CASE REPORT

Lingual thyroid and hyperthyroidism: A new case and review of the literature

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ABSTRACT. Lingual thyroid is the result of a defective migration of the thyroid anlage occurring between the 3rd and 7th week of gestation. Whereas mutations in the transcription factor-2 (TTF-2) and PAX8 and in the TSH receptor genes (TSH-R) have been reported in a minority of patients with thyroid dysgenesis, the etiopathogeny of the majority of cases, and in particular of thyroid ectopy, remains unclear. The majority of patients with thyroid ectopy are asymptomatic, but obstructive symptoms as well as hypothyroidism have been observed. Hyperthyroidism is an exceptionally rare finding. To our knowledge, only 2 cases have been reported in the literature to date. Herein, we describe an unusual case of thyrotoxicosis related to a nodular lesion in a lingual thyroid. Treatment consisted in restoration of a euthyroid state with thionamide followed by surgical removal of the ectopic gland. The underlying molecular cause of the ectopic lingual thyroid and the toxic adenoma in this case could not be identified. We speculate that abnormally early differentiation of the thyroid gland could interfere with the migration process, a hypothesis yet to be confirmed.

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INTRODUCTION

Ectopic thyroid tissue is the result of abnormal migration of the gland from the foramen caecum to its final pre-tracheal position. It may be found in four major regions: lingual, sublingual, thyroglossal, and intralaryngotracheal (1). Other locations have also been documented including mediastinum (2), esophagus (3), heart (4), and cervical lymph nodes (5).

Lingual thyroid, first described by Hickman in 1869 accounts for approximately 90% of ectopic thyroid tissue (6). However, it is a rare entity found in 1/100.000 people with a female preponderance (7). Together with thyroid agenesis and hypoplasia, thyroid ectopy is classified as thyroid dysgenesis, in opposition to dyshormonogenesis. While mutations in a series of genes involved in thyroid hormone synthesis have been identified in the latter [TG, Thyroid peroxidase (TPO), Sodium dependent iodide symporter (NIS), Pendrin], only rare cases of mutations in PAX8, transcription factor-2 (TTF-2) and TSH receptor genes have been found in the former.

Although clinical manifestations of obstruction and bleeding have been observed (8, 9), the majority of patients with this condition are asymptomatic. In other patients, subclinical and overt hypothyroidism are present at the time of diagnosis (6), whereas hyperthyroidism is uncommon. To our knowledge, thyrotoxicosis related to a nodular lesion in a lingual thyroid has not been reported.

CASE STUDY

A 26-year-old woman was seen in an outpatient endocrinology clinic in 1995 because of excessive weight loss. She complained of palpitations, heat intolerance, insomnia, diaphoresis and nervousness. Personal past medical history was not significant. Thyroid gland could not be palpated on physical examination. Laboratory findings revealed a thyrotoxicosis with a low TSH <0.03 mU/l (normal range

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(N)=0.2-4), and high free thyroid hormone levels FT4: 19 pg/ml (N=7-15), FT3: 5.38 pg/ml (N=2-4.1). Thyroid stimulating immunoglobulins (TSI) were undetectable and erythrocyte sedimentation rate (ESR) was normal. Technetium scintiscan showed no uptake in the pretracheal area while TG level was 94 µg/l (N<25). No thyroid ultrasound was performed at that time, and the diagnosis of silent thyroiditis was retained. Carbimazole treatment was started, and the patient went into euthyroid state but discontinued the medication on her own a few months later.

In November 1996, the patient was referred to our hospital because symptoms of hyperthyroidism recurred. She denied dysphagia or dyspnea. Thyroid function tests revealed a new episode of hyperthyroidism (TSH <0.05 mU/l, FT4: 21.4 pg/ml, TG:127 µg/l and undetectable TSI). Urinary iodine excretion was normal. Technetium scintiscan revealed no uptake in the pretracheal area and ultrasound confirmed the absence of the thyroid gland in its normal anatomical position. An ectopic thyroid tissue was suspected: a total body I123 scan was done and showed an uptake of 6.4% at 5 h just below the chin.

An oropharyngeal examination revealed a pinkish red mass at the base of the tongue. MRI of the neck disclosed a mass of 4 cm in diameter, isointense in T1, protruding into the oropharynx and displacing the tongue anteriorly (Fig. 1).

The patient was treated with Carbimazole (20 mg/day) which improved her symptoms and normalized her thyroid tests. She was referred to surgery 8 months later.

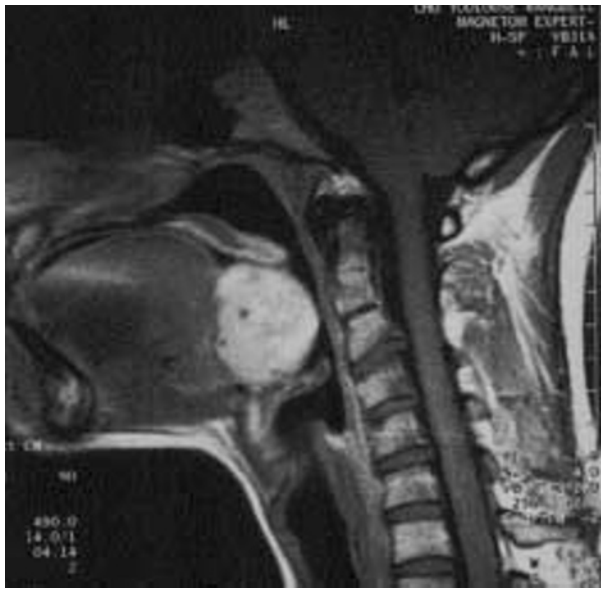

Fig. 1 - *T1 sagittal MRI of the neck showing an isointense 4 cm mass protruding into the oropharynx.*

Intraoperatively, a supra hyoid mass was discovered and resected along with the hyoid bone and the previously identified ectopic thyroid tissue. Histology showed an encapsulated nodular lesion consisting of benign thyroid tissue. No hemorrhage or inflammatory cellular infiltration was noted. Postoperatively the patient received thyroid replacement therapy. Since then, she has been free of symptoms and doing well on LT_4 (150 µg/day).

DISCUSSION

Thyroid primordium begins as a thickening of the epithelium in the pharyngeal floor that later forms a diverticulum and starts its descent caudally towards its final pretacheal position. This process is regulated by a gene encoding TTF-2 as evidenced from knock-out mice, showing impaired migration (10, 11). Recently, a transcription factor FKHL15 was reported as the human homologue of mouse TTF-2. A missense mutation within its forkhead domaine was identified in 2 siblings with thyroid agenesis, cleft palate and cloanal atresia, underlining its potential role in thyroid embryogenesis (12).

Functional thyroid differentiation and development require coordinate expression of TSH and its receptor (13, 14), as well as transcription factors TTF-1, TTF-2 and PAX8. Up to now, only rare patients with thyroid dysgenesis have been found to bear mutations in one of these genes. While Macchia *et al.* (15) found 3 infants with mutations in the PAX8 gene out of 145 infants with thyroid dysgenesis, Lapi *et al.* (16) failed to find TTF-1 mutation in 61 infants with congenital hypothyroidism. Perna *et al.* (17) studied 15 patients with thyroid agenesis, sublingual ectopic thyroid, and severe hypoplasia. The molecular analysis did not identify any TTF-1 mutation among these patients. In the face of these conflicting data, the etiopathogeny of the majority of the cases of thyroid dysgenesis remains to be identified.

Among patients with lingual thyroid, hypothyroidism was documented in approximately 30% of the cases (6). Subclinical hypothyroidism as well as compressive symptoms (18-21) related to the gland size and the presence of other acute process such as bleeding (9) have also been reported. However, most lingual thyroid glands are asymptomatic (22, 23), and hyperthyroidism has been described in only few patients. In 1966, Kuehn *et al.* (24) reported a case of Graves' disease in a hyperplastic ectopic thyroid tissue in the subhyoid

area, which was removed surgically but recurred in the lateral thyroid lobe and at the base of the tongue 3 yrs later. A similar case of Graves' disease involving an ectopic subhyoid thyroid was described by Azzam *et al*. (25). Recently, an unusual case of T_3 toxicosis with low thyroid RAIU due to a large *struma ovarii* was published making ovaries an additional but rare ectopic site of hyperfunctioning thyroid tissue (26).

To our knowledge, a case like ours has not been published. Our patient presented two episodes of thyrotoxicosis related to a toxic adenoma in a lingual thyroid. The diagnosis was missed the first time. Therefore, we stress the considerable benefit of ultrasound study in hyperthyroid patients with unpalpable thyroid, absent cervical uptake on scintiscan and detectable thyroglobulin level.

Germline gain of function mutations of the TSH-R gene have been identified as the cause of hereditary (27-29) and sporadic (30, 31) non autoimmune toxic thyroid hyperplasia, whereas somatic mutations in the TSH-R gene and Gs alpha protein (gsp) are considered the major molecular cause of toxic adenomas (32-34). The frequency with which these activating mutations are found in autonomously functioning thyroid nodules is variable, ranging from as high as 80% (35) to as low than 10% (36). One potential reason suggested for this apparent discrepancy is related to differences in iodine exposure. Patients from iodine deficient areas appear to have a higher frequency of TSH-R mutations, whereas those from iodine sufficient regions, where toxic adenomas, are scarce, have fewer. It should be noted that urinary iodine excretion in our patient was normal. Unfortunately, fixation of the thyroid tissue obtained at surgery has not made it possible to search for gain of function mutations of the TSH receptor or the gsp, and the underlying genetic basis of hyperthyroidism in this patient remains unknown.The observation that ectopic thyroid tissue produces adequate amounts of thyroid hormones in the majority of cases (22, 23) and, as in the present case, can even lead to autonomy and thyrotoxicosis, demonstrates that migration of the tissue to its normal location is not a prerequisite to normal tissue differentiation. Whereas several cases with mutations in the TSH-R (13, 14) or TSH beta (37-39) genes indicate that the TSH-cyclic cAMP regulatory pathway is not involved in migration of the thyroid, it can be hypothesized, in contrast, that abnormally early differentiation of the gland could interfere with the migration process. Whether the present case is an illustration of this hypothesis or not, will have to await molecular analysis of further such cases.

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REFERENCES

1. Dossing H., Jorgensen K.E., Oster-Jorgensen E., Krogdahl A., Hegedüs L. Recurrent pregnancy-related upper airway obstruction caused by intratracheal ectopic thyroid tissue. Thyroid 1999, *9:* 955-958.
2. Basaria S., Cooper D. Grave's disease and recurrent ectopic thyroid tissue. Thyroid 1999, *9:* 1261-1264.
3. Noyek A.M., Friedberg J. Thyroglossal duct and ectopic thyroid disorders. Otolaryngol. Clin. North Am. 1981, *14:* 187-201.
4. Pollice L., Caruso G. Struma cordis. Ectopic thyroid goiter in the right ventricle. Arch. Pathol. Lab. Med. 1986, *110:* 452-453.
5. Roth L.M. Inclusions of non-neoplastic thyroid tissue within cervical lymph nodes. Cancer 1965, *18:* 105-111.
6. Neinas F.W., Gorman C.A., Devine K.D., Woolner L.B. Lingual thyroid: clinical characteristics of 15 cases. Ann. Intern. Med. 1973, *79:* 205-210.
7. Devos H., Rodd C., Gagne N., Laframboise R., Van Vliet G. A search for the possible molecular mechanisms of thyroid dysgenesis: Sex ratios and associated malformations. J. Clin. Endocrinol. Metab. 1999, *84:* 2502-2506.
8. Arancibia P., Veliz J., Barria M., Pineda G. Lingual thyroid: report of three cases. Thyroid 1998, *8:* 1055-1057.
9. Maurice N., Makeieff M., Delol J., *et al.* La thyroïde ectopique linguale à propos de trois cas. Ann. Otolaryngol. Chir. Cervicofac. 1995, *112:* 399-405.
10. Macchia P.E., Mattei M.G., Lapi P., Fenzi G., Di Lauro R. Cloning, chromosomal localization and identification of polymorphism in the human thyroid transcription factor 2 gene (TITF2). Biochimie 1999, *81:* 433-440.
11. De Felice M., Ovitt C., Biffali E., *et al.* A mouse model for hereditary thyroid dysgenesis and cleft palate. Nat. Genet. 1998, *19:* 395-398.
12. Clifton-Bligh R.J., Wentworth J.M., Heinz P., *et al.* Mutation of the gene encoding human TTF-2 associated with thyroid agenesis, cleft palate and choanal atresia. Nat. Genet. 1998, *19:* 399-401.
13. Gagne N., Parma J., Deal C., Vassart G., Van Vliet G. Apparent congenital athyreosis contrasting with normal plasma thyroglobulin levels and associated with inactivating mutations in the thyrotropin receptor gene: Are athyreosis and ectopic thyroid distinct entities? J. Clin. Endocrinol. Metab. 1998, *83:* 1771-1775.
14. Abramowicz M.J., Duprez L., Parma J., Vassart G., Heinrichs C. Familial congenital hypothyroidism due to inactivating mutation of the thyrotropin receptor causing profound hypoplasia of the thyroid gland. J. Clin. Invest. 1997, *99:* 3018-3024.

15. Macchia P.E., Lapi P., Krude H., *et al.* Pax8 mutations associated with congenital hypothyroidism caused by thyroid dysgenesis. Nat. Genet. 1998, *19:* 83-86.
16. Lapi P., Macchia P.E., Chiovato L., *et al.* Mutations in the gene encoding thyroid transcription factor -1 (TTF-1) are not a frequent cause of congenital hypothyroidism with thyroid dysgenesis. Thyroid 1997, *7:* 383-387.
17. Perna M.G., Civitareale D., De Filippis V., *et al.* Absence of mutations in the gene encoding thyroid transcription factor-1 (TTF-1) in patients with thyroid dysgenesis. Thyroid 1997, *7:* 377-381.
18. Koch C.A., Picken C., Clement S.C., Azumi N., Sarlis N.J. Ectopic lingual thyroid: An otolaryngologic emergency beyond childhood. Thyroid 2000, *10:* 511-514.
19. Chanin L.R., Greenberg L.M. Pediatric upper airway obstruction due to ectopic thyroid: classification and case reports. Laryngoscope 1988, *98:* 422-427.
20. Guerin N., Urtasun A., Chauveau E., *et al.* Thyroïde linguale et kyste thyreo-glosse basi-lingual. A propos de deux cas. Rev. Laryngol. Otol. Rhinol. 1997, *118:* 183-188.
21. Turgut S., Murat Ozcan K., Celikkanat S., Katirci H., Ozdem C. Diagnostic et traitement de la thyroïde linguale: revue de la littérature. Rev. Laryngol. Otol. Rhinol. 1997, *118:* 189-192.
22. Kamat M.R., Kulkarni J.R., Desai P.B., Jussawalla D.J. Lingual thyroid: A review of 12 cases. Br. J. Surg. 1979, *66:* 537-539.
23. Kaplan M., Kauli R., Lubin E., Grunebaum M., Laron Z. Ectopic thyroid gland. A clinical study of 30 children and review. J. Pediatr. 1978, *92:* 205-209.
24. Kuehn P.G., Newell R.C., Reed J.F. Exophtalmos in a woman with lingual, subhyoid and lateral lobe thyroid glands. N. Engl. J. Med. 1966, *274:* 652-654.
25. Azzam A., Nitunga N., Baulieu J.L., *et al.* Ectopie thyroïdienne et maladie de Basedow. Presse Med. 1988, *17:* 383-385.
26. Simkin P.H., Ramierz L.A., Zweizig S.L., *et al.* Monomorphic teratoma of the ovary: a rare cause of triiodothyronine toxicosis. Thyroid 1999, *9:* 949-954.
27. Grüters A., Schöneberg T., Biebermann H., *et al.* Clinical Case Seminar: Severe congenital hyperthyroidism caused by a germ-line neo mutation in the extracellular portion of the thyrotropin receptor. J. Clin. Endocrinol. Metab. 1998, *83:* 1431-1436.
28. Duprez L., Parma J., Van Sande J., *et al.* Germline mutations in the thyrotropin receptor gene cause non-autoimmune autosomal dominant hyperthyroidism. Nat. Genet. 1994, *7:* 396-401.
29. Tonacchera M., Van Sande J., Cetani F., *et al.* Functional characteristics of three new germline mutations of the thyrotropin receptor gene causing autosomal dominant toxic thyroid hyperplasia. J. Clin. Endocrinol. Metab. 1996, *81:* 547-554.
30. Kopp P., Jameson L., Roe T. Congenital nonautoimmune hyperthyroidism in a nonidentical twin caused by a sporadic germline mutation in the thyrotropin receptor gene. Thyroid 1997, *7:* 765-770.
31. Esapa C.T., Duprez L., Ludgate M., *et al.* A novel thyrotropin receptor mutation in a infant with severe thyrotoxicosis. Thyroid 1999, *9:* 1005-1010.
32. Van Sande J., Parma J., Tonacchera M., *et al.* Somatic and germline mutations of the TSH receptor gene in thyroid diseases. J. Clin. Endocrinol. Metab. 1995, *80:* 2577-2585.
33. Führer D., Kubisch C., Scheibler U., *et al.* The extracellular thyrotropin receptor domain is not a major candidate for mutations in toxic thyroid nodules. Thyroid 1998, *8:* 997-1001.
34. Duprez L., Parma J., Van Sande J., *et al.* Pathology of the TSH receptor. J. Pediatr. Endocrinol. Metab. 1999, *12:* 295-302.
35. Parma J., Van Sande J., Swillens S., *et al.* Somatic mutations causing constitutive activity of the thyrotropin receptor are the major cause of hyperfunctioning thyroid adenomas: identification of additional mutations activating both the cyclic adenosine 3',5'-monophosphate and inositol phosphate-Ca^{2+} cascades. Mol. Endocrinol. 1995, *9:* 725-733.
36. Takeshita M., Nagayama Y., Yokoyama N., *et al.* Rarity of oncogenic mutations in the thyrotropin receptor of autonomously functioning thyroid nodules in Japan. J. Clin. Endocrinol. Metab. 1995, *80:* 2607-2611.
37. Biebermann H., Liesenkotter K.P., Emeis M., Oblanden M., Grüters A. Severe congenital hypothyroidism due to a homozygous mutation of the beta TSH gene. Pediatr. Res.1999, *46:* 170-173.
38. Doeker B.M., Pfaffle R.W., Pohlenz J., Andler W. Congenital central hypothyroidism due to a homozygous mutation in the thyrotropin beta-subunit gene follows an autosomal recessive inheritance. J. Clin. Endocrinol. Metab. 1998, *83:* 1762-1765.
39. Medeiros-Neto G., Herodotou D.T., Rajan S., *et al.* A circulating, biologically inactive thyrotropin caused by a mutation in the beta subunit gene. J. Clin. Invest. 1996, *97:* 1250-1256.