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Case 12-2023: A 44-Year-Old Woman with Muscle Weakness and Myalgia

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PRESENTATION OF CASE

Dr. Chidiebere D. Akusobi (Medicine): A 44-year-old woman was evaluated in the rheumatology clinic of this hospital because of proximal muscle weakness and myalgia.

The patient had been in her usual state of health until 5 years before the current presentation, when morning stiffness and pain developed in the small joints of both hands. Laboratory evaluation reportedly revealed elevated blood levels of anti-cyclic citrullinated peptide (CCP) antibodies and rheumatoid factor, as well as an elevated erythrocyte sedimentation rate. Rheumatoid arthritis was diagnosed, but the patient chose not to begin specific therapy for rheumatoid arthritis. Instead, she began taking selenium, cod-liver oil, and turmeric as home remedies for joint pain. Morning stiffness and joint pain resolved after 4 weeks.

Four years before the current presentation, treatment with hydroxychloroquine was started after the occurrence of another episode of morning stiffness and pain in the small joints of the hands. Three years before the current presentation, treatment with hydroxychloroquine was stopped after melasma developed. Treatment with methotrexate was initiated, but morning hand stiffness and pain recurred; methotrexate was replaced with leflunomide, and the symptoms in the hands subsequently decreased.

Six months before the current presentation, the patient began to have myalgia in the arms and thighs, as well as generalized fatigue. She had difficulty raising her arms above her head, and she could no longer independently brush her hair or apply makeup. Myalgia worsened with exercise and was worst at the end of the day. The patient reported episodes of tingling in the hands and feet, but she had no stiffness or pain in the small joints of her hands.

Three months before the current presentation, the patient was evaluated by a local rheumatologist and laboratory testing was performed. The blood level of creatine kinase was 422 U per liter (reference range, 40 to 150) and the lactate dehydrogenase level 509 U per liter (reference range, 110 to 210). Antinuclear antibodies (ANA) were detected at a titer of 1:320 in a nuclear homogenous pattern,

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and anti-U1-ribonucleoprotein (U1-RNP) antibodies were present. The blood levels of C3 and C4 were normal, and testing for anti-double-stranded DNA (dsDNA) and anti-Smith antibodies was negative. Two months before the current presentation, treatment with azathioprine was started, and the patient was referred to the rheumatology clinic of this hospital.

In the rheumatology clinic, the patient reported ongoing myalgia and tingling in the hands and feet but had noticed an improvement in her ability to raise her arms above her head after starting treatment with azathioprine. Two weeks earlier, episodes of muscle spasms in the hands and fingers had developed; massage of the hands had been performed to relax the spasms.

The patient had a history of Graves' disease, which had been complicated by ophthalmoplegia and had been treated with methimazole for 2 years, followed by radioactive iodine ablation 11 years before this presentation; hypothyroidism had developed after radioactive iodine ablation therapy. Other history included latent tuberculosis infection, which had been treated with a 3-month course of isoniazid and rifampin, and hypoparathyroidism that had developed 9 years before this presentation. Medications included azathioprine, levothyroxine, calcium supplements, and calcitriol; the patient was unsure of the formulation and dose of calcium supplementation. She lived outside the United States and traveled intermittently to Boston for specialized medical care. She lived with her mother and worked in information technology. She drank alcohol occasionally, smoked cigarettes, and used no illicit drugs. A sibling had systemic lupus erythematosus (SLE).

On examination, the temporal temperature was 36.3°C, the blood pressure 145/70 mm Hg, the pulse 72 beats per minute, the respiratory rate 18 breaths per minute, and the oxygen saturation 100% while the patient was breathing ambient air. She had mild exophthalmos in both eyes. There was an area of hyperpigmentation on the face. The joints had a normal range of motion without tenderness on palpation; there was no synovitis. Neck flexion was mildly weak, as was hip flexion; strength was otherwise normal, as was sensation. There was no rash. The remainder of the examination was normal.

Diagnostic tests were performed, and management decisions were made.

DIFFERENTIAL DIAGNOSIS

Dr. Marcy B. Bolster: This 44-year-old woman with seropositive rheumatoid arthritis presented to the rheumatology clinic with a recent onset of fatigue, proximal muscle weakness, myalgia in the arms and legs, paresthesia in the hands and feet, and muscle spasms in the hands. The available laboratory data showed elevated levels of creatine kinase and lactate dehydrogenase, as well as the presence of rheumatoid factor, anti-CCP antibodies, ANA, and anti-U1-RNP antibodies.

RHEUMATOID ARTHRITIS

When I evaluate a patient with a history of a rheumatic disease, I first establish whether I agree with the previous diagnosis before proceeding with evaluation of the patient's current presentation. Five years before this patient's current presentation, she had symmetric small-joint polyarthritis and was found to have positive tests for rheumatoid factor and anti-CCP antibodies. The specificity of a positive test for anti-CCP antibodies for the diagnosis of rheumatoid arthritis is 95%; in combination with a positive test for rheumatoid factor, the specificity increases to 98%.¹ Her presentation 5 years before the current presentation is clinically and serologically consistent with a diagnosis of rheumatoid arthritis.² She had temporary abatement of arthritis after treatment with hydroxychloroquine followed by methotrexate. More recently, her rheumatoid arthritis was well managed with leflunomide therapy, and at the time of the current presentation, she had no symptoms or findings involving the joints.

Now that I am comfortable with the previous diagnosis of rheumatoid arthritis, the next step is to determine whether the current presentation could be related to rheumatoid arthritis, a coexisting condition, or a new condition. I will begin by considering categories of diseases that are associated with proximal muscle weakness and myalgia.

AUTOIMMUNE DISEASES

Proximal muscle weakness and myalgia are not characteristic clinical manifestations of rheumatoid arthritis. However, other rheumatic conditions are high on the differential diagnosis in this patient with evidence of autoimmunity, on

the basis of her diagnoses of rheumatoid arthritis, Graves' disease, and hypoparathyroidism (which can be caused by an autoimmune process) and given the fact that a first-degree relative has SLE. With overlap syndromes, a patient meets classification criteria for two or more rheumatic conditions. Patients with rheumatoid arthritis can have an overlap syndrome comprising rheumatoid arthritis plus one or more other rheumatic conditions such as SLE, idiopathic inflammatory myopathies, Sjögren's syndrome, or systemic sclerosis. SLE, idiopathic inflammatory myopathies, and systemic sclerosis can be associated with proximal muscle weakness. This patient did not have clinical features that would suggest Sjögren's syndrome (e.g., keratoconjunctivitis sicca symptoms) or systemic sclerosis (e.g., Raynaud's phenomenon or skin thickening); other overlap syndromes merit consideration.

OVERLAP SYNDROME OF RHEUMATOID ARTHRITIS AND SLE

Could this patient have an overlap syndrome of rheumatoid arthritis and SLE? She is known to have had a positive ANA test; such antibodies can be present in patients with SLE. However, this autoantibody has low specificity and can also be present in patients with rheumatoid arthritis, idiopathic inflammatory myopathies, overlap syndromes, mixed connective-tissue disease, and Graves' disease, as well as in first-degree relatives of patients with SLE. A positive anti-U1-RNP antibody test can also occur in patients with SLE. However, this patient did not have the typical clinical features of SLE, such as oral ulcers, serositis, rash, and cytopenias. In addition, she recently had negative tests for anti-dsDNA and anti-Smith antibodies, and she had normal C3 and C4 levels. Overall, an overlap syndrome of rheumatoid arthritis and SLE is unlikely.

OVERLAP SYNDROME OF RHEUMATOID ARTHRITIS AND IDIOPATHIC INFLAMMATORY MYOPATHY

The classification criteria for idiopathic inflammatory myopathies include proximal muscle weakness, laboratory abnormalities (e.g., a positive anti-Jo-1 antibody test or elevated blood levels of creatine kinase, aldolase, lactate dehydrogenase, alanine aminotransferase, or aspartate aminotransferase), rash (e.g., Gottron's papules, Gottron's sign, or heliotrope rash), esophageal dysmotility or dysphagia, and pathological find-

ings on muscle biopsy.³ An overlap syndrome of rheumatoid arthritis and one of the idiopathic inflammatory myopathies is possible in this patient who presented with proximal muscle weakness and elevated blood levels of creatine kinase and lactate dehydrogenase.

There are several diagnoses within the spectrum of idiopathic inflammatory myopathies to consider in this patient. Juvenile dermatomyositis can be ruled out on the basis of her age. Although patients with inclusion-body myositis can have symptoms that involve the hands, this patient did not have the characteristic weakness in the finger flexors that is associated with inclusion-body myositis. In addition, she had a decrease in her symptoms after treatment with azathioprine was started, whereas patients with inclusion-body myositis typically do not have a rapid or strong clinical response to therapy. She did not have a rash, which makes dermatomyositis unlikely. She was not taking a statin, and although statin use is not a requisite for the development of immune-mediated necrotizing myositis, it is a common association.⁴ Antisynthetase syndrome is associated with inflammatory arthritis and proximal muscle weakness, as well as Raynaud's phenomenon, fever, interstitial lung disease, mechanic's hands (rough, cracking, dry skin most commonly located over the distal aspects of the fingers and particularly involving the index finger [radial side] and thumb [ulnar side]), and the presence of an anti-transfer RNA synthetase antibody.^{5,6} The patient's inflammatory arthritis was due to rheumatoid arthritis, and she did not have other clinical features that would suggest antisynthetase syndrome.

An overlap syndrome of rheumatoid arthritis and polymyositis remains a possible diagnosis in this patient. Electromyography (EMG) and nerve-conduction studies, magnetic resonance imaging (MRI) of the muscles, serologic testing to include evaluation for myositis-associated or myositis-specific autoantibodies, or a muscle biopsy could be pursued for further investigation. However, polymyositis is typically characterized by proximal muscle weakness without myalgia, paresthesia, or muscle spasms.

MIXED CONNECTIVE-TISSUE DISEASE

Proximal muscle weakness is also a manifestation of mixed connective-tissue disease. Mixed connective-tissue disease is characterized by the

presence of anti-U1-RNP antibodies in association with features of several different rheumatic conditions, without meeting classification criteria for any one disease. Although we know that this patient had a positive anti-U1-RNP antibody test, we do not know the titer. If the titer of anti-U1-RNP antibodies was low, it would have minimal clinical significance. Regardless, in this patient with a diagnosis of rheumatoid arthritis, an overlap syndrome is more likely than mixed connective-tissue disease.

INFILTRATIVE DISEASES

Both amyloidosis and sarcoidosis can be manifested by proximal muscle weakness and can be associated with carpal tunnel syndrome, which could explain the paresthesia in this patient's hands. Although a diagnosis of either amyloidosis or sarcoidosis could explain her proximal muscle weakness and paresthesia, muscle spasms would be an unusual feature of either disease. The patient did not have any known chronic inflammatory conditions, chronic kidney disease, rash, or macroglossia, features that would be suggestive of amyloidosis. In addition, she did not have lymphadenopathy, uveitis, or rash, which would be suggestive of sarcoidosis. I will consider other explanations for her presentation, but I would reconsider infiltrative disease if an alternative diagnosis were not identified.

MEDICATIONS

Many medications have been associated with myalgia or proximal muscle weakness. The patient's current medications included azathioprine (started 2 months before the current presentation for muscle weakness) and longer-standing treatment with leflunomide (for rheumatoid arthritis), calcium supplementation and calcitriol (for hypoparathyroidism), and levothyroxine (for hypothyroidism that developed after treatment for Graves' disease). The patient's symptoms predated azathioprine treatment, and she felt better after starting this medication; thus, an adverse effect from azathioprine would be unlikely to explain her presentation. Leflunomide can cause myalgia, but it has not specifically or commonly been associated with muscle weakness. Calcium supplements, calcitriol, and levothyroxine are not known to cause proximal muscle weakness.

Previous medications have included methotrexate, rifampin, isoniazid, methimazole, and hydroxychloroquine. Methotrexate and rifampin

are not typically associated with muscle-related adverse effects. Although isoniazid, methimazole, and hydroxychloroquine can have myopathic adverse effects, the use of each of these medications by this patient was remote and thus was not likely to have contributed to her current presentation.

INFECTIONS

The bacterial infections that are most commonly associated with myalgia and proximal muscle weakness are those related to contiguous spread of *Staphylococcus aureus* infection. Infection with coxsackievirus B, influenza virus, parainfluenza virus, cytomegalovirus, Epstein-Barr virus, hepatitis B and C viruses, or severe acute respiratory syndrome coronavirus 2 can also be associated with myalgia and proximal muscle weakness. Fungal pathogens to consider include aspergillus, cryptococcus, and *Pneumocystis jirovecii*, and parasites to consider include trichinella and *Toxoplasma gondii*. The patient had been taking azathioprine for 2 months, so she was immunocompromised. However, she did not have fever or other infectious signs or symptoms; thus, although an infectious process is possible, I think that it is unlikely to explain her current presentation.

METABOLIC DERANGEMENTS

Patients with metabolic myopathies that are related to disorders of carbohydrate, lipid, or purine metabolism often have proximal muscle weakness. However, I would have expected this patient to have had symptoms earlier in life if a metabolic myopathy was the cause.

Proximal muscle weakness can manifest in patients deficient in vitamin D, phosphorus, or calcium, as well as in patients with hypothyroidism or hyperthyroidism. This patient presented with not only muscle symptoms but also nerve symptoms (paresthesia and muscle spasms); therefore, I will focus on conditions that could explain both muscle and nerve symptoms.

Hypothyroidism can be associated with both muscle symptoms and paresthesia, particularly in the context of carpal tunnel syndrome. This patient's treatment for Graves' disease resulted in hypothyroidism, and her levothyroxine replacement dose could be too low. In addition, she has hypoparathyroidism, for which she was prescribed calcium supplementation and calcitriol. She was uncertain of the formulation and

dose of her calcium supplementation regimen, so it is possible that the calcium supplementation has not been adequate. Hypoparathyroidism, with associated hypocalcemia, can be manifested by proximal muscle weakness and myalgia with the additional symptom of muscle spasms. Patients with profound hypocalcemia can have elevated creatine kinase levels. Overall, I suspect that hypocalcemia resulting from hypoparathyroidism is the most likely explanation for her presentation. I suspect that the diagnostic test was a comprehensive metabolic panel, which would include measurement of blood levels of calcium and albumin.

DR. MARCY B. BOLSTER'S DIAGNOSIS

Hypoparathyroidism with symptomatic hypocalcemia.

ENDOCRINOLOGY DIAGNOSTIC TESTING

Dr. Steven K. Grinspoon: Diagnostic laboratory test results obtained at the rheumatology clinic included a blood calcium level of 5.9 mg per deciliter (1.5 mmol per liter; reference range, 8.5 to 10.5 mg per deciliter [2.1 to 2.6 mmol per liter]) and a blood phosphorus level of 4.5 mg per deciliter (1.5 mmol per liter; reference range, 2.6 to 4.5 mg per deciliter [0.8 to 1.5 mmol per liter]). The ionized calcium level, which reflects biologically active calcium, was low, at 0.77 mmol per liter (reference range, 1.14 to 1.30). The blood level of creatine kinase was 2645 U per liter.

The patient was instructed to present to the emergency department of this hospital for further evaluation and treatment of severe hypocalcemia with symptoms. Additional test results included normal blood levels of albumin, creatinine, 25-hydroxyvitamin D, and thyrotropin. The blood level of parathyroid hormone (PTH) was inappropriately normal, at 35 pg per milliliter (reference range, 10 to 60), which indicated hypoparathyroidism. The phosphorus level, which was at the upper limit of the reference range, was also consistent with hypoparathyroidism.

DISCUSSION OF ENDOCRINOLOGY MANAGEMENT

Dr. Grinspoon: The patient's severe hypocalcemia with associated symptoms was initially treated

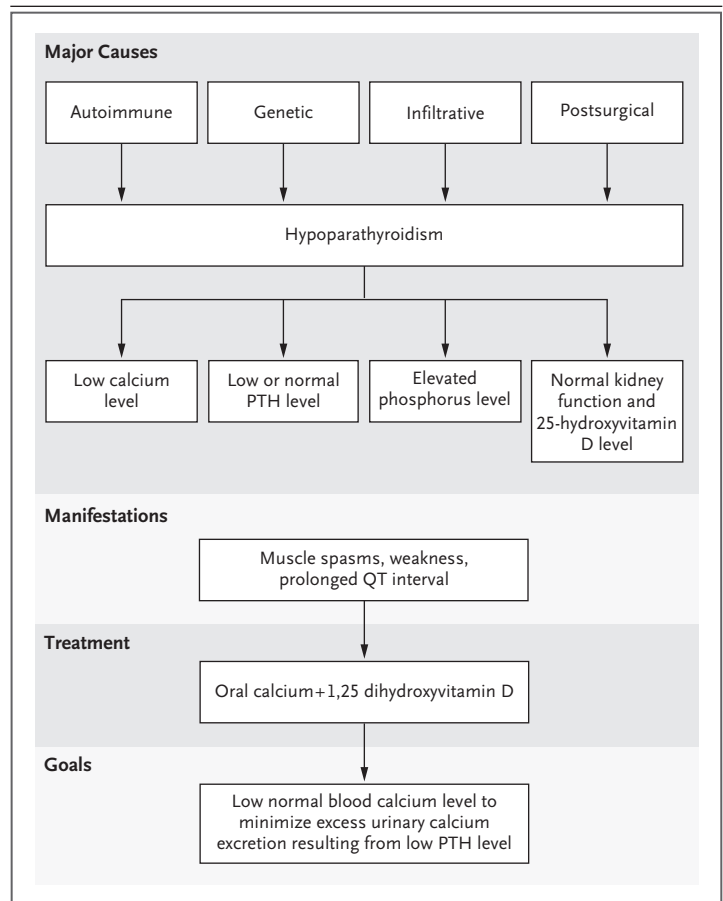


Figure 1. Major Causes, Manifestations, Treatment, and Goals of Treatment in Patients with Hypoparathyroidism.

Hypoparathyroidism is commonly caused by neck surgery, infiltrative or destructive diseases, autoimmune diseases, or genetic or developmental conditions, but it can be idiopathic. Typically, the calcium level is low, and parathyroid hormone (PTH) levels are low or inappropriately normal; the phosphorus level is either elevated or at the upper limit of the reference range. Hypocalcemia can lead to muscle spasms, muscle weakness, and myalgia, as well as a prolonged QT interval on electrocardiography. Treatment includes calcium and vitamin D supplementation. In patients with hypoparathyroidism, conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D is impaired, and treatment with calcitriol is needed for vitamin D replacement. Treatment of hypoparathyroidism can be difficult because calcium is not reabsorbed in the distal nephron owing to the low PTH levels, and the urinary calcium level can increase and ultimately lead to nephrolithiasis. Patients are often treated with a goal of a low normal calcium level to simultaneously minimize symptoms and avoid excess urinary calcium excretion.

with intravenous calcium. Intravenous calcium gluconate is usually used to avoid irritation from extravasation of intravenous fluid.

The cause of the hypoparathyroidism in this patient was not entirely clear. The differential diagnosis of hypoparathyroidism includes neck surgery, infiltrative and destructive diseases, autoimmune diseases, and genetic and develop-

mental conditions (Fig. 1). She had no family history of hypocalcemia. There was no history that was consistent with autoimmune polyglandular syndrome type 1, nor was there a history of early development of hypocalcemia in childhood. She was not receiving any medications that were known to be associated with hypocalcemia. She had been treated with radioactive iodine ablation for Graves' disease, and rare case reports have described the development of hypoparathyroidism in such circumstances.^{7,8} Acquired hypoparathyroidism can be due to autoimmune mechanisms, including activating autoantibodies to the calcium-sensing receptor in the context of ongoing autoimmune disease, which may be of relevance to this patient, given her underlying autoimmune diagnosis.

In patients with hypoparathyroidism, conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D is impaired, and treatment with calcitriol (synthetic 1,25-dihydroxyvitamin D) is needed for vitamin D replacement. This patient was transitioned to a stable dose of oral calcium citrate–cholecalciferol and calcitriol, with subsequent normalization of her calcium level to 8.4 mg per deciliter (2.1 mmol per liter). Treatment of hypoparathyroidism can be difficult because calcium is not reabsorbed in the distal

nephron owing to the low PTH levels, and the urinary calcium level can increase and ultimately result in nephrolithiasis. Currently, patients are typically treated with supplemental calcium and calcitriol, with a goal of a low normal calcium level to minimize symptoms and avoid excess urinary calcium excretion. Thiazide diuretic agents can help to reduce urinary calcium excretion but were not used in this patient. PTH replacement therapy is approved by the Food and Drug Administration but is not currently available; however, this may be a promising treatment option in the future.⁹

RHEUMATOLOGY DIAGNOSTIC TESTING

Dr. Eli M. Miloslavsky: When we first evaluated the patient, the available test results included the calcium level of 5.9 mg per deciliter, as well as a markedly elevated creatine kinase level. Proximal muscle weakness, myalgia, and a substantially elevated creatine kinase level increased our suspicion for idiopathic inflammatory myopathies. However, the presence of hypocalcemia in the context of hypoparathyroidism would explain the patient's muscle spasms and paresthesia, as well as her myopathy. Some endocrinopathies, such as hyperthyroidism, typically cause myopathy in patients with a normal creatine kinase level. In contrast, patients with hypoparathyroid myopathy typically present with an elevated creatine kinase level; thus, hypoparathyroid myopathy was considered to be the most likely diagnosis in this case.¹⁰

The diagnosis of hypocalcemic hypoparathyroid myopathy could have been confirmed by monitoring the patient's symptoms and creatine kinase level after calcium repletion therapy was started. However, because of the facts that her symptoms resulted in hospitalization, that the morbidity associated with untreated idiopathic inflammatory myopathies is high, and that she lived outside the United States, we chose to further evaluate the possibility of idiopathic inflammatory myopathies.

Commercially available myositis panels include both myositis-specific and myositis-associated antibodies (Table 1).¹¹ The presence of a myositis-specific antibody would have suggested idiopathic inflammatory myopathies in this case;

Table 1. Myositis-Specific and Myositis-Associated Antibodies.

Myositis-specific antibodies

Anti-tRNA synthetase antibodies (associated with interstitial lung disease): anti-Jo-1, anti-PL-7, anti-PL-12, anti-EJ, anti-OJ, anti-KS, anti-Ha, and anti-Zo

Anti-MDA-5 (associated with rapidly progressive interstitial lung disease)

Anti-TIF-1γ (associated with cancer)

Anti-SRP (associated with necrotizing myopathy)

Anti-Mi-2 (associated with frequent cutaneous manifestations)

Anti-HMG-CoA reductase (associated with statin-induced necrotizing autoimmune myopathy)

Anti-NXP-2 (associated with frequent cutaneous manifestations)

Anti-SAE (associated with frequent cutaneous manifestations)

Anti-cN1A (associated with inclusion-body myositis)

Myositis-associated antibodies

Anti-U1-RNP

Anti-Ro

Anti-PM-Scl

Anti-Ku

the presence of such an antibody can also be helpful in predicting the phenotype and severity of disease. However, these antibodies are absent in approximately 40% of patients with idiopathic inflammatory myopathies.¹² Furthermore, positive myositis antibody tests must be interpreted carefully, with particular attention to the pretest probability of an inflammatory myositis and the specificity of the antibody.

MRI and EMG are relatively sensitive methods for detecting muscle injury, particularly in patients with idiopathic inflammatory myopathies.¹³ However, the presence of myopathy on the basis of either method is nonspecific and does not confirm the cause of muscle injury. Both are also important for identifying which muscle groups are involved to determine the appropriate site for a muscle biopsy. When obtaining an EMG for this purpose, we typically perform unilateral EMG, followed by a biopsy on the contralateral side because idiopathic inflammatory myopathies tend to be symmetric and muscle stimulation during EMG can affect muscle biopsy results. In this case, we chose to obtain an MRI of the left arm.

Dr. Alexis M. Cahalane: MRI of the left arm was performed without the administration of intravenous contrast material (Fig. 2). T2-weighted fat-saturated images showed no bone marrow, muscle, or fascial edema. T1-weighted images showed no evidence of fatty infiltration or atrophy of the muscles. No fracture or marrow-replacing lesion was identified.

Dr. Miloslavsky: Given the negative MRI results, which further decreased the probability of idiopathic inflammatory myopathies, we chose not to pursue a muscle biopsy. After calcium repletion therapy, the patient's symptoms abated rapidly, and by the time she was discharged from the hospital, the creatine kinase level had decreased to 227 U per liter. The results of the myositis panel, which became available after her discharge, did not identify any additional positive antibodies. Therefore, the response to calcium repletion therapy and the negative MRI and myositis panel were all consistent with hypocalcemic hypoparathyroid myopathy. Although the reason she felt better after treatment with azathioprine was unclear, we recommended discontinuation of azathioprine and resumption of leflunomide because her rheumatoid arthritis

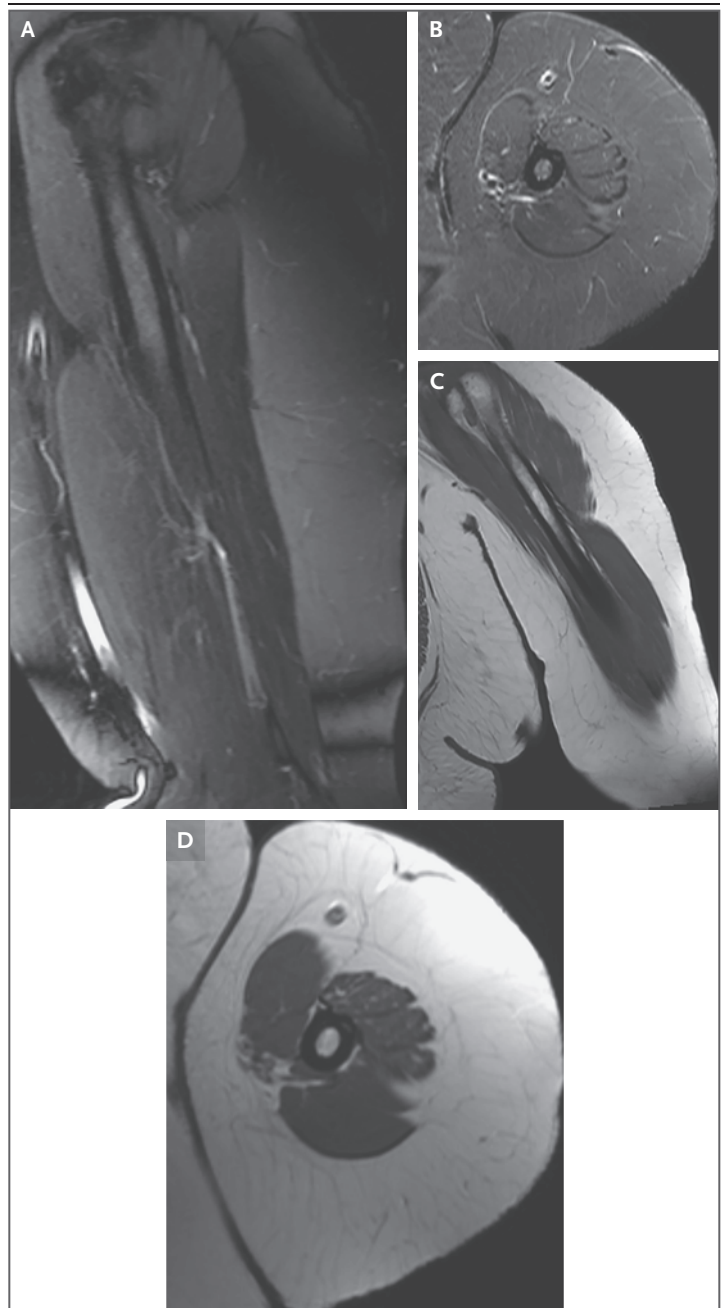


Figure 2. MRI of the Arm.

Sagittal (Panel A) and axial (Panel B) T2-weighted fat-saturated images of the left arm show no bone marrow, muscle, or fascial edema. Coronal (Panel C) and axial (Panel D) T1-weighted images of the left arm show no evidence of fatty infiltration or atrophy of the muscles. No fracture or marrow-replacing lesion is present.

had been in remission with the use of leflunomide therapy and because her myopathy was not inflammatory in nature.

FOLLOW-UP

Dr. Grinspoon: The importance of routine appointments with the patient's local endocrinologist was emphasized so that her doses of calcium and calcitriol could be adjusted appropriately, her urinary calcium level could be monitored, and any new prospective therapeutic options, including PTH replacement therapy, could be discussed. After the patient was discharged, we recommended an additional outpatient workup that included genetic testing for a possible activating mutation in the calcium-sensing receptor and for mutations associated with autoimmune hypoparathyroidism; however, such mutations

were probably unlikely to be present, given that symptoms did not develop in this patient until later in life. Assessment of autoantibodies to the calcium-sensing receptor in the context of her autoimmune disease might also be useful.¹⁴

FINAL DIAGNOSIS

Hypocalcemic myopathy due to hypoparathyroidism.

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.

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REFERENCES

1. Nishimura K, Sugiyama D, Kogata Y, et al. Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. *Ann Intern Med* 2007;146:797-808.
2. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum* 2010;62:2569-81.
3. Lundberg IE, Tjärnlund A, Bottai M, et al. 2017 European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups. *Ann Rheum Dis* 2017;76:1955-64.
4. Pinal-Fernandez I, Casal-Dominguez M, Mammen AL. Immune-mediated necrotizing myopathy. *Curr Rheumatol Rep* 2018;20:21.
5. Chatterjee S. Mechanic's hands. *N Engl J Med* 2021;384(6):e16.
6. Sohara E, Saraya T, Sato S, et al. Mechanic's hands revisited: is this sign still useful for diagnosis in patients with lung involvement of collagen vascular diseases? *BMC Res Notes* 2014;7:303.
7. Burch WM, Posillico JT. Hypoparathyroidism after I-131 therapy with subsequent return of parathyroid function. *J Clin Endocrinol Metab* 1983;57:398-401.
8. Jialal I, Pillay NL, Asmal AC. Radioiodine-induced hypoparathyroidism: a case report. *S Afr Med J* 1980;58:939-40.
9. Khan AA, Guyatt G, Ali DS, et al. Management of hypoparathyroidism. *J Bone Miner Res* 2022;37:2663-77.
10. Policepatil SM, Caplan RH, Dolan M. Hypocalcemic myopathy secondary to hypoparathyroidism. *WMJ* 2012;111:173-5.
11. McHugh NJ, Tansley SL. Autoantibodies in myositis. *Nat Rev Rheumatol* 2018;14:290-302.
12. Mammen AL. Autoimmune myopathies: autoantibodies, phenotypes and pathogenesis. *Nat Rev Neurol* 2011;7:343-54.
13. Tomasová Studynková J, Charvát F, Jarosová K, Vencovsky J. The role of MRI in the assessment of polymyositis and dermatomyositis. *Rheumatology (Oxford)* 2007;46:1174-9.
14. Tomar N, Gupta N, Goswami R. Calcium-sensing receptor autoantibodies and idiopathic hypoparathyroidism. *J Clin Endocrinol Metab* 2013;98:3884-91.

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