>
<td>74</td>
</tr>
<tr>
<td>Aspartate aminotransferase, IU/L</td>
<td>0–50</td>
<td>313</td>
<td>82</td>
</tr>
<tr>
<td>Total bilirubin, mmol/L</td>
<td>0–19</td>
<td>12</td>
<td>153</td>
</tr>
<tr>
<td>Potassium, mmol/L</td>
<td>3.5–5.5</td>
<td>3.8</td>
<td>7.5</td>
</tr>
<tr>
<td>Bicarbonate, mmol/L</td>
<td>22–30</td>
<td>26</td>
<td>9</td>
</tr>
<tr>
<td>Creatinine, mmol/L</td>
<td>0.05–0.11</td>
<td>0.10</td>
<td>0.20</td>
</tr>
</tbody>
</table>

NOTE. Results obtained in Oct 2001 were obtained 2 months before presentation. Results obtained in Dec 2001 were obtained at admission to the hospital.