

Approach to inflammatory breast cancer

ANDREA MOLCKOVSKY¹, MD, BARBARA FITZGERALD¹, RN, ORIT FREEDMAN¹, MD, RUTH HEISEY¹, MD, MARK CLEMONS¹, MD, Drs MOLCKOVSKY¹, FREEDMAN¹, CLEMONS¹, Ms FITZGERALD¹, Dr HEISEY²

¹Division of Hematology and Medical Oncology at Princess Margaret Hospital in Toronto, Ont, and in the Department of Medicine at the University of Toronto

²Department of Family and Community Medicine at the University of Toronto

The average family physician will see 2 new cases of breast cancer each year. (1) Inflammatory breast cancer (IBC) is a rare subgroup of breast cancer that presents particular challenges. Although few women presenting with inflammation of the breast have cancer, family physicians must recognize warning signs and differentiate IBC from the more common benign disorders.

One of the main challenges of IBC is prompt recognition of disease symptoms. Inflammatory breast cancer often presents with diffuse erythema of the breast in the absence of a discrete breast lump, which might not be recognized by patients as a “warning sign” for aggressive breast cancer, thus delaying presentation. (2) Clinicians might not recognize IBC warning signs if women are younger, pregnant, or breastfeeding. (3) Because IBC is a rapidly progressing form of cancer, it is essential that family physicians be familiar with its clinical presentation and make timely referrals. Following diagnosis, family physicians play an important role in symptom control and supportive care.

In this article we will expound upon basic principles surrounding diagnosis and management of IBC in primary care.

CASE 1

Callie is a 36-year-old who gave birth to her first child 2 months ago. Five days ago she noticed

redness and tenderness in her left breast. She has no relevant personal past medical history; however, her mother and maternal aunt were both diagnosed with breast cancer in their 60s. Callie presents to your office with visible erythema of the left breast in the upper outer quadrant and concomitant tenderness. She is concerned about infection and breast-feeding on that side. Should you be concerned about IBC? □

CASE 2

Edith is a 76-year-old widow. She presents to your office complaining of a 3-month history of enlargement of the right breast. Physical examination reveals that her right breast is enlarged and red, and the skin is firm, with pitting (Figure 1). She has palpable axillary lymph nodes. You suspect IBC. What are your next steps in diagnosis and management?



Figure 1. Right breast is enlarged and red, and the skin is firm, with pitting

Sources of information

Data for this review were identified by a search of MEDLINE (January 1950 to April 2008) using search terms *inflammatory breast cancer, detection, differential, risk factors, family physician, and survival*. References were hand-searched for relevance and limited to English-language articles. Evidence is level II (epidemiologic studies) and III (reviews based on retrospective case series and expert opinions).

Definition

Inflammatory breast cancer is a clinical diagnosis. Patients typically present with a rapidly progressing, tender, firm, enlarged breast (Table 1). This presentation is due to the invasion of skin dermal lymphatics by breast cancer cells. The obstructed lymph channels produce characteristic skin changes – erythema, warmth, edema, and induration – that mimic an inflammatory process, except cancer cells rather than inflammatory infiltrate are seen under the microscope. (4) These changes are sometimes, but not always, demonstrated on skin biopsy.

Epidemiology

Inflammatory breast cancer is not common, representing anywhere from 1% to 6% of all breast cancer diagnoses (level II evidence). (5) A recent review suggested that the incidence of IBC could be rising; authors found an incidence of 2% from 1988 to 1990 and 2.5% from 1997 to 1999. (5)

Inflammatory breast cancer is more common among black women and is associated with younger age at diagnosis (mean age 50 to 58 years compared with 50 to 64 years among those diagnosed with noninflammatory breast cancer). (6) Studies based on cases in North Africa, where for unknown reasons 50% of breast cancer cases

present as IBC, have suggested an association with obesity and younger age at first giving birth. (6) However, there are no validated risk factors that might aid in raising suspicion for IBC. (6,7)

Inflammatory breast cancer is commonly diagnosed in women who have never had breast cancer, but it can also develop in a breast that contains a known tumour or that has been previously treated. These “secondary” cases of IBC behave similarly to “primary” cases of IBC, and therefore a diagnosis of IBC cannot be excluded in a woman with a known history of breast cancer. (8)

Clinical presentation

Patients with IBC usually present with a complaint of colour change in 1 breast, usually pink that evolves into a darker red and spreads over the entire breast. The patient might describe a sensation of heat in the breast, and the breast itself enlarges rapidly over a period of only a few weeks (Table 1 and Figure 2). Patients usually do not experience fever. (9)



Figure 2. Patients with inflammatory breast cancer Patients usually present complaining of colour change in one breast, usually pink that evolves into a darker red and spreads over the entire breast. The patient might describe a sensation of heat in the breast, and the breast itself enlarges rapidly.

Table 1. Clinical features of inflammatory breast cancer

OBJECTIVE SIGNS	SYMPTOMS
<ul style="list-style-type: none"> • Absence of fever 	<ul style="list-style-type: none"> • Affected breast is often "heavier" than the unaffected breast
<ul style="list-style-type: none"> • Warmth of the breast 	<ul style="list-style-type: none"> • Breast enlargement
<ul style="list-style-type: none"> • Edema involving more than two-thirds of the breast 	<ul style="list-style-type: none"> • Sensation of heat, possibly tenderness
<ul style="list-style-type: none"> • Skin thickening or peau d'orange 	<ul style="list-style-type: none"> • Rapid onset and progression
<ul style="list-style-type: none"> • Ridges dividing areas of induration and more normal areas of skin 	
<ul style="list-style-type: none"> • Diffuse firmness on palpation 	
<ul style="list-style-type: none"> • Might or might not be an underlying mass 	
<ul style="list-style-type: none"> • Might be axillary adenopathy 	
<ul style="list-style-type: none"> • Mottled erythema over at least one-third of the breast 	

Physical examination should focus on assessing warmth, swelling, induration, erythema, and peau d'orange. Nipple changes such as crusting and retraction might be seen but are not criteria for diagnosis. (9) Underlying tumour masses might be palpable in IBC, but up to 30% of patients will present with no underlying masses. Instead, such a patient will have a diffusely enlarged breast. (9) Given the rapid spread of this type of tumour, it is not uncommon to find axillary adenopathy. Rarely, patients might have signs or symptoms of metastatic spread (Table 2).

Certain warning signs in a woman with a red breast increase the likelihood of IBC (Table 3). These include a personal history of breast cancer, nonlactational status, and palpable axillary adenopathy. Unless a clear alternative diagnosis is present, these women should be referred immediately to surgical oncologists.

Table 3. Red-flag warning signs of inflammatory breast cancer

WARNING SIGNS
Previous history of breast cancer. Symptoms of mastitis in a nonlactating woman. Palpable adenopathy.

Differential diagnoses

The differential diagnoses for inflammation of the breast include benign diseases and other malignancies, and can be stratified by lactation status (Table 4).

Lactation mastitis occurs in up to 10% of lactating women and is associated with localized tenderness, fever, and leukocytosis – features that help to distinguish it from IBC. (10) Mastitis develops rapidly over a few days. The erythema is

associated with tenderness and occupies a wedge-shaped quadrant of the breast, and the patient feels unwell. Infection is usually caused by *Staphylococcus aureus* and improvement occurs within 24 to 48 hours of initiating antibiotics.

Duct ectasia is a benign entity of the nonlactating breast that affects perimenopausal and postmenopausal women. It occurs when ducts beneath the nipples become clogged with fatty material, producing a lump. There is frequently itching or burning around the nipple and a thick discharge. (11) These changes are well demarcated and involve less than one-third of the breast. (12) Duct ectasia is usually a self-limited disease but might lead to subareolar abscesses that require surgical resection. (11)

Other benign entities that can be confused with IBC include Mondor disease and fat necrosis. Mondor disease, or phlebitis of the thoraco-epigastric vein, usually presents as a painful, possibly palpable, cord and is usually preceded by trauma. (10) Because there is a possible association with malignancy, a mammogram is suggested for women older than 35 years of age. Treatment includes reassurance and nonsteroidal anti-inflammatory drugs. Fat necrosis can occur spontaneously or as a result of trauma. (10) The usual presentation of fat necrosis is a palpable lump, and a biopsy might be required to differentiate it from malignancy. Neither Mondor disease nor fat necrosis will result in enlarged lymph nodes, another clue to diagnosis of IBC. (11)

Malignant entities that mimic IBC include leukemic infiltration of the breast. These patients are usually systemically unwell, and a peripheral blood smear usually confirms this rare diagnosis.

Generally, benign breast conditions will resolve with appropriate treatment. Most experts recommend waiting 7 days before initiating further investigations, unless the clinical suspicion of IBC

Table 2. Signs and symptoms of met

SITE OF SPREAD	SYMPTOM	SIGN
Lymph nodes	Pain and swelling in axillary, supraclavicular, or infraclavicular areas	Axillary, supraclavicular, or infraclavicular adenopathy
Bone	Pain in bones out of keeping with patients' usual pain, without previous trauma and not responding to medication	Tenderness on percussion of the spine
Liver	Abdominal pain, early satiety	Enlarged liver on palpation, with a firm liver edge
Lung	Shortness of breath	Auscultation and percussion of lungs compatible with pleural effusion or pulmonary edema
Brain	Morning headache, vomiting	Neurologic symptoms, papilledema

Table 4. Differential diagnoses of inflammation. Entities in boldface are common

STATUS OF BREAST	BENIGN CONDITIONS	MALIGNANT CONDITIONS
Lactating	Acute mastitis	Inflammatory breast cancer
	Abscess	
	Galactocele	
Nonlactating	Duct ectasia	Inflammatory breast cancer
		Lymphoma
Nonspecific	Generalized dermatitis (insect bite, sunburn, allergy)	Leukemia
	Fat necrosis	
	Tuberculosis	
	Sarcoidosis	
	Cat-scratch disease	
	Syphilis	

is high (classic breast appearance, axillary nodes, no history of lactation or trauma).

Investigations

If clinical suspicion of IBC is high, prompt referral to a surgeon should be made. Otherwise the first investigation ordered is generally a mammogram. The classic changes that can be seen on a mammogram in IBC are skin thickening, trabecular and stromal thickening, and increased breast density. (13) Inflammatory breast cancer, as mentioned, might not be associated with a breast mass, and concomitant high breast density can obscure masses as well; therefore, absence of suspicious masses on the mammogram is not helpful in ruling out IBC.

Ultrasound of the breast and axillary lymph nodes can be useful when IBC is suspected. Ultrasound imaging might detect masses that were not obvious on palpation or mammography, or reveal axillary adenopathy, and thereby facilitate biopsy for diagnosis. (13)

If results of these investigations do not suggest a benign diagnosis (such as fat necrosis), and the patient's symptoms persist beyond 3 weeks despite appropriate investigations and conservative treatment (such as nonsteroidal anti-inflammatory drugs and antibiotics), prompt referral to a surgeon is necessary.

Management

Patients with IBC need to be treated promptly, ideally in a multidisciplinary breast oncology clinic that specializes in the treatment of IBC. This patient group requires coordination of medical, surgical, and radiation oncology care as well as nursing and other supportive disciplines. These clinics are usually only found within cancer centres affiliated with tertiary hospitals, and might require patients to travel substantial distances.

Management of IBC encompasses combined-modality therapy. Owing to the skin involvement of IBC, the risk of loco-regional and distant recurrence is too high to justify immediate mastectomy. Preoperative chemotherapy is therefore standard care. (14) Before initiating chemotherapy, a core biopsy is performed to confirm the diagnosis and determine hormone-receptor and HER-2/*neu* status of the tumour. A metastatic workup completes staging. This workup includes bone scans, chest x-ray scans, and abdominal ultrasound scans (with more focused tests if there are any additional symptoms).

The purpose of chemotherapy up front (also known as *neoadjuvant* or *preoperative chemotherapy*) is to eliminate micrometastatic disease and reduce inflammation in the breast, making tumours amenable to surgery and radiation. Response to chemotherapy also tells oncologists about the aggressiveness of tumours, providing clues to patients' ultimate prognoses. After chemotherapy, patients undergo mastectomy and axillary lymph node dissection, followed by radiation therapy to the chest wall and regional lymph nodes. (15) The final component of treatment includes endocrine therapy and targeted therapy, such as trastuzumab, depending on receptor status. In total, the active treatment of IBC takes about 1 year.

Common side effects of chemotherapy include alopecia, nausea and vomiting, and risk of febrile neutropenia. Patients are advised to promptly visit the nearest emergency department if they experience a fever (higher than 38°C for at least 1 hour, or 1 reading above 38.2°C). Some patients receiving taxane chemotherapy experience bony pain or myalgias. This pain often responds to treatment with acetaminophen, but can be severe enough to require opioid treatment as well. (16) Long-term effects include increased

risk of cardiac damage (due to anthracycline therapy) and increased risk of leukemia.

Prognosis

When compared with other breast cancer patients presenting at the same stage, women with IBC have worse prognoses. Moreover, up to 25% of women present with metastatic, incurable disease. (17) Median overall survival for IBC patients is 2.9 to 4.2 years, (18,19) with lower survival rates among black women and those with estrogen receptor-negative tumours. (5) These survival rates have not changed significantly over the past 30 years, emphasizing the aggressive nature of the disease. (19) Newer biologic agents such as trastuzumab and lapatinib might improve outcomes for patients with IBC. (14) Given the baseline poor prognosis of IBC, eligible patients are offered inclusion in clinical trials if possible.

Family physicians' role in management

Family physicians are gatekeepers: they play a crucial role in identifying IBC and referring patients appropriately. The oncology team treats the cancer and related problems; however, the family doctor manages nononcologic diagnoses that were present before diagnosis of IBC. Some conditions might be affected by treatment; for instance, blood-glucose control in patients with diabetes often worsens during chemotherapy, owing to steroids given adjunctively. The family doctor often needs to provide psychological support to the patient and her family. Once treatment is finished, close clinical surveillance and annual mammography are shared responsibilities of the oncologist and family doctor. The family doctor also monitors for long-term side effects of treatment (Table 5).

Table 5. Family physician follow-up of women treated for breast cancer. The goals of follow-up are to provide support and counseling, to detect metastatic disease and ensure appropriate treatment is initiated promptly, and to provide patient education as new information about breast cancer becomes available.

FOLLOW-UP ACTIVITIES	RECOMMENDATIONS FOR EXAMINATION
Medical history	Bone pain
	Dyspnea
	Weight loss
	Abdominal symptoms
	New nodules or masses
	Vaginal bleeding if taking tamoxifen*
Physical examination	Breast and chest wall
	Axilla
	Supraclavicular nodes
	Arm lymphedema
	Hepatomegaly
	Ascites
	Leg swelling if taking tamoxifen**
Mammograms	Annually
Routine laboratory and radiological tests	As clinically indicated by signs or symptoms
Bone mineral density scans for women at risk of osteoporosis or starting aromatase inhibitors	At completion of adjuvant chemotherapy and before initiation of aromatase inhibitors
	Repeat in 12-18 mo
	Advise lifestyle modification (reduce alcohol and caffeine intake, stop smoking, increase weight-bearing exercise, take calcium and vitamin D supplements)
Consequences of disease or treatment	Menopausal symptoms
	Cognitive functioning
	Fatigue
	Weight gain
	Sexual functioning
	Fertility
	Arthralgias
	Lymphedema
	Psychosocial distress

* If vaginal bleeding is present in patients taking tamoxifen, a trans-vaginal ultrasound is recommended. Refer to a gynecologist if the endometrial thickness is > 10 mm or if there is persistent bleeding with thickness > 5 mm.

**If a patient experiences a thrombotic event while taking tamoxifen, a referral back to the oncologist is recommended.

Often the family physician is not only the patient's doctor but also her whole family's doctor. If the patient is the primary caregiver in the family, a shifting of roles needs to occur, and coping can be difficult. Previous relationship difficulties are often exacerbated by the stress of a new diagnosis. Children of any age are substantially affected. (20) Family physicians should inquire about children's health and development; some warning signs include somatic complaints, difficulties with school, depression, and anxiety. Some families might benefit from multidisciplinary support teams that include family physicians, oncologists, nurses, and social workers. Internet resources can also be helpful (Table 6).

Given the poor prognosis of IBC, family doctors might need to help with palliative care as well. Communication with a patient's oncologist is essential for optimizing symptom management and organizing end-of-life care. Palliative care clinics affiliated with cancer centres are excellent referral centres that organize home nursing and social work, and they will liaise with family doctors to provide comprehensive and consistent care. □

CONCLUSION

Family physicians are uniquely positioned to assure timely diagnosis of IBC, which is an aggressive form of breast cancer. Prompt recognition of symptoms and signs suggestive of IBC, referral to a multidisciplinary team for treatment, and support of women and their families throughout treatment and beyond

assures optimal management of this potentially fatal disease.

Case 1 resolution

Callie has a low-grade fever, and her baby is not feeding properly from the affected breast. Examination reveals a focal area of pain, redness, and induration in the outer upper quadrant, with no palpable lymphadenopathy. Bloodwork results show leukocytosis and left shift. You instruct Callie about compresses, ibuprofen, and continued breastfeeding, and prescribe a 14-day course of oral cloxacillin. (11) You expect improvement within 48 hours; if there is no response within 7 days you will reconsider the diagnosis, perform a mammogram and an ultrasound, and, depending on the results, refer Callie to a breast cancer centre.

Case 2 resolution

Edith has many worrisome features of IBC, and prompt mammogram and ultrasound are performed. She is immediately referred to a tertiary oncology centre when pathology from the ultrasound-guided lymph node biopsy reveals breast adenocarcinoma. You help manage her pain and symptoms throughout her ordeal, but despite optimal treatment her cancer spreads and she dies peacefully, pain-free, at a hospice.

Levels of evidence

Level I: At least one properly conducted randomized controlled trial, systematic review, or meta-analysis.

Table 6. Internet resources

RESOURCE	WEBSITE	DESCRIPTION OF RESOURCE
General information		
Canadian Cancer Society	www.cancer.ca	Information and resources across Canada
Canadian Breast Cancer Network	www.cbcn.ca	Database of support groups and information
National Cancer Institute	www.cancer.gov	US website with up-to-date clinical information for patients and health professionals, clinical trials
Support groups		
Willow	www.willow.org	Support groups and support information across Canada
Princess Margaret Hospital Survivorship Program	www.caringvoices.ca	Support groups and support information
Families with children		
Gilda's Club	www.gildasclubtoronto.org	On-line resources for children
We Can Cope	http://wecancope.com	Information and frequently asked questions
Palliative care		
Princess Margaret Hospital Palliative Care	www.caringtotheend.ca	Information for health professionals and patients

Level II: Other comparison trials, non-randomized, cohort, case-control, or epidemiologic studies, and preferably more than one study.

Level III: Expert opinion or consensus statements.

EDITOR'S KEY POINTS

- Inflammatory breast cancer (IBC) is a rare type of breast cancer, accounting for between 1% and 6% of all breast cancer diagnoses. Because IBC is aggressive, however, the prognosis is poorer than for women with other types of breast cancer. Up to 25% of women present with metastatic, incurable disease. Median overall survival for IBC patients is 2.9 to 4.2 years.
- Patients will usually present with inflammation of the breast. Physical examination should focus on assessing warmth, swelling, induration, erythema, and peau d'orange. Nipple changes might be seen but are not criteria for diagnosis. Up to 30% of patients will not have

underlying masses. It is not uncommon to find axillary adenopathy, and signs or symptoms of metastatic spread are rare.

- Warning signs in a woman with a red breast include a personal history of breast cancer, non-lactational status, and palpable axillary adenopathy. Unless a clear alternative diagnosis is present, these women should be referred immediately to surgical oncologists.

Footnotes

Cet article a fait l'objet d'une révision par des pairs.

Contributors

Drs Molckovsky, Freedman, Heisey, and Clemons and Ms Fitzgerald contributed to the concept of the article, the literature search, the review of selected articles, and preparing the manuscript for submission.

Competing interests

None declared.

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Studies point to viruses as cause of diabetes

Two studies published on Thursday provide evidence that common viruses may cause childhood diabetes, paving the way for potential vaccines against the life-threatening condition, researchers said.

One team showed that enteroviruses – which normally cause colds, vomiting or diarrhea – were found frequently in the pancreases of young people who had recently died from type 1 diabetes, sometimes called juvenile diabetes, but not in healthy samples.

This suggests a virus could trigger the disease in children genetically predisposed to the condition, which affects an estimated 440,000 people worldwide, said Alan Foulis of the Royal Infirmary in Glasgow, who worked on one of the studies.

“The story that is emerging is there is a virus infection that precedes the onset of autoimmunity,” he told a news conference. “There is a thought that we are looking at the culprit.”

Type 1 diabetes is caused by the destruction of beta cells of the pancreas that produce the insulin necessary to regulate blood sugar levels. The autoimmune disease is different from

the far more common type 2 diabetes, which is strongly associated with obesity.

Genetics play a role in diabetes but researchers know other factors such as diet are also important, with viruses long suspected as a possible trigger, researchers said.

Foulis and colleagues examined 73 pancreas samples of young people who had died from diabetes and found that 60 percent of the donated organs contained evidence of enteroviral infection of beta cells.

By contrast, the researchers hardly ever saw infected beta cells in tissue samples taken from 50 children without diabetes, they reported in the journal *Diabetologia*.

They also found a large proportion of these infected cells in adults with the more common type 2 diabetes, suggesting that viruses may also trigger this form of the disease in some people.

A second study from Cambridge University researchers found that rare genetic mutations in a gene involved with the body’s response to viruses reduce the risk of juvenile diabetes.

They looked at 480 young people with type 1 diabetes and another 480 healthy people to identify the gene and the variants involved.

“We have pinpointed a specific gene, which acts as a warning report for virus infection,” John Todd, a Cambridge University researcher, who worked on a study published in the journal *Science*. “Not only have we found a specific gene but this gene also has an intriguing function in dealing with virus infection.”

While Todd cautioned that many environmental factors besides viruses could contribute to type 1 diabetes, Foulis and his team said they wanted to whittle down the some 100 enteroviruses to find which ones played the main roles.

Doing this, and better understanding of how cells respond to viral infection, are steps toward a vaccine that could one day protect children against diabetes, Foulis said.

“The aim would be for a vaccine that would prevent many cases of type 1 diabetes,” he added.

Source: REUTERS HEALTH – London

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