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Case 32-2026: A 50-Year-Old Man with Recurrent Cardiomyopathy

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PRESENTATION OF CASE

Dr. Christopher H. Newton-Cheh: A 50-year-old man was evaluated at this hospital because of recurrent systolic heart failure.

The patient had a history of hypertension, hypercholesterolemia, and obstructive sleep apnea. Eleven years before the current presentation, he was admitted to this hospital because of fever, chills, and dyspnea after a trip to the Caribbean. Laboratory testing showed leukocytosis, acute kidney injury, and increased levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), troponin T, and N-terminal pro–B-type natriuretic peptide; laboratory test results are shown in Table 1. An electrocardiogram (ECG) was normal. Transthoracic echocardiography revealed a left ventricular ejection fraction of 21% with moderately reduced right ventricular systolic function; no ventricular dilatation or myocardial wall thickening was noted. The patient had progressive cardiogenic shock in the first hours after admission, and venoarterial extracorporeal membrane oxygenation (ECMO) was initiated.

On hospital day 3, the patient was weaned from ECMO, and the ventricular function normalized. Blood cultures showed no growth, and an extensive infectious disease workup was negative, except for a mildly elevated level of anti–streptolysin O antibodies. A presumptive diagnosis of poststreptococcal myocarditis was made. The patient completed a 14-day course of amoxicillin, and treatment with an oral beta-blocker and an angiotensin-converting–enzyme inhibitor was initiated.

Approximately 2 years later, and 9 years before the current presentation, the patient was evaluated at another hospital because of acute abdominal and leg pain on the right side. Computed tomography (CT) of the abdomen, performed after the administration of intravenous contrast material, reportedly showed an infarct in the right kidney, along with a filling defect and possible focal dissection in the right renal artery. Ultrasonography of the right leg reportedly showed no venous thrombi. Treatment with warfarin was initiated.

Transthoracic and transesophageal echocardiography reportedly showed low-normal ventricular function. No valvular vegetations, intracardiac thrombi, or intracardiac shunts were detected. Blood cultures showed no growth. Magnetic resonance

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Table 1. Laboratory Data.*

Variable	Reference Range, Adults, This Hospital†	11 Yr before Current Presentation, This Hospital	4 Yr before Current Presentation, Primary Care Clinic	4 Yr before Current Presentation, Endocrinology Clinic	3 Yr before Current Presentation, Hematology Clinic	On Current Presentation, Emergency Department	Hospital Day 2
Hemoglobin (g/dl)	13.5–17.5	17.5	18.1	—	18.8	15.3	15.5
Hematocrit (%)	41.0–53.0	50.0	53.4	—	56.7	48.5	49.3
Red-cell count (per μl)	4,500,000–5,900,000	5,430,000	5,680,000	—	6,340,000	5,380,000	5,500,000
Mean corpuscular volume (fl)	80.0–100.0	92.0	94.0	—	89.4	90.1	89.6
Mean corpuscular hemoglobin (pg)	26.0–34.0	35.0	31.9	—	29.7	28.4	28.2
White-cell count (per μl)	4500–11,000	21,500	7360	—	10,170	14,230	12,730
Platelet count (per μl)	150,000–400,000	288,000	238,000	—	310,000	400,000	369,000
Sodium (mmol/liter)	135–145	135	139	—	141	135	129
Potassium (mmol/liter)	3.4–5.0	5.1	4.7	—	4.2	4.7	4.4
Chloride (mmol/liter)	98–108	96	98	—	100	95	101
Carbon dioxide (mmol/liter)	23–32	28	28	—	27	20	20
Urea nitrogen (mg/dl)	8–25	16	18	—	14	22	19
Creatinine (mg/dl)	0.60–1.50	2.07	1.33	—	1.42	1.45	1.38
Glucose (mg/dl)	70–110	150	89	—	94	106	84
Albumin (g/dl)	3.3–5.0	3.3	4.4	—	4.7	3.9	3.6
Alanine aminotransferase (U/liter)	10–55	63	67	—	58	195	173
Aspartate aminotransferase (U/liter)	10–40	62	50	—	38	129	98
Alkaline phosphatase (U/liter)	45–115	83	66	—	73	169	176
Total bilirubin (mg/dl)	0.0–1.0	1.4	0.8	—	0.9	1.1	1.3
Direct bilirubin (mg/dl)	0.0–0.4	0.5	—	—	—	0.4	0.4
Lactate (mmol/liter)	0.5–2.2	3.1	—	—	—	1.9	—
Troponin T (ng/ml)	<0.03	0.71	—	—	—	—	—
High-sensitivity troponin T (ng/liter)	0–9	—	—	—	—	25	20
N-terminal pro–B-type natriuretic peptide (pg/ml)	<900	3178	—	—	—	3494	—
Coxsackievirus B2 antibody (titer)	<1:8	1:8	—	—	—	1:16	—
Coxsackievirus B3 antibody (titer)	<1:8	1:8	—	—	—	1:16	—

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Coxsackievirus B5 antibody (titer)	<1:8	1:8	—	—	—	1:8	—
Coxsackievirus B6 antibody (titer)	<1:8	1:8	—	—	—	1:8	—
Anti–streptolysin O antibody (U/ml)	<530	672	—	—	—	—	—
Anti–DNase B antibody (U/ml)	<300	725	—	—	—	—	—
Anti–smooth-muscle antibody (titer)	<1:20	Negative	—	—	—	—	1:40
C-reactive protein (mg/liter)	<8.0	—	—	—	—	—	67.1
Erythropoietin (mIU/ml)	2.6–18.5	—	—	—	5.9	—	—
Lactate dehydrogenase (U/liter)	110–210	—	—	—	150	—	—
D-dimer (ng/ml)	<500	—	—	—	—	718	—
Thyrotropin (μIU/ml)	0.40–5.00	2.96	1.99	—	2.25	—	0.64
Glycated hemoglobin (%)	4.3–5.6	—	5.4	—	—	—	5.8
Cholesterol (mg/dl)	0–200	—	216	—	212	—	90
Low-density lipoprotein cholesterol (mg/dl)	50–129	—	128	—	107	—	49
High-density lipoprotein cholesterol (mg/dl)	35–100	—	36	—	35	—	22
Triglycerides (mg/dl)	0–150	—	260	—	349	—	93
Iron (μg/dl)	30–160	—	131	—	—	—	30
Total iron-binding capacity (μg/dl)	230–404	—	310	—	—	—	332
Ferritin (μg/liter)	10–200	—	164	—	116	—	43
Total testosterone, morning (ng/dl)	249–836	—	95	187	130	—	—
Free testosterone (ng/dl)	6.16–19.40	—	—	3.65	2.84	—	—
Sex hormone–binding globulin (nmol/liter)	13–71	—	—	29	24	—	—
Normetanephrine (nmol/liter)	<0.90	—	—	—	—	—	0.92
Metanephrine (nmol/liter)	<0.50	—	—	—	—	—	0.33

* To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for bilirubin to micromoles per liter, multiply by 17.1. To convert the values for lactate to milligrams per deciliter, divide by 0.1110. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for iron and iron-binding capacity to micromoles per liter, multiply by 0.1791.

† 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.

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imaging of the legs reportedly showed patchy perivascular inflammation of the lower legs. A diagnosis of polyarteritis nodosa was considered, and empirical treatment with a tapering course of prednisone, followed by azathioprine, was prescribed.

Subsequent evaluation included renal arteriography, which reportedly showed tapering of the right renal artery without dissection or microaneurysm. No evidence of microaneurysm, narrowing, or dissection of the superior mesenteric, celiac, splenic, hepatic, iliac, or femoral arteries was noted. Genetic testing for variants associated with aortopathy was negative. A biopsy of the gastrocnemius muscle showed no vasculitis.

During the next 5 years, the patient was followed in the primary care, cardiology, nephrology, rheumatology, general medicine, sleep medicine, and psychiatry clinics of this hospital. He made the decision to stop taking azathioprine, and treatment with warfarin was discontinued after a spontaneous muscle hematoma occurred.

Four years before the current presentation, the patient was evaluated by his primary care physician for fatigue. The physical examination was reportedly normal. The blood level of thyrotropin was normal, but the total testosterone level was decreased; laboratory test results are shown in Table 1.

Three months later, the patient was evaluated by an endocrinologist at this hospital. He reported poor sleep, reduced libido, and intermittent fatigue. The physical examination was normal; the testicular volume, as measured by a Prader orchidometer, was 15 ml on both sides (reference range, 15 to 25). The levels of follicle-stimulating hormone and luteinizing hormone were normal; other laboratory test results are shown in Table 1. Treatment for obstructive sleep apnea, which is a risk factor for low testosterone levels, was recommended.

Three years before the current presentation, the patient was evaluated by a hematologist after routine laboratory testing showed erythrocytosis (red-cell count, 6,340,000 per microliter; reference range, 4,500,000 to 5,900,000). The blood pressure was 150/108 mm Hg; the remainder of the physical examination was normal. The carboxyhemoglobin level was normal, and testing for the V617F mutation in the gene encoding Janus kinase 2 (*JAK2*) was negative; other laboratory test results are shown in Table 1. Erythrocytosis was attributed to obstructive sleep apnea and renal-artery stenosis.

On the current presentation, the patient was evaluated in the emergency department of this hospital because of 5 days of progressive chest congestion and tightness, fatigue, leg edema, and progressive dyspnea after a trip to the Caribbean. He also noted that his pulse had been 130 beats per minute, as compared with his baseline pulse of 80 beats per minute. The patient reported several years of erectile dysfunction and decreased libido. He reported no known sick contacts, illicit drug use, exposure to animals or insects, or consumption of raw, undercooked, new, or unusual foods during his recent travel. He noted that he had previously used a tanning bed and applied spray tan.

The patient's medical history also included hepatic steatosis, diverticulosis, anxiety, and surgical repairs for a rotator-cuff injury and traumatic tears of the biceps tendon and a knee ligament. Medications included amlodipine and hydrochlorothiazide. The patient had been vaccinated against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during the 3 months before the current presentation. He had no known adverse reactions to medications. He worked as a facility manager. He lived with his wife and children in eastern Massachusetts. He drank beer occasionally and smoked marijuana several times per year; he was a lifelong nonsmoker. He drank four to six caffeinated beverages daily. The patient described himself as a workout "fanatic" and exercised most days of the week. Multiple family members had hypertension and diabetes. His father had coronary artery disease, and his maternal grandfather had died from heart failure.

On examination, the temporal temperature was 35.8°C, the heart rate 134 beats per minute, the blood pressure 148/106 mm Hg, the respiratory rate 28 breaths per minute, and the oxygen saturation 99% while the patient was breathing ambient air. The weight was 83.5 kg, and the body-mass index (the weight in kilograms divided by the square of the height in meters) was 29.7. He was muscular, tanned, anxious, and in mild distress. The cardiac examination was notable for tachycardia, a systolic murmur at the base, and an S3 heart sound. The jugular venous pressure was not elevated. The lungs were clear on auscultation, without rales or wheezes. Symmetric

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edema was present in the legs. The remainder of the examination was normal.

An ECG (Fig. 1) showed sinus tachycardia, left atrial abnormality, delayed R-wave progression, and nonspecific ST-segment and T-wave changes. A urine toxicology screening test was negative. Other laboratory test results are shown in Table 1.

Dr. Shahmir C. Kamalian: A chest radiograph (Fig. 2A) showed mild enlargement of the cardiac silhouette. Ultrasonography of the legs showed no deep venous thrombi. CT of the chest, performed after the administration of intravenous contrast material timed to detect pulmonary embolism (Fig. 2B and 2C), showed a mildly enlarged pulmonary artery without pulmonary embolism. There was also evidence of focal coronary calcifications, perihilar bronchial-wall thickening, mild gynecomastia that was more prominent on the left side than on the right side, and a left renal cyst. Ultrasonography of the right upper abdomen showed small gallbladder polyps but otherwise showed normal results.

Dr. Newton-Cheh: The patient was admitted to the hospital. Echocardiography revealed severe diffuse left ventricular dysfunction (left ventricular ejection fraction, 20%) with no dilatation, right ventricular dilatation and dysfunction, biatrial dilatation, moderate mitral regurgitation, and trace pericardial effusion. Oral captopril and hydralazine were administered.

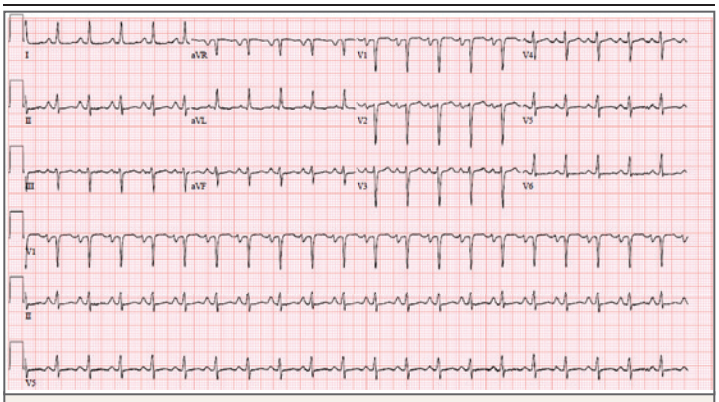


Figure 1. Electrocardiogram Obtained at the Current Presentation.
An electrocardiogram shows sinus tachycardia, left atrial abnormality, poor R-wave progression, and nonspecific ST-segment and T-wave changes.

On hospital day 2, the heart rate was 119 beats per minute, the blood pressure 126/94 mm Hg, and the oxygen saturation 100% while the patient was breathing ambient air. Tests for antineutrophil cytoplasmic antibodies (ANCA), antinuclear antibodies, cytomegalovirus (CMV) IgM, hepatitis B virus core IgM and surface antigen, hepatitis C virus (HCV) antibodies, human herpesvirus 6 (HHV-6) IgM, parvovirus B19 IgM, *Trypanosoma cruzi* antibodies, and varicella–zoster virus IgM were negative, as were screening tests for *Borrelia burgdorferi* and human immunodeficiency virus (HIV) types 1 and 2. Testing for SARS-CoV-2 RNA was also negative. The blood

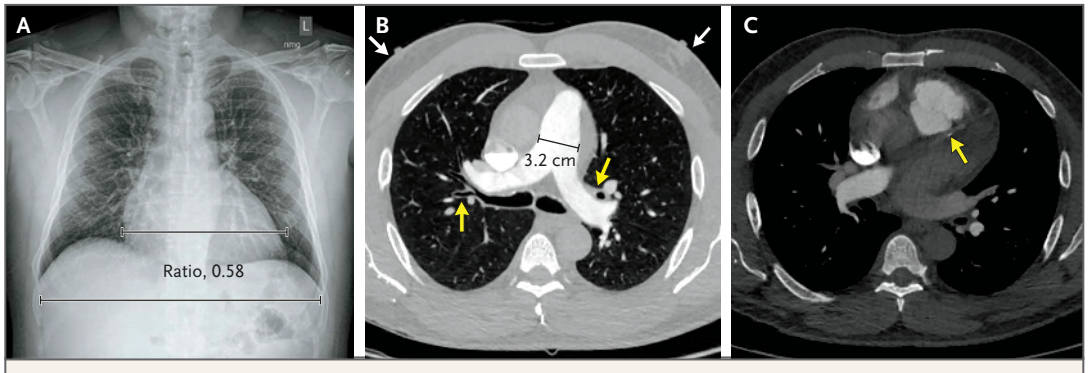


Figure 2. Chest Imaging Studies Obtained at the Current Presentation.
A posteroanterior chest radiograph (Panel A) shows a cardiothoracic ratio that exceeds 50%, which indicates enlargement of the cardiac silhouette. The lungs are clear, and no other abnormalities are seen. Representative axial images from a pulmonary CT angiogram with lung and bone window settings (Panels B and C, respectively) show enlargement of the pulmonary trunk (3.2 cm in width), which exceeds the upper limit of the normal range (2.9 cm). Subtle peribronchial cuffing is present (Panel B, yellow arrows), which is a nonspecific finding associated with conditions such as pulmonary edema or reactive airway disease. Asymmetric bilateral glandular breast tissue, which is more prominent on the left side, is present (Panel B, white arrows), a finding suggestive of gynecomastia. Coronary calcifications are seen (Panel C, arrow). There is no evidence of pulmonary embolism.

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levels of angiotensin-converting enzyme, rheumatoid factor, and selenium were normal; other laboratory test results are shown in Table 1.

A diagnosis was made.

DIFFERENTIAL DIAGNOSIS

Dr. Dale S. Adler: This 50-year-old man, who describes himself as an exercise enthusiast, initially presented with cardiac dysfunction and cardiogenic shock after returning from a trip to the Caribbean at 39 years of age. At that time, the cardiac dysfunction resolved rapidly after the patient received brief mechanical circulatory support. He now presents with biventricular dysfunction after another trip to the Caribbean.

During the 11 years between these fulminant cardiac presentations, the patient had fatigue, insomnia, and loss of libido. Medical evaluations revealed hypertension, impaired glucose tolerance, reduced high-density lipoprotein (HDL) cholesterol levels, elevated AST and ALT levels, erythrocytosis with a normal erythropoietin level, low-normal testicular volumes, and a low level of testosterone.

The patient's initial presentation of heart failure, 11 years before the current presentation, was characterized by biventricular dysfunction without chamber dilatation or wall thickening, findings suggestive of an acute cardiac process. The patient's current presentation includes right ventricular dilatation that could be related to long-standing obstructive sleep apnea, hypertension, or diastolic dysfunction. However, the current left ventricular dysfunction without dilatation again suggests an acute cardiac process. Acute coronary syndrome is unlikely with either presentation, given the absence of ischemic ECG changes. I will begin by considering syndromes that cause fulminant myocarditis that can be reversible and recurrent,[1] with the understanding that the correct diagnosis will probably also account for the patient's most prominent symptoms in the intervening years.

CAUSES OF MYOCARDITIS

The patient's initial presentation of heart failure predated the coronavirus disease 2019 (Covid-19) pandemic, and myocarditis due to Covid-19 is unlikely to explain the patient's current presentation in the absence of other manifestations of Covid-19, such as sore throat, nasal congestion, or fever. HHV-6 and parvovirus B19 infections are associated with local myocardial damage involving the septum and posterolateral wall, respectively. Infections with adenovirus, influenza virus, coxsackievirus, CMV, Epstein–Barr virus (EBV), HIV, and HCV are associated with diffuse cardiac dysfunction, similar to the findings noted in this patient. Most of these infections were ruled out with testing performed during the initial presentation, the current presentation, or both, although testing for EBV antibodies was not performed. The low titers of antibodies against coxsackievirus are most consistent with previous infection.

Lyme disease is a well-described cause of myocarditis that was ruled out during both presentations of heart failure in this patient. Fulminant myocarditis has been described with anaplasmosis in an immunocompromised patient,[2] but anaplasmosis is unlikely in this patient's case in the absence of neutropenia and thrombocytopenia. *Babesia microti* and rickettsia infections are unlikely in the absence of hemolytic anemia and rash.

Staphylococcal infection, especially that involving toxin production, can be associated with fulminant myocarditis. Blood cultures showed no growth during the patient's initial presentation of heart failure 11 years earlier. At that time, a presumed diagnosis of poststreptococcal myocarditis was made. Although streptococcal pharyngitis is common, poststreptococcal myocarditis is rare. The condition is distinguished from rheumatic manifestations of streptococcal infection by the timing relative to pharyngitis, with a reported mean onset of 3.1 days after pharyngitis.[3] ST-segment changes that are characteristic of myocarditis are usually seen on ECG, and the left ventricular ejection fraction is either normal or slightly reduced.[3] This patient did not have pharyngitis or characteristic ST-segment changes and had a severely reduced ejection fraction, features that make poststreptococcal myocarditis an unlikely explanation for either of his presentations of heart failure. The elevated level of anti–streptolysin O antibodies that was observed during the patient's first presentation of heart failure is a nonspecific finding that can occur in the context of any immune activation.

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AUTOIMMUNE MYOCARDITIS

Autoimmune causes of fulminant myocarditis include giant-cell arteritis, sarcoidosis, celiac disease, and systemic lupus erythematosus. Hallmark features of giant-cell arteritis and sarcoidosis are conduction alterations and arrhythmia, neither of which was present in this patient. None of these autoimmune conditions would be expected to resolve quickly without specific treatment.

EOSINOPHILIC MYOCARDITIS

Causes of eosinophilic myocarditis include hypersensitivity reactions, hypereosinophilic syndromes, ANCA-positive diseases, and cancers. Use of hydrochlorothiazide has been associated with eosinophilic myocarditis, but this patient's first presentation of heart failure preceded treatment with this medication. We are not provided with the white-cell differential count, which would allow us to evaluate for peripheral eosinophilia, although eosinophilia is not always present in patients with eosinophilic myocarditis. Similar to autoimmune myocarditis, eosinophilic myocarditis would be unlikely to resolve rapidly without specific treatment.[4]

TOXIN- OR MEDICATION-RELATED MYOCARDITIS

The urine toxicology screening test, which at this hospital includes testing for cocaine, was negative in this patient; therefore, several causes of toxin-related myocarditis were ruled out. Alcohol can also cause cardiomyopathy, but the reported consumption was not substantial enough to be causal in this patient's case. No insect bites or scorpion bites were reported. The patient had no exposure to chemotherapy or immune checkpoint inhibitor treatment.

ANABOLIC–ANDROGENIC STEROIDS

Bioavailable testosterone levels decrease with age, particularly in patients with obesity, diabetes, or obstructive sleep apnea. Indeed, the low testosterone level that had been reported in this patient 4 years before the current presentation was attributed to obstructive sleep apnea. Medically supervised testosterone replacement and supplementation have been used to improve sexual interest and performance, reduce anemia, increase bone density, and address depressive symptoms.[5]

Although judicious supplementation of testosterone has favorable effects in patients with hypogonadism, it may be associated with an increased risk of cardiac events and death, especially in those of advanced age, those with only moderately reduced free testosterone levels, or those with underlying cardiac disease. Testosterone supplementation may also be associated with erythrocytosis and resultant hyperviscosity syndromes and thrombosis. Erythrocytosis is thought to be related to a reset of the erythropoietin–hemoglobin axis, with inhibition of hepcidin without an associated change in erythropoietin levels.[6,7] In addition, testosterone supplementation has been associated with hypertension, atrial fibrillation, and acute kidney injury.[5,8]

Synthetic versions of testosterone have become common drugs of abuse, taken at doses far exceeding those used for medically supervised testosterone replacement or supplementation. These anabolic–androgenic steroids (AAS) are used by an estimated 2.9 to 4 million people in the United States, most of whom are male recreational athletes, to increase strength, lean mass, and performance.[9] AAS use is estimated to account for 1.5% of cases of cardiomyopathy among persons younger than 65 years of age.[10,11] Cardiac toxic effects can include severe reversible cardiomyopathy, and this patient's recurrent episodes of cardiomyopathy may have been triggered by the use of AAS before or during trips to the Caribbean.

AAS use has been associated with decrements in left ventricular ejection fraction, impaired myocardial relaxation, and increases in longitudinal strain, left ventricular end-systolic diameter and volume, left ventricular mass, and coronary plaque volume.[11] Additional deleterious effects include decreased HDL cholesterol levels, liver steatosis, hyperviscosity, mural endocardial thrombosis, and inhibition of extraneuronal uptake of amines, with the possibility of sudden cardiac death.[10,12]

Illicit use of AAS could explain several of this patient's noncardiac findings, including his current hypertension, gynecomastia, progressive insulin resistance, and elevated levels of AST, ALT, and alkaline phosphatase. The previous episodes of ligament tears and erythrocytosis may also be associated with AAS use. The insomnia, fatigue, and low testosterone levels, which had been attributed to obstructive sleep apnea, may instead be due to hypogonadism after discontinuation of AAS.

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The diagnostic evaluation in this patient's case could involve a careful discussion with the patient to assess for surreptitious use of AAS. Commercially available toxin screening tests typically do not detect AAS, but special assays for measurement of the total testosterone level could be considered.

CLINICAL IMPRESSION

Dr. Newton-Cheh: While we were assessing the patient in the hospital, we inquired about the use of AAS. The patient disclosed long-standing intermittent use of high doses of AAS to boost muscularity; most recently, he had taken trenbolone (a synthetic AAS approved for use in veterinary medicine only) in the weeks before his vacation in the Caribbean. Laboratory testing targeted to evaluate for AAS use was performed on the morning of hospital day 2.

CLINICAL DIAGNOSIS

Cardiomyopathy related to androgen excess.

DR. DALE S. ADLER'S DIAGNOSIS

Excess use of anabolic–androgenic steroids.

DIAGNOSTIC TESTING

Dr. Soma Jobbagy: The diagnostic test was measurement of the total testosterone level in the blood. The testosterone level was greater than 1500 ng per deciliter, which exceeded the reportable range of the assay (reportable range, 12 to 1500; reference range, 249 to 836).

The immunoassay that was used to measure the testosterone level has cross-reactivity with multiple structurally similar compounds. Some types of AAS, such as methyltestosterone, boldenone, and 19-norclostebol, have strong-to-moderate cross-reactivity with testosterone. Other types of AAS, such as trenbolone, have only weak cross-reactivity.[13] However, the extent of cross-reactivity has not been determined for all the possible metabolites of AAS in this assay, and the cross-reactivity may be higher or lower than that of the parent compounds.

LABORATORY DIAGNOSIS

Androgen excess–related cardiomyopathy.

DISCUSSION OF MANAGEMENT

Dr. Margaret F. Lippincott: Cessation of AAS use is the recommended treatment for cardiomyopathy due to androgen excess. Use of AAS suppresses the reproductive endocrine axis (hypothalamic–pituitary–gonadal axis) and spermatogenesis through negative feedback at the level of the hypothalamus; if the compound is able to be converted into an aromatic compound, the pituitary gland can also be affected.[14,15] As a result, cessation of AAS use typically leads to anabolic steroid–induced hypogonadism.[15-18]

Recovery from anabolic steroid–induced hypogonadism is lengthy and varied; however, full recovery is possible.[19-24] Negative predictors of recovery include preexisting dysfunction of the reproductive endocrine axis, an age older than 35 years, a duration of AAS use of more than 1 year, and use of high doses of AAS, all of which are relevant in this patient.[19-23,25] Normalization of testosterone levels typically occurs within 3 months to 1 year after cessation of AAS use; however, testosterone levels may remain low for up to 3 years.[21,22,26] Recovery of spermatogenesis typically occurs within 1 to 3 years; testosterone production and restoration of follicle-stimulating hormone levels are both required for spermatogenesis.[20,21]

Watchful waiting for endogenous recovery of the reproductive endocrine axis is recommended after cessation of AAS use,[19,27] although this approach results in prolonged symptoms associated with anabolic steroid–induced hypogonadism in a majority of users of illicit AAS. These symptoms include loss of sexual desire, erectile dysfunction, gynecomastia, reduced orgasmic satisfaction, and ejaculatory disorders.[28] Patients who remain symptomatic and hypogonadal at least 3 to 6 months after cessation of AAS use may be offered treatment on the basis of the patient's goals involving fertility, restoration of sexual function, or both.[19]

Therapies approved by the Food and Drug Administration for anabolic steroid–induced hypogonadism are lacking; however, established treatment options, such as human chorionic gonadotropin or testosterone-replacement therapy, result in normalization of testosterone levels and central suppression of the endogenous reproductive endocrine axis.[19,27] Clomiphene is a selective estrogen-receptor modulator that has been used off-label for stimulation of the reproductive en-

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docrine axis with preservation of fertility in men with secondary hypogonadism, which is typically related to age or obesity.[29] Short-term treatment with clomiphene can be considered in men with anabolic steroid–induced hypogonadism, although patients should be cautioned about the increased risk of venous thromboembolism.[19]

Dr. Harrison G. Pope, Jr.: There is an upper limit to the muscularity that a lean man can attain without pharmacologic agents — typically a fat-free mass index (the lean body mass in kilograms divided by the square of the height in meters) of 26.[30] Therefore, if a patient is relatively lean and his muscularity is conspicuously above this threshold, a tentative diagnosis of illicit AAS use can often be made on the basis of observation alone.[31]

When AAS first became widely available in the 1950s, athletes quickly discovered the muscle-building powers of these drugs, and AAS use spread throughout elite sports. In the 1980s and 1990s, AAS use began to spread to the general population. Use of AAS has now become a major international substance use disorder.[15] The estimated number of men in the United States with a history of AAS dependence is now similar to the number of U.S. men with HIV infection.[9] Clinicians should be prepared to encounter increasing numbers of patients presenting with the long-term effects of AAS exposure, including cardiomyopathy, atherosclerotic disease, and anabolic steroid–induced hypogonadism.

FOLLOW-UP

Dr. Newton-Cheh: Treatment with metoprolol, sacubitril–valsartan, empagliflozin, and spironolactone was initiated in this patient. Four months later, echocardiography showed a left ventricular ejection fraction of 49%, with normal chamber sizes and wall thickness. The blood levels of AST, ALT, and alkaline phosphatase had normalized with cessation of AAS use.

Dr. Lippincott: Six months after AAS cessation, the patient continued to have symptomatic anabolic steroid–induced hypogonadism with a low testosterone level (<100 ng per deciliter) despite normalization of the gonadotropin levels. Given the severity of his ongoing symptoms, he opted for a short course of clomiphene. No improvement in the testosterone level was observed after 1 month, and he opted to start topical testosterone-replacement therapy with a plan for a future tapering course. His testosterone level normalized, but he continued to have erectile dysfunction. This effect is consistent with reports of ongoing sexual dysfunction even after normalization of the testosterone level after cessation of AAS use.[18]

Dr. Newton-Cheh: Eight months after the current presentation, the patient had not restarted AAS use. He continued to exercise with cycling, an elliptical machine, and a jump rope, and he had no heart-failure symptoms.

FINAL DIAGNOSIS

Androgen excess–related cardiomyopathy.

This case was presented at the Massachusetts General Hospital and Harvard Medical School postgraduate course "Internal Medicine: Comprehensive Review and Update 2023."

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

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