Case 7-2011: A 52-Year-Old Man with Upper Respiratory Symptoms and Low Oxygen Saturation Levels

J. Carl Pallais, M.D., M.P.H., Bonnie T. Mackool, M.D., M.S.P.H., and Martha Bishop Pitman, M.D.

PRESENTATION OF CASE

Dr. Roby P. Bhattacharyya (Medicine): A 52-year-old man was seen in the urgent care outpatient medical clinic at this hospital because of upper respiratory symptoms.

The patient had been in his usual state of health until 3 days earlier, when subjective fever, fatigue, headache, nasal and sinus congestion, sore throat, and a non-productive cough developed. Three days later, he came to the outpatient clinic. He did not have chills, gastrointestinal symptoms, shortness of breath, wheezing, night sweats, or chest discomfort, and he reported that his respiratory symptoms were not as severe as those he had had during a previous episode of pneumonia.

The patient had had type 1 diabetes mellitus for 17 years, for which he was followed at another hospital. Control of blood glucose levels had been poor, despite low hemoglobin A\textsubscript{1c} measurements; glycemic control was followed by measuring the levels of plasma fructosamine. Eight years before this evaluation, he had an episode of prolonged altered consciousness and somnolence, associated with a fasting blood sugar level of 49 mg per deciliter (2.7 mmol per liter); his condition improved slowly after the administration of glucagon and intravenous glucose. Eighteen months before this evaluation, he had an episode of transient expressive aphasia and was treated briefly with valproic acid. He also had hypertension, exercise-induced angina, hyperlipidemia, hyperbilirubinemia of more than 8 years’ duration, glaucoma, and dermatitis herpetiformis, for which he had taken dapsone for more than 8 years. Testing for serum endomysial antibodies had been positive, and he had briefly tried a gluten-free diet but had not adhered to it. He had migraine headaches, atypical chest pains, and peripheral neuropathy with mildly diminished vibratory sensation in his feet. Episodes of elevated aminotransferase levels had occurred 18 months, 8 months, and 2 months before this evaluation, after the initiation of valproic acid, simvastatin, and atorvastatin, respectively. A screening colonoscopy had revealed diverticulosis and a tubular adenoma (4 mm in diameter), which had been excised.

Medications included the human insulin analogue lispro, insulin glargine, dapsone (200 mg daily), lisinopril, metoprolol succinate, and nitroglycerin as needed for chest pain. The patient reported omitting his antihypertensive medications for the 3 days preceding the current evaluation, and he had not taken...
atorvastatin for the previous 2 weeks, nor had he taken aspirin, ranitidine, or latanoprost ophthalmic drops recently. He had received influenza and pneumococcal vaccines in the past. He lived with his wife and worked in an office. His wife had been ill with respiratory and gastrointestinal symptoms approximately 1 week before this evaluation. He drank alcohol moderately, had never smoked, and did not use illicit drugs. His father had died at 52 years of age from metastatic colon cancer, both parents had had hypertension, his mother and sister had migraines, and an uncle had type 1 diabetes; there was no other family history of autoimmune diseases.

On examination, the patient appeared to be comfortable, without respiratory distress. The skin was pale. The blood pressure was 164/75 mm Hg, the pulse 81 beats per minute, the temperature 37.7°C, the respiratory rate 12 to 16 breaths per minute, and the oxygen saturation (tested on multiple digits of both hands and feet) 85 to 90% while the patient was breathing ambient air. The body-mass index (BMI) (the weight in kilograms divided by the square of the height in meters) was 32. Capillary refill occurred in 2 to 3 seconds, and there was no clubbing, cyanosis, or ulcerations. The remainder of the examination was normal. On further review of the patient’s record, the oxygen saturation had been 89% and 86%, 17 months and 15 months before this evaluation, respectively, as measured by pulse oximetry (most likely with different oximeters) while he was breathing ambient air.

The white-cell count, differential count, platelet count, and levels of total protein, albumin, globulin, alkaline phosphatase, and aspartate and alanine aminotransferases were normal; other laboratory-test results are shown in Table 1. A chest radiograph was normal. Fluticasone nasal spray was prescribed, and the patient was discharged with instructions to follow up with his internist for additional laboratory studies.

Two months later, he returned to the outpatient clinic for routine follow-up; he had resumed taking atorvastatin. On examination, he appeared to be comfortable. The respiratory rate was 12 to 16 breaths per minute, and the oxygen saturation 88% while he was breathing ambient air. The BMI was 32.8, and the blood pressure, pulse, and temperature were normal. The remainder of the examination was normal. The white-cell count, differential count, and platelet count were normal. The levels of electrolytes, protein, albumin, globulin, alkaline phosphatase, aspartate

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference Range, Adults†</th>
<th>On Evaluation</th>
<th>2 Mo Later</th>
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<tbody>
<tr>
<td>Hematocrit (%)</td>
<td>41.0–53.0 (men)</td>
<td>41.7</td>
<td>37.8</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>13.5–17.5 (men)</td>
<td>13.8</td>
<td>12.3</td>
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<tr>
<td>Mean corpuscular volume (μm³)</td>
<td>80–100</td>
<td>92</td>
<td>92</td>
</tr>
<tr>
<td>Erythrocyte count (x10⁶/liter)</td>
<td>4.50–5.90 (men)</td>
<td>4.54</td>
<td>4.13</td>
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<td>Red-cell distribution width (%)</td>
<td>11.5–14.5</td>
<td>14.2</td>
<td>15.9</td>
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<tr>
<td>Reticulocytes (%)</td>
<td>0.5–2.5</td>
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<td>6.6</td>
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<tr>
<td>Hemoglobin A₁c (%)</td>
<td>3.80–6.40</td>
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<td>4.70</td>
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<tr>
<td>Calculated mean blood glucose (mg/dl)</td>
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<td></td>
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<tr>
<td>Glucose (mg/dl)</td>
<td>70–110</td>
<td>227</td>
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</tr>
<tr>
<td>Fructosamine (μmol/liter)</td>
<td>200–285</td>
<td>403</td>
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<tr>
<td>Bilirubin (mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>0.0–1.0</td>
<td>2.4</td>
<td>2.6</td>
</tr>
<tr>
<td>Direct</td>
<td>0.0–0.4</td>
<td>0.7</td>
<td>0.8</td>
</tr>
<tr>
<td>Lactate dehydrogenase (U/liter)</td>
<td>110–210</td>
<td>405</td>
<td></td>
</tr>
</tbody>
</table>

* 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.
† 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.
and alanine aminotransferases, calcium, iron, iron-binding capacity, and ferritin were normal, as were hemoglobin electrophoresis, the anion gap, and tests of renal function; other test results are shown in Table 1.

A diagnostic test was performed.

**Differential Diagnosis**

Dr. J. Carl Pallais: I am aware of the diagnosis in this case. Two striking features are the repeatedly low oxygen saturation levels as measured by pulse oximetry (SpO₂), despite the patient’s normal physical examination and chest radiograph, and the unexpectedly low hemoglobin A₁c measurements, despite the patient’s reportedly poor glycemic control and elevated fructosamine levels.

**Causes of Low Oxygen Saturation on Pulse Oximetry**

**Hypoxemia**

Pulse oximeters rely on the differential absorption of oxyhemoglobin and reduced hemoglobin at two wavelengths of light, 660 nm and 940 nm, to estimate the functional saturation of oxygen (oxygen saturation in arterial blood). The functional saturation of oxygen is calculated as oxyhemoglobin divided by the sum of oxyhemoglobin and reduced hemoglobin. By measuring the amount of light absorbed at each wavelength during arterial pulses and factoring out the “static” background absorption, pulse oximeters calculate an arterial absorption ratio that is then converted to oxygen saturation readings with the use of empirically derived data.

Low SpO₂ measurements are a common indicator of hypoxemia. Acute (as opposed to chronic) causes of hypoxemia (e.g., pneumonia and pulmonary embolism) are frequently associated with clinical signs and symptoms, such as air hunger, diaphoresis, tachypnea, and tachycardia. These clinical markers may be masked in several chronic pulmonary and cardiovascular conditions, despite low SpO₂ readings. In this patient, the repeatedly low pulse oximetry measurements over the course of months to years, without acute signs of hypoxemia, suggest a chronic cause. However, the absence of clubbing, jugular venous distention, abnormal cardiac or lung findings on examination, and polycythemia, as well as the normal appearance of the heart and lungs on chest radiographs, argue strongly against chronic hypoxemia. Although chronic hypoxemia can be associated with remarkable clinical compensation, it still leaves patients with limited reserves. In this patient, who probably has a viral infection of the upper airway, the normal vital signs and unremarkable examination provide additional support for the supposition that hypoxemia was not the cause of his low SpO₂ values.

**Measurement Errors**

Without other evidence of hypoxemia, factors that interfere with pulse oximetry measurements need to be considered in this case. The normal physical examination and the multiple low SpO₂ measurements that were made with different devices at different times make it unlikely that technical artifacts or inadequate detection of arterial pulse waves explains the low readings. The normal hemoglobin electrophoresis rules out rare hemoglobin variants that can alter the light-absorption spectra of hemoglobin and produce falsely low SpO₂ readings. Some hemoglobin species, such as sulfhemoglobin and methemoglobin, have characteristic light-absorption spectra that can result in falsely low SpO₂ values. This patient had not been exposed to sulfonamides, but he did take dapsone, which suggests that methemoglobinemia is the cause of the low SpO₂ values.

**Dapsone and Methemoglobinemia**

Methemoglobin is formed when the iron molecule in heme is oxidized from its ferrous (Fe²⁺) form to its ferric (Fe³⁺) state. Methemoglobin normally accounts for less than 2% of total hemoglobin. It is formed at a low rate through the process of oxygen transport, and the rate of formation is balanced by its reduction back to the ferrous state by cytochrome-b₅ reductase. Although methemoglobinemia can be caused by inherited mutations affecting its reduction, acquired causes are much more common and result from increased methemoglobin formation. Dapsone use is one of the most common causes of acquired methemoglobinemia, accounting for nearly half the cases in a large case series. Dapsone undergoes N-hydroxylation by various P-450 enzymes in the liver to form N-hydroxy dapsone, and it is this metabolite, rather than the drug itself, that results in methemoglobinemia. This hydroxylamine product mediates the oxidation of the iron molecule of heme to produce methemoglobin in a dose-dependent fashion.
In the ferric form, the iron in heme cannot bind oxygen and changes the absorption spectrum of hemoglobin, resulting in inaccurate oxygen saturation measurements by pulse oximetry. Since methemoglobin has similar absorption at the 660-nm and 940-nm wavelengths, it alters the absorption ratio of the pulse oximeter and biases it toward an 85% reading. The result is an underestimation of the $SpO_2$ when the true values are above 85%, and an overestimation of the oxygen saturation in patients with hypoxemia below this level. This patient’s $SpO_2$ measurements were all in the range of 85 to 90% and were performed while he was receiving dapsone for dermatitis herpetiformis. These findings point to methemoglobinemia as the most likely cause of his low $SpO_2$ values.

**Methemoglobinemia Symptoms**

Although the presence of methemoglobinemia underestimates the true oxygen saturation in most cases, it can still have clinically significant consequences, as I believe it did in this patient. Methemoglobinemia results in a functional anemia due to the inability of methemoglobin to bind oxygen. In addition, the allosteric effect of methemoglobin on neighboring oxyhemoglobin molecules shifts the oxyhemoglobin dissociation curve to the left, increasing the risk of tissue hypoxia and worsening the clinical effect of anemia. Various clinical manifestations can arise, ranging from asymptomatic cyanosis to death, depending on the degree of methemoglobinemia. During the previous several years, the patient reportedly had headaches, altered mental status, a possible seizure, and chest pain. It is possible that methemoglobinemia contributed to this constellation of symptoms.

**FALSELY LOW HEMOGLOBIN $A_{ic}$ LEVELS**

**Fructosamine and Glycated Hemoglobin**

In this patient with diabetes, the hemoglobin $A_{ic}$ levels were unexpectedly low despite poor glycemic control suggested by the elevated blood glucose and fructosamine levels. The levels of hemoglobin $A_{ic}$ and fructosamine depend on the ability of glucose to covalently bind to free amine groups on proteins. Glycation of circulating proteins produces fructosamine, whereas glycation of the N-terminal valine of the hemoglobin β chain produces hemoglobin $A_{ic}$. Since the rate-limiting step in the formation of both fructosamine and glycated hemoglobin is the glucose level, measurements of both fructosamine and hemoglobin $A_{ic}$ are useful for monitoring glycemic control in patients who have diabetes. Large-scale studies have shown that hemoglobin $A_{ic}$ levels not only accurately reflect the average glucose levels for the preceding 2 to 3 months but are also closely correlated with clinical outcomes. In addition, hemoglobin $A_{ic}$ levels can be used to screen for the presence of diabetes. Although there is a good correlation between hemoglobin $A_{ic}$ and fructosamine levels, measurement of fructosamine provides an estimate of the level of glycemic control during only the previous 2 to 3 weeks; furthermore, the association between fructosamine levels and estimated average glucose levels or clinical outcomes has not been extensively studied, and the fructosamine assays have not been universally standardized. Therefore, fructosamine testing is not widely used to monitor glycemic control and cannot be used to diagnose diabetes.

In this patient, the elevated fructosamine and blood glucose levels were consistent with poor glycemic control, meaning that the hemoglobin $A_{ic}$ readings were likely to be falsely low. Many factors alter hemoglobin $A_{ic}$ measurements (Table 2). The intracellular accumulation of glycated hemoglobin depends on both the glucose level and the red-cell age — young cells will have lower hemoglobin $A_{ic}$ levels than will older cells. Therefore, any process that lowers the average age of the red-cell population by increasing the destruction or production of erythrocytes will lower the hemoglobin $A_{ic}$ levels. In contrast, conditions that permit an increase in the average age of red cells will artificially increase hemoglobin $A_{ic}$ levels. Unlike hemoglobin $A_{ic}$ levels, fructosamine levels are not affected by changes in red-cell survival or production.

**Dapsone and Red-Cell Destruction**

In this patient, dapsone-induced hemolysis and increased reticulocytosis most likely explain the falsely low glycated hemoglobin levels. Just as N-hydroxy dapsone causes oxidation of the heme moiety, it also induces erythrocyte destruction by the formation of reactive oxygen species. The primary defense against oxidative injury in erythrocytes is the glucose-6-phosphate dehydrogenase (G6PD)–NADPH–glutathione pathway, which neutralizes free radicals. In persons with G6PD...
deficiency, dapsone causes severe hemolysis, since less reduced glutathione is available to handle the oxidative injury. Unlike substances that cause hemolysis only in persons with G6PD deficiency, dapsone can cause hemolysis in persons with normal G6PD levels, albeit in a less severe form. Older erythrocytes may be more susceptible to dapsone-induced destruction, owing to waning G6PD activity. This patient had many markers of hemolysis, including unconjugated hyperbilirubinemia, an elevated lactate dehydrogenase level, and reticulocytosis. Since he had only mild anemia despite the moderately high dapsone dose, it is likely that he had normal G6PD activity.

Because older erythrocytes are more susceptible to oxidative injury and contain more glycated hemoglobin than do younger cells, the mechanism by which dapsone induces red-cell destruction may have a particularly profound effect in lowering hemoglobin A\textsubscript{1c} levels. Several case reports have shown that dapsone artificially lowers hemoglobin A\textsubscript{1c} levels.\textsuperscript{24–27} One study of patients with diabetes in whom dapsone was administered after islet-cell transplantation showed that dapsone lowered hemoglobin A\textsubscript{1c} levels but had no effect on fructosamine levels.\textsuperscript{28} This result is consistent with the findings in this patient, who had low-to-normal hemoglobin A\textsubscript{1c} levels despite elevated fructosamine levels.

**SUMMARY**

In summary, dapsone is the likely cause of this patient’s low SpO\textsubscript{2} levels and falsely low hemoglobin A\textsubscript{1c} levels (Fig. 1). This case illustrates the importance of understanding potential pitfalls in the measurement of such values as oxygen saturation and hemoglobin A\textsubscript{1c} and reminds us that clinically significant hemolysis can occur with the use of dapsone, even in patients without G6PD deficiency.

*Dr. Nancy Lee Harris (Pathology): Dr. Bhattacharyya, would you tell us your thinking when you saw this patient?*

*Dr. Bhattacharyya: My reasoning was similar to that of Dr. Pallais. The discordance between the patient’s hemoglobin A\textsubscript{1c} level and his glucose and fructosamine readings, as well as his unconjugated hyperbilirubinemia, made me suspect that dapsone-induced hemolysis was causing the low hemoglobin A\textsubscript{1c} measurements and unconjugated hyperbilirubinemia. A review of hospital records from 2001 subsequently confirmed that his hemoglobin A\textsubscript{1c} level was markedly elevated before he started dapsone therapy. Venous blood showed a methemoglobin level of 9.7%, as measured by CO-oximetry. A subsequent arterial sample showed a partial pressure of arterial oxygen (PaO\textsubscript{2}) that was normal at 83 mm Hg (reference range, 80 to 100) and an oxygen saturation of 96%. The sample was obtained while the patient was breathing ambient air and had an oxygen saturation of 87% as measured by pulse oximetry. A subsequent arterial sample showed a partial pressure of arterial oxygen (PaO\textsubscript{2}) that was normal at 83 mm Hg (reference range, 80 to 100) and an oxygen saturation of 96%. The sample was obtained while the patient was breathing ambient air and had an oxygen saturation of 87% as measured by pulse oximetry, confirming the incorrect pulse oximetry reading. The arterial blood methemoglobin level was 16.5%, and the venous level, in a sample drawn at the same time, was 11.5%. Despite the normal PaO\textsubscript{2} value, the arterial sample had a dark appearance that is characteristic of methemoglobinemia.*

<table>
<thead>
<tr>
<th>Table 2. Factors Affecting Hemoglobin A\textsubscript{1c} Measurements.\textsuperscript{9}</th>
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<tbody>
<tr>
<td><strong>Factors that decrease hemoglobin A\textsubscript{1c} levels</strong></td>
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<tr>
<td>Decreased mean red-cell age</td>
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<tr>
<td>Increased % of young red cells (reticulocytes) owing to erythropoietin therapy, hemorrhage, or hemolysis</td>
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<td>Transfusions</td>
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<td>High doses of vitamins C and E</td>
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<td>Human immunodeficiency virus infection</td>
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<td>Dialysis</td>
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<td>Pregnancy</td>
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<tr>
<td><strong>Factors that increase hemoglobin A\textsubscript{1c} levels</strong></td>
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<tr>
<td>Increased red-cell life span owing to hemolysis (from congenital causes, immune-mediated causes, drugs, or illness such as disseminated intravascular coagulation or malaria), liver disease, or splenomegaly</td>
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<tr>
<td>Iron deficiency</td>
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<td>Increasing age of person</td>
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<tr>
<td><strong>Factors with various effects on hemoglobin A\textsubscript{1c} levels</strong>\textsuperscript{†}</td>
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<tr>
<td>Hemoglobinopathies</td>
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<td>Nonglucose adducts</td>
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<td>Carbamylation (uremia)</td>
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<td>Acetylation (salicylates)</td>
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<td>Acetaldehyde (alcohol)</td>
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<td>Hypertriglyceridemia</td>
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<td>Opiate addiction</td>
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<td>Potential variants</td>
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<tr>
<td>Red-cell permeability</td>
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<td>Glycation efficiency</td>
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\* Data are from Nathan et al.,\textsuperscript{14} Bloomgarden,\textsuperscript{19} NGSP,\textsuperscript{20} and Saudek et al.\textsuperscript{22} \† The effects largely depend on the assay method.*

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DISCUSSION OF MANAGEMENT

Dr. Bhattacharyya: After the diagnosis was established, the issue of how to manage the dermatitis herpetiformis became critical.

Dr. Bonnie T. Mackool: This patient has dermatitis herpetiformis, an intensely pruritic, papulovesicular eruption (called “herpetiform” because of the grouped distribution of vesicular lesions)\textsuperscript{28,30} that typically develops between 30 and 40 years of age, more commonly in men.\textsuperscript{31} Although this patient does not have the gastrointestinal symptoms of celiac disease,\textsuperscript{32-36} dermatitis herpetiformis is an autoimmune condition related to gluten sensitivity,\textsuperscript{34} and as many as 92% of patients reportedly have evidence of gluten-sensitive enteropathy on endoscopy.\textsuperscript{35,36} The intense pruritus and sometimes the burning or stinging associated with lesions of dermatitis herpetiformis severely affect the quality of life, as they did in this patient.

Since dermatitis herpetiformis is a manifestation of gluten sensitivity, the mainstay of treatment is a lifelong gluten-free diet, just as it is for celiac disease.\textsuperscript{37-40} Dietary treatment may alleviate the gastrointestinal symptoms of celiac disease after as short a period as 2 weeks, but cutaneous symptoms typically require 5 to 12 months for partial improvement and up to 2 years for complete improvement with a gluten-free diet alone.\textsuperscript{41} For this reason, dapsone is used during the first several months of a gluten-free diet, until the diet controls the symptoms. Dapsone provides dramatic improvement within 24 to 36 hours, often after the first dose. Side effects, in addition to methemoglobinemia and hemolysis, include agranulocytosis, liver dysfunction, and peripheral neuropathy. Since most side effects are dose-related, the aim is to decrease the dose after several months of a gluten-free diet and eventually eliminate the use of dapsone.\textsuperscript{42,43} A complete blood count and liver-function tests should be performed regularly, and the methemoglobin level should be monitored according to the patient’s symptoms and coexisting conditions.\textsuperscript{43} All potential side effects of dapsone should be discussed with the patient.

Other medications, such as sulfapyridine,\textsuperscript{44,45} colchicine, azathioprine, cyclosporine, tetracycline, nicotinamide, and topical and systemic glucocorticoids, and ultraviolet light may offer some relief from dermatitis herpetiformis, but they are less effective than dapsone. It is crucial that this patient be persuaded to adhere to a gluten-free diet, which will not only prevent the recurrence of dermatitis herpetiformis and eliminate the need for dapsone but also provide protection against the development of gastrointestinal lymphoma, a known and often fatal complication of untreated gluten sensitivity.\textsuperscript{46}

Dr. Bhattacharyya: Dapsone had dramatically improved the patient’s disabling cutaneous symptoms, and he was unwilling to discontinue the medication, despite the associated complications. He indicated that he would rather give up insulin than dapsone. Repeat testing for endomysial antibodies and testing for tissue transglutaminase were positive. Nevertheless, he was strongly opposed to initiating a gluten-free diet, since his diet was already restricted by the diabetes. In consultation with a gastroenterologist, a duodenal biopsy was recommended.

PATHOLOGICAL DISCUSSION

Dr. Martha Bishop Pitman: The patient’s diagnosis of dermatitis herpetiformis had been established 8 years earlier by examination of a 3-mm punch-biopsy specimen of the skin, which revealed accumulations of neutrophils and eosinophils that formed small microabscesses at the tips of adjoining dermal papillae (Fig. 2A). Direct immunofluorescence staining for IgA highlighted a granular deposition pattern at the dermal–epidermal junction, which is the diagnostic hallmark of the disease.\textsuperscript{32,34}

Upper gastrointestinal endoscopy revealed mild erythema and nodularity and subtle scalloping of the plicae circulares in the duodenum. Histologic examination of a biopsy specimen showed blunted and atrophic villi, crypt hyperplasia, and marked intraepithelial lymphocytosis, features that are diagnostic of celiac disease (Fig. 2B, 2C, and 2D).

The patient now has three diagnoses — type 1 diabetes mellitus, dermatitis herpetiformis, and celiac disease — but does he really have three diseases, or just one? Dermatitis herpetiformis is the cutaneous manifestation of celiac disease. Patients with celiac disease, our patient, and most patients with dermatitis herpetiformis have elevated tissue transglutaminase levels, as well as anti–endomysial IgA antibodies in their serum.\textsuperscript{32,47,48} Patients with dermatitis herpetiformis also have antibodies to the closely related epidermal trans-
glutaminase, the purported autoantigen in the skin and the most sensitive serologic marker for dermatitis herpetiformis.\textsuperscript{11,49,50}

In the majority of patients with dermatitis herpetiformis, enteropathy is mild or asymptomatic, resulting in the under diagnosis of celiac disease. After a diagnosis of celiac disease has been established, a diagnosis of dermatitis herpetiformis is made in approximately 5 to 10\% of patients.\textsuperscript{51,52} Examination of intestinal-biopsy specimens obtained from patients with dermatitis herpetiformis and symptoms suggestive of celiac disease has shown that 69\% of these patients have classic evidence of intestinal injury mimicking that of celiac disease, and 93\% have evidence of mucosal injury manifested as intraepithelial lymphocytosis.\textsuperscript{32}

An association between type 1 diabetes mellitus and celiac disease has long been well established, but the high prevalence (approximately 10\% of children and 2\% of adults with type 1 diabetes also have celiac disease) has been reported more recently.\textsuperscript{53} The relationship between these two inflammatory diseases is believed to have both a genetic and an environmental basis. The diseases share an association with the HLA class II locus HLA-DQB1 on chromosome 6p21. Genomewide association studies have identified 8 chromosome regions outside the HLA region in celiac disease\textsuperscript{54} and 15 non-HLA regions in

**Figure 2. Biopsy Specimens and Findings from Upper Gastrointestinal Endoscopy.**

A punch-biopsy specimen of a skin lesion from 8 years earlier (Panel A, hematoxylin and eosin) shows spongiosis of the epidermis and small subepidermal vesicles (inset), with an accumulation of neutrophils and eosinophils forming small microabscesses at the tips of adjoining dermal papillae (arrow), features that are consistent with dermatitis herpetiformis. Upper gastrointestinal endoscopy (Panel B) revealed mild erythema and nodularity and subtle scalloping (arrows) of the plicae circulares in the duodenum. (Image courtesy of Dr. Michael Thiim.) The duodenal-biopsy specimen (Panel C, hematoxylin and eosin) shows blunted and atrophic villi (long arrow), crypt hyperplasia (short arrows), and marked intraepithelial lymphocytosis, features that establish the diagnosis of celiac disease. Immunoperoxidase staining with anti-CD3, which stains T cells brown, highlights the marked intraepithelial lymphocytosis in the damaged villi (Panel D).
patients with type 1 diabetes mellitus.\textsuperscript{55,56} Another study showed seven shared alleles in these two disorders, which suggested a common biologic mechanism.\textsuperscript{57} Combinations of specific alleles, together with epigenetic influences and chance, lead to these various autoimmune-related inflammatory conditions, which may appear as a single condition in some persons and as combined diseases in others.

Thus, this patient may have just one underlying pathobiologic condition, manifested as type 1 diabetes mellitus, dermatitis herpetiformis, and celiac disease.

\textit{Dr. Harris:} Dr. Bhattacharyya, would you tell us what happened with this patient?

\textit{Dr. Bhattacharyya:} Since the patient initially declined to discontinue or lower the dapsone dose, we started treatment with cimetidine. Cimetidine has been shown to decrease dapsone-induced methemoglobinemia by reducing the formation of the toxic hydroxylamine metabolite through the inhibition of several cytochrome P-450 enzymes, without affecting the therapeutic activity of dapsone.\textsuperscript{44} When the patient was receiving high doses of cimetidine, the methemoglobin levels dropped from a range of 9 to 16\% to approximately 6\%. After the results of the duodenal biopsy were reported, the patient’s wife removed gluten-containing foods from the house, so that the patient is on a gluten-free diet at least on weekends. Even though he does not adhere to the diet while at work, we were able to successfully reduce his dose of dapsone to 100 mg per day. One year after the diagnosis, his methemoglobin level was 2.1\%. The lactate dehydrogenase and bilirubin levels have improved but continue to be slightly elevated, and the hemoglobin A\textsubscript{1c} level continues to be low, despite poor glycemic control, so the patient still has dapsone-induced hemolysis. His caregivers are encouraging better adherence to the gluten-free diet.

\textit{Dr. Lloyd Axelowd} (Diabetes Unit): Given the high sensitivity and specificity of serologic tests for celiac disease, what was the indication for a duodenal biopsy?

\textit{Dr. Pallais:} Intestinal biopsy remains the definitive method of establishing the diagnosis of celiac disease, although its role in high-risk persons such as this patient is debated. Since the patient was asymptomatic, he may not have fully appreciated his risk of enteropathy, and this probably contributed to his resistance to start a gluten-free diet. Indeed, after the biopsy, we heard that he modified his diet to decrease his gluten intake.

\textit{Dr. Axelowd:} If a patient adheres to and has a therapeutic response to a gluten-free diet, would it perhaps not be necessary to do a biopsy?

\textit{Dr. Pallais:} That is probably correct.

\section*{ANATOMICAL DIAGNOSES}

Gluten sensitivity, with dermatitis herpetiformis and celiac disease.

Methemoglobinemia and nonimmune hemolysis due to dapsone, resulting in falsely low oxygen saturation levels as measured by pulse oximetry and falsely low hemoglobin A\textsubscript{1c} levels.

This case was presented at the Medical Case Conference.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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