

Recurrent Renal Hyperparathyroidism due to A Subcutaneous Parathyroid Lesion: Report of A Case

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Abstract

Failure of a primary operation to control renal hyperparathyroidism is usually due to inadequate resection of hyperplastic tissue or previous undetected ectopic parathyroid gland. We describe a patient with recurrent renal hyperparathyroidism, who presented with a subcutaneous neck nodule. A 49-year-old woman had a history of systemic lupus erythematosus, papillary thyroid carcinoma, and end-stage renal disease with renal hyperparathyroidism, for which she subsequently received percutaneous ethanol infusion therapy to bilateral hyperplastic parathyroid lesions, a subtotal thyroidectomy and parathyroidectomy. Despite aggressive treatment with phosphate binders and vitamin D3 supplements, the levels of intact parathyroid hormone, calcium and phosphorus kept elevating during the follow-up period. Thyroid sonography revealed neither thyroid nor parathyroid tissue in the thyroid bed. Physical examination showed a palpable subcutaneous nodule at the right neck, which was hyperechoic and heterogeneous on soft tissue sonography. Technetium (^{99m}Tc) sestamibi scan showed a focal hot spot at the same site. She received complete surgical resection of the neck nodule. Histopathological analysis showed parathyroid hyperplasia. Two years after removal of the nodule, the patient was well. In conclusion, to avoid recurrent hyperparathyroidism, a meticulous surgical technique is vital to successful parathyroid surgery. On the other hand, alcohol injection is not recommended for renal hyperparathyroidism if the patient can tolerate operation, because alcohol injection can cause fibrosis which makes further operation difficult in processing. We should also keep subcutaneous parathyroid lesions in mind when we perform neck re-exploration for recurrent hyperparathyroidism. (J Intern Med Taiwan 2011; 22: 206-211)

Key words: Hyperparathyroidism; Recurrence; Subcutaneous tissue

Introduction

The number of patients with long-term hemodialysis increases gradually, and renal hyperparathyroidism (HPT) has become widely recognized as a complication of chronic renal failure. In patients with chronic renal failure, parathyroid cells are stimulated by vitamin D deficiency, hyperphosphatemia, and hypocalcemia¹. With time, progressive alteration of calcium and vitamin D receptors of the parathyroid cell leads to inappropriate and uncontrolled hypersecretion of parathyroid hormone, causing renal hyperparathyroidism (HPT)²⁻³. Despite advances in medical prophylaxis and treatment, many patients with renal HPT are refractory to medical treatment, and parathyroidectomy is required. However, parathyroidectomy is not always successful, and HPT relapses frequently. Preoperative diagnosis to identify supernumerary or residual glands in ectopic sites is helpful for preventing persistent/recurrent HPT, but it is difficult to identify ectopic glands of less than 500 mg by any preoperative imaging procedure⁴. The parathyroid glands may be located anywhere near or even within the thyroid or thymus. Other locations of supernumerary parathyroid glands, including the external aspect of prethyroidal muscles, the carotid sheath, and the inferior and superior thyroid poles have been described and may give rise to persistent or recurrent HPT⁵. However, it is rare that recurrent renal HPT is due to subcutaneous parathyroid lesions. Here we describe a patient with recurrent renal HPT, who presented with a subcutaneous neck nodule.

Case report

A 49-year-old woman was admitted to the hospital because of recurrent renal hyperparathyroidism.

The patient had a history of systemic lupus erythematosus and end-stage renal disease with

renal HPT. Two consecutive attempts to control HPT by using percutaneous ethanol infusion therapy to bilateral hyperplastic parathyroid lesions failed to significantly decrease intact parathyroid hormone (iPTH) level. Eventually, she underwent cervical exploration at the age of 35. The right superior and right inferior parathyroid glands were removed. A subtotal thyroidectomy was also performed because the parathyroid lesions were densely adhesive to the thyroid and multiple small thyroid nodules were noted. No mention of spillage of parathyroid tissue during removal was made in the operative notes. Postoperatively, the calcium decreased from 2.59 mmol/L to 2.11 mmol/L and iPTH level decreased from 1561 pg/mL to 60.6 pg/mL. Pathology revealed papillary thyroid carcinoma in bilateral thyroid gland and chief cell hyperplasia in parathyroid lesions. After operation, she had regular follow-up in our clinics.

She had been admitted at the age of 48 because of recurrent HPT, with a high level of calcium (2.73 mmol/L; normal range, 2.02 to 2.60), markedly increased levels of alkaline phosphatase and iPTH (1572 pg/mL; normal range, 12 to 72). Ultrasonography of the neck revealed a 2.5 × 1.6 × 1.6 cm remnant parathyroid tissue on the left inferior thyroid lobe. Technetium (^{99m}Tc) sestamibi scan showed a focal hot spot in the lower pole of the left thyroid lobe. Cervical exploration revealed a cystic parathyroid adenoma involving the inferior aspect of the left thyroid lobe. Marked hemorrhagic degeneration was present. No other parathyroid tissue was identified. The cystic adenoma was removed along with the left thyroid tissue because of inextricable adherence to the surrounding tissues. According to the operative note, the cystic lesion was ruptured with spillage of the cystic contents during removal. Microscopic examination demonstrated that the tumor, 2.3 cm in diameter, was a chief cell hyperplasia of the parathyroid gland. Postoperatively, the calcium decreased from 2.73 mmol/L to 2.3 mmol/L

L and iPTH level decreased from 1572 pg/mL to 295 pg/mL.

The patient was well until 6 months after second operation, when the iPTH, calcium and phosphorus levels elevated gradually despite aggressive treatment with phosphate binders and vitamin D3 supplements. No goiter was palpable on physical examination. Thyroid sonography revealed neither thyroid nor parathyroid tissue in the thyroid bed. Eight months after second operation, she had paresthesia of both hands. The calcium level was 2.91 mmol/L, and phosphorus level of 6.4 mg/dL with an iPTH level of 577 pg/mL. Further physical examination showed a palpable, movable, soft, and non-tender subcutaneous nodule at the right lateral

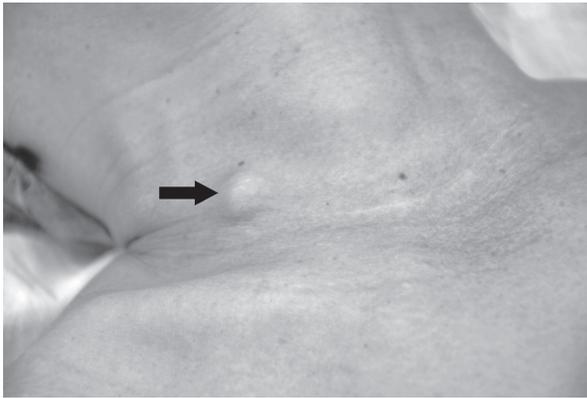


Figure 1. A small, movable, soft, and non-tender nodule is noted at the lateral side of the right neck (arrow).

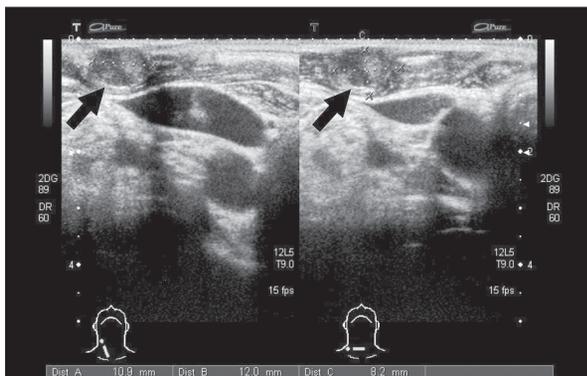


Figure 2. Neck ultrasonography. One $1.09 \times 1.20 \times 0.82$ cm isolated hyperechoic lesion (arrows) is seen in the subcutaneous plane of the right neck, but with no other visible thyroid or parathyroid tissue in the thyroid bed. (Left panel: oblique view. Right panel: transverse view).

neck (Fig. 1, arrow), which was heterogeneous and hyperechoic on soft tissue sonography (Fig. 2, arrow). Actually, this nodule had been noted since 6 months after second operation and was diagnosed as lipoma initially, based on the clinical judgment. Technetium (^{99m}Tc) sestamibi scan showed an area of intense delayed tracer activity at the right lateral neck and no definite tracer accumulation at the thyroid bed (Fig. 3). To resolve the dilemma of the palpable neck nodule being of soft tissue origin or a parathyroid neoplasm, fine needle aspiration cytology (FNAC) of the nodule was performed. Smears obtained were moderately cellular, with clusters of mildly anisomorphic cells in the absence

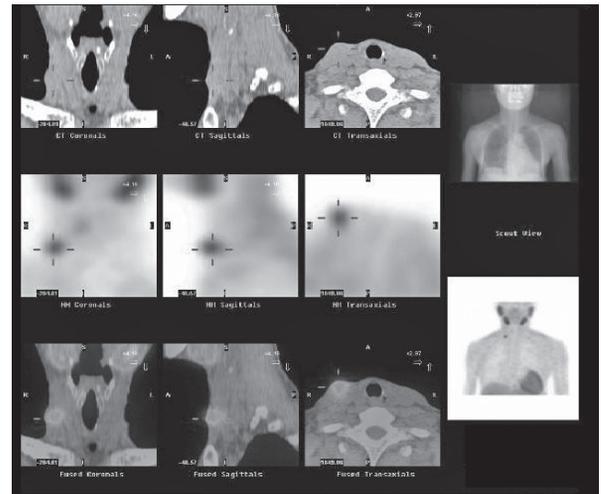


Figure 3. Technetium (^{99m}Tc) sestamibi scan. A focal hot spot is seen at the lateral side of the right neck.

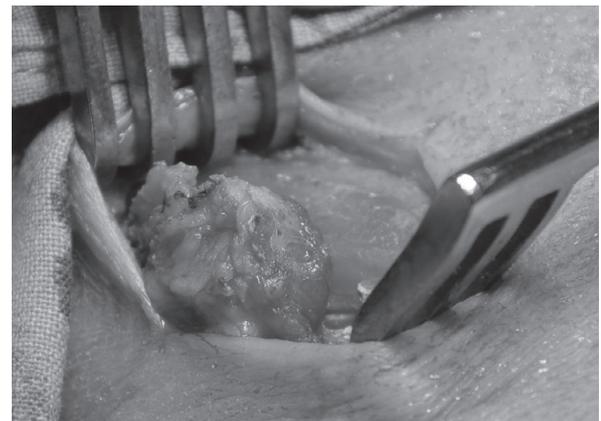


Figure 4. An intraoperative photograph taken from the right side of the neck. A parathyroid gland is being extracted from the subcutaneous plane.

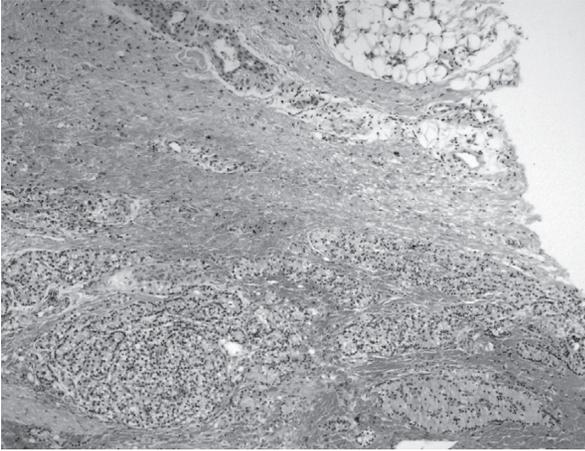


Figure 5. Multiple foci of hyperplastic parathyroid tissue infiltrating the fibrous tissue. (H & E, original magnification $\times 40$).

of colloid and were reported as consistent with parathyroid lesion. At cervical exploration, a $1.0 \times 1.0 \times 1.0$ cm round nodule densely adherent to the subcutaneous tissue was found. She received complete surgical resection of the neck nodule (Fig. 4). Pathology showed variably sized nodules of hyperplastic parathyroid tissue with an ill-defined border on the fibrotic tissue (Fig. 5). Mixed chief cells, water clear cells and oxyphil cells with a solid and trabecular growth pattern were noted in the nodules. The day after the operation, the calcium decreased to 2.3 mmol/L and iPTH level decreased to 58 pg/mL. In the 2-years follow-up after excision of the nodule, the patient was well under the treatment with phosphate binders and vitamin D3 supplements with no clinical, biochemical or investigative suspicion of recurrent HPT.

Discussion

A successful initial parathyroidectomy is very important to avoid uncontrolled persistent and/or recurrent HPT⁶. The four most common causes, either alone or in combination, of persistent or recurrent HPT are inadequate resection of hyperplastic tissue, failure to find ectopic or supernumerary parathyroid glands, multiglandular disease, and parathyroid carcinoma⁷. Failed neck explo-

ration for HPT is almost always associated with persistent rather than recurrent hypercalcemia, and the problem is almost always evident within the first postoperative week. Although the return of serum iPTH level to normal after successful parathyroidectomy may be delayed in cases of renal insufficiency⁸, the iPTH level of our case did not drop significantly after second parathyroidectomy at the age of 48, probably due to parathyroid tissue remaining in the surrounding muscular or fat tissue, which was left at the first operation due to fibrosis after alcohol injection and complete resection was impossible, and finally became obvious as subcutaneous nodule. This is also supported by the pathology which showed variably sized nodules of hyperplastic parathyroid tissue with an ill-defined border on the fibrotic tissue.

In the absence of definitive criteria to identify patients at risk of recurrence, some studies demonstrated that some morphologic aspects (primarily diffuse vs. nodular enlargement, but also proliferative cellular activity) can be used to distinguish patients at increased risk. The nodular form, as in this case, is more frequent in recurrent HPT than the diffuse form (95.6% vs. 74%); the recurrences have a higher proliferative activity than the controls; and a nodular form with an elevated proliferative index ($>1.5\text{--}2\%$) indicates a high risk of recurrence⁹. This could explain why our patient had experienced so many instances of recurrent HPT. However, the fibrosis caused by alcohol injection is also an important cause of incomplete resection.

In this case, the subcutaneous nodule of hyperplastic parathyroid tissue also could be thought to have been caused by implantation of tissue spilled from the second operation of cystic parathyroid lesion at lower pole of the left thyroid lobe. Although cystic adenomas may appear solid, they are extremely friable. If not handled with meticulous surgical technique, rupture with spillage of the cyst and its cellular contents are likely

to occur¹⁰. However, the pathology of the third operation did not support this thinking.

Parathyromatosis is a rare but problematic cause of recurrent HPT and is a serious complication after parathyroidectomy for both primary and secondary HPT. It consists of hyperfunctioning parathyroid tissues scattered throughout the neck, due either to intraoperative tissue spillage and subsequent implantation or to hyperplasia of parathyroid rests from embryologic development¹¹⁻¹². These lesions are typically inextricable adhesive to surrounding tissues and scars, making complete excision very difficult. In the previous study, the total frequency of parathyromatosis at neck re-exploration was 10%¹³.

This is a case of recurrent hyperparathyroidism due to hyperfunctioning parathyroid tissue presenting with a subcutaneous nodule. This case illustrates the difficulty of determining which of a patient's parathyroid glands may become hyperfunctioning. Effort must be made to identify the anatomical site(s) of the hyperfunctioning parathyroid tissue. Even though radiographic imaging procedures are the mainstay of localization before the cervical exploration, one palpable nodule in the neck could be found on physical examination in this case. The diagnosis was made preoperatively by cytological examination of a fine-needle aspiration (FNA). Parathyromatosis after FNA of potential parathyroid adenomas is a theoretical concern that to date has not been documented. A retrospective review of 81 patients diagnosed with HPT undergoing FNA of suspected parathyroid tissue documented no significant correlation exists between FNA of suspected parathyroid tissue and subsequent development of parathyromatosis¹⁴. However, most patients in this study are diagnosed as primary HPT, in which the pathophysiological mechanisms are different from those in secondary HPT. Therefore, we need more evidences to determine whether parathyromatosis develops in

patients undergoing FNA for secondary or tertiary HPT.

This case also demonstrates the importance of an experienced physical examination when clarifying the cause of recurrent HPT, and the need for long-term follow-up before a patient is considered "cured" of hyperparathyroidism.

In conclusion, healthy and pathologic parathyroid tissue can implant in the neck or mediastinum if spilled during parathyroidectomy, and these implants can cause recurrent or persistent hypercalcemia. To avoid the risk of iatrogenic parathyromatosis, a meticulous surgical technique and careful tissue handling are vital to successful parathyroid surgery. On the other hand, alcohol injection is not recommended for hyperparathyroidism if the patient can tolerate operation, because alcohol injection can cause fibrosis which makes further operation difficult in processing. We should also keep subcutaneous parathyroid lesion in mind when we perform neck re-exploration for recurrent renal hyperparathyroidism.

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復發性腎性高副甲狀腺血症是 因皮下副甲狀腺病灶所致：病例報告

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摘 要

造成腎性高副甲狀腺血症開刀後失敗的原因，通常是因為缺乏足夠的增生組織切除或以前未被發現的異位性副甲狀腺殘留。在此，我們描述一個復發的腎性高副甲狀腺血症病人，她一開始表現為頸部皮下結節。一個49歲的女性病患過去有紅斑性狼瘡、甲狀腺乳頭狀癌、末期腎病變併有腎性高副甲狀腺血症，為此她陸續接受了增生性副甲狀腺病灶酒精注射、甲狀腺次全切除及副甲狀腺切除，在追蹤期間，儘管積極得使用磷結合劑治療和維生素D3補充，病患的副甲狀腺激素、血鈣、血磷仍不斷升高。甲狀腺超音波檢查並未在甲狀腺床的部位發現甲狀腺或副甲狀腺組織。身體檢查顯示在右頸部有明顯的皮下結節，且這在軟組織超音波檢查下呈現高迴音和異質性。Sestamibi掃描顯示在同一部位有熱點。她接受了頸部結節的切除手術，病理組織學顯示為副甲狀腺增生。結節切除後的兩年追蹤期間，病人未再復發。總之，為了避免經常性高副甲狀腺血症復發，小心且有經驗的副甲狀腺開刀技術是很重要的。另一方面，因為酒精注射會造成組織纖維化，進而增加後續手術的困難度，因此針對腎性高副甲狀腺血症患者，除非是病人無法接受手術，否則通常不建議使用酒精注射治療。除此之外，當我們遇到復發性高副甲狀腺血症時，在手術前須將皮下副甲狀腺病變考慮進去。