Successful Treatment by Radiation and Hormone Therapy of Isolated Local Recurrence of Breast Cancer 24 Years After Mastectomy Accompanied by Immune Thrombocytopenia: a Case Report

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We report a case of isolated local recurrence of breast cancer, which was accompanied by idiopathic thrombocytopenic purpura (ITP) and benign monoclonal gammopathy that presented 24 years after the patient underwent mastectomy. A 72-year-old female patient with a chest wall tumor was referred to our hospital in November 1994. Twenty-four years previously she had surgically treated breast cancer, of which the pathology was scirrhous carcinoma. Needle biopsy of the tumor revealed tubular carcinoma, which is compatible with local recurrence of breast cancer. She had no evidence of regional lymph node involvement or distant metastasis. Hematological and serological examination revealed a low platelet count accompanied by M-proteinemia (IgG, \( \kappa \)-type) and a mild increase in platelet-associated IgG. She was initially treated with extensive-field chest wall radiation (60 Gy), followed by systemic administration of tamoxifen. Complete local control of isolated local recurrence (LR) was achieved after radiation therapy (RT) and the patient has been progression-free for more than 2 years. Platelet count recovered gradually to a normal level after achievement of complete remission induced by radiation and tamoxifen. This may be the first case suggestive of a paraneoplastic syndrome of immune thrombocytopenia accompanied by local recurrence of breast cancer.

Key words: local recurrence - breast cancer - idiopathic thrombocytopenic purpura - radiation

INTRODUCTION

Idiopathic thrombocytopenic purpura or immune thrombocytopenia associated with solid tumor rarely occurs and its cause remains unclear (1–3). Autoimmune disorders usually accompany lymphoid malignancies which have disordered immune regulation (4,5). Several reports have suggested that immune thrombocytopenia with accelerated platelet destruction is combined with elevated platelet-associated antibodies or plasma anti-glycoprotein autoantibodies, the absence of disseminated intravascular coagulation (DIC) and normal bone marrow function (2,3,5–8). However, in advanced or recurrent breast cancer, thrombocytopenia occurs commonly in dissemination of metastatic disease and is difficult to differentiate from chronic DIC and immune mediated thrombocytopenia, both of which may occur during disease progression (9).

We report a successfully treated case of local recurrence of breast cancer, which presented 24 years after mastectomy and which was accompanied by thrombocytopenia. Thrombocytopenia improved dramatically after achieving complete remission of breast cancer. The clinical relevance of the association between recurrence of breast cancer and thrombocytopenia is discussed.

CASE REPORT AND METHOD

ASSAY FOR MEMBRANE-BOUND IgG

Antiplatelet membrane-bound IgG was measured by the quantitative antiglobulin consumption assay as described by Kaden et al. (5).
In November 1994, a 72-year-old Japanese woman was referred to our hospital presenting with a 4-month history of an erythematous skin nodule and persistent thrombocytopenia. The skin nodule was associated with cutaneous redness and itching of the scar from surgery for left breast cancer. Before visiting our hospital, her platelet count was $13 \times 10^3/\text{mm}^3$ on October 3, 1994 when she visited the hospital for the first time. Apparent bleeding tendency had not yet been manifested. She had had a mastectomy 24 years previously (May 28, 1970) in Kotoh Hospital (Kotoh-ku, Tokyo) for a scirrhous adenocarcinoma 35 $\times$ 25 $\times$ 15 mm in size with one ipsilateral axillary lymph node metastasis. She was diagnosed as stage IIB breast cancer. After surgery, she received adjuvant radiation therapy without subsequent chemotherapy. She also had a recent history of essential hypertension and angina pectoris and had received long-acting nitroglycerine and calcium antagonists for more than 10 years without hematological complications. Her mother died of uterine cervical cancer, but otherwise her family history was negative for cancer or autoimmune diseases.

On physical examination, the patient appeared well nourished and in no apparent distress. Neither anemia nor icterus was detected. Her body weight was 49.7 kg and her height was 144.5 cm. Blood pressure was 158/88 mmHg and the pulse was 78 without irregular rhythm. The left breast had been removed and on the left chest there was an $18 \times 28$ mm erythematous, flat indurated nodule which was palpable and seemed to be fixed to the chest wall (Fig. 1). Computerized tomograms of the chest revealed tumor involvement of the chest wall. The thyroid of her neck showed mild diffuse enlargement on palpation. There was no evidence of axillary, cervical or inguinal lymphadenopathy and no hepatosplenomegaly or skin petechiae or ecchymosis. Needle aspiration was performed to obtain cytological diagnosis, which was adenocarcinoma of the papillotubular type (Fig. 2).

Findings from the skin nodule were compatible with breast cancer recurrence. X-ray films of systemic bones showed no osteolytic or punched-out lesions. Systemic screening included computerized tomograms of the abdomen and pelvic region, whole bone scintigram, magnetic resonance imagegram of the brain and vertebral bone and bone marrows; these produced negative results. The disease appeared to be localized and the patient was diagnosed as having solitary local recurrence of breast cancer.

Results of routine blood chemistry studies were within the normal range. Results of CBC (complete blood counts) were as follows. The WBC count was 4100/mm$^3$ with 68% neutrophils, 18% lymphocytes, 12% monocytes and 2% eosinophils (November 21, 1994). There were 0.8% reticulocytes. Hemoglobin was 10.8 g/dl and the platelet count was $26 \times 10^3/\text{mm}^3$. Low platelet count and lymphocytopenia were detected and CBC were closely followed for 1 month without any medication. Subsequently, it was found that the WBC count was $3400/\text{mm}^3$ with 59% neutrophils, 32% lymphocytes, 7% monocytes and 2% eosinophils (December 19, 1994). There were 0.8% reticulocytes. Hemoglobin was 11.6 g/dl and the platelet count was $34 \times 10^3/\text{mm}^3$. Although lymphocytopenia improved spontaneously, the low platelet count still continued. Peripheral blood smear did not show platelet aggregation which would suggest pseudothrombocytopenia, or fragmented RBC which would suggest underlying chronic DIC. The laboratory data for the coagulation system were within normal limits except for a slight increase in D-dimer. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) were 11.3 s and 35.4 s (normal), respectively. Fibrinogen was 293 mg/dl and the activity of antithrombin III was 103%. FDP was 1.9 $\mu$g/ml (normal limits, <10 $\mu$g/ml). D-dimer was 0.6 $\mu$g/ml (normal limits, <0.5 $\mu$g/ml). Direct and indirect Coombs tests were both negative. Serological tests revealed elevation of IgG (3304 mg/dl) and M-proteinemia (IgG, $\kappa$-type) (Fig. 3). IgA, IgM and complements (C3, C4) were normal. Platelet-associated IgG (PA-IgG) was elevated at 40.2 ng/10$^7$ platelets (normal limits, 5.0–25.0). Serological examination of
tumor markers, CEA, NCC-ST-439 and CA15-3, did not reveal elevated values. Bone marrow examination revealed normocellular marrow, normal count and appearance of megakaryocytes and normal myeloid and erythroid differentiation (Fig. 4a and c). The plasma cell percentage in the bone marrow was within normal limits. Megakaryocytes were producing platelets and were compatible with ITP (Fig. 4b).

After obtaining informed consent for radiotherapy, the patient underwent local electron-beam radiation therapy which extended to the whole left chest wall for a total dose of 50 Gy given in 20 fractions and boost radiation of an additional 10 Gy on the residual chest nodule. Six weeks after the completion of the radiation, response of the localized tumor to radiation therapy was achieved with complete local control and no evidence of disease. From April 1995, tamoxifen (20 mg/day) was administered for systemic treatment and continues to the present. The patient presented with pigmented skin lesions that gradually disappeared within 6 months. She received no subsequent chemotherapy in addition to the tamoxifen and 2.5 years later showed no evidence of other organ involvement. Concomitantly, her platelet counts were monitored and ranged between $70 \times 10^3$ and $100 \times 10^3/\text{mm}^3$ during the first 6 months and returned to normal ($130-150 \times 10^3/\text{mm}^3$) 8 months after the initiation of treatment. Following this gradual recovery from thrombocytopenia, her platelet count reached $170 \times 10^3/\text{mm}^3$ in January 1997 (Fig. 5).

Systemic examinations performed in 1997 showed no systemic recurrence and normal tumor markers have persisted for 2.5 years. However, M-proteinemia (IgG, k-type) persisted. The PA-IgG value was still elevated at 121.7 ng/10^7 platelets. She subsequently suffered from cervical cancer of the uterus and underwent subtotal hysterectomy on February 7, 1997. The operation revealed the findings of stage Ib cervical cancer (squamous cell carcinoma and leiomyoma of the uterus) with no lymph node metastasis.

Figure 3. Immunoelectrophoresis of patient’s serum which showed IgG, k-type M-proteinemia (arrow).

Figure 4. (a) Light microscopy of aspirated bone marrow particle smear and (b) megakaryocytes which produce platelets were seen [May–Giemsa staining; original magnification, (a) x80 and (b) x240]. (c) Light microscopy of posterior iliac bone marrow biopsy. Normal cellularity and abundant normal megakaryocytes were observed (HE; original magnification, x33).

DISCUSSION

A syndrome resembling ITP with cancer has been reported by Kim and Boggs (1) and an ITP-like syndrome can be secondary to various forms of carcinoma (2,3,10–13) or lymphoid tumors, which suggests that it may be due to an antiplatelet antibody (3,5,7,10). Thrombocytopenia occurring in cancer patients is
usually related to chemotherapy, radiotherapy or underlying DIC. In breast cancer, it is commonly seen in patients with disseminated disease accompanied by DIC (9) or is sometimes related to splenic metastasis of breast cancer (14). It has been reported that 4–10% of cases of unexplained thrombocytopenia were associated with cancer (1–3). A syndrome resembling ITP is frequently reported in association with lymphoid malignancies, such as CLL and Hodgkin's disease, in which immune disorders are speculated as the causative mechanism, but rarely in solid tumors (4,7,15,16). The diagnosis of an ITP-like syndrome is usually made on the basis of thrombocytopenia without leukopenia or anemia, normal peripheral blood smear, normal bone marrow cellularity, normal or increased numbers of normal-appearing megakaryocytes on marrow aspirate or biopsy, no evidence of drug use which may induce thrombocytopenia, such as the use of thiazide diuretics or quinidine, and no evidence of DIC or infectious diseases (17,18). The present case had platelet counts under $30 \times 10^3/mm^3$, which occurred concomitantly with local recurrence of breast cancer. No evidence to support the cause of thrombocytopenia was obtained and this patient did not use thiazide diuretics or quinidine, nor was the presence of DIC or severe infection noted. The ITP practice guideline panel recently published defined ITP as isolated thrombocytopenia (low platelet count with otherwise normal results on complete blood count and peripheral blood smear) in a patient with no clinically apparent associated conditions or factors that can cause thrombocytopenia, such as lymphoproliferative disorders, systemic lupus erythematosus, DIC or myelodysplasia (18). Bone marrow aspiration is appropriate to establish the diagnosis in patients older than 60 years in order to rule out myelodysplastic syndrome or bone marrow metastasis of tumors (18,19). Although the number of megakaryocytes producing platelets in the patient was within normal limits, which was not necessarily compatible with typical ITP according to the classical definition, bone marrow aspiration and bone marrow biopsy did not reveal the presence of myelodysplasia or metastasis of breast cancer.

Thrombocytopenia with recurrent breast cancer is usually associated not only with chronic DIC caused by systemic dissemination of cancer but also with diffuse splenic involvement of breast cancer (14). Microscopic focus of a tumor has frequently been found in the excised spleen in lymphoid malignancies associated with ITP when splenectomy was performed as a surgical treatment of ITP (4,7). Splenic involvement in breast cancer could not be completely ruled out in this patient; however, it appeared unlikely because echogram and CT scan examinations on admission revealed no visceral involvement in addition to normal tumor markers. The patient had received no antineoplastic therapy before admission.

The cause of immune thrombocytopenia in patients with carcinoma remains unknown. ITP or autoimmune hemolytic anemia has been reported in association with lymphoid malignancies or solid tumors (Table 1). Immune thrombocytopenia with platelet destruction is strongly suggested by the combination of elevated PA-IgG or -lgM or antibodies against platelet glycoprotein Ib or IIb/IIIa (6–8,10,20). The levels of PA-IgG or -lgM may correlate with tumor mass or with progressive disease (3,7), although our patient did not show such a clear correlation. It has also been reported that the amount of membrane-bound IgG in ITP patients is increased and varies inversely with the platelet count (2). Disordered immune regulation could be present in any patient with recurrent cancer, predisposing to autoimmune disease (16). In addition to elevated platelet-associated autoantibodies, immune complexes in the cancer state may also bind to autologous platelets to promote destruction (16).

An immune mechanism as the etiology of thrombocytopenia in the present case was suggested, since the PA-IgG level was high at the presentation of the recurrence of breast cancer, in addition to an underlying latent immune disorder, such as benign monoclonal gammapathy, which was evident at presentation. However, the patient did not show a clear correlation between the amount of PA-IgG and the platelet count recovery. The PA-IgG value increased after treatment (from 42 to 121.7 ng/10^7 platelets). On the other hand, the platelet count recovered and the tumor disappeared. One of the explanations of this disagreement is the reliability of the assay method, which may be non-specific for the detection of membrane-bound IgG of platelets in the presence of IgG-type M-proteinemia in the plasma, because non-specific binding of platelets and IgG in vitro after blood sampling might occur and be enhanced after platelet count recovery. Second, total PA-IgG might not be necessarily responsible for platelet destruction in the presence of IgG-type M-proteinemia, but might reflect only non-specific binding of IgG to platelets. Third, unknown specific antibodies against the antigen which expressed on platelets and tumor cells might be responsible for the development of ITP. Recent investigation has suggested the presence of adhesive glycoprotein antigens which are expressed on platelets and also on tumor cells (breast cancer cell lines) or the presence of cytoadhesive proteins, such as thrombospondin, although the association of the development of platelet-associated autoantibodies with recurrence of breast...
cancer remains to be explored (21,22). To date, antiplatelet antibodies have not been fully studied with tests of antibody cross-reactivity with tumor cells. In addition to thrombocytopenia, CBC of the patient showed mild anemia, leukopenia and lymphocytopenia at presentation, suggesting the destruction of the blood cells other than platelets by the autoantibodies. Although she showed neither clinical nor laboratory evidence of systemic lupus erythematosus, Sjögren's syndrome or autoimmune hemolytic anemia, this possibility of the transient concomitant development of the autoantibody to leukocyte could not be excluded.

Generally, for the treatment of ITP, administration of corticosteroid therapy or a splenectomy is recommended (5,18,19). Rarely, administration of immunosuppressive agents or androgens such as Danazol is indicated (18), if appropriate, in addition to specific therapy for primary cancer, although the effect of tumor treatment alone on thrombocytopenia is still unknown. Recently, Calderoni et al. (23) reported cases of familial breast cancer with the autoimmune processes as a paraneoplastic syndrome which developed in the course of the disease manifestations. They successfully obtained regression of the autoimmune disease solely by the administration of tamoxifen and chemotherapy towards the breast cancer. The ITP-like syndrome in this patient began to improve after the initiation of radiation, which resulted in shrinkage of the local recurrent tumor (24,25). As the tumor size decreased after radiation therapy, so did the severity of the thrombocytopenia. This clinical course also implies the activation of an underlying autoimmune mechanism evoked by the recurrence of breast cancer, retrospectively. It is speculated that the patient had an underlying immune disorder which may have evoked the ITP associated with the onset of cancer.

The median survival of isolated loco-regional recurrence of breast cancer is reported to be 2–3 years, with a 5-year survival rate of 10–20%. Only 5–10% of patients would survive 10 years with progression free after local recurrence (26). The standard therapy for recurrence of isolated local disease is local chest wall radiation with or without local surgery (25–33). Systemic therapy added to local therapy is likely to increase the CR rate of loco-regional recurrence of breast cancer (29,34). However, the addition of systemic chemotherapy is still controversial in both LR after mastectomy and LR after conservative surgery and radiation, except for the systemic administration of tamoxifen for patients with estrogen receptor-positive tumors or unknown receptor status (25,29). Local therapy, surgery or radiation resulted in up to 90% local control. However, from the point of view of quality of life, radiation therapy is preferred over extensive field surgery (25,35). Our patient was initially treated with extensive field radiation for the malignancy rather than being treated for ITP. Tamoxifen was added after completion of radiation (60 Gy). Thrombocytopenia improved spontaneously after radiation therapy and administration of tamoxifen without administration of immunosuppressive agents, such as prednisolone. The choice of therapy toward the breast cancer rather than the ITP appeared to be successful, but whether ITP should be treated directly must be addressed in cases in which the thrombocytopenia does not improve or worsen (36).

### Table 1. ITP associated with solid tumor (not including malignant lymphomas)

<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>Tumor type (number)</th>
<th>Presence of platelet-associated autoantibodies</th>
<th>Therapy of ITP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim and Boggs (1979)</td>
<td>Lung ca. (2), rectal ca. (2), sarcoma, testicular ca. and gall bladder ca.</td>
<td>Unknown</td>
<td>PSL and/or splenectomy</td>
</tr>
<tr>
<td>Schwartz et al. (1982)</td>
<td>Ovarian ca. (2)*, vaginal ca., breast ca., bronchogenic ca., lung ca. and basal cell ca.</td>
<td>Yes (IgG)</td>
<td>PSL and/or splenectomy or chemotherapy*</td>
</tr>
<tr>
<td>Saunders and Warenius (1982)</td>
<td>Ureter ca., breast ca., lung ca.</td>
<td>Yes (IgG)</td>
<td>PSL or splenectomy</td>
</tr>
<tr>
<td>Bellone et al. (1983)</td>
<td>Primary unknown ca., larynx ca. and pancreatic ca.</td>
<td>Yes (IgG and IgM)</td>
<td>PSL and/or splenectomy</td>
</tr>
<tr>
<td>Kobayashi et al. (1993)</td>
<td>Malignant thymoma</td>
<td>Yes, Antibody to platelet glycoprotein IIb/IIIa</td>
<td>Splenectomy and cyclosporine</td>
</tr>
<tr>
<td>Kaneko et al. (1993)</td>
<td>Bladder ca.</td>
<td>Yes (IgG). Monoclonal gammopathy</td>
<td>PSL</td>
</tr>
<tr>
<td>Ohura et al. (1996)</td>
<td>Lung ca.</td>
<td>Unknown</td>
<td>High-dose γ-globulin</td>
</tr>
<tr>
<td>This case</td>
<td>Breast ca. (local recurrence)</td>
<td>Yes (IgG). Monoclonal gammopathy</td>
<td>Radiation therapy and tamoxifen</td>
</tr>
</tbody>
</table>

Abbreviations: ca., cancer; PSL, prednisolone. *It was reported that ITP was improved by chemotherapy alone.
Recent investigations of breast cancer tumor dormancy suggested that the balance between cell proliferation and cell death (apoptosis) is maintained, which may result in a long period of tumor latency (37,38). In our patient, we could speculate on an identical clonal tumor emergence since the adenocarcinoma cells were found only in the area of the scar from the resection rather than re-metastasis from an unknown metastatic site of the breast cancer. The proliferation of breast cancer cells requires estrogen and withdrawal of estrogen results in the shrinkage of the tumor. Therefore, anti-estrogen therapy acts as a primary systemic therapy. When considering the addition of cytotoxic chemotherapy, one must estimate the prognostic factors of the patient. Although we did not have information on estrogen receptors in this patient, the choice of systemic treatment with hormone therapy seemed reasonable, because of her age and good prognosis based on the previous long disease-free period (35). The present case was in a favorable group according to established prognostic factors, because of the long duration of the latent phase before LR. Radiation alone can achieve 40–80% of complete local control and may achieve 5-year survival in 20–30% of patients. For complete local control of recurrent tumor, at least 55 Gy are required in addition to boost radiation (24,29). In spite of thrombocytopenia, our patient was able receive this dose of radiation. In addition, her platelet count recovered gradually. In conclusion, to our knowledge this is the first case indicating paraneoplastic syndrome of immune thrombocytopenia accompanied by recurrence of breast cancer which appeared as an isolated loco-regional recurrence.

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References