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CASE REPORT

Heart Block and Acute Kidney Injury Due to Hyperparathyroidism-Induced Hypercalcemic Crisis

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We describe a patient who presented with multi-system organ failure due to extreme hypercalcemia (serum calcium 19.8 mg/dL), resulting from primary hyperparathyroidism. He was found to have a 4.8 cm solitary atypical parathyroid adenoma. His course was complicated by complete heart block, acute kidney injury, and significant neurocognitive disturbances. Relevant literature was reviewed and discussed. Hyperparathyroidism-induced hypercalcemic crisis (HIHC†) is a rare presentation of primary hyperparathyroidism and only a small minority of these patients develop significant cardiac and renal complications. In cases of HIHC, a multidisciplinary effort can facilitate rapid treatment of life-threatening hypercalcemia and definitive treatment by surgical resection. As such, temporary transvenous cardiac pacing and renal replacement therapy can provide a life-saving bridge to definitive parathyroidectomy in cases of HIHC.

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†Abbreviations: HIHC, hyperparathyroidism-induced hypercalcemic crisis; PHPT, primary hyperparathyroidism; PTH, parathyroid hormone; ECG, electrocardiogram; AV, atrioventricular.

Keywords: hyperparathyroidism, hypercalcemic crisis, heart block, acute kidney injury

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INTRODUCTION

Primary hyperparathyroidism (PHPT) is a common endocrine disorder, affecting approximately 0.1 percent to 0.3 percent of the population [1]. PHPT is most commonly caused by a single parathyroid adenoma (85 percent), followed by multiple adenomas or four gland hyperplasia (15 percent), and rarely parathyroid carcinoma (<1 percent) [1]. Hyperparathyroidism-induced hypercalcemic crisis (HIHC) is a rare but life-threatening presentation of PHPT. The patient's course can be complicated by multiple concurrent co-morbidities, including cardiac arrhythmias, acute kidney injury, severe hypovolemia, obtundation, and various gastrointestinal disturbances [2,3]. In addition, these patients are more likely to have larger, atypical glands present in ectopic locations, as well as a higher incidence of parathyroid carcinoma [2,3]. Despite these challenges, patients presenting with HIHC can be successfully treated with intensive medical support and emergent parathyroidectomy, producing long-term, durable results [2,3].

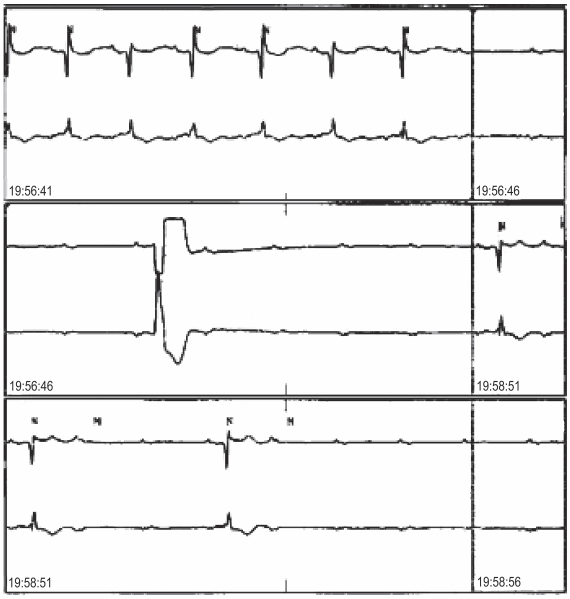

Figure 1. Electrocardiogram (ECG) of patient. The ECG demonstrates a symptomatic episode of complete heart block prior to pacemaker placement and parathyroidectomy.

CASE PRESENTATION

A 70-year-old gentleman from Ecuador presented to Yale-New Haven Hospital following several days of worsening weakness, fatigue, anorexia, and constipation. He also noted 15 pounds of unintentional weight loss over the past 6 months. His initial laboratory evaluation was remarkable for a significantly elevated serum calcium level of 19.8 mg/dL (8.4 – 10.2 mg/dL), a parathyroid hormone (PTH) level of 1,650 pg/mL (10.0 – 65.0 pg/dL), and a serum creatinine level of 3.0 mg/dL (0.6 – 1.2 mg dL). His medical history included hypertension, hyperlipidemia, and gastroesophageal reflux disorder, all well controlled medically. He denied a prior history of hypercalcemia or related symptoms. Of note, despite complaints of weakness and fatigue, he completed a hike to the summit of a local mountain in Connecticut several days prior to admission.

The patient was admitted to the medical intensive care unit in hypercalcemic crisis, accompanied by acute kidney injury. His hypercalcemia was emergently treated with aggressive intravenous fluid resuscitation, calcitonin, bisphosphonates, and renal replacement therapy via a temporary venous catheter. On surgical evaluation, the patient was also noted to be lethargic with some mental slowing. His course was then complicated by symptomatic paroxysmal atrioventricular (AV) block that required the placement of a temporary transvenous pacemaker (Figure 1). An ultrasound of the neck demonstrated a 4.8 x 4.0 x 2.9 cm mass in the right neck, consistent with an enlarged right parathyroid gland (Figure 2a). A sestamibi scan demonstrated focal radiotracer uptake, corresponding to the region of the enlarged parathyroid gland.

With a working diagnosis of PHPT due to a parathyroid adenoma and concern for potential parathyroid carcinoma, he underwent a focused parathyroidectomy after his

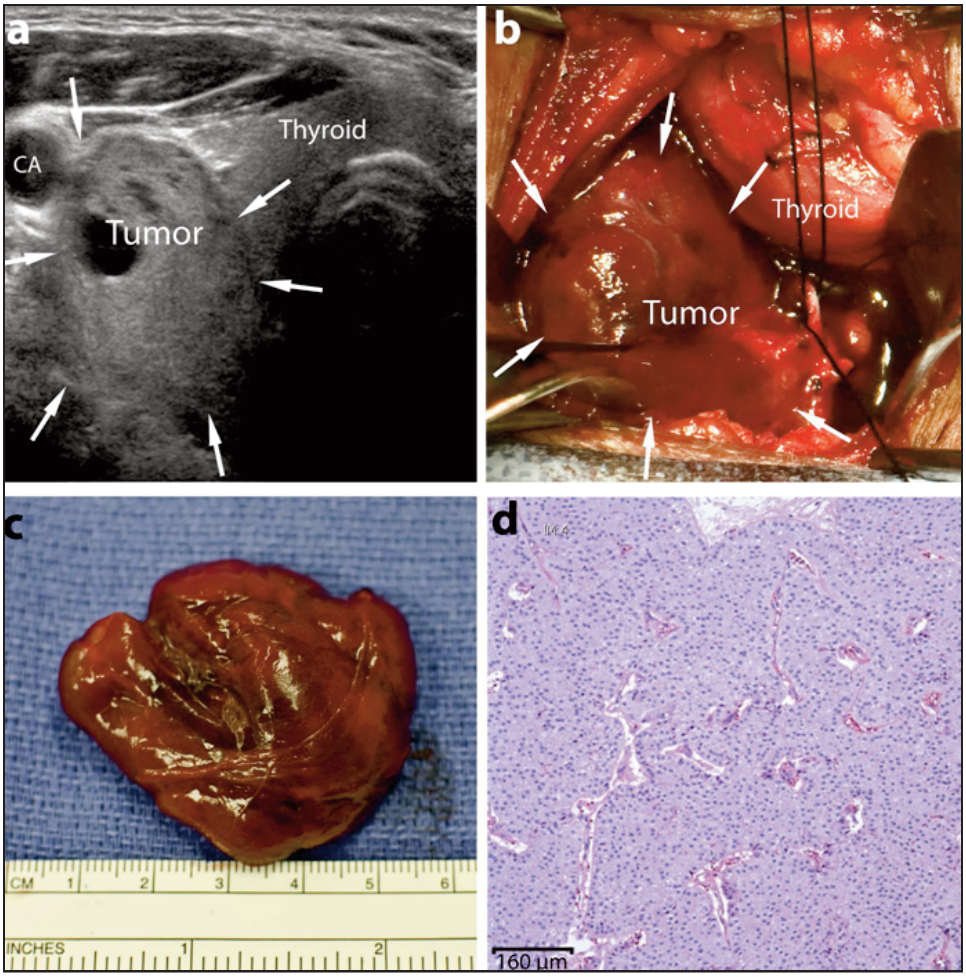

Figure 2. Ultrasound (US), intra-operative, and histological images of parathyroid adenoma. Arrows denote tumor boundaries. **a)** A pre-operative US demonstrates an enlarged right parathyroid gland containing a cystic component and abutting the carotid artery (CA). **b)** The intra-operative photograph is of the enlarged parathyroid gland with its major vascular pedicle isolated prior to ligation. **c)** The intra-operative photograph is of the excised parathyroid adenoma. **d)** The microphotograph at 10X magnification is of a H&E stain of the tumor demonstrating a cellular parathyroid gland, composed of a uniform population of oncocytic cells in a solid, nested, and trabecular growth pattern.

arrhythmia was stabilized. An enlarged parathyroid gland, spanning the entire length of the right thyroid lobe, was readily identified (Figure 2b). The gland was soft and contained a large inferior cystic component. The tumor easily dissected free from surrounding tissues, and there was no gross evidence of malignant invasion (Figure 2b and 2c). Intra-operative intact PTH levels were measured, and a baseline level of 5,200 pg/ml decreased to a nadir of 507 pg/ml 40 minutes following resection of the parathyroid adenoma. Pathological examination of the gland did not identify any features of malignancy, including capsular invasion, prominent nucleoli, thick fibrous bands, or vascular invasion, and the tumor was classified as an atypical parathyroid adenoma (Figure 2d).

After successful parathyroidectomy, the arrhythmia and renal dysfunction abated, and his pacemaker and dialysis catheters were removed on post-operative day 4 and 5, respectively. He was discharged to his

home. Two months after surgery, the patient's calcium and PTH level were 9.6 mg/dL and 32 pg/mL, respectively, consistent with resolution of PHPT. At that time, the patient's symptoms had resolved, and he was feeling well.

DISCUSSION

One notable aspect of the patient's course was the development of heart block, requiring temporary transvenous pacemaker placement. Most cases of PHPT present with mild-to-moderate hypercalcemia with limited effect on cardiac function. In one study that assessed electrocardiogram (ECG) changes in patients with PHPT and modest hypercalcemia, patients demonstrated QT and QTc interval shortening that resolved after parathyroidectomy. These patients never developed significant cardiac dysfunction or arrhythmias, such as supraventricular or ventricular arrhythmias, or high-grade AV-block. The authors concluded that moderate hypercalcemia had no immediate, clinically significant effects on cardiac conduction [4]. Patients with chronic, mild-to-moderate hypercalcemia due to PHPT, however, have been shown to demonstrate subtle changes in cardiac structure and physiology, including left ventricular hypertrophy, cardiac and vascular calcifications, and diastolic dysfunction [5]. Furthermore, patients with symptomatic PHPT have been shown to be at higher risk of cardiac death before and after parathyroidectomy [5].

Significant cardiac arrhythmias, including heart block and ventricular arrhythmias, although rare, are known complications of hypercalcemic crisis. In one retrospective study of 67 patients presenting with HIHC, only two patients (3 percent) suffered from cardiac arrhythmias [2]. In a similar study of 34 patients presenting with HIHC, no patients demonstrated evidence of cardiac arrhythmia [3]. Most other reports of HIHC-induced cardiac arrhythmia are annotated in case reports. A review of these demonstrates that the presentation of significant cardiac arrhythmia associated with HIHC can be highly variable, including tachy-brady syndrome, ventricular tachycardia, ventricular fibrillation, and paroxysmal atrioventricular block [6-9]. While life-threatening cardiac arrhythmias are rare during HIHC, ECG changes, including QT interval shortening, are frequent [4].

Our patient required the placement of a temporary transvenous pacemaker to treat complete heart block secondary to hypercalcemia. This intervention stabilized the patient's cardiac arrhythmia and allowed for emergent parathyroidectomy. Increasingly, temporizing pacemaker placement is being used in critically ill patients as a bridge to definitive therapy or recovery of non-compromising heart rhythm [10]. Life-threatening cardiac arrhythmias are rare complications of HIHC, and our experience demonstrates that placement of a temporary pacemaker can serve as a critical adjunct to treatment.

The patient's course was also notable for non-oliguric acute kidney injury, requiring emergent hemodialysis due to refractory hypercalcemia. In chronic PHPT, renal dysfunction is reported to have a prevalence of approximately 16 to 17 percent [11]. In mild, asymptomatic cases of PHPT, significant renal impairment is infrequently noted, and renal function usually does not deteriorate over time. In contrast, moderate to severe symptomatic PHPT is frequently associated with renal impairment, and renal function usually deteriorates over time if left untreated [12]. Indeed, higher levels of PTH are associated with an increased risk of developing end-stage renal disease due to PHPT [13].

The acute effects of HIHC upon renal function are less understood. In one case series of 67 patients with HIHC, 20.8 percent were noted to be suffering from nephrolithiasis, but serum creatinine levels were not noted [2]. In a similar case series of 34 patients presenting with HIHC, the mean preoperative creatinine level was significantly higher than observed in non-crisis patients with PHPT. However, after parathyroidectomy, both groups' creatinine levels returned to normal, indicating that the more severe renal impairment observed in HIHC is reversible [3]. In neither case series was use of renal replacement therapy noted.

The patient's presentation was also notable for neurocognitive disturbances that included anorexia, fatigue, and lethargy. Neurocognitive disturbance occur frequently in PHPT but have been shown to occur at a higher rate and of a greater severity in the setting of HIHC [3]. Though the exact mechanism remains incompletely understood, these changes have been attributed to hypercalcemia altering neurotransmitter function [14]. It has been shown that parathyroidectomy reduces mood and anxiety symptoms in PHPT patients [15]. Due to the patient's acute kidney injury, he also suffered from additional metabolic derangements that could have also contributed to his neurocognitive changes.

CONCLUSIONS

In summary, we present a unique case of hypercalcemic crisis caused by PHPT. The patient's presenting hypercalcemia of 19.8 mg/dL was significantly higher than noted in previous case series of HIHC, which had reported values of 13.95 ± 0.19 md/dL and 15.8 ± 2.1 md/dL [2,3]. As a result, the patient suffered multi-system organ failure, including life-threatening heart block and acute kidney injury. As such, the patient's care required a multi-disciplinary effort that included endocrine surgery, endocrinology, nephrology, interventional cardiology, internal medicine, and critical care specialists.

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