Incidence of Malignant Tumors in Patients with Acromegaly

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Abstract. Neoplasms may be one of the systemic complications to which we attribute high mortality in acromegaly. The present study was designed to investigate the incidence of malignant tumors in patients with acromegaly in the Japanese population. In this report, 44 patients (25 men and 19 women) with biochemically proven acromegaly were studied retrospectively and had a total 670 patient years of the duration of acromegaly. We investigated the incidence of malignant tumors. There were 5 patients with malignant tumors (5 in men) in this study (11%). Male patients with acromegaly had nearly a 3.5 times higher ratio of malignancy than expected and this increased cancer incidence was considered significant (P=0.01). There was no significant increase in cancer incidence of either the total patient population or female patients. The malignant tumors were two thyroid cancers and one colon, one gastric and one bladder cancer. It is of note that the colon cancer of one patient was diagnosed 2 years after transsphenoidal surgery even though the levels of serum GH and insulin-like growth factor (IGF-1) were reduced to normal after operation. This preliminary study has suggested that male patients with acromegaly might have a high risk of malignancy and that careful screening for tumors is needed both before and after surgical and medical treatment, even in patients with normalized serum GH and IGF-1 levels.

Key words: Acromegaly, Cancer incidence, Colon cancer, Malignant tumors, Thyroid cancer

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STUDIES on systemic complications have been extensively attempted and there have been reports on cancer incidence and mortality in acromegaly. The overall increase in incidence of cancer in acromegaly has been reported [1, 2]. However, since some authors did not support those findings [3], the prevalence of malignant diseases in acromegaly is contentious. We performed a retrospective study for neoplasms in patients with acromegaly and investigated the incidence of malignant tumors.

Methods

The medical records of 48 patients with diagnosis of acromegaly treated at Chiba University Hospital and tertiary referral hospitals between 1976 and 1998 were reviewed. The diagnosis of acromegaly is based on the presence of clinical features of acromegaly and a high level of growth hormone (> 5 ng/ml) or IGF-1 (> 400 ng/ml). The duration of acromegaly was estimated by history from the time somatic changes
began to occur, or from the appearance of related symptoms (acromegalic features, headache, visual field defects, irregular menstruation and amenorrhea in women). Patients with multiple endocrine neoplasia type I or McCune-Albright syndrome were excluded (4 patients).

The incidence rates of malignancy in the subjects with acromegaly were calculated per person-years of known acromegaly. Expected cancer incidence was calculated by multiplying age-, sex-, and period-specific person-years at risk corresponding to the Cancer Registry in Chiba in 1993. Standardized incidence ratios (SIRs) were calculated, and significantly excess cancer incidence was determined by calculating a Poisson probability. Ninety-five percent confidence intervals for SIRs were calculated and the significance was assumed when $P < 0.05$.

### Results

The descriptive characteristics of the patients with acromegaly are shown in Table 1. There was no significant difference in the mean age at onset, diagnosis and last follow up between men and women with acromegaly. We also found no significant difference in the basal level of GH or IGF-1 between men and women with acromegaly.

We observed 5 cases of cancer in men. Male patients with acromegaly had nearly a 3.5 times higher ratio of malignancy than expected and this increased cancer incidence was considered significant (Table 2). There was no significant increase in cancer incidence of either the total patient population or female patients.

The individual malignancies are detailed in Table 3. The malignant tumors were two thyroid cancers and one colon, one gastric and one bladder cancer. One patient who developed gastric cancer died from disseminated cancer. The other patients are in disease remission. It is of note that the colon cancer of one patient was diagnosed 2 years after transsphenoidal surgery even though the levels of serum GH and IGF-1 were reduced to normal immediately after the operation.

<table>
<thead>
<tr>
<th>Table 1. Patient characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male: 25</td>
</tr>
<tr>
<td>Age at onset</td>
</tr>
<tr>
<td>Age at diagnosis</td>
</tr>
<tr>
<td>Age at last follow up</td>
</tr>
<tr>
<td>GH at diagnosis (ng/ml)</td>
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<tr>
<td>IGF-1 at diagnosis (ng/ml)</td>
</tr>
</tbody>
</table>

Previous treatment:
- Surgery: 22 | 17
- Radiation: 5 | 3
- Radiosurgery: 0 | 2
- Bromocriptin only: 0 | 1
- Nil: 2 | 0

Age, the serum level of GH and IGF-1 are represented as mean ± standard deviation.

<table>
<thead>
<tr>
<th>Table 2. Incidence of cancer in acromegaly compared with the local population</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
</tr>
<tr>
<td>All</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
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</table>
INCIDENCE OF MALIGNANT TUMORS IN ACROMEGALICS

Discussion

Attention has been called to the prevalence of malignancy in patients with acromegaly and the association between the excess of GH secretion and tumorigenesis [4]. Therefore, to evaluate the basal GH and IGF-1 levels in our study population, we needed to compare cancer incidence in the present study to previous reports. Most of previous reports, however, have described GH and IGF-1 levels measured by different assay or have not described them. We could not assess the basal levels of GH or IGF-1 at diagnosis in our results compared with those in previous reports.

Previous studies have shown that cancer incidence was significantly increased in patients with acromegaly [1, 2, 5]. In this study, the high incidence of malignant tumors was confirmed in men, but not in the overall patient population or in women with acromegaly.

In our results, the thyroid was the organ most commonly affected by cancer in acromegaly. Nine cases of thyroid cancer in acromegalic patients were reported in previous reports [3, 5-9]. The mechanism of the association between acromegaly and thyroid cancer is unclear, but previous reports have demonstrated that IGF-1 had a stimulatory effect on growth and proliferation in rat thyroid cells [10] and could bind to IGF-1 receptors expressed on human thyroid cancer cells [11]. These studies suggested a high serum level of IGF-1 played an important role in the growth of thyroid cancer in acromegalic patients. Barzilay et al. opined that malignancy should be considered in clinically suspicious nodules even though goiter was prevalent in acromegaly. Our results provide some support to this recommendation.

We found only one patient who had colonic carcinoma and did not observe a higher incidence of colonic carcinomas as described in some previous reports [12, 13]. The reason for the difference regarding colonic carcinoma between our results and recent studies is unclear. In mainly epidemiologic studies, colonic cancer has been found to be closely related to environmental factors, including dietary habits as carcinogenic factors in general population [14]. In particular, the mortality of colonic cancer is low in Japanese population compared with that of foreign countries [15]. Ladas et al. noted that environmental and hereditary factors might be more important than the presence of acromegaly in prevalence of colonic carcinoma [16]. Environmental factors might be involved in low incidence of colonic cancer for acromegalics in our study. However, the mortality and incidence rate for colonic cancer has rapidly been increasing in Japan recently [14]. We should continue to pay attention to colonic cancer in acromegals.

The colon cancer of one patient was diagnosed 2 years after transsphenoidal surgery even though the GH and IGF-1 levels were reduced to normal after the operation. A previous report showed that there was no relationship between cancer incidence and post-treatment GH levels [3]. This suggests that careful screening for tumors is needed both before and after surgical and medical treatment, even in patients with normalized GH and IGF-1 levels.

In conclusion, this study suggests that male patients with acromegaly might have a high risk for malignancy and that careful screening for tumors, especially thyroid cancer, is needed both before and

<table>
<thead>
<tr>
<th>No. (gender)</th>
<th>Malignancy</th>
<th>Age (years)</th>
<th>GH level (ng/ml)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Acromegaly</td>
<td>Tumor</td>
</tr>
<tr>
<td></td>
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<td>Onset</td>
<td>Diagnosis</td>
</tr>
<tr>
<td># 2 (M)</td>
<td>Thyroid</td>
<td>33</td>
<td>53</td>
</tr>
<tr>
<td># 12 (M)</td>
<td>Thyroid</td>
<td>42</td>
<td>48</td>
</tr>
<tr>
<td># 14 (M)</td>
<td>Colon</td>
<td>21</td>
<td>47</td>
</tr>
<tr>
<td># 18 (M)</td>
<td>Bladder</td>
<td>41</td>
<td>42</td>
</tr>
<tr>
<td># 30 (M)</td>
<td>Stomach</td>
<td>35</td>
<td>50</td>
</tr>
</tbody>
</table>

R, remission; D, deceased from dissemination.

Table 3. Malignant tumors in patients with acromegaly
after surgical and medical treatment, even in patients with normalized serum GH and IGF-1 levels.

References