Bone Marrow-Related Syncope

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Multiple myeloma is a disease presenting with anemia and renal failure, which is usually diagnosed late and has a poor prognosis. We report the case of a 63 year old man who was hospitalized in the Cardiology division due to syncope, and present the rare diagnosis made by cardiologists after a thorough differential diagnosis and describe the work of a multidisciplinary team.

PATIENT DESCRIPTION

A 63 year old healthy man was admitted due to syncope and urine loss for the first time in his life, which occurred while walking and with a prodrome of chest pain for half a minute.

His past medical history was remarkable for effort-related chest pain. Stress echocardiography (sEcho) was performed which demonstrated anterior wall hypokinesis, and he was referred for invasive coronary angiography (ICA). A drug-eluting stent was deployed on a 60% stenosis in the left anterior descending coronary artery (LAD). During the next 3 months he reported the same symptoms. He was referred for stress single-photon emission cardiac tomography, which was normal. The physician's recommendation was to intensify anti-anginal medications due to the working diagnosis of small vessel coronary artery disease (CAD).

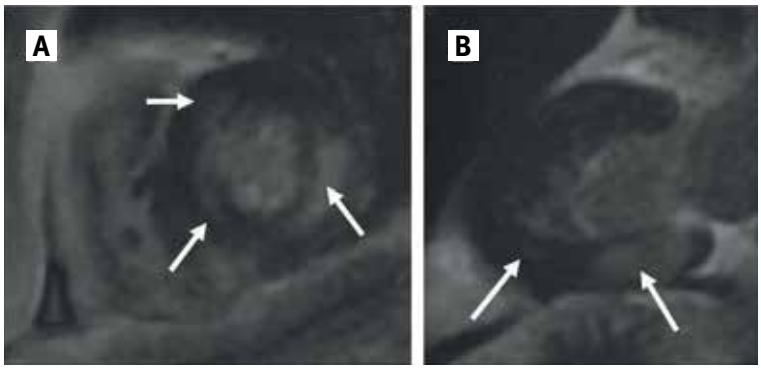
On physical examination, blood pressure was 137/82 mmHg, pulse 72 beats/minute and saturation 98%. Laboratory examination showed normal blood count, and normal renal, liver and thyroid function. Troponin-I levels were mildly elevated at 0.24 pg/dl (normal range < 0.05 pg/dl). Electrocardiogram (ECG) showed normal sinus rhythm and axis without signs of acute ischemia, arrhythmia or conduction defects. There were T-wave inversions in leads II, III, aVF and V4-6. A head computed tomography (CT) scan, which was ordered to rule out an organic pathology that might explain syncope and to rule out head trauma or bleeding, was normal.

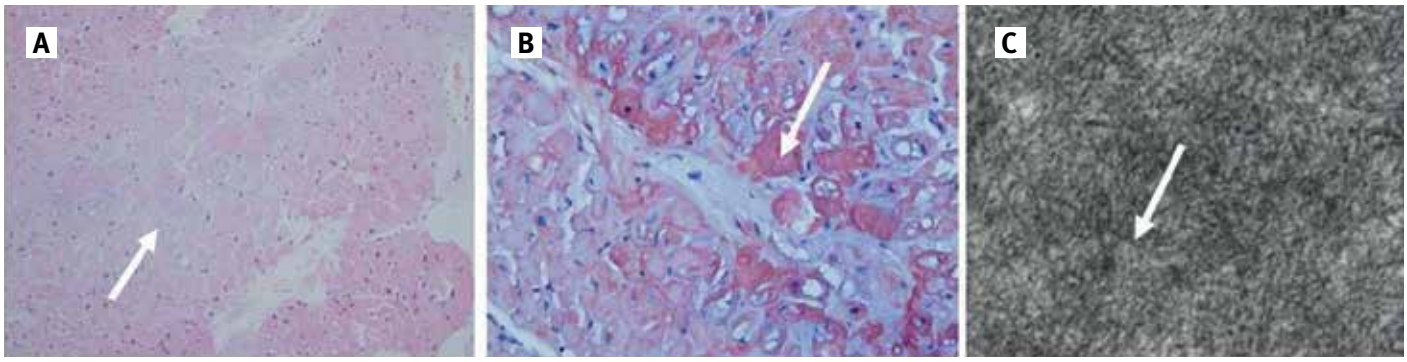
At this point, we tried to address the differential diagnosis of syncope. Syncope is defined as a transient loss of consciousness. Cardiac and neurological diseases are the main causes, with vasovagal syncope, arrhythmia, conduction defects and myocardial infarction in the former, and cerebrovascular accident, transient ischemic attack (TIA) or epilepsy in the latter [1]. A history of urine loss points to a neurological entity such as epilepsy. However, the patient denied an aural-like prodrome and post-ictal state. Epilepsy does not usually begin at this age unless there is a structural defect in the brain. A history of effort-related chest pain with non-specific ECG changes may point to a cardiogenic reason – coronary artery disease, cardiomyopathy, or arrhythmia.

The management of his recent chest pain was reasonable. The type of chest pain was suggestive of CAD and he had an intermediate pre-test probability of significant CAD, making the choice of sEcho appropriate. Therefore, when the test revealed anterior wall hypokinesis, the referral for ICA was correct. A 60% stenotic lesion in the LAD could explain his symptoms and sEcho results, necessitating stent implantation. However, the stent did not alleviate his symptoms. This can happen when the stent is not deployed properly, or diffuse small vessel disease is present. We had to bear in mind the possibility of another etiology to explain his effort-related chest pain, such as valvular or myocardial disease.

A neurological consultation requested an electroencephalogram to rule out epilepsy, and a carotid artery Doppler to rule out the possibility of TIA. Both studies were normal, whereupon he was referred for echocardiography. Echocardiography showed normal systolic function with a grade II diastolic dysfunction and borderline left ventricular hypertrophy (LVH) with a septum width of 12 mm (probably normal for his body surface area of 2.23 m^2). A 24 hour ECG Holter recording failed to reveal an arrhythmia. An ECG-gated cardiac CT-angiogram ruled out significant CAD or pulmonary embolism. An exercise tolerance test was performed to a reasonable effort of 9 METs, which did not provoke chest pain or ST changes but demonstrated some multifocal premature ventricular complexes. The possibility of arrhythmia was raised and the patient was discharged with the recommendation for a loop-recorder implantation.

Ten days later, he was readmitted due to syncope with the same prodrome and loss of urine. Physical examination and neurological consultation were again normal, and laboratory tests again showed only a mild elevation of troponin levels, 0.16 pg/dl. ECG showed the same T-wave changes and a repeat 24 hour ECG recording failed to show any rhythm abnormality. At this point we reevaluated his workup. We were bothered by the grade II diastolic dysfunction which was out of proportion to his borderline (if any) left ventricular hypertrophy. The other differential diagnosis of diastolic





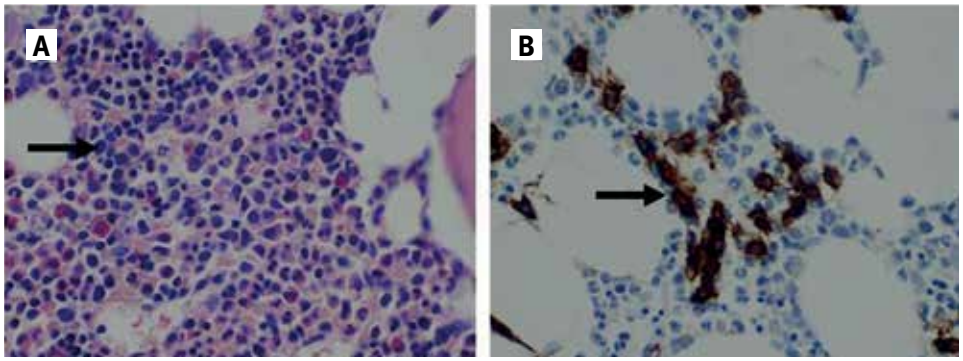


Figure 1.
Top panel: Cardiac magnetic resonance imaging. **[A]** Cardiac short axis. **[B]** Cardiac long axis. Arrows indicate late gadolinium enhancement in a non-coronary, mid-wall, patchy distribution. Septal width was 16 mm

Middle panel: Microscopy of endomyocardial and bone-marrow biopsy. **[A]** Light microscopy x20, hematoxylin & eosin staining showing islands of amorphous matter between normal appearing myocardium (arrows). **[B]** Light microscopy x40, Congo-red staining showing positive staining (arrows) of those amorphous islands. **[C]** Electron microscopy x250 showing straight, non-bifurcating lamella (arrows)

Lower panel: Microscopy of bone marrow biopsy (x40). **[A]** Abundance of plasma cells with atypical, eccentric and hyperchromatic nuclei with basophilic cytoplasm (arrows). **[B]** Anti CD-138 staining showing plasma cells with eccentric nucleus (arrows) positively stained

dysfunction consists of status-post myocardial infarction, old age, obesity and diabetes mellitus, which did not apply to him.

In view of another etiology – restrictive cardiomyopathy caused by infiltrative disease [2] – he was therefore referred for cardiac magnetic resonance imaging (CMR) which is a robust and well-validated imaging modality for myocardial tissue characterization. CMR showed an ejection fraction of 67%, and diffuse late-gadolinium enhancement, in a non-coronary artery distribution. It was patchy and mid-wall [Figure 1, top panel]. A septum width of 16 mm was measured, leading to the working diagnosis of hypertrophic cardiomyopathy as a cause of syncope due to malignant ventricular arrhythmia, necessitating a defibrillator implantation [3].

However, at this stage, we were troubled by another finding. When looking carefully at his ECG, besides the T-wave inversion, there was a pattern of low voltage amplitude of QRS complexes, which is unusual in hypertrophied hearts, unless there is a myocardial infiltrative disease. Here the differential diagnosis comprised amyloidosis, sarcoidosis, Fabry's disease, hemochromatosis and myocarditis. The patient was referred for endomyocardial biopsy.

Hematoxylin-eosin staining showed amorphous loci between normally apparent myocardial fibers and blood vessel walls. Congo-red staining was positive and electron microscopy showed amyloid lamella. Immunostaining for amyloid A was negative. A diagnosis of cardiac amyloidosis [4] was made with arrhythmia-related syncope as the presenting symptom. Of note, the common presenting symptom of cardiac amyloidosis is heart failure [5]. The patient was referred to the hematology department for bone marrow and urine analysis, which revealed 12% monoclonal plasma cells in the former and a high content of

kappa-chains in the latter, culminating in the diagnosis of multiple myeloma. He was prescribed a regimen of corticosteroids and proteasome inhibitor with the option for bone marrow transplant if it failed.

CONCLUSIONS

The importance of this case report with its unique diagnosis is to emphasize the importance of being alert to subtle findings and working with a multidisciplinary approach. Attention to the differential diagnosis of diastolic dysfunction and subtle "non-specific" changes on ECG is crucial. This patient did not have any of the presenting symptoms of multiple myeloma, general amyloidosis or cardiac amyloidosis, and this early diagnosis may have saved his life or at least prolong it.

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