Unexplained Hemolytic Anemia with Multiorgan Failure

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CASE

A 51-year-old white male with history of osteoarthritis, hypertension, and insomnia presented to the hospital with a 1-month history of fatigue, as well as a 1-week history of back pain, nausea, and dark urine. The patient worked as a construction contractor and lived with his wife. His family history was limited to his mother having diabetes. He was taking scheduled hydrochlorothiazide and celecoxib and taking zolpidem as needed. In addition, he was also taking a wide variety of nonprescribed nutritional supplements.

At presentation, the patient had a decreased hemoglobin concentration of 3.5 g/dL [reference interval (RI), 13.5–17.5 g/dL, with a baseline hemoglobin value of 12 g/dL obtained 6 months previously], a reticulocyte count of 1.2% (RI, 0.7%–3.2%), a total bilirubin value of 17.6 mg/dL (RI, 0.2–1.2 mg/dL), a direct bilirubin value of 4.6 mg/dL (RI, 0–0.5 mg/dL), a lactate dehydrogenase activity of 693 U/L (RI, 0–248 U/L), and a positive result in a direct antiglobulin test for IgG. His haptoglobin concentration was <30 mg/dL (RI, 48–224 mg/dL). A peripheral blood smear from the patient had 1 or 2 schistocytes and 1 or 2 spherocytes per high-power field, a typical platelet morphology, and hyperlobated neutrophils. He was transferred to an intensive care unit 2 days after presentation.

Treatment with intravenous immunoglobulin and methylprednisolone was initiated for immune hemolytic anemia. A bone marrow biopsy showed erythroid hyperplasia. His values for red blood cell folate, serum vitamin B12, C3, C4, rheumatoid factor, and red blood cell glucose-6-phosphate dehydrogenase activity were within their respective RIs, and the results of serum cell glucose-6-phosphate dehydrogenase were received rituximab, cyclophosphamide, and then plas-}

QUESTIONS TO CONSIDER

1. What are the symptoms and laboratory test results associated with AIHA?
2. Are the laboratory test results and the clinical course of this case consistent with AIHA?
3. What additional laboratory testing should be performed on available antemortem blood samples in this case to explore potential causes of the patient’s symptoms?

mapheresis, in addition to methylprednisolone and intravenous immunoglobulin to treat his ongoing anemia. The patient was given transfusions of packed red blood cells as needed. His hemoglobin concentration increased to 8 g/dL. A course of antibiotics was started for presumed sepsis, although initial blood and urine cultures did not yield any evidence of infection.

Despite continued aggressive treatment for presumed autoimmune hemolytic anemia (AIHA), the patient developed progressive hepatic, renal, and respiratory problems with marked acidosis requiring multiple transfusions of platelets and fresh frozen plasma, hemodialysis, and endotracheal intubation. Before dialysis, the patient’s serum creatinine concentration rose to 3.6 mg/dL from 1.1 mg/dL (RI, 0.6–1.3 mg/dL) at transfer 3 days previously. The patient’s alanine aminotransferase and aspartate aminotransferase activities, although within the RIs at the time of transfer, increased slightly to 86 U/L (RI, 5–45 U/L) in the case of alanine aminotransferase and substantially to 257 U/L (RI, 15–41 U/L) for aspartate aminotransferase. Samples submitted for electrolyte analysis consistently exhibited hemoglobin concentrations >200 mg/dL (RI, 0–10 mg/dL) according to spectrophotometric index analysis (Synchron DxC; Beckman Coulter). The direct bilirubin concentration increased to >50 mg/dL (RI, 0–0.5 mg/dL). His platelet count decreased from 247 × 10^3/μL to 108 × 10^3/μL (RI, 150–500 × 10^3/μL). Additionally, the patient experienced respiratory failure. His refractory multiorgan system dysfunction continued its aggressive course until his death 4 days after transfer.

The postmortem examination revealed organizing thrombi and multifocal hemorrhages with acute inflammatory infiltrates in most organs, including myocardium, brain, bowel, lungs, and spleen. The liver ex-
hibited diffuse centrilobular congestion and necrosis, and the kidneys exhibited bilateral cortical infarcts and acute tubular necrosis. Cultures of blood and lung tissue were negative.

**DISCUSSION**

The initial symptoms and laboratory findings of hemolytic anemia, depressed hemoglobin and haptoglobin concentrations, increased lactate dehydrogenase, increased indirect bilirubin, and an IgG-positive result in a direct antiglobulin test were all consistent with those typically indicative of warm antibody AIHA, although the reticulocytosis often also associated with AIHA was not noted (1). Antinuclear antibodies sometimes associated with warm antibody AIHA were not observed. Importantly, the speed and severity of the patient’s clinical course and his nonresponsiveness to steroid and rituximab treatment were highly atypical for AIHA (1).

Further laboratory studies were conducted on residual premortem samples to identify processes that might have contributed to the patient’s severe and persistent hemolytic anemia and multiorgan failure. Heavy-metal poisoning is a known potential cause of intravascular hemolysis (2). Heavy-metal testing was performed via inductively coupled plasma mass spectrometry (ICP-MS) analysis of a residual sample of whole blood (containing sodium EDTA) drawn the day before the patient’s death.

Notably, this testing revealed a highly increased cadmium concentration in whole blood of 106.5 µg/L (RI for whole blood, 0–5 µg/L). No increases for other toxic trace elements (lead, mercury, and arsenic) were observed (Table 1). Acute cadmium toxicity is considered to occur at blood concentrations >50 µg/L. Occupational Safety and Health Administration guidelines mandate worker removal from potential sources at a blood concentration of 10 µg/L, which has been demonstrated to cause progressive tubular dysfunction (3, 4).

Cadmium concentrations were also measured in postmortem formalin-fixed tissue sections embedded in paraffin blocks. Two unique formalin-fixed tissue samples (2–4 mg) per organ were digested in equal amounts (0.5 mL) of trace element-grade concentrated nitric acid and hydrogen peroxide at 80 °C for 20 min, and an internal standard (yttrium; Inorganic Ventures) was added. Cadmium concentrations were measured by conventional ICP-MS (PerkinElmer 9000) that had been calibrated from 1–30 µg/L for 114Cd. The results are summarized in Table 2 as the cadmium concentration per dry weight of digested tissue.

A high cadmium concentration was found in 2 kidney cortex sections (mean, 5944 µg/g dry weight). The presence of high cadmium concentrations in tissue samples from the patient effectively ruled out possible contamination of the original blood sample. Formalin fixation of tissue samples has been demonstrated not to affect measured cadmium concentrations (5). Expected results for individuals who have no occupational exposure to cadmium are given in Bush et al. (5).

**Table 1. Results of antemortem heavy-metal testing of whole blood by ICP-MS.**

<table>
<thead>
<tr>
<th>Metal</th>
<th>Result, µg/L</th>
<th>RI, µg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead</td>
<td>3</td>
<td>0–24.9</td>
</tr>
<tr>
<td>Mercury</td>
<td>3</td>
<td>1–10</td>
</tr>
<tr>
<td>Arsenic</td>
<td>4.8</td>
<td>0–62</td>
</tr>
<tr>
<td>Cadmium</td>
<td>106.5</td>
<td>0–5</td>
</tr>
</tbody>
</table>

**Table 2. Cadmium measurements of postmortem tissue sections.**

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Cadmium concentration, µg/g dry weight</th>
<th>(Sample no.)</th>
<th>Mean</th>
<th>Expected value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver (1)</td>
<td>14.8</td>
<td>(1)</td>
<td>13.0</td>
<td>&lt;15</td>
</tr>
<tr>
<td>Heart (1)</td>
<td>7.9</td>
<td>(1)</td>
<td>9.7</td>
<td>&lt;1.0</td>
</tr>
<tr>
<td>Kidney (cortex) (1)</td>
<td>5908</td>
<td>(1)</td>
<td>5944</td>
<td>&lt;200</td>
</tr>
<tr>
<td>Brain (1)</td>
<td>2.8</td>
<td>(1)</td>
<td>3.0</td>
<td>&lt;1.0</td>
</tr>
</tbody>
</table>

* Cadmium concentrations from 2 postmortem formalin-fixed tissue samples from the patient were measured by ICP-MS. As a negative control, 5 additional liver tissue samples from unrelated patients were also tested; these samples exhibited cadmium concentrations <1.3 µg/g dry weight. Expected results for individuals who have no occupational exposure to cadmium are given in Bush et al. (5).
toxicity of cadmium in these tissues is less well described, although hepatotoxic effects have been recognized. Typical nonkidney cadmium concentrations in individuals lacking occupational exposure are <1 μg/g dry weight for brain and cardiac tissue, and <15 μg/g dry weight for hepatic tissue (5).

Severe cadmium poisoning is known to cause substantial renal impairment, nausea, liver damage with increased liver enzymes, pulmonary impairment in cases of inhalation, hemolytic anemia, and thrombosis (3, 4, 6, 7). Long-term poisoning may cause osteomalacia (3). Cadmium exposure also has been associated with anemia by its induction of oxidative stress in red blood cells, reduction of antioxidant enzyme activity, and inhibition of protein synthesis, and it can lead to direct hemolysis, as well as to an increased susceptibility to extravascular lysis (8). In this case, anemia and in vivo hemolysis were noted; these observations are consistent with cadmium poisoning. Concurrent AIHA cannot be excluded, especially in view of the positive IgG result in the direct antiglobulin test, and may have contributed to the severity of the patient’s hemolytic anemia. Furthermore, a wide variety of drugs and other disorders are known to induce AIHA, although cadmium has not been linked directly to AIHA to date (1).

While cadmium is not a common severe toxicant in the general population, there are several potential environmental and occupational sources. Smokers and older individuals can exhibit relatively higher blood concentrations of cadmium, but they generally remain <10 μg/L. Cadmium has a long half-life in the body (>10 years) (3). Although cadmium is found in some soils and phosphate fertilizers, more common industrial sources of cadmium include pigments in organic compound–based paints and in batteries (3). Severe or chronic exposure can be caused by such activities as electroplating, soldering, welding, making pottery, and auto painting. Ingestion and inhalation are the usual modes of toxic exposure to cadmium. Fumes containing cadmium can lead to pneumonitis, nasal epithelial degradation, and pulmonary congestion resembling emphysema (3, 7). Cadmium contamination has been observed in food and dietary supplements (9).

The clinical symptoms observed in this case, which were consistent with previous reports of cadmium toxicity, manifested primarily as hemolytic anemia and acute tubular necrosis. Although the autopsy report identified the presence of toxic amounts of cadmium in multiple biological samples, the origin of the exposure in this case remains undetermined. Activities related to this patient’s occupation as a construction contractor might have led to occupational exposure to cadmium; other sources cannot be excluded. To our knowledge, the history obtained from the patient and family gave no specific indications regarding the source of cadmium poisoning. Access to the nonprescribed nutritional supplements was not obtained. In the absence of hair samples (not available in this case) or a known source of exposure, one cannot determine definitively whether the exposure was chronic or acute; however, the rapid course of severe symptoms and the observed high concentration of cadmium in the blood are consistent with acute exposure.

Management of severe acute cadmium poisoning is mainly supportive and dependent on the mode of exposure. Chelation therapy with calcium disodium EDTA or dimercaptosuccinic acid may promote cadmium elimination in some cases after acute exposures, but chelation has not been shown to effectively reduce the body burden in cases of chronic exposure (10). Cadmium testing should be considered in cases of unexplained multiorgan failure, hemolytic anemia, and renal impairment.

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or revising the article for intellectual content; and (c) final approval of the published article.

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References


Commentary

Michael E. Mullins*

Humans generally accumulate cadmium extremely slowly throughout their lives. Cadmium concentrations are higher among cigarette smokers than non-smokers, but even tobacco use does not explain this patient’s scenario.

Occupational exposures to cadmium occur primarily in certain industries involving soldering, welding, or other processes with cadmium-containing metal products. This patient’s occupation as a construction contractor does not easily fit this description, however.

The patient’s hobbies, if any, are unknown to us. Even if his hobbies included metal work, it is still unlikely that these activities could have produced cadmium concentrations in the ranges found in this case.

It is possible that one or more of the nutritional supplements could have contributed to the cadmium poisoning. Under federal law, products marketed as dietary supplements are explicitly not regulated by the US Food and Drug Administration. Some dietary supplements have occasionally been the source of poisoning by heavy metals or other toxic substances. However, we have no information that more strongly implicates the dietary supplement, which was not tested for cadmium, so the link remains circumstantial at best. Furthermore, if the patient’s death was due only to contaminated dietary supplements, we would expect others to have been sickened also.

The blood and tissue concentrations were extremely high, and the reported symptoms apparently progressed in the week preceding his presentation for care. Both their acuity and severity suggest acute poisoning.

Was the patient the victim of malicious poisoning by someone with access to cadmium? A few milligrams of cadmium or even less than a milligram of a cadmium salt may be enough to produce fatal toxicity.

With the limited available information, the exact manner of the fatal cadmium exposure remains undetermined.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

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