

Incidental Growth Hormone Producing Pituitary Adenoma in a Case of Recurrent Nodular Goiter and Thyroid Carcinoma

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Rec date: Jan 10, 2015, Acc date: Feb 28, 2015, Pub date: Mar 03, 2015

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Abstract

Objective: Studies report an increased prevalence of thyroid tumors among patients with acromegaly. Acromegaly often has a subtle presentation and is likely underdiagnosed. This report highlights the development of recurrent thyroid neoplasia in a patient with undiagnosed acromegaly and raises awareness of thyroid malignancy in patients with acromegaly.

Case report: Mrs. R is a 47-year-old woman who presented with a recurrent goiter following two partial thyroidectomies, then was diagnosed with acromegaly and subsequently papillary thyroid cancer.

Methods: A review of the English-language literature on the PubMed database of acromegaly and thyroid cancer was performed. DNA from the tumor and adjacent benign thyroid tissue was tested by polymerase chain reaction (PCR)/direct sequencing of genomic DNA for genetic abnormalities.

Results: The relationship between the Growth Hormone (GH)/Insulin-like Growth Factor 1 (IGF-1) axis and the thyroid hyperplasia and neoplasia was detailed. The increased risk of malignancy occurs under the influence of specific goitrogens namely, prolonged GH/IGF-1 exposure.

Conclusion: The reported link between acromegaly and thyroid tumors should raise suspicion of malignancy in acromegalic patients with thyroid nodules. Additionally, an increased suspicion of acromegaly should be entertained in patients with recurrent thyroid nodular hyperplasia following partial thyroidectomy.

Keywords: Goiter; Acromegaly; Thyroid cancer

Introduction

Several studies have reported on the high prevalence of goitrous disorders [1] and increased rates of thyroid malignancy among patients with acromegaly [2-4]. In most studies, patients were only included in cancer estimates if they presented with acromegaly and were then found to have a malignancy. However, clinical features of acromegaly are nonspecific and similar to other disorders, thus the prevalence is possibly greater than previously thought [5]. In this report, we aim to raise awareness of the presence of subtle or undiagnosed acromegaly among patients assessed for thyroid neoplasia.

Case Report

Mrs. R., a 47-year-old female, was assessed for a recurrent nodular goiter. She had a right hemithyroidectomy for local compression symptoms related to a nodular goiter in 2002 in the Philippines. The excised specimen revealed benign hyperplasia. Two years post-resection, the symptoms of local neck pressure recurred and again the excised nodular goiter revealed benign tissue.

She presented to this Endocrinology Clinic with recurrent neck pressure characterized by difficulty swallowing, and occasional

choking on food. Furthermore, she admitted to daily headaches, blurred vision, a 10-year history of increasing ring and shoe size. She had also recently been diagnosed with diabetes mellitus type II, hypertension, and hypothyroidism. As well she reported that her menses had stopped after her surgery for fibroids in November 2011. Examination revealed normal visual fields, warm and diaphoretic skin, increased hand size, widely spaced teeth, coarse facial features and palpable nodular thyroid tissue in the left neck extending towards the isthmus. In addition, a discrete 2cm firm, mobile and non-tender isthmic nodule was palpated.

This constellation of signs and symptoms suggested acromegaly and diagnostic laboratory studies were ordered. She was found to have an insulin-growth factor-1 (IGF-1) level of 1351.14 ng/mL (normal 64.12-225.19 ng/ml), growth hormone (GH) level of 226.38 ng/ml (normal 0.03-4.0 ng/ml), an impaired oral glucose tolerance test (OGTT) with unsuppressed serum GH levels (> 1 ng/ml) and thyroid stimulating hormone (TSH) of 7.75 mU/L (normal 0.4-4.50 mU/L). A magnetic resonance imaging (MRI) of the brain revealed a mass lesion in the sella turcica of 3.2 × 2.4 × 1.8 cm with suprasellar extension and partial effacement of the optic chiasm. Ultrasound (US) of the thyroid showed nodular thyroid tissue on the left with a left isthmus complex (mixed solid and cystic) nodule. Fine needle aspiration and biopsy (FNAB) disclosed an indeterminate lesion (atypia of undetermined significance), Bethesda category III [6]. She first underwent transsphenoidal adenomectomy followed 3 months later by

completion thyroidectomy. The pituitary lesion was consistent with a GH-producing macroadenoma and the thyroid lesion in addition to recurrent nodular hyperplasia revealed papillary thyroid carcinoma (PTC), follicular variant (tumour 1 × 2 cm). DNA from the tumour and adjacent benign thyroid tissue was tested by polymerase chain reaction (PCR)/direct sequencing of genomic DNA for specific oncogenes. The thyroid carcinoma and adjacent hyperplastic thyroid tissue did not display the BRAF mutation V600E as well as the K-RAS mutation.

Discussion

This report showcased a patient with undiagnosed acromegaly who developed benign nodular hyperplasia of the thyroid and papillary carcinoma. The hyperplastic goiter caused local symptoms of pressure that recurred after two partial thyroidectomies. Papillary thyroid carcinoma of a suspicious thyroid nodule within the goitrous tissue was confirmed at the time of the completion thyroidectomy. The frequently described point mutations of the BRAF and KRAS genes were not identified in the malignant thyroid tissue. We suspect that the protracted mitogenic effect of elevated GH and IGF-1 levels acting synergistically with elevated TSH levels lead to recurrent nontoxic multinodular and papillary thyroid carcinoma.

It has been well documented that there is an increased prevalence of benign thyroid lesions in patients with acromegaly [1,2,4,5,7,8]. A connection between acromegaly and malignant thyroid disease remains controversial, as several studies have found such a link (2.5% to 7%) [4,8-11], while others have not [12]. One of the first prospective studies in the area, did find an increase in thyroid cancer in acromegalic patients, which found a prevalence of thyroid cancer of 11% in this group [4]. Gullu et al., (2010) found a much lower rate of thyroid cancer in acromegaly of 4.7%, but found it to be the malignancy with the greatest prevalence in that study population [10]. Interestingly, they did find that initial study GH levels were positively correlated with development of cancer ($P=0.046$), however they found no significant difference in IGF-1 levels in patients with cancer. More recently dos Santos et al (2013) performed a cross-sectional study, which included a control group and found a statistically significant difference (7.2% vs 0.7%, $P=0.0011$) between acromegalic and non-acromegalic patients with respect to incidence of thyroid cancer [7].

One of the common proposed mechanisms for this association is the hypersecretion of GH, which induces hepatic secretion of IGF-1, and promotes thyrocyte proliferation by increasing mitosis and decreasing apoptosis. In vitro studies have shown that tumors express IGF-1 receptors that are stimulated by the excess IGF-1 in acromegaly, stimulating mitosis and tumor growth and proliferation [10]. As well, Dogan et al (2013) found that longer disease duration, and hence prolonged exposure to elevated GH/IGF-1 serum levels led to significantly more thyroid nodules on palpation ($P=0.043$) [2]. However, other studies found no significant difference in GH levels at diagnosis in patients with acromegaly with thyroid cancer compared to those without thyroid cancer [2,8]. Dogan et al also found no difference in IGF-1 levels neither pre-treatment nor post-treatment between the acromegalic and non-acromegalic groups, indicating that GH and IGF-1 levels cannot be the sole determining factor as to whether a goiter progresses to malignancy or not [2].

The role of the GH/IGF-1 pathway in carcinogenesis is quite complex involving many pathways and cell signaling mechanisms. Much experimental and epidemiological research has been done in the

area and concludes that increased circulating levels of GH/IGF-1 contribute to tumor progression and possibly even tumor initiation. However, in addition to the endocrine effect of GH/IGF-1, they also exert an autocrine and paracrine effect, which may blunt or stimulate this carcinogenic response in some individuals with acromegaly [12].

After review of the natural progression of thyroid tissue from normal to malignant under the influence of goitrogens, several reasons for Mrs. R's recurrent thyroid growths can be seen. With prolonged acromegaly, her thyroid follicular cells were under the influence of elevated GH and IGF-1 levels. As well, there may have been a synergistic mitogenic effect of a mildly elevated TSH level, which has also been reported to constitute a risk factor for thyroidal malignancy [13]. As she was from the Philippines, her exact nutritional status cannot be definitively determined; a possible contributing factor of iodine deficiency is plausible. The clinical scenario suggests that the strongest goitrogens in this case derived from the synergistic mitogenic effect of the chronic elevations of GH, IGF-1 and TSH.

Due to the link between acromegaly and some forms of thyroid disease, an increased awareness for thyroid neoplasia inpatients with acromegaly should be acknowledged. In those with no obvious cause for goitrous disease, a search for subtle signs of acromegaly and a serum IGF-1 screen is suggested. As well, due to evidence of the increased risk of thyroid malignancy in acromegaly, a strong suspicion for thyroid malignancy should be maintained in all acromegalic patients with thyroid nodules, especially those with indeterminate results on FNAB.

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