Case Report

Nicotinic Acid-Induced Toxicity Associated With Cytopenia and Decreased Levels of Thyroxine-Binding Globulin

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We report the occurrence of cytopenia and hypothyroxinemia attributed to decreased levels of thyroxine-binding globulin in patients receiving nicotinic acid. We describe two patients in whom hypothyroxinemia developed while they were taking nicotinic acid; these patients also had decreased levels of thyroxine-binding globulin. Results of all thyroid function tests returned to normal when use of the nicotinic acid was discontinued. In one patient, leukopenia and thrombocytopenia developed during nicotinic acid therapy alone. These conditions were reversed after the drug regimen was discontinued. In another patient, leukopenia and thrombocytopenia developed during combination nicotinic acid and lovastatin therapy. When administration of both drugs was discontinued, the hematologic abnormalities, which could have been due to either nicotinic acid or lovastatin, diminished. We suggest that cytopenia may develop in patients receiving nicotinic acid; thus, thyroid function tests should be interpreted in light of a possible decreased level of thyroxine-binding globulin.

The cholesterol-lowering effect of nicotinic acid was first described by Altschul and associates in 1955. Use of nicotinic acid decreased the incidence of nonfatal myocardial infarction, as shown in the Coronary Drug Project. In a long-term follow-up study, the overall mortality was 11% lower in the group treated with nicotinic acid than in the group that received placebo. Nicotinic acid is inexpensive and available without a prescription; these factors increase the potential for unsupervised use. The associated side effects include hepatotoxicity, intolerance of glucose, hyperuricemia, and gastrointestinal upset. Investigators have shown that if the dose of the drug is initially low and then gradually increased, it is well tolerated. Herein we report three cases of toxic manifestations not previously ascribed to nicotinic acid.

REPORT OF CASES

Case 1.—A 66-year-old woman was referred to the Mayo Lipid Clinic in May 1990 because of a 12-year history of hyperlipidemia and a 3-month period of fatigue and weight loss. She had been treated with diet alone for 10 years. She had had a myocardial infarction in 1979 and had undergone angioplasty in 1988 for recurrent chest pain. Squamous cell carcinoma of the anus was diagnosed in 1987, for which she received radiotherapy—4,500 rad to the pelvis and 1,800 rad to the anus between July and September 1987.

A regimen of slow-release nicotinic acid (Goldline, 500 mg three times a day) was begun in July 1988. Laboratory values obtained before initiation of nicotinic acid therapy were as follows: total cholesterol, 263 mg/dl (upper 75th percentile, 265); triglycerides, 148 mg/dl (upper 95th percentile, 140); high-density lipoprotein cholesterol, 50 mg/dl (normal, 35 to 85); hemoglobin, 12.4 g/dl (normal, 11.6 to 14.9); platelet count, 205 × 10³/mm² (normal, 196 to 451 × 10³); leukocyte count, 6.2 × 10³/mm² (normal, 4.0 to 10.4 × 10³); aspartate aminotransferase, 18 U/liter (normal, 12 to 31); and total thyroxine, 7.8 µg/dl (normal, 5.0 to 12.5) (Table 1).

In September 1988, she returned for a follow-up examination. Laboratory studies yielded the following results: total cholesterol, 268 mg/dl; triglycerides, 153 mg/dl; high-density lipoprotein cholesterol, 48 mg/dl; hemoglobin, 13.2 g/dl; platelet count, 205 × 10³/mm²; leukocyte count, 2.8 × 10³/
mm\(^3\); and aspartate aminotransferase, 17 U/liter. Cholestyramine was added to the treatment regimen, and the dosage of nicotinic acid was increased to 500 mg four times a day. Because of the development of constipation, cholestyramine therapy was discontinued, and treatment with lovastatin (20 mg daily) was instituted in December 1988. The dose of nicotinic acid was unchanged.

In April 1989, laboratory values were as follows: total cholesterol, 109 mg/dl; triglycerides, 52 mg/dl; high-density lipoprotein cholesterol, 57 mg/dl; hemoglobin, 13.6 g/dl; platelet count, 151 x 10\(^3\)/mm\(^3\); and aspartate aminotransferase, 72 U/liter. Lovastatin therapy was discontinued, but the dose of nicotinic acid remained unchanged. The level of the aspartate aminotransferase returned to normal, but the leukocyte count remained between 2.5 and 2.9 x 10\(^3\)/mm\(^3\) and the platelet count between 129 and 158 x 10\(^3\)/mm\(^3\).

In May 1990, when she came to the Mayo Lipid Clinic, laboratory values were as follows: total cholesterol, 103 mg/dl; triglycerides, 63 mg/dl; high-density lipoprotein cholesterol, 29 mg/dl; hemoglobin, 11.8 g/dl; platelet count, 112 x 10\(^3\)/mm\(^3\); leukocyte count, 2.5 x 10\(^3\)/mm\(^3\); aspartate aminotransferase, 92 U/liter; and alkaline phosphatase, 455 U/liter (normal, 119 to 309). Serum total thyroxine was 2.6 \(\mu\)g/dl, and thyroxine-binding globulin was 3.1 \(\mu\)g/dl (normal, 16 to 24). Nicotinic acid therapy was discontinued; 4 months later, results of liver function tests and thyroid function tests were normal (total thyroxine, 6.8 \(\mu\)g/dl). Six months after use of the drug had been discontinued, the leukocyte count had increased to 3.5 x 10\(^3\)/mm\(^3\), and the platelet count was 181 x 10\(^3\)/mm\(^3\). The automated differential count was 54.4% granulocytes, 38% lymphocytes, and 7.6% monocytes. Eleven months after the nicotinic acid therapy was discontinued, the leukocyte count was 4.3 x 10\(^3\)/mm\(^3\), and the platelet count was 239 x 10\(^3\)/mm\(^3\).

**Case 2.**—A 51-year-old man was referred to the Mayo Lipid Clinic for evaluation of hyperlipidemia in August 1990. His main complaints were fatigue and weight loss. He had undergone coronary artery bypass grafting procedures in 1980 and in 1987. A strong family history of hyperlipidemia was noted. In 1987, he was treated with cholestyramine, but development of fecal impaction necessitated a change to lovastatin therapy. The dosage was gradually increased to 40 mg twice a day. Slow-release nicotinic acid (KAL) was added, and the dosage was increased to 2.5 g/day.

At the time of examination, laboratory values were as follows: alkaline phosphatase, 33 U/liter (normal, 98 to 251); aspartate aminotransferase, 92 U/liter; cholesterol, 112 mg/dl (upper 75th percentile, 246); triglycerides, 40 mg/dl (upper 95th percentile, 195); platelet count, 92 x 10\(^3\)/mm\(^3\) (normal, 184 to 370 x 10\(^3\)); leukocyte count, 2.1 x 10\(^3\)/mm\(^3\) (normal, 4.1 to 10.9 x 10\(^3\)) with a differential count of 61% granulocytes, 6% bands, 29% lymphocytes, 3% monocytes, and 1% eosinophils. The hemoglobin concentration was normal. No prior laboratory data were available. Both the lovastatin and nicotinic acid regimens were discontinued. Two months later, results of liver function tests were normal; the leukocyte count was 3.4 x 10\(^3\)/mm\(^3\), and the platelet count was 118 x 10\(^3\)/mm\(^3\). At that time, lovastatin therapy (20 mg daily at bedtime) was reintroduced by his local physician. Despite this regimen, the leukocyte and platelet counts continued to increase to 4.6 x 10\(^3\)/mm\(^3\) and 128 x 10\(^3\)/mm\(^3\), respectively. Use of lovastatin was then discontinued because of a rash.

**Case 3.**—In a 62-year-old woman with hyperlipidemia, a regimen of slow-release nicotinic acid (unknown generic

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### Table 1.—Laboratory Findings Related to Various Drug Regimens in 66-Year-Old Woman With Hyperlipidemia (Case 1)*

<table>
<thead>
<tr>
<th>Date</th>
<th>Medications</th>
<th>Leukocyte count ((4.0-10.4 \times 10^3/\text{mm}^3)^{\dagger})</th>
<th>Platelet count ((196-451 \times 10^3/\text{mm}^3)^{\dagger})</th>
<th>Thyroxine-binding globulin ((16-24 \mu\text{g/dl})^{\dagger})</th>
<th>Total thyroxine ((5.0-12.5 \mu\text{g/dl})^{\dagger})</th>
<th>Aspartate aminotransferase ((12-31 \text{U/liter})^{\dagger})</th>
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<tbody>
<tr>
<td>July 1988</td>
<td>None</td>
<td>6.2</td>
<td>205</td>
<td>...</td>
<td>7.8</td>
<td>18</td>
</tr>
<tr>
<td>September 1988</td>
<td>Slow-release nicotinic acid (500 mg t.i.d.)</td>
<td>2.8</td>
<td>205</td>
<td>...</td>
<td>...</td>
<td>17</td>
</tr>
<tr>
<td>April 1989</td>
<td>Slow-release nicotinic acid (500 mg q.i.d.) + lovastatin (20 mg/day)</td>
<td>2.9</td>
<td>151</td>
<td>...</td>
<td>4.4</td>
<td>72</td>
</tr>
<tr>
<td>June 1989</td>
<td>Slow-release nicotinic acid (500 mg q.i.d.)</td>
<td>2.5</td>
<td>129</td>
<td>...</td>
<td>...</td>
<td>18</td>
</tr>
<tr>
<td>May 1990</td>
<td>Slow-release nicotinic acid (500 mg q.i.d.)</td>
<td>2.5</td>
<td>112</td>
<td>3.1</td>
<td>2.6</td>
<td>92</td>
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<tr>
<td>November 1990</td>
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<td>3.5</td>
<td>181</td>
<td>16.4</td>
<td>6.8</td>
<td>20</td>
</tr>
<tr>
<td>May 1991</td>
<td>None</td>
<td>4.3</td>
<td>239</td>
<td>...</td>
<td>...</td>
<td>20</td>
</tr>
</tbody>
</table>

* q.i.d. = four times a day; t.i.d. = three times a day.

† Normal range.
label, 500 mg three times a day) was initiated in September 1989. In October, she complained of fatigue; laboratory studies obtained by her local physician yielded the following results: total thyroxine, 2.0 μg/dl; thyroid-stimulating hormone, 1.0 mIU/liter (normal, 0.4 to 8.0); and aspartate aminotransferase, 70 U/liter. She underwent an extensive assessment by her local physician, including a thyrotropin releasing hormone test and magnetic resonance imaging of the head; results of both were normal. A regimen of levothyroxine sodium was initiated, and she was referred to our institution with a diagnosis of central hypothyroidism.

After levothyroxine therapy was discontinued, laboratory results were as follows: aspartate aminotransferase, 45 U/liter; alanine aminotransferase, 109 U/liter (normal, 9 to 29); alkaline phosphatase, 209 U/liter (normal, 108 to 282); total cholesterol, 231 mg/dl; triglycerides, 109 mg/dl; total thyroxine, 3.5 μg/dl; thyroxine-binding globulin, 3.5 μg/dl; and leukocyte count, 4.3 x 10^3/mm^3. The nicotinic acid therapy was discontinued, and results of liver function tests and thyroid function tests returned to normal or near-normal values 1 month later (total thyroxine, 7.2 μg/dl; thyroxine-binding globulin, 14.6 μg/dl). The patient's symptoms resolved completely.

DISCUSSION
We report three cases of nicotinic acid-induced toxicity associated with cytopenia and hypothyroxinemia. Our three patients also had abnormal results of liver function tests, a finding that has previously been reported in association with nicotinic acid therapy. As in other studies, the hepatotoxicity was reversible after withdrawal of nicotinic acid.

Cytopenia has not previously been reported in patients taking nicotinic acid or a combination of lovastatin and nicotinic acid. Leukopenia and thrombocytopenia are listed in the Physicians’ Desk Reference as possible hypersensitivity reactions to lovastatin. A recent study of 8,425 patients managed with lovastatin, however, detected no evidence of hematologic toxicity. Lovastatin treatment in patients who had undergone renal transplantation caused a 27% increase in the leukocyte count. Cytopenia attributed to drug-induced lupus erythematosus was recently described in two patients receiving only lovastatin.

In our first patient, leukopenia developed after therapy with slow-release nicotinic acid was instituted. The patient was also taking lovastatin, but the neutropenia was present before this regimen was initiated and persisted after it was discontinued. The patient had received radiotherapy for carcinoma of the anus, but the leukocyte count and platelet count returned to normal after withdrawal of the nicotinic acid. The fact that her blood cell count was normal before and low during nicotinic acid therapy and that it returned to normal after the therapy was discontinued suggests that the hematologic abnormality was drug induced.

Our second patient was taking both nicotinic acid and lovastatin. The blood cell count improved when use of these drugs was discontinued. The hematologic toxicity in this patient may have been due to nicotinic acid, but a hypersensitivity reaction to lovastatin cannot be ruled out. Most likely, either drug or a combination of both drugs caused the abnormal blood cell count.

Two of our patients had hypothyroxinemia. One patient (case 3) underwent an extensive workup for central hypothyroidism. Both patients had low levels of thyroxine-binding globulin, which have been shown to be increased in acute hepatitis. In our patients, however, these low levels led to a low concentration of total serum thyroxine. Unlike other types of hepatitis, nicotinic acid-induced hepatotoxicity is associated with a low level of thyroxine-binding globulin. Cashin-Hemphill and colleagues reported a decrease in levels of thyroxine-binding globulin in patients receiving combination colestipol and nicotinic acid therapy. They suggested that this finding may have been due to the combination therapy because decreased levels of thyroxine-binding globulin had not been reported previously in patients taking either drug independently. Our patient was not receiving colestipol; to our knowledge, this is the first reported case of decreased levels of thyroxine-binding globulin in a patient taking only nicotinic acid. Thus, the decrease in the level of thyroxine-binding globulin in the study by Cashin-Hemphill and colleagues may have been due to nicotinic acid and not colestipol. Results of thyroid function tests in patients taking nicotinic acid should be interpreted in light of a possible decrease in the level of thyroxine-binding globulin. Although a decreased level of thyroxine-binding globulin in association with nicotinic acid therapy is rare, knowledge of this effect is important; it would have eliminated extensive and costly diagnostic intervention in one of our patients (case 3).

CONCLUSION
We report the occurrence of nicotinic acid-induced hepatotoxicity in association with cytopenia and hypothyroxinemia attributed to low levels of thyroxine-binding globulin. We suggest that results of thyroid function tests be interpreted cautiously in patients taking nicotinic acid. Clinicians should be aware that cytopenia may be a manifestation of nicotinic acid-induced toxicity.

REFERENCES


