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Case Report

Persistent Serum p53 Antibody Titer Following Mastectomy for Locally Advanced Breast Cancer Is Associated with the Recurrence of Cancer in the Central Nervous System

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ABSTRACT: Serum p53 antibody (s-p53-Abs) is induced by p53 overexpression in cancer cells. Therefore, residual cancer cells may be the cause of seropositivity even after radical surgery. Only few reports have evaluated perioperative changes and long-term monitoring of s-p53-Abs titers in patients with breast cancer. This case report presents long-term monitoring of s-p53-Abs titers in a patient with locally advanced breast cancer who developed recurrence in the central nervous system after radical surgery. The s-p53-Abs titer was monitored for 3 years during neoadjuvant chemotherapy and radical surgery in a 38-year-old woman with clinical stage IIB (T2N1M0) breast cancer. The levels of both the carcinoembryonic antigen (CEA) and cancer antigen 15-3 (CA15-3) were within the normal range, but s-p53-Abs test result (54.8 U/ml) was positive. Neither computed tomography nor bone scintigraphy showed any distant metastasis before treatment. The patient received neoadjuvant chemotherapy (epirubicin, 100 mg/m^2; cyclophosphamide, 500 mg/m^2; and fluorouracil, 500 mg/m^2; followed by docetaxel, 75 mg/m^2). One and a half year after surgery, s-p 53-Abs results remained positive (5.66 U/ml), and brain metastasis was found. Despite resection for brain metastasis, s-p53-Abs titer remained high (5.88 U/ml), and carcinomatous meningitis was found. During the entire clinical course, although s-p53-Abs titers reflected the presence of residual cancer cells, both CEA and CA15-3 results were negative. The perioperative s-p53-Abs titer might be a useful marker for monitoring residual cancer cells in a patient with breast cancer. Recurrence in the central nervous system might be detected using s-p53-Abs monitoring.

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KEYWORDS: serum p53 antibody, breast cancer, metastasis

The overexpression of mutant p53 protein in cancer cells has been shown to induce serum p53 immunoglobulin G antibodies (s-p53-Abs) in patients with breast cancer.[1–4)] Because such an antibody reaction is independent of conventional serum tumor markers, s-p53-Abs may be useful for the detection of tumors that are negative for conventional serum markers. Our previous reports showed that s-p53-Abs monitoring is useful for predicting tumor recur-

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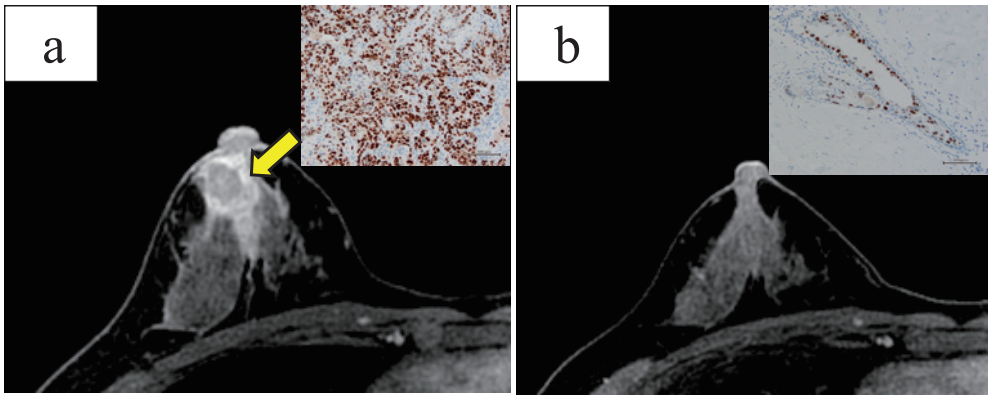

Fig. 1 Immunoreactivities of p53 (brown precipitate) and MRI. (a) biopsy specimen and (b) resected breast tissue.

rence in patients with esophageal squamous cell carcinoma, possibly because the antibody response is due to the presence of residual cancer cells.[5,6] Therefore, s-p53-Abs monitoring may detect recurrent breast cancer cells in an early phase. Although several reports have shown the clinicopathological significance of s-p53-Abs in patients with esophageal squamous cell carcinoma[7] or colon adenocarcinoma,[8] there is little information regarding the clinical significance of perioperative changes in s-p53-Abs titers in patients with breast cancer. This case report provides information regarding long-term monitoring of s-p53-Abs in a patient with locally advanced breast cancer who was surgically treated after neoadjuvant chemotherapy.

Case Report

A 38-year-old woman with a breast tumor and an axillary tumor was referred to our hospital. The breast tumor was 20 mm in diameter and was located in the right upper outer quadrant without skin invasion. The axillary tumor was 30 mm in diameter. A mammogram showed a cluster of fine pleomorphic calcification on right mediolateral oblique view. Ultrasonography revealed an irregularly shaped tumor, 20 mm in diameter, with calcification in the right C area and swollen lymph nodes at the axilla. A needle biopsy showed a histologically invasive ductal carcinoma of the schirrhous type, with positive for estrogen receptor, progesterone receptor, human epidermal receptor 2 and p53 (Fig. 1a). The Ki-67 index was approximately 70%. The cancer subtype was identified as luminal B. The serum tumor marker levels were within normal ranges: cancer antigen 15-3 (CA15-3), 8.0 U/ml (normal range, $<$25.0 U/ml) and carcinoembryonic antigen (CEA), 1.6 ng/ml (normal range, $<$5.0 ng/ml), with the exception of s-p53-Abs titer of 54.8 U/ml (normal range, $<$1.31 U/ml), which was positive before the neoadjuvant chemotherapy. Neither computed tomography nor bone scintigraphy showed any distant metastasis. Based on the clinical staging of the tumor (IIB; cT2, N1, M0), the patient received neoadjuvant chemotherapy (epirubicin, 100 mg/m^2; cyclophosphamide, 500 mg/m^2; and fluorouracil, 500 mg/m^2; followed by docetaxel, 75 mg/m^2). After the neoadjuvant chemotherapy, s-p53-Abs titer decreased to 9.91 U/ml; at this point, a total mastectomy with axillary lymph node dissection was performed. Based on the Japanese Classification of Breast Cancer,[9] which is based on the histology of the resected tissue, the tumor was defined as a ductal carcinoma, and the effectiveness of the chemotherapy was defined as grade 3. The overexpression of p53, as demonstrated by immunostaining, is shown in Fig. 1b. After surgery, adjuvant molecule target therapy comprising trastuzumab was administered for 1 year along with a total of 50 Gy (2 Gy $\times$25 fractions) of radiation applied to the supraclavicular fossa and chest wall. Despite receiving radiation therapy, s-p53-Abs titer remained positive (5.66 U/ml). Two months later, the patient complained of headache. At this point, a brain tumor was detected on magnetic resonance imaging (MRI). Tumorectomy was performed, and the histopathology of tumor mass revealed metastatic breast cancer with p53 overexpression (Fig. 2a). Radiation was applied to the entire brain. Despite tumorectomy and radiation therapy, s-p53-Abs titer remained positive (5.88 U/ml). The changes in the s-p53-Abs levels are shown in Fig. 3. At 24 months after surgery, the patient reported neck/back pain. At this point, fludeoxyglucose (^{18}F) positron emission tomography (FDG-PET) and MRI showed carcinomatous meningitis (Fig. 2b, c). Then, radiation was

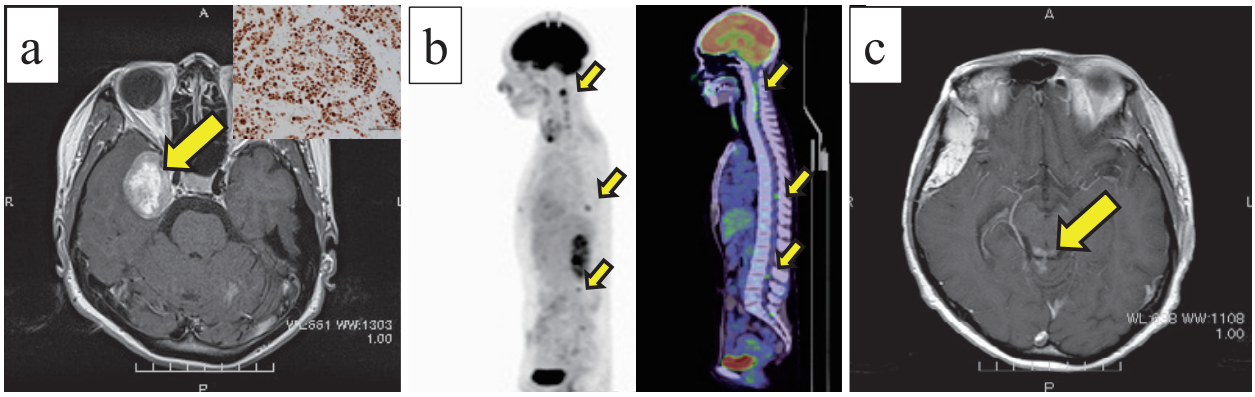

Fig. 2 Immunoreactivities of p53 (brown precipitate), MRI, and FDG-PET. (a) brain metastasis, (b) FDG-PET image of carcinomatous meningitis, and (c) MRI of meningitis carcinomatosa.

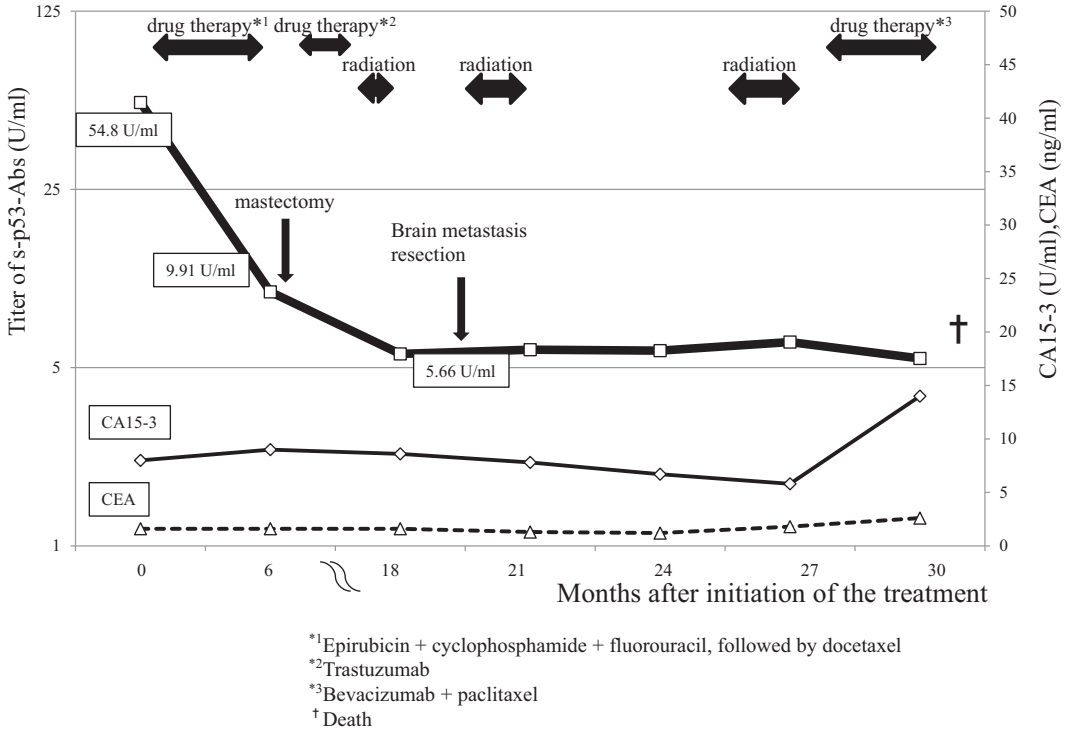

Fig. 3 Three-year monitoring of s-p53-Abs titers (U/ml) and CEA (ng/ml) and CA15-3 (U/ml) levels.

applied to the spinal cord (L1-S3). After completion of radiation, the patient was administered chemotherapy consisting of bevacizumab (10 mg/kg) and paclitaxel (90 mg/m^2). The patient's s-p53-Abs titers (6.30 U/ml) did not decrease despite radiotherapy and chemotherapy. Finally, treatment was stopped due to disease progression. Due to rapid tumor progression, the patient died 3 years after the initiation of the neoadjuvant chemotherapy.

Discussion

Serum tumor markers in cancer patients are useful for monitoring the treatment efficacy and detecting tumor recurrence.[7,10] In the present case, the persistency of s-p53-Abs might reflect the presence of residual cancer cells after surgery. As the rate of false positive results in healthy subjects was $<5\%$, the specificity of this marker is $>95\%$.[4] We believe that s-p53-Abs may be useful for detecting residual cancer cells. Indeed, this patient may have had another cancer which induced s-p53-Abs, rather than breast cancer recurrence.[11] Although postoperative FDG-PET did not show any other tumors, we could negate any subclinical p53-positive tumors. In our previous study to

evaluate the clinical impact of s-p53-Abs on patients with esophageal carcinoma, we observed that patients whose s-p53-Abs titers did not decrease after treatment were significantly less likely to survive than those with decreased s-p53-Abs titers.[5] In the present case, the s-p53-Abs titer was persistently positive, even after surgery. As all other conventional tumor markers were negative throughout the clinical course, the monitoring of s-p53-Abs was helpful for assessing the patient's tumor burden. An enzyme-linked immunosorbent assay is a quick and easy method for detecting p53 alterations in cancer cells; thus, perioperative monitoring of s-p53-Abs titers may prove to be useful for identifying the presence of residual cancer cells and for predicting a recurrent disease.

The patient developed brain metastasis as the first recurrent lesion. Such associations between p53 alterations and brain metastasis from breast cancer have been reported.[12–14] Moreover, our recent study showed that s-p53-Abs-positive patients significantly more frequently showed brain as the first site of recurrence.[15] Hence, persistent s-p53-Abs seropositivity, even after radical surgery, may be a potential predictive indicator for brain metastases. Although the present case suggests the significance of s-p53-Abs monitoring after surgery, further studies are required to gain more precise understanding of the clinical implications of s-p53-Abs in breast cancer.

Consent

Informed consent was obtained from the family of the patient for publication of this case report and any accompanying images. A medical record of the consent is available for review by the Editor-in-Chief of this journal.

Conflicts of interest: Hideaki Shimada received research grants from Medical & Biological Laboratories Co., Ltd., Nagoya, Japan. Other authors declare that they have no conflicts of interest.

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