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CASE REPORT

Parathyroid Carcinoma Causing Mild Hyperparathyroidism in Neurofibromatosis Type 1: A Case Report and Systematic Review

Vincenzo Triggiani[1,*], Marco Castellana[2], Paolo Basile[3], Giuseppina Renzulli[4] and Vito Angelo Giagulli[1]

[1]*Section of Internal Medicine, Geriatrics, Endocrinology and Rare Diseases, Interdisciplinary Department of Medicine, University of Bari, School of Medicine, Policlinico, Bari, Italy;* [2]*Via Turi 44 Rutigliano, Bari, Italy;* [3]*University of Bari, Bari, Italy;* [4]*Pathology Unit, Policlinico, Bari, Italy*

Abstract: ***Background:*** Neurofibromatosis type 1 is an autosomal dominant disorder characterized by an increased incidence of tumors, including endocrine ones. Primary hyperparathyroidism can be rarely caused by a parathyroid carcinoma; these patients are generally characterized by severe symptoms, large neck lesions and high levels of PTH and calcium. We report a case of hyperparathyroidism due to parathyroid carcinoma in a patient affected by neurofibromatosis type 1. A systematic review of the literature was also conducted.

Patient Findings: A 56-year-old woman was referred for a 13 mm-nodular lesion of the neck incidentally discovered on ultrasound examination and mild hyperparathyroidism. A 99mTc-tetrofosmin/pertechnetate subtraction scintigraphy was negative for parathyroid disease. Given the absence of suspicious ultrasound finding, a fine-needle aspiration cytology was performed with iPTH determination in the aspirate, confirming the parathyroid origin of the lesion. The patient underwent left inferior parathyroidectomy with intraoperative monitoring of iPTH and became normocalcemic. On histopathological examination, parathyroid carcinoma presenting at the resection margin was diagnosed, thus a surgery revision was requested.

Conclusion: Even if literature does not support a syndromic association between neurofibromatosis type 1 and primary hyperparathyroidism, the benefit of precociously diagnosing and treating this condition may outweigh costs associated with screening. This case report moreover demonstrates that sometimes clinical, laboratory and imaging aspects suspicious for cancer may be missing. A prompt referral to a high-volume center is crucial for the management of those cases of incidental histopathological diagnosis.

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1. INTRODUCTION

Neurofibromatosis type 1 (NF1) is a multi-system disorder caused by the mutation of neurofibromin (NF1) with a global prevalence of 1 case per 3,000 individuals. It is characterized by an autosomal dominant inheritance and extreme variability in clinical features. The diagnosis is based on family history and physical examination, according to 1987 National Institutes of Health Consensus Development Conference Criteria; genetic testing may clinch the diagnosis in classical phenotype and is mandatory in patients with unusual clinical presentations [1, 2]. NF1 has been associated with an increased incidence of both benign and malignant tumors, including endocrine ones such as pheocromocytoma and thyroid cancer [3, 4].

*Address correspondence to this author at the Section of Internal Medicine, Geriatrics, Endocrinology and Rare Diseases, Interdisciplinary Department of Medicine, University of Bari, School of Medicine, Policlinico. P.O. Box: 70124, Bari, Italy; Tel/Fax: ++39-080-547-8814;
E-mail: vincenzo.triggiani@uniba.it.

Primary hyperparathyroidism (PHPT) is an endocrine disorder characterized by hypercalcemia and elevated or inappropriately normal levels of parathyroid hormone (PTH). Incidence varies from 0.4 to 82 cases per 100,000. A solitary parathyroid adenoma accounts for 80% of cases, whereas four-gland hyperplasia for 15% and multiple adenomas for 5%. Less than 1% of cases are caused by parathyroid cancer; the clinical presentation is similar (*i.e.*, weakness, fatigue, anorexia, bone and joint pain, bone fractures, renal stones), but with higher serum calcium and intact parathyroid hormone (iPTH) (>300 pg/ml) levels than in parathyroid benign disease. In 40-70% of patients a firm palpable mass, 3.3 cm in median size, is found in the neck; lymph nodes are involved in 15-30% at presentation; up to 30% may present with symptoms of metastases usually in lungs, liver, and bone. The disease has a slowly progressive course with frequent local recurrence and/or metastases; most of the patients die due to complications of hypercalcemia [5, 6].

We report a case of concomitant NF1 and mild PHPT caused by parathyroid carcinoma. Since over 90% of para-

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thyroid carcinomas are hormonally functional, a systematic review of PHPT in NF1 was also conducted [5].

2. PATIENT

A 56-year-old woman was referred to our institution because of a neck nodular lesion incidentally discovered on ultrasound (US) examination and mild hyperparathyroidism (Fig. **1**). The patient had been complaining of hypertension for 2 years. A family history of NF1 in the mother, of type 2 diabetes mellitus and hypertension in the father was reported. The medical history recorded a diagnosis of NF1 at 25 years of age, breast cancer G3 pT1N1 because of which she underwent surgery and chemotherapy at 46 years of age, paroxysmal tachycardia at 49 years of age. She was on bisoprolol and flecainide. A routine thyroid ultrasound performed at the age of 55 showed multiple bilateral hypoechoic nodules (the largest of 8 mm) and an ovoid well-defined solid hypoechoic lesion of 13 mm, which was likely attributable to an enlarged left parathyroid gland. Laboratory findings were consistent with primary hyperparathyroidism: serum calcium was slightly above the normal range (10.7 mg/dl; n.r. 8.5-10.5), serum phosphate 3.6 mg/dl (n.r. 1.5-6.8), urinary calcium 359 mg/24h (n.r. 50-300), urinary phosphorus 0.5 g/24h (n.r. 0.3-1.0), 25OH vitamin D <8 ng/ml (n.r. 30-100), iPTH 140 pg/ml (n.r. 4-40); estimated glomerular filtration rate was 85 ml/min. Thyroid hormones, thyrotropin, calcitonin and anti-thyroid peroxidase antibody were in the normal range. Osteoporosis was found on Hologic Explorer dual-energy X-ray absorptiometry (DEXA): bone mineral density was -3.3 at lumbar spine, -2.7 at femoral neck; nephrolitiasis and nephrocalcinosis were excluded by US. A 99mTc-tetrofosmin/pertechnetate subtraction scintigraphy didn't show images possibly referred to parathyroid lesions.

On admission, the patient was afebrile, had a blood pressure of 140/80 mmHg, a pulse of 88 beats/min, a respiratory rate of 16 breaths/min, a pulse oximetry of 97% in room air. Anthropometric data were: height of 152 cm, body weight of 53 kg, body mass index of 22.9 kg/m^2. The general examination was characterized by kyphoscoliosis, cutaneous neurofibromas (Fig. **2a**), café-au-lait pigment spots and freckles of skinfolds. Given the history of NF1 and hypertension, urinary metanephrine testing, urinary normetanephrine testing, aldosterone-to-renin ratio and overnight dexamethasone suppression test were requested and resulted negative; hyperparathyroidism was confirmed. The hypoechoic solid nodule, 8 x 8 x 15 mm in size, with scanty vascularization flow was confirmed on neck US; no suspicious lymph nodes were found. US-guided fine-needle aspiration cytology (FNAC) was performed; iPTH determination in the aspirate was >1800 pg/ml, confirming the parathyroid nature of the lesion. The cytological smears were hypercellular and consisted of oxyphil cells with nuclear monomorphism in overcrowded papillary and syncytial aggregates; a cytopathological diagnosis of indeterminate oncocytic neoplasm was given (Fig. **2b**, **2c**).

The patient underwent left inferior parathyroidectomy with intraoperative monitoring of iPTH and the specimen was sent for histopathological confirmation. Serum calcium was 9.7 mg/dl, urinary calcium 257 mg/24h and iPTH 36.3 pg/ml, thus cholecalciferol 50 000 IU twice a month for two months (followed by a once a month regimen) and calcium carbonate 500 mg/day were started.

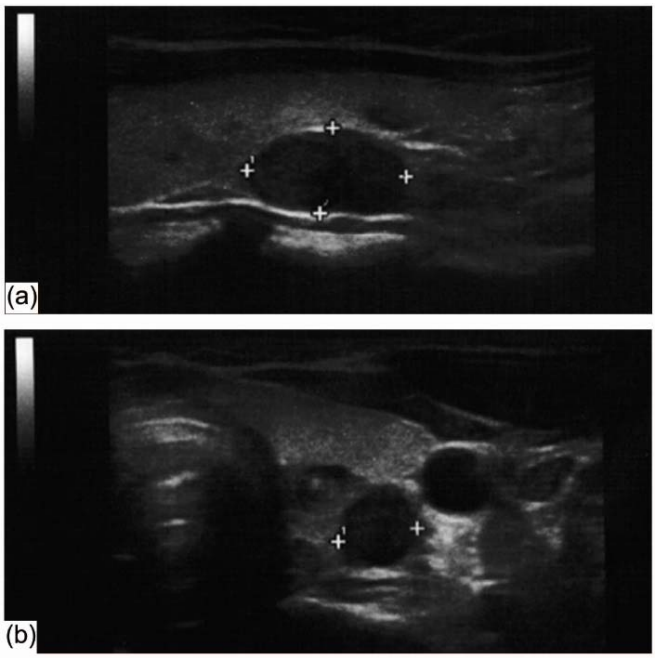

Fig. (1). Neck US showed a hypoechoic solid nodule, 8 x 8 x 15 mm in size, with scanty vascularization flow, in the posterior aspect of the left thyroid lobe suggesting a parathyroid origin of the lesion. Longitudinal scan (**a**); transverse scan (**b**).

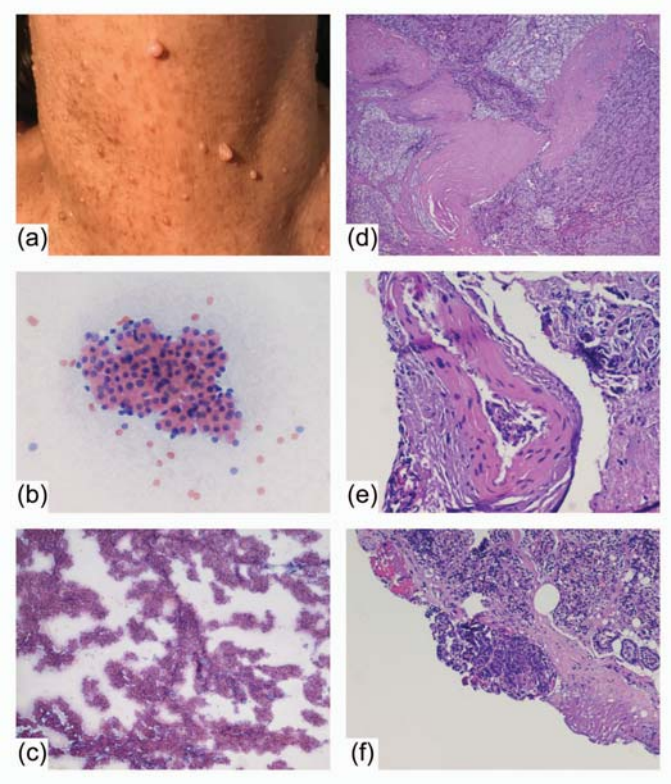

Fig. (2). Cutaneous neurofibromas of the neck (**a**). Cytologic smears – Papanicolaou staining: oxyphil cells with nuclear monomorphism (200×) (**b**) in overcrowded papillary and syncytial aggregates (40×) (**c**). Histopathologic examination - hematoxylin and eosin staining: parathyroid carcinoma with capsular (40×) (**d**) and vascular invasion (200×) (**e**) presenting at the resection margin (R1) (100×) (**f**).

On histopathological examination, a parathyroid carcinoma with oncocytic and water-clear cell aspects was diagnosed; signs of malignancy were capsular and vascular invasion (Fig. **2d**, **2e**). The labeling index, evaluated with MIB-1, was very low (Ki67=2%). Since tumor presented at the resection margin (R1) (Fig. **2f**), a total thyroidectomy with left perirecurrential lymph nodes dissection was performed and an intrathyroid focus of parathyroid carcinoma 1 mm in size with no cancer cells seen at the resection margin (R0) was found.

After surgical intervention, levothyroxine 125 μg/die was started. Serum calcium was 9.2 mg/dl and iPTH 27.1 pg/ml. The patient was then in a good general condition and with blood pressure in the normal range.

3. METHODS FOR SYSTEMATIC REVIEW OF LITERATURE

PRISMA checklist was used to present the findings of this systematic review.

To extent to the best of published literature on PHPT in NF1, a three-step search strategy was planned. Firstly, we identified keywords and MeSH terms in Pubmed. Secondly, the terms were searched in Pubmed. Thirdly, according to our aim, original case reports and case series reporting PHPT in NF1 were included for the present review. Fourthly, references of included studies were searched for additional papers. The last search was performed on 1st November 2017. No language restriction was adopted.

Data were extracted in a piloted form. The following data were reported: 1. General information of the paper (first author, year of publication, country); 2. Patient data (age at diagnosis, gender, clinical presentation, cause of PHPT, location and size of the lesion, therapy); 3. Laboratory findings (serum total and 24h urinary calcium, iPTH); 4. Type of imaging for PHPT and complications (US, computed tomography (CT), magnetic resonance imaging (MRI), scintigraphy, single photon emission computed tomography (SPECT-CT), DEXA). If a full-paper could not be retrieved, information was extracted from the abstract. Discrepancies were resolved by a mutual consensus between all the authors.

4. RESULTS OF THE SYSTEMATIC REVIEW

The search revealed 102 potentially relevant articles. One additional paper was found in a personal database. By reading title and abstract, 54 studies were excluded. The full text of the remaining 49 papers was found and evaluated, and 19 articles were excluded because of several reasons (*i.e*., no NF1 and PHPT, reviews, secondary hyperparathyroidism, no full-text available). Finally, 30 papers were included in the present review.

The characteristics of the included articles are summarized in Table **1**. The papers were published between 1950 and 2015; 11 in Europe, 10 in Asia, 8 in North America, 1 in South America. A total of 32 patients with NF1 and PHPT were reported, of which 17 were female. The median age at diagnosis was 52 years (range 18-71). In most patients, PHPT was suspected following the complaining of bone pain or the finding of renal stones. PHPT was caused by adenoma in 21 patients, atypical adenoma in 2, four-gland hyperplasia in 2, carcinoma in 1; no evidence of parathyroid adenoma was reported in one patient, even if described as marked hypercalcemic with elevation of the iPTH [30]. In single-gland disease, a lesion was located in the right inferior parathyroid in 7 patients, right superior in 3, left inferior in 3, mediastinum in 2. The median largest diameter was 30 mm (range 10-57). Two patients presented as normocalcemic, with one of them having ionized calcium measured and found persistently elevated [23, 34]; serum total calcium ranged from 11.0 to 19.0 mg/dl in adenomas, from 15.8 to 21.9 mg/dl in the case with carcinoma [18]. iPTH levels ranged from 153 to 29 800 pg/ml in adenomas, only three of which with iPTH less than 300 pg/ml; from 84 to 117 pg/ml in four-gland hyperplasia and from 466 to 1 967 pg/ml in the carcinoma. Imaging was represented by scintigraphy in 12 patients, neck US in 8, CT in 5, MRI in 2, SPECT-CT in 1; one patient was submitted to FNAC [13]. All adenomas were excised, a 3/4 excision was performed for four-glands hyperplasia, while the carcinoma was treated with en-bloc resection of parathyroid and thyroid.

5. DISCUSSION

The aim of the current case report and systematic review was to identify the best available evidence on the characteristics of PHPT in NF1. To the best of our knowledge, we reported the first case of parathyroid carcinoma causing mild PHPT in NF1 and performed the first systematic review on PHPT in NF1. We planned a literature search to find the largest number of case reports and case series of both functioning and nonfunctioning parathyroid tumors, then selected relevant articles. The vast majority of papers found was represented by single case reports.

Traditionally, NF1 has been considered as a neural crest disease; since parathyroid principal cells derive from neural crest too, an association of NF1 and PHPT can be expected [15, 37]. Reported data on NF1, however, didn't support this hypothesis: a retrospective study among 1,404 NF1 patients in Finland didn't find any case of parathyroid cancer; a prospective study among 448 in the United Kingdom reported one case [3, 4]. In the present systematic search, only 32 cases of PHPT were found. For this reason in NF1 patients not affected by syndromes known to be associated with PHPT such as Multiple Endocrine Neoplasia (MEN) type 1 and 2A, PHPT should be exclusively regarded as a coexisting disease rather than a syndromic condition.

Parathyroid carcinoma has been associated with moderate-to-severe signs and symptoms of hyperparathyroidism, in particular, combined renal and bone involvement. On examination, a palpable firm cervical mass and laryngeal nerve palsy can be found; laboratory findings include markedly elevated levels of serum total calcium (>14-15 mg/dl) and iPTH (3-10 times above the upper normal limit); neck US generally shows a nodule larger than 3 cm in size, with lobulated non-homogeneous pattern, marked hypoechogenicity, degenerative changes, calcifications, irregular halo sign or local infiltration; as already stated, lymph nodes may be involved.

The combined finding of serum calcium higher than 12 mg/dl (3 mmol/l) and a parathyroid lesion larger than 3 cm (the so-called >3 + >3 rule) should raise the suspicion of

Table 1. Primary hyperparathyroidism (PHPT) in patients with neurofibromatosis type 1.

Author or Principal Investigator	Year	Country	Age	Gender	Clinical Presentation	Cause of PHPT	Location of Lesion	Size of Lesion (mm)	Serum Total Calcium (mg/dl)	PTH (pg/ml)	US	FNAC	CT	MRI	scitigraphy	SPECT-TC	DEXA
Abdel-Wanis [7]	2001	Japan	31	F	back pain due to kyphoscoliosis	adenoma	right inferior		12.5	29800	x						
Altinova [8]	2006	Turkey	37	M	headache, hypertensive attacks and palpitation	adenoma	right inferior		12.9	198	x				x		x
Al-Wahhabi [9]	2005	Saudi Arabia	65	M		adenoma	right inferior		11.8	153	x				x		
Bahadir [10]	2009	Turkey	52	F	widespread pain and muscle weakness	adenoma	right	13x11x9	11.1	322	x				x		x
Behera [11]	2013	India	33	M	low back ache with headache	atypical adenoma	left inferior		12.0	741	x			x	x	x	
Bretagne [12]	1980	France															
Buderi [13]	2014	UK	65	F		adenoma						x	x		x		
Caniggia [14]	1966	Italy	61	F	back pain, muscular weakness, mild polyuria, renal stones, osteitis fibrosa cystica	adenoma			14.0								
Chakrabarti [15]	1979	USA		F	renal colic	adenoma	right inferior	10x8x3	11.4								
Chakrabarti [15]	1979	USA		F	renal colic	adenoma	left inferior	20x15x5	13.9								
Cinamon [16]	2002	Israel	47	F	swelling in left parotid region	adenoma	left				x		x		x		
Daly [17]	1970	Canada	59	M	foot and back pain, fractures, osteitis fibrosa cystica	adenoma	right superior		11.9								
Daly [17]	1970	Canada	34	F	epulis, probable osteitis fibrosa cystica	adenoma	right inferior		11.0								
Demirjian [18]	2008	USA	31	F	nausea, vomiting, fatigue, mental status changes	carcinoma	right superior	40x30x25	15.8-21.9	466-1967			x		x		
Dieter [19]	2002	USA	50		nephrocalcinosis, renal failure	adenoma	mediastinal	57x45x29	19.0								
Doerffel [20]	1961	Germany			osteitis fibrosa cystica	adenoma											
Duquenne [21]	1994	France															
Favere [22]	2015	Brazil	62	F	bone pain, asthenia, weight loss, brown tumor in femur and tibia	atypical adenoma	right inferior	45x40x33	13.5	1933	x				x		
Gkaliagkousi [23]	2009	Greece	70	F	abdominal discomfort, sweating, headache	4-gland hyperplasia	right inferior		9.8	157					x		

Table (1) contd….

Author or Principal Investigator	Year	Country	Age	Gender	Clinical Presentation	Cause of PHPT	Location of Lesion	Size of Lesion (mm)	Serum Total Calcium (mg/dl)	PTH (pg/ml)	US	FNAC	CT	MRI	scitigraphy	SPECT-TC	DEXA
Godlewski [24]	1989	France				adenoma											
Hoppe [25]	1986	USA															
Kodama [26]	2007	Japan	18	F	renal stones	adenoma	right superior	50x33x30	11.6	356	x				x		
Moiton [27]	2002	France															
Popescu [28]	2007	Romania	41		masticatory impairment, brown tumors	adenoma											
Rokke [29]	1990	Norway		F	bone pain, fractures, osteitis fibrosa cystica	adenoma	left inferior										
Rosenberg [30]	1988	USA	44	F	muscle weakness	no evidence of adenoma			↑	↑							
Spektorova [31]	1950	Russia				tumor											
Troitskaia [32]	1964	Russia				adenoma											
Vogelzang [33]	1989	USA	62	M		adenoma			↑	↑			x	x	x		
Weinstein [34]	1990	USA	61	F	bone pain and muscle weakness	4-gland hyperplasia		20x10x5	9.1-9.8	84-116							
Yamamoto [35]	2015	Japan	60	F	melena	adenoma	anterior mediastinum		11.8	427			x		x		
Zoller [36]	1996	Sweden	71	F		adenoma											
Triggiani	2017	Italy	56	F	hypertension	carcinoma	left inferior	8x8x15	10.7-11.5	131-140	x	x					x

parathyroid carcinoma. On the other hand, the presence of a homogeneous nodule with a thick capsule and a non-suspicious vascularity should be regarded as a benign lesion [38]. In the present review, these aspects showed a poor accuracy: serum total calcium, iPTH and size overlapped between adenoma and carcinoma; US aspects were not extensively reported. Demirjian *et al.* described a case of parathyroid carcinoma in NF1, showing characteristics in line with the ones reported above: the patient complained of nausea, vomiting, fatigue, and mental status changes; a palpable neck mass was found; serum total calcium was 21.9 mg/dl and PTH 466-1,967 pg/ml; a neck exploration was performed and a 40 x 30 x 25 mm parathyroid carcinoma was excised en-bloc with the right lobe of the thyroid [18]. In our case, none of the characteristics at presentation could raise the suspicion of parathyroid carcinoma.

Parathyroid glands are characterized by high heterogeneity in both number and position [39]. In sporadic PHPT, current evidence supports the use of minimally invasive parathyroidectomy instead of bilateral neck exploration because of smaller incisions, lesser dissection, eligibility for outpatient surgery and cost savings, thus preoperative localization and intraoperative adjuncts are strongly recommended [40]. We have previously reported the advantages of iPTH determination in the aspirates in the differential diagnosis of neck masses: in our series of 46 cases, a value over 245 pg/ml was constantly associated to the parathyroid lesions [41]. In the reported case, the neck US showed a 15 mm hypoechoic solid nodule; the 99mTc-tetrofosmin/pertechnetate subtraction scintigraphy was negative for parathyroid disease. In order to better characterize the neck lesion, a FNAC was performed confirming its parathyroid origin; the mass was thus excised. Following the histopathological examination, a surgical revision was requested. Of course, when a parathyroid lesion is suspected to be cancer, FNAC with measurement of iPTH should be avoided because of the potential seeding of malignant cells along the needle track; for the same reason, the gold standard treatment is the en-bloc resection of the tumor, the ipsilateral thyroid lobe with gross clear margins and the adjacent involved structures, considering lymph node excision due to the high risk of local recurrence and metastases [38].

This review has several limitations. The first limitation relates to the database search: there may be studies published in databases other than Pubmed. A case series on 20 cases with NF1, osteomalacia, osteoporosis and hyperparathyroidism could not be retrieved in full-text and this is a second limitation [42]. A third limitation was represented by the characteristics of the included papers: most of them reported imaging technique but not the findings. Lastly, we did not plan to perform analyses for gene mutations.

CONCLUSION

In conclusion, this is the first well-documented report of a parathyroid carcinoma causing mild PHPT in NF1. To date, literature data do not support the syndromic association of PHPT and NF1, but the benefit of diagnosis and treatment of PHPT may outweigh costs associated with screening. A significant clinical, laboratory and imaging overlap between parathyroid adenoma and carcinoma may be present, thus a pre-operative differential diagnosis of parathyroid carcinoma is challenging. Therefore, even among small sporadic lesions, the clinician should consider the possibility of parathyroid carcinoma in initial evaluation as well as during follow-up.

LIST OF ABBREVIATIONS

CT	=	Computed Tomography
DEXA	=	Dual-Energy X-Ray Absorptiometry
FNAC	=	Fine-Needle Aspiration Citology
iPTH	=	Intact Parathyroid Hormone
MEN	=	Multiple Endocrine Neoplasia
MRI	=	Magnetic Resonance Imaging
NF1	=	Neurofibromatosis Type 1
PHPT	=	Primary Hyperparathyroidism
PTH	=	Parathyroid Hormone
SPECT-CT	=	Single Photon Emission Computed Tomography
US	=	Ultrasound

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

The case report was performed in accordance with the Helsinki Declaration of 1975, as revised in 2008 (http://www.wma.net/en/20activities/10ethics/10helsinki/).

STANDARD FOR REPORTING

CARE guidelines and methodology were followed to conduct the study.

CONSENT FOR PUBLICATION

A written informed consent was obtained from the patient prior to publication of this paper.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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