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Thyroid cancer is the most common cancer associated with acromegaly

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Abstract The aim of the study was to screen the malignancy in an acromegalic patient group and to determine whether there was any increased risk and the incidence of malignancy and its association with disease characteristics such as duration of disease, latency in diagnosis, and GH and IGF-1 levels. One hundred-five (65 female, 40 male) patients with acromegaly followed and treated at Cerrahpasa Medical School, Endocrinology and Metabolism outpatient clinic between 1983 and 2007 were included in this study. The patients were screened with colonoscopy, mammography, and thyroid and prostate ultrasonography (US). Malignancy was detected in 16 (15%) patients. Thyroid cancer was found in 5 patients (4.7%), breast cancer in 3 (2.8%), colon cancer in 2 (1.9%), lung cancer in 2 (1.9%), cervix cancer in 1 (0.9%), myelodysplastic syndrome (MDS) in 1 (0.9%), *cholangiocarcinoma* in 1 (0.9%), *and* multiple endocrine neoplasm (MEN) type 1 in 1 patient (0.9%). Cancer was more common in the male patients ($P = 0.046$) and high levels of GH increased the risk of cancer development ($P = 0.046$). In this series, the most commonly detected cancer types were thyroid followed by breast and colon cancers. Although high levels of initial GH seemed to increase the risk of cancer development in acromegalic patients, age, gender, age at the time of diagnosis, duration of disease, and initial IGF-I levels were not associated with cancer development.

Keywords Acromegaly · Malignancies · GH · IGF-I · Thyroid cancer

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Introduction

Mortality is high among patients with acromegaly compared with healthy age and gender matched controls [1, 2]. Although the most important three causes of mortality are cerebrovascular, cardiovascular, and pulmonary disease, malignancies are the cause of death in 15% of acromegalic patients [2, 3].

The association between tumor growth and growth hormone (GH), insulin like growth factor-1 (IGF-1) axis is well established [4, 5]. GH is mitogenic and anti-apoptotic in many tissues [5, 6]. IGF-1 is an important mitogen required by some cell types to progress from the G1 phase to the S phase of the cell cycle [6]. IGF-1 exerts powerful effects on each of the key stages of cancer development and behaviour: cellular proliferation and apoptosis, angiogenesis and metastasis, and more recently, development of resistance to chemotherapeutic agents [7]. It is a potent proliferative agent affecting almost every cell type, an effect predominantly mediated via the mitogen-activated protein (MAP) kinase signaling pathway. In addition to these proliferative actions, IGF-1 is also a powerful anti-apoptotic agent influencing the apoptotic responses to a variety of agents of numerous cell types [6, 7]. Indeed, many types of neoplastic cells express or overexpress IGF-1 receptors, which stimulate mitogenesis when activated by IGF-I in vitro. In vivo, tissue IGF bioactivity is determined not only by circulating IGF-1 and IGFBP levels, but also

by local production of IGFs, IGFBPs, and possibly IGFBP proteases that enhance IGF-1availability by cleaving IGFBPs [4–7].

However, several reports did not support the increased risk of developing cancer in patients with acromegaly [3, 8]. Most studies reported a moderately increased relative risk for acromegalic patients to develop tumors, mainly of the colon/rectum, breast, prostate, thyroid, and hematological system [9–15].

The aim of our study was to determine the malignancy rate in acromegalic patients at a single center and to determine whether there was any increased risk and the incidence of malignancy and its association with disease characteristics such as duration of disease, latency in diagnosis, and GH and IGF-1 levels.

Patients and method

One hundred-five patients with acromegaly (60 female and 45 male; mean age: 47.9 ± 11.5 SD years) followed and treated at Cerrahpasa Medical Faculty, Endocrinology and Metabolism outpatient clinic between 1998 and -2007 were included in this study. All the patients were invited to the hospital by phone. The patients were enrolled into the study upon their informed consent. Although colonoscopy, mammography, thyroid US and prostate US were planned for all the patients according to gender, only 70 patients completed the screening. Among the patients, 15 refused colonoscopy, 15 refused mammography, 5 refused thyroid US, and 1 male patient refused prostate US. In the patients diagnosed with thyroid nodule, a fine-needle aspiration biopsy (FNAB) was performed on all the thyroid nodules with a diameter ≥1 cm and which showed suspicious US characteristics. At the end of these examinations, the patients were treated with the appropriate treatments. Age at the time of diagnosis, gender, duration of the disease, size of pituitary adenoma, surgery, treatments received, the most recent activation of illness, and the disease activation at the time of cancer diagnosis were evaluated. The diagnosis of active disease was determined by the presence of clinical findings and failure to suppress nadir GH level less than 1 ng/dl during OGTT and as well as high levels of IGF-1 adjusted for age and gender. Acromegaly was 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 ng/ml during OGTT [16].

GH and IGF-1 levels were determined by the immunolight method (BIO-DPC, Los Angeles, USA). The normal values were accepted as 0–5 ng/dl for GH. The data on normal IGF-1 ranges adjusted for age and gender in Turkish population were obtained from a pervious study by Tiryakioğlu et al. [17]. Thyroid US and prostate US were performed using 7.5 MHz 70 mm linear transducer device (Siemens Sonoline Sienna). Mammography examination was performed with Siemens Nova 3000 device, and colonoscopy, with Pentaks device. The study was approved by the Ethics Committee of Cerrahpasa Medical School, Istanbul University.

SPSS 15.0 software package was used in statistical analysis of the data. Chi square test was used in the comparisons of categorical variables. When continuous variables were compared, the Mann–Whitney *U* test was used for independent groups. To assess the factors that affect cancer development, logistic regression analysis was used. $P < 0.05$ was considered statistically significant.

Results

The general characteristics of the patient groups with cancer and without cancer are shown in Table 1. Eighty three percent of the patients had macroadenomas, and 17% of the patients had microadenomas. The average duration of the disease was 13.02 ± 7.1 SD years. During screening for malignancy, cancer was found in 16 acromegalic patients (15.2 %). Thyroid cancer was found in 5 patients (4.7%), breast cancer in 3 (2.8%), colon cancer in 2 (1.9%), lung cancer in 2 (1.9%), cervix cancer in 1 (0.9%), myelodysplastic syndrome (MDS) in 1 (0.9%), *cholangiocarcinoma* in 1 (0.9%), *and* multiple endocrine neoplasm (MEN) type 1 in 1 patient (0.9%) (Fig. 1). There was no statistical significant difference between the ages of the patients with (52.10 ± 3.50 SD years) and without- cancer (47.13 ± 1.20 SD years) ($P = 0.313$).

Of the patients who developed cancer, 11 were male (68%) and 5 were female (32%) ($P = 0.046$). Eighty one percent of the patients had macroadenomas. Logistic regression analysis showed that age, gender, age at the time

Table 1 General characteristics of the groups with or without cancer

	Without-cancer		With-cancer		*P*
	Median	IQR	Median	IQR	
Age at diagnosis (year)	39	30–48.5	39	30–50	0.65
Latency in diagnosis (month)	48	12–84	60	24–60	0.90
Duration of illness (month)	132	84–186	144	96–252	0.50
Last IGF-1(ng/dl)	264	155–419	319	186–543	0.27
Last GH (ng/dl)	1.74	0.7–4.3	1.2	0.6–2.5	0.80
Remission time (month)	12	12–24	42	18–48	0.048

IQR Interquartile range

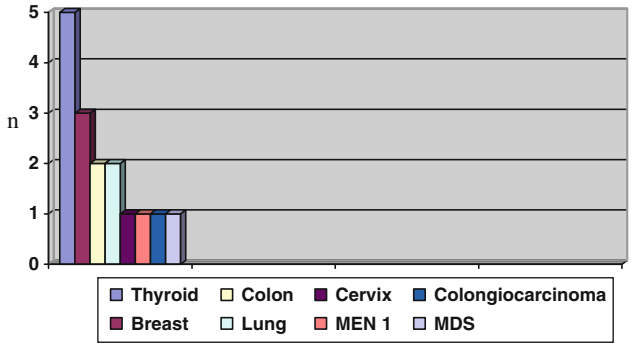

Fig. 1 The types of cancer detected in the acromegalic patients

of diagnosis, duration of illness and initial IGF-I level were not associated with cancer development. Initial GH levels seemed to be associated with an increased risk of cancer development ($P = 0.046$). The remission time was found to be significantly longer for the patients diagnosed with cancer ($P = 0.048$).

Thyroid US was performed in 100 patients and nodules were found in the thyroid gland in 62 patients (62%). Single nodule was found in 36% and multiple nodules were found in 26% of these patients. Size of the thyroid nodule was <10 mm in 29 (47%) patients, between 10 and 20 mm in 21 (34%) patients, and over 20 mm in 12 (19%) patients. FNAB was performed in 27 patients with a nodule size ≥10 mm which had suspicious US features in the thyroid gland. Although the findings of 22 patients were benign in nature, 5 patients had thyroid cancer. The incidence rate of thyroid cancer was 5% for all of the patients and 8% for the patients who had a nodule in the thyroid gland. All the patients who were diagnosed with thyroid cancer were male, and all of the pathological subtypes were papillary thyroid cancer. There was no statistically significant difference between the IGF-1 levels of the group of patients with thyroid cancer (median IGF-1: 600 IQR [506-777]) and the group of patients without thyroid cancer (median IGF-1: 569 IQR [438.5-713]) ($P = 0.61$). One patient was diagnosed with Graves Disease and one patient, with Hashimoto disease.

Fifty-nine female and 31 male (total $n = 90$ patients) underwent mammography. Malignancy was found in three female patients whose pathological subtypes were invasive ductal carcinoma, in-situ ductal carcinoma, and mixed type ductal carcinoma, and their stages were stage 0, stage 1 and stage 2, respectively.

Fifty-three female and 37 male (total $n = 90$ patients) underwent colonoscopy. There were no pathological findings in 55 patients; a polyp was detected in 23 (26%), and colon cancer was found in 2 patients (2%). The tumor stages of these patients were stage 2 and stage 3, and pathological subtypes of tumors were adenocarcinoma and mucinouscarcinoma. The distribution of the pathological findings in the patients who underwent colonoscopy has been shown in Table 2.

Table 2 Pathological findings of the patients who underwent colonoscopy

Pathological findings	*n* (25)	%
Hyperplastic polyp	2	8
Tubular adenomatous polyp	5	20
Adenomatous polyp	2	8
Tubulovillous adenoma low grade dysplasia	3	12
Serrated adenoma	1	4
Sessile polyp	9	36
Dimmunitive polyp	1	4
Mucinous adenocarcinoma	1	4
Adenocarcinoma	1	4

Thirty-nine male patients were performed prostate US. The mean age of these patients was 44.36 ± 1.79 SD years. Prostate hypertrophy was detected in 26 patients (67%), and no pathologies were found in the prostate gland of 13 patients (33%). None of these patients was diagnosed with prostate cancer.

Except for the screening tests, during the follow up, two lung cancers, one colongiocarcinoma, one MDS, one MEN type 1 and one cervix cancer were determined. These patients were treated according to their cancer stages. Four patients from the acromegalic patient group died. The cause of death was lung cancer in two patients, cholangiocarcinoma in one patient, and MEN type 1 in one patient.

In the evaluation of remissions at the time of cancer diagnosis of the patients, there was remission in 1 patient (6.25%), and there were no remissions in 13 patients (81.25%). The remission status of two patients (12.5%) could not be evaluated because they could not be contacted.

Discussion

Cancer was detected in 16 (15.2%) of all the acromegalic patients in this study. Thyroid cancer was the most common cancer type among acromegalic patients. Five of 16 patients who were diagnosed with cancer in the acromegalic patient group had thyroid cancer.

The results of epidemiological studies indicating that acromegaly may increase the neoplastic risk have been controversial. In their study conducted between 1937 and 1955, Mustacchi and Shimkin analyzed 223 patients who were diagnosed with acromegaly and did not find an increased cancer incidence compared to incidence rates for the population [18]. A significant contribution to this

debate was made by Orme et al. [8] who retrospectively examined the cancer incidence and mortality in a cohort of 1,362 acromegalic patients. They reported that the overall cancer incidence rate was lower than that in the general population of the United Kingdom, and there was no significant increase in site-specific cancer incidence rates. The authors also stated that there was no increase in mortality rate from malignant disease in general, but the colon cancer mortality rate was higher than expected. In 1982 Klein et al. [19] studied 44 acromegalic patients and reported 11 cases of cancer, predominantly colon cancer. Brunner et al. [20] demonstrated an increased risk only for colon cancer in 52 acromegalic patients compared to population tumor incidence rates. Subsequently, Barzilay et al. Popovich et al. and Higuchi et al. [12, 15, 21] found an increased cancer incidence compared to population tumor incidence rates in their smaller series. Recently, Barıs et al. [22] confirmed an increased risk for all cancers in 1,634 acromegalic patients from Sweden and Denmark especially colon and rectum cancers. Experimental in vitro and in vivo studies have provided the first evidence of the association between the GH/IGF-1 system and cancer. In 1950, Moon et al. [23] applied chronic high dose treatment with extracted GH in female rats and determined that it caused the development of tumors in lungs, adrenals, ovaries, and breast. Transgene expression of bovine GH was not shown to be carcinogenetic; however, studies in which transgenic mice expressing human GH developed mammary tumors confirmed the role of GH in animal tumorigenesis [24]. In vitro studies showed that GH stimulated the proliferation of several cancer cell lines, while studies on GH synthesis in a number of extra pituitary organs have suggested that GH may have local paracrine/autocrine effects [23]. For example, in mammary carcinoma cell lines, autocrine GH creates a direct proliferative stimulus and decreases apopitotic activity, with marked synergism with tropic agents such as IGF-1 [25]. Cancer development risk increased in parallel with baseline GH enhancement. Orme et al. [8] have also concluded that high post-treatment GH levels are associated with an increased overall mortality rate and increased mortality rates due to colon cancer, cardiovascular disease, and all malignant diseases. Post-treatment GH levels less than 2.5 ng/ml (5 mU/l) result in an overall mortality rate similar to that in the general population.

The effects of GH are mediated by GH receptor. Binding of GH to the GHR activates signal transduction pathways critical 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. Upregulation of components of this pathways has been observed in a wide range of malignancies [26]. GH also induces early response genes that precede cell growth and differentiation signals mediated by CCAT enhancer-binding protein β and serum response element sites on the c-fos promoter [27].

GH shows its effects on somatic growth by induction of hepatic IGF-1 secretion. The tumoregenic process is modulated by IGF-1 system at different levels. In experimental studies, which reported that knockout of IGF-1R gene was capable of decreasing cell proliferation and increasing apoptosis, IGF-1/IGF-1R involvement in cancer cell proliferation was shown [23]. Moreover, the IGF-1/IGF1R system has been suggested to influence cancer progression by promoting adhesion and migration of cells, as well as angiogenesis within tumoral tissues and in the surrounding areas [28]. Likewise, because IGF-1 is widely synthesized locally, it has an autocrine/paracrine effect in tissues. IGF-1/IGF-1R-mediated autocrine/paracrine effect is responsible for regulation of cancer growth based on the demonstration of IGF-1R mRNA expression in colon cancer as well as on the surface of malignant breast epithelial cells where IGF-1R was shown to have an effect [23]. In addition, IGFBP-3 has been held responsible for apoptosis development and proliferation of numerous tumor cell lines.

The most common cancer types were thyroid, breast, and colon cancers in our study. It was found that the risk of malignancy development was higher in acromegalic male than in female patients. Age, gender, age at the time of diagnosis, duration of the disease and initial IGF-I were not associated with cancer development, but the level of initial GH was found to be important in tumor genesis. Furthermore, the size of adenomas was not found to be associated with tumor genesis ($P = 1.0$).

To date, no real rate of cancer incidence has been established for a defined population in Turkey despite several studies. A “passive cancer registration system” was established for the entire country by Turkish Ministry of Health in 1983. However, because it is a passive system, a gap exists between the recorded and expected numbers of cancer cases. In addition, irregular information on the incidence rates (including Hacettepe and Ege Universities) from pathology departments are available in the current literature; nevertheless, there are several selection biases in these studies, and they represent only a determined region. The data on mortality in Turkey are also incomplete and available only for selected urban areas [29]. A population-based cancer registry, covering the province of Izmir (population 2.7 million, 1993–1994) in Western Turkey was established in 1992. Overall cancer incidence was higher in males than in females [age-standardized rates (ASR) 157.5 and 94.0 per 100.000, respectively], as in previous non-population- based series. The principal cancers in male were lung (ASR 61.6), bladder (ASR 11.0), larynx (ASR 10.6) cancers respectively. On the other hand,

thyroid cancer (ASR 0.5) and gastrointestinal cancers especially colon/rectum cancer (ASR 7) were relatively rare in males. In women, breast cancer was by far the most common malignancy (ASR 24.4) followed by corpus uteri (ASR 6.4), ovary (ASR 5.9), and cervix uteri (ASR 5.4) cancers. Age-standardized rates for thyroid and colon/rectum cancers were 1.1 and 5.6% in Turkish women respectively [29].

In our study, the frequency of nodules in the acromegalic patients was 62% and the frequency of thyroid cancer in the patients with a thyroid nodule was 8%. No statistically significant difference was found between the median serum IGF-I levels of the patients with thyroid cancer and of the patients without thyroid cancer. The carcinogenic mechanism of thyroid adenoma and cancer in acromegaly is not clear. However, this may be associated with increased guatrogenic effect in acromegaly [30]. This effect is induced by TSH and IGF-1 at receptor level [30, 31]. In acromegaly, an increase in the frequency of goiter was detected as well as in benign and malign thyroid lesions [31]. In recent epidemiological studies, it has been found that the risk of thyroid cancer increases depending on duration of illness in acromegalic patients who have past history of goiter or thyroid nodule [32, 33]. In a study by Gaspari et al. [34] in 2002, 258 patients with active acromegaly were evaluated for the presence thyroid disorders, and the thyroid cancer rate was found to be 1.2%. Tita et al. [30] performed a retrospective study on 125 acromegalic patients and reported that the frequency of thyroid cancer was 5.6% in comparison to the estimated prevalence in the general population. Kurimato et al. [35] detected thyroid cancer using ultrasonograpy in 4.8 % of 140 acromegalic patients (60% male and 40% female). Barıs et al. [22] reported that a risk for thyroid carcinoma was significantly elevated exclusively in women with acromegaly. Similarly, in our study, a high incidence of thyroid cancer was determined in acromegalic patients.

During our study, mammography was performed to investigate the risk of probable breast cancer in men as well as in women, and only three women (3.3%) had pathological masses in the breast. Thus, breast cancer screening may not be recommended for men. Our study is consistent with the prior studies [36, 37] in that it confirms that high levels of premenopausal GH and IGF-I increase the risk of breast cancer because 65% of the patients with breast cancer are diagnosed in premenopausal period and initial GH and IGF-I levels of all the patients with breast cancer are high. In a study of Nabarro et al. [11] it was shown that there was a four-fold increase in breast cancer incidence in acromegalic patients. In a case control study of Hankinson et al. [38] on patients with breast cancer, in previously collected and stored serum samples, IGF-1 levels were higher and IGFBP-3 levels were lower compared to those of the controls. Similarly, Li et al. [36] showed that there was a high risk of breast cancer in premenopausal women with increased IGF-1 and decreased IGFBP-3 levels. In our study, the rate of breast cancer was 2.8% in the acromegalic patients.

Renehan et al. [39] using cumulative data in the published literature from 8 autopsy studies and 4 screening colonoscopy studies, reported adenocarcinomas in 3 (2.6%), and at least 1 adenoma in 11 patients, reaching an overall prevalence of neoplasia in 12 % of 115 acromegalic patients compared to the general population. According to Jenkins et al. [40] macroscopic colorectal carcinoma was found in 5.1% and tubullar adenoma was found in 25.1% of 155 acromegalic patients and their IGF-1 levels were higher than those of the patients without polyp or cancer. Prospectively in an average of 33-month follow-up, the rate of detection of a new polyp was calculated as 14% in repeated colonoscopy. In our study, the colon cancer was determined in 0.9% of the acromegalic patients.

In contrast to some studies in the literature, in the present study, prostate hypertrophy was detected in 67% of the patients; none of the patients had prostate cancer. It was reported that in patients with progressed prostate cancer, the serum levels of IGF-1 increased and the IGFBP-3 levels decreased significantly compared with the patients with benign prostate hyperplasia [41, 42]. In an earlier study, blood samples of 14,916 patients were collected and stored. After 10 years, when serum levels of IGF-1 and IGFBP-3 of the patients diagnosed with prostate cancer were compared with the control group, it was found that the IGF-1 levels in the group having a higher risk for prostate cancer were significantly higher compared with the group having a low risk for cancer [44]. In several epidemiological studies, it was observed that the frequency of prostate cancer in general population increased along with the increased IGF-1 levels [41–44]. Prostate cancer is rare in people <60 years of age. In this study, we did not detect prostate cancer in any of the acromegalic patients. One of the reasons why prostate cancer was not detected in acromegalic patients in our study might have been that the mean age of the men was <50.

In our study, lung cancer was determined in two male patients (1.9%) and both died during the study period. In several prospective studies, no significant relationship was detected between prediagnosis IGF-I level and lung cancer. In general population, risk of lung cancer was found to be higher than that for acromegalic patients, and this was attributed to smoking habit and lower rates of exposure to environmental pollution and radiation [8].

It was concluded in our study that high levels of GH increased the possibility of cancer development. Age at the time of disease, gender, age at the time of diagnosis, duration of disease, and initial IGF-I levels did not play a role in cancer development.

Earlier studies have yielded conflicting results on the increased cancer incidence in acromegalic patients; thus, there is no consensus on a specific rate. Contrary to the literature and acromegaly algorithms that suggest colon cancer as the most common type, in our study, thyroid cancer was the most common type of cancer in acromegalic patients [1, 27]. Our data suggest that the patients who are followed for acromegaly should be screened for thyroid nodule and cancer by US, and FNAB when required. In the present study, compared to previous studies, colon polyp and cancer in acromegalic patients were detected to be in lower rates than expected. In addition, we recommend annual mammography for female patients with acromegaly.

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