

## CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

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## Case 4-2025: A 41-Year-Old Man with Syncope, Ankle Swelling, and Abnormal Chest Imaging

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### PRESENTATION OF CASE

*Dr. William J. Lu-Culligan (Medicine):* A 41-year-old man was evaluated at this hospital because of swelling in both ankles and episodes of syncope.

The patient had been in his usual state of health until approximately 4.5 months before the current presentation, when exertional dyspnea and a burning sensation in the chest developed. The symptoms lasted for several weeks, and the patient was admitted to another hospital. Radiography and computed tomography (CT) of the chest reportedly showed no abnormalities. Coronary angiography showed severe stenosis of the right coronary artery, and a stent was placed. The patient's symptoms resolved after the procedure; he was able to walk for 30 minutes daily without a recurrence of symptoms.

Ten days before the current presentation, the patient had worsening fatigue. During the next 3 days, fever, diffuse myalgia, anorexia, mild headache, new scattered ecchymoses, and arthralgia in the wrists and ankles developed. Antigen testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was reportedly negative. Symptoms abated on the fourth day. However, on the fifth day, he had a temperature of 38.2°C, and syncope occurred when he stood up from a chair, causing a fall that resulted in an injury to the right knee. The next morning, while the patient was urinating, he became nauseated, diaphoretic, and light-headed. He tried to lower himself to the ground and called for his family; then, witnessed syncope occurred, and he hit his head. He regained consciousness after a few seconds, and soon afterward, he presented to the emergency department of this hospital.

On examination, the temporal temperature was 36.3°C, the heart rate 79 beats per minute, the blood pressure 121/72 mm Hg, and the oxygen saturation 99% while the patient was breathing ambient air. He had dry mucous membranes. His right knee was tender and had limited range of motion during flexion. Ecchymoses were noted on the left hip and right biceps. Laboratory test results are shown in Table 1. Nucleic acid testing for SARS-CoV-2 and influenza types A and B was negative. An antibody test for Lyme disease was nonreactive. An electrocardiogram was normal.

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N Engl J Med 2025;392:495-503.

DOI: 10.1056/NEJMcpc2412513

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**Table 1. Laboratory Data.\***

Variable	Reference Range, Adults†	5 Days before Current Presentation	On Current Presentation
Hemoglobin (g/dl)	13.5–17.5	13.3	11.7
Hematocrit (%)	41.0–53.0	39.6	35.5
White-cell count (per $\mu$ l)	4500–11,000	8840	9500
Platelet count (per $\mu$ l)	150,000–400,000	262,000	297,000
Sodium (mmol/liter)	135–145	130	132
Potassium (mmol/liter)	3.4–5.0	5.0	4.0
Chloride (mmol/liter)	98–108	98	98
Carbon dioxide (mmol/liter)	23–32	23	24
Urea nitrogen (mg/dl)	8–25	13	12
Creatinine (mg/dl)	0.60–1.50	1.02	1.00
High-sensitivity troponin T (ng/liter)	0–14	6	6
N-terminal pro-B-type natriuretic peptide (pg/ml)	<900	—	107
Erythrocyte sedimentation rate (mm/hr)	0–14	—	42
C-reactive protein (mg/liter)	<8.0	—	113.7

\* 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.

† 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.

*Dr. Sadia Sultana:* A chest radiograph obtained in the emergency department was reportedly normal. A radiograph of the right knee reportedly showed a joint effusion without evidence of fracture or dislocation.

*Dr. Lu-Culligan:* Lactated Ringer's solution was administered intravenously, and the patient was discharged home. During the next 4 days, the patient reported new erythema and edema in the ankles. Ankle arthralgia persisted; it was worst in the morning and did not abate with the administration of acetaminophen. On the day of admission, the patient had a temperature of 39.4°C, and he returned to the emergency department of this hospital.

Review of systems was notable for brief heart palpitations that had occurred over a period of several weeks, as well as chronic snoring. The patient reported no chest pain, dyspnea, orthopnea, paroxysmal nocturnal dyspnea, abdominal pain, diarrhea, vomiting, dysuria, cough, rhinorrhea, neck stiffness, dry mouth, mouth ulcer, lymphadenopathy, Raynaud's phenomenon, vision changes, weakness, or paresthesia. He had no sick contacts.

The patient's medical history was notable for coronary artery disease, hypertension, hyperlipidemia, impaired glucose tolerance, obesity, erectile dysfunction, hepatic steatosis, rosacea, and anxiety. Medications included aspirin, ticagrelor, atorvastatin, metoprolol, amlodipine, and escitalopram. There were no known adverse reactions to medications.

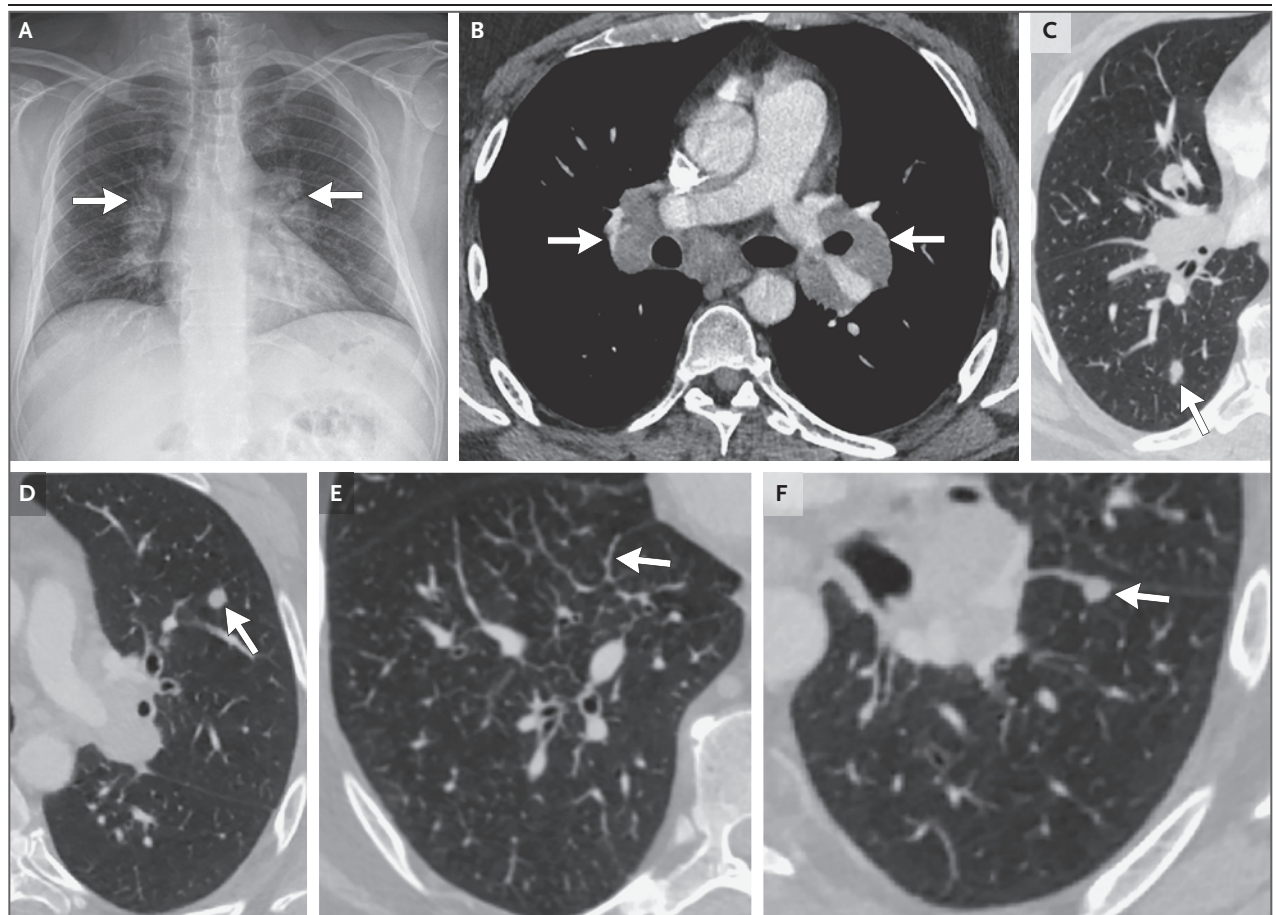
The patient worked in an office and lived in an urban area of New England with his spouse and a cat; the cat had scratched his left wrist approximately 6 months earlier. He had smoked a half pack of cigarettes daily for 12 years and had tried marijuana. He did not currently smoke cigarettes, drink alcohol, or use other substances. His travel history included visits to coastal New England, mid-Atlantic states, and the southeastern United States. For 2 years in the remote past, he had lived in the United Kingdom. His family history was notable for hyperlipidemia, hypertension, and systemic sclerosis in his mother; pulmonary fibrosis in a maternal aunt; smoking-related lung cancer in his maternal grandmother; and pancreatic cancer in his maternal grandfather.

On examination, the temporal temperature was 37.6°C, the heart rate 88 beats per minute, the blood pressure 132/62 mm Hg, and the oxygen saturation 96% while the patient was breathing ambient air. The body-mass index (the weight in kilograms divided by the square of the height in meters) was 31.4. No lymphadenopathy was noted in the cervical, supraclavicular, submental, submandibular, axillary, or inguinal areas. The wrists were tender and swollen, with pain on extension and flexion. There was edema in the ankles, and erythematous macules were noted on the ankles. Rosacea was present, but no other skin or nail changes were noted. The rest of the examination was normal.

Laboratory test results are shown in Table 1. Blood levels of calcium, magnesium, phospho-

rus, albumin, globulin, and total protein were normal, as were the white-cell count, the differential count, and blood levels of aspartate aminotransferase, alanine aminotransferase, bilirubin, and alkaline phosphatase. Urinalysis was normal. A blood specimen was obtained for culture. A nucleic acid test for SARS-CoV-2 was negative. Antibodies to human immunodeficiency virus and syphilis were not detected. An electrocardiogram was normal. Point-of-care ultrasonography reportedly showed normal ventricular function, no pericardial effusion, and no B lines. The next morning, no thrombus was identified on ultrasonography of the lower legs.

*Dr. Sultana:* Chest radiography (Fig. 1A) revealed bilateral hilar enlargement and otherwise clear lung fields. Given this finding, the chest



**Figure 1. Chest Imaging Studies.**

A chest radiograph shows bilateral hilar enlargement (Panel A, arrows). A contrast-enhanced CT image shows diffuse mediastinal and bilateral, symmetric hilar lymphadenopathy (Panel B, arrows). CT images in lung windows show multiple pulmonary nodules (Panels C and D, arrows). Subtle nodular interlobular septal thickening is present in the right lower lobe (Panel E, arrow). A perifissural nodule is present along the left major fissure (Panel F, arrow).

radiograph that had been previously obtained in the emergency department was again reviewed, and on retrospective assessment, bilateral hilar prominence was noted. CT of the chest and abdomen (Fig. 1B through 1F), performed after the intravenous administration of contrast material, showed diffuse mediastinal and bilateral hilar lymphadenopathy, a finding that had not been present on CT performed 4.5 months earlier. There were also multiple pulmonary nodules, including perifissural nodules and an 8-mm nodule in the right lower lobe that had increased in size since the previous study. Interlobular septal thickening in the right lower lobe was noted, as was diffuse bronchial-wall thickening, hepatic steatosis, and coronary-artery calcification.

*Dr. Lu-Culligan:* A diagnosis and management decisions were made.

#### DIFFERENTIAL DIAGNOSIS

*Dr. Daniel Restrepo:* When we engage in clinical reasoning, it is important for us to be aware of the cognitive paths that we take to reach a diagnosis. The diagnostic process begins when we learn a patient's story, connecting the background to the clinical presentation. Then, the process evolves as we gather data at the bedside using hypothesis-driven questioning and examination.

#### PROBLEM REPRESENTATION

Central to the diagnostic process is framing the clinical problem that needs solving. "Problem representation" refers to the way in which physicians frame a case. We highlight the most salient features of the presentation in order to reach a diagnosis. A problem representation is derived by asking three questions: First, who is the patient? Second, what is the tempo of the disease process? Third, what is the syndrome at hand?<sup>1</sup>

In answering the first question, we focus on host-specific factors that increase or decrease the probability of certain diagnoses, such as known medical conditions, current medications, anatomical variants, or travel history. In answering the second question, we characterize the pace of the disease (acute, subacute, or chronic) and identify other temporal features (recurrence, recrudescence, or intermittence), given that certain diseases have characteristic tempos. Finally,

in answering the third question, we distill the salient features of the case in a way that will best enable us to solve the problem, whether by stating the clinical problem or by referencing a known syndromic diagnosis. For example, a patient who is taking several antidepressants and presents with pyrexia and clonus (clinical problem) can also be described as a patient with serotonin syndrome (syndromic diagnosis).

In this case, a 41-year-old man with coronary artery disease presents with subacute fever, bilateral hilar lymphadenopathy, inflammatory arthritis, and an erythematous lower-leg rash. Although his two episodes of loss of consciousness are probably clinically significant, I will revisit them later in the discussion. At this point in the diagnostic process, we can use either the syndromic approach or the checklist approach.

#### SYNDROMIC APPROACH

The word "syndrome" — derived from the Greek *sun*, which means "together," and *dramein*, which means "to run" — encapsulates the intention of the syndromic approach. If we can recognize the constellation of symptoms and signs that "run together" in the patient, we may be able to rapidly reach a diagnosis.

When I consider the problem representation in this case, specifically noting the phenomena that are manifesting simultaneously, the diagnosis that comes to mind is Löfgren's syndrome. This syndrome is an acute manifestation of sarcoidosis that is characterized by erythema nodosum, bilateral hilar lymphadenopathy, and bilateral ankle arthritis.<sup>2</sup>

#### CHECKLIST APPROACH

Numerous studies in the surgical and intensive care literature have shown that checklists decrease process errors and prevent harm.<sup>3,4</sup> Checklists have also been posited to reduce diagnostic errors.<sup>5</sup> After identifying the salient features of the case, we can create a differential diagnosis for each feature. We can then cross-reference each differential diagnosis, in a checklist fashion, to ensure that an extensive search for the correct diagnosis has been conducted.

In this case, the four salient features noted in the problem representation are fever, bilateral hilar lymphadenopathy, inflammatory arthritis, and lower-leg rash. Although each feature has a long list of potential causes, we need to focus



our attention only on the disorders that can cause all four salient features. Thus, we can tailor our efforts to explore three disease categories: infection, cancer, and autoimmune disease.

#### INFECTION

Possible infectious causes of this patient's clinical syndrome include both tuberculous and nontuberculous mycobacterial infections, as well as both endemic and ubiquitous mycoses. His history of travel to the southeastern United States confers a predisposition to blastomycosis, which can manifest with cutaneous and pulmonary findings. Infection with another yeast, *Cryptococcus neoformans*, can result in clinical manifestations similar to those of *Blastomyces dermatitidis* infection and is not endemic to a specific region. However, the patient's disease process is more rapid than would be expected with these infections. In addition, his extrapulmonary findings would suggest a disseminated infection, which is most often seen in persons with impaired immunity. Given that this patient is not overtly immunosuppressed, an invasive fungal infection is unlikely.

Another infectious cause that is an important diagnostic consideration in this case is *Mycobacterium tuberculosis* infection. Tuberculosis commonly causes fever, pulmonary nodules, and bilateral hilar lymphadenopathy. In addition, tuberculosis can cause reactive arthritis (Poncet's disease) as well as various cutaneous manifestations, including erythema nodosum and hypersensitivity reactions (tuberculids). However, this patient has no apparent epidemiologic risk factors that would confer a predisposition to tuberculosis, which substantially decreases the probability of this diagnosis.

Finally, another granulomatous infection that merits consideration in this case is bartonellosis, given the patient's history of a cat scratch occurring 6 months earlier. Infection with *Bartonella henselae* can result in fever and both regional and generalized lymphadenopathy. However, pulmonary manifestations and symmetric oligoarthritis are both rare findings in this context and thus would be quite unlikely to occur simultaneously. Furthermore, the timing of this patient's presentation is not consistent with bartonellosis, given that fever and regional lymphadenopathy did not occur in association with the cat scratch.

#### CANCER

Among the various types of cancer that could result in this patient's syndrome, lymphoproliferative disorders are the most likely possibilities. Such disorders, including Hodgkin's disease and diffuse large B-cell lymphoma, can cause fever and hilar lymphadenopathy. However, the tempo of this patient's illness, with symptoms developing only 10 days before presentation, is uncharacteristic of lymphoproliferative disorders, even an aggressive lymphoma. In addition, the patient had no night sweats or clinically significant weight loss, and these findings would be expected in a patient with an aggressive lymphoma. Patients with cancer may have paraneoplastic inflammatory polyarthritis, an entity that usually mimics rheumatoid arthritis, but it is reported rarely and is more likely to occur in patients with lymphoma or leukemia than in patients with other types of cancer.<sup>6</sup> Overall, this patient's syndrome would be an exceedingly uncommon manifestation of a lymphoproliferative disorder.

#### AUTOIMMUNE DISEASE

Autoimmune or rheumatologic conditions that manifest with pulmonary disease, lymphadenopathy, arthritis, and fever include systemic lupus erythematosus, small- and medium-vessel vasculitides, and idiopathic inflammatory myopathies. Polyarticular crystalline diseases, such as gout and calcium pyrophosphate deposition disease, could result in fever with articular and periarticular symptoms but would not explain the thoracic findings seen in this patient.

Given the tempo of the patient's illness and the constellation of findings manifesting simultaneously, the most likely autoimmune disorder in this case is sarcoidosis. This multisystem granulomatous disorder can involve any organ and has a wide spectrum of severity, with manifestations ranging from incidental imaging findings with no associated symptoms to fulminant life-threatening disease. The diagnosis is typically clinicopathological, requiring the presence of nonnecrotizing granulomas on tissue biopsy, except in the case of three distinct clinical manifestations of sarcoidosis: uveoparotid fever, lupus pernio, and Löfgren's syndrome.

Both the syndromic approach and the checklist approach have led us to sarcoidosis as the cause of the patient's presentation. Although I

would recommend that glucocorticoid therapy be initiated in this patient, I would posit that we are not yet done with the case.

#### DIAGNOSTIC RECONCILIATION

The practice of medication reconciliation is a crucial step in the care of hospitalized patients and is known to reduce medication errors among inpatients.<sup>7</sup> However, the practice of diagnostic reconciliation is performed far less frequently. Before immunosuppressive therapy is initiated, it is important for us to delineate the facts of the case as well as the assumptions that we are making in our reasoning. Thus, I will perform diagnostic reconciliation by answering three questions: First, what do I know to be true? Second, what do I believe to be true? Third, what have I yet to explain?

Thus far, what we know for certain is that this patient has an acute-to-subacute inflammatory process with lymph-node, joint, and skin involvement. Given the tempo of his illness and the absence of epidemiologic risk factors for atypical infection, we may infer that these findings are caused by a benign, noninfectious process. What remains to be explained is his recurrent loss of consciousness, which will bring us to the final step in the diagnostic process.

#### ITERATIVE PROBLEM REPRESENTATION

As the case unfolds and new information is acquired, it is important for us to iteratively reframe the problem. At first, the patient's episodes of syncope might have suggested either neurocardiogenic syncope during micturition or orthostatic syncope from hypovolemia in the context of a protracted illness. However, now that we have determined that other features of his presentation are highly suggestive of sarcoidosis, we can update our problem representation.

I would now describe the patient as a 41-year-old man with probable sarcoidosis who presents with recurrent syncope and palpitations. This framing prompts consideration of cardiac sarcoidosis, which frequently manifests with ventricular tachyarrhythmias.<sup>8</sup> A more intensive cardiovascular investigation is warranted, including cardiac magnetic resonance imaging (MRI) and <sup>18</sup>F-fluorodeoxyglucose (FDG) positron-emission tomography (PET) with CT.

#### DR. DANIEL RESTREPO'S DIAGNOSIS

Sarcoidosis (Löfgren's syndrome).

#### DIAGNOSTIC TESTING

*Dr. Jeffrey A. Sparks:* This patient presented with pain in the wrists and ankles with a subacute onset, as well as systemic features. The differential diagnosis includes causes of polyarthritis, such as rheumatoid arthritis, spondyloarthritis, systemic lupus erythematosus or another systemic rheumatic disease, crystalline arthritis, infection, or a paraneoplastic process. The involvement of both ankles increases suspicion for sarcoidosis, given that Löfgren's syndrome has a predilection for this joint area, resulting in either synovitis or peri-arthritis of the soft tissue surrounding the ankles.

The patient has the classic features of Löfgren's syndrome, and the diagnosis can be made clinically without the need for additional testing. Löfgren's syndrome is a form of acute sarcoidosis that is characterized by the triad of erythema nodosum, hilar lymphadenopathy, and inflammatory joint pain (Table 2). Löfgren's syndrome was first described by Sven Halvar Löfgren and Holger Lundbeck in 1946 while they were reviewing cases of erythema nodosum.<sup>9</sup> There are no formal diagnostic criteria for

**Table 2. Classic Triad of Löfgren's Syndrome.**

Feature	Present in This Patient
Erythema nodosum: a painful erythematous patch that often involves the anterior legs	Yes: involvement of the anterior lower legs
Hilar lymphadenopathy	Yes: hilar and mediastinal lymphadenopathy
Inflammatory joint pain: inflammatory arthritis or soft-tissue peri-arthritis that often involves the ankles	Yes: ankle peri-arthritis and wrist synovitis

Löfgren's syndrome. Unlike most other manifestations of sarcoidosis, Löfgren's syndrome does not require a tissue diagnosis unless the manifestations are atypical or the patient does not have a response to treatment. Ankle involvement is a particularly prominent feature of Löfgren's syndrome and has high specificity for the diagnosis.<sup>10</sup> In rare cases, patients may present with incomplete Löfgren's syndrome, without the full triad.<sup>11</sup> Although serologic testing may be helpful to rule out other causes, no specific biomarkers are used for the diagnosis of Löfgren's syndrome.

#### CLINICAL DIAGNOSIS

Sarcoidosis (Löfgren's syndrome).

#### DISCUSSION OF MANAGEMENT

*Dr. Sparks:* Löfgren's syndrome is typically initially treated with nonsteroidal antiinflammatory drugs, but many patients also receive a short course of glucocorticoid therapy. Approximately 90% of patients with Löfgren's syndrome have resolution of symptoms within 6 weeks after the onset of symptoms.<sup>2</sup> The diagnosis should be reconsidered if the patient does not have a response to appropriate treatment. In a minority of patients, chronic sarcoid arthropathy later develops, and treatment with disease-modifying antirheumatic drugs such as methotrexate, hydroxychloroquine, or tumor necrosis factor inhibitors may be indicated. In rare cases, refractory erythema nodosum may lead to treatment with colchicine or dapsone. When pulmonary nodules or lymph nodes enlarge over time, biopsy may be considered to rule out alternative causes. Most patients with Löfgren's syndrome have a good prognosis, without other serious features of sarcoidosis, but other manifestations can develop in some patients even years later.<sup>5</sup> In this patient, prednisone therapy (20 mg daily) was initiated for presumptive sarcoidosis (Löfgren's syndrome), with a plan to administer a tapering course of prednisone over a period of 7 weeks.

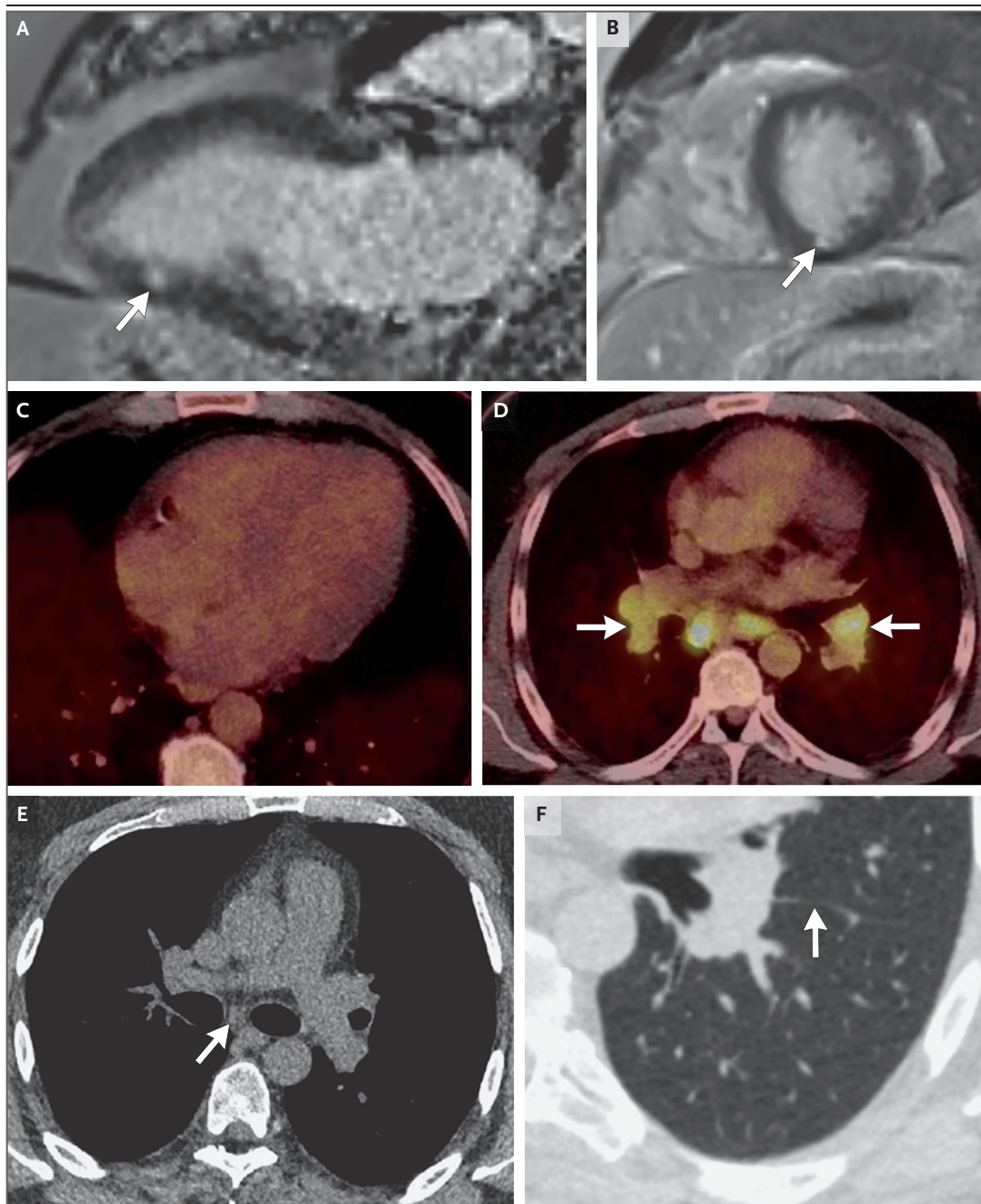
*Dr. Sanjay Divakaran:* The prevalence of cardiac involvement in patients with systemic sarcoidosis is estimated to be 20 to 25%.<sup>12-14</sup> However, clinically significant cardiac involvement occurs in approximately 5% of patients with systemic

sarcoidosis. Some patients have sarcoidosis that is confined to the heart at presentation, a condition that is commonly referred to as isolated cardiac sarcoidosis. The three principal clinical manifestations of cardiac sarcoidosis are high-grade conduction-system disease (e.g., high-grade atrioventricular block), ventricular arrhythmias, or left ventricular systolic dysfunction.<sup>14</sup>

The Heart Rhythm Society Expert Consensus Statement on the Diagnosis and Management of Arrhythmias Associated with Cardiac Sarcoidosis provides two pathways for making the diagnosis.<sup>15</sup> The first involves obtaining histologic confirmation by means of endomyocardial biopsy. The second involves the following three steps: obtaining histologic confirmation by means of extracardiac biopsy; identifying the presence of at least one clinical or imaging criterion, such as unexplained high-grade atrioventricular block, abnormal FDG uptake on PET-CT in a pattern consistent with cardiac sarcoidosis, or late gadolinium enhancement on cardiac MRI in a pattern consistent with cardiac sarcoidosis; and ruling out other causes of cardiac manifestations. Diagnosis through the first pathway can be challenging because endomyocardial biopsy is not without risk and cardiac sarcoidosis is often a patchy disease, which results in a low diagnostic yield.<sup>16</sup> Therefore, cardiovascular imaging plays an important role in making the diagnosis of cardiac sarcoidosis through the second pathway.

Echocardiography is of limited value in the diagnosis of cardiac sarcoidosis owing to its poor sensitivity.<sup>17</sup> Therefore, at most centers, cardiac MRI is the initial study performed in cases of suspected cardiac sarcoidosis owing to its high sensitivity, prognostic value, and ability to identify alternative causes of cardiac manifestations.<sup>18,19</sup> PET-CT provides complementary diagnostic value, as well as the ability to identify metabolically active cardiac and extracardiac disease.<sup>20,21</sup> This patient was referred for cardiac MRI for the evaluation of syncope.

The patient's cardiac MRI study (Fig. 2A and 2B) would be interpreted as indicating that cardiac sarcoidosis is possible but unlikely<sup>16,20</sup> and that a more likely alternative diagnosis that is associated with late gadolinium enhancement may be present,<sup>19</sup> particularly in light of the known coronary artery disease involving the right-coronary-artery territory. His PET-CT study



**Figure 2. Cardiac Imaging Studies.**

Cardiac MRI images were obtained with a single-shot phase-sensitive inversion recovery (PSIR) sequence in the two-chamber view (Panel A) and with a segmented PSIR sequence in the short-axis view (Panel B). Small, focal areas of late gadolinium enhancement are present in the mid-to-apical inferior wall (Panels A and B, arrows). Images from  $^{18}\text{F}$ -fluorodeoxyglucose (FDG) positron-emission tomography with CT were also obtained (Panels C and D). Myocardial suppression is adequate, with no evidence of abnormal myocardial uptake that would be suggestive of active cardiac sarcoidosis (Panel C); mediastinal and hilar lymph nodes have intense FDG uptake (Panel D, arrows). Follow-up, post-treatment CT images were obtained 6 months after the initial presentation in the mediastinal window (Panel E) and in the lung window (Panel F). The previously enlarged mediastinal and hilar lymph nodes have decreased in size (Panel E, arrow), as has the perihilar pulmonary nodule (Panel F, arrow).



(Fig. 2C and 2D) showed evidence of metabolically active extracardiac sarcoidosis but showed no evidence of myocardial inflammation. Taken together, these findings do not support cardiac sarcoidosis as the cause of this patient's syncope.

*Dr. Lu-Culligan:* The patient completed the tapering prednisone course in 7 weeks, with resolution of the musculoskeletal pain and rash, along with normalization of the erythrocyte sedimentation rate and C-reactive protein level. Follow-up chest CT (Fig. 2E and 2F) performed

6 months after the initial presentation showed that the previously enlarged mediastinal and hilar lymph nodes, the right-lower-lobe nodule, and the perifissural nodules had all decreased in size.

#### FINAL DIAGNOSIS

Sarcoidosis (Löfgren's syndrome).

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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