Follicular Carcinoma of the Thyroid with Hyperthyroidism

A Case Report

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BACKGROUND: Follicular carcinoma of the thyroid in association with hyperthyroidism is rare. The malignant lesion may remain occult for a long time. Certain clinical and cytologic features may be helpful in raising the alarm.

CASE: An elderly male with a history of occupational exposure to X rays, long-standing toxic multinodular goiter and clinical hyperthyroidism presented with a rapidly enlarging mass in the neck. Cytologic smears showed a prominent microfollicular pattern, scanty colloid, anisonucleosis and nuclear overlapping. The noteworthy feature was the presence of marginal vacuoles. The cytologic diagnosis of follicular neoplasm with highly suggestive malignancy was made. Subsequently, multiple pulmonary nodules provided radiologic evidence of possible metastatic spread.

CONCLUSION: This case report demonstrates the rare association of follicular carcinoma of the thyroid with hyperthyroidism and analyzes certain high-risk clinical and cytologic features to be considered in the follow-up of long-standing hyperfunctioning multinodular goiter. (Acta Cytol 2004;48: 219–222)

Even in the setting of hyperthyroidism, all thyroid nodules require long-term follow-up and careful FNA sampling.

Keywords: thyroid cancer, hyperthyroidism, aspiration biopsy, follicular carcinoma.

Follicular carcinoma of the thyroid typically manifests under euthyroid conditions with a scan showing a cold nodule.[1,2] Its association with hyperthyroidism is considered an infrequent relationship of uncertain nature; the reported incidence ranges from 0.3% to 16.6%.[3,4] In such cases the follicular carcinoma usually remains hidden and is diagnosed only postoperatively on histopathologic examination.[1,5] Many such instances of malignancy being missed on preoperative cytology have been reported.[4]

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We report a case of follicular carcinoma in a toxic, multinodular goiter.

Case Report

A 65-year-old male with a history of mild thyromegaly and documented hyperthyroidism of 7 years' duration was referred to our center for an alarming enlargement of the gland over the previous year. It was associated with increasing anxiety, palpitations and breathlessness. A previous fine needle aspiration (FNA) at a different center 2 years previously was reported as adenomatous goiter. A thyroid hormone profile done 1 year earlier showed a free T_4 level of 77 nmol/L (laboratory reference range, 12–22) and TSH level < 0.005 mU/L (laboratory reference range, 0.27–4.2). The patient was on irregular medical treatment for hyperthyroidism and hypertension.

On examination, the patient was emaciated, markedly dyspneic and agitated. The thyroid was strikingly enlarged, multinodular, firm to hard and nontender and measured 8×10×12 cm. The overlying skin was focally stretched out. Movement with deglutition could not be detected. The resting pulse rate was 110/min, and blood pressure was 150/100 mm Hg. A tremor in the outstretched fingers was observed. Eye signs, muscle weakness and cardiac rhythm anomalies were not found.

FNA performed from multiple sites yielded a thick, whitish aspirate that was processed for Giemsa staining. The smears were hypercellular and showed a closely packed, microfollicular pattern in a background containing scanty colloid. In focal areas follicular cells showed moderate to marked anisokaryosis, nuclear overlapping and a few atypical giant cells. Marginal vacuoles (Mv) were prominent (Figure 1). A cytologic diagnosis of follicular neoplasm was suggested, and further investigations were advised to confirm the malignant nature.

Subsequent radiography and ultrasonography of the neck revealed a large soft tissue swelling arising from the thyroid compressing and displacing the trachea to the left (Figure 2). No calcification or cystic areas were present. Chest radiography showed multiple discrete, nodular opacities in bilateral lung fields with a pleura-based opacity in the left upper zone, consistent with metastases. No other factor to which these nodules could be ascribed was found on further workup.

On detailed questioning it was found that the patient had worked as a radiography technician for 25 years until his retirement 7 years earlier. He was found unfit to undergo general anesthesia due to airway compromise. He declined any other treatment, including radioablation using iodine isotopes, and soon afterward left the hospital against medical advice.

Discussion

There is high prevalence of benign (both toxic and nontoxic) thyroid nodules in India due to the en-

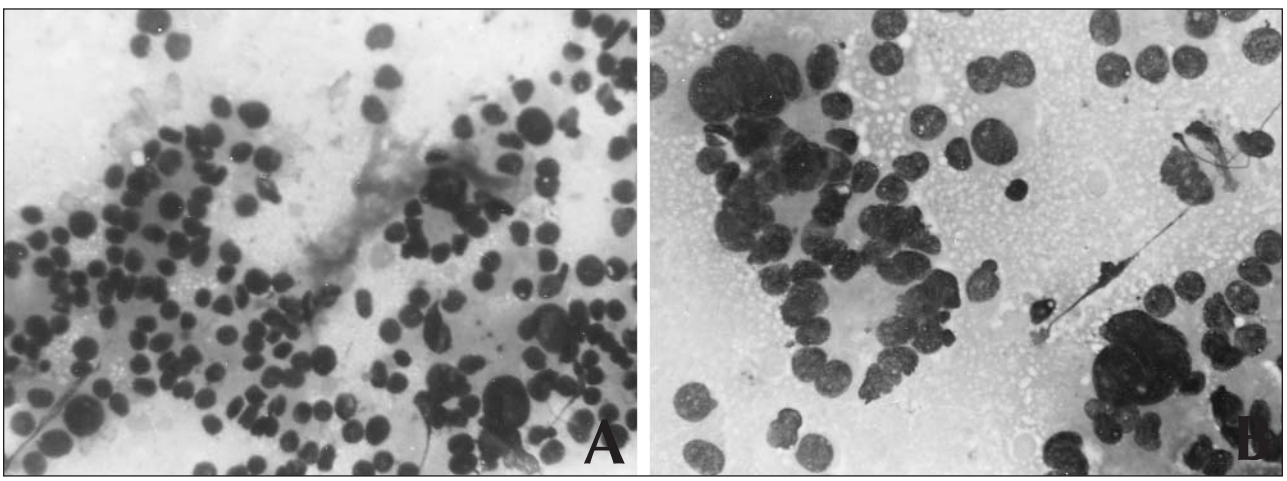

Figure 1 (A) Aspirate smear showing microfollicular pattern with anisokaryosis and prominent Mv (Giemsa stain, x 400). (B) Marked anisonucleosis, nuclear overlapping and giant cell formation (Giemsa stain, ×480).

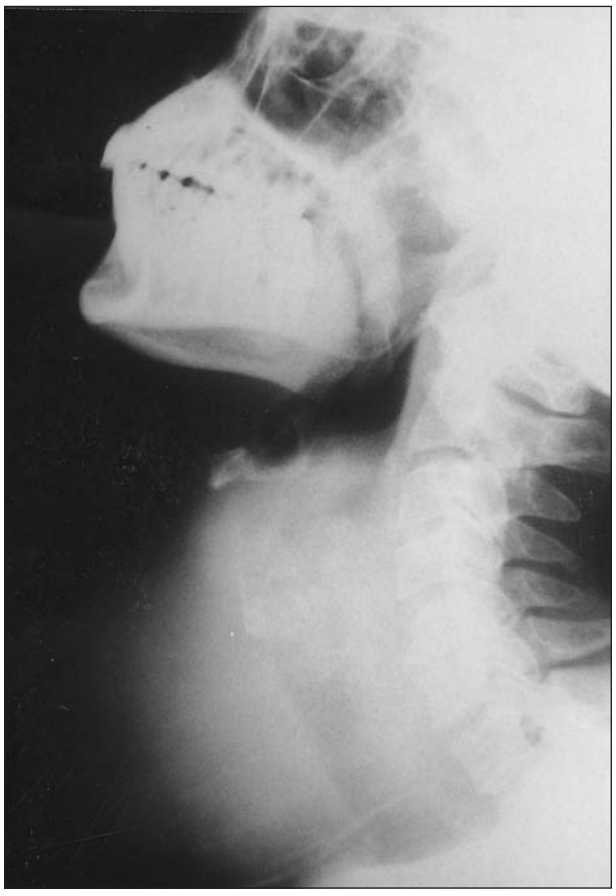

Figure 2 Radiograph of the neck showing massive, homogeneous soft tissue swelling causing tracheal displacement.

demic iodine deficiency. However, the frequency of thyroid malignancy is low.[6] Moreover, malignant lesions occurring in a previously diseased thyroid are very rare.[3-5,7,8] The different histologic types have different risk factors, and their rarity makes them difficult to study. Pooling data from studies of the etiologies of thyroid carcinoma becomes necessary to determine the role of previous thyroid diseases, iodine intake, and other dietary and genetic factors. In most histologically documented studies, papillary carcinoma was the most common thyroid malignancy followed by follicular carcinoma found in association with hyperthyroidism.[3-5,8] Most of them were clinically occult, and preoperative detection on ultrasonography or FNA was only occasional. In the present case, suspicion of follicular carcinoma was raised on FNA.

The possibility of prolonged occupational exposure to radiation is another noteworthy feature in our case. The relationship between external radiation and thyroid carcinoma has been confirmed by many studies.[9-12] Mostly these are papillary carcinoma and rarely follicular type. RET protooncogene–activating rearrangements (mostly RET/PTC1 and RET/PTC3) have been found to play a crucial role in papillary carcinoma and follicular adenoma, appearing after accidental or therapeutic irradiation.[11,12] The transmembrane and extracellular domains of RET are lost and are replaced by parts of other genes at the 5′ end.[11] Mutations in the RAS oncogene (codon 12, 13, 61), p53 (exons 5 to 8) and Gs-α (codon 201 and 227) also occur in papillary carcinoma.[11] These studies could not be done in the present case due to the lack of facilities.

FNA is currently the most reliable diagnostic method of managing thyroid masses. The neoplastic nature of a thyroid nodule may be missed on FNA due to a low index of suspicion and inadequate sampling of a large mass. In 1 large series, 849 patients, with initial cytologic diagnoses of benign thyroid lesions, 0.85% were subsequently found to have thyroid malignancy on repeat FNA after ≥6 months.[13] Initial cytodiagnosis in the present case was adenomatous goiter. The rarity of the association of hyperthyroidism with follicular carcinoma could have been responsible for the low index of suspicion.

Clinically, elderly age, male sex, a solitary nodule, size >4 cm and recent growth in a longstanding goiter suggest a higher risk of malignancy.[14,15] All of these except a solitary nodule were present in our case and were taken into account at the time of repeat FNA at our center; extensive sampling was done. The cytologic features of scanty or absent colloid, prominent microfollicular pattern, nuclear overlapping and anisokaryosis in the present case are considered high-risk features for malignancy.[16] In this clinicocytologic setting the multiple pulmonary nodules on chest radiography provided strong circumstantial evidence of metastases from a thyroid primary. Thus, the case appears to be a highly invasive follicular carcinoma. FNA of lung lesions was advised for confirmation but could not be performed as the patient declined any further intervention.

Mv in cytologic preparations have been linked to thyroid hormone overproduction and have been observed in both toxic and nontoxic goiter.[17] Although the rate is significantly higher in thyrotoxic goiter, they are seen infrequently in neoplastic goiter. Das et al reported Mv in 13.3% of neoplastic goi-

ter out of 441 cases of solitary nodules and noted that they were limited to tumors with a follicular component.[18]

Even in the setting of hyperthyroidism, all thyroid nodules require long-term follow-up and careful FNA sampling. High-risk clinical and cytologic features, as seen in this case, should raise a high index of suspicion of malignancy to achieve an early and specific diagnosis.

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