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DIFFICULT CASES IN ENDOCRINOLOGY

Large Goiter and Multiple Rib Tumors

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We report an interesting case of a 47-yr-old who had a large goiter and multiple rib tumors. The patient was initially suspected of having thyroid cancer, which had metastasized on the ribs, based on imaging studies. However, laboratory tests revealed a high level of ionized calcium and parathyroid hormone (PTH). The large goiter was diagnosed as having parathyroid tumors owing to the high level of PTH in the tissue fluid. The biopsy specimen from a rib tumor was diagnosed as containing brown tumors associated with primary hyperparathyroidism (PHP). The patient also had prolactinoma and pancreatic gastrinoma. Her daughter had both prolactinoma and PHP, and her brother and her father had PHP. Thus, the patient was diagnosed as having multiple endocrine neoplasia type 1.

Key Words: Goiter; rib; brown tumor; hyperparathyroidism; parathyroid hormone; multiple endocrine neoplasia type 1.

Introduction

Brown tumors, focal bone lesions in hyperparathyroidism, were first described in 1891 by von Recklinghausen as osteitis fibrosa cystica. The brown tumors, so-called because of the reddish-brown color of their tissue, rarely occur with both primary and secondary hyperparathyroidism *(1–4)*. Histologically, brown tumors consist of multinucleated giant cells admixed with mononuclear stromal cells and areas of hemorrhage. On purely histological grounds, brown tumors resemble giant cell tumors and other giant cell bone lesions, such as giant cell reparative granuloma. The giant cells have certain morphological similarities to osteoclasts. Brown tumors in hyperparathyroidism are not genuine tumors, but represent a special type of benign reactive cellular process. Parathyroid hormone (PTH) may play an important role in the pathogenesis of brown tumors, as it is well known that high PTH secretion in hyperparathyroidism is associated with an increased number of osteoclasts *(5–8)*.

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant disorder characterized by primary hyperparathyroidism (PHP), tumors of the anterior pituitary, and gastroenteropancreatic endocrine tissues *(9)*. Other less common lesions are carcinoid tumors, adrenal tumors, thyroid diseases, and lipomas. PHP is usually expressed at an early age and has a high penetration in MEN1. MEN1-related PHP is often asymptomatic and most parathyroid tumors are tiny and not palpable. The bone change most frequently found in MEN1 is osteopenia as well as in sporadic PHP. To our knowledge, the presence of brown tumors has not been reported in MEN1 to date, because fully developed changes in brown tumors are seen only in late and severe cases of PHP. In the present articles, we describe a patient with a large goiter consisting of parathyroid tumors and multiple brown tumors associated with MEN1.

Case Report

A 47-yr-old woman was referred to our hospital because of a large goiter and multiple rib tumors. In the past, she had undergone minor surgery to remove an SC mass on the jaw. Physical examination revealed a large goiter in her neck. Laboratory tests showed high levels of alkaline phosphate (682 U/L; normal:100–280) and ionized calcium (3.55 meq/dL; normal:2.24–2.58). Chest X-rays showed multiple tumors in the chest wall (Fig. 1A) and a chest computed tomography (CT) scan disclosed a tumor in the left rib (Fig. 1B). A bone scan showed increased uptake in multiple areas of her ribs (Fig. 1C). A CT scan of her neck revealed solid tumors in the right lobe and a cystic mass in the left lobe of the thyroid gland (Fig. 2A). Thyroid cancer and multiple bone metastasis were initially suspected. However, laboratory tests revealed an extremely high level of PTH (1000 pg/mL; normal:15.0–50.0 pg/mL). Aspiration biopsy cytology of the goiter found no malignancy, and PTH levels were very high in the tissue fluid from the solid tumors. The large goiter was diagnosed as having parathyroid tumors. The biopsy specimen from a rib lesion

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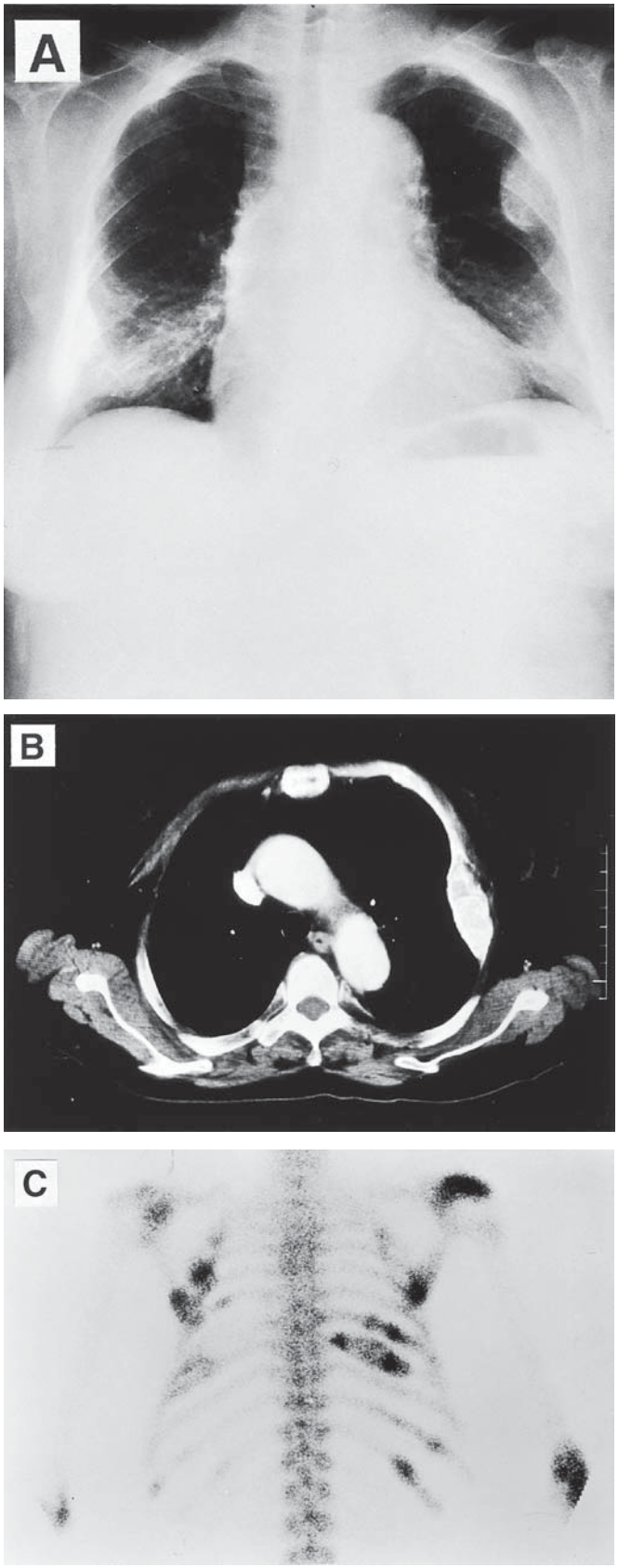

Fig. 1. (A) Chest radiograph showing multiple tumor-like shadows in the chest wall. **(B)** Computed tomographic scan of the chest demonstrating an intramedullary mass in the left rib. **(C)** Bone scan demonstrating increased uptake in multiple areas of the ribs.

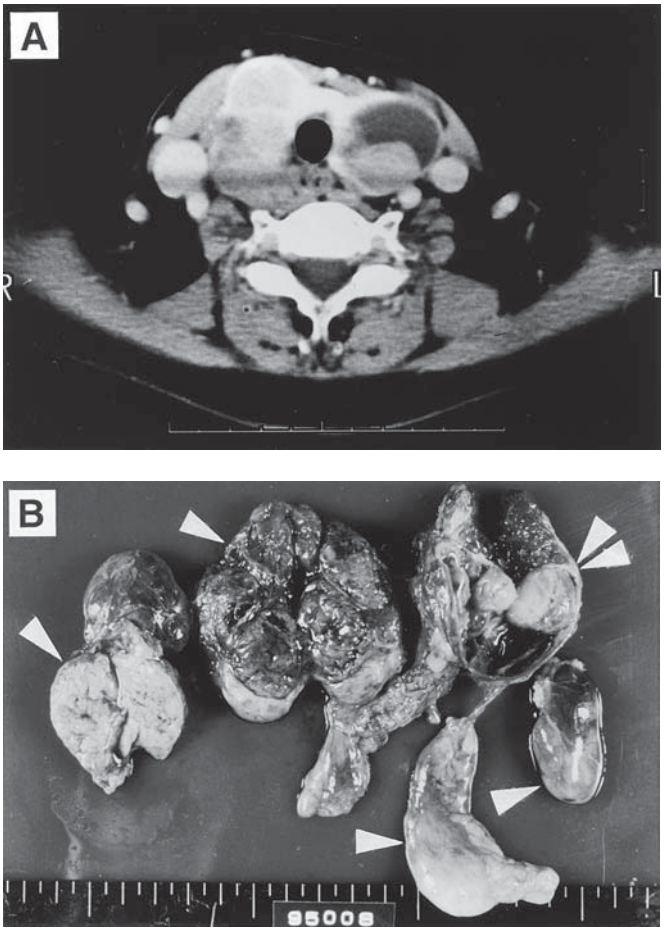

Fig. 2. (A) CT scan of the neck demonstrating solid tumors in the right lobe and a cystic mass in the left lobe of the thyroid. **(B)** Cross-section of the resected large goiter showing markedly enlarged parathyroid glands (two sectioned tumors from the left and two unsectioned tumors from the right) and the thyroid gland with a cystic nodule (upper right). A single arrow indicates parathyroid tumor and double arrows indicate thyroid tumor.

had a solid and brownish appearance. Histologically, the lesion had solid proliferation multinucleated giant cells of an osteoclastic type and fibrohistiocytic cells with fibrosis (Fig. 3). No cellular atypism was observed in either cell type. Mitotic figures were not observed in the specimen. Lymphoid cell infiltration and hemosiderin deposition were noted in the spindle-cell areas. The pathological findings were compatible with brown tumors associated with hyperparathyroidism. The patients hypercalcemia became worse and did not respond to conservative treatment. The patient therefore underwent total parathyroidectomy with autoplantation. All parathyroid glands were markedly enlarged and a cystic nodule was noted in the left lobe of the thyroid (Fig. 2B). The pathological diagnosis was hyperplasia of four parathyroid glands and adenomatous goiter. After the surgery, serum calcium and PTH returned to normal levels.

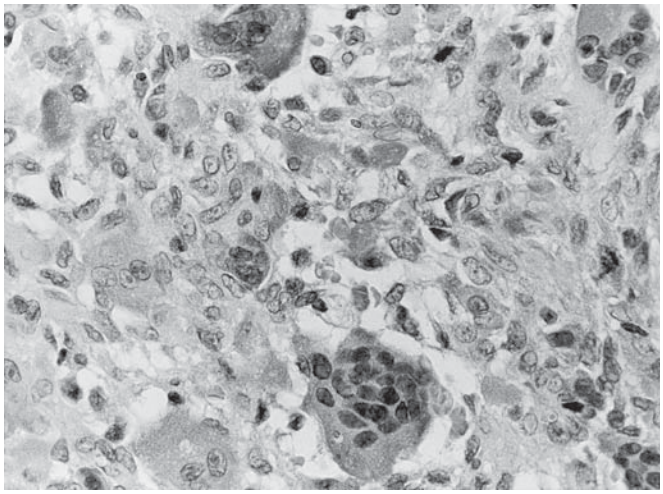

Fig. 3. Photomicrograph of a biopsy specimen from the patient's rib tumor, demonstrating a composition of multinucleated giant cells of an osteoclastic type and spindle-shaped cells, typical of brown tumors in hyperparathyroidism.

Further tests showed hyperprolactinemia (prolactin [PRL] 300.0 ng/mL; normal:1.4–14.6) and hypergastrinemia (gastrin, 310.0 ng/mL; normal:0.0–200.0 pg/mL). Brain magnetic resonance imaging revealed a pituitary tumor. Serum PRL levels decreased with bromocriptine (BRC). Abdominal CT revealed a pancreatic tumor. Although she was diagnosed as having pancreatic gastrinoma, surgical treatment was not chosen because of chronic renal failure related to hypercalcemia. Upper gastrointestinal (GI) endoscopy revealed gastric and duodenal polyposis, and gastric histology showed a GI carcinoid. The patient's brother (45-yr-old) visited our hospital for family screening and was diagnosed as having PHP. His PRL and gastrin levels were normal. He refused to undergo surgery for PHP. The proband's younger daughter (24-yr-old) also visited our hospital for family screening and was diagnosed as having PHP and prolactinoma (PRL, 110.0 ng/mL). She was treated with BRC and her serum PRL levels decreased to normal. The proband's father (88-yr-old) was diagnosed as having PHP when he visited a local hospital. Genomic DNA was extracted from the peripheral blood of the proband for genetic analysis on a germline mutation of the *MEN1* gene. No mutation was detected in the coding region of the *MEN1* gene.

Discussion

The patient had a large goiter that showed as a heterogeneous pattern in radiographic examinations. In general, most parathyroid tumors are tiny and not palpable. However, in the case of marked progression, a mistaken diagnosis of goiter can be made. There were no differences between goiter of thyroid and parathyroid origin under radiographic examination, except for parathyroid scanning (sestamibi scanning). In addition, the multiple rib tumors confused our diagnosis. Our first impression was therefore thyroid cancer and bone metastasis. Biochemical findings such as high calcium and PTH levels suggested that PHP may be present in this patient. Measurement of PTH in the tissue fluid from the large goiter also suggested that parathyroid tumors were included in the goiter. The operative findings revealed that all the parathyroid glands were markedly enlarged, and the pathological diagnosis was hyperplasia of four parathyroid glands and adenomatous goiter. Although this case was uncommon, parathyroid tumors must not be overlooked in goiter cases.

The bone lesions associated with PHP are diffuse osteopenia *(10)*. Very rarely, a tumor-like lesion occurs known as "brown tumor" because of its color *(1–4)*. The radiographic changes may be confused with that of a tumor, either primary or metastatic *(11)*. On microscopic examination, the characteristic finding is increased osteoclastic activity associated with multinuclear giant cells *(12)*. A differential diagnosis with giant cell tumor is very difficult because of its histological similarity *(13)*. Only clinical findings make a differential diagnosis possible. In our case, the pathological diagnosis was a giant cell tumor in the biopsy specimen from the rib tumor. The diagnosis of a brown tumor was made on the basis of the clinical finding that PHP was present in this patient. Common sites for brown tumors include the metacarpals, phalanges, jaw, rib, pelvis, and femur, but they may be found in any bone and cause various clinical symptoms *(1–4)*. In our case, the patient had a past history of minor surgery at a local hospital to remove a SC mass on the jaw. This may have been the first clinical manifestation of the disease, although the histology of that mass is unknown.

Brown tumors occur in both primary and secondary hyperparathyroidism, but the incidence is low (2–3%) *(1–4)*. High PTH secretion in hyperparathyroidism appears to play an important role in the pathogenesis of brown tumors. It is known that injecting PTH into experimental animals and adding PTH to bone cell cultures increases the number of osteoclasts and osteoclast precursors or preosteoclasts *(5–8)*. Fully developed changes in brown tumors may only be seen in late and severe cases of hyperparathyroidism. This is why the incidence of brown tumors is low in primary and secondary hyperparathyroidism. In our case, the PTH levels were extremely high (more than 20 times the normal value), and the parathyroid tumors were very large. It is likely that persistent high levels of PTH secretion were directly involved in the formation of brown tumors in our case. Brown tumors are known to have a good prognosis because no malignant degeneration occurs and regression or complete disappearance following parathyroidectomy is common *(14,15)*. Similarly, in our case, the rib tumors showed marked regression after parathyroidectomy.

Familial MEN1 is an autosomal dominant disorder, the classical spectrum of which includes PHP and tumors of the anterior pituitary and endocrine pancreas *(9)*. Less frequently observed associations include foregut carcinoids, lipoma, thyroid diseases, and adrenal tumors. The *MEN1*

gene has recently been cloned as a responsible gene for *MEN1*, and its germline mutations were identified in a number of familial *MEN1* patients *(16–24)*. On the other hand, mutation-negative cases have been reported in some *MEN1* familes *(16,20,21)*. In such cases, it is possible that mutations in the promoter and 5' or 3' untranslated region of the *MEN1* gene are present. In our case, germline mutation of the *MEN1* gene was not detected. Nevertheless, the diagnosis of familial *MEN1* was confirmed, because four family members, of whom two (proband and her daughter) had at least two major *MEN1* lesions, had PHP in the present case. To our knowledge, this is the first report of brown tumors in *MEN1*. PHP is usually expressed at an early age and has a high penetration in *MEN1*. *MEN1*-related PHP is often asymptomatic, and hypersecretion of PTH is usually modest in most cases *(10)*. However, in more severe cases, brown tumors may occur, making misdiagnosis possible. Because *MEN1* has recently been highlighted because of the discovery of the *MEN1* gene, brown tumors as PHP-related bone lesions should not be overlooked.

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