Case Report

Granulosa Cell Tumor of the Ovary in a Patient with Adjuvant Tamoxifen Use for Breast Cancer: An Extremely Rare Case Report

Meme Kanseri Tedavisinde Adjuvan Tamoksifen Kullanan Bir Hastada Ovaryan Granüloza Hücreli Tümör: Oldukça Nadir Görülen Bir Vaka

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ABSTRACT

Tamoxifen use can cause gynecologic tumors like uterine sarcomas. However, the relationship between tamoxifen use and adult granulosa cell tumors (AGCTs) is uncertain. Here we report a case of AGCT in a 57-year old patient with antecedent tamoxifen use for hormone-receptor positive breast cancer. After 22 months of tamoxifen use, the patient had diagnosed with a stage 1a granulosa tumor. To our knowledge, there are only four cases previously published about the relationship between the development of granulosa cell tumors and the use of tamoxifen. It is very difficult to say that there is a certain relationship between tamoxifen use and AGCT because of the rarity of the condition.

Keywords: Breast cancer, granulosa cell tumor, tamoxifen

ÖZET

Tamoksifen kullanımı uterin sarkomlar gibi jinekolojik tümörlere yol açabilir. Ancak tamoksifen kullanımının yetişkin granüloza hücreli tümör (AGCT) etiyolojisindeki yeri kesin değildir. Biz burada, hormon pozitif meme kanseri nedeniyle adjuvan tamoksifen tedavisi almakta olan 57 yaşındaki bir hastada gelişmiş olan AGCT vakasını bildirmek istiyoruz. Hastamız evre 1a AGCT tanısı aldığında 22 aydır tamoksifen kullanmaktaydı. Bildiğimiz kadarıyla, tamoksifen kullanımı altında gelişen AGCT' ler ile ilgili daha önce yayımlanmış 4 adet vaka bildirimi mevcuttur. Bu tip vakalarının çok nadir olması nedeniyle AGCT gelişimini tamoksifen kullanımı ile ilişkilendirmenin oldukça zor olduğunu söylemek isteriz.

Anahtar kelimeler: Meme kanseri, granüloza hücreli tümör, tamoksifen

Introduction

Breast cancer is the most common cancer type among women worldwide. Selective estrogen receptor modulators are widely used for treating hormone receptor-positive breast cancer. One of their mechanisms of action is that; it competes with estradiol for estrogen receptors. However, their pharmacodynamics are complex. They can also act as a partial estrogen agonist in certain tissues. So,

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sometimes detrimental effects can be developed with these drugs. For example, tamoxifen is known as an important risk factor for endometrial cancer [1].

Ovarian sex cord-stromal tumors (SCSTs) are a group of tumors that originates from the sex cord-stromal cells (Leydig, Sertoli and, Granulosa cells). They are less common when compared with epithelial and germinal origin ovarian tumors. According to Surveillance, Epidemiology and End Results United States national database, the incidence of SCSTs was 0.20 per 100,000 women [2]. Recent studies suggest that sex cord-stromal tumors might be associated with certain genetic syndromes like Peutz-Jeghers syndrome, Ollier Disease, Maffucci syndrome, and DICER1 syndrome [3]. However, the etiology of these tumors remains uncertain.

To our knowledge, they are only a few cases formerly reported about the relation of tamoxifen use and adult granulosa cell tumor (AGCT). Here, we report a case of AGCT with antecedent tamoxifen use for breast cancer.

Case Report

A 57-year-old postmenopausal woman with a history of breast cancer presented with abnormal uterine bleeding and an ovarian mass. Two years ago, the patient had undergone breast-conserving surgery due to intramammarian mass. Her pathology report was given as invasive ductal carcinoma, ER-positive, PR-positive, HER2-negative. Positron emission tomography/computed tomography scan had shown no distant metastasis. She had been diagnosed with hormone receptor-positive breast cancer. The patient was evaluated as T1N0M0, stage 1a breast cancer according to the TNM staging system. After breast-conserving surgery, she had received adjuvant radiotherapy. She has been receiving adjuvant tamoxifen for 22 months since her diagnosis. In June 2021, the patient was admitted to the hospital with abnormal uterine bleeding. Ultrasound showed a nodular mass in her left ovary. Therefore, she underwent an adnexal hysterectomy and salpingo-oophorectomy. On gross examination, 30x21x12 mm diameter of the left ovary with an intact capsule was seen. On the cut surface, an 18 mm yellow and nodular mass with a soft surface adjacent to ovarian stroma was observed. Microscopically, at small magnification, a moderately cellular tumor characterized by solid, microfollicular, insular and trabecular patterns localized at the ovarian stroma was observed. At high magnification, tumor cells showed pale to eosinophilic

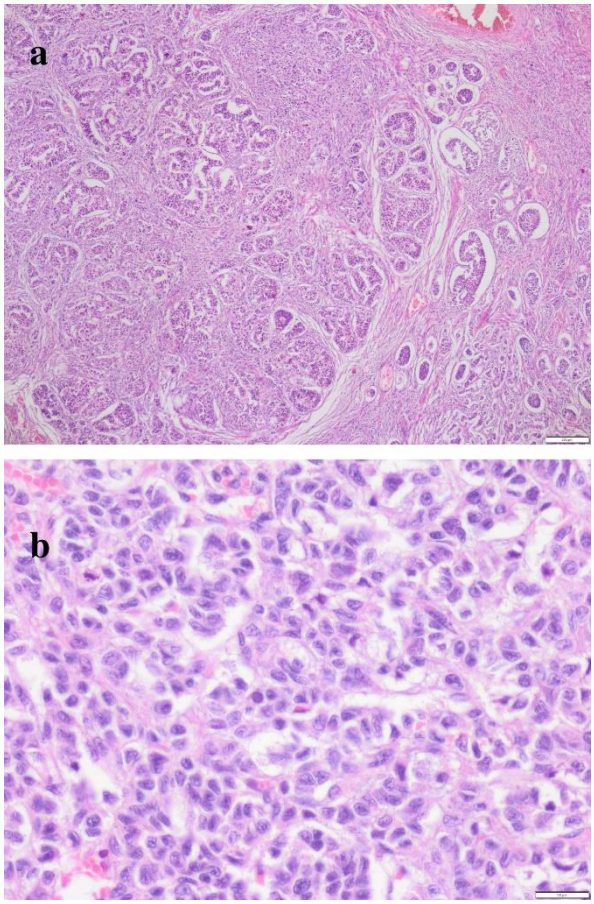

Figure 1a. Trabecular pattern of the tumor can be observed, especially at the right side of the image (HE x40). 1b. Trabecular pattern of the tumor can be observed (HE x100).

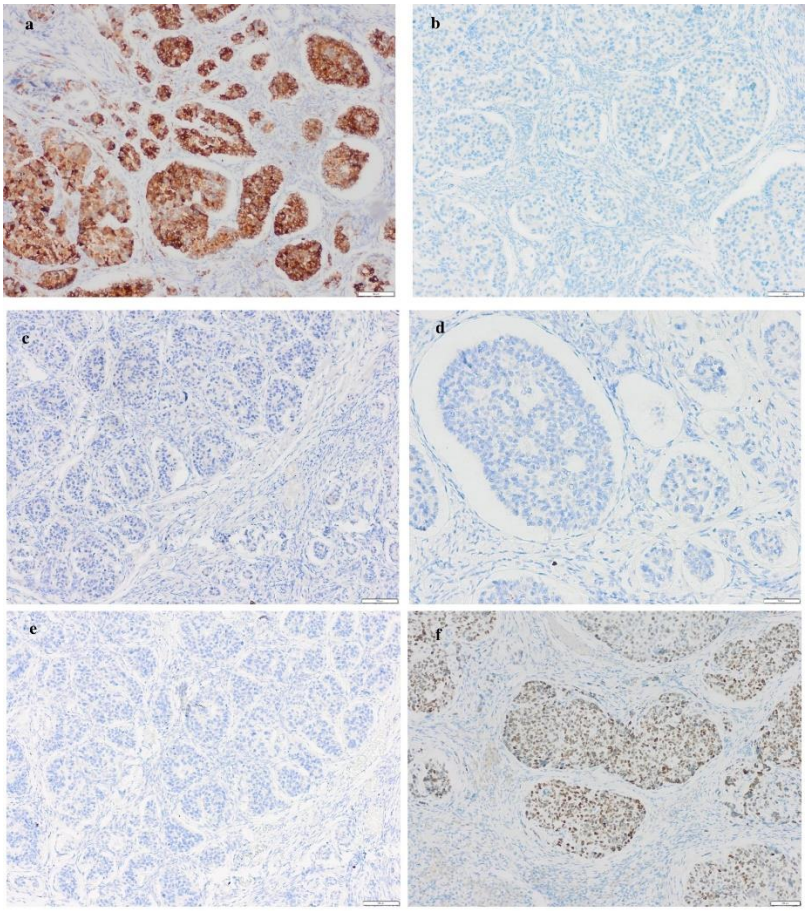

Figure 2a. Tumor cells showed cytoplasmic positivity for Inhibin (x100). b. Tumor cells stained negative for CK7 (x100). c. Tumor cells stained negative for PAX8 (x100). d. Tumor cells stained negative for GCDFP15 (x200).e. Tumor cells stained negative for Mammoglobulin (x100). f. Tumor nuclei stained positive for PR (x100).

cytoplasm and pale, oval nuclei with an irregular border. Some tumor cells had nuclear grooves (Figure 1). On 10 high magnification fields, 13 mitoses were counted. Immunohistochemically tumor cells stained positive for inhibin whereas they stained negative for CK7and PAX8. Since the patient had a breast cancer history differential diagnosis was made with negative staining for GCDFP15, Mammoglobulin, ER, and Cerb B2. PR showed immunopositivity with tumor cells (Figure 2). Inhibin positivity and pale cytoplasm ruled out poorly differentiated adenocarcinoma and small cell carcinoma. A final diagnosis of adult granulosa cell tumor was rendered based on morphology and immunohistochemical stains. The peritoneal washing cytology was negative. The stage of disease was classified as 1A according to FIGO. No adjuvant therapy was suggested. Keeping her on a close follow-up is decided. Tamoxifen therapy is continued since there is no clarity about the relation between tamoxifen use and AGCT. The patient is still in remission for both breast cancer and AGCT. An informed consent form was obtained from the patient.

Discussion

The adult granulosa cell tumor is relatively uncommon cancer type among women cancers [2,4]. Based on a few cases in the literature, it is considered that tamoxifen might play a role in the pathogenesis of AGCT. The studies designed to prove the relationship between tamoxifen use and

Table 1. The clinical and pathological characteristics of the patients

References	Age	Duration of Treatment	FIGO Classification	Mitotic index	ER	PR
Gherman et al.	52	11 months	1c	5	Unknown	Unknown
Arnould et al.	63	4 years	1c	2	-	+
Abhassian et al.	47	5 years	1c	3-5	Unknown	Unknown
Tanaka et al.	58	5 years*	1c	5	-	+
Our current case	57	22 months	1a	13	-	+

*2 years of torefemine use after 5 years of tamoxifen theraphy

uterine sarcomas are first failed due to the rarity of cases [5]. But recently, tamoxifen is known to be a risk factor for uterine sarcomas [1].

To our knowledge, AGCT with antecedent tamoxifen use has been described in only four cases previously. The first case of all was reported by Gherman et al in 1994. It was a 52-old woman with liver disfunction. The authors concluded that the hepatic failure may have resulted in changes in tamoxifen metabolism, therefore AGCT may be developed [6]. The second case was a case of breast carcinoma metastasis within AGCT, reported by Arnould et al in 2002. This time the patient had no signs of hepatic failure [7]. Then in 2010 Abahssain et al reported the third case of AGCT with antecedent tamoxifen use. They presumed that considering worldwide tamoxifen use among women AGCT development might be random [8]. Finally, in 2020, Tanaka et al reported AGCT in a 58-year old female patient with long-term tamoxifen use [9]. We report the fifth case of AGCT in a 57-year old patient after 22 months of tamoxifen use. We also emphasize that the AGCT cases may be incidental. The clinical and pathological characteristics of these patients are summarized in Table 1.

At least in the cases in which we can reach the hormone receptor information, we can see that ER was negative in ovarian GCTs. If tamoxifen acted through only hormone receptors, ER-receptor would have been positive in these GCTs. On the other hand, in 2009 Merglen et al represented that, the risk of death from breast cancer significantly increases in patients with ER-negative breast cancer who were treated with tamoxifen. And they also concluded that, besides its remarkable impact on ER-positive breast cancer, tamoxifen may cause carcinogenesis of ER-negative tumors [10]. Some of the studies demonstrated that tamoxifen's impact on the hormone receptors is not its only mechanism of action. Tamoxifen also can act on growth factor signaling pathways, therefore it can be detrimental effects [11]. Moreover, metabolites like metabolite E and bisphenol derived from tamoxifen can have alternative mechanisms of action for ER-negative cells. For example, Wiebe et al identified metabolite E and bisphenol in tamoxifen resistance MCF-7 human breast tumor implanted in athymic nude mice, as well as tumors from patients with tamoxifen resistance [12]. Due to the multifocal effects of tamoxifen, we think that it may be related to cancers such as AGCT, although it is not certain.

Considering the widespread use of tamoxifen all around the world, among women with breast carcinoma, the development of AGCT

seems to be incidental, but these results show the importance of proper surveillance especially for women on tamoxifen and the early diagnosis of gynecological tumors. Our current case and these results show that it is very difficult to say there is a certain relationship between tamoxifen use and AGCT because of the rarity of the condition

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