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Case 38-2014: An 87-Year-Old Man with Sore Throat, Hoarseness, Fatigue, and Dyspnea

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PRESENTATION OF CASE

Dr. Leigh H. Simmons: An 87-year-old man with multiple chronic medical problems was seen in an outpatient clinic of this hospital because of sore throat and fatigue.

The patient had been in his usual health until several weeks before presentation, when hoarseness, sore throat, and increasing fatigue developed. At the urging of his family, he was seen by his physician in an outpatient clinic of this hospital. He reported hoarseness, increasing facial puffiness, and periorbital swelling, with no chest pain, dyspnea, or new joint pains or muscle aches.

The patient had hypertension, hyperlipidemia, and chronic kidney disease. Two months earlier, the creatinine level was 2.22 mg per deciliter (196 μmol per liter; reference range, 0.60 to 1.50 mg per deciliter [53 to 133 μmol per liter]), which was stable, as compared with values obtained the previous year. He also had hypothyroidism, with a normal thyrotropin level 8 months earlier (3.38 μU per milliliter [reference range, 0.40 to 5.00]), as well as gastroesophageal reflux disease, esophageal motility disorder, an abdominal aortic aneurysm, chronic back pain, depression related to the death of his wife several years before, and recurrent urinary tract infections. In the past, he had had pneumonia and had undergone angioplasty of the right renal artery (10 years earlier), a cholecystectomy, a lobectomy of the right middle lobe due to a spiculated nodule that was found to be benign, photoselective vaporization of the prostate due to obstructive benign prostatic hypertrophy (2 months before this presentation), and wrist surgery. Medications included atenolol, vitamin D_3, a fluticasone propionate and salmeterol inhaler, aspirin, citalopram, a fluticasone nasal spray, atorvastatin, omeprazole, and levothyroxine. Lisinopril had caused a cough, and zolpidem tartrate had caused nightmares.

The patient was retired and lived alone. He could independently perform activities of daily living, and he managed his own medications. His three children lived nearby and were in frequent contact with him, but he came to most medical appointments unaccompanied. He was under the regular care of an internist, a nephrologist, a cardiologist, and a urologist. Immunizations were up to date. He had stopped smoking many years earlier and did not drink alcohol. His father had died of liver cancer, and a son had sarcoidosis; his two other children were healthy.

On examination, the patient was pleasant, smiling, and in no distress; he spoke

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Table 1. Laboratory Data.*

Variable	Reference Range, Adults†	On Presentation	11 Days after Presentation
Erythrocyte sedimentation rate (mm/hr)	0–13		19
Sodium (mmol/liter)	135–145	137	134
Potassium (mmol/liter)	3.4–4.8	4.2	4.5
Chloride (mmol/liter)	100–108	101	96
Carbon dioxide (mmol/liter)	23.0–31.9	22.3	24.5
Urea nitrogen (mg/dl)	8–25	28	33
Creatinine (mg/dl)	0.60–1.50	3.04	3.08
Alkaline phosphatase (U/liter)	45–115	49	43
Aspartate aminotransferase (U/liter)	10–40	90	163
Alanine aminotransferase (U/liter)	10–55	46	72
Creatine kinase (U/liter)	60–400	2713	5358
Triglycerides (mg/dl)	40–150	190	
Cholesterol (mg/dl)	<200 (desirable)	203	
High-density lipoprotein	35–100	52	
Low-density lipoprotein	<130 (desirable)	113	

* 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 triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.

† 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.

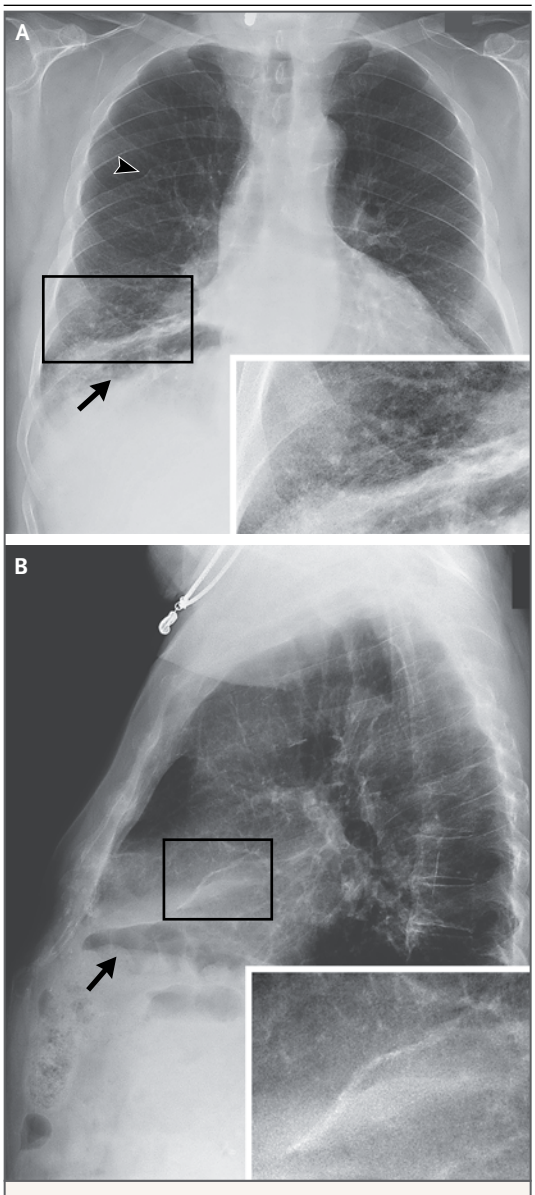

Figure 1. Chest Radiographs.

Frontal and lateral chest radiographs (Panels A and B, respectively) were obtained 11 days after presentation. The box in each panel shows the area that is enlarged in the inset. There are reticulonodular opacities at the base of the right lung (Panel A, inset) and chain sutures from a lobectomy of the right middle lobe (Panel B, inset). Incidentally noted are a healed right-rib fracture (Panel A, arrowhead) and interposition of the transverse colon between the liver and the right hemidiaphragm (Panels A and B, arrows).

with a hoarse voice. The blood pressure was 130/72 mm Hg, the pulse 59 beats per minute, the oxygen saturation 96% while he was breathing ambient air, the weight 86.8 kg (approximately 4.5 kg greater than it had been 1 month earlier), and the body-mass index (the weight in kilograms divided by the square of the height in meters) 29.9. There was facial swelling and periorbital edema; the remainder of the examination was normal. Blood levels of glucose, total protein, albumin, globulin, calcium, phosphorus, and total bilirubin and the plasma anion gap were normal; other test results are shown in Table 1. An appointment with an otolaryngologist was scheduled, and the patient returned home. Two days later, when the results of the laboratory tests were known, he was instructed by his physician to stop taking atorvastatin, and a follow-up appointment was scheduled for 9 days later in the outpatient clinic for repeat blood tests.

Seven days after presentation, the patient called his doctor's office at his daughter's urging to report persistent hoarseness and swelling of his face and abdomen, which he indicated had been present for months but had, according to his daughter, worsened recently. Four days later, 11 days after presentation, he was seen in the outpatient clinic, where he reported markedly worsening fatigue, especially after walking, with associated dyspnea, facial edema, weight gain, cough that produced white mucus, and laryngitis. He reported no chest pain or worsening arthralgias and stated that he was taking all his medications. Chest radiographs were obtained.

Dr. Florian J. Fintelmann: Frontal and lateral chest radiographs (Fig. 1) showed no changes, as compared with chest radiographs and computed tomographic scans obtained 9 months previously. In addition to sutures from the lobectomy of the right middle lobe, there were small reticulonodular opacities at the right base, findings suggestive of scarring due to recurrent aspiration or prior infection. No evidence of pulmonary edema, lymphadenopathy, or a mediastinal mass was seen.

Dr. Simmons: A complete blood count and a white-cell differential count were normal, as were blood levels of glucose, calcium, total protein, albumin, globulin, total bilirubin, and C-reactive protein; other test results are shown in Table 1. A diagnostic test result was received.

DIFFERENTIAL DIAGNOSIS

Dr. Christiana A. Iyasere: This 87-year-old man with multiple long-standing medical problems presented with an illness that progressed over a period of several weeks. Through careful attention to the patient's symptoms, signs, and history (Table 2), we can build an analytic framework on which to base our differential diagnosis. In particular, it is important that we establish the tempo of disease progression, determine whether the disease process is global or local, and identify the salient clinical features that our diagnosis must account for.

Approximately 2 months before presentation, the patient was well enough to undergo a semielective surgical procedure, and his laboratory values at that time were at his baseline. However, several weeks later, fatigue, hoarseness, and periorbital edema developed. Eleven days after presentation, the symptoms worsened, new dyspnea on exertion and cough developed, and weight gain had occurred. I would describe the tempo of this disease process as subacute with acceleration.

Table 2. Symptoms, Signs, and History.

Symptoms
Fatigue
Sore throat
Periorbital and facial edema
Hoarse voice
Abdominal swelling
Dyspnea on exertion
Weight gain
Signs
Persistently elevated levels of creatine kinase, aspartate aminotransferase, and alanine aminotransferase
Worsening renal function
History
Hypertension
Hyperlipidemia
Hypothyroidism
Gastroesophageal reflux disease
Multiple medications
Multiple providers

The patient described symptoms involving multiple organ systems, including hoarseness suggesting possible involvement of the vocal cords or larynx, edema of multiple distinct body regions, shortness of breath and dyspnea on exertion, fatigue, and weight gain. Furthermore, the abnormally elevated levels of creatine kinase and aspartate aminotransferase (AST) suggest ongoing muscle inflammation or breakdown. As a result, we are looking for a global disease process with protean manifestations.

Despite the progressive nature of the disease process, there is a surprising lack of abnormal laboratory findings. The patient's renal function has declined, but the only additional notable laboratory findings are elevated levels of creatine kinase, AST, and alanine aminotransferase (ALT). Although AST and ALT are commonly thought of as liver enzymes and markers of hepatic injury, they are not tissue-specific; AST in particular is also found in numerous other organ systems, including skeletal and cardiac muscle. I suspect that in this patient, the mildly elevated AST and ALT levels are reflective of an ongoing myopathic process rather than hepatocellular injury.

The patient's laboratory values are not striking, but his clinical symptoms are. The combination

of hoarseness and periorbital edema is relatively uncommon and specific. In the context of an active myopathic process, these findings constitute a compelling description of the disease process.

In summary, we are looking for a disease entity with protean manifestations that can occur subacutely but can accelerate rapidly. Furthermore, the diagnosis must explain hoarseness, periorbital edema, and muscle injury or inflammation.

CANCER

Because of the patient's age, it is reasonable to consider cancer as the underlying disease process, particularly if there is an obstructive mass associated with a paraneoplastic syndrome. Patients with tumors of the anterior mediastinum or with tumors of the right lung and associated clinically significant hilar lymphadenopathy can present with mechanical obstruction of the superior vena cava leading to edema of the head and neck, which may be associated with a narrowing of the trachea and esophagus that is manifested by cough, hoarseness, or dyspnea.[1]

An associated paraneoplastic myositis might explain the myopathic component of this patient's presentation. In particular, polymyositis and dermatomyositis are associated with an increased incidence of cancer; the standardized incidence ratios for cancer among patients with these conditions are 6.2 and 2.0, respectively.[2]

However, we are told that the patient has facial and periorbital edema, not the swelling of the head and neck, facial plethora, or dilated veins of the arms that would be expected in a patient with the superior vena cava syndrome. Abnormalities on chest radiography, although a relatively insensitive marker, are seen in the majority of patients with a superior vena cava syndrome that is due to cancer-related vascular compression,[3] whereas the chest radiograph was normal in this case. Cancer with associated myopathy remains a plausible diagnosis, but because of the inconsistent findings, we should explore alternative explanations.

INFLAMMATORY MYOPATHY

Could an inflammatory myopathy in the absence of overt cancer explain this patient's symptoms? Polymyositis and dermatomyositis, which are both systemic inflammatory processes of the skeletal muscle, are characterized by proximal muscle weakness and laboratory evidence of increased muscle-enzyme levels. These diseases can develop gradually, with symptoms occurring over a period of weeks or months. Dermatomyositis, unlike polymyositis, is associated with classic skin findings, including an erythematous-to-violaceous eruption on the eyelids (heliotrope rash), skin changes on the dorsal aspects of the metacarpophalangeal and interphalangeal joints (Gottron's papules), and abnormal pigmentation of the skin, particularly on exposed areas ("shawl sign"). Both disorders have a variety of extramuscular manifestations, including interstitial lung disease and involvement of the gastrointestinal tract.[4]

This patient is described as having fatigue rather than overt weakness; a variety of symptoms can be described as fatigue. Patients with an inflammatory myopathy commonly present with dysphagia when the gastrointestinal tract is affected but can present with hoarseness as a consequence of involvement of the skeletal muscle of the larynx.[5] Could the periorbital edema and facial swelling be manifestations of dermatomyositis? Periorbital edema, although uncommon, has been described as an initial manifestation of dermatomyositis that can occur in the absence of other skin changes.[6] Although many of the features of this patient's presentation can be explained by dermatomyositis, this would be an atypical case. Thus, before invoking a diagnosis of an inflammatory myopathy, we must rule out other explanations of a myopathic process, such as hypothyroidism.

HYPOTHYROIDISM

The patient has a history of hypothyroidism. Patients with hypothyroidism commonly report muscle-related symptoms, such as nonspecific muscle stiffness, diffuse myalgias, or proximal muscle weakness.[7] In one prospective cohort study involving patients with hypothyroidism, 40% of patients reported muscle weakness.[8] In particular, weakness after exertion, which was seen in this patient, is uncommon among patients with an inflammatory myopathy but is consistent with neuromuscular disease that has a metabolic cause. Furthermore, hoarseness and periorbital edema have been described as manifestations of matrix glycosaminoglycan accumulation in the interstitium of tissues in patients with hypothyroidism.[9]

Could severe hypothyroidism explain the majority of the symptoms in this patient? Fatigue, weight gain, and dyspnea are all well-recognized

Figure 2. The Patient's Medications.

consequences of generalized slowing of metabolism due to thyroid hormone deficiency. Abdominal swelling may be caused by constipation due to decreased gut motility, which is often seen in patients with hypothyroidism; a less likely cause is ascites, which can be a rare complication of severe thyroid hormone deficiency that mimics intra-abdominal cancer.[10] Finally, the serum creatinine level may be elevated in patients with severe thyroid hormone deficiency, as it was in this patient.[11]

How can we reconcile the diagnosis of severe hypothyroidism with the fact that the patient is receiving thyroid hormone–replacement therapy? There are two possible scenarios to consider. First, it is possible that the patient was not taking the prescribed levothyroxine. Alternatively, the levothyroxine could have been taken but not absorbed. Given the patient's age and the fact that he had been taking multiple similar-appearing oral medications (Fig. 2), it is easy to imagine him being confused about which medication to take. The patient is cared for by at least four providers, which adds a layer of complexity to his medical care that could precipitate a medication error. Finally, levothyroxine absorption is affected by common foods and medications if they are taken at the time of levothyroxine administration. Coffee, fiber, and calcium have all been shown to decrease levothyroxine absorption.[12] This patient was also taking omeprazole, a medication thought to alter thyroid hormone absorption.[13]

Finally, we should consider whether concomitant statin administration exacerbated the degree of skeletal-muscle injury in this patient. Hypothyroidism is a known risk factor for statin-induced myopathy.[14] However, the elevated creatine kinase level in this case is consistent with hypothyroid myopathy alone.[15]

In summary, severe hypothyroidism is a global disease process that can develop insidiously, with symptoms that can progress quickly over time. This diagnosis explains all the key features of this patient's presentation. Thyroid hormone–replacement therapy had been prescribed for the patient, but I believe we have sufficient evidence to conclude that either he was not taking the medication or it was malabsorbed.

Dr. Eric S. Rosenberg (Pathology): Dr. Simmons, would you tell us your impression when you initially evaluated this patient?

Dr. Simmons: When I initially saw this patient, the salient features of his illness were severe fatigue, hoarseness, worsening renal function, edema, and depression. Keeping in mind that coexisting long-term conditions are common among geriatric patients, I considered the following possible causes of his fatigue, hoarseness, and elevated creatine kinase level: statin-induced rhabdomy-

olysis, autoimmune myositis, and hypothyroidism. We reviewed his medication list, and he confirmed that he was taking all his medications as prescribed. I asked him to stop taking his statin medication and to return to the office for follow-up testing in 1 week. On follow-up testing, his creatine kinase level remained elevated, and I was concerned about another cause of rhabdomyolysis. I then checked his thyrotropin level.

CLINICAL DIAGNOSIS

Statin-induced rhabdomyolysis and possible hypothyroidism.

DR. CHRISTIANA A. IYASERE'S DIAGNOSIS

Severe hypothyroidism, possibly complicated by statin-induced myopathy.

PATHOLOGY

Dr. Anand S. Dighe: The patient's thyrotropin level was highly elevated, at 144.10 μU per milliliter. Additional thyroid hormone testing was not performed. The highly elevated thyrotropin level suggests that the patient had not been taking his thyroid hormone–replacement therapy and thus had resultant hypothyroidism. Given the elimination half-life of thyroid hormones (up to 2 weeks, depending on thyroid status), it would probably take many weeks of treatment nonadherence for the patient to have a highly elevated thyrotropin level and presumably very low levels of thyroid hormones. A positive correlation between creatine kinase and thyrotropin levels has been seen in patients with hypothyroidism; the majority of patients with overt hypothyroidism and a highly elevated thyrotropin level also have a highly elevated creatine kinase level.[16,17] Before the diagnosis of hypothyroidism was made, the question of a statin-induced myopathy was raised, since the patient was taking atorvastatin at presentation. Although hypothyroidism alone is associated with myopathy, hypothyroidism is also a known risk factor for the development of statin-induced myopathy.[14]

FOLLOW-UP

Dr. Simmons: When I received the thyrotropin test result, I called the patient's son, who assists in organizing the patient's medications. The son later called with confirmation: he said, "My father stopped taking levothyroxine 6 months ago. He says you asked him to stop taking it." I had not, of course, advised him to do so. However, there had been a few intervening events in the previous 6 months that might have caused confusion regarding the patient's medication management. Our office has a system of medication reconciliation; at each visit, all patients are asked to review and confirm their medications. This patient would frequently decline to reconcile his medications, stating that "nothing has changed." However, during two hospitalizations this year, one for pneumonia and one for photoselective vaporization of the prostate, his medicine list did include some changes. One set of discharge instructions indicated that the patient should take 100 μg of Synthroid daily, and another indicated that he should take 100 μg of Levoxyl daily — Synthroid and Levoxyl are both brand-name versions of levothyroxine. The patient takes a generic form of levothyroxine. It is at least possible that he no longer saw levothyroxine listed specifically on his medicine list and thought that he was supposed to stop taking it.

A review of recent medical records also gave hints that such an error could have easily happened. This patient regularly sees an internist (me), a nephrologist, a cardiologist, and a urologist. He uses both a mail-order pharmacy and a local pharmacy for medication refills. He keeps all his pills in one pillbox. Two years before the current presentation, he presented to my office with orthostasis and near-syncope, and we discovered that he was taking both tamsulosin (a medication that had been newly prescribed by his urologist) and doxazosin (a long-standing medication); neither of the prescribing physicians had been aware of the full medication list.

Thus, this patient had profound hypothyroidism because he had not taken his prescribed thyroid hormone–replacement therapy for an unknown amount of time, probably for at least several weeks before presentation. He had hypothyroid myopathy and mild rhabdomyolysis. The thyroid hormone–replacement therapy was reinitiated, and the patient's son watched over the patient's medications very closely. Within 1 month, his fatigue and dyspnea decreased markedly, and after 4 months, with a small increase in the dose of levothyroxine, to 112 μg daily, his thyrotropin level was back to normal.

The patient continues to live independently and

is doing reasonably well. We check his thyrotropin level on a quarterly basis to confirm adherence to the regimen. His son's assistance with medication management has led to the early detection of two additional medications being stopped abruptly; these problems were quickly resolved after his son called the office to confirm his father's medications.

A Physician: Does muscle pain or tenderness typically occur in patients with hypothyroid myopathy, as it does in patients with dermatomyositis?

Dr. Iyasere: Patients with hypothyroidism can present with frank myalgias but they more commonly present with nonspecific muscular symptoms. The majority of patients with moderate-to-severe hypothyroidism have some form of fatigue or muscular discomfort. It may be difficult to distinguish an inflammatory myopathy from a hypothyroid myopathy on the basis of the presence or absence of muscle pain; however, muscle fatigue after exertion is more consistent with a metabolic (hypothyroid) myopathy than with an inflammatory myopathy. Furthermore, muscle weakness, rather than muscle pain, is characteristic of inflammatory muscle disease.

FINAL DIAGNOSIS

Severe hypothyroidism.

This case was discussed at the Medical Case Conference.

No potential conflict of interest relevant to this article was reported.

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

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