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Case report

Thyroid hemiagenesis, Graves' disease and differentiated thyroid cancer: a very rare association: case report and review of literature

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ABSTRACT

OBJECTIVE: Thyroid hemiagenesis is a rare congenital disorder characterized by the absence of a lobe and/or of isthmus. Studies on the association between thyroid hemiagenesis, Graves' disease and differentiated thyroid cancer are rare. CASE PRESENTATION: We describe the medical and surgical history of a patient in whom a molecular evaluation was performed. A 36-year-old man presented with symptoms and signs of hyperthyroidism of a few months' duration. Hyperthyroidism was confirmed biochemically and anti-TSH-receptor antibodies were positive. Thyroid ultrasonography showed no left lobe and demonstrated a diffused enlargement of the right lobe; an ipoechoic, non-homogenous nodule 15 millimeters in size was identified in the middle part of the lobe. A ^{99m}Tc-pertechnetate thyroid scintigraphy (111 MBq) confirmed thyroid hemiagenesis due to the absence of the left lobe. Treatment with methimazole (30mg/day) was started. As the patient's hyperthyroidism improved, he underwent fine-needle needle aspiration cytology (FNAC) of the right nodule. Cytology was suspicious for malignancy (THY4) and the patient was referred for surgery. Histopathological findings revealed a papillary thyroid carcinoma. The molecular analysis did not show PAX8 or TSHR mutations in the thyroid tissue nor mutations of BRAF, H-RAS, N-RAS or K-RAS genes in the tumor. CONCLUSION: Though thus far studies on the association of thyroid hemiagenesis, Graves' disease and differentiated thyroid cancer are extremely rare, the possibility of the development of thyroid cancer must be taken into account in patients affected by thyroid hemiagenesis and the nodular variant of Graves' disease.

Key words: Differentiated thyroid cancer, Graves' disease, Radioiodine treatment, Thyroid hemiagenesis

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INTRODUCTION

Thyroid hemiagenesis is a rare congenital anomaly in which one lobe and/or isthmus fail to develop. This condition was described for the first time by Handfield-Jones in 1866.

The etiology of thyroid hemiagenesis is unknown, with postulations of failure of descent from the foramen cecum to the trachea,[1] defects in lobulation[2] or genetic mechanisms.[3-5] Many genes have been identified as important contributors to proliferation and migration of thyroid cells precursors, acting during embryogenesis (NKX2-1, PAX8, FOXE1, NKX2-5, TSHR). However, mutations in such genes playing a role in thyroid morphogenesis have been reported in only a small minority of patients. In particular, a heterozygous mutation of the PAX8 gene has been proposed as being responsible for some familial cases.[6] However, Castanet et al,[7] having found no PAX-8 mutations in 22 patients with hemiagenesis, proposed other mutations (i.e. TTF-1, FOXE-1, TTF-2). It is likely that sporadic cases of hemiagenesis are caused by epigenetic factors rather than by mutations in thyroid transcription factors or genes involved in thyroid development.

Thyroid hemiagenesis is often discovered incidentally,[2,8] its incidence ranging from 0.025% to 0.16%.[3] Searching in the literature from 1970 and up to the present day, we have noticed how the association of thyroid hemiagenesis and differentiated thyroid cancer is rare,[4] while it is relatively common with Graves' disease (GD).

To date, only one female patient has been described in whom all three conditions were present.[5] Herein we report, for the first time, a male patient with thyroid hemiagenesis associated with GD and differentiated thyroid cancer and review the pertinent literature.

CASE PRESENTATION

Patient findings

A 36-year-old-man was referred to our outpatient clinic in July 2013 because of fatigue, palpitations, tremor, insomnia, sweating and weight loss of a few months' duration. Physical examination revealed warm, moist skin and hyper-reflexia; moreover, a diffuse enlargement of the right thyroid lobe was observed, while the left lobe was not-detected. His heart rate was 98 beats/minute and his mean blood pressure was 145/70 mmHg.

No photophobia and/or eyelid retraction were present on ophthalmological examination. Funduscopic and visual field examinations were within the normal range.

The serum TSH was 0.012 mU/l (normal range 0.270–4.2) and the serum free triiodothyronine (FT3) and free thyroxine (FT4) levels were elevated (FT3: 22.6 pg/ml, range 2.2–4.2; FT4: 34.4 pmol/L; normal range 9.0–16.0). Serum anti-TSH-receptor antibodies (TRAb) were markedly increased (20 IU/L; range 0-1.5), whereas anti-thyroglobulin antibodies (Tg-Ab) and anti-peroxidase antibodies (TPO-Ab) were absent.

Thyroid ultrasonography (US) did not show the left lobe and demonstrated a diffused enlargement of the right lobe, associated with hypoechogenicity and an increased thyroid blood flow. An ipoechoic, non-homogenous nodule (15 millimeters in size), with nodular microcalcifications and high intranodular blood flow by color-Doppler, was identified in the middle part of the lobe. The isthmus was not observed. A 99mTc-pertechnetate thyroyd scintigraphy (111 MBq), performed a few days later, confirmed thyroid hemiagenesis due to the absence of the left lobe. In the right lobe, the 99mTc-pertecnetate uptake was non-homogeneous and a cold nodule was detected in the middle part (Figure 1). No other family members were affected by thyroid hemiagenesis.

All findings were consistent with GD, nodular variant, in a patient affected by left thyroid lobe hemiagenesis and treatment with methimazole [MMI (20 mg/day)] was started. After several weeks, we observed a progressive improvement of symptoms and signs of thyrotoxicosis, as well as normalization of FT3 and FT4 values. Some weeks later, the patient underwent fine-needle aspiration cytology (FNAC) of the nodule located in the right lobe. Cytology was suspicious for malignancy (THY4) and the patient underwent surgery. Histopathological findings were conclusive for papillary thyroid carcinoma (PTC) associated with diffused hyperplasia and hypertrophy of follicular cells, without lymph-node metastases (pT1aN0Mx) (Figure 2).

After surgery, the patient was maintained on levothyroxine (L-T4) suppressive therapy, with serum

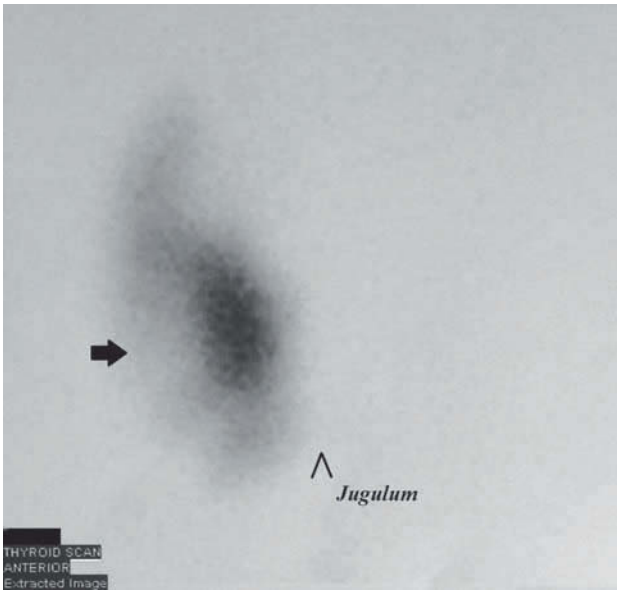

Figure 1. ^{99m}Tc-pertecnetate scintigraphy. Only the right thyroid lobe shows uptake (being intense and non-homogeneous) while no uptake was evident on the left side. The black arrow indicates a cold nodule corresponding to the finding of U/S.

TSH values <0.2 mUI/L and serum levels of FT3 and FT4 within the normal range. Serum levels of thyroglobulin (hTg) were undetectable (<0.15 ng/ml) and Tg-Ab were absent.

Three months later, neck US showed a right thyroid remnant but did not reveal any findings suspicious for neoplastic/metastatic disease in the lymph nodes. The patient underwent radioiodine treatment (RaIT) with ablative activity of 131I (2220 MBq) on levothyroxine therapy and after recombinant human TSH (rhTSH) stimulation (0.9 mg daily for two consecutive days administered by intra-muscular injections). The post-therapy whole body scan, performed 5 days later, showed an intense and well defined radioiodine uptake located in the right thyroid bed, consistent with thyroid remnant tissue At the time of the RaIT, serum peak level of TSH and hTg were 117 mU/l and 31 ng/ml, respectively. In the absence of Tg-Ab (<4 UI/ml), hTg levels were consistent with the persistence of the thyroid remnant only.

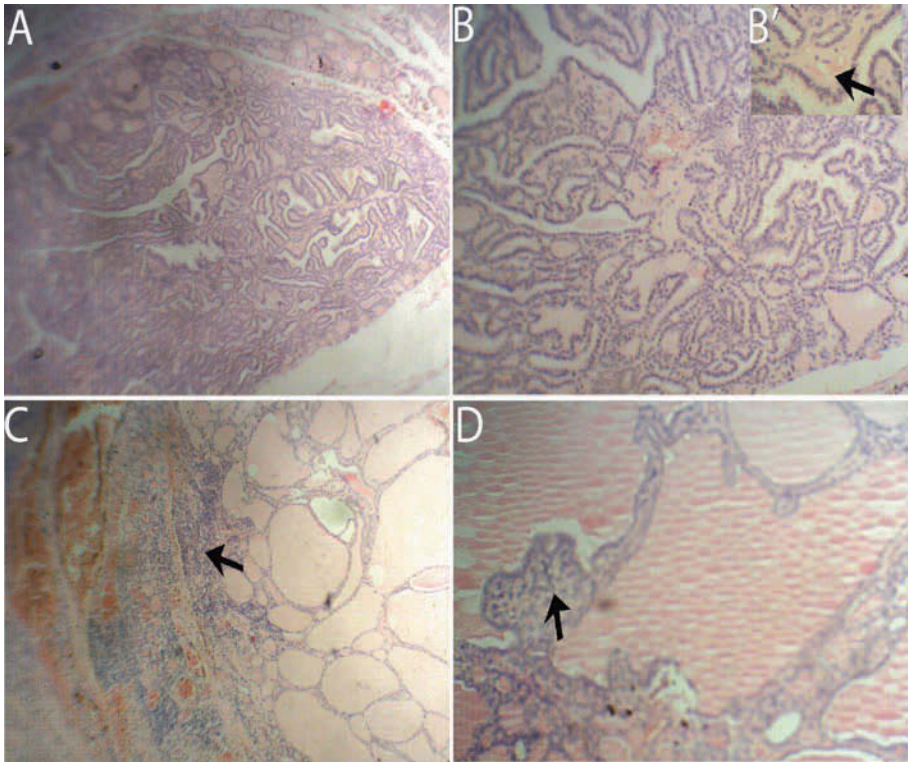

Figure 2. Histological features of papillary thyroid microcarcinoma occurring in the context of Graves' disease**. Panel A**: Unifocal papillary carcinoma (pT1aNxMx) (Ob. X4, Oc. X10). **Panel B**: Papillary architecture of the carcinoma with branching (Ob. X10, Oc.X10). **Panel B´**: Fibrovascular core of papillae (arrow) covered by cells with eosinophilic cytoplasm and enlarged nuclei with nuclear clearing (Ob. X40, Oc. X10). **Panel C**: Macrofollicular goiter with peripheral areas of moderate lymphocitic infiltration (arrow) (Ob. X4, Oc. X10). **Panel D**: Pseudopapillary architecture without a fibrovascular core of papillae (arrow) and nuclear clearing of cells (Ob. X10, Oc. X10).

Twelve months later, basal and stimulated serum levels of hTg (after rhTSH-stimulation) were undetectable and Tg-Ab were absent. Neck US was negative for thyroid remnant tissue and/or loco-regional metastases. Thus, the patient was declared "disease free".

Molecular studies

The surgical thyroid specimens were analyzed for mutations of the PAX8 gene, since PAX8 is considered the main regulator of thyroid morphogenesis. The TSH receptor (TSHR) gene was also studied. Moreover, the tumour nodule was examined for activating mutations of H-RAS, N-RAS, K-RAS and BRAF genes by direct sequencing.

Extraction of somatic DNA from the surgical specimens was performed with the Nucleospin Tissue Kit (Macherey-Nagel, Germany), according to the manufacturer's instructions.

The DNA samples were used for directly sequencing exon 15 of the BRAF gene, exons 1 and 2 of the H-RAS, K-RAS and N-RAS genes, exons 1-10 of the TSHR gene and exons 3-12 of the PAX8 gene. Direct sequencing of polymerase chain reaction (PCR) products was performed using the Big Dye Terminator v1.1 cycle sequencing kit (Applied Biosystems, Foster City, CA) and an automatic ABI310 sequencer (Applied Biosystems). The employed primers are shown in Table 1. All the above exons were ampli-

Table 1. Sequences (5'-3') of the primer pairs employed.

Gene/Exon	Forward oligo	Reverse oligo
TSHR Ex 1	GATTTCGGAGGATGGAGA	ACACTCACACACTACTTCGG
TSHR Ex 2	GCCCAATGATTAAAACTCTAA	ACTGCCATTGATTTATGCAAG
TSHR Ex 3	ATCTGGGAAGCGCATAAC	GCTTAGGTCTATGCTGCACT
TSHR Ex 4	CCTGTGGCGTAAATGCATA	CCAGAAAAGTAGGATGGGA
TSHR Ex 5	GAAGGTGTTGGGAGTTTG	CAACCTACCCTCATGACTGT
TSHR Ex 6	TAAGTGCATATGCGCAGC	GGAGGGAGTAGAACTGGTAA
TSHR Ex 7	CAACTCTCCAGAAACAGGC	CATTGGATGGTTAGGGTAAGG
TSHR Ex 8	TCTCTCTCTCCCTCTAGAAGC	AAAGAGGGACTTGCAGAAGC
TSHR Ex 9	CTCACTGCCTCTCTGCATTT	ATTCCACTTCCACCAAGGTC
	GGATTACAGTCATGAGCCACT	GGTGTCATGGGATTGGAA
TSHR Ex 10	TATCGGTGTATACGCTGACG	GGCGAAGGTGATGGCATA
	AGATCATTGGTTTTGGCCAG	CTGGAAGGCCTTGGTGAA
PAX-8 Ex 3	CATAGCTAATCCCCACCCAAAC	GCCTGCGGTGAATTTCGT
PAX-8 Ex 4	ATTGGGTAATTCTTTGGGATTC	CCAGGCCTTTCTTGTCTCTT
PAX-8 Ex 5	AGGGGTGTCAAAAAGGCGACTG	TGGGTATGCTGGGGGAGGTG
PAX-8 Ex 6	TCTCCCTCTCCCCCACTG	GCAGAGCCCCTACAAAGTCC
PAX-8 Ex 7	GAGCATGAATGATAGGTCCC	CACAGGCTCATTTGGAGAAT
PAX-8 Ex8	GTCTCTGTGCGCTGACTTCT	CACACCTTCCGCCTGAC
PAX-8 Ex 9	CCTCCCCGCCATCTCACACC	TCCCACCCGCCGCCATAG
PAX-8 Ex10	CCCCCATGGTCCAACTGAC	CCTCTTGCTCCTTGTGTCCCAC
PAX-8 Ex 11	TGCATTGATGCCCTTCACCTCA	AGGTAACCTTTGACCCACCCTT
PAX-8 Ex 12	AAAGGTCAGCAGATGCAGGGAA	CGCAATGCTGGACTTTGTGGTTA
H-RAS Ex 1	ATGACGGAATATAAGCTGGT	CTCTATAGTGGGGTCGTATT
H-RAS Ex 2	AGGTGGTCATTGATGGGGAG	AGGAAGCCCTCCCCGGTGCG
K-RAS Ex 1	GGCCTGCTGAAAATGACTGAA	GGTCCTGCACCAGTAATATGC
K-RAS Ex 2	CAGGATTCCTACAGGAAGCAAGTAG	CACAAAGAAAGCCCTCCCCA
N-RAS Ex 1	ATGACTGAGTACAAACTGGT	CTCTATGGTGGGATCATATT
N-RAS Ex 2	TCTTACAGAAAACAAGTGGT	GTAGAGGTTAATATCCGCAA
B-RAF Ex 5	GCTTGCTCTGATAGGAAAATG	GTAACTCAGCAGCATCTCAG

fied by PCR as follows: initial denaturation for 5 min (94˚C), followed by 30 cycles of 30 sec at 94˚C, 30 sec at the appropriate annealing temperature and 30 sec at 72˚C, followed by a final 5-min elongation at 72˚C. The annealing temperature was 53° C for N-RAS exon 2; 55˚C for BRAF exon 15, H-RAS and K-RAS exon 1, TSHR exons 1-8, PAX8 exon 4; 57° C for H-RAS exon 2, N-RAS exon 1 and PAX8 exon 3; 58° C for K-RAS exon 2 and PAX8 exons 7 and 8; 59˚C for TSHR exons 9 and 10, and for PAX8 exon 11; 61° for PAX8 exons 5 and 9; 62 °C for PAX8 exon 10; 63 °C for PAX8 exon 12. The PCR products were purified using the Nucleospin Extract II kit (Macherey-Nagel, Germany).

The full-length TSHR and PAX8 sequence and the RAS and the BRAF sequences present in the GenBank database were used for mutagenesis analysis.

However, no genetic alterations were found either in the tumour or in the surrounding thyroid tissue.

DISCUSSION

Thyroid hemiagenesis is a rare developmental anomaly, with a female predominance (F:M ratio 3:1),[9] the most common feature being absence of the left lobe (L:R ratio 4:1).[1] The presence or absence of the isthmus is variable (50% of cases).[9] Currently, the prevalence of thyroid hemiagenesis is estimated to be from 0.025% to 0.16%, according to the literature,[9] and it seems to be higher in iodine-deficient areas.[10] However, a true incidence of thyroid hemiagenesis is very difficult to verify, since the absence of a lobe and/or isthmus is often clinically irrelevant and the diagnosis is frequently incidental in the setting of accompanying thyroid disorders.

We have searched the literature which includes approximately 350 cases described to date. In the majority of patients (195/350 or 56%), the hemiagenesis was associated with another thyroid disease, hypothyroidism and/or Hashimoto thyroiditis being the most common. The associations, however, include a wide range of thyroid diseases: euthyroid multinodular goiter,[1] Hashimoto thyroiditis,[1] congenital hypothyroidism,[3] hypothyroidism,[10] hyperthyroidism (due to GD or nodular toxic goiter), differentiated thyroid cancer,[10,11] accessory lingual thyroid[1] and thyroglossal duct cyst.[1]

Only 40 patients (33 F and 7 M, mean age 37.2 ± 14.2, range 7-63 years) with thyroid hemiagenesis and GD have been reported in the literature to date (Table 2). With the exception of a case in which data were missing, the thyroid hemiagenesis was on the left in 29 patients (74.4%) and on the right in 9 (23.1%), while isolated isthmus absence was present only in one patient (2.5%). All patients with right hemiagenesis were women, while 7 men (24.1%) and 22 women (75.9%) had a left hemiagenesis. The only patient with isolated isthmus agenesis was a woman. Thus, 82.5% of patients with association of hemiagenesis and GD were women, they were younger than the men (p=0.20) and the hemiagenesis was prevalently on the left lobe (76.3%).

Searching for the association between thyroid hemiagenesis and cancer, we found 15 patients (14 females and 1 male, mean age 48.57±15.9, range 14 to 74 years)[2,4,5,8,10-20] (Table 3). Thyroid hemiagenesis was on the left in 8 cases (7 F and 1 M, mean age 50.5±17.1, range 14-69) and on the right in 6 (all women; mean age 47.8±16.5, range 30-74), while only one woman presented isolated isthmus absence. Among these patients, 12 (80%; 11 females aged 30-70 yr and 1 54-yr-old male) were affected by PTC, a woman had a follicular thyroid cancer (FTC) and another woman a medullary thyroid carcinoma (MTC), while the coexistence of PTC and FTC was observed in a third woman. Once again, the above mentioned conditions were significantly prevalent in the female gender.

Limiting the research to patients with GD, hemiagenesis and thyroid cancer, only one case was reported in the literature.[5] Ammaturo et al described a 39-year-old woman with GD, left hemiagenesis and papillary thyroid cancer. As in our patient, the diagnosis of thyroid hemiagenesis was incidentally obtained via instrumental thyroid studies performed to better define a hyperthyroid state. No molecular studies were performed in this patient.

In conclusion, we describe the first case of a male patient affected by thyroid hemiagenesis, GD and differentiated thyroid cancer. To date, only one female patient has previously been reported in the literature. In our patient we failed to identify any gene mutation. Although this condition is extremely rare, the

Table 2. Thyroid hemiagenesis associated with Graves' disease

Patient n	Gender	Age	Thyroid Hemiagenesis Tomography	Isthmus	Image Studies
1	F	N/S	Left	N/S	S
2	F	28	Left	NO	S
3	F	39	Left	NO	S
4	F	21	Left	NO	S
5	F	28	Right	NO	S
6	F	58	Left	YES	S
7	M	53	Left	N/S	S
8	F	28	Right	N/S	S
9	F	40	Left	YES	S
10	F	41	Left	YES	S
11	F	58	Left	N/S	S
12	F	55	Left	N/S	S
13	F	30	Right	N/S	S
14	F	23	Right	N/S	S
15	M	52	Left	N/S	S
16	F	28	Right	N/S	S
17	F	20	Left	N/S	S
18	F	35	Left	N/S	S
19	M	30	Left	YES	S
20	F	43	Left	N/S	S
21	F	16	Left	N/S	S
22	F	47	Right	N/S	S; US
23	M	31	Left	YES	S
24	M	17	Left	YES	S
25	N/S	N/S	N/S	N/S	N/S
26	F	42	Right	N/S	N/S
27	M	57	Left	NO	S; US
28	F	35	Left	N/S	N/S
29	N/S	N/S	N/S	N/S	N/S
30	F	31	Left	YES	S; US
31	F	44	N/S	N/S	S; US
32	F	29	Left	NO	S; US
33	F	28	Right	N/S	S; US
34	F	41	Left	YES	S; US
35	F	49	Left	YES	S; US
36	F	7	Left	N/S	S; US
37	F	55	Left	NO	S; US
38	F	43	Left	N/S	S; US
39	M	63	Left	NO	S; US
40	F	8	Left	YES	S; US
41	F	41	Isthmus	NO	S; US
42	F	50	Right	NO	S; US

N/S: not specified; US: thyroid ultrasonography; S: thyroid scintigraphy.

Table 3. Thyroid hemiagenesis associated with Thyroid cancer

Study	Patients n.	Age	Gender	Thyroid Hemiagenesis	Nodule Tomography	Thyroid tumor
Hamburger JI et al, 1970 (13)	1	14	F	Left	Right Lobe	PTC+FTC
Harada T et al, 1972 (14)	1	74	F	Right	Left Lobe	PTC
Greening WP et al, 1980 (2)	1	51	F	Left	Right Lobe	PTC
Khatri VP et al, 1992 (15)	1	41	F	Right	Left Lobe	PTC
McHenry CR et al, 1995 (11)	1	58	F	Left	Right Lobe	FTC
Shaha AR et al, 1997 (4)	1	30	F	Right	Left Lobe	PTC
Huang SM et al, 2002 (16)	1	47	F	Right	Left Lobe	PTC
Pizzini AM et al, 2005 (8)	1	54	M	Left	Right Lobe	PTC
Ammaturo C et al, 2007 (5)	1	39	F	Left	Right lobe	PTC
Lee YS et al, 2008 (12)	1	69	F	Left	Right Lobe	PTC
Berni Canani F et al, 2008 (17)	1	35	F	Right	Thyroglossal duct	PTC*
Wang J et al, 2013 (20)	2	49 (60)#	F (F)#	Right (Left)#	Left Lobe (Right lobe)#	MTC (PTC)#
Karatag GY et al, 2013 (18)	1	59	F	Left	Right Lobe	PTC
Vayisoglu Y et al, 2013 (19)	1	N/S	F	Isthmus	Right Lobe	PTC

N/S: not specified; FTC: follicular thyroid carcinoma; PTC: papillary thyroid carcinoma; MTC: medullary thyroid carcinoma.
*Papillary carcinoma of a thyroglossal duct cyst; #Second patient.

possibility of developing a thyroid cancer must be taken into account in patients affected by thyroid hemiagenesis and the nodular variant of GD.

CONFLICT OF INTEREST

There is no potential conflict of interest and the authors have nothing to disclose.

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