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CASE REPORT: CLINICAL CASE

ST-Segment Elevation

Hypocalcemia or Takotsubo Syndrome? A Diagnostic Dilemma

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ABSTRACT

A wide range of etiologies, both ischemic and nonischemic, can produce an electrocardiographic pattern of ST-segment elevation (STE), including Takotsubo syndrome (TTS) and electrolyte imbalances. Instances of hypocalcemia-induced TTS and STE are exceedingly rare in medical literature. This paper presents the case of a 75-year-old woman with advanced ovarian cancer and no prior heart issues, who exhibited diffuse STE on electrocardiogram, resembling acute coronary syndrome. Additionally, echocardiography suggested left ventricle apical ballooning, as per TTS, in the context of severe hypocalcemia and elevated troponin I level. After confirming no coronary artery disease via angiography, we administered calcium supplementation. Subsequently, the electrocardiogram displayed widespread giant T-wave inversions, and the patient's cardiac function fully recovered on normalization of calcium levels within few days. This case serves to highlight the importance of recognizing rare causes of STE (eg, hypocalcemia-induced cardiomyopathy), particularly in patients with neoplastic condition. However, the precise mechanism underlying a potential hypocalcemia-induced TTS remains to be elucidated, and there are only a limited number of case reports in the literature. In light of the aforementioned considerations, we propose a comprehensive examination of cases associated with hypocalcemia and STE and left ventricular systolic impairment. (JACC Case Rep. 2024;29:102795) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

ST-segment elevation (STE) is an electrocardiographic pattern that must be promptly identified because it can be indicative of an ongoing transmural myocardial infarction. According to the current European Society of Cardiology guidelines,[1] percutaneous coronary reperfusion must be performed in these patients within 2 hours from the diagnosis. Therefore, electrocardiogram (ECG) represents a key tool for the diagnosis and therapeutical management of these patients.[1] However, STE is not always caused by obstructive coronary artery disease (CAD). The STE morphology (concave vs convex) can assist the clinician in the differential diagnosis.

TAKE-HOME MESSAGES

- STE is a rare occurrence in cases of hypocalcemia, and the precise mechanism responsible for the ECG pattern resembling a heart attack is not yet fully understood.
- We discuss a complex case of hypocalcemia-induced STE in the context of concomitant TTS, which may be associated with either a paraneoplastic process or directly with hypocalcemia.
- Due to the extreme rarity of the combination of these conditions, a definite diagnosis remains challenging.

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ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

ECG = electrocardiogram

hs-TnI = high sensitive troponin I

LV = left ventricular

STE = ST-segment elevation

TTS = Takotsubo syndrome

Conversely, there are other conditions that can completely mimic the STE-myocardial infarction ECG pattern.[2] In these cases, a coronary angiography is generally performed to rule out a ST-segment elevation myocardial infarction.

Hypocalcemia is characterized by a total serum calcium concentration <8.8 mg/dL (<2.20 mmol/L), with normal plasma protein concentrations, or a serum ionized calcium concentration of <4.7 mg/dL (<1.17 mmol/L). The most common electrocardiographic variations in patients with hypocalcemia affect the ST-segment and QTc interval. STE is a rare finding during hypocalcemia.[3]

Takotsubo syndrome (TTS) is an acquired cardiopathy thought to be induced by increased catecholamines secretion due to severe physical or emotional stress. In patients with TTS, STE can be found, typically of <2 mm in the inferior leads and V_3. After the acute phase, several electrocardiographic changes can be found: QTc prolongation and the emergence of negative T waves are the most common. The typical echocardiographic finding is apical ballooning, consisting in the akinesia of the left ventricular (LV) apex and middle segments, with a hypercontractility of the LV base.[4]

Only 2 cases of TTS associated with hypocalcemia have been reported in the literature.[5,6] We present a case of STE mimicking acute coronary syndrome in the setting of hypocalcemia, with an echocardiographic aspect of apical TTS.

CASE REPORT

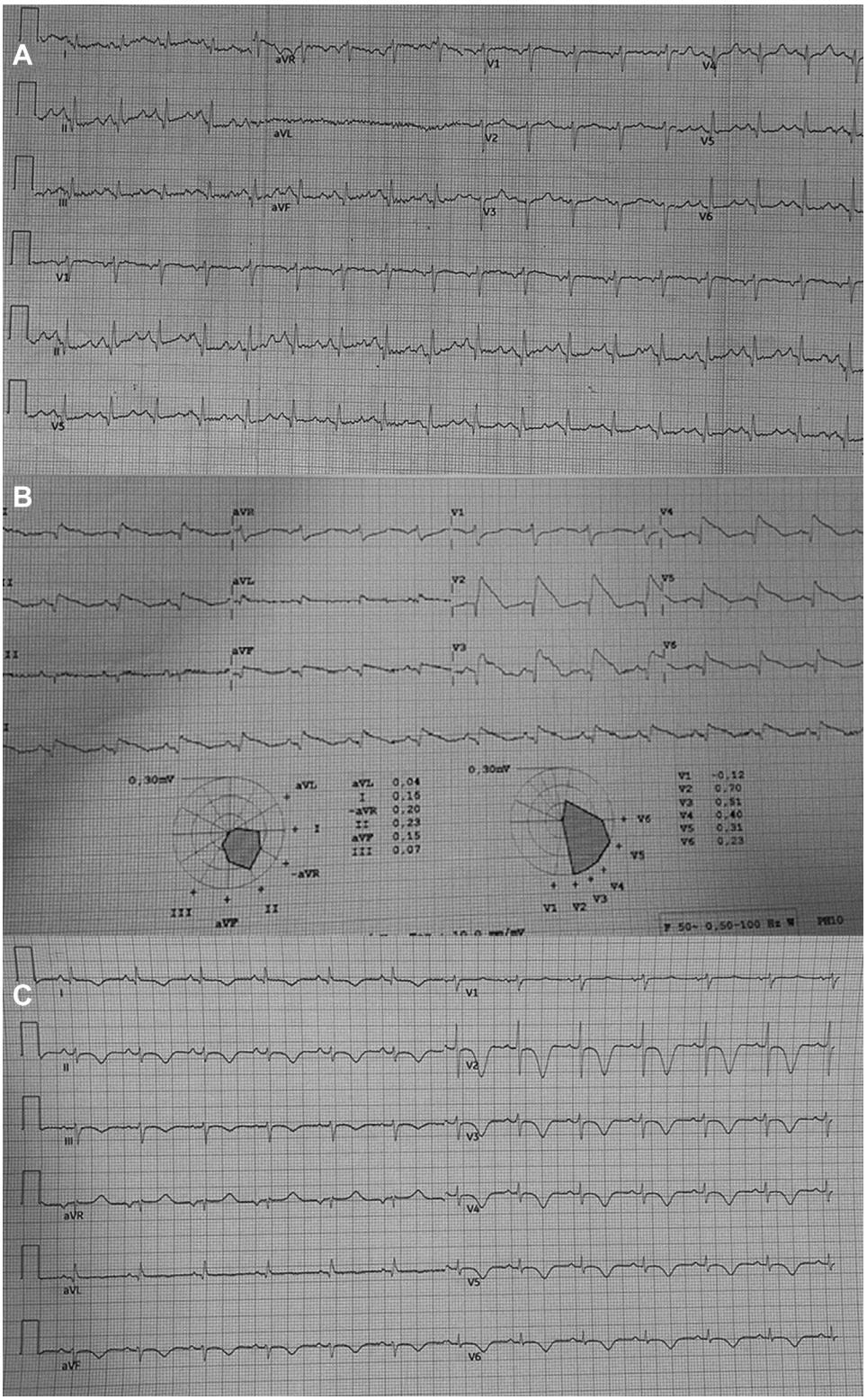
A 75-year-old woman was admitted to our emergency department due to the sudden onset of a painful muscle spasm associated with a burning sensation in her hands and feet. She also complained of perioral numbness, dysphagia, and nausea. Her medical history included immunoglobulin A monoclonal gammopathy of undetermined significance. At 68 years of age, she was diagnosed with stage IV metastatic serous ovarian cancer (*BRCA* wild-type) treated with gynecologic surgery, and neoadjuvant and adjuvant chemotherapy, using the carboplatin-paclitaxel-bevacizumab regimen. Her only cardiovascular risk factor was hypertension, and she had no history of previous cardiac diseases. Two months before, she had undergone surgery for intestinal obstruction secondary due to peritoneal carcinomatosis, without complications. At presentation, she was hemodynamically stable and with normal vital parameters. She was receiving only palliative care because of her end-stage cancer. She denied chest pain and dyspnea. Physical examination revealed Chvostek and Trousseau sign, indicating an electrolyte imbalance. A left pleural effusion was evidenced at chest radiograph. Laboratory tests confirmed severe hypocalcemia: total calcium serum level was 6.8 mg/dL (normal range: 8.7-10.4 mg/dL) and free ionized calcium was 3.09 mg/dL (reference range: 4.6-5.3 mg/dL). Magnesium, potassium, sodium, high sensitive troponin I (hs-TnI) (first dosage), and inflammatory markers were normal; creatinine was 1.39 mg/dL with an estimated glomerular filtration rate of 37 mL/min.

ECG demonstrated sinus tachycardia, low voltage QRS complex in peripheral leads, and poor R-wave progression from V_1 to V_4 lead. QT interval was normal (**Figure 1A**). The second dosage of hs-TnI was 7058.6 ng/mL. Still no chest pain was reported. On bedside echocardiography, LV systolic function was severely impaired, with akinesia of the apical and middle segments and hypercontractility of the basal ones (**Figure 2**). The LV ejection fraction was estimated to be 25%, whereas no signs of LV hypertrophy and/or dilation were detected. Neither valvular disease nor pericardial effusion was identified.

Given the clinical suspicion of acute coronary syndrome, the patient was transferred to our cardiology department. ECG at this time revealed diffuse STE with concomitant ST-segment depression in leads aVR and V_1 (**Figure 1B**). Consequently, an invasive coronary angiography was performed, which revealed normal coronary arteries (**Figure 3**). Thus, given the exclusion of CAD, the apical ballooning, the hs-TnI increase, and the electrocardiographic alterations, in the suspicion of TTS, the patient was monitored, while serum calcium was corrected.

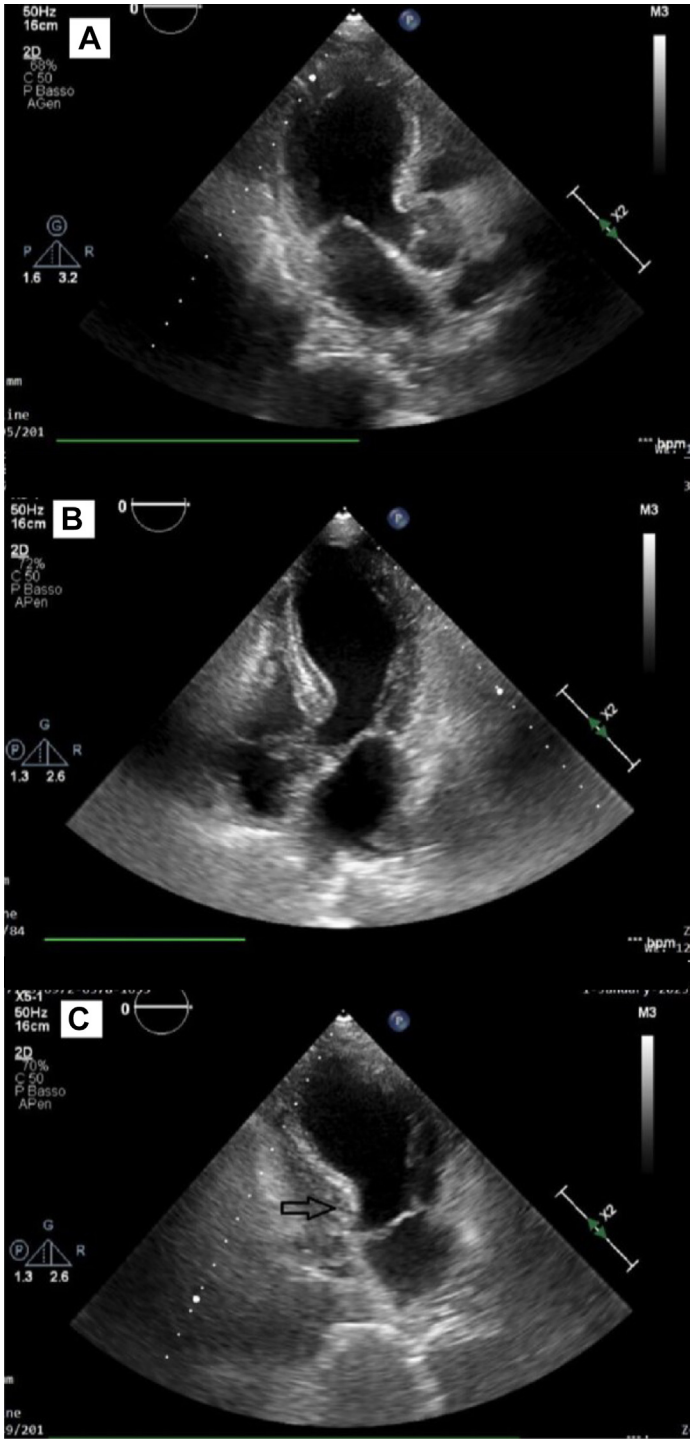
After a few days, ECG revealed the presence of global giant T-wave inversions (**Figure 1C**). The patient's conditions improved rapidly, and no other signs or symptoms of hypocalcemia were reported. Furthermore, a progressive improvement in kidney function was registered. On the ninth day of hospitalization, echocardiography demonstrated a complete resolution of the regional wall motion abnormalities of the left ventricle, with an ejection fraction of 55%. The patient was discharged with normal laboratory values in phospho-calcium metabolism. hs-TnI concentration progressively decreased. The patient is currently in good health and cardiologic status at periodic follow-up.

FIGURE 1 **Evolution of Electrocardiogram During the Patient's Hospitalization**



(A) Admission 12-lead electrocardiogram (ECG) showing sinus tachycardia, low voltage QRS complexes in peripheral leads, and poor R-wave progression from lead V_1 to lead V_4. (B) 12-lead ECG performed after a few hours from admission showing diffuse ST-segment elevation with concomitant ST-segment depression in lead aVR. (C) 12-lead ECG performed after the normalization of calcium levels showing giant T-wave inversions, with a complete recovery of ST-segment elevation.

FIGURE 2 Apical Echocardiographic Images Showing Apical Ballooning Typical of Takotsubo Syndrome



(A) Echocardiogram 3-chamber apical view showing hypocontractility of the left ventricle basal segments. (B) Echocardiogram 4-chamber apical view demonstrating the suggestive Takotsubo apical type morphology. (C) Echocardiogram 2-chamber apical view, evidencing left ventricular basal segments akinesia.

DISCUSSION

If an STE is present on ECG, careful attention to the ST-T segment and QRS complex morphology must be paid to differentiate between the possible underlying causes. The differential diagnosis includes ischemic and nonischemic causes (eg, ST-segment elevation myocardial infarction, early repolarization, myopericarditis, pulmonary embolism, hypothermia, preexcitation).[2] Of the known electrolyte abnormalities affecting the ST-segment, hypocalcemia is one of the rarest.[7] In fact, the most common electrocardiographic finding in hypocalcemia is QTc prolongation. The T-wave is usually normal but may also be flattened or inverted.[3] However, the mechanism by which low serum calcium can lead to a pseudoinfarct pattern on ECG is not fully understood. One plausible explanation is that hypocalcemia increases the permeability of the cell membrane to sodium ions, causing progressive depolarization. Depolarization from an epicardial to an endocardial region is likely to generate the ST-segment deflection on ECG.[7]

Some authors have also suggested an association between hypocalcemia and coronary vasospasm resulting in STE on ECG, but the underlying pathophysiological mechanism has not yet been identified.[8]

Rare cases of hypocalcemia presenting with an STE simulating acute myocardial infarction have been described in the literature. Very few have shown a concomitant alteration in LV contractile function on echocardiogram in the absence of CAD.[7,9-11]

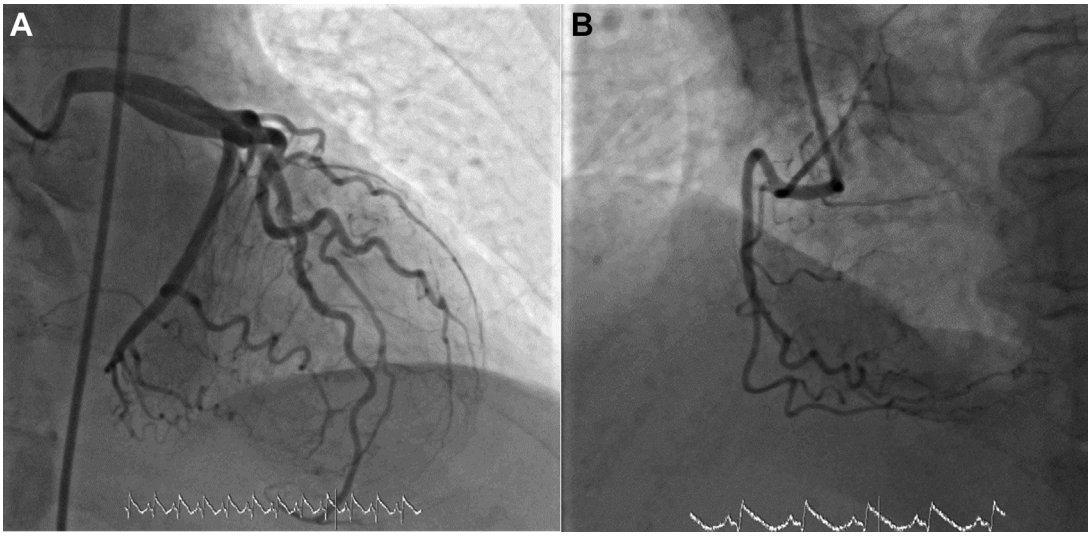
Lehmann et al[10] presented the case of a woman with chest pain, severe hypocalcemia, and STE in the anterior leads of ECG due to what the authors considered to be resultant coronary vasospasm. However, the patient also had hypomagnesemia, hypokalemia, and hyperphosphatemia, which may have contributed to the electrocardiographic changes.[10]

Conversely, our patient presented without any other electrolyte disturbances, making hypocalcemia the most likely cause of the changes.

In addition, as in the Andreozzi et al[6] paper, our case is quite atypical: first, it is only a calcium disorder without QT-segment alterations and, second, the LV abnormalities resemble a Takotsubo-like pattern.

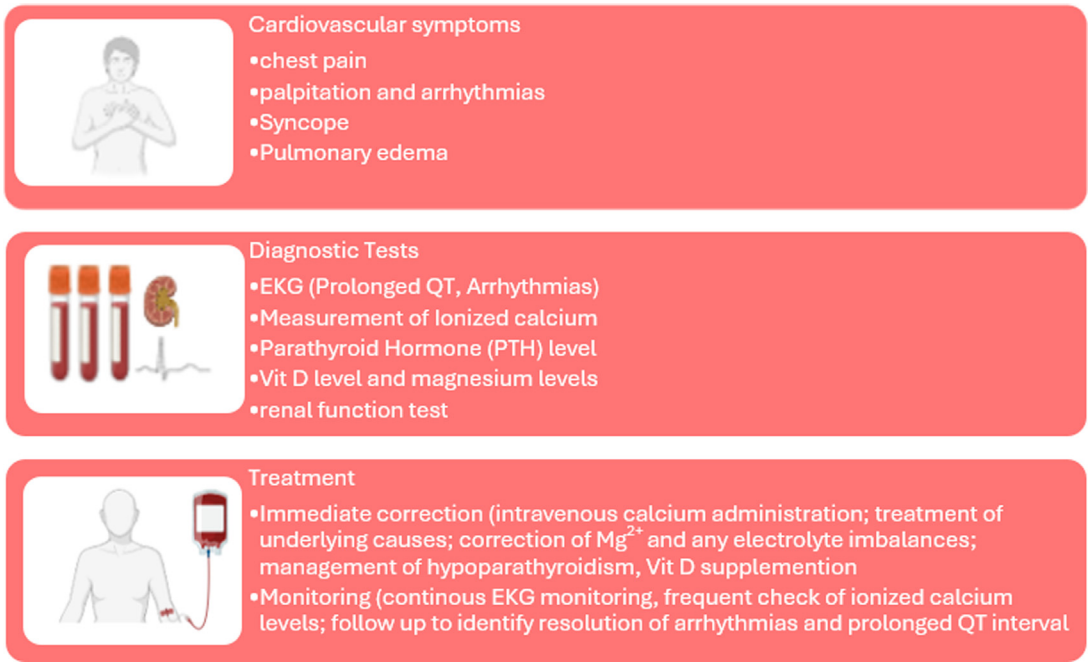
A recent review of the literature[3] found a total of 7 cases of hypocalcemia-related STE, with a wide age range and no significant differences between genders. In all of them, the admission ECG showed STE, most frequently in the lateral leads, and QTc prolongation. Normalization of serum calcium levels reversed symptoms and electrocardiographic manifestations.[3] Coronary angiography showed normal

FIGURE 3 Coronarography Showing No Obstructive Coronary Artery Disease



(A) Angiographic right cranial view demonstrating no critical stenoses on the left main, left anterior descendent, and left circumflex arteries. (B) Angiographic left cranial view showing no obstruction on the right coronary artery.

FIGURE 4 Flowchart to Guide Diagnosis and Treatment of Hypocalcemia



coronary arteries. LV systolic dysfunction was found in 4 of 7 cases.[3] A possible explanation may be found in the key role played by calcium in cardiac depolarization and consequent myocardial cell contraction: indeed, there is no correlation between the electrocardiographic location of STE and the LV low-contractile regions. This condition has been termed hypocalcemic cardiomyopathy[12] and must be distinguished from the echocardiogram features of TTS.[13,14]

Between the well-known triggers of TTS (emotional stress, cerebrovascular accidents, invasive procedures), which were not reported by our patient, electrolyte disturbances are not usually described. Although the exact pathogenesis remains unclear, catecholamine-induced cardiotoxicity and microvascular dysfunction are considered the most common causes.[4,6]

Burgdorf et al[15] observed an association between TTS and underlying malignancies, suggesting that it may be the consequence of paraneoplastic phenomena (eg, increase in cardiac adrenoceptor sensitivity). Furthermore, we presume that also the chronic inflammatory state associated with cancer may contribute to this process. We observed a segmental echocardiographic impairment of LV ejection fraction, whereas the cardiotoxic effect of chemotherapy drugs usually results in a global defect of LV contractility and does not recover completely in few days. Therefore, we excluded the latter; however, a paraneoplastic increase in adrenoceptor sensitivity could be hypothesized.

The link between electrolyte abnormalities and TTS is not well established; however, they may contribute to cardiac impairment. A profound and prolonged reduction in serum calcium levels can lead to contractile dysfunction of the myocardium. However, the so-called hypocalcemia-induced cardiomyopathy usually presents with diffuse LV hypokinesia rather than LV apical ballooning.[13,14]

In this case, we can also assume that the observed motion abnormalities were the result of both intense sympathetic activation and hypocalcemia. Indeed, an improvement in apical ballooning was achieved after calcium replacement. Moreover, we cannot exclude that the terminal cancer may have produced a prolonged psychological stress, which in turn may have caused TTS. For the treatment of hypocalcemia-induced cardiomyopathy, calcium replacement is pivotal: clinical and hemodynamic improvement could not have been achieved with standard heart failure therapy if the serum calcium deficiency had not been corrected (**Figure 4**).

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