

Clinically occult breast lesions A histopathologic study

OBJECTIVE With the increasing use of mammography in screening programs growing numbers of breast biopsies are performed on clinically nonpalpable lesions in asymptomatic women. The purpose of this study was to describe the histopathologic findings of clinically occult, mammographically detected breast lesions. **METHOD** During the last eight years 178 hook-wired needle-guided biopsies were performed on 175 women with nonpalpable mammographically detected breast lesions. The median age was 52 (range 25–75) years. Mammographic findings included 76 cases with microcalcifications, 89 cases with tissue density and 13 cases with both features. Surgical specimens were radiographed and sampled accordingly. The mammographic and histologic material of all cases was reviewed retrospectively. **RESULTS** Microscopically, 22.5% of the biopsies revealed the presence of carcinoma that was invasive in 62.5% of the cases. Benign lesions, most frequently fibrocystic changes, were identified in 73% of the biopsies, while 4.5% disclosed other findings. Sixty percent of the cancers were associated with radiographic calcifications. Calcium deposits were located within the tumor (62.5%) or in the adjacent non-neoplastic breast tissue (37.5%). Axillary lymph node dissection was performed in 26 patients with carcinoma and metastatic disease was found in 42% of these cases. **CONCLUSIONS** This study indicates that nonpalpable breast lesions exhibit a wide spectrum of histopathologic findings. Carcinoma is not an uncommon occurrence, which although clinically occult does not preclude the possibility of metastases in the axillary lymph nodes. Microcalcifications are more frequent in benign breast lesions while their presence in the non-neoplastic tissue surrounding a tumor indicates the need for a thorough histopathologic examination of the surgical specimen.

The use of mammography for the screening of asymptomatic women has increased steadily in recent years, with its merits widely accepted. As a result growing numbers of breast biopsies are performed on clinically nonpalpable lesions. In most cases, the needle localization technique is used to guide the surgeon to the area of the mammographically detected breast lesion. The most frequent mammographic abnormalities prompting biopsy are microcalcifications, soft tissue density or a combination of both. These abnormalities may or may not be

associated with a grossly visible lesion in the biopsy specimen.

Most reports selectively analyze the incidence and the morphologic features of nonpalpable mammographically detected breast lesions, with emphasis on atypical hyperplasia and intraductal carcinoma.^{1–6}

The purpose of the present study was to examine the morphologic spectrum of clinically occult breast lesions and to evaluate their histopathologic and mammographic characteristics.

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Μη ψηλάφητες βλάβες στο μαστό.
Ιστοπαθολογική μελέτη

Περίληψη στο τέλος του άρθρου

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MATERIAL AND METHOD

From January 1992 through December 1999 (8 years) a total of 178 needle-guided biopsies were performed on 175 women with nonpalpable mammographically detected breast lesions. The median age was 52 years with a range of 25 to 75 years. Three patients underwent bilateral biopsies; each biopsy has been considered and evaluated as a separate mammary lesion.

Abnormal mammographic findings included microcalcifications in 76 biopsies, soft tissue density in 89 biopses and breast tissue density associated with microcalcifications in 13 biopsies. The lesions were localized preoperatively using a hook-wired needle, and confirmation of excision was obtained by specimen radiography in all cases (fig. 1). In every case, the tissue specimen was submitted to the pathology laboratory intact in the fresh state, in most cases with the guiding wire *in situ*. The specimen margins were painted with Indian ink, the tissue was serially sectioned at about 4–5 mm intervals and the slices were re-X-rayed. Abnormalities on the radiographed slices were labeled and placed in correspondingly labeled cassettes, for microscopic examination. The lesions in question were entirely blocked. The tissue adjacent to the suspicious area was also sampled.

The tissues were fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned at 4 μ m and stained with hematoxylin-eosin (HE). Six to 15 HE stained slides from each biopsy specimen were examined under conventional and polarized light microscope (fig. 2). In cases where the initial slides failed to reveal microscopic calcifications, multiple levels from the blocks in question were obtained.

Twenty-six patients with malignant tumors underwent breast surgery (19 modified radical mastectomy and 7 segmentectomy with axillary node dissection) as part of the treatment. The average number of lymph nodes removed per case was 17.

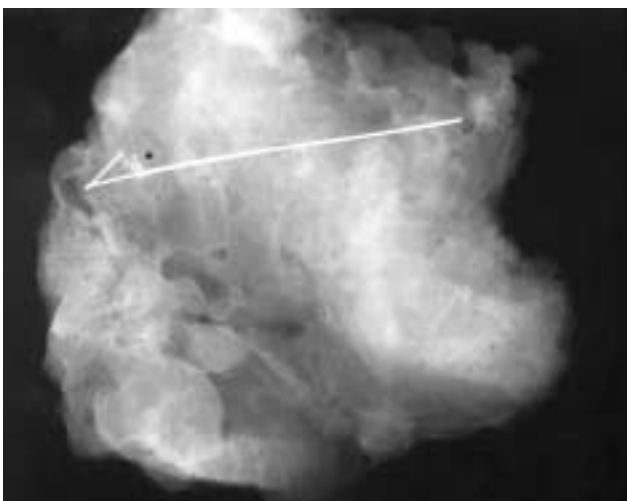


Figure 1. Radiography of the surgically excised lesion with hook-wire in place. Note the microcalcifications (asterisk).

RESULTS

Microscopic examination of 178 biopsies of nonpalpable breast lesions, performed on 175 women, revealed 40 cases of cancer (22.5%) and 138 of benign lesions (77.5%) (tabl. 1). The malignant lesions included 22 cases of infiltrating ductal carcinoma (fig. 2f), 13 cases of ductal carcinoma *in situ* (fig. 2e), 3 cases of infiltrating lobular carcinoma and 2 cases of lobular carcinoma *in situ* (fig. 2d). Multicentricity was found in 9 of the 22 (41%) mastectomy specimens. Multifocal growth, defined as the presence of separate foci of carcinoma in the same quadrant, was encountered in four cases: two cases of ductal carcinoma *in situ* and two of infiltrating ductal carcinoma. In the remaining nine cases the tumor presented as a solitary mass. Of the 138 benign lesions 111 (80%) revealed fibrocystic changes, 19 (14%) fibroadenomas and 8 (6%) variable findings such as papilloma (1 case), intramammary lymph node (1 case), mastitis (1 case), lipoma (2 cases) and normal breast tissue (3 cases).

In the specimens with fibrocystic changes the whole spectrum of morphologic changes was encountered including cyst formation, fibrosis of the stroma, mild to florid epithelial hyperplasia, atypical hyperplasia (ductal or lobular), apocrine metaplasia, adenosis (blunt duct adenosis or sclerosing adenosis were categorized as adenosis) and fibroadenomatoid change (fig. 2a–c). Fibrocystic changes to some extent were also noted in the peritumoral breast tissue in 26 cases. Of the various histologic patterns seen in a breast biopsy with fibrocystic changes associated with malignancy were those of fibrosis and cystic dilatation, followed by atypical hyperplasia.

Well-circumscribed small (1–1.3 cm) nodules, with fibroadenomatoid changes, were classified as fibroadenomas. Thirteen of the 19 fibroadenomas occurred on a background of fibrocystic changes. Two fibroadenomas were detected in two cases of ductal carcinoma *in situ*. No associated lesions were found in the remaining four cases.

The size of the carcinomas, measured on the histological sections, ranged from 0.4 cm to 1.5 cm, while larger or diffuse lesions were mainly accounted for by fibrocystic changes. Table 2 shows the mammographic and relevant histologic findings. Of the 89 cases with calcium deposits on mammography (76 calcifications alone, 13 calcifications associated with tissue density) only 76 contained microscopic calcifications. Examination of the sections under polarized light failed to detect any crystal deposits in the remaining 13 cases. Among the 76 cases with microscopic calcifications, fibrocystic changes

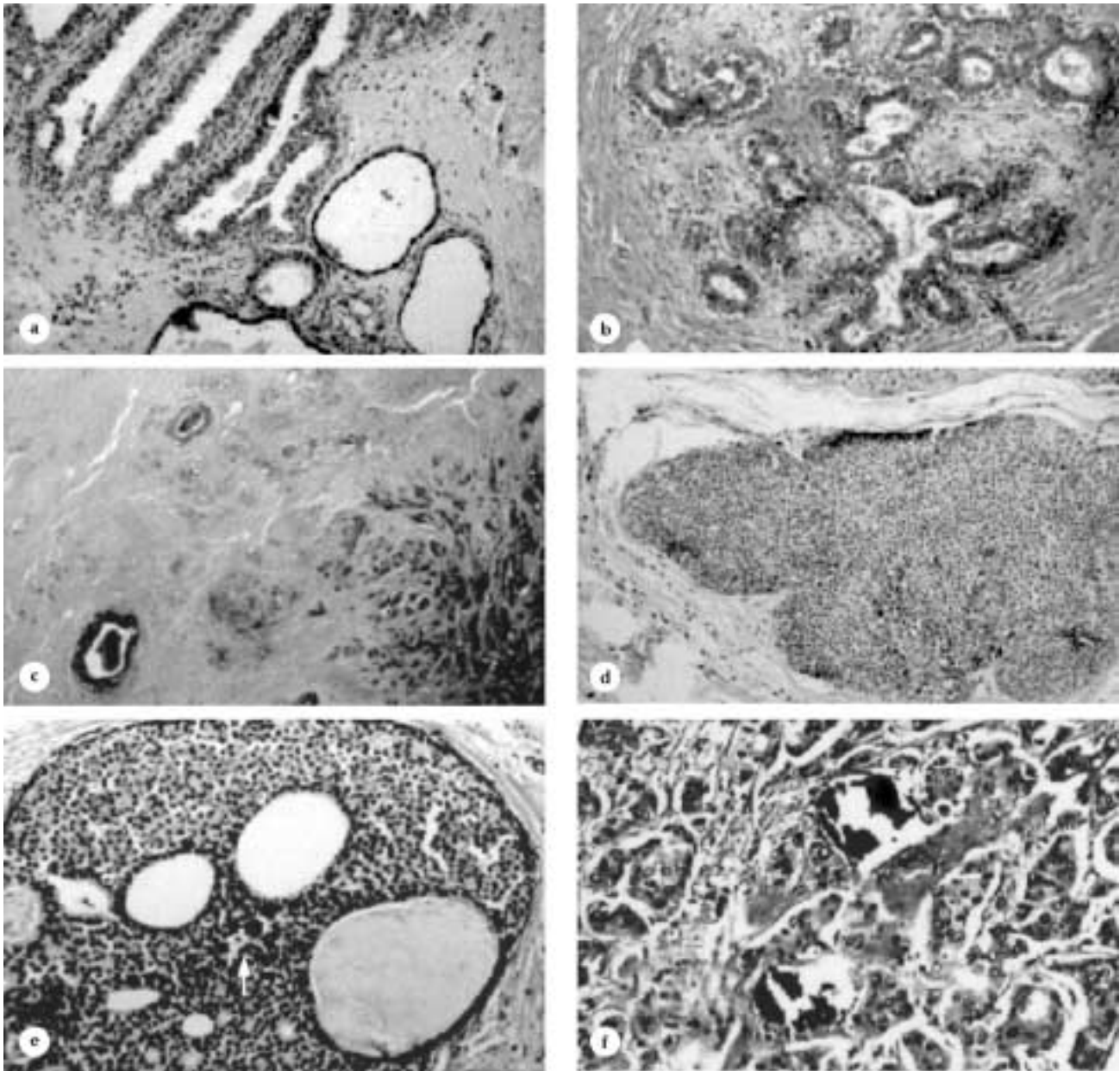


Figure 2. Microscopic findings in cases presenting as tissue density (a–d) or calcifications (e, f) on mammography (hematoxylin-eosin). (a) Fibrocystic changes, predominantly cyst formation ($\times 100$). (b) Fibrocystic changes, ductal hyperplasia ($\times 100$). (c) Sclerosing adenosis ($\times 100$). (d) Lobular carcinoma *in situ* ($\times 100$). (e) Ductal carcinoma *in situ* with microcalcification (arrow, $\times 200$). (f) Invasive ductal carcinoma, with calcifications (arrows, $\times 200$).

were found in 49 cases (64.5%), carcinoma in 24 (31.5%) and fibroadenoma in 3 (4%).

Microcalcifications were present as coarse-granular amorphous deposits, or small laminated structures resembling psammoma-like bodies. They were located mainly within the lumen of neoplastic ducts (fig. 2e, f), in benign microcysts and small ducts, and occasionally

in the stroma. The latter had a sand-like appearance and was observed in specimens with fibrocystic changes. In one case microcalcifications were detected within a hyalinized fibroadenoma.

Of the 88 cases with mammographically detected soft tissue density, 50 (57%) exhibited fibrocystic changes, 15 (17%) were found to contain cancer, 16 (18%) cor-

Table 1. Histologic findings in 178 nonpalpable breast lesions.

	Number	(%)
Fibrocystic changes	111	62
Fibroadenoma	19	11
Carcinoma	40	22,5
<i>In situ</i>	15	37,5
Invasive	25	62,5
Other*	8	4,5
Total	178	100

* Papilloma, lymph node, lipoma, mastitis, normal breast

responded to a fibroadenoma and 7 (8%) other benign lesions (tabl. 2).

Axillary lymph node metastases were detected in 11 of the 26 (42%) mastectomy specimens. All of the tumors with lymph node involvement were invasive carcinomas with a coexisting *in situ* component in six of them. An extensive (>25% of the tumor area) ductal *in situ* carcinoma, most frequently of comedo type, was observed in four of these six cases (67%). In one case micropapillary and clinging types were noted in the same tumor.

Table 2. Histologic and mammographic findings.

Histology	Mammography			Total
	Ca ⁺⁺	Td	Ca ⁺⁺ /Td	
Fibrocystic changes	53	50	8	111
Cancer	22	16	2	40
Fibroadenoma	–	16	3	19
Other	1*	7**	–	8
Total	76	89	13	178

Ca⁺⁺: Calcifications, Td: Tissue density

* Mastitis, ** Papilloma, lymph node, lipoma, normal breast

DISCUSSION

With the increased use of mammography, smaller, often nonpalpable, breast lesions are being biopsied. The percentage of malignancy detected in these biopsies varies from 10% to 32%, in different reports.^{1,3,4,7-10} This variability largely depends on the experience of the radiologist and the achieved quality of the mammograph. In the present study 22.5% of the biopsies performed for a nonpalpable mammographic abnormality proved to be malignant, with a higher frequency of invasive carcinomas (62.5%, 25/40). There was no difference in size between invasive and noninvasive carcinomas.

Intraductal carcinoma was the most common observed noninvasive neoplastic lesion, probably because lobular carcinoma *in situ* is usually not detectable mammographically.¹¹ In 16 cases of infiltrating ductal carcinoma an *in situ* component, mostly of the comedo type, was also present; it occupied the largest area of the tumor or was present in the grossly normal breast tissue adjacent to the tumor. An *in situ* component of the same histologic type with the main tumor was also detected in two cases of infiltrating lobular carcinoma.

The presence of extensive intraductal carcinoma, in excisional biopsy specimens, within the tumor or in the breast tissue adjacent to the invasive neoplasm, has been related to the presence of intraductal carcinoma in the rest of the breast.^{12,13} On the other hand, the presence of intraductal carcinoma as a potential prognostic parameter in patients with invasive ductal carcinoma has been evaluated by several authors.¹⁴⁻¹⁶ These authors noted a better prognosis and a decreased frequency of nodal metastases in cases of invasive tumors harboring a prominent intraductal component. In the present study the frequency of lymph node involvement was slightly higher in those tumors with an *in situ* component compared with the tumors that lacked the *in situ* feature (55%, 6/11 vs 45%, 5/11). However, the limited number of cases studied does not allow any definite conclusion.

Multicentricity of breast cancer is defined as the occurrence of more than a single focus of carcinoma, in more than one quadrant of the breast. A high incidence of multicentricity in nonpalpable breast cancer was noted by Schwartz et al.⁷ They found foci of invasive or noninvasive ductal or lobular carcinoma in 44.2% of the specimens examined. In the present study a relatively high rate (41%) of multicentric growth was found in the mastectomy specimens. In three cases an *in situ* component of various morphologic types (comedo, cribriform, solid, micropapillary, clinging) was also present. In another case, the biopsy specimen revealed an invasive ductal carcinoma while in the mastectomy specimen foci of infiltrating lobular carcinoma were found in another quadrant. These carcinomas were considered as two separate neoplasms, of different microscopic appearance, present in the same breast.

It has long been recognized that the distinction between intraductal hyperplasia with atypia and intraductal carcinoma may present a difficult pathologic decision, especially when dealing with well-differentiated non-comedo intraductal carcinoma. Tavassoli et al¹⁷ suggest that the diagnosis of intraductal carcinoma should be limited to lesions with aggregate diameter of at least 2 mm, regardless of the number of ducts involved. Based

on these criteria three of the cases of atypical intraductal hyperplasia in this study qualified as intraductal carcinoma.

It has been reported that mammographically detected small breast cancers, although invasive, are generally neoplasms that lack the morphological and biologic features of aggressive behavior.¹⁸ In the present material 38% (5/13) of the *in situ* ductal carcinomas were of high grade (comedo type), while a grade II and III were found in 50% (11/22) and 23% (5/22) of the infiltrating ductal carcinomas, respectively.

Nonpalpable breast lesions should not be viewed as a synonym for inconsequential. In a recent study of 558 patients with nonpalpable, mammographically detected, invasive carcinomas who were subjected to axillary dissection, 27.1% had at least one positive node,¹⁰ while a higher metastatic rate of up to 31%, at the time of diagnosis, has been reported.^{19,20} The rate in the present study is much higher, accounting for 42% of the mastectomy specimens. In addition, one more case of a grade II infiltrative ductal carcinoma with no lymph node involvement exhibited neoplastic emboli into blood vessels. The size of these tumors ranged from 0.5 cm to 1.5 cm (mean 1.2 cm). Interestingly, the case with the two different histologic types of cancer showed extensive lymph node metastases (in 12 out of 15 lymph nodes), composed entirely of lobular carcinoma. Axillary node dissection was also performed in four patients with ductal carcinoma *in situ* and all lymph nodes were free of metastasis.

The disagreement of our findings with other series could be partially explained; if lymph node positivity was estimated in tumors of <1 cm, the metastatic rate would be 18%. However, most of the invasive cancers with axillary lymph node metastases in the present study were ≥ 1 cm (median 1.3 cm). In addition, 45% (5/11) of these tumors were located in the outer quadrants, a site that has been reported to be related with axillary lymph nodes metastases more frequently than lesions of the inner quadrants.²¹ In the present study, the metastatic rate is particularly high for clinically occult lesions and some of these might actually have been palpable on careful examination. However, in large breasts, common in Greek women, tumors of up to 2 cm in diameter (T1) can easily be missed on palpation, even by experienced surgeons (DK and ET), whose clinical practice is restricted to breast disease. In addition, these particular patients had no clinically suspicious axillary lymph nodes on physical examination.

Breast cancer is one of the malignant neoplasms which can stimulate calcium formation. Today, the increasing

use of mammographic screening has shown that the presence of calcifications in breast tissue is of great importance, since they are one of the signs routinely used in the diagnosis of breast cancer. The most common type of microcalcifications is composed of amorphous calcium phosphate, while less frequently calcium oxalate may be present. The latter is rarely associated with malignancy.²² It has been suggested that microcalcifications are associated with epithelial secretions or necrosis, and hence reflect a product of the living cell or a cellular degenerative process.²³⁻²⁵

Calcifications are present in a variety of benign and malignant lesions of the breast. In a series of breast biopsies performed for mammographically identified microcalcifications, it was shown that the incidence of carcinoma was lower than that of benign lesions (32% vs 68%).⁹ A slight difference from the above mentioned data was noted in the present study, where the rate of carcinoma in the biopsies was 27% (24/89) while benign lesions accounted for 72% (64/89). On the other hand, 60% (24/40) of carcinomas were detected on biopsies performed for calcifications while 40% (16/40) were identified on biopsies performed for tissue density. Hall et al²⁶ found an almost equal percentage of cancer in biopsies performed for calcifications (30%) and in those performed for masses (29%). In the present series, microcalcifications were identified histologically within the tumor mass in 62.5% of the cases, while in the remaining 37.5% the calcium deposits were present only in benign breast tissue adjacent to the tumor.

The incidence of fibrocystic changes in this series was found at a range between 62% (150/178) to 84% (86/134); it was higher in cases where such lesions were present in association with other findings, such as tumors and fibroadenomas.

Previous studies showed a 10–19% overall incidence of atypical hyperplasia in biopsy specimens of mammographically detected breast lesions.^{2,4,9} The lower limits of these rates are in accordance to the 10% (18/178) overall rate in the present series; the latter was found to be higher than the 2–4% incidence of atypical hyperplasia reported in the literature, in cases of breast biopsies performed due to a clinically palpable mass.^{4,27} Of interest is the fact that nine of the 18 cases (50%) with atypical hyperplasia were associated with malignancy. In three cases the criteria of carcinoma *in situ* were fulfilled. This finding is suggestive of a close relation between carcinoma and atypical hyperplasia of the breast.

Microscopic calcifications in specimens with solely fibrocystic changes were detected in all, except for 11, biopsies obtained due to microcalcifications on mam-

mography. Calcium deposits were also found microscopically in six more cases, whereas mammography had failed to demonstrate the presence of this finding. Calcifications are commonly identified histologically in breast biopsies performed for indications other than mammographic microcalcifications. This is due to the fact that single calcium particles as small as 0.1 mm cannot be seen on a conventional mammogram.⁵ In this study, microscopic calcium deposits represent tiny sand-like aggregations in the stroma of the fibrocystic lesions.

Large-core needle biopsy has been used as a feasible alternative sampling technique to formal biopsy for evaluation of palpable breast lesions.^{28,29} Recently, image-guided large-core needle biopsy of nonpalpable, mammographically detected breast abnormalities has become an alternative to wire localization biopsy.³⁰⁻³⁵ Non-image-guided large-core needle biopsy has a reported sensitivity of 89% to 90% and a specificity of 100%, while the sensitivity of stereotactic core needle biopsy ranges from 84% to 96.9% and the specificity from 98.6% to 100%.^{28,29,32,33,35,36}

Although core needle biopsy is a reliable, less invasive and compared with excisional biopsy, less costly method for evaluation of palpable and nonpalpable breast lesions,³³ some diagnostic pitfalls have to be taken in con-

sideration, due to the small tissue volume removed and to the underestimation of certain pathologic conditions. It has been shown in the literature that because of the small size of the sample it is difficult to determine the type of carcinoma, ductal vs lobular, or to differentiate fibroadenoma from phylloides tumor.^{28,33} The most common underdiagnosed cases (25–70%) seem to be atypical ductal hyperplasia and ductal carcinoma *in situ*.^{33,37} Furthermore, a core biopsy diagnosis of ductal carcinoma *in situ* does not preclude the discovery of invasive carcinoma at surgical biopsy.^{33,38}

In conclusion, the present study of 178 hook-wired needle-guided biopsies for nonpalpable mammographically detected breast lesions revealed a wide spectrum of histopathologic findings. Breast carcinoma was not uncommon (22.5%).

A relatively high proportion (42%) of patients with nonpalpable carcinoma had axillary node metastases. Microcalcifications were present in a variety of breast lesions, mostly benign, with fibrocystic changes being the great majority. The pathologist should always keep in mind that microcalcifications detected in cases of breast cancer could also be present in the adjacent non-neoplastic tissue.

ΠΕΡΙΛΗΨΗ

Μη ψηλαφητές βλάβες στο μαστό. Ιστοπαθολογική μελέτη

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ΣΚΟΠΟΣ Με την όλο και αυξανόμενη χρήση της μαστογραφίας σε ασυμπτωματικές γυναίκες, σε προγράμματα μαζικού ελέγχου, σήμερα ένας μεγάλος αριθμός βιοψιών μαστού γίνονται σε μη ψηλαφητές, κλινικά, βλάβες. Σκοπός της παρούσας αναδρομικής εργασίας ήταν η περιγραφή των ιστοπαθολογικών ευρημάτων σε υποκλινικές βλάβες του μαστού που ανιχνεύονται μαστογραφικά. **ΥΛΙΚΟ-ΜΕΘΟΔΟΣ** Με τη βοήθεια συρμάτινου οδηγού, τα τελευταία οκτώ χρόνια έγιναν 178 κατευθυνόμενες βιοψίες σε 175 γυναίκες, οι οποίες είχαν μαστογραφικά ανιχνεύσιμες βλάβες στο μαστό. Η ηλικία των ασθενών κυμαινόταν από 25–75 χρόνια (διάμεση 52 χρόνια). Τα μαστογραφικά ευρήματα περιελάμβαναν 76 περιπτώσεις με μικροαποπιτανώσεις, 89 περιπτώσεις με πύκνωση των μαλακών μορίων και 13 περιπτώσεις με αμφοτέρα τα ευρήματα. Στα χειρουργικά παρασκευάσματα γινόταν ακτινογραφία και ακολουθούσε δειγματοληψία για ιστολογική εξέταση. Σε όλες τις περιπτώσεις συνεκτιμούνταν τα μαστογραφικά και ιστοπαθολογικά ευρήματα. **ΑΠΟΤΕΛΕΣΜΑΤΑ** Η μικροσκοπική εξέταση των βιοψιών απέδειξε την ύπαρξη καρκινώματος σε 22,5% των περιπτώσεων, από τις οποίες 62,5% αφορούσαν σε διηθητικό καρκίνωμα. Καλοήθεις βλάβες, κυρίως ινοκυτικές αλλοιώσεις, ανευρέθηκαν στο 73% των

βιοψιών, ενώ 4,5% εμφάνιζαν άλλα ευρήματα. Το 60% των καρκίνων συνδυαζόταν με την παρουσία αποπιτανώσεων στη μαστογραφία. Οι εναποθέσεις ασβεστίου εντοπίζονταν μέσα στον όγκο (62,5%) ή στο γειτονικό μη νεοπλασματικό ιστό (37,5%). Σε 26 ασθενείς με καρκίνωμα η εξέταση των σύστοιχων μασχαλιαίων λεμφαδένων απέδειξε την ύπαρξη μεταστατικής νόσου στο 42% των περιπτώσεων. **ΣΥΜΠΕΡΑΣΜΑΤΑ** Η παρούσα εργασία έδειξε ότι οι μη ψηλαφητές βλάβες στο μαστό περιλαμβάνουν ένα ευρύ φάσμα ιστοπαθολογικών αλλοιώσεων. Το καρκίνωμα δεν αποτελεί ασύνηθες εύρημα και παρά το ότι οι βλάβες αυτές είναι υποκλινικές, δεν αποκλείουν την πιθανότητα μεταστατικής λεμφαδενικής νόσου. Οι μικροαποπιτανώσεις είναι πιο συχνές στις καλοήθεις βλάβες του μαστού, ενώ η παρουσία τους στο μη νεοπλασματικό ιστό, που περιβάλλει τον όγκο, δείχνει την αναγκαιότητα της λεπτομερούς ιστοπαθολογικής εξέτασης του χειρουργικού παρασκευάσματος.

Λέξεις ευρητηρίου: Αποπιτανώσεις, Καρκίνωμα, Μαστογραφία, Μαστός, Μη ψηλαφητές βλάβες

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