Parathyroid Adenoma Complicated with Severe Hypercalcemia, Encephalopathy and Pancreatitis

Ciddi Hiperkalsemi, Ensefalopati ve Pankreatit ile Komplike Olmuş Paratiroid Adenomu


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Abstract

Primary hyperparathyroidism is the most frequent cause of hypercalcemia in adults. Primary hyperparathyroidism generally leads to mild-moderate hypercalcemia. Severe hypercalcemia in these cases is rare. Coexistence of severe hypercalcemia and hypercalcemic encephalopathy is very unusual with very limited number of reported cases. Our case is a 50-year-old female who presented to the emergency department with the complaints of nausea and severe abdominal pain. Her serum calcium level was 19.7 mg/dL (8.8-10.2 mg/dL) and her PTH level was 73.5 ng/dL (15-65) on presentation. After her hospitalization, she was treated with saline infusions and furosemide, however, her calcium level increased to 22.4 mg/dL. Her calcium levels were also refractory to subcutaneous calcitonin 200 mg twice a day and zoledronic acid 4 mg. Ultrasonography of the neck revealed a 3.2x2.7x4.6 cm mass suspicious for a left parathyroid adenoma hardly being distinguished from a left thyroid nodule. Considering her general situation getting worse despite maximum medical treatment, she underwent an emergency parathyroidectomy and total thyroidectomy. Early postoperatively, the patient’s general condition deteriorated reaching a precoma state. Cranial computed tomography (CT) at this point revealed periventricular ischemia compatible with metabolic encephalopathy. During the follow-up postoperatively, the patient’s serum calcium levels normalized eventually requiring active vitamin D and calcium pills and she no longer had symptoms of encephalopathy. The pathology specimen was reported as a parathyroid neoplasm compatible with atypical parathyroid adenoma. Although mild-moderate hypercalcemia is frequent in primary hyperparathyroidism, it should be noted that it can be severe and refractory to maximum medical treatment requiring emergency surgical intervention. In addition, not being one of the most frequent reasons, severe hypercalcemia due to primary hyperparathyroidism should be considered as an important cause of metabolic encephalopathy. Turk J Em 2015; 19: 105-108

Key words: Hypercalcemia, encephalopathy, primary hyperparathyroidism

Anahtar kelimeler: Hiperkalsemi, ensefalopati, primer hiperparatiroidi
Introduction

Primary hyperparathyroidism (PHP) is a generalized disorder resulting from excessive secretion of parathyroid hormone (PTH) by one or more of the parathyroid glands (1). Solitary parathyroid adenomas represent approximately up to 85% to 90% of cases with PHP (2,3). The majority of the remainder is either parathyroid hyperplasia or multiple parathyroid adenomas (4,5). Parathyroid carcinoma rarely occurs and is responsible for only 0.7% of all cases (3). With increased detection by means of routine calcium screening, the clinical profile of PHP in Western countries has shifted from a symptomatic disease, characterized by hypercalcemic symptoms; nephrolithiasis, overt bone disease, and neuromuscular symptoms to one with subtle or no specific symptoms (asymptomatic primary hyperparathyroidism). In the developing world, the symptomatic variant still dominates (6).

In this report, we present a case of PHP presenting and progressing with severe neurological symptoms together with acute pancreatitis.

Case Report

A 50-year-old female was admitted to the emergency department with the complaints of severe abdominal pain and nausea lasting several weeks which recently increased in intensity. She mentioned hospital admission with similar complaints eleven years ago when she underwent cholecystectomy. She had no recent history of drug use and no history of chronic diseases. She recalls her laboratory tests being completely normal eleven years ago at the time of her cholecystectomy, but the laboratory report was unavailable at present time. On her admission to our hospital, she had abdominal tenderness on palpation and leucocytosis, hypercalcemia and elevated serum amylase levels (Table 1).

She was then hospitalized at the department of general surgery with a prediagnosis of acute pancreatitis. Intravenous hydration and antibiotics were initiated. The PTH level was 73.5 ng/dL (15-65) (Electrochemiluminescence immunoassay), thus, a neck ultrasonography (USG) was performed. The neck USG revealed a 3.2x2.7x4.6 cm homogenous, hyperechoic mass suspicious for a parathyroid adenoma hardly being distinguished from a left thyroid nodule. Despite maximum medical therapy, consisting of intravenous hydration, furosemide, calcitonin and zoledronic acid, the serum calcium level increased to 22.9 mg/dL. Thyroid function tests were normal.

In less than a 24-hour period, her calcium level reached 24 mg/dL and her clinical condition deteriorated reaching a precoma state. Considering her general condition and severe hypercalcemia, emergent surgical intervention was planned with the prediagnosis of malignant hypercalcemia, hypercalcemic encephalopathy and PHP with the suspicion of parathyroid carcinoma as the cause of malignant hypercalcemia. Total thyroidectomy and left parathyroidectomy were performed.

Early after the operation, the calcium levels were still above 24 mmol/L. In addition, the patient’s general condition got even worse; confusion and loss of cooperation continued. The cranial computed tomography scan at this point revealed periventricular ischemia which was compatible with metabolic encephalopathy due to hypercalcemia.

On the third day, the renal function tests and calcium levels improved. Her neurological symptoms no longer existed. Eventually, her serum calcium levels decreased to 8.1 mg/dL requiring oral calcium and active vitamin D supplementation. The pathology report described parathyroid neoplasm compatible with atypical parathyroid adenoma because of its cellularity and some atypical features of the cells. No necrosis, atypical mitosis and capsular invasion were present. The Ki-67 proliferative index was 2%. Neoplastic cells stained positive with chromogranin (Figures 1, 2, 3).

Table 1. Significant laboratory tests on presentation. Normal range for each entity is expressed in parenthesis

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>White Blood Cells</td>
<td>13000 /mm³ (4-10000)</td>
</tr>
<tr>
<td>Serum Calcium</td>
<td>19.7 mg/dL (8.8-10.2)</td>
</tr>
<tr>
<td>Serum Sodium</td>
<td>136 mEq/L (135-145)</td>
</tr>
<tr>
<td>Serum Potassium</td>
<td>2.8 mmol/L (3.5-5.1)</td>
</tr>
<tr>
<td>Serum Albumin</td>
<td>3.7 g/dL (3.5-5.0)</td>
</tr>
<tr>
<td>Serum Amylase</td>
<td>361 U/L (25-125)</td>
</tr>
<tr>
<td>Serum Phosphorus</td>
<td>2.4 mg/dL (2.3-4.7)</td>
</tr>
<tr>
<td>Serum Creatinine</td>
<td>0.9 mg/dL (0.6-1.1)</td>
</tr>
<tr>
<td>Serum Blood Urea Nitrogen (BUN)</td>
<td>22 mg/dL (10-20)</td>
</tr>
<tr>
<td>Alkaline Phosphatase (ALP)</td>
<td>120 IU/L (44-147)</td>
</tr>
<tr>
<td>Alanine Transaminase (ALT)</td>
<td>30 IU/L (10-40)</td>
</tr>
</tbody>
</table>

Discussion

The incidence of pancreatitis in hyperparathyroidism is controversial (7,8). Recent studies have stated that hyperparathyroidism is rarely associated with pancreatitis (1-7% of cases), but when such a combination does occur, pancreatitis is severe (9).
The pathogenesis of pancreatitis in the course of hyperparathyroidism is not well defined. Hyperparathyroidism is believed to cause pancreatitis by several mechanisms, the most common of which is hypercalcemia. The other hypercalcemic states, such as malignant diseases, vitamin D intoxication, hyperthyroidism, excessive calcium intake and parenteral nutrition, may also result in pancreatitis (10). Animal studies have suggested that long-standing hypercalcemia directly affects pancreatic functions. According to some researchers, hypercalcemia secondary to hyperparathyroidism causes decreased pancreatic volume whereas pancreatic enzyme activity is not affected. These findings suggest that hypercalcemia may have some influence on exocrine pancreatic function (11). Persistent hypercalcemia may also result in an increased calcium concentration in pancreatic juice, and activate pancreatic trypsinogen to trypsin resulting in pancreatic ductal and parenchymal damage and pancreatitis (7,8,12). Long-standing hypercalcemia may also decrease the volume of pancreatic secretions leading to protein plugs in the pancreatic duct eventually obstructing the pancreatic flow leading to pancreatic inflammation (13).

On the other hand, PTH itself has been suggested to be a cause of pancreatitis. The hormone may inhibit pancreatic blood circulation directly or by means of pancreatic ductal and blood vessel narrowing mediated by hypercalcemia. Some authors have also indicated that PTH itself may act as a toxin causing local thromboendarteritis and necrosis of pancreatic tissue (7,8). Microembolisms due to hyperparathyroidism have also been reported. All of which may result in pancreatic tissue necrosis (7). PHP and acute pancreatitis are rarely expected to co-exist (9). In our case, acute pancreatitis was the presenting feature. Hypercalcemic crisis is an infrequent manifestation of PHP which calls for urgent surgical attention. The published reports of such cases clearly indicate that the syndrome of hypercalcemic crisis occurring in the course of PHP is almost uniformly fatal unless recognized early and the hyper functioning parathyroid tissue is promptly removed (14).

Central nervous system symptoms can vary from tiredness, headache to depression and even loss of initiative (15). According to an article that was presented at the 67th Annual Meeting of the Central Surgical Association in 2010, subjects with hypercalcemic crisis had a greater incidence of mental status changes, fatigue, ectopic glands, and pancreatitis (16).

In this case we studied, the increase in serum calcium level correlated with acute psychomotor deterioration and alteration in the level of consciousness. This finding was attributed to metabolic encephalopathy secondary to hypercalcemic crisis. Posterior reversible encephalopathy syndrome (PRES) is a clinico-radiological entity which has been described since the mid-90’s (17). It is characterized by an acute alteration in the level of consciousness frequently accompanied by headache, seizures and focal neurological signs such as visual field defects (18).

This syndrome has been described in a wide variety of settings, most commonly, solid organ transplantation, hypertensive crisis, and immunosuppressive drug administration (18). In the literature, 8 cases of hypercalcemia related to PRES have been reported (19,20), only 2 of which were due to parathyroid adenomas (21,22). Since then, a case report by Giani et al., announced a new case of PRES in association with parathyroid adenoma (23).

The physiopathological mechanisms of PRES are still debated (18). There have been two main theories suggested to explain the condition. The first theory focuses on severe hypertension as the triggering condition of overflow edema, by disturbance in autoregulatory mechanism of the cerebral blood vessels. A second theory emphasizes the importance of altered blood brain barrier function resulting from a combination of endothelial dysfunction, hypoperfusion and vasoconstriction (24). Hypercalcemia and elevated PTH levels have been shown to induce the production of vascular endothelial growth factor (VEGF) and nitric oxide (NO) by way of which they can alter vascular permeability (25,26,27) as mentioned in the second theory.

In PRES, symptoms develop sub-acutely or acutely, often with seizures at onset (24). Imaging studies (both CT and magnetic resonance imaging) demonstrate focal regions of symmetric hemispheric edema in the brain (28,29) which usually reverses...
completely [30] with early identification of the underlying etiology and its effective treatment [31]. Neurological symptoms that developed during the follow-up complicated the case. Considering severe hypercalcemia insensitive to medical therapy and the neurological symptoms accompanying, two main entities were suspected: hypercalcemic crisis and PRES. The level of consciousness deteriorated progressively and acutely in correlation with progressively increasing levels of calcium and only moderately high PTH levels. This dramatically worsening of the patient’s general condition made emergent surgical intervention inevitable. The underlying etiology of severe hypercalcemia was established to be a parathyroid adenoma. Furthermore, the progression of the case and acute regression after surgery, strongly suggested PRES. Due to the necessity of emergent surgery, radiological imaging studies could not be performed before surgery.

Generally, PTH levels are frankly elevated in cases with PHP, but in our case it was mildly elevated despite marked calcium elevation. This was unexpected, but in a study that compared patients with PHP having normal PTH levels with those having elevated PTH levels, the mean serum calcium levels and subjective symptoms were similar [32]. Although mild-moderate hypercalcemia is frequent in PHP, it should be noted that it can be severe and refractory to maximum medical treatment requiring emergency surgical intervention. In addition, not being one of the most frequent reasons, severe hypercalcemia due to PHP should be considered as an important cause of metabolic encephalopathy.

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**References**