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Case Report

Endometrial cancer after tamoxifen-containing adjuvant treatment for breast cancer

Johan Kurnianda[1], Syahru A Setiawan[2]*

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Authors' affiliations:
[1]Division of Hematology and Medical Oncology, Department of Internal Medicine, Sardjito General Hospital, Yogyakarta/
[2]International Graduate Program in Medicine, College of Medicine, Taipei Medical University, Taipei City, Taiwan

Corresponding author:
Johan Kurnianda
E-mail: *johan.kurnianda@yahoo.com*

Abstract

Background: Breast cancer is the most predominant cancer among women globally, including in Indonesia, and has been recognized as a heterogeneous disease. Hormone-receptor positive breast cancer is the major subtypes of breast cancer which expresses estrogen and/or progesterone receptors and has unique characteristics of favorable prognosis despite predisposes to have a higher risk of late recurrence. Tamoxifen is a selective estrogen receptor modulator (SERM) which has become a drug of choice for adjuvant hormonal therapy to reduce the recurrence risk of hormone-receptor positive breast cancer in pre- or postmenopausal women. Therefore, current clinical guidelines recommend to extend the duration of tamoxifen to increase the benefit of reducing the risk of recurrence. On the other hand, the long-term side effects of tamoxifen are also increasing, including the incidence of tamoxifen-induced endometrial cancer.
Case: This case report presents a clinical case of endometrial cancer emerged in a survivor of hormone-receptor positive breast cancer who previously underwent tamoxifen adjuvant therapy.
Discussion: Eventually, this case report may increase awareness of secondary malignancy and review the incidence, underlying mechanism, risk factors, prevention measures, and current management of tamoxifen-induced endometrial cancer.

Keywords: *breast cancer, tamoxifen, endometrial cancer, estrogen receptor, hormonal therapy*

Abstrak

Latar Belakang: Kanker payudara merupakan kanker terbanyak pada wanita di seluruh dunia, termasuk di Indonesia, dan telah dikenal sebagai suatu penyakit yang heterogen. Kanker payudara hormon reseptor positif yang mengekspresikan baik reseptor estrogen dan/atau progesteron merupakan subtipe mayor dari kanker ini dengan karakteristik unik berupa prognosis yang lebih baik tetapi di sisi lain memiliki risiko rekurensi lambat yang cukup tinggi. Tamoxifen merupakan agen modulator anti-estrogen selektif yang menjadi salah satu pilihan utama sebagai terapi hormonal ajuvan untuk menurunkan kejadian kekambuhan pada kanker payudara bertipe hormon reseptor positif baik pada wanita pre- atau pascamenopause. Oleh karena itu, *guidelines* klinis terkini merekomendasikan untuk memperpanjang durasi pemberian tamoxifen untuk semakin menurunkan risiko rekurensi tersebut. Di sisi lain, efek samping jangka panjang akibat tamoxifen juga berisiko meningkat, termasuk di antaranya kejadian kanker endometrium yang diinduksi oleh tamoxifen.
Kasus: Laporan kasus ini menyajikan suatu kasus kanker endometrium yang muncul pada penyintas kanker payudara bertipe hormon reseptor positif dan sebelumnya menjalani terapi ajuvan tamoxifen.
Diskusi: Hal tersebut untuk meningkatkan kewaspaadan akan risiko keganasan sekunder serta membahas kembali mengenai insidensi, mekanisme, faktor risiko, pencegahan, dan manajemen terkini seputar kanker endometrium yang diinduksi tamoxifen.

Kata Kunci: *kanker payudara, tamoxifen, kanker endometrial, reseptor estrogen, terapi hormonal*

Background

Global cancer report in 2018 has highlighted breast cancer as the most predominant cancer among women with incidence number reached to two million cases (24.2%) and mortality rate of six hundred thousand cases.[1] Moreover, breast cancer has been marked as cancer with the highest incidence in Indonesia, with 58000 of new cases and 22000 of dead cases. In addition, the case fatality rate of breast cancer in Indonesia has reached 38.9%, higher than other Southeast Asian countries such as Thailand, Philippines, and Malaysia, which count of 38.1%, 32.5%, and 38.1% respectively.[1] The high case fatality rate is apparently contributed by several factors, including initial presentation of most patients with advanced-stage, suboptimal treatment compared with international standards, and a growing number of younger breast cancer cases.

In the early of 2000, breast cancer has been known as heterogeneous disease, both molecularly and genetically. This has brought breast cancer to be classified into 4 distinct subtypes which are luminal A or B, triple-negative, and human epidermal growth factor receptor-2 (Her-2) overexpressed.[2] Each subtype has different characteristics that requires differential approach.[3] Luminal or hormone-receptor positive breast cancer is the major subtype of breast cancer in which estrogen and/or progesterone become oncogenic drivers.[4] This predominant subtype has a unique biological features, in particular for favorable prognosis but higher rate of late recurrence (after five years of disease). Therefore, recurrent disease is also marked as a critical problem in this subtype without failing to notice the patient's survival.

Tamoxifen has been a pivotal drug as adjuvant hormone therapy for early-stage of breast cancer, both in pre-menopause and post-menopause women, alongside with aromatase inhibitors, and gonadotropin-releasing hormone (GnRH) agonist [2,3]. Several meta-analyses have mentioned tamoxifen to effectively prevent breast cancer recurrence.[5,6] However, late recurrence rate remains high even after a 5-year use of tamoxifen which initiates other trials to extend hormone treatment duration for 10 years to reach an optimum benefit.[6–9] Furthermore, tamoxifen response among young women (<35 years) in term of recurrent reduction is considered deficient and the incident of long-term adverse events such as venous thromboembolism and endometrial cancer is regarded as high.[6,10]

In order to improve awareness of the endometrial cancer risk among tamoxifen user women in breast cancer, this study reported a clinical case of endometrial cancer in a patient previously treated with tamoxifen for breast cancer and reviewed for incidence, risk factor, proposed mechanism, and management, along with preventive measures.

Case Illustration

In the mid of 2002, a 42-year-old, pre-menopause woman came to Sardjito General Hospital and complained about a lump palpated in left breast for 5 years. Initially, the lump only felt pain in each of her period, but later progressed into a constant pain. Mass diameter of approximately 2-2.5 cm. With a favorable initial Karnofsky performance status of 90%, lumpectomy was then performed and biopsy concluded as ductal infiltrative breast cancer. Mammography of her right breast found insignificant findings. The breast cancer was then concluded as stage IIIA T3N1M0. Subsequently, the patient received adjuvant chemotherapy with CAF regiment (Cyclophosphamide, Doxorubicin, and Fluorouracil) for 6 cycles. After adjuvant chemotherapy, the patient underwent routine follow-up of abdominal and breast sonography which was found to be normal.

The patient has remained disease-free for three years until she complained a new lump on her left breast. The lump was then evaluated by sonography which was suggested as a residual mass, and performed fine-needle aspiration biopsy (FNAB) which was found malignant cells, giving a conclusion of relapsing breast cancer. A modified-radical mastectomy (MRM) procedure was performed, with the biopsy resulted in moderate differentiation of ductal infiltrating carcinoma. No metastases were found in the contralateral breast or other organs. Immunohistochemistry examination resulted positive expression of estrogen and progesterone receptors in approximately 35% of the tumor cell population, but negative in Her-2 (figure 1, 2, and 3). The patient then received second-line chemotherapy with paclitaxel and carboplatin for 6 cycles and radiotherapy with total dose of 30 Gy. After chemoradiotherapy, patients were initiated tamoxifen adjunctive therapy for 5 years (2006-2011). Routine control was performed including breast and abdominal sonography which resulted insignificant result, and assessment of CA 15.3 and CEA level reached within normal range. Abdominal sonography surveillance during tamoxifen therapy found no abnormalities in the uterus including the size of uterus. Patient was again declared to achieve disease-free after the first episode of relapse.

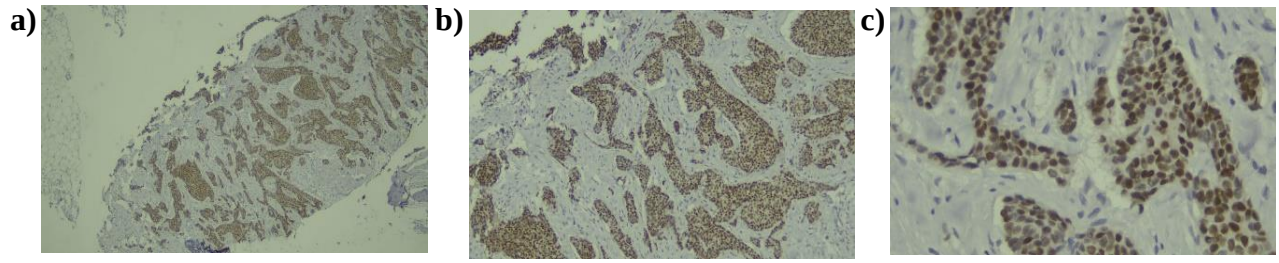

Figure 1. Estrogen receptor showed positive expression in ± 35% of tumor cells in breast cancer case, (a) low magnification, (b) medium magnification, (c) high magnification.

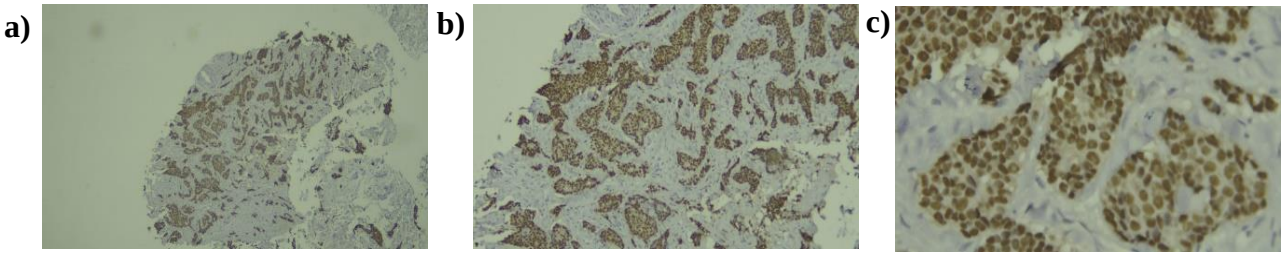

Figure 2. Progesterone receptor showed positive expression in ± 35% of tumor cells in breast cancer case, (a) low magnification, (b) medium magnification, (c) high magnification.

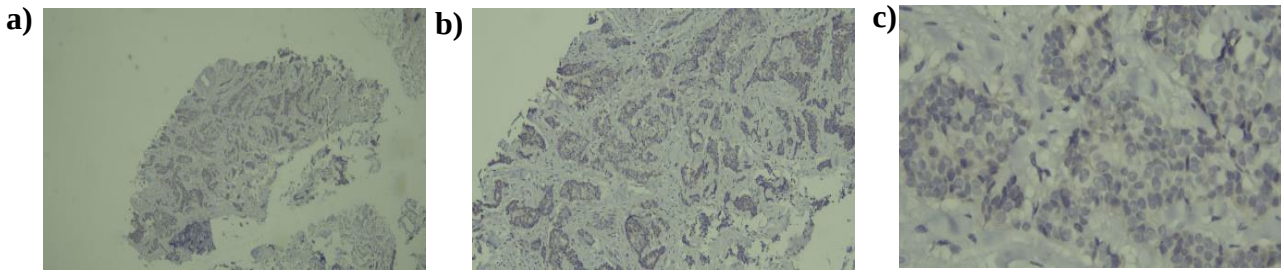

Figure 3. Her-2 Receptor showed negative expression among tumor cells in breast cancer case, (a) low magnification, (b) medium magnification, (c) high magnification.

Within a year after previous use of five-year tamoxifen, the patient, who at the time has achieved post-menstrual status, complained episode of heavy vaginal bleeding for 5 months, with gynecological evaluation was found a lesion on the cervical portion. Pap smear examination showed low-grade squamous intraepithelial lesion (LSIL) and continued with cervical biopsy concluded endometrioid carcinoma nuclear grade 3. During this moment, the Karnofsky performance status was 90%. Total Abdominal Hysterectomy and Bilateral Salpingo-oophorectomy (TAH-BSO) procedure were then performed on the patient. Uterine biopsy showed a poorly differentiated adenocarcinoma which invaded into myometrium, without the involvement of adnexa and omentum (figure 4), and later concluded as stage II T2N0M0 of endometrial carcinoma. Patient received 6 cycles of adjuvant chemotherapy with carboplatin. After chemotherapy, the patient underwent surveillance of abdominal and breast sonography, in addition to assessment of CEA, CA 125, and CA 15-3 which fell within normal range. Patient has remained in disease-free for breast cancer and endometrial cancer until her last recent visit in February 2020 (8 years for endometrial cancer, 15 years for breast cancer).

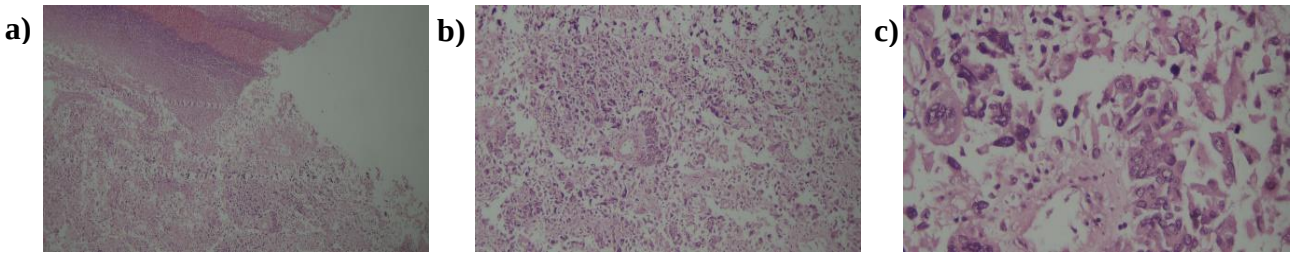

Figure 4. Pathological examination of uterine showed poorly differentiated adenocarcinoma, (a) low magnification, (b) medium magnification, (c) high magnification.

Discussion

The incidence of endometrial cancer among breast cancer patients with known using tamoxifen for hormonal treatment is considered rare and varies within studies, for about 2-8 per 1000 women.[6,11,12] Indeed, there is no specific study on the incidence of endometrial cancer related to tamoxifen in Indonesia. The estimated risk of endometrial cancer in breast cancer patients with tamoxifen use is also wide-ranging with a significant result reported by prospective study of tamoxifen (RR 2.53; 95% CI 1.35-4.47). Moreover, the risk is considered to be higher among patient over 50 years (RR 4.01; 95% CI 1.70 - 10.90).[12] On the other hand, most retrospective studies do not provide significant results for tamoxifen as a risk factor associated with endometrial cancer, seemingly due to limited number of endometrial cancer events compared with prospective studies.[11,13]

Tamoxifen is a selective estrogen receptor modulator (SERM) which has been proved to effectively reduce breast cancer recurrence and the risk of contralateral breast cancer events significantly. Five years of tamoxifen therapy could reduce the risk of relapse after 10 years by 37% among women aged 50-59 years, and as much as 54% among women aged 60-69 years.[14] In breast tissue, tamoxifen will provide anti-estrogen effects by blocking estrogen receptors (ER), thereby inhibiting the growth of estrogen-dependent breast neoplastic cells. On the other hand, the agonistic effects of estrogen would be seen in other tissues that also have estrogen receptors, including endometrial tissue which is stimulating both benign and neoplastic transformation.[15]

Tamoxifen selectively induces estrogen receptors with different characteristics between alpha estrogen receptors (α-ER) and beta (β-ER). The underlying mechanism of tamoxifen in breast cancer originates from the antagonistic effect of α-ER on breast tissue, but its agonistic effect via endometrial β-ER is related to hyperplasia and malignancy, even atypia in the endometrium.[16] Heterogeneity of this effect cannot be explained yet, but a proposed theory states that it depends on endogenous estrogen circulation. In an estrogen-rich environment, tamoxifen could act as a primary antagonist, while in an environment lacking of estrogen, the primary effect tends to be agonistic rather than antagnositic.[14,15,17]

Use of tamoxifen for three years or more is known to have a significant risk of endometrial cancer (OR 2.94; 95% CI, 2.13-4.06) which represents prolonging duration of estrogenic stimulation to endometrium.[18,19] In addition, women older than 35 years are also posed a higher risk of endometrial cancer (OR 4.08; 95% CI 1.67 - 9.93). However, other factors such as previous hormone exposure, hypertension, and diabetes insignificantly increase the incidence of endometrial cancer among breast cancer patients receiving tamoxifen.[18] In line with previous statement, both age factor and duration of tamoxifen therapy, which are confirmed within this case, are presumed to increase the patient's risk of endometrial cancer.

Heavy vaginal bleeding or menorrhagia is the main symptom and accounts for 62% of endometrial carcinoma among previous use of tamoxifen which was also presented in this case.[19] On the other hand, abnormality or any changes in term of uterine enlargement is rarely presented in tamoxifen-induced endometrial carcinoma. Instead, the previous sign is frequently presented in more benign cases such as leiomyomatosis, adenomyosis, and uterine polyp as also being other implications of tamoxifen-driven estrogenic stimulation in endometrium.[19–21] Thus, it seems to be fairly difficult to conduct surveillance of endometrial cancer among tamoxifen user sonographically.

The endometrial cancer presented in this case was staged as FIGO II and T2N0M0. The management was conducted with total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO),

followed by adjuvant chemotherapy with carboplatin for six cycles. NCCN Guidelines has recommended surgical procedure in resectable endometrial cancer, followed by adjuvant radiotherapy by using extended-beam radiotherapy (EBRT) with or without systemic chemotherapy in FIGO stage II.[22] Generally, endometrial cancer is classified into two Bokhman's subtypes. The first type which is often referred as endometrioid, which is occurred in this case, is an estrogen-dependent and has more favorable prognosis with 5-year overall survival (OS) of around 85%. In contrast, the second type, known as non-endometrioid types (including, serous and clear-cell) is more estrogen-independent type and frequently has worse prognosis with 5-year OS of around 55%.[23]

Extending tamoxifen duration from five to ten years has been shown to reduce breast cancer recurrence, for which NCCN guidelines has considered extending hormonal treatment for pre- and postmenopausal women with breast cancer.[7–9,24,25] Nevertheless, the consequence is also detrimental which is reported by other studies regarding the doubling risk of endometrial cancer when tamoxifen is extended to another five years.[24] Therefore, any measures to prevent or decreasing the cancer risk is invaluable in this scenario.

At present, the consensus issued by ESMO-ESGO-ESTRO still does not recommend routine surveillance of endometrial cancer other than routine gynecological care in pre-menopausal tamoxifen user women. However, postmenopausal women using tamoxifen are expected to be informed regarding long-term adverse events and also the cancer risk with providing to report any symptoms and signs that are correlated with endometrial hyperplasia or cancer such as vaginal bleeding.[26,27] Other clinical evidence of any measure to reduce the risk of endometrial cancer is still absent. For instance, a trial to combine tamoxifen and medroxyprogesterone has not been proven to effectively protect against endometrial carcinoma due to lower incidence of endometrial cancer than expected which is unable to make a robust conclusion.[28]

The evaluation of endometrial cancer among pre- and postmenopausal women is different. Generally, it requires transvaginal ultrasonography (TVS) and/or endometrial sampling. Women on tamoxifen therapy who have abnormal uterine bleeding (AUB) or are known to have endometrial thickening sonographically require pathological evaluation of the uterus. Endometrial thickness ≤ 4 mm based on TVS results in postmenopausal woman is sufficient to exclude endometrial cancer. However, a thickness of more than previous cut-off in post-menopausal women who are known as tamoxifen users is recommended to have an endometrial biopsy rather than TVS alone. Due to limitation of endometrial biopsy in detecting focal pathology, it is necessary to do a hysteroscopic endometrial biopsy along with TVS.[29]

Conclusion

Tamoxifen is still being drug of choice as hormonal therapy that is effectively reducing recurrence risk for hormone-receptor positive breast cancer. Due to this success, tamoxifen therapy has been extended from five to ten years. However, recent finding notifies for the doubling risk of endometrial cancer along with extension of tamoxifen therapy. Therefore, the risk must be properly handled, including screening, diagnosis, and management of endometrial cancer among women using tamoxifen. Clinical evidence in preventing the risk of endometrial cancer is still demanding to mitigate the risk along with arising practices of extending tamoxifen duration among breast cancer survivor.

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Conflict of Interest

The authors have no conflict of interest to declare.

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