

Current Research in Surgery

Case Report

Isolated Extra-Axillary Lymph Nodes in a Case of Invasive Ductal Carcinoma of the Breast: Case Report and Literature Review

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ABSTRACT

Background: Lymphatic drainage of each breast is estimated to be 75% to the ipsilateral axillary lymph nodes while extra-axillary lymph nodes make up the remaining. On lymphoscintigraphy, it is common to see a combination of axillary and extra-axillary lymph node drainage and much less common to see drainage isolated to extra-axillary lymph nodes.

Materials and Methods: This case report and literature review discusses an unusual case of invasive ductal breast carcinoma with only internal mammary and intra-mammary lymph nodes visualized on lymphoscintigraphy. This review discusses the importance of lymphoscintigraphy technique, the risk versus benefit of performing internal mammary lymph node (IMLN) biopsy, and determining operative management.

Results: There is an estimated 1-8% chance of IMLN drainage in cases of invasive ductal breast carcinoma. The rate of metastatic disease to IMLNs is significantly lower than axillary lymph nodes making biopsy of questionable benefit and the risks of performing such must be considered due to the complexity of the procedure. Overall, there is not a general consensus on the significance, excision practices or treatment of extra-axillary lymph nodes.

Conclusion: There are currently no clear guidelines regarding the management of extra-axillary lymph nodes making it an important topic for study. More research is needed to improve lymphoscintigraphy visualization and create a safe technique for IMLN biopsy. This could potentially aid in staging and help to formulate new treatment plans and radiotherapy protocols.

Introduction

Our current understanding of breast lymphatics originally began in the 1850's by anatomist Marie Philibert Constant Sappey. In 1874, he established one of the most comprehensive and influential studies characterizing the lymphatic system by injecting mercury into the interstitial tissues and lymphatic vessels of cadavers to produce an extensive lymphatic atlas. He explained that breast lymphatics were separate from the underlying torso lymphatic system. Additionally, he displayed a subareolar lymphatic subplexus of the breast and a small system of large breast lymphatic vessels draining into the axillary lymph nodes (Figure 1). From these findings he subsequently created the anatomical basis of axillary lymph node drainage claiming

that the lymphatic drainage on the trunk of the body from the skin was symmetric between the two sides of the body and never crossed the vertical midline. On each truncal side the lymphatic zones were divided into four regions from the skin level. These lines of division were coined "Sappey's lines" and presumptively defined which axillary or groin nodal region lymphatic drainage would occur [1].

Sappey's conclusions were widely accepted and followed by the scientific and medical community for over a hundred years until the 1970's when they were challenged. Further studies were carried out with contradictory conclusions, particularly in melanoma patients, but, ultimately, Sappey's theory, with a few exceptions, was re-demonstrated showing the lymphatic drainage system of the skin

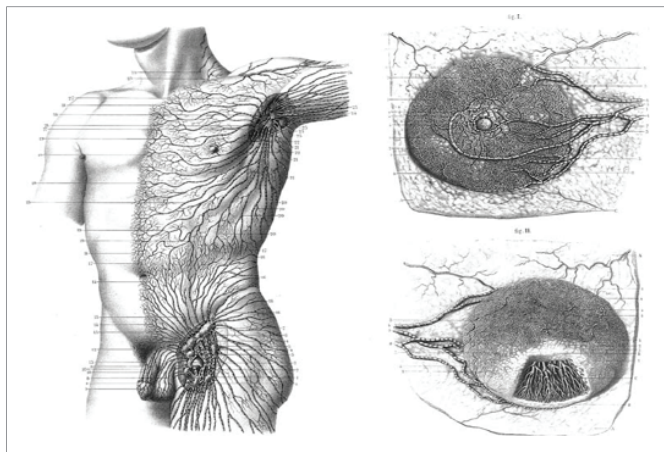


Figure 1: Sappey's drawing of superficial lymphatics of the male upper torso and female breast in 1874 [1].

is symmetric. In an analysis of breast cancer patients with axillary nodal drainage, one of the exceptions to this symmetric drainage theory, showed that there are more axillary lymph nodes on the left side of the body compared to the right; however, the lymph nodes on the left are smaller than the lymph nodes on the right. With this new understanding along with Sappey's anatomical basis of axillary lymph nodal clearance, a further understanding of breast lymphatics and how it is affected in breast cancer patients has continued to be studied [2].

The lymphatic drainage of the breast begins in an avascular capillary network at the superficial dermis and is carried to the subcutaneous lymphatics [2]. An estimated 75% of the breast lymphatic drainage is to the axillary lymph nodes which has been described in approximately 90% of the patient population in random studies. The remaining lymphatic drainage is to the internal mammary lymph nodes, intramammary, interpectoral, intercostal, supraclavicular and infraclavicular lymph nodes, termed extra-axillary lymphatic drainage of the breast [3]. Lymphatic drainage may be impacted by the location of the breast tumor as well as depth of the tumor, particularly when examining palpable versus non-palpable lesions. Anatomic studies on the arrangement of breast lymphatics show that retromammary lymphatics, which supply the internal mammary and interpectoral lymph nodes, arise from breast lobules and run along the pectoral fascial plane. They accompany the blood vessels that penetrate the pectoral and intercostal muscles. Non-palpable lesions have been found to have less drainage to the axilla and more to the internal mammary lymph nodes, irrespective of the breast quadrant of focus. A suggested explanation is that non-palpable lesions are generally deeper within the breast and closer to the deep fascial planes. The depth of tumor and its relationship to these lymphatics, may explain the difference in drainage to extra-axillary sentinel lymph nodes [3]. In one study the visualized extra-axillary sentinel lymph nodes in cancer patients with non-palpable tumors were reported at 43%, which was significantly different than the palpable tumor visualization of extra-axillary sentinel lymph nodes at a rate of 24% [3].

Lymphatic drainage in breast cancer patients is most commonly explored through sentinel lymph node biopsy. Lymphoscintigraphy is a nuclear medicine modality that has the potential to identify the lymphatic system in its earliest stages and to some extent estimate

the number of sentinel lymph nodes. Breast lymphoscintigraphy demonstrates that the axilla is the most common site for a sentinel lymph node(s) to appear. On lymphoscintigraphy, it is common to see a combination of axillary and extra-axillary lymph node drainage and much less common to see drainage isolated to extra-axillary lymph nodes [3]. In this case report, we have visualization of isolated internal mammary and intramammary lymph nodes on the lymphoscintigram in a case of invasive ductal carcinoma with no axillary sentinel lymph node visualization.

Case Presentation

An obese 71-year-old female with history of right lung cancer with partial lung resection presented to breast clinic with diagnosis of invasive ductal carcinoma of the right breast. She had not received chemotherapy or radiation treatment for her lung cancer. Her (living) sister was diagnosed with breast cancer at age 40. Her screening bilateral mammogram showed a focal asymmetry and microcalcifications at the 10:00 aspect of the right breast (Figure 2). A targeted ultrasound with core needle biopsy was performed (Figure 3).

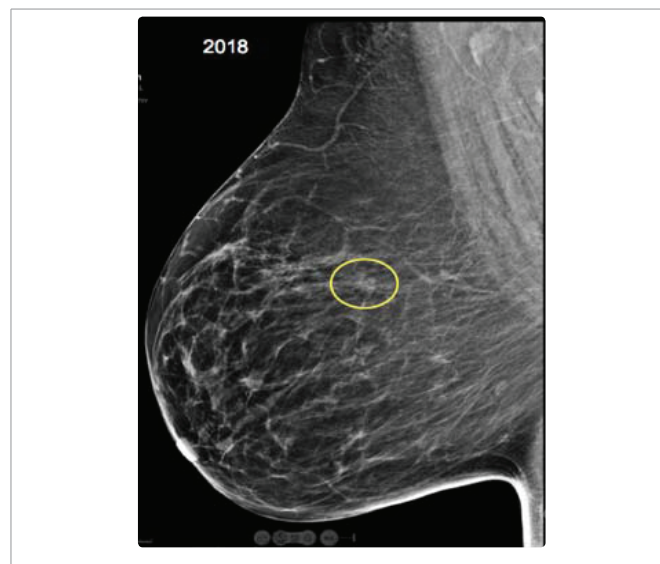


Figure 2: Mammography of the right breast with a focal asymmetry and microcalcifications at the 10:00 aspect.

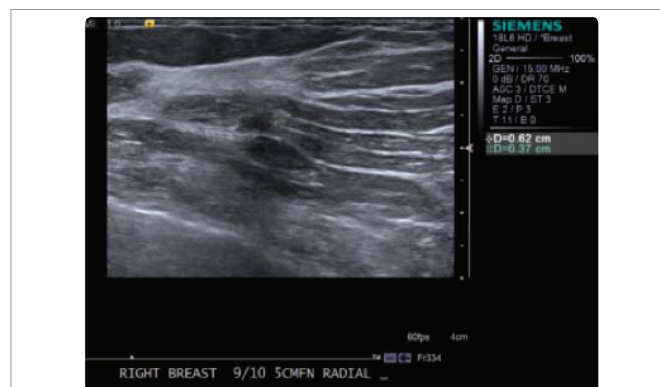


Figure 3: Right breast, spiculated, 6mm ill-defined suspicious solid nodule, BIRADS 4.

Pathology revealed a well-differentiated invasive ductal carcinoma, ER/PR positive, Ki-67 10%, and HER2 negative. MRI revealed the biopsy proven cancer and no additional findings (Figure 4). A PET /CT was unremarkable. Her clinical breast exam was unremarkable.

Management and Outcome

Five hundred mCi of Technetium-99m (Tc-99m) tilmanocept was administered intradermally with four injections into the right breast and lymphoscintigraphy was performed (Figure 5).

There are multiple lymph nodes in the right internal mammary region and additional uptake on the medial aspect of the breast in the right intramammary region. No axillary lymph nodes are identified. Delayed 17 hour imaging was taken the following day (not pictured) and again did not reveal axillary lymph nodes.

In the operating room no nuclear activity was detected in the axillary region by the Geiger counter. The active sites correlated precisely with the lymphoscintigram (Figure 5). Five mL of Lymphazurin blue dye was injected into the retroareolar area. A faint area of blue lymphatics was visualized traveling towards the upper outer quadrant, perhaps the axilla (Figure 6).

She underwent a right partial mastectomy with preoperative placement of radioactive seed, intramammary lymph node biopsy, which was a sentinel node with benign pathology, and right axillary exploration for attempted right axillary sentinel lymph node biopsy however no blue nodes were visualized and there was no nuclear uptake in the axilla. The internal mammary lymph nodes were not pursued due to the potential complication risk and it is not current standard of care.

Surgical incisions include: medially at the active intramammary site where sentinel lymph node biopsy was performed; laterally where lumpectomy was performed; and the axilla where sentinel lymph node biopsy was attempted. The surgical markings along the chest wall correlate to the internal mammary lymph nodes active on the Geiger counter that match the lymphoscintigram. Note how the blue dye mostly travels medially; however there is a small focus traveling laterally.

Surgical pathology showed a 1.2 cm well-differentiated invasive

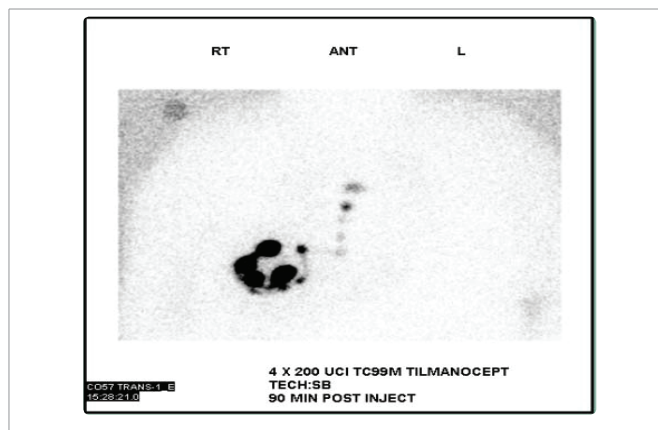


Figure 5: Right Breast Lymphoscintigraphy.



Figure 6: Intraoperative picture of the patient's right breast.

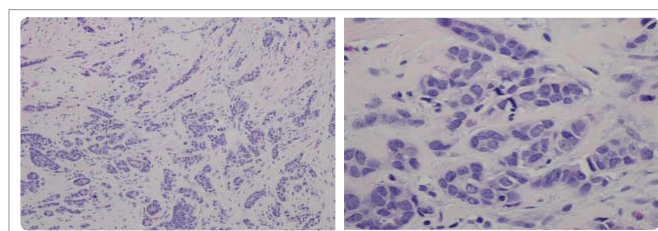


Figure 7: Invasive ductal carcinoma well differentiated. Left: 40X, Right: 100X.

ductal carcinoma. One sentinel lymph node, intramammary, was negative for carcinoma (Figure 7).

Discussion

It is more common for both axillary and extra-axillary lymph nodes to be visualized on lymphoscintigraphy and rare to find isolated extra-axillary lymphatic drainage.

Drainage to intramammary lymph nodes (intraMLNs) has been detected anywhere from 28-47% of breasts, with only a small portion linked to metastatic breast disease [5]. Reports describing intramammary sentinel nodes (intraSLNs) are relatively rare in

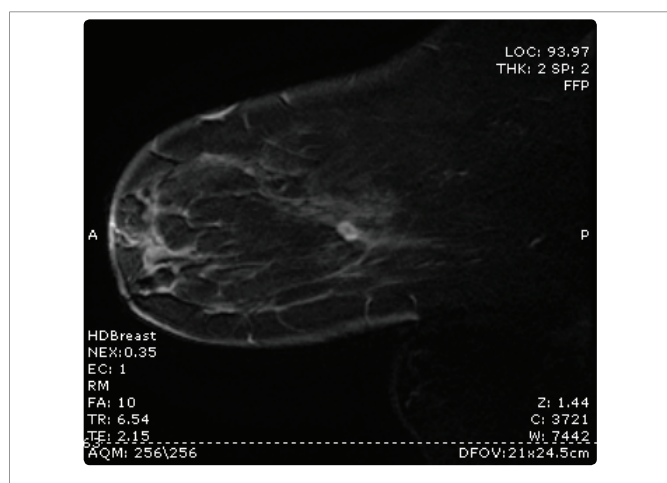


Figure 4: MRI: A 10 x 7 x 8 mm rim enhancing mass in the upper outer quadrant of the right breast at 10:00, 10 cm from the nipple.

an estimated less than 1% of cases, and the clinical significance of metastases in intraSLNs is unclear [6]. There is no general consensus on the significance, excision practices or treatment of extra-axillary lymph nodes; however, it is advocated that when there is a presence of an intraSLN in conjunction with axillary sentinel lymph nodes, that biopsies of both sites should be performed. When an isolated intraSLN is present, biopsy is also recommended [5].

There is an estimated 1-8% chance of isolated internal mammary lymph node (IMLN) drainage with the overall rate of nodal metastasis less than 5% compared to the rate of axillary nodal metastasis reported at 34% [7]. It is widely accepted that prophylactic IMLN excision is not the current standard surgical treatment. However, some researchers have attempted internal mammary sentinel lymph node biopsy (IM-SLNB) stating it is important for accurate staging and prognostic factors [7]. There are currently no clear guidelines on the operative management of internal mammary sentinel lymph nodes (IM-SLN) and further studies are warranted. Most surgeons, though, currently disagree with surgical excision of IMLN and radiation to this area and literature remains controversial [5].

A Korean study carried out from 2001 - 2006, retrospectively analyzed 525 patients with early stage breast cancer and investigated clinical features of tumors with IMLN drainage while determining the clinical significance and long-term outcomes. Two groups were studied, one with only axillary lymph node drainage and the other with either combined axillary and IMLN or isolated IMLN drainage. Amongst these, 14.7% had combined axillary and IMLN drainage and 2.1% had isolated drainage to the IMLN. Follow-up results for early stage breast cancer, recurrences, and deaths showed no statistically significant difference in survival outcome or recurrence rates in patients with or without IMLN drainage [7].

Another study looked at 470 cases that underwent autologous reconstruction surgery at the time of breast cancer surgery between 2002 - 2014 and looked at the incidence of IMLN metastases. Of these, 157 cases had confirmed IMLN removal during the reconstruction and 6% of these were metastatic resulting in the upstaging of 2 patients. Interestingly, 3% of patients had isolated IMLN metastases with no axillary involvement. It was noted there was significant association of metastatic disease in patients less than 40 years old with lymphovascular invasion and negative PR status. The study suggested selectively performing IMLN biopsy in younger patients with lymphovascular invasion and negative PR status to assist in guiding adjuvant treatment [8].

In 2009, the American Joint Committee on Cancer, AJCC, incorporated the IM-SLNB concept into their management practices and guidelines for breast cancer; however, without significant change in operative management [9]. Between 2012 to 2015 the National Comprehensive Cancer Network (NCCN) Breast Cancer Clinical Practice Guidelines recommended internal mammary lymph node irradiation (IMLNI) for patients with axillary node metastasis after lumpectomy or mastectomy [4]. Subsequent to this trial, in 2016, the NCCN strongly recommended IMLNI in patients with ≥ 4 positive axillary lymph nodes (ALNs), and to strongly consider IMLNI for patients with 1-3 positive ALNs, both after mastectomy and lumpectomy [10]. Most recently, in 2017, the AJCC added internal mammary lymph nodes into their definition for clinical and pathological regional lymph nodes, impacting the overall staging and prognosis of breast cancer [9]; however, to date, there have not

been any studies to evaluate a change in surgical practices and further research is needed.

It is important to carefully consider the risk versus benefit of performing extra-axillary lymph node biopsy, particularly IMLN. Tan, Caragata and Bennett reviewed biopsy outcomes in a series of breast cancer patients of which 95 out of 581 (16.4%) had drainage to the internal mammary lymph node chain. Of these, 51 were surgically explored and 35 were found to have IM-SLNs. Only three patients (0.08%) had metastatic involvement within this group. A complication rate of 7.8% was reported secondary to pneumothorax concluding that the risk of performing the procedure outweighed the benefit [11]. Another group of researchers speculated that the perceived complexity of the procedure and potential risk of complications including bleeding and chylothorax is another reason IM-SLNB is not routinely performed. Advances in technique along with surgeon's experience and technical skill may lower these rates overtime [12]. Currently, though, further research is warranted before incorporating this procedure into practice.

Proper injection technique is also important. Superficial injections are most frequently used and improper technique can affect the range of visualization, particularly within the extra-axillary lymph nodes. Studies suggest visualization of IMLN ranges from 0-37%, with an average of 13% [13]. It is unknown whether this range of discrepancy is secondary to technique or anatomical factors [2,13].

The amount of radioisotope injection and time interval between the injection and imaging performed may affect these detection rates [7]. In this case, however, a standard amount of Tc-99m was used and the patient was re-imaged 17 hours later showing the same results. Researchers have suggested that a modified high volume radiotracer injection under ultrasound guidance in the periareolar intraparenchymal region would significantly improve the IMLN visualization rate [13]. Better visualization with proven safe biopsy technique could lead to individualized minimally invasive staging with the potential for creating internal mammary radiotherapy regimens and protocols [13].

Furthermore, the depth of the tumor and its relationship to lymphatics may explain drainage to extra-axillary sentinel lymph nodes. A suggested explanation is that non-palpable lesions generally lie deeper within the breast and closer to the deep fascial planes [2]. They are thought to drain less to the axilla and more towards the extra-axillary lymph nodes, including IMLNs irrespective of the breast quadrant of focus [3]. In this case, the tumor was deep and non-palpable which correlates with this relationship.

Conclusion

In summary, there are currently no clear guidelines regarding the management of extra-axillary lymph nodes making it an important topic for study. It is recommended, however, to excise intramammary lymph nodes when visualized on lymphatic mapping. Most surgeons currently do not pursue IMLNs because the current literature shows no increased survival rates or decrease in recurrence. There is also an increased complication rate to benefit ratio when pursuing IM-SLNB. More research is needed to improve lymphoscintigraphy visualization and to create a safe technique for IMLN biopsy. This could potentially aid in staging and help to formulate new treatment plans and radiotherapy protocols. Overall, more research is warranted before incorporating a new standard into the current practice guidelines.

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