CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 15-2018: An 83-Year-Old Woman with Nausea, Vomiting, and Confusion

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PRESENTATION OF CASE

Dr. Andrew S. Hoekzema (Medicine): An 83-year-old woman was admitted to this hospital in the winter because of nausea, vomiting, diarrhea, and confusion.

One week before admission, rhinorrhea, sore throat, and nonproductive cough developed. The patient felt feverish but did not measure her temperature at home. No family members or recent contacts had been ill. Two days before admission, nausea, vomiting, and diarrhea developed. One day before admission, the patient asked her daughter repetitive questions and appeared to not recognize family members. On the day of admission, the patient reported global weakness and was brought by her daughter to the emergency department of this hospital for evaluation.

In the emergency department, the patient reported no headache, changes in vision, chest pain, shortness of breath, or abdominal pain. She had a history of rheumatic heart disease, with mitral-valve stenosis and regurgitation, atrial fibrillation, and heart failure with a preserved ejection fraction of 60%. Other medical history included osteoporosis, compression fracture of thoracic vertebrae, and chronic kidney disease with a creatinine level of 1.2 mg per deciliter (106 μmol per liter; reference range, 0.6 to 1.5 mg per deciliter [53 to 133 μmol per liter]) and an estimated glomerular filtration rate (GFR) of 50 ml per minute per 1.73 m^2 of body-surface area (reference range, >60) according to the Modification of Diet in Renal Disease (MDRD) formula. Fifteen years earlier, she had undergone open mitral-valve commissurotomy and ring annuloplasty, procedures that were complicated by the development of recurrent severe mitral-valve regurgitation, which led to pulmonary hypertension, right ventricular dilatation and hypokinesis, and severe tricuspid-valve regurgitation. Nine years earlier, she had undergone bioprosthetic mitral-valve replacement and tricuspid-valve reconstruction with annuloplasty, with placement of a permanent pacemaker for persistent atrial fibrillation with bradycardia. Eight years earlier, transthoracic echocardiography had revealed a well-seated prosthetic mitral valve, an annular ring in the tricuspid position, mild tricuspid-valve regurgitation, and normal right ventricular size and function. In

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Table 1. Laboratory Data.*

Variable	Reference Range, Adults†	On Presentation
Sodium (mmol/liter)	135–145	132
Potassium (mmol/liter)	3.4–5.0	5.1
Chloride (mmol/liter)	98–108	87
Carbon dioxide (mmol/liter)	23–32	28
Glucose (mg/dl)	70–110	101
Urea nitrogen (mg/dl)	8–25	44
Creatinine (mg/dl)	0.6–1.5	1.6
N-terminal pro–B-type natriuretic peptide (pg/ml)	0–1800	4999
Troponin T (ng/ml)	<0.3	0.01

* To convert the values for glucose to millimoles per liter, multiply by 0.05551. 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.

addition, 10 years earlier, a cholecystectomy had been performed.

The patient lived at home with one of her grown children, was independent in activities of daily living, and walked for 30 minutes daily. Medications included furosemide, spironolactone, metoprolol, digoxin, and warfarin. She took her daily medications from a pillbox organizer that her daughter filled on a weekly basis. Warfarin therapy was monitored monthly with measurement of the prothrombin time and international normalized ratio; almost all results had been in the therapeutic range. The patient was born in Uganda but had moved to New England when she was 64 years of age to live with her children. She did not smoke tobacco, drink alcohol, or use illicit drugs.

On examination, the temperature was 36.9°C, the blood pressure 153/60 mm Hg, the pulse 64 beats per minute, the respiratory rate 18 breaths per minute, and the oxygen saturation 100% while the patient was breathing ambient air. The weight was 39.2 kg, and the body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) 18.7. The patient was cachectic and appeared ill. She was awake but lethargic, and she responded to questions with nonsensical answers in her native language. She intermittently followed simple one-step commands and could move her arms and legs. Results of cranial-nerve examinations were normal (although the function of the first cranial nerve was not tested). The mucous membranes were dry. Bowel sounds were present, and the abdomen was nondistended, soft, and nontender on palpation. The cardiac rhythm was irregularly irregular, with a loud S_2 heart sound and a systolic murmur throughout the precordium; the jugular vein was nondistended. Crackles were present in the lower lung fields. There was no leg edema. The complete blood count was normal, as were results of liver-function tests and blood levels of calcium, phosphorus, and lipase. Urinalysis was normal, except for the presence of 1+ ketones (reference range, negative). Nucleic acid testing of a nasal-swab specimen for influenza A and B viruses and respiratory syncytial virus was negative. Other laboratory test results are shown in Table 1.

Dr. Victorine V. Muse: Chest radiography (Fig. 1) revealed wires associated with median sternotomy, a single-lead pacemaker on the left side of the heart, and evidence of mitral-valve and tricuspid-valve repairs. There was evidence of stable, massive, global cardiomegaly and mild interstitial pulmonary edema. Computed tomography (CT) of the head, performed without the administration of intravenous contrast material, revealed prominent ventricles and sulci, as well as nonspecific, scattered periventricular white-matter hypodensities; there was no evidence of intracranial hemorrhage, large territorial infarction, or intracranial mass lesion.

Dr. Hoekzema: The patient was admitted to the hospital, and a diagnostic test was performed.

DIFFERENTIAL DIAGNOSIS

Dr. Melissa L.P. Mattison: This 83-year-old woman was brought by her family to this hospital for an evaluation of global weakness in the context of nausea, vomiting, and diarrhea, which began to occur after she had had symptoms that were suggestive of an upper respiratory infection for several days. She was newly unable to recognize family members and to answer questions. Using the common classification of organ failure as acute, chronic, or acute-on-chronic, I would characterize her condition as acute brain failure.[1,2]

The patient's daughter had set out the patient's

pills, but I do not know whether she did this because the patient was no longer capable of doing so owing to cognitive impairment or because the patient had a low level of health literacy or language-barrier issues. Although the patient clearly had an acute alteration of mental status, I would need more background information to determine whether her current condition could represent an acute-on-chronic process. Regardless, the features of her presentation are consistent with delirium according to the Confusion Assessment Method (CAM) definition.[3] She had acute inattention (intermittent following of commands), disorganized thinking (inability to recognize family members), and an altered level of consciousness (global weakness and lethargy).

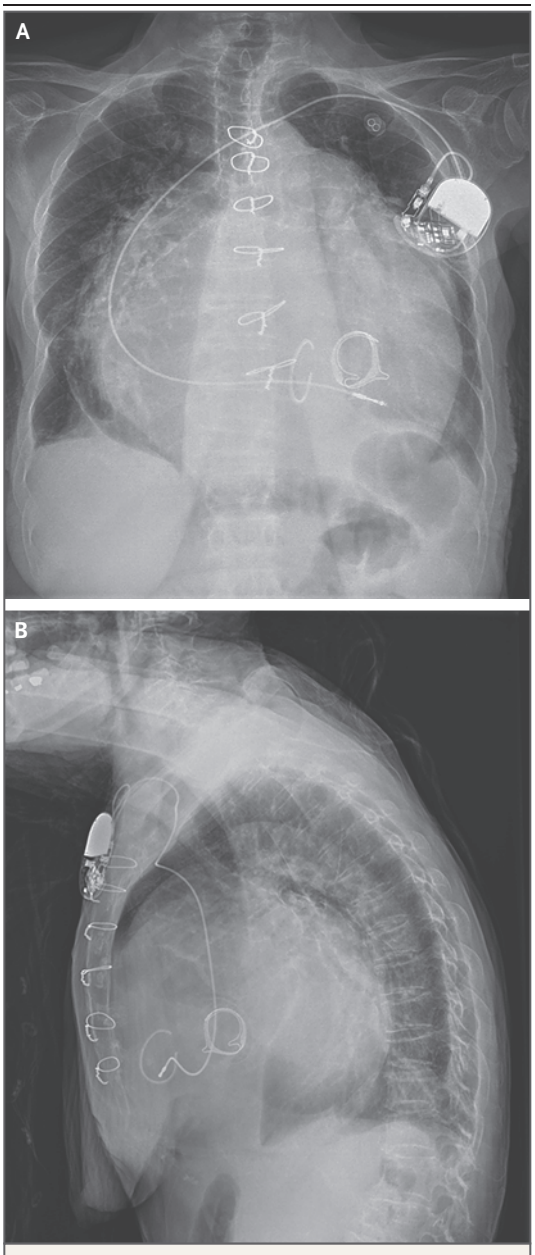

Figure 1. Chest Radiographs.
Posteroanterior and lateral chest radiographs (Panels A and B, respectively) show evidence of marked cardiomegaly, with a cardiothoracic ratio of more than 80%, and mild interstitial pulmonary edema.

DELIRIUM

The diagnosis of delirium in this patient is a cause for alarm, since delirium is associated with increased mortality during hospitalization[4,5] and at 1 year after diagnosis.[6] The most important step after the recognition of delirium is to identify the underlying cause, which involves consideration of common reversible conditions that have been described in hospitalized older adults.[7]

DRUGS

Medications are a common cause of delirium, particularly in older adults. Although this patient was receiving warfarin, her international normalized ratio was almost always in the therapeutic range, indicating that she had adhered to the prescription and seemed to have taken the medication correctly. Although psychoactive drugs had not been prescribed in the patient, she took multiple medications — including anticoagulants, diuretics, and several cardiac medications — that increased her risk of adverse drug events. Withdrawal syndromes can cause delirium, but this patient did not drink alcohol or use medications, such as benzodiazepines, that are associated with withdrawal syndromes. However, it remains possible that a drug effect could have contributed to her delirium.

ELECTROLYTE AND METABOLIC DISTURBANCES

This patient's calcium level is not reported, but she had mild hyponatremia and her urinalysis was notable for the presence of ketones. On physical examination, she had dry mucous membranes and no leg edema or jugular venous distention. Taken together, these findings are suggestive of volume depletion. I suspect her hyponatremia was due to an inadequate effective arterial blood volume, leading to the ongoing release of antidiuretic hormone. The hyponatremia was not severe enough to fully explain her delirium, but

it can be a marker of underlying volume depletion, which can contribute to delirium.

This patient's glucose level was normal. The thyrotropin level is not available, but she did not have symptoms that were suggestive of either hypothyroidism or hyperthyroidism. The combination of hyponatremia, hyperkalemia, and global weakness can indicate adrenal insufficiency, a very uncommon cause of delirium that may also explain the nausea, vomiting, and fatigue. However, the absence of hypotension makes adrenal insufficiency unlikely.

CARDIOPULMONARY DISORDERS

Cardiac and pulmonary disorders can lead to delirium through hypoxemia or hypercarbia. Although I do not have access to results of tests of arterial blood gases for this patient, there is no history of lung disease that would raise suspicion for these abnormalities. In addition, I have not seen the results of electrocardiography for this patient, but she did not report chest pain and she had a normal troponin T level, and these findings make myocardial infarction unlikely. She had evidence of rales on pulmonary auscultation, mild pulmonary vascular congestion on chest radiography, and an elevated level of N-terminal pro–B-type natriuretic peptide, findings that indicate a component of congestive heart failure. However, her oxygen saturation was normal, and thus it is unlikely that a cardiac or pulmonary process would be the main driver of her delirium.

INFECTION

Infection involving the central nervous system is a serious consideration in patients with delirium, especially those with an abnormal neurologic examination or with no more likely cause of the condition. It is reassuring that this patient's neurologic examination was unremarkable and that the history did not raise concerns about seizure activity. In addition, non–contrast-enhanced CT of the head revealed only prominent ventricles and nonspecific periventricular white-matter hypodensities.

Infections outside the central nervous system can also lead to delirium. Two common culprits, urinary tract infection and pneumonia, are unlikely in the absence of pyuria and of consolidation on chest radiography, respectively. Although this patient had no known sick contacts, she presented in the winter after she had had an upper respiratory infection. Tests for influenza A and B viruses and respiratory syncytial virus were negative, but other influenza-like illnesses remain possible. More remotely acquired infections, such as human immunodeficiency virus and *Mycobacterium tuberculosis* infections, are also possible in this patient who had emigrated from Uganda 19 years before admission. Weight loss is not reported, but she was described as being cachectic and she had a BMI of 18.7 (with values of <18.5 indicating underweight status).[8] However, she had normally walked for 30 minutes daily, indicating that she was physically robust, so perhaps she was just a very thin person.

NARROWING THE DIFFERENTIAL DIAGNOSIS

Can any features of this case help us to determine the most likely diagnosis? The most striking laboratory finding is the blood creatinine level of 1.6 mg per deciliter (141 μmol per liter), which had increased from a baseline level of 1.2 mg per deciliter and is consistent with acute kidney injury. However, despite the normal baseline blood creatinine level, this patient also had chronic kidney disease with a reduced estimated GFR.

The GFR decreases naturally with age, even in the absence of renal disease, with a 35% decrease between 20 years and 70 years of age.[9,10] Estimating the GFR is difficult, particularly in people with an older age, low muscle mass, or a low-protein diet.[10] Because creatinine comes from muscle, people with lower muscle mass should normally have a lower blood creatinine level. In this patient, the baseline estimated GFR according to the MDRD formula was 50 ml per minute per 1.73 m^2, a finding consistent with stage 3A chronic kidney disease. However, this estimated GFR is inaccurate, since the MDRD formula assumes a body-surface area of 1.73 m^2. Because this patient weighed 39.2 kg, she would need to be more than 7 ft (2.15 m) tall to have a body-surface area of 1.73 m^2. She had a BMI of 18.7 and a height of 4 ft 9 in. (1.45 m), and she most likely had a very low muscle mass. The Cockcroft–Gault equation can also be used to calculate creatinine clearance in estimating the GFR. This equation takes weight into account and can be helpful in patients whose weight is extremely low. According to the Cockcroft–Gault equation, this patient's baseline creatinine clearance was 22 ml per minute, indicating stage 4 chronic kidney disease.

The combination of chronic kidney disease, acute renal failure, and older age increases this

patient's risk of adverse drug events. Adverse drug events are common, occurring in at least 5% of hospitalized patients,[11,12] and they are more common among patients in the outpatient setting. Medications that commonly cause adverse events include oral hypoglycemic agents, oral anticoagulants, antiplatelet drugs, and opiates. This patient was taking spironolactone, which is contraindicated in patients older than 65 years who have a creatinine clearance of less than 35 ml per minute and is associated with ataxia, confusion, lethargy, hyperkalemia, nausea, vomiting, diarrhea, and acute kidney injury.[13] Another possible cause of this patient's condition is digoxin toxicity, which is characterized by confusion, dizziness, nausea, vomiting, diarrhea, weakness, and visual disturbances.[14] The major route of elimination of digoxin is through renal excretion, and the blood level of digoxin can rise in the context of a reduced GFR. Approximately 20 to 30% of digoxin is bound to blood albumin, and factors such as older age, congestive heart failure, and renal failure reduce the volume of distribution, contributing to an increased risk of toxic effects.

This patient did not have the ataxia that is associated with spironolactone toxicity or the visual disturbances that are associated with digoxin toxicity, but otherwise, the features of her presentation fit well with both conditions. Therefore, drug toxicity, probably from digoxin, is the most likely diagnosis in this case. I suspect the diagnostic test was an immunoassay to determine the blood digoxin level.

Dr. Meridale Baggett (Medicine): Dr. Simmons, what was your clinical impression when you initially evaluated this patient?

Dr. Leigh H. Simmons: This patient had been under my care for several years, but I saw her in the office very infrequently after she lost Medicaid coverage, which was not reinstated for unclear reasons. Despite our requests that her family bring her in for routine checks and for assistance with exploring options for health insurance, her family declined to do so because of concerns about the cost of medical visits. Through our anticoagulation-management service, her international normalized ratio was checked regularly and was nearly always in the therapeutic range. Her family consistently refilled her medicines, which were available in generic form and were relatively inexpensive.

When the patient presented to the emergency department, I learned from her attentive daughters that she had been doing well at home until this sudden decline and that they thought she had a viral illness. I was especially concerned, because the patient rarely sought medical attention for illnesses. During my initial assessment in the emergency department, I thought a viral illness could have precipitated heart failure or renal failure. However, her confusion was the most worrisome feature of her presentation, and it prompted me to consider the possibility of digoxin toxicity and to request a digoxin immunoassay.

CLINICAL DIAGNOSIS

Digoxin toxicity.

DR. MELISSA L.P. MATTISON'S DIAGNOSIS

Delirium due to an adverse event related to digoxin and possibly spironolactone.

DIAGNOSTIC TESTING

Dr. Rory K. Crotty: The diagnostic test in this case was a digoxin immunoassay. Testing of a blood sample obtained in the emergency department revealed a digoxin level of 9.0 ng per milliliter (therapeutic range, 0.9 to 2.0). The international normalized ratio was more than 16.

The digoxin level is frequently monitored because of the narrow therapeutic range and the potential for serious adverse drug events. This patient was also taking spironolactone, which has historically been reported to interfere with testing of the digoxin level by acting as a digoxin-like immunoreactive substance. The term digoxin-like immunoreactive substance encompasses a broad range of substances, both exogenous and endogenous in origin, that may interfere with digoxin immunoassays.[14] Endogenous digoxin-like immunoreactive substances may be found in patients with volume expansion and appear to have natriuretic effects. Exogenous digoxin-like immunoreactive substances include spironolactone, canrenone, and Chinese herbal medications. However, spironolactone and related medications are not known to cause interference with the current generation of digoxin immunoassays that are used at this hospital.

In cases in which the desired diagnostic test is a digoxin immunoassay, a blood sample must

be obtained before the administration of digoxin-binding antibody fragments. The digoxin level cannot be meaningfully measured until these antibody fragments are eliminated from the body, which may take days to more than a week in patients with severe kidney dysfunction.

DISCUSSION OF MANAGEMENT

Dr. Christopher Newton-Cheh: I met this patient shortly after her emigration from Uganda, 19 years before this admission. She reportedly had had persistent atrial fibrillation for years, which was not surprising given her symptomatic mitral-valve stenosis, left atrial enlargement, and resultant scarring from chronic pressure overload. I presume that digoxin and a beta-blocker had initially been prescribed in Uganda for control of the heart rate in the context of atrial fibrillation and that these treatments were continued when heart failure subsequently developed.

Cardiac glycosides, such as digoxin, were first used for the treatment of heart failure many years ago,[15] well before the molecular actions of these drugs were understood. If this patient presented today with atrial fibrillation and heart failure, it is unlikely that digoxin would be prescribed. The use of digoxin therapy for the treatment of atrial fibrillation has decreased as alternative therapeutic approaches with greater efficacy and reduced toxic effects have been recognized. Nondihydropyridine calcium-channel blockers and beta-blockers slow the ventricular response at rest and during exertion. Digoxin is sometimes added if these agents do not adequately control the heart rate at maximal doses. However, the vagotonic effect of digoxin is overcome by the adrenergic surge that occurs during exercise, and therefore, digoxin is of limited use in preventing uncontrolled heart rates during exercise. The use of digoxin for the treatment of heart failure has also decreased because of the rise of more effective and less toxic therapies, including angiotensin-converting–enzyme inhibitors, angiotensin-receptor blockers, neprilysin–angiotensin-receptor inhibitors, beta-blockers, and mineralocorticoid-receptor antagonists. A trial conducted by the Digitalis Investigation Group did not show a benefit from digoxin with respect to mortality in patients with symptomatic heart failure and a reduced ejection fraction, and the trial results also suggested harm from digoxin when it was present at high levels in the blood.[16]

The administration of digoxin-binding antibody fragments (i.e., digoxin immune Fab) is not necessarily indicated for several nuisance consequences of digoxin toxicity, including xanthopsia (yellow vision), nausea, bradycardia, and confusion. Life-threatening consequences of digoxin toxicity include ventricular tachycardia, severe bradycardia, complete heart block, and shock. The administration of digoxin immune Fab, which binds to digoxin and clears the drug from tissues, is indicated for the treatment of life-threatening arrhythmias and shock, as well as for the prevention of these events when hyperkalemia is present.

This patient had a blood potassium level of more than 5 mmol per liter, which is associated with an increased risk of life-threatening arrhythmias or death. She was treated with digoxin immune Fab; the dose was calculated on the basis of the blood digoxin level and body weight with the use of a dosing nomogram for chronic toxicity. Adverse events associated with the administration of digoxin immune Fab include heart failure, hypokalemia, and hypersensitivity to ovine Fab epitopes; none of these events occurred in this patient.[17]

Dr. Simmons: Before the patient was discharged from the hospital, we performed a careful assessment of her home situation. We learned that some memory deficits had developed in the patient and that her daughters were concerned that she had not been managing her medicines well. Her daughters did not think that this was a suicide attempt, and once the patient's mental status had improved, information obtained during an interview did not suggest depression. However, a cognitive evaluation indicated that she had deficits in short-term memory and executive functioning. Warfarin and digoxin were discontinued, and apixaban was initiated for stroke prevention. Medicaid coverage was reinstated. The patient was discharged home. Adjustments have been made to the doses of diuretics for heart failure, but otherwise, her medical condition has been stable. During the 12 months after her hospital stay, she had 19 telephone calls and 11 scheduled or urgent office visits to primary care and cardiology but had no hospitalizations or emergency department visits.

Our experience with this patient highlights several of the well-studied health consequences of being uninsured. Avoidable causes of death occur disproportionately in patients who do not

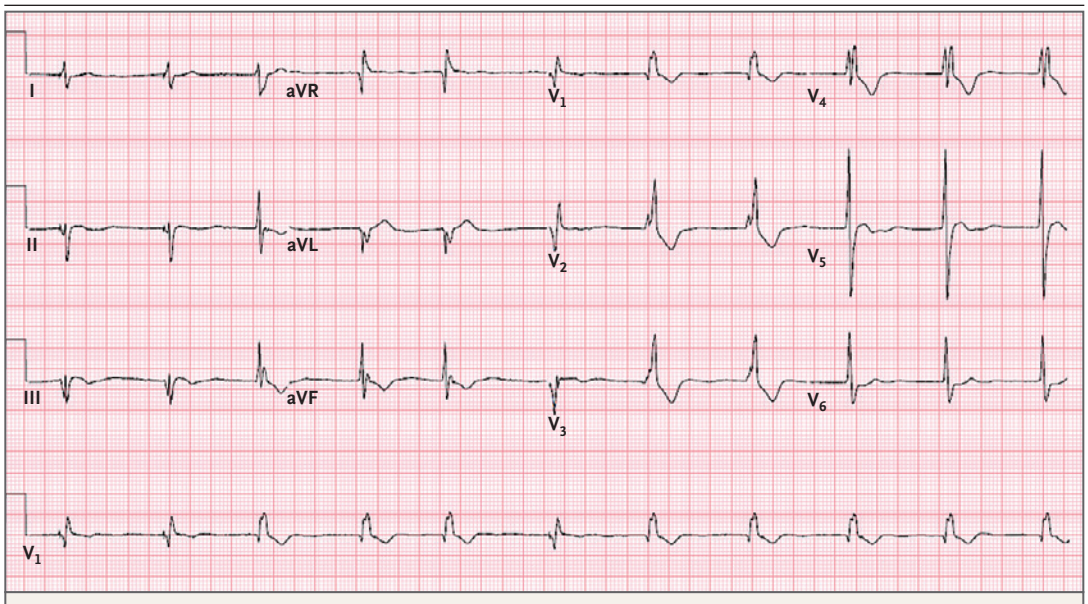

Figure 2. Electrocardiogram.

An electrocardiogram, obtained on admission, shows an underlying rhythm of atrial fibrillation with ventricular-demand pacing at a rate of 60 beats per minute. When atrioventricular conduction is present, at a rate slightly higher than 60 beats per minute, there is evidence of a regularized ventricular response with a pattern of right bundle-branch block.

have health insurance. Patients who regain insurance after being previously uninsured start to use outpatient services more often (as this patient did). Studies suggest that there are mortality benefits from acquiring health insurance.[18] For me, the particularly distressing component of this patient's story is that she had survived a complex cardiac operation and had undergone advanced cardiac procedures, including pacemaker placement, only to subsequently lose access to her regular health coverage. Routine visits for primary care before this admission might have resulted in conversations about her cognitive functioning and her ability to manage medicines on her own, as well as a review of essential medications and perhaps the discontinuation of higher-risk medications, such as digoxin.

A Physician: What did this patient's initial electrocardiogram show?

Dr. Randall M. Zusman (Cardiology): I cared for this patient at the hospital. The electrocardiogram obtained on admission (Fig. 2) showed an underlying rhythm of atrial fibrillation with ventricular-demand pacing at a rate of 60 beats per minute. When atrioventricular conduction was present, there was evidence of a regularized ventricular response that was consistent with an excess of digoxin, but the ST-segment changes were more consistent with the underlying conduction-system disease than with classic digoxin toxicity. After digoxin immune Fab was administered, the patient was less dependent on the pacemaker; the cardiac rhythm was more irregular and the delay in the conduction system was less marked. In this case, the diagnosis of digoxin toxicity was based on the clinical features of an electrolyte disorder, acute renal insufficiency, and the suspected inadvertent administration of an excess of digoxin rather than on the development of classic findings on electrocardiography.

FINAL DIAGNOSIS

Digoxin toxicity.

This case was presented at the Internal Medicine Case Conference.

Dr. Newton-Cheh reports receiving consulting fees from Novartis and Ironwood and consulting fees and advisory board fees from GE Healthcare. No other potential conflict of interest relevant to this article was reported.

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

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