Case Report
Spontaneous regression of breast cancer with axillary lymph node metastasis: a case report and review of literature

Eriko Tokunaga1, Shinji Okano2, Yuichiro Nakashima1-3, Nami Yamashita1, Kimihiro Tanaka1, Sauri Akiyoshi1, Kenji Taketani1, Mitsunori Shirouzu4, Hidetaka Yamamoto3, Masaru Morita1, Yoshihiko Maehara1

Departments of 1Surgery and Science, 2Innovative Applied Oncology, 3Anatomic Pathology, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan; 4Shirouzu Breast Surgery Clinic, 3-67 Kasuga, Kasuga, Fukuoka, Japan

Received April 28, 2014; Accepted May 13, 2014; Epub June 15, 2014; Published July 1, 2014

Abstract: Spontaneous regression (SR) of cancer is a rare but well-documented biological phenomenon. However, the mechanism remains to be elucidated. We herein report a case of the SR of breast cancer at both the primary site and metastatic axillary lymph node with spontaneously-induced T cell-mediated immunological responses. A 52-year-old female with a lump in the left axilla was diagnosed to have a small breast carcinoma with a distinct axillary lymph node metastasis. During the preoperative systemic examination, she was diagnosed to have severe type 2 diabetes mellitus, was treated with insulin, and the hyperglycemia was normalized after one month. Surgery for left breast cancer was then performed. The postoperative histopathological examination revealed the SR of breast cancer at both the primary site and metastatic axillary lymph node. Immunohistochemical studies revealed that estrogen receptor positive, AE1/AE3-positive ductal carcinoma completely underwent necrosis associated with extensive infiltration of CD3-positive T cells in the tumor nodule in the lymph node. In addition, primary ductal carcinoma cells also underwent single cell necrosis with infiltration of T cells with lymph follicle-like organization of B cells in the mammary gland. The features were suggestive that the tumor eradication in the metastatic lymph node and regression of the primary ductal carcinoma could be due to host T cell response to the ductal carcinoma. As far as we know it is the first report that shows the spontaneous regression of breast cancer, probably due to the spontaneously-induced T cell response.

Keywords: Spontaneous regression, breast cancer, cancer immunology, T cell response

Introduction

Spontaneous regression (SR) of cancer is a rare but well-documented biological phenomenon. SR is defined as “the partial or complete disappearance of a tumor in the absence of any treatment capable of regression” [1, 2]. It is very rare and occurs in less than 1 in 100000 cases [2]. However, it has been reported in various types of human cancer. SR of breast carcinoma is also extremely rare, despite the high frequency of detection of breast cancers, and the number of the well-documented cases is small. Various mechanisms are considered to be associated with this phenomenon, including immune mediation, tumor inhibition by growth factors and/or cytokines, induction of differentiation, hormonal mediation and tumor necrosis. Spontaneously induced T cell-mediated immunological responses are recently paid attention in multidisciplinary cancer treatment since more than thirty percentages of durable clinical responses including complete response are observed just administration of antibody to block the inhibitory immunological check point signal, PD-1/PD-L1 in various cancer patients [3, 4]. Therefore, spontaneously-induced immunological responses could be an important mechanism also in the SR of the cancer. We herein report a case of the spontaneous regression of breast cancer at both the primary site and metastatic axillary lymph node. Immunohistochemically, we confirmed that estrogen receptor positive, AE1/AE3-positive ductal car-
Spontaneous regression of breast cancer

Correspondence: Yasuyuki Terrai, Department of Surgery, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo, 113-0033, Japan (Tel: +81-3-3815-9551, Fax: +81-3-3815-9557, Email: terrai@ch.u-tokyo.ac.jp)

Received for publication: June 11, 2014
Accepted for publication: August 15, 2014

Abstract
Spontaneous regression (SR) of breast cancer is a rare and poorly understood process in which the tumor is eliminated without the intervention of surgery, chemotherapy, or radiotherapy. We report a case of SR of breast cancer in a 52-year-old woman who presented with a lump in the left axilla diagnosed to have lymph node metastasis of adenocarcinoma with unknown origin by fine needle aspiration cytology (FNAC). She was referred to our hospital for diagnosis and treatment. A physical examination disclosed a solid mass 3 cm in diameter in the left axilla; however, no mass was palpable in either breast. The mammographic findings demonstrated a well-defined mass in the left axilla, however, no mass was detected in both breasts (Figure 1A and 1B). A swollen lymph node was detected in the left axilla by ultrasonography (Figure 1C). The ultrasonogram also revealed an irregularly shaped hypoechoic mass, 0.7 × 0.7 cm, in the left breast (Figure 1D). Magnetic resonance imaging (MRI) showed a small irregular mass, 0.9 cm in diameter, with early enhancement after injection of gadolinium-diethylenetriaminepentaacetic acid (Gd-DTPA) was recognized in the left breast. Rt; right, Lt; left.

Figure 1. Preoperative imaging findings. A. A craniocaudal mammogram. No obvious abnormalities were recognized. B. A mediolateral oblique mammogram. A swollen lymph node was recognized in the left axillary lesion. C. An ultrasonogram of the swollen lymph node in the left axillary lesion. D. An ultrasonogram of the left breast mass. A small hypoechoic mass was recognized in the outer side of the nipple. E. Magnetic resonance imaging (MRI) findings. A small irregular mass, 9 mm in diameter, with early enhancement after injection of gadolinium-diethylenetriaminepentaacetic acid (Gd-DTPA) was recognized in the left breast. Rt; right, Lt; left.

Case report
A 52-year-old female with a lump in the left axilla was diagnosed to have lymph node metastasis of adenocarcinoma with unknown origin by the fine needle aspiration cytology (FNAC). She was referred to our hospital for diagnosis and treatment. A physical examination disclosed a solid mass 3 cm in diameter in the left axilla; however, no mass was palpable in either breast. The mammographic findings demonstrated a well-defined mass in the left axilla, however, no mass was detected in both breasts (Figure 1A and 1B). A swollen lymph node was detected in the left axilla by ultrasonography (Figure 1C). The ultrasonogram also revealed an irregularly shaped hypoechoic mass, 0.7 × 0.7 cm, in the left breast (Figure 1D). Magnetic resonance imaging (MRI) showed a small irregular mass, 0.9 cm in diameter, with early enhancement after injection of gadolinium-diethylenetri-
aminepentaacetic acid (Gd-DTPA) (Figure 1E). Based on the physical examination, mammographic, ultrasonographic and MRI findings, small breast carcinoma with a distinct axillary lymph node metastasis was suspected. FNAC was performed for both the breast and axillary mass. For the breast mass, atypical epithelial clusters with hyperchromatic nuclei were seen, and the cytological diagnosis was class V (A) × 40, (B) × 400. (C) The cytology of the left axillary lymph node from FNAC performed by the previous doctor. Atypical epithelial clusters with hyperchromatic nuclei were seen, and the cytological diagnosis was metastatic adenocarcinoma, class V. (D) The cytology of the left axillary lymph node from FNAC performed at our hospital on her first visit. Atypical ductal cells with necrotic changes were recognized, and the diagnosis of the left axilla was class III.

During the preoperative systemic examination, severe hyperglycemia was revealed, and she was diagnosed to have type 2 diabetes mellitus. She was treated with insulin, and the hyperglycemia was improved and was normalized after one month. Surgery for left breast cancer was then performed. The proposed operation was a left partial mastectomy and left axillary lymph node dissection. We performed ultrasonography just before the surgery in order to confirm the location and size of the breast cancer, however, it was difficult to
detect. In addition, the axillary lymph node, which had been swollen to 3 cm, was reduced in size to 1.5 cm. The resection area of the breast was determined according to the preop-
Figure 4. Immunohistochemical staining for the primary breast cancer. (A-E) CD3-positive (A), CD4-positive (B), and CD8-positive T-cells (C), aggregation of CD20-positive B-cells showing lymph follicle-like organization (D), and few CD56-positive NK cells are detected (E). (F, G) The ductal carcinoma cells are immunopositive for ER in the nuclei (F), and are immunonegative for PgR in the nuclei (G). All the original magnification are × 400 (A-F).
Figure 5. Immunohistochemical staining for the lymph node affected by metastatic ductal carcinoma. (A-G) AE1/AE3-positive cytoplasm (A, B) and ER-positive nuclei (C, D) are detected in the swollen axillary lymph node, completely undergoing coagulation necrosis. PgR-positive nuclei are not detected (E). Infiltration of CD3-positive T cells, but not CD20-positive B cells, are detected in the necrotic area of the lymph node (F, G). The original magnification is as follows: (A) × 100, (B) × 400, (C) × 100, (D) × 400, (E) × 100, (F) × 400, (G) × 400.
Spontaneous regression of breast cancer

The postoperative histopathological examination of the resected breast tissue showed a very small focus of atypical ductal cells, accompanied by massive lymphocytes aggregation (Figure 3A-C). The features indicated invasive ductal carcinoma with nuclear atypia 2, and the tumor was found to be 2 mm in diameter. The histological diagnosis was performed by three independent pathologists. It is noteworthy that the carcinoma cells showed eosinophilic changes of the cytoplasm and chromatin condensation of the nuclei, suggestive of degenerative changes (Figure 3C). Intriguingly, a significant aggregation of lymphocytes was observed around the tumor cells, which consists of CD3-positive CD4-positive or CD8-positive T cells (Figure 4A-C) admixed with lymph follicle-like organization of aggregation of CD20-positive B-cells (Figure 4D), but there were few CD56-positive NK cells (Figure 4E). On the other hand, all 31 dissected lymph nodes were free of carcinoma cells. However, the largest lymph node was focally replaced by a massive necrotic tissue and granulation tissue (Figure 3D, 3E). This lymph node was considered to be a swollen one, due to metastasis of the adenocarcinoma. Because residual antigens can be occasionally detected even in the necrotic tissue with immunohistochemical studies for some antigens, we tried to detected antigens for hormone receptors including ER, PgR, and pancytokeratin AE1/AE3. As a result, immunohistochemical studies revealed the presence of nuclear ER-positive and AE1/AE3-positive cells in the necrotic area (Figure 5A-D). The PgR expression was not detected in the necrotic area in the lymph node (Figure 5E), and the profiles of ER- and PgR-expression are similar to the ductal carcinoma within the breast (Figure 4F, 4G). Therefore, the final histopathological findings concluded that the lymph node with massive metastatic invasive ductal carcinoma cells underwent necrosis. It is noteworthy that CD3-positive T cells infiltrate admixed with a few CD20-positive B cells in the necrotic area of the metastatic carcinoma in the lymph node, suggestive of T-cell response to the carcinoma cells, but not residual lymphocytes undergoing necrosis (Figure 5F, 5G).

Usually, adjuvant systemic therapy and radiotherapy to the whole breast are added for node-positive breast cancer after a partial mastectomy and axillary lymph node dissection. However, in this patient, the primary breast cancer lesion and axillary lymph node metastasis had spontaneously regressed. We discussed the use of adjuvant therapy with our medical staff and the patient, and decided that no adjuvant therapy would be added. The postoperative recovery of the patient was uneventful. The patient is being followed closely, with examinations every 3-4 months, undergoes regular breast examinations, breast ultrasonography, mammography and tumor marker evaluations (CA 15-3 and CEA). After 60 months of follow-up, we have not observed any signs of cancer relapse, and the patient has remained free of the disease.

Discussion

SR of cancer is a very rare, but well-documented biological event [1, 2]. Although it is difficult to determine the scientific and definitive mechanism of the SR of cancer, many of the studies reviewed proposed possible causative mechanisms. The postulated mechanisms affecting the SR of cancer in general are as follows; immunological, endocrine, metabolic, surgical, postoperative events, elimination of a carcinogen or an antigen, inhibition of angiogenesis, tumor necrosis, oncogene, growth factor, or cytokine changes, genetic and epigenetic factors, induction of benign differentiation, apoptosis and psychological factors [1, 2, 5]. In this case, we demonstrated that the distinct metastatic carcinoma underwent complete necrosis with massive infiltration with CD3-positive T cells in the lymph node. The invasive ductal carcinoma in the breast, considerable primary site in this case, also underwent degenerative changes, accompanied with massive infiltration of CD3-positive T cells and lymph follicle-like formation (Figures 2, 3). These findings suggest that immunological response is the most important mechanism in the SR in this case.

In a review of 741 cases of the SR of cancer from 1900 to 1987, the incidence of SR of hypernephroma, lymphoma, malignant melanoma, leukemia and neuroblastoma was much higher than that of more common cancers,
Spontaneous regression of breast cancer

such as colorectal, lung and breast cancer [6]. Among the cases reviewed, there were only 41 cases (5.5%) of breast cancer with SR. In addition, only two cases of SR of breast cancer have been reported since 1987 [7, 8]. On the other hand, there have been some reports regarding the SR of malignant lymphoma of the breast [9-11]. Malignant lymphoma of the breast is rare, however, the incidence of SR of lymphoma is much higher than that of breast cancer [6].

Recently, Dussan et al. reported a case of invasive ductal carcinoma that spontaneously regressed after an arm injury occurred while the patient was awaiting surgical treatment. The authors hypothesized that the tumor disappeared due to immunological and local inflammatory reactions involved in the healing process induced by local tissue trauma, injury of the primary lesion after core and fine needle biopsy, and the background of generally increased healing and reparative mechanisms in the patient’s body, which started after the arm injury [7]. Regarding another possible mechanism of SR, sudden tumor regression with enhanced NK cell accumulation in a patient with stage IV breast cancer was reported [8]. In that case, after the treatment with dexamethasone alone, a SR was seen both in the primary tumor and in metastasis in the clavicular region. A biopsy from the primary region revealed no malignant cells, but a large number of inflammatory cells, mainly of NK cells. The biopsy from the subcutaneous metastasis in the supraclavicular area also showed clustered neoplastic tumor cells and lymphocyte infiltration. Repeated bone scans revealed a slight but unusual regression in the bone metastasis. It is conceivable that corticosteroids could cause the redistribution of lymphocytes to lymph nodes and tumor tissues [8]. Immune-mediated host responses and humoral factors were also reported to play a central role in the SR of solid tumors, such as renal cell carcinoma and malignant melanoma [1, 12].

In our case, the patient received only insulin therapy for blood glucose control before surgery. The cancerous tissue was significantly regressed during the month prior to the surgery, and the postoperative histopathological examination revealed that a significant aggregation of lymphocytes was observed around atypical ductal cells. The aggregated cells were mainly CD3-positive, CD8- or CD4-positive T-cells, while CD56-positive NK cells were not observed in our case. It is unclear when the immunological response the accumulation of lymphocytes occurred; however, neither lymphocytes nor necrotic cells were recognized in the breast sample obtained by FNAC that was performed on the day of her first visit. It is therefore possible that the accumulation of lymphocytes started after that. On the other hand, the SR of the metastatic lymph node might have started before she visited our hospital, because necrotic changes were already detected in the lymph node by the FNAC performed at our hospital on the day of her first visit to our clinic. The largest lymph node was composed of massive necrosis and granulation tissue without viable cancer cells after the surgery. Immunohistochemical studies revealed the presence of the pan-cytokeratin marker, AE1/AE3-positive cancer cells with ER-positive nuclei, which finally underwent massive necrosis after FNAC. There is a difference in the histological findings of the necrosis between the carcinoma cells within the breast and those in the lymph node. The former shows degenerative changes with eosinophilic changes of the cytoplasm and nuclear chromatin condensation. On the other hand, the latter shows massive coagulation necrosis with the infiltration of CD3-positive T cells within the metastatic cancer tissue, probably due to vascular disturbance. It is unlikely that the CD3-positive T cells could be preexisting of the lymphocytes of the lymph node, because there is few CD20-positive B cells follicular component near the area with scattered T cells. There have been several reports in which the SR of hepatocellular and renal cell carcinomas were associated with tumor necrosis related infarction [13], and the massive necrosis with CD3-positive T cell infiltration was induced after peptide vaccination [14, 15]. Taken together, we suggests of the following scenario in our case: at first, the metastatic ductal carcinoma in the lymph node had undergone degenerative changes due to unknown cause, and subsequently T cell responses were induced in the lymph node, resulted in the vascular disturbance of the metastatic cancer tissue and massive necrosis; next, the activated T cell against the ductal carcinoma infiltrate the primary ductal carcinoma within the breast and induced apoptosis of the carcinoma cells as a effector T cells through
the killing mechanism such as Fas-Fas ligand, TNFα-TNFα receptor, and perforine-granzyme system [16].

In conclusion, we herein reported a case of SR of breast cancer with axillary lymph node metastasis. As far as we know it is the first report that show the spontaneous regression of breast cancer, and the eradication mechanism could be spontaneously induced T cell response to the breast cancer. While the SR of breast cancer is a rare event, it is important to recognize that it might happen, at least to some extent. There has been a small number of well-documented cases of SR of breast cancer, and recent research suggests that the natural course of some screening-detected invasive breast cancers might be to spontaneously regress, although there is controversy regarding this point [17]. Our case distinctly indicates that SR of breast cancer exists associated with probable adaptive immunological response to the carcinoma. Spontaneously occurring immunological response to cancer is an important mechanism in the SR of cancer and the spontaneous response to cancer are paid the most attention and are essential also in the cancer vaccination at present, after reports of targeted molecular treatment for immunological check point signals such as PD1-PD1 ligand interaction [3, 4]. Therefore, it is important to recognize the presence of SR of the breast cancer and further understanding of the mechanism of SR would provide significant implications for cancer prevention and therapeutics.

Acknowledgements

This study was supported by grants from the Ministry of Education, Culture, Sports Science, and Technology of Japan. We are grateful to Mr. Fumihiko Ohkubo and Ms. Yuko Kubota for their valuable technical assistance.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Shinji Okano, Department of Innovative Applied Oncology, Graduate School of Medical Sciences, Kyushu University, 3-1-1, Maidashi, Higashi-ku, Fukuoka 812-8582, Japan. Tel: 81-92-642-5466; Fax: 81-92-642-5482; E-mail: okap@surg2.med.kyushu-u.ac.jp

References

Spontaneous regression of breast cancer


