Reversible Mental and Behavioral Disturbances due to Giant Mediastinal Parathyroid Adenoma-Induced Hypercalcemia

Heschi H. Rotmensch MD, Ilan Kitzes MD, Gideon Charach MD and Moshe Weintraub MD

Department of Medicine C, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
Affiliated to Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

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In 1925, DeQuervain [1] was the first to report the removal of a non-functioning parathyroid cyst from the mediastinum. Since then, 96 patients with functioning and non-functioning cystic parathyroid tumors located in the mediastinum have been described [2]. We report on a young woman with excessive hypercalcemia associated with mental and behavioral disturbances that was due to a giant mediastinal cystic parathyroid adenoma. Following resection of the tumor, the patient's symptoms – that had persisted for over a decade – completely resolved.

Patient Description

A 22 year old woman was referred to our department because of an excessively elevated serum calcium concentration of 18.7 mg/dl that was detected on routine laboratory examinations. Her parents revealed that at age 9 years the child was noted to have difficulty concentrating and subsequently developed significant learning disability and behavioral disturbances that had been interpreted as an adaptation disorder requiring transfer to a specialized education facility. In her early teens, the patient began suffering from intermittent fatigue, lack of energy, emotional instability, obscure thoughts, lethargy, and intermittent confusion that typically lasted for several days to weeks. Her non-verbal and social skills were reported to be adequate. At age 13, the girl had undergone a nutrient mineral analysis of her hair by a certified laboratory, which detected a very high calcium content of 1,350 parts per million, representing more than two standard deviations above the mean population value. No further laboratory work-up was conducted and the parents did not consult a physician during those years, assuming that the child's complaints were attributable to a congenital mental impairment.

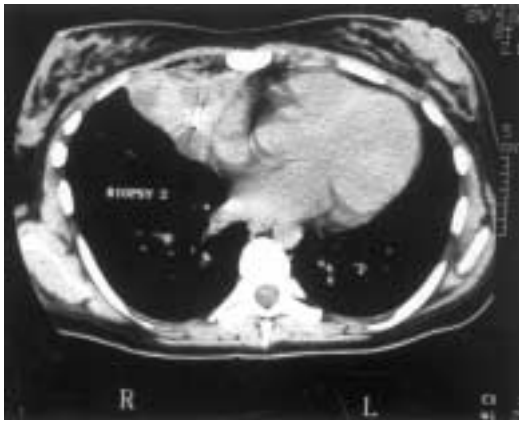
Twelve months prior to admission, the patient's condition gradually worsened, with the familiar episodes of emotional outbursts, lethargy and confusion becoming more severe and sustained. In addition, she began suffering from nausea, vomiting, constipation, and an 8 kg weight loss. Due to this deterioration, the patient had started to self-administer a variety of supplemental nutrients including vitamin D and A, as well as calcium. She had no past history of peptic ulcer disease, hypertension, bone pain, renal disease, or a family history of hypercalcemia or endocrinopathy, nor had she been administered lithium.

On admission the patient appeared well nourished, had a normal stature without any abnormal craniofacial features, and no overt signs of dehydration or acute distress but was moderately confused and her speech slurred. Her vital signs were normal. There was no palpable neck mass or lymphadenopathy, and the cardiac examination was normal. Intermittent jerky movements of both arms were noted without any focal neurologic signs, including vocal cord paralysis; muscle strength was preserved, and tendon reflexes were normal. The remainder of the physical examination was unremarkable.

Blood chemical values revealed a serum calcium concentration of 17.9 mg/dl and a normal serum albumin level. Serum alkaline phosphatase was 288 mU/ml (normal 15–85), and serum phosphorous and magnesium were 3.0 mg/dl (normal 2.5–4.5) and 1.3 mg/dl (normal 1.8–2.2), respectively. Creatinine clearance was 106 ml/min and immunoreactive parathyroid hormone 541 pg/ml (normal 12–72 pg/ml). On 24 hour urinary excretion, calcium and phosphorous were 355 mg (normal 100–300) and 180 mg (normal 900–1,300), respectively. The results of thyroid function tests, plasma 1,25 hydroxy-vitamin D and 24,25 dihydroxy-vitamin D, and protein electrophoresis were normal. Morning serum cortisol and gastrin concentrations and 24 hour urinary catecholamines were within normal limits.

An electrocardiogram showed a normal sinus rhythm and a short QTc interval. Ultrasound of the neck revealed a solid mass, 1.5 x 1.0 x 0.4 cm, within the inferior right thyroid lobe, and chest X-ray demonstrated a mediastinal mass that was confirmed by computerized tomography (10 x 6 x 5 cm) and displacing the great vessels [Figure]. Within the mass there were large, irregular cystic areas. A technetium-MIBI SPECT showed marked, non-homogenous uptake within a large area of the right anterior mediastinum and in the area of the right inferior parathyroid gland. An ultrasound showed normal sized kidneys and multiple echogenic foci compatible with medullary nephrocalcinosis.

Treatment with intravenous fluids and bifosphonates was begun immediately after admission, resulting in a gradual decline of serum calcium levels to 11.2 mg/dl over a 3 day period. Transcutaneous biopsy of the mediastinal mass was performed under CT guidance and the histopathology showed a tumor composed of closely packed cells with faintly eosinophilic cytoplasm, but no signs of inflammation, atypia or mitosis. Immunohistochemical analyses of the tissue were



Chest CT scan showing a mediastinal mass (10 x 6 x 5 cm) with large, irregular cystic areas. Pathology revealed a cystic parathyroid adenoma.

positive for PTH, chromogranin A, as well as high and low molecular weight keratin, and negative for somatostatin, synaptophysin, non-specific esterase, S-100, calcitonin and beta-human chorionic gonadotropin.

Surgical exploration of the neck showed no evidence of abnormal parathyroid tissue in multiple frozen sections. Following median sternotomy, a large well-circumscribed, encapsulated cystic mass (14 x 6 x 4 cm) weighing 134 g was removed from the mediastinum. The mass did not penetrate any adjacent structures, was covered by a thin capsular layer, and contained several cysts filled with brownish-colored fluid. The histologic picture was indicative of parathyroid tissue displacing some thymic tissue.

Postoperatively the patient's serum calcium decreased to 8.8 mg/dl and the postoperative period was uneventful with the patient recovering fully. Serum calcium and PTH concentrations returned to normal. During the 24 month follow-up period, serum calcium and PTH levels were within normal limits and the patient's general and mental condition had improved substantially. Her parents witnessed a remarkable change in her behavior and intellectual capabilities; the young lady regained normal energy levels and started an academic career.

PTH = parathyroid hormone

Comment

This young woman presented with hypercalcemic crisis apparently superimposed on long-standing moderate hypercalcemia due to a giant mediastinal cystic parathyroid adenoma. The progression to hypercalcemic crisis might have been due to ingestion of supplemental calcium and vitamin D preparations for several months and/or partial necrosis of the large adenoma. The complete regression of symptoms following surgical cure of the hyperparathyroidism, coupled with the indirect evidence of an increased tissue calcium content (by hair analysis) 9 years prior to admission, raise the possibility that the patient's long-lasting mental and behavioral disturbances might have been causally related to hypercalcemia that remained undiagnosed for over a decade.

Initially, in light of the hypercalcemia in association with emotional and behavioral disturbances since childhood, the diagnosis of Williams syndrome [4] seemed appealing. This gene deletion syndrome is characterized by distinctive craniofacial features, congenital cardiovascular abnormalities, mental retardation, growth deficiency, and transient hypercalcemia in about 20% of children. In the absence of these typical findings of Williams syndrome, other etiologies for the hypercalcemia were investigated resulting in the diagnosis of parathyroid adenoma.

Parathyroid cysts and cystic parathyroid adenomas located in the mediastinum are rare but well-defined clinical and pathologic entities [2,3]. Since the first case report in 1925 [1], a total of 96 patients have been reported [2]. In about 60% of these cases the cystic tumor was non-functioning, and in only 13 cases was the tumor considered large or giant, i.e., at least 10 cm in its largest dimension. Seven of the 39 patients with functioning tumors (18%) presented with hypercalcemic crisis. Thymic involvement (either intrathymic or attached to the thymic residue) was observed in 7 of the 12 patients in whom the tumor was located in the anterior mediastinum. These tumors must be differentiated from true ectopic secretion of authentic PTH by a thymoma [5] or other non-parathyroid, usually malignant tumors.

We described a young female with a long-standing history of mental and behavioral disturbances that completely resolved following resection of a giant mediastinal PTH-producing cystic adenoma. It is conceivable that the patient's long-lasting mental and behavioral disturbances were causally related to hypercalcemia secondary to the slowly growing mediastinal adenoma. Mental and behavioral disturbances may be another protean clinical manifestation of hypercalcemia, which should be routinely assessed in patients with behavioral disturbances.

References

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Correspondence: Dr. H.H. Rotmensch, Dept. of Medicine C, Tel Aviv Sourasky Medical Center, 6 Weizmann St., Tel Aviv 64239, Israel.
Phone: (972-3) 644-9522
Fax: (972-3) 644-9523
email: hrotmensch@cato.co.il

Riches serve a wise man but command a fool

English proverb