Inflammatory breast cancer: Pathology and molecular pathogenesis

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Literature review current through: **Oct 2023.**
This topic last updated: **Apr 04, 2022.**

INTRODUCTION

Inflammatory breast cancer (IBC) is an aggressive form of locally advanced breast cancer. De novo IBC refers to primary disease. These patients typically present with pain and a tender, firm, and enlarged breast. The skin over the breast is reddened, warm, and thickened, with a "peau d'orange" (orange skin) appearance (picture 1). In comparison, the inflammatory recurrence of a noninflammatory breast cancer is called secondary disease. It usually develops on the chest wall at the site of previous mastectomy, but can also occur rarely as a distant cutaneous recurrence. The signs and symptoms of IBC arise rapidly compared to non IBC, typically within weeks to six months.

Primary IBC is a relatively rare disorder accounting for approximately 1 to 5 percent of invasive breast cancers [1,2]. However, because of its aggressive nature, it accounts for a greater proportion of cases presenting with more advanced disease. In one report of 752 patients with stage III breast cancer, for example, 24 percent had IBC [3].

At presentation, almost all women with primary IBC have lymph node involvement and approximately one-third have distant metastases. The long-term prognosis is also relatively poor, which has led to the development of combined modality treatment regimens consisting of neoadjuvant chemotherapy to maximize clinical response, followed by locoregional treatment, and then consolidation chemotherapy [4,5]. (See "Inflammatory breast cancer: Clinical features and treatment".)

BASIC FEATURES

The 2017 American Joint Committee on Cancer and the International Union for Cancer Control (AJCC-UICC) Tumor, Node, Metastasis (TNM) breast cancer staging system defines IBC as a clinical-pathologic entity characterized by diffuse erythema and edema (peau d'orange) involving a third or more of the skin of the breast (table 1). These "inflammatory" skin changes are not due to infiltration of inflammatory cells but rather to lymphedema caused by tumor emboli within the dermal lymphatics. However, the diagnosis is based upon the clinical presentation. Although dermal lymphatic involvement supports the diagnosis of inflammatory breast cancer, it is neither necessary nor sufficient in the absence of classical clinical findings.

IBC is designated as primary tumor stage T4d. Tumor presentation with ulceration and/or ipsilateral satellite skin nodules and/or edema are T4b. Not all skin changes qualify as IBC or even locally advanced breast cancer (LABC). Invasion of the dermis alone, such as dimpling of the skin or nipple retraction does not qualify as T4 and may occur in T1, T2, or T3 without changing the classification.

Of note, if a cancer is designated as inflammatory before therapy, the patient will be designated to have inflammatory breast cancer throughout, even if the patient has complete resolution of inflammatory findings.

Primary IBC has several characteristic biologic features:

- It is rapidly progressive
- It is highly angiogenic and angioinvasive; these features account for the high metastatic potential
- The aggressive behavior and angiogenicity are intrinsic features of the tumor [6]

The last characteristic was demonstrated in a unique human xenograft model, the SCID (severe combined immune deficiency) mouse. Implantation of noninflammatory human tumors into the mammary fat pad in these mice resulted in the growth of isolated subcutaneous nodules [6]. By contrast, implantation of an IBC resulted in exclusive growth within lymphatic and blood vessels, with marked erythema of the overlying skin.

Given these data, an international expert panel proposed the following consensus-based criteria for the diagnosis of IBC in 2011 [7]:

- 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 no more than six months
- Erythema occupying at least one-third of the breast
- Pathologic confirmation of invasive carcinoma (see "Inflammatory breast cancer: Clinical features and treatment", section on 'Diagnostic criteria')

Primary IBC refers to a de novo IBC. Secondary IBC is the inflammatory recurrence of a noninflammatory primary breast carcinoma. Secondary IBC usually occurs on the chest wall at the site of previous mastectomy for a noninflammatory breast cancer, but occasionally may be found at a distant cutaneous recurrence [8].

PATHOLOGY

The classic histologic finding in IBC on biopsy of affected skin is dermal lymphatic invasion by tumor cells; this change can also be seen in areas of skin that are clinically normal (picture 2). These malignant cells form tumor emboli, which are responsible for both the local signs and symptoms and for the development of metastatic disease [9,10]. Thus, the term "inflammatory" breast cancer is actually a misnomer since the clinical signs suggesting inflammation are not due to infiltration of inflammatory cells. Invasion of the dermis outside the lymphatics is uncommon in primary IBC but can be seen in secondary IBC.

Several caveats need to be kept in mind when evaluating the skin biopsy:

- Dermal lymphatic invasion is not always found in patients with primary IBC, primarily due to sampling error.
- Dermal lymphatic invasion can be an incidental finding in patients with breast cancer who do not have clinical evidence of IBC [11,12]; such tumors are not considered to be inflammatory cancers.
- Rarely, women with clinical features suggestive of IBC have other disorders; these include acute mastitis, diffuse infiltration by lymphoma or leukemia cells, and advanced noninflammatory breast cancer.

Primary IBC is not a specific histologic subtype of breast cancer, but the tumor is often of the ductal type (see "Pathology of breast cancer"). These tumors generally have a high histologic grade, with pleomorphic tumor cells, highly atypical mitotic figures, and a high intratumoral microvessel density [9,13]. It has been suggested that secondary IBC is more likely to be seen in recurrences of primary breast cancers with prominent apocrine features [10].

MOLECULAR GENETICS

As noted above, the angioinvasive nature of primary IBC appears to be intrinsic to the tumor [6,14]. Experimental studies have begun to shed light on the pathogenetic factors that may be involved in the development and progression of this disorder [8]. Among the factors that have been evaluated are hormone receptor status, the *p53* tumor suppressor gene, other genetic determinants, and cytokines.

Hormonal receptors and other tumor markers — Breast cancers that do not express estrogen or progesterone receptors (ER and PgR) are generally associated with a shorter disease-free survival and a worse prognosis than receptor-positive tumors. The majority of IBCs are hormone receptor-negative [6,15-17]. In one report of 60 patients with locally advanced breast cancer (LABC) of any type, both response to treatment and overall survival were significantly correlated with ER and PgR positivity as well as a lower mitotic index, histologic grade, and diploid tumors [18]. (See "Prognostic and predictive factors in early, non-metastatic breast cancer".)

IBCs are also characterized by a high proliferative rates [16,17]. Approximately 60 percent of IBCs overexpress the epidermal growth factor receptor (EGFR) and the type EGFR, also called HER2 [19]. Although not specific for IBC, these molecular markers may identify patients who have a worse prognosis.

Genetic changes — Loss of heterozygosity (LOH) is detected in approximately one-half of IBCs, and the most frequently lost alleles are at 3p, 6p, 8p, 11q, 13q, and 17q [20]. Lack of expression of genes at some of these loci may have phenotypic and prognostic importance. As an example, in one series of 64 patients with IBC who were treated homogeneously at a single institution between 1988 and 1999, women who presented with extensive inflammation and who had a poor overall outcome had both a significantly higher overall frequency and a different pattern of intratumoral LOH compared to those who presented with localized inflammation and who had a better prognosis [21].

p53 tumor suppressor gene — Mutations in the *p53* tumor suppressor gene or accumulation of p53 protein have been reported in 20 to 50 percent of human breast cancers [22,23]. These abnormalities are more often seen in patients with familial/hereditary breast cancer syndromes (such as the familial breast and ovarian cancer and Li-Fraumeni syndromes) than in those with sporadic breast cancer. (See "Li-Fraumeni syndrome".)

The *p53* status in IBC was evaluated by immunohistochemistry in a series of 27 patients [22]. Three groups of almost equal size were identified: tumors with high levels of p53 in the nucleus,

tumors with no detectable p53, and tumors with p53 in the cytoplasm. The last two groups had only wild-type *p53*, while the samples with intense nuclear staining had a variety of missense mutations. These findings suggest that two mechanisms, direct mutation and cytoplasmic sequestration of wild-type protein, can subvert the normal role of p53 in IBCs.

A subsequent study by the same group evaluated 24 additional patients with IBC in an attempt to determine the prognostic significance of p53 [24]. Those patients with a *p53* gene mutation and nuclear overexpression of p53 protein had an 8.6-fold higher risk of death compared with patients that had neither mutation nor protein overexpression. There was an important prognostic interaction with ER expression. The subset of patients who were both ER-negative and had nuclear p53 overexpression had a 17.9-fold higher risk of death, compared to 2.8-fold for women with tumors that had p53 nuclear overexpression alone.

Similar findings were noted in a study of 39 LABCs, 32 of which were confirmed as IBCs by clinical and pathologic criteria [25]. *p53* mutations were detected in 41 percent of the tumors analyzed, all but three of which had intense p53 nuclear staining. The presence of *p53* mutations was significantly associated with large tumor size and disseminated disease at diagnosis. There was also a nonsignificant trend toward an association between *p53* mutation, negative ER status and a lower rate of response to therapy.

RhoC GTPase and WISP3 — In an effort to identify new genes that may contribute to the rapidly growing and metastatic features of IBCs, we compared the genes expressed in two cells lines: an IBC cell line (SUM149) and two human mammary epithelial (HME) cell lines [26]. Seventeen transcripts were identified as being differentially expressed, eight solely by the normal cell lines, and nine solely by the tumor cell line. This was followed by a blinded analysis of the seventeen transcripts in 20 archival IBCs and 30 stage-matched non-IBCs. The following findings were noted:

- Two genes, *RhoC GTPase* and a novel gene called WNT1-inducible-signaling pathway protein 3 (*WISP3*) or lost in inflammatory breast cancer (*LIBC*), were concordantly altered in 91 percent of the IBC specimens compared to none of the controls.

- The putative *RhoC GTPase* oncogene was more often overexpressed (90 versus 38 percent) and *WISP3* was commonly lost in the IBCs (80 versus 21 percent).

- Role of *RhoC GTPase* – *RhoC GTPase* is a member of the Ras superfamily of small GTP-binding proteins [27,28]. It is involved in cytoskeletal reorganization, via regulation of the actin cytoskeleton [29]. Transfection of the *RhoC GTPase* gene into human mammary epithelial cells leads to enhanced invasiveness, motility, and the release of angiogenic cytokines (eg, vascular endothelial growth factor), at least partially recapitulating the IBC

phenotype (see 'Cytokines' below) [30,31]. The additional observation that overexpression of RhoC GTPase correlates with tumor progression in aggressive ductal pancreatic cancer [32] is consistent with the hypothesis that *RhoC GTPase* is an important contributor to the IBC metastatic phenotype.

- Role of *WISP3* – The product of the *WISP3* gene is an insulin-like growth factor binding protein-related protein (IGFBP-rP) called IGFBPrP-9 [33]. It has been suggested that both the high-affinity IGF binding proteins (IGFBPs) and the IGFBPrPs modulate the availability of insulin-like growth factor to the cell surface IGF receptors [34]. If so, they could potentiate IGF-mediated proliferative actions; they may also promote tumor cell growth by IGF-independent effects [35].

There is suggestive evidence that at least some IGFBPrPs play a role in tumor progression. Downregulation or loss of IGFBPrP-1 expression has been associated with progression of breast cancer and prostate cancer [36,37], while transfection of *WISP3* into breast cancer cells inhibits tumor cell growth, invasiveness, and angiogenic potential [38]. Thus, the *WISP3* gene appears to act as a tumor suppressor gene in breast cancer.

Others — Several studies have performed next-generation sequencing on IBC versus non-IBC tumors. Although considerable overlaps in the mutational spectrum were found, some characteristics are salient in IBC. IBC has a higher mutational burden than non-IBC [39]. Although phosphoinositide-3 kinase (*PI3K*), tumor protein p53 (*TP53*), breast cancer susceptibility gene 2 (*BRCA2*), fibroblast growth factor receptor 3 (*FGFR3*), and c-ROS oncogene 1 (*ROS1*) were more commonly mutated in IBC versus non-IBC, these gene mutations are not specific for IBC and thus do not contribute at this time to a molecular definition of IBC.

Germline alterations in a subset of IBC — Overall, 14 percent of cases of IBC at a single institution had germline mutations [40]. Mutations in *BRCA1* and *BRCA2* accounted for approximately one-half of these germline mutations, whereas the other half was distributed amongst several genes, notably partner and localizer of BRCA2 (*PALB2*), checkpoint kinase 2 (*CHEK2*), ataxia-telangiectasia mutated (*ATM*), and BRCA1-associated RING domain 1 (*BARD1*). Further studies are needed across institutions and ethnicities to evaluate if, indeed, germline mutations in cancer susceptibility genes are more common than in non-IBC.

Cytokines — As noted above, the term inflammatory is a misnomer in IBC since the clinical signs suggesting inflammation are due to tumor cell invasion of dermal lymphatics, not infiltration of inflammatory cells [9]. In addition, IBCs produce negligible levels of most inflammatory cytokines such as interferon-gamma, interleukin-1 (IL)-1, and IL-12.

However, other cytokines may be important. As mentioned above, IBCs tend to be highly vascular tumors because of their angiogenic and angioinvasive potential [9]. In preclinical models, IBC tumor cell lines and tumor specimens release increased amounts of vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF, FGF-2), IL-6, and IL-8; increased release of these cytokines also occurs in human mammary epithelial cells that are transfected with and overexpress the *RhoC GTPase* gene, a gene specifically associated with IBC [31]. (See 'RhoC GTPase and WISP3' above.)

The VEGF receptor-3 (VEGFR-3) is expressed in the lymphatic endothelium, plays an important role in lymphatic development, and is activated after binding to VEGF-C and VEGF-D. The VEGFR-3 pathway also may play an important role in tumor lymphangiogenesis and subsequent metastasis [41,42]. As an example, VEGF-C is overexpressed in some breast cancer cells, promoting both intratumoral lymphangiogenesis and metastases to the regional lymph nodes and lungs [41]. By contrast, VEGF ligands to VEGFR-2 do not stimulate lymphangiogenesis [42]. (See "Clinical features and diagnosis of peripheral lymphedema".)

These observations appear to be applicable to human disease. One study screened breast cancer cell lines for expression of members of the VEGF family [43]. The following findings were noted:

- Expression of VEGF-A and VEGF-B, which play a role in tumor angiogenesis, was seen in both node-positive and node-negative tumors
- Expression of VEGF-C, a ligand for VEGFR-3, was detectable in some node-positive breast cancers but not in node-negative tumors
- Expression of VEGF-D, another ligand for VEGFR-3, was detected only in an inflammatory breast cancer cell line and in a tumor cell line that was developed from an inflammatory skin metastasis

Thus, activation of VEGFR-3, particularly by VEGF-D in IBC, may be specifically involved in the lymphotactic process through the development of new lymphatic vessels near the tumor.

NEW TARGETS IN IBC WITH THERAPEUTIC IMPLICATIONS

Although not specific for IBC, epidermal growth factor receptor (EGFR), janus kinase/signal transducer and activator of transcription 3 (JAK1/2/STAT3), and tunica interna endothelial cell kinase 2 (TIE2) can be dysregulated in IBC, notably triple-negative IBC [44]. To address the possibility that targeting these signaling alterations may prove efficacious, there are several

ongoing clinical trials of panitumumab [45] and neratinib [46], targeting EGFR, which are open to patients with IBC. The JAK2/STAT3 signaling pathway activated by interleukin-6 modifies the differentiation to macrophages in the tissue microenvironment. In turn, the mesenchymal stromal cells that come under the influence of M2 macrophages may mediate resistance and promote metastases; this biology is addressed in trials of ruxolitinib to modulate the JAK/STAT axis [47]. The TIE2 kinase, part of the family of angiopoietin receptors, may participate in angiogenic progression in IBC. To target TIE2, a clinical trial of the inhibitor rebastinib, phase 1b/2, is ongoing [48]. Increasingly, there are more diverse trials that allow enrollment of patients with IBC, when the targeted molecules have been shown to play a role in the phenotypic and clinical features of IBC. This breakthrough in the inclusion of patients with IBC on clinical trials of aggressive breast cancers is due, in large part, to concerted international advocacy and academic efforts to increase representation of patients with IBC in novel trials.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Breast cancer".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Inflammatory breast cancer (The Basics)")

SUMMARY

Inflammatory breast cancer (IBC) is a rare and aggressive form of breast cancer, characterized by its inflammatory appearance with diffuse erythema and edema.

- The classic histologic finding on biopsy of affected skin is dermal lymphatic invasion by tumor cells, which causes the inflammatory changes. (See 'Pathology' above.)
- Although dermal lymphatic involvement supports the diagnosis of inflammatory breast cancer, it is neither necessary nor sufficient in the absence of classical clinical findings. (See 'Basic features' above.)
- Investigations into the molecular basis of IBC and its rapidly progressive and highly angiogenic and angioinvasive features have focused on hormone receptors, overexpression of the epidermal growth factor receptor and vascular endothelial growth factor, and the contributory role of the *p53* tumor suppressor gene, *RhoC GTPase* oncogene (a member of the Ras family of small GTP-binding proteins), and the *WISP3* gene and its protein product, an insulin-like growth factor binding protein-related protein. (See 'Molecular genetics' above.)

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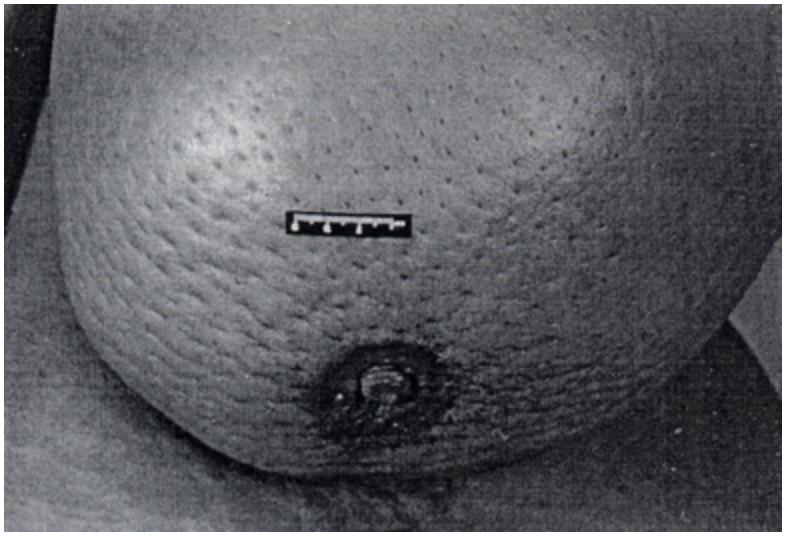
Topic 742 Version 20.0

GRAPHICS

Clinical presentation of inflammatory breast cancer



The characteristic "peau d'orange" appearance of the breast skin, which is similar to the appearance of the skin of an orange, is apparent.

Graphic 70894 Version 4.0

Breast carcinoma TNM anatomic stage group AJCC UICC 8th edition

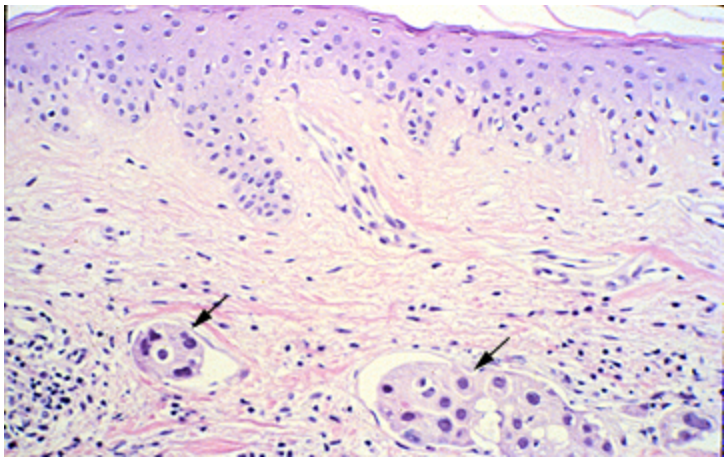
When T is...	And N is...	And M is...	Then the stage group is...
Tis	N0	M0	0
T1	N0	M0	IA
T0	N1mi	M0	IB
T1	N1mi	M0	IB
T0	N1	M0	IIA
T1	N1	M0	IIA
T2	N0	M0	IIA
T2	N1	M0	IIB
T3	N0	M0	IIB
T0	N2	M0	IIIA
T1	N2	M0	IIIA
T2	N2	M0	IIIA
T3	N1	M0	IIIA
T3	N2	M0	IIIA
T4	N0	M0	IIIB
T4	N1	M0	IIIB
T4	N2	M0	IIIB
Any T	N3	M0	IIIC
Any T	Any N	M1	IV

- The anatomic stage group table should only be used in global regions where biomarker tests are not routinely available.
- Cancer registries in the US must use the prognostic stage group table for case reporting.

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

Graphic 110848 Version 8.0

Inflammatory carcinoma of the breast



The skin of the breast with an inflammatory carcinoma shows dermal lymphatic invasion by carcinoma cells (arrows).

Courtesy of Stuart Schnitt, MD.

Graphic 60801 Version 1.0

Contributor Disclosures

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