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Prevalence of neoplasms in acromegaly: a Turkish single-center retrospective study

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ABSTRACT

Aims: This study aimed to investigate the prevalence of benign and malignant neoplasms and to assess associated clinical conditions in patients with acromegaly.

Methods: In this single center, retrospective and observational study, data from 71 patients with acromegaly followed at an endocrinology and metabolism diseases outpatient clinic between January 2010 and December 2023 were reviewed through the hospital's electronic database. Patients' medical histories, demographic data, blood examinations, medications, pituitary MRI scans, thyroid ultrasound, mammography, colonoscopy, endoscopy, and pathology reports were evaluated. Acromegaly diagnosis was based on elevated insulin-like growth factor-1 (IGF-1) levels and unsuppressed growth hormone (GH) levels after oral glucose tolerance testing. The chi-square test and Mann-Whitney U test were used to compare patients with malignancy to other patients in terms of demographic and clinical characteristics.

Results: The study included predominantly female patients (60.6%) with an average age of 55.6 years. The mean age at diagnosis was 44.3±11.3 years, and the mean disease duration was 11.3±8.4 years. Malignancies, including breast, thyroid, and colorectal cancers, were detected in 9.9% of patients. Additionally, thyroid nodules were present in 62% of patients, and colon polyps in 14.1%. No significant differences were observed in clinical features including age, gender, disease duration, GH levels, IGF-1 levels, adenoma size, or remission frequency between patients with and without malignancy ($p>0.05$ for all).

Conclusion: This study reveals an increased prevalence of breast, colon, and thyroid cancers in patients with acromegaly. Performing cancer screenings in patients with acromegaly more comprehensively and at an earlier stage compared to the normal population may be beneficial.

Keywords: Acromegaly, neoplasm, cancer screening

INTRODUCTION

Acromegaly is an uncommon disease marked by increased growth hormone (GH) and insulin-like growth factor-1 (IGF-1), typically resulting from the presence of a pituitary adenoma.[1] Its incidence ranges from 3-4 per million per year, with a prevalence of 40 to 70 per million.[2] Acromegaly is typically diagnosed between the ages of 40 and 50. Its insidious onset, slow progression, and variable clinical presentation frequently lead to delayed diagnosis.[3]

Patients with acromegaly face an increased risk of morbidity and mortality due to cardiovascular, respiratory, and metabolic complications.[4] Moreover, the anti-apoptotic and pro-angiogenic effects of IGF-1 are known to contribute to an elevated risk of neoplasms in patients with acromegaly.[5] While conflicting results exist, most studies have shown an increased incidence of malignancies in patients with acromegaly.[6,7] Additionally, an increased frequency of benign tumors in organs such as the thyroid gland, colon, and gallbladder has been reported.[8,9]

With the rise in life expectancy and improved treatment options for acromegaly over the years, malignancies have become one of the leading causes of mortality in these patients.[10] However, there are limited studies investigating the risk of malignancy in Turkish individuals with acromegaly.

This study aims to investigate the prevalence of benign and malignant neoplasms in patients with acromegaly followed at a tertiary care hospital and to elucidate related clinical conditions.

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METHODS

Design and study population

In this single-center retrospective observational study, data from 71 patients with acromegaly followed at our endocrinology and metabolism diseases outpatient clinic between January 2010 and December 2023 were evaluated. The medical histories, demographic data, blood tests, medications, pituitary MRI scans, and pathology results of the patients were reviewed retrospectively. At our center, routine follow-up for acromegaly patients involves colonoscopy and thyroid ultrasound for all patients, and mammography for female patients, as part of standard clinical practice, and the results of these procedures were also reviewed. Because the study was designed retrospectively, no written informed consent form was obtained from patients. The study was conducted following ethical standards outlined in the Helsinki Declaration, with approval from İstanbul Medeniyet University Clinical Researches Ethics Committee (Date: 18.06.2021, Decision No: 2022/0636).

Clinical Assessment

Laboratory examinations were conducted after 8-12 hours overnight fasting. Serum IGF-1 and GH levels measured using chemiluminescence immunoassay. Acromegaly diagnosis was based on elevated IGF-1 levels and unsuppressed GH levels after oral glucose tolerance testing (OGTT).

Patients were classified into remission or active disease groups based on treatment response criteria. Remission was defined as GH suppression to <0.4 µg/L following an OGTT or GH <1 µg/L with normal IGF-1 levels. Active disease was characterized by GH >1 µg/L and elevated IGF-1 levels.

Height (in centimeters) and weight (in kilograms) were measured using a height scale and an automated weight machine, and body-mass index (BMI) was subsequently calculated.

Statistical Analysis

Descriptive statistics for study participant characteristics included mean, standard deviation (SD), and % frequencies. Numerical data were analyzed using the Mann-Whitney U test for independent variables, and categorical data were analyzed using the chi-square test or Fisher's test when chi-square test conditions were not met. SPSS 28.0 software was used for statistical analysis, with a significance level set at $p<0.05$.

RESULTS

The mean age of the patients was 55.6±11.4, with a female predominance (60.6%). The mean age at diagnosis was 44.3±11.3 years, and the mean disease duration was 11.3±8.4 years. At the time of diagnosis, the mean GH and IGF-1 values were 5.3±9.0 µg/L and 410 ± 329 µg/L, respectively. Sixty-two patients (87.3%) underwent transsphenoidal surgery, ten (14.1%) received radiotherapy, and 29 (40.8%) had recurrence or residual adenomas. Medical treatment was administered to 57 patients (80.3%), with 53 (74.6%) achieving remission. Detailed demographic characteristics and clinical features of the patients are presented in Table 1.

Table 1. Demographic and clinical characteristics of patients

Variable (n=71)	Value
Age (year)	55.6±11.4
Female	43 (60.6)
Body-mass index (kg/m^2)	29.1±5.4
Age at diagnosis (year)	44.3±11.3
Disease duration (year)	11.3±8.4
Diabetes mellitus	34 (47.9)
Hypertension	35 (49.3)
Coronary artery disease	11 (15.5)
Chronic obstructive pulmonary disease	7 (9.9)
Size of pituitary adenoma (mm)	16±9.9
GH level at diagnosis (µg/L)	5.3±9
IGF-1 level at diagnosis (µg/L)	410±329
Transsphenoidal surgery	62 (87.3)
Radiotherapy	10 (14.1)
Residue or nux	29 (40.8)
Follow up	14 (19.7)
Dopamine agonist	2 (2.8)
Somatostatin analogue	45 (63.4)
Dopamine agonist+somatostatin analogue	10 (14.1)
Remission	53 (74.6)

Data are presented as mean±standard deviation or as n (%), GH: Growth hormone, IGF-1: Insulin-like growth factor-1

Malignancies were detected in seven patients (9.9%), including two colorectal cancers, two papillary thyroid cancers, and three breast cancers. Additionally, polyps were found in 13 patients (14.1%) in the colon, intestinal metaplasia in one patient (1.4%) in the gastric antrum, and thyroid nodules in 44 patients (62%). The frequencies of benign and malignant tumors detected in patients are shown in Table 2.

Table 2. Prevalence of benign and malignant tumors

Thyroid US±biopsy	Normal	25 (35.2)
	Nodule/MNG	44 (62)
	Papillary carcinoma	2 (2.8)
Colonoscopy±biopsy	Normal	56 (78.9)
	Inflammatory polyp	7 (9.9)
	Hyperplastic polyp	6 (8.4)
	Colorectal cancer	2 (2.8)

US: Ultrasound, MNG: Multinodular goiter, Data were presented as n, (%)

When comparing patients with malignancies (n=7) to the others, no statistically significant differences were observed between the groups in terms of age, gender, comorbid features, disease duration, GH levels, IGF-1 levels, adenoma size, or remission frequency ($p>0.05$ for all) (Table 3).

Table 3. Comparison of demographic and clinical characteristics between patients with malignancy and those without malignancy

Variable	Malignancy (-) n=64	Malignancy (+) n=7	p value
Age (year)	55±11.6	61.1±6.9	0.097
Age at diagnosis (year)	44.1±11.4	46.6±11	0.657
Female	38 (59.4)	5 (71.4)	0.536
Body-mass index (kg/m^2)	29.1±5.5	28.9±4.4	0.309
Disease duration (year)	11±8	14.6±12	0.543
Size of adenoma (mm,)	16.4±9.9	12.4±9.2	0.938
GH level at diagnosis (µg/L)	5.4±9.5	4.2±3.5	0.623
IGF-1 level at diagnosis (µg/L)	422±342	293±133	0.335
Remission (n, %)	49 (76.6)	4 (57.1)	0.359

Data are presented as mean±standard deviation or as n (%), GH: Growth hormone, IGF-1: Insulin-like growth factor-1

DISCUSSION

In this study, we found that one out of every ten patients with acromegaly who were followed at our hospital has malignancy. Additionally, we found that, apart from malignant tumors, thyroid nodules were present in 62% of patients, and colon polyps were found in 14.1% of them.

Untreated acromegaly is associated with a reduction in life expectancy by approximately 10 years and leads to various complications.[11] Among these complications, an increased risk of malignant tumors is of paramount importance. Malignancies are the third leading cause of death in patients with acromegaly, following cardiovascular and respiratory diseases.[12,13]

Numerous studies have investigated the frequency of benign and malignant tumors in acromegaly. Thyroid cancer is believed to be the most prevalent malignant neoplasm in patients with acromegaly.[14] In a study by Woliński et al.[15] involving 205 patients with acromegaly, the frequency of thyroid cancer was reported as 5.4%. The estimated risk of developing thyroid cancer in individuals with acromegaly was found to be 2.5-4.3 times higher than that in the general population.[16] A large cohort study by Baris et al.[7] involving 1634 acromegaly patients reported a statistically significant increase in thyroid cancer incidence compared to the general population. In our study, papillary thyroid cancer was observed in 2.8% of patients, indicating a higher prevalence compared to the general population, although it was not directly compared with a control group.[17]

The association between acromegaly and an increased risk of breast cancer is a subject of debate. Several studies have shown no significant difference in the frequency of breast cancer between patients with acromegaly and control groups.[18,19] However, according to Nabarro, the risk of breast cancer development in acromegaly increases fourfold.[20] Baris et al.[7] observed a slight rise in breast cancer incidence among female patients with acromegaly below the age of 50. In our study, the occurrence of breast cancer in 3 out of the female patients (7%) suggests an increased frequency of breast cancer in patients with acromegaly, emphasizing the need for more vigilant mammography screenings in women with acromegaly.

The prevalence of colorectal cancer in acromegaly has been shown to be elevated in several studies. A British prospective study involving 129 acromegaly patients indicated a significantly higher incidence of colorectal carcinoma.[21] A meta-analysis by Rokkas et al.[9] reported a colorectal cancer incidence ratio of 4.6% in patients with acromegaly, significantly higher than that in control groups. In our study, colorectal cancer was observed in 2.8% of patients, supporting the notion that colorectal cancer incidence is higher in acromegaly, and earlier colonoscopy screening may be beneficial for this patient group.

In addition to malignant tumors, it is well-established that the frequency of benign lesions increases in acromegaly. Our study revealed that 62% of patients had thyroid nodules, 14.1% had colon polyps, and 7% of female patients had breast masses. A study by Can et al.[22] involving 56 patients with acromegaly and an equal number of control subjects, found that 55.4% of patients had thyroid nodules, which was statistically significantly higher compared to the control group. In light of the aforementioned results, it is recommended that patients with acromegaly undergo routine thyroid ultrasound examinations, and biopsies should be considered for thyroid nodules with suspicious features.

Comparative studies on the prevalence of colon polyps in patients with acromegaly and control groups are limited, as performing colonoscopy on asymptomatic individuals in the control group solely for research purposes raises ethical concerns. A meta-analysis conducted by Rokkas et al.[9] which included nine studies and 701 patients, demonstrated a statistically significant higher incidence of both adenomas and hyperplastic polyps in patients with acromegaly. According to both this meta-analysis and other prospective studies, benign colonic neoplasms are estimated to be present in around half of the patients.[9,23,24] In our study, the presence of colon polyps in 14.1% of patients appears to be consistent with the findings of these studies. Based on these findings, colonoscopy at the time of diagnosis is recommended for patients with acromegaly, and our center has data on endoscopy and colonoscopy for all patients with acromegaly. However, some authors argue that, in the absence of evidence supporting an increased risk of developing colorectal cancer, patients with acromegaly should follow guidelines for the general population, which recommend the first colonoscopy after the age of 50.[25]

The most discussed mechanism for the increased malignancy risk in acromegaly is the elevated level of GH, followed by IGF-1. A positive correlation between circulating IGF-1 levels and the risk of colorectal, breast, or thyroid cancer has been established in the general population.[26,27] However, in our study, we did not observe any significant differences in IGF-1 and GH levels between patients with malignancy and those without. We believe that this may be primarily attributed to the retrospective design of our study, which did not account for variables that could affect IGF-1 levels, as well as the relatively small sample size.

Limitations

Our study has certain limitations. Firstly, it was conducted retrospectively at a single center, and its findings cannot be extrapolated to the general population. Secondly, due to the design of our study, there was no control group, and the results could not be compared to those of healthy individuals. Thirdly, there was a lack of detailed evaluation of genetic and environmental factors that may contribute to cancer development in patients. Finally, the endoscopic, colonoscopic, mammographic, and thyroid ultrasound examinations were performed by different physicians over the years, and biopsy results were evaluated by different pathologists, which may have led to variations in the interpretation of the results.

CONCLUSION

In conclusion, our study demonstrated an increased prevalence of breast, colon, and thyroid cancer in acromegaly patients. However, no significant differences in clinical features related to acromegaly were observed between patients with and without malignancy. Considering these results, we believe that cancer screenings in acromegaly patients may be

beneficial if conducted earlier or at more frequent intervals. Nevertheless, these findings need further support from more comprehensive prospective and randomized controlled studies.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the İstanbul Medeniyet University Clinical Researches Ethics Committee (Date: 18.06.2021, Decision No: 2022/0636).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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