

Case Report



Bilateral Metachronous Paget's Disease of the Accessory Breasts in a Male

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OPEN ACCESS

Received: Apr 23, 2020

Accepted: May 21, 2020

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Conflict of Interest

The authors declare that they have no competing interests.

ABSTRACT

Bilateral axillary Paget's disease in men is a rare occurrence with limited reports on its diagnosis, treatment, and prognosis. Here, we report the case of a 55-year-old Korean male, who presented with a palpable mass and eczematous skin lesion on the left axilla. An incisional biopsy and histopathologic examination indicated invasive ductal carcinoma with Paget's disease arising in the accessory breast. Magnetic resonance imaging and positron emission tomography revealed no malignancy in the normal breast and other organs. The patient was subjected to a wide excision, wherein the left axillary lymph node was dissected, followed by the administration of adjuvant chemotherapy and radiation therapy. After 17 months of disease-free survival, the patient was diagnosed with Paget's disease of the contralateral accessory breast. He underwent wide excision surgery along with radiation therapy. To the best of our knowledge, this is the first report of bilateral extramammary Paget's disease in a male.

Keywords: Axilla; Breast neoplasms, male; Paget's disease, mammary

INTRODUCTION

Male breast cancer is a rare disease, accounting for approximately 0.5% of all breast cancer cases in South Korea. The incidence of accessory breast cancer in men is even lower, and only a few cases have been reported [1]. The scant prevalence of the ailment has often resulted in delayed diagnoses of accessory breast cancer in men, predominantly in the late stages, as indicated in early case reports [2]. Breast cancer in the axilla presenting with Paget's disease in male patients is an extremely rare occurrence and has not been reported sufficiently in scientific literature. Here, we report a case of male breast cancer that initially presented with axillary skin changes. The patient was diagnosed with axillary breast cancer with Paget's disease that later recurred as metachronous Paget's disease in the contralateral axilla. This study was approved by the institutional review board of Asan Medical Center (No. 2018-0079), informed consent was obtained from the patient.

Author Contributions

Conceptualization: Lee YJ, Jung JM, Kim EK, Jung J, Jeong JH, Gong G, Ko B; Data curation: Lee YJ, Shin J, Jung JM, Kim EK, Jung J, Jeong JH, Gong G, Ko B; Supervision: Gong G, Ko B; Validation: Ko B; Visualization: Ko B; Writing - original draft: Lee YJ, Shin J; Writing - review & editing: Lee YJ, Ko B.

CASE REPORT

A 55-year-old man with no prior history of diseases, barring gout, developed erythematous skin lesions on his left axilla, a year before diagnosis. The mass became palpable and occasionally painful. The patient was diagnosed with intertrigo and was treated by his primary physician for a year before the current diagnosis. The patient showed no improvement and was referred to our dermatology department with suspicion of fibrosis or squamous cell carcinoma. Physical examination showed a 6.0 × 5.0 cm eczematous lesion with erythema in the left axilla (**Figure 1A**). An incisional biopsy of the lesion was performed, and histopathologic examination yielded a diagnosis of invasive ductal carcinoma arising in the accessory breast with Paget's disease (cytokeratin 7 [diffuse +], S-100 protein [-]). The patient refused chromosomal and genetic studies. Careful physical examination of the entire body, including imaging studies, was performed to evaluate the extent of the lesion and occult primary malignancies. The physical examination did not reveal any abnormal findings except the lesion in the affected left axilla, while no abnormalities in the external genitalia were observed. Magnetic resonance imaging (MRI) of the breast showed focal skin thickening in the left axilla and several enlarged lymph nodes in level I. Accessory breast tissue did not show any definite features in the MRI (**Figure 1B**). However, F-18-fluorodeoxyglucose positron emission tomography revealed several hypermetabolic (SUV = 2.0) lymph nodes (**Figure 1C**). There was no evidence of malignancy in the normal breast parenchyma or distinct primary malignancy, except in the left axillary region. The patient underwent wide excision with axillary lymph node dissection, including axillary levels I

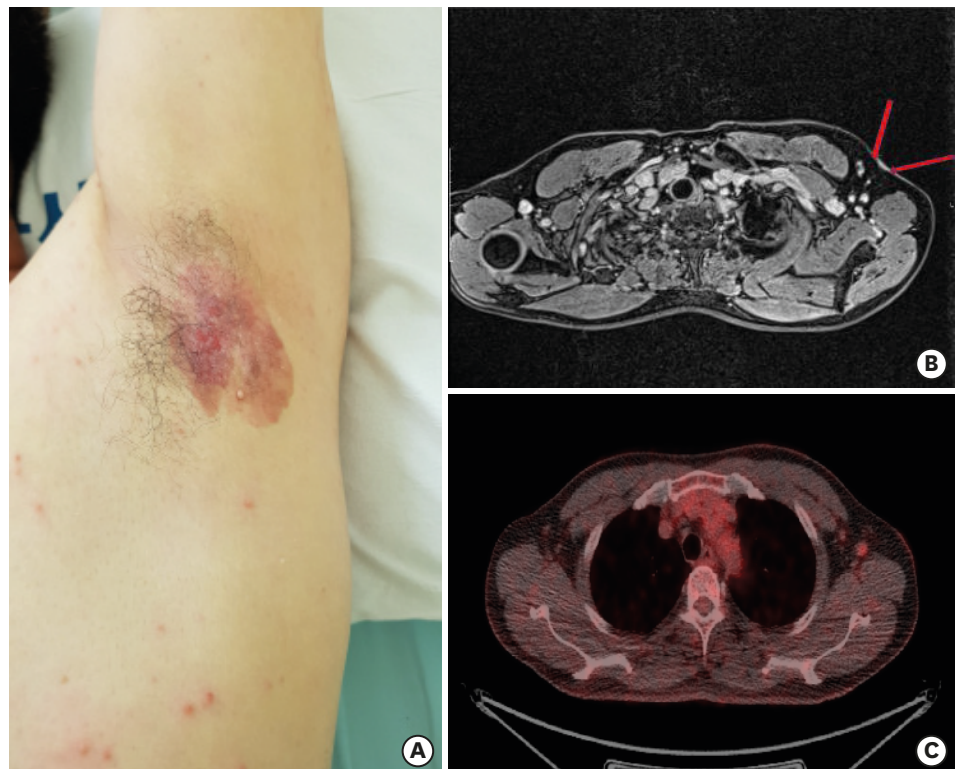


Figure 1. Visual and radiological findings of accessory mammary carcinoma. (A) Eczematous skin lesion with a mass on the left axilla. (B) MRI revealed focal skin thickening with several enlarged lymph nodes on the left axilla. (C) Positron emission tomography showed several mild hypermetabolic lymph nodes on the left axilla. MRI, magnetic resonance imaging.

and II. Since the affected skin lesion was wide (**Figure 2A**), a plastic surgeon reconstructed the axilla with a myocutaneous flap using the latissimus dorsi muscle (**Figure 2B**). The final diagnosis was invasive ductal carcinoma grade 2 with Paget's disease of the skin. The sizes of the invasive tumor and Paget's skin lesion were $1.5 \times 1.1 \times 0.6$ cm and 5.7×4.2 cm, respectively (**Figure 2C**). Lymphovascular invasion was evident, and 9 out of 15 retrieved lymph nodes were positive for malignancy, with the largest metastatic tumor measuring 1.5 cm. Immunohistochemical analysis showed that the lesion was estrogen receptor (ER) negative (-), progesterone receptor (PR) (-), and C-erbB2 (2+), with negative silver *in situ* hybridization (SISH) results. The Ki-67 proliferation index was 30%–40%. The patient received 4 cycles of adjuvant doxorubicin plus cyclophosphamide, followed by four cycles of docetaxel and adjuvant intensity-modulated radiation therapy (IMRT). Radiation was administered at 46 Gy in 23 fractions to the left chest wall, axilla, and supraclavicular area, with a simultaneous integrated boost of 55.2 Gy in 23 fractions to the tumor bed. The post-surgical follow-up image is shown in **Figure 3**.

At 17 months after surgery, the patient presented with a similar skin erythematous lesion in the contralateral right axilla (**Figure 4**). A skin incisional biopsy confirmed Paget's disease (cytokeratin 7 positive). Preoperative enhanced breast MRI showed skin thickening with enhancement. The patient underwent wide excision of the left axilla, and the final diagnosis was Paget's disease in the accessory breast. The lesion measured $1.9 \times 1.5 \times 0.2$ cm with similar immunohistochemistry results (ER [-], PR [-], C-erbB2 [2+], SISH [-], Ki-67 [10%–30%]). The patient received adjuvant IMRT to the right axilla and chest wall with a total dose of 50 Gy in 25 fractions. The pathologic results are shown in **Figures 5 and 6**.

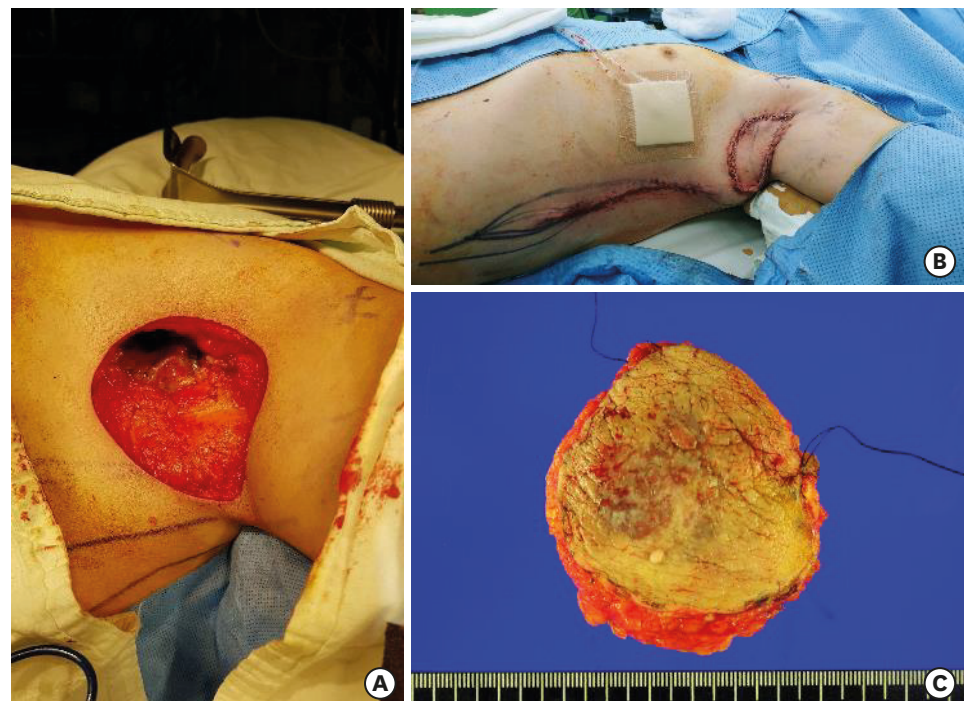


Figure 2. Gross appearance of specimen and operation fields. (A) Gross appearance of the epidermal surface of Paget's disease. Ill-defined erosion and crusting, measuring 5.7×4.2 cm. (B) A 10×10 cm skin defect after wide excision. (C) The plastic surgeon performed reconstruction surgery with a myocutaneous flap using the latissimus dorsi muscle.

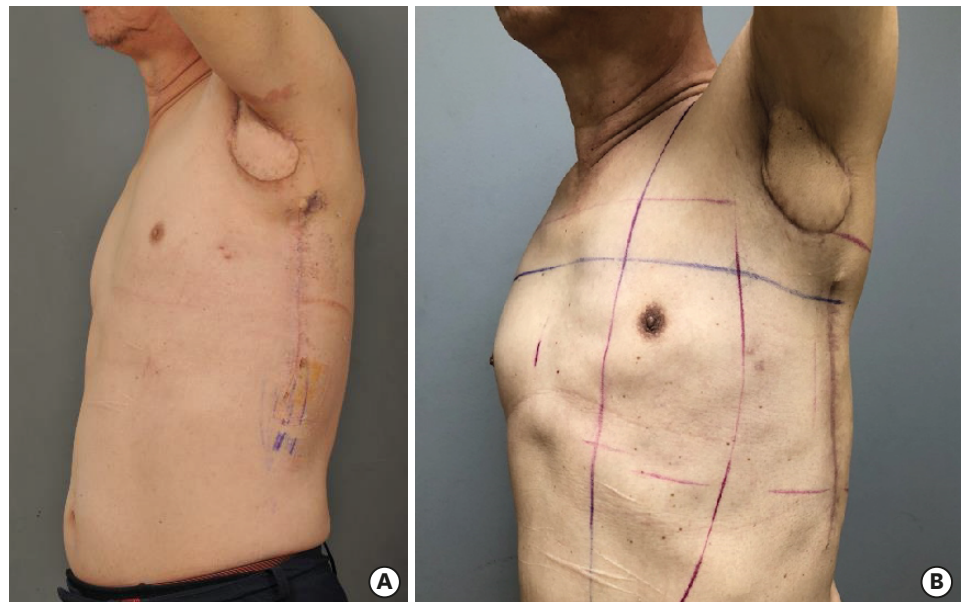


Figure 3. Post-operative wound. (A) One month after surgery. (B) Eight months after surgery.



Figure 4. Contralateral axilla (right-side) recurrence with Paget's disease at 1.5 years after the initial surgery.

DISCUSSION

Male accessory mammary carcinoma is a very rare disease. A survey of literature on the PubMed identified less than 10 reports on this disease. The incidence of accessory breast cancer in all populations is extremely rare; however, studies suggest that the incidence is higher in men [3]. Risk factors for male breast cancer include genetic mutations, obesity, alcohol intake, testicular damage, liver disease, and radiation therapy to the chest wall [4]. In the present case, there were no predisposing factors predicting a higher risk of breast cancer. Unlike typical breast cancer arising in the female breast, male breast cancer and accessory breast cancer are often misdiagnosed or have a delayed diagnosis. The differential diagnosis

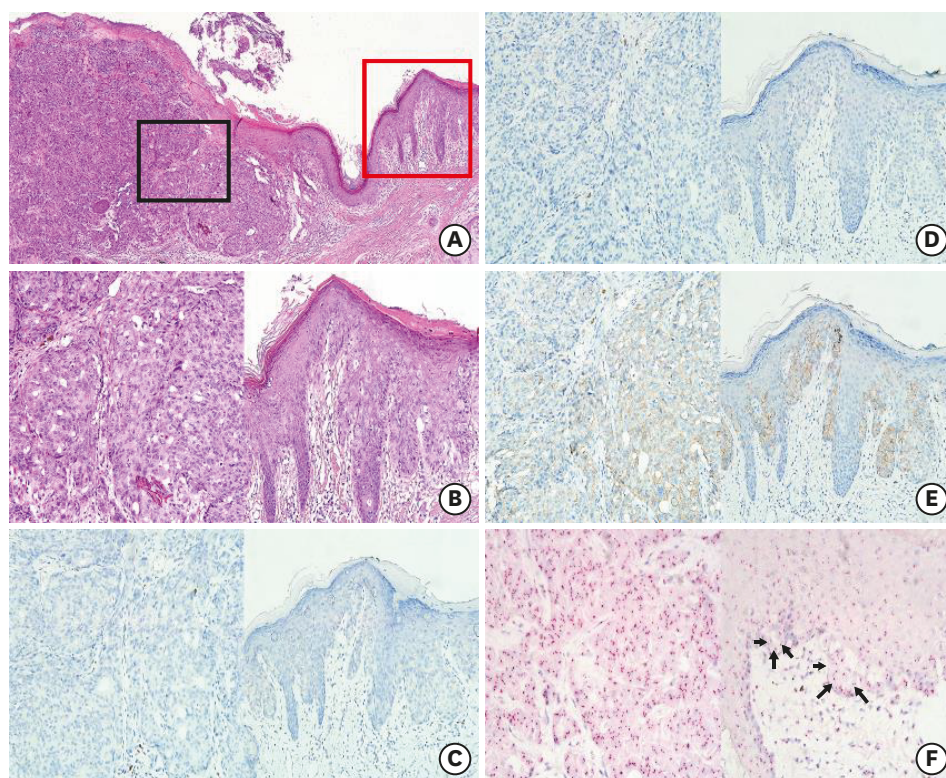


Figure 5. Pathologic image of the initial surgery. (A) Invasive ductal carcinoma with Paget's disease (H&E, magnification $\times 40$). (B) Magnified image (left) of invasive ductal carcinoma (black square from A) (right), Paget's disease (red square from A), (H&E, $\times 200$). The tumors show immune-negativity for estrogen receptor (C) and progesterone receptor (D), and equivocal positivity for HER2 (E) (IHC, $\times 200$). Absence of HER2 amplification is confirmed by SISH (F). (SISH, $\times 400$, tumor cells, black arrow).
H&E, hematoxylin and eosin; IHC, immunohistochemistry; SISH, silver *in situ* hybridization.

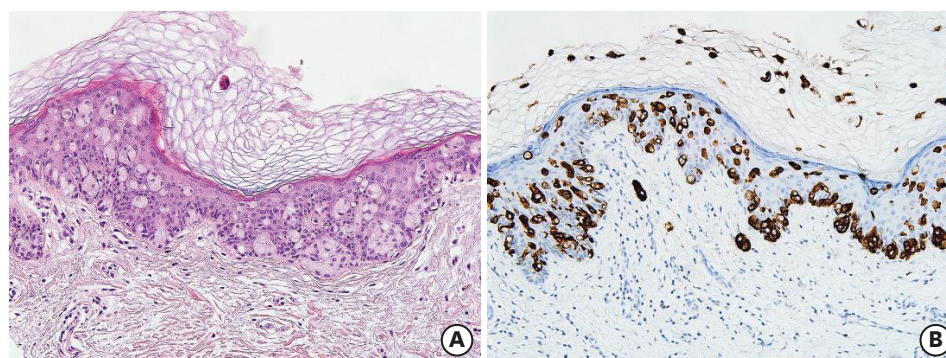


Figure 6. Pathologic image of contralateral Paget's disease. (A) Large and pale eosinophilic cells extend throughout the entire thickness of the epidermis. The nuclei are hyperchromatic and displaced peripherally (H&E, $\times 200$). (B) Tumor cells show immunoreactivity for cytokeratin 7 (IHC, $\times 200$).
H&E, hematoxylin and eosin; IHC, immunohistochemistry.

of an axillary nodular mass should include other axillary masses such as fibroadenoma, lipoma, abscess, sebaceous cyst, hidradenitis, and lymphadenopathies [5]. The detection of metastatic nodes from chest and breast cancer, skin cancer, Hodgkin disease, or soft tissue tumors is also important. The ipsilateral breast, upper extremity, and chest wall need to be examined carefully, and a biopsy should be performed, if there are any abnormal observations [6]. In patients with axillary disease who present with a mass or skin change or report of a

failed initial treatment, further evaluation and differential diagnosis are recommended. In the present patient, the diagnosis was delayed because the clinical symptoms were limited to erythematous skin changes, which were treated as a dermatologic disease. The treatment is similar to that of accessory breast cancer in women and consists of surgical removal of the tumor followed by adjuvant therapy. When lymph node metastasis is confirmed, axillary lymph node dissection is performed. However, a protocol for sentinel lymph node biopsy has not been established. It remains controversial as to whether the ipsilateral normal breast, including the nipple-areolar complex should be removed [7]. Cogswell and Czerny [8] and Evans and Guyton [9] reported that ipsilateral mastectomy might not be necessary to improve survival outcomes in patients with ectopic breast carcinoma. Wide excision of the tumor and surrounding tissues including involved regional nodes has been proposed as a treatment strategy when there is no sign of occult disease upon clinical examination, mammography, and ultrasonography. Omission of mastectomy should be followed by careful physical examination and imaging studies to detect potential malignant breast disease. The distribution of cancer subtypes by immunohistochemistry is similar between male and female breast cancers. In the Korean male breast cancer population, ER and PR negativity is reported in 10.5%–15.0% of cases [1]. In the cases of hormone receptor-positive male breast cancer, adjuvant endocrine therapy is recommended, and tamoxifen is the treatment of choice and the most widely studied therapy. Most male breast cancer patients with hormone receptor-positive disease are treated with tamoxifen, and studies show that adjuvant tamoxifen has long-term survival benefits [10]. Paget's disease of the breast is commonly associated with a high rate of epidermal growth factor receptor 2 (HER2) overexpression; however, the present case was HER2-negative [11]. Besides, the present patient had a triple negative subtype with multiple metastatic lymph nodes (pN2), and was therefore treated with adjuvant chemotherapy with anthracycline plus cyclophosphamide followed by taxane. The benefits of adjuvant chemotherapy in male breast cancer are not well established, albeit several studies suggesting some benefit. A 20-year follow up of patients receiving 12 cycles of adjuvant cyclophosphamide, methotrexate, and fluorouracil (CMF) showed that the overall survival probability is 64.5% at 10 years, 51.6% at 15 years, and 42.4% at 20 years, thereby indicating certain benefit from adjuvant chemotherapy in patients with axillary lymph node metastasis [12]. A report from the MD Anderson Cancer Center analyzing men with positive lymph node status indicated that adjuvant chemotherapy is associated with a lower risk of death (hazard ratio, 0.78); but there was no statistically significant difference [13].

The role of radiation therapy in male breast cancer is not well established. Retrospective studies indicate that the 5-year locoregional recurrence rates of male breast cancer patients range from 3% to 20% [4]. Women with accessory breast cancer are usually treated by wide excision rather than total mastectomy. In a series of Japanese women diagnosed with accessory breast cancer, only 22 out of 94 underwent mastectomy. There was no information on whether the patients had adjuvant radiation therapy after wide excision [3]. As there are no indications regarding the surgical boundary in accessory breast cancer, adjuvant radiation therapy to the tumor bed may be beneficial for local control. Further studies are necessary to establish guidelines for wide excision followed by radiotherapy.

The overall survival of male breast cancer cases is comparable to that of female breast cancer cases when adjusted for stage and age at diagnosis [14]. A recent large population-based retrospective analysis performed by a French group showed that local recurrence, regional recurrence, and metastasis occurred in 2%, 5%, and 22% of patients, respectively; while the incidence rates of contralateral breast cancer and secondary malignancy were 2% and 10%,

respectively. The results indicated that the use of endocrine therapy, systemic cytotoxic therapy, and radiation therapy improved the long-term outcomes of male breast cancer [15]. The risk factors for poor prognosis in addition to advanced stage are comorbidities, which increase with age. Long-term survival data for male accessory breast cancer are lacking because of the rarity of this disease, and the outcomes of this patient population remain unclear. Furthermore, there are no established guidelines for the diagnosis and treatment of male accessory breast cancer. Multicentric and worldwide case acquisition is necessary to understand the natural course of this unique type of male breast cancer. The present case showed some peculiarities including male gender, accessory breast cancer, bilateral Paget's disease, and triple negative breast cancer, which are all rare clinical manifestations of breast cancer.

REFERENCES

1. Choi MY, Lee SK, Lee JE, Park HS, Lim ST, Jung Y, et al. Characterization of Korean male breast cancer using an online nationwide breast-cancer database matched-pair analysis of patients with female breast cancer. *Medicine (Baltimore)* 2016;95:e3299.
[PUBMED](#) | [CROSSREF](#)
2. Deutsch M, Yeh J, Grunes D, Horowitz E, Johnson E, Joseph KA. Clinical presentation of extramammary Paget disease of the axilla in a male patient. *Clin Breast Cancer* 2015;15:e159-61.
[PUBMED](#) | [CROSSREF](#)
3. Nihon-Yanagi Y, Ueda T, Kameda N, Okazumi S. A case of ectopic breast cancer with a literature review. *Surg Oncol* 2011;20:35-42.
[PUBMED](#) | [CROSSREF](#)
4. Fentiman IS, Fourquet A, Hortobagyi GN. Male breast cancer. *Lancet* 2006;367:595-604.
[PUBMED](#) | [CROSSREF](#)
5. Ghosn SH, Khatri KA, Bhawan J. Bilateral aberrant axillary breast tissue mimicking lipomas: report of a case and review of the literature. *J Cutan Pathol* 2007;34 Suppl 1:9-13.
[PUBMED](#) | [CROSSREF](#)
6. Velanovich V. Fine needle aspiration cytology in the diagnosis and management of ectopic breast tissue. *Am Surg* 1995;61:277-8.
[PUBMED](#)
7. Zhang S, Yu YH, Qu W, Zhang Y, Li J. Diagnosis and treatment of accessory breast cancer in 11 patients. *Oncol Lett* 2015;10:1783-8.
[PUBMED](#) | [CROSSREF](#)
8. Cogswell HD, Czerny EW. Carcinoma of aberrant breast of the axilla. *Am Surg* 1961;27:388-90.
[PUBMED](#)
9. Evans DM, Guyton DP. Carcinoma of the axillary breast. *J Surg Oncol* 1995;59:190-5.
[PUBMED](#) | [CROSSREF](#)
10. Ribeiro G, Swindell R. Adjuvant tamoxifen for male breast cancer (MBC). *Br J Cancer* 1992;65:252-4.
[PUBMED](#) | [CROSSREF](#)
11. Sek P, Zawrocki A, Biernat W, Piekarski JH. HER2 molecular subtype is a dominant subtype of mammary Paget's cells. An immunohistochemical study. *Histopathology* 2010;57:564-71.
[PUBMED](#) | [CROSSREF](#)
12. Walshe JM, Berman AW, Vatas U, Steinberg SM, Anderson WF, Lippman ME, et al. A prospective study of adjuvant CMF in males with node positive breast cancer: 20-year follow-up. *Breast Cancer Res Treat* 2007;103:177-83.
[PUBMED](#) | [CROSSREF](#)
13. Giordano SH, Perkins GH, Broglio K, Garcia SG, Middleton LP, Buzdar AU, et al. Adjuvant systemic therapy for male breast carcinoma. *Cancer* 2005;104:2359-64.
[PUBMED](#) | [CROSSREF](#)
14. Guinee VF, Olsson H, Moller T, Shallenberger RC, van den Blink JW, Peter Z, et al. The prognosis of breast cancer in males. A report of 335 cases. *Cancer* 1993;71:154-61.
[PUBMED](#) | [CROSSREF](#)
15. Cutuli B, Le-Nir CC, Serin D, Kirova Y, Gaci Z, Lemanski C, et al. Male breast cancer. Evolution of treatment and prognostic factors. Analysis of 489 cases. *Crit Rev Oncol Hematol* 2010;73:246-54.
[PUBMED](#) | [CROSSREF](#)