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Severe Hypocalcemia Causing Acute Heart Failure Decompensation with Exacerbation of Mitral and Tricuspid Regurgitation

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Abstract

Hypocalcemia can lead to arrhythmias and to left ventricular dysfunction. We present herein this case of a 93 years old man with multiple myeloma (MM) who developed severe hypocalcemia secondary to treatment with Zoledronic acid. The severe hypocalcemia induced by Zoledronic acid led to acute decompensation of stable heart failure (HF) and to an increase of the mitral and tricuspid regurgitation severity with pulmonary edema requiring intubation, mechanical ventilation and inotropic support. Correction of the hypocalcemia using intravenous calcium gluconate reversed the cardiac decompensation and improved the mitral and tricuspid regurgitation as demonstrated by transthoracic echocardiography, with an improvement in the clinical condition of the patient.

Keywords: hypocalcemia; heart; mitral and tricuspid regurgitation

Introduction: Case Presentation

This is a 93 years old man with long standing history of congestive heart failure (CHF) and reduced ejection fraction (EF) at 30%, coronary artery disease (CAD) with a history of coronary artery bypass grafting (CABG) twenty years ago and a history of percutaneous coronary intervention (PCI) to the diagonal artery branch of the left anterior descending (LAD) artery seven years ago, chronic kidney disease (CKD), diabetes mellitus (DM) , dyslipidemia and MM for which he was treated with intravenous

Bortezomib plus dexamethasone cycles, subcutaneous erythropoietin and packed RBC transfusion as required. His medication consisted of: Bisoprolol 2.5 mg orally daily, spironolactone 25 mg orally daily, Empagliflozin 10 mg orally daily, Ramipril 2.5 mg orally daily, Furosemide 60 mg orally daily, Atorvastatin 20 mg orally daily and Linagliptin 5 mg orally daily. The timeline of patient's medical conditions with the treatment offered is depicted in table *1*.

Table 1: Table *1* depicts the timeline of patient's medical conditions with the treatment offered

Disease	Date of onset	Treatment
Dyslipidemia	20 years ago	Atorvastatin 20 mg orally
CAD	20 years ago	CABG
Unstable angina	7 years ago	PCI of the diagonal branch of the LAD artery.
Diabetes mellitus	7 years ago	Linagliptin 5 mg orally daily.
		Empagliflozin 10mg orally daily.
CHF	3 years ago	Bisoprolol 2.5 mg orally daily.
		Spironolactone 25 mg orally daily.
		Empagliflozine 10 mg prally daily.
		Ramipril 2.5 mg orally daily.
		Furosemide 60mg orally daily.
CKD	3 years ago	Empagliflozin 10 mg orally daily
		Ramipril 2.5 mg orally daily
Multiple myeloma	2 years ago	Intravenous bortezomib plus dexamethasone cycles on weekly basis.
		Sub cutaneous erythropoietin and packed RBC transfusion as required.

CAD=coronary artery disease; CABG=coronary artery bypass grafting; PCI=percutaneous coronary intervention; CHF=congestive heart failure; LVEF=left ventricular ejection fraction. CKD=chronic kidney disease.

Patient received Zoledronic acid to treat severe osteoporotic lesions of the lumbar vertebrae leading to multiple fractures (3rd and 4th lumbar vertebrae) and causing severe pain despite analgesics and a kyphoplasty of 4th lumbar vertebrae (L4); The oncologist recommended Zoledronic acid to prevent further episodes of fractured Lumbar vertebrae; after treatment with Zoledronic acid the patient was observed for 4 days in hospital and then discharged home; the calcium, phosphorus, magnesium, creatinine, electrolytes and albumin levels four days after zoledronic acid treatment were all normal (table 2); during this admission, patient was in New York heart association (NYHA) II classification of heart failure, his left ventricular (LV) ejection fraction (EF) was reported at 30%.

Table 2: Laboratory results showing calcium. phosphorus, magnesium, creatinine, electrolytes and albumin levels four days after Zoledronic acid treatment.

Laboratory results	4 days after Zoledronic acid treatment	Normal range
Calcium mg/dl	8.6	8.5-10.5
Phosphorus mg/dl	3.1	2.5-4.4
Magnesium g/dl	2.1	1.5-2.5
Creatinine mg/dl	1.28	0.7-1.3
Sodium meq/l	133	135-145
Potassium meq/l	4.4	3.5-5.0
Chloride meq/l	96	96-106
CO2 meq/l	26	22-28
Albumin g/l	41	3.5-5

He presented to our emergency room (ER) three days post discharge from our hospital (seven days after zoledronic acid treatment) with severe dyspnea tachypnea at rest and hypoxemia plus hypotension (blood pressure at 75 / 55mm Hg); he was intubated with mechanical ventilation using continuous mandatory ventilation (CMV) mode, sedated using intravenous (IV) midazolam plus fentanyl (midazolam at the dose of 3mg/hour IV and fentanyl at a dose of 150microgram/hour IV) and supported with inotropes (Dobutamine at the dose of 3 microgram/kilogram/minute and Noradrenaline at the dose of 0.5 microgram/minute); his ECG showed LBBB and there was no ECG changes compared to previous ECG (Figure 1). He was admitted to the intensive care unit.
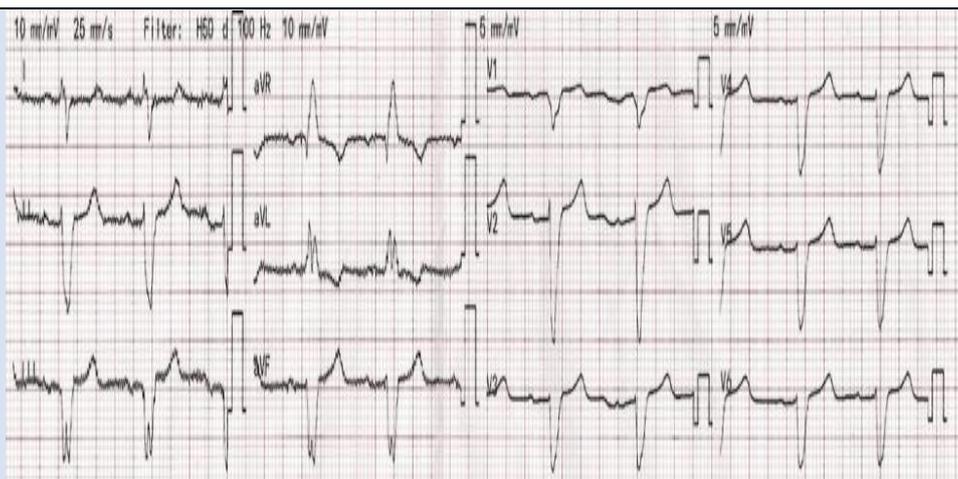
Figure 1: Electrocardiogram (ECG) showing left bundle branch block.

His Chest x ray (Figure 2) showed pulmonary edema and cardiomegaly.

Figure 2: Chest x ray showing cardiomegaly and pulmonary edema.

Echocardiography done urgently, while patient was receiving inotropic support, and showed a reduced LVEF at 19% (Figure 3).
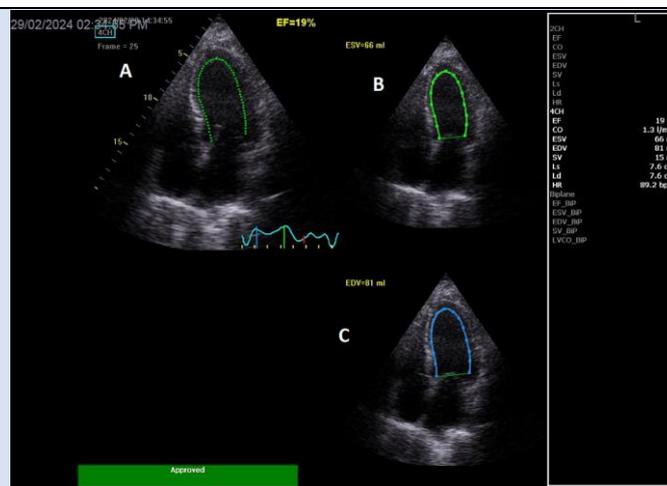

Figure 3: A: Apical 4 chambers view showing automatic left ventricular ejection fraction at 19%. B: LV end systolic volume at 66ml. C: LV end diastolic volume at 81ml.

LA=left atrium; LV=left ventricle; RA=right atrium; RV=right ventricle; EF=ejection fraction; ESV = end systolic volume; EDV = end diastolic volume.
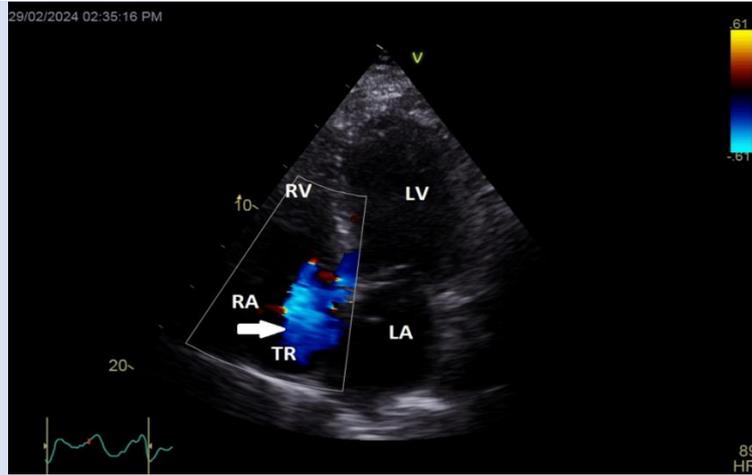
Color Doppler mapping of the mitral valve showed severe mitral regurgitation (MR) (Figure 4).

Figure 4: Apical long axis view still frame showing severe mitral regurgitation (white arrow)
LA=left atrium; LV=left ventricle; MR=mitral regurgitation

Color Doppler mapping of the tricuspid valve showed severe tricuspid regurgitation (TR) (Figure 5).

Figure 5: Apical 4 chambers view showing severe tricuspid regurgitation (white arrow).
LA=left atrium; LV=left ventricle; RA=right atrium; RV=right ventricle; TR=tricuspid regurgitation

Continuous wave (CW) Doppler interrogation of the tricuspid regurgitant jet yielded a jet velocity at 3.85 m/sec allowing calculation of systolic pulmonary artery pressure(SPAP) at 67 mmHg with estimated right atrial pressure at 8 mmHg (Figure 6); the inferior vena cava was normal in size at 1.6 cm and collapsing normally with inspiration.
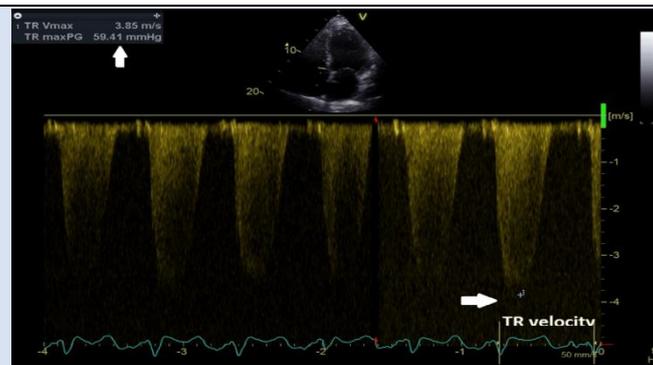
Figure 6: CW Doppler interrogation of the tricuspid regurgitant jet yielded a jet velocity at 3.85 m/sec (white arrows) allowing calculation of SPAP at 67 mmHg with estimated right atrial pressure at 8 mmHg; the inferior vena cava was normal in size at 1.6 cm and collapsing normally with inspiration.
CW=continuous wave Doppler; m/s=meter/second; SPAP=systolic pulmonary artery pressure.

Blood test showed a calcium level of 4.3 mg/dl (normal level is from 8.5-10.5 mg/dl) and albumin level of 33 mg/dl (normal level 35-50 g/l) indicating a severe drop of free calcium because the albumin level was normal. Immediate intravenous calcium replacement was done: calcium gluconate at the dose of 300mg in 50 cc D5W was given urgently intravenously over 30 minutes then an intravenous drip of calcium gluconate was started at 1mg/kg/hour using an electric pump; the aim was to reach a low normal blood level of calcium at 8-8.4 mg/dl; Noradrenalin at the dose of 0.5 microgram/minute and Dobutamine at the dose of 3 microgram/kilogram/minute were continued. On the third day the calcium level increased to 7.4mg/dl (Table 3) and patient condition improved markedly.

his blood pressure improved 110 / 70 mmHg so continuous intravenous furosemide at the dose of 120 mg/24 hours by electric pump was started; on the 4th day the Ca level was 8 mg/dl, and patient was weaned off inotropes, sedation and mechanical ventilator (patient was extubated) with stable blood pressure at 110/65 mmHg, improved arterial blood gases (ABG's) and a saturation at 98% with oxygen delivered via nasal cannula at 1.0 liter/minute (table 3). Table 3 summarizes the blood test of the patient and it shows the correction, over four consecutive days, of serum calcium using intravenous calcium gluconate, also it shows the improvement of ABG's of the patient after extubation on the day four of admission (Table 3).

Table 3: Shows creatinine, electrolytes, calcium, albumin, phosphorus, magnesium, TSH, PTH and vitamin D level, and ABG's during the correction of hypocalcemia (PaO2 measures the partial pressure of oxygen in arterial blood, while PaCO2 measures the partial pressure of carbon dioxide in arterial blood).

Laboratory result	3 days before discharge	2 days before discharge	24 hours before discharge	Normal range
Creatinine mg/dl	1.38	1.18	1.28	0.7-1.3mg/dl
BUN mg/dl	56	29	37	7-20mg/dl
Na meq/l	134	134	133	135-145 meq/L
K meq/l	3.7	4	4.4	3.5-5 meq/L
Cl meq/l	97	99	96	96-106 meq/L
CO2 meq/l	27	24	26	22-28 meq/L
Calcium mg/dl	9.0	9.0	8.6	8.5-10.5 mg/dl
Albumin mg/dl	41	(-)	(-)	3.5-5 g/dl
Globulin mg/dl	26	(-)	(-)	2.0-2.5 g/dl
Phosphorus mg/dl	3.8	4.2	3.1	2.5-4.4 mg/dl
Magnesium mg/dl	3.08	2.41	2.1	1.5-2.5 mg/dl
HT %	24.7	29.5	10.3	38.3-55
Hb g/dl	8.7	10.7	30.2	13.2-17.5
WBC / microl	6980	9430	9220	4500-11000
Neutrophiles %	90.2	86.4	85.2	40-60
Lymphocytes %	5.47	6.46	6.44	20-40
Monocytes %	3.93	6.44	7.14	4-8
Platlets / microl	136000	141000	124000	140-450000
PaO2 mmHg	96	83	97	75-100
PaCO2 mmHg	37	43	36	35-45
Saturation %	99	97	98	95-100
PH	7.5	7.48	7.45	7.35-7.45

TSH=thyroid stimulating hormone; PTH=parathyroid hormone; Vit D25_OH=25 hydroxy vitamin D level

Table 4 shows the results of cardiac troponin I level during the first four days of admission; it was slightly elevated on admission and returned to normal the next day. The changes in cardiac troponin I level at presentation was attributed to the hypotension and not to acute coronary syndrome.

Table 4: Shows the cardiac troponin I level on admission and in the next four days.

Cardiac troponin I level	First day	Second day	Third day	Fourth day	Normal cTnI
cTnI ng/ml	0.057	0.038	0.024	0.015	< 0.035

After the 4th day intravenous calcium gluconate was stopped and patient was started on oral calcium carbonate (Caltrate) at a dose of 600mg every 6 hours orally with 1,25 hydroxy vitamin D (One-Alfa at a dose of 1 microgram daily orally) with a target Calcium level at 8-8.4mg/dl; also, intravenous furosemide was changed to oral furosemide at a dose of 100 mg orally daily. Repeat echocardiography after extubation and after weaning off inotropes showed an improvement in LVEF at 32% (Figure 7).
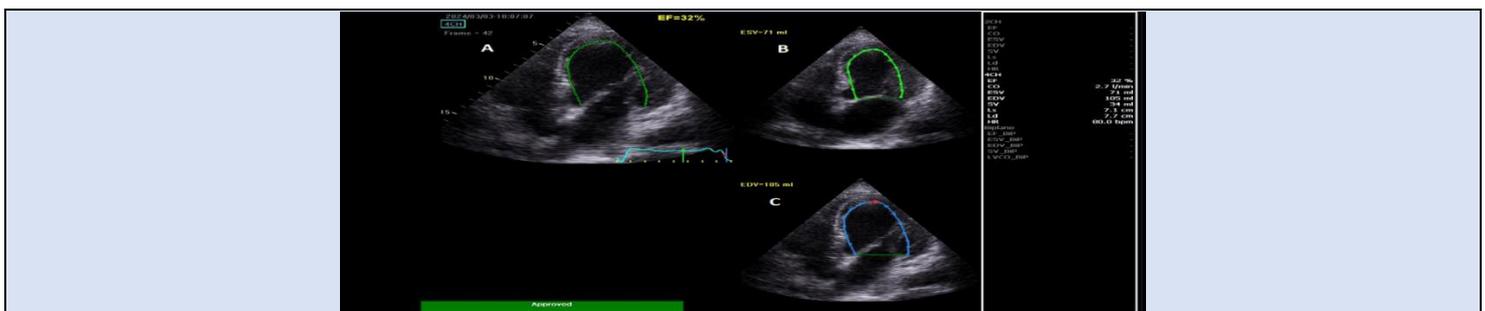
Figure 7: A: Apical 4 chambers view after correction of hypocalcemia showing a left ventricular ejection fraction at 32%. B: LV end systolic volume at 71ml; C: LV end diastolic volume at 105ml
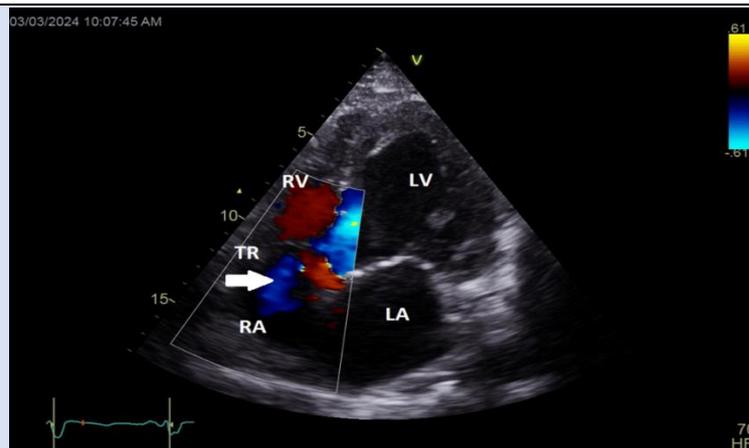
LA=left atrium; LV=left ventricle; RA=right atrium; RV=right ventricle; EF=ejection fraction; ESV=end systolic volume; EDV= end diastolic volume.

Color Doppler mapping of the mitral valve showed a decrease in MR severity with only grade I mitral regurgitation noted after correction of hypocalcemia (figure 8).
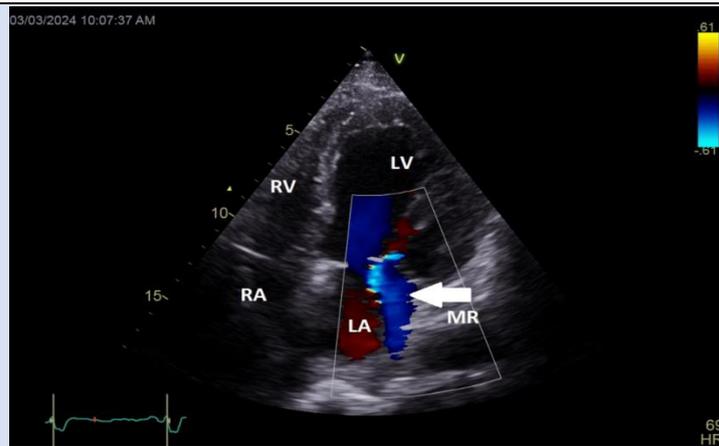
Figure 8: Apical 4 chambers view showing the decrease in mitral regurgitation severity (white arrow) after correction of hypocalcemia. LA=left atrium; LV=left ventricle; RA=right atrium; RV=right ventricle; MR=mitral regurgitation

Color Doppler mapping of the tricuspid valve showed a decrease in TR with only grade I tricuspid regurgitation noted after correction of hypocalcemia (Figure 9).

Figure 9: Apical 4 chambers view showing decrease of the tricuspid regurgitation severity (white arrow) after correction of hypocalcemia. LA=left atrium; LV=left ventricle; RA=right atrium; RV=right ventricle; TR=tricuspid regurgitation.

CW interpretation of the tricuspid regurgitant jet showed a decrease in TR velocity at 3.09 m/sec and thus an improvement of the SPAP at 43.1 mmHg with estimated RA pressure at 5 mmHg after correction of the hypocalcemia (figure 10).
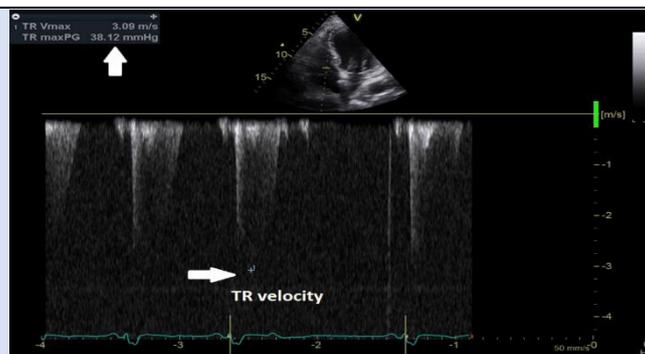
Figure 10: Continuous wave doppler interpretation of the tricuspid valve showing a decrease of the tricuspid regurgitant velocity (white arrows) at 3.09 m/sec; with a subsequent decrease of systolic pulmonary artery pressure at 43.1 mmHg. TR velocity=Tricuspid regurgitation velocity

All cultures including blood cultures deep tracheal aspirate (DTA) cultures and urine cultures taken during this admission were negative. Patient's HF medications were restarted in the few days that followed. He was also started on oral calcium and active vitamin D (1.25 hydroxy vitamin D); with monitoring of serum calcium level and a target of calcium level at around 8-8.4mg/dl, he was discharged home 3 weeks after presentation to ER. Before discharge from hospital (after 3 weeks) patient was in stable clinical condition not requiring oxygen therapy and was able to ambulate unassisted.

Discussion

Our patient was a very elderly man with CKD and CHF, he was treated with guideline directed medical therapy for heart failure (the four pillars): angiotensin converting enzyme inhibitor (ramipril), beta blocker (bisoprolol), mineralocorticoid antagonist (spirolnolactone) and sodium glucose co-transporter inhibitor 2 (empagliflozin); he also had multiple myeloma and severe bone pain related to vertebral fracture that was refractory to analgesics and kyphoplasty so treatment with zoledronic acid was advised by the oncologist to prevent further bone fracture in vertebral bodies of the spine [8], this treatment led to severe hypocalcemia [2] and acute cardiac decompensation with reduction in LVEF from 30% to 19% during hypocalcemia, LVEF improved to 32% after correction of hypocalcemia with intravenous calcium gluconate. It is likely that the patients age and CKD predisposed him to severe hypocalcemia despite the fact that calcium level was normal 4 days after treatment with zoledronic acid and even though vitamin D and PTH levels were normal (usually these levels should be optimized before treatment with intravenous bisphosphonate). These warrants monitoring of calcium level for longer period after treatment with zoledronic acid in this patient population.

Calcium is essential for excitation-contraction coupling in the myocardium. Because the calcium confined within the sarcoplasmic reticulum is inadequate to begin contraction, extracellular calcium influx is primarily responsible for the initiation and extent of cardiac contraction [2]. Severe hypocalcemia will affect the calcium influx from the SR into the myocyte's cytoplasm thus decreasing activating actin myosin complex by binding with troponin [2]. A severe decrease in serum calcium level will affect early the excitation-contraction coupling by decreasing calcium entry through the surface membrane and transverse tubules (opened L-type Ca channels) leading to a decrease in calcium-induced calcium release mechanism thus decreasing calcium release from the SR [2]. Also the decrease of overall calcium availability will lead to decrease in contractility; These findings establish biologic plausibility and provide an approach to understanding the pathophysiologic relationship between extracellular hypocalcemia, and reversible heart failure; reports have shown that severe acute hypocalcemia will lead to a decrease in myocardial contractility, a decrease in left ventricular function and a decrease in LVEF by echocardiography; correction of hypocalcemia with intravenous calcium gluconate will improve left ventricular function and LVEF [3-7].

Hypocalcemia may cause severe ventricular arrhythmias [9] and supraventricular arrhythmias [10].

In ischemic and dilated cardiomyopathy (CMP) mitral regurgitation (MR) is called functional MR, is due mainly to mitral annular dilatation, lack of contraction of the mitral valve ring, malalignment of the papillary muscles and dysfunction of the papillary muscles [11,12]; a further decrease in myocardial annular contractility or papillary muscle contraction seen with acute severe hypocalcemia will exacerbate mitral regurgitation severity as in our patient.

The most common cause of functional tricuspid regurgitation is left heart failure and pulmonary diseases leading to pulmonary hypertension causing a dilatation of the right ventricle due to the eccentric forces applied to its wall ending in tricuspid annular dilation [12,13]; also tricuspid leaflet tethering as a result of papillary muscle displacement in lateral and apical directions (due to RV dilatation and strain on the right ventricular free wall) or papillary muscle dysfunction will cause an increase in tricuspid regurgitation [12,13]; a further decompensation of the left ventricular function, right ventricular function or papillary muscle function due to hypocalcemia will exacerbate tricuspid regurgitation severity as in our patient.

Echocardiography is an important tool to assess left ventricular function and regurgitation of the mitral and tricuspid valves; in our patient correction of hypocalcemia with intravenous calcium gluconate resulted in rapid improvement in myocardial

contractility an improvement in LVEF from 19% to 32% by echocardiography and a decrease in severity of mitral and tricuspid regurgitation, also there was a decrease in systolic pulmonary artery pressure form 67mm Hg to 43mmHg correlating with improvement in patient clinical status and hemodynamics. This marked rapid clinical and echocardiographic improvement in LVEF and mitral plus tricuspid regurgitation severity, without further need for inotropic support, reinforce the fact that severe hypocalcemia was the cause of cardiac decompensation. Other cause leading to decompensation of left ventricular function and a decrease in LVEF such as acute coronary syndrome and hypothyroidism were excluded based on normal troponin and TSH levels.

Few cases have reported hypocalcemia causing left ventricular dysfunction [3-7]; however echocardiographic documentation of severe mitral and tricuspid regurgitation that improve after correction of existing hypocalcemia with intravenous calcium gluconate is rarely described.

The improvement in mitral regurgitation after correction of hypocalcemia with intravenous calcium gluconate is secondary to the increase in left ventricular function and to better mitral annular contraction and papillary muscle function; this beneficial effect on mitral regurgitation (MR) is similar, in concept, to performing a mitral annuloplasty in patient with CHF and severe functional MR [14].

The improvement in TR after correction of hypocalcemia with calcium gluconate is secondary to improvement of RV function, decreased strain on the RV (with improvement in LV function and decrease in systolic pulmonary artery pressure) leading to a better tricuspid annulus contraction and papillary muscle function.

Conclusion

Intravenous use of bisphosphonate in patients with malignancies and bone involvement may lead to acute severe hypocalcemia. Patients at risk to develop hypocalcemia should be identified before the drug is administered and should be monitored carefully after treatment and given calcium and vitamin D (active form or 25 hydroxy calciferol). Severe acute hypocalcemia secondary to intravenous bisphosphonate can cause acute HF, so it should be recognized and treated very early since early intravenous calcium administration will prevent and even reverse the acute HF or the decompensation of already established stable HF. Functional mitral and tricuspid regurgitation will increase with the decompensated HF leading to exaggeration of symptoms and Guideline-directed drug therapy (GDMT)remains the first-line treatment for functional regurgitation across all HF phenotypes, followed by cardiac resynchronization therapy (CRT) in appropriately selected patients. Behind GDMT and CRT, surgical or trans-catheter valve therapy is a valuable option for patients remaining symptomatic. Pharmacological and non-pharmacological treatments are complementary and can interrupt valvar-driven HF progression in appropriately selected patients; however, when acute or subacute hypocalcemia develops due to other non-cardiac therapies the patient is receiving and leads to acute heart failure exacerbation with increase in valvar regurgitation, then correction of hypocalcemia should be done urgently first to see if it reverses the acute HF exacerbation. In conclusion, severe hypocalcemia as a possible cause of heart failure should be considered in the differential diagnosis of all individuals with congestive heart failure. The correction of serum calcium level results in the improvement of heart function and electrical activity.

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