47-Year-Old Man With Dizziness and Palpitations

Ikram-Ul Haq, MBBS; Roberto Herrera, MD; and Ammar M. Killu, MBBS

A 47-year-old man with no significant past medical history presented to the emergency department with sudden-onset palpitations. He denied any recent fevers, chills, or unexpected weight loss. He had no recent sick contacts and no pertinent travel. He reported moderate alcohol intake, did not smoke, and was not on any medications at the time.

On examination, he was afebrile, normotensive (118/59 mm Hg) but tachycardic with a pulse rate of 177 beats per minute (bpm). Cardiac auscultation revealed no murmurs, clicks, or rubs. The lungs were clear to auscultation bilaterally, and his abdomen was soft and nontender, with bowel sounds present. There were no focal neurologic deficits, and there was no peripheral edema or peripheral lymphadenopathy.

Laboratory studies yielded the following values (reference ranges shown parenthetically): hemoglobin, 14.9 g/dL (13.5 to 17.5 g/dL); leukocytes, 9.7 X 10^9/L (3.5 to 10.5 X 10^9/L); platelet count, 191 X 10^9/L (150 to 450 X 10^9/L); potassium, 4.0 mmol/L (3.5 to 5.2 mmol/L); magnesium, 2.2 mg/dL (1.7 to 2.3 mg/dL); calcium, 9.7 (9.0 to 11.0 mg/dL); N-terminal b-type Natriuretic Peptide (NT Pro BNP), 43 (<125 pg/mL); troponin I, 0.0025 (0-0.0028 ng/mL) and thyroid-stimulating hormone, 0.7 mIU/L (0.3 to 5.0 mIU/L).

Chest x-ray revealed an enlarged cardiac silhouette with splaying of the carina without hilar lymphadenopathy or pulmonary venous congestion. An electrocardiogram (ECG) revealed a wide-complex tachycardia with a right bundle branch block pattern and left axis deviation. This rhythm was unsuccessfully treated with adenosine and metoprolol before he was sedated with propofol and electrically cardioverted. His repeat ECG after cardioversion is shown in the Figure.

1. Which one of the following options best describes this ECG?
   a. Atrial flutter with 3:1 atrioventricular conduction
   b. Sinus rhythm with Mobitz type 1 (Wenckebach) atrioventricular block
   c. Sinus rhythm with Mobitz type 2 atrioventricular block
   d. Sinus rhythm with complete heart block and junctional escape rhythm
   e. Sinus rhythm with complete heart block and ventricular escape rhythm

Atrial flutter refers to a form of supraventricular tachycardia caused by a reentry circuit in the atrium. Typical (cavotricuspid isthmus) atrial flutter has a “sawtooth” pattern of flutter waves, with a continuously undulating baseline that is best appreciated in the inferior (II, III, aVF) and V1 leads. The ventricular rate is determined by the degree of atrioventricular (AV) block. A 3:1 AV block refers to one conducted beat for every 3 preceding atrial flutter waves.

Sinus rhythm is the intrinsic pacemaker rhythm of the heart where the origin of cardiac impulse arises from the sinoatrial node. It is characterized by a regular rhythm of 60 to 100 bpm. The P-wave morphology is typically upright in the inferior leads (high-to-low activation), positive in lead I (right-to-left activation), and positive-negative in lead V1 (posterior to anterior, and right to left).

Mobitz type 1 (Wenckebach) and type 2 are examples of second-degree heart blocks. Mobitz type 1 is caused by block at the AV node. This manifests as progressive prolongation of the PR interval followed by a
nonconducted P wave. The following conducted beat has a shorter PR interval than the last conducted beat before AV block. In Mobitz type 2, there is damage to the His-Purkinje system, which can suddenly and unexpectedly fail. This results in a nonconducted P wave without progressive PR prolongation. In Mobitz type 1, there is progressive R-R interval shortening with an R-R interval length around the dropped beat less than twice the shortest R-R cycle. In Mobitz type 2, the R-R interval around the dropped beat is usually twice the length of the preceding R-R interval.

Complete heart block (CHB) refers to an absence of AV conduction, and the rhythm is maintained by a junctional or a ventricular escape rhythm. If the sinoatrial node fails to depolarize, the junctional tissue (AV node, His bundle) may depolarize instead, producing an escape rhythm with a narrow QRS complex. Ventricular escape rhythms occur when pacemaker cells in the ventricles depolarize because of a failure of pacemaker cells in the upstream conduction system. Typically, the rhythm has a rate of 20 to 40 bpm, and QRS complexes are wide (>120 ms).

In this case, the ECG demonstrates normal sinus rhythm with complete dissociation of the P waves and QRS complexes, suggestive of CHB with a wide QRS complex of right bundle branch block morphology and a ventricular escape rhythm of 38 bpm. After the patient was stabilized, a dual-chamber pacemaker was implanted.

2. What is the single next best step to evaluate this patient?
   a. Transthoracic echocardiogram (TTE)
   b. Cardiac stress test
   c. Cardiac magnetic resonance imaging (MRI)
   d. 18fluoro-D-glucose positron emission tomography/computed tomography (18F-FDG PET/CT)
   e. Multigated acquisition (MUGA) scan

Transthoracic echocardiogram is a low-cost, noninvasive, and routinely available imaging modality. It is an appropriate next test in this case, as it will help evaluate for structural heart disease, valvular heart disease, and cardiac function. Cardiac stress testing is useful in the diagnosis, prognosis, and risk stratification of ischemic heart disease and cardiomyopathies. It also helps evaluate for stress-induced ischemia and arrhythmias. However, there is low suspicion for myocardial ischemia with the absence of characteristic anginal symptoms, normal troponins, and no evidence for ischemia on the ECG. A cardiac MRI is a noninvasive imaging modality, which not only provides anatomic and functional data but allows for tissue characterization. This is helpful in identifying myocardial edema, fibrosis, and infiltrative processes. However, it is costly,
difficult to obtain, and takes longer to perform; hence, a TTE should be obtained initially. 18F-FDG PET/CT uses radiolabeled glucose to detect active myocardial inflammation, providing morphologic and metabolic delineation of tissue. Without TTE and limited evidence to suggest a cardiovascular inflammatory disorder, the utility of obtaining a PET/CT scan as the initial imaging choice is uncertain. Multigated acquisition scanning is a nuclear imaging modality using radioisotopes to evaluate the heart’s structural and dynamic properties and is used with scenarios in which initial imaging options suggest discrepancies in gauging cardiac function.

In our case, the next most appropriate investigation was to obtain a TTE. It revealed a normal LV chamber size with an ejection fraction of 59%, regional wall-motion abnormalities not in a coronary distribution, with interventricular septum wall thickening. An 18F-FDG PET/CT was performed, which revealed a large perfusion defect with associated FDG uptake in the anteroseptal, inferoseptal, and inferolateral segments. Numerous hypermetabolic, symmetric nodules and infiltrates were also found in both lungs and in mediastinal, axillary, and supraclavicular lymph nodes.

At this time, further laboratory work-up was obtained, including a serum angiotensin-converting enzyme, 45 (8 to 53 U/L); C-reactive protein, 12.3 (<8 mg/L); erythrocyte sedimentation rate, 6 (0 to 22 mm/1h); total ferritin, 150 (24 to 336 µg/L); kappa-free light chain, 1.77 (0.33 to 1.94 mg/dL); lambda-free light chain, 1.74 (0.57 to 2.63 mg/dL), and a serum protein electrophoresis, which did not reveal evidence of monoclonal proteins.

3. Which one of the following is the most likely etiology for this patient’s arrhythmia?
   a. Cardiac amyloidosis
   b. Systemic lupus erythematosus (SLE)
   c. Idiopathic degeneration (Lenegre-Lev disease)
   d. Tuberculosis (TB)
   e. Cardiac sarcoidosis (CS)

Cardiac amyloidosis involves the deposition of fibrillar proteinaceous material in the heart that is most commonly from light-chain (AL) or transthyretin (ATTR) protein. It often presents with restrictive cardiomyopathy and right ventricular failure but can also present with bradyarrhythmias or advanced atrioventricular block.1 A hallmark of cardiac amyloidosis is increased left ventricular wall thickness with reduced QRS voltage on ECG.1 Other cardinal echocardiographic findings include a reduction in global longitudinal strain with apical sparing (“bullseye appearance”), biaatrial enlargement, and diastolic dysfunction.1 Cardiac MRI is a useful confirmatory imaging test when late gadolinium enhancement (LGE) suggests amyloidosis.1 In this case, the patient did not present with right ventricular failure, did not endorse systemic amyloid findings, and had normal serum free light chains and serum protein electrophoresis.

Systemic lupus erythematosus is a chronic autoimmune disease that can rarely affect the heart’s conduction system and present with arrhythmias.2 However, our patient did not endorse any other constitutional symptoms, including arthralgias, and did not have evidence of serositis, cytopenia, renal, or neurologic disease. Hence, the suspicion for SLE was low. Lenegre-Lev disease is acquired CHB from idiopathic fibrosis and degeneration of the conducting system and is a diagnosis of exclusion seen in the elderly. This is unlikely in our relatively young patient. Tuberculosis can affect any organ system, including the heart where it commonly causes pericarditis, myocarditis, or aortitis and rarely affects the conduction system.3 Our patient did not endorse other systemic symptoms such as fevers, chills, or weight loss.

Sarcoidosis can affect the heart with septal predilection, causing AV block, ventricular arrhythmias, and heart failure.4 Three major guidelines exist to help guide the diagnosis of CS: World Association of Sarcoidosis and Other Granulomatous diseases (WASOG), 2014 Heart Rhythm Society (HRS), and Japanese Ministry of Health and Welfare (JMHW).5-7
Both WASOG and HRS propose diagnostic criteria, which require histologic evidence of disease.\(^5,6\) However, cardiac biopsies are marred by a low sensitivity (estimated to be 25%); high false negative rates; and complications associated with the procedure including conduction abnormalities, tricuspid valve apparatus injury, and cardiac tamponade.\(^4\) Although electrogram-guided biopsies have been shown to be safe at the time of ablation or device implantation, its efficacy remains slightly limited.\(^8-10\) As our patient had evidence of hypermetabolic supraclavicular lymphadenopathy, these were biopsied and found to consist of noncaseating granulomatous inflammation concerning for sarcoidosis. Hence, a cardiac biopsy was not required. In 2017, the JMHW guidelines were revised to not require histologic confirmation for diagnosis and instead suggested myocardial uptake with \(^{18}\)F-FDG PET/CT and LGE on cardiac MRI are the major diagnostic criteria of disease.\(^7\)

Gadolinium is an extracellular contrast agent that is used in cardiac MRI to allow better tissue characterization. It washes out more slowly from expanded extracellular spaces, such as areas of inflammation and scar, leading to LGE where different disease processes exhibit different patterns of LGE. In CS, there is often LGE in the mid-wall and subepicardial regions with septal predication.

18-Fluorodeoxyglucose (FDG) is a glucose analog that remains trapped in cells after glycolysis. Inflammatory cells within a sarcoid granuloma take up large amounts of \(^{18}\)F-FDG, and this accumulation is detected by the PET/CT scan; \(^{18}\)F-FDG PET/CT is useful in detecting active inflammation and monitoring treatment response.

4. **For initial treatment of this patient’s symptoms, which one of the following is most appropriate?**
   a. Hydroxychloroquine
   b. Prednisone
   c. Leflunomide and prednisone
   d. Cyclophosphamide
   e. Tafamidis

Hydroxychloroquine impairs antigen processing in antigen presenting cells and has been found to reduce autoimmune responses against autoantigenic peptides.\(^2\) It is used in various rheumatic diseases including rheumatoid arthritis (RA), SLE, and Sjogren syndrome.\(^11\) It can be used in sarcoidosis but is more often used in cutaneous sarcoidosis and in some cases of neurosarcoidosis.\(^11\) Prednisone is used in a variety of disease processes as an anti-inflammatory and immunosuppressive agent. Studies suggest higher doses (>30 mg per day), combined with other anti-inflammatory agents, are more effective than monotherapy in CS.\(^12\)

Leflunomide is a novel isoxazole derivative that has anti-inflammatory and immunomodulatory mechanisms.\(^13\) It is commonly used in RA to delay articular cartilage disintegration but is a viable alternative to methotrexate for pulmonary and extrapulmonary sarcoidosis. In our patient, leflunomide and prednisone is an appropriate initial combination therapy. Cyclophosphamide is an alkylating agent that inhibits protein synthesis by cross-linking DNA and RNA.\(^14\) It is used in the treatment of autoimmune diseases such as multiple sclerosis, vasculitis, and SLE as well as in neoplasms.\(^14\) Tafamidis is used to treat transthyretin (ATTR) amyloidosis;\(^1\) ATTR is a tetramer protein synthesized in the liver. When it destabilizes and dissociates into monomers, it can deposit as amyloid fibrils in the heart, leading to ATTR cardiac amyloidosis. Tafamidis is a benzoxazole derivative that stabilizes and inhibits the dissociation of transthyretin.\(^1\)

5. **Which one of the following would be the most reasonable follow-up plan for this patient?**
   a. No further follow-up is necessary
   b. ECG in 3 months
   c. Stress test in 6 months
   d. \(^{18}\)F-FDG PET/CT in 6 months
   e. TTE in 6 months

Aside from fatigue, the patient was asymptomatic without chest pain,
palpitations, dyspnea, or clinical evidence of heart failure after pacemaker placement. However, follow-up is warranted after starting cytotoxic treatment for CS. A repeat ECG alone would not be sufficient but is important to monitor underlying rhythm and pacemaker function. A stress test would help to evaluate for coronary artery disease, but this would be unlikely to develop in the short intervening follow-up period, especially without symptoms. An $^{18}$F-FDG PET/CT scan would be most useful to monitor cardiac inflammation, treatment response, and guide further treatment. A repeat TTE is not sensitive in assessing CS inflammation, and many patients with cardiac involvement can have normal findings.15

After initiating leflunomide and a prednisone taper, the patient was followed up in clinic with serial $^{18}$F-FDG PET/CT scans. His 6-month follow-up scan revealed decreased inflammation, and at 12 months his inflammation had resolved.

DISCUSSION

Sarcoidosis is a multisystem disorder defined histologically by the presence of noncaseating granulomas. In the United States, its incidence is estimated to be 10.9 in 100,000 in White Americans and 33.5 in 100,000 in African Americans.5 Cardiac involvement is a common sequela of disease, affecting 25% of patients with systemic sarcoidosis, and there is a growing appreciation for a subset of patients with isolated CS who are inevitably more challenging to diagnose and manage.16,17 The clinical manifestations of CS depend on the location and extent of myocardial inflammation. There is a predilection of the interventricular septum, thereby explaining why conduction-system abnormalities—such as CHB—are common manifestations. The most common symptoms of CS are palpitations, presyncope, and syncope. However, approximately 20% to 25% of patients remain asymptomatic.18

Initial evaluation and management of CHB is focused on ensuring the patient is hemodynamically stable. Unstable patients require immediate pharmacologic therapy or temporary cardiac pacing. In our case, the patient was first stabilized before an assessment, and evaluation for reversible etiologies was made. Examples of potentially reversible etiologies include myocardial ischemia, infections (such as Lyme carditis), electrolyte derangements, and hypervagotonia. In such cases, treating the underlying cause can resolve the heart block and the 2018 American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) guidelines only recommend inserting a permanent pacemaker (PPM) when CHB persists despite medical therapy.19 If no reversible etiology is identified, a PPM should be inserted.

The decision to implant a PPM or an implantable cardioverter defibrillator (ICD) in CS is nuanced. During active inflammation, ventricular tachyarrhythmias may occur, including ventricular fibrillation. Moreover, initiating high-dose steroids may precipitate ventricular tachycardia (VT), and following resolution of inflammation, scar maturation may ensue, providing a nidus for reentrant ventricular arrhythmias. The 2018 guidelines recommend ICD implantation as a class 2A recommendation in patients with CS who have indications for PPM implantation.19 The 2014 HRS expert consensus statement details patients with CS who have had sustained ventricular arrhythmias or previous cardiac arrest warrant ICD implantation for secondary prevention with a class 1 indication.5 Implantation of an ICD is also a class 1 indication for primary prevention in patients with CS and ejection fractions of less than 35% despite optimal medical therapy.5

Our patient was initially implanted with a dual chamber PPM at an outside institution at the time of CHB diagnosis. This was upgraded to an ICD when the diagnosis of sarcoidosis with cardiac involvement was made. After resolution of the inflammation, the patient’s AV conduction did not improve, and he experienced several nonsustained VT episodes and one episode of sustained VT necessitating an ICD shock, suggesting scar-mediated VT.
POTENTIAL COMPETING INTERESTS
The authors report no competing interests.

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Correspondence: Address to Ammar M. Killu, MBBS, Department of Cardiovascular Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905 (Killu.ammar@mayo.edu; Twitter: @akillumd, @IkramHaq).

ORCID
Ikram-Ul Haq: https://orcid.org/0000-0003-3574-5814

REFERENCES

CORRECT ANSWERS: E A E C D