Case Report

Serum p53 Antibody is a Useful Biomarker for Long-Term Monitoring of Breast Cancer: Report of a Recurrent Case After Surgery

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ABSTRACT: Serum p53 antibody (s-p53-Ab) is the most recently developed biomarker for breast cancer. Only a few studies have evaluated perioperative s-p53-Ab titers in patients with breast cancer. S-p53-Ab titers were monitored for over 4 years, during the perioperative period and after surgery, in a 75-year-old woman with clinical stage IIA (T2N0M0) breast cancer. The results of screening tests were negative for cancer antigen 15-3, carcinoembryonic antigen (CEA), and National Cancer Center-Stomach-439; only s-p53-Ab level (10.1 U/ml) was positive preoperatively. S-p53-Ab titer remained positive (9.1 U/ml) after radical surgery. Pathologic analysis of surgically resected specimens showed a stage IIB tumor (pT2N1M0). Two years postoperatively, CEA level had increased to 5.9 ng/ml. At this time, liver metastases were detected by computed tomography. Neither chemotherapy nor hormone therapy were effective against this recurrence, and the patient died 3 years after surgery. Perioperative s-p53-Ab titer was a useful marker for long-term monitoring of residual cancer cells in a patient with stage IIA breast cancer.

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KEYWORDS: serum p53 antibody (s-p53-Ab), breast cancer, surgery, monitoring

Overexpression of mutant p53 protein in cancer cells stimulates production of serum p53 antibodies (s-p53-Abs) in patients with breast cancer,[1–4)] including those with stage I disease.[1)] Because this antibody reaction is completely independent of conventional serum tumor markers, s-p53-Abs may be useful in discovering tumors those are not detectable by conventional markers. Our previous report showed that monitoring of s-p53-Abs is useful for predicting tumor recurrence in patients with esophageal squamous cell carcinoma, possibly because antibody response is caused by the presence of residual cancer cells.[5, 6)] Therefore, s-p53-Abs monitoring can detect recurrent breast cancer cells at an early phase. Although several reports have shown the clinicopathologic importance of s-p53-Abs in patients with esophageal squamous cell carcinoma[7)] and colon adenocarcinoma,[8)] few studies have evaluated the clinicopathologic significance of perioperative s-p53-Ab titer in patients with breast cancer. This

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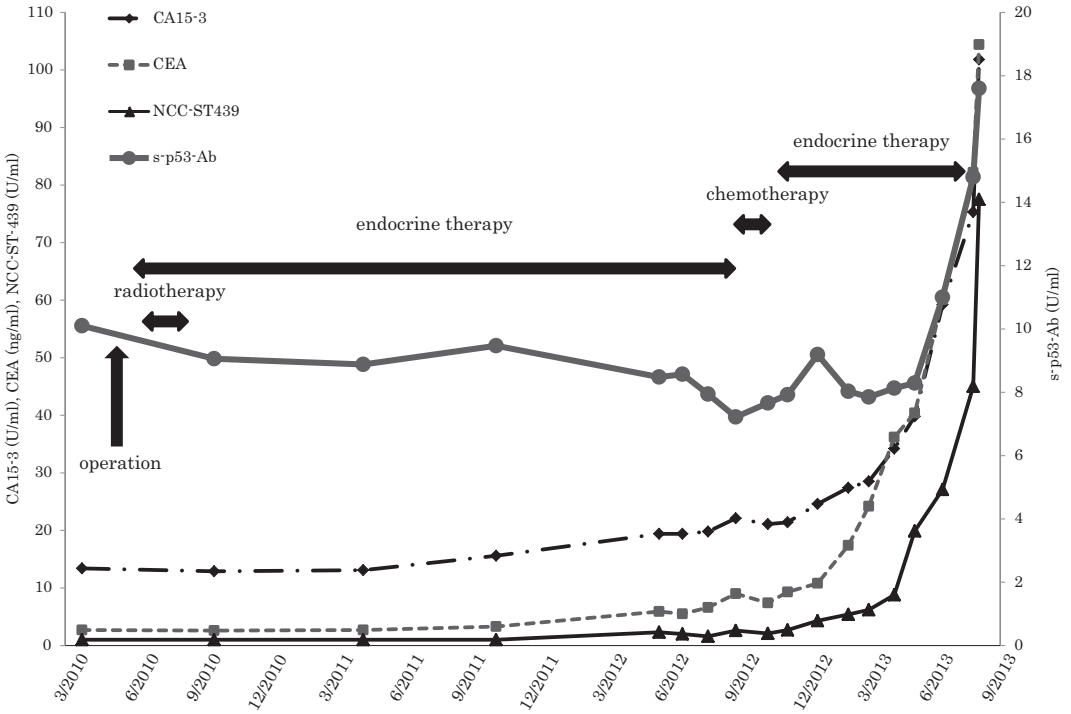

Fig. 1 Changes in serum tumor markers after radical surgery. s-p53-Abs remained positive until liver metastases were identified.
s-p53-Ab: serum p53 antibody, CA15-3: cancer antigen 15-3, CEA: carcinoembryonic antigen, NCC-ST-439: National Cancer Center-Stomach-439

case report presents the results of long-term monitoring of s-p53-Ab in a patient with breast cancer treated by radical surgery without neoadjuvant chemotherapy. To the best of our knowledge, this is the first case report to show the results of long-term (>3 years) postoperative monitoring of s-p53-Ab titers in a patient with breast cancer.

Case Report

A 75-year-old woman with a breast tumor was referred to our hospital. The tumor was 30 mm in diameter and was located at the right upper outer quadrant, without skin invasion. Most serum tumor markers were within normal ranges, as follows: cancer antigen 15-3 (CA15-3), 13.4 U/ml (normal range, <25.0 U/ml); carcinoembryonic antigen (CEA), 2.7 ng/ml (<5.0 ng/ml); and National Cancer Center-Stomach-439 (NCC-ST-439), <1.0 U/ml (<4.5 U/ml). Only the result for s-p53-Abs was positive (10.1 U/ml; <1.31 U/ml) before surgery. Although mammography showed no abnormal features, ultrasonography revealed an irregularly shaped tumor, 27 mm in size, with calcification in the right C area (Fig. 1). Neither computed tomography (CT) nor bone scintigraphy showed any distant metastases. Histologic analysis of a needle biopsy specimen showed scirrhous invasive ductal carcinoma. On the basis of the clinical staging of the tumor (IIA; cT2, N0, M0), a partial mastectomy with axillary lymph node dissection was performed on May 2010, without neoadjuvant chemotherapy. Using the Japanese Classification of Breast Cancer,[9] we analyzed the resected tissue and diagnosed the tumor as an invasive ductal carcinoma, solid-tubular carcinoma, with lymphatic and venous invasion, nuclear grade: 2, estrogen receptor (Allred score: 3 + 5 = 8), progesterone receptor (Allred score: 0 + 0 = 0), and human epidermal receptor 2 score: 0, with a Ki-67 index of approximately 25%. The subtype was classified as luminal B. Histologic evaluation showed invasive growth and an alveolar pattern, with variably sized cancer cell nests, a trabecular pattern, and a solid pattern with lymphatic and venous permeation. Three lymph nodes were involved (Fig. 2). The cancer cells had oval, polyhedral hyperchromatic nuclei with prominent nucleoli. Adjuvant hormone therapy with an aromatase inhibitor was administered for 2 years. Radiotherapy (50 Gy; 2 Gy × 25 fractions) was selected for treatment of remnant breast tissue. The s-p53-Ab titer re-

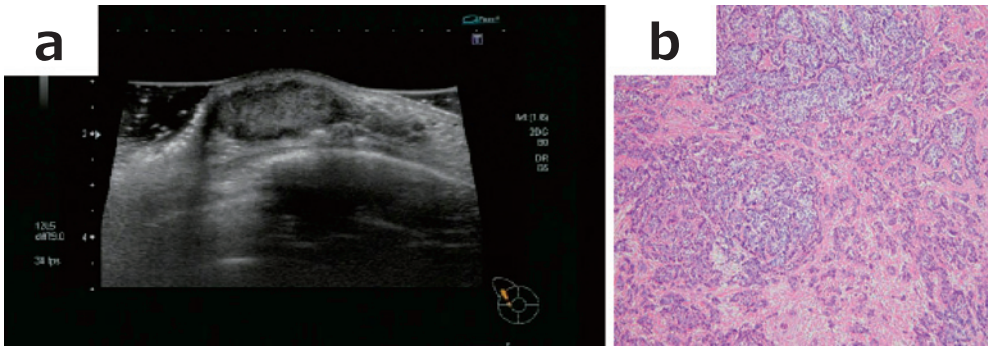

Fig. 2 (a) Ultrasonography shows a 30-mm tumor with calcification in the C area.
(b) A histologic specimen from a needle biopsy shows scirrhous invasive ductal carcinoma (hematoxylin and eosin stain, × 100).

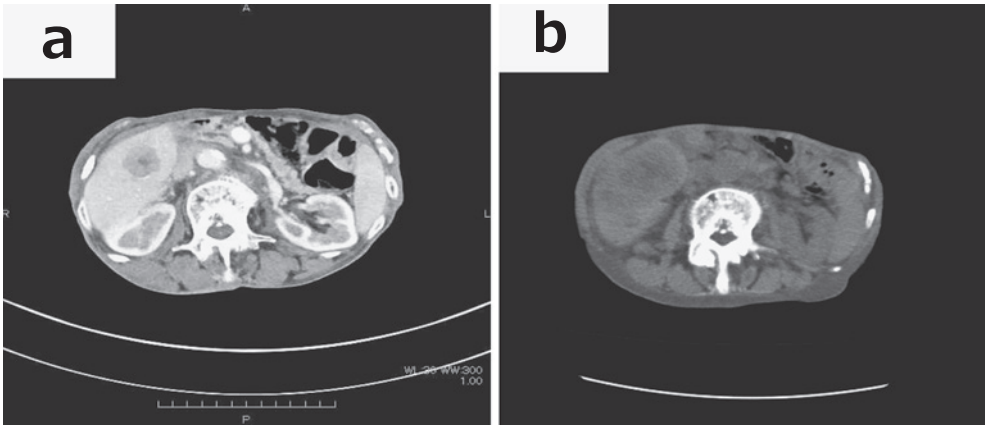

Fig. 3 Computed tomography (CT) images show liver metastases before chemotherapy (a) and after chemotherapy (b).

mained positive (9.06 U/ml) even after radiotherapy (Fig. 1). Two years later, in May 2012, CEA and CA15-3 levels were elevated, and liver metastases were detected by CT (Fig. 3a). Change in s-p53-Ab level is shown in Fig. 1. Levels of tumor markers consistently increased, even after administration of chemotherapy and aromatase inhibitor. The patient was started on eribulin (1.4 mg/m^2/day) in September 2012. Although levels of serum tumor markers seemed to stabilize, we stopped treatment in October 2012 because of adverse effects. Fulvestrant (500 mg) was started in December 2012, but the disease rapidly progressed and she died of liver dysfunction in August 2013, 3 years after surgery (Fig. 3b).

Discussion

Serum tumor markers are useful for monitoring treatment effectiveness and detecting tumor recurrence in cancer patients.[7, 10] In the present case, residual cancer cells may have been detected during monitoring of s-p53-Abs after radical surgery. Because the specificity of this marker is greater than 95%,[4] we believe that s-p53-Abs is useful for detecting residual cancer cells and for identifying patients who require further adjuvant treatment. Of course, s-p53-Abs may have been induced by a cancer other than the breast cancer in our patient. Although preoperative computed tomography showed no other tumor, we cannot exclude the possibility of other, subclinical, p53-positive tumors. In a previous study, we observed that patients with s-p53-Ab titers that did not decrease after treatment were significantly less likely to survive than were those with decreasing s-p53-Ab titers.[5] In the present case, s-p53-Ab titer was consistently positive, even after radical surgery. As the results for all other conventional tumor markers were negative in this case, monitor-

ing of s-p53-Abs was helpful in assessing the patient's tumor burden.

Kulić et al reported that tumor size and number of positive axillary lymph nodes were significantly associated with the presence of s-p53-Abs.[3] Associations of s-p53-Abs with estrogen and/or progesterone receptor-negative tumors have also been reported.[11–13] Moreover, triple-negative, estrogen receptor (−), progesterone receptor (−), and human epidermal growth factor receptor 2 (−), cancer was reported to be significantly correlated with s-p53-Abs.[1] The hormone status of the present case was estrogen receptor (+), progesterone receptor (−), and human epidermal growth factor receptor 2 (−). Because her cancer was classified as intermediate risk, we believed that hormonal therapy alone would not be sufficient. Although we suggested adjuvant chemotherapy, the patient selected hormone therapy alone. As cancer cells at the sites of liver metastases may have been p53-mutated, neither hormone therapy nor chemotherapy would have been effective against the metastases. Therefore, patients with high s-p53-Ab titers are more likely to have tumors that are resistant to chemotherapy and/or radiation therapy.[14, 15] Enzyme-linked immunosorbent assays are a quick and easy method for detecting p53 alterations in cancer cells. Thus, perioperative monitoring of s-p53-Ab titers may prove useful for identifying residual cancer cells and predicting recurrent disease. Even after radical surgery, seropositive patients may be good candidates for adjuvant chemotherapy. Further studies are required for a more precise understanding of the clinical implications of s-p53-Ab titers in breast cancer. Nevertheless, the present case suggests that postoperative monitoring of s-p53-Ab titers is useful for detecting residual cancer cells.

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