Case 21-2012: A 27-Year-Old Man with Fatigue, Weakness, Weight Loss, and Decreased Libido

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Dr. Fernando M. Contreras (Medicine): A 27-year-old man with a history of obesity was seen in the endocrinology clinic at this hospital because of fatigue, myalgias, weakness, weight loss, and loss of libido.

Thirteen months before presentation, the patient reported weighing 108.9 kg (body-mass index [BMI, the weight in kilograms divided by the square of the height in meters], 35.4) and began aerobic exercises, 2 hours daily, and a calorie-restricted diet (2400 kcal daily), resulting in a loss of 36.3 kg in 10 months. Two months before evaluation, arm weakness, numbness and aching in his legs, decreased libido with loss of morning erections, and a faint lacy rash on his legs developed. He reportedly stopped aerobics, began lifting weights, and increased his caloric intake, without improvement in his symptoms. On evaluation by his physician at another hospital, the white-cell and differential counts and blood levels of calcium, lipids, prolactin, thyrotropin, and vitamin D were normal; testing for IgA autoantibodies to transglutaminase and screening tests for antinuclear antibodies, the human immunodeficiency virus (HIV), viral hepatitis (types A, B, and C), and Lyme disease were negative; and testing for parvovirus suggested past infection.

Other test results are shown in Table 1. Topical testosterone gel was prescribed.

During the next 3 weeks, additional consultations and testing were obtained. Serum levels of alpha-fetoprotein and complement (C3 and C4) were normal; testing for autoantibodies to double-stranded DNA, rheumatoid factor, Ro (SSA), and La (SSB) were negative; other test results are shown in Table 1. Computed tomography (CT) of the chest, abdomen, and pelvis reportedly revealed multiple small gas bubbles in the mediastinum (a finding consistent with pneumomediastinum), decreased intraabdominal and intrapelvic fat, and opacities suggestive of stool throughout the colon. A magnetic resonance imaging (MRI) scan of the pituitary gland was normal. An MRI scan of the abdomen and liver, obtained after the administration of gadolinium, reportedly showed higher signal intensity in the liver than in the spleen, with no evidence of masses, iron overload, ascites, or lymphadenopathy.
Table 1. Laboratory Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference Range, Adults†</th>
<th>Physician's Office</th>
<th>Other Hospital</th>
<th>This Hospital</th>
<th>Other Hospital</th>
<th>This Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8 Wk before Presentation</td>
<td>7 Wk before</td>
<td>5 Wk before</td>
<td>10 Days before</td>
<td>3.5 Wk after</td>
<td>6 Wk after</td>
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<td></td>
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<td>Presentation, Outpatient</td>
<td>Presentation, on Admission</td>
<td>Presentation, on Admission</td>
<td>Presentation, Endocrinology Clinic</td>
<td>Presentation, 2nd Admission</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>41.0–53.0 (men)</td>
<td>42.5</td>
<td>30.3</td>
<td>31.2</td>
<td>29.6</td>
<td>34.3</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>13.5–17.5 (men)</td>
<td>15.3</td>
<td>10.6</td>
<td>10.5</td>
<td>10.1</td>
<td>11.9</td>
</tr>
<tr>
<td>White-cell count (per mm³)</td>
<td>4500–11,000</td>
<td>4400 (ref 4800–10,800)</td>
<td>6000</td>
<td>11,300</td>
<td>5400</td>
<td>6900</td>
</tr>
<tr>
<td>Mean corpuscular volume (μm³)</td>
<td>80–100</td>
<td>88.3</td>
<td>91</td>
<td>91</td>
<td>92</td>
<td>92.8</td>
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<tr>
<td>Platelet count (per mm³)</td>
<td>150,000–400,000</td>
<td>187,000</td>
<td>149,000</td>
<td>344,000</td>
<td>322,000</td>
<td>103,000</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (mm/hr)</td>
<td>0–11 (men)</td>
<td>7 (ref 0–15)</td>
<td>84</td>
<td>20.1</td>
<td>20.6</td>
<td></td>
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<tr>
<td>Prothrombin time (sec)</td>
<td>10.8–13.4</td>
<td></td>
<td>84</td>
<td>20.1</td>
<td>20.6</td>
<td></td>
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<tr>
<td>International normalized ratio for prothrombin time</td>
<td></td>
<td></td>
<td>84</td>
<td>20.1</td>
<td>20.6</td>
<td></td>
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<tr>
<td>Sodium (mmol/liter)</td>
<td>135–145</td>
<td>138</td>
<td>136</td>
<td>136</td>
<td>137</td>
<td>137</td>
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<tr>
<td>Potassium (mmol/liter)</td>
<td>3.4–4.8 (ref 3.6–5.0)</td>
<td>5.3</td>
<td>4.5</td>
<td>4.1</td>
<td>4.1</td>
<td>4.0</td>
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<tr>
<td>Chloride (mmol/liter)</td>
<td>100–108</td>
<td>99</td>
<td>97</td>
<td>97</td>
<td>95</td>
<td>93</td>
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<td>Carbon dioxide (mmol/liter)</td>
<td>23.0–31.9 (ref 22–30)</td>
<td>36</td>
<td>35</td>
<td>37</td>
<td>29.4</td>
<td>35.0</td>
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<tr>
<td>Urea nitrogen (mg/dl)</td>
<td>8–25</td>
<td>37</td>
<td>34 (ref 9–20)</td>
<td>25</td>
<td>29</td>
<td>13</td>
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<tr>
<td>Creatinine (mg/dl)</td>
<td>0.60–1.50</td>
<td>1.22</td>
<td>0.92</td>
<td>0.56</td>
<td>0.69</td>
<td>0.70</td>
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<tr>
<td>Glucose (mg/dl)</td>
<td>70–110</td>
<td>71</td>
<td>75 (ref 75–110)</td>
<td>55</td>
<td>67</td>
<td>73</td>
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*Unless otherwise indicated, reference ranges are from laboratory standards.**
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<tr>
<th>Protein (g/dl)</th>
<th>6.0–8.3</th>
<th>7.1 (ref 6.3–8.2)</th>
<th>7.0</th>
<th>5.1</th>
<th>6.0</th>
<th>7.0</th>
<th>5.9</th>
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<td>Total</td>
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<td>Albumin</td>
<td>3.3–5.0</td>
<td>4.4 (ref 3.5–5.0)</td>
<td>4.4</td>
<td>2.8</td>
<td>3.1</td>
<td>3.8</td>
<td>3.5</td>
<td>3.2</td>
<td>3.5</td>
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<td>Total bilirubin (mg/dl)</td>
<td>0.0–1.0</td>
<td>0.8 (ref 0.2–1.3)</td>
<td>0.8</td>
<td>0.6</td>
<td>0.8</td>
<td>0.8</td>
<td>0.4</td>
<td>2.1</td>
<td>2.8</td>
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<tr>
<td>Direct bilirubin (mg/dl)</td>
<td>0.0–0.4</td>
<td>0</td>
<td>0</td>
<td>0.2</td>
<td>0.1</td>
<td>1.4</td>
<td>2.1</td>
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<td>Alkaline phosphatase</td>
<td>45–115</td>
<td>80 (ref 38–126)</td>
<td>79</td>
<td>138</td>
<td>289</td>
<td>196</td>
<td>109</td>
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<td>(U/liter)</td>
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<td>Aspartate aminotransferase (U/liter)</td>
<td>10–40</td>
<td>97 (ref 17–59)</td>
<td>234</td>
<td>229</td>
<td>103</td>
<td>23</td>
<td>16</td>
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<td>Alanine aminotransferase (U/liter)</td>
<td>10–55</td>
<td>248 (ref 11–66)</td>
<td>382</td>
<td>474</td>
<td>335</td>
<td>57</td>
<td>17</td>
<td>2427</td>
<td>2576</td>
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<td>Lactate dehydrogenase</td>
<td>110–210</td>
<td>855</td>
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<td>(U/liter)</td>
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<td>Creatine kinase (U/liter)</td>
<td>60–400 (men)</td>
<td>210 (ref 55–170)</td>
<td>39</td>
<td></td>
<td>29</td>
<td>752</td>
<td>847</td>
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<td>Creatine kinase isoenzymes (ng/ml)</td>
<td>0.0–6.9</td>
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<td>IgE (IU/ml)</td>
<td>324.0 (ref &lt;114.0)</td>
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<tr>
<td>25-hydroxyvitamin D (ng/ml)</td>
<td>&gt;32</td>
<td>40.11 (ref 30–100)</td>
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<tr>
<td>Follicle-stimulating hormone (mIU/ml)</td>
<td>0.85 (ref 1.4–18.1, men)</td>
<td></td>
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<td></td>
<td></td>
<td>&lt;0.3</td>
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<tr>
<td>Luteinizing hormone (mIU/ml)</td>
<td>0.29 (ref 1.5–9.3, men ages 20–70 yr)</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td>&lt;0.07</td>
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<tr>
<td>Total testosterone (ng/dl)</td>
<td>270–1070</td>
<td>58.04 (ref 241–827)</td>
<td>394 (ref 240–950)</td>
<td>707</td>
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<td>5020 (ref 274–1194)</td>
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<td>Test</td>
<td>Value (Units)</td>
<td>Reference Range</td>
<td>Notes</td>
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<tr>
<td>Free testosterone (ng/dl)</td>
<td>14.6 (ref 9–30)</td>
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<tr>
<td>Aldolase (U/liter)</td>
<td>&lt;7.7</td>
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<tr>
<td>Ferritin (ng/ml)</td>
<td>1520.9 (ref 20–350)</td>
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<tr>
<td>Iron (μg/dl)</td>
<td>45–160</td>
<td>223 (ref 49–181)</td>
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<tr>
<td>Total iron-binding capacity (μg/dl)</td>
<td>230–404</td>
<td>218 (ref 250–450)</td>
<td>Unable to perform test</td>
<td></td>
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<tr>
<td>Transferrin (mg/dl)</td>
<td>170–340</td>
<td>11,063</td>
<td></td>
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<tr>
<td>Corticotropin (pg/ml)</td>
<td>26 (ref 6–43)</td>
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<tr>
<td>Cortisol, morning (μg/dl)</td>
<td>35.43 (ref 4.2–22.4)</td>
<td>35.27</td>
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<tr>
<td>Free triiodothyronine (pg/ml)</td>
<td>1.56 (ref 2.3–4.2)</td>
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<tr>
<td>Free thyroxine (ng/dl)</td>
<td>0.9–1.8</td>
<td>0.8 (ref 0.89–1.76)</td>
<td>1.0</td>
<td></td>
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<tr>
<td>Total triiodothyronine (ng/dl)</td>
<td>60–181</td>
<td>38</td>
<td>42</td>
<td></td>
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<td></td>
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<tr>
<td>Insulin (μU/ml)</td>
<td>2.6–25</td>
<td>2.4</td>
<td></td>
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<tr>
<td>C-reactive protein (mg/liter)</td>
<td>&lt;8.0 for inflammation</td>
<td>8.0 (ref 0–10)</td>
<td>50.1</td>
<td></td>
<td></td>
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<tr>
<td>Total complement (U/ml)</td>
<td>63–145</td>
<td>225</td>
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<tr>
<td>Lipase (U/liter)</td>
<td>13–60</td>
<td>1239 (ref 23–300)</td>
<td>132</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Amylase (U/liter)</td>
<td>3–100</td>
<td>130 (ref 30–110)</td>
<td>118</td>
<td></td>
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<td></td>
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<tr>
<td>Myoglobin (ng/ml)</td>
<td>&gt;1000 (ref 0–110)</td>
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</table>

* Ref denotes reference range at the other facility. To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for bilirubin to micromoles per liter, multiply by 17.1. To convert the values for 25-hydroxyvitamin D to nanomoles per liter, multiply by 2.496. To convert the values for testosterone to nanomoles per liter, multiply by 0.03467. To convert the values for iron and iron-binding capacity to micromoles per liter, multiply by 0.1791. To convert the values for corticotropin to picomoles per liter, multiply by 0.2202. To convert the values for cortisol to nanomoles per liter, multiply by 27.59. To convert the values for free thyroxine to picomoles per liter, multiply by 12.87. To convert the values for free triiodothyronine to picomoles per liter, multiply by 1.536. To convert the values for total triiodothyronine to nanomoles per liter, multiply by 0.01536. To convert the values for insulin to picomoles per liter, multiply by 6,945.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.
Approximately 5 weeks before this presentation, the patient was admitted to the other hospital because of a submandibular abscess in the neck, associated with dental caries. The abscess was incised and drained, and antibiotics were administered, with improvement. Pathological examination of a biopsy specimen of a lymph node showed areas of infarction, necrosis, and acute inflammation, without evidence of cancer. Culture of the tissue grew alpha-hemolytic streptococci. He was discharged on the third hospital day.

The patient reportedly stopped exercising but continued to lose weight. Echocardiography revealed normal left ventricular size and function, and a small pericardial effusion, without tamponade. Two weeks after discharge, a biopsy of the liver was performed; pathological examination of a specimen showed moderate hepatic siderosis, mostly involving macrophages but with a minor hepatocellular component. He was referred to the endocrinology clinic at this hospital.

The patient reported fatigue, intermittent abdominal pain, constipation (one bowel movement weekly for months), swelling in his feet, and decreased testicular size. Pubertal development and previous sexual function had been normal. He had asthma. Medications included transdermal testosterone gel, gabapentin, morphine sulfate as needed for pain, and albuterol by inhalation as needed for asthma. He had no allergies. He had stopped smoking and drinking 1 year earlier. He did not use illicit drugs, including anabolic steroids. He lived with his girlfriend and was receiving disability payments because of his illness; he owned rabbits. His father had type 2 diabetes mellitus, cirrhosis, and hepatitis C virus infection; his mother had anemia; and his son and half-siblings were well. There was no family history of autoimmune disease.

On examination, the patient was cachectic (Fig. 1), with bitemporal wasting. The abdomen was flat and nontender, with striae without pigmentation; the feet were slightly edematous, with a blanching erythematous macular rash on the dorsal surface. Proximal muscles were weak, with severe wasting in the thighs. The pubic-hair distribution was classified as Tanner stage 5; phallic length was 4 cm, and testicular volume was 15 ml (estimated) bilaterally. Urinalysis and blood levels of globulin, phosphorus, vitamin B₁₂, thyroxine, and leptin were normal; other test results are shown in Table 1.

Twelve days later, on evaluation by a rheumatologist, the patient reported diffuse pain (especially in the feet), which he rated at 8 on a scale of 1 to 10, with 10 indicating the most severe pain. On examination, the blood pressure was 103/55 mm Hg, the pulse 56 beats per minute, the temperature 36.6°C, and the weight 51.3 kg (BMI, 16.7). There was poor dentition, severe diffuse muscle tenderness, edematous ankles, decreased strength (4 out of 5) in the ankles and lower legs, nonblanching macular erythematous rash on the thighs, and decreased sensation of light touch over the legs. Testing for antinuclear antibodies was positive at a 1:40 dilution, in a speckled pattern; blood levels of C₃, C₄, vitamin C, cryoglobulins, and immunoglobulins were normal, as were serum protein electrophoresis and urinalysis; and screening for other autoantibodies, antibodies to HIV, and urinary Bence Jones proteins was negative. The patient declined admission for further evaluation.

On follow-up 6 days later, the weight had decreased to 50.2 kg (BMI, 16.3); the patient was admitted to this hospital. Examination revealed painful pitting (1+) edema to the mid-
shins; tenderness of the Achilles’ tendons; xerosis of the legs with nearly platelike scaling, blanchable eczematous erythema on the feet and legs, sparse petechiae and reticulate violaceous discoloration, vertical striae on the abdomen, mild hyperkeratosis with fissuring of both soles, and diminished hair growth on the lower legs. Strength was diminished in the legs more than in the arms; the proximal and distal muscles were affected. Sensation and reflexes were normal. Blood levels of carcinoembryonic antigen and tissue transglutaminase IgA antibodies were normal, as were protein electrophoresis and immunofixation; testing for cryoglobulins and urine porphobilinogens was negative; additional test results are shown in Table 1. Pathological examination of a skin-biopsy specimen was thought to be consistent with morphea. Neuromuscular electromyography revealed bilateral peroneal mononeuropathies, a finding consistent with a focal demyelinating process. The patient was discharged on the second hospital day. Additional testing was performed (Table 1). One month after discharge, examination of biopsy specimens of the sural nerve and skeletal muscle revealed a mild demyelinating neuropathy and myopathic and neurogenic changes in the muscle.

Five days later, the patient felt weak while showering; after lying down, he was unable to arise. Emergency medical services personnel were called. On examination, the capillary blood glucose was reportedly 26 mg per deciliter; glucose was administered intravenously, with a follow-up level of 88 mg per deciliter. He was taken to the other hospital. Respirations were normal. The blood pressure was 114/76 mm Hg, the pulse 42 beats per minute, and the temperature 34.6°C. He was cachectic and had a depressed affect. The oral mucosa was dry. The abdomen was scaphoid (i.e., it had a concave anterior wall) and soft, with a palpable liver edge 3 cm below the costal margin; a lymph node was palpated in the right inguinal region. The skin was slightly jaundiced, with a bleeding laceration on the head, a healed laceration on the arm, petechiae and edema (1+) of the legs, and a stage II sacral decubitus ulcer. The extremities were cool to palpation. Levels of fibrinogen, calcium, magnesium, lactic acid, ammonia, vitamin B₁₂, folate, thyrotropin, thyroxine, troponin T, ceruloplasmin, and alpha₁-antitrypsin were normal; other laboratory-test results are shown in Table 1. An electrocardiogram showed sinus rhythm at 43 beats per minute and T-wave abnormalities in the inferior and anterolateral leads. A barium-swallow examination was normal. CT of the chest revealed extensive pneumomediastinum and associated subcutaneous emphysema. Lung windows revealed bilateral patchy ground-glass opacities, without air bronchograms, and diffuse, bilateral bronchial-wall thickening, with a thin-walled cyst or bulla in the right lower lobe. Soft-tissue windows were notable for marked cachexia and a loss of subcutaneous fat.

After review of the patient's history, findings on examination, and test results, a diagnosis was made.

**Differential Diagnosis**

*Dr. Daniel P. Hunt:* May we review the radiology studies?

*Dr. Alexander R. Guimaraes:* Coronal and sagittal reformatted images of the thorax from a contrast-enhanced CT examination of the chest at the level of the carinal bifurcation show extensive gas throughout the middle and posterior mediastinum, dissecting into the fascial planes of the neck (Fig. 2A and 2B). No evidence of...
pneumoperitoneum or pneumothorax is identified. From the same CT examination, axial images at the level of the lung bases show a pneumatocele at the right lung base and patchy, reticulonodular opacities at the left lung base, in addition to the previously mentioned pneumomediastinum. Differential considerations for pneumomediastinum include post-traumatic causes and postinfectious causes, as well as hyperemesis (in patients with Boerhaave’s syndrome).

Ultrasonography performed for the evaluation of abdominal pain revealed a cystic mass adjacent to the gallbladder, which was incompletely characterized on this examination. As a result, MRI was performed for further characterization. Coronal and axial $T_2$-weighted half-

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**Figure 2. Imaging Studies.**

Coronal (Panel A) and sagittal (Panel B) reformatted CT images of the thorax, obtained in lung windows, show extensive pneumomediastinum (arrows) surrounding the esophagus and trachea and extending to the fascial planes of the neck. Coronal (Panel C) and axial (Panel D) $T_2$-weighted half-Fourier single-shot turbo spin–echo and forced recovery images of the upper abdomen show abnormally low $T_2$-weighted signal in the liver and spleen (white arrows), without a clinically significant loss of signal in the pancreas (black arrows).
Fourier single-shot turbo spin–echo images (Fig. 2C and 2D) show a T₂-weighted, hyperintense mass in the liver, adjacent to and inseparable from the gallbladder. The mass shows mild heterogeneity on T₂-weighted imaging, with no enhancement on T₁-weighted axial images obtained at the level of the mass after the administration of gadolinium. Differential considerations of this mass include a duplicated gallbladder, a complex cyst, or possibly an old hematoma, all benign causes. Incidental note is also made of low signal intensity in the liver and spleen in a pattern that is consistent with hemosiderosis and iron, or heavy metal, in the reticuloendothelial system. The absence of low signal in the pancreas, concomitant with the low signal in the spleen, makes this finding not compatible with primary hemochromatosis.

**Table 2. Problem List.**

- Profound weight loss
- Weakness of the extremities
- Numbness and aching of the legs and abnormal biopsy specimens of the nerves and muscles
- Decreased libido, loss of morning erections, and low levels of follicle-stimulating hormone, luteinizing hormone, and testosterone
- Pneumomediastinum
- Hypotension on evaluation 6 wk before this admission
- Hypothermia
- Hypoglycemia
- Normocytic anemia
- Hypoalbuminemia
- Elevated liver-enzyme levels, with severe elevations at this admission
- Elevated lactate dehydrogenase level
- Mildly elevated lipase and amylase levels
- Episode of submandibular abscess requiring drainage, before this admission
- Poor dentition
- Constipation
- Painful pitting edema of the lower extremities
- History of asthma
- Skin findings, including xerosis, hyperkeratosis of soles, and a sacral ulcer
- Bradycardia
- Thrombocytopenia (late development)
- Elevated prothrombin time
- Abnormal thyroid-function test results
- Abnormal cortisol level

**Medical Differential Diagnosis**

*Dr. Hunt:* This young man has a progressive, severe, subacute illness affecting multiple systems. It is essential to construct a “problem list” (Table 2) of all the issues we need to address to arrive at a unifying diagnosis.

I would like to approach the differential diagnosis for this patient’s underlying illness by using two different constructs. Assuming that each approach yields a similar diagnosis, we will then return to the problem list and make sure that the proposed diagnosis accounts for each problem. It is critical that we maintain an open mind about the diagnosis and not ignore or discard inconsistencies that might point us in a different direction.

**Pneumomediastinum**

It is highly unusual for air in the mediastinum to be incidentally detected in a young man during evaluation for weakness, myalgias, weight loss, and loss of libido. This finding is inconsistent with simple, intended weight loss. There are well-described causes of pneumomediastinum, including exercise or retching¹⁻⁶; however, spontaneous pneumomediastinum has been associated with interstitial lung disease, asthma, bronchiolitis obliterans, chronic obstructive pulmonary disease, cystic lung lesions, or malignant conditions. This patient does not appear to have severe symptomatic asthma or any of the other conditions. There are multiple case reports of spontaneous pneumomediastinum occurring in association with anorexia nervosa.¹⁻³,⁵⁻⁷⁻⁹ Does this patient have anorexia nervosa?

**Weight Loss**

This patient’s illness extended over a period of at least 13 months, and he reported that his weight fell by 33% during a period of 10 months. This is well outside normal weight change for a healthy adult.¹⁰,¹¹ Perhaps it is a consequence of a rigorous exercise program and moderate caloric restriction. However, weight loss continued at a rapid pace even after the patient reported reduced exercise, and it was not recognized as an illness until it impaired his normal function. His physicians were appropriately concerned about many systemic or malignant illnesses. The patient was described as being cachectic, but did he in fact have symptoms of cachexia or, rather, of starva-
morning erections are common in men with anorexia nervosa.

14 of eating disorders include mucosal atrophy, den- 
ing.

elevated ferritin level that improves with refeed-

notable that about one third of patients have an

mia is common in anorexia nervosa, and it is

36.1°C is an indication for hospitalization.

Hypothermia is well described in patients with

anorexia nervosa and may include isolated pero-

cardia, hypotension, diminished cardiac output,

conduction delays, and ventricular arrhythmias.

15 Hypothermia is well described in patients with

anorexia nervosa, and a temperature below

36.1°C is an indication for hospitalization. 16 Anem-

ia is common in anorexia nervosa, and it is

notable that about one third of patients have an

elevated ferritin level that improves with refeeding.

17 Mild thrombocytopenia occurs in 5 to 11% of

patients with anorexia nervosa. 17 Dermato-

logic signs of anorexia nervosa include xerosis,

telogen efflulium, lanugo-like body hair, purpura,

acne, and carotenoderma. 18 Oral manifestations

of eating disorders include mucosal atrophy, den- 
tal erosions, caries, gingivitis, periodontitis, sial-

adenosis, and necrotizing sialometaplasia. 19 Endo-

crine abnormalities in anorexia nervosa include

hypogonadotropic hypogonadism, hypercorti- 
solism, and transient depression of the hypotha-

lamic–pituitary–thyroid axis in nonthyroidal ill-

ness (formerly called euthyroid sick syndrome),

all of which are present in this patient. 20

The final remaining problems on our list in-

clude abnormal liver-enzyme levels and elevated

levels of amylase and lipase. Among patients

with anorexia nervosa, there may be an inverse

relationship between BMI and the degree of eleva-

tion of aminotransferase levels. Several case se-

ries have described marked abnormalities in

liver- and pancreatic-enzyme levels in patients

with anorexia nervosa. 21,22 Encouragingly, refeed-

ing in these case series resulted in prompt im-

provement.

In summary, I believe this young man has

anorexia nervosa. The condition is clearly ad-

vanced, and there is great urgency to begin re-

feeding, with careful monitoring.

PSYCHIATRIC DIFFERENTIAL DIAGNOSIS

Dr. Anne E. Becker: I am aware of the diagnosis in

this case. This patient's medically unexplained,

continued rapid weight loss after presentation

raised concern about an eating disorder. In par-

ticular, his self-reported dietary restriction in the

context of his extremely low weight suggested a

diagnosis of anorexia nervosa, although men do

not usually present with this disorder. 23

Many of the patient's physical findings on

presentation are consistent with severe nutritional

compromise associated with anorexia nervosa

but are diagnostically nonspecific. Although the

patient reported that he had no history of purg-

ing, the finding of dental caries in the context of

these other findings also raises clinical suspi-

cion for undisclosed chronic induced vomiting.

Pneumomediastinum associated with induced

vomiting in patients with anorexia nervosa has

been reported. 24 This patient's reportedly good

appetite was inconsistent with the anorexia of

major depression, and both major depressive

disorder and factitious disorder were ruled out

as the primary diagnosis.

Although a diagnosis of an eating disorder

was suspected, the intense fear of weight gain

that is the sine qua non of anorexia nervosa and
is intrinsic to the core psychopathology of the condition could not be established with certainty for this patient. He reported that he had no history of an eating disorder, rationalized his previous diet and exercise regimen as being motivated by a goal of a “healthier lifestyle,” re- canted his initial report of calorie restriction before this admission, and asserted his intention to gain weight. He even articulated a weight goal of 170 lb (77 kg), which at his height of 175 cm, would have resulted in a BMI of 25.1, a value slightly higher than the ideal range. He described increasing his caloric intake before this admission and adjusting his exercise regimen in order to regain weight. Taken together, his history appeared inconsistent with that of a patient with an intense fear of weight gain.

During the hospital course, however, several behaviors were observed that contradicted and undermined the patient’s stated desire to gain weight. His nurse reported that he was eating only 50% of his meals and that nutritional supplements ordered for him were found, uncon- sumed, in a drawer in his room. On one occasion, vomitus was discovered in the patient’s bathroom, although he denied emesis then and a history of purging. He repeatedly requested to be discharged, despite having been informed of his serious risk of refeeding complications requir- ing inpatient care. This patient’s poor cooperation and limited insight were consistent with his lack of recognition of the serious medical con- sequences of his extremely low weight, a manifesta- tion of a body-image disturbance character- istic of anorexia nervosa.

This patient’s clinical presentation met the definition of eating disorder not otherwise specified (EDNOS), according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR).25 EDNOS is a heterogeneous residual category comprising, among other presentations, subthreshold anorexia nervosa, and it is the most prevalent clinical diagnosis made for an eating disorder.26 However, under proposed criteria for DSM-5, evidence of this patient’s persistent behaviors that interfere with weight gain would most likely support a diagnosis of anorexia nervosa, even without his acknowledgment of any concern about weight.27

### DR. DANIEL P. HUNT’S DIAGNOSES

- Anorexia nervosa.
- Severe malnutrition.
- Acute liver dysfunction due to anorexia nervosa.

### DR. ANNE E. BECKER’S DIAGNOSIS

- Eating disorder not otherwise specified (EDNOS).

### PATHOLOGICAL DISCUSSION

Dr. Joseph Misdraji: A liver-biopsy specimen shows mildly increased lipofuscin pigment in hepa- cytes (Fig. 3A). Prussian blue staining reveals an increased deposition of iron in Kupffer cells and periportal hepatocytes (Fig. 3B). Increased lipofuscin has been reported in cases of anorexia nervosa,22 but it is a common finding in liver bi- opsies and offers little or no diagnostic informa- tion. Increased deposition of iron has also been reported in anorexia nervosa,22,28 although the cause is uncertain. In other forms of starvation, increased iron in the liver has been described, presumably because protein deficiency leads to decreased substrate for hemoglobin synthesis and a reduced demand for iron in the body. Since iron excretion is limited, the unused iron accum- ulates in the liver.

Dr. Anat Stemmer-Rachamimov: Sections of the peripheral-nerve (sural-nerve) biopsy specimen show rare degenerating axons and regenerating clusters, features consistent with active axonal neuropa thy (Fig. 3C). In addition, there are occa- sional lipid-laden macrophages and thinly myelin- ated large axons, features suggestive of a second- ary ongoing demyelinating process. The histologic changes in the peripheral nerve in cases of star- vation or malnutrition are not specific; axonal, demyelinating, and mixed neuropathies may occu- r, since deficiencies of multiple nutrients (min- erals and vitamins) may be involved.29-32

Sections of the gastrocnemius-biopsy specimen show marked variation in fiber size with many scattered atrophic type II fibers. In addition, NADH staining shows a targetoid pattern (cen- tral clearing) that is consistent with neurogenic changes. However, periodic acid–Schiff staining highlights the most striking finding — marked depletion of glycogen in all muscle fibers (Fig.
This finding was confirmed on electron microscopical examination. Glycogen depletion can be seen after intense exercise and may be more pronounced when coupled with magnesium deficiency. Atrophy of type II fibers may be seen in anorexia nervosa, and the neuro-
genic changes are consistent with the axonal neuropathy.

Finally, the skin-biopsy specimen shows clinically significant serous atrophy of the subcutaneous fat, with marked deposition of extracellular mucopolysaccharides (Fig. 3E). These findings are similar to the serous atrophy described in the bone marrow in cases of starvation. In summary, examination of this patient’s skin, muscle, and nerve shows changes that have been reported in starvation. In addition, the muscle-biopsy specimen shows the effects of intense exercise.

Taken together, these findings are consistent with severe malnutrition and starvation.

**DISCUSSION OF MANAGEMENT**

**Dr. Becker:** Acute management priorities in this case of severe nutritional compromise are medical stabilization, treatment of associated complications, and nutritional rehabilitation, preferably by oral refeeding in conjunction with behavioral management. The last intervention requires formulation and implementation of a dietary and behavioral plan to meet energy requirements that result in adequate and controlled weight gain and to correct deficiencies in micronutrients. Hospital-level care is required for medically safe and effective nutritional rehabilitation, since the refeeding syndrome, a potentially lethal complication of anorexia nervosa, can occur in the early stages of refeeding.

Psychosocial intervention in the acute care setting should focus on supporting the immediate medical and nutritional goals, evaluating and treating coexisting mental illness, and engaging the patient in the transition to postdischarge treatment for the eating disorder. Expectations for his participation in weight regain should be made clear to the patient. These expectations would include adherence to a prescribed meal plan, caloric supplements, and restrictions on physical activity or unsupervised bathroom use. This patient may have subverted therapeutic interventions by discarding food and vomiting; clinicians should maintain vigilance for surreptitious behaviors and be prepared to respond therapeutically with psychosocial support and appropriate behavioral interventions.34

**Dr. Rosenberg:** Dr. Contreras, would you tell us how you treated this patient and how he is now?

**Dr. Contreras:** Once we started feeding him, the levels of liver aminotransferases rapidly improved. He remained in the hospital for 25 days and insisted on being discharged. At the time of discharge, his weight was 51 kg. He refused to pursue additional inpatient psychiatric treatment for his eating disorder. He was referred to outpatient treatment with a multidisciplinary team from the psychiatry and nutrition departments, as well as his primary care physician.

**FINAL DIAGNOSIS**

Eating disorder not otherwise specified (EDNOS).

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**REFERENCES**

sign of multiorgan-disorders in severely


