CASE REPORT

A systemic disease un...suspected by physical examination

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SUMMARY

A 73-year-old man was admitted to the cardiology department with unstable angina. He had a history of macroglossia with 3 years of development, attributed to hypothyroidism. On physical examination, he presented an exuberant macroglossia. The following diagnostic procedures were performed—ECG, in sinus rhythm with low voltage criteria, and transthoracic echocardiography, which revealed a left ventricle with preserved function and marked wall thickening, with low strain values in basal segments. The coronary angiography confirmed a lesion of 90% in the right coronary artery, treated with two stents. Suspecting a systemic infiltrative disease, additional tests were performed and these revealed the presence of systemic amyloid light-chain (AL) amyloidosis with cardiac involvement, associated with multiple myeloma. The patient was sent to a consult of haematology to begin chemotherapy.

BACKGROUND

The aim of this report is to present a case of systemic amyloidosis with cardiac involvement, describing the diagnostic route in a case of irregular contours, whose diagnostic clues emerged about 3 years before diagnosis. This was performed after the patient had been admitted to hospital due to a probable epiphenomenon—disease of right coronary epicardial artery, responsible for unstable angina.

CASE PRESENTATION

The authors present a case of a 73-year-old man, an ex-smoker (stopped 15 years ago) with a history of hypothyroidism (in the context of thyroiditis), treated with levothyroxine.

The patient was hospitalised in the cardiology department with unstable angina. When assessing the history of present illness, the patient's history was as follows:

- ▶ Three years before hospital admission, macroglossia had appeared with a progressive increase, attributed to hypothyroidism;
- ▶ Six months previously, his angina appeared and was precipitated with moderate physical effort, increasing in frequency and intensity, appearing for minimal exertion a few days before hospital admission.
- ▶ Fifteen days previously, the emergence of fatigue, orthopnoea and oedema of the lower limbs.

His general practitioner requested an exercise stress test that was positive for myocardial ischaemia, with some criteria of severity. For this reason, the patient was referred to the emergency department.

Figure 1 Exuberant macroglossia of the patient.

On physical examination, the following were noted: an exuberant macroglossia ([figure 1](#)); rhythmic S1 and S2 on cardiac auscultation; abolition of breath sounds in the right pulmonary base on pulmonary auscultation; oedema of the lower limbs, with no other alterations in the examination (including in skin/appendages and on neurological examination).

INVESTIGATIONS

The investigations performed at the hospital were:

- ▶ A 12-lead ECG that showed a sinus rhythm with a heart rate of 90 bpm, left deviation of the axis and low voltage criteria ([figure 2](#)).
- ▶ A transthoracic echocardiography that revealed a left ventricle with preserved global function and a marked wall thickening, especially of the midbasal septum level (20 mm), with a sparkling appearance ([figure 3](#)); the strain of the left ventricle, when evaluated by Speckle-Tracking Echocardiography, had a strain global longitudinal of 13.4, with low strain in the basal segments ([figure 4](#)).
- ▶ A chest X-ray which showed an opacity of the right pulmonary base, compatible with a right pleural effusion.

For suspected coronary artery disease due to unstable angina, it was performed, during hospitalization, a coronary angiography which showed a lesion of 90% in middle segment of right coronary artery ([figure 5A](#)), treated with two drug eluting stents ([figure 5B](#)).

The conjunction of macroglossia with low voltage criteria in the 12-lead ECG and a marked wall thickening of left ventricle, with sparkling appearance, and low strain values in basal segments, suggested an infiltrative systemic disease, and the following additional tests were performed:

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Figure 2 The 12-lead ECG.

- Analytical study, which revealed: positive free light chains in serum and urinary immunofixation; positive Bence Jones protein in urine; proteinuria (24 h) of 575 mg/day, with no other alterations in complete blood count, renal and hepatic function, B-type natriuretic peptide, troponin I or C reactive protein.
- Cardiac MRI showed no other structural cardiac changes beyond those already highlighted by echocardiography, with no specific pattern of delayed enhancement ([figure 6](#)).

Before high suspicion of systemic amyloidosis with cardiac involvement, an abdominal fat biopsy was requested which showed extensive deposits of amyloid in subcutaneous adipose tissue (colouring with H&E and congo red). Additionally, bone marrow biopsy revealed cellular changes compatible with multiple myeloma.

DIFFERENTIAL DIAGNOSIS

- The patient was admitted to the cardiology department with a diagnosis of unstable angina. Coronary angiography confirmed a disease of the right coronary artery.
- The macroglossia could have hypothyroidism as aetiology; however, the conjunction of macroglossia with low voltage criteria in the 12-lead ECG and a marked wall thickening of the left ventricle with low strain values in basal segments suggested the presence of an infiltrative systemic disease, particularly amyloidosis with cardiac involvement, confirmed by examinations performed.
- The diagnosis of hypertrophic cardiomyopathy, although considered, was unlikely taking into account the echocardiographic findings.
- It was diagnosed concomitantly a multiple myeloma.

Figure 3 The transthoracic echocardiography revealed a left ventricle with a marked wall thickening, especially of the mid-basal septum level.

Figure 4 The strain of the left ventricle, when evaluated by Speckle-Tracking Echocardiography, had a strain global longitudinal of 13.4, with low strain in the basal segments.

TREATMENT

During coronary angiography, the right coronary artery lesion was treated with two drug eluting stents and the patient was medicated with double antiaggregation (aspirin and clopidogrel).

Symptomatic therapy was optimised in the context of heart failure (with a preserved ejection fraction).

After diagnosis of systemic amyloidosis, the patient was sent to a consult of haematology to begin chemotherapy.

OUTCOME AND FOLLOW-UP

Six months after hospitalisation, patient presented dyspnoea and fatigue for large physical efforts (New York Heart Association class I), having no symptoms of angina.

DISCUSSION

Systemic amyloidosis is a rare, multisystemic disorder characterised by the extracellular deposition of insoluble fibrillar proteins in various tissues and organs, leading to progressive lesions.¹⁻⁵

Systemic amyloid light-chain (AL) amyloidosis is the most common form of amyloidosis in developed countries.¹ Virtually any plasma cell dyscrasia affecting B lymphocytes (myeloma, lymphoma, macroglobulinaemia) can produce these monoclonal proteins and trigger amyloidosis. The disease usually appears after age 50, but can develop earlier.¹ Its distribution is similar in both genders, with a slightly higher prevalence in men.¹ The multi-organ involvement is the most frequent presentation, although in 5% of cases the heart is the only organ involved.¹ In 90% of cases,

Figure 5 (A) The coronary angiography showed a lesion of 90% in the middle segment of the right coronary artery. (B) The lesion of the middle segment of the right coronary artery was treated with two drug eluting stents.

Figure 6 Cardiac MRI showing no other structural cardiac changes beyond those already highlighted by echocardiography, with no specific pattern of delayed enhancement.

there are deposits in the heart, but only 50% of patients have symptoms or signs of cardiac involvement when diagnosis is made.¹⁻³ Cardiac involvement is crucial in patients' prognosis.¹⁻³

Stenoses and obstructions in coronary arteries by amyloid deposits can lead to ischaemic disease, which differs in terms of prognosis.² Vascular involvement is very common (about 90%), affecting especially small arteries and average and large arterioles.² Amyloid proteins are usually deposited in tunica media and adventitia, leading to a thickening of walls.² Epicardial coronary arteries are involved in a mild or even absent manner.²

Many dermatological signs were associated with cardiac amyloidosis.¹⁻³ Periorbital purpura and capillary fragility are the most distinctive features.¹⁻³ The presence of macroglossia (in 10–20% of patients with AL amyloidosis) can cause a change in taste or dysphonia.¹⁻³ The combination of macroglossia and periorbital purpura is not a very sensitive indicator, but it is highly specific for the diagnosis.¹ Some patients report nail fragility.¹ Neurological symptoms include carpal tunnel syndrome, as well as sensorial and autonomic polyneuropathy.¹⁻³

The low voltage on ECG with poor progression of R waves in precordial leads occurs in 50% of patients with cardiac amyloidosis AL.¹⁻⁴ The presence of low voltage ECG in conjunction with concentric thickening of the ventricular wall is highly suspect of the pathology, but the low voltage may not always occur.⁴

The typical echocardiographic findings include ventricular concentric thickening with right ventricular involvement.¹⁻⁴ A diastolic dysfunction is one of the earlier findings and may occur before cardiac symptoms.¹⁻⁴ The sparkling appearance of the myocardium is not specific of amyloidosis.¹⁻⁴ The most advanced echocardiographic techniques are beginning to reveal important findings.⁴ The strain and strain rate imaging can help differentiate amyloidosis from hypertrophic cardiomyopathy.³⁻⁴ Typically, there is a greater restriction of basal motion relative to the apical movement in amyloidosis.⁴ The basal left ventricular strain is an independent predictor of mortality of cardiac and global causes.⁴

Other imaging modalities such as cardiac MRI may show, in amyloidosis, a pattern of late global subendocardial enhancement.³⁻⁴

The diagnosis of amyloidosis requires a biopsy of the tissue.¹⁻⁵ It is not required to perform a biopsy of heart if echocardiographic findings are typical of cardiac amyloidosis and histological diagnosis was made by biopsy of another tissue.¹⁻³ A biopsy of abdominal fat is a simple procedure, positive for amyloid deposits in more than 70% of patients with AL amyloidosis.¹⁻³ If diagnosis is not confirmed by other tissue biopsy, an endomyocardial biopsy should be performed.¹⁻³

Once there is confirmation of AL amyloidosis, the presence of concomitant blood cell dyscrasia should be investigated.³ Serum

Learning points

- ▶ This report highlights the diagnostic journey in a case of systemic amyloidosis with cardiac involvement, in which macroglossia appeared years before diagnosis, indicating the importance of a high degree of suspicion towards some signs and symptoms.
- ▶ The disease is usually diagnosed late, often after the onset of signs and symptoms suggestive of heart disease, when clinical and additional tests performed raise strong suspicion of an infiltrative disease.
- ▶ The usual late diagnosis and cardiac involvement affect the prognosis of these patients.
- ▶ In amyloidosis it is uncommon for there to be involvement of the major epicardial vessels, more commonly affecting the small arteries due to infiltration of amyloid proteins. Coronary heart disease in this patient eventually translates into an epiphenomenon, resulting in an earlier diagnosis of amyloidosis.

and urine immunofixation should be performed instead of serum and urine electrophoresis, because the amount of serum and urinary paraprotein may be low and immunofixation is a much

more sensitive test.^{1 3} A bone marrow biopsy is required to exclude the presence of multiple myeloma and other less common diseases such as Waldenstrom's macroglobulinaemia.³

The approach to take for a patient with amyloidosis requires the monitoring of cardiac symptoms and treatment mainly with diuretics as well as an investigation of the underlying cause in order to control the production of paraproteins responsible for amyloid formation.¹⁻⁴ Chemotherapy with melfalan seems to have a higher success rate, with a complete haematological response in 40% of patients who survive for about 1 year after the chemotherapy.³

Competing interests None.

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