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The inflammatory breast: Management, decision-making algorithms, therapeutic principles

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Breast; Inflammation; Diagnostic strategy; Treatment

Abstract
Inflammatory syndrome is one of the rare emergency breast situations. Its etiology is benign, infectious in most cases. The clinical examination is often self-evident and suggests the diagnosis. But alone it is insufficient, and diagnostic tests are necessary to guide therapy. As essential as it is, mammography’s limitations reinforce the benefit of ultrasonography, which in all cases reveals an abscess and has greater sensitivity for detecting a malignant tumor. If the etiology is benign, clinical signs will disappear with medical treatment, with no need for further investigation. While it is legitimate to initiate a trial treatment, it must not delay oncologic management, because of the severity of inflammatory cancer.

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Since the breast is a superficial organ, inflammation or mastitis results in classical clinical signs: redness, heat, and pain. It is a rare reason for consultation with a physician. Mastitis has several possible etiologies: pure inflammatory, infectious, or malignant [1,2]. It is an emergency breast situation. Any picture of mammary infection that initially appears to be benign but resists appropriate treatment should suggest a malignant lesion.

There are few series in the literature addressing the value of various imaging studies for diagnosing inflammatory syndrome, whose management includes the possibility of surgical procedures. When malignancy is confirmed, it must be managed in an oncologic setting on an emergency basis.

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Figure 1. Age 47. Left breast red, taut, entirely indurated: a: mammogram, standard lateral: marked sloping skin thickening, areolar appearance of the structure, focal increase supra-areolar density at mid third of the gland, cluster of irregular microcalcifications; b: lateral image enlarged to better analyze the microcalcifications. The increased focal density is located at the upper edge of the film; c: ultrasound: irregular 35 mm supra-areolar mass. Ultrasound-guided microbiopsy: invasive ductal carcinoma.

Overview: contribution and limitations of the clinical examination and conventional imaging

The clinical examination

Redness, measured in centimeters, is not marked, and is localized in inflammatory cysts and diabetic mastopathy; however, redness or lack thereof is not proof positive of benignity. "Orange peel" (pitting) edema may or may not be present in benign causes, and is significantly more marked in infectious and malignant mastitis than in purely inflammatory mastitis [3].

The abscess presents as a classically fluctuating tumor, but this sign is actually rare here, since the Cooper's ligaments act as a barrier against the spread of infection to the surface, and the infection most often spreads inside the gland, which cannot be judged from its external appearance [4]. Purulent discharge, fever, and laboratory signs are generally absent with mammary abscesses.

Palpation of a thickness or mass(es) is not necessarily a bad sign, and may reflect dilated pseudocystic ducts or diabetic mastopathy. Conversely, in inflammatory cancer, an underlying mass is not always palpated. Whence the importance of imaging in making an etiologic diagnosis.

Imaging

Priority of studies

Mammography is essential in adult females. It can be difficult to perform and interpret if there is insufficient compression and if there is marked edema, giving the structure a mesh-like appearance. When clinical and ultrasound signs are in favor of benignity, it is better to perform one
secondarily, after the inflammation resolves, in order to obtain a good quality study. Mammograms are typically performed in women after 30 years of age [5], but should be performed in a young woman under 30 when there are suspicious clinical signs or persistent inflammation.

The signs of edema are often mild, predominantly in the periareolar area and in the inferior quadrants due to gravity; sometimes it is necessary to make a comparison with the opposite side. By increasing the contrast, digital mammography facilitates the detection of subtle signs.

We look for the following signs, which are then described using the BI-RADS lexicon:

- dilated retroareolar ducts;
- calcifications;
- focal asymmetric density (Fig. 1a and b);
- mass.

Ultrasonography is the first-line method used when mammography is not feasible, or in addition to mammography (Fig. 1c). The signs common to all inflammation are: skin thickening to more than 3 mm, a hyperechoic appearance of the fat lobules due to edema, visibility of the subcutaneous lymphatic vessels in the form of tubular structures that
follow the path of the crests of Duret (Fig. 2). We look for the following signs [3]:
- dilated lactiferous ducts (more than 3 mm in diameter);
- cysts (by analyzing echogenicity, wall thickness)
- fluid collections and fistulas (Fig. 3);
- solid masses (Fig. 4);
- enlarged axillary lymph nodes.

Contribution and limitations of imaging in reaching an etiologic diagnosis

The imaging signs of edema are significantly more marked in infectious and malignant mastitis than in purely inflammatory mastitis [3]. A benign inflammatory lesion generally has no suspicious manifestation [4].

**Mammography**

The mammogram may be normal (ACR 1). The abscess is occult in one-third of all cases on the mammogram [4,6]. The mammogram’s sensitivity for detecting inflammatory cancer varies in the literature, firstly due to technical differences and secondly due to the individualization of primary inflammatory cancer as compared to locally advanced cancer with secondary inflammatory changes. Mammography does not necessarily reveal a mass that correlates with the palpable mass found in most patients. In the study by Le-Petross [7], compared with other imaging methods, mammography had the lowest cancer detection rate (43% of single and multiple masses detected). But in those cases, the edema was often marked and the gland had increased density: the mammogram could not be considered normal.

The mammogram may show signs of duct ectasia (ACR 2). In that case it is necessary to ascertain that the ectasia is the only causal mechanism of the inflammatory syndrome, since it is commonplace to see these signs without any symptoms.

The mammogram may show changes in gland density. Very moderate diffuse edema and a focal increased density that is difficult to isolate argue in favor of benignity. A diffuse increase in density is more suspicious and can mask a malignant mass, as mentioned above [7–9].

There may be an architectural distortion (ACR 4), which may be slight, due to plasmacytic mastitis with fibrosis, or marked, posing a more acute problem for differential diagnosis versus malignant disease. Percutaneous biopsies are necessary when there is image distortion, and the choice of technique is determined based on whether or not the image appears on the ultrasound.

The mammogram may be classified ACR 5 from the outset (Fig. 2). Technological progress has contributed to its better sensitivity in malignant inflammatory syndrome.

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**Figure 3.** Age 32. Smoker: a: right periareolar inflammatory syndrome; b: first-line ultrasound: dilated duct with thick contents. Periareolar abscess resolved with medical treatment.

**Figure 4.** Age 46; localized left supra-areolar inflammatory syndrome. Mammogram: dense breasts, mild signs of edema, ACR 2. Ultrasound: moderate skin thickening, dilatation of subcutaneous lymphatic vessels, irregular 30 mm mass, ACR 5. Ultrasound-guided microbiopsy: grade 2 invasive ductal carcinoma.
Ultrasonography

The ultrasound signs are mild or even absent when the abscess is in the presuppurative stage. However an abscess with collection of pus always appears on the ultrasound [6] (Fig. 5). While the analysis of a mass is based on the BI-RADS lexicon and classification, management should reflect the clinical context, since the ultrasound signs of an abscess (echogenic halo, etc.) have a high positive predictive value for malignancy. An inflammatory syndrome manifesting as a very hypoechoic or irregular anechoic area that appears benign or indeterminate on the mammogram, is assumed to have a benign etiology [4].

The abscess may still pose a differential diagnosis problem versus a malignant mass due to its irregular shape and ill-defined margin [5]. It should be borne in mind that rapidly progressive cancers (with a triple-negative phenotype and/or occurring in mutated women in whom malignant tumors with a pseudo-fluid appearance on the ultrasound have been reported) are very hypoechoic in nature [10,11]. Finally, necrotic cancer can have a pseudo-fluid appearance with swirling echoes (Fig. 6).

Even in patients who have only a mild image on the mammogram, the ultrasound can show a mass with all the criteria for malignancy, or extensive architectural disorganization. The sensitivity of ultrasonography in inflammatory syndrome is 65% [9]. It is therefore an alternative to mammography when the latter is not technically feasible.

Diagnostic strategy

This is summarized in Fig. 7.
Benign-appearing inflammatory syndrome

An emergency trial treatment is prescribed for 10–15 days after which the patient is seen again for a clinical examination and follow-up ultrasound (as well as a mammogram, if one was not done originally). The need for follow-up should be clearly indicated in the conclusion of the radiology report and, ideally, an appointment should be scheduled for the patient.

When the clinical radiology aspect suggests an abscess, a bacteriology specimen is not essential, but makes it possible to adjust the antibiotic therapy. The puncture is done with an 18G or 20G needle; the specimens are cultured on aerobic and anaerobic media.

Persistent clinical inflammation or mass-type abnormalities on the ultrasound are indications for an ultrasound-guided 14G biopsy. A residual granuloma is simply monitored (Fig. 8).

A 14G biopsy sometimes reveals cystic and ectatic features, but the clinical signs improve without disappearing, suggesting inflammatory cancer. Possible options are:

- macrobiopsies to provide larger samples;
- or an MRI, which is indicated after treatment of inflammatory syndrome, if in doubt about the diagnosis, even...
if differentiation between benign and malignant mastitis remains difficult [12] (Figs. 9 and 10).

A suspicion of diabetic mastopathy leads to an ultrasound-guided 14G microbiopsy and, if the diagnosis is histologically confirmed, it seems possible to avoid a surgical procedure [13].

In the context of a treated breast (conservative treatment), the diagnostic process is different, since post-radiation inflammation is the initial hypothesis (Fig. 11). A normal workup supports that hypothesis, and medical treatment (nonsteroidal anti-inflammatories and ice) should make the clinical signs disappear.

**Ambiguous or suspicious-appearing inflammatory syndrome**

An ultrasound-guided microbiopsy is the rule. Targeting is sometimes difficult, since this is a poorly defined mass with posterior acoustic shadowing. Radiologic/histologic reconciliation becomes very important and, if negative, further micro- and macrobiopsies or skin biopsies must be taken.

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**Figure 8.** Age 45. Follow-up on an abscess after 10 days of medical treatment. Ultrasound: solid 1 cm mass with well defined margins. Ultrasound-guided microbiopsy: granuloma. Follow-up: 4 months, 6 months, then usual.

**Figure 9.** Slightly marked localized inflammatory syndrome, persisting for 15 days despite medical treatment, in a patient with breast augmentation implants. Ultrasound: bilateral intracapsular rupture. MRI, transaxial slices. Silicone-only sequences: siliconoma at the lower part of the implant. a: T1-weighted, without injection: the siliconoma is moderately hyperintense; b: after injection: moderate enhancement of the siliconoma, due to inflammatory phenomena. Regression of signs with anti-inflammatory treatment extended 10 days.

**Figure 10.** Age 52. Right breast globally red, hard, very enlarged. Mammogram not feasible. Ultrasound difficult to read. No regression with medical treatment. An MRI was ordered. a: MRI of right breast, T2-weighted coronal slice: thickening of the skin and dilation of the lymphatic vessels that “outline” the path of the crests of Duret; b: MRI, coronal slice after injection. Irregular masses in the superior lateral quadrant are heterogeneously enhanced. ACR 5. Blind microbiopsy at right superior lateral quadrant: grade 3 invasive ductal carcinoma.
Figure 11. Age 55. History of conservative treatment 1 year earlier. Redness around scar on left superior lateral quadrant with cutaneous edema. Mammogram and ultrasound normal, other than mild signs of edema. Resolved with anti-inflammatories.

Absence of a target, a blind microbiopsy may be done, preferably in the retroareolar area if the entire breast is red, or in a localized inflammatory area. As a last resort, a skin biopsy may be done under local anesthesia in an inflammatory area. An aspiration biopsy of a suspicious enlarged lymph node may be appropriate when the breast workup is normal.

**Treatment**

**Benign inflammatory syndrome**

For puerperal mastitis, broad-spectrum antibiotic therapy is initiated (erythromycin, dicloxacillin, cephalaxin). Breastfeeding may be continued [7].

For mastitis with duct ectasia, treatment consists of nonsteroidal anti-inflammatories, or steroidal anti-inflammatories when the clinical signs are marked (palpable pseudocystic dilatations).

When the clinical radiology aspect is suggestive of an abscess, a trial treatment prescribed on an emergency basis is the rule for 10–15 days, with a combination of antibiotics (pristinamycin, amoxicillin, metronidazole) and anti-inflammatories, (steroidal or nonsteroidal). The bacterial flora of abscesses that occur outside of lactation is often mixed: Staphylococcus aureus, aerobic and anaerobic streptococcus, Enterococcus, Proteus mirabilis, Escherichia coli... Broad-spectrum antibiotic therapy is indicated, particularly in patients at high risk for recurrence (smokers, obese subjects) [14]. The symptoms should improve and disappear after that time period, and the ultrasound must be repeated at the end of treatment to be sure the signs have disappeared.

For a recurrent fistulized periareolar abscess, the conventional treatment is surgical excision of the duct once it is quiescent; the quality of the excision is fundamental to avoid recurrence. In fact, management of these patients is quite difficult, since once quiescent, it is often impossible for the surgeon to find the causal duct. Any associated nipple inversion should be corrected. It is necessary to convince the patient — and this is essential — that it is absolutely mandatory to stop smoking to prevent the condition from becoming chronic [14,15] (Fig. 12).

Some authors suggest ultrasound-guided percutaneous drainage for abscesses larger than 3 cm [8]. In the Berna series [8], 15 out of 17 abscesses improved, and in two cases, a persistent mass required a histologic diagnosis; one was an inflammatory granuloma and the other was cancer.

In the case of Mondor’s disease, the diagnosis is clinical and the inflammation resolves spontaneously [16]; nonsteroidal anti-inflammatories may be prescribed; a clotting workup is recommended.

**Malignant inflammatory syndrome**

Based on its histopathologic features — dermal lymphovascular invasion is pathognomonic of the condition — inflammatory breast cancer should be considered a local/regional disease as soon as it is diagnosed. This serious condition is totally different from other locally advanced breast cancers (with attachment to deep structures or skin ulceration) and management by a trained multidisciplinary team is essential. Staging should be done before treatment is initiated, since metastatic disease is found at the outset in approximately 30% of cases. The standard workup consists of a thoracic and abdominopelvic CT scan and a bone scan.

Figure 12. Age 33. Smoker. Right periareolar redness. a: first-line ultrasound: dilated sub-areolar lactiferous duct with thick contents. Periareolar abscess; b: follow-up ultrasound after 10 days of medical treatment. Disappearance of clinical signs. Persistence of visible duct. Medical treatment continued for 8 days with recommendation that patient completely stop smoking.
Based on the currently available data, a PET scan is not part of the standard workup.

In the absence of confirmed metastatic disease, surgery and radiation therapy are part of the treatment plan [17]. Skin involvement at the time of diagnosis represents a contraindication to initial surgery, due to the major risk of tumor residue being the cause of early cutaneous recurrences. Neoadjuvant chemotherapy is therefore routinely given, in order to achieve sufficient tumor regression to allow a subsequent surgical procedure.

Due to the rarity of the disease, there have been no randomized studies comparing different treatment regimens, and the choice of chemotherapy is therefore based on retrospective analyses, small prospective studies, and extrapolation from randomized studies comparing different neoadjuvant chemotherapies for noninflammatory tumors. The standard treatment currently consists of a combination of an anthracycline and a taxane (six courses). In half the cases, the tumor shows HER-2 amplification, and treatment with trastuzumab is then added [18]. The preliminary results of a French study suggest that for HER-2 tumors, the addition of an antiangiogenic, bevacizumab, may significantly increase the efficacy of chemotherapy and trastuzumab in this type of tumor subgroup [19].

If there is good response to chemotherapy, particularly with regression of inflammatory signs, surgery should routinely be considered based on retrospective studies. Due to the characteristics of these tumors, that surgery should consist of a radical mastectomy without preservation of the skin. Due to the wide tumor dissemination in the breast and the frequency of axillary lymph node involvement (55–85% of cases), axillary resection with sentinel lymph node dissection is not a consideration. Lymph node dissection is routinely done. This surgery is always followed by radiation of the entire chest wall as well as the supra- and sub-clavicular and internal mammary lymph node areas. Immediate breast reconstruction is not recommended, but may be done subsequently.

Surgery is contraindicated as long as the inflammatory phenomena persist and, if neoadjuvant chemotherapy fails, radiation therapy should be given before subsequently reconsidering a surgical procedure.

One-third of all tumors express steroid receptors (estradiol and/or progesterone) and hormone therapy for at least 5 years is then suggested after local/regional treatment is completed [20].

Subsequent monitoring includes a clinical examination every 4–6 months, as well as an annual contralateral mammogram. Despite a more severe prognosis, all learned societies agree not to recommend any other routine diagnostic tests since no benefit has ever been found from early diagnosis of metastatic dissemination for which there is no known cure.

**Conclusion**

Inflammatory syndrome is one of the rare emergency breast situations. It has a benign infectious etiology in most cases and disappears with medical treatment, with no need for further investigation [21]. A trial treatment should not delay oncologic management.

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**TAKE-HOME MESSAGES**

**Diagnosis:**
- The term mastitis describes an inflammation, but is not synonymous with infection.
- Infection is the most common cause of inflammatory syndrome.
- History-taking is essential in the search for an infectious risk factor.
- A mammary abscess is always visible on the ultrasound.

**Strategy:**
- Clinical and ultrasound follow-up should be scheduled after the medical trial treatment.
- Percutaneous biopsies are required when clinical or radiological signs persist despite 15 days of medical treatment.

**Treatment:**
- Since a significant association has been found between smoking and periareolar abscesses, cessation is imperative.
- Neoadjuvant chemotherapy is administered in cases of inflammatory breast cancer.

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**Clinical case**

Mrs. B., age 57, had 2 years of conservative treatment for grade 2 invasive ductal carcinoma of the right inferior lateral quadrant. Her last follow-up breast sonogram was done 10 months earlier.

She was seen for a moderate inflammatory syndrome of that inferior lateral quadrant; the scar was thickened but there was no palpable mass. No enlarged axillary lymph nodes. No fever.

**Question 1**

What imaging studies do you order?

1. None.
2. Ultrasound.
3. Mammogram.
4. MRI.

**Answer**

2, 3. It is legitimate to redo a full conventional workup, inasmuch as the due date for the annual follow-up is approaching. An MRI would be indicated immediately only if the mammogram and ultrasound were difficult to read.

**Question 2**

Based on the mammogram (Fig. 13) and the ultrasound (Fig. 14) you do, what do you suggest to Mrs. B.?

2. An MRI.
3. An ultrasound-guided biopsy.
4. Nothing; monitoring at 1 year.
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Answer

1. The mammogram (Fig. 13) shows moderate post-treatment aspects and a clear image of a fatty cyst, which appears to have mixed echogenicity on the ultrasound (Fig. 14). Subcutaneous lymphatic vessels are visible, indicating edema.

This inflammatory syndrome should be treated for 10–15 days, followed by clinical and ultrasound follow-up.

Question 3

The inflammatory syndrome clearly regresses but does not completely disappear.

An MRI is done. You have a T2-weighted image (Fig. 15) and a late image after fat saturation injection (Fig. 16). What is your course of action?

1. ACR 2. Continue anti-inflammatory therapy for 1 week and repeat the annual follow-up.
2. ACR 3. Follow-up MRI in 4 months.

Answer

1. The MRI was done because the inflammatory syndrome had not completely disappeared. It shows a T2 hypersignal with mass effect, therefore fat content (Fig. 15), with fine annular enhancement indicating inflammation (Fig. 16). There is no sign of recurrence.

This was an inflammatory reaction to fatty necrosis. The inflammatory syndrome finally disappeared in a total of 1 month.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


