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Case series

HYPERCALCEMIC CRISIS AS A PRESENTATION OF PRIMARY HYPERPARATHYROIDISM

IVÁN BEDINI[1], GUSTAVO SYLVESTRE BEGNIS[1], FERNANDO POENITZ[2], DAVID C. POLILLO[1], MARÍA CECILIA VARGAS[1], DIAMELA BOLZÁN[1], LUIS A. RAMÍREZ STIEBEN[1]

[1]Unidad de Tiroides y Paratiroides del Grupo Gamma, Rosario, Santa Fe,
[2]Servicio de Cirugía de Cabeza y Cuello, Sanatorio Británico, Rosario, Santa Fe, Argentina

Postal address: Luis A. Ramírez Stieben, Pte. Roca 2440, 2000 Rosario, Santa Fe, Argentina
E-mail: lramirez@grupogamma.com
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Abstract

Hyperparathyroidism-induced hypercalcemic crisis (HIHC) is an unusual state of marked progressive primary hyperparathyroidism (PHPT). Patients have severe hypercalcemia and may have severe symptoms such as kidney failure, acute pancreatitis, and mental changes. PHPT is due to the presence of a single gland adenoma/disease in 80 to 85%; parathyroid carcinoma is reported in <1%. Among patients with adenoma, atypical parathyroid tumor can be found infrequently. Parathyroidectomy is the only curative approach for PHPT. In this report we present three cases of HIHC due to giant parathyroid adenomas (GPAs), one of them with histopathological characteristics of an atypical parathyroid tumor, with satisfactory evolution after parathyroidectomy.

Key words: primary hyperparathyroidism, hypercalcemic crisis, parathyroid adenoma, acute kidney disease

Resumen

Crisis hipercalcémica como presentación de hiperparatiroidismo primario

La crisis hipercalcémica inducida por hiperparatiroidismo (HIHC) es un estado inusual de hiperparatiroidismo primario progresivo y marcado (HPTP). Los pacientes tienen hipercalcemia grave y pueden tener síntomas graves como insuficiencia renal, pancreatitis aguda y cambios mentales. El HPTP se debe a la presencia de un adenoma/enfermedad de una sola glándula en 80 a 85%; el carcinoma de paratiroides se informa en <1%. Entre los pacientes con adenoma, el tumor paratiroideo atípico se puede encontrar con baja frecuencia. La paratiroidectomía es el único abordaje curativo del HPTP. En este reporte presentamos tres casos de HIHC por adenomas paratiroideos gigantes (APGs), uno de ellos con características histopatológicas de tumor paratiroideo atípico, con evolución satisfactoria luego de paratiroidectomía.

Palabras clave: hiperparatiroidismo primario, crisis hipercalcémica, adenoma paratiroideo, insuficiencia renal aguda

Hyperparathyroidism-induced hypercalcemic crisis (HIHC) is a rare manifestation of primary hyperparathyroidism (PHPT) occurring in approximately 1% of patients[1]. Patients usually have profound hypercalcemia (serum ≥14 mg/dl) along with rapid deterioration of central nervous system, cardiac, gastrointestinal, and renal functions[2].

The size of the parathyroid adenoma correlates with calcium and PTH levels. Although several studies have demonstrated that the average elevation in PTH and calcium is significantly higher in parathyroid carcinomas than in benign adenomas, most patients with severe elevations in PTH and calcium still have benign disease[1,3,4]. We report three cases of PHPT presenting as HIHC and satisfactory evolution after parathyroidectomy.

Clinical case 1

A 59-year-old man who was admitted due to asthenia, poor general condition, generalized myalgia, hyporexia, decreased diuretic rate, nausea, and vomiting of bilious content for three days. He reported constipation and goat feces associated with a loss of 8 kg of body weight of approximately one year of evolution.

During the physical exam the patient was found to have decreased skin turgor, blood pressure of 140/90 mmHg, heart rate of 110 beat per minute, respiratory rate of 20 breath per minute, and an axillary temperature of 36.3°C. The patient was alert and oriented in time, place and person, generalized hyperreflexia, and distal fine tremor were confirmed.

The biochemical reports showed a calcium level of 24.7 mg/dl, a PTH level of 2416 pg/ml, and a serum creatinine level of 2.84 mg/dl. Table 1 (case 1) summarizes the biochemical findings. Biochemical reports suggested PHPT. Ultrasonography (USG) did not reveal any parathyroid lesions, while parathyroid scan coupled with SPECT using 99mTc-sestamibi tracer showed a 30 mm mass in superior mediastinum, to the right of the esophagus and in contact with the posterior edge of the trachea. Hydration was started with crystalloids and, later, loop diuretics. Due to the persistence of severe hypercalcemia, emergency hemodialysis was performed. Finally, minimally invasive parathyroidectomy was performed with normalization of calcium levels. Pathology revealed a lesion with a maximum diameter of 25 mm, 4 grams, without signs of malignancy, compatible with a giant parathyroid adenoma (GPA).

At the follow-up three year later, a recurrence of hyperparathyroidism was confirmed due to a hyperplasia of two parathyroid glands.

Clinical case 2

A 67-year-old man with a history of arterial hypertension, bipolar disorder, and benign prostatic hyperplasia, who was admitted with a two-week history characterized by alteration in his behavior over the past two weeks, in the form of apathy, irritability, and decreased alertness. In treatment with valproic acid, lamotrigine, quetiapine, terazosin, tamsulosin, and amlodipine. Physical examination: dry mucosa, decreased skin turgor. Blood pressure 100/70 mmHg, heart rate 100 /min, respiratory rate 16 /min. Bradypsychia, irrelevant talk, without neck stiffness. A 30-mm elastic, a palpable nodule was detected in projection of the right thyroid lobe. Biochemical reports showed a serum calcium level of 14.1 mg/dl, serum phosphate of 2.47 mg/dl, PTH of 1143 pg/ml, and serum creatinine of 1.73 mg/dl (Table 1). USG revealed a 25-mm nodular mass behind the upper pole of the left thyroid lobe. Parathyroid scan coupled with SPECT using 99mTc-sestamibi tracer showed a nodular image of approximately 20 mm, suggesting the presence of a left upper parathyroid adenoma. Hydration with crystalloids was started and 48 hours after admission parathyroidectomy was performed. Pathology study revealed a parathyroid adenoma of 8 grams, 40 mm by 20 mm, without signs of malignancy, compatible as GPA. After surgery, a normalization of calcium and PTH levels was found. These findings suggested HC due PHPT.

After one year of follow-up, the patient is in remission, with normal levels of serum calcium, serum phosphate, and PTH.

Clinical case 3

A 58-year-old man with a history of hepatic transplant for non-alcoholic steatohepatitis complicated with post-

Tabla 1 | Biochemical characteristics of patients before surgery and at discharge

	Case 1		Case 2		Case 3	
	Before surgery	At discharge	Before surgery	At discharge	Before surgery	At discharge
Parathyroid hormone (pg/ml)	2416	224	1143	22	764	16
Corrected calcium (mg/dl)	24.70	10	13.20	8.80	23.46	8.86
Phosphorus (mg/dl)	3.70	3.54	2.47	2.16	2.59	2.31
Serum 25-hydroxyvitamin D (ng/ml)	13.9	-	30.6	-	41.3	-
Alkaline phosphatase (IU/l)	216	148	185	120	762	1250
Serum urea (mg/dl)	105	41	55	59	95	40
Serum creatinine (mg/dl)	2.84	1.98	1.77	2.18	1.94	1.38
Intraoperative PTH criteria	Miami		Dual		Dual	

Miami criterion: decrease of >50% in PTH levels compared to the highest hormonal level obtained before incision or excision. Dual criterion: >50% decrease in PTH levels to the normal range

surgical stricture of the bile duct, undergoing hospitalization for acute cholangitis, with percutaneous drainage placement and antimicrobial treatment. The patient evolved with acute confusional state. The biochemical report showed a serum calcium adjusted for albumin of 23.46 mg/dl, PTH of 764 pg/ml, and serum creatinine of 1.94 mg/dl (Table 1, case 3). USG revealed an 18-mm hypoechoic nodular lesion adjacent to the right thyroid lobe. Magnetic resonance imaging (MRI) of the cervical region showed a mass measuring 50 by 18 mm, hypointense on T1 and hyperintense on T2, in low right laterocervical topography. Hydration was started to reduce pre-surgical serum calcium levels and parathyroidectomy was performed. Pathology showed a parathyroid adenoma of 7 grams, 40 mm by 30 mm, with extensive hemorrhage, and solid/trabecular growth patterns compatible with an atypical giant adenoma. After surgery, calcium and PTH levels returned to normal range (Table 1).

The publication was approved by the Ethics Committee of the Grupo Gamma, and written informed consent was obtained from each participant.

Discussion

HIHC is an unusual state of progressive and marked of PHPT. Patients with HIHC have profound hypercalcemia (serum calcium ≥14 mg/dl) resulting in anorexia, vomiting, dehydration, decreased renal function, impaired mental status, confusion, coma, and if untreated, death[1,2,5]. In this report, we present three cases of PHPT that presented with severe hypercalcemia with satisfactory evolution after parathyroidectomy.

Patients with HIHC may have severe symptoms such as renal failure, acute pancreatitis, and mental changes[5]. In our report, the most frequent symptoms were dehydration with renal failure and altered mental status. These symptoms improved markedly after parenteral hydration and as expected, after parathyroidectomy.

HIHC demands an accelerated approach and requires immediate improvement within hours. Conservative management strategy for HIHC includes rapid intravascular volume expansion with isotonic saline solution, and loop diuretics as furosemide to induce calciuresis[1-3]. Most patients presenting with severe hypercalcemia have intravascular volume depletion. This situation exacerbates hypercalcemia by altering renal calcium clearance. Isotonic saline solution for 24 to 48 hours corrects possible volume depletion and consequently lowers calcium levels. In some cases, hemodialysis may be considered[6], as in one of our patients. On the other hand, the use of bisphosphonates is controversial and may be associated with an increased risk of hypocalcemia in the postoperative period[7]. However, although medical treatment can rapidly reduce serum calcium levels, the definitive approach is urgent parathyroidectomy due to the life-threatening risk to patients.

Ultrasonography (USG) and (99mTc)-sestamibi scintigraphy (with SPECT) are recommended as first-line imaging methods, with the goal of obtaining preoperative localization. If two studies are concordant, the positive predictive value for the correct localization of the parathyroid tumor is close to 97%[8], and one can go for minimally invasive or focused parathyroidectomy. This technique has modified the management of hypercalcemic crisis, due to a shorter operating time, smaller incision, and less perioperative pain[2]. Our patients underwent a focused parathyroidectomy, achieving biochemical remission of the disease in the short term and without complications associated with the surgical procedure, such as hematoma/bleeding in the surgical bed or neuronal damage.

PHPT is due to the presence of an adenoma/single-gland disease in 80-85%. Although parathyroid carcinoma is a rare cause of PHPT, it can be seen in about 5% cases of HIHC[1,4,9]. However, the most common pathological finding in HIHC is a solitary parathyroid adenoma. Other types of tumors, such as GPA and atypical parathyroid tumors, are less frequent. Interestingly, our patients had GPAs adenomas and one of them had a GPA with characteristics of an atypical parathyroid tumors. None of our patients presented histopathological findings compatible with parathyroid carcinoma.

GPA is a rare type of parathyroid adenoma defined as weighing >3.5 g, and consequently, only a few cases of GPA have been reported. A systematic review by Wong et al. identified 65 GPAs[10]. Subsequently, four more cases were published[11,12]. They manifest as PHPT but exhibit elevated laboratory parameters and severe clinical manifestations[5,13], bearing a closer resemblance to parathyroid carcinoma rather than a typical benign adenoma. This should draw attention to the potential malignant nature of the tumor[14].

Furthermore, histopathological analysis of parathyroid tumors of HIHC may display some unique features which include necrosis, fibrosis, extensive hemorrhage, microcystic pattern, and presence of intracytoplasmic vacuoles[9]. Some reports have suggested that hemorrhage within an intact parathyroid gland may precipitate HIHC. Only one of our patients (case 3) showed evidence of intratumoral hemorrhage in the pathology.

In 2022, the WHO reclassified atypical parathyroid adenomas now as atypical parathyroid tumors due to their potential for malignant behavior15. These tumors display some histologic features that can often be seen in parathyroid carcinoma, such as cytologic atypia, sheet-like or trabecular growth, adherence to adjacent structures, fibrosis (which may be band-like, tumor cells extend towards the tumor capsule but not through it) and mitotic activity, but do not present other signs such as full-thickness capsular invasion, vascular invasion, perineural invasion or invasion of adjacent structures[15]. One of our patients (case 3) presented a GPA with a solid trabecular growth pattern. In these situations, parafibromin immunohistochemistry is recommended to appreciate the risk of recurrence and to estimate de possibility of an underlying CDC73 mutation[15]. However, we do not have this immunohistochemistry panel to estimate these issues. To date, the patient has not presented signs of recurrence.

Hungry bone syndrome is a rapid, severe, and prolonged hypocalcemia following parathyroidectomy, caused by an abrupt drop in PTH levels and osteoclastic resorption. Risk factors include a PTH level >1000 pg/ml, and alkaline phosphatase levels three times higher than the normal upper limit[13]. Although our patients had low calcium levels during follow-up, they did not present this syndrome, possibly due to routine administration of calcitriol and calcium after surgery.

Conflict of interest: None to declare

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