The Prevalence of Benign and Malignant Tumors in Patients with Acromegaly at a Single Institute

Makiko Kurimoto, Izumi Fukuda, Naomi Hizuka and Kazue Takano

Department of Medicine, Institute of Clinical Endocrinology, Tokyo Women’s Medical University, Tokyo, 162-8666, Japan

Abstract. It has been reported that patients with acromegaly may have an increased risk of developing several types of cancers, such as colorectal, breast and prostate tumors. However, some reports do not support these findings and therefore the prevalence of cancers in patients with acromegaly remains controversial. In this study, we determined the prevalence of benign and malignant neoplasms in patients with acromegaly. A retrospective chart analysis was performed on 140 patients with active acromegaly who had attended our outpatient clinic (M/F 54/86, age 55 ± 25 yr, range 21–86). Colon cancer was found in 10 patients, thyroid cancer in 5, breast cancer in 4 and gastric cancer in 2. When compared with the local population, the standardized incidence ratios (SIRs) for thyroid cancer in patients with acromegaly were 61.74 (95% confidence interval (CI): 0.51–114.63) for females and 272.4 (95% CI: 29.12–876.71) for males. The SIRs for colon cancer in the acromegalic patients were 17.4 (95% CI: 4.74–44.55) for females and 19.0 (95% CI: 5.18–48.64) for male patients in comparison with the local population. Of the benign tumors, multinodular goiter and colonic, gastric and gallbladder polyps were observed in 57% (47/83), 39% (31/80), 21% (8/39), and 15% (10/65) of the patients, respectively. This study suggested that patients with acromegaly have an increased risk of colon cancer and polyps. Moreover, it is speculated that the risk for thyroid cancer is increased in male patients. It is therefore recommended that patients with acromegaly should undergo screening colonoscopy and ultrasonography of the thyroid.

Key words: Acromegaly, Malignant Tumors, Thyroid cancer

THE association between tumor growth and growth hormone (GH)-insulin-like growth factor-I (IGF-I) axis is well established [1, 2]. It has also been shown that the overall increase in incidence of malignant disease in acromegaly is a consequence of excessive levels of GH and IGF-I [3–7]. Ezzat et al. suggested that patients with acromegaly are at increased risk of developing cancer, particularly colorectal, but possibly also breast, prostate and haematological malignancies [8]. A report from Japan showed that malignant diseases were found in 5% of acromegalic patients and were the fourth most common complications after diabetes mellitus (37%), hypertension (23%) and hyperlipidemia (6%) [9]. However, several other reports did not support these findings and therefore it still remains controversial whether or not acromegaly is associated with an increased prevalence of cancer [10, 11]. In this study, we determined the prevalence of benign and malignant neoplasm in patients with acromegaly at a single institution.

Subjects and Methods

The medical records of 140 patients with active acromegaly (54 males and 86 females; mean age 55 ± SD 25 year, range 21–86 year) who had attended the Tokyo Women’s Medical University Hospital in Japan up to 2002 were reviewed. The diagnosis of acromegaly was based on the following criteria; 1) the presence of clinical features of acromegaly; 2) an abnormal GH response to a 75 g oral glucose tolerance test; 3) high
levels of serum IGF-I; 4) the presence of a pituitary adenoma confirmed by either computed tomography (CT) or magnetic resonance imaging (MRI). Patients with multiple endocrine neoplasia type 1 were excluded. The duration of acromegaly was estimated by the clinical history from either the time somatic changes occurred, when diabetes mellitus was diagnosed, or from the appearance of related symptoms such as acromegalic features and irregular menstruation and amenorrhea in women. The study had the aim of determining the prevalence of benign or malignant tumors by reviewing the medical records. In order to investigate gastrointestinal neoplasms, 87 of the patients had a colonoscopy, while 43 patients had a fiber gastroscopy procedure. Abdominal CT, abdominal ultrasonography, or both, were performed in 77 patients to survey abdominal benign and malignant neoplasms. Thyroid ultrasonography was also performed in 83 patients.

Statistical analysis

The incidence rates of malignancy in the patients with acromegaly were calculated per person-years of known acromegaly. The expected cancer rates by age and sex, divided into 10-yr age groups, were obtained from a survey carried out in 1999 on the general population in Japan [12], and were used for comparison with rates observed in this study. The age at the diagnosis of malignancy was used for the comparison. The patients were divided into two groups according to the estimated duration of acromegaly was shorter than 10 years (group S) or longer (group L). The difference in the cancer incidence between group S and L was evaluated by partitioning analysis. Statistical analysis was performed using StatView 5.0 (SAS Institute Inc., Cary, NC, USA), with statistical significance established at P<0.05. The difference between the observed and expected ratios was tested using the exact probabilities of the Poisson distribution, with 95% confidence intervals (CI).

Results

In this study, the median duration of acromegaly was 11.8 years (range; 2–43years). Colonoscopy was performed in 87 patients, with colonic polyps, colon cancers and carcinoid tumors being found in 35 (40.2%), 9 (10.3%) and 1 (1.2%) patients, respectively. Fiber gastrosopy was performed in 43 patients, and gastric polyps, gastric cancers, duodenum polyps, gastric leiomyosarcoma and submucous tumors of the stomach were found in 10 (23.3%), 2 (4.7%), 2 (4.7%), 3 (7.0%) and 2 (4.7%) patients, respectively. Seventy-seven patients had either abdominal ultrasonography or CT, with 11 patients (14.3%) having gallbladder polyps, 2 patients (2.6%) having adrenal adenoma and 1 (1.3%) patient having a benign renal tumor. As shown in Table 1, thyroid ultrasonography was performed in 83 patients, and adenomatous nodules, diffuse goiters, multiple thyroid nodules and thyroid cancers were found in 47 (56.6%), 14 (16.9%), 11 (13.3%) and 4 (4.8%) patients, respectively.

In addition to the above findings, 6 cancers were

\[
\text{Table 1. Thyroid diseases detected by ultrasonography} \\
\begin{array}{|c|c|}
\hline
\text{Thyroid disease} & \text{Incidence} \\
\hline
\text{Adenomatous nodules} & 47/83 (56.6\%) \\
\text{Diffuse goiter} & 14/83 (16.9\%) \\
\text{Thyroid nodules (multiple)} & 11/83 (13.3\%) \\
\text{Thyroid cancer} & 4/83 (4.8\%) \\
\text{Hashimoto disease} & 4/83 (4.8\%) \\
\text{Follicular adenoma} & 3/83 (3.6\%) \\
\text{Thyroid nodule (solitary)} & 2/83 (2.4\%) \\
\text{AFTN*} & 2/83 (2.4\%) \\
\hline
\end{array}
\]

*Autonomous functioning thyroid nodule

\[
\text{Table 2. The number of neoplasms observed in 140 acromegalic patients} \\
\begin{array}{|c|c|c|}
\hline
\text{Neoplasm} & \text{Male} & \text{Female} \\
\hline
\text{Colon cancer} & 5 & 5 \\
\text{Thyroid cancer} & 2 & 3 \\
\text{Gastric cancer} & 1 & 1 \\
\text{Gastric leiomyosarcoma} & 1 & 0 \\
\text{Breast cancer} & 4 & 4 \\
\text{Total} & 9 & 13 \\
\hline
\end{array}
\]

\[
\text{Table 3. Incidence of thyroid cancer in patients with acromegaly compared with the local general population} \\
\begin{array}{|c|c|c|}
\hline
\text{Parameter} & \text{Male} & \text{Female} \\
\hline
\text{Number} & 54 & 86 \\
\text{Person-years} & 351 & 408.5 \\
\text{Expected} & 0.008241 & 0.048593 \\
\text{Observed} & 2 & 3 \\
\text{Standardized incidence ratios} & 242.7 & 61.7 \\
\text{95% confidence interval} & 29.12–876.71 & 0.51–114.63 \\
(P<0.05) & & \\
\hline
\end{array}
\]
newly diagnosed during the observation period at other hospitals (1 colon cancer, 1 thyroid cancer and 4 breast cancers). Those cancers were found at other hospitals before the diagnosis of acromegaly. Overall the number of cancers found in the 140 acromegalic patients comprised 10 colon, 5 thyroid, 4 breast and 2 gastric tumors, including one patient who had double cancer (thyroid and colon). A gastric leiomyosarcoma was found in one patient (Table 2). The malignancy was newly diagnosed in six and four patients in group S ($n = 71$) and L ($n = 69$), respectively. The prevalence of malignancy did not differ significantly between these groups.

The evidence is strongest for an increased risk of colorectal cancer in patients with acromegaly. We also found many of these patients had thyroid cancer. Therefore, we determined the standardized incidence ratios (SIRs) for colon and thyroid cancer in acromegaly. The SIRs for colon cancers associated with acromegaly were 17.4 (95% confidence interval (CI): 4.74–44.55) for females and 19.0 (95% CI: 5.18–48.64) for males when compared with the general population. The SIRs for thyroid cancer in patients with acromegaly when compared against the general population were 61.74 (95% CI: 0.51–114.63) for females and 272.4 (95% CI: 29.12–876.71) for males (Table 3).

The characteristics of the four patients with thyroid cancers are summarized in Table 4. Thyroid papillary carcinoma was detected in one male and three female patients. The levels of serum thyroglobulin ranged from 27 to 130 ng/ml. All patients underwent a thyroidectomy that resulted in a cure from their thyroid cancers. As shown in Table 4, the diameter of resected thyroid cancer ranged from 1.0 cm to 3.5 cm, and no patient had a microcarcinoma.

**Table 4.** Thyroid cancer in patients with acromegaly

<table>
<thead>
<tr>
<th>No.</th>
<th>Age/Sex</th>
<th>GH level (ng/ml)</th>
<th>IGF-I level</th>
<th>Duration of Acromegaly (years)</th>
<th>Tg* (ng/ml)</th>
<th>Maximal Tumor Size (cm)</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>36/F</td>
<td>27.8</td>
<td>910 (ng/ml)</td>
<td>10</td>
<td>72.9</td>
<td>3.5</td>
<td>cured</td>
</tr>
<tr>
<td>#2</td>
<td>43/F</td>
<td>7.2</td>
<td>344 (ng/ml)</td>
<td>20</td>
<td>27</td>
<td>2.5</td>
<td>cured</td>
</tr>
<tr>
<td>#3</td>
<td>43/F</td>
<td>21</td>
<td>880 (ng/ml)</td>
<td>5</td>
<td>130</td>
<td>1.0</td>
<td>cured</td>
</tr>
<tr>
<td>#4</td>
<td>63/M</td>
<td>13.8</td>
<td>3.60 (U/ml)</td>
<td>unknown</td>
<td>78</td>
<td>3.0</td>
<td>cured</td>
</tr>
</tbody>
</table>

Tg*; Thyroglobulin

**Discussion**

Of all cancers, patients with acromegaly have an increased risk of developing colorectal cancer, as a consequence of the excessive levels of growth hormone. These tumors are now regarded as a major complication of acromegaly by many researchers and consensus working groups, although there is some disagreement in the literature as to the prevalence of the lesions. In a review of the literature, the overall prevalence of colon tubulo-villous adenoma was reported to be 21% in acromegaly and 9% in controls, a difference that was highly significant [11]. In contrast, Lieberman and co-workers reported that the incidence of colon adenoma was not increased in patients with acromegaly [13]. Moreover, a meta-analysis of 13 prospective studies on colonoscopy showed the incidence of colon cancer was 3.7% in acromegaly patients and 0.5% in controls [11].

In this study, we found colon polyps and cancers in 40% (35/87) and 10% (9/87) of acromegalic patients, rates that are higher than other published retrospective epidemiological data [7]. As we did not investigate the incidence of asymptomatic colonic polyps or colon cancer in age-, sex- and ethnically-matched controls, we were unable to evaluate whether or not the incidence of colon disease in patients with acromegaly was significantly higher than in the normal population. However, when the high incidence of asymptomatic colon cancer found in our series is taken into consideration, it suggests that it is important to perform screening colonoscopy in patients with active acromegaly. Current guidelines suggest that colon surveillance for high-risk groups should also be applied to patients with acromegaly [14].

Acromegaly has been associated with goiter as well as with benign and malignant tumors [15–17]. As reported previously, we found an increased prevalence of thyroid disorders detected by ultrasonography, parti-
cularly multinodular goiter. Kasagi et al. detected thyroid goiter associated with acromegaly using ultrasonography [18]. They reported that diffuse goiter and adenomatous goiter was detected 31.8% and 29.5%, respectively. The prevalence of diffuse goiter and adenomatous goiter were 16.9% and 69.9%, respectively, in our study. In 1999, newly classification for thyroid nodules was proposed by the Japan Society of Ultrasonics in Medicine [19]. Therefore, the different results in the two studies might be due to the different criteria applied. We also found thyroid carcinoma in 4.8% (4/83) of acromegalic patients. Gasperi et al. detected thyroid cancer using ultrasonography in 1.2% of 258 acromegalic patients, a prevalence that was slightly, but not significantly increased, compared to 150 control subjects with prolactin-secreting or non-functioning pituitary adenomas [20]. The rate we measured in our series was surprisingly high compared with the data of Gasperi et al. Recently, Tita et al. reported a prevalence of thyroid carcinoma in 5.6% of 58 acromegalic patients, a result that was close to that measured in our study. Baris et al. reported that a risk for thyroid carcinoma was significantly elevated exclusively in women with acromegaly in Sweden [22]. However, in our series, no significant increase in risk was observed for thyroid carcinoma among women (SIR 61.74, 95% 0.51–114.63). It is possible the high prevalence of thyroid cancer we observed may have been attributable to increased surveillance of the thyroid. However, it is unlikely this was the main reason, as papillary thyroid cancer was palpable by clinical examination in the majority of patients and no patient in our series had a microcarcinoma.

With regard to the pathogenesis of papillary thyroid carcinoma in acromegaly, presumably chronic excess of IGF-I has a role in the development of these carcinomas by stimulating cell proliferation and inducing anti-apoptotic effects in a variety of cells and tissues, including thyroid cancer cells [23, 24].

In this study, the relationship between the duration of acromegaly and the prevalence of cancer was not clear. However, Jenkins et al. reported that the patients in whom serum IGF-I remained elevated were regarded as high risk for the repeated development of colorectal neoplasma [25]. Therefore, early detection of acromegaly and keeping post-treatment lower GH/IGF-I levels is important for preventing the progression of complications of acromegaly. Furthermore, we did not study the prevalence of benign and malignant neoplasm in patients with inactive acromegaly. Further study is required for confirming whether or not the activity of acromegaly affects the incidence of newly developed neoplasm.

In conclusion, this study suggested that patients with acromegaly have an increased risk of colon cancer and polyps. Moreover, it is speculated that the risk of thyroid cancer is increased, especially in male patients. It is recommended that patients with acromegaly undergo screening colonoscopy and ultrasonography of the thyroid.

Acknowledgments

This work was supported in part by Grants-in-Aid for Scientific Research (C) (No. 17590968, 16590913) from The Ministry of Education, Science and Culture, a research grant from the Foundation for the Growth Science, Japan and a research grant from the Ministry of Health, Labour and Welfare, Japan.

References