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Case Report

Hypertrophic cardiomyopathy in a patient with secondary hypoparathyroidism: A case report ☆,☆☆

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ABSTRACT

Parathyroid hormone (PTH) has direct and indirect actions on cardiovascular cells. The effects of chronic hypoparathyroidism on cardiac morphology, function, and conduction are still unclear. Low PTH states are associated with multiple manifestations in the heart, acute or chronic. Acute hypocalcemic cardiomyopathy is a transient dilated cardiomyopathy with reduced ejection fraction and diffuse left ventricular hypokinesia. Chronic hypoparathyroidism-associated cardiomyopathy is a rare disease that may cause reduced myocardial tension, cardiac cavity enlargement, arrhythmias, and congestive heart failure. Here, we describe a 73-year-old woman with chronic hypoparathyroidism and hypocalcemia, who developed a hypertrophic cardiomyopathy, and not a dilated hypocalcemia-associated cardiomyopathy, which would be usually the case.

Introduction

Hypoparathyroidism is a rare disorder characterized by low or absent concentrations of circulating parathyroid hormone (PTH), leading to hypocalcemia, hyperphosphatemia, and elevated urine fractional excretion of calcium [1]. With an estimated prevalence of 23-37 cases per 100,000 person-years [2], the major cause is iatrogenic, since 78% of the cases occur as a complication of anterior neck surgery [2,3]. Most of car-

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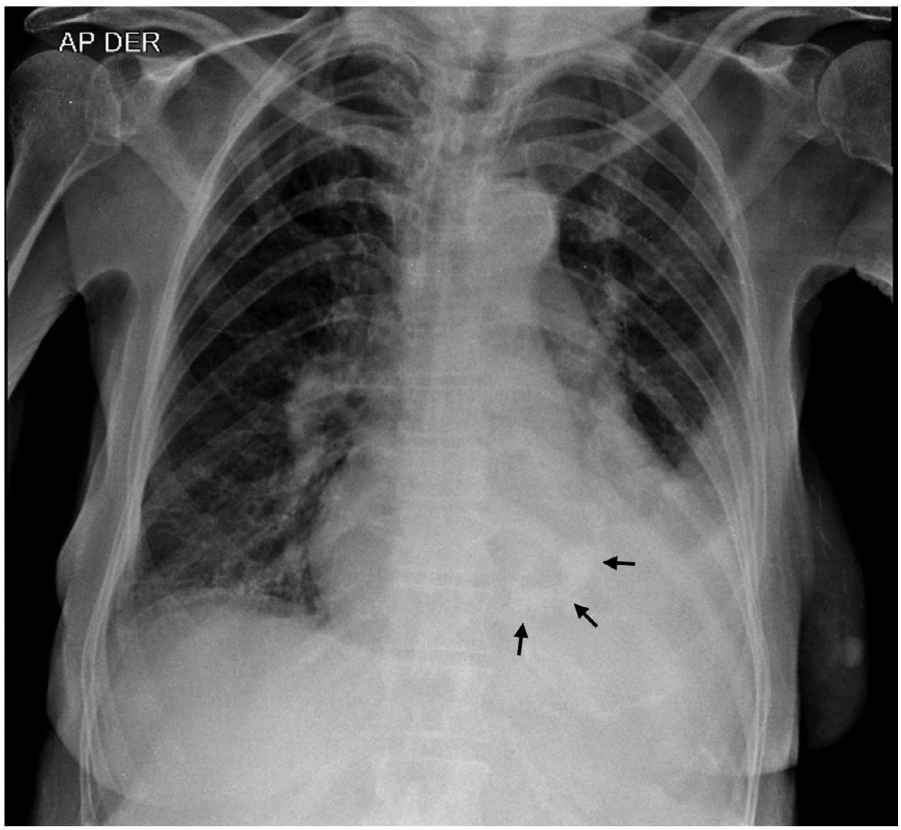

Fig. 1 – Chest X rays. Band of coarse calcification over the expected location of the annulus of the mitral valve (black arrows), cardiomegaly, and left pleural effusion.

diac effects from hypoparathyroidism stem from the resulting hypocalcemia. PTH also appears to have an independent effect on cardiac cells, which has to be elucidated [4].

Case presentation

A 73-year-old woman was repeatedly admitted due to recurrent transudate-type pleural effusions, dyspnea, and hypocalcemia. She had a previous history of hypertension, bilateral cataracts, epilepsy, cognitive impairment, and secondary hypoparathyroidism after subtotal thyroidectomy 54 years ago. The patient was under treatment due to chronic heart failure, so she attended our institution because of suspected decompensated heart failure. Physical examination revealed Trousseau and Chvostek signs. Relevant test results showed: corrected calcium 5.42 mg/dL (8.8-10.2), phosphate 7 mg/dL (2.5-4.5), calcium/phosphate product 37.94 (less than 55), TSH 1.65 mUI/L (0.350-4.94), and parathyroid hormone <3 pg/mL (15-65).

Chest X-ray (Fig. 1) disclosed cardiomegaly, left pleural effusion, and a band of coarse calcification over the expected location of the mitral valve annulus. *Transthoracic echocardiography* showed a non-dilated left ventricle with an ejection fraction of 65%, hyperdynamic systolic function with obliteration of the middle ventricular third in the apical portion, and a maximum gradient of 8 mmHg. The mitral valve had severe calcification of the posterior ring. There was tricuspid valve regurgitation with mild right ventricle dilatation. Left and right atrium presented mild and severe dilatation respectively. The pulmonary artery pressure was 75 mmHg. A predominantly apical hypertrophic cardiomyopathy was diagnosed, due to obliteration of the apical cavity of the left ventricle during systole. *Gadolinium cardiac MRI (CMRI)* (Fig. 2) demonstrated normal biventricular systolic function—with an ejection fraction of 89% and 68% in the left and right ventricle respectively—restrictive pattern with bi-auricular dilatation, and mid-diastolic collapse of the left ventricle with flow acceleration. There was interatrial septal thickness and hypointense nodular thickening of the mitral valve suggestive of calcification. Myocardial perfusion was normal. *Non-contrast Brain CT* (Fig. 3) showed bilateral symmetric calcifications on basal ganglia compatible with Fahr syndrome. *Congo red and crystal violet stains* of the periumbilical skin and rectal mucosa were negative, ruling out amyloidosis. Other hypertrophic cardiomyopathy phenocopy conditions like Fabry, glycogen, and lysosomal storage diseases were also ruled out.

The patient was treated with calcium, calcitriol, and recombinant human PTH (rhPTH) 1-34 fragment (teriparatide, Forteo by Lilly France SAS, Fegersheim, France), at a dose of 20 μg twice daily, as an off-label use due to unavailability of rhPTH 1-84 fragment. These interventions al-

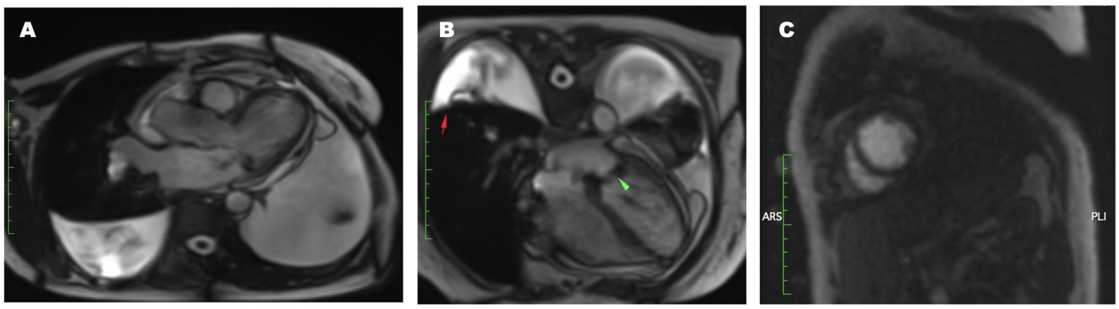

Fig. 2 – Gadolinium cardiac MRI (CMRI). Three-chamber view, cine steady-state free precession (SSFP) show hypertrophied basal septal myocardium and turbulence jet across the mitral valve suggestive of mitral valve stenosis (panel A). Four-chamber view displays a loss of signal on T1-weighted images compared to the adjacent myocardium compatible with Mitral annular calcification (green arrowhead), and a pleural effusion is also present (red arrow) (panel B). Midventricular short-axis image show no contrast uptake during first pass or late gadolinium enhancement (LGE) sequences (panel C).

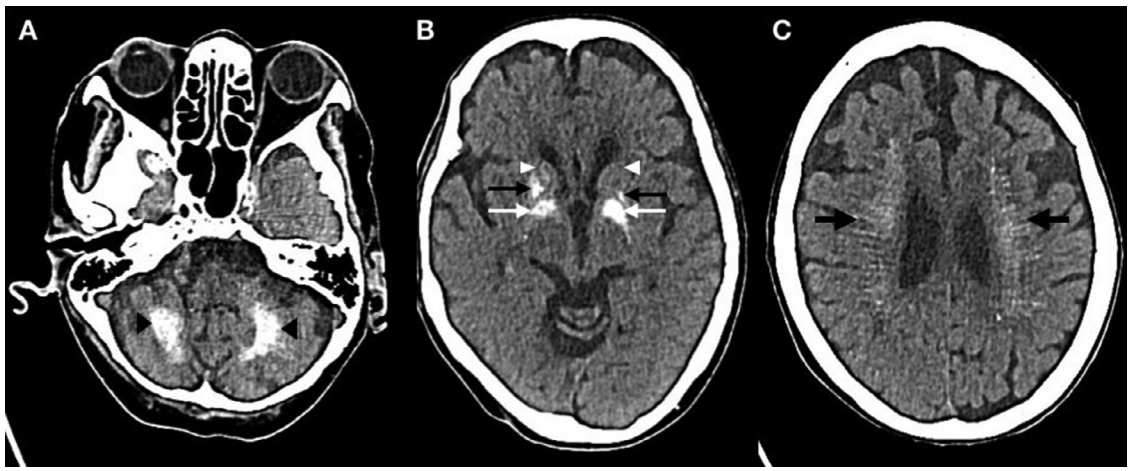

Fig. 3 – Axial non-contrast brain CT. Bilateral symmetric calcifications on dentate nuclei (Black arrowheads) (panel A). Head of the caudate nuclei (white arrowheads), Putamina (thin black arrow), Globus pallidus (thin white arrows) (panel B). And Corona radiata (thick black arrows) (panel C).

lowed us to reach therapeutic targets of serum total calcium slightly below the lower limit of the normal range, serum phosphate in the upper limit, and a total calcium phosphate product less than 55 mg^2/dL^2. Her condition improved, so that there was a decrease in the frequency of readmissions.

Discussion

Parathyroid hormone has direct and indirect actions on cardiovascular cells (cardiomyocytes and smooth muscle cells) through downstream signaling of heart G protein-coupled receptors. Such actions exert changes in contractility, proliferation, and hypertrophy of the cardiac myocytes [4,5] On the vasculature, PTH is a vasorelaxant agent acting directly on vascular smooth muscle cells [4,5]. The effects of excess PTH on the cardiovascular system are well-known and are associated with a higher incidence of hypertension, left ventricular hypertrophy, heart failure, arrhythmias, and calcific valve disease [4]. On the other hand, the effects of the chronic deficit of PTH on cardiac morphology, function and conduction is still unclear.

Hypoparathyroidism is an uncommon condition characterized by low or absent PTH levels, hypocalcemia, and hyperphosphatemia; its etiology can be either congenital or acquired [1]. Low PTH states are associated with multiple manifestations on the heart, either acute or chronic. The hypocalcemic cardiomyopathy is an acute, transient, dilated cardiomyopathy with reduced ejection fraction and diffuse left ventricle hypokinesia. It is associated with brain calcifications: Fahr Syndrome (20%), cataracts (20%), and cognitive dysfunction (16.5%). Other acute manifestations include Takotsubo cardiomyopathy and arrhythmias [6]. These manifestations share the same physiopathology and are caused by acute effects of hypocalcemia, hypomagnesemia, vitamin D deficiency, and hypoparathyroidism on cardiomyocytes and calcium channels. They are reversible by restoring serum calcium levels [6].

The cardiac manifestation of chronic hypoparathyroidism, with hypocalcemia, is an associated cardiomyopathy with reduced myocardial tension, cardiac cavity enlargement, arrhythmia, and congestive heart failure [6–8]. Hypoparathyroid cardiomyopathy is probably caused by other factors different from the low PTH state, such as an elevated calcium phosphate product, chronic hyperphosphatemia, and elevated levels of Fibroblast growth factor-23 (FGF-23). Here, we presented a patient with chronic hypoparathyroidism and hypocalcemia who developed a hypertrophic cardiomyopathy, and not a dilated hypocalcemia-associated cardiomyopathy, which usually would be the case.

Goals of treatment in hypoparathyroid patients aim to maintain serum calcium levels slightly below the normal range (8.0-8.5 mg/dl), and to keep the calcium phosphate product below 55 mg^2/dL^2 (a threshold extrapolated from patients with chronic kidney disease that prevents the calcium and phosphate in soft tissues). In hypoparathyroid patients, higher product levels are associated with vascular and mitral valve calcification; but even a calcium phosphate product more than 34.5 mg^2/dL^2 is associated with calcification of the basal ganglia. Another goal aims to maintain fasting serum phosphate within normal range or slightly elevated [9]. In hypoparathyroid patients, hyperphosphatemia might act as a cardiac stressor, increasing FGF-23—a bone-secreting hormone that lowers serum phosphate levels—leading to mitral annular calcification and cardiac hypertrophy [10–14].

Fibroblast growth factor-23 might have general pro-inflammatory features that could contribute to cardiac inflammation associated with pathologic hypertrophy. FGF-23 activates fibroblast growth factor receptor 4 (FGFR4) on cardiac myocytes to stimulate the phospholipase Cγ/calcineurin/Nuclear factor of activated T cell signaling axis in myocytes, thereby promoting cardiac hypertrophy [14,15]. Although the prevalence of hypoparathyroidism is low, in cohorts of patients with this condition, the low occurrence of cardiomyopathy suggests that there must be a subtype of vulnerable patients, with risk factors not yet defined [1,16].

Conclusion

The hypoparathyroidism-associated hypertrophic cardiomyopathy is an exotic manifestation of chronic hypoparathyroidism; it is even rarer than hypocalcemic dilated cardiomyopathy. It seems to be the consequence of hypoparathyroidism, a high calcium phosphate product, and hyperphosphatemia, leading to increased FGF-23 and posterior activation of intracellular pathways, causing cardiac hypertrophy.

Patient consent

Informed written consent was obtained from the patient for publication of the case report and all imaging studies. Consent form on record.

Compliance with ethical standards

This article does not contain any studies involving animals, performed by any of the authors.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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