Acromegaly and papillary thyroid carcinoma: A case series

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INTRODUCTION

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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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 no notable for hemoglobin (Hb): A1c: 5.4% (4%–6.5%), fasting blood sugar (F BS): 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),
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: 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),

### 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 | Left thyroid nodule | Left thyroid nodule |
| | Enlarged nose | Weight gain | Weight gain |
| | Protruded chin, feet, and hands | Increased size of hands, nose, and feet | |
| | Deep voice | | |
| | Thickened lips | | |
| | Coarse skin | | |
| | Excessive sweating | | |
| **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 | TSS | TSS |
| | NTT: PTC 31 mm | NTT: PTC with ETE | Sandostatin LAR 30 mg every 4 weeks |
| | No ETE | I-131 100 mCi | 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
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for HbA1c: 6%

presented to our department with neck swelling. A 3
enanthate was administered. Prednisolone
uptitrated to a maximum dose of 30
mg, every 4 weeks and then
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 thyrxine 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
gingollicular cells.

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. 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.

Thyroid cancer was reported as the most
common cancer type in these patients. 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%). A meta-analysis of case-
control studies showed an increased risk of thyroid cancer in
acromegaly. In addition, the rate of thyroid cancer varied
from 1.2% to 10.6% in different studies. 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. Indeed, in some studies, the
prevalence of thyroid cancer was reported only slightly
higher than the general population. Furthermore, we
need to take into consideration that prolonged and close
follow-up of the acromegalic patients in endocrinology

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 transphenoidal 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 ng/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,
GT (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. Transphenoidal surgery was performed
in September 2006. After surgery, the patient’s symptoms
relied, 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, GT (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


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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