# Spontaneous Complete Regression of Breast Cancer: Two Case Report

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Spontaneous regression (SR) is a tumor's partial or complete disappearance without any treatment. In the literature, it has been documented that SR is uncommon in breast cancer (BC) and other types of cancer. Multiple mechanisms are believed to contribute to the development of SR. However, its mechanism still needs to be clearly demonstrated.

Although two SR patients were presented in our study, the evidence needed to be more sufficient to determine the mechanism. However, due to Programmed Death-Ligand 1 (PD-L1) negativity in both patients, the hypothesis in the literature that PD-L1 has strong antitumoral activity was not supported. In addition, it was determined that the patient in case 2 was the first Cerb B2 positive case reported in the literature and had the earliest SR period. Due to this, it has been disclosed that the SR mechanism of BC will be concluded within 21 days at the earliest. This situation suggests that breast surgeons, in particular, should conduct a thorough physical examination and, if necessary, re-radiological examination before surgery on patients for whom surgery is decided after diagnosis. Being careful in this regard may increase the number of SR in BC cases and allow molecular investigations on living tissue samples to reveal the underlying mechanism.

**Keywords:** breast; cancer; spontaneous; regression

## Introduction

Breast cancer (BC) is the most commonly diagnosed malignancy in women and a leading cause of death worldwide [1]. In the literature, it has been documented that spontaneous regression (SR) is uncommon in BC and other types of cancer [2]. SR is a tumor's partial or complete disappearance without treatment [3, 4]. SR is a rare condition, occurring in approximately 1 out of every 60,000–100,000 cases [3, 5]. Cancer regressing on its own is a rare and well-documented biological phenomenon [4]. It is stated that SR can be multifactorial [5]. Multiple mechanisms, including immune mediation, tumor inhibition by growth factors and/or cytokines, induction of differentiation, hormonal mediation, and tumor necrosis, are believed to contribute to the development of SR. However, its mechanism has not yet been clearly demonstrated [4]. For this reason, discussions regarding SR remain current, and it is acknowledged that additional studies and patient reports are required [6].

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Based on our review of the English literature, it is believed that with these two cases, the total number of reported cases of SR in BC patients now stands at eleven, including nine cases reported in the literature since 1987. In Turkey, these are the first SR cases of BC to be reported. In this investigation, two complete SRs in patients with BC were analyzed in light of the literature.

## Case Report

In this case report, written informed consent and institutional approval for the investigation were obtained from two patients. In this study, patients with BC who had undergone two complete SR were presented.

### *Case 1*

A 65-year-old female patient complained of a palpable mass in the right breast. Only hypertension and appendectomy surgery were identified in the patient's medical history. On physical examination, a 2 × 3 cm, irregularly circumscribed, painless, mobile mass was palpated in the 11 o'clock position of the patient's right breast. The patient's mammogram revealed a 2.5 × 2.5 cm Breast Imaging Reporting and Data Systems (BIRADS) V lesion with irregular borders in the upper outer quadrant (UOQ) of the right breast. Benign axillary lymphadenopathy (LAP) was present, with nipple retraction and increased skin thickness

prominent in the periareolar region. Fig. 1 depicts an image of the patient's mammogram. On breast ultrasonography (USG), a 24-mm irregularly contoured hypoechoic mass was detected in the UOQ of the right breast, as well as a hypoechoic LAP with a diameter of 18 × 11 mm, the greatest of which was found in the right axilla. The breast magnetic resonance imaging (MRI) examination identified a 2.5 × 2 cm lobulated contoured mass with Type 3 pattern enhancement in the right breast UOQ and a 2 × 1.5 cm suspicious LAP in the right axilla regarding invasion. Fig. 2 depicts the breast MRI image of the patient.

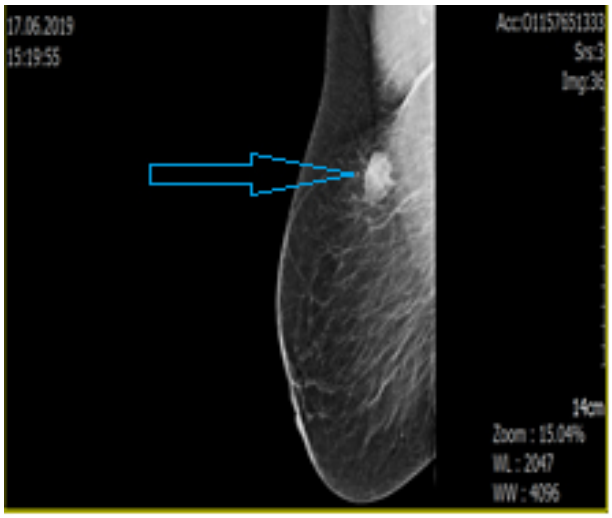


**Fig. 1. Mammography image of Case 1.** Blue arrow: Breast Imaging Reporting and Data Systems (BIRADS) V breast mass.

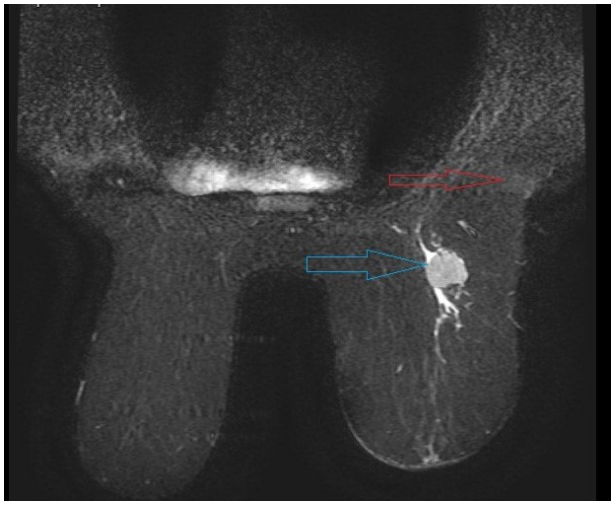

**Fig. 2. Magnetic resonance imaging (MRI) image of Case 1.** Blue arrow: Type 3 pattern breast mass. Red arrow: suspicious axillary lymphadenopathy.

Under USG guidance, the patient underwent a tissue biopsy of the breast mass and Fine needle aspiration cytology of the lymph node in the right axilla. The breast biopsy revealed invasive ductal carcinoma with a prominent lymphocytic response, while the axilla biopsy yielded negative results for malignancy. The histopathology of breast tissue revealed estrogen receptor (ER) positive, progesterone receptor (PR) positive, CerbB2-negative, Ki 67: 7–8%, AE1-AE3-positive, cytokeratin 7 (CK7) focal weak-positive, and Gata-3-positive. The patient was evaluated within the multidisciplinary breast council. Breast-conserving surgery and axillary sentinel lymph node biopsy were planned for the patient. She was scheduled for surgery 46 days after the date of the biopsy. The mass was not palpable during the preoperative physical exam. A USG examination was carried out. Since no mass could be detected sonographically, the patient underwent quadrenectomy and sentinel lymph node biopsy (SLNB), including UOQ. The axillary lymph node was reported to be reactive. No cancer was detected in the breast pathology sample. There were reports of focal periductal chronic inflammation, focal fat necrosis, fibrocystic changes, and columnar cell changes. A breast MRI was performed on the patient on the first postoperative day. No sign of cancer was detected radiographically. Fig. 3 depicts the patient's postoperative MRI image. A second opinion was obtained from another center for each patient's radiological and histopathological examinations, and the results were confirmed. The patient was diagnosed with complete SR of BC. Blood was drawn from the patient and compared to histopathological tissue samples. As confirmed by chimerization and DNA analysis, all tissues are genetically identical to the same individual. By the decision of the oncology council, palliative radiotherapy was applied in the postoperative period. Chemotherapy treatment was not deemed necessary. During the patient's 34-month follow-up, there were no signs of a BC recurrence.

*Case 2*

A 57-year-old female complained about a mass in her right breast. The patient had a history of diabetes, hypertension, and the use of metformin for diabetes. On physical examination, a 2.5 × 3 cm, irregularly circumscribed, painless, mobile mass was found in the 10 o'clock position of the right breast. The patient's breast USG examination revealed a 20 × 10 mm mass with irregular contours and spicular extension at 10 o'clock on the right breast, a 23 × 16 mm hypoechoic lesion with irregular borders in the deep plane of this lesion, and a 13 × 7 mm mass with irregular borders at 12 o'clock (satellite lesion). It was designated sonographically as BIRADS 4C. Fig. 4 depicts a sonographic image of the patient. The mammographic examination reported an asymmetrical density increase that did not show sharp borders in the right breast UOQ, and the lesion was mammographically compatible with BIRADS 4C.

A core biopsy was performed on a 2.5 × 3 cm malignant breast mass on the right side. Based on histopathology, medullary pattern invasive carcinoma was reported.

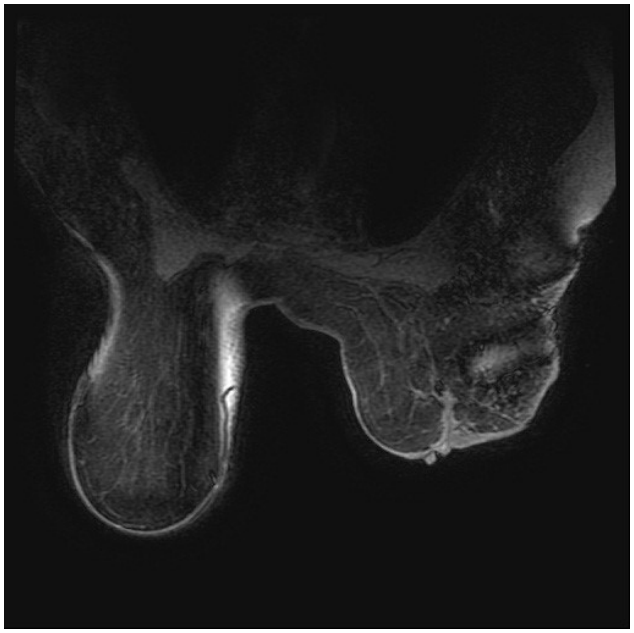

**Fig. 3. Postoperative MRI image of Case 1.**

Tumor-infiltrating lymphocyte (TIL) was 80%, ER was 5% positive, PR was negative, CerbB2 was positive, Ki 67 was 80%, P63 staining was present in a limited number of tumor cells, and Gata-3 was positive. With the present findings, it was decided to evaluate the patient in the breast council. However, it was determined that 22 days after the breast core biopsy, the patient underwent a mastectomy and axillary lymph node dissection at another center without being evaluated by the breast council. According to the patient's surgical pathology report, no metastatic lymph nodes in the axilla and no tumor cells could be detected in the mastectomy specimen. When the patient reapplied for follow-up at our clinic, the surgical specimen obtained at another facility was evaluated histopathologically. In our center's examination of the axilla, no evidence of metastasis was identified. A malignant epithelial cell islet was detected in a 0.7 cm focus during the examination of the mastectomy specimen. Blood samples were extracted from the patient to conduct chimerization and DNA analysis on histopathological tissue samples. It was determined that all tissue samples were genetically identical. The patient has been classified as BC complete SR. By the decision of the oncology council, postoperative radiotherapy and chemotherapy treatment was not deemed necessary. During the patient's 22-month postoperative follow-up, no signs of BC recurrence were detected.

## Discussion

BC, SR is uncommon, and there are few case reports in the medical literature [4]. No data regarding its incidence has been found in the literature. However, based on the study by Challis and Stam [2], it was found that 5.8% of all SR-detected cancers were cases of BC. Challis and Stam [2] reported that between 1900 and 1987, SR was observed in 741 cancer patients, 43 of whom had BC. Following that period, a total of nine additional cases of SR in BC patients, including eight females and one male, were reported in the English literature available on PubMed. Both patients in our study were women. CerbB2 was negative in all nine recently reported patients whose receptor information was shared histopathologically in the literature. In our investigation, while the patient in Case 1 was negative for Cerb B2, the patient in Case 2 was positive. Therefore, the patient in Case 2 is deemed to be the first CerbB2-positive patient described in the literature. However, the Cerb B2 positivity was not regarded as a data point that would help explain the SR mechanism. Case reports in the literature indicate that the mechanism of SR is unclear. Even though numerous mechanisms have been discussed, adequate evidence for receptor positivity has not been demonstrated [5, 7]. Because the most obvious claim about receptor positivity was made in the case report by Cserni *et al*. [7]. High levels of Programmed Death-Ligand 1 (PD-L1), normally expressed by tumor cells, transmit negative regulatory signals that lead to immune evasion. Although it is known that high PD-L1 level is associated with poor prognosis, in the case report by Cserni *et al*. [7], it was stated that high PD-L1 level has a better prognosis in triple negative, lymphocyte dominant breast carcinomas. However, the mechanism behind this observation was not elucidated. In contrast to their findings, both patients in our study tested negative for PD-L1.

Although the mechanism of SR is not a clearly established phenomenon, it is thought to be possibly related to trauma or infection [4]. Considering the case reports in the literature and the fact that SR was observed after biopsy in two patients in our study, the hypothesis that it may be related to trauma is strengthened. Regression is generally observed 30–53 days after the date of breast biopsy in patients with CR detected after surgery or without surgery, according to case reports in the medical literature [4, 5]. In our study, it was found that the patient in case 2 had complete regression 22 days after the biopsy. Therefore, this patient is believed to have the earliest SR detected after biopsy in the published literature. Considering the case reports in the literature and the regression periods in case 2 of our study, we can conclude that SR of BC is a process completed on average 3–4 weeks after the biopsy.

Although it was reported by Ohara *et al*. [4] that SR may be associated with immunological cell death (ICD), sufficient evidence and molecular markers for ICD could not be identified. According to Maiche *et al*. [8], dexamethasone's antitumor mechanism of action was described. Nonetheless, such an effect has yet to be established. Similarly, another case report indicated that it may be related to the use of metformin in a diabetic patient; sufficient evidence could not be presented [7]. In case reports found in the scientific literature, the immunological response is the SR mechanism that is most frequently highlighted. In addition, the local inflammation-induced immune response is also men-

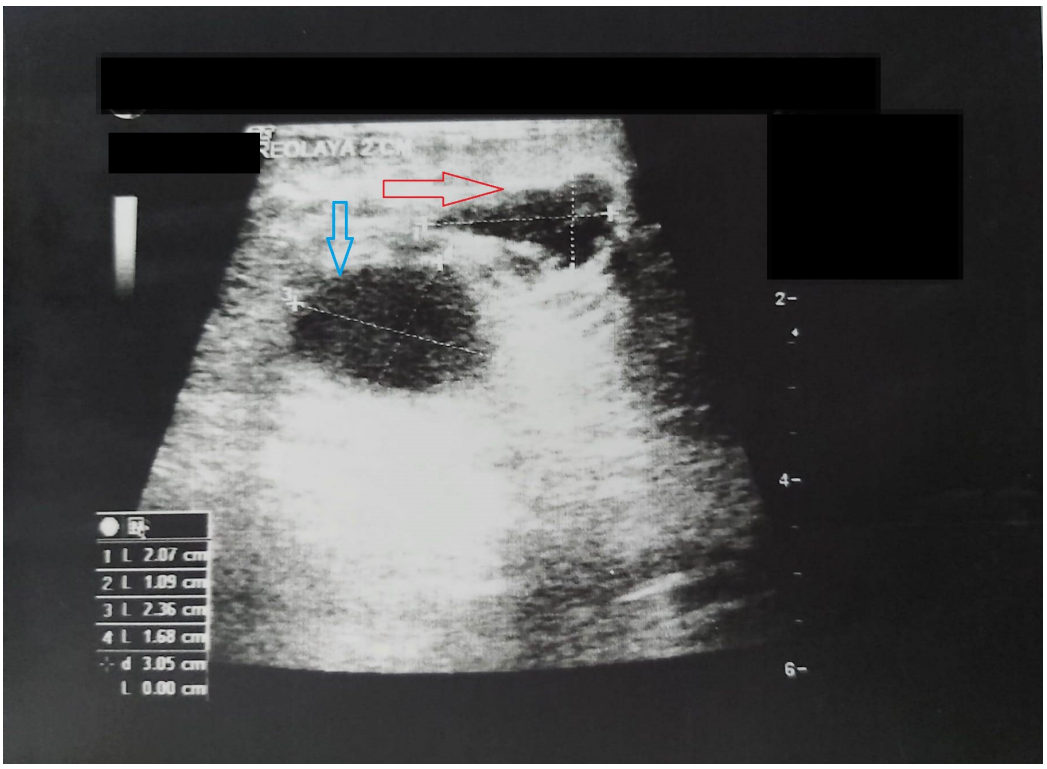


**Fig. 4. Sonographic image of Case 2.** Blue arrow: malign breast mass. Red arrow: satellite lesion.

tioned [6]. Regarding patients with regression of axillary metastases, it is recognized that a systemic immunological response theory comes to the forefront. Although the mechanism eliciting this immunologic response is unclear, its occurrence in all case reports following a biopsy strengthens the theory that it is a reaction triggered by local inflammation. Although we believed there was an immunological response due to local inflammation, sufficient evidence could not be presented due to the observation of SR after biopsy in two of our patients.

There is no definitive consensus regarding the treatment of patients with SR of BC. In line with case reports in the literature, it is seen that surgical treatment is generally applied to patients [3, 5, 7, 9, 10]. However, Katano *et al*. [6] reported that no surgical treatment was applied; only adjuvant tamoxifen treatment was given. Although postoperative systemic therapy (ST) and radiotherapy (RT) are generally recommended for patients undergoing surgery, the practices in reported case reports vary from giving only RT, only chemotherapy (CT), CT and RT together, or no treatment [3, 5, 7, 9, 10]. Adjuvant chemotherapy was not administered to the two patients in our study in the postoperative period, according to the decision of the oncology council. However, while postoperative RT was applied to the patient in Case 1, who underwent breast-conserving surgery, RT was not applied to the patient in Case 2, who underwent mastectomy. For this reason, the increase in the number of cases in the literature may contribute to establishing a consensus on treatment, considering disease-free survival times.

## Conclusions

In conclusion, the SR mechanism of BC is a biological phenomenon that has yet to be fully elucidated. Even though two SR patients were presented in our study, the evidence needed to be more sufficient to determine the mechanism. However, it was determined that the patient in case 2 was the first Cerb B2 positive case reported in the literature and had the earliest SR period. Due to this, it has been disclosed that the SR mechanism of BC will be concluded within 21 days at the earliest. This situation suggests that breast surgeons, in particular, should conduct a thorough physical examination and, if necessary, re-radiological examination before surgery on patients for whom surgery is decided after diagnosis. Being careful in this regard may increase the number of SR in BC patients and allow molecular investigations on living tissue samples to reveal the underlying mechanism. Because by revealing the mechanism, it can contribute to the prevention and treatment of BC.

## Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

## Author Contributions

OY1: Analysis, interpretation, writing the article, critical revision of the article, and literature review. UK: Study design, analysis, interpretation, writing the article, critical revision of the article, and literature review. MGD: Literature review, English editing, critical revision. OYu: Lit-

erature review, critical revision. AE: Data collections, radiological examinations, literature review. PON: Literature review, histopathological examinations, critical revision. All authors: Analysis and interpretation of data. All authors revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

Signed informed consent was obtained from the patient included in this case report and is available upon request. The Ethic approval is exempted by Prof. Dr. Cemil Tascioglu City Hospital. The study was conducted in accordance with the Declaration of Helsinki.

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## Conflict of Interest

The authors declare no conflict of interest.

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