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ORIGINAL ARTICLE

High incidence of thyroid cancer among patients with acromegaly

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Summary

Purpose: *Several studies have suggested that patients with acromegaly have an increased risk of thyroid, colorectal, breast and prostate cancers. In this study we determined the prevalence of malignant neoplasms in patients with acromegaly.*

Methods: *Cancer risk was evaluated in a cohort of 110 patients (M/F 48/62, age 58.63±13.8 years, range 30–86) with acromegaly. Mean age at diagnosis of acromegaly was 46.37±13.11 years. Mean period of time since diagnosis of acromegaly was 12.26±9.6 years.*

Results: *From 110 patients, cancer was diagnosed in 26 (23.6%) patients. Thyroid cancer was the most common cancer and was diagnosed in 13 patients (11.8%); other cancers encountered were gastric cancer (N=2), endometrial cancer (N=2), and breast cancer, colon cancer, prostate cancer (N=2), myelodysplastic syndrome, renal cell carcinoma, lung cancer and pancreatic carcinoma, one case each. Age, gender, age at the time of diagnosis of acromegaly, tumor size of pituitary adenoma and duration of disease were not associated with cancer development.*

Conclusions: *This study suggests that patients with acromegaly have an increased risk of thyroid cancer and therefore they should undergo regular screening with hormonal and ultrasound evaluation of the thyroid and FNAB when required.*

Key words: *acromegaly, colon cancer, GH, IGF-1, thyroid cancer*

Introduction

Acromegaly is characterized by excessive levels of circulating growth hormone (GH) and its tissue mediator, insulin-like growth factor (IGF-1). Prior to effective treatment and lowering of GH and IGF-1, the majority of patients with the disease died by the age of 60 years, mainly because of diabetes mellitus, cerebrovascular and cardiovascular diseases. More recently, it has become evident that patients with acromegaly may also have an increased prevalence of multiple cancers. IGF-1 and GH have been correlated with tumor growth [1,2]. For some of these patients, the cause of death is attributed to malignancy [3]. Due to the improved management of the disease nowadays and the longer survival of patients, the increased risk of cancer development should be taken into consideration. Most common cancers related with acromegaly are predominantly located in the thyroid, breast, prostate, kidney, intestine, brain, uterus and skin [4,5]. In this study, we deter-

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mined the prevalence of malignant neoplasms in patients with acromegaly in a single Greek Cancer Centre, Metaxa Cancer Hospital, Piraeus.

Methods

Study population

This cross-sectional study evaluated retrospectively 110 patients with acromegaly who were treated and followed-up conducted at the department of Endocrinology of Metaxa Cancer Hospital during 1995-2015. The diagnosis of acromegaly was based on clinical features of the disease and the following criteria: 1) abnormal GH response to a 75 g oral glucose tolerance test; 2) high levels of serum IGF-I; and 3) presence of a pituitary adenoma confirmed by either computed tomography (CT) or magnetic resonance imaging (MRI).

All the subjects read and signed informed consent forms before enrolling in the study, which was approved by the local Ethics Committee and the Athens University Medical School. Demographic characteristics and a medical history, which included history of surgery and radiotherapy, medical treatment, duration of medical therapy, disease duration and status of the pituitary functions, were recorded in all patients. The diagnosis of cancer was histologically documented. Also, the presence of comorbidities (diabetes mellitus, hypertension, coronary artery disease), mortality and state of remission or disease control at last visit were also recorded. Patients were considered to be in remission when circulating IGF-1 level was within age and gender adjusted normal ranges and nadir GH was less than 1 μg/L during oral glucose tolerance test. A comparison was made between patients who had been operated on, had radiation treatment and medical therapy and those who had not.

Statistics

Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS, Inc. Chicago, ILL, USA) (version 22.0). Values are presented as mean±SD (median;min–max) for continuous variables and as numbers (percents) for categorical data. Differences between biochemically controlled and uncontrolled patients for demographic variables were analyzed using x^2 test and independent samples *t*-test. Significance was set at $p< 0.05$.

Results

A total of 110 patients with acromegaly were retrospectively assessed (48 males and 62 females, mean age 58.63 ± 13.8 years, range 30–86) with average disease duration 12.26 ± 9.61 years. Mean age at diagnosis of acromegaly was 46.37 ± 13.11 years. Forty two patients had a microadenoma and 68 had a macroadenoma. Mean period of time since diagnosis of acromegaly was 12.26 ± 9.6 years. At baseline, all patients were biochemically controlled. A hundred and eight patients were treated with somatostatin analogues. Only 2 patients were successfully treated with pituitary transsphenoidal surgery and received no medical treatment afterwards. Additionally, 31 patients were treated with pegvisomant and 6 patients with dopamin agonists. Eighty eight patients underwent pituitary transsphenoidal surgery, 13 of them underwent supplementary radiotherapy also, and 1 patient underwent radiotherapy only. Of those who had surgery, 15.9% had second and 2.2% had third operation. Associated hypopituitarism after pituitary surgery was treated with hormonal replacement therapy in 16 patients. A total of 58 patients had also hypertension, 56 had diabetes mellitus and 22 had cardiovascular diseases. Hypopituitarism was present in 16 patients.

From 110 patients, cancer was diagnosed in 26 (23.6%). Thyroid cancer was the most prevalent cancer diagnosed in 13 patients (11.8%). All of them had papillary thyroid carcinoma and received radioactive iodine ablation and all are in remission regardless of their acromegaly control. The mean age of patients with cancer was not statistically different when compared with the mean age of those without cancer. There was also no significant difference in disease duration, pituitary tumor size, or age at onset between them. No significant difference was found in the prevalence of hypertension, coronary heart disease and treatment modalities between the patients with/without cancer, whereas cancer was significantly more common in patients with diabetes.

Table 1 shows the patient characteristics and the differences between those with cancer and those without cancer and Table 2 shows the number of malignancies observed in patients with acromegaly.

Discussion

In this study of 110 acromegalic patients, histologically confirmed cancer was detected in 26 (23.6%) of them. Thyroid cancer was the most common cancer type with 13 of 26 acromegalic patients (50%) diagnosed with cancer had thyroid cancer. It was found that the risk of cancer development was not associated with age, gender, age at the time of diagnosis and disease duration. Additionally, the size of pituitary adenomas was not found to be related to cancer presence.

The association of acromegaly and cancer has only been recognized recently, since the improved

Table 1. The general characteristics of the patient groups with cancer and without cancer

Characteristics	*All patients (N=110)*	*Patients with cancer (N=26) N (%)*	*Patients without cancer (N=84) N (%)*	*p value*
Total number	110	26 (23.6)	84 (76.3)	
Females / Males	62/48	18 (29.0) / 8 (16.6)	44(70.9) / 40 (83.3)	0.106
Age (years, mean ±SD)	58.63±13.8	63.69±13.5	57.06±13.6	0.718
Age at onset (years, mean ±SD)	46.37±13.11	51.77±10.86	44.70±13.36	0.301
Disease duration (years, mean ±SD)	12.26±9.61	11.92±10.7	12.37±9.3	0.400
Tumor size (mm, mean ±SD)	16.32±8.82	15.96±9.73	16.43±8.5	0.598
Macroadenoma	68	14	54	0.338
Subjected to operation	88	21	67	0.911
On acromegaly medication	108	25	83	0.376
Received radiotherapy	13	3	10	0.960
Hypertension	58	16	42	0.303
Diabetes mellitus	56	18	38	0.032
Cardiovascular disease	22	6	16	0.654

Table 2. The number of neoplasms observed in 110 acromegalic patients

	Males (N=48) N	*Females (N=62) N*	*Total (N=110) N (%)*
Thyroid cancer	2	10	12 (10.9)
Coexistence of thyroid, prostate and lung cancer	1	0	1 (0.9)
Endometrial cancer	0	2	2 (1.8)
Gastric cancer	1	1	2 (1.8)
Gastrimona	0	1	1 (0.9)
Colon cancer	0	1	1 (0.9)
Breast cancer	0	1	1 (0.9)
Renal cell cancer	1	0	1 (0.9)
Pancreas cancer	1	0	1 (0.9)
Prostate cancer	1	0	1 (0.9)
Meningioma	0	1	1 (0.9)
Paraganglioma	1	0	1 (0.9)
Myelodysplastic syndrome	0	1	1 (0.9)

management of acromegaly offers longer survival and thus longer follow up in patient health status [6]. The association of acromegaly and cancer is controversial. Some studies indicate no increased risk for patients with acromegaly [3,7-9], whereas others report increased risk only for colon cancer [10]. Nevertheless, several studies found an increased cancer prevalence in patients with acromegaly compared to the tumor prevalence in the general population [4,5,11-13]. The differences between different studies may be due to the low prevalence of acromegaly *per se*, due to the retrospective nature of studies or due to differences in study designs.

The most common cancer type was thyroid cancer in our study, diagnosed in 11.8% of all patients. In Greece the incidence of thyroid cancer in the general population was 0.7/100,000 for men and 3.1/100,000 for women in 2012 according to the International Agency for Research on Cancer of the World Health Organization [14]. Thyroid cancer is the commonest cancer in patients with acromegaly ranging from 3.5 to 10.6% in several studies [5,15-18].

An uncontrolled hyperactive GH-IGF-1 axis may play a dominant role in the development of primary thyroid carcinoma rather than the BRAFV600E mutation in patients with acromegaly [19]. The effects of GH effects are mediated by GH receptor. When GH binds to its receptor, signal transduction pathways are activated which are important for cell growth and survival, including the Janus kinase-2/signal transducers and activators of transcription (JAK-2/STAT), the c-Src p44/42 mitogen activated protein kinase (MAPK), and the phosphoinositide 3-kinase (PI3 K) pathways. Many malignancies are associated with up-regulation of components of these pathways [20]. Moreover, GH shows its actions on somatic growth by induction of hepatic IGF-1 secretion and the IGF-1 and its receptor has been suggested to affect cancer devel-

opment by promoting adhesion and migration of cells, apart from angiogenesis in tumors [21].

Acromegaly is associated with different pathologies of the thyroid gland. Long-lasting stimulation of the follicular epithelium by GH and IGF-1 can alter thyroid function and morphology, such as increased mass and the development of goitre. Acromegalic patients develop more often non-toxic multinodular goitre and nodules [22]. Palpable thyroid nodules occur more often in acromegalic patients and the risk of malignancy in acromegalic patients with thyroid nodules is higher [23]. Acromegaly has goitrogenic-effect on the thyroid which is induced by TSH and IGF-1 [17,24].

Additionally, in our study only one female patient was diagnosed with breast cancer, although acromegaly has been associated with increased risk for breast cancer development [25], whereas other studies showed no increased risk [5,7]. IGF-1 causes marked proliferation of breast cancer cell lines which can be inhibited by anti-IGF1-receptor antibody [26].

Likewise, in this study we detected prostate cancer in only 2 of the acromegalic patients. Several authors have reported that IGF-1 may increase the risk of prostate cancer in humans [27,28]. Prostate enlargement in young acromegalic patients with low testosterone levels due to central hypogonadism supports the hypothesis that chronic GH and IGF-I excess cause prostate hyperplasia [29].

Colorectal cancer was thought to be the most frequent malignancy in acromegaly in the past. Nevertheless, in our study, colon cancer was determined in 0.9% of the acromegalic patients although the association between colon cancer and acromegaly has been emphasized in many studies [30,31]. In patients with acromegaly, the length of the colon is generally greater than in healthy people and epithelial cells of sigmoid crypts show increased pattern of proliferation, positively correlated to circulating IGF-1 levels and decreased apoptotic activity [32,33]. Possible mechanisms underlying the increased risk in patients with acromegaly include direct actions as a consequence of increased levels of serum GH and IGF-I and/or other perturbations within the IGF system. Additional possible mechanisms are altered bile acid secretion, altered cellular immunity, hyperinsulinaemia and shared genetic susceptibility [34].

In our study diabetes mellitus was more common in patients with cancer as in another epidemiological study [35] and no significant differences in age and sex of the acromegalic patients with/without cancer were reported in this study as well as in other ones [17,35]. Both glucose intolerance and diabetes mellitus are frequent complications of acromegaly.

In the present study we showed that the patients with cancer were older compared with those without and similar results were reported in one more study [35]. Cancer incidence rates increase with age for most cancers, especially in ages above 50 years.

Limitations of our study included its retrospective nature and the small number of patients. Another limitation was the lack of control group to compare the risk with the general population. Moreover, the patients came mostly from a single center, a Cancer Hospital, where many patients with thyroid carcinomas are treated every year, and the present results may be due to increased awareness of cancer in acromegalic patients and thus increased surveillance. In addition, FNAB for thyroid nodules has been performed routinely in recent years to detect malignancy.

In this study, thyroid cancer was the most common type of cancer in acromegalic patients, contrary to the acromegaly algorithms and the literature that show colon cancer as the most common type [36] and suggest regular colonoscoping screening [37]. In fact, the risk of thyroid cancer in acromegaly seems to be greater than it is reported in the literature. In conclusion, each individual diagnosed with acromegaly requires a hormonal assessment, ultrasound evaluation of the thyroid and FNAB if necessary, and an accurate evaluation during further observation and treatment. It is particularly essential to diagnose the patients early and to rule out thyroid cancer.

Conflict of interests

The authors declare no confict of interests.

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