Case Report

Acromegaly and papillary thyroid carcinoma: A case series

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Acromegaly is a rare chronic disease and associated with an increased risk of malignancy. The issue of the risk of thyroid cancer in these patients is a topic of debate, and the number of large case–control studies is very limited. Several studies indicated that a chronic excess insulin-like growth factor-1 stimulates the proliferation of various cell types and induces an antiapoptotic effect in thyroid follicular cells. In the literature, the risk of thyroid cancer was reported greater than five-fold. In this review, we will briefly summarize the studies available regarding thyroid cancer in patients with acromegaly and present three case reports.

Key words: Acromegaly, malignancy, thyroid cancer

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INTRODUCTION

Acromegaly is a rare chronic disease, characterized by excessive production of growth hormone (GH) and insulin-like growth factor-1 (IGF-1). Acromegaly is associated with increased morbidity and mortality. Cardiovascular complications have historically been reported contributing to half of the deaths. However, Ritvonen *et al*. according to a 20-year follow-up study reported that cardiovascular disease and malignancy accounted for 23% and 35% of deaths during the second decade, respectively.[1] The relationship between GH/IGF-1 and tumor growth has been reported, and thyroid cancer was one of the most common cancer types in patients with acromegaly. The issue of the risk of thyroid cancer in these patients is a topic of debate, and the number of large case–control studies is very limited. In the literature, the risk of thyroid cancer was reported greater than five-fold.[2] In this review, we will briefly summarize the studies available regarding thyroid cancer in patients with acromegaly and present our new case reports [Table 1]. It should be noted that the patients gave their informed consent for participation in the research.

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CASE REPORTS

Case 1

A 42-year-old male was referred to the endocrinology clinic in 2012 due to a thyroid nodule. The patient also complained of weight gain. Thyroid ultrasonography showed a 24 mm × 30 mm nodule in the middle of the left lobe with a hypoechoic pattern, irregular outline, and microcalcification. Fine-needle aspiration (FNA) was done, and papillary thyroid carcinoma (PTC) was reported. The physical appearance of the patient was suspected to be acromegaly. He had protruded chin, thickened lips, enlarged nose, deep voice, enlarged hand and feet, coarse skin, and excessive sweating. Laboratory values were notable for hemoglobin (Hb) A1c: 5.4% (4%–6.5%), fasting blood sugar (FBS): 94 mg/dl (77–99 mg/dl), IGF-1: 542 ng/dl (140–405 ng/dl), basal GH: 8.4 ng/ml (normal values were <1 ng/ml), oral glucose tolerance test (OGTT) (1 h after 75 mg oral glucose): 6.8 ng/ml, OGTT (2 h after 75 mg oral glucose): 5.7 ng/ml (normal value <1 ng/ml), thyroid-stimulating hormone (TSH): 1.2 mIU/ml (0.27-4.2 mIU/ml), free T4: 0.9 ng/dl (0.7-1.9 ng/dl), follicle-stimulating hormone (FSH); 9.1 mIU/ml (4.7–21.5 mIU/ml),

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Table 1: Characteristics of our patients with acromegaly and thyroid cancer

Characteristics	Case number 1	Case number 2	Case number 3
Sex	Male	Female	Male
Age	42	28	40
Presenting symptoms and signs	Left thyroid nodule Enlarged nose Protruded chin, feet, and hands Deep voice Thickened lips Coarse skin Excessive sweating	Left thyroid nodule Weight gain Increased size of hands, nose, and feet	Weight gain Low libido Low sexual desire Excessive sweating Frontal bossing Macrognathia Coarse facial features
FNA	PTC	PTC	PTC
IGF-1 (ng/dl)	542	1416	951
Basal GH (ng/ml)	8.4	7.9	5.2
OGTT-GH (ng/ml)			
1 h	6.8	6.4	4.3
2 h	5.7	6	3.5
TFT			
Free T4 (ng/dl)	0.9	1.9	0.7
TSH (mIU/ml)	1.2	1	0.5
Other axis	Normal	Normal	Hypogonadotropic hypogonadism
Pituitary MRI	Macroadenoma	Macroadenoma	Macroadenoma
Treatment	TSS NTT: PTC 31 mm No ETE I-131 100 mCi	TSS NTT: PTC with ETE I-131 100 mCi	TSS Sandostatin LAR 30 mg every 4 weeks Testosterone 200 mg every 3 weeks NTT: PTC (37mm) without ETE I-131 100 mCi
Postoperatively (3 months)			
IGF-1 (ng/dl)	460	385	683
GH (ng/ml)	1.1	1	5.2
OGTT (ng/ml)			
1 h	0.6	6.8	4.3
2 h	0.7	5.7	3.5
Final laboratory results			
IGF-1 (ng/dl)	257	385	215
GH (ng/ml)	1	1	1.6
Thyroglobulin	0.7	-	0.2
Antithyroglobulin	Negative	-	Negative

PTC=Papillary thyroid cancer; OGTT=Oral glucose tolerance test; GH=Growth hormone; TSS=Transsphenoidal surgery; IGF-1=Insulin-like growth factor 1; ETE=Extrathyroidal extension; TFT=Thyroid function test; MRI=Magnetic resonance imagery; FNA=Fine-needle aspiration

luteinizing hormone (LH): 2.8 IU/L (0.5–16.9 IU/L), testosterone: 2.5 ng/ml (2–6.9 ng/ml), cortisol: 11 μg/dL at 8 am (10–20 μg/dL), and prolactin: 12 ng/ml (4–23 ng/ml). Brain magnetic resonance imaging (MRI) was performed and showed a macroadenoma in the pituitary gland. One month later, transsphenoidal surgery was done, and 8 months later, the patient underwent thyroidectomy and PTC was confirmed in the pathology report. On microscopic examination, there was no lymphovascular or capsular invasion. In the macroscopic evaluation of the lesion, the maximum mass diameter was 31 mm. Postoperatively, he received 100 mCi radioactive iodine and then he was put on 0.15 mg thyroxine once a day. Three months after thyroidectomy, laboratory values were notable for GH: 1.1 ng/ml, IGF-1: 460 ng/dl, OGTT (1 h): 0.6 ng/ml, OGTT (2 h): 0.7 ng/ml, and TSH: 0.1 mIU/ml. In late 2018, the patient's overall clinical condition was improved, and the laboratory test results showed prominent improvements, basal GH: 1 ng/ml, IGF-1: 257 ng/ml, thyroglobulin (on-levothyroxine): 0.7 ng/ml, and negative antithyroglobulin antibody. Now, the patient is feeling well.

Case 2

A 28-year-old female was referred to the endocrinology clinic in 2017 due to a thyroid nodule. She also complained of size and weight gain gradually over the past 3 years. Thyroid ultrasound showed a 15 × mm 8 × mm × 18 mm hypoechoic nodule without calcification in the left thyroid lobe. FNA report was suspicious for PTC. Laboratory values were notable for FBS: 117 mg/dl, IGF-1: 1416 ng/dl (115–310 ng/dl), basal GH: 7.9 ng/ml (normal values were <1 ng/ml), OGTT (1 h): 6.4 ng/ml, OGTT (2 h): 6 ng/ml, TSH: 1 mIU/ml (0.27–4.2 mIU/ml), free T4: 1.9 ng/dl (0.7–1.9 ng/dl), prolactin: 12 ng/ml (4–23 ng/ml),

cortisol: 17.5 μg/dL at 8 am (10–20 μg/dL), FSH: 9 mIU/ml (4.7–21.5 mIU/ml), LH: 8.1 IU/L (0.5–16.9 IU/L), and estradiol: 115 pg/ml. Brain MRI was performed and showed a macroadenoma in the pituitary gland. The patient underwent transsphenoidal surgery, and 4 months later, thyroidectomy was done. PTC was confirmed in pathology report, and there was lymphovascular and capsular invasion with two cervical lymph node metastases. Therefore, she received 100 mCi radioactive iodine. Three months later, laboratory values were notable for HbA1c: 5.8% (4%–6.5%), FBS: 90 mg/dl (77–99 mg/dl), IGF-1: 385 ng/dl (140–405 ng/dl), basal GH: 1 ng/ml (normal values were <1 ng/ml), OGTT (1 h after 75 mg oral glucose): 6.8 ng/ml, OGTT (2 h after 75 mg oral glucose): 5.7 ng/ml (normal value <1 ng/ml), TSH: 1.8 mIU/ml (0.27–4.2 mIU/ml): and free T4: 1.1 ng/dl (0.7–1.9 ng/dl). Now, the patient's general condition is favorable.

Case 3

A 40-year-old male was referred to the endocrinology clinic in August 2006. The patient complained of weight gain, low libido, low sexual desire, and excessive sweating. Physical examination was notable for frontal bossing, macrognathia, coarse facial features, large hand, and feet. The thyroid examination and visual field test results were normal.

Laboratory values were notable for HbA1c: 6% (4%–6.5%), FBS: 124 mg/dl, IGF-1: 951 ng/dl (140–405 ng/dl), basal GH: 8.2 ng/ml (normal values were <1 ng/ml), GTT (1 h): 5.6 ng/ml, GTT (2 h): 4.7 ng/ml, FSH: 3.2 mIU/ml (4.7–21.5 mIU/ml), LH: 1 IU/L (0.5–16.9 IU/L), prolactin: 8 ng/ml (4–23 ng/ml), adrenocorticotropic hormone (ACTH): 15.1 pg/ml at 8 am (7.1–63 pg/ml), cortisol: 11 μg/dL at 8 am (10–20 μg/dL), testosterone: 0.6 ng/ml (2–6.9 ng/ml), TSH: 0.5 mIU/ml (0.27–4.2 mIU/ml), and free T4 of 0.7 ng/dl (0.7–1.9 ng/dl). Brain MRI was performed and revealed a macroadenoma in the pituitary gland. Transsphenoidal surgery was performed in September 2006. After surgery, the patient's symptoms relieved, but the disease was not controlled biochemically. Three months later, laboratory values were notable for IGF-1: 683 ng/dl (87–220 ng/dl), basal GH: 5.2 ng/ml, GTT (1 h); 4.3 ng/ml, GTT (2 h): 3.5 ng/ml, FSH: 2 mIU/ml (4.7–21.5 mIU/ml), LH: 0.9 IU/L (0.5–16.9 IU/L), testosterone: 0.5 ng/ml (2–6.9 ng/ml), prolactin: 7.8 ng/ml (4–23 ng/ml), ACTH: 10.2 pg/ml at 8 am (7.1–63 pg/ml), cortisol: 5 μg/dL at 8 am (10-20 μg/dL), TSH: 0.4 mIU/ml (0.27–4.2 mIU/ml), and free T4 of 5.7 ng/dl (0.7–1.9 ng/dl). Therefore, Sandostatin LAR (start at a dose of 20 mg, every 4 weeks and then uptitrated to a maximum dose of 30 mg, every 4 weeks) was administered. Prednisolone (5 mg/day), testosterone enanthate (200 mg every 3 weeks), and levothyroxine (100 μg daily) were also prescribed. In late 2015, the patient presented to our department with neck swelling. A thyroid nodule was detected during the physical examination, and PTC was detected by FNA biopsy. Therefore, the patient was scheduled for a total thyroidectomy. In macroscopic evaluation of lesion, maximum nodule diameter was 37 mm, and in microscopic evaluation, PTC without any extrathyroidal invasion was confirmed. Postoperatively, the patient received 100 mCi radioactive iodine, and then, he received on 0.15 mg thyroxine once a day. Now, the patient's general condition is favorable, and the last laboratory data reveal a GH of 1.6 ng/ml, IGF-1: 215 ng/dl (87–220 ng/dl), thyroglobulin (on-levothyroxine): 0.2 ng/ml, and negative antithyroglobulin antibody. Now, he is receiving Sandostatin LAR (30 mg every 4 weeks).

DISCUSSION

In acromegalic patients, thyroid disturbance occurs as a thyroid dysfunction as well as benign or malignant structural disease. Several studies indicated that a chronic excess IGF-1 stimulates the proliferation of various cell types and induces an antiapoptotic effect in thyroid follicular cells.[3,4] Some studies have suggested the potential role of pituitary irradiation, obesity, insulin, insulin resistance, leptin, IGF-binding proteins (BP) 1, and IGF-BP3 in inducing thyroid cancers.[5,6] It is important to keep in mind that genetic susceptibility to pituitary tumors with overproduction of GH can also increase the risk of other tumors such as thyroid cancer due to epigenetic mechanisms.[7] Thyroid cancer was reported as the most common cancer type in these patients.[2,8,9] We describe three patients with acromegaly and papillary thyroid cancer. None had previous radiotherapy or family history of thyroid malignancy. In all the patients, the thyroid cancer was the papillary type. In two patients, acromegaly and PTC were simultaneously diagnosed, and in the third case, the PTC was diagnosed when the acromegaly was not controlled biochemically. Therefore, in all the patients, PTC was diagnosed in the presence of elevated IGF-1 levels. Recently, Tirosh and Shimon *et al*. summarized the main studies reporting rates of thyroid cancer among patients with acromegaly. They deduced that patients with acromegaly had higher rates of thyroid cancer compared with controls (3.2% vs. 0.3%).[10] A meta-analysis of case–control studies showed an increased risk of thyroid cancer in acromegaly.[11] In addition, the rate of thyroid cancer varied from 1.2% to 10.6% in different studies.[10] Of course, some of the studies enrolled patients with small thyroid nodules for cytology evaluation. Therefore, this contributes to the diagnosis of thyroid microcarcinomas which are known as very low-risk tumors.[10,12] Indeed, in some studies, the prevalence of thyroid cancer was reported only slightly higher than the general population.[13,14] Furthermore, we need to take into consideration that prolonged and close follow-up of the acromegalic patients in endocrinology

clinics can lead to overdiagnosis of thyroid cancers. In some studies, there was no relationship between age, sex, disease duration or IGF-1 levels, and cancer developments,[2,12,14] but others reported gender-related differences.[9] Higuchi *et al*. reported that male acromegalic patients might have a higher risk for thyroid malignancy.[9] In general, although most patients with acromegaly were visited regularly by an endocrinologist and the thyroid cancer is often considered as a less aggressive tumor, routine thyroid examination may be necessary.

CONCLUSION

In the series of patients reported here, the size of papillary thyroid cancers was >1 cm and extrathyroidal extension was observed. It seems that extra attention should be paid on thyroid examinations in patients with acromegaly so that these thyroid complications should be discovered in earlier stages.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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