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Giant malignant phyllodes tumor of the breast: A rare case report and literature review

MIN LIU[1*], SHUO YANG[1*], BIN LIU[2], LIANG GUO[3], XUEYING BAO[1], BAILONG LIU[1] and LIHUA DONG[1]

Departments of [1]Radiation Oncology, [2]Hand Surgery and [3]Pathology, The First Hospital of Jilin University, Changchun, Jilin 130021, P.R. China

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Abstract. Malignant phyllodes tumor of the breast (MPTB) is rarely encountered in clinical practice. Preoperative diagnosis is challenging due to nonspecific radiological and histological features, and the prognostic factors and optimal treatment remain controversial. The current report describes the case of a middle-aged female with giant MPTB who underwent multidisciplinary intervention, including surgery, postoperative chemotherapy and radiotherapy. To date, the disease-free survival (DFS) of the patient has reached 18 months. Furthermore, a related literature review summarize the clinicopathological characteristics and treatment progress regarding MPTB is presented, along with an analysis of the indications for therapeutic strategy in the current case. In the future, multi-center clinical trials must be initiated to identify the criteria for diagnosis and optimal treatment consensus for MPTB. In conclusion, the present case highlights that multi-disciplinary management may contribute to DFS following the treatment of giant MPTB.

Introduction

Malignant phyllodes tumor of the breast (MPTB) is a rare but distinct clinicopathological entity. MPTB typically occurs in middle-aged women (1), and has an average annual age-adjusted incidence of 2.1 per million females (2). As far as the etiology is concerned, Li-Fraumeni syndrome (germline TP53 mutation) has been reported to increase the risk of phyllodes tumors (3,4). Surgery is the typical initial treatment option for MPTB and radiotherapy is recommended for individuals with a high local recurrence risk. Chemotherapy is used to treat patients with a high systemic metastatic risk (3). Given its rarity, decisions regarding treatment options are based on small-scale retrospective clinical trials or case reports (5,6,7). A rapidly-growing breast mass is the most typical symptoms of MPBT and postoperative pathology is the most accurate method of diagnosis (3). Surgery is regarded as the primary method of management of MPBT. The clear margin achieved by surgery rather than the surgery type (breast conserving surgery or total mastectomy) determines the local recurrence rate (6). The five-year disease-free survival (DFS) is 60-90% (6). A previous study observed that 14.3% of patients died of metastatic MPTB 5 years following initial diagnosis (6). To date, the optimal intervention strategy has not been established. Herein, the case of a giant MPTB (the postoperative specimen measured 14.5x10.5x4.5 cm), in which surgery, adjuvant chemotherapy and radiotherapy was performed, is presented. Written informed consent was obtained from the patient for the publication of her data in the present case report. In addition, the related literature was reviewed in order to expand our understanding of this unique breast malignancy.

Case report

A 43-year-old female was referred to The First Hospital of Jilin University in August, 2014 with a history of a painless lump in the right breast for 9 months. She had no other discomfort. Her past history was unremarkable, except allergies to starch and penicillin.

On physical examination, a large firm mass measuring about 11x4.5 cm was palpated in the upper outer quadrant of right breast. A skin ulcer of 1.4 cm was present on the surface of the mass. In the bilateral supra- and subclavicular regions and axillas, there were no palpable enlarged lymph nodes.

Laboratory investigations revealed that the complete blood cell count and serum biochemical profile were normal. Ultrasound (Philips iU22; Philips Medical Systems, Inc., Bothell, WA, USA) of the breast demonstrated an 11.2x4.54-cm, heterogeneous, hypoechoic mass in the upper outer quadrant of right breast with blood flow. Mammography (Selenia Dimensions mammography system; Hologic Corporation, Bedford, MA, USA) also revealed an 11.0x4.5 cm irregular mass of high density. The BI-RADS stage (8) was determined to be 4B due to the observations of an unclear border and irregular lesion

Correspondence to: Dr Bailong Liu or Dr Lihua Dong, Department of Radiation Oncology, The First Hospital of Jilin University, 71 Xinmin Street, Changchun, Jilin 130021, P.R. China
E-mail: bailong3385@163.com
E-mail: lijie200461@126.com

*Contributed equally

Abbreviations: BCS, breast conserving surgery; MPTB, malignant phyllodes tumor of the breast; PT, phyllodes tumor

Key words: malignant phyllodes tumor, breast, radiotherapy

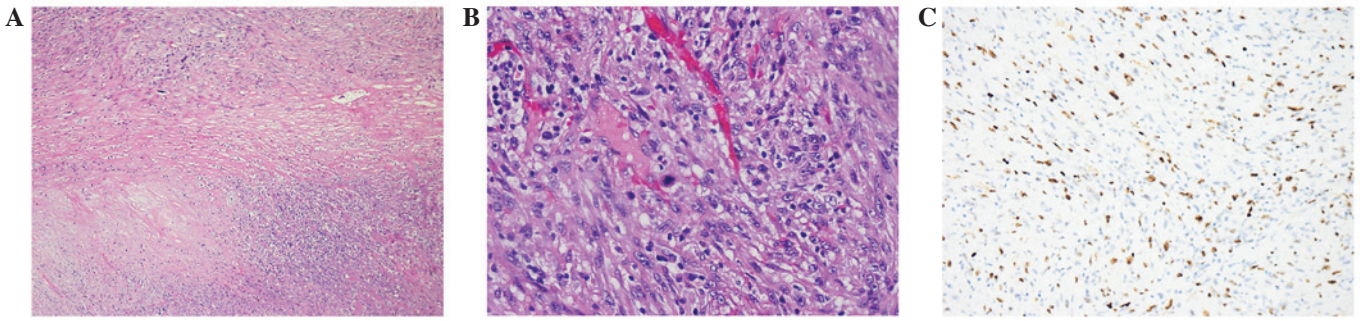

Figure 1. Pathological results of the postoperative specimen. (A) The tumor showed apparent necrosis (H&E staining; magnification, x100). (B) The neoplastic cells demonstrated a high mitotic rate (2-5 per high-power field), indicating highly aggressive behavior (H&E staining; magnification, x400). (C) Ki-67 was positive in the nuclei of 30% of the neoplastic cells (immunostaining; magnification, x200). H&E, hematoxylin and eosin.

shape revealed by the ultrasound. The subsequent biopsy indicated mesenchymal malignancy, as hematoxylin and eosin staining revealed spindle neoplastic cells and immunohistochemistry demonstrated Ki-67 (30%+) and AE1/AE3 (-). An abdominal ultrasound and bone scan yielded unremarkable results.

The patient's performance status was evaluated as 1 based on Eastern Cooperative Oncology Group criteria (9). The patient subsequently underwent a simple mastectomy plus sentinel lymph node biopsy. Biopsy and postoperative specimens were fixed in formalin, embedded in paraffin, sliced and stained by hematoxylin and eosin (10). Immunohistochemistry was performed using the dex-tran-polymer method (EnVision+; Dako, Glostrup, Denmark) (10) using the following monoclonal mouse anti-human antibodies against Ki-67 (dilution, 1:200; catalog no., RMA-0542), AE1/AE3 (dilution, 1:200; catalog no., MAB-0049), cluster of differentiation (CD)34 (dilution, 1:200; catalog no., MAB-0034), desmin (dilution, 1:200; catalog no., MAB-0055), leukocyte common antigen (LCA; dilution, 1:200; catalog no. MAB-0037), smooth muscle actin (SMA; dilution, 1:200; catalog no., MAB-003), estrogen receptor (ER; dilution, 1:200; catalog no., MAB-0062), S-100 (dilution, 1:200; catalog no., RAB-0150), CD68 (dilution, 1:200; catalog no., MAB-0041) and cytokeratin (dilution, 1:200; catalog no., MAB-0049). All the antibodies were purchased from Fuzhou Maixin Biotechnology Development Co., Ltd., Fuzhou, China. Goat anti-mouse IgG horseradish peroxidse-conjugated secondary antibodies (MaxVision™ kit; catalog no., KIT-5010/5020/5030; Fuzhou Maixin Biotechnology Development Co., Ltd.) were incubated with the samples according to the manufacturer's protocol. The 3,3'-diaminobenzidine chromogenic reagent kit was also purchased from Fuzhou Maixin Biotechnology Development Co., Ltd., and used according to the manufacturer's protocol. The postoperative pathology revealed a high-grade malignant phyllodes tumor with multifocal necrosis (Fig. 1A). The primary tumor measured 14.5x10.5x4.5 cm, with involvement of the skin, tissue beneath the nipple and superficial fascia, and a high mitotic rate (2-5 per high power field; Fig. 1B). There was no evidence of lymphovascular or neural invasion. The final immunohistochemistry results demonstrated a Ki-67 index of 30%+ (Fig. 1C); negative reactivity for cytokeratin, AE1/AE3, CD34, desmin, LCA, SMA and ER(-); and diffuse positive reactivity for S-100 and CD68. Two sentinel lymph nodes proved negative for metastasis.

Postoperatively, 4 cycles of chemotherapy were administered. The first 2 cycles were as follows: Pirarubicin, 80 mg (50 mg/m^2), day 1; cyclophosphamide, 800 mg (500 mg/m^2), day 1; and liposomal paclitaxel, 270 mg (175 mg/m^2), day 2. The 3rd and 4th cycles consisted of the following: Pirarubicin, 70 mg, day 1; cyclophosphamide, 700 mg, day 1; liposomal paclitaxel, 270 mg, day 2. Prophylactic chest irradiation was subsequently performed, with a dose of 60 Gy/30 fractions. To date, the patient has a good quality of life and has demonstrated DFS for 18 months.

Discussion

Phyllodes tumors (PTs) are rather rare entities, accounting for only 1% of all breast tumors (1). In 2003, the World Health Organization classified PTs into three subtypes, designated benign, borderline and malignant, according to various clinicopathological characteristics, including the degree of stromal cell atypia and stromal overgrowth, tumor necrosis, the status of mitosis and the tumor margin. (11-13). An extensive literature review was performed in the Pubmed database (www.ncbi.nlm.nih.gov/pubmed) using the following key terms: 'Malignant phyllodes tumor and breast'. The search was performed on the titles of English language articles published between 1993 and 2015. The relevant literature was studied to gain a full-scale understanding of MPTB. In the United States, ~500 new MPTB cases are diagnosed annually (14). A fast-growing breast mass is the most common manifestation. Giant MPTB can lead to the development of hypoglycemia, which results from increased insulin-like growth factor 2 levels produced by the tumor (15,16). Metastasis from MPTB occurs in 6.2-25% of cases (17), most frequently metastasizing to the lung, bone and liver (18,19).

Imaging procedures, such as ultrasound and mammography, are barely able to differentiate PT from fibroadenoma (3,20). In a previous study, mammography diagnosed PT in only 32% of cases (20). In addition, fine needle aspiration cytology or even core biopsy are usually inadequate for accurate diagnosis of PT (20). According to the report by Salvadori *et al* (20), cytology was performed on 30 patients in their study, and was suggestive of PT in only 4 cases.

Surgery is the primary option for the treatment of MPTB. For a long time, the extension of resection, namely the choice between breast-conserving surgery (BCS) and mastectomy,

has remained controversial. Wide resection with clear margins of ≥1 cm has been recommended (21,22). However, research by Belkacémi *et al* (23) revealed that, for borderline and malignant PTs of the breast, total mastectomy was superior to BCS in order to guarantee adequate safe margins. Mituś *et al* (6) supported that a tumor-free margin of ≥1 cm is critical for favorable local control following mastectomy or BCS. MPTB has a propensity for rare metastasis to the axillary lymph nodes, described in <10% of cases; therefore, axillary dissection is not routinely performed (24,25).

Positive surgical margins and large primary tumor have been proved to be poor prognostic factors for local recurrence (1). For patients with MPTB measuring >2 cm after lumpectomy, or tumors >10 cm after mastectomy, adjuvant radiotherapy is strongly recommended to control the high local relapse rate of ≥15% (26). Barth Jr *et al* (14) held the view that, for all the borderline and malignant breast PTs after margin-negative BCS, radiotherapy should be initiated. In their multi-institutional study, despite a median negative margin of 0.35 cm after BCS, the local relapse rate was unexpectedly high at 21%. Postoperative radiotherapy was effective in reducing the local recurrence, which is considered to be a strong indicator of distant metastases (23,26,27) and is associated with significantly increased risk of mortality (26). Furthermore, given the fact that the most common local relapses occurred in the site of initial resection by BCS, partial breast irradiation may be as effective as whole breast irradiation (14). In the current case, the giant primary tumor (14.5x10.5x4.5 cm) and close margin (involvement of superficial fascia) indicated a high risk of local recurrence, making timely radiotherapy important for local control. Radiotherapy is also an effective treatment for symptomatic metastases of MPTB (28).

To date, the role of adjuvant chemotherapy remains controversial; cisplatin and etoposide, and ifosfamide alone or in combination with doxorubicin have been proven to be effective (29,30). For large tumors (>5 cm) or recurrent MPTB, chemotherapy is beneficial (29). The epithelial element of PT partially expresses ER (58%) or progesterone receptor (75%); however, there is no evidence that endocrine therapy is beneficial for treating PTs (31).

In conclusion, MPTB is a rare entity with distinct clinicopathological features. There is no established consensus regarding the optimal type of surgery and indications for radiotherapy and chemotherapy regimens. In the current case of a giant MPTB, multidisciplinary interventions contributed to favorable outcomes. In the future, large-scale multi-institutional clinical trials should be launched to clarify the indication for radiotherapy for MPTB.

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