Post Total Thyroidectomy Hypocalcaemia - Induced Cardiomyopathy: Case Presentation and Literature Review

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ABSTRACT

Calcium ions play an important role in the contractility of cardiac muscle. Severe extracellular hypocalcaemia impairs cardiac contractility and results in ventricular dysfunction known as hypocalcemia induced cardiomyopathy. Hypocalcemia induced cardiomyopathy after total thyroidectomy is rare with only few cases reported in the literature. We report a case of post thyroidectomy Hypocalcaemia induced cardiomyopathy in a 45 years old lady who was successfully treated with calcium and vitamin D supplement with complete recovery of her left ventricular function.

Keywords: Total thyroidectomy; hypocalcaemia; cardiomyopathy

Introduction:

Total thyroidectomy is considered as the standard procedure in the management of thyroid cancer and increasingly used nowadays for benign thyroid diseases. Although total thyroidectomy is considered a safe procedure however it carries a significant risk of injury to the inferior laryngeal nerve if not identified intraoperatively as well as morbidity associated with inadvertent parathyroidectomy leading to hypocalcemia.

We report a case of a 45-year-old female who had total thyroidectomy for multinodular goiter and presented three years later with progressive shortness of breath and syncope associated with severe hypocalcaemia and left ventricular dysfunction. We reviewed the literature for etiology, prediction, and prevention of this serious complication of thyroid surgery.

Case Report:

A 45-year-old female was admitted to our ICU because of progressive shortness of breath for a week and a syncopal attack on the day of admission associated with severe electrolyte imbalance. She had no history of orthopnea or paroxysmal nocturnal dyspnea, or chest pain.

She had a history of total thyroidectomy 3 years before admission for multinodular goiter and she was on levothyroxine 100 mg /day, calcium and vitamin D supplements but she was not compliant with medications. She had no history of hypertension, diabetes mellitus or other medical diseases. On physical examination, she was fully conscious, oriented with normal oxygen saturation at room air. Her pulse rate was 90/min, blood pressure 110/70 mmHg, and temperature 37.5℃. On chest examination, there was basal crepitation, coarse breathing sounds on both lung fields, and a systolic murmur on the apex of the heart. Abdomen was soft and non- tender. There was trivial pedal edema.

Laboratory investigations revealed hemoglobin, complete blood count, urea and creatinine within normal values. Magnesium was 0.57 mmol/L (reference range; 0.66-1.07 mmol/L), albumin of 39 g/L (reference range; 35-50 g/L), adjusted calcium of 1.38 mmol/L (reference range; 2.10-2.50 mmol/L), and ionized calcium of 1.36 mmol/L (2.10-2.50). Troponin-I was 0.023 ug/L (reference range; <0.016 ug/L), C-reactive protein of 72.1 mg/L (reference range; 0.0-5.0 mg/L), and brain natriuretic peptide (BNP) 1277 pg/mL (reference range; <100 pg/mL)

The thyroid profile revealed free T4 of 18.6 pmol/L (reference range; 9-19 pmol/L) and thyroid stimulating hormone (TSH) 1.54 miu/L (reference range; 0.53-4.94 miu/L). The parathyroid hormone (PTH-I) was 23.7 pg /mL (reference range; 26.1-37 pg /mL) and Vitamin D level was in normal range.

The chest radiograph showed mild cardiomegaly, bilateral pleural effusions and increased lung markings on both lung fields (figure 1) which was confirmed by chest CT scan which showed bilateral pleural effusions, right lower lung lobe consolidation/collapse and scattered ground glass haziness in both lung fields alongwith mild cardiomegaly (figure 2)

Figure 1: Chest radiograph showing mild ccardiomegaly, bilateral pleural effusions and increased lung markings on both lung fields.

Figure 2: Chest CT image showing the ground-glass appearance of both lungs and bilateral pleural effusions.

The electrocardiogram (Figure 3) showed normal Sinus rhythm with 1st degree AV block, prolonged PR interval (232 m-seconds), and prolonged QTc interval (467 m-seconds)

Figure 3: The electrocardiogram (Figure 3) showed normal sinus rhythm with 1st degree AV block, prolonged PR interval (232 m-seconds), and prolonged QTc interval (467 m-seconds) (figure 3).

The transthoracic echocardiography showed global hyperkinesia of the left ventricle with left ventricular ejection fraction of about 40% (figure 4).

Figure 4: Transthoracic echocardiography with reduced left ventricular ejection fraction at about 40%.

The patient was treated with intravenous calcium gluconate, vitamin D and with aggressive treatment for congestive heart failure. She responded well to the treatment with improvement in cardiac symptoms. She was discharged home on calcium and vitamin D supplement (oral calcium carbonate 100 mg/kg/d in three divided doses and oral calcitriol 0.125 μg/daily) and advised to monitor her serum calcium weekly. She reported significant symptomatic improvement during her follow-up after discharge a month later. Serum calcium level at that time improved to1.96 mmol/L. The chest x-ray showed no evidence of pulmonary vascular congestion, cardiomegaly or pleural effusions and the echocardiogram showed significant improvement of the left ventricular functions with a left ventricular ejection fraction of 59%. (Figure 5)

Figure 5: Transthoracic echocardiography showing the improvement of the left ventricular functions.

Discussion:

Calcium plays a key role in a wide range of biological functions including extra- and intracellular signaling, nerve impulse transmission, muscle contraction etc [1, 2]. The vast majority of total body calcium (more than 99%) is present in the skeleton, and serves to provide skeletal strength, and represent a dynamic store to maintain the intra- and extracellular calcium pools [3, 4].

Blood calcium represents less than 1% of total body calcium and approximately half of the total serum calcium is bound to protein (mainly albumin and globulin), with the remaining free ionized calcium represents the physiologically active calcium [5]. Serum ionized calcium is mainly regulated by parathyroid hormone, 1, 25-dihydroxy vitamin D, calcitonin and serum ionized calcium itself, which together regulate calcium transport at the gut, kidney, and bone [4].

Parathyroid hormone (PTH) plays a major role in regulating ionized serum calcium. The hormone is secreted primarily by the chief cells of the parathyroid glands in response to hypocalcemia. It is a polypeptide containing 84 amino acids acts to increase serum calcium by mobilization calcium from bone, increase absorption of calcium from the small intestine and reduce calcium loss in urine by increasing calcium reabsorption by renal tubules.

Hypocalcemia is defined as a total serum calcium concentration less than the lower limit of the normal range (8.8 mg/dL / 2.20 mmol/L) in the presence of normal plasma protein concentrations or as a serum ionized calcium concentration less than (4.7 mg/dL / 1.17 mmol/L).

Vitamin D deficiency and hypoparathyroidism are the commonest cause of hypocalcaemia although it can be caused by many other conditions including renal disease, end-stage liver disease causing vitamin D inadequacy, Fanconi syndrome, and Hungry bone syndrome. It is also

associated with many drugs, including bisphosphonates, cisplatin, anti-epileptics, and aminoglycosides, diuretics, and proton pump inhibitors [6].

Hypoparathyroidism is most commonly seen following inadvertent removal of or damage to the parathyroid glands or their vascular supply during a total thyroidectomy. Persistent hypocalcemia six months after surgery confirms the diagnosis of hypoparathyroidism in the presence of low or inappropriately normal PTH levels [7].

Total thyroidectomy is considered as the standard procedure in the management of thyroid cancer and increasingly used nowadays for benign thyroid diseases. The optimal surgical treatment of patients with multinodular goiters is still debatable. Although the recent European and American guidelines recommend total thyroidectomy for management of the multinodular due to increased reported safety of the procedure, subtotal thyroidectomy is still in common practice in several centers worldwide [8].

Some authors [9-13] advocates' subtotal thyroidectomy for surgical management of multinodular goiter as they believe that total thyroidectomy increases the rates of recurrent laryngeal nerve and parathyroid injuries in addition to the lifelong need for hormone replacement therapy. On the other hand, others advocate total thyroidectomy because of the significant risk of recurrence in patients undergoing thyroid surgery [14-17].

Recent European and American guidelines recommend total thyroidectomy for the treatment of multinodular goiter as it is the most reliable approach in preventing the high recurrence rate associated with a less invasive approach (18).

Although total thyroidectomy is a safe procedure under the skilled surgeon's hands, it carries a significant risk of morbidity associated with hypoparathyroidism and injury to the inferior laryngeal nerve.

Hypocalcemia remains a major postoperative complication of total thyroidectomy. The primary cause of post thyroidectomy hypocalcemia is damage to the parathyroid blood supply and/or inadvertent excision of one or more glands. [19]. Post thyroidectomy hypocalcemia can be transient or permanent.

Transient biochemical or symptomatic hypocalcemia is common after thyroid surgery. It is of not known or fully understood etiology and can occur despite careful preservation of the parathyroid glands and their blood supply. The reported incidence of post thyroidectomy transient hypocalcemia ranges between 6.9 and 49% [20-23]. It tends to develop during the first 24 to 48 hours after surgery, responds favorably to replacement therapy, and recovered during the first month in (79%) of the patients without serious consequences apart from delaying patient's discharge [24].

Post thyroidectomy hypocalcemia is considered permanent when it does not return to normal within 6 months of surgery [25]. It has a negative impact on the quality of life of the patients as patients suffer from lifelong therapy, re-admissions to the hospital, disabilities to perform household activities and poor quality of life [26]. The incidence of permanent post thyroidectomy hypoparathyroidism varies from one study to another and found to be much higher from national registries and large multicenter studies than from single-center studies, ranging from 6% to 12%[(27].

Post thyroidectomy hypocalcemia can be asymptomatic, particularly if calcium levels are only mildly reduced, or symptomatic with typical symptoms including numbness and tingling in fingertips, toes, and the perioral region, paresthesia of the extremities, muscle cramps and weakness, carpal spasm, anxiety, and mental confusion. The typical clinical signs including Chvostek's and Trousseau's signs, muscle spasms and paresthesia. Diagnosis of post thyroidectomy hypocalcemia in the early postoperative period is straight forward and can easily be made from patient symptoms and signs with measurement of serum calcium level.

Many studies [28-32] investigated the early predictive factors for development of transient and permanent post total thyroidectomy hypocalcemia with consensus that measurement of intact parathyroid hormone (intact PTH) intraoperative or 1 to 24 hours postoperatively is the most cost-effective and reliable screening predictor for development of hypocalcemia with no consensus on the optimal time for (intact PTH) measurement. Some authors (33, 34) suggested that greater specificity can be achieved by combining (intact PTH) measurement with serum calcium measured 6-24 hours after surgery.Australian endocrine surgeons' guidelines recommended that (intact PTH) levels should ideally be measured four hours postoperatively and patients with normal (intact PTH) can be safely discharged on the first postoperative day [35].

Early anticipation of patients who are going to develop transient or permanent hypocalcemia following total thyroidectomy is important as it helps with early safe discharge of patients with normal intact PTH and with early commencement of replacement therapy in those at high risk of this complication with abnormal low intact PTH or normal intact PTH in the face of hypocalcemia.

Calcium plays a crucial role in myocardial contractility. Extracellular calcium is of vital importance for myocardial contraction since the amount of calcium ion in the sarcoplasmic reticulum is not sufficient to initiate contraction. The influx of extracellular calcium ions into the myocytes during membrane depolarization triggers the release of calcium from sarcoplasmic reticulum which through further steps stimulates muscle contraction [36]. Calcium ion fluxes also link contraction to the wave of excitation (excitation-contraction coupling) [37]. The strength of myocardial contraction is influenced by the magnitude of the influx of extracellular calcium. Thus,

the concentration of the extracellular calcium ion has a direct effect on the strength of myocardial contraction [38]. These observations explain myocardial dysfunctions associated with hypocalcemia as severe extracellular calcium depletion impairs cardiac contractility because the sarcoplasmic reticulum is unable to maintain a sufficient amount of calcium content to initiate myocardial contraction [39].

Hypocalcemia lowers the cell membrane potential of myocardial muscles which reflected on electrocardiogram (ECG) as intermittent QT prolongation, or intermittent prolongation of the QTc (corrected QT interval) secondary to a lengthened ST segment [40]. Significant hypercalcemia can cause ECG changes that mimic an acute myocardial infarction [40, 41].

Although the physiological role of calcium in muscle contraction is well-known, the pathophysiology of hypokalemic (CMP) is not yet fully understood. Adult hypocalcaemia cardiomyopathy (CMP) is rare with only a few cases reported in the literature [42-46] since Hegglin R et al reported the first case in 1939 [47]. Post thyroidectomy hypocalcaemia induces (CMP) is even more rare with only 7 cases reported in the literature to the best of our knowledge [48-54]. In adults, hypocalcaemia CMP is usually a result of hypoparathyroidism, with or without concomitant vitamin D deficiency [55].

Diagnosis of hypocalcemia induced CMP should be suspected in all cases of unexplained severe LV systolic dysfunction especially when it is refractory to conventional treatment.

Calcium and vitamin D treatment play an important role in the treatment of hypocalcemia induced cardiomyopathy as correction of hypocalcemia usually restore the left ventricular geometry and systolic function.

Although correction of serum calcium level can be achieved rapidly, restoration of myocardial function would take a few months, as restoration of intracellular calcium level is more important to restore cardiac function and usually takes time to be normalized [56].

Conclusions:

Hypocalcaemia is a rare treatable cause of CMP that should be suspected in all unexplained cases of severe LV systolic dysfunction in post thyroidectomy patients. Surgeons should be aware of this serious complication and pay more attention to careful identification, dissection, and preservation the parathyroid glands and their blood supply during thyroid surgery. Intraoperative, 1-24 hours postoperative measurement of (intact PTH) with or without serial measurement of the serum calcium in the first postoperative day is a sensitive predictor of the risk of post thyroidectomy hypocalcaemia. Early prediction of patients at high risk of hypocalcaemia is vitally important in making a decision about the early discharge of patients at low risk and commencement of replacement therapy on those at high risk. Early institution of appropriate replacement therapy

together with regular follow up of patients at high-risk is the only safeguard against chronic post thyroidectomy hypocalcaemia and its serious cardiac complications.

Conflict of Interest: None

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