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Breast Cancer with Internal Mammary Node Metastases: A Case Presented in a Tumor Board Session and decision making

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ABSTRACT

Background: There are several therapeutic options available for breast cancer treatment, now incorporating innovative targeted molecular therapies. Metastatic breast cancer is usually treated with chemotherapy and/or hormonotherapy. Surgery has not been shown to improve survival. Adjuvant radiotherapy (RT) has been proven to be effective in the treatment of locally advanced breast cancer, reducing locoregional recurrence. The optimal treatment of internal mammary lymph nodes (IMN) metastases remains controversial.

Case presentation: A 48-year-old woman was diagnosed with invasive breast cancer with ipsilateral metastases to axillary lymph nodes and a contralateral IMN metastasis. This case was presented twice during the tumor board sessions of the Surgical Oncology Service at the *Centre hospitalier de l'Université de Montréal* (CHUM), Montréal, Canada.

Question: Does the internal mammary chain (IMC) dissection could be used as a treatment approach in breast cancer with IMC metastasis?

Conclusion: Internal mammary chain dissection should be discussed in tumor board sessions on a case-by-case basis. There are no strong guidelines on the management of IMN metastasis in breast cancer, but there is growing evidence that these women should be treated with curative intent.

Introduction

Breast cancer affects 1 woman in 8 during their lifetime. In the last two decades, major advances have been achieved in breast cancer diagnosis and treatment, reducing mortality by 20%.[1] Amongst others, the recent advent of innovative targeted molecular therapies, such as PARP and CDK 4/6 inhibitors, seems promising. Metastatic breast cancer is usually treated with chemotherapy and/or hormonal therapy if the hormone-dependent disease is present: surgery has not been shown to improve survival in stage IV disease. On the other hand, adjuvant radiotherapy (RT) has been proven to be effective in the treatment of locally advanced breast cancer, reducing locoregional recurrence rates and improving survival as well.[2-5]

The majority of breast cancers (> 90%) demonstrate primary drainage to axillary lymph nodes.[6] Their crucial contribution to staging, treatment and prognosis is well established and is widely accepted nowadays. The second group of lymph nodes, the internal mammary nodes (IMN), receive a significant proportion of primary drainage from breast

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tissue as well, accounting for approximately 20% of tumors, depending on tumor location within the breast.[7-8] However, although IMNs are the first nodal draining basin in breast cancer and are considered locoregional nodes according to the latest AJCC classification, their involvement in breast cancer influences therapy and staging in a very controversial fashion. Breast cancer patients with IMN metastases without distant metastases are rare and carry worse prognosis in terms of overall survival (OS) and distant recurrence free survival (RFS), irrespective of the axillary status.[9] The conflicting evidence regarding the optimal treatment of IMN involvement in breast cancer remains a highly controversial topic in the current literature.

Case presentation

A 48-year-old premenopausal woman without notable medical, surgical and family history was referred to our institution with a six-centimeter mass located in the lower outer quadrant of the right breast. A core needle biopsy of the mass and axillary lymph node confirmed a grade 2 invasive ductal carcinoma with axillary metastases, with hormone-positive receptors and HER-negative status. A breast magnetic resonance imaging (MRI) demonstrated a neoplastic cutaneous extension with suspected pectoral involvement, suspicious level I, II and III right axillary lymph nodes, two suspicious right IMN with a diameter of 5 mm and one left IMN measuring 9 mm. The neoplastic cutaneous invasion was demonstrated by thickened skin adjacent to the tumor and accompanied by a cutaneous retraction zone. A positron emission tomography (PET scan) was performed, confirming hypermetabolism of the breast mass, right axillary nodes and left IMN, with standardized uptake values (SUV) of 12, 6 and 2.8, respectively. The pathology report of fine needle biopsy of left IMN revealed metastatic cells from breast cancer. The extension was assessed with thoracic, abdominopelvic and bone scans, and showed no distant metastasis except for the left IMN. (Figure 1)

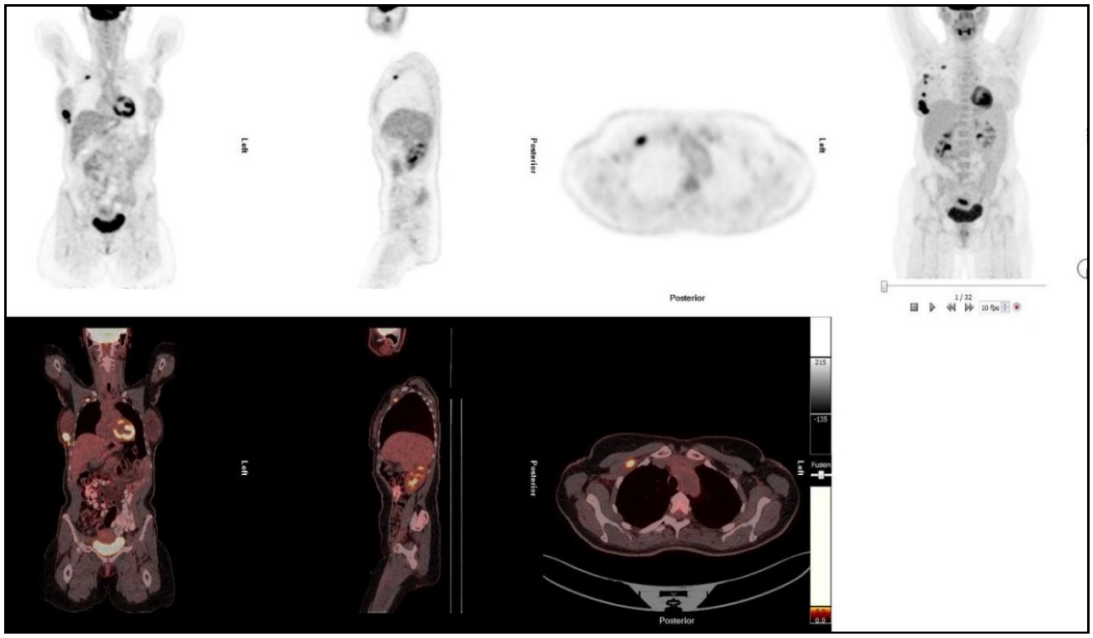

Figure 1. PET Scan Before Treatment, Confirming a Hypermetabolism of the Right Breast Mass, Right Axillary Nodes and Left IMN.

The genetic work-up was negative. Chemotherapy with dose-dense AC (doxorubicin/cyclophosphamide) was initiated, followed by the first discussion at our institutional tumor board meeting. By mutual agreement, despite a stage IV breast cancer, given the limited disease to regional lymph nodes, curative treatment was continued. After a total of 5 months, neoadjuvant chemotherapy composed of dose-dense AC followed by weekly paclitaxel was completed with an excellent clinical and radiological response and complete normalization of the left IMN disease. After a second discussion, surgical oncology, thoracic surgery and plastic surgery combined their technical skills to perform a right modified radical mastectomy with partial excision of the pectoralis major muscle, a left internal mammary chain (IMC) dissection, and a right-breast immediate reconstruction with a latissimus dorsi flap for defect closure and reconstruction. The thoracoscopic approach was used for the left IMN removal which the patient clearly favored over watchful waiting or post-operative radiotherapy alone. Surgery was well tolerated without complications. Final pathology showed 5 out of 12 metastatic axillary lymph nodes, but a left IMC free of disease, corresponding to a pathologic stage IIIA (ypT1cN2a) according to latest AJCC

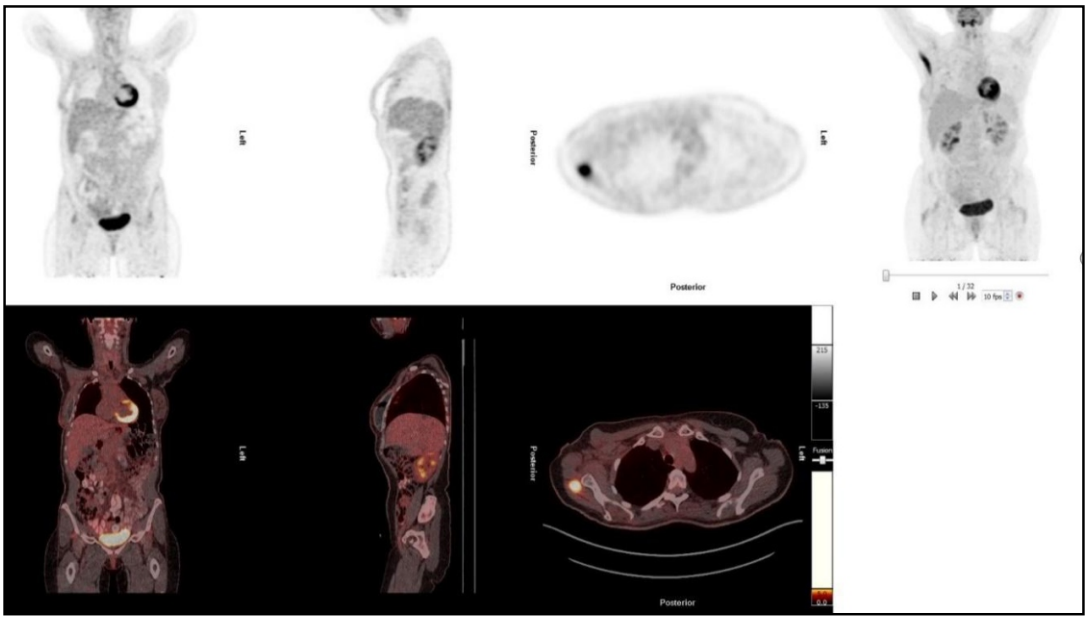

Figure 2. PET Scan After Treatment, Showing the Excellent Radiological and Surgical Response.

classification. Radiotherapy covering the right chest wall, right axillary and supraclavicular lymph nodes as well as both IMCs was initiated a few weeks after surgery. Since the breast cancer tumor was hormone receptor positive and the patient was premenopausal with a high residual burden of disease, Zoladex and Letrozole were started. Six months after surgery, follow-up clinical examination, as well as PET and thoracic scans, revealed no evidence of locoregional or distant recurrence. Bilateral breast MRI and mammograms are scheduled. (Figure 2)

Question

This case was presented at the weekly breast cancer tumor board session at the Centre hospitalier de l'Université de Montréal, Canada, gathering experts in the field, such as surgical oncologists, medical oncologists, radiation oncologists, radiologists and pathologists. Two main questions were debated. First, should we treat this patient with curative or palliative intent, given the contralateral positive IMN? Second, should we offer IMN dissection as an option to this woman after neoadjuvant chemotherapy?

Discussion

According to NCCN recommendations, inoperable, non-inflammatory, locally advanced breast cancer at presentation should be treated with neoadjuvant anthracycline-based chemotherapy, with or without a taxane. A monoclonal antibody such as trastuzumab and possibly pertuzumab for locally advanced breast cancer that is HER2-positive should be added to the preoperative systemic regimen. Surgical options following a clinical response to initial chemotherapy include 1) modified radical mastectomy or 2) partial mastectomy and level I/II axillary dissection. NCCN guidelines state that these patients, regardless of chosen local therapy, have significant local recurrence risks that warrant the use of adjuvant RT. Standard therapy includes RT to chest wall or breast and supraclavicular nodes. Based upon lower-level evidence (category 2B), there is an NCCN consensus that IMN radiation should be considered even without IMN metastasis. IMN should be included in the RT field if positive for cancer. Endocrine therapy consists of adjuvant therapy in the event of hormone-receptor positive disease.[10]

Patients with metastatic breast cancer are unlikely to be cured of their disease and complete remissions are rare with current therapies. However, with advances in the multimodal treatment of breast cancer, patients can hope to live for many years nowadays. Although in many types of cancer removing the primary tumor provides survival benefits even in the presence of distant metastases, for metastatic breast cancer, most oncologists agree that aggressive local therapy is futile in terms of survival. [11] On the other hand, there is increasing evidence that women with a solitary metastasis, or a few metastases at a single organ site, could live longer following surgical control of the metastatic disease. A recent study showed a durable response to therapy with a significant survival benefit in metastatic breast cancer patients treated with aggressive surgical removal of oligometastases. This subgroup of patients shared some important characteristics, such as an excellent response to systemic therapy before surgery and adequate locoregional treatment of breast and lymph nodes, in order to attain the status of no evidence of disease.[12] HER2 and hormone-receptor positivity were associated with an improvement in overall survival

and progression-free survival, respectively. These findings could potentially guide clinicians in their selection of patients for this novel approach incorporating curative metastasectomy.

After three randomized clinical trials failed to show any benefit in terms of overall survival between Halsted or extended mastectomy and radical or modified radical mastectomy while incurring significant operative morbidity, IMN dissection was abandoned. It is mandatory to note that only a small percentage of patients in those studies had positive IMN. Moreover, the diagnostic and therapeutic management of breast cancer patients at that time were different from the current management of the disease. A few retrospective studies tried to demonstrate OS and RFS benefits from IMN dissection, but these were underpowered.[13-16] Following these publications, the interest of clinicians for IMN in breast cancer treatment had waned, and this issue was almost ignored for a few years. IMNs have regained popularity as a result of the development and increasing use of lymphoscintigraphy and the demonstration of the importance of locoregional control on long-term survival, among others.[2-3] As a consequence of renewed interest, there has since been a small increase in studies on IMN in the early 2000s with ongoing interest. Literature has since demonstrated that elective biopsy of internal mammary chain sentinel nodes (IMCSn) affects cancer stage, prognosis, and overall management strategy.[7-17] In the same vein, a recent study assessed the effect of IMCSn biopsy on OS and RFS.[17] It showed that lower survival of patients with IMN metastases was attributable to distant metastasis. Predictive factors were suggested to determine who could be spared the possible RT side effects and who could benefit from this treatment modality. Recommendations from this group are to perform IMCSn biopsy for patients younger than 70 years old with a breast tumor larger than 1.5 cm. In their hands, the procedure was shown to be safe, with a low rate of complications. However, despite great advances toward uncovering the best indications for IMN biopsy and surgical resection, controversy still resides in that no modern clinical trials are assessing OS and RFS benefits from IMN dissection in patients with proven preoperative IMN metastases, without the distant disease.

On the other hand, recent studies demonstrated encouraging results on OS, RFS and distant metastasis-free survival of breast cancer patients with IMN metastasis treated with adjuvant RT after 10 years of follow-up.[18-19-20] Nonetheless, concerns have been raised by multiple authors regarding long-term morbidity resulting from RT, such as cardiac toxicity and pulmonary fibrosis. There is no minimum threshold for the risk of cardiotoxicity with left-sided IMN radiation with the probability of major coronary events increasing proportionally with the mean dose to the heart.[21] In our institution, radiation oncologists use a novel RT technique, namely helical tomotherapy (HT), in left-sided breast cancer or when IMN incorporation in the radiotherapy field is required. HT enables excellent conformity of dose distribution with treatment delivery from 360 degrees around the patient with coverage of complex zones while providing maximal noble organs sparing.

Breast cancer patients with IMN involvement should all be discussed at tumor board sessions on a case-by-case basis because there are no strong guidelines in current literature assessing IMN metastasis management. Patient's age and comorbidities, molecular subtype and risk of distant micrometastases are all but a few examples of factors that we think should be included in the pro- and con discussions. Each proposed treatment should be evaluated according to expected patient benefit weighted against potential complications. Recent studies pave the way to prospective trials assessing predictors that would tip the scale towards choosing a more aggressive multimodal treatment, such as extended surgery to IMN.

For this patient with contralateral IMN metastasis, tumor board experts in the CHUM suggested IMN dissection during mastectomy, despite stage IV breast cancer. Arguments raised in favor of surgery were the lack of clear guidelines, age and overall health of the patient, limited disease to lymph nodes, luminal A molecular subtype, thoracoscopic minimally-invasive surgical approach, and patient's concern about residual disease. Longer follow-up with serial and close imaging will be essential for this patient. At last, follow up 6 months after surgery, the patient has no locoregional or distant cancer recurrence.

Ethical Consideration

The ethics committee from CHUM Hospital was consulted and it was suggested that written or verbal consent be obtained. Verbal consent was obtained from the patient whose case inspired the discussion.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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