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CASE REPORT

A rash with a heavy heart

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Summary

Cardiac amyloidosis (CA) is relatively rare and frequently misdiagnosed. Other disorders presenting with increased left ventricular (LV) mass can mimic its diagnosis. This case illustrates unique findings of primary light chain (AL) amyloidosis in a patient with remarkable signs of CA. Here, we report a 49-year-old male with prior diagnosis of hypertrophic cardiomyopathy (HCM) based on an echocardiogram performed 1 year earlier, which presented with 8 weeks of periorbital rash. The patient had numbness in the past 3 years. More recently, the patient presented with shortness of breath. Physical examination was remarkable for periorbital purpura, macroglossia and orthostatic hypotension. Cardiac auscultation showed S3 and S4. Electrocardiography showed diffuse low-voltage QRS complexes. Echocardiography revealed severe diastolic impairment; granular 'sparkling' pattern of the myocardium with thickened walls, interatrial septum and valves; and pericardial effusion. Diastolic dysfunction and thick walls with low ECG voltage are compelling diagnostic findings. Laboratory workup showed increased free light chain-differential (FLC-diff), N-terminal fragment of brain natriuretic peptide (NT-BNP) and cardiac Troponin T (cTnT). Bone marrow biopsy confirmed AL amyloidosis. A diagnosis of AL amyloidosis with cardiac involvement mimicking HCM was made. The patient died during hospitalization due to sudden cardiac death. This case illustrates the importance of the combination of clinical, serological, and electro- and echocardiographic findings to establish the diagnosis of CA.

Key Words

- cardiac amyloidosis
- 2D echocardiography
- light-chain amyloidosis
- cardiomyopathy
- hypertrophic cardiomyopathy

Learning points:

- Several disorders presenting with increased LV mass can mimic CA.
- Echocardiography is one of the most important methods to diagnose CA and HCM.
- Signs of CA include LV wall thickness; thickening of interatrial septum, valves and right ventricular free wall; and pericardial effusion. Diastolic dysfunction and thick walls on echocardiography with low ECG voltage are the hallmark of disease.
- CA is a major prognostic factor in AL amyloidosis.
- Signs of HCM on echocardiography include several patterns of LV hypertrophy, such as sigmoidal, reverse curve, neutral and apical morphologies; LV outflow tract or mid-cavity obstruction; systolic anterior motion of mitral leaflets; mitral regurgitation and diastolic dysfunction.
- The combination of clinical and serological features, along morphological and functional structures, has an important role for establishing diagnosis and predicting prognosis.

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Background

CA presentation is often progressive and insidious, which makes its early diagnosis challenging. In addition, there are several other diseases/disorders presenting with increased ventricular mass that can mimic CA. In the heart, amyloid protein deposition leads to thick walls and small ventricles, and carries a poor prognosis. Once heart failure occurs, life expectancy decreases considerably. Thus, early detection of cardiac involvement is crucial (1, 2).

Case presentation

A 49-year-old male was referred to Mayo Clinic for diagnostic evaluation of hypertrophic cardiomyopathy (HCM) based on an ECG 1 year earlier presented with 8 weeks of a periorbital rash. An ECG from that time noted concentric LV wall thickening, normal LV systolic function and grade 2 diastolic dysfunction. A trial treatment with angiotensin-receptor blockers and β-blockers was initiated, which had resulted in recurrent syncopal episodes. The patient had numbness of hands and erectile dysfunction, and recently presented with shortness of breath and orthopnoea. The patient's physical examination was remarkable for orthostatic hypotension, periorbital purpura (Fig. 1A), and macroglossia with indentation marks (Fig. 1B). Respiratory examination showed bibasilar pulmonary crackles. Cardiac auscultation revealed S3 and S4 (although the latter is almost rarely present, presumably due to atrial dysfunction secondary to amyloid infiltration); neck examination showed increased jugular venous pressure of 15 cm H_2O with profound peripheral oedema.

Investigation

Echocardiography was repeated, which revealed granular 'sparkling' appearance of myocardium, biventricular wall thickening, and thickening of interatrial septum and valves; severe diastolic dysfunction with moderately reduced LV ejection fraction; mild decrease in right ventricle systolic function; and small pericardial effusion (Fig. 1C; Videos 1 and 2). Electrocardiography showed low-voltage QRS complexes in the peripheral limbs (Fig. 1D). Laboratory workup was remarkable for free light chain (FLC) monoclonal protein in serum and urine; slight impairment of renal function and significant proteinuria. FLC-differential (FLC-diff) was 34.11 mg/dL, N-terminal fragment of brain natriuretic peptide (NT-BNP) was 11,518 pg/L, and cardiac Troponin T (cTnT) was 0.04 µg/L. Bone marrow biopsy was positive for Congo red staining (Fig. 1E), and the diagnosis of AL amyloidosis was confirmed with mass spectrometry. A diagnosis of CA mimicking HCM was made.

Video 1
Apical 4-chamber and parasternal long axis two-dimensional transthoracic echocardiography showing sparkling pattern of myocardium and concentric biventricular wall thickening, moderately reduced LV ejection fraction, mildly reduced right ventricular function, enlarged and thickened atria, and a small pericardial effusion. Used with permission of Mayo Foundation for Medical Education and Research. View Video 1 at http://movie-usa.glencoesoftware.com/video/10.1530/ERP-17-0021/video-1.

Video 2
Apical 4-chamber and parasternal long axis two-dimensional transthoracic echocardiography showing sparkling pattern of myocardium and concentric biventricular wall thickening, moderately reduced LV ejection fraction, mildly reduced right ventricular function, enlarged and thickened atria, and a small pericardial effusion. Used with permission of Mayo Foundation for Medical Education and Research. View Video 2 at http://movie-usa.glencoesoftware.com/video/10.1530/ERP-17-0021/video-2.

Treatment and outcome

The patient received chemotherapeutic workup following heart failure treatment. The patient died 1 week after admission due to ventricular tachycardia.

Discussion

AL amyloidosis is a clonal bone marrow plasma cell disorder that produces monoclonal immunoglobulin light chains. This disorder is closely related to, but generally distinct from, myeloma and/or other B-cell dyscrasias. Whilst almost any B-cell dyscrasias are associated with AL amyloidosis, not all immunoglobulin light chains are

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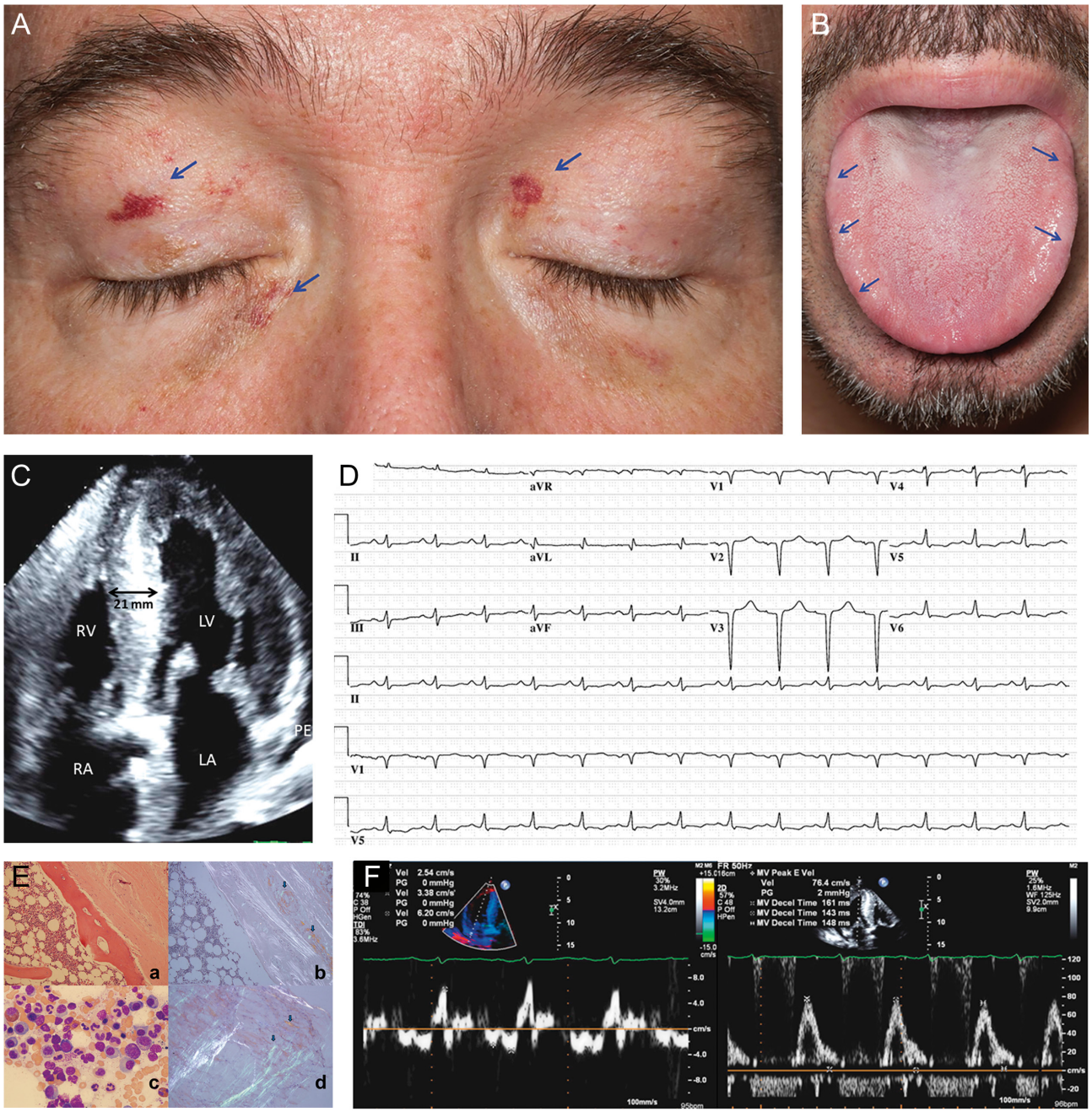

Figure 1
(A) Periorbital purpura. Arrows indicate purpura. (B) Macroglossia. Tongue shows lateral indentation marks (arrows). (C) Transthoracic apical 4-chamber showing a speckled pattern of myocardium and increased wall thickness (interventricular septum of 21 mm); thickening of interatrial septum, valves and right ventricular free wall; biatrial enlargement; and small pericardial effusion. (D) Electrocardiography showing low-voltage QRS in the limb leads. (E) Bone marrow core biopsy (haematoxylin and eosin, original magnification ×100) showing thickened periosteal blood vessels (a), with bone marrow core biopsy (Congo red, original magnification ×100) (b) in which arrows point to amyloid deposits in periosteum and blood vessel wall. Bone marrow aspirate (Wright–Giemsa, original magnification ×600) shows moderate increase in plasma cells (c), and subcutaneous fat aspirate (Congo red, original magnification ×100) (d) shows amyloid deposits (arrows). (F) Tissue and mitral Doppler inflow showing grade 3 diastolic dysfunction with a sharp deceleration time and low e′ with a high E/e′ ratio of 25, suggesting high LV filling pressures.

equally amyloidogenic, given that the majority of AL cases are associated with a subtle monoclonal gammopathy and only 10–15% are associated with myeloma (1, 2). The light chain protein misfolds and forms a β-pleated sheet configuration that deposits in several organs, including the interstitium of the heart. In light of cardiac

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involvement, not only does AL amyloidosis affect the heart, it is important to recognise that the wild-type transthyretin-associated amyloidosis (TTR) has a greater predilection for the heart despite slower progression and better survival. Additionally, the prevalence of wild-type TTR has increased considerably due to population ageing and thus has higher prevalence in the elderly (1, 2).

CA is a condition characterized by extracellular amyloid protein deposition that stiffens the heart without compensatory dilation, which results in increased wall stress and, if not treated in a timely manner, cardiac function deteriorates (2, 3, 4). Early symptoms and signs are often nonspecific; typical features are rare and frequently occur at late stage of disease. Dyspnoea and peripheral oedema are common cardiac manifestations. Skin, kidney, and peripheral and autonomic nerves are classically affected resulting in symptoms. AL amyloidosis typically presents with nephrotic syndrome, periorbital purpura, macroglossia, numbness and orthostatic hypotension. Periorbital purpura and macroglossia are pathognomonic and strongly suggest the diagnosis (Fig. 1A and B). The former is a typical feature almost exclusive to disease, and primarily results from fragile skin capillaries damaged by amyloid protein deposition (1, 3).

Echocardiography is a noninvasive and reproducible tool, and one of the most important methods of assessing CA. In the heart, signs suggesting CA are the presence of granular 'sparkling' pattern of the myocardium, especially in advanced amyloid, although it is nonspecific and less reliable when using harmonic imaging; LV wall thickness; and thickening of interatrial septum (the latter is specific in late stages), valves, papillary muscle, and right ventricular free wall as well as pericardial effusion (2, 3, 4) (Fig. 1C). The most common echocardiographic finding is wall thickening often incorrectly referred as hypertrophy, since there is myocyte/interstitial infiltration rather than hypertrophy as the underlying pathology. Pericardial effusion and thickened valves are described in 40–60% of patients (4). Diastolic dysfunction is the hallmark and the earliest echocardiographic finding. Abnormal relaxation is usually observed in early stages, while restrictive filling with short deceleration time is seen as myocardial infiltration progresses (Fig. 1F). Tissue Doppler velocities are often reduced, even at early stages with mild wall thickening. Diastolic dysfunction and thick walls on echocardiography with low ECG voltage (Fig. 1D) are compelling diagnostic findings; systolic impairment usually occurs at the late stage of disease (Videos 1 and 2). Of note, AL amyloidosis may present with low stroke volume despite preserved LV ejection fraction resulting from reduced LV cavity size. The low ECG voltage is present in 46% of amyloid patients, although it may reach up to 74% (4). The combination of increased LV mass in the absence of high ECG voltage may be more specific.

CA is the major prognostic factor in AL amyloidosis. Once heart failure occurs, life expectancy markedly decreases to 6 months (2, 3, 4, 5). Traditionally, NT-BNP, cTnT and FLC-diff have been major prognostic markers in the disease with profound impact on risk-adapted therapies (6). In addition, speckle-tracking echocardiography derived strain has been shown to be a powerful predictive tool, especially in those at early stages of disease (7). Notably, speckle-tracking echocardiography derived strain appears to play an important role to detect early cardiac infiltration (7). Other disorders presenting with increased wall thickness, such as HCM, infiltrative cardiomyopathies (Fabry disease, Danon disease, mucopolysaccharidoses, myocardial oxalosis, Friedreich ataxia, etc.), and hypertensive and renal heart disease, can mask its diagnosis (8). Here, we illustrate typical findings of CA amyloidosis.

In comparison, HCM is relatively more common and associated with a more favourable prognosis, although the manifestation and prognosis of HCM depend upon the degree of hypertrophy and symptoms. LV hypertrophy is characterized by heterogeneous morphologies, such as sigmoidal, reverse curve, neutral and apical patterns (9), although concentric distribution (neutral) is the most important mimicker of amyloidosis. Additionally, HCM with increased septal wall thickness may be associated with systolic anterior motion of the mitral valve, which usually leads to dynamic LV outflow tract obstruction and mitral regurgitation. Although HCM is associated with obstruction at the LV outflow tract, there can be other levels of obstruction such as in the mid-cavity. Of note, patients with apical or septal asymmetric HCM have pronounced strain reduction in these segments. Conversely, patients with amyloidosis typically present with a basal-apical strain gradient, i.e., they have lower global longitudinal strain values at the basal and spared or less attenuated values at the apical segments (7). In addition, amyloid patients usually present with greater impairment in global longitudinal strain compared to other cardiomyopathies with the same degree of wall thickness, such as asymmetric HCM pattern (7, 10). Interestingly, despite the heterogeneity in phenotypic expression of LV hypertrophy, diastolic dysfunction is noted in almost all HCM patients.

As discussed, several findings should alert the physician to consider investigating CA. Because AL amyloidosis is relatively rare, its presentation is insidious and progressive and depends on the extension of organ involvement, which may delay its diagnosis. In addition, CA can mimic other disorders with increased wall thickness (8). The combination of clinical, serological and echocardiographic features has an important role for predicting the outcome and establishing an accurate diagnosis.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this case report.

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Patient consent
Informed written consent to publish was obtained.

Author contribution statement
Study conception and design: Drs Barros-Gomes and Villarraga. Writing the manuscript and figures: Drs Barros-Gomes and Villarraga. Drs Naksuk and Jevremovic assisted with writing and figures. Drs Naksuk contributed to patient care. Dr Jevremovic interpreted bone marrow biopsy. All authors accessed the data, revised the manuscript and approved the final manuscript.

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