Anaplastic Thyroid Carcinoma with Prominent Cardiac Metastasis, Accompanied by a Marked Leukocytosis with a Neutrophilia and High GM-CSF Level in Serum

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Cardiac metastasis of thyroid carcinoma is extremely rare. We treated a case of anaplastic thyroid carcinoma with prominent cardiac metastasis. The 61-year-old male was admitted because of high fever. Investigations revealed a cardiac mass and anaplastic thyroid carcinoma. Resection of the cardiac mass revealed that it was metastasis from the thyroid carcinoma. After 4 months, he died in spite of intensive therapy. Marked leukocytosis was observed during the clinical course, and a concomitant increase of granulocyte macrophage-colony stimulating factor (GM-CSF) level was demonstrated in the sera. It was suggested that the high GM-CSF level in serum contributed to leukocytosis.

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**Key words:** high fever, cytokine

**Case Report**

A 61-year-old male with high fever was admitted to our hospital. From 2 months prior to admission, he had had a fever of above 38.0°C. He first consulted another doctor and received antibiotic therapy because of an elevated peripheral white blood cell (WBC) count. However, there was no response, and he was referred to our hospital for investigation of fever of unknown origin. At the age of about 30 years, he was noted to have a nodular goiter, but since he was asymptomatic, no treatment was sought. He had no noteworthy family history.

On admission, his temperature was 36.0°C, which later increased. His pulse was 90/min, and blood pressure was 104/58mmHg. In the left lobe of the thyroid gland, there was an elastic hard tumor of about 50mm in diameter, which was mobile and non-tender. No superficial lymph nodes were palpable. On examination, there were no specific findings in the heart, lungs, and abdomen.

Laboratory investigations revealed the following values: hemoglobin, 11.0g/dl; red blood cell count, 3,970,000/mm³; platelet count, 153,000/mm³; WBC count, 35,300/mm³ (segmented neutrophil, 65%; band neutrophil, 23%; lymphocyte, 8%; monocyte, 3%; metamyelocyte, 1%); total protein, 5.0g/dl; albumin, 2.5g/dl; glutamate oxaloacetate transaminase, 12 IU/l (normal, 7–27); glutamate pyruvate transaminase, 59 IU/l (normal, 0–24); lactate dehydrogenase, 526 IU/l (normal, 213–397); alkaline phosphatase (ALP), 331 IU/l (normal, 39–118); leucine aminopeptidase, 113 IU/l (normal, 31–54); gamma-glutamyl transpeptidase (γ-GTP), 190IU/l (normal, 5–42); serum calcium, 4.0 milliequivalent/l. Serum creatinine, blood urea nitrogen, and other electrolytes were within the normal range. The prothrombin time and activated partial thromboplastin time were also within the normal range. The erythrocyte sedimentation rate was 74mm/h and C-reactive protein was 13.6mg/dl (normal, less than 0.3). Serum thyroid stimulating hormone, free thyroxine, and free triiodothyronine level were respectively 0.67μIU/l (normal, 0.35–3.78), 0.90pg/ml (normal, 0.93–1.73), and 0.61ng/ml (normal, 2.7–5.0). Serum carcinoembryonic antigen, calcitonin, and thyroglobulin were respectively 0.6ng/ml (normal, less than 4.0), 110pg/ml (normal, less than 100), and 3,000ng/ml (normal, less than 30). Urinary examination revealed no abnormality, and venous blood culture was negative for bacteria. Bone marrow aspiration revealed the following values: nucleated cell count, 158,000/mm³; megakaryocyte count, 90/mm³; granulocyte erythrocyte ratio, 7.7. It was myeloid cell dominant but there was no pathological cell.

Chest X-ray film showed tracheal deviation to the...
right at the level of the thyroid. Ultrasonography and computed tomography of the cervical region showed a tumor in the left lobe of the thyroid gland, measuring about 30 × 50 mm (Fig. 1A). The tumor had ringed-calcification of its lateral side. Aspiration biopsy of the lesion showed anaplastic thyroid carcinoma. Ultrasonography of the abdomen showed three small space-occupying lesions (maximum diameter 7 mm), which were suspected to be metastases. 99mTechnetium bone scan showed no abnormality. Electrocardiogram showed the same pattern as old inferior myocardial infarction.

To rule out infectious endocarditis, a possible cause of fever, echocardiography was performed. This demonstrated a huge mass filling the right ventricle and partially projecting into the right atrium (Fig. 1B). Although it could not be determined whether this was a myxoma or a metastasis, surgery to remove the intracardiac tumor was performed to prevent sudden death. The tumor projected from the right ventricle into the right atrium through the tricuspid valve, and invaded the tricuspid valve, septum, and anterior wall of the apex. It was resected as extensively as possible, and tricuspid valve replacement was performed. Histological examination of the resected tumor revealed metastasis of anaplastic thyroid carcinoma.

After the surgery, three courses of chemotherapy consisting of cisplatin, doxorubicin, cyclophosphamide, and prednisolone were given (1, 2), followed by radiotherapy with 60 Cobalt (3, 4) (Fig. 2). Following chemotherapy, the fever was resolved and WBC count decreased. However, WBC count rapidly increased soon after each course, and the main tumor in the neck gradually enlarged. Swelling of lymph nodes around the main tumor began to develop, and on chest X-ray film, multiple small nodular shadows were recognized in the bilateral lung fields. Radiotherapy was effective in reducing the lymph node swelling around the main tumor, and the main tumor itself was also slightly reduced in size. However, during the course of radiotherapy, the WBC count markedly increased and the condition of the patient rapidly deteriorated and he finally died about 4 months after surgery.

To investigate the cause of the increase in the WBC count, especially the rapid increase just before death, granulocyte macrophage-colony stimulating factor (GM-CSF) activity in preserved sera was measured by the enzyme-linked immunosorbent assay. The results are shown in Table 1. In comparison to the mean normal control value (28 pg/ml), the patient’s value was markedly elevated, and the value changed in parallel with the WBC count in the peripheral blood. When the peripheral WBC count was 105,600/mm³ (neutrophil, 97%), GM-CSF activity showed a maximum value of 106.4 pg/ml. Staining for GM-CSF was performed by immunohistochemical method (avidin-biotin-peroxidase complex method) on a tumor sample, but the result was not positive.

At autopsy, a large part of the thyroid gland was replaced by diffusely proliferating tumor cells, and invasion of adjacent structures was recognized (Fig. 3A). Histological examination revealed many large cells with marked atypia (Fig. 3B). Inside the ringed calcification, no cell components were identified, however, the presence of large degenerated follicles containing remnant colloid suggested that it may have been an adenomatous goiter (Fig. 3C).

In the heart, a large part of the right ventricle was replaced by tumor, and marked pericarditis carcinomatosa was observed (Fig. 4A). Histological examination revealed the same cells that were observed in the thyroid gland (Fig. 4B). No direct invasion via the superior vena cava was recognized, but there were many tumor
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Fig. 2. The clinical course of the patient from admission to death. The upper panel shows the chemotherapy and radiotherapy performed after surgery. The middle panel shows body temperature during the clinical course. The lower panel shows WBC count (solid line) and serum granulocyte macrophage-colony stimulating factor activity (broken line) during the clinical course. CDDP: cisplatin, Co: cobalt, CPA: cyclophosphamide, DXR: doxorubicin, GM-CSF: granulocyte macrophage-colony stimulating factor, Gy: gray, M: month, PSL: prednisolone, WBC: white blood cell.

Table 1. Serum GM-CSF Activity Measured by Enzyme-Linked Immunosorbent Assay and WBC Count During the Clinical Course

<table>
<thead>
<tr>
<th>Date (days before death)</th>
<th>GM-CSF* (pg/ml)</th>
<th>WBC (/mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>56.1</td>
<td>37,300</td>
</tr>
<tr>
<td>11</td>
<td>69.8</td>
<td>57,600</td>
</tr>
<tr>
<td>5</td>
<td>106.4</td>
<td>105,600</td>
</tr>
<tr>
<td>3</td>
<td>41.3</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>59.6</td>
<td>89,600</td>
</tr>
<tr>
<td>1</td>
<td>43.3</td>
<td>52,500</td>
</tr>
</tbody>
</table>

* The mean normal control value of GM-CSF is 28 pg/ml.
GM-CSF: granulocyte macrophage-colony stimulating factor, WBC: white blood cell.

thrombi within myocardial vessels, and it was considered that cardiac metastasis had occurred via the blood stream.

Metastases to the lungs, liver, bladder, and lymph nodes were also recognized, but no metastasis was recognized in the bone marrow.

Discussion

Although metastatic cardiac tumor is more frequent than primary cardiac tumor, its absolute incidence is very low. It is generally considered to frequently occur during the terminal stage of malignant disease in association with total body metastasis, and is found at autopsy. The most common primary tumors are reported to be carcinoma of the lung and breast, malignant lymphoma, and malignant melanoma (5-10). Prichard reported that among 4,375 autopsy cases with death due to malignant disease, 146 cases had recognized cardiac metastasis, including 23 cases of carcinoma of the breast, 16 cases of carcinoma of the lung, 18 cases of lymphoma, and 8 cases of malignant melanoma (5). Although the reported incidences vary, cardiac metastasis due to carcinoma of the thyroid gland comprised 0 to 2 cases among 37 to 146 autopsy cases (5-10).

Thus, cases of thyroid carcinoma with clinically apparent cardiac metastasis are very rare; we could find only 5 cases reported in Japan (11-15), which consisted of one case of papillary adenocarcinoma (11), one case of clear cell carcinoma (12), and the others were anaplastic carcinoma (13-15). In 4 of these cases, cardiac metastasis seemed to be spread hematogenously (12-15), as in our case, and in the case of papillary adenocarcinoma, direct invasion via the superior vena cava was recognized (11). However, Kim et al reported that of 7 cases of thyroid carcinoma with cardiac metastasis, 6 cases had direct invasion via the superior vena cava (16). The 4 Japanese cases died without surgery or soon after cardiac surgery (11, 13-15). It is notable that the present case survived almost 4 months after cardiac surgery.

Recently, many cases of colony stimulating factor
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Fig. 3. Macroscopic transection view of the neck at the level of the thyroid gland at autopsy. The scale is represented in cm. "RT" denotes the right side of the body (A). Photomicrograph of the thyroid carcinoma at autopsy shows large cells with marked atypia (HE stain, 3.3 x 40) (B). Photomicrograph of the lesion inside the ringed calcification located in the lateral side of the left lobe of the thyroid gland at autopsy shows degenerated large follicles containing residual colloid and no cell components, suggestive of necrotic adenomatous goiter (HE stain, 3.3 x 40) (C).

Fig. 4. Macroscopic transection view of the heart at autopsy. The right ventricle is replaced by tumor, and marked pericarditis carcinomatosa (whitish regions) is observed. The dark regions represent residual myocardium. The scale is the same as Fig. 3A (A). Photomicrograph of the heart at autopsy shows the same tumor cells in the myocardium. Destructive change with fibrosis and fragmentation of muscle fibers is also observed (HE stain, 3.3 x 10) (B).

(CSF)-producing tumor have been reported. Among them, there have been 7 cases of CSF-producing thyroid carcinoma: 3 cases were squamous cell carcinoma (17–19), 3 cases were anaplastic carcinoma (20–22), and 1 case was papillary adenocarcinoma with bone metastasis partially transformed to anaplastic carcinoma (23). It is not clear why these anaplastic or squamous cell carcinoma produce CSF, but it is possible that when well-differentiated carcinoma transform to these types of tumors, they acquire the capability to produce CSF (18).

Also in the present case, an increased serum level of GM-CSF and a concomitant increase of WBC count were observed during the clinical course. This finding suggests that this tumor produced GM-CSF. However, we were unable to prove whether or not the tumor directly produced CSF. Possible reasons why the tumor was not stained by anti-GM-CSF antibody are as follows. First, the antigenicity of GM-CSF may have been destroyed. Although the autopsy specimen was properly preserved as −80°C, the autopsy was performed about 10 hours after death, and this time period may have seriously affected the antigenicity. Secondly, the effect
of intensive chemotherapy and radiotherapy on GM-CSF production should be considered. Particularly, the last course of chemotherapy, which was given urgently, caused a marked decrease in WBC count, suggesting massive destruction of the tumor. The specimen was obtained from the primary tumor, however, the cardiac metastasis, which did not receive radiotherapy, may have been preferable. Finally, it is possible that other cytokines that induce leukocytosis or increase the GM-CSF level may have been produced in the tumor. Dinarello reported that interleukin-1 may induce leukocytosis (24). Other cytokines are often produced by undifferentiated thyroid carcinoma cell lines (20, 25).

It was reported that some cases of GM-CSF-producing tumor were accompanied by hypercalcemia. In the present case, the serum ALP was elevated, however, serum calcium was within the normal range. As serum γ-GTP was elevated concomitantly, elevation of serum ALP might be due to cholangitis or cholecystitis.

In conclusion, in this extremely rare case of anaplastic thyroid carcinoma with a huge cardiac metastasis, interestingly, the marked leukocytosis corresponded to an increase of GM-CSF in patient’s sera.

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