Continuing Medical Education

Benign Breast Disease in Women

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Summary

Background: Most clinical breast changes in women are benign; in only 3% to 6% of cases are they due to breast cancer. However, there is a lack of up-to-date, evidence-based treatment recommendations for the various benign differential diagnoses.

Methods: Selective literature search of PubMed from 1985 to May 2019, including current national (AWMF, *Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften* [Association of Scientific Medical Societies in Germany]) and international guidelines.

Results: Mastalgia and fibrocystic changes are common (around 50% of all women over the age of 30). Fibroadenomas occur in 25% of women; they are the most common benign tumors of the breast and do not require treatment. With most benign breast changes the risk of dedifferentiation is very low. However, it is important in the differential diagnosis to distinguish between such benign changes and breast cancer or changes that carry a risk of malignancy. Complex cysts, for example, carry a risk of malignancy of 23% to 31%, papillary lesions 16%, and radial scars 7%. Where there is doubt, histological confirmation should be sought by means of percutaneous biopsy.

Conclusion: Benign breast changes can be definitively distinguished from malignant lesions through the selective use of available diagnostic investigations and interdisciplinary collaboration. When lesions of uncertain malignant potential are found (B3 in the biopsy classification), complete excision is indicated. Prospective studies on the early diagnosis of breast cancer in lesions carrying a risk of malignancy are desirable.

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According to data from the Netherlands and the USA, around 3% of women's consultations with their general practitioners (GPs) are about breast symptoms (1, e1). At around 70 000 new cases a year, breast cancer is the most common form of cancer in women in Germany, occurring in approximately one in eight women at some time during their lives. For this reason, breast changes are a cause of anxiety in patients and require a carefully targeted diagnostic process (2). Although breast cancer is detected in only 3% to 6% of women with clinical symptoms, and in most cases the cause of the symptoms is benign, no evidence-based recommendations for the management of benign disease have been produced because the focus has been on the diagnosis and treatment of breast cancer (1, 3) (e1). Benign breast changes are more common in women of child-bearing age, peaking between the ages of 30 and 50, whereas the incidence of

breast cancer peaks during the postmenopause (e2, e3). The management of benign breast changes includes clinical, radiological, and if necessary histological diagnostic investigations to rule out malignancy; palliation of symptoms; and counseling and monitoring of patients at increased risk of breast cancer. Typical presenting symptoms such as pain, a palpable mass, and nipple discharge can be caused by a wide array of benign differential diagnoses (*Table 1*) and require targeted diagnostic imaging in addition to a comprehensive history and clinical examination (e4). The BI-RADS ("breast imaging reporting and data system") classification—the standardized description of radiological findings—offers the clinician recommendations for action (*Table 2*) (4). Today's minimally invasive techniques for achieving a confirmed histological diagnosis mean that surgical excision, previously common, can now be avoided in most cases.

Prevalence

Benign breast changes are more common in women of child-bearing age, peaking between the ages of 30 and 50, whereas the incidence of breast cancer peaks during the postmenopause.

Diagnosis

In addition to a comprehensive history and clinical examination, diagnostic imaging (ultrasonography, mammography as indicated) is important for ruling out breast cancer.

TABLE 1

Differential diagnoses of benign breast changes, classified by main symptom

Symptom	Benign causes	Incidence of breast cancer
Pain (unilateral)	<ul style="list-style-type: none"> – Cysts – Fibrocystic breast disease – Hyperplasia of the breast – Mastitis – Postoperative changes 	2% to 7% (7)
Palpable mass	<ul style="list-style-type: none"> – Cysts – Fibrocystic breast disease – Fibroadenoma – Lipoma – Hamartoma – Pseudoangiomatous stromal hyperplasia (PASH) – Intramammary lymph nodes 	8% (1, e1)
Nipple discharge	<ul style="list-style-type: none"> – Hypothyroidism – Galactorrhea – Intraductal papilloma – Periductal mastitis – Ductal ectasia 	5% to 21% (29, e26)

Method

The literature review performed for this article was based on a selective literature search of PubMed from 1985 to May 2019 including current national (AWMF, Association of Scientific Medical Societies in Germany) and international guidelines (EUSOMA, WHO, American College of Obstetricians and Gynecologists, American College of Radiology). This article discusses selected benign breast changes according to their incidence and significance in everyday clinical routine, grouping them by their main presenting symptoms.

Learning goals

After reading this article, readers should:

- Be familiar with the symptoms, diagnosis, and management of the most common benign breast diseases of women (mastalgia, fibrocystic changes, benign tumors, mammary duct ectasia, mastitis);
- Be able to distinguish benign breast changes from malignant findings;
- Know the breast cancer risk associated with certain benign breast conditions.

Mastalgia

Mastalgia (also called mastodynia) is the name given to pain related to the mammary gland occurring either spontaneously or in response to touch. Mastalgia is

classified as cyclic and noncyclic. Differential diagnoses to rule out are chest pain of extramammary origin such as intercostal neuralgia and pain from cardiac or vertebrogenic causes.

Surveys have shown that more than half of all women report significant breast pain, which in 30% to 40% of cases impairs their everyday and sexual life (e5). In two-thirds of cases, the pain is cyclic and is worst a week premenstrually and perimenstrually. Cyclic mastalgia manifests at around 30 years of age; the onset of noncyclic mastalgia is notably later, at a mean age of 41. What causes mastalgia is unknown. The fact that cyclic mastalgia improves in association with hormonal changes such as when the menopause is reached, and during pregnancy and lactation, suggest a hormonal cause (e5). In a woman with noncyclic mastalgia, inflammatory, neoplastic, and vascular breast disease needs to be ruled out (e6). In cases with no underlying pathology, rates of spontaneous remission within a few months to up to 3 years are high (5). After breast cancer treatment, 30% of women have persistent noncyclic mastalgia, especially those who are premenopausal, have a high body mass index, or have a concomitant psychological condition (6, e7).

Diagnostic investigations include obtaining a comprehensive history and clinical exam. Palpation will reveal the localization of the pain, any mass or

Mastalgia

In two-thirds of cases, mastalgia is cyclic. Differential diagnoses for noncyclic mastalgia include inflammatory, neoplastic, and vascular breast disease.

Fibrocystic changes and risk of breast cancer

Of the common fibrocystic breast changes, only proliferating lesions with atypia are associated with a clearly increased risk of breast cancer. These include flat epithelial atypia, atypical ductal hyperplasia, and atypical lobular hyperplasia.

masses, and any swollen lymph glands. In women from the age of 40 onward, or those with additional risk factors such as any abnormal clinical findings or a family history of breast cancer, unilateral noncyclic mastalgia should prompt mammography (supplemented by ultrasonography) to rule out breast cancer, which is the underlying cause in 2% to 7% of cases (7). Once malignancy has been excluded, most women do not require treatment for alleviation of the painful symptoms (e8).

The range of options for relieving symptoms in cyclic mastalgia includes wearing a well-fitting bra (in 85% of patients this reduces the pain within 3 months), intermittent analgesics, relaxation techniques (autogenic training, progressive muscle relaxation), and regular physical exercise such as swimming, walking, or gymnastics (8, e9). Among herbal preparations, flaxseed (also called linseed; 25 g ground flaxseed daily) and monk's pepper (*Vitex agnus castus* 3.2 to 4.8 mg/day), taken for 2 to 3 months, are suitable for reducing cyclic mastalgia; their efficacy has been demonstrated in randomized controlled studies (9, e10, e11). In terms of local treatment, in a recent meta-analysis diclofenac gel 3 × 20 mg/day for 2 months was shown to reduce pain by around 60% (10, e12). Another option is black cumin oil (*Nigella sativa*) 2 × 600 mg/day; topical progesterone gel, although commonly used, has not been scientifically validated (e13). Systemic treatment with tamoxifen 10 mg/day (off-label use) for 3 to 6 months resulted in significant pain reduction in placebo-controlled studies, but should only be considered in cases where symptoms are severe and other treatments have failed (11, e14). Treatment with dopamine agonists such as bromocriptine, lisuride, or cabergoline for 2 to 6 months relieves symptoms in 47% to 88% of patients with hyperprolactinemia. This treatment may be limited by unwanted effects such as dizziness and headache (10, 11, e15, e16).

Fibrocystic changes

“Fibrocystic changes” is the term used to designate a variety of clinical and histopathological changes of the female mammary gland, some of which should be regarded not so much as a disease, more as a disordering of physiological development, maturation, and involution. In the histological classification by Dupont and Page (1985), fibrocystic changes are divided according to risk into proliferative changes and nonproliferative changes (12). More recent publications also include forms of cellular atypia, because these are associated

TABLE 2

BI-RADS assessment categories for the classification of radiological findings in the breast and resulting recommendations for management, adapted from (4)

BI-RADS category	BI-RADS code	Recommendation
Assessment incomplete	0	Comparison with previous images or further diagnostic investigations may be necessary
Negative	1	Refer for breast cancer screening
Benign	2	Refer for breast cancer screening
Probably benign	3	Shortened-interval follow-up (in 6 months)
Suspect	4	Histological study recommended
Highly suggestive of malignancy	5	Histological diagnostic confirmation and initiation of therapy required

BI-RADS, „breast imaging reporting and data system“

with a markedly raised risk of breast cancer and require intensive monitoring (Table 3) (13, e17). Forms of cellular atypia are included in the biopsy classification (Table 4) under lesions with uncertain biological potential (B3) and are not counted among the purely benign lesions (14, 15).

From the age of 30, about 50% of women develop fibrocystic breast disease, and in 20% of them macrocysts cause symptoms (pain, palpable mass). Sclerosing adenosis is found in 10% to 30% of all women (e18). The pathophysiology of these changes is probably related to an imbalance in the female sex hormones, with predominance of estrogen stimulation and relative progesterone deficiency.

Breast cysts are fluid-filled widenings of the terminal duct lobular units (TDLU), lined with a single layer of epithelium. They are discovered by palpation of a mass (smooth, elastic, mobile) as an incidental finding during imaging or on histological study of a breast biopsy specimen. Ultrasonography is pathognomonic, showing cysts as well-circumscribed, oval to round, anechoic or hypoechoic foci of variable size. Aspiration is only necessary for large lesions that cause persistent symptoms. Cyst fluid varies widely in color and viscosity, from a clear, thin content to a whitish, opaque secretion to a dirty-green, bluish, or gray secretion; the color has no diagnostic significance. Cysts form as a result of hormonal changes and generally regress in the postmenopause. Simple cysts must be distinguished on ultrasonography from so-called complex cysts, which present a 23% to 31%

Options for relief of symptoms in cyclic mastalgia

- Wearing a well-fitting bra
- Intermittent use of analgesics
- Relaxation techniques
- Regular physical exercise

Biopsy classification

Histological findings after minimally invasive biopsy are categorized according to the biopsy classification, where B1 is a normal result, B2 a definitely benign lesion, and B3 a benign lesion of uncertain malignant potential.

TABLE 3

Fibrocystic breast changes and associated risk of developing breast cancer, adapted from (12, 13)

Lesion type	Histopathological diagnosis	Relative risk of developing breast cancer in the future compared to the risk in the normal population [95% confidence interval]
Nonproliferating	<ul style="list-style-type: none"> – Simple cysts – Papillary apocrine metaplasia 	1.17 [0.94; 1.47]
Proliferating without atypia	<ul style="list-style-type: none"> – Usual hyperplasia (UDH) – Columnar cell hyperplasia (blunt duct adenosis) – Sclerosing adenosis – Radial scar 	1.76 [1.58; 1.95]
Proliferating with atypia	<ul style="list-style-type: none"> – Flat epithelial atypia (FEA) – Atypical ductal hyperplasia (ADH) – Atypical lobular hyperplasia (ALH) 	3.93 [3.24; 4.76]

UDH („usual ductal hyperplasia“):

Cell proliferation in the ducts without cellular atypia; simple hyperplasia (3 to 4 cell layers), florid hyperplasia (>4 cell layers)

Blunt duct adenosis:

Increase in size and number of epithelial cells, typical cylindrical differentiation with monomorphic cell nuclei and without atypia (columnar cell hyperplasia)

Sclerosing adenosis:

Increase in size and number of acini in the TDLU (terminal ductal lobular unit) accompanied by proliferation of the surrounding stroma

risk of malignancy and must be histologically investigated (16).

Usual ductal hyperplasia (UDH) is characterized by cell proliferation within the ducts without cellular atypia. Blunt duct adenosis is characterized by an increase in the size and number of epithelial cells. Sclerosing adenosis features increased number and size of the acini within the TDLU accompanied by stromal hyperplasia. Because of their intraluminal (UDH) or subepithelial calcifications (blunt duct adenosis), these two forms of adenosis are often detected in the context of minimally invasive biopsies of suspect microcalcifications identified on mammography and according to the biopsy classification are classed as benign (B2) (17, e19). Radial scars are benign changes which on imaging show as suggestive of malignancy; histologically they show a stellate fibroelastic core with entrapped ducts and radial epithelial structures. Frequently, benign changes are found within this, as in usual ductal hyperplasia, adenosis, or ductal ectasia, and occasionally also in atypical epithelial hyperplasia. Lesions >1 cm are termed complex sclerosing lesions (CSL) (18). Radial scars discovered incidentally and removed completely during minimally invasive diagnostic procedures are classified as B2 lesions; otherwise they are considered as B3 (Table 4). After surgical excision of

minimally invasively diagnosed radial scars, the overall malignancy rate according to a recent meta-analysis is 7%, and after vacuum-assisted biopsy and without atypia it is only 1% (19, 20).

After histological evidence of usual ductal hyperplasia, sclerosing or blunt duct adenosis, and radial scar after percutaneous biopsy, it is important to correlate clinical, imaging, and pathology findings at a postinterventional case conference, in order to avoid a false-negative biopsy result. It is equally important to distinguish these conditions by histological study from atypical and malignant breast lesions (21, 22).

Proliferative changes without atypia are associated with only a slightly increased risk of breast cancer (e17). Chemoprevention, e.g., with raloxifen or tamoxifen, is not indicated because of the unfavorable risk–benefit ratio (e20).

Similarly, if there is no family history and no clinical symptoms, no particular investigations are needed outside the officially recommended breast cancer screening program (screening every 2 years from age 50 to age 69).

Benign tumors (neoplastic changes)

With an incidence of 25%, fibroadenoma is the most common benign tumor of the breast; peak onset is

Ductal hyperplasia

Usual ductal hyperplasia is characterized by cell proliferation within the ducts without cellular atypia. Blunt duct adenosis is characterized by an increase in the size and number of epithelial cells.

Multidisciplinary case conference

To avoid a false-negative biopsy finding, clinical, imaging, and pathology results all need to be discussed at a postinterventional case conference.

TABLE 4

Biopsy classification, adapted from (15)

Category	Definition	Diagnoses
B1	Tissue normal or cannot be assessed	<ul style="list-style-type: none"> – Adipose tissue only (exception: lipoma, categorize as B2) – Regressive changes/involution – Lactational changes
B2	Benign lesion	<p>Mass:</p> <ul style="list-style-type: none"> – Fibroadenoma, adenoma – Fibrocystic lesions, adenosis – Hamartoma – Small papilloma retrieved in toto – Pseudoangiomatous stromal hyperplasia (PASH) – Mastitis, abscess – Fat necrosis <p>Radiologically significant microcalcification(s):</p> <ul style="list-style-type: none"> – Fibrocystic breast disease/(papillary) apocrine metaplasia – Blunt duct adenosis, sclerosing adenosis – Calcified fat necrosis
B3	Benign lesion of uncertain malignant potential	<p>Lesions with increased risk of associated DCIS or invasive carcinoma:</p> <ul style="list-style-type: none"> – Atypical ductal hyperplasia (ADH) – Flat epithelial atypia (FEA) – Classical lobular neoplasia (LN; ALH and LCIS) <p>Potentially heterogeneous lesions with the risk of incomplete sampling:</p> <ul style="list-style-type: none"> – Cellular fibroepithelial lesion or phyllodes tumor – Intraductal papilloma with/without atypia, incompletely sampled – Radial scar or complex sclerosing lesion
B4	Suspect lesion	
B5	Malignancy	<p>B5a: In situ carcinoma</p> <p>B5b: Invasive carcinoma</p> <p>B5c: Cannot be subcategorized as invasive or in situ carcinoma</p> <p>B5d: Malignancy of other histogenesis or metastasis</p>

ALH, atypical lobular neoplasia; DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ (classical); LN, lobular neoplasia

between 15 and 35 years of age (23). In terms of etiology and pathogenesis, a hormonally triggered mechanism is likely, as suggested by early onset during the premenopause, growth during pregnancy or estrogen therapy, and regression during the menopause (24, e21). A striking clinical characteristic is a palpable mass measuring up to 3 cm. Sonographically, fibroadenomas appear as oval, well-circumscribed, hypoechoic focal masses that displace the surrounding parenchyma. Fast-growing breast carcinomas in younger women can look like fibroadenomas on ultrasonography. Asymptomatic fibroadenomas are often discovered as incidental findings during screening mammography. Fibroadenoma typically appears on a mammogram as a well-circumscribed mass, with or without popcorn-like calcifications, is pathognomonic and needs no further investigation (25). In the presence of the following

findings, histological diagnostic confirmation by means of percutaneous biopsy is advisable:

- Inconclusive ultrasound findings (BI-RADS 4)
- Evidence of tendency to grow (clinical or sonographic)
- New palpable mass in a menopausal patient
- Firm mass found in a patient with risk factors in her history (positive family history, BRCA mutation)
- Mass with suspect microcalcifications on mammography.

Histologically there is a typical pattern of stromal proliferation with slit-like compressed epithelial components. It is important to distinguish this pattern from phyllodes tumors (incidence: 0.3% to 1% of all breast tumors), which are characterized by stromal hypercellularity, increased mitoses, and in some cases

Fibroadenomas

With an prevalence of 25%, fibroadenomas are the most common benign tumors of the breast; peak onset is between 15 and 35 years of age.

Detection of fibroadenomas

Asymptomatic fibroadenomas are often discovered as incidental findings during screening mammography. The typical appearance on mammography is that of a well-circumscribed mass with or without popcorn-like calcifications.

stromal cell atypia (24). Whereas asymptomatic fibroadenoma does not require any treatment, phyllodes tumors should if possible be excised with clear margins of 10 mm, as they can only be classified histologically as benign, malignant, or borderline on the basis of the surgical specimen. Phyllodes tumors have a high tendency to recur and high metastatic potential: 0.1% in benign phyllodes tumors, 1.6% in borderline tumors, and 16.7% in malignant tumors (26, e22). Symptomatic fibroadenomas can be removed by surgical excision (a good option if the mass measures >2 cm) or by ultrasound-guided vacuum-assisted biopsy. Cryoablation and treatment with high-intensity focused ultrasound (HIFU) are experimental techniques (e23, e24).

In patients with a palpable breast tumor, the rare differential diagnosis of pseudoangiomatous stromal hyperplasia (PASH) is also a possibility. The radiological appearance is similar to that of fibroadenoma and the diagnosis is made by percutaneous core biopsy (e25). If there is evidence of a tendency to grow, or a discrepancy between clinical findings, imaging findings, and histology, extirpation with wide margins should be carried out; if the tumor is progressive, this could mean complete mastectomy (27). For PASH discovered incidentally on biopsy without any corresponding clinical or imaging findings, ultrasound follow-up will suffice, as the risk of breast cancer is not increased (28).

Pathologic nipple discharge is the name given to spontaneous, often unilateral release of fluid from the nipple. In 50% of cases the cause is intraductal papilloma, in 25% to 35% of cases ductal ectasia, and in 5% to 15% of cases breast carcinoma (29, e26). Papillomas are relatively common, making up 5% to 10% of benign breast tumors. They can occur as centrally located, solitary masses or as multiple, usually peripherally located lesions (“intraductal papillomatosis”) (30). In 80% of cases papillomas are clinically identified because of a spontaneous blood-stained or serous discharge from the nipple; less often they will be picked up by palpation or as an incidental finding on mammography. In a patient with low breast density, solitary papillomas appear on the mammogram as rounded masses, in some cases with internal calcifications. Galactography shows papillomas as a filling defect or complete obstruction. On ultrasonography, papillomas show as rounded, well-circumscribed, hypoechoic masses, but intraductal or intracystic proliferations may also be seen (e27). Histological study shows ragged, branching epithelial

protrusions intruding into a dilated duct, with a fibrovascular stromal core. As a result of the stromal sclerosis, microcalcifications are often present. The epithelial components can show a wide spectrum of morphological changes including atypical ductal hyperplasia and ductal carcinoma in situ (DCIS) (e28). If the diagnosis is made histologically by minimally invasive biopsy, the papilloma is classified as a lesion of uncertain malignant potential (B3). Because of the lesion’s heterogeneity, it is possible that even if the core or vacuum-assisted biopsy was performed correctly, an area of higher-grade malignancy was missed (“sampling error”). The upgrade risk of papillary lesions confirmed by core biopsy—i.e., the risk that they will be identified at subsequent surgery as DCIS or invasive cancer—was reported in a recent meta-analysis as 16% (31). For this reason, it is recommended that a biopsy-confirmed, incompletely removed papilloma without atypia should be completely excised. Papillary lesions showing atypia should always be surgically excised. No treatment is required for papillomas without atypia that are removed in toto, which are classified as B2 (*Table 4*) (20, e29). Because papillomas are so heterogeneous, postinterventional management should be determined in a multidisciplinary case conference (radiology, gynecology, pathology).

Galactorrhea is the name used to describe a milky secretion, which is often bilateral. The important differential diagnoses are listed in *Table 5*. Galactorrhea is often caused by dopamine antagonists such as tricyclic antidepressants or selective serotonin reuptake inhibitors (SSRI). A serum prolactin concentration >200 ng/mL indicates the presence of a prolactinoma in the pituitary gland, and the patient should be referred for cerebral MRI and consultation with an endocrinologist (e30). If the prolactin concentration is normal and the secretion only occurs on pressure, no further diagnostic investigations are needed.

Inflammatory breast disease

Inflammatory breast conditions that occur in association with lactation are referred to as puerperal mastitis. Nonpuerperal mastitis is a collective term applied to all forms of mastitis occurring outside the lactation period, the most common of which are bacterial mastitis (59%), nonbacterial mastitis (25%), and special forms of nonpuerperal mastitis (14%) (e31).

Puerperal mastitis generally occurs during the first 3 months after delivery. Depending on study protocol,

Phyllodes tumors

Whereas asymptomatic fibroadenomas do not require treatment, phyllodes tumors should if possible be excised with clear margins of 10 mm, as they can only be histologically classified as benign, malignant, or borderline on the basis of the surgical specimen.

Galactorrhea

Galactorrhea is the name used to describe a milky secretion, which is often bilateral. It is often caused by dopamine antagonists such as tricyclic antidepressants or selective serotonin reuptake inhibitors.

TABLE 5

Differential diagnoses of galactorrhea

Physiological	Medication-related	Neoplastic	Endocrine
<ul style="list-style-type: none"> – Pregnancy and lactation – (Occasional) persistence after weaning – Puberty – Stress 	<ul style="list-style-type: none"> – Neuroleptics (phenothiazine, risperidone) – Metoclopramide – SSRI – Tricyclic antidepressants – Opiates – Methyldopamine – Clonidine – Verapamil – Cimetidine, ranitidine – Estrogens, oral contraceptives 	<ul style="list-style-type: none"> – Prolactinoma – Prolactin-secreting tumors (e.g., of the lung) 	<ul style="list-style-type: none"> – Hypo- and hyperthyroidism – Renal failure

SSRI, selective serotonin reuptake inhibitors

its incidence worldwide has been reported at between 2% and 50%, and in selective cohorts a higher incidence has been observed (32, e32). A prospective study of 420 breastfeeding women in Glasgow found a cumulative incidence within 6 months of 18% (e33). According to the WHO definition, the symptoms of puerperal mastitis are:

- Pain
- Local redness, warmth, and swelling of the breast, usually unilateral
- Fever ($>38.4^{\circ}$) and aching limbs
- General feeling of illness (32).

Diagnosis is based on the typical clinical symptoms. Risk factors include incorrect breastfeeding technique, stress, and lack of sleep (33). In many cases, epithelial lesions in the nipple area form an entry portal for pathogens from the infant's nasopharynx, which in the presence of blocked ducts can ascend and cause an infection (e34). In $>90\%$ of cases, the cause is *Staphylococcus aureus*; more rarely, coagulase-negative staphylococci, streptococci, *Pseudomonas aeruginosa*, or *Escherichia coli* are the cause. Bacterial culture of the milk for diagnostic purposes is reserved for the following situations:

- Symptoms remain uncontrolled after 48 h antibiotic treatment
- Recurrent puerperal mastitis
- Patient needs hospitalization.

Histologically, puerperal mastitis is a phlegmon that can lead to the formation of abscess and fistula (e35). The risk of abscess increases with the duration of symptoms before treatment starts, so early diag-

nosis and initiation of treatment are important (e36). Puerperal mastitis needs to be distinguished from milk stasis, a common condition the clinical symptoms of which are much less severe and systemic symptoms are often absent altogether (e37). The most important steps for the treatment of puerperal mastitis are regular emptying of the breast (evidence level 2b) and early antibiotic therapy (33, 34, e38). Paracetamol (max. 4×1 g/day) or ibuprofen (3×500 – 800 mg/day) are suitable for relief of the general symptoms (e39). Local antiphlogistic measures include the application of heat immediately before feeding and cooling the inflamed area during the breaks in feeding (33, e39, e40). If symptomatic treatment fails, after no more than 48 h calculated antibiotic therapy with an oral β -lactamase-resistant penicillin, e.g., flucloxacillin 3×1 g/day or dicloxacillin 4×1 g/day, or a first- or second-generation cephalosporin should be started (evidence level 2b). In patients allergic to penicillin, macrolide antibiotics (e.g., clarithromycin 4×500 mg/day or clindamycin 3×600 mg/day) are indicated. Treatment should be continued for at least 10 (to 14) days (33). If no improvement is seen within 48 to 72 h, ultrasonography should be carried out to check for abscess formation. Should an abscess be shown, it must be aspirated under ultrasonographic guidance (33, 35, e41). Surgical incision and drainage of an abscess should be done only if the abscess persists despite repeated aspiration, or is extensive, or is in an unfavorable location (36). Continued breastfeeding or expression of milk may be possible. Secondary weaning is reserved for treatment-resistant cases and is carried out using orally administered

Symptoms of puerperal mastitis

Puerperal mastitis is accompanied by fever, a general sense of illness, pain, and usually unilateral local redness and swelling of the breast.

Treatment of puerperal mastitis

In puerperal mastitis, which in most cases is caused by *Staphylococcus aureus*, early initiation of treatment with an oral β -lactamase-resistant penicillin is the therapy of choice. As an alternative in patients allergic to penicillin, macrolide antibiotics or clindamycin may be given.

bromocriptine (2×1.25 mg day 1, 2×2.5 mg day 2 to day 14). Prevention is about education in the right technique for breastfeeding:

- A calm environment, switching sides when breastfeeding
- Avoiding milk stasis, e.g., by stroking the breast towards the nipple during feeding
- Optimal technique for attaching the baby (e42)
- Treating nipples with lanolin ointment to prevent fissuring (33).

Nonpuerperal mastitis includes all forms of periductal mastitis, the rarer granulomatous mastitis, and iatrogenic inflammation after surgery or radiotherapy. In patients over the age of 35 with nonpuerperal mastitis, breast carcinoma should be excluded by a careful history and clinical examination followed by the selective use of mammography and/or ultrasonography. Periductal mastitis is an inflammatory condition of the subareolar ducts and has a prevalence in nonbreastfeeding women of 5% to 9% (e43). It often occurs in women who are overweight with macromastia and nicotine abuse. The etiology is presumed to be nicotine-induced damage to the ducts with tissue necrosis and consequent infection (e44). The clinical manifestation of periductal mastitis is of periareolar signs of inflammation (redness, swelling, warmth). Secondary bacterial infection can lead to abscess and fistula formation. Treatment involves relief of symptoms, antibiotic therapy, and, if there is abscess formation, aspiration and drainage (36, e43, e45). A prospective study of 151 patients showed complete resolution of symptoms in 81% after a single aspiration and antibiotic treatment (e46). For this reason, in cases of abscess-forming nonpuerperal mastitis, ultrasound-guided abscess aspiration and antibiotic therapy are the treatment of choice. The pathogen spectrum corresponds to the normal flora of the breast and nipple area. If *S. aureus* is shown to be present, it should be assumed that in more than 50% of cases it will be MRSA (e47). The drug of choice is clindamycin 3×600 mg/day, or alternatively amoxicillin/clavulanic acid $2 \times 875/125$ mg (e43). Treatment should be continued for at least 7 days (e47). Recurrent nonpuerperal mastitis is often caused by a ductal fistula exiting close to the areola, and this requires surgical revision with extirpation of the fistula (37, e48).

Necrotizing nonpuerperal mastitis is an extremely rare and life-threatening disease in a category of its own; it occurs in multimorbid patients and those under immune suppression or with diabetes mellitus.

Typical pathogens are group A β -hemolytic streptococci, or combined infections with *Bacteroides* species or *Escherichia coli*. Clinical features in the early stage are edema, pain, skin pallor, and formation of blisters; later in the course, deep necrosis takes place. Since the inflammation will follow a fulminant course if untreated, spreading along the fascia and resulting in sepsis and multi-organ failure, immediate therapy with penicillin G 0.5–1 million IU i.v. (or alternatively broad-spectrum antibiotics) is required, as is meticulous surgical removal of necrotic tissue, even mastectomy if necessary (38, e49, e50).

Granulomatous mastitis is a rare inflammatory breast disease of women of childbearing age; its etiology is unknown (e51). Associations with lactation, hyperprolactinemia, and the presence of *Corynebacterium kroppenstedtii* have been described (e52). The main symptom is a painful palpable mass, often with redness and swelling, and sometimes also skin retraction. The symptoms and appearance on imaging are similar to those of diffuse breast cancer (39). In some cases abscess formation can be seen on ultrasonography. Diagnosis is via percutaneous core biopsy. On histological study, the presence of granulomas with multinucleated giant cells indicates the diagnosis.

There are two treatment strategies:

- Surgical excision (for small masses)
- Systemic high-dose glucocorticoid therapy with prednisolone 30 mg/day for at least 2 to 6 months followed by slow tapering with monitoring of the lesion (40).

According to a recent meta-analysis, the rate of complete remission after surgical intervention is 90.6% (95% confidence interval [83.8; 95.7]); after oral steroid therapy it is 71.8% [67.1; 76.3], and after combined treatment it is 94.5% [88.9; 98.3] (e53). In cases where there is extensive inflammation, glucocorticoid therapy, despite its associated unwanted effects such as weight gain, hyperglycemia, gastroduodenal ulcer, and the risk of Cushing syndrome, is regarded as the treatment of choice. Within a year after the cessation of treatment, a 20% recurrence rate has been reported (e53, e54). If symptoms are not severe and the patient rejects systemic glucocorticoid therapy, topical treatment with hydrocortisone acetate 0.5% 1 $\times$ daily may be attempted (e55). If glucocorticoid therapy fails, low-dose methotrexate (7.5 to 25 mg/week + folic acid supplementation) is an option for treatment (e56).

Nonpuerperal mastitis

Nicotine abuse, overweight, and macromastia are regarded as risk factors for nonpuerperal mastitis. The differential diagnosis should include consideration of inflammatory breast cancer. Failure of antibiotic therapy may be due to the presence of an abscess, which can be diagnosed by ultrasound followed by aspiration.

Granulomatous mastitis

Because the symptoms and appearance on imaging of granulomatous mastitis are similar to those of breast cancer, the diagnosis is made on the histology after minimally invasive biopsy. Treatment is with prednisolone 30 mg/day given orally for at least 2 months.

Conflict of interest statement

The authors declare that no conflict of interest exists.

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► Supplementary material

eReferences:
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Case Study:
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CME credit for this unit can be obtained via cme.aerzteblatt.de until 10 November 2019.
Only one answer is possible per question. Please select the answer that is most appropriate.

Question 1

A patient is suffering from cyclic mastalgia. It mainly troubles her during her weekly session at the gym. You advise her to wear a well-fitting bra.

What topical medication would you recommend?

- a) Diclofenac gel
- b) Rosemary oil
- c) Flaxseed oil
- d) Prednisolone cream
- e) Progesterone gel

Question 2

Which of the diagnoses included under fibrocystic breast changes represents a four-fold increased risk of breast cancer compared to the normal population, and therefore requires more intensive screening for breast cancer?

- a) Sclerosing adenosis
- b) Atypical ductal hyperplasia
- c) Radial scar
- d) Blunt duct adenosis
- e) Papillary apocrine metaplasia

Question 3

A nonproliferating form of benign breast disease is diagnosed by screening mammography in a 52-year-old patient with no relevant personal or family history. What further investigations do you recommend in terms of breast cancer screening?

- a) Mammography every 12 months
- b) Breast ultrasound every 12 months
- c) Breast MRI every 12 months
- d) Clinical examination of the breast every 6 months
- e) Attending screening mammography every 2 years

Question 4

What are the most important therapeutic measures in a patient with incipient puerperal mastitis?

- a) Apply vaseline to the nipples and use yogurt compresses
- b) Start calculated oral antibiotic treatment and regular milk expression
- c) Cool and compress the breast
- d) Secondary weaning; discard the remaining milk
- e) Use nipple shields and oral nonsteroidal analgesics

Question 5

A 22-year-old patient with puerperal mastitis in the upper lateral quadrant of the left breast shows no clear improvement of symptoms after 3 days of treatment. What diagnostic investigation should you now carry out without further delay?

- a) Take blood for blood count and CRP determination to check the diagnosis
- b) Galactography to rule out blocked ducts
- c) Breast ultrasound to rule out an abscess
- d) Mammography to rule out inflammatory breast cancer
- e) Core biopsy of the area involved to rule out breast cancer

Question 6

When should a bacterial culture of the breast milk be performed in the case of a patient with puerperal mastitis?

- a) When symptom control has not been achieved after 48 h antibiotic treatment
- b) When the analgesics administered make breastfeeding impossible
- c) When cooling the affected breast fails to relieve symptoms within 24 h
- d) When the patient has had puerperal mastitis after previous deliveries
- e) When there is a family history of puerperal mastitis

Question 7

What is the treatment of choice for abscess-forming nonpuerperal mastitis?

- a) Ultrasound-guided aspiration of the abscess and antibiotic therapy
- b) Expression of milk and cooling of the affected breast
- c) Mastectomy
- d) Galactography to rule out blocked ducts
- e) Low-dose glucocorticoid therapy

Question 8

In a 35-year-old patient with the BRCA1 mutation, breast ultrasonography is carried out for a newly discovered palpable mass and fibroadenoma is suspected. What should be done next?

- a) Mammography
- b) Follow-up breast ultrasonography in 6 to 12 months
- c) Ultrasound-guided core biopsy of the mass
- d) Surgical excision of the mass
- e) Prophylactic bilateral mastectomy and reconstruction with implants

Question 9

For what diagnosis is spontaneous blood-streaked or serous nipple discharge the main symptom?

- a) Breast cancer
- b) Phyllodes tumor
- c) Blunt duct adenosis
- d) Lactating adenoma
- e) Papilloma

Question 10

With which class of drugs can galactorrhea occur as an unwanted effect?

- a) Nonsteroidal anti-inflammatories
- b) Selective serotonin reuptake inhibitors
- c) Thyroid hormone
- d) Proton pump inhibitors
- e) ACE inhibitors

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Supplementary material to:

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by Angrit Stachs, Johannes Stubert, Toralf Reimer, and Steffi Hartmann

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