Case report

A Case of Raynaud's Disease with Uterine Cancer Producing Interleukin-6

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Summary

A case of cervical cancer of the uterine producing interleukin-6 (IL-6) in a patient who suffered from Raynaud's phenomenon is described. Her serum contained anti SS-A antibody. The cancer was removed surgically. High level of IL-6 activity was detected in the culture supernatant of the resected cancer cells. After operation, Raynaud's phenomenon had improved and anti SS-A antibody had disappeared. This case shows us that IL-6 produced by malignant tumour might induce autoimmune connective tissue disease-like symptoms.

Key words

Cervical Cancer of the Uterine, Interleukin-6 (IL-6), Raynaud's Phenomenon, Anti SS-A Antibody.

INTRODUCTION

The quiescent B cell requires several signals to pass through stages of activation (1,2). Interleukin-6 (IL-6) acts in the late stage of B cell differentiation leading to the synthesis of immunoglobulins (3). IL-6 has been proposed to explain hypergammaglobulinemia and autoantibodies in patients with connective tissue diseases. The patients with benign tumours, cardiac myxoma and giant lymph node hyperplasia (Castleman's disease), were reported as human examples which suggested the relation of IL-6 and connective tissue disease like symptoms (4-6). We describe a case of Raynaud's disease with IL-6 producing uterine cervical cancer.

CASE REPORT

A 65-year-old woman was admitted to Juntendo University Hospital in June 1986 for the evaluation of Raynaud's phenomenon. She was in good health until November 1984, when she sustained numbness and coldness of her right hand. In December, she noticed that her right middle and ring fingers lost their color. Despite several visits to various hospitals, she could not get a diagnosis. From September 1985, she became easily fatigued. In May 1986, she was found to have an elevated sedimentation rate. Two months prior to her admission, a numbness developed in her left hand.

On admission, she was afebrile, and her blood pressure was 138/76 mmHg. Neither lymphadenopathy nor a thyroid goiter was found. Her lungs were clear, and her heart sound was normal. Pigmentation and erythema were negative. Neurological examination revealed that a sense of vibration and pain dulled centripetally in graded "glove" fashion. Muscle weakness was not present, and deep tendon reflexes were normal except that the Achilles tendon reflexes were absent bilaterally. Laboratory studies revealed the following values. The white blood cell count was 12,800/mm³. Platelet count was 259,000/mm³, and the sedimentation rate was 46 mm per hour. Blood chemical analysis was within normal limits. Serum γ-globulin was 21.7% (1.61 g/dl). Volume of immunoglobulin G, A, and M were 1822 mg/dl, 365 mg/dl, 180 mg/dl, respectively. Rheumatoid factor and LE cells were negative. No cryoglobulins were detected. Antinuclear antibodies were present in a titer of 1:20 with a speckled pattern. Standard immunodiffusion showed that her serum contained SS-A antibody (anti-Ro) but not SS-B antibody (anti-La). Urinalysis results were normal. Plethysmography showed a specific wave form pattern including low amplitude, delayed upslope, and rounded peak (Fig. 1A). Angiography of right brachial artery demonstrated the narrowing of the deep and superficial palmer branch. The proper palmer digital artery was not recognized. After injection of vasodilator,
Raynaud’s disease with uterine cancer

Fig. 1: Plethysmogram of the left middle finger performed before and after treatment. (A) shows low amplitude and rounded peak. After treatment amplitude was increased (B). The paper speed was 50 divisions per second.

Table I: Laboratory data before and after treatment

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
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<tbody>
<tr>
<td>WBC</td>
<td>12800/mm³</td>
<td>8600/mm³</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>3008/mm³</td>
<td>1806/mm³</td>
</tr>
<tr>
<td>γ-globulin</td>
<td>1.61 g/dl</td>
<td>1.43 g/dl</td>
</tr>
<tr>
<td>(21.7%)</td>
<td>(20.5%)</td>
<td></td>
</tr>
<tr>
<td>ANA</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>α-SS-A Ab</td>
<td>4</td>
<td>–</td>
</tr>
<tr>
<td>CEA</td>
<td>11 ng/ml</td>
<td>1.4 ng/ml</td>
</tr>
</tbody>
</table>

WBC: white blood count; TP: total protein; ANA: antinuclear antibodies; α-SS-A Ab: anti SS-A antibodies; CEA: carcinoembryonic antigen.

20 mg of tolazoline hydrochloride, the proper palmer branch was recognized in spite of its narrowness. These findings were interpreted as vasospasms which was compatible for Raynaud’s phenomenon. Although this patient had autoantibodies, especially SS-A antibody in her serum, she was not diagnosed as having a definite connective tissue disease.

Values of tumour markers were elevated; carcinoembryonic antigen (CEA) was 11 ng/ml (normal, less than 2.5 ng/ml); and coelomic epithelium related antigen (CA125) was 150 U/ml (normal, less than 50 U/ml). The general examinations to search for neoplasms revealed cervical cancer of the uterine in Stage IIIb. Radical hysterectomy was performed. Aseptically resected tissue was used for detecting IL-6 activity. Carcinoma cells were minced and cultured in RPMI 1640 containing 10% fetal calf serum at the cell concentration of 2 × 10⁶ cells/ml for 2 days. IL-6 activity was studied by the bioassay reported by Hirano et al (7). The IL-6 activity in this culture supernatant was 154 units which was more than 10-fold higher than that in culture supernatant of phytohemagglutinin (PHA)-stimulated tonsilar lymphocytes.

Five months later, she recognized an improvement with respect to the coldness and numbness of her hand. Plethysmography revealed that amplitude became higher and recovery time became shorter, compared to that before the operation (Fig. 1B). CEA had decreased to 1.4 ng/ml and leukocytosis had improved. In addition, antinuclear antibody and SS-A antibody had disappeared in her serum. Hypergammaglobulinemia had slightly improved (Table I).

DISCUSSION

The case we presented here was cervical cancer of the uterine with Raynaud’s phenomenon and SS-A antibody. To study the relationship between the cancer and the connective tissue disease-like symptoms, the IL-6 activity in culture supernatant of carcinoma cells was examined and detected in a high titer. In this case, we could compare the clinical features before and after the removal of the cancer. After the operation of uterine cancer, Raynaud’s phenomenon improved and anti SS-A antibody disappeared. These findings strongly suggested that cancer producing IL-6 participates in the pathogenesis of connective tissue disease-like symptoms.

This case gave us one more important suggestion concerning the mechanism, whereby, Raynaud’s phenomenon was caused by malignant diseases such as cancer of the uterine body, malignant ovarian cyst, and pancreatic or ovarian neoplasm. However, the mechanism of this as-