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CASE REPORT
Electrophysiology

Complete heart block associated with paraneoplastic hypercalcemia: a case report

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Background Complete heart block (CHB) means a lack of association between the atrium and the ventricle. Hypercalcemia is an electrolyte disorder that rarely causes CHB.

Case summary Hereby, we report the case of a 59-year-old male who was admitted with general weakness. The electrocardiography (ECG) changes revealed CHB, short QT interval due to short ST segment, and generalized ST elevation. The initial calcium level was 15.8 mg/dL (high), and serum levels of parathyroid hormone (PTH), vitamin D, and phosphorus were normal. A chest computed tomography scan showed a large, central mass with cavitation in the right lung. After an initial diagnosis of lung cancer and paraneoplastic hypercalcemia, the patient was treated with normal saline, calcitonin, and zoledronic acid, whose calcium levels decreased to 10.4 mg/dL after 4 days. Pathological ECG findings were also resolved after the correction of serum levels of calcium.

Discussion Hypercalcemia sometimes occurs as a paraneoplastic syndrome following the production of PTH-related peptide by malignant cells, including squamous cell carcinoma of the lung. Complete heart block associated with paraneoplastic syndrome has been reported so far in only one study.

Keywords Complete heart block • Hypercalcemia • Squamous cell carcinoma • Paraneoplastic syndrome • Case report

ESC Curriculum 5.7 Bradycardia • 5.6 Ventricular arrhythmia

Learning points

- Complete heart block (CHB) can be associated with hypercalcemia in the context of squamous cell carcinoma of the lung.
- Hypercalcemia occurs as a paraneoplastic syndrome following the production of parathyroid hormone–related peptide by malignant cells.
- Cardiovascular complications of hypercalcemia include coronary artery or heart valvular calcification, hypertension, various arrhythmias, and the effect of myocardial contractility at very high levels of calcium.
- Pathological electrocardiography findings in hypercalcemia (short QT, ST elevation, and CHB) resolved after the correction of serum calcium levels.

Introduction

Complete heart block (CHB) means a lack of electrical association between the atrium and the ventricle. The clinical presentation of CHB varies; from asymptomatic to cardiac death. The signs and symptoms of CHB are general weakness, hypotension, dizziness, nausea and vomiting, syncope, and sudden cardiac death.[1] The aetiology of CHB contains electrolytes disturbance, structural heart disease, infection, ischaemic heart disease, cardiac surgery, drugs, autoimmune, infiltrative conditions, and hyperthyroidism.[2] Electrolyte disturbances that cause CHB include hypo- and hyperkalaemia and hypo- and hypermagnesaemia. Hypercalcemia is also an electrolyte disorder that rarely causes CHB.[3]

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Hereby, we report a case of CHB associated with hypercalcemia in the context of squamous cell carcinoma (SCC) of the lung.

Timeline

Timeline	Events
During the 3 months before hospitalization	General weakness and 12 kg weight loss
A week before hospitalization	Aggravation of weakness
Initial presentation	General weakness and cachexia
Initial paraclinic investigations	Complete heart block and ST elevation (STE) in electrocardiography (ECG). Hypercalcemia with NI parathyroid hormone. Large mass with cavitation in chest computed tomography
Day 2	Beginning of normal saline, calcitonin, and *zoledronic* acid
Day 4	Calcium levels decreased to 10.4 mg/dL
Day 5	Pathological ECG findings were resolved and the ECG was normal sinus rhythm (NSR)
Day 9	The patient underwent bronchoscopy
Day 11	He was discharged with an ECG showing NSR and a calcium level of 8.9 mg/dL
After discharge	He never came for follow-up

Case presentation

A 59-year-old male was admitted to our emergency department with general weakness and 12 kg weight loss over 3 months. He had been a heavy smoker (45 packs per year); however, he did not have any past medical condition. He also denied taking any medication. The patient had no personal or family history of heart disease based on previous electrocardiography (ECG), echocardiographic examination, and other documents. On examination at first hospitalization, he was afebrile with a respiratory rate and blood pressure of 16 breaths/min and 125/74 mmHg, respectively. He had a widespread wheeze of auscultation of the chest. His skin had no special lesions. There was no lymphadenopathy in the examination. The thyroid was of normal size and consistency with no nodules. An abdominal examination showed no organomegaly.

The ECG on admission revealed atrioventricular (AV) dissociation with an atrial rate of 68 b.p.m. and ventricular rate of 50 b.p.m., a normal axis, normal P wave, normal PR interval, normal QRS voltage and duration, and R-wave progression, a short QT interval (293 ms) due to a short ST segment, a generalized ST elevation (STE) and normal T wave (*Figure 1*). Echocardiography ruled out any cardiac structural, valvular, or functional abnormalities. The initial complete blood count revealed a haemoglobin count of 9.2 g/dL (reference range: 14–17.5 g/dL) with an mean corpuscular volume of 87.1 (reference range: 80–100), which suggested chronic disease anaemia. The initial calcium level was 14.2 mg/dL (reference range: 8.4–10.2 mg/dL). Serum levels of parathyroid hormone (PTH), vitamin D, and phosphorus were 29 pg/dL (reference range: 14–65 pg/dL), 19 mg/dL (reference range: 30–55 mg/dL), and 4.9 mg/dL (reference range: 3.5–6 mg/dL), respectively. A complementary laboratory workup showed a normal range of potassium, magnesium, urea, creatinine levels, serum levels of albumin, erythrocyte sedimentation rate, and C-reactive protein. Also, the

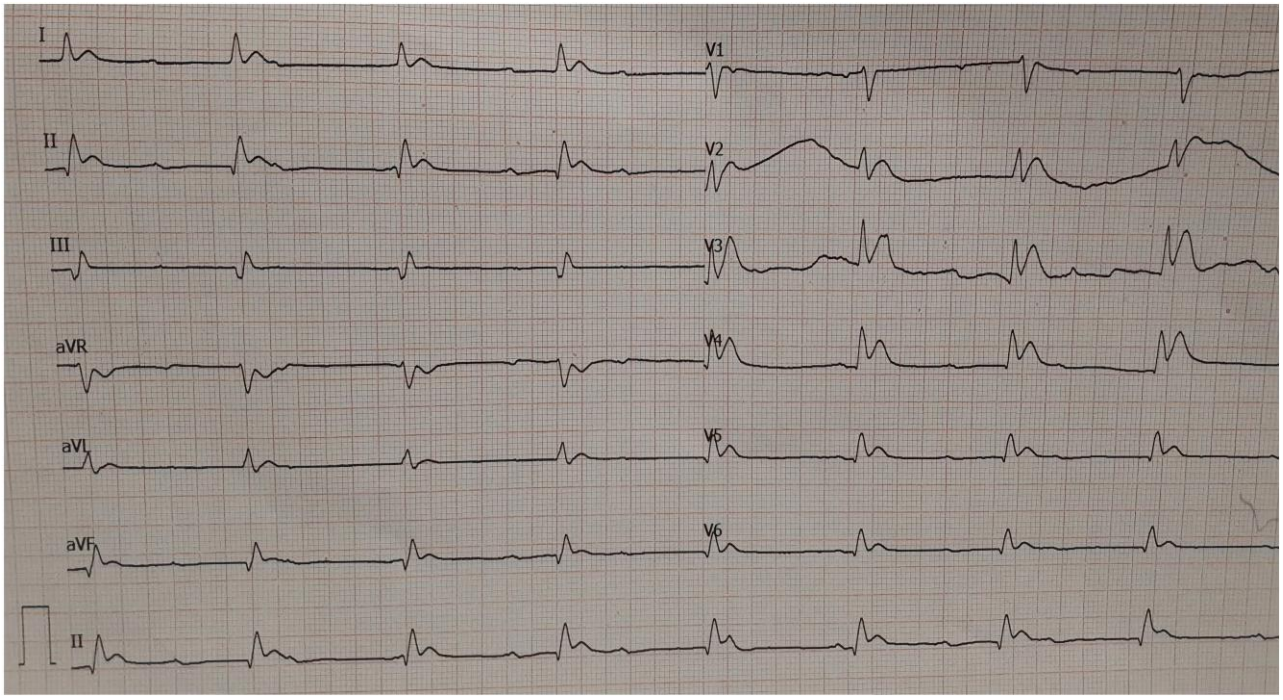

Figure 1 Atrioventricular (AV) dissociation with an atrial rate of 68 b.p.m. and ventricular rate of 50 b.p.m., a normal axis, normal P wave, normal QRS voltage and duration, and R-wave progression, a short QT interval (293 ms) due to a short ST segment, a generalized ST elevation and normal T wave.

liver function test and thyroid function test results were normal. Following the results of the lab tests, a chest computed tomography (CT) scan was performed with a suspicion of paraneoplastic hypercalcemia. Chest CT showed a large, central mass with cavitation in the right lung. Evidence of hyper-inhalation and emphysema was also seen in both lungs (*Figure 2*).

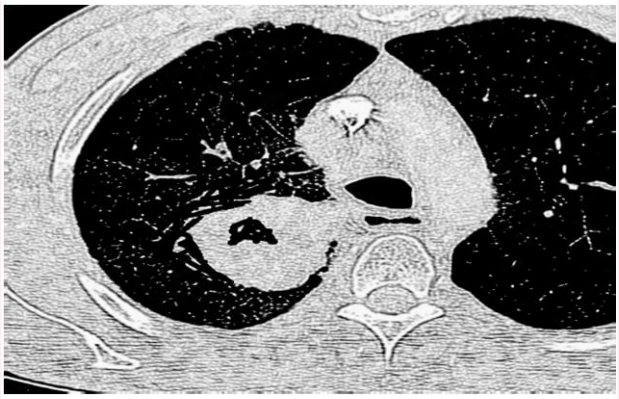

Figure 2 Central and large mass with a cavitation in the right lung in favour of squamous cell carcinoma of the lung. Evidence of hyper-inhalation and emphysema was also seen in both lungs.

Following a diagnosis of lung cancer and paraneoplastic hypercalcemia, the patient was treated with normal saline, calcitonin (200 IU every 6 h, subcutaneous injection), and zoledronic acid (4 mg, a single dose), whose calcium levels decreased to 10.4 mg/dL after 3 days. Pathological ECG findings (short QT, ST elevation, and CHB) were also resolved after the correction of serum calcium levels (*Figure 3*). The patient underwent bronchoscopy, and finally, SCC of the lung was confirmed based on pathological findings (*Figure 4*). He was discharged with an ECG showing normal sinus rhythm (NSR) and a calcium level of 8.9 mg/dL. Unfortunately, he never came for follow-up and for starting cancer treatment.

Discussion

We reported a case of CHB associated with hypercalcemia in the context of SCC of the lung. CHB and other ECG pathological findings were resolved after the correction of serum levels of calcium.

Hypercalcemia often occurs due to hyperparathyroidism. But it can occur in the context of malignancy, including SCC of the lung. This phenomenon occurs as a paraneoplastic syndrome following by the production of PTH-related peptide by malignant cells.[4] Cardiovascular complications of hypercalcemia are coronary artery or heart valvular calcification,[3] hypertension,[5] various arrhythmias, and myocardial contractility disorder in very high levels of calcium.[6] As observed in our patient, the common electrocardiographic presentations of hypercalcemia include a short corrected QT interval (QTc), and rarely, ST segment or J-point elevation. These changes

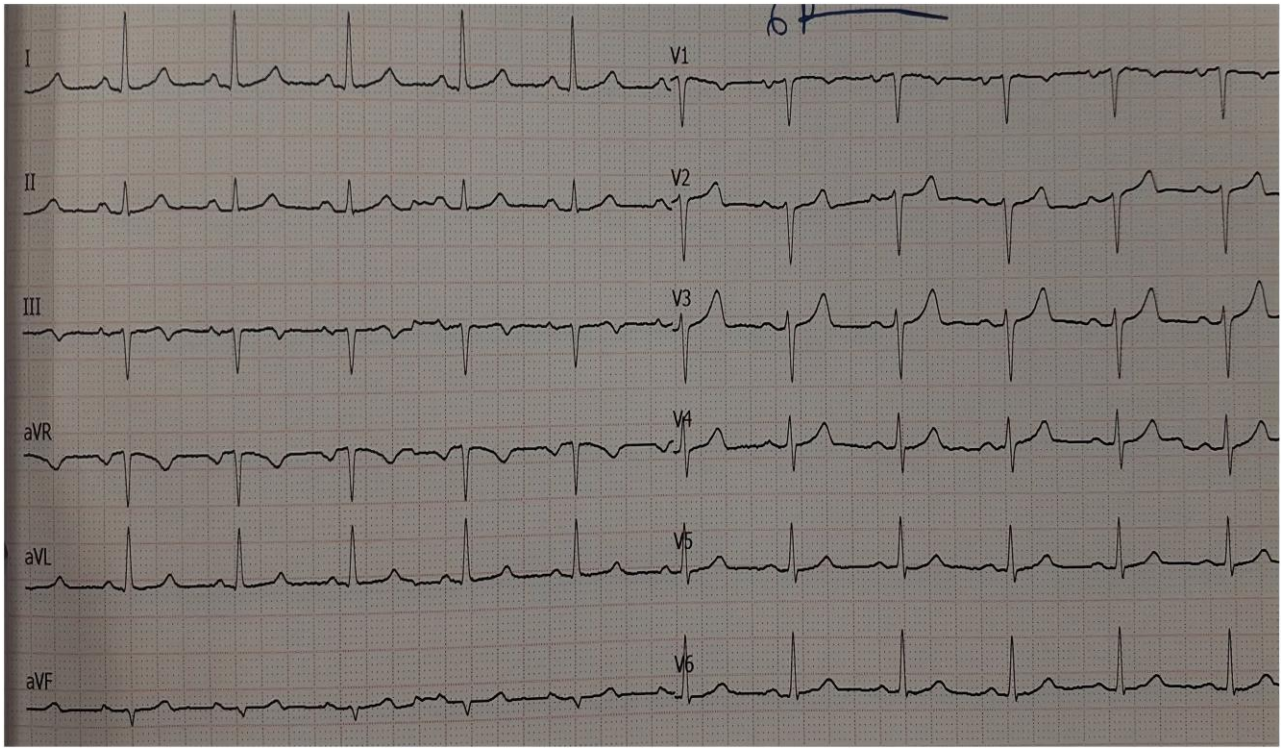

Figure 3 Electrocardiography pathological findings (short QT, ST elevation, and complete heart block) were also resolved after the correction of serum levels of calcium.

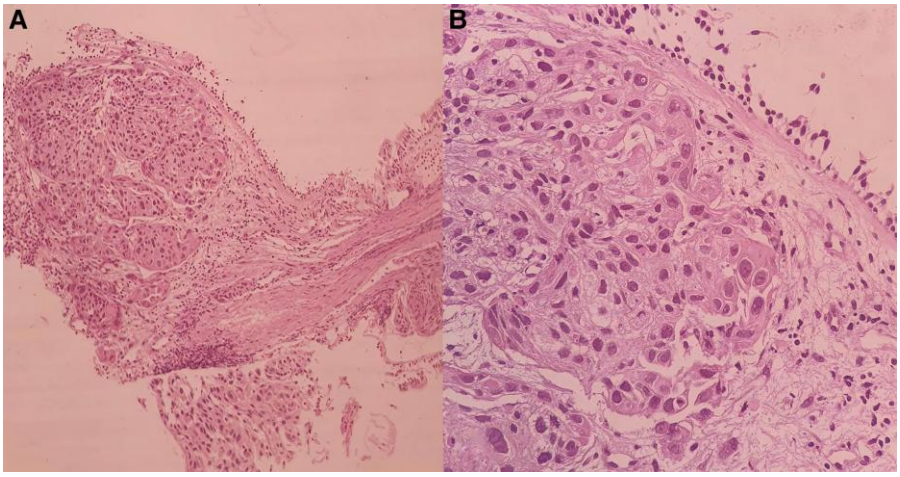

Figure 4 Moderately to poorly differentiated bronchial squamous cell carcinoma revealing bronchial tissue surrounded by sheets and islands of large polygonal malignant cells with intercellular bridges, showing focal areas of intra-cytoplasmic mucin (*A*; ×200 and *B*; ×400, H&E-stained slides).

are caused by the effect of ionized-free calcium on the action potential.[7]

The human body has a large reservoir of calcium (Ca^{2+}), which is mostly stored in the skeletal bones. Of all 1–2 kg of calcium in the whole body, only 1 g is in plasma, of which ~55% is bound to albumin and <1% is ionized-free calcium. The gradient of free-ionized intracellular and extracellular calcium is 1000–10 000 times, which causes rapid transmembrane shifts through 'gated' channels.[3] In previous studies, it was found that changes in the intracellular calcium concentration of cardiomyocytes actually affected the length of the action potential. Phase 2 is the plateau phase determined by a balance between inward Ca^{2+} and outward K^+ currents. In hypercalcemia, the slope of Phase 2 of the action potential becomes steeper, and simultaneous ECG recording showed Osborn waves and ST elevation. Phase 3 is maintained by competing inward currents mediated by the voltage-gated L-type Ca^{2+} channel (ICa,L) and Na^+–Ca^{2+} exchanger (INCX) and outward currents mediated by the voltage-gated-delayed rectifier K^+ channels (IK). Hypercalcemia stimulates 'calcium-activated potassium channels', which would increase the outward potassium currents during Phase 3 of the action potential, accelerating the process of repolarization, which appears as a short QT in the surface ECG.[8]

Various heart rhythm abnormalities and arrhythmias associated with hypercalcemia have been reported, including sinus bradycardia in two cases following i.v. infusion of calcium gluconate[9] or sinus node dysfunction and first-degree heart block in two patients with hypercalcemia due to hyperparathyroidism.[10] Complete heart block has also been reported in very rare cases.[1] Hypercalcemia-induced CHB has been reported mostly in the context of hyperparathyroidism or vitamin D toxicity.[2,11] Complete heart block associated with hypercalcemia due to malignancy has been reported so far in only one study, in which the patient also had hypokalaemia.[1] Our case is the second reported case of hypercalcemia-induced CHB associated with malignancy that was resolved after the correction of serum levels of calcium. The pathophysiology of AV node conduction system disease in hypercalcemia remains unknown. However, it may be due to calcium deposition in the heart conduction system.[11] Change in the electrochemical gradient of myocyte cells is another theory, in which the increased intracellular calcium activates the sodium channel, resulting in impaired conduction of myocyte cells.[12]

Lead author biography

Hamid Khederlou is Resident of Cardiology at the Tehran Heart Center. He is also a researcher in cardiovascular disease.

Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports*.

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Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

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