Preoperative double adenoma upgraded to a triple adenoma after intraoperative sonographic evaluation of the neck

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ABSTRACT

Solitary parathyroid adenomas are a common cause of primary hyperparathyroidism (pHPT). Double parathyroid adenomas have a reported frequency of under 12% in primary hyperparathyroidism. We present the case of a 45-year-old female patient admitted with weakness, fatigue, and generalized bone pain. She had been treated for nephrolithiasis five times in the last two years, had high levels of serum calcium and parathyroid hormone, a low level of 25-hydroxy vitamin D, and osteopenia diagnosed by bone densitometry. Neck ultrasonography revealed bilateral parathyroid adenomas, confirmed by technetium-99m-sestamibi scintigraphy on the left. Findings on the right were suspicious, but not diagnostic. The parathyroid hormone washout concentrations were 1989 pg/mL (left) and 2097 pg/mL (right). A bilateral parathyroidectomy was performed. Intraoperative ultrasonography revealed a third retrosternal lesion, which was removed. All three specimens were confirmed as parathyroid adenomas on histological evaluation. Intraoperative neck ultrasonography thus played a crucial role in preventing secondary surgical intervention.

Keywords: Double adenoma, intraoperative ultrasonography, parathyroid adenomas, triple adenoma

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INTRODUCTION

Primary hyperparathyroidism (pHPT) resulting from the overproduction of parathyroid hormone (PTH) is associated with hypercalcemia and hypophosphatemia. Most patients with pHPT are diagnosed incidentally and do not display classic symptoms such as recurrent nephrolithiasis, peptic ulcers, mental disorders, weakness, or bone and muscle pain. Current guidelines recommend parathyroidectomy for surgical management of pHPT (1). The causes of pHPT include solitary adenoma (80%-85%), multi-gland hyperplasia (15%), and rarely, carcinoma (1%). Double adenomas have been found in 3%-12% of patients undergoing surgery for pHPT. Other rare causes include double and ectopic adenomas (2-5).

CASE PRESENTATION

A 45-year-old female patient was referred to Bülent Ecevit University Hospital, Department of Urology for evaluation of an adrenal incidentaloma. She had been diagnosed with bilateral adrenal adenomas by abdominal computerized tomography during an evaluation of renal colic episodes one month previously. She was not aware of any hypercalcemia, but had generalized bone pain, muscle weakness, and fatigue, together with the history of recurrent nephrolithiasis five times in the past two years that was managed by means of extracorporeal shock wave lithotripsy. She has had no history of head or neck irradiation, thyroid problems, pancreatitis, or any family history of multiple endocrine neoplasia syndromes, or parathyroid or calcium disorders. She had type 2 diabetes mellitus that was controlled by sitagliptin-metformin therapy. Patient's physical examination revealed nothing significant.

Biochemical investigations revealed the following: serum calcium, 12.3 mg/dL (normal range, 8.8-10.6 mg/dL); phosphorus, 2.9 mg/dL (normal range, 2.4-5.1 mg/dL); albumin, 4.1 g/dL (normal range, 3.5-5.3 g/dL); PTH, 237 pg/mL (normal range, 12-88 pg/mL); glomerular filtration rate, 75 mL/min/m2; alkaline phosphatase, 99 IU/L; 25-hydroxy vitamin D, 6.4 ng/mL (normal range, 30-100 ng/mL); 24-h urine calcium, 483 mg/day. Other laboratory examination results were within normal ranges (Table 1). The analysis of the adrenal mass was consistent with benign adenomas.

Renal ultrasonography (USG) demonstrated bilateral nephrolithiasis. Bone densitometry measurements revealed that she had osteopenia, with a T score of −1.2. Two smooth, ovoid, hypoechoic lesions with sonographic features of parathyroid adenoma were observed in the neck ultrasonography. . The lesions were measured 15×11×8 mm on the right and 18×12×7 mm on the left (Figure 1). A technetium-99m-sestamibi scan of the left lower lobe of the thyroid confirmed the ultrasonography findings. However, uptake by the lesion on the right side was suspicious, but not diagnostic of an adenoma (Figure 2). Analysis of the washout from ultrasound-guided fine-needle aspiration of the suspected lesions dem-

Table 1. Laboratory results of the patient

| Laboratory parameters	Patient's result	Normal range
Glucose (mg/dL)	122	80-100
Creatinine (mg/dL)	0.9	0.5-1.2
Calcium (mg/dL)	12.3	8.8-10.6
Albumin (gr/L)	4.1	3.5-5.3
Phosphorus (mg/dL)	2.9	2.4-5.1
Alkaline phosphatase (U/L)	99	60-105
Parathormone (PTH) (pg/mL)	237	12-88
25-hydroxy-vitamin D (25-OH-D) (ng/mL)	6.4	20-30
24-urine calcium (mg/day)	483	50-300 mg/day
GFR (mL/min)	75	80-110
Thyroid-stimulating hormone (TSH):(μIU/mL)	2.18	0.35-4.94
Free thyroxine (FT4) (pmoL/L)	0.77	0.55-1.2
Prolactine (mg/mL)	26	5-26

GFR: glomerular filtration rate
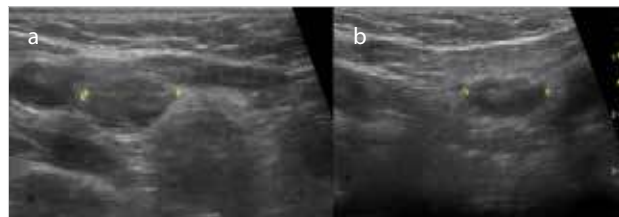
Figure 1. a, b. US images show right parathyroid adenoma (a) and left parathyroid adenoma (b)
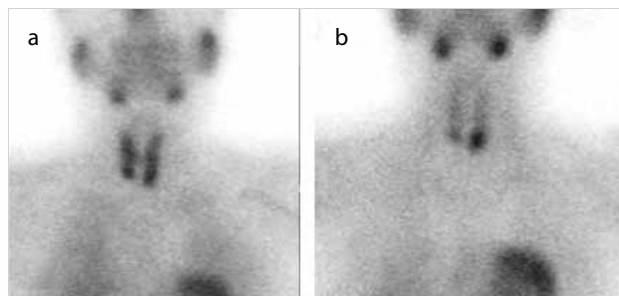

Figure 2. a. b. Scintigraphic images show early phase (a) and late phase (b)

onstrated a PTH concentration of 2097 pg/mL and 1989 pg/mL for the right and left lesions, respectively.

Accordingly, a diagnosis of pHPT due to double adenoma was determined and surgical intervention was planned. An intraoperative ultrasound-guided double adenoma excision was performed and confirmed by frozen-section analysis. During intraoperative ultrasonographic evaluation of the neck, the surgeon saw a third lesion, with a retrosternal location posterior to the trachea. The lesion had the sonographic appearance of an adenoma and was, therefore, also removed by the surgeon. Subsequent histologic analysis confirmed the finding of three parathyroid adenomas (Figure 3).

After surgery, patient's serum calcium was 9.3 mg/dL. The patient was discharged on postoperative day three without any signs of hypocalcemia and a total serum calcium of 9.3 mg/dL. Serum calcium level had normalized to 9.3 mg/dL, and PTH to 66 pg/mL. Informed consent from patient was taken.

DISCUSSION
The widespread use of PTH as a diagnostic test allows clinicians to diagnose pHPT before the occurrence of clinical symptoms, including kidney stones, overt bone disease, or neuromuscular dysfunction. Over the last few decades, increasing numbers of patients have been referred to surgeons for parathyroidectomy with biochemically mild pHPT (1).

Currently, surgery is the mainstay of treatment in pHPT. Nevertheless, surgeons should also diagnostically exclude other possible causes of hypercalcemia and syndromes associated with familial hyperparathyroidism, such as multiple endocrine neoplasia type I, multiple endocrine neoplasia type IIa, and familial hypocalciuric hypercalcemic hyperparathyroidism. As the gold standard surgical management of pHPT, bilateral neck exploration (BNE) has a cure rate of up to 98%. After the introduction of localizing imaging modalities, such as sestamibi-[99m]Tc (MIBI) scintigraphy and ultrasonography, and with the availability of PTH washout samples and intraoperative PTH monitoring associated with intraoperative ultrasonographic evaluation, minimally invasive parathyroidectomy (MIP) has become the preferred choice of treatment, with cure rates approaching BNE levels (6, 7). The reported accuracy rate of ultrasonography is 79%-86% and that of MIBI is 88%-90% (8). The positive predictive values of PTH washout concentrations has been reported to be up to 100% (9).
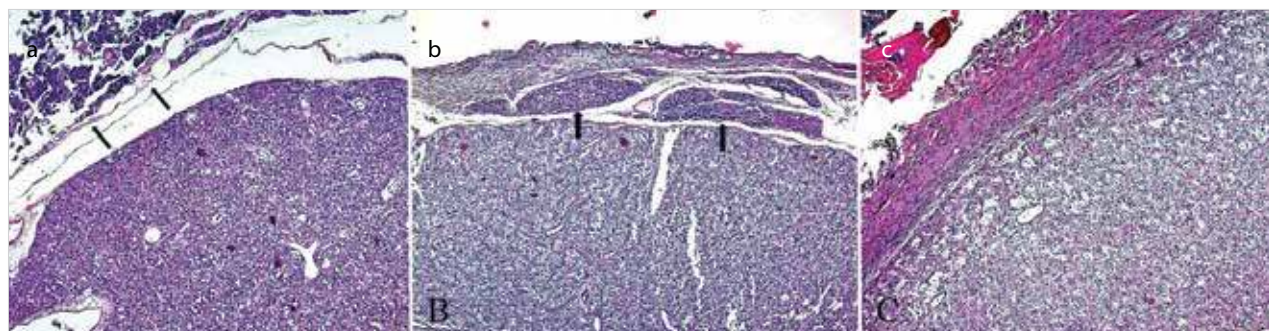

Figure 3. a-c. Pathological examinations of parathyroid adenomas show chief cells (a), clear cells (b, c). Note the normal parathyroid tissue on the top left in A (thin arrows) and compressed normal parathyroid remnants on the top in B (thick arrows)

Primary hyperparathyroidism is caused by a single adenoma in 80%-85 % of cases. The remaining cases are composed of four-gland hyperplasia, double adenomas, and much less commonly, parathyroid carcinoma (2, 3, 10). Multiple parathyroid adenomas were defined as the enlargement of more than one and less than four glands parathyroid glands, with at least one normal parathyroid gland on operation, evidence of neither multiple endocrine neoplasia nor familial hyperparathyroidism; and achievement of normocalcemia after resection of all glands (11).

Double adenomas have been found in 3%-12% of patients undergoing surgery for pHPT (2-5). A double adenoma was first described in 1977 by Wang and Reider (12); then Cope (13) reported similar findings in 1978. In a recent prospective evaluation of 100 patients with pHPT, only 65 patients were found to have a single adenoma: 15 patients had two enlarged glands and 10 patients had three or four enlarged glands (14). In another study, 20%-25% of patients had a multiple adenoma form of pHPT (15).

Surgery is currently the only available cure for pHPT (16). In selected patients, MIP offers the benefits of decreased morbidity and a shorter hospital stay compared with BNE and four-gland evaluation (17). MIP depends on successful preoperative imaging and localization of the abnormal gland using ultrasonography and technetium-99m-MIBI scanning with single-photon emission tomography (18). Using a combination of these imaging modalities, an adenoma can be localized with 95% accuracy (19). However, the accuracy of these modalities is decreased in a multi-glandular disease (20). Double adenomas can be missed in up to 15% of patients diagnosed with a single adenoma by MIBI scan (21, 22). They have a non-uniform distribution and likely involve both sides of the neck, and thus, can easily be missed when a focused MIP approach is employed. Similar to retrosternal thyroid goiters, parathyroid adenomas can also be located below the manubrium, and in such cases, are called ectopic retrosternal parathyroid adenomas. Intraoperative ultrasonography is a useful tool to detect these cases when preoperative procedures are not sufficient (21-25). Intraoperative evaluation ofthe neck after removing the suspicious lesions was of paramount importance in decreasing the need for BNE.

Intraoperative ultrasonography in operations of parathyroid glands was used for the first time by Siegel in 1981. He used this technique for the localization of an adenoma of upper right parathyroid gland (26). However, in 1986, Norton et al. (27) published a study concerning usefulness of IOUS in re-operations due to primary hyperparathyroidism. Intraoperative ultrasonography has some advantages as it is an accurate, safe, cheap, repeatable, and non-invasive method. In centers where intraoperative quick PTH assessment cannot be performed, intraoperative ultrasonography is useful for BNE.

CONCLUSION

In conclusion, the introduction of intraoperative ultrasonography has largely replaced more invasive approaches like BNE. It is a more focused procedure and can be used in conjunction with preoperative imaging to confirm disease location and carry out an intraoperative evaluation to ensure that all parathyroid lesions within the neck have been removed before completing an MIP.

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