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CHALLENGES IN MANAGING PAPILLARY CARCINOMA THYROID COEXISTING WITH HYPERTHYROIDISM – CASE REPORT AND REVIEW OF LITERATURE

Abstracts:

Papillary carcinoma of thyroid can rarely coexist with hyperthyroidism and the reported incidence varies widely across the literature. It requires very high degree of suspicion to recognise the malignant nodule preoperatively. We are presenting a case that was initially being treated with carbimazole for hyperthyroidism and he was found to have papillary carcinoma of thyroid on FNAC from cold nodule detected in thyroid scan, probably the first case report from Nepal. Total thyroidectomy with level VI neck dissection followed by radioiodine ablation was performed. The approach to thyroid nodule in hyperthyroid patients is no different than euthyroid or hypothyroid patients as the risk of malignancy is similar. Thyroid scan is useful for classifying the different causes of hyperthyroidism and hence its management but for characterisation of nodule in terms of benign or malignant, ultrasonography is superior. Fine needle aspiration cytology of any suspicious nodule, in patient with hyperthyroidism, should be advised.

Keywords: Hyperthyroidism, Differentiated thyroid carcinoma, Graves' disease, Thyroid scan

INTRODUCTION:

Hyperthyroidism can rarely coexist with thyroid cancer. The incidence reported in the literature varies widely ranging from 0.1-21%.^{1,2,3} Carcinoma of thyroid can exist either with toxic multinodular goitre (MNG), Graves' disease (GD) or toxic adenoma (TA). Any of the histological forms of thyroid malignancy can exist with hyperthyroidism as the association of any of the particular histological forms has not been established yet.² Papillary carcinoma thyroid, being the commonest thyroid malignancy, is found to be more commonly associated with hyperthyroidism than other carcinomas of thyroid. Detection of thyroid malignancy in hyperthyroid patient is often missed. In most of the cases, carcinoma is detected only in the histopathology postoperatively in patient undergoing thyroidectomy for hyperthyroidism.^{2,4} Hence the detection of malignancy in large proportion of patient receiving nonsurgical management may be delayed and will have to face the consequences. On the other hand, screening all the hyperthyroid patients for malignancy as done for hypothyroid patients may not be practical. The aim of this article is to discuss the approach to hyperthyroidism for early detection of coexisting malignancy in cost-effective way in the setup with limited resources and its management.

CASE REPORT:

A 24 year gentleman, who had recently returned from abroad, presented to Patan hospital with the complaints of neck swelling for 5 months and feeling feverish for 2 months. He also gave history of palpitation, bleeding from nostrils on and off and multiple pruritic papulovesicular rashes over different parts of body. On examination, he was afebrile, pulse rate was 108 bpm and blood pressure was 150/70 mmHg. Tremor, exophthalmos and lid lag were present. Neck examination revealed enlarged and firm right lobe of thyroid gland (5x4 cm) and no other swellings were noted. Thyroid function test showed TSH - 0.015 (0.46-4.68 IU/mL), free T3-22.8 (2.77-5.27 pg/mL) and free T4-6.50 (0.78-2.19 ng/mL). Heterogeneous nodule of size 3.3 x 2.5 cm, with calcified foci in right lobe of thyroid was noted in ultrasonography (USG) (Figure 1) whereas isthmus and left lobe appeared normal. On the basis of above findings, differential diagnoses of Graves' disease with hypo-functional (benign) nodule, Toxic adenoma, Marine-Lenhart syndrome, and Graves' disease with malignant nodule were considered. ⁹⁹Tc pertechnetate thyroid scan showed cold nodule (Figure 2) in right lobe with diffuse increased uptake. Fine needle aspiration cytology (FNAC) of cold nodule was suggestive of papillary carcinoma of thyroid. Therefore the provisional diagnosis of Graves' disease with papillary carcinoma thyroid was

made and total thyroidectomy with level VI neck dissection followed by radioiodine ablation was planned. Considering the risk of thyroid storm, the patient had to be made euthyroid to safely proceed towards surgery. Carbimazole and propranolol were prescribed for one month and then 10 days prior to surgery potassium iodide was started in order to make patient euthyroid. At the time of surgery, TSH was 0.015 (0.46-4.68 IU/mL), free T3 was 5.97 (2.77-5.27 pg/mL), and free T4 was 1.61 (0.78-2.19 ng/mL). Even though TSH was not normalised, free T4 was within the normal range and free T3 was slightly above normal range, we decided to go ahead with total thyroidectomy with level VI neck dissection after communicating with anaesthetist. Intraoperative and immediate postoperative periods were uneventful. Bilateral vocal cords were mobile and patient had normal serum calcium level postoperatively. Histopathology was reported as papillary carcinoma of thyroid with maximum tumour dimension 4cm in right lobe with extracapsular and lymphatic invasion but without vascular invasion. Eight out of 12 level VI lymph nodes showed metastatic deposit (pT2N1a). Diagnostic whole body scan after 4 weeks showed faint tracer uptake in thyroid bed (Figure 3). Serum TSH level was 45 IU/mL, thyroglobulin (Tg) was 27 ng/mL and antithyroglobulin antibody was negative. On this basis, patient received 110 mCi ¹³¹I and post therapy scan showed uptake in thyroid bed (Figure 4) suggestive of some remnant. Patient was prescribed with thyroxine 125 mcg daily. Patient is doing well till now in the 10 months of follow up with TSH maintained in the lower reference range.

Figure 1. Ultrasonography of right thyroid nodule



Figure 2. 99Tc Pertechnetate thyroid scan showing cold nodule in right lobe

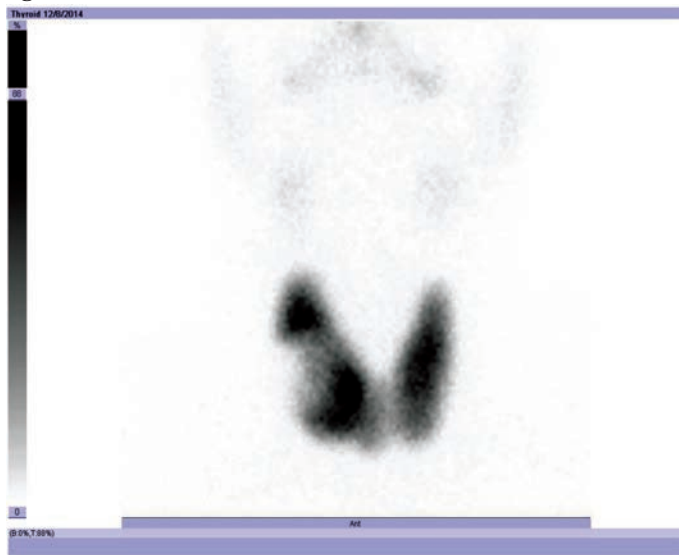


Figure 3. Diagnostic whole body scan

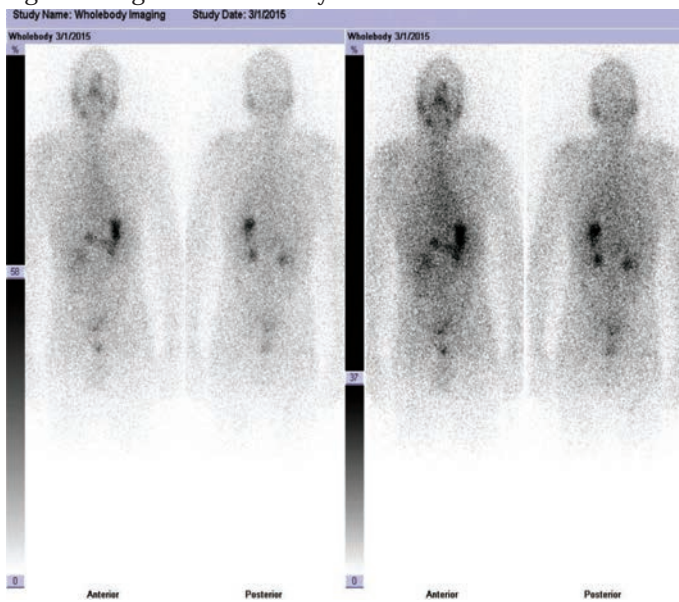
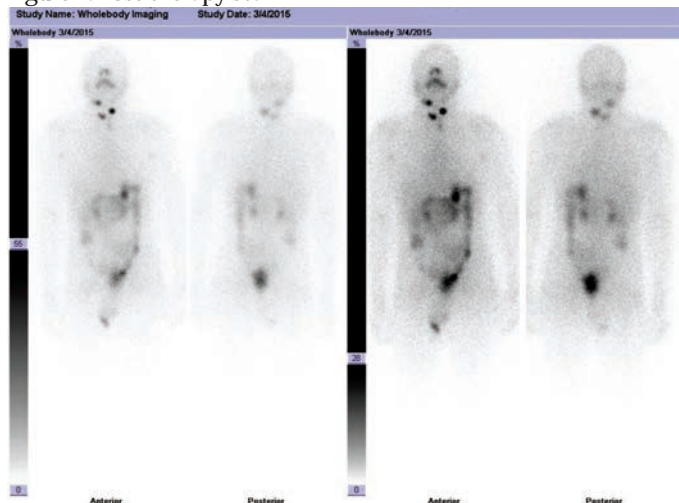


Figure 4. Post-therapy scan



DISCUSSION:

Though once thought as if hyperthyroidism could be protective against thyroid cancer, the coexistence of thyroid cancer with hyperthyroidism is well established with the incidence ranging from 0.1-21%.² Thyroid carcinoma is reported with any of the causes of hyperthyroidism e.g. GD, Toxic MNG, TA with variable incidence across the literature (Table 1). Thyroid nodule in GD is reported as 10-15% and the incidence of malignancy in this group of patients may be higher than without GD.⁵ It has been postulated that thyroid stimulating immunoglobulin (TSI) might have a role in triggering the growth of malignant cells in GD.⁶ Some authors suggest that the thyroid cancer associated with hyperthyroidism is more aggressive⁷ but others do not agree.⁸ Moreover, clinical signs of malignancy e.g. hardness, fixation, cervical lymphadenopathy, hoarseness etc. which are late features may not be obvious early in the presentation. Small nodules are difficult to find out clinically by palpation in large thyroid gland of GD and also to suspect malignant nodule clinically in MNG is particularly challenging. Most of the patients with toxic MNG and TA would undergo surgery eventually as long term management with antithyroid drugs is not recommended as these patients do not go into remission.⁹ On the other hand patients with GD are preferably managed either with antithyroid drugs or radioactive iodine (RAI) ablation.⁹ The hyperthyroid patients who are managed nonsurgically should be evaluated properly for coexisting malignancy, which is not a rare phenomenon, not only in the initial evaluation but also in the follow ups¹⁰ as delay in the diagnosis will cause the patient to suffer. Thyroid scan is valuable in diagnosing different causes of hyperthyroidism and hence its management.¹¹ When a clinical presentation of hyperthyroidism is not diagnostic of GD and in the presence of thyroid nodularity, thyroid scan should be performed.⁹ In thyroid scan, nodule may appear as hot (hyper-functioning), warm (iso-functioning) or cold (non-functioning). The chance of cold nodule being malignant is 10-20%^{11,12,13} whereas hot nodules rarely harbour malignancy.¹⁴ Cold nodules are frequently found in hyperthyroid patients in endemic iodine-deficient regions.¹² Cold nodules in older patients (>/=50 years) is significant risk factors for malignancy in patients with hyperthyroidism.¹² Small nodules may not be detected by thyroid scan and its sensitivity and specificity to predict malignancy is very low.¹¹ USG can detect the small nodules which are even clinically impalpable and the various characteristics of thyroid nodules like hypoechoogenicity, increased intranodular vascularity, irregular infiltrative margins, presence of microcalcifications, absent halo, and a shape taller than the width measured in the transverse dimension are associated with higher likelihood of malignancy.¹⁵ The increased incidence of microcarcinomas of thyroid is partly due to better evaluation of nodule by USG.^{9,16} FNAC has very high sensitivity and specificity in detecting thyroid cancer preoperatively thus avoiding the biopsy.¹⁵ USG is also useful to guide FNAC from the suspicious nodule in GD. USG guided FNAC of not only dominant nodule but also suspicious nodule in toxic MNG is recommended.¹² As the hot nodules rarely harbour malignancy and the characteristics of malignant hot nodule is still uncertain by USG, FNAC is not recommended routinely.¹⁴ Sometimes even if FNAC is negative for malignancy, surgery should be advised in the presence of suspicious cold nodule.¹² Antithyroid drugs (e.g. carbimazole or Propylthiouracil) and beta blocker should be initiated prior to surgery to avoid thyroid storm, aiming to correct the serum T₃/T₄ level rather than TSH level which takes time to normalise. Potassium iodide is also beneficial to prevent thyroid storm in GD if initiated a week before surgery because of Wolff-Chaikoff effect.¹⁷ On the contrary, due to Jod-Basedow effect¹⁷ in patient with MNG from iodine deficient area, serum T₃/T₄ level may further increase and hence increasing the risk of thyroid storm. Thyroidectomy is recommended in hyperthyroidism with nodule if there is relatively low uptake of radioactive iodine or presence of large nonfunctioning, photopenic, or hypofunctioning nodule in thyroid scan or when thyroid malignancy is documented or suspected (e.g., suspicious or indeterminate cytology) by USG or FNAC.¹⁵ The clinical course does not differ significantly in long term follow up between the patients of thyroid cancer with and without hyperthyroidism.^{8,18} The coexistence of thyroid cancer with hyperthyroidism raises the question against TSH suppression which is recommended in high risk patients. In GD, it is hypothesised that TSI stimulates cancer cells⁶ but why do cancer cells proliferate in toxic MNG or TA remains unanswered.

CONCLUSION:

Thyroid cancer in patients with hyperthyroidism, though once thought as rare, is not uncommon. Any suspicious nodule in hyperthyroid patient should be investigated to rule out malignancy.

Table 1. Incidence of thyroid cancer in patients undergoing thyroidectomy. Figures in (%) indicates specific incidence.

Author	Number of cases (Surgery for hyperthyroidism)	Thyroid cancer	GD with Thyroid cancer	Toxic MNG with thyroid cancer	TA with thyroid cancer	Types of thyroid cancer
Cappelli et al, 2006 ⁷	691	32	9(6.5%)	13(3.9%)	10(4.4%)	
Senyurek et al, 2008 ¹²	817	53	13(3.8%)	19(6.4%)	21(12%)	
Karagulle et al, 2009 ¹⁹	344	35	4(7.1%)	26(11.6%)	5(7.7%)	Papillary - 35
Ardito et al, 1997 ²⁰	408	23	5(3.8%)	13(12.5%)	5(2.8%)	Papillary - 19 Follicular - 3 Medullary - 1
Calo et al, 2005 ³	71	15				
Vaiana et al, 1999 ²¹	512	24	7(6.4%)	10(3.9%)	8(4.4%)	
Nicolosi et al, 1994 ²²		11	2	9		Papillary - 8
Bolko et al, 2002 ²³		20	3	17		Papillary - 16
Soh et al, 1993 ²⁴	545	11				

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