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Differences in Microcalcification in Breast Tumors

Carl Michael Büsing[1], Ulrich Keppler[2], and Volker Menges[3]

[1] Institute of Pathology, Klinikum Mannheim (Director: Prof. U. Bleyl, MD), Mannheim, Federal Republic of Germany
[2] Laboratory for Materials Research, D-7036 Schönaich, Federal Republic of Germany
[3] Central Institute for Radiology, Theresien-Krankenhaus
(Direktor: Priv.-Doz. Dr. V. Menges), Mannheim, Federal Republic of Germany

Summary. Microcalcifications in benign and malignant tumors can be analyzed by X-ray diffraction and electron microprobe analysis in human specimen. Our systematic investigations revealed calcium hydroxyapatite in cases of invasive carcinoma but calcium oxalate (weddelite) in proliferating but non-invasive diseases. The differences in calcification depending on the underlying disease may indicate basic differences in cell metabolism.

Key words: Microcalcification – Mastopathy – Breast cancer – X-ray diffraction

Introduction

Calcification in benign and malignant breast tumors has been known to occur for a long time (Hamperl 1969). Different calcification patterns are found by X ray and in some cases, have great significance for the diagnosis of malignant tumors of the breast (Menges et al. 1973). Although their diagnostic value is of great importance, the genesis of these calcifications is not clear and in particular, the question as to whether it is a sign of degeneration or of an active cell processes is still open.

In light microscopy, there are also differences to be found in the distribution pattern and the appearance or the relationship of the calculi to surrounding cells and tissue. Previous investigations have shown that there seem to be differences in the chemical composition and crystallographic lattice of these calcifications (Hassler 1969; Ahmed 1975; Barth et al. 1977; Keppler et al. 1979), but there has been as yet no systematic investigation (Gros 1981). We have examined whether there is some relationship between the histological appearance of the tumor (malignant or benign) and the chemical nature or the deposit.

Offprint requests to: Priv.-Doz. Dr. C.M. Büsing, Pathologisches Institut, Klinikum der Stadt Mannheim, Theodor-Kutzer-Ufer, D-6800 Mannheim 1, Federal Republic of Germany

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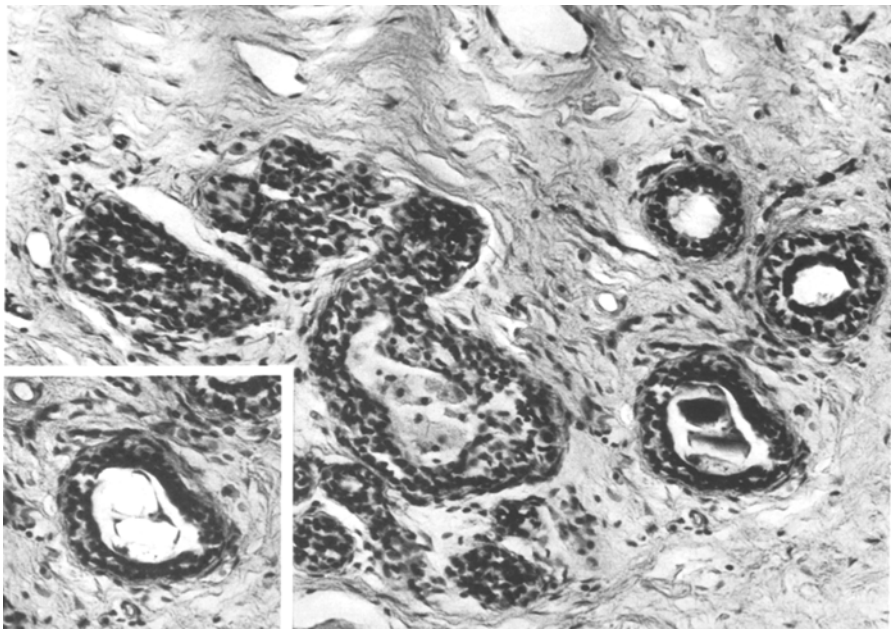

Fig. 1. Oxalate crystal in lobular neoplasia (lobular carcinoma in situ); 52 year old woman. Inset: photography with polarized light. Formalin, Paraffin, hematoxylin-eosin, magn. ca. 1:

Table 1. Results of X-ray diffraction analysis and microprobe investigations of calcifications in different breast tumors

Age	Histological diagnosis	Type of calcification
67	invasive ductal carcinoma	apatite + amorphous
39	invasive ductal carcinoma	apatite + amorphous
59	invasive ductal carcinoma	apatite + amorphous
40	invasive ductal carcinoma	apatite + amorphous
40	invasive ductal carcinoma	apatite + amorphous
41	proliferating mastopathy	oxalate
43	proliferating mastopathy	oxalate
52	right: proliferating mastopathy	oxalate
52	left: carcinoma lobulare in situ	oxalate
44	invasive ductal carcinoma	amorphous
51	proliferating mastopathy	amorphous

Materials and Methods

Our investigations have been performed on breast tumors with extensive microcalcification (Fig. 1). After embedding in paraffin and histological investigation, we performed specimen radiography in two directions on the paraffin blocks, using the remaining tissue for the demonstration and localization of the remaining calcifications, which were dissected with fine pins and knives under a stereomicroscope.

On these tiny specimens crystallographic analysis by X-ray diffraction was performed. The diffraction pattern was recorded by a film technique. In cases with amorphous material without refraction, chemical analysis by electron microprobe was performed. Crystallographic and microprobe results were then compared with the light microscopic appearance of calcification in the related histological slide and with the histocalcification of the tumor.

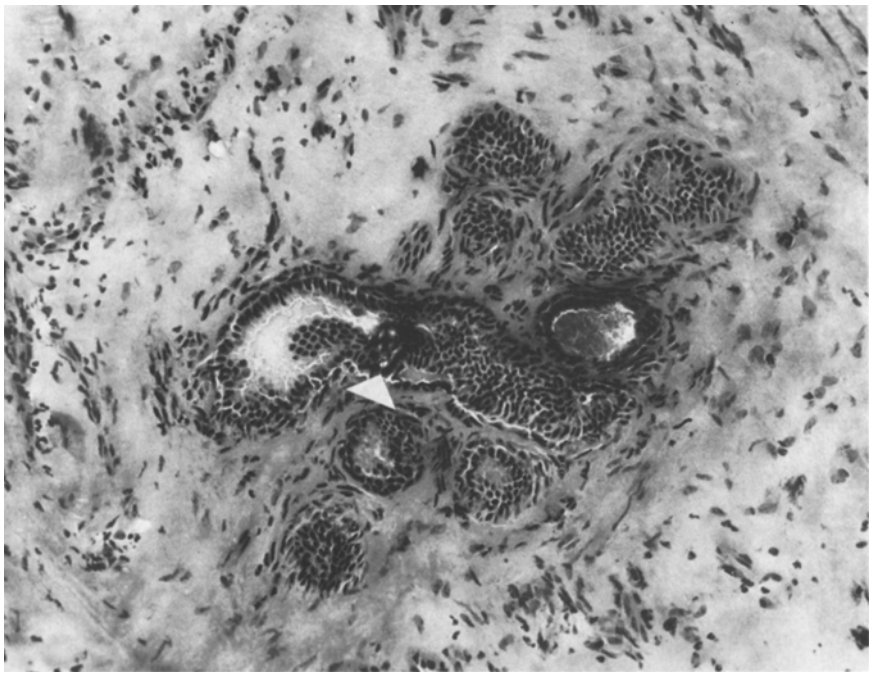

Fig. 2. Oxalate crystal in proliferating mastopathy; 43 year old woman. Quick frozen section, hematoxylin-eosin, polarized light, magn. ca. 1:

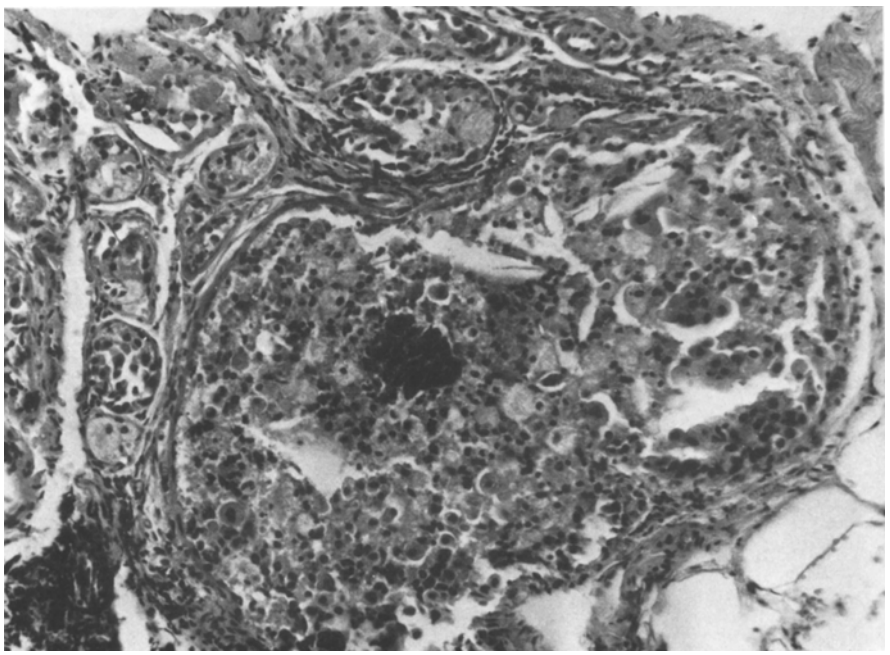

Fig. 3. Amorphous calcium deposits in cellular debris of an invasive ductal carcinoma; 59 year old woman. Formalin, paraffin, hematoxylin-eosin, magn. ca. 1:

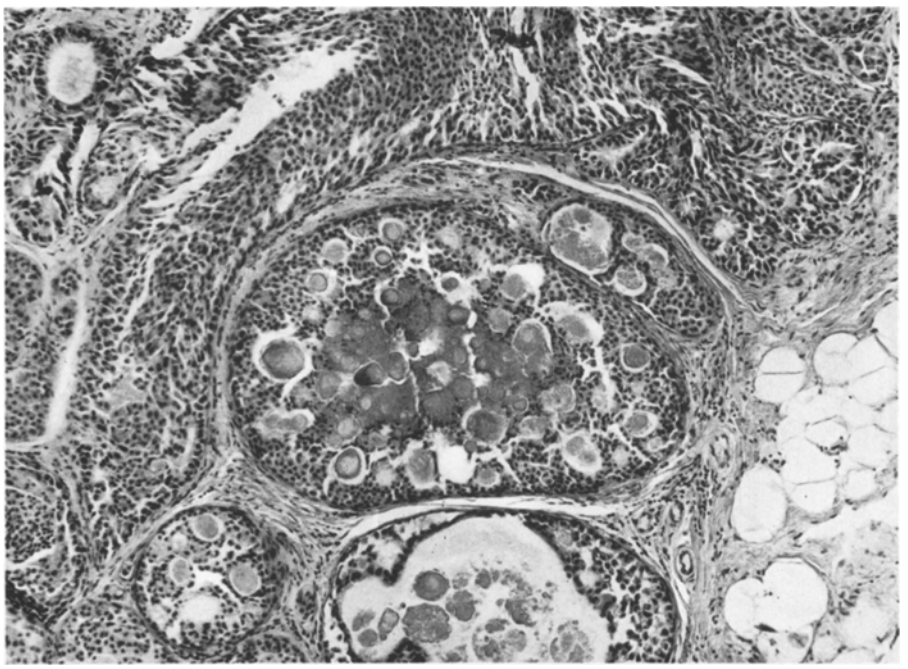

Fig. 4. Amorphous calcium deposits in thickened glandular secretions in an invasive ductal carcinoma of a 40 year old woman. Formalin, paraffin, hematoxylin-eosin. magn. ca. 1:

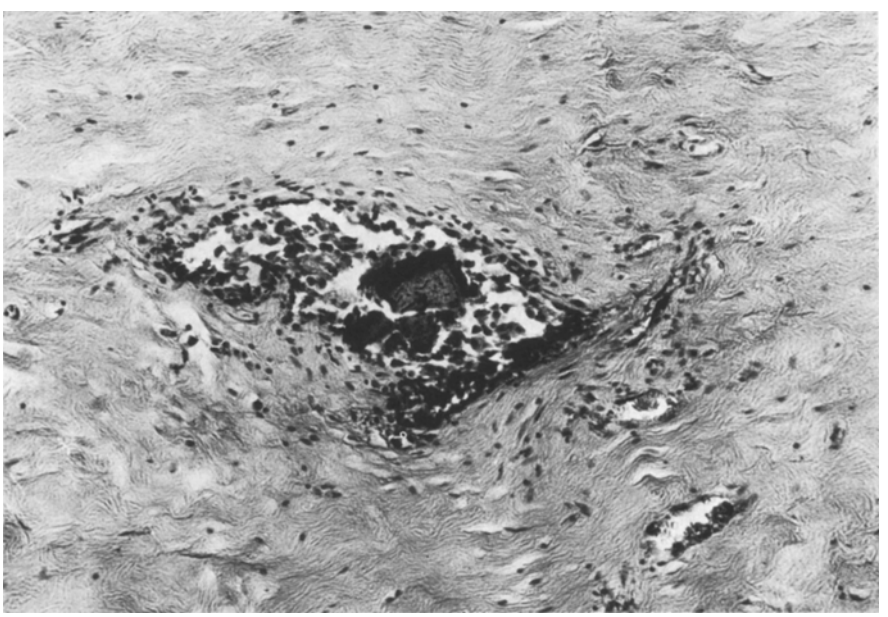

Fig. 5. Calcium apatite deposit, weakly laminated-like psammoma body in a case of invasive ductal carcinoma; 67 year old women. Formalin, paraffin, hematoxylin-eosin, magn. ca. 1:

Results

We investigated the calcification in 11 specimens (Table 1). In four cases, X-ray diffraction analysis revealed calcium oxalate in the crystalline form of weddelite. In the histological slide, these deposits appeared as poorly stained well-limited bodies which showed a marked double refraction in polarized light (Fig. 1) which can also be observed in quick frozen sections (Fig. 2). The histological diagnosis in cases with these calcium oxalate bodies had been a non-invasive carcinoma lobulare in situ in one case and proliferating mastopathy with more or less severe epithelial atypia in three others. The two last specimens were from the same patient.

In two cases, only amorphous material was found. The histological classification of these cases was invasive ductal carcinoma. In electron microprobe analysis, these calcifications revealed mainly calcium phosphate. Under the light microscope, these often seemed to be the result of degenerative impregnation of cellular debris (Fig. 3) or of thickened glandular secretion (Fig. 4).

In five cases, apart from amorphous clacium deposits the X-ray investigation revealed calcium phosphate in the form of calcium hydroxyapatite, a well studied material. In the histological slides, these calcifications have the appearance of irregular clumps, often closely interlocked with the surrounding cells (Fig. 5).

Discussion

The analysis of microcalcification in breast tumors demonstrated both amorphous and crystalline deposits. Although there is controversy over the genesis of calcification, we consider that amorphous deposits conform very well with the interpretation that they are of a secondary dystrophic or degenerative nature (Brandt et al. 1969, 1972). We did not find a relationship to vessels such as Johannessen et al. (1980) described around calcifications in thyroid tumors. Calcium apatite might also be of degenerative, or dystrophic nature, since it seems possible that at the beginning of the crystalline deposition there may be a gel phase.

The crystalline calcifications in the form of oxalate, are probably the product of an active cellular process according to the investigations of Stegner et al. (1972). Furthermore, in our investigations there seems to be a direct connection between the cancer risk of the tumor and this kind of crystalline calcification. Oxalate in the form of weddelite was only found in proliferating but not in invasive diseases of the breast. However, apatite crystals were only found in invasive malignant breast tumors. The number of cases in our series is too small for statistical appraisal, so we have made a compilation of the occasional investigations in the literature concerning this subject (Table 2). Besides our six cases, Barth and coworkers (1977) have investigated a case of proliferative mastopathy and found oxalate. Hassler (1969) has reported on three invasive carcinomas in which calcium apatite was found. Keppler and Nitsche (1979) have investigated two further cases of invasive carcinomas and also found apatite. Ahmed (1975) found calcium apatite in his cases of infiltrative carcinoma without specifying the number of tumors investigated in his study. In the contin-

Table 2. Compilation of our own investigated cases of breast tumors with crystalline calcium deposits and the cases found in the literature

Author	Disease of the breast	Number of cases with apatite	Number of cases with oxalate
Own material	proliferating disease		4
	invasive tumor	5	
Barth	proliferating disease		1
Hassler	invasive tumor	3	
Ahmed	invasive tumor	1	
Keppler	invasive tumor	2	
Total		11	5

Table 3. Two-by-two table of all the cases shown in Table 2. Strong correlation between the results of X-ray analysis and the nature of the tumor

	Apatite	Oxalate
Proliferating disease	0	5
Invasive tumor	11	0

$P=0.001$

gency table (Table 3), there is a high significance ($P=0.001$). Oxalate calcifications are correlated with proliferating but noninvasive diseases of the breast, e.g. proliferative mastopathy or lobular carcinoma in situ, but calcium phosphate in the crystalline form of apatite is correlated to invasive malignant tumors, e.g. undifferentiated ductal carcinoma in our cases.

This raises an interesting point: if there is no exception to this rule, we can conclude that either the definitive carcinoma has destroyed the formerly proliferating epithelial cells and the oxalate crystals presumably present, or that the invasive carcinoma does not develop at the site of the proliferating cells. The term "precancerous epithelial atypia" would thus subject to discussion.

In our investigations, one point is unsatisfactory: the cells and the calcium-bearing granules in the histologically investigated slides and in the remaining tissue for X-ray refraction analysis were very close together but are not identical. Thus our comparison of the histological appearance and chemical analysis can only be statistical. In the future, we should look for methods which avoid this disavantage.

We may also consider the diagnostic and prognostic significance of histologically demonstrated microcalcifications. Oxalate deposits demonstrate double-refraction in polarized light well, even in quick frozen sections, but further cases have to be investigated to decide on whether this will be an additional diagnostic criterion in distinguishing benign and malignant breast diseases.

Finally, we suggest that there is a difference in cell metabolism between proliferative diseases and malignant invasive diseases of the breast which also involves the formation of calcium salts. From our results, this appears to be a very constant difference.

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