JBUON 2013; 18(3): 798-801
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
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LETTERS TO THE EDITOR

Medullary carcinoma of the breast: A brief report from a tertiary care center

Dear Editor,

Medullary carcinoma comprises 3-5% of all breast cancer patients. It is easily identified by prominent syncytial growth, well-circumscribed margins, nuclear pleomorphism, diffuse lymphoid infiltrate and absence of an intraductal component or microglandular features [1]. Studies have shown that despite the common occurrence of large tumor size, high nuclear grade, and hormone receptor negativity, medullary carcinomas of the breast have a good pronosis; up to 84% 10-year survival [2].

We retrospectively investigated the files of 2003 patients and found 16 patients diagnosed with medullary carcinoma. We looked up some parameters in the patient files as follows: age, menopausal state, oral contraceptive use, TNM classification of the tumors, receptor positivity, follow up period, survival, and the treatment modalities they had received. The mean age was 47 years (range 28-73), with median 46 years. All of the patients were women; 7 were postmenopausal and 9 premenopausal. Three of the patients had a history of oral contraceptive use and the remaining denied any use of oral contraceptives. Nine patients had a family history of malignancy, 2 were estrogen receptor positive, 3 were progesterone receptor positive, 4 were HER2 positive, however, one patient's chart did not include the information regarding any receptor positivity and 3 patient's charts did not indicate any information regarding HER2 positivity. Six patients had triple negative medullary breast cancer. Regarding histological grade, 10 patients had grade III and 1 grade II; 4 patients lacked information on grade. Regarding staging, 2 patients had T1, 12 T2, and 1 T3 tumors. Ten patients did not have lymph node metastasis (LNM), 4 had N1 and 1 N4 nodal disease. All of the patients had M0 stage at the time of diagnosis and all received adjuvant chemotherapy; none of them received neoadjuvant chemotherapy. Five patients received hormone therapy and 10 had adjuvant radiotherapy. The mean follow up period was 44.8±22.2 months (range 4.2 months -10.5 years). During follow up, 2 patients died and 2 had disease progression (one of them after 8.4 months and 2nd after 17.7 months).

Medullary carcinoma of the breast stands apart from other subtypes, with its easily distinguishable histological appearance and its good prognosis. LNM has been shown to be an important prognostic factor of this disease. Fisher et al. have demonstrated that the 10-year survival rates for those without LNM were 68.7–80.2%, whereas for patients with LNM not receiving chemotherapy this ratio was 44.4%–50.0% [3]. Metastasis, as demonstrated in our analysis is rare in this subtype. In addition, a recent study has also shown that ER positivity is infrequent, and that there are racial disparities in survival. Moreover, it has been shown that inadequate lymphadenectomy may lead to understaging, as the survival increases with increasing lymph node yield [4]. Furthermore, Pinto et al. reported no survival difference between ER+ and ER- patients, suggesting hormone therapy resistance [5]. To conclude, medullary breast carcinoma has unique characteristics of its own which need to be taken into consideration during diagnosis and selection of treatment modalities. In this study we presented a brief report of our experience and a concise summary of the current information about this uncommon pathology.

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I. Petekkaya, T. Babacan, F. Sarici, G. Gezgen, E.C. Roach, M.C. Kizilarslanoglu, K. Altundag

Department of Medical Oncology, Hacettepe University Institute of Oncology, Ankara, Turkey.

Correspondence to: Kadri Altundag, MD.
E-mail: altundag66@yahoo.com

Successful treatment of benign metastasizing leiomyoma with oral alternated chemotherapeutic agents

Dear Editor,

Benign metastasizing leiomyoma (BML) is a rare variant of uterine leiomyoma [1]. BML could spread to different organs but lung is the most common site of involvement. Patients with pulmonary BMLs are almost always asymptomatic with incidental identification of the pulmonary lesions.

In March 2003 a 52-year-old woman was referred to hospital, since a routine chest X-ray had previously revealed multiple, bilateral suspect pulmonary tumor masses. She had a history of hysterectomy at the age of 41 because of a uterus myomatosus. A video-assisted thoracoscopy with biopsy of a pulmonary nodule was performed. Pathologic evaluation showed bundles of spindle-shaped, smooth-muscle cells staining positive for desmin and actin. Based on these findings and the accompanying symptoms the patient diagnosed with pulmonary BML. She refused surgical intervention and hormone treatment was abandoned because of severe menopausal disorders. As the patient was asymptomatic and malignant transformation of BML is uncommon, no further therapeutic actions were taken and regular control chest roentgenograms were agreed on. However, the patient was lost to follow-up until August 2005. She was referred to our outpatient clinic with cough and dyspnea that lasted for several weeks. Blood tests, including tumor markers, inflammation and liver enzymes were all within normal limits. A thoracic computed tomography (CT) scan identified multiple bilateral pulmonary nodules with a maximum diameter of 75 mm. She was treated with cyclophosphamide 50 mg /5 p.o. days a week. After therapy was initiated, she underwent thoracic and pelvic examinations, blood tests, and periodical diagnostic imaging every 3-6 months. Although the response was evaluated as "stable disease" according to the Response Evaluation Criteria for Solid Tumors, the size of the nodules reduced slightly during treatment and no new lesions were observed. At the end of one year cyclophosphamide therapy, her treatment was replaced with etoposide 50 mg p.o. daily x14 days every 3 weeks due to the stability of disease. After 3 years of etoposide therapy, the disease remained stable and asymptomatic, and we decided to return to cyclophosphamide therapy owing to the risk of leukemia due to etoposide with a rearranged schema (50 mg p.o./5 days a week). She was on cyclophosphamide during the 6 years of follow-up, she remained asymptomatic and there was a valuable regression in lung fibrosis.

There is no standard treatment guideline for BML currently. Reported treatment modalities include careful observation, surgical resection, progestins, aromatase inhibitors and medical castration using luteinizing hormone releasing hormone analogues [2-5]. A radical surgical resection, if possible, has been advocated as primary treatment. Hormonal therapy has been suggested as the best option for unresectable metastatic disease [3]. However, not all patients seem to respond to hormone treatment and side effects including flushes, fatigue, and nausea can be aggravating. As our patient refused to undergo surgery and a hormone treatment was not an option due to menopausal disorders, a wait-and-see strategy was decided.

Depending on the locations of the metastases and the hormone receptor status, we believe that treatment should be individualized for each patient. Because of the limited therapeutic options, new drugs or new therapeutic modalities should be considered. In the future, studies with long-term follow-up may be helpful for their implication in clinical practice. In cases where the patients deny the surgical resection and face adverse effects with hormonal therapy, it is possible to initiate patient-oriented oral metronomic treatment regimens. Further randomized and blind trials are required to verify the findings of this paper.

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F. Sarici[1], T. Babacan[1], K. Altundag[1], O. Balakan[2], I. Gullu[1]

[1]*Department of Medical Oncology, Hacettepe University Institute of Oncology, Ankara;* [2]*Department of Medical Oncology, Gaziantep University Faculty of Medicine, Gaziantep, Turkey*

Correspondence to: Kadri Altundag, MD.
E-mail: altundag66@yahoo.com

Lung tuberculosis causing false positivity on positron emission tomography

Dear Editor,

Positron emission tomography (PET) with 18 flurodeoxyglucose (FDG) is a very useful imaging modality which can be used for diagnosis, staging, and monitoring treatment of cancers, particularly in Hodgkin's and non Hodgkin's lymphoma, and lung cancer [1]. Additionally, FDG-PET has been shown to play an important role in revealing metastases, or for recurrence after a known highly-active primary tumor is removed. Besides evaluation of many malignancies, FDG can also accumulate intensely in inflammatory lesions and some false-positive findings, such as in tuberculosis (TBC), may occur [2].

A 55-year-old man presented with night sweats, loss of appetite, weight loss, pallor, and easy fatigue for the last 6 months; cough with hemoptysis were added in the last month. On admission his blood pressure was 130/80 mmHg, pulse rate 105/min, and temperature 37oC. Body weight was 65 kg and height 174 cm. Lung auscultation was normal. Lab tests revealed WBC 11,000, increased erythrocyte sedimentation rate at 65 mm/h, increased fasting blood sugar at 155 mg/dl, urea 36 mg/dl (upper limit of normal/ULN 40) , creatinine 1.1 mg/dl (ULN 1.4), AST 22 (ULN 34), ALT 41(ULN 43), LDH 350 (ULN 200). Sputum smears and cultures were negative. Chest X ray showed a 3x3 cm nodule in the left upper lobe. Chest computerized tomography revealed a 2x3 cm mass in the left upper lobe posteriorly and a 8x7 mm nodule in the right upper posterior lobe of the lung. No endobronchial lesion was seen on bronchoscopy. The mass was very stiff and the transthoracic fine needle aspiration was not sufficient for evaluation. FDG-PET/CT scan showed a 21x30 mm mass with standard uptake values (SUV) max early 2.5 and late 3.1 at the posterior segment of the upper lobe of the left lung. There was also a 8x7 mm nodule at the upper lobe (upper-posterior) of the right lung which did not hold FDG. The patient was operated on and a 3x3 cm firm mass was resected from the left upper posterior lobe of the lung. Histopathological examination was consistent with TBC.

The goals for imaging in patients with undetermined pulmonary nodules are to distinguish between benign and malignant lesions in the least invasive way and to make a specific diagnosis. PET/CT performed for cancer evaluation may detect asymptomatic infection and guide definitive diagnosis. The objective of PET before exploratory thoracotomy in patients with benign solitary nodules is to determine appropriateness for surgery as well as prevent unnecessary complications that may occur in a significant fraction of patients [3]. However, it is frequently hard to differentiate tuberculomas from malignant nodules radiologically. Active TBC, including asymptomatic and extrapulmonary disease may be detected with FDG-PET/CT. It may also be a useful tool in the assessment of latent TBC, to exclude active disease prior to treatment [4]. A threshold SUV of 2.5 at FDG-PET has been reported to provide optimal sensitivity (83–100%) and specificity (67–90%) in differentiating benign from malignant nodules in patients with solitary pulmonary nodules [1,3,5]. In this report we showed a SUV max which is expected for malignant but not for benign lesions like TBC. We would like to point out that in endemic regions TBC should always be kept in mind when dealing with lung masses. PET/CT may be used in patients with difficulties in diagnosing TBC, but this topic needs further investigations.

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S. Muallaoglu[1], I. Ustun[2], Y. Kaya[3], I. Leblebici[4]

[1]*Department of Medical Oncology, Baskent University Faculty of Medicine, Adana;* [2]*Department of Endocrinology, Mustafa Kemal University Faculty of Medicine Antakya;* [3]*Department of Thoracic Surgery, Mersin State Hospital, Mersin;* [4]*Department of Pulmonary and Critical Care Medicine, Mersin State Hospital, Mersin, Turkey*

Correspondence to: Sadik Muallaoglu, MD.
E-mail: smuallaoglu@hotmail.com

Does trastuzumab-emtansine have better cardiac safety profile in contrast to trastuzumab?

Dear Editor,

Trastuzumab is the first agent developed to target the HER2 pathway. The use of trastuzumab in the adjuvant and metastatic treatment of HER2 positive breast cancer is associated with both symptomatic and asymptomatic cardiotoxicity. The incidence rates of trastuzumab-mediated cardiotoxicity were 27% with anthracycline combination and 13% when it was administered with paclitaxel [1]. The incidence of ejection fraction decline of 10% or 15% was 3-34% of trastuzumab recipients in the 5 major randomized adjuvant trials [1]. The incidence of severe congestive heart failure was 0-3.9% in the trastuzumab arms vs 0-1.3% in the control arms in these 5 trials [1]. Despite the proven efficacy of anti-HER2 humanized monoclonal antibody trastuzumab plus chemotherapy, a proportion of patients with HER2-positive breast cancer will not respond, while the majority of patients with metastatic breast cancer will progress within 1 year. Thus new therapies directed at HER2 were developed.

Trastuzumab-emtansine (T-DM1), a novel antigen-drug conjugate (ADC) that targets HER2-positive tumors, is highly promising. T-DM1 is the first ADC targeting HER2-positive tumor cells. The chemical structure of T-DM1 consists of trastuzumab and a maytansinoid derivative. Trastuzumab, besides providing many important clinical benefits itself, is an ideal ADC antibody to target HER2-positive tumor cells. The DM1, a maytansinoid derivative, is a highly potent antimicrotubule drug with a low therapeutic index [2]. This targeted chemotherapy delivery system optimizes the delivery of both the monoclonal antibody trastuzumab and the chemotherapeutic agent DM1 minimizing the systemic side-effects of chemotherapy. In a recent, phase III trial (EMILIA), Verma and colleagues reported that in patients with HER2-positive advanced breast cancer after failure of trastuzumab and taxane treatment, trastuzumab emtansine (T-DM1) significantly prolonged progression-free survival and overall survival compared to lapatinib plus capecitabine combination [2]. In this study, only in 1.7% of patients in the T-DM1 group experienced a decreased ejection fraction at least 15% below the baseline value. Grade III left ventricular ejection fraction (LVEF) developed only in one patient (0.2%) in T-DM1 group whereas no grade III congestive heart failure was reported in the lapatinib plus capacitabine group. In a phase II study, 3.6 mg/kg T-DM1 was administered intravenously every 3 weeks to 110 patients with HER2-positive metastatic breast cancer who had been previously treated with anthracycline, taxane, capecitabine, trastuzumab and lapatinib [3]. T-DM1 was well tolerated in this heavily pretreated population, with no cardiac events requiring dose adjustment. Another phase II study (TDM4258g) further evaluated the safety and efficacy of T-DM1 [4]. In this single-arm trial, 112 HER2-positive metastatic breast cancer patients with tumor progression after prior treatment with HER2-directed therapy and prior chemotherapy were administered T-DM1. T-DM1 has been shown to be well tolerated and no cardiac toxicity was reported. In another phase II study (TDM4450) (first-line setting, randomized, open-label, two-arm, multicenter study) the efficacy and safety of T-DM1 and trastuzumab plus docetaxel was assessed in recurrent, advanced or metastatic breast cancer patients [5]. T-DM1 had a better safety profile compared to trastuzumab, with no significant cardiotoxicity. Additional results of the previous studies showed that T-DM1 can induce QT prolongation than decrease in LVEF. The exact mechanism for T-DM1-induced QT interval prolongation is not known.

T-DM1 has shown favorable cardiac safety and efficacy profiles in clinical trials. Clinical studies have shown that continuing T-DM1 beyond progression on other HER2-directed therapy is a feasible strategy; preclinical and pharmacokinetic data support that, although trastuzumab is one of its components, T-DM1 is a completely different molecule with a cardiac safety profile. The evidently favorable safety profile of T-DM1 is probably related to the mechanism of intracellular delivery of a maytansinoid cytotoxic agent directly into HER2-expressing tumor cells. In the light of the previous studies, cardiac safety profile of T-DM1 should be evaluated carefully.

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M.A.N. Sendur[1], S. Aksoy[2], Y. Ozdemir[1], N. Zengin[1], K. Altundag[2]

[1]*Ankara Numune Education and Research Hospital, Department of Medical Oncology, Ankara;* [2]*Hacettepe University Cancer Institute, Department of Medical Oncology, Ankara, Turkey*

Correspondence to: Mehmet Ali Nahit Sendur, MD.
E-mail: masendur@yahoo.com.tr