Graves' disease and papillary thyroid cancer

An association that can be missed

Ahmad A. Al-Omari, *JBIM, MRCP (UK),* ***Fares H. Haddad,*** *JBIM, FRCP (Edin),*
Haytham M. Khushman, *MD, JBIM,* ***Omar M. Malkawi,*** *MD, JBIM.*

ABSTRACT

Thyroid nodules are frequently found in association with Graves' disease. Papillary carcinoma can arise from these nodules. We report a 65-year-old gentleman who presented with classical features of Graves' disease. Technetium 99 scintigraphy revealed diffuse goiter with a cold nodule over the isthmus. Papillary thyroid cancer was suggested by the enlarging thyroid gland, and by the presence of cold nodule, and was proven by fine needle aspiration biopsy of this nodule. The diagnosis was confirmed by histopathology of thyroid specimen after total thyroidectomy, which also showed local invasion; metastatic work up revealed pulmonary and liver metastasis. Despite treatment by total thyroidectomy, twice radioactive iodine I^{131} ablation and levothyroxine replacement in a thyroid stimulating hormone suppressive dose, he still harbors metastases with elevated thyroglobulin level. This case should raise the index of suspicion of the treating physician to consider similar association, and to prompt early diagnosis and surgical treatment to prevent dreadful consequences that might adversely affect the outcome.

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Nodules are a frequent finding in patients with Graves' disease.[1] Their incidence ranges from 10.3-35.1%.[2,3] Most of the nodules are larger than 5 mm.[4] The presence of thyroid nodules in Graves' disease raises the suspicion of thyroid carcinoma.[2] The incidence of carcinoma in these nodules has increased recently due to early diagnosis by ultrasonography and fine needle aspiration (FNA) biopsy.[4] It varies from 3.8-15% in different studies.[1,3] The relation between Graves' disease and thyroid carcinoma is still unclear.[5] There is no consensus about the natural history of thyroid carcinoma coexisting with Graves' disease; while some authors believe it is a more aggressive cancer,[6] others do not support this belief.[7] In this report, we present an aggressive type of papillary thyroid cancer that was associated with Graves' disease.

Case report. A 65-year-old gentleman was referred to our endocrine clinic from the gastroenterology clinic with abdominal pain, weight loss >6 kg, palpitation, and insomnia for 2 months prior to presentation. He is a retired officer in the Kuwaiti army who has smoked 20 cigarettes/day for 8 years and quit 4 years ago, there was no history of radiation exposure or previous medical or surgical history. Clinical examination revealed a body weight of 71.5 kg, regular pulse of 112 beats/minute, bilateral proptosis (right 31 mm, left 27 mm, distance 63 mm) with lid lag, and lid retraction, diffuse goiter with audible bruit over both lobes, a palpable nodule of 1.9 x 2.1 cm over the isthmus with no retrosternal extension or cervical lymphadenopathy, his hands were hot, sweaty with a fine tremor, palmar erythema, and

From the Division of Endocrinology and Diabetes (Al-Omari, Haddad, Malkawi), and the Division of Chest Medicine (Khushman) and the Department of Internal Medicine, King Hussein Medical Center, Amman, *Jordan.*

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Address correspondence and reprint request to: Dr. Fares H. Haddad, PO Box 967, Amman 11118, *Jordan.* Tel. +962 777790910. Fax. +962 (6) 4619499. E mail: Haddf@hotmail.com

thyroid acropachy were noted. The rest of the physical examination was normal. Laboratory work-up of this patient showed high free thyroxine (T4) = 5.9 ng/dl. (Normal range [N]: 0.8-2.1) and free triiodothyronine (T3) = 14 pg/dl (N: 1.3-4.1), and suppressed thyroid stimulating hormone (TSH) of 0.009 mIU/L (N: 0.4-4.5), normal fasting blood glucose, full blood count, liver function tests, kidney function tests, and calcium profile, his ECG was normal. Technetium 99 isotope scan showed diffuse goiter with a cold nodule over the isthmus, 20-minute uptake was 4.5% (N: 0.4-4). He was started on methimazole 30 mg daily. Follow up visit after 8 weeks revealed euthyroid clinical status with suppressed TSH (Free T4 1.6 ng/dl, Free T3 3.1 pg/dl, and TSH 0.004 Miu/l), his current dose was maintained and he later developed rapid relapses on reducing the methimazole treatment below 20 mg. During follow up, he complained of an annoying tinnitus, and hoarseness of voice for which an ENT evaluation by indirect laryngoscope showed paralyzed left vocal cord with a nodule; biopsy of which revealed a benign nodule. He was offered ablative treatment with radioactive iodine I^{131} or surgery, but he declined for over a two-and-half year follow up. In the last year, and despite becoming euthyroid, his goiter was getting bigger, with a progressive sensation of breathlessness, and hoarseness of voice, so thyroid FNA was performed, and cytological examination of the aspirate was suggestive of papillary thyroid cancer **(Figure 1a).** Total thyroidectomy was performed, and histopathological examination confirmed the diagnosis of papillary thyroid cancer invading adjacent soft tissue structures with lympho-vascular invasion **(Figure 1b & 1c).** Further evaluation including chest, and abdominal CT scan showed multiple lung, and liver metastases **(Figure 2)**. He received 150 miCu radioactive iodine ablation, and was then started on levothyroxine to suppress his TSH < 0.1 miu/l. Follow up visit after 6 months showed a high serum thyroglobulin 300 mg/dl (N:

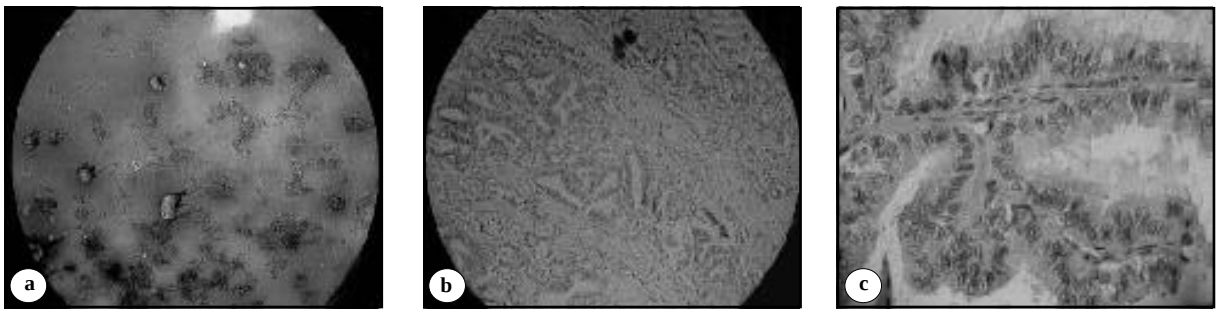

Figure 1 - Cytohistopathological specimens showing : **a)** (Diff Quik stain); fine needle aspiration showing cellular aspirate with sheets of papillary fragments on a thick colloid background. **b)** Thyroid tissue with papillary structures, note the typical overlapping, grooved ground glass nuclei with inclusion bodies. **c)** Higher view of the papillary structures with inclusion bodies.

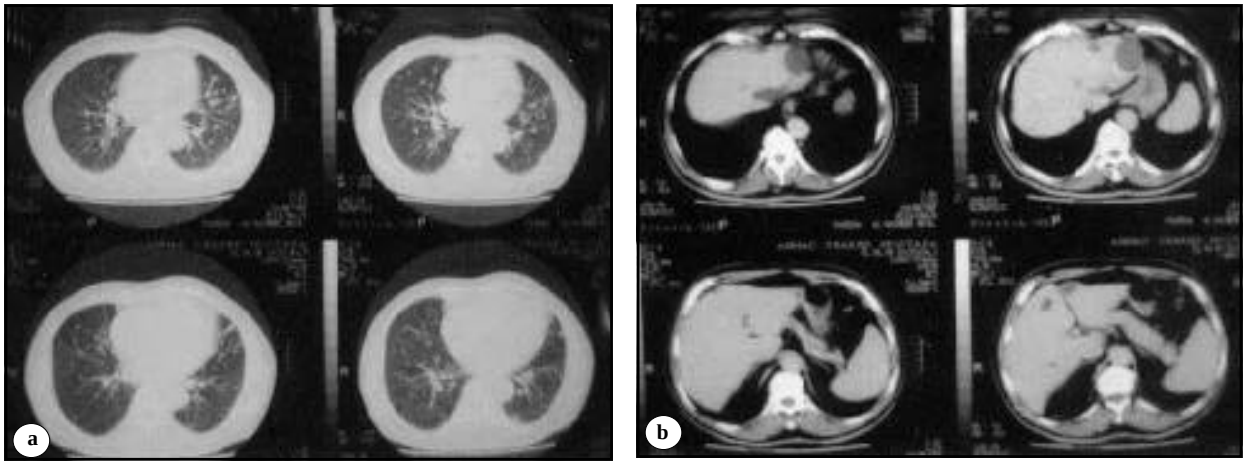

Figure 2 - Chest and abdominal CT scan showing **a)** multiple lung and **b)** liver metastases.

<10), iodine whole body scan showed abnormal uptake over the thyroid and no uptake by the lungs, despite the persistence of lung metastasis on chest CT scan that was proved by CT scan guided FNA cytology. A second dose of 150 miCu radioactive iodine was given, and followed by another third dose of 150 miCu due to persistent high thyroglobulin level. His general condition is satisfactory so far with no specific complaints apart from dry cough, his thyroglobulin level nevertheless, is still high, and he is under close scrutiny.

Discussion. Hyperthyroidism and papillary thyroid carcinoma is not an uncommon association.[1] Studies have suggested that thyroid cancer is found more frequently during surgery for hyperthyroidism than in euthyroidism.[8] The incidence of thyroid nodules, and of thyroid cancer in patients with Graves' disease has increased, with cancer rates varying from as low as 1% to as high as 9% of cases.[9] Ultrasonography is the most important investigation to detect thyroid nodules,[2] but since these nodules are a frequent ultrasonic finding, their clinical significance remains controversial.[2] Fine needle aspiration cytology is the best single investigation in the work-up of thyroid nodules; it is better to be carried out under ultrasound guidance to increase the diagnostic yields.[2,4] A FNA cytology is sometimes difficult to interpret in small nodules, in the presence of hemorrhage, and in the presence of hyperplastic nodules in Graves' disease especially after radioactive iodine ablation.[10] Treatment of hyperthyroidism coexisting with thyroid nodules is influenced by the result of FNA cytology. Definitely benign nodules favor nonsurgical treatment, while surgery is advised in suspicion of malignancy.[2]

The biological behavior of thyroid carcinoma coexisting with Graves' disease is still controversial. Some authors believe that there is a high incidence of local invasiveness, lymph node involvement, and distance metastases in thyroid carcinoma with Graves' disease,[3] a good outcome was reported by others.[1,7] The definite treatment of thyroid cancer is thyroid surgery followed by radioactive iodine ablation that has an impact on overall survival.[11] Young age at presentation and more aggressive treatment are possible contributing factors of high survival and low incidence of recurrence. The recurrence free interval, mainly in patients over 40 years of age and invasive papillary thyroid cancer may be improved by external radiation,[12] patients with microscopic residual papillary thyroid cancer after surgery are more commonly rendered disease free by external radiation (90%) than without it (26%).[13]

Our case belongs to the poor prognosis group due to older age, local invasion at presentation and persistence of pulmonary and liver metastases, proven by high thyroglobulin. Nodules are frequently found in association with Graves' disease; early diagnosis by FNA cytology, and early thyroidectomy in those with carcinoma is highly recommended. This case should raise the index of suspicion of treating physicians toward early diagnosis and intervention.

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