Hypercalcemia syndrome

Coexisting hyperthyroidism, primary hyperparathyroidism and cancer of the gallbladder

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ABSTRACT

Hypercalcemia is a frequent finding in clinical practice. All possible causes must be considered in a patient with hypercalcemia. The association between both benign or malignant thyroid disease and primary hyperparathyroidism is well recognized. Up to 65% with primary hyperparathyroidism have associated thyroid abnormality. Hypercalcemia has also been associated with many malignant conditions. But, it is rarely seen in digestive tract cancer, such as carcinoma of gallbladder. Hypercalcemia syndrome is an absolutely rare entity. It is coexisting with hyperthyroidism, primary hyperparathyroidism and cancer of the gallbladder.

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Hypercalcemia is a frequent finding in clinical practice. It causes are manifold and include primary hyperparathyroidism, malignant disease, hyperthyroidism, immobilization, vitamin D and vitamin A overdose, familial hypocalciuric hypercalcemia, diuretic phase of acute renal failure, chronic renal failure, thiazide diuretics, sarcoidosis or other granulomatous diseases, milk-alkali syndrome, Addison's disease, and Paget's disease.[1] All these possible causes must be considered in a patient with hypercalcemia. However, in practice, 90% of cases are due to either primary hyperparathyroidism or malignancy. Therefore, the differential diagnosis of these 2 causes is of paramount importance. Although significant hypercalcemia was considered to be rare complication of thyrotoxicosis, since it was first reported in 1937, there have been numerous reports in the literature of widely discrepant incidence ranging from 2-51%.[1] The association between both benign or malignant thyroid disease and primary hyperparathyroidism is well recognized. Up to 65% with primary hyperparathyroidism have associated thyroid abnormality.[2] Hypercalcemia is a well-recognized complication of neoplastic disorders. It has been associated with a large number of malignant conditions ranging from solid tumors, predominantly breast carcinoma, squamous carcinomas of the lung, head and neck, and renal adenocarcinoma, to hematological malignancies: multiple myeloma and lymphoma. More rarely, hypercalcemia is seen in digestive tract cancer, mainly squamous cell carcinoma of the esophagus and carcinoma of the gallbladder.[3]

Case Report. An 83-year-old woman was referred to the University Hospital of Suleyman Demirel, Isparta, Turkey for evaluation of weakness, nausea, vomiting, weight loss, lack of

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appetite and tremulousness associated with elevated serum calcium. The patient exhibited sinus tachycardia of 120 beats per minute, and mild exophthalmia. In addition, her thyroid gland was enlarged. Pertinent laboratory studies yielded the following values: FT3: 4.95 pg/ml (range, 1.71-3.71 pg/ml), FT4: 2.57 ng/dl (range, 0.7-1.48 ng/dl), thyroid stimulating hormone: 0.013 mIU/ml (range, 0.35-4.94 units/ml), ionized calcium: 2.97 mEq/L (range, 2.3-2.54 mEq/L), phosphorus: 2.3 mg/dl (range, 2.7-4.5 mg/dl), parathormone: 752 pg/ml (range, 12-65 pg/ml) calcitonin: 8 pg/ml (range, 0-30 pg/ml), alkaline phosphatase: 76 U/L (range, 0-270 units/L). A thyroid ultrasonography showed the gland to be enlarged, multinodular and heterogeneous with a 2.5 cm mass at the left inferior pole area consistent with parathyroid adenoma. These findings were confirmed with thyroid and parathyroid scintigraphy. Severe osteoporosis was detected by the measurement of bone mineral densitometry. Cholelithiasis was found by upper abdominal ultrasonogram. She was treated with 300 mg propylthiouracil daily and 80 mg propranolol twice per day for 6 weeks. After the euthyroidism was achieved, she underwent a cervical exploratory operation and laparoscopic cholecystectomy. It revealed a markedly enlarged left inferior parathyroid gland and diffusely enlarged and multinodular thyroid gland. Three other parathyroid glands were normal. An uneventful left inferior parathyroidectomy, left total and right subtotal thyroidectomy were performed. Laparoscopic cholecystectomy was also performed uneventfully. The final pathologic situation of the left inferior parathyroid was consistent with an adenoma **(Figure 1)**; the thyroid gland exhibited colloidal nodular goiter **(Figure 2).** The pathologic report of the gallbladder was consisted with well-differentiated adenocarcinoma of the gallbladder **(Figure 3)**, and the cancer was revealed at stage-II. Both extended cholecystectomy, and the dissection of the hepatoduodenal lymph node with laparotomy were performed during re-operation. The patient was discharged on the 9th postoperative day without any complications and external-beam radiation therapy was performed. One month after surgery the patient was without thyroid and parathyroid symptoms with normal laboratory values.

Discussion. Hypercalcemia occurs in up to 51% of patients with hyperthyroidism.[2] The mechanism by which thyrotoxicosis induces hypercalcemia has been discussed by various investigators. It is thought to be caused by activation of osteoblastic bone resorption.[1,2] Since hypercalcemia complicating thyrotoxicosis is rarely symptomatic, the presence of signs and symptoms of hypercalcemia, should alert the investigator to the

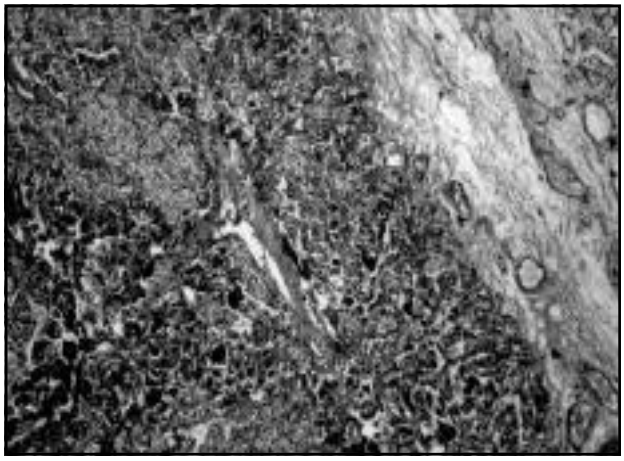

Figure 1 - Parathyroid adenoma (Hematoxylin and eosin x 40).

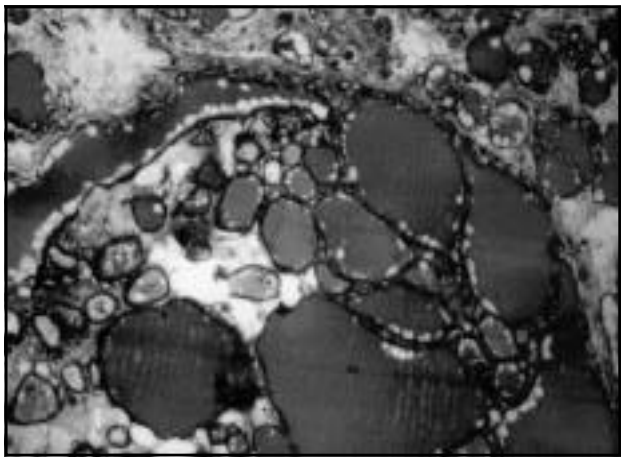

Figure 2 - Colloidal thyroid nodule (Hematoxylin and eosin x 40).

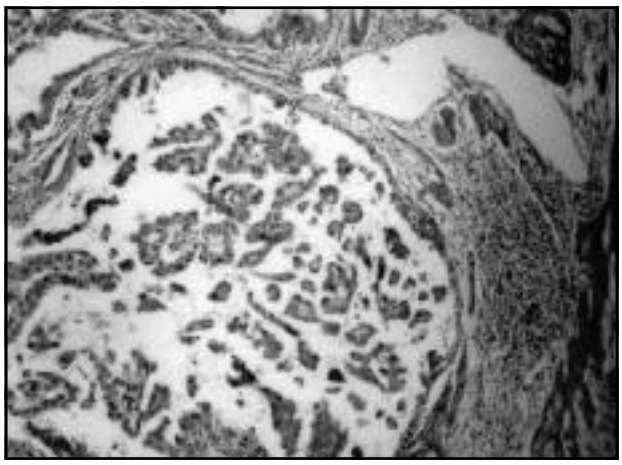

Figure 3 - Well differentiated adenocarcinoma of gallbladder (Hematoxylin and eosin x 40).

possibility of concomitant disease.[1] Due to the overt symptoms of hyperthyroidism often mask the usually vague symptoms of primary hyperparathyroidism, routine laboratory screening is important if the presence of coexistent disease is to be shown. Hypercalcemia in patient with hyperthyroidism should prompt measurement of parathormone levels.[4] In a small percentage of cases, the hypercalcemias are attributable to concomitant parathyroid disease. Bouillon et al[5] note that primary hyperparathyroidism probably accounts for hypercalcemia in more than 1% of patients with thyrotoxicosis. Should a patient with thyrotoxicosis continue to be hypercalcemic after achievement of an euthyroid state with antithyroid therapy, then the diagnosis of concurrent or latent primary hyperparathyroidism should be seriously considered, and appropriate measurement of serum parathormone levels should be obtained as the initial step in a search for the cause of hypercalcemia.[5] Direct measurement of parathyroid function by determination of serum parathyroid hormone levels is the most useful laboratory parameter in the differential diagnosis of hypercalcemia.[5] In this patient, severely elevated parathyroid hormone level was detected.

The relevance between hyperthyroidism and hyperparathyroidism is still unclear. Some believed that a relationship exists between both disorders.[5,6] The 2 organs are from the same origin, namely, branchial structures. Hence, the concomitance might occur as part of the syndrome of multiple endocrine adenomas resulting from the presence of the abnormal gene responsible for this syndrome. Furthermore, hyperparathyroidism might be produced by a long-standing effect of excess thyroid hormone on adrenergic receptors.[6] If this was the case, parathyroid hyperplasia should be almost universal in hyperthyroidism whereas in most cases, including this case described here of concomitant hyperparathyroidism and hyperthyroidism, the parathyroid has been adenomatous.[7]

Hypercalcemia coexisting gallbladder carcinoma has previously been observed in 2 cases in the literature.[3,8] Classically, 2 mechanisms have been proposed to explain the development of hypercalcemia in malignancy. The most common is metastatic bone involvement. In the absence of bony metastases, several circulating substances, other than parathormone have been described, which presumably alter metabolism resulting in calcium release.[9] It seems that one of the causes of hypercalcemia in gallbladder cancer is the ectopic production and secretion by the tumor of parathyroid hormone related proteins (PTHrP). Our case could not be placed in these categories as the patient had parathyroid adenoma and hyperthyroidism. Nevertheless, gallbladder cancer should be included in the growing list of tumors documented to secrete PTHrP.[3] Carcinoma of the gallbladder is associated with gallstones (90%), older age and female gender. The present patient was also female, older age and associated with gallstones. Adenocarcinomas represent 90% of gallbladder cancers. Squamous cell carcinomas, anaplastic carcinomas, adenosquamous carcinomas, and sarcomas comprise the remainder of malignant gallbladder tumors. In this patient, the postoperative histopathologic report of gallbladder was consistent with well-differentiated adenocarcinoma of the gallbladder **(Figure 3),** and the gallbladder cancer was diagnosed by histopathology specimen examination.

Only rarely hyperthyroidism, primary hyperparathyroidism and cancer of the gallbladder occur concurrently. Only one case has been reported previously as named hypercalcemia syndrome.[10] The present case is the second in the English literature.

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