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Spontaneous Regression of a Breast Carcinoma: A Case Report

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Key Words
Spontaneous remission · Breast cancer · Apoptosis · Cancer behavior

Abstract
Spontaneous regression of malignant tumors is a rare event. It is defined as partial or total disappearance of a proven malignant tumor without adequate medical treatment. The causes of this phenomenon are various. Nevertheless, malignant tumors do regress occasionally for no apparent reason, as evidenced by many clinical observations. We report a case of a 68-year-old woman, who was presented with a several-month history of a painless firm lump, initially of 1 cm in diameter and growing to a large solid regular tumor of 2.5 × 2.5 cm in size, in the upper outer quadrant of her right breast. Preoperative histopathological diagnosis revealed ductal invasive carcinoma. Later on, while awaiting surgical treatment, she suffered an arm injury requiring a 1-month delay of surgery. After recovery, on the date of surgery the tumor disappeared, and, in addition, it was not found in tissue specimens obtained from quadrantectomy. After 78 months of follow-up there was no evidence of relapse. In this report, we discuss clinical and histopathological findings, patient management and possible mechanisms of cancer regression.

Introduction

Spontaneous cancer regression is an extremely rare phenomenon. In these cases, the malignant tissue mass partially or completely disappears without any treatment, or as a result of a therapy inadequately influencing systemic neoplastic growth. This definition makes it clear that the term 'spontaneous regression' applies to a neoplasm in which the overall malignant disease is not necessarily treated and to cases where regression may not be complete or permanent [1]. It has been estimated that it occurs not more than once in 60,000–100,000 cases, and is reported in all types of human cancer [2]. The cause of the phenomenon may be multifactorial. Mechanisms proposed for spontaneous regression of human cancer include: immune mediation, tumor inhibition by growth factors and/or cytokines, induction of differentiation, hormonal mediation, and elimination of a carcinogen, tumor necrosis and/or angiogenesis inhibition, psychological factors, apoptosis and epigenetic mechanisms [3]. A number of possible mechanisms of spontaneous regression are still under debate, with the understanding that no single mechanism can completely account for this phenomenon. Spontaneous remission among gynecological malignancies, including breast cancer, is rare despite their frequency.

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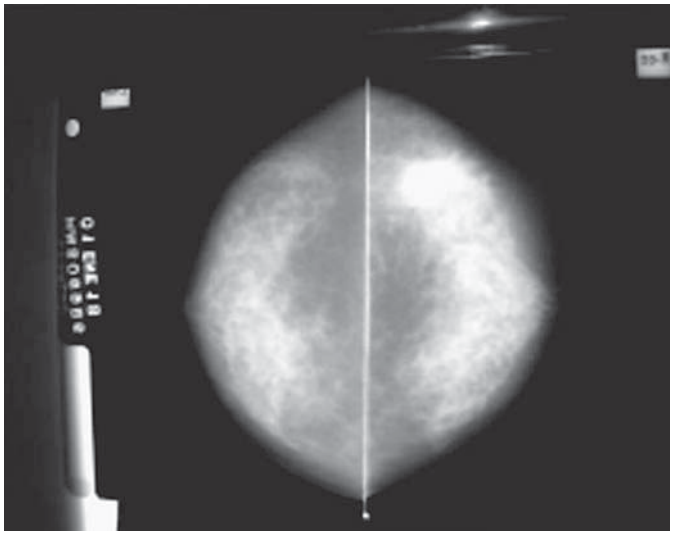

Fig. 1. Preoperative craniocaudal mammogram (presence of a solid lesion in the UOQ of the right breast).

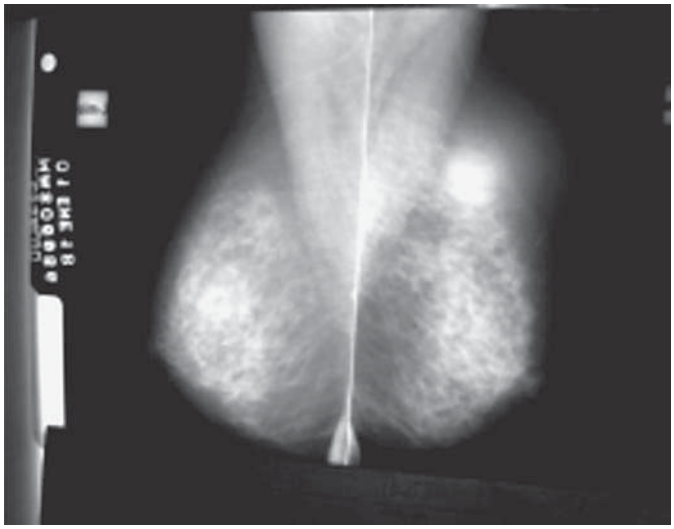

Fig. 2. Preoperative mediolateral oblique mammogram (presence of a solid lesion in the UOQ of the right breast).

We report a case of spontaneous breast cancer remission in a postmenopausal woman, rarely discussed in the literature.

Case Report

A 68-year-old woman with a history of a rapidly growing painless firm lump, initially of 1 cm in diameter extending to a large solid regular tumor in the upper outer quadrant of her right breast, was referred for surgical treatment. Physical examination disclosed a 2.5 × 2.5 cm, solid, painless, partially mobile tumor of regular shape localized in the region of the upper outer quadrant of the right breast with local skin retraction. Examination of the ipsilateral regional lymph nodes in the axilla revealed a palpable tumor of 1 × 1 cm in size, vs. a metastasis. Breast mammography was compatible with the neoplastic lesion disclosed by palpation and showed a well-circumscribed lesion with tiny asymmetric margins that dispersed at the edges of the breast tissue without the presence of microcalcifications. Breast imaging reporting and data system (BI-RADS) concluded category 5 classification (fig. 1 and 2). Laboratory biochemical evaluations, blood cell count and hemocoagulation parameters were all within normal ranges. Tumor markers were not investigated. Gynecological examination of the internal genital was standard, appropriate for age. She was a nonsmoker multipara (3 births) with a regular menstrual period since the age of 14 years and a history of oral contraceptive age for 6 years, without any long-time medication, chronic disease or history of repeated chest X-ray examinations, breast injury or clinical mastalgia. Her family history was otherwise unremarkable.

The patient underwent fine needle and core breast biopsy. Four slides for cytology (fig. 3) and one 4-mm-long tissue fragment for histological examination (fig. 4) were obtained. The results concluded a poorly differentiated (grade 3) ductal invasive carcinoma with negative progesterone and estrogen receptor status. Based on this conclusion, together with clinical examination, quadrantectomy (UOQ) with axillary dissection was recommended to the patient.

During the following 2 weeks, she was prepared for the operation. However, 3 days before the planned breast surgery the patient sustained a serious arm injury with complicated fracture of the forearm. This event caused a 4-week delay in her surgical intervention. During this delay, she used nonsteroidal anti-inflammatory medication (diclophenac 100 mg daily) for 1 week. No other (e.g. hormonal, steroid, homeopathic) medication was administered. At the end of the arm-healing period (nearly 6 weeks after the initial visit) she was rehospitalized, but the previously described breast tumor was not clearly palpable any more. Based on this and previous findings, UOQ with a 1-cm healthy right breast tissue demarcation margin and regional axillary dissection was recommended. However, on gross pathology during the surgery the tumor was not found. Similarly, frozen biopsy excluded the presence of a malignant lesion. The conclusion was also the same at the definitive histological report. For verification, repetitive blind re-evaluations of specimen slides by other breast pathologists were performed. All excluded the finding of breast carcinoma. Additionally, mammography 6 months after surgery also showed no presence of tumor (fig. 5).

Postoperative recovery of the patient was uneventful. The patient is followed every 4–6 months, takes regular breast examination, including mammography, tumor markers (Ca 15-3, CEA), abdominal sonography, chest X-ray and total body bone scintigraphy. After 78 months of follow-up, we did not reveal any sign of cancer relapse and the patient has remained free of the disease until present.

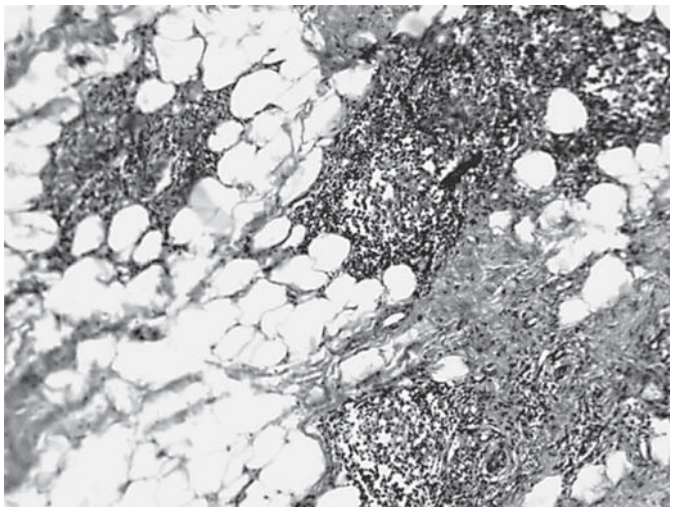

Fig. 3. Tumor cytology (from FNC).

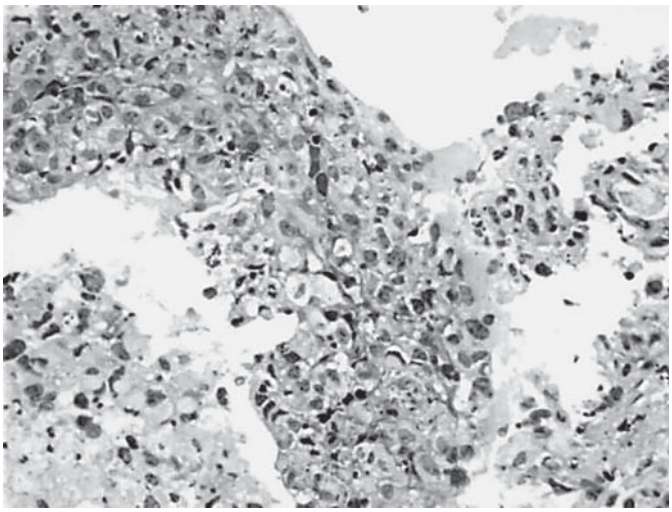

Fig. 4. Tumor histology (from core biopsy).

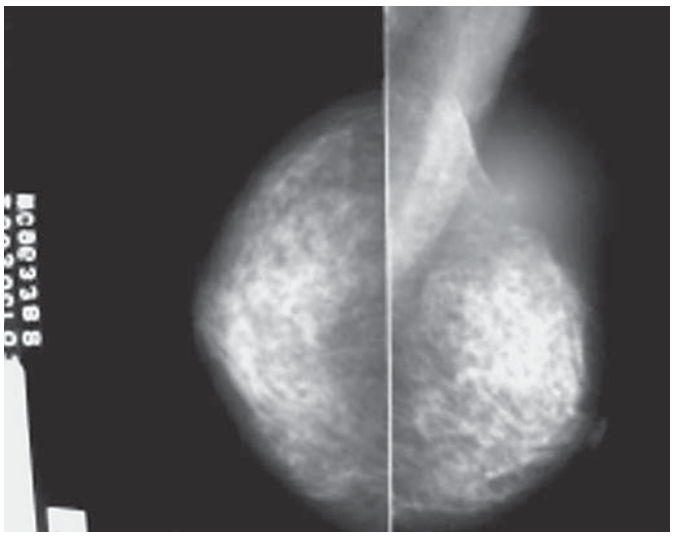

Fig. 5. Follow-up mammogram after 6 months (absence of solid lesion in the UOQ of the right breast).

Discussion

The phenomenon of spontaneous regression of benign and malignant tumors is documented in the literature and is commonly attributed to the induction of apoptosis [4, 5], the activation of the immune system [3, 6], or to necrosis and cell death. Recent data suggest that breast cancer has a very variable natural course, and a small fraction of patients may survive 10–15 years without treatment. An exceptional course could be misinterpreted as effective alternative treatment in the absence of strict criteria [7].

Various attempts to explain this unusual biological cancer behavior have been made. The present hypothesis about spontaneous remission proposes that tumor regression is the consequence of induction of the process of planned cellular death in tumors [8]. Apoptosis in general requires the activation of intracellular proteases called caspases. Their activation takes place in two ways (extrinsic and intrinsic). The extrinsic way consists of the activation of proapoptotic transmembrane receptors, transmission by means of adaptation proteins and the activation of caspases. The intrinsic way consists of the liberation of mitochondrial proteins to the cytosol (such as cytochrome C) and subsequent activation of caspase 9 and 3. Any alteration in caspase activity may then affect cell apoptosis. Another cell cycle regulating structure is the p53 gene that encodes the main apoptotic regulating protein: the tumor suppressor protein p53 [9]. Its overexpression or structural abnormality may lead to changes in its functions, which can result in various cellular changes including death or tumor regression.

Tonini et al. [10] in a study of DNA fragmentation concluded that in the course of neuroblastoma progression, apoptosis seems to take place with about an equal frequency for both favorable and unfavorable stages with an exception for the 4th stage. Since DNA fragmentation re-

mained undetected in stage IV, Tonini et al. [10] suggested that apoptosis was not a mechanism of spontaneous regression for these patients. Otherwise, there is evidence in favor of the hypothesis that spontaneous regression of tumors may be mediated immunologically. Halliday et al. [11] observed a larger number of CD4+ T lymphocytes infiltrating primarily regressing melanomas and basal cell carcinomas than their non-regressing counterparts. The number of T cells positive for interleukin-2 receptor, but not for transferring receptor, was also increased, indicating that the infiltrating T lymphocytes were in the early stage of their activation.

Another attempt to explain cancer remission is to evaluate the role of random effects taking part in this phenomenon. The authors [12] consider a stochastic model of tumor growth, which is descriptive of the fact that tumors are inherently prone to spontaneous regression due to the nature of their random development. Clearly, one has to rely on mathematical modeling as the only way to evaluate the role of random effects in this process, especially when we know that the tumor initially grows rapidly (exponentially or superexponentially), but increasingly slows down its growth as it becomes larger, so that the mean tumor size tends to be constant as time progresses. Thus, a retardation of growth rate can be seen even in early stages of carcinogenesis, as the Gompertz growth kinetics of expected number of tumors cells is consistent with this pattern [13].

It has been shown that 2 out of 3 patients going through spontaneous remission are experiencing spiritual awakening before remission happens [14]. Ventegodt et al. found it extremely interesting that the size of a tumor could be reduced dramatically within a few hours of holistic treatment, when the patient was highly motivated for personal development. The reduction of tumor size is in accordance with the holistic view that many types of cancer are caused by emotional and existential disturbances. From a holistic point of view, cancer can be understood as a simple disturbance of cells, arising from the tissue holding on to a trauma with strong emotional content. This is called a 'blockage', where the function of the cells is changed to a function of holding emotions. Holistic medical research meets both ethical dilemmas and practical difficulties, as it is obviously important for induced spontaneous remissions that surgery and chemotherapy are not used, unless it is absolutely necessary. On the other hand, it is important for the patients' survival that they receive a well-documented treatment as soon as possible [14]. Additionally, some patients combine conventional therapy with alternative treatment forms, and it has been claimed that some of those can have an antineoplastic effect. It is still unknown whether this might be another cause of cancer remission. Therefore the role of alternative treatment forms requires close examination.

Although spontaneous tumor regression is an extremely rare finding, it has been reported in several cancers, including gynecological malignancies. Gynecologists can occasionally see regression of cervical intraepithelial neoplasia [15, 16], rarely of ovarian [17] or breast cancer. Kadish et al. [18] examined cell-mediated immune responses to human papillomavirus 16 E6 and E7 peptides and the outcome of cervical lesions and provided an important insight to the tumor biology. They revealed a significant correlation between cell-mediated immune responses to specific E7 peptides (37–54) and disease regression and resolution of viral infection. These findings encouraged scientists to identify and map the 'protective' epitopes in the oncoproteins, which could lead to the development of immunological assays determining the risk of any neoplastic lesion and the development of immunotherapeutic protocols for their management and, ultimately, for the prevention of cancer.

There is only a single meta-analysis in the English literature from Larsen and Rose [7] who reported on the natural history of breast cancer and the degree of spontaneous remission. Literature search revealed 32 cases of spontaneous breast cancer remissions, and only 6 cases were sufficiently documented including histological confirmation of the diagnosis [7]. These results confirm that the phenomenon of cancer remission is very rare and the natural course is varied and unclear. Apart from solid breast lesions, spontaneous resolution of breast microcalcifications or in situ breast cancer was also rarely reported [19–21], mainly at the time of menopause as a result of falling estrogen levels. Thus, this phenomenon should trigger full investigation and close follow-up or excision. There are still significant proportions of disappearing indeterminate microcalcifications in association with malignancies.

The problem of breast cancer regression is complex. We know that more breast cancer is diagnosed among screened than unscreened women [22], and this breast cancer rate in the invited age groups is about 50% higher than the background level prior to the introduction of the screening program [23, 24]. Zahl et al. [23] suggest that as many as one third of all invasive breast cancers detected by mammography screening in the age group 50–69 years would not have been detected in the patients' lifetime without screening, and therefore represent overdiagno-

sis. Additionally, in another study they concluded that 73% of the 'latent cancers' are no longer detectable in the mammograms of women at age 70 [25]. This suggests that many subclinical invasive and noninvasive cancers, including breast cancer, regress spontaneously without treatment and offer an explanation for the excellent prognosis of tumors detected by mammography screening. The same conclusion is supported by similar calculations from other studies [26].

The exact mechanism regarding spontaneous regression of tumors is not fully understood. Molecular events regulating cell survival, apoptosis, growth arrest as well as cell differentiation, are important contributors to the overall kinetics and turnover of malignant cell growth and play a role in their development, progression or regression. Failure of these cell cycle pathways can result in loss of control over proliferation. In our case, we hypothesize that the tumor disappeared due to immunological and local particular inflammatory and healing mechanisms induced by local tissue trauma, injury of the primary lesion after core and fine needle biopsy on the background of generally increased healing and reparative mechanisms in the patient's body, which started after the arm injury. Cole and Everson [27] showed some possible factors that can be implicated in the phenomenon of spontaneous tumor regression in such situations (endocrine influence, surgical removal, unusual sensitivity to inadequate irradiation, fever or acute infection, allergic reaction, interference with nutrition of the tumor, removal of carcinogenic agents and incorrect diagnosis).

In conclusion, while spontaneous breast cancer remission is an extremely rare finding, it is necessary to consider it when definitive results of histology are negative after a previously positive finding. Diagnostic and operative mistakes have to be excluded when counseling patients' status and management. More cases with subsequent follow-up are needed for a better understanding of the natural history of this rare cancer behavior. Additionally, the need for investigation of molecular biology features of breast tumors and their tendency to undergo apoptosis is obvious.

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