A Case Report of Double Primer Cancer: Malignant Phyllodes Tumor and Invasive Ductal Carcinoma

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INTRODUCTION

In some cases, multiple primary malignancies are common, and the number has been increasing due to improvements in diagnostic technology [1]. Nevertheless, multiple primary malignancies have happened in multiple organs. Billroth described this phenomenon at the end of the nineteenth century, and several cases of double or triple primary malignancies have been reported since then [2]. Epidemiological studies have shown the frequency of some area codes in the range of 2–17% [3]. The interval between those tumors diagnosed divides into two categories that are synchronous malignancy and metachronous malignancy. Secondary tumors that appeared at the same time as or within six months of the first malignancy were referred to as synchronous malignancies, and secondary tumors that occurred more than six months after the first malignancy were referred to as metachronous malignancies [1].

The most common area of primary tumors is in the head and neck (34.15%), followed by gynecologic cancer (21.95%), breast (17.07%), lung cancer (14.9%), esophageal cancer (7.3%), and then other tumors (14.6%). Of the secondary malignancies, breast cancer (21.95%) and gastrointestinal tract (21.95%) are the most common, and lung cancer (17.07%) and gynecologic cancer (12.20%) followed [1]. One case of double primary cancer is often found in melanoma. Patients with cutaneous melanoma (CM) include primary-secondary malignancies, especially secondary primary melanoma, lymphoma, and various other cancers (breast, thyroid, or prostate). It has been reported that the risk is high [4].

Multiple primaries have been reported in patients with breast cancer in the range of 4.1% to 16.4%. The median time from the first malignancy to the second malignancy was five to eight years [3]. Many risk factors have been identified, including early onset menstruation, late menopause, childbirth, and family history. First-
degree relatives are about twice as likely to develop the disease. Many highly permeable breast cancer susceptibility genes include BRCA1 and BRCA2. These genes increase the risk of breast and ovarian cancer. P53 (Li Fraumeni Syndrome) and PTEN (Cowden Syndrome), two genes linked to rare cancer syndromes, have also been linked to an increased risk of breast cancer [5]. For the breast, the percentage of a double primary is 10% [6]. This study presents a case of a double primary tumor that occurred in the same organ and is the synchronous malignancy that rarely happens these days.

CASE PRESENTATION

The patient was a 45-year-old woman with a breast lump in the right breast near the armpit in the last five years. The initial size of the lump was about a grape size, painful, and enlarged slowly. At the end of 2020, a lump appeared on the left breast around 12 o’clock. The left lump widened faster, with an initial size as big as a corn seed and grown as big as a ping pong ball. The patient claimed no history of pregnancy during her 18 years of marriage. Also, the patient used no hormonal contraception and had no history of breast cancer in her family. The patient had regular monthly menstruation but always be accompanied by pain in the breast, starting from two weeks before until the end of menstruation.

Physical examination found asymmetrical breasts, right and left breast mass, left lump size 3 x 2 x 3 cm, right lump size 4 x 2 x 4 cm, non-mobile consistency, and not-clear boundaries. The patient had no enlargement of lymph nodes. Sores, nipple retraction, and peau d’orange appearance were denied.

The patient did a mammary ultrasound examination at Indriati Hospital in February 2021 (Figure 1). On the right mammary examination, the lesion appeared solid, multiple, lobulated, and conglomerated with an irregular border. The lesion was located around 9 o’clock with a size ± 4.34 x 2.23 x 4.08 cm (Birads 4A). On the left mammary examination, the lesion appeared solid and immobile, with an irregular border and regular contours. The lesion was located at the upper outer of the left mammary with a size ± 2.82 x 2.12 x 2.96 cm (Birads 4C). Thus, from the ultrasound examination, the patient decided to pursue a biopsy of the mentioned lesion.

The patient underwent a right mammary biopsy at Indriati Hospital on February 2021. On the microscopic view, the lesion showed mesenchymal tumor tissue composed of spindle cells, infiltrative, atypical cells, and pleomorphic with round, oval, and spindle with binucleated and multinucleated, coarse chromatin and myxoid stroma between the swollen connective tissues and glands with partially differentiated rhabdoid cells (Figure 2). Macroscopic examination showed one piece of tissue with I-IV thread markings measuring 6.5 x 5 x 2 cm, white color, supple. Cleavage obtained a mass size of 2.5x2x5.5 cm. The examination concluded that the patient had a malignant phyllodes tumor with Rhabdoid differentiated on the right mammary (Figure 3). The patient’s cancer stage was T2N0.

Figure 1. Ultrasound Examination at Indriati Hospital on February 2021. (A) Right breast; (B) Left breast

Figure 2. (A) Histopathology slide of infiltrative ductal carcinoma; (B) Histopathology of malignant phyllodes.

Figure 3. (A) Right Mammary Biopsy at Indriati Hospital in February 2021; (B) Left Mammary Biopsy at Indriati Hospital in March 2021

Figure 4. Clinical appearance after undergoing mastectomy surgery on both breasts
The patient received three chemotherapy cycles with paclitaxel and epirubicin since April 9, 2021, along with mastectomy surgery of the left breast in June 2021. In addition, the patient received another three cycles of chemotherapy with the same antineoplastic agents and completed on August 13, 2021, followed by mastectomy surgery of the right breast in September 2021.

Definitive treatment was done to the patient, and currently, she is under evaluation post-surgery. So far, for nine months postoperatively, the patient has not felt any significant complaints and has not complained of any residing lumps on both breasts (Figure 4).

DISCUSSION

This report tells cases of patients with two histologically distinct malignancies. Since some patients had no family history of malignant tumors, the researchers were urged to consider the presence of inherent and extrinsic risk factors that could explain the sporadic occurrence of double primary cancer. The most important hazard factors for double primary cancer are tobacco, alcohol, or radiation exposure. The second primary breast cancer can be synchronous or metachronous in the contralateral breast. Most are metachronous. Meta synchronous breast cancer accounts for 5% to 6% of cancer cases and about 1% to 2% of women with breast cancer [7].

Breast cancer patients have been reported to have multiple primary tumor incidence rates ranging from 4.1% to 16.4%. The median time for secondary malignancies was between five and eight years, but this case shows that the secondary malignancy happened almost simultaneously. Double primary cancer is a synchronous category rarely reported in the literature. Reproductive or hormonal and hereditary variables (e.g., BRCA1, BRCA2) and corpulence are common chance variables for double primaries [3]. One study revealed that the prevalence of primary doubles varied from 1% in the initial liver primary to 16% in the initial bladder primary. In the case of breasts, the percentage of double primary is 10% [7].

The breast is one of the anatomical sites of most cancers classified because of the world-main threatful neoplasm and nonetheless disadvantageous for some of the damaging effects of desperation in a woman [8]. The pathway of breast malignant neoplastic disease is multidimensional and inefficaciously learned; however, the bound disposal of a variable is known. Advancing age and female gender are the most common predisposing factors. Genic changes, especially BRCA 1 and 2, make up 10% of breast cancers [9]. Other rare but highly permeable genes include PTEN, TP53, CDH1, and STK11, each leading to a different clinical syndrome [10].

Phosphatase and tensin homolog (PTEN) localized on chromosome 10 (10q23.3) and recognized as tumor suppressor genes. It acts as an inhibitor of the PI3K/AKT/mTOR signaling pathways that control angiogenesis and cell proliferation [11]. Mutations of PTEN are related to an elevated risk of malignant and benign tumors [12]. Loss of PTEN activity increases the phosphorylation of various cellular proteins, affecting growth, migration, and apoptosis [13]. To diagnose the mutations of PTEN, DNA was extracted from peripheral blood leukocyte samples. Germline variants were assessed in PTEN exons (along with the intron-exon boundary) by PCR and sequencing [14].

Epithelial cadherin (CDH1) is a member of classical cadherin (the others are Neural cadherin (N-cadherin) and Vascular Endothelial cadherin (VE-cadherin)). These single-pass transmembrane glycoproteins are found in many tissues and play a role in Ca2+- dependent intercellular adhesion [15]. Immunohistochemical staining is used to diagnose [16]. Understanding how cadherin affects cell behavior can help regulate cadherin activity and design potential therapeutic interventions to prevent tumor cell growth, infiltration, and metastasis. The therapeutic target may be epigenetic E-cadherin activation or N-cadherin inactivation. In diverse types of cancer, increased infiltration is associated with the downregulation of the gene encoding E-cadherin (CDH1). The CDH1 promoter is hypermethylated in human breast cancer, hepatocellular carcinoma, and prostate cancer. Decreased DNA methylation in mouse models of colorectal tumors has been reported to result in inhibition of tumor growth. Therefore, it may be a new target for cancer treatment. For example, thymine DNA glycosylase (TDG) directly targets specific sequences of DNA, causing local DNA demethylation at key regulatory sequences and enhancing gene induction. Another idea is to target the intramembrane proteases of the rhombic family RHBDL2 to regulate the migration of cancer cells by E-cadherin functional inactivation [17].

The pathophysiology of multiple primary malignancies has been proposed as a combination of common-carcinogen-induced multiple cancers in an exposed epithelial surface, known as “field-cancerization,” and a genetic predisposition to neoplasia [6]. A combination of some factors contributes to multiple cancers in most patients. Genetic predisposition for double primary breast cancer can be seen with germline mutation BRCA1/2 and possibly other mutations. After ten years of breast cancer diagnosis, 30% of patients with this mutation would be diagnosed with contralateral breast cancer [18].

In common, malignant phyllodes growth are one-sided and unifocal. However, some may be as reciprocal and multifocal lesions. Histologically, malignant phyllodes neoplasm is biphasic fibroepithelial tumors comprising the tissue and stromal parts. The epithelial ducts are organized into crevices and cystic structures surrounded by a leaf-shaped stroma. The stromal component shows different histological manifestations. In general, the
stroma of benign phyllodes malignant tumors shows regular spindle-shaped fibroblasts. In contrast, the stroma of phyllodes malignant tumor usually has high cellular atypia, expanded stromal cellularity, and mitotic number. From alternative perspectives, chronic changes are often seen together with bleeding, cystic degeneration, and sphacelus [19].

USG and mammography are applied as preparatory imaging modalities. MRI can be applied in particular circumstances, including in sufferers with thick breasts and people with records of breast cancer. These individuals are being assessed for contralateral contamination and people with a high-chance danger of breast cancer. MRI also can be used for operative designing of carcinoma confirmed by a diagnostic test or evaluating dense breasts, contralateral lesions, or patients with previous breast surgery or radiotherapy. Imaging can distinguish skin changes common in fiery breast cancer more precisely than skin intrusion [9]. A tissue diagnostic assay confirms the disease. Samples may be obtained by connective tissue ultrasound-guided core needle biopsy, excision biopsy, stereotactic biopsy, or MRI-guided biopsy. The biopsy results can contain data on growth grade, immunohistology, and Oncotype DX breast return score [9].

The microscopic appearance of infiltrative ductal carcinoma is highly variable. The degree of tumor cellularity, growth pattern, the extent of associated in situ carcinoma component, degree of cytologic atypia, mitotic activity, amount of stroma, presence or absence of necrosis, and the presence and amount of lymphocytic infiltrate in the stroma. Among tumor cells, all differ significantly between tumors. Most infiltrative ductal carcinoma show dilated ducts with intermediate and high-grade ductal carcinoma in situ of cribriform and micropapillary type with microcalcification. In this patient, the lesion showed epithelial tumor tissue composed of solid, trabecular, papillary, tubular, infiltrative, atypical cells, pleomorphic, eosinophilic cytoplasm, round nucleus, oval, vesicular, and coarse chromatin. Nucleus clear with stroma desmoplastic and partially myxoid. The closest distance from the operating limit is 5 mm.

Phyllodes tumors show an increase in intratumoral growth patterns with leaf-like appearance into variously dilated elongated lumens. The epithelial component consists of luminal and myoepithelial cells that extend into arched columns and overhang the interstitial leaves [20]. In this patient, the lesion showed mesenchymal tumor tissue composed of spindle cells, infiltrative, atypical cells, and pleomorphic with round, oval, and spindle with binucleated and multinucleated, coarse chromatin and myxoid stroma between the swollen connective tissues and glands with partially differentiated rhabdoid cells.

In this case, the interdisciplinary team decided to begin neoadjuvant chemotherapy to reduce the two tumors and achieve better local disease control, followed by the definitive therapy of mastectomy of both breasts. The therapy was chosen to ensure the patient’s more prolonged survival and better prognosis. The limitation of this study is that the patient is still in the evaluation period of post-operative treatment and has not been subjected to a detailed genetic examination.

CONCLUSIONS

This case highlighted multiple primary cancers that are common these days, especially in the same organ, the breast. Nevertheless, medical literature rarely presents a case of synchronous malignancy, prompting us to publish this case. With improved cancer treatment and more prolonged survival, the number of patients with double cancers is increasing.

DECLARATIONS

Ethics approval and consent to participate
All participating patients provided written informed consent.

Competing interest
The authors declare no competing interest in this study.

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REFERENCES