CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 32-2024: A 72-Year-Old Woman with Dyspnea, Dysphagia, and Dysarthria

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PRESENTATION OF CASE

Dr. Lucas X. Marinacci: A 72-year-old woman was evaluated for dysarthria and respiratory failure during an admission to this hospital, which had occurred before the coronavirus disease 2019 pandemic.

Two years before the current evaluation, the patient presented to her primary care physician at this hospital with subacute exertional dyspnea, which had been present for more than a year but had progressively worsened during the past several months. The oxygen saturation was 91 to 94% while she was walking. She had edema in both legs. The white-cell count, platelet count, and blood levels of electrolytes, aspartate aminotransferase, alanine aminotransferase, bilirubin, albumin, and hemoglobin were normal, as were test results for kidney function.

Dr. Sandra P. Rincon: A chest radiograph showed an enlarged cardiac silhouette and bilateral interstitial opacities.

Dr. Marinacci: Hydrochlorothiazide was prescribed. At a follow-up evaluation 2 weeks later, the patient's weight had decreased by 5 kg, but the exertional dyspnea and bilateral leg edema were unchanged. The N-terminal pro–B-type natriuretic peptide level was normal, and the D-dimer level was 3259 ng per milliliter (reference value, <500).

Dr. Rincon: Computed tomographic angiography (CTA) of the chest, performed after the administration of intravenous contrast material, showed no pulmonary emboli. A dilated main pulmonary artery, mosaic attenuation of the lungs, and coronary-artery calcifications were present.

Dr. Marinacci: Four weeks later, the patient presented to her primary care physician with increased exertional dyspnea. Her weight had decreased by 2 kg. The peak expiratory flow was 220 liters per second (expected value according to age, sex, and height, 350). A tapering course of prednisone and inhaled albuterol were prescribed, and her condition improved initially.

The patient was lost to follow-up; her next visit took place 10 months before the current evaluation. At that time, the patient reported recurrent exertional dyspnea, which occurred when she moved from room to room. She reported an episode of

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Table 1. Laboratory Data.*

Variable	Reference Range, Adults†	10 Mo before Admission, Outpatient Clinic	On Presentation, Emergency Department	Hospital Day 2	Hospital Day 3
Sodium (mmol/liter)	135–145	143	139	142	142
Potassium (mmol/liter)	3.4–5.0	3.8	4.7	3.5	3.4
Chloride (mmol/liter)	98–108	99	98	98	94
Carbon dioxide (mmol/liter)	23–32	30	22	28	32
Urea nitrogen (mg/dl)	8–25	29	16	17	16
Creatinine (mg/dl)	0.60–1.50	0.89	0.86	0.83	0.78
Glucose (mg/dl)	70–110	171	120	110	156
N-terminal pro–B-type natriuretic peptide (pg/ml)	<900	1908	2000	—	—
High-sensitivity troponin T (ng/liter)	0–9	—	16	18	—
Erythrocyte sedimentation rate (mm/hr)	0–20	—	—	39	—
Venous blood gas					
pH	7.30–7.40	—	7.33	7.33	—
Partial pressure of carbon dioxide (mm Hg)	38–50	—	63	71	—
Arterial blood gas					
Fraction of inspired oxygen	—	—	—	—	0.45
pH	7.35–7.45	—	—	—	7.32
Partial pressure of carbon dioxide (mm Hg)	35–42	—	—	—	74
Partial pressure of oxygen (mm Hg)	80–100	—	—	—	89

* 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.
† 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.

transient facial asymmetry with saliva dripping from the left side of her mouth that had developed while she was washing herself; later that day, her sister had noticed that she was slurring words during a telephone call. The white-cell count, platelet count, and blood levels of thyrotropin, glycated hemoglobin, aspartate aminotransferase, alanine aminotransferase, bilirubin, albumin, and hemoglobin were normal; other laboratory test results are shown in Table 1. Furosemide was prescribed.

Two months later, the patient presented to her primary care physician with throat pain and dyspnea that had been present for 3 weeks. An examination was notable for diffuse crackles in both lung fields.

Dr. Rincon: A chest radiograph showed pulmonary edema and a small right pleural effusion.

Dr. Marinacci: Intravenous furosemide was administered. Transthoracic echocardiography showed normal biventricular wall thickness, size, and function. Mild biatrial enlargement, a patent foramen ovale with mild left-to-right shunting, moderate tricuspid regurgitation, and a right ventricular systolic pressure of 60 mm Hg were noted.

On the day before the current evaluation, the patient called her primary care physician to report sore throat with difficulty swallowing that had started 2 days earlier. Because she had slurred speech over the phone, she was referred to the emergency department of this hospital.

In the emergency department, the patient reported dysphagia with food, liquids, and medications. Her daughter reported that her voice had sounded "garbled" and "soft" during the preceding days and also during an episode of transient dysarthria that had developed a few months earlier. Dyspnea and mild leg edema had been present for at least 3 years, along with some orthopnea and an intermittent nonproductive cough.

The patient had started using a walker in the past year owing to exertional fatigue, arthritic pain, and weakness in both legs. Two falls had occurred in the previous 8 months. In addition, the patient reported increased generalized weakness and limb weakness, daytime somnolence, and fatigue. She had no diplopia, numbness, dizziness, headache, chest pain, palpitations, bleeding, nausea, abdominal pain, constipation, diarrhea, or urinary symptoms.

The patient's medical history was notable for severe obesity, coronary-artery calcifications, hypertension, hyperlipidemia, atrial flutter, and hyperparathyroidism. Medications included furosemide, apixaban, aspirin, amlodipine, lisinopril, metoprolol, lovastatin, metformin, and sertraline. She had had no known adverse drug reactions. The patient was retired and divorced, and she lived alone in an assisted-living community. She had smoked two packs of cigarettes daily for 15 years but had quit smoking 20 years earlier, and she did not drink alcohol or use other substances. Her family history was notable for ischemic heart disease. Her father had had myocardial infarctions; a paternal cousin had systemic lupus erythematosus.

On examination, the temporal temperature was 36.2°C, the heart rate 76 beats per minute, the blood pressure 154/88 mm Hg, the respiratory rate 21 breaths per minute, and the oxygen saturation 84% while the patient was breathing ambient air. The weight was 124 kg, and the body-mass index (the weight in kilograms divided by the square of the height in meters) was 53.1. The patient was appropriately oriented, and her speech was fluent. She appeared to have increased work of breathing. The oropharynx was clear; no stridor was noted. Auscultation revealed an irregular heart rhythm with a systolic murmur at the base of the left sternal border and crackles in both lungs. The patient had pitting edema in both legs with venous stasis dermatitis and had tenderness of the knees with mild crepitus but no erythema or effusion.

The white-cell count, platelet count, and blood levels of calcium, magnesium, phosphate, creatine kinase, lactate, aspartate aminotransferase, alanine aminotransferase, bilirubin, albumin, globulin, lipase, and hemoglobin were normal; other laboratory test results are shown in Table 1. Urinalysis showed 1+ protein. Testing of an oropharyngeal swab for group A streptococcal antigen was negative, and a throat culture showed no growth.

Dr. Rincon: A chest radiograph showed an enlarged cardiac silhouette, low lung volumes, and bilateral interstitial opacities (Fig. 1A).

Dr. Marinacci: Electrocardiography was notable for atrial flutter with a ventricular rate of 75 beats per minute, a rightward axis, and low precordial QRS voltage. On the first night in the emergency department, the patient was unable to lie flat to sleep because of dyspnea. Intravenous furosemide was administered, along with continuous positive airway pressure (with a pressure of 10 cm of water and a rate of 4 liters of oxygen per minute). Cardiology and neurology consultations were requested.

Dr. Rincon: Computed tomography (CT) of the head and CTA of the head and neck showed chronic lacunar infarcts and chronic hypertensive microangiopathy (Fig. 1B). No high-grade stenosis or large-vessel occlusion was noted. CT of the neck and mediastinum showed no mass or lymphadenopathy (Fig. 1C).

Dr. Marinacci: On the second day, the patient was admitted to the hospital because of slurred speech, voice changes, and dyspnea. The examination was notable for tachypnea and a new onset of forgetfulness. The dysarthria was most pronounced with guttural sounds. She also had facial droop on the right side, subtle ptosis in the right eye, slight weakness in the proximal muscles on both sides, pronator drift on the left side, and the Babinski reflex in the right foot. Laboratory test results are shown in Table 1.

Dr. Rincon: Magnetic resonance imaging (MRI) of the head and magnetic resonance angiography (MRA) of the head and neck showed findings similar to those seen on CT. No evidence of acute infarction was noted (Fig. 1D). Scattered foci of susceptibility signal were present in the cerebral hemispheres, basal ganglia, and thalami, findings consistent with chronic microhemorrhages. MRA showed widely patent intracranial and cervical arteries (Fig. 1E and 1F).

Dr. Marinacci: On the third day, the patient was somnolent and was using accessory muscles for breathing until bilevel positive airway pressure was initiated. An evaluation revealed weak cough and delayed swallow initiation. Owing to the degree of dysphagia, it was recommended that the patient avoid oral medications and food. The thyrotropin level was normal; other laboratory test

results are shown in Table 1. Direct laryngoscopy showed an impaired swallow, normal vocal cords, and no mass or other source of obstruction. Intravenous furosemide and piperacillin–tazobactam and inhaled ipratropium were administered.

Diagnostic tests were performed, and management decisions were made.

DIFFERENTIAL DIAGNOSIS

Dr. Stephanie V. Sherman: In a complex case, it can be helpful to identify the features in the background, middle ground, and foreground that form the overall clinical landscape. This 72-year-old woman presented with dyspnea and leg swelling that had occurred for several years and had prompted consideration of multiple cardiopulmonary conditions (background). During the months preceding the current evaluation, episodes of slurred speech, facial asymmetry, and falls had occurred (middle ground). At the time of the current evaluation, sore throat, difficulty swallowing, and increased generalized weakness, including dysarthria, facial droop and ptosis on the right side, and weakness in both legs, had been present for several days (foreground). Neuroimaging

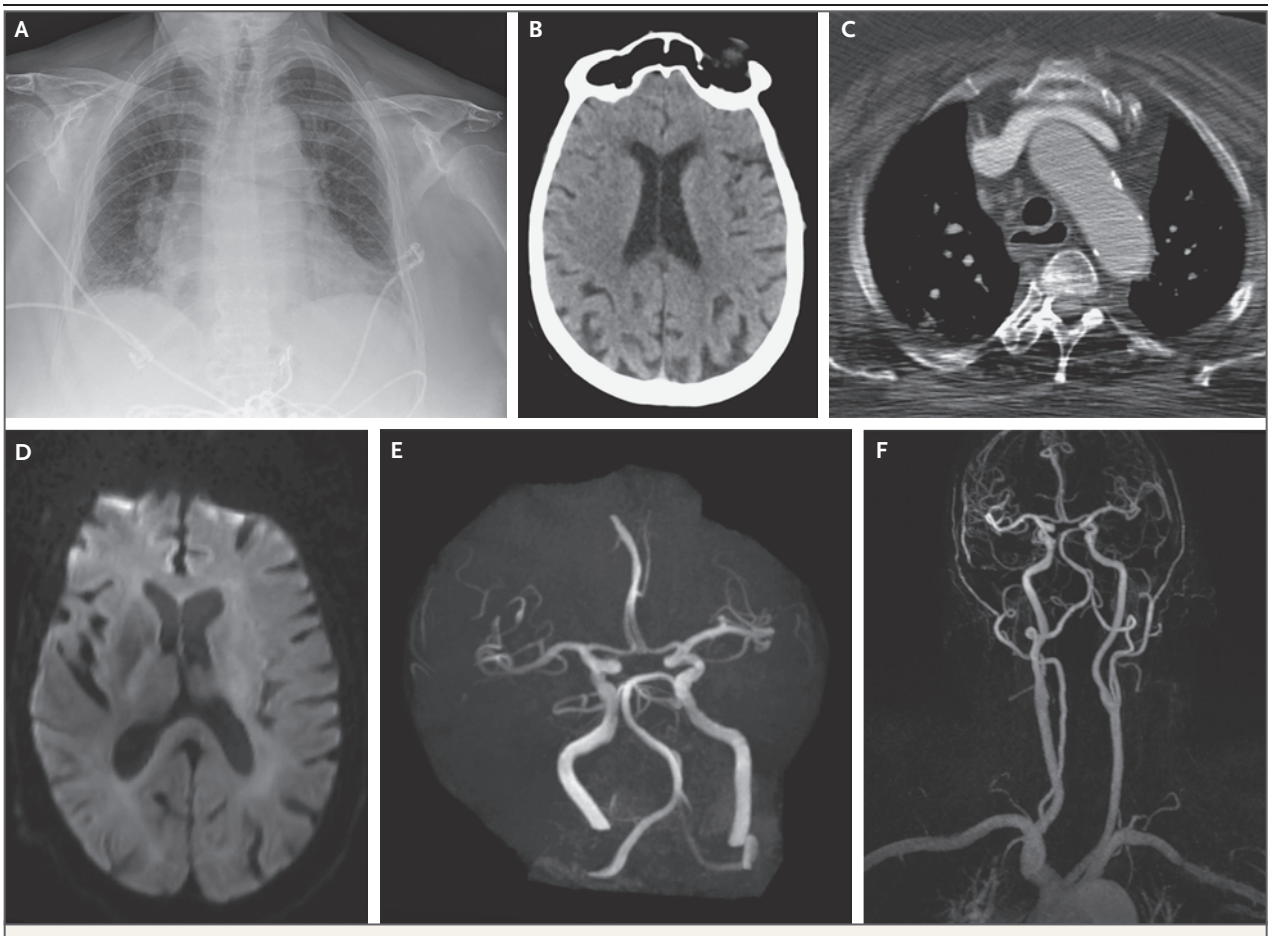

Figure 1. Imaging Studies.

Portable chest radiography was performed on presentation. The chest radiograph (Panel A) shows an enlarged cardiac silhouette and mild pulmonary edema. Neuroimaging studies were obtained the next day. An axial image from CT of the head (Panel B) shows diffuse brain parenchymal volume loss, chronic lacunar infarcts, and chronic white-matter changes; no acute intracranial abnormality is present. An axial image from CT of the mediastinum (Panel C), obtained after the administration of contrast material, shows no mass or lymphadenopathy; aortic-arch calcification is noted. An axial diffusion-weighted image from MRI of the head (Panel D) shows no restricted diffusion that would be suggestive of acute infarction. Maximum-intensity-projection images from three-dimensional time-of-flight magnetic resonance angiography (MRA) of the head (Panel E) and from gadolinium-enhanced MRA of the neck (Panel F) show no high-grade stenosis or occlusion of the major intracranial or cervical arteries.

showed no acute changes, and the respiratory status rapidly worsened despite the administration of diuretic agents and noninvasive positive-pressure ventilation.

When a patient's condition is rapidly worsening and the diagnosis is uncertain, it is important to focus on the foreground — in this case, the acute onset of dysphagia, dysarthria, and respiratory failure. Dysphagia can be categorized as oropharyngeal or esophageal, and then a problem in the structure or motility can be identified. In this patient, findings from the bedside assessment, laryngoscopy, and imaging are consistent with oropharyngeal dysphagia from impaired motility, which is derived from incoordination or weakness of the muscles of swallowing. Dysarthria also results from incoordination or weakness of muscles. When the patient's dysphagia and dysarthria (also known as bulbar symptoms) are layered onto the findings of facial droop, ptosis, decreased leg strength, and respiratory failure, a syndrome of weakness becomes apparent.

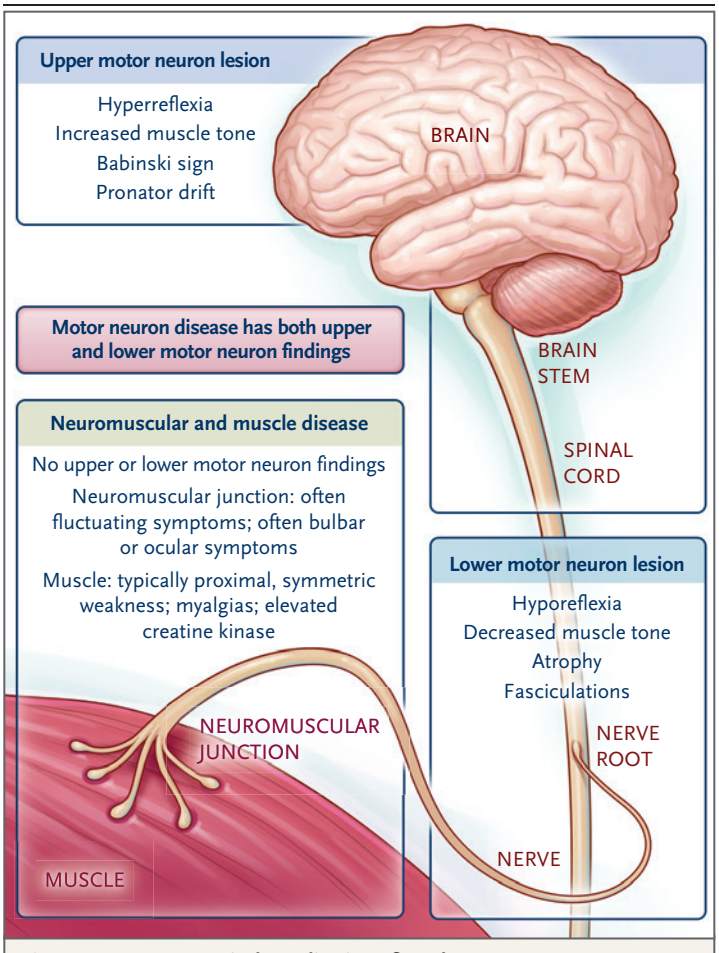

Figure 2. Neuroanatomical Localization of Weakness.
Upper and lower motor neuron findings can be used to localize where the problem lies neuroanatomically.

NEUROANATOMICAL LOCALIZATION OF WEAKNESS

In neurology, one diagnostic approach is to first localize where the problem lies neuroanatomically, according to the upper or lower motor neuron findings present on examination (Fig. 2), and to then consider specific diseases, according to the time course of the syndrome.[1] For example, vascular events are prioritized when hyperacute symptoms are present, whereas neurodegenerative problems are considered when chronic symptoms are present. For an older woman with a history of intermittent facial droop and dysarthria who presents with acute bulbar, ocular, facial, leg, and respiratory-muscle weakness, the differential diagnosis can be constructed by localizing her findings along the neuroaxis.

BRAIN AND BRAIN STEM

Could this patient's weakness be caused by acute strokes? The previous bouts of dysarthria could be consistent with transient ischemic attacks, owing to her risk factors for stroke (age, hypertension, hyperlipidemia, obesity, and atrial flutter). However, to account for this patient's weakness, the pattern of the strokes would need to be multifocal, involving territories in both the cerebral cortex and the brain stem. The many foci involved would generate even more neurologic deficits than those observed in this case. It is important to note that no evidence of acute strokes was identified on neuroimaging. On MRI with diffusion-weighted imaging, false negative results for acute strokes are uncommon (occurring in 6.8% of cases) and are most likely to occur with posterior circulation strokes, which would not fit with this patient's presentation.[2]

MOTOR NEURONS

The patient's prominent dysphagia and dysarthria prompt consideration of motor neuron disease. Amyotrophic lateral sclerosis (ALS) is a motor neuron disorder that manifests with bulbar, limb, and respiratory-muscle weakness. The presentation of ALS is heterogeneous; a pure brainstem variant manifests with progressive bulbar

symptoms.[3] Patients with ALS have both upper and lower motor neuron signs, but this combination of findings was not convincingly present in this patient. Although she had the Babinski reflex on the right side, she did not have other signs of hyperreflexia. In addition, she did not have atrophy or fasciculations, which are lower motor neuron findings. The acute onset of this patient's syndrome, combined with the history of self-resolving episodes of dysarthria, would not fit with the chronic, progressive course of ALS.

NERVE ROOTS

When the nerves exit the central nervous system at the brain stem or spinal cord, they traverse the subarachnoid space. Inflammation of the meninges can cause neuropathies that result in weakness. Could leptomeningeal disease, such as that caused by cancer, be a consideration in this patient? The presentation of leptomeningeal disease is heterogeneous, with possible manifestations including headache, cerebrospinal fluid obstruction, and cranial neuropathies. Neuropathies involving cranial nerves III and VII, which lead to ptosis and facial droop, respectively, can occur in patients with leptomeningeal disease; however, neuropathies involving cranial nerves IX and X, which lead to dysarthria and dysphagia, are uncommon.[4] In addition to the patient's clinical syndrome not fitting with the illness script for leptomeningeal disease, no meningeal enhancement was seen on MRI.

PERIPHERAL NERVES

A few peripheral nerve diseases could explain the bulbar, ocular, facial, and limb weakness observed in this case. Sarcoidosis results in multisystem granulomatous inflammation that could unify the cardiac, pulmonary, and neurologic symptoms. However, the patient's presentation does not fit well with neurosarcoidosis, in which bulbar cranial neuropathies are rare and sensory deficits are common.[5]

The Guillain–Barré syndrome (GBS) is an immune-mediated, demyelinating polyneuropathy with an acute onset that is preceded by infection in two thirds of cases.[6] This patient had a sudden onset of neurologic symptoms after a recent sore throat. Although GBS often manifests as an ascending paralysis with associated sensory symptoms, there are pure motor variants.[7] Ptosis, however, is a rare finding with GBS.[8,9] The patient's history of intermittent facial droop and dysarthria would also not be explained by a diagnosis of GBS.

In light of the patient's preceding sore throat, diptheric neuropathy is a consideration. Weeks to months after causing an upper respiratory infection, diphtheria can cause a toxin-mediated polyneuropathy that manifests with bulbar, ocular, and facial cranial neuropathies and later progresses to a polyneuropathy.[10,11] However, this patient was immunocompetent and had normal results on a throat examination and culture, features that render diptheric neuropathy unlikely.

NEUROMUSCULAR JUNCTION

Myasthenia gravis and the Lambert–Eaton myasthenic syndrome (LEMS) are two autoimmune neuromuscular junction disorders to consider in this case. Myasthenia gravis is caused by antibodies against the postsynaptic acetylcholine receptor and is characterized by bulbar, ocular, facial, limb, and axial weakness. In 60% of patients, the presenting sign is asymmetric ptosis, diplopia, or both; approximately 10% of patients have an associated thymoma.[12,13] A hallmark of myasthenia gravis is fatigable weakness.

LEMS is caused by antibodies against presynaptic voltage-gated calcium channels and is characterized by lower-leg weakness and later by dysautonomia and hyporeflexia. The syndrome is paraneoplastic in 50% of cases. Ocular and bulbar symptoms are less prominent with LEMS than with myasthenia gravis[14]; therefore, LEMS is a less compelling diagnosis in this case. In addition, the incidence of the most common type of myasthenia gravis is 20 times that of LEMS.[15]

MUSCLE

Skeletal muscle is the final "stop" along the neuroaxis, but myopathy does not fit well with this patient's presentation. Many myopathies manifest with proximal muscle weakness, elevated creatine kinase levels, and myalgias; none of these findings were noted in this patient. Oculopharyngeal muscular dystrophy is a muscle disease with a late onset (after 40 years of age) that causes ptosis, dysphagia, proximal limb weakness, and respiratory failure, but it has a chronic, progressive course that does not fit with the patient's clinical history.[16]

SUMMARY

This older woman with a history of intermittent facial droop and dysarthria presented with acute bulbar, ocular, facial, leg, and respiratory-muscle weakness. The history of self-resolving neurologic symptoms and the current asymmetric ptosis, bulbar weakness, and respiratory failure make myasthenia gravis with impending crisis the most compelling diagnosis. This case highlights the challenge of making the diagnosis of myasthenia gravis in older, medically complex patients, especially when the only hallmark ocular finding is subtle.[17,18] The neurologic findings in this case that do not fit with a diagnosis of myasthenia gravis — such as the Babinski reflex and pronator drift — were probably distracting features. These findings may be related to the previous strokes noted on neuroimaging.

Two subtypes of myasthenia gravis are compatible with this patient's presentation. The first is late-onset myasthenia gravis, which occurs in persons older than 50 years of age who have antibodies to the acetylcholine receptor. The second is myasthenia gravis associated with antibodies to muscle-specific kinase; more than 40% of patients with this subtype first present with prominent dysphagia or dysarthria, have minimal or no ocular symptoms, and have little variation in muscle strength throughout the day.[13]

What would have triggered such a severe case of myasthenia gravis? In one study, 30% of myasthenia gravis flares were preceded by infection.[19] The patient's recent sore throat may point toward the trigger. Alternatively, the sore throat could have been related to discomfort from oropharyngeal dysphagia or could have been a manifestation of neck-muscle weakness and soreness.

To establish the diagnosis of myasthenia gravis, I would recommend repetitive nerve stimulation studies and serum testing for autoantibodies related to myasthenia gravis.

CLINICAL IMPRESSION

Dr. Marinacci: Given the progressive hypercapnic respiratory failure that was refractory to medical therapy and the constellation of findings on examination, imaging, and laryngoscopy, we suspected that the patient had an acute worsening neuromuscular process that was superimposed on a chronic underlying cardiopulmonary disease. The ptosis waxed and waned; the patient could not maintain an upward gaze, and the negative inspiratory force was markedly reduced. Of the diagnostic considerations, which included myasthenia gravis and GBS variants, myasthenia gravis best accounted for her presentation and subsequent clinical deterioration.

CLINICAL DIAGNOSIS

Respiratory failure due to myasthenic crisis.

DR. STEPHANIE V. SHERMAN'S DIAGNOSIS

Myasthenia gravis with impending crisis.

DIAGNOSTIC TESTING AND MANAGEMENT

Dr. Elizabeth M. Raynor: Analysis of a specimen of cerebrospinal fluid revealed a nucleated-cell count of 1 per microliter, a red-cell count of 4 per microliter, a protein level of 39 mg per deciliter (reference range, 5 to 55), and a glucose level of 73 mg per deciliter (4.0 mmol per liter; reference range, 50 to 75 mg per deciliter [2.7 to 4.2 mmol per liter]). The results of routine nerve conduction studies and needle electromyography were normal. These initial studies ruled out GBS variants, inflammatory myopathy, and motor neuron disease, as well as presynaptic neuromuscular transmission disorders such as LEMS and botulism. Repetitive nerve stimulation studies and serum testing for myasthenia-related autoantibodies were performed.

Examples of repetitive nerve stimulation studies with normal and myasthenic responses are shown in Figure 3. The patient's repetitive nerve stimulation studies showed the hallmark decremental response seen with myasthenia gravis; the amplitude decrement was 18% on a study obtained before exercise and worsened on a study obtained after exercise. Although other rare neuromuscular transmission disorders may be associated with similar findings on low-frequency (3 Hz) repetitive nerve stimulation studies, the overall electrodiagnostic findings were not suggestive of such conditions in this patient. Abnormal results on repetitive nerve stimulation studies reflect conduction failure (known as "block") of impulses between nerve and muscle fibers, which occurs as the demand for acetylcholine

increases under the stress of successive nerve stimulation; this instability of the neuromuscular junction correlates clinically with muscular fatigue and weakness, as seen in this case.[20]

Myasthenia-related autoantibodies were measured. The level of acetylcholine receptor–binding antibodies was 12.5 nmol per liter (reference value, ≤0.02). Acetylcholine receptor–binding antibodies have high sensitivity (85%) and specificity (90%) for the diagnosis of generalized myasthenia gravis.[21,22] These pathogenic antibodies lead to dysfunction of the acetylcholine receptor through functional blocking of the receptor and complement-mediated destruction of the postsynaptic membrane. Other pathogenic antibodies directed against structural proteins of the acetylcholine receptor include anti–muscle-specific kinase antibodies,[21,22] which were not detected in this patient. The titer of antistriational antibodies was 1:30,720 (reference value, <1:120). These nonpathogenic antibodies are seen in approximately 36% of patients with myasthenia gravis and correlate with increased age and disease severity; in younger patients, these antibodies correlate with the presence of thymoma.[21] Given that myasthenia gravis can be associated with thymoma (in approximately 10% of all patients with myasthenia gravis),[13,23] this patient underwent screening with mediastinal CT, which was negative for a thymic mass.

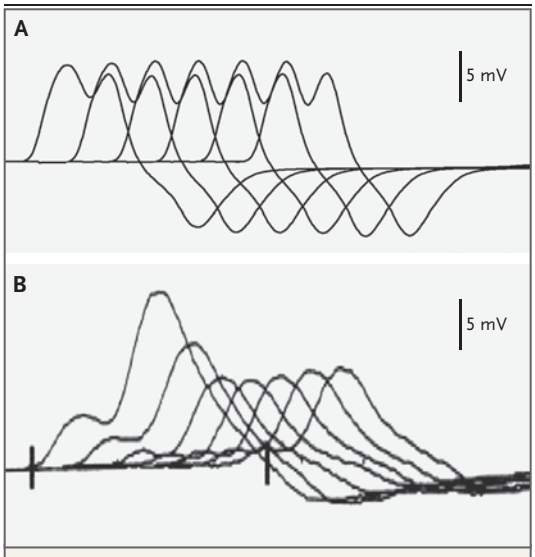

Figure 3. Electrodiagnostic Studies.

Repetitive nerve stimulation is a specialized nerve conduction technique designed to rule out myasthenia gravis and other neuromuscular transmission disorders. A motor nerve is stimulated repetitively for 2 seconds at a rate of 3 Hz, and a train of six responses is obtained from the corresponding muscle. A reliable amplitude decrement between the first response and the fifth response of more than 10% is evidence of a neuromuscular transmission disorder. Worsening of the decrement after exercise is a characteristic feature of myasthenia gravis. To test for exercise-induced worsening, the muscle is exercised for 30 to 60 seconds, and then repetitive nerve stimulation is performed in 1-minute intervals for up to 5 minutes. Panel A shows an example tracing of the normal response to stimulation. Panel B shows an example tracing of the myasthenic response. When presynaptic neuromuscular transmission disorders are a clinical consideration, additional testing may be performed to distinguish between presynaptic and postsynaptic disorders. The panels are courtesy of Dr. Pushpa Narayanaswami of Beth Israel Deaconess Medical Center.

The patient had evidence of clinically significant respiratory-muscle weakness on presentation — including labored breathing, accessory-muscle use, hypercapnia, and rapidly evolving hypoxemia — that was consistent with impending myasthenic crisis. Myasthenic crisis is defined as life-threatening, rapid worsening of myasthenia gravis with airway compromise from respiratory-muscle or bulbar weakness that leads to intubation or noninvasive ventilation.[24] The management of myasthenic crisis in patients with previously untreated myasthenia gravis is highly complex. The patient's antibody status, age, and coexisting conditions guide the overall approach to treatment. Efficacy is based on clinical response instead of antibody titers.[13]

Figure 4 outlines the treatment strategy for a patient in myasthenic crisis,[24-26] as well as the therapies administered to this patient. The treatment approach involves first stabilizing life-threatening respiratory-muscle weakness and then addressing the underlying autoimmune disorder, with the goal of restoring neuromuscular function sufficiently to minimize symptoms and prevent relapse. Immediate measures include intensive care and ventilatory support with either mechanical ventilation or noninvasive positive-pressure ventilation, which was initiated in this patient. Rapid-acting treatment options for myasthenic crisis are plasma exchange and the administration of intravenous immune globulin (IVIG).[13,24-26] This patient received a standard, 5-day course of IVIG. Although short-acting therapy with pyridostigmine can be administered to manage symptoms in patients with myasthenia gravis, such

treatment is avoided in patients in myasthenic crisis, owing to the possible induction of increased bronchial secretions and cardiac arrhythmias.[24-26]

Additional immunotherapy is recommended once the patient's condition is medically stable.[13,25,26] Prednisone is used as a first-line immunosuppressive agent.[24-26] High doses of prednisone are recommended for patients in myasthenic crisis to allow for a shorter time to clinical effect (2 to 4 weeks). However, high-dose glucocorticoid therapy leads to transient disease exacerbation in nearly half of patients with myasthenia gravis who receive such treatment, typically within the first 1 or 2 weeks after the initiation of therapy.[13,24,27] This patient received a daily dose of prednisone beginning on hospital day 9, and she had worsening of bulbar and limb weakness that led to repeat hospitalization and treatment with IVIG 2 weeks later, a scenario suggestive of glucocorticoid-induced exacerbation.

In patients with severe myasthenia gravis, including those in myasthenic crisis, nonsteroidal immunosuppressants can be administered early, in addition to prednisone.[13,26] First-line nonsteroidal immunosuppressive agents used for the treatment of myasthenia gravis include mycophenolate mofetil, azathioprine, calcineurin inhibitors, and methotrexate; rituximab is typically reserved for patients with refractory disease.[13,24,28] Newer antibody-based biologic agents, including complement inhibitors and Fc receptor antagonists, are becoming less costly and more readily accessible as glucocorticoid-sparing medications. This patient received azathioprine concurrently with prednisone. Rituximab was added when her condition worsened; she received her first dose of rituximab in the hospital after a 5-day course of IVIG, and she received her second dose as an outpatient 2 weeks later. At a follow-up visit 6 weeks after her initial presentation, the patient's condition had improved markedly, with minimal bulbar, ocular, and limb weakness.

Dr. Marinacci: Several days after the 6-week follow-up visit, the patient had acute shortness of breath after taking medication in the evening. She was transported to this hospital and underwent emergency intubation and mechanical ventilation. Imaging findings were suggestive of a massive aspiration event. Owing to refractory shock, the patient's treatment was transitioned to comfort-focused care, and she died within 24 hours after arrival.

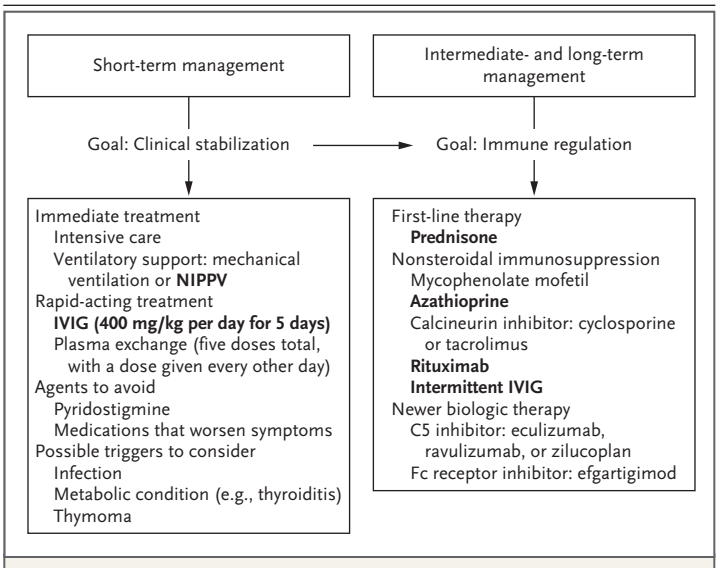

Figure 4. Treatment Strategy for Myasthenic Crisis.

Approaches to the short-term management of myasthenic crisis (left side) and to the intermediate- and long-term management of myasthenia gravis (right side) are shown. The therapies administered to this patient are shown in bold. For patients with previously untreated myasthenia gravis who have moderate-to-severe weakness but are not in myasthenic crisis, the same approach to the intermediate- and long-term management can be used. Drug choice is individualized on the basis of the expected time to clinical effect, the side-effect profile, and the patient's risk with respect to coexisting conditions. IVIG denotes intravenous immune globulin, and NIPPV noninvasive positive-pressure ventilation.

CASE RECORDS EDITORS' NOTE — LESSONS LEARNED

1. Several findings on physical examination are highly suggestive of myasthenia gravis: improvement of ptosis with ice placed over the affected eye ("ice pack test"), limb fatigue with repetitive motion, and the development of ptosis or diplopia with repetitive eye movements.

2. The presence of acetylcholine receptor–binding antibodies has high sensitivity (85%) and specificity (90%) for the diagnosis of generalized myasthenia gravis.

3. Myasthenic crisis is a medical emergency that often leads to mechanical ventilation and critical care management.

FINAL DIAGNOSIS

Myasthenia gravis.

This case was presented at the Medicine Case Conference.

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

REFERENCES

1. Berkowitz AL. Clinical neurology and neuroanatomy: a localization-based approach. 2nd ed. New York: McGraw Hill, 2022 (https://www.mhprofessional.com/clinical-neurology-and-neuroanatomy-a-localization-based-approach-second-edition-9781260453362-usa-group).
2. Edlow BL, Hurwitz S, Edlow JA. Diagnosis of DWI-negative acute ischemic stroke: a meta-analysis. Neurology 2017;89:256-62.
3. Brown RH, Al-Chalabi A. Amyotrophic lateral sclerosis. N Engl J Med 2017;377:162-72.
4. Kesari S, Batchelor TT. Leptomeningeal metastases. Neurol Clin 2003;21:25-66.
5. Kidd DP. Neurosarcoidosis: clinical manifestations, investigation and treatment. Pract Neurol 2020;20:199-212.
6. Doets AY, Verboon C, van den Berg B, et al. Regional variation of Guillain-Barré syndrome. Brain 2018;141:2866-77.
7. Leonhard SE, Mandarakas MR, Gondim FAA, et al. Diagnosis and management of Guillain-Barré syndrome in ten steps. Nat Rev Neurol 2019;15:671-83.
8. Teng H-W, Sung J-Y. Ptosis as the initial presentation of Guillain-Barré syndrome. J Emerg Med 2012;43(5):e283-e285.
9. Imam YZ, Deleu D. Isolated bilateral ptosis as an early sign of Guillain-Barré syndrome. Case Rep Neurol Med 2013;2013:178291.
10. Sanghi V. Neurologic manifestations of diphtheria and pertussis. Handb Clin Neurol 2014;121:1355-9.
11. Sharma NC, Efstratiou A, Mokrousov I, Mutreja A, Das B, Ramamurthy T. Diphtheria. Nat Rev Dis Primers 2019;5:81.
12. Gilhus NE, Verschuuren JJ. Myasthenia gravis: subgroup classification and therapeutic strategies. Lancet Neurol 2015;14:1023-36.
13. Gilhus NE. Myasthenia gravis. N Engl J Med 2016;375:2570-81.
14. Titulaer MJ, Lang B, Verschuuren JJ. Lambert–Eaton myasthenic syndrome: from clinical characteristics to therapeutic strategies. Lancet Neurol 2011;10:1098-107.
15. Punga AR, Maddison P, Heckmann JM, Guptill JT, Evoli A. Epidemiology, diagnostics, and biomarkers of autoimmune neuromuscular junction disorders. Lancet Neurol 2022;21:176-88.
16. Yamashita S. Recent progress in oculopharyngeal muscular dystrophy. J Clin Med 2021;10:1375.
17. Spillane J, Higham E, Kullmann DM. Myasthenia gravis. BMJ 2012;345:e8497.
18. Vincent A, Clover L, Buckley C, Grimley Evans J, Rothwell PM. Evidence of underdiagnosis of myasthenia gravis in older people. J Neurol Neurosurg Psychiatry 2003;74:1105-8.
19. Gummi RR, Kukulka NA, Deroche CB, Govindarajan R. Factors associated with acute exacerbations of myasthenia gravis. Muscle Nerve 2019;60:693-9.
20. AAEM Quality Assurance Committee. Literature review of the usefulness of repetitive nerve stimulation and single fiber EMG in the electrodiagnostic evaluation of patients with suspected myasthenia gravis or Lambert–Eaton myasthenic syndrome. Muscle Nerve 2001;24:1239-47.
21. Meriggioli MN, Sanders DB. Muscle autoantibodies in myasthenia gravis: beyond diagnosis? Expert Rev Clin Immunol 2012;8:427-38.
22. Keller CW, Pawlitzki M, Wiendl H, Lünemann JD. Fc-receptor targeted therapies for the treatment of myasthenia gravis. Int J Mol Sci 2021;22:5755.
23. Priola AM, Priola SM. Imaging of thymus in myasthenia gravis: from thymic hyperplasia to thymic tumor. Clin Radiol 2014;69(5):e230-e245.
24. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis: executive summary. Neurology 2016;87:419-25.
25. Lacomis D. Myasthenic crisis. Neurocrit Care 2005;3:189-94.
26. Claytor B, Cho S-M, Li Y. Myasthenic crisis. Muscle Nerve 2023;68:8-19.
27. Pascuzzi RM, Coslett HB, Johns TR. Long-term corticosteroid treatment of myasthenia gravis: report of 116 patients. Ann Neurol 1984;15:291-8.
28. Narayanaswami P, Sanders DB, Wolfe G, et al. International consensus guidance for management of myasthenia gravis: 2020 update. Neurology 2021;96:114-22.