
Mammographic findings in pseudoxanthoma elasticum

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Background: There have been isolated case reports of arterial and skin calcification in mammograms of patients with pseudoxanthoma elasticum (PXE), and unpublished anecdotes of many women with PXE undergoing breast biopsy for evaluation of microcalcifications.

Objective: Our aim was to systematically evaluate mammography and breast pathology in PXE.

Methods: The mammograms of 51 women with confirmed PXE were compared with those of a control sample of 109 women without PXE, noting each of the following characteristics on each mammogram: breast density, skin thickening, skin microcalcifications, vascular calcification, breast microcalcifications and macrocalcifications, and masses. The characteristics of the 2 samples were compared using the 2-tailed *t* test with a pooled estimate of variance. The indications for mammography and data for each of the mammographic findings were analyzed using the χ^2 test. Available breast biopsy material was reviewed.

Results: The PXE and control groups were similar in age and indications for mammography. There was a statistically significant increase in skin thickening, vascular calcification, and breast microcalcifications in the PXE group ($P < .001$ each). Breast density, masses, macrocalcifications, and skin calcification did not differ statistically in the 2 groups, but no control patient had axillary calcification, or both vascular calcification and microcalcifications ($P < .001$). Nearly 1 in 7 of the patients with PXE demonstrated at least 3 of the following: microcalcifications, skin calcifications, vascular calcification, and skin thickening; whereas none of the control group did. Histopathologic findings of breast tissue showed calcification of dermal elastic fibers, subcutaneous arteries, and elastic fibers of the deep fascia and interlobular septae of the fat adjacent to breast parenchyma.

Conclusion: Breast microcalcification and arterial calcification are not rare in the normal population and are not of diagnostic value. The presence of both of these findings, especially with skin thickening or axillary skin calcification, should suggest a diagnosis of PXE. The majority of breast calcifications in PXE are benign. (*J Am Acad Dermatol* 2003;48:359-66.)

Pseudoxanthoma elasticum (PXE) is a genetic disorder characterized by calcification of elastic fibers within the dermis; internal elastic lamina and media of arteries; and Bruch's membrane, an elastin-rich layer of the choroid of the eye. As a result, PXE is complicated by skin changes leading to lax and redundant skin, especially of the neck and axillae (Fig 1); arterial occlusive changes

manifested by absent pulses, intermittent claudication, premature coronary and cerebrovascular disease, and gastrointestinal bleeding; and by loss of central vision as a result of bleeding of fragile choroidal vessels growing through breaks in the calcified Bruch's membrane known as angioid streaks.¹ PXE occurs both sporadically and as an autosomal recessive disorder.¹ Although several families with 2

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Fig 1. Characteristic skin changes of pseudoxanthoma elasticum in axilla. Note papules and skin redundancy.

affected generations have been described, compound heterozygosity and pseudodominance have accounted for all those studied and true dominant inheritance has not been documented.² The gene responsible for PXE encodes the intracellular membrane transport protein, ABCC-6, and several mutations in this gene have been described.²⁻⁵ PXE is rare, having an estimated incidence of 1:100,000,⁶ although the true incidence may be as high as 1:25,000.

Mammography is a radiographic technique particularly suited to the detection of soft-tissue changes. Although there have been isolated case reports of mammograms of patients with PXE demonstrating arterial calcification within the breast⁷ and skin calcification,⁸ no studies of mammography in PXE have been undertaken. Unpublished anecdotes suggest that many women with PXE have undergone breast biopsy for evaluation of radiographic microcalcifications that proved to be benign. A study was, therefore, undertaken to systematically evaluate mammography in PXE.

Table I. Characteristics of pseudoxanthoma elasticum and control groups

	PXE (n = 51)	Control patients (n = 109)
Age (y)	54.3 ± 11.4	55.8 ± 13.1 (<i>P</i> > .05)
Reasons for mammography		
Screening (%)	39 (76.5)	92 (84.4)
Follow-up (%)	10 (19.9)	12 (11.0)
Mass, symptoms (%)	2 (3.9)	5 (4.6)
		(<i>p</i> > 0.05)*

* χ^2 test.

MATERIAL AND METHODS

Mammograms were obtained from 51 patients with confirmed PXE (diagnostic skin biopsy and angioid streaks) in the database of PXE International Inc (Sharon, Mass) and the private medical practices of 2 of the investigators. The control sample consisted of 109 consecutive mammograms blindly selected from the files of a hospital-based breast imaging center. Each mammogram was independently examined by 2 radiologists, noting each of the following characteristics: breast density, skin thickening, skin microcalcifications, vascular calcification, breast microcalcifications and macrocalcifications, and masses.

The characteristics of the 2 groups were compared using a 2-tailed *t* test with a pooled estimate of variance. The indications for mammography and the data for each of the mammographic findings were analyzed using the χ^2 test.

Breast biopsy specimens from 5 patients with PXE were reviewed by one of the authors, a pathologist, who had no access to the mammographic findings. Among the histologic parameters evaluated were the presence or absence of (1) breast parenchymal calcifications, and if present, the localization of such deposits; (2) calcification in the fatty and fibrous tissue overlying or deep to the breast parenchyma; (3) calcified fragmented, degenerated elastic fibers in overlying skin; and (4) vascular calcification.

RESULTS

The characteristics of the PXE and control groups and the indications for ordering the mammograms are summarized in Table I. None of the patients in the PXE group were known to have diabetes. The mammographic findings are outlined in Table II. There was a statistically significant increase in the occurrence of skin thickening (Fig 2), breast microcalcifications (Fig 3), and vascular calcification (Fig 4) (*P* < .001 each) among patients with PXE. Breast density, macrocalcifications, and masses were not

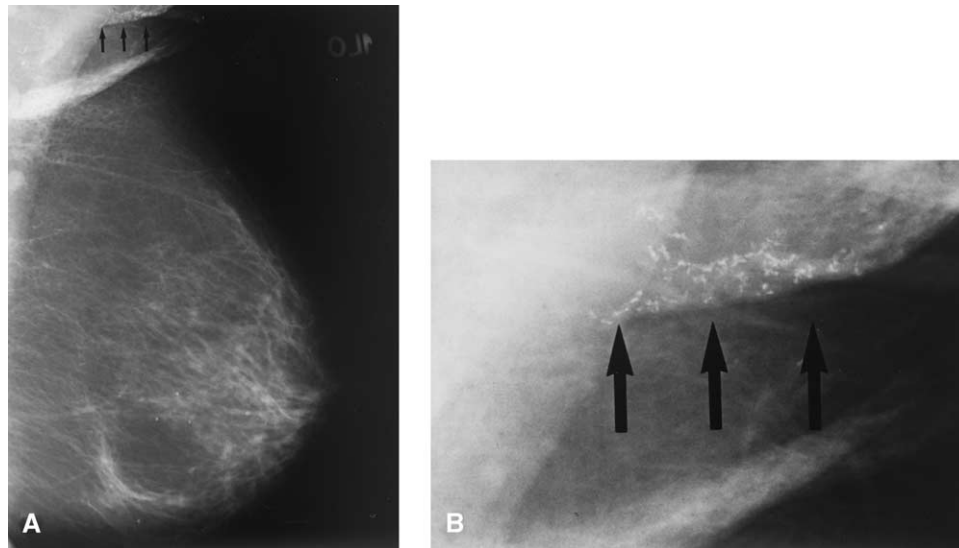


Fig 2. **A,** Skin thickening and skin calcifications in axilla (*arrows*). **B,** Magnified view of thickened axillary skin with calcification (*arrows*).

Table II. Mammographic findings in pseudoxanthoma elasticum

	PXE (n = 51)	Control (n = 109)	
Breast microcalcifications (%)	27 (52.9)	12 (11)	$P < .001$
Skin thickening (%)	12 (23.5)	1 (0.9)	$P < .001$
Skin calcifications (%)	6 (11.8)	4 (3.7)	$P > .05$
Axillary skin calcifications (%)	6 (11.8)	0 (0)	$P < .001$
Macrocalcifications (%)	20 (39.2)	35 (32.1)	$P > .05$
Vascular calcification (%)	26 (51)	16 (14.7)	$P < .001$
Mean age (y)			
Vascular calcification	60.2 ± 10.2	69.4 ± 11.0	$P < .05$
No vascular calcification	50.1 ± 9.7 ($P < .05$)	54.2 ± 10.2 ($P < .001$)	$P > .05$
Mass (%)	4 (7.8)	14 (12.8)	$P > .05$
Breast density (%)			
Fatty	5 (9.8)	9 (8.5)	
Normal	26 (51)	59 (54.1)	$P > .05^*$
Dense	20 (39.2)	41 (37.6)	
Skin thickening + skin calcification (%)	5 (9.8)	0 (0)	$P < .001$
Vascular calcification + breast microcalcification (%)	17 (33.3)	0 (0)	$P < .001$
3/4: Skin thickening, skin calcification, vascular calcification, or breast microcalcification (%)	7 (13.2)	0 (0)	$P < .001$

* χ^2 test.

statistically different between the 2 groups. Although the incidence of skin calcification was not significantly increased in the PXE group ($P > .05$), no patient in the control group had axillary skin calcification ($P < .001$), and none of the control patients had both axillary skin calcification and thickening, whereas 9.8% of the PXE mammograms showed both ($P < .001$). One third of patients with PXE demonstrated both vascular and breast microcalcifications whereas this combination was not noted in

the control group ($P < .001$). Nearly 1 in 7 of the PXE sample (in contrast to none of the control group) demonstrated at least 3 of the following: breast microcalcifications, skin calcifications, vascular calcifications, and skin thickening ($P < .001$).

Skin thickening in the PXE sample was seen only in the axilla, as was skin calcification (Fig 2).

One breast biopsy specimen from a patient with PXE showed classic changes of PXE in breast skin, including calcification of clumped and degenerated

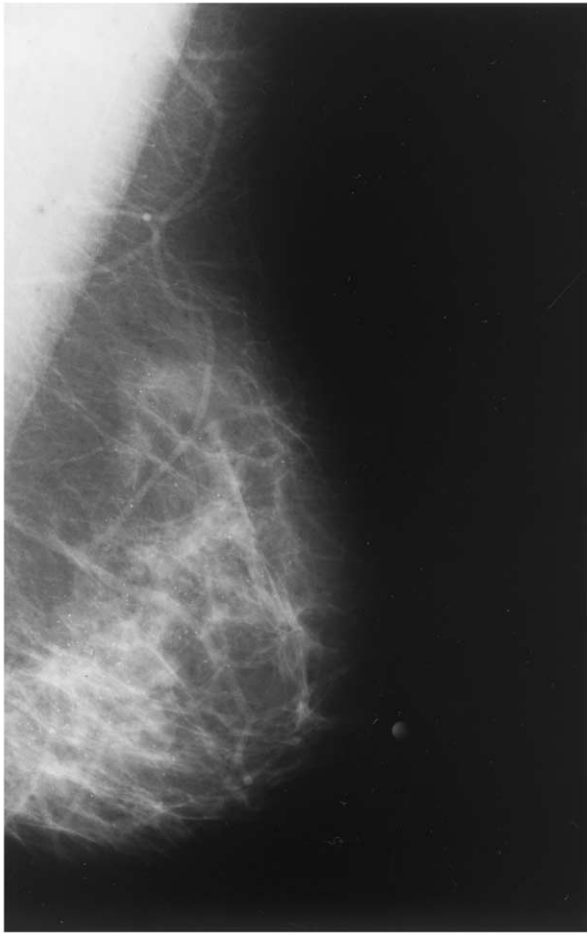


Fig 3. Multiple scattered microcalcifications in breast.

dermal elastic fibers in the dermis (Fig 5, *A* and *B*), and calcification and fragmentation of the internal elastic lamina of a subcutaneous artery (Fig 5, *C*). Although neither elastic-tissue abnormalities nor calcification of elastic fibers were noted in the breast parenchyma, the deep fascia and the interlobular septae manifested multiple foci of small, thin-caliber, granular amphophilic elastic fibers that stained intensely for calcium (Fig 6). Although the hematoxylin and eosin light microscopic findings were very subtle, affecting in any one examined microscopic field only a small percentage of sampled elastic fibers, such findings were present in most randomly examined high-power fields. The wide extent of this change was best appreciated on von Kossa-stained material. The other 4 breast biopsy specimens showed fibrocystic disease. Two showed intraluminal microcalcifications, psammomatous calcification of ductal epithelial cells, or lamellated rounded calcific concretions interposed between the basement membrane zone of the ducts and glands, and the ductal epithelial cells. Neither vascular calcification

nor foci of elastic tissue calcification were seen in any of these 4 biopsy specimens but the authors were unable to examine the overlying skin or surrounding soft tissue and, because of the unavailability of tissue blocks, special stains for elastic tissue and calcium could not be conducted. Radiologic-pathologic correlation is summarized in Table III.

DISCUSSION

Because of the occurrence of calcification within the dermis and internal elastic lamina and media of arteries in PXE, it is not surprising that calcifications were observed more frequently in mammograms of patients with PXE. James et al⁹ first observed the following findings in patients with PXE: intramural calcification of arteries and veins of the upper and lower extremity; arteriographic evidence of occlusion of either radial or ulnar arteries with extensive collateral circulation; atherosclerotic occlusion of the femoral arteries in young patients; and ischemic resorption of the terminal phalangeal tufts.

Soft-tissue findings that have been reported in PXE include tumoral calcinosis,¹⁰ ligamentous calcification (possibly nonspecific),¹¹ and skin microcalcifications seen on mammography.^{8,11} Prick and Thijssen¹¹ examined the skin of the axillae, groin, and both upper and lower extremities using xeroradiography and mammography techniques, and were unable to detect calcium deposits. However, they did note axillary cutaneous microcalcification in one patient's mammograms. In addition, one patient with PXE has been shown to have arterial calcification within the breast on mammography.⁷

Isolated mammographic microcalcifications in the skin have been described in osteoma cutis, Albright's hereditary osteodystrophy, and chronic folliculitis,¹² and are noted in patients with renal failure, and a variety of metabolic and endocrine disorders such as hyperparathyroidism, milk-alkali syndrome, and hypervitaminosis D. These can occur after operation and are commonly associated with sebaceous glands, either as grouped, diffuse, or isolated calcifications.¹³ Metallic skin deposits from deodorants, tattoos, and skin creams can mimic intracutaneous microcalcifications.¹⁴ Other causes of extramammary calcification include pectoral muscle microcalcification, possibly as a result of old trichinosis, and dermatomyositis.¹⁵ Skin calcifications may be confirmed with tangential mammographic images, the use of a skin marker, or both.¹²

Arterial changes in PXE include not only calcification of the media and internal elastic lamina but also thickening of the intima and media secondary to segmental fibroplasia, development of atheromatous plaques, and subsequent occlusion of the vas-

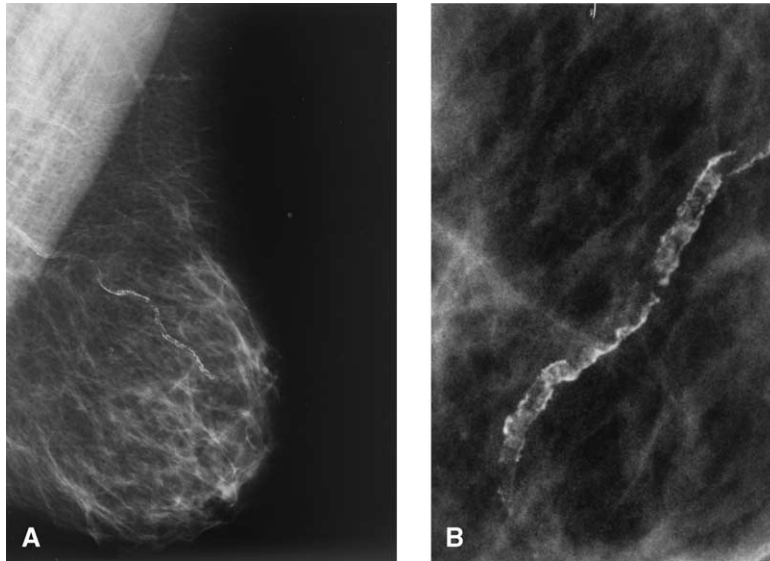


Fig 4. **A**, Arterial calcification in breast. **B**, Magnified view of breast arterial calcification.

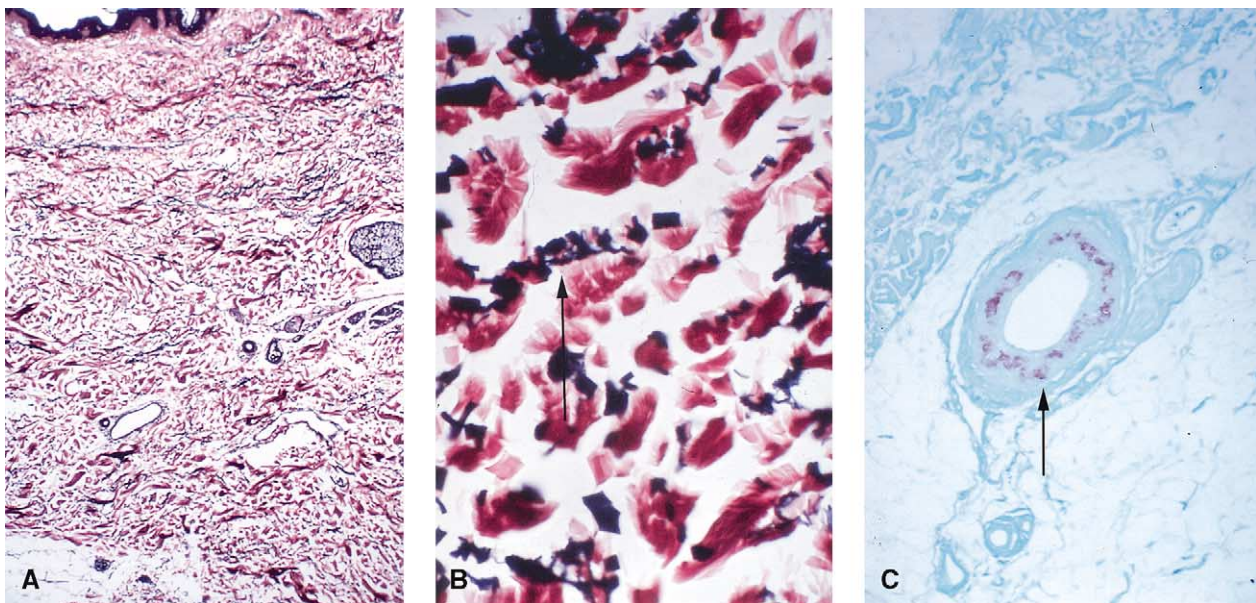


Fig 5. Biopsy specimen of breast skin showing **A** and **B**, calcified clumped elastic fibers in reticular dermis (*arrow*, **B**) (von Kossa's stain; original magnification $\times 40$ [**A**] and $\times 100$ [**B**]); **C**, calcification (*arrow*) and fragmentation of internal elastic lamina of subcutaneous artery (alizerin red stain; original magnification $\times 100$).

cular lumen.¹⁶ These findings have been described primarily in the medium-sized arterial branches of the aorta. Because the breast is supplied by the internal mammary artery, thoracic branches of the axillary artery, and the intercostal arteries,¹⁷ one would expect to find vascular pathology in the breast as well.

Radiographic demonstration of arterial calcification on mammography has been extensively stud-

ied. The radiographic appearance of arterial medial wall calcification on mammography is that of 2 parallel calcific lines with linear amorphous calcification in between,^{18,19} or a calcific ring when viewed head on.¹⁸ In contrast, calcification of the intima, as seen in atherosclerosis, tends to produce relatively large and discontinuous calcific deposits.²⁰

Arterial calcification in the breast has been reported in the setting of diabetes mellitus.²¹ A large-

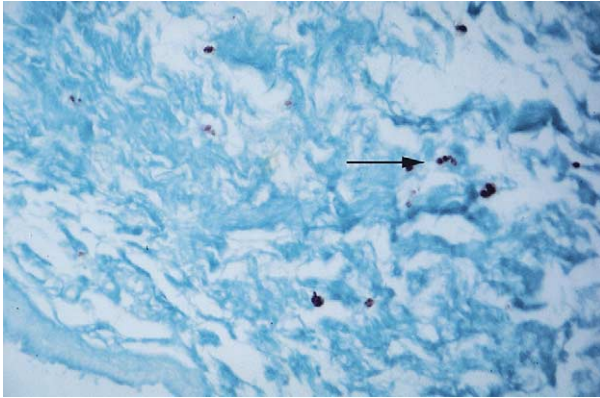


Fig 6. Biopsy specimen of deep fascial tissue adjacent to breast parenchyma showing clumped elastic fibers that stain for calcium (*arrow*) (alizarin red stain; original magnification $\times 100$). Calcium stain highlights greater percentage of affected fibers than is apparent in routine light microscopic examination.

scale study showed that although its prevalence was almost 5 times higher among patients who are diabetic than those who are not, fewer than 10% of patients whose mammograms demonstrated arterial calcification were found to have diabetes, and the association was thought to be too weak to be of clinical use.²² In addition, none of the patients with PXE in this study were known to have diabetes. The presence of arterial calcification was thought to be more strongly correlated with advancing age.²²

Another study showed a significant correlation of breast arterial calcification with coronary artery disease in women under age 59 years, and that the positive predictive value of diabetes for coronary artery disease increased to 1.00 when breast arterial calcification was present.¹⁹ However, because most women younger than 59 years with coronary artery disease did not have breast arterial calcification, it was not thought to be a useful screening tool.

One of the most common causes of benign vascular calcification of the breast is medial calcific sclerosis (Mönckeberg's arteriosclerosis).²³ In very early cases confirmed by breast biopsy, the mammographic features of parallel linear and central amorphous ("pipestem") calcification are not seen, and the findings may be indistinguishable radiographically from microcalcifications as a result of ductal calcifications.²³ This correlates with the histopathologic finding of discrete focal and discontinuous calcific deposits within the media of the vessel wall. Because of the similar localization and discontinuous pattern of vascular calcification in early PXE, one might also expect to see breast microcalcifications rather than pipestem calcification in early vascular disease.

There has been one previous report of breast arterial calcification associated with PXE in the radiologic literature⁷ and reference is made to an additional case diagnosed on biopsy.¹ However, because benign vascular calcification of the breast is a common finding, the value of anecdotal reports is questionable and finding arterial calcification on mammography is not specific for PXE. The current study not only showed a statistically significant increase in the occurrence of breast arterial calcification in PXE, but also it occurred on the average nearly 10 years earlier among patients with PXE than in control patients. Those patients in both groups having arterial calcification were significantly older than those without it, supporting the finding in other studies^{21,22} that it correlates with advancing age. Because breast arterial calcification occurred in nearly 15% of the control sample, it lacks diagnostic sensitivity.

Thickening of the skin seen on mammography may have several causes.^{13,17} It may be generalized or localized. Generalized thickening may be a result of edema, an infiltrative process such as a leukemia or lymphoma, or inflammatory carcinoma. Localized thickening may be a result of postoperative scarring, postirradiation change, postinflammatory change, localized thrombophlebitis (Mondor's disease), infection, tumor, or a variety of skin lesions. However, in the absence of the above conditions, skin thickening localized to the axilla appears to be specific for PXE. The radiographic appearance of skin thickening in PXE is likely a result of a combination of redundant skin and prominent pseudoxanthomatous elastosis.

Breast microcalcification occurred in more than 50% of study patients with PXE. In most cases, the microcalcifications were scattered, and in a few patients, clustering occurred. No particular pattern of microcalcification was either diagnostic or suggestive of PXE, although only in the PXE sample was the combination of breast microcalcification and vascular calcification observed.

The causes of breast microcalcification in PXE have not been systematically studied. Presumably, some of the calcifications observed in this study are associated with benign fibrocystic disease, probably unrelated to PXE, and represent intraductal calcification or milk of calcium in microcysts.¹⁸ However, in at least 1 case, microscopic calcification was localized to degenerated elastic fibers of the deep, soft tissue and interlobular fat septae.

Elastic tissue is present in small quantities around ducts and within vessel walls in normal breast tissue,²⁴ and in increased amounts around ducts in benign proliferative breast disease, and around

Table III. Radiologic-pathologic correlation

Mammographic finding	Histopathologic correlates
Arterial calcification	Calcification of fragmented internal elastic or of dystrophic elastic fibers in media of medium-sized arteries in breast
Breast microcalcification	Calcification of elastic fibers in reticular dermis, deep fascia, interlobular septae Early, discontinuous calcification of arterial walls Ductal calcifications of fibrocystic disease
Skin thickening	Carcinoma Redundant, lax axillary skin with calcified dystrophic elastic fibers in reticular dermis
Skin calcification	Calcified dystrophic elastic fibers in reticular dermis Calcified internal elastic lamina in subcutaneous arteries

the invasive portion of intraductal carcinoma.²⁵⁻²⁷ It is believed that the elastin is secreted by myofibroblasts, possibly under the influence of epithelial cells.²⁶ The periductal connective tissue of the breast has been likened to papillary dermis whereas the interlobular stroma is said to resemble reticular dermis (where the diagnostic dermal elastin calcification occurs in PXE).²⁸ It can be postulated that some of the breast microcalcification seen in PXE may be the result of calcified stromal elastin fibers, although this hypothesis could not be confirmed on any of the biopsy material available to us for study.

In one case, the calcifications were indeed typical for PXE, affecting not only the dermis and subcutaneous arteries, but also the deep, soft tissue overlying and subjacent to breast parenchyma, a finding hitherto not described in this disorder. Although the findings were very subtle on hematoxylin and eosin-stained material, special stains for calcium showed the findings to be widespread, although it is not known if these are above the resolution of mammography. In the remaining cases, the calcifications and other histopathologic findings were typical of fibrocystic disease, but tissue blocks were not available for special stains, and the biopsy specimens contained no skin. A prospective study of a larger sample of breast pathology in women with PXE would be helpful in understanding the basis of mammography findings in PXE.

One factor that might have influenced the results is selection bias. Women whose films were in the study were required to meet 2 conditions: having confirmed PXE and having had a mammogram. It is certainly possible that women who knew of mammographic abnormalities might be more likely to volunteer for such a study. Indeed, 13 of the 51 patients with PXE reported having had a breast biopsy (almost all benign), a large fraction of a group with a condition not known to be associated with

breast disease, although not surprising considering the more than 50% incidence of breast microcalcifications in the PXE sample. However, the majority of the women in the study seemed to be unaware of the results of their mammograms (other than the fact that the studies showed no findings suspicious for malignancy), and the reasons for ordering mammograms were similar in both PXE and control groups. It is unlikely that selection bias could have accounted fully for the striking differences in breast microcalcification, vascular calcification, skin thickening, and axillary skin microcalcification. In fact, in all cases, the latter 2 findings were not noted by the radiologist who initially interpreted the mammograms, so it would have been impossible for the study patients with PXE to have been aware of this finding.

It appears that PXE is associated with a significantly increased incidence of breast microcalcifications, vascular calcification, axillary skin thickening, and microcalcifications, and that although no particular mammographic finding is diagnostic of PXE, the finding of axillary skin abnormalities or any 3 of the above findings on mammography might suggest PXE in a differential diagnosis. It is hoped that further study of breast biopsy material might shed light on the mammographic findings reported in this study.

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