CASE REPORT

# Aggressive behavior of papillary microcarcinoma in a patient with Graves' disease initially presenting as cystic neck mass

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**ABSTRACT. Prognosis of papillary carcinoma of the thyroid associated with Graves' disease is controversial; nevertheless, tumors smaller than 1 cm (microcarcinoma) are usually considered to render a good prognosis. We describe a patient with Graves' disease who developed a lateral cystic neck mass that was later confirmed to be a metastatic lymph node from papillary thyroid microcarcinoma. Contrary to having a good prognosis with a microcarcinoma, our patient developed bilateral lung metastases. The possible role of thyroid stimulating immunoglobulins in the aggressive course of the tumor is discussed.**

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## INTRODUCTION

The course of papillary thyroid carcinoma in patients with Graves' disease is considered to be more aggressive than in euthyroid patients (1), although controversy exists on this issue (2). Thyroid stimulating antibodies (TSI) are presumed to play an important role in the aggressive nature of these tumors in patients with Graves' disease. These antibodies increase cAMP production and stimulate thyrocyte proliferation and tumor growth in some differentiated tumors expressing TSH receptors (3, 4).

Cystic lymph node metastases are an unusual initial manifestation of papillary microcarcinoma and are usually associated with a good prognosis (5). The association of Graves' disease with papillary microcarcinoma presenting as cystic lymph node metastases has not been previously reported. We herein describe the occurrence of an aggressive papillary microcarcinoma presenting initially as a large cystic mass in association with Graves' disease. The possible role of thyroid stimulating antibodies in promoting the aggressiveness of the tumor is discussed.

## CASE DESCRIPTION

A 28-yr-old woman presented to an outside hospital in March 1998 with 1-yr history of a progressively enlarging mass on the right side of the neck along with signs and symptoms of hyperthyroidism. She denied any hoarseness, dyspnea or dysphagia. Initial laboratory results were as follows: $T_3$=526.8 ng/dl (normal range 45 to 137 ng/dl), total $T_4$>24 µg/dl (4.5 to 12 µg/dl) and TSH<0.01 mU/l (0.5 to 5 mU/l). A technetium scan was consistent with Graves' disease without evidence of any focal abnormalities. Antithyroid antibodies were negative and TSI were elevated at 20.9 U/l (positive higher than 10 U/l).

The patient was started on propylthiouracil 300 mg 3 times a day. An ultrasound of the neck showed a diffusely enlarged thyroid gland without any nodules, with a hypoechoic and heterogeneous pattern. A 3.0x1.4 cm cystic lesion in the right lateral aspect of the neck was noted along with a vascular solid component. The chest X-ray was normal. In January 1999, she was referred to us for further evaluation.

*Key-words:* Cystic metastatic lymph node, papillary thyroid carcinoma, papillary thyroid microcarcinoma, Graves' disease.

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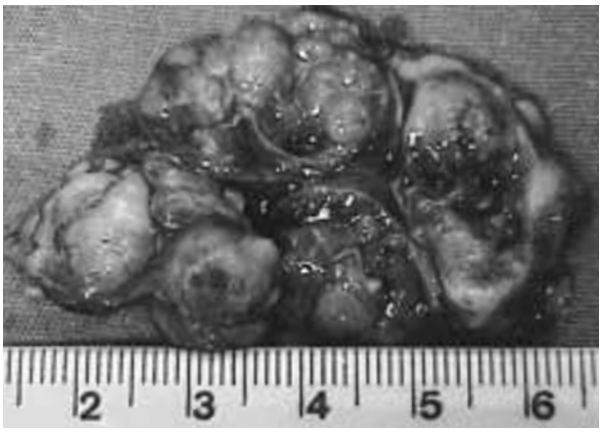

Fig. 1 - *Cystic mass fused with lymph nodes.*

Fig. 2 - *Right lobe showing the primary lesion and intra-thyroidal metastases.*

On physical examination, her pulse rate was 96 beats/min and blood pressure 120/90 mmHg. The skin was warm and moist and the patient was tremulous. Her extraocular movements were normal without lid lag or retraction. The thyroid gland was diffusely enlarged, soft and without palpable nodules, with an estimated weight of 80 g. A 4-cm tender and mobile mass was palpable anterior to the right sternocleidomastoid muscle along with two lymph nodes, each 1-2 cm in diameter.

A repeat ultrasound confirmed the cystic component of the lesion, measuring 4.0 x 2.3 cm. A fine needle aspiration biopsy was performed and 3 ml of brownish fluid was aspirated and a few thyroid follicular cells without any atypia were seen on the smear. The TG content of the fluid was 1,469,646 ng/ml. The patient was prepared for surgery with propranolol 40 mg twice a day and Lugol's solution 5 drops 3 times a day for 7 days.

In April 1999, excision of the cystic mass was performed with an extended McFee incision. The lesion was a 3.5 x 3 x 1 cm multiloculated cystic mass fused with 3 lymph nodes and was resected from the right upper jugular chain (Fig. 1). Frozen section showed metastatic papillary thyroid carcinoma. Total thyroidectomy was performed which showed a 1.0-cm papillary carcinoma in the right lobe, limited to the thyroid, with another small focus in the same lobe (Fig. 2). A right modified neck dissection was performed and lymph node metastases in the right anterior cervical chain were identified and resected.

The patient was discharged 3 days after surgery on levothyroxine 0.1 mg/day. In July 1999, after levothyroxine withdrawal (TSH=48 mU/l), she received 150 mCi of radioactive iodine. The post-therapy scan showed uptake in the anterior part of the neck and diffuse uptake in both lungs. The patient was started on levothyroxine and her TSH was adequately suppressed. On follow-up visits her thyroglobulin was 1.2 ng/ml (IRMA) on suppression. The patient felt well and clinically there was no evidence of recurrence. In April 2000, the patient was withdrawn from levothyroxine. On withdrawal, her TSH was 56 mU/ml and serum thyroglobulin was 4.82 ng/ml. An $^{131}I$ scan showed persistent uptake in the neck and in the lungs. Chest X-ray was negative. Another radioactive iodine treatment with 200 mCi was administered. The patient was restarted on levothyroxine and her TSH levels were adequately suppressed.

## DISCUSSION

To the best of our knowledge, this is the first case in the endocrine literature delineating the aggressiveness of a papillary microcarcinoma in a patient with Graves' disease presenting as a cystic neck mass.

Aggressive behavior of papillary thyroid cancer has been reported in patients with Graves' disease (1), although not confirmed by others (2). Since some of these differentiated tumors express TSH receptors, TSI present in Graves' disease may stimulate adenylate cyclase activity and hence tumor cell growth (4). Filetti *et al.* (3) demonstrated that IgG (TSI) from patients with Graves' disease stimulated thyroid tumor cells *in vitro*. Whether patients with Graves' disease and a concurrent papillary carcinoma have a worse prognosis is still unclear. If TSH receptor antibodies act as growth factors for cancer cells, then TSH suppression alone would not be adequate to prevent tumor growth in patients with Graves' disease and possible benefits of immunosuppression should be studied.

Aggressive nature of papillary thyroid cancer in patients with Graves' disease has been reported in a few studies. Belfiore *et al.* (1) described extrathyroidal tumor invasion in 62% of patients with Graves' disease when compared to 11% in euthyroid patients, even though the tumor size was significantly larger in the euthyroid group. When compared to euthyroid patients matched for tumor size, patients with Graves' disease had more frequent distant metastases on follow-up and developed more recurrences (31% compared to 15%). Increased aggressiveness of microcarcinomas was also reported by Ozaki *et al.* (6) who described significant extracapsular invasion among 19 patients with papillary thyroid cancer and Graves' disease. Forty-eight percent of the tumors were smaller than 10 mm. On the contrary, Hales *et al.* (2) did not find increased aggressiveness of papillary thyroid cancer in patients with Graves' disease when compared to euthyroid patients, although in the Graves' disease group, fewer patients had tumor size larger than 10 mm (13 *vs* 74% in the euthyroid group).

Papillary carcinomas with cystic lymph node metastases generally have a benign course, even in the presence of long standing metastases. Hwang *et al.* (5) described a female patient with a 14-yr history of cystic neck mass which was later found to be a metastatic focus to the cervical lymph node from a 1.2-cm primary thyroid tumor. Long-term follow-up of such euthyroid patients show absence of distant metastases (7). Apart from having Graves' disease, our patient should be considered a low-risk because of the small tumor size and the cystic nature of the lymph node metastases. Despite these benign characteristics, our patient had distant metastases to the lungs. In the absence of any other potentially unfavorable prognostic factor in this case, we propose that thyroid stimulating antibodies may have played a role in the aggressiveness of the tumor.

Cystic transformation of lymph node metastases from papillary thyroid cancer is infrequent and is considered to be secondary to subcortical liquefication of the node (8). The main differential diagnosis includes the branchial cleft cyst. It appears commonly in the third decade of life and may be easily mistaken for metastases on ultrasound if the solid portion of the metastatic focus is not visible (9, 10). In our patient, the presence of follicular cells and TG in the cyst strongly suggested metastases from papillary thyroid carcinoma. Kawamura *et al.* (11) showed that a high concentration of thyroglobulin in cystic lymph node metastases from papillary thyroid carcinomas is helpful in differentiating them from other cystic neck masses. Pacini *et al.* (12) observed the presence of elevated amounts of thyroglobulin in the wash-out of fine needle aspiration cytology from enlarged lymph nodes of unknown origin in all patients with metastatic differentiated thyroid cancer. The authors concluded that these findings are highly suspicious for metastatic thyroid disease. A thickened irregular wall and necrosis also suggests metastatic disease. Ahuja *et al.* (10) reported that among 70 patients with metastatic lymph nodes from papillary thyroid cancer, 21% had undergone cystic degeneration. Up untill now, 17 patients have been reported in the literature in English with cystic lymph node metastases as being the initial presentation of a papillary microcarcinoma (7, 9, 10, 13). Most were diagnosed in men (male/female ratio=2.2/1) and were predominantly on the right side. Intraglandular dissemination was a prominent feature in most of the lesions. Although high resolution ultrasound is generally able to detect lesions as small as 1.5 to 2 mm (14), it failed to detect any abnormality in all the patients, even in those with primary lesions larger than 5 mm. In our patient, the presence of autoimmune thyroid disease represents a potential pitfall for ultrasound diagnosis of the lesion. Malignant tumors are usually hypoechoic because of their high cellular content. Thyroid glands affected by autoimmune disease are also hypoechoic. Thyroid scanning was not helpful in detecting the primary lesion in the thyroid in our patient. The reason for this being that the normal thyroid tissue may overlay these lesions with low uptake, hence rendering then not visible. Ozaki *et al.* (6) recently showed that soft tissue X-rays may be helpful in a small group of patients with Graves' disease and papillary carcinoma, with a fine pattern of calcification suggesting the neoplastic lesion. However, this did not prove to be a sensitive method for detecting small papillary cancers.

In conclusion, we describe a patient with an aggressive papillary microcarcinoma and concurrent Graves' disease who initially presented with cystic lymph node metastases. Although small papillary carcinomas generally have a benign course in euthyroid patients, our patient had bilateral lung metastases. The relationship between TSI and aggressiveness of differentiated thyroid tumors is controversial, however in our patient, the presence of TSI may be related to the aggressive behavior of the tumor.

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## REFERENCES


1. Belfiore A., Garofalo M.R., Giuffrida D., Runello F., Filetti S., Fiumara A., Ippolito O., Vigneri R.
Increased aggressiveness of thyroid cancer in patients with Graves' disease.
J. Clin. Endocrinol. Metab. 1990, *70:* 830-835.
2. Hales I.B., McElduff A., Crummer P., Clifton-Bligh P., Delbridge L., Hoschl R., Poole A., Reeve T.S., Wilmshurst E., Wiseman J.
Does Graves' disease or thyrotoxicosis affect the prognosis of thyroid cancer?
J. Clin. Endocrinol. Metab. 1992, *75:* 886-889.
3. Filetti S., Belfiore A., Amir S.M., Daniels G.H., Ippolito O., Vigneri R., Ingbar S.H.
The role of thyroid-stimulating antibodies of Graves' disease in differentiated thyroid cancer.
N. Engl. J. Med. 1988, *318:* 753-759.
4. Clark O.H., Gerend P.L., Cote T.C., Nissenson R.A.
Thyrotropin binding and adenylate cyclase stimulation in thyroid neoplasms.
Surgery 1981, *90:* 252-261.
5. Hwang C.F., Wu C.M., Su C.Y., Cheng L.
A long-standing cystic lymph node metastases from occult thyroid carcinoma – report of a case.
J. Laryngol. Otol. 1992, *106:* 932-934.
6. Ozaki O., Ito K., Kobayashi K., Toshima K., Iwasaki E., Yashiro T.
Thyroid carcinoma in Graves' disease.
World. J. Surg. 1990, *14:* 437-441.
7. Verge J., Guixá J., Alejo M., Basas C., Quer X., De Castro J., Autonell J., Serra C.
Cervical cystic lymph node metastases as first manifestation of occult papillary thyroid carcinoma: report of seven cases.
Head Neck 1998, *21:* 370-374.
8. Micheau C., Cachin Y., Caillou B.
Cystic metastases in the neck revealing occult carcinoma of the tonsil – a report of six cases.
Cancer 1974, *33:* 228-233.
9. Loughran C.F.
Cystic lymph node metastases from occult thyroid carcinoma: a sonographic mimic of a branchial cleft cyst.
Clin. Radiol. 1991, *43:* 213-214.
10. Ahuja A., NG C.F., King W., Metreweli C.
Solitary cystic nodal metastases from occult papillary carcinoma of the thyroid mimicking a branchial cyst: a potential pitfall.
Clin. Radiol. 1998, *53:* 61-63.
11. Kawamura S., Kishino B., Miyauchi A., Takai S., Tajima K., Mashita K., Tarui S.
The differential diagnosis of cystic neck masses by the determination of thyroglobulin concentrations in the aspirates.
Clin. Endocrinol. (Oxf.) 1984, *20:* 261-267.
12. Pacini F., Fugazzola L., Lippi F., Ceccarelli C., Centoni R., Miccoli P., Elisei R., Pinchera A.
Detection of thyroglobulin in fine needle aspirates of nonthyroidal neck masses: a clue to the diagnosis of metastatic differentiated thyroid cancer.
J. Clin. Endocrinol. Metab. 1992, *74:* 1401-1404.
13. Tovi F., Zirkin H.
Solitary lateral cervical cyst: presenting symptom of papillary thyroid adenocarcinoma.
Ann. Otol. Laryngol. 1983, *92:* 521-524.
14. Jennings A.S.
Non-isotopic techniques for imaging the thyroid.
In: Braverman L.E., Utiger R.D. (Eds.), Werner and Ingbars' The thyroid: a fundamental and clinical text, ed. 7.
Lippincott Raven, Philadelphia, 1996, p. 433-446.