Clinical Approach to Breast Disorders: A Primer for Internists

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Abstract

Women with breast disorders often present first to their internists for evaluation. A delay in accurate diagnosis could often result in worsening of prognosis for the patient. Common diagnostic problems include evaluation of a breast lump, nipple discharge and breast pain. Internist now has a choice of several diagnostic modalities to evaluate breast disorders. An evidence-based approach to common breast symptoms and advances in breast diagnostic techniques has been described to enable early diagnosis of breast cancer, thereby reducing the need for intensive treatments and improve patient satisfaction and clinical outcome.

INTRODUCTION

Breast cancer is the second most common cancer among women in India, with locally advanced breast cancer comprising the majority of patients presenting for treatment. The outlook for breast cancer appears promising though, with tremendous advances being made over the recent years in early diagnosis as well as treatment of breast cancer. Improved breast health awareness, routine screening procedures, and a thorough assessment of clinical breast problems can enable early diagnosis of breast cancer, thereby reducing the need for intensive treatments and improve patient satisfaction and clinical outcome. In the present review, we will discuss an evidence-based evaluation of common breast symptoms and advances in breast diagnostic techniques.

EVALUATION OF A BREAST ABNORMALITY

Palpable mass

A palpable breast lump is a common clinical breast problem and often associated with immense anxiety for the patient. In a retrospective cohort study of a health maintenance organization in New England, Barton et al reported, 16 percent of women ages 40 to 69 sought physician advice about breast complaints over a 10-year period for a rate of 23 visits per 1000 woman years. In 40 percent the complaint was for a breast lump or lumpiness that breast mass was the second most common presenting symptom, after pain, and that 10.7% of the visits for breast mass resulted in the diagnosis of breast cancer. Most breast lumps are benign, but a thorough work up is necessary to rule out breast cancer (Fig.1 and Fig.2).

Detailed history includes the location of the mass, change in size, relationship with the menstrual cycle, pain, and overlying skin changes. In addition, breast cancer risk factors should be assessed including family history of breast or ovarian cancer with relative risk (RR) of 2.6, prior history of atypical hyperplasia (RR, 3.7) or breast cancer, age at menarche (RR, 1.5), age at first parity (RR, 1.5), prior use of oral contraceptives (RR 1.07), use of hormone replacement therapy (RR, 1.2) and prior breast biopsies (RR, 1.7). In the United States, the Gail model was created using a cohort of women in the Breast Cancer Detection and Demonstration Project and is used to calculate an estimate of a woman’s 5-year and lifetime risk of invasive breast cancer, thus providing an assessment of the risk status. However, it is necessary to bear in mind that evaluation of a breast mass should be undertaken independent of the patient’s risk status.

The next step is a comprehensive clinical breast examination, including inspection of the breast in both the upright and supine positions for asymmetry, nipple/ skin changes, erythema or peau d’orange, and palpation of the breasts for a discrete or dominant mass. An assessment of the axillary and supra-clavicular lymph node regions is also important to rule out lymphadenopathy.

Imaging assessment of a palpable breast mass includes
a bilateral diagnostic mammogram (in women 30 years and older) and a breast ultrasound. A mammogram can identify an area of asymmetric density, the extent of a breast lesion, or pleomorphic calcifications associated with breast cancer. The sensitivity of a mammogram is reduced in younger women or women with dense breast tissue. Therefore, it is of immense importance to understand that normal mammogram findings do not rule out a malignancy. A focused ultrasound of the area of a palpable mass can differentiate a cyst from a solid lesion. Simple cysts (thickened wall or echogenic cyst contents) should be biopsied particularly if a solid component is noted on imaging. Solid breast masses may be benign such as fibroadenomas or hamartomas, or be malignant. A solid or indeterminate mass seen on breast ultrasound requires a biopsy to establish a tissue diagnosis.

**Non-palpable Mammographic Abnormality**

Mammographic breast abnormality can be classified as ‘benign’, ‘indeterminate’ or ‘suspicious’ for an underlying malignancy. Most of the mammographic breast abnormalities may result in benign findings on additional work-up. However, when a mammogram reveals a ‘suspicious’ finding that is non-palpable, a biopsy is necessary. Image-guided core needle biopsy involves either a stereotactic biopsy when the lesion is only seen on a mammogram (such as pleomorphic microcalcifications), or an ultrasound-guided biopsy when the lesion is detectable on ultrasound. If these options are not available, the patient should be referred for an image-guided wire localization of the lesion prior to an open surgical biopsy. Indication for open surgical biopsy also include atypical hyperplasia on core-needle biopsy (to rule out associated ductal carcinoma in situ), calcifications poorly visualized under stereotactic technique, failed prior attempt at stereotactic biopsy, discordant results between pathology and breast imaging, and if the patient is unable to lie prone for the stereotactic biopsy.

Mammographically indeterminate findings can be subject to a biopsy to rule out cancer or can be reassessed in six months for stability if there is a low suspicion of cancer.

**Nipple discharge**

Majority of women presenting with nipple discharge have a benign etiology. Murad et al found that about 5% of women presenting with nipple discharge have breast cancer, but the risk increases to 60% for women with both nipple discharge and a breast mass. Causes of nipple discharge are outlined in Table 1. Features of pathologic nipple discharge that may suggest an associated malignancy include spontaneous, persistent, bloody or watery, single duct discharge. The age at presentation may also be a predictor of underlying malignancy. In one study, 3% of women below age 40 with nipple discharge had breast cancer compared to 32% of women older than 60 years. An evidence-based approach to a case with spontaneous nipple discharge follows a step-wise strategy (Fig. 3).

Nipple discharge in a non-lactating woman must therefore, be evaluated with a mammogram to rule out a mass lesion, except in women younger than 30 years. Breast ultrasound is a reasonable option for women below age 30 and sub-areolar breast ultrasound.
can identify underlying mass lesions. When breast imaging identifies an abnormal lesion, biopsy is recommended.

Milky, bilateral nipple discharge suggests galactorrhea and is secondary to medication use such as psychotropic agents or hyperprolactinemia. Medical work-up is appropriate in such instances and includes assessment of prolactin and TSH.

Women with multi-duct, non spontaneous, non-bloody nipple discharge and negative clinical exam and imaging can be reassured. Patients with pathologic nipple discharge require duct excision, both for diagnostic and therapeutic purposes, even if breast imaging is normal.

Nipple/ areolar abnormality

The differential diagnosis of a nipple/ areolar rash includes benign causes such as eczema or dermatitis, as well as malignant cause such as Paget’s disease of the breast. Clinical breast examination and breast imaging with mammogram and ultrasound are indicated for work-up. If initial evaluations reveal negative findings, initiation of treatment for dermatitis is appropriate, but follow-up of these patients is mandatory until complete resolution. A non-resolving nipple or areolar rash

must be subject to biopsy to rule out Paget’s disease of the breast. Studies have demonstrated that Paget’s disease of the breast may be associated with underlying breast cancer even in the absence of clinical or imaging abnormalities.10

Nipple inversion may be congenital or acquired. Acquired nipple inversion requires clinical breast assessment, and a mammogram to rule out breast cancer.

Breast Pain

Mastalgia is a common breast symptom in clinical practice and may be cyclical when it occurs in relation to the menstrual cycle, or non-cyclical mastalgia.13 Cyclic mastalgia is common among premenopausal women, who experience breast pain in the premenstrual phase of the menstrual cycle, and symptoms resolve with menstruation. Mastalgia is often related to fibrocystic changes in the breast and large breast cysts can be a cause of breast pain. Non-cyclical mastalgia is unrelated to the menstrual cycle, is often unilateral and in some women may be associated with fibrocystic breast changes, fibroadenomas, lipomas, Mondor’s disease (thrombophlebitis of the thoraco-epigastric vein) or breast infections. Chest wall pain from costochondritis, radiculopathy, trauma, etc. as well as other causes such as referred pain from gastroesophageal reflux disease, and cardiac causes will need to be excluded during the history and physical examination. Although breast pain is associated with many benign breast conditions, the presence of pain does not preclude a diagnosis of cancer.

In the absence of a palpable or imaging breast abnormality, several modalities have been suggested for treatment of mastalgia. Women with mastalgia and negative clinical exam and breast imaging can be reassured11. Initial management of mastalgia involves measures such as the use of a fitted bra, dietary changes (avoidance of methylxanthines,12 and dietary fat13), gentle massage, and exercise. Non-steroidal anti-inflammatory agents may help relieve pain in some patients.

Hormonal therapy for breast pain has been studied. Cessation or altering the dose of estrogen therapy may be considered for women taking exogenous estrogen. Danazol, the only FDA-approved agent for the treatment of mastalgia, is an option for women with refractory mastalgia, but has limited use due to side-effects.14 Other agents that have been reported to be effective in small studies include tamoxifen,15 bromocriptine,16 luteinizing hormone releasing hormone agonist analogs 17 and toremifene18, but their use is limited due to adverse effects.

BREAST DIAGNOSTIC TECHNIQUES

Mammography / Ultrasonography

Diagnostic mammography is performed to evaluate

Table 1: Causes of nipple discharge

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<th>Physiologic</th>
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<td>Duct abnormalities</td>
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<tr>
<td>Intralobular papilloma</td>
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<td>Duct ectasia</td>
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<td>Periductal mastitis</td>
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<td>Carcinoma</td>
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<td>Galactorrhea</td>
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<td>Hyperprolactinemia</td>
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<td>Hypothyroidism</td>
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<td>Medications: oral contraceptives, cimetidine, verapamil, phenoxybenzamine, metoclopramide, alpha-methyldopa</td>
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<td>Conditions that may mimic nipple discharge</td>
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<td>Eczema with drainage</td>
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<td>Paget’s disease of the breast</td>
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<td>Nipple adenoma</td>
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Fig. 3: Approach to case with nipple discharge.
symptomatic women 30 years or older to identify features suggestive of breast cancer and to screen the surrounding breast tissue as well as the contralateral breast for non-palpable abnormalities (Fig. 4a). Diagnostic mammogram is often combined with a focused breast ultrasound that can differentiate solid from cystic lesions (Figs. 5 and 6). Ultrasound features indicative of a simple cyst include lack of internal echoes, well defined margins, round or oval shape and posterior acoustic enhancement.

Breast tissue is composed of fat, fibroglandular tissue, and stroma. Fatty tissue is radiolucent enabling the detection of masses and calcifications in a predominantly fat-replaced breast. However, in younger women, the tissue is predominantly fibroglandular and radiodense, reducing the sensitivity of the mammogram (98% in fatty breast pattern compared to 50-60% in dense breasts) to detect abnormal lesions. Abnormal findings on mammogram may include mass lesions, calcifications with irregular features (Fig. 4b), asymmetric fibroglandular tissue, architectural distortion, nipple retraction or axillary lymphadenopathy.

**Breast Biopsy**

Breast biopsy may be done as a core-needle biopsy (CNB) or an open surgical biopsy (incisional or excisional). The core-needle biopsy (using a 14-, 16- or 18-gauge needle) is performed under stereotactic/mammography guidance for non-palpable lesions only seen on a mammogram. An ultrasound-guided biopsy is done under ultrasound guidance and is the procedure of choice to biopsy palpable lesions and those detected on breast ultrasound. These procedures are associated with a lower false-negative rate compared to fine-needle biopsies (10% versus 25-30%, respectively). In the event that the needle biopsy reveals findings that are not concordant with the imaging findings, further evaluation with an open surgical biopsy is warranted.

The procedure of fine needle aspiration biopsy (FNAB) is sometimes performed in situations where the core needle biopsy procedure is not available or if imaging would result in significant delay in treatment. However, there is a risk of a false-negative result with this approach. Grant et al demonstrated that FNAB had a false-positive rate of 6% with no false-positive results. The accuracy of FNAB is variable and dependent on the expertise of the cytologist/ institution. A negative FNAB result from a suspicious mass must, therefore, be further evaluated with additional tests.

Excisional breast biopsy is a surgical procedure that
can diagnose and treat focal breast lesions. If a lesion is non-palpable, preoperative wire localization is recommended to ensure accurate excision of the lesion. With the ease, and decreased risks associated with CNB procedure, there has been a trend to decreasing frequency of excisional breast biopsy and increasing CNB.

**Magnetic Resonance Imaging (MRI) as a diagnostic tool**

Breast MRI is increasingly being used in the assessment of patients with breast concerns. Studies have demonstrated that the sensitivity of the breast MRI for detection of invasive breast cancer ranges from 95 to 100%.

However, the specificity of this test is low resulting in high false positives requiring additional evaluations. In addition, the test is expensive and cannot be performed on patients with indwelling metal devices.

Breast MRI has a role in specific clinical situations. A woman with evidence of axillary metastatic breast cancer and occult primary lesion not detectable on clinical exam, mammogram or ultrasound (Fig. 7); in women with suspected breast implant rupture; suspicious mass on clinical exam with negative findings on mammogram and ultrasound as may occur with invasive lobular carcinoma or young women with dense breast tissue; and suspected multifocal breast cancer are some clinical scenarios where the breast MRI can be beneficial.

**Molecular breast imaging** is an area of ongoing research using technetium Tc 99m scintimammography. Preliminary studies reveal a high sensitivity for small lesions (92% overall sensitivity; 86% for lesions ≤1cm) making it a potentially useful tool for evaluation of women with dense breast tissue.
In summary, careful assessment with history and detailed breast examination followed by appropriate breast imaging are essential components of the clinical breast evaluation. Follow-up until resolution of certain breast conditions can prevent delayed diagnosis and improve patient outcomes.

REFERENCES
27. Rhodes DJ, O’Connor MK, Phillips SW, et al. Molecular...