Case Report

Remission of Primary Hyperparathyroidism Following Fine-Needle Aspiration Biopsy: A Case Report and Review of the Literature

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ARTICLE INFO

ABSTRACT

Background: Spontaneous or fine-needle aspiration biopsy (FNAB)-induced remission of primary hyperparathyroidism (PHPT) is an extremely rare and generally transient phenomenon.
Methods: A 40-year-old woman with a history of recurrent kidney stones was diagnosed with PHPT (serum calcium, 14.2 mg/dL; parathyroid hormone [PTH], 380 pg/mL). Ultrasonography and scintigraphy findings were consistent with a left enlarged parathyroid. Ultrasound-guided-FNAB cytology of the lesion did not confirm a parathyroid nature. However, levels of PTH within the needle-washing fluid were elevated.
Results: After few days, there was evidence of biochemical remission of the hypercalcemia (calcium, 8.1 mg/dL), and at subsequent follow-up visits, the enlarged parathyroid showed progressive shrinkage with eucalcemia and normalized PTH levels throughout 12 months of follow-up.
Conclusions: Rarely, remission of PHPT may occur after ultrasound-guided-FNAB performed on a hyperfunctioning parathyroid lesion.

Introduction

Primary hyperparathyroidism (PHPT) is the most common cause of hypercalcemia and caused by a single adenoma (85%), 4-gland hyperplasia (10%), or double adenoma (3%). In contrast, atypical parathyroid adenoma and carcinoma are rarer, the latter accounting for less than 1% of all cases of hypercalcemia.[1,2] In about 80% of all cases, PHPT is asymptomatic, so the diagnosis is essentially based on biochemical data. Parathyroid ultrasonography (US) and scintigraphy with sestamibi represent the first-line imaging procedures for parathyroid localization.[1] US is a noninvasive and easy technique to perform in skilled hands, with an excellent positive predictive value. However, it is operator-dependent, and the presence of concomitant thyroid diseases (eg, chronic lymphocytic thyroiditis) can lead to false-negative results. Parathyroid cytology has a low diagnostic value because it can be easily confused with

that of the thyroid.[3] For these reasons, measurement of parathyroid hormone (PTH) in washout fluid might increase the positive predictive value of US and might be considered in selected cases to make an easier differential diagnosis of neck lesions on ultrasound-guided fine-needle aspiration biopsy (FNAB). Of note, although rare, ultrasound-guided FNAB of the parathyroid can lead to histologic aberrations and has an intrinsic risk of parathyroid tissue seeding (parathyromatosis); therefore, it is not recommended by current guidelines.[4] At present, parathyroidectomy is the treatment of choice for patients with symptomatic PHPT and for those with asymptomatic PHPT who meet the criteria recommended by the latest guidelines.[4] Reports of spontaneous and ultrasound-guided-FNAB-induced remission of PHPT are extremely rare. We present a case of PHPT due to an enlarged parathyroid hyperfunctioning lesion that underwent persistent biochemical remission and ultrasonographic shrinkage after an ultrasound-guided-FNAB procedure.

Case Report

A 40-year-old woman was admitted to an outpatient clinic for hypercalcemia. Her past medical history was remarkable for recurrent right kidney stones, treated with lithotripsy and a

Table 1
Biochemical Data During the Follow-up

Parameter	At diagnosis	Before FNAB	6 d after FNAB	1 mo after FNAB	6 mo after FNAB	12 mo after FNAB	Normal values
Calcium, mg/dL	14.2[a]	12.3[a]	8.1[a]	9.1[b]	9.3[b]	9.4[b]	8.4-10.2[a] 8.5-10.5[b]
Phosphorus, mg/dL	…	...	...	2.7	2.6	2.4	2.5-4.5
PTH, pg/mL	380[c]	310[c]	188[c]	127[d]	54[d]	30[d]	10-65[c] 8-40[d]
25(OH)D, µg/L	8	…	…	10.9	32.2	29.4	>20
Albumin, g/dL	3.9	3.9	4.0	…	3.8	4.1	3.5-5.0

Abbreviations: FNAB = fine-needle aspiration biopsy; PTH = parathyroid hormone.
[a] Other institution.
[b] Our institution.
[c] Second-generation assay.
[d] Third-generation assay.

ureteral stent in 2017. There was no familial history of hypercalcemia or kidney stones. Her body mass index was 23.2 kg/m^2. Upon neck examination, a solid mass of nearly 2 cm was palpable in the left thyroid lobe. In November 2018, routine blood tests revealed a serum calcium level of 14.2 mg/dL (normal, 8.4-10.2 mg/dL), PTH level of 380 pg/mL (normal, 10-65 pg/mL), and normal renal function (serum creatinine, 0.6 mg/dL, and estimated glomerular filtration rate [Chronic Kidney Disease Epidemiology Collaboration equation], 114 mL/min/m^2). Table 1 illustrates all biochemical data recorded for this patient.

The neck US scan displayed a 24 × 21 × 17 mm highly vascularized mixed cystic/solid thyroid nodule of the left lobe (Fig. 1 A and B). The patient was initially treated with massive intravenous hydration, leading to a progressive decrease of serum calcium to 12.8 mg/dL, and discharged home after 2 days. One month after the initial diagnosis, serum calcium level was 12.3 mg/dL, and PTH level was 310 pg/mL. ^{99m}Tc sestamibi scintigraphy was performed and showed high uptake in the left posterior thyroid region, suspicious for a parathyroid lesion (Fig. 1 C and D). After 2 days, the patient underwent ultrasound-guided FNAB, performed elsewhere. Five passes were made into the mass with a 20-gauge needle, and 2 cytologic specimens of nonfluid material over 2 slides were sent for analysis. The PTH level in the washout fluid was 181 pg/mL, suggesting the parathyroid nature of the lesion. FNAB cytology showed a cluster of oncocytic cells with large and hyperdense nuclei (PTH$^-$,
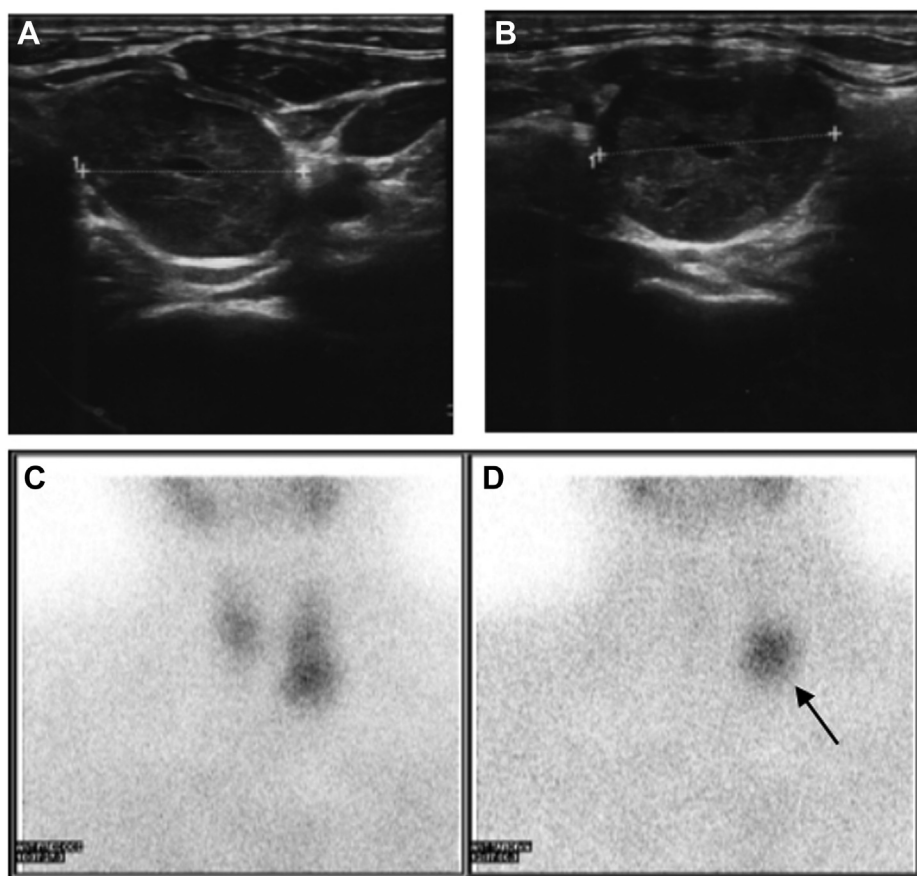

Fig. 1. Neck ultrasound and ^{99m}Tc sestamibi scintigraphy parathyroid scan images of the neck. A, Transverse and B, longitudinal ultrasound images of the neck performed at the time of diagnosis, showing a 24 × 21 × 17 mm solid lesion located in the lower pole of the left thyroid lobe. C, Early and D, delayed images of ^{99m}Tc sestamibi scintigraphy displaying a high uptake area in the lower pole of the left thyroid lobe, consistent with hyperfunctioning parathyroid tissue (arrow).
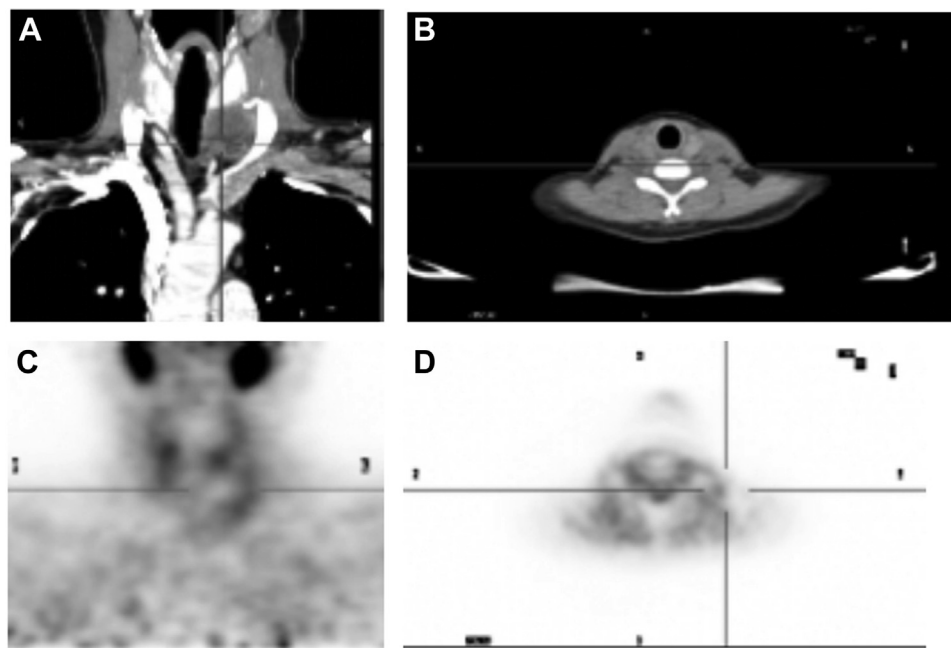
Fig. 2. ^{18}F-choline positron emission tomography/computed tomography scan of the neck. *A*, Coronal and *B*, transverse images of low-dose computed tomography scan of the neck. *C*, *D*, Positron emission tomography images showing an increased uptake at the lower pole of the left thyroid lobe, consistent with autonomous parathyroid tissue.

PAX8⁻, CD10⁻, and thyreoglobulin⁻), consistent—per the outside hospital pathology report—with a diagnosis of a benign thyroid lesion with pseudopapillary features. Laboratory testing performed 6 days after the FNAB revealed a calcium level of 8.1 mg/dL (normal, 8.4-10.2 mg/dL) and albumin level of 4.0 g/dL (normal, 3.5-5.0 g/dL), in the absence of signs and symptoms of hypocalcemia. Twenty days after the FNAB, an ^{18}F-choline-positron emission tomography scan was performed, which showed a metabolically active (standardized uptake value, maximum 5.9) hypodense nodule of 23 × 16 × 18 mm below the left thyroid lobe, with extensive necrotic phenomena consistent with a diagnosis of hyperfunctioning parathyroid tissue (Fig. 2).

After 1 month, she was referred to our center. At the time of our evaluation, the patient was in good health. On physical examination, no nodule was palpable at the left lobe of the thyroid, and there was no evidence of enlarged lateral cervical lymph nodes. Biochemical workup revealed normal renal function, with PTH levels of 127 pg/mL (normal, 8-40 pg/mL); calcium, 9.1 mg/dL (normal, 8.5-10.5 mg/dL); phosphorus, 2.7 mg/dL (normal, 2.5-4.5 mg/dL); and 25(OH)D, 10.9 μg/L. The neck US showed a slightly hypoechoic nodule of 14 × 19 × 22 mm below the left thyroid lobe, with absent vascularity on color Doppler (Fig. 3 *A*). Unfortunately, the original cytologic specimen was unavailable, so we were unable to perform a pathologic revision. Because the calcium levels were within normal values, active surveillance was advised. Cholecalciferol 25 000 IU monthly was started for vitamin D deficiency. Blood tests performed after 6 months of follow-up showed calcium, 9.3 mg/dL; ionized calcium, 1.23 mEq/L; phosphorus, 2.6 mg/dL; albumin, 3.8 g/dL; PTH, 54 pg/mL; and 25(OH)D, 32.2 μg/L. The neck US revealed a reduction of the lesion to 14 × 19 × 14 mm), which appeared markedly hypo-anechoic (Fig. 3 *B*). After 1 year, biochemical parameters were in the normal range: PTH, 30 pg/mL; serum calcium, 9.4 mg/dL; ionized calcium, 1.24 mEq/L; albumin, 4.1 g/dL; and 25(OH)D, 29.4 μg/L (Table 1). The neck US showed evidence of further dimensional reduction of the lesion, measuring 9 × 10 × 13 mm (Fig. 3 *C*).

Written informed consent was obtained from the patient for publication of the submitted article and accompanying images.

Discussion

We described a rare case of biochemical remission of PHPT after an FNAB was performed on a hyperfunctioning enlarged parathyroid lesion. Only 3 similar cases have been reported to date,[5-7] of which 1 is a case of long-lasting FNAB-induced PHPT remission.[7] Our patient went into PHPT remission, given that her PTH and calcium levels dropped from 380 to 188 pg/mL and from 14.2 to 8.1 mg/dL, respectively, following the FNAB, with complete normalization of PTH levels 12 months after the biopsy.

Autoinfarction (necrosis without hemorrhage) or acute hemorrhage of the lesion have been suggested as the most common mechanisms involved in the pathogenesis of autoparathyroidectomy.[8] However, the exact etiology remains unclear because most cases lack histologic confirmation. Parathyroid autoinfarction usually leads to an acute and dramatic reduction of calcium and PTH levels, while in some cases, the decrease is much less pronounced and entirely asymptomatic. After the FNAB, our patient experienced a rapid fall in serum calcium concentrations despite reduced but still high levels of PTH, the latter arguably due to the presence of concomitant vitamin D deficiency. Several reports in the literature have described the reoccurrence of PHPT after spontaneous[9] or FNAB-induced parathyroidectomy.[5,6,9] Indeed, in 2 of the cases of FNAB-induced remission of PHPT reported,[5,6] the resolution of PHPT was only transient. At the same time, the patient described by Kara et al[7] showed a long-term (9 years) normalization of calcium and PTH levels. Rarely, FNAB can cause resolution of hypercalcemia without hemorrhage or hematoma formation, as in the case reported by Ing and Pelliteri,[5] in which the complete aspiration of an intrathyroidal parathyroid cyst resolved hypercalcemia for at least 16 months of post-FNAB follow-up. However, the PTH levels remained above the upper limit of the normal value, likely consistent with the persistence of PHPT. Remarkably, hypercalcemia and exacerbation of PHPT might be a transient
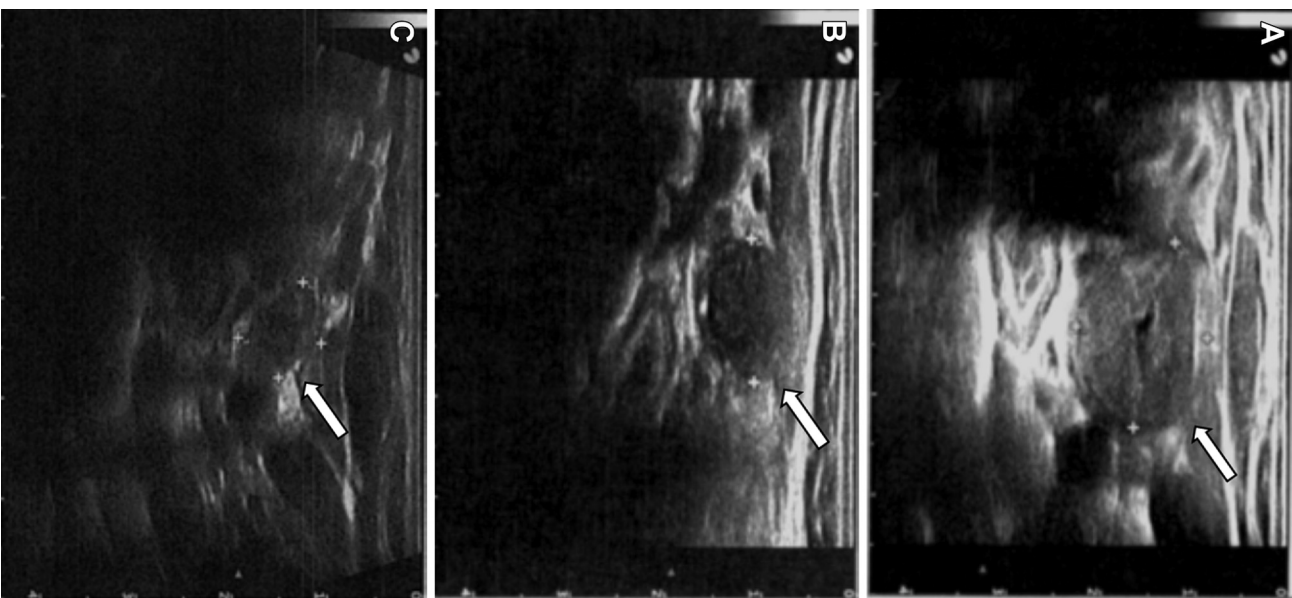
Fig. 3. US of the study patient's neck showing the evolution of the parathyroid lesion during the follow-ups. A. Neck US performed 1 month after the fine-needle aspiration biopsy, displaying a 14 × 19 × 22 mm mixed lesion apparently embedded in the left thyroid lobe (arrow). B. Neck US performed 6 months after the fine-needle aspiration biopsy, showing a 14 × 19 × 14 mm markedly hypoechoic lesion (arrow). C. After 1 year, the lesion showed a further size reduction, measuring 9 × 10 × 13 mm (arrow). US = ultrasonography.

phenomenon, spontaneously going into a long-term remission even in the absence of FNAB or other invasive procedures.[10-12] While the measurement of PTH in washout fluid combined with FNAB can help clinicians to accurately diagnose parathyroid incidentalomas at the time of ultrasound-guided FNAB in selected cases, we must emphasize that FNAB does not form part of the standard diagnostic workup in cases of suspected PHPT,[4] and its indication in these circumstances is still a matter of debate. Furthermore, parathyroid FNAB is not free of disadvantages. Indeed, it can cause worrisome histologic alterations (ie, fibrosis,

Table 2
Clinical and Biochemical Features of Reported FNAB-Induced PHPT Remission

Authors	Age/sex	Measurements of parathyroid lesion at diagnosis	Measurements of parathyroid lesion at the end of follow-up	Calcium/albumin/ PTH before FNAB	PTH washout levels	First measured calcium/PTH after FNAB	Calcium/albumin/ PTH at the end of follow-up	Reoccurrence	Length of follow-up (mo)	Symptoms after FNAB
Ing and Pelliteri[5]	74/M	24 × 23 × 26 mm apparently intrathyroidal complex nodule	8 × 9 mm	16.2/NA/341	1800	7.9/NA (2 wk after FNAB)	9.8/NA/83	Yes	16	No
Maxwell et al[6]	63/F	39 mm intrathyroidal nodule	Surgery	12.4/NA/247	…	10.4/22 (4 d after FNAB)	9.2/NA/71	Yes	1	Neck pain, dysphagia, and voice modification
Kara et al[7]	67/F	5 × 16 × 29 mm hypoechoic extrathyroidal fusiform nodule	Disappeared	11.1[a]/NA/249	808	9.3/90 (3 mo after FNAB)	9.1*/NA/53	No	105	Asymptomatic neck swelling
Present case	40/F	24 × 21 × 17 mm apparently intrathyroidal complex nodule	9 × 10 × 13 mm	14.2/3.9/380	181	8.1/NA (6 d after FNAB)	9.4/4.1/30	No	12	No

Abbreviations: F = female; FNAB = fine-needle aspiration biopsy; M = male; NA = not available; PHPT = primary hyperparathyroidism; PTH = parathyroid hormone.
Calcium presented as mg/dL, albumin as g/dL, and PTH as pg/mL.
PTH assays: second-generation for [6] and [7], third-generation for [5] and the present case.
Reference range for PTH: 6-40 pg/mL,[5] 10-65 pg/mL,[6] and 15-88 pg/mL.[7]
Reference range for serum calcium: 8.3-10.5 mg/dL,[5] 8.4-10.2 mg/dL,[6] and 8.5-10.6 mg/dL.[7]
[a] Corrected calcium using the following formula: corrected calcium (mg/dL) = total serum calcium (mg/dL) + 0.8 × (4 − serum albumin [g/dL]).

pseudoinvasion of the capsule, and cellular atypia) resembling those of parathyroid malignancy[13,14] and, although rare, parathyromatosis, which is benign parathyroid tissue seeding and a potential cause of recurrent or persistent PHPT.[15] We reported that the cytologic specimen was initially diagnosed as a benign thyroid lesion with pseudopapillary features. Although some studies have shown good reliability of cytologic diagnosis in parathyroid adenomas, several possible diagnostic pitfalls need to be considered,[3] especially in intrathyroidal parathyroid adenomas, like in the case described here. Parathyroid and thyroid lesions share several cytologic features,[3] and this might be especially true for oncocytic parathyroid adenomas, being most often misinterpreted as Hurtle cell thyroid carcinoma. However, the lack of histologic verification in our patient did not allow us to confirm this finding.

Immunocytochemical staining for PTH can help pathologists identify a parathyroid lesion. Still, the application of this technique might be difficult due to the low rate of hormone storage within individual cells.[3] In keeping with the studies mentioned previously, the immunocytochemical analysis in our report was negative for PTH staining. Conversely, clearly detectable PTH in the washout fluid was consistent with the parathyroid nature of the aspirated mass. The case described here, along with a literature review of similar cases (Table 2), suggest that hyperfunctioning parathyroid lesions are prone to necrotic infarction due to their high vascularization and fragility. In addition, we cannot exclude that in this particular case, the size of the needle and number of needle passes might have contributed to PHPT remission. Taken together, all these data may also explain why minimally invasive alternative treatments to surgery can be effective in obtaining PHPT remission.[16] Percutaneous ethanol ablation,[17] ultrasound-guided high-intensity focused ultrasound,[10] and laser ablation[18] have been reported as effective treatments in PHPT, especially in patients who refuse or have contraindications for surgery and in those with recurrent multiple endocrine neoplasia type 1-related PHPT.[17] However, these techniques often produce only a transient resolution of hypercalcemia and cannot be proposed as a definitive treatment of PHPT.[16,18]

Conclusion

Here, we reported the case of a cured PHPT because of FNAB-induced damage of an intrathyroidal parathyroid adenoma. The results of this case, as well as other similar reported cases, suggest that hyperfunctioning parathyroid lesions might be susceptible to FNAB-induced damage, although this procedure is not recommended in cases of suspected PHPT. Because injured parathyroid adenomas frequently relapse, adequate long-term surveillance remains mandatory in all of these cases.

Disclosure

The authors have no multiplicity of interest to disclose.

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