Case report

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Acromegalic cardiomyopathy: a neglected cause of cardiomyopathy

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Abstract

Acromegaly represents a rare endocrine condition characterized by an excessive secretion of the growth hormone (GH) and the insulin-like growth factor-1 (IGF-1), mostly subsequent to a pituitary adenoma. Acromegaly affects 40-60 people per million without significant difference between men and women, with an average age of onset of 44. The slow progression of the disease leads to a delay in diagnosis of 4 to 10 years from the onset of the hormonal imbalance. The increase of the GH and IFG-1 levels is associated with cardiac, respiratory, metabolic and rheumatic disorders. The cardiac involvement, also called acromegalic cardiomyopathy, causes a serious deterioration of the prognosis quoad vitam. An early diagnosis and a targeted treatment at the initial stage of the myocardial damage can enable the reversibility of the structural alterations. ***Clin Ter 2022; 173 (1):31-34 doi: 10.7417/CT.2022.2387***

Key words: *Acromegalic cardiomyopathy, structural dilatative cardiomyopathy, stress echocardiography*

Case Description

We describe the case of a 66 year old man who came to the first cardiac evaluation after observation of frequent supra- and ventricular extra-systoles at the monitoring during orthopaedic surgery. The patient had excellent general condition, had never complained about cardiovascular symptoms, reported to be very active, with multiple sports activities during the week. His cardiac risk factors were dyslipidemia, on therapy with low dose simvastatin, and a positive family history (father died following a cardiac arrest at the age of 39 years and a brother affected by coronary heart disease). At the clinical examination: height 190cm, weight 84 Kg, BMI of 22.7 Kg/m2, arterial pressure 142/82 mmHg, normal pulse-rate. Cardiac and lung examination were normal, without signs of congestion.

The electrocardiogram registered a normo-cardic sinus rhythm with complete right bundle branch block and left anterior fascicular block, with negative T wave from V1 to V3 (Fig. 1).

The transthoracic rest echocardiography showed a slightly dilated left ventricle (end-diastolic diameter: 62mm, end-diastolic volume: 200ml), with a calculated biplane ejection fraction of 45-50%, lateral and anterior middle-apical hypokinesia. During stress-echocardiography with physical exercise the patient reached 225 Watts (133% of predicted) with maximal cardiac frequency of 148 bpm (94% of max according to his age), arterial pressure reached 202/102 mmHg, without insurgence of relevant symptoms, but with appearance of polymorphic ventricular extra-systoles and ventricular bigeminism during exercise. Slow return to normal pulse rate in the course of the recovery phase. At the stress echocardiography no-significant increase of the ejection fraction and a diffuse development of hypokinesia were observed. To exclude a coronary artery diseases, a cardiac magnetic resonance with pharmacological stress was performed, which confirmed a light dilation of both ventricles with a slightly reduced ejection fraction but without alterations of the regional kinesis or perfusion defects. ACE inhibitor was introduced, and it was recommended the optimal control of the cardiovascular risk factors.

He presented to cardiac follow-up one year later and he was found asymptomatic and in good health. Due to a trauma, the patient had abstained from any sports activities in the last 4 months. The clinic examination and the electrocardiography were unchanged, with respect to the previous year. The trans-thoracic echography was unchanged, except for the appearance of the tissues, a slow progression of the ventricular hypertrophy and a grade 2 diastolic dysfunction. These findings were no more compatible with "athlete's heart", since the patient had stopped any physical exercise in the previous 4 months, which is a time-period enough for the regression of a possible exertional hypertrophy.

To investigate secondary causes of cardiomyopathy, screening tests were conducted: autoimmune diseases were excluded; thyroid function, protein electrophoresis, ferritin, and serologies for Borellia were normal. During the visit, the patient reported intolerance to heat and the increase

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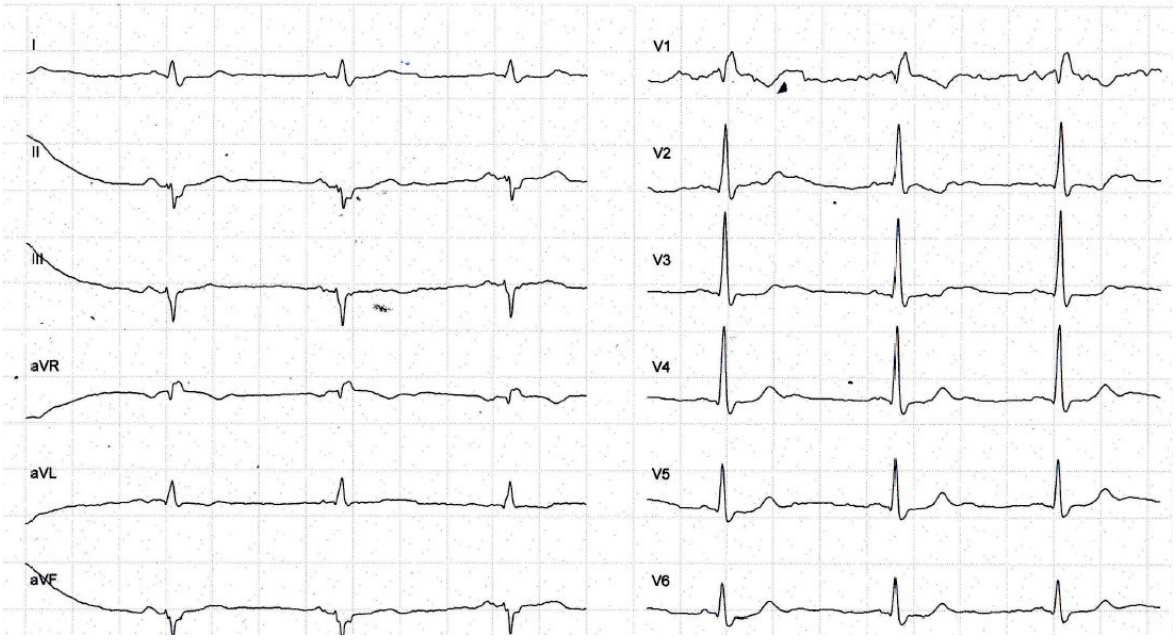

Fig.1. Sinus bradycardia, normal PR interval, complete right bundle branch block and anterior hemiblock

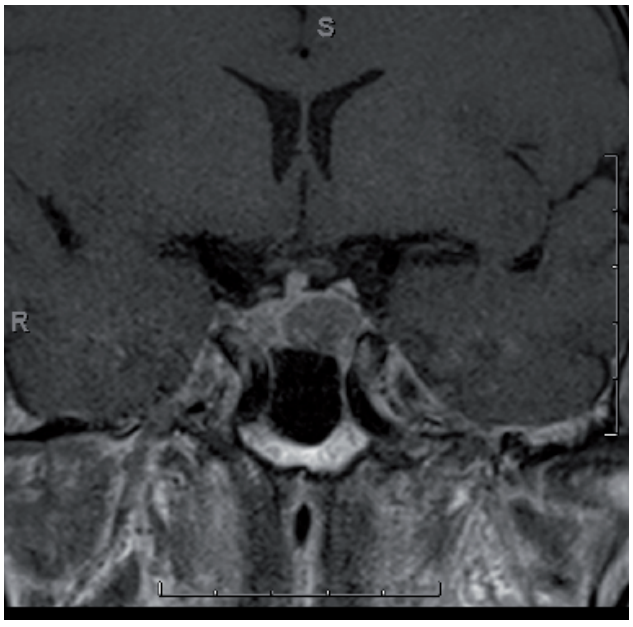

Fig. 2. T1 weighted MRI sequence after gadolinium administration shows a left lateralised pituitary macroadenoma in the suprasellar cistern without mass effect on suprasellar structures. Slight shift off the midline of the pituitary stalk.

by one of his shoes size in the last two years. Hence, an endocrinological evaluation was prompt performed; the findings showed an increase of the growth hormone and of the insulin-like growth factor levels (GH 7.80 ng/L, IGF-1612 ng/L).The MRI brain scan confirmed the presence of a 12 mm pituitary adenoma, which was surgically excised through trans-sphenoidal trans-nasal access (Fig. 2).

The immunohistochemistry resulted positive for GH and synaptophysin. No post-surgical residues were detected during the follow-up MRI brain scan, six monthes after surgery.

The haemato-chemical tests showed persistent elevated GH and IGF-1 levels. The patient started a therapy with cabergoline 0.75 mg/day. At following haemato-chemical tests a decrease of the GH levels (5.41 ng/L) and the normalization of the IGF-1 values (209 ng/L) were observed.

The following cardiologic evaluation showed no change of the left ventricular ejection fraction.

Discussion

Since 1886, following the Pierre Marie's studies, cardiomegaly and heart failure have been recognized as complications of acromegaly, a rare endocrine condition characterized by excessive secretion of the growth hormone (GH) and insulin-like growth factor-1 (IGF-1), mostly subsequent to a pituitary adenoma originated from somatotropic cells (> 98% of the cases).

The clinical symptoms depend from the levels of GH and IGF-1, the age and exposure time of the organs to the elevated hormonal levels. The diagnosis arrives often many years after the onset of the endocrine alteration. The acromegalic patients' life expectancy is around 10 years lower compared to the rest of the population, with a two times higher risk of mortality due to cardiovascular, cerebrovascular, respiratory and metabolic causes. Cardiovascular disorders represent a frequent comorbidity in patients affected by acromegaly, representing the 80% of the complications, and the second mortality cause after cancer (1-3).

The "acromegalic cardiomyopathy" develops through three phases: the first phase shows a biventricular hypertrophy and an increase in myocardial contractibility, secondarily to the stimulation of the myocardiocytes by the raised levels of GH and IGF-1 and to the increased flux of calcium ion inside the myocytes as an effect of IGF-1. It follows a reduction of the elasticity of the ventricular walls, with consequent diastolic dysfunction (second phase), and a ventricular dilation with systolic dysfunction (third phase) (4-6).

Histologically it is characterized by an alteration of cardiac muscle architecture with extracellular collagen depositions, disarray of the myofibril, progressive lymphocytic and monocytic infiltration and finally necrosis with interstitial fibrosis. The evolution of the damage until congestive cardiac failure is however rare (1-4% of acromegalic patients), and associated with a long-standing, not treated endocrine disease (3)

The early treatment (surgical or pharmacological with somatostatin-analogues or pegvisomant, a GH receptor antagonist) can induce the regression of the ventricular hypertrophy and improve the cardiac function (3-5).

The excess of GH causes: growth of the smooth muscle cells (with consequent increase of the vascular resistance), hyper activation of the renin-angiotensin- aldosterone system and altered production of nitric oxide with following altered vasodilation, insulin resistance. The acromegaly therefore frequently causes hypertension (in up to 50% of the acromegaly patients) and diabetes, indirectly acting as a cardiovascular risk factor (4).

Another feature and cause of mortality in acromegalic patients is the high incidence of ventricular arrhythmias. It leads in fact to a high incidence of ventricular premature beats (on interstitial fibrosis), a high variability of the QT interval and presence of late potentials, which are all correlated with ventricular tachyarrhythmia. There is furthermore an altered variability of the cardiac frequency due to a dysfunction of the cardiac autonomic system and of the sympato-vagal system (3, 7-8).

The aim of the therapy in acromegalic patients is the normalization of the GH and IGf-1 levels, removal or reduction of pituitary tumors, maintenance of a normal pituitary residual function, comorbidity control and reduction of mortality rate. The therapeutic approach consists of transnasal-transsphenoidal surgery, radiotherapy and pharmacological therapies with analogues of somatostatin, dopamine agonists and GH receptor antagonist (9).

The regression of the hypertrophy and ventricular dysfunction depends not only on the correction of the hormonal levels but also on the patient's age, the duration of the disease and the control of the metabolic panel: the control of endocrinal alterations after 12 months of therapy with analogues of somatostatin has proved a normalization of the left ventricle mass in the 100%of the young patients and 50% of the middle-age and elderly patients with correspondent improvement of the ejection fraction in the 80% of young patients and in the 50% of the remaining patients.

For patients who are resistant of somatostatin-analogues it is indicated a long-term treatment with Pegvisomant. So far no study has described the effects of cabergoline on cardiovascular complications in acromegaly (5-9). In the advanced phase of the cardiomyopathy, even after treatment of acromegaly, there isn't a regression of the myocardial damage (10).

Due to unfavourable risk-factor ratio, by our patient it was decided to not perform endomyocardial biopsy, which would have provided a histological diagnosis of acromegalic cardiomyopathy and it is not certain whether his cardiopathy was related or not to the acromegaly. However, after successful surgical treatment of the condition and normalization of GH and IGF-1 values, at the following cardiac visits, we did not observe any worsening.

Conclusions

The cardiac involvement in acromegalic patients is the result of different concomitant and probably interdependent pathophysiological aspects. Altogether, hypertension, cardiac hypertrophy with dilatative and congestive evolution, coronary artery disease and an high incidence of ventricular arrhythmias represent the clinical spectrum of the disease and concur to determine its dismal prognosis. These elements contribute to the increased mortality rate in these patients, compared to the general population, with a 10-year reduction in life expectancy. An early diagnosis is essential to reverse or reduce the development of cardiac complications and to improve the prognosis.

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Authors' contribution

The presented idea of the study was conceived by T Bonora and ML De Perna. T Bonora wrote the manuscript with support from E Rigamonti and ML De Perna. M Capoferri supervised the project.

All authors read and approved the final version of the manuscript.

Learning points

Acromegalic cardiomyopathy includes dilatative cardiomyopathy, congestive heart failure, hypertension, coronary artery disease and a high incidence of ventricular arrhythmias.

These elements contribute to the increased mortality rate in these patients, compared to the general population, with a 10-year reduction in life expectancy.

An early diagnosis is essential to reverse or reduce the development of cardiac complications and to improve the prognosis.

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