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Contralateral Axillary Lymph Node Metastasis in Breast Cancer, an Unusual Clinical Scenario: A Case Report and Review of the Literature

A. Ali Assarian^a, Ahmad Elahi*^a^a Department of Surgery, Tehran University of Medical Sciences, Tehran, Iran

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ABSTRACT

Background: Contralateral axillary metastasis (CAM) is a rare entity in patients with breast cancer which can occur during the primary breast cancer or its follow-up. Different treatment modalities include surgery, radiotherapy, and chemotherapy, but there is no agreement on them. In our review, we found 12 series with available data, 82 patients with synchronous or metachronous contralateral axillary node involvement with no primary cancer in the contralateral breast.

Case Presentation: Our patient was a 50-year-old woman who presented with locally advanced right breast cancer with no distant metastasis. After treatment including neoadjuvant chemotherapy, MRM, and radiotherapy, her contralateral axillary lymph node was involved with metastatic carcinoma compatible with ductal carcinoma of the breast with similar IHC results. Evaluation of the contralateral breast was negative for occult lesions and metastatic workups were negative for malignancy. We assumed this presentation as a CAM and planned the treatment accordingly.

Conclusion: CAM without systemic metastasis might be considered a regional disease because in many cases the spread is lymphatic and not hematogenous. The new concept of lymphatic invasion instead of hematogenous spread has changed the intent of palliative to curative treatment. According to our study, CAM patients were mostly managed with chemotherapy (96%), ALND (45%), contralateral breast and axillary radiation (35%). The prognosis of CAM is usually poor with a high relapse rate (>60%) and a mortality rate of 15% in our review after 14-43 months follow-up, but it is better than the prognosis of the patients with systemic metastasis.

Introduction

Contralateral axillary lymph node metastasis (CAM) is an unusual clinical scenario which challenges the patient's treatment. More cases are documented as a result of the increasing use of high resolution ultrasound; therefore, clinicians who deal

with breast cancer should be more aware. During the last 6 months, we had 3 documented cases at our center that were mainly detected by ultrasonography. We have the data of one patient available which we will present it in this report. We have reviewed the available data, and discussed the pathophysiology, diagnostic workup, and treatment options.

Breast cancer contralateral axillary lymph node metastasis (CAM) is rare, with an incidence of 1.9% – 6%.¹⁻⁷ This condition can be synchronous (at the same time as primary breast cancer diagnosis) or metachronous (following prior treatment of breast cancer as a recurrence).³ Kiluk *et al.* used the term synchronous when CAM was diagnosed within one

Address for correspondence:

Ahmad Elahi, MD
Address: Department of Surgery, Imam Khomeini Hospital,
Keshavarz Blvd., Tehran, Iran
Tel: +98 21 88871785
Fax: +98 21 88871698
Email: elahi84@gmail.com



year of the breast cancer diagnosis and metachronous when CAM was detected after one year.⁸ Traditionally, CAM has been considered a systemic condition (stage IV) and treated as a widespread metastatic disease.⁴ Some authors believe in a new concept of regional disease rather than a distant disease that may have a better outcome.⁸ Jaffer *et al.* reported a case of contralateral axillary metastasis as the first evidence of recurrent breast carcinoma.⁹ Kinoshita S. *et al.* reported a case of second new primary breast cancer with CAM 4.5 years after the treatment of the breast cancer with breast conserving therapy.¹⁰ Herold CI *et al.* reported a case of new primary breast cancer with synchronously CAM in a patient 9 years after breast conserving surgery of the primary breast cancer.¹¹ In all of these cases, the management of such patients is controversial in terms of the curative or palliative intent.³

Case presentation

In February 2015, a 50-year-old woman presented with a right breast mass. There was no family history or any risk factor of breast cancer. On physical examination, she had a locally advanced breast cancer. Tissue diagnosis with core needle biopsy of the mass confirmed grade 2 invasive ductal carcinoma that was ER (estrogen receptor) positive, PR (progesterone receptor) negative, and HER-2 negative, with 15-18% ki-67. Staging did not show any evidence of distant metastasis. The patient was referred for neoadjuvant chemotherapy and after 8 courses, she underwent mastectomy and axillary lymph node dissection. After surgery, she was referred for radiotherapy. Few months after adjuvant treatment, she was referred to the surgical department with a suspicious contralateral axillary lymph node and core needle biopsy of the lymph node confirmed metastatic carcinoma compatible

with ductal carcinoma of the breast that was ER positive, PR positive, and HER-2 negative (similar to the primary tumor). Evaluation of the left breast with physical examination, ultrasonography, mammography, and MRI was negative for occult lesions and again metastatic workup was negative for malignancy. We assumed this presentation as a CAM and planned the treatment accordingly.

Discussion

We reviewed the available published studies of the patients with CAM in the databases of PubMed and Science Direct. All case or series reports of CAM patients from 1995 to 2014 were included. Both synchronous and metachronous CAM were included in this study. None of the patients in the study had evidence of cancer in the contralateral breast. The data of these studies were analyzed according to age, follow-up, treatment options, and survival. Unfortunately, other data such as tumor IHC and location were not available in all reports. We found 12 studies including 82 patients with documented CAM whose information has been showed in Table 1 and 2 and the final results summarized in Table 3.

There are three possible clinical scenarios for explaining CAM: 1) Hematogenous spread, 2) Regional involvement due to occult ipsilateral breast cancer, 3) Regional metastasis to the contralateral side from the deep fascial plexus, anterior chest wall lymphatics that cross the midline.^{2,7}

Barranger *et al.* reported a case of breast cancer in a 70-year-old female (with a history of bilateral mammoplasty) in whom preoperative lymphoscintigraphy above the tumor revealed one sentinel lymph node in the contralateral axilla but axillary dissection showed no node involvement.¹² Some reports have confirmed the contralateral lymphatic

Table 1. Demographic information of CAM reports

	Publication Year	Number of Patients	Median Age	Incidence	Family History (1 st , 2 nd)	Tumor Position	Primary tumor	Pathology	Hormone Receptor	Her-2
Jaffer <i>et al.</i> ⁹	1995	1	50			1 Outer				
Dauod <i>et al.</i> ¹⁷	1998	6		4.9%		5 Inner & central				
Allweis <i>et al.</i> ¹⁴	2003	1	48			Inner		IDC	Positive	Negative
Barranger <i>et al.</i> ¹²	2004	1	70			Outer	Left	IDC	Positive	Negative
Huston <i>et al.</i> ⁴	2007	7	49		6 (86%)	3 Outer 3 Inner 1 Central	All in Left	7 IDC		
Kinoshita <i>et al.</i> ¹⁰	2010	1	60			6 Outer	Left	IDC	Positive	Positive
Morocos <i>et al.</i> ¹⁵	2011	21	51	1.9%		3 Inner 12 Central or diffuse		20 IDC 1 ILC	10 (48%) Positive	8 (42%) Positive
Zhou <i>et al.</i> ³	2013	1				Outer	Left	IDC	Negative	
Kim <i>et al.</i> ⁷	2013	1	52			Inner		IDC	8 (62%) Positive	2 (15%) Positive
Kiluk <i>et al.</i> ⁸	2014	13	53					11 IDC 2 ILC	12 (42.8%) Positive	8 (28.5%) Negative
Dayyat <i>et al.</i> ²	2014	1	63	0.8%		Outer	Left			
Wang <i>et al.</i> ¹	2014	28	47			2 Central 12 Inner 13 Outer		21 IDC 6 ILC 1 other		

Abbreviations: IDC: Invasive Ductal Carcinoma; ILC: Invasive lobular carcinoma



Table 2. Summary of treatment modalities in CAM reports

	Number of Patients	Median Interval (Months)	Median Follow Up (Months)	Lymph Node Surgery	Mastectomy (Contralateral)	Hormone Therapy	Chemotherapy	Radiotherapy (Contralateral)	Survival
Jaffer <i>et al.</i> ⁷	1	metachronous		Yes	Yes	No	Yes	No	Good
Dauod <i>et al.</i> ¹⁸	6	3 synch 3 meta (12 m)		5 (83%)	(no tumor)		5(83%)	5 Axilla (83%)	2 NED 4 AWD
Allweis <i>et al.</i> ¹⁵	1	synch		ALND(limited)	No	Yes	Yes	No	
Barranger <i>et al.</i> ¹⁴	1	synch		No	No	2 (28%)	Yes	No	
Huston <i>et al.</i> ⁸	7	6 metha 71 m 1 synchr (14%)	35 m	Node Excision 1 (14%) ALND 5(86%)	Mastectomy 1 (14%) free tumor		7 (100%) (1 NAC)	6 Breast & Axilla (85%) 1 Chest wall (15%)	2 NED 3 AWD 2 DOD
Kinoshita <i>et al.</i> ¹¹	1	Metha 60 m	36	Yes	No		Yes	Yes Breast	NED
Morocos <i>et al.</i> ¹⁰	21	17 m (10 sync 11 meta)	27	4 (19%)	No	10 (84%)	21 (100%) (5NAC)	No	5 NED 12 AWD 4 DOD
Zhou <i>et al.</i> ⁶	1	Synchronous	27	Yes (ALND)	Yes (no tumor)	Yes	NEC	Bilateral chest wall Not midline	Preasternal recurrence 27 month AWD
Kim <i>et al.</i> ¹⁶	1	Metha 52 m	13	ALND & Supraclavicular LND	No	Yes	Yes	Yes Axilla	
Kiluk <i>et al.</i> ¹²	13	5 (38%) sync 8 meta	43	10 (77%)	No	5 (38%)	100%	5 Axilla (38%)	3 NED 10 AWD
Dayyat <i>et al.</i> ⁵	1	Meta 48m	14	ALND	No	Yes	Yes	Yes	NED
Wang <i>et al.</i> ⁴	28	All methachronous	29	6 (21%) ALND	6 (7%)		26	7 Axilla 1 Breast	3 NED 19 AWD 6 DOD

Abbreviations: NED: No evidence of disease; AWD: Alive With Disease; DOD: Dead Of Disease; BCS: Breast Conserving Surgery; NAC: Neo-Adjuvant Chemotherapy

Table 3. Results of available data in our review

	Number of Included Patients	Overall result in review
Tumor position	61	Inner: 21 (34.4%) Outer: 25 (41%) Central: 15 (24.6%)
Tumor side	7	All in left breast
Histopathology	74	IDC: 64 (86.4%) ILC: 10 (13.6%)
Hormone receptor	67	Positive: 34 (50.7%) Negative: 33 (49.3%)
Her2	66	Positive: 19 (28.7%) Negative: 47 (71.3%)
Time of axillary recurrence	82	Synchronous: 22 (26.8%) Methachronous: 60 (73.2%) (Interval 12-71 months)
ALND(contralateral)	82	Yes: 37 (45.1%) No: 45 (54.9%)
Mastectomy(contralateral)	82	Yes: 5 (6%) (No tumor found) No: 77 (94%)
Hormone therapy	82	All hormone receptor positive
Chemotherapy	82	Yes: 79 (96.3%) No: 3 (3.7%)
Radiotherapy (contralateral)	82	Breast: 5 (6%) Breast & axilla: 11 (13.5%) Axilla: 13 (15.8%) No: 53 (64.7%)
Survival	80	No evidence of disease: 18 (22.5%) Alive with disease: 50 (62.5%) Dead of disease: 12 (15%)

drainage through the deep dermal lymphatic plexus.^{4,8} In a study by Gauthier *et al.*, lymphoscintigraphy of the right breast (in patient with right breast cancer), after periareolar injection, revealed lymphatic drainage from the right breast into the left contralateral axillary lymph node.¹³

Allweis *et al.* reported a case of breast cancer in a 48-year-old female that revealed 2 SLNs, one in the ipsilateral and one in the contralateral axilla, consistent with breast cancer metastasis.¹⁴

Involvement of the dermis in CAM was proved in a study by Kiluk *et al.* in 77% of the patients (10 from

13 patients).⁸ Alternative routes of lymphatic drainage might be prompted by damage to the usual lymphatic drainage (such as irradiation or previous axillary surgery). However, alternative lymphatic drainage routes might also be present in patients without previous surgery or radiotherapy.^{3,12,13}

In a review by Pentheroudakis *et al.*, CAM patients were mostly managed with axillary lymph node dissection and mastectomy (59%), primary breast irradiation (26%), or observation (15%).¹⁵

In a systematic review of the literature by M. Moosdorff *et al.*, 48 patients with contralateral



axillary lymph node recurrence were included and classified them into 3 categories: 1) Isolated contralateral lymph node recurrence (26 patients), 2) Ipsilateral breast tumour recurrence and synchronous contralateral lymph node recurrence, 3) Ipsilateral breast tumour recurrence and subclinical synchronous contralateral lymph node recurrence (15 patients).⁶

Morocos *et al.*, compared 21 patients with CAM with 401 breast cancer patients without CAM. They demonstrated that breast cancer patients with CAM had significantly worse histopathological features, such as a higher tumor grade (81% grade 3 carcinomas), lymphovascular invasion (81%), larger primary breast tumors (95% T3/T4 breast carcinoma), ER-receptor negativity (52%), and HER-2 overexpression (42%).^{3,5}

Wang *et al.* evaluated 28 patients with pathologically confirmed metachronous CAM: 26 patients with CAM were treated with chemotherapy and hormonal therapy, and 2 refused any treatment.¹

Hiram S *et al.* believed that ALND was indicated for patients who experienced relapse in the contralateral axilla and did not have other distant sites of the disease.¹⁶ In a considerable part of our study, ALND was performed and acceptable results were obtained. Contralateral axillary dissection can be a good option which results in excellent axillary control.¹³

Mastectomy has been traditionally performed in patients with occult primary tumor with ipsilateral axillary metastasis. This strategy is based on the observation that approximately 50% of the patients who do not receive therapy to the breast will develop clinically evident disease in the breast. However, in CAM, surgery on the contralateral breast in which physical examination and imaging studies all are without any footprint of an occult cancer is controversial. Routine contralateral mastectomy is probably not indicated.⁴

In all series, chemotherapy was recommended in most patients and hormone therapy was advised in hormone receptor positive patients. Radiation therapy can provide additional help for local control.⁷ In a study by Wang *et al.*, 7 patients underwent ALND, and no difference in median DFS was noted between patients who underwent ALND and those who did not.¹ According to Kim *et al.*, if there is no evidence of other metastatic lesions, lymph node dissection needs to be carried out, and radiation therapy can be added following proper systemic therapy.⁷ In our review, a minority of CAM patients underwent breast radiotherapy (6%).

The rate of the patients that were alive without any evidence of the disease during the follow-up period is less than 30% in most studies. According to these findings, it seems that the overall survival is poorer in breast cancer patients with contralateral axillary metastases, but they have a better outcome

compare to patients with distant metastasis.⁸

In conclusion, CAM without systemic metastasis might be considered a regional disease because the spread is lymphatic and not hematogenous in many cases. These patients should be discussed in breast multidisciplinary meetings to individualize the management of each patient. A significant proportion of the patients had ALND (45.1% of the patients) and systemic treatment (96.3%), suggesting a curative instead of palliative intent. Mastectomy of the contralateral breast was not performed in most reports (6% - all of them were done together with ALND) but breast radiation (with or without axillary radiation) was performed in about 19.5% of the cases.

Chemotherapy and hormone therapy are very important and effective factors in the management of CAM patients but the effectiveness of radiotherapy requires more investigations.

The prognosis of CAM is usually poor with a high relapse rate (>60%) and a mortality rate of 15% in our review after 14-43 months follow-up, but it is better than the prognosis of the patients with systemic metastasis.

We recommend thorough evaluation of the contralateral axilla during the follow-up of breast cancer to rule out contralateral axillary lymph node involvement.

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