

Title: Aberrant Lymphatic Drainage of Primary Invasive Lobular Carcinoma with Concurrent Primary Lung Adenocarcinoma: A Case Report

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| Contributor Role | Role Definition | Authors | |
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| | | 1 | 2 |
| Conceptualization | Ideas; formulation or evolution of overarching research goals and aims. | X | X |
| Data Curation | Management activities to annotate (produce metadata), scrub data and maintain research data (including software code, where it is necessary for interpreting the data itself) for initial use and later reuse. | X | |
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Highlights:

- This is a case report of a patient, with no known genetic abnormalities, who was found to have two primary carcinomas, invasive lobular carcinoma and adenocarcinoma of the lung, after workup of a breast mass found during self-examination.
- The lymphatic drainage of the invasive lobular carcinoma was found to be atypical, spreading to the contralateral lymphatic beds without involvement of the ipsilateral lymphatic beds.
- Furthermore, the case points to the use of imaging techniques in the diagnosis and treatment of cancers.

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40

41 **Discussion Points:**

42 1. Lymphatic drainage pattern of invasive lobular carcinoma.

43 2. most likely cause of the aberrant lymphatic drainage

44 3. Impact on workup guidelines of suspected cancers (with extensive lymphatic spread).

45 4. Role of biopsy in diagnosis and cancer staging

46

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53 **ABSTRACT.**

54

55 **Background:** Lymphatic spread of breast cancer is currently well understood and can be assessed in breast
56 cancer patients through the use of lymphatic mapping with sentinel node biopsy, CT or PET.

57

58 **The Case:** A 73-year-old female with two distinct primary carcinomas, right-sided invasive lobular carcinoma
59 of the breast and left-sided adenocarcinoma of the lung. We discuss the predictable and unpredictable lymphatic
60 drainage of the lobular carcinoma, including ipsilateral drainage to the axillary chain and suspected contralateral
61 hilar and mediastinal lymph node metastasis.

62

63 **Conclusion:** The unique lymphatic spread of the breast cancer in this case emphasizes the use of lymphatic
64 mapping for staging of disease and staining biopsied tissue samples for tumor markers to guide treatment.
65 Additional anatomic research in this patient or supporting reported cases are needed to determine the frequency
66 and cause of aberrant lymphatic drainage of primary invasive lobular carcinoma of the breast.

67

68 **Key Words:** lobular carcinoma, adenocarcinoma of lung (Source: MeSH-NLM).

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70 **INTRODUCTION.**

71 Invasive lobular carcinoma (ILC) comprises around 10% of all breast cancers.¹ The malignant cells line up in a
72 single file in the stroma and usually do not form a distinct, palpable mass. Overall, the prognosis tends to be
73 good, due to the low grade of the tumor and its nature of being estrogen receptor positive (ER +).² However,
74 ILC tends to be multifocal and multicentric and can involve both breasts.³ Such characteristics have led to cases
75 of distant metastases involving the peritoneum, ovaries, and uterus.⁴ The vast majority of breast malignancies
76 tend to spread via axillary lymph nodes, but there can also be nodal metastases outside of the axillary lymph
77 nodes, involving the internal mammary, infraclavicular, and supraclavicular lymph nodes.⁵ Furthermore, breast
78 malignancies, using lymphatic and hematogenous routes, can have pulmonary involvement, called pulmonary
79 lymphangitic carcinomatosis.⁶

80

81 Adenocarcinoma of the lung is the most common type of lung cancer and can quickly spread to distant sites via
82 lymphatic and hematogenous routes, which often results in stage IV disease by the time of patient presentation.⁷

83

84 Here, we present an interesting case of a primary, right-sided invasive lobular carcinoma with ipsilateral axillary
85 nodal involvement and primary, left-sided adenocarcinoma of the lung with suspected ipsilateral hilar and
86 mediastinal lymph node metastasis, which actually turned out to be invasive lobular carcinoma. Informed
87 consent of publication was obtained from the patient prior to submission/publication.

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89 **THE CASE.**

90 The patient is a 73-year-old African American female with no family history of breast or ovarian cancer, who
91 initially presented due to a right breast mass palpated upon routine self-breast examination. She had a
92 screening mammogram completed, which showed a 2.5cm spiculated mass in the right breast at the 6 o'clock
93 position, 16cm from the nipple along with a 1.1cm asymmetry anterior to the mass and a 0.8cm asymmetry in
94 the right retroareolar region (**Figure 1**). The radiologist assessment was BI-RADS 0 (Breast Imaging Reporting
95 and Database System), and additional imaging was recommended.

96
97 Two weeks later, the following diagnostic mammogram showed a 2.3cm irregular, spiculated mass in the right
98 breast at the 9 o'clock position, 17cm from the nipple along with a 0.7cm mass, 2cm from the nipple. Whole
99 breast ultrasound showed a solid mass in the right 8 to 9 o'clock position, highly suspicious for malignancy
100 along with an abnormal lymph node in the right axilla. The radiologist assessment this time was BI-RADS 5:
101 highly suggestive of malignancy, so biopsies of the lesion and lymph node were recommended.

102
103 The patient was seen by a breast surgeon, who examined the patient and noted the patient's breasts to be
104 enormous and very pendulous with palpation of some nodularity in the extreme outer right breast, but no lymph
105 nodes were palpated in the axillary and supraclavicular regions.

106
107 The following day, patient underwent an ultrasound-guided core biopsy with multiple cores taken from the
108 primary lesion in the right breast at the 8 o'clock position, 13cm from the nipple (**Figure 2**). The 5-6mm satellite
109 lesion was seen 3-4mm away from the primary lesion, but no biopsy samples were taken. Multiple cores were
110 taken from an enlarged right axillary lymph node, which showed cortical thickening with compromise of the hilum
111 that measured 1cm. The pathology report that followed showed invasive lobular carcinoma with positive axillary
112 metastasis.

113
114 Breast-specific gamma imaging (BSGI) and Positron emission tomography-computed tomography (PET-CT)
115 were ordered one week later. The BSGI showed a 2cm diameter area of intense focal uptake in the right breast
116 at 9 o'clock, 15cm from the nipple with no evidence of multifocal, multicentric disease. The PET-CT findings
117 included: an irregular right lateral breast mass, consistent with known right breast carcinoma, mildly enlarged
118 right axillary lymph nodes consistent with nodal metastases (**Figure 3**), and an irregular nodule within the
119 superior segment of the left lower lobe, which was concerning for metastasis or concurrent primary
120 bronchogenic carcinoma (**Figure 4**).

121
122 Based on such findings, the breast surgeon and interventional radiologist agreed upon a CT-guided biopsy of
123 the left pulmonary lesion (**Figure 5**) two weeks after the imaging studies were completed. Two 20-gauge core
124 biopsy specimens were obtained with no complications, and the pathologist reported well differentiated
125 pulmonary adenocarcinoma with predominant lepidic growth pattern. The specimens stained positively for
126 cytokeratin 7, napsin-A, and TTF-1 (thyroid transcription factor-1). The major risk factor for the patient was a
127 history of tobacco use, which started at 17 years of age.

128

129 At this point, the patient's diagnoses were stage II carcinoma of the breast and a primary tumor of the left lung.
130 Three weeks later, the patient subsequently underwent a right needle-localized lumpectomy and axillary
131 dissection. The pathology report confirmed invasive lobular carcinoma, and 2 of the 2 lymph nodes tested
132 positive for metastatic lobular carcinoma. The tumor was ER (estrogen receptor) positive, PR (progesterone
133 receptor) negative, and HER2 (human epidermal growth factor receptor 2) negative. The staging of the breast
134 cancer was T1c N1 M0 stage IIa invasive lobular carcinoma.

135
136 The patient was referred to an oncologist and cardiothoracic surgeon. One month later, she had a left lower
137 lobectomy and mediastinal lymph node dissection performed. An 18.5 x 12.0 x 4.0cm lobe of the left lung that
138 weighed 173.4g was removed. The pathology report showed moderately differentiated adenocarcinoma with
139 lepidic predominance; all the vascular and bronchial margins were free of tumor. However, the pathology report
140 showed the left mediastinal lymph nodes to actually be invasive lobular carcinoma: 1 of 1 peribronchial, 5 of 6
141 interbronchial, 1 of 1 subcarinal, 1 of 1 aortopulmonary window, 1 of 1 left inferior pulmonary ligament, and 1 of
142 1 hilar. The hilar lymph nodes stained positive for pankeratin and GATA3 (transcription factor and breast cancer
143 marker) (Takaku) and negative for TTF-1 (Schilsky) and CD68. They were strongly positive for ER 100%,
144 positive for PR 2%, and HER2 negative. Based on such histological characteristics, the left hilar lymph nodes
145 were most consistent with metastatic invasive lobular carcinoma and not lung adenocarcinoma. The patient's
146 diagnoses were changed to stage IV carcinoma of the breast and stage IA2 (T1b, N0, M0) carcinoma of the
147 lung. She is currently undergoing chemotherapy with letrozole and Ibrance (palbociclib).

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148 **DISCUSSION.**

149 Here we presented a unique case of primary lobular carcinoma of the right breast, primary invasive
150 adenocarcinoma of the left lower lung lobe with pankeratin positive, GATA3 positive, ER positive left
151 peribronchial lymph node involvement. Lymphatic spread of breast cancer is thought to be well understood.
152 This case highlights a unique pattern of lymphatic spread of unknown etiology. Review of other case reports
153 indicates the pattern of lymph node involvement in this patient with invasive lobular carcinoma of the breast is
154 quite unique. While other cases were found on spread of invasive lobular carcinoma to the contralateral breast
155 and aberrant lymphatic drainage patterns in recurrent breast cancer after treatment, no additional cases were
156 found in the literature of spread of invasive lobular carcinoma to contralateral hilar and mediastinal lymph nodes
157 in a patient with no previous history or treatment of breast cancer.

158
159 Lymphatic drainage of the breast drains ipsilaterally through the axillary, transpectoral and internal mammary
160 pathways.⁸ Further drainage occurs into “lymphatics that course along the axillary and contiguous subclavian
161 vein. From here, the lymphatics may drain directly into the jugulosubclavian confluence or initially pass through
162 the jugular and bronchomediastinal lymphatics.”⁸ The variance of lymphatic drainage seen in various tumors
163 may be attributed to the quality of the lesions, whether it is palpable or nonpalpable, and the location of the
164 lesion within the breast, either in the right outer, right inner, left outer, or left inner quadrant or in the center.
165 According to Estourgie et al, both palpable and nonpalpable lesions can drain toward the internal mammary
166 chain, but this pattern is more commonly seen with nonpalpable lesions.⁹ Furthermore, Estourgie et al. reveals
167 97.1% of palpable lesions in the left outer quadrant should be expected to drain to the axillary lymphatic bed
168 while 26.1% of palpable lesions in the same location drained to the internal mammary chain of lymphatics.⁹
169 Because of the location of the primary breast tumor in the left outer quadrant (9 o'clock position of the right
170 breast), the most predictable pattern of lymphatic drainage in this patient would be to the axillary nodes. While
171 this patient had involved lymph nodes in the axillary chain, including sentinel nodes, stain positive for the
172 invasive lobular carcinoma, additional lymphatic drainage to the contralateral hilar and mediastinal lymph nodes
173 without ipsilateral hilar and mediastinal lymph node involvement was unique and not currently explained by the
174 literature.

175
176 The question raised by the physicians caring for this patient was, how did the breast cancer spread to a single,
177 contralateral region of lymph nodes without involvement of other ipsilateral or contralateral lymph node beds?
178 Could this be an anatomic variant in this patient? Were there additional factors that allowed the spread of the
179 tumor to a contralateral lymphatic bed, or was the cancer undiagnosed for a length of time adequate enough
180 for the lobular carcinoma to contralaterally spread? According to Sharma et al.,⁸ obstruction of normal lymphatic
181 flow allows for development of collateral lymphatic drainage pathways, including internal mammary and
182 mediastinal lymphatics. Lymphatic mapping with sentinel node identification in this patient identified drainage
183 of the primary tumor to the axillary nodes. An anatomical variant or development of collateral pathways not
184 assessed during the lymphatic mapping could explain the unique spread of the invasive lobular carcinoma in
185 this patient. This case may support the expansion of lymphatic mapping into further lymphatic regions to identify
186 spread of the tumor and may prompt further developments and advancements in lymphatic mapping as it
187 pertains to breast cancer. The unpredictable lymphatic spread in this case prompts the discussion of the
188 appropriateness of routine PET scans prior to treatment in breast cancer patients with no evidence of additional

189 lymphatic spread on CT. CT is commonly used in cancer imaging to determine lymph node involvement.
190 Because involved lymph nodes appear normal on CT, fluorine-18 fluorodeoxyglucose (FDG) PET can be used
191 for more accurate detection of lymphatic spread of the primary tumor and relevant lymph node involvement.⁸
192 Additional reports and studies are needed to determine the incidence of contralateral spread of lobular
193 carcinoma of the breast to unusual lymphatic beds to determine the benefit of FDG-PET in conjunction with
194 current CT scanning on patients with suspected additional extra-axial or contralateral lymph node involvement.
195
196 During the initial assessment of the patient, the involved hilar and mediastinal lymph node was suspected to be
197 secondary to the primary adenocarcinoma of the left lung by the treatment team. Only through further staining
198 and discussion was the origin of the carcinoma in the hilar and mediastinal lymph nodes discovered.
199
200 The complexity of this case illustrates the importance of staining biopsied tissue samples for tumor markers to
201 accurately stage the disease and to ensure a chemotherapy regimen and further treatment is appropriate.
202 Further research is needed to determine the impact of the aberrant lymphatic drainage of primary invasive
203 lobular carcinoma as seen in this patient.

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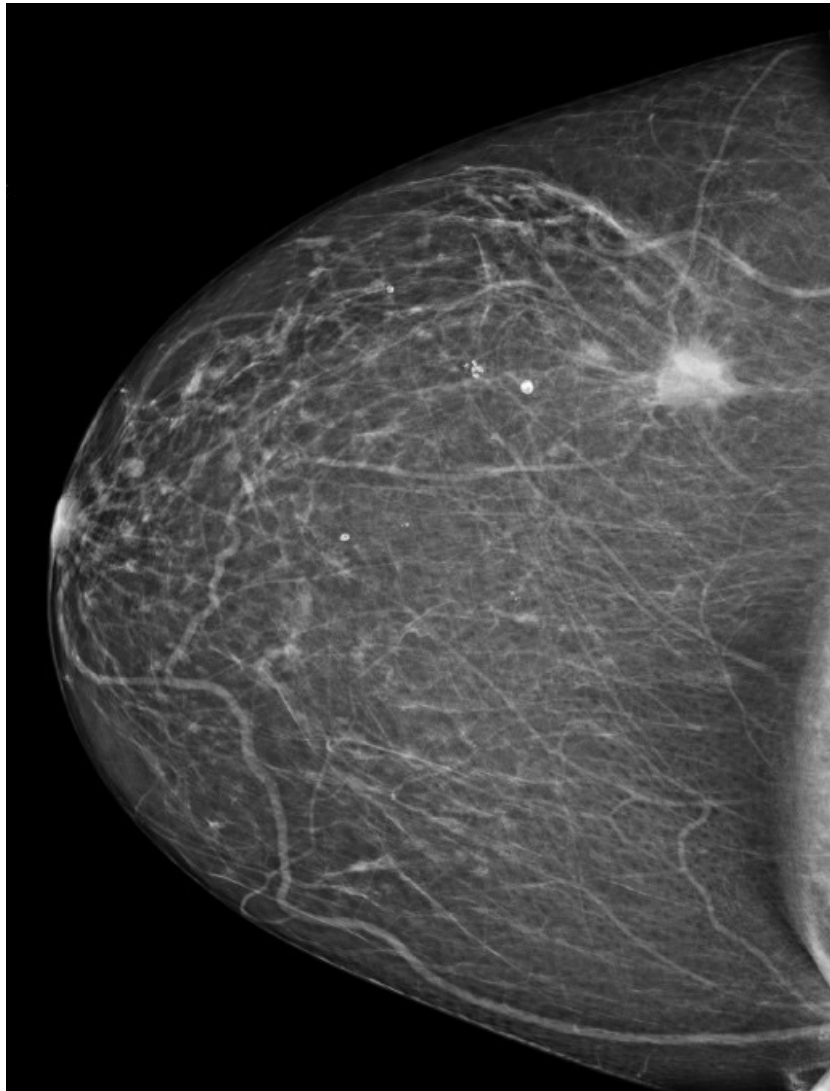
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232

FIGURES AND TABLES.

233

Figure 1: Screening mammogram showing spiculated mass in right breast.



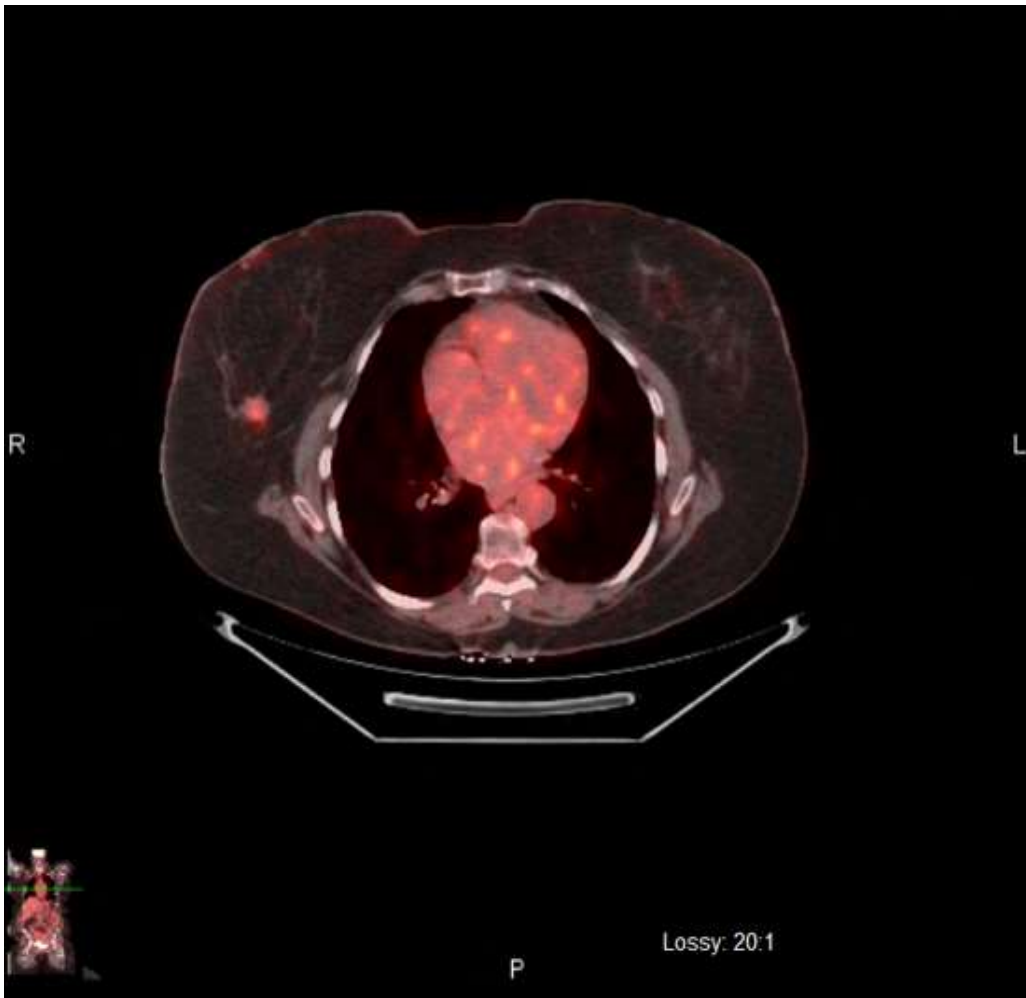
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234 **Figure 2:** Ultrasound image showing right breast mass prior to biopsy.



235 **Figure 3:** PET image showing right lateral breast mass with fluorodeoxyglucose uptake.



236 **Figure 4:** PET image showing fluorodeoxyglucose uptake in superior segment of left lower lobe.



237 **Figure 5:** CT showing left lung lesion prior to biopsy.

