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Clinicopathologic and Mammographic Characteristics of Inflammatory and Non-Inflammatory Breast Cancer at Six Centers in North Africa

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Abstract

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Ethical approval: All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committees.

Informed consent: Informed consent was obtained from all study participants.

Purpose: We describe the clinico-pathologic and mammographic characteristics of inflammatory breast cancer (IBC) and non-IBC cases enrolled in a case-control study. Because IBC is a clinico-pathologic entity with rapid appearance of erythema and other signs, its diagnosis is based on clinical observation and thus, by necessity, subjective. Therefore, we evaluate our cases by photographic review by outside expert clinicians and by degree of adherence to the two most recent definitions of IBC: the international expert panel consensus statement and American Joint Committee on Cancer (AJCC) 8th edition (we used the slightly less restrictive 7th edition definition for our study).

Methods: We enrolled 267 IBC and 274 age- and geographically-matched non-IBC cases at 6 sites in Egypt, Tunisia, and Morocco in a case-control study of IBC conducted between 2009–2015. We collected clinic-pathologic and mammographic data and standardized medical photographs of the breast.

Results: We identified many differences between IBC and non-IBC cases; 54.5% versus 68.8% were estrogen receptor-positive, 39.9% versus 14.8% human epidermal growth factor receptor 2-positive, 91% versus 4% exhibited erythema, 63% versus 97% had a mass, and 57% versus 10% had mammographic evidence of skin thickening. Seventy-six percent of IBC cases adhered to the expert panel consensus statement and 36% to the AJCC definition; 86 percent were confirmed as IBC by either photographic review or adherence to the consensus statement.

Conclusions: We successfully identified distinct groups of IBC and non-IBC cases; the reliability of IBC diagnosis would benefit from expert review of standardized medical photographs and associated clinical information.

Keywords

inflammatory breast cancer; diagnostic criteria; Egypt; Tunisia; Morocco

Introduction

Inflammatory breast cancer (IBC) is a rare, aggressive clinico-pathologic form of breast cancer characterized by the rapid clinical appearance on the breast of erythema (redness), edema (swelling), and peau d'orange (a dimpled condition, resembling the skin of an orange); these signs are thought to be due to lymphedema caused by tumor emboli in the breast dermal lymphatics (1, 2). Major differential diagnoses for IBC are mastitis and neglected locally advanced breast cancer (3), the latter being a distinct clinicopathologic entity (4) in which there are often skin changes that present late in the disease process. Currently there are no credentialed molecular factors that distinguish IBC from non-IBC tumors (3). In the United States, IBC accounts for a disproportionate number of breast cancer deaths (7%) given that it constitutes only approximately 2% of breast cancer cases (4).

Because IBC is a clinico-pathologic entity, its diagnosis is, by necessity, subjective. Diagnostic criteria have changed over time (6) and are not entirely consistent among recent iterations (1–2, 7). Between 2009–2015 we conducted a case-control study of IBC in Egypt, Tunisia, and Morocco with the diagnosis of IBC based on the American Joint Committee on Cancer (AJCC) 7th edition definition (1). The study also included a group of non-IBC cases

and controls without breast cancer. For both groups of breast cancer cases we collected information on tumor characteristics, initial symptoms and signs of the breast cancer and their duration, signs evident upon clinical examination, health care seeking history for the breast cancer, mammographic features, and digital photographs of the breast (8).

Here we describe the clinico-pathologic and mammographic characteristics of the IBC and non-IBC cases included in this study, expanding upon previous studies (9–20). We also evaluate cases by photographic review and adherence to the two most recent definitions of IBC: the international expert panel consensus statement for standardized diagnosis (7) and the American Joint Committee on Cancer (AJCC) 8th edition definition, which expands on the 7th edition definition (which we used in our study) by considering duration history of symptoms/signs (2).

Methods:

We conducted a case-control study of IBC at six large cancer referral centers in Egypt, Tunisia, and Morocco (8). Informed consent was obtained for all participating cases. Institutional Review Board (IRB) approval was obtained from the National Cancer Institute-U.S.A., other U.S. collaborating institutions, and IRBs in the participating countries. We enrolled 267 women with IBC aged 18 or older that study clinicians considered IBC based on the following general guidelines from the AJCC 7th edition definition of IBC: exhibited erythema, edema, and peau d'orange over approximately a third or more of the breast (1), with a pathologic diagnosis of invasive breast cancer, and without a prior mastectomy or treatment with chemotherapy (with 4 exceptions). Cases with extensive ulceration were generally excluded to avoid including non-IBC locally advanced breast cancer in the IBC case group, although such cases with ulceration that also exhibit erythema and other clinical signs of IBC are included as IBC according to the AJCC definitions (1–2). Prior to study initiation, we used photographs from our pilot study (9) as training for the participating physicians to standardize the visual assessments contributing to the IBC diagnosis across study centers. IBC cases were enrolled at the time of diagnosis from the surgery departments at Tanta Cancer Center and the Gharbiah Cancer Society (from 03/2009 to 07/2013) (N = 63), and from medical oncology departments of the National Cancer Institute-Cairo (from 03/2009 to 9/31/2013) (N = 60), the Institut Salah Azaiz in Tunis, Tunisia (from 11/2009 to 10/2013) (N = 57), Ibn Rochd Oncology Center in Casablanca, Morocco (from 01/2011 to 08/2015) (N = 57), and University Hospital Center Mohammed VI in Marrakech, Morocco (from 01/2011 to 09/2015) (N=30).

The case-control study also included a comparison group of 274 female breast cancer cases without erythema, edema and peau d'orange (non-IBC cases) matched to the IBC cases on age (within 5-year categories, e.g. 40–44, 45–49), study hospital, and metropolitan catchment area surrounding the study hospital (except for the Tanta Cancer Center/Gharbiah Cancer Society where matching was the Gharbiah governorate) or other area of the country, and accrued over the same time period as the IBC cases. Non-IBC cases were identified from outpatient surgery clinics at the Tanta Cancer Center/Gharbiah Cancer Society (N = 64) and at the NCI-Cairo (N = 56), and from the medical oncology departments at the Institut Salah Azaiz (selected from women having their initial consultation with the study

medical oncologists) (N = 57), the Ibn Rochd Oncology Center (N = 70) and University Hospital Center Mohammed VI (N = 27). Non-IBC cases at the Ibn Rochd Oncology Center were also selected from the gynecologic surgery department. Our goal was to recruit cases before treatment, but at least 22 (8%) non-IBC cases were recruited post-mastectomy or chemotherapy (information on prior treatment was not available for 46 non-IBC cases).

Pathology reports were retrieved for 247 (93%) IBC cases and 255 (93%) non-IBC cases. Standardized forms were used to record presence of tumor emboli in the dermal lymphatics (available for 149 [56%] of IBC cases and 170 [62%] of non-IBC cases), tumor histology (available for 246 [92%] IBC cases and 256 [93%] non-IBC cases), grade (available for 196 [73%] IBC cases and 228 [83%] non-IBC cases), and stage (able to code localized [no regional lymph node or distant metastases], regional [if T4 and no distant metastases or > N0 and no distant metastases or no distant metastases] and distant disease [evidence of distant metastases] for 203 [76%] IBC cases and 206 [75%] non-IBC cases). Estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression were obtained for 177 (66%), 175 (66%), and 138 (52%) of IBC cases, respectively, and for 231 (84%), 230 (84%), and 182 (66%) of non-IBC cases. We categorized cases with an immunohistochemistry (IHC) score of 0 to 1+ as “HER2 negative”, and those with a score of 2+ “equivocal”, and a score of 3+ “HER2 positive.” If the IHC scoring was missing, HER2 status was considered unknown. Receptor tests were not done for a higher percentage of IBC cases than non-IBC cases (6% vs. 2% for ER and PR status and 7% vs 3% for HER2). Mammography reports were retrieved and information from the report coded on standardized forms for 192 (72%) of IBC cases and 185 (68%) of non-IBC cases. If information on a specific feature was not mentioned in the report, we assumed that feature was not present.

The diagnosing clinicians used standardized forms to record patient-reported initial breast cancer signs and symptoms and their duration, care seeking and treatment prior to reaching the study hospital, and presence and extent of signs and symptoms upon clinical examination. The clinical examination was completed for 256 (96%) IBC cases and 243 (89%) non-IBC cases.

Based on clinical information, we evaluated our cases against the two most recent definitions of IBC: 1) the International Expert Panel on Inflammatory Breast Cancer Consensus Statement for Standardized Diagnosis (7), which requires as minimum criteria the rapid onset of breast erythema, edema and/or peau d’orange, and/or warm breast, with or without an underlying palpable mass, duration of history of no more than 6 months, erythema occupying at least one-third of the breast, and pathologic confirmation of invasive carcinoma, and; 2) the AJCC 8th edition definition requiring diffuse erythema and edema (peau d’orange) (this phrasing implies that edema is always accompanied by peau d’orange) involving approximately a third or more of the skin of the breast and less than 6 months from first symptom to breast cancer diagnosis (2). We used 30% to approximate a third of the breast and based duration history on the maximum reported duration of any of the following symptoms/signs: pain, itching, erythema, edema, peau d’orange, mass, ulceration, bruising, palpable axially and supra-clavicular lymph nodes, nipple retraction, warmth, thickening of the skin, and other unspecified symptoms.

Standardized digital photographs of the breast (a full-frontal photograph of both breasts from the mid-neck to the waist with arms by the side and a close-up of the affected breast) taken by diagnosing clinicians were obtained for 196 (74%) IBC cases and 94 (34%) non-IBC cases. The discrepant percentages are largely a result of not starting collection of photographs for non-IBC cases at the beginning of the study. We entered photographs into the National Institutes of Health National Library of Medicine Interaction Tool for review by two board-certified medical oncologists who were experts in IBC and breast cancer in general in the United States (SDM and SMS). They evaluated the photographs for erythema, edema, and peau d'orange without reviewing the clinical data.

Using SAS version 9.3 (SAS Institute, Inc. Cary, NC) we obtained p-values from chi square tests to compare the percentages of IBC and non-IBC cases with certain symptoms/signs. We also used proc corr to obtain Spearman rank correlation coefficients (r) between extent and duration of selected signs.(20). A two-sided p-value .05 was considered statistically significant.

Results

The median ages (ranges) of the 267 IBC cases and 274 non-IBC cases were 50.0 (23–77) years and 50.0 (27–80) years, respectively. Although the majority of both case groups were regional stage at diagnosis, the stage distributions were significantly different ($p < .001$). A significantly higher percentage of IBC cases had evidence of tumor emboli in the dermal lymphatics, a significantly lower percentage were ER+ and PR+ and a significantly higher percentage were HER2+ (Table 1). There were no significant differences between IBC and non-IBC cases according to breast side, histology, or grade.

The initial symptom or sign most frequently reported by IBC cases was erythema (79.2%) and by non-IBC cases was a lump (81.3%) (Table 2). All initial signs except for bruising, palpable lymph nodes, and other signs were statistically significantly different for IBC and non-IBC cases. Of IBC cases reporting erythema or edema as an initial sign, 88–89% reported that the condition arose within a month (data not shown in table).

A statistically significantly higher percentage ($p < .0001$) of IBC cases (69%; $N = 183$) than non-IBC cases (50%; $N = 137$) had first sought medical care for their breast condition at a hospital/clinic other than the study hospital. Fifteen percent ($N = 40$) of IBC cases versus 5% of non-IBC cases ($N = 14$) reported prior antibiotic treatment for their breast cancer ($p = .0001$).

Based on the clinical examination, a statistically significantly greater percentage of IBC cases than non-IBC cases reported pain and itching and had erythema, edema, peau d'orange, palpable axillary lymph nodes and supra-clavicular lymph nodes, nipple retraction, warmth, and thickening of the skin (Table 3). A statistically significantly higher percentage of non-IBC cases (96.7%) compared to IBC cases (62.5%) had a mass. Ninety-four percent of IBC cases versus 61 percent of non-IBC cases had a known duration history from first symptom/sign to diagnosis; the median (range) was 2 months (.03–48) for

IBC cases and 3 months (.07–36) for non-IBC cases. Eighty-seven percent of IBC cases versus 74 percent of non-IBC cases had a duration history of less than 6 months.

Among IBC cases, the extent and duration of erythema were not correlated, but extent and duration of peau d'orange were positively and statistically significantly correlated (Table 4). Clinical size and duration of the mass were not correlated for IBC cases, but were statistically significantly positively correlated for non-IBC cases ($p=.0004$). Among IBC cases, the median duration of signs of erythema, edema, and peau d'orange did not vary by presence of a mass or stage (regional vs. distant) at diagnosis.

Mammographic evidence of skin thickening, axillary adenopathy, stromal coarsening/thickened trabeculations and nipple-areolar swelling was statistically significantly more frequent in IBC cases than non-IBC cases, while evidence of a mass was more frequent in non-IBC cases (Table 5).

Case evaluation

IBC

Seventy-six percent of IBC cases with available clinical information (189/267–19) adhered to the international expert panel consensus statement on diagnostic criteria for IBC and 36% (88/267–24) to the AJCC 8th edition definition of IBC (Table 6). Eighty-six percent of IBC cases (168+46+15/267) were confirmed as IBC by either photographic review or reported adherence to the international consensus statement definition (Table 6) (Figure 1a).

A major reason cases did not meet the international consensus definition was because signs of erythema were reported to cover less than 30% of the breast (Figure 1b); similarly, cases that did not meet the AJCC 8th edition definition of IBC often did not have all three signs (erythema, edema, and peau d'orange) over at least 30% of the breast (Figure 1c). Cases that were considered non-IBC/uncertain by one or both photographic reviewers, but otherwise met at least one of the definitions for IBC, sometimes had apparent ulceration of the breast (Figure 1d – in this case the ulceration on the affected right breast is an allergic reaction, 1e), or had a breast that was contracted (Figure 1f). Of the 10 cases with reported duration of erythema of 6 or more months, 7 reported that erythema arose within 1 month (Figure 1g). Some cases did not meet either definition of IBC or photographic review (Figure 1h). Four of 15 cases that were considered IBC by the international consensus definition but not on photographic review had evidence of tumor emboli in the dermal lymphatics; 4 had no evidence, and 7 had no information.

A secondary review of photographs for IBC cases without reported signs of erythema, edema, or peau d'orange (available for 18 of 24 cases without reported erythema, 16 of 22 cases without reported edema, and 21 of 31 cases without reported peau d'orange) by one author (CS) found erythema (sometimes very faint) for 61% of those without recorded erythema; corresponding percentages for edema and peau d'orange were 31.3%, and 14.3%.

Non-IBC

Of the 94 non-IBC cases with photographs, 60 (64%) were considered non-IBC by at least one of the reviewers, 19 (20%) were considered IBC by both reviewers, and 15 (16%) were considered uncertain (data not shown). Of the 19 non-IBC cases classified as IBC by both U.S. reviewers, 1 met the international consortium definition of IBC and 18 did not. One of the 18 had duration of signs over 6 months. Of the 17 others, a secondary review of photographs by one author (CS) suggested possible erythema for 9, edema for 10, and peau d'orange for 7, although signs were not recorded by the clinicians and were often ambiguous. Three (15.8%) had evidence of tumor emboli in the dermal lymphatics. Thirteen had information on mammographic characteristics. Of these, 3 (23.1%) had skin thickening, 12 (92.3%) had a mass, 7 (53.8%) had axillary adenopathy.

Discussion

In this case-control study of IBC in North Africa, we identified distinct differences between the two case groups (IBC and non-IBC) in the presence of tumor emboli in the dermal lymphatics, hormone receptor status, clinical history and characteristics, and mammographic features. Photographic review and adherence to the international consensus conference definition of IBC confirmed 86 percent of diagnoses, but it also identified a small percentage of cases (IBC and non-IBC) that were ambiguous.

Our findings with regard to hormone receptor expression, tumor histology, and presence of tumor emboli in the dermal lymphatics in IBC and non-IBC cases are similar to other studies (11–14,19,22). Mammographic evidence of skin thickening and stromal coarsening/thickened trabeculations among IBC cases was less common and axillary adenopathy (17,23) and a detected mass (17,20,23) were more common than reported in other studies. In our study, a larger percentage of IBC cases reported a discrete mass, inverted nipple, warmth and pain, and a slightly smaller percentage reported itching compared to a U.S. study (24). However, the percentage of IBC cases reporting pain and skin thickening in our study was similar to that in a French study (16). Significant erythema of the skin was the most frequent initial symptom reported by cases in the U.S. Inflammatory Breast Cancer Registry (24). In another U.S. study, the majority of women reported that the “triggering event” that led to diagnosis was a self-discovered breast lump (34%) or pain (19%) (15), percentages that are similar to the percentages reporting an initial mass and pain in our study.

The prevalence of erythema, edema, and peau d'orange was generally higher and duration of these signs among IBC cases generally shorter in our study than in other studies in North Africa (10–12), which were based on medical record review (except for the Egyptian cases in reference 11). Notably, deficiencies in the information in medical records needed to identify IBC cases have been described (25). Our findings do not support the conclusions that erythema spreads diffusely throughout the entire breast as disease advances (3). However, they possibly support the suggestion by others that the extent of peau d'orange may be associated with advanced aggressive disease (3).

Our results are comparable to the 20% of patients in the Inflammatory Breast Cancer Registry in the United States whose initial clinical diagnosis was infection (24). Although

we do not know the duration of the non-neoplastic specific treatments received initially, these results emphasize the need for continuing physician and patient education to effect prompt diagnosis of IBC by shortening the time to obtain a tissue biopsy to confirm presence of cancer to no more than 7–10 days (7, 26).

Our evaluation of cases by photographic review and adherence to two definitions of IBC (2,7) revealed aspects of the definitions that need further assessment. The international consensus definition requires only erythema over at least a third of the breast along with the presence of either edema, peau d'orange, or warmth but without specifying the extent of these signs. Duration of history should be 6 months or less (7). The AJCC definition requires erythema and edema (peau d'orange) over at least a third of the breast with duration of first symptom to diagnosis of less than 6 months (2). Our results lead us to question several aspects of these definitions. Are edema and peau d'orange equivalent contributors to an IBC diagnosis, as implied by the AJCC definition (1,2)? Meeting this restriction eliminated many cases from the AJCC definition that were considered IBC by reviewers of the photographs. Must a third of the breast be affected by erythema alone or all three signs, particularly given that specifying the percentage of an irregularly shaped organ like the breast is difficult and subjective? Would not how quickly signs arise rather than the duration of signs/history at the time of diagnosis be the more relevant diagnostic factor (2, 7)? For instance, signs could arise within a month, but seeking medical care could be delayed for more than 6 months. At a minimum, the guidance in the international consensus definition and the AJCC definition should be made consistent with regard to history duration. Also of concern are cases where the affected breast appears constricted or shrunken, but signs of erythema and peau d'orange cover at least a third of the breast. Others have suggested that patients without erythema, but who present with rapid breast swelling, peau d'orange and nipple retraction should be diagnosed with IBC (26).

Several issues may affect the interpretation of our results. Case ascertainment at each of the sites was affected by geopolitical events or resource shortages that precluded or reduced case ascertainment during certain periods of time. Thus, the total number of IBC cases at each study site should not be viewed as a complete enumeration of IBC cases over the study period at that site. Hormone receptor reports were sometimes missing due to delays in the results arriving at the diagnosing department and occasionally medical records were unavailable because they were in the possession of the patient rather than the study hospital or were retained by other hospitals. The original pathology and mammography reports were not standardized for this study; thus, the presence of tumor emboli in the dermal lymphatics was not routinely recorded by all pathologists. Our photographic review suggests the somewhat subjective nature of the recording of signs of IBC, particularly erythema, by diagnosing physicians and the difficulty of accurately diagnosing IBC in a small percentage of cases. It is also possible that patient recall or reporting of duration of symptoms and signs is not accurate.

In summary, we identified many differences between the two case groups, albeit none that were exclusive to one group. We also suggest questions for consideration regarding the diagnosis of IBC. As has been recommended (26), medical photographs of the breast should be standard procedure in diagnosing IBC and other types of locally advanced breast cancer.

Further standardization of the diagnosis of IBC would benefit from an expert panel review of medical photographs of IBC cases and their clinical information, such as from this and possibly other studies. Early and accurate diagnosis of IBC is critical because of the rapid systemic and loco-regional progression of the disease; survival rates and quality of life of IBC and non-IBC patients depend on access to appropriate clinical management, clinical trials, and symptom palliation.

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Figure 1.

a. IBC case with erythema, edema, peau d'orange $\geq 30\%$ of breast; duration of signs < 6 months; b. IBC case with erythema (20%), edema (20%), peau d'orange (20%); duration of

signs < 6 months, no tumor emboli in dermal lymphatics; c) IBC case with erythema and edema 30% of the breast but no peau d'orange; tumor emboli in the dermal lymphatics; duration of signs less than 6 months; d) IBC case with erythema, edema, and peau d'orange 30% of the breast, duration of signs less than 6 months, tumor emboli in the dermal lymphatics, skin lesions due to allergic reaction; e) IBC case with erythema, edema, peau d'orange 30% of the breast, duration less than 6 months, tumor emboli in the dermal lymphatics, ulceration; f) IBC case with signs reported as 30% of the breast, duration of signs < 6 months, retraction of the breast, classified as uncertain whether IBC by photo reviewers; g) IBC case - erythema and edema arose within a month but duration of signs was 8 months; tumor emboli in the dermal lymphatics; h) IBC case not meeting definitions of IBC and considered non-IBC by photo reviewers.

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Table 1.

Tumor characteristics of IBC and Non-IBC cases

Characteristic	IBC (N = 267) N (%) ^a	Non-IBC (N = 274) N (%) ^a	p-value from chi-square test ^b
Breast side		121 (47.8)	
Left	138 (53.7)	130 (51.4)	.26
Right	115 (44.9)	2 (0.8)	
Both	4 (1.6)	21	
Unknown	10		
Stage			
Localized			<.0001
Regional	0 (0)	50 (24.3)	
		134 (65.1)	
Distant	160 (78.8)	22 (10.7)	
Unknown	43 (21.3)	68	
	64		
Tumor emboli in dermal lymphatics			
No	66 (24.8)	133 (48.5)	
Yes			
	83 (31.2)	37 (13.5)	<.0001
Unknown			
	118	104	
Histology ^c			
Any Ductal NOS	214 (87.0)	234 (91.4)	.13
Any Lobular but no ductal	12 (4.9)	12 (4.7)	
Other/unspecified			
	20 (8.2)	10 (3.9)	
Unknown			
	21	18	
Grade ^d			
1	7 (3.6)	12 (5.3)	.25
2	142 (72.5)	175 (76.8)	
	47 (24.1)	41 (18.0)	
3	71	46	
Unknown			
Estrogen receptor			
Negative	81 (45.8)	72 (31.2)	
Positive/borderline		159 (68.8)	
	96 (54.5)		.002
Unknown		43	

Characteristic	IBC (N = 267) N (%) ^a	Non-IBC (N = 274) N (%) ^a	p-value from chi-square test ^b
Progesterone receptor	90		
Negative	95 (54.0)	80 (34.8)	<.0001
Positive/borderline	80 (46.0)	150 (65.2)	
Unknown	92	44	
HER2			
Negative/equivocal	83 (60.1)	155 (85.2)	<.0001
Positive	55 (39.9)	27 (14.8)	
Unknown	129	92	
Combined receptor status			
ER+ and/or PR+ and Her2-	61 (34.5)	127 (54.7)	.0001
ER+ and/or PR+/HER2+ or missing	41 (23.2)	44 (19.0)	
ER- and PR- and Her2+	32 (18.1)	16 (6.9)	
ER-/PR-/Her2-	21 (11.9)	27 (11.6)	
Other combinations	23 (12.9)	18 (7.8)	
Unknown	89	42	

^a Percentages are of those with known values.

^b Chi-square test based on those with known values.

^c Categories are mutually exclusive.

^d The Modified Scarff-Bloom-Richardson system was the most commonly used (27).

Table 2.

Self-reported initial symptoms and signs for IBC and non-IBC cases Initial Signs/Symptoms

	IBC (N=267) N (%) ^a	Non-IBC (N = 274) N (%) ^a	p-value for chi-square test ^b
Symptoms			
Pain	71 (27.8)	35 (14.2)	.0002
Signs			
Erythema	202 (79.2)	4 (1.6)	<.0001
Edema	168 (65.9)	60 (24.3)	<.0001
Peau d'orange	85 (33.3)	27 (10.9)	<.0001
Mass	98 (38.4)	200 (81.0)	<.0001
Bruising	3 (1.2)	0	.09
Palpable lymph nodes	48 (18.8)	34 (13.8)	.13
Nipple retraction	50 (19.6)	31 (12.6)	.03
Warmth	62 (24.3)	1 (0.4)	<.0001
Other	2 (0.8)	0 (0.0)	.16
Initial symptoms/signs were not reported	12 (4.5)	27 (9.9%)	

^aPercentages are of the 255 (96%) IBC cases or 247 (90%) non-IBC cases with known information for initial signs/symptoms.^bChi-square test based on those with known values.

Table 3.

Symptoms and signs for IBC and non-IBC cases based on clinical examination

Sign/symptom	IBC (N = 266) N (%) ^a	Non-IBC (N=274) N (%) ^a	p-value from chi- square test ^b
Symptoms			
Pain	112 (43.8)	48 (19.8)	<.0001
Itching	30 (11.7)	9 (3.7)	.0009
Signs			
Erythema	232 (90.6)	9 (3.7)	<.0001
Edema	233 (91.0)	38 (15.6)	<.0001
Peau d'orange	224 (87.5)	40 (16.5)	<.0001
Mass	160 (62.5)	235 (96.7)	<.0001
Ulceration	18 (7.0)	8 (3.3)	.06
Bruising	5 (2.0)	2 (0.8)	.28
Palpable axillary lymph nodes	172 (67.2)	102 (42.0)	<.0001
Palpable supra-clavicular lymph nodes	20 (7.8)	4 (1.7)	.001
Nipple retraction	128 (50.0)	43 (17.7)	<.0001
Warmth	134 (52.3)	4 (1.7)	<.0001
Thickening of the skin	137 (53.5)	23 (9.5)	<.0001
Other	6 (2.3)	7 (2.9)	0.71
Clinical examination was not done	11 (4.0)	31 (11.0)	

^aPercentages are of the 256 (96%) IBC cases or 243 (89%) non-IBC cases who underwent a clinical examination. If data for a particular symptom/sign was missing, it was set to "no".

^bChi-square test based on those with known values.

Table 4.

Extent and duration of selected signs for IBC and non-IBC cases

Sign	Extent of sign (% of breast) Mean, Median (range) ^a	Duration of sign (months) Mean, Median (range) ^a	Spearman correlation coefficient of extent and duration of signs ^b	P-value for correlations statistic ^b
IBC		2.1, 2.0 (0.03–13)		
Erythema (N = 232)	60.9, 60 (5–100)	2.1, 2.0 (0.23–13)	.10	.14
Peau d'orange (N=224)	49.9, 50 (10–100)		.22	.003
	Clinical size (cm) Mean, Median (range) ^c	Duration (months) Mean, Median (range) ^c	Spearman correlation coefficient of size and duration ^d	P-value for correlations statistic ^d
IBC		2.8, 2.0 (0.25–18.0)	.12	
Mass (N = 160)	5.8, 5.0 (1.0–17.0)			.21
Non-IBC				
Mass (N = 235)	4.7, 4.0 (0.7–20.0)	5.4, 3.0 (0.75–36.0)	.30	.0005

^a Among IBC cases with erythema, data are missing on percent and duration of erythema for 5 and 4 cases, respectively; among IBC cases with peau d'orange, data are missing on percent and duration of peau d'orange for 4 and 41 cases, respectively;

^b Correlations and p-values for extent and duration of erythema and extent and duration of peau d'orange are based on 223 and 180 cases, respectively.

^c Among those with a mass data on size and duration of mass are missing for 16 and 35 IBC cases, respectively and 31 and 89 non-IBC cases, respectively.

^d Correlations and p-values for size and duration of mass are based on 120 IBC and 134 non-IBC cases

Table 5.

Mammographic features of IBC and non-IBC cases

Mammographic feature	IBC (N=267) N (%)^a	Non-IBC (N=274) N (%)^a	P-value for chi- square test for IBC vs. non-IBC^b
Mass	135 (70.3)	171 (92.4)	<.0001
Skin thickening	109 (56.8)	18 (9.7)	<.0001
Calcifications	51 (26.9)	38 (20.5)	0.17
Axillary adenopathy	119 (62.0)	74 (40.0)	<.0001
Fat necrosis characteristic of trauma	1 (0.5)	2 (1.1)	0.54
Stromal coarsening/thickened trabeculations	21 (11.0)	0 (0.0)	<.0001
Nipple-areolar swelling	9 (4.7)	2 (1.1)	0.04
Nipple inversion	20 (10.4)	18 (9.7)	0.82
Mammographic information not available	75 (28.1)	89 (32.5)	

^aPercentages are of the 192 (72%) IBC cases or 185 (68%) non-IBC cases for whom mammographic reports were retrieved. If data for a particular characteristic was missing, it was set to "no".

^bChi-square test based on those with known values.

Table 6.

Evaluation of IBC cases by photographic review and adherence to the International Consensus^a definition of IBC and the American Joint Committee on Cancer (AJCC) 8th Edition^b definition of IBC

International consensus definition of IBC ^a	Photographic review			Total
	No photographs	IBC by at least one reviewer	Non-IBC/uncertain by one or both reviewers	
	N (%)	N (%)	N (%)	N (%)
Missing clinical information	8	9	2	19 (7.1)
Yes	46	128	15	189 (70.8)
No	17	31	11	59 (22.1)
Total	71 (26.6)	168 (62.9)	28 (10.5)	267 (100)
AJCC 8th edition definition of IBC^b				
Missing clinical information	10	12	2	24 (9.0)
Yes	24	60	4	88 (33.0)
No	37	96	22	155 (58.1)
Total	71 (26.6)	168 (62.9)	28 (10.5)	267 (100)

^aErythema over at least one-third of the breast (here $\geq 30\%$ to approximate one-third) and either edema or peau d'orange or warmth and maximum history ≤ 6 months.

^bErythema and edema and peau d'orange over at least one-third of the breast (here $\geq 30\%$ to approximate one-third) and maximum history < 6 months.