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Parathyromatosis after parathyroidectomy because of primary hyperparathyroidism: A case report

Case Report

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Abstract: Introduction: Differential diagnosis and treatment of recurrent hyperparathyroidism are complicated. Materials and methods: A 62-year-old female patient was reoperated for primary hyperparathyroidism after suspected relapse of missing parathyroid adenoma. Biochemical blood and urine analyses, neck sonography, neck and chest computed tomography (CT), magnetic resonance tomography (MRT), 99mTc – MIBI scintigraphy, and bilateral jugular venous sampling were performed. After reoperation, the extirpated tissues were examined histologically. Results: Hyperparathormonemia (PTH, 159.4 pg/ml), hypercalcemia (Ca^{++}, 1.38 mmol/l) was statei. Neck and chest CT and MRT no pathological findings were found. Parathyroid glands 99mTc - MIBI scintigraphy showed more intense accumulation of tracers in the left thyroid gland lobe and nearby. After blood sampling the bilateral jugular venous for PTH levels, the left hemithyroidectomy with surrounding fat tissues and lymph nodes was performed because the cause of recurrent hyperparathyroidism during the operation was not obvious. The histological findings indicated parathyromatosis. Conclusion: Bilateral jugular venous sampling for PTH levels influence the choice of reoperation side. If the cause of recurrent hyperparathyroidism during the operation is not discernable, ipsilateral lobisthmectomy and complete ipsilateral central neck dissection should be performed.

Keywords: *Parathyroid carcinoma • Primary hyperparathyrosis • Recurrent hyperparathyroidism • Parathyromatosis Bilateral jugular venous sampling*

1. Introduction

Both recurrent and persistent hyperparathyroidism (HPT) are uncommon but potentially difficult, problems following initial cervical exploration for primary HPT. Persistent HPT is hypercalcemia occurring within six months of surgical intervention for primary HPT and is predominately the result of a missed parathyroid adenoma. Recurrent HPT is defined as hypercalcemia recurring after at least a six-month period of normocalcemia following surgical intervention for primary HPT. The most common causes of recurrent HPT are, in order of frequency: 1) a missed parathyroid adenoma; 2) insufficient removal of hyperplastic parathyroid tissue; 3) parathyroid carcinoma; and 4) parathyromatosis [1].

Parathyromatosis, a rare parathyroid disorder, is one possible cause of recurrent or persistent hyperparathyroidism. There are three theories regarding the origin of parathyromatosis: 1) it is a low-grade parathyroid malignancy; 2) it results from seeding after the fracture of the parathyroid gland capsule during surgical removal of a parathyroid neoplasm; or 3) it is an overgrowth of embryologic rests of parathyroid tissue [2]. Diagnostic of parathyromatosis is always complicated; final differentiation from carcinoma is possible only after histopathology examination.

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2. Materials and methods

We examined a 62-year-old female patient with recurrent hypercalcemia who 9 years previously had had a surgical intervention for primary hyperparathyroidism (HPT).

Biochemical blood and urine tests: Ionized calcium (Ca^{++}) and serum calcium (Ca), phosphorus (P), urea, creatine concentration in blood, calcium and phosphorus concentration in a 24-hour urine sample, as well as parathyroid hormone (PTH) concentration in the blood, were measured.

Instrumental investigations: For purposes of diagnosis, we performed ultrasonography of the thyroid gland and parathyroid glands; x-ray of the hand bones; bone densitometry measurements; neck and chest CTs; magnetic resonance tomography (MRT); and parathyroid gland 99mTc - MIBI scintigraphy (Figure 1). The patient was operated following the diagnosis of recurrent hypercalcemia and hyperparathormonemia on August 22, 2010.

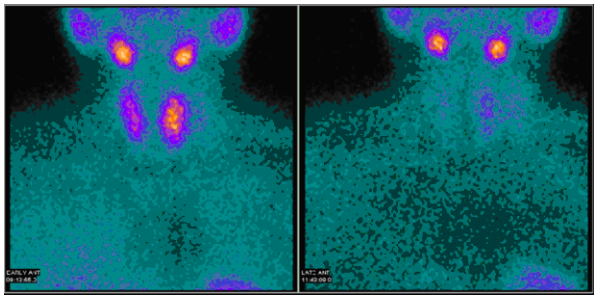

Figure 1. Parathyroid 99mTc sestamibi scan (MIBI scintigraphy) - increased accumulation of tracers in the middle and bottom of the left thyroid thirds projection.

Intraoperative findings: Bilateral jugular venous sampling for PTH levels was done before the incision. The excision of scarified tissue, left thyroid gland and six neck region lymph nodes was performed. Ten minutes after the PTH concentration in v. jugularis int. sin. blood was measured again. The removed tissues were examined histologically. After the operation, the concentrations of ionized calcium, serum calcium and PTH in blood were measured every two months.

3. Results

3.1 Clinical presentation

In March 21, 2001, a female patient age 62 years was operated for a mandibular tumor. Histological findings showed a giant cell granuloma. In July 5, 2001, osteosynthesis was performed because of a pathological right tibial bone fracture. During the operation, a thinned and spongy cortical bone layer (Figure 2) was

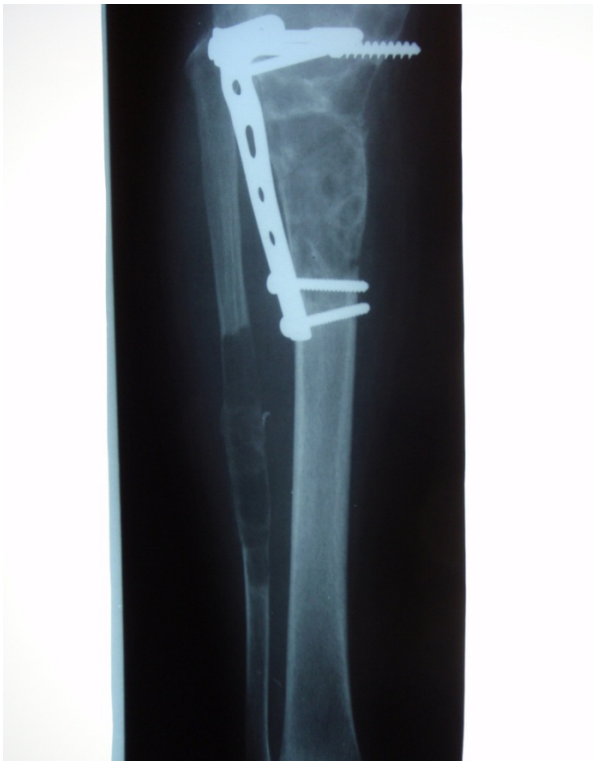

Figure 2. Pathological bone fracture due to tibia and fibula cystic fibrosis.

detected. The histological investigation of the bone biopsy led us to suspect metastasis of kidney light-cell carcinoma. This diagnosis was not confirmed by successive examinations at National Center of Pathology (NCP). X-RAYs of spine, skull and pelvis bones showed no changes. The results of performed biochemical blood tests were as follows (normal ranges in parentheses): ionized Ca^{++}, 1.85 mmol/L (1.0-1.37); serum Ca, 4.0 mmol/L (2.15-2.5); PTH, 889.4 pg/ml (15-65); P, 0.81 mmol/L (0.87-1.45); urea, 6.4 mmol/L (2.5 – 7.5); creatine, 73 µmol/L (53-97); Ca concentration in 24-hour urine sample, 7.6 mmol/24h (2.5-7.5); P concentration in 24-hour urine sample, 20.9 mmol/24h (12.9-42). The results of ultrasonography of the thyroid and parathyroid gland found the size of right thyroid lobe to be 18.5x20.9x46 mm; it detected an izoechogenious, a low-vasculated node of 5 mm diameter in the medial part. The size of left lobe was 17.4x20x44 mm; in its frontal medial part, a low-vasculated node of 4.7 mm diameter was detected. Near the left lobe lower pole of the parathyroid gland, a 30x15x21 mm hypoechogenious hypervascular node was detected. Primary hyperparathyroidism was identified.

The patient was operated August 22, 2001. Conventional parathyroid glands revision was made and an adenoma of 30 mm diameter was removed from underneath the left side of the parathyroid. The other three

parathyroid glands showed no changes. Histological findings of the parathyroid adenoma indicated a parathyroid mixed-cell solid adenoma. We noted that the investigative material material was fragmentated. Histology showed lymphoplasmic infiltration with lymphoid follicles in the left thyroid gland lobe. Parathyroid gland fragments were found near the thyroid gland in fatty tissues between the striated muscles. Single parathyroid gland tissue fragments were found between the thyroid lobules. The parathyroid gland tissue was mostly hyperplastic, formed from primary or oncocyte cell nests, trabecules, and rare tubules. The structure of single fragments was normal. There was no mitotic figures or intravascular spreading in parathyroid gland tissue. An imunohistochemical test described Ki67 proliferative activity at <1% in parathyroid gland tissue. Hyperplasia was identified in all 12 lymph nodes follicules analyzed. These histological findings confirmed parathyromatosis, focal lymphoid thyroiditis, and reactive lymphadenopathy (Figure 3A, 3B, 3C, respectively).

3.4 Postoperative follow-up

During the first 24 hours after operation, the PTH concentration in blood was 8.74 pmol/L, Ca^{++} was 1.27 mmol/L. The patient was repeatedly examined after 2 months, during which time blood sample tests showed Ca^{++} at 1.18 mmol/L and a PTH concentration in blood, 14.3 pmol/L (slight hyperparathormonemia and normocalcemia).

4. Discussion

In patients with persistent (<6 months from initial exploration) or recurrent disease (>6 months from initial exploration) after unsuccessful parathyroidectomy, the diagnosis of primary hyperparathyroidism should be reconfirmed, and the surgical indications should be re-evaluated. The causes of recurrent of primary hyperparathyroidism may be parathyroid carcinoma, parathyroid hyperplasia or supernomeroty parathyroid gland adenoma, and very rarely, parathyromatosis. There are three theories regarding the origin of parathyromatosis: 1) it is a low-grade parathyroid malignancy; 2) it results from seeding after the fracture of the parathyroid gland kapsule during surgical removal of a parathyroid neoplasm; or 3) it is an overgrowth of embryologic remains of parathyroid tissue [3-5].

Parathyroid carcinoma is a rare cause of hyperparathyroidism. In one review of 4239 patients with hyperparathyroidism, 2.1% had functioning parathyroid carcinomas [6]. A systematic literature review of 22,225 cases of primary hyperparathyroidism reported between

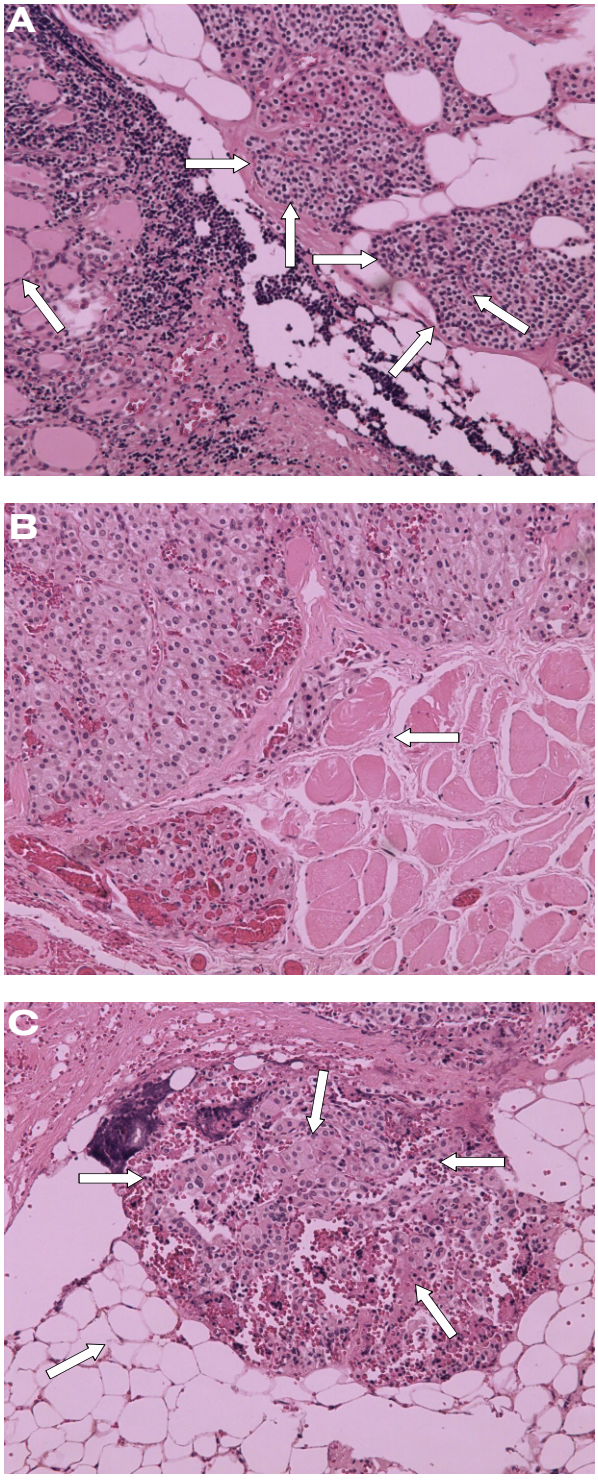

Figure 3. A Parathyroid gland cells (arrows) in surrounding tissues, thyroid gland (arrow).
B Parathyroid gland cells (arrows) in neck muscles (arrow).
C Parathyroid gland cells (arrows) in fatty tissues (arrow).

1995 and 2003 revealed that parathyroid carcinoma accounted for 0.74% of the cases [16]. It is important to note that very few patients with parathyroid carcinoma will be asymptomatic, while most patients with primary hyperparathyroidism are now diagnosed quite early and will not have the "classic" symptoms of advanced hypercalcemia [7]. A negative 99mTc sestamibi scan does not preclude the diagnosis of primary hyperparathyroidism. Sestamibi scanning is often unrevealing in patients with parathyroid hyperplasia, multiple parathyroid adenomas, and in those with coexisting thyroid disease, CT or MRI can be useful for identifying a recurrent tumor in the neck or mediastinum [3,8].

Controversy continues regarding the criteria for classification of parathyroid tissue as benign or malignant. The characteristic histopathology of parathyroid carcinoma consists of uniform sheets of cells arranged in a lobular pattern separated by dense fibrous trabeculae, mitotic figures in the tumor cells, and capsular and blood vessel invasion. However, these features have been noted occasionally in parathyroid adenomas. Because of the lack of reliable microscopic features differentiating benign and malignant parathyroid tumors, frozen section analysis has been found to be minimally useful for distinguishing between the two entities [2]. Thus, because of the nonspecificity of these histological features, the two criteria upon which a definitive diagnosis of parathyroid carcinomas can be made are local invasion of contiguous structures, or lymph node or distant metastases. When the surgeon observes a white, firm, fibrous, hypervascular, and/or adherent, enlarged parathyroid gland, this is a parathyroid carcinoma [9]. While benign parathyroid tumors are typically soft, beefy red-brown in color, well encapsulated, and minimally adherent to surrounding structures, parathyroid cancers are frequently hard, whitish-gray, poorly encapsulated, and stuck to or invading adjacent structures [10]. In our patient, we did not find local invasion of contiguous structures at the time of the primary and secondery operations. Histopathologic examination didn't describe any mitotic activation. In the iterative operation, we proceeded without strict localization of the hyperfunction focus. The success rate of reoperative surgery without preoperative localization is only 60 percent [11]. Selective venous catheterization is invasive, and is utilized only if noninvasive imaging is inconclusive for identifying recurrent parathyroid carcinoma [12].

A unilateral elevation of PTH concentration in jugular venous sampling raises suspicions of a hyperfunctioning gland on that side. Bilateral PTH levels that are equivocal may be suggestive of hyperfunctioning parathyroid disease in the mediastinum [13]. In the left side of the neck, in which jugular venous sampling PTH levels were higher than normal and no supernumerary parathyroid gland was found, thus raising the possibility of an undiagnosed parathyroid gland cancer relapse after first operation; the left thyroid gland lobe with surrounding fatty tissues and with lymph nodes was removed. When parathyroid carcinoma is suspected from preoperative clinical or biochemical features or from intraoperative findings, the recommended operation is *en bloc* resection of the parathyroid tumor with complete ipsilateral thyroid lobectomy and isthmusectomy; in addition, a complete ipsilateral central neck dissection from the upper mediastinum to the larynx should be performed with the goal of removing all potential tumor-bearing tissues on the tracheoesophageal groove [14]. From results of the histological analysis, parathyromatosis was diagnosed. Despite the normocalcemia after 2 months postoperative, disease relapse may be expected. Careful dissection, avoidance of capsular fracture, and preservation of structures such as the recurrent laryngeal nerve are the keys to successful operation. Intraoperative parathyroid hormone measurement can assist in determining whether resection of hyperfunctioning tissue is complete, but is not likely to predict a long-term cure because this condition frequently recurs. Parathyromatosis is defined as the overgrowth of multiple small hyperfunctioning nodules of parathyroid tissue. However, the nodules of parathyromatosis may be too small or too well incorporated into the surrounding tissues to be detected by ultrasound. Sestamibi scanning will demonstrate abnormal uptake in hyperfunctioning parathyroid tissue, but as with ultrasound, the small size of the nodules seen in parathyromatosis may render them undetectable. However, when positive, preoperative imaging studies can help to guide operative planning for surgical treatment of this condition. The aim of surgical therapy is to remove all hyperfunctioning parathyroid tissue; this may be especially difficult in the reoperative setting when the tumor nodules could have been incorporated into scar tissue or surrounding structures and *en bloc* resection is required [7]. Repeated surgery often is necessary, but generally is unsuccessful [15].

5. Conclusion

Bilateral jugular venous sampling for PTH levels should be performed at the time of reexploration. A unilateral elevation of PTH concentration in jugular venous sampling may indicate hyperfunctioning tissue on that side and can help to guide operative planning for surgical treatment of recurrent hyperpathyroidism. If the cause of recurent hyperparathyroidism at the time of operation is not discovered, ipsilateral thyroid lobe-isthmusectomy, a complete ipsilateral central neck dissection from the upper mediastinum to the larynx, should be performed.

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