

## **Lobular Endocrine Neoplasia in a Fibroadenoma of the Breast**

### **An Ultrastructural Study**

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**Summary.** The authors report a case of lobular endocrine neoplasia within fibroadenoma of the breast. The main pathological differences to similar cases previously described are discussed.

The histochemical and ultrastructural findings suggest that, in our case, the neoplasia may be a variant of lobular carcinoma in situ.

**Key words:** Breast – Fibroadenoma – Lobular carcinoma in situ – Lobular endocrine neoplasia – Dense-core granules

### **Introduction**

Fibroadenoma of the breast is rarely associated with a lobular carcinoma (Azzopardi 1979). Recently Eusebi and Azzopardi (1980) have described a new pathological entity associated with fibroadenoma which has been defined as “lobular endocrine neoplasia”.

Herein we report the light and electron microscopic study of a similar lesion which expands the spectrum of both morphological and clinical knowledge.

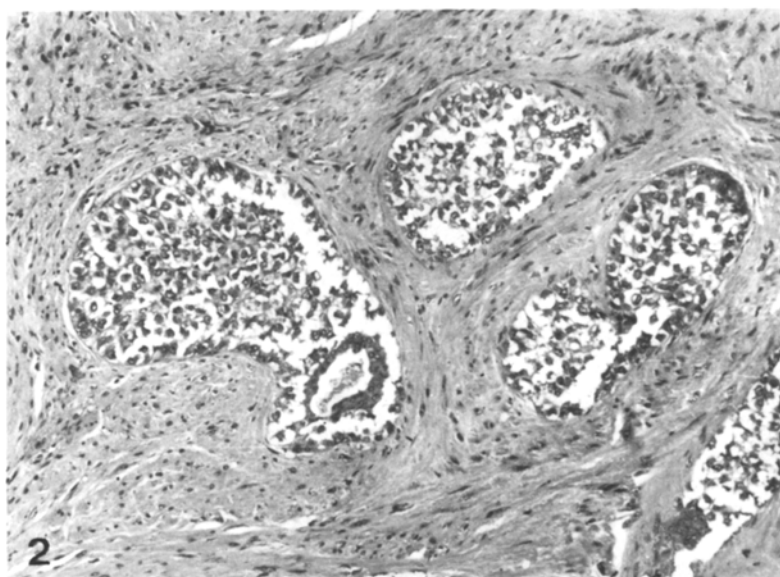
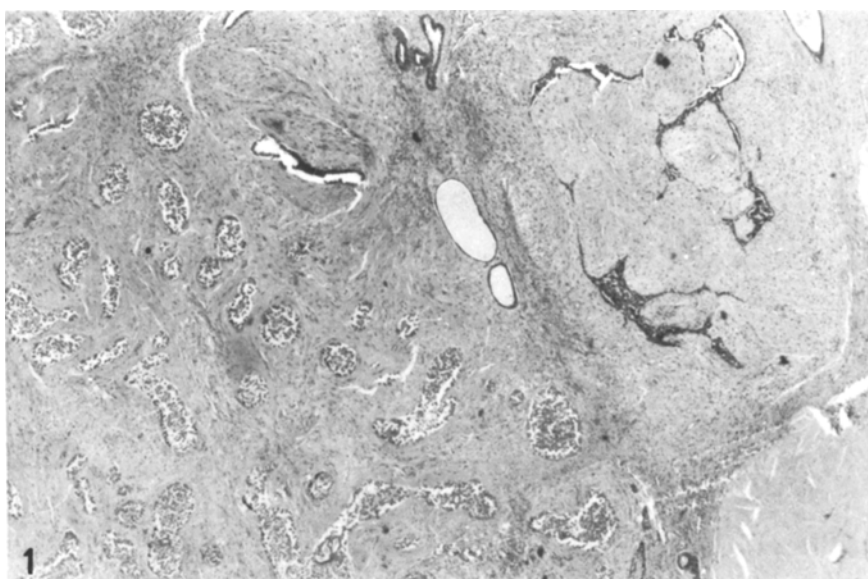
### **Case Report**

A 40 year-old female was admitted to the Policlinico S. Orsola, Bologna University, in May 1980.

The patient showed a nodule of the right breast in the same site as a previous biopsy for fibrocystic disease. Mammography revealed a benign lesion, while an aspiration biopsy was doubtful for carcinoma. The nodule was excised and dissection of enlarged axillary lymph nodes was performed. Macroscopically, the breast-mass was irregularly ovoidal and measured  $2.5 \times 2 \times 2.5$ . A histological diagnosis of lobular endocrine neoplasia in fibroadenoma was made. The axillary lymph nodes were negative for tumor. The patient is alive and well after 11 months.

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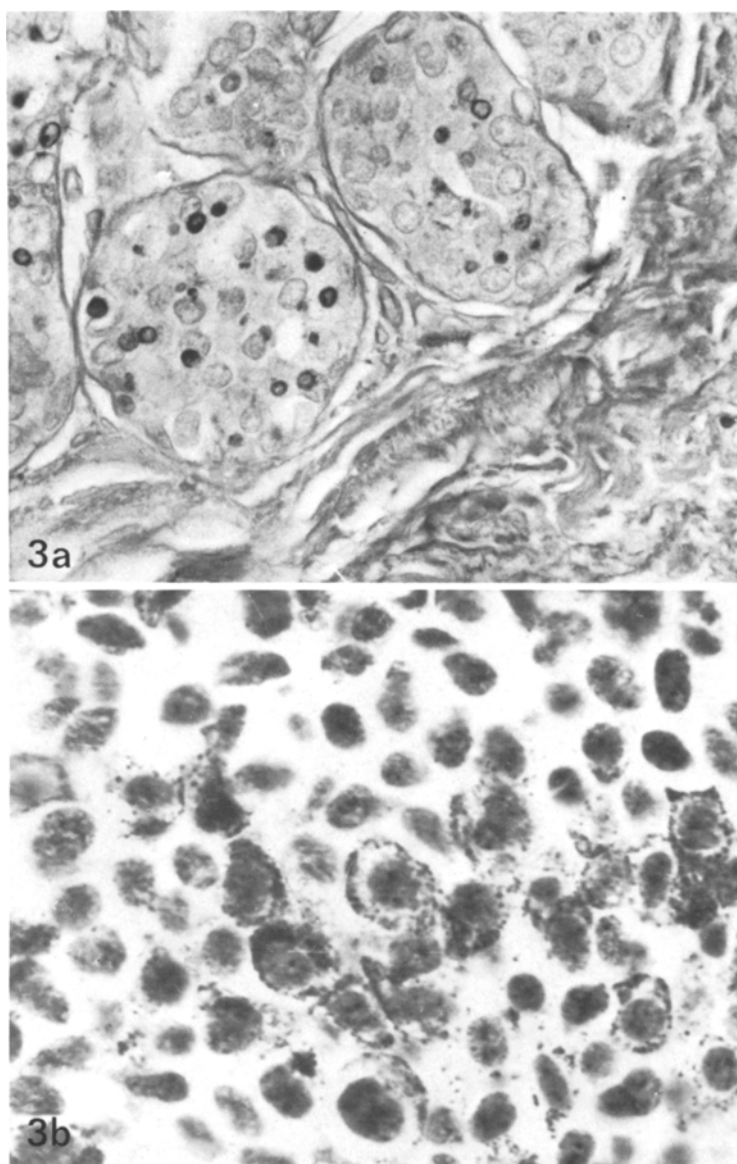
**Fig. 1.** Marked dilatation of the ductules by tumor cells in a fibroadenoma variant. H.E.,  $\times 26.4$

**Fig. 2.** Prevalently solid pattern of proliferation. There is lack of cellular cohesion. H.E.  $\times 105.6$

### Materials and Methods

Sections of formalin fixed paraffin embedded breast tissue were stained according to the following methods: H.E.; Weigert-Van Gieson; Congo redstain; periodic acid-Schiff with and without diastase pretreatment; Alcian blue/PAS; Grimelius, Bodian and Masson-Fontana.

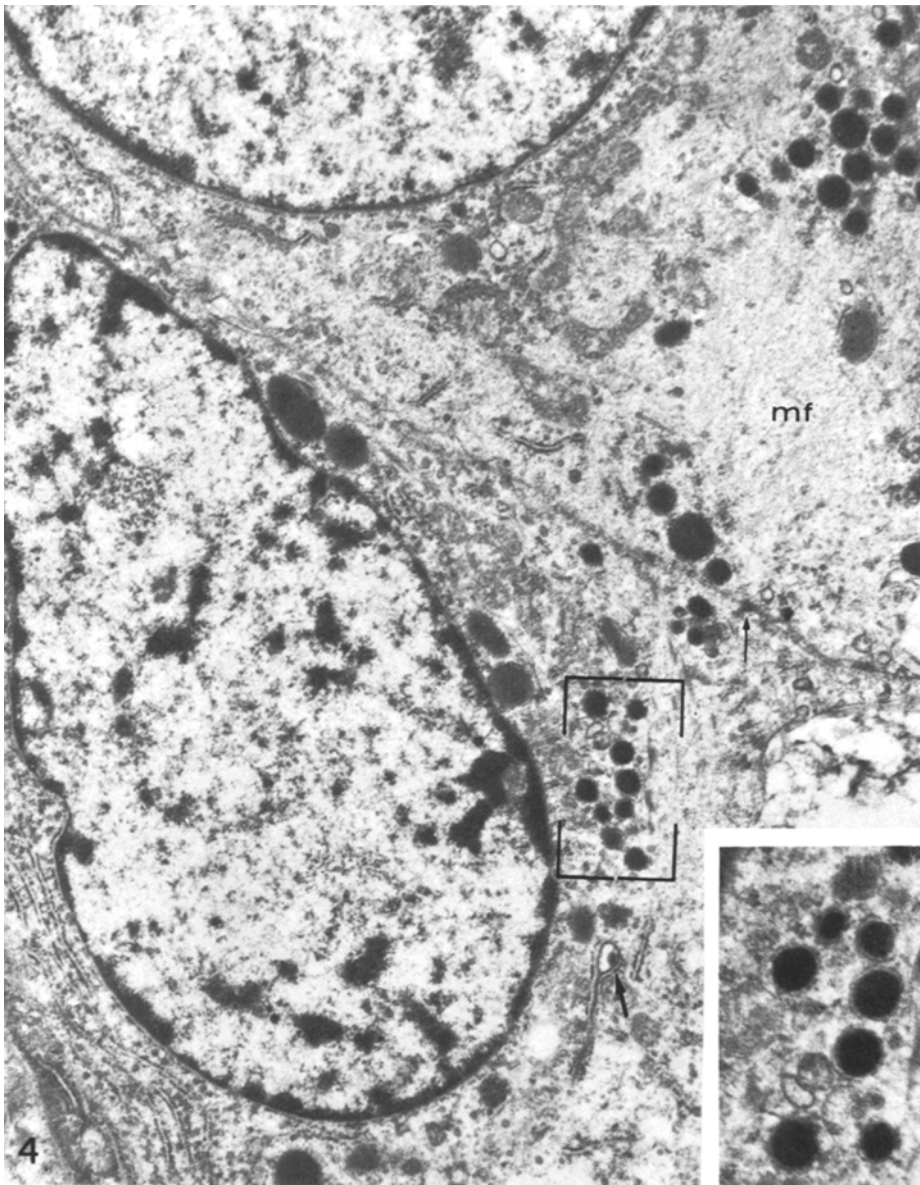
For electron microscopy, some formalin-fixed blocks were postfixes in 1% osmium tetroxide and embedded in epoxy resin (Araldite). Ultrathin sections were stained with uranyl acetate-lead citrate.



**Fig. 3. a** Intracytoplasmic alcianophilic vacuoles. Alcian blue PAS.  $\times 264$ . **b** Argyrophilia of tumoral cells. Bodian silver impregnation.  $\times 1,056$

#### *Light Microscopy*

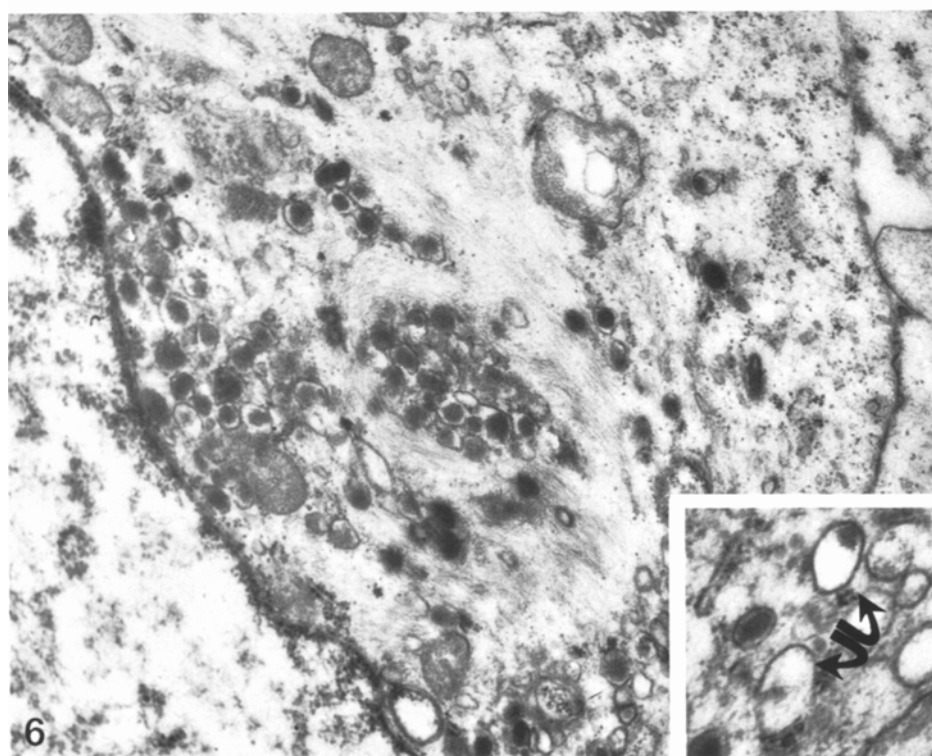
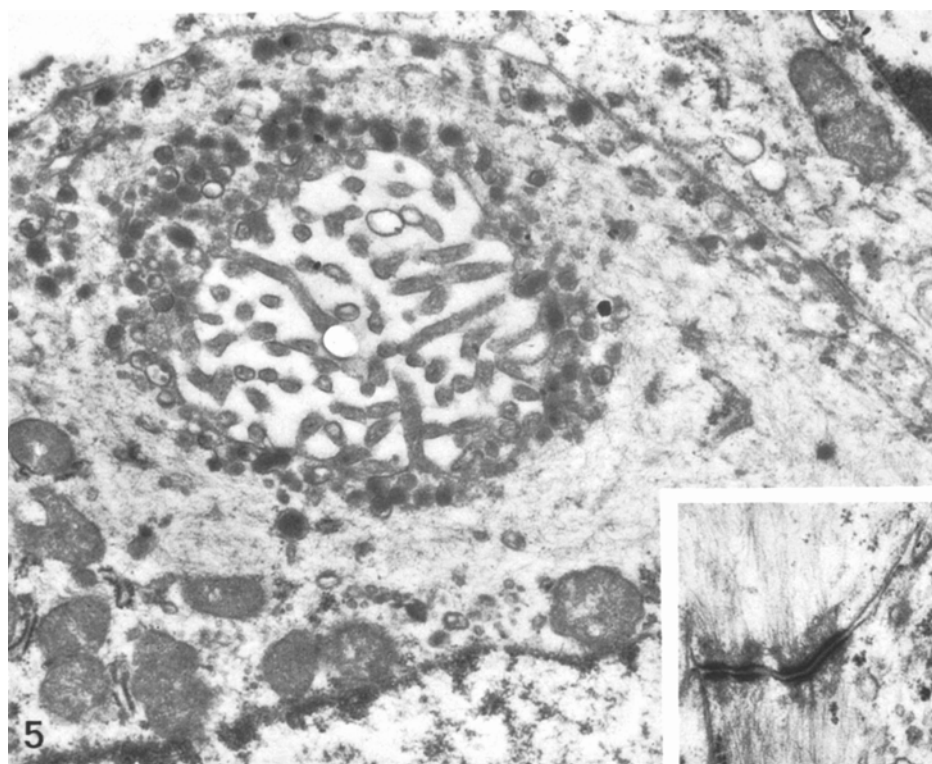
The examination of the breast sections stained with H.E. reveals a “fibroadenoma variant” (Azzopardi 1979). In some areas the ductular structures are filled and obliterated by enlarged polygonal tumor cells (Fig. 1). These cells are often not cohesive (Fig. 2) and sometimes circumscribe a lumen lined by a darker epithelium, so giving a pagetoid appearance. Cytologically, they are large and polymorphic. The cytoplasm is eosinophilic, granular and rarely clear or vacuolated. The nuclei are round and show delicate chromatin and small nucleoli. The mitotic figures are

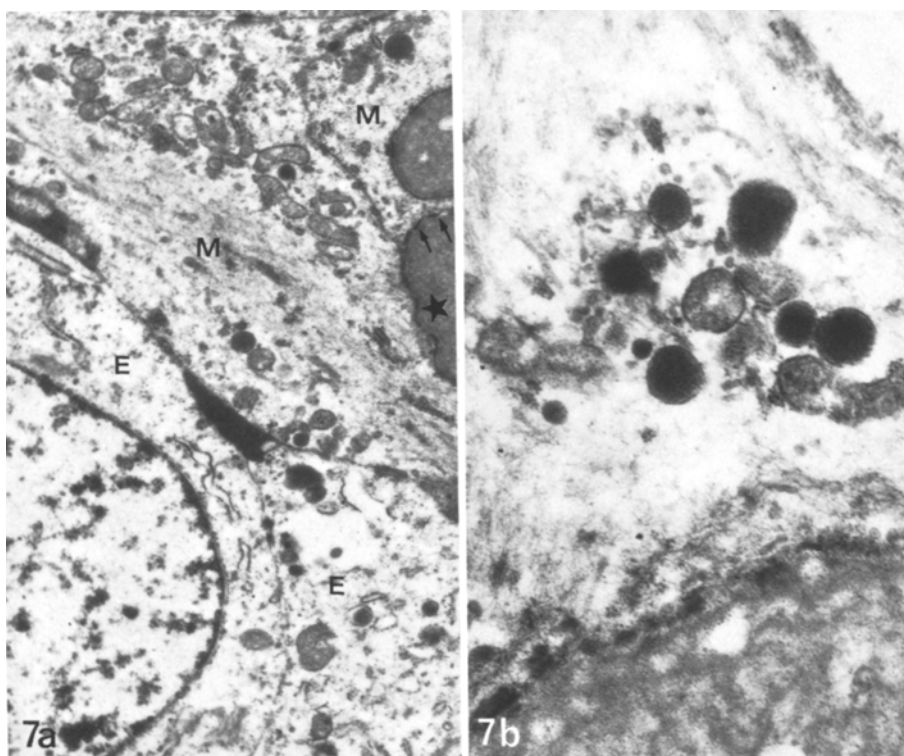


**Fig. 4.** Two epithelial-type cells showing round-oval electron dense secretory granules and rare secretory vesicles of mucinous type (*thick arrow*). The cell sap contains microfilaments sometimes arranged in swirls (*mf*). The adjacent cells are joined by desmosomes (*thin arrow*) ( $\times 16,800$ ). Inset: enlargement of rectangle in Fig. 4. The secretory granules consist of a central electron dense core with a narrow clear halo between the core and the distinct limiting membrane ( $\times 33,000$ )

**Fig. 5.** Epithelial-type tumor cell with dense core granules arranged around an intracytoplasmic lumen lined by microvilli ( $\times 25,333$ ). Inset: microfilaments on well developed desmosomes joining adjacent cells ( $\times 24,500$ )

**Fig. 6.** Dense core secretory granules are trapped, together with mucinous-like vesicles and membranous profiles in a whorl of microfilaments ( $\times 20,769$ ). Inset: secretory mucinous-like vacuoles show an electron lucent matrix containing eccentrically located electron dense spherules (*arrows*) ( $\times 53,333$ )





**Fig. 7.** **a** Neoplastic ductular structure peripherally displaying myoepithelial-type cells (*M*) showing hemidesmosomes (*arrows*) and resting on a well-developed basal lamina (*asterisk*). The myoepithelial-type cells are joined with desmosomes to epithelial-type cells (*E*) containing rare dense core granules ( $\times 13,230$ ). **b** Cluster of dense core granules in a myoepithelial-type cell ( $\times 28,140$ )

rare. Characteristically, in some areas hyaline bodies are present among the tumor cells. These structures are Alcian blue/PAS positive and PAS diastase-resistant. The Congo red and Weigert-Van Gieson stains are negative. Intracytoplasmic alcianophilic vacuoles are also observed in a few cell-clumps (Fig. 3a). Argentaffin reactions are negative, while the Bodian silver impregnation method is positive (Fig. 3b).

In ductular structures filled by tumor cells myoepithelial elements are detected.

#### *Electron Microscopy*

Low-power views show dilated ductular structures filled with cells having either epithelial (secretory) or myoepithelial appearance.

The elements of the epithelial-type (secretory type) are round-polygonal with abundant cytoplasm (Fig. 4). The nuclei contain small nucleoli and have marginated chromatin. The rough endoplasmic reticulum (RER) is well represented and the mitochondria are irregularly distributed through the cytoplasm. The hyaloplasm contains numerous microfilament-laden zones; the microfilaments are arranged in parallel bundles or in swirls (Fig. 4). Some cells reveal intracytoplasmic lumina containing microvillous projections (Fig. 5). Scattered membrane-bounded vacuoles showing an electron lucent or a finely granular/cloudy matrix with eccentrically electron dense particles are observed in some cells (Fig. 6, inset). The adjacent elements are joined by desmosomes. Occasionally, filaments are inserted in well-defined desmosomes (Fig. 5 inset). Furthermore, granules consisting of a central electron dense core, a pale halo and a single delimiting membrane (secretory granules) are observed in 20–30% of the epithelial-type cells (Fig. 4, inset). These granules range from 200 to 330 nm

in diameter (mean diameter: 207.9 nm) and are mostly round in shape. Sometimes they are arranged around the intracytoplasmic lumena (Fig. 5) or are trapped in bays of microfilaments (Fig 6) together with membranous profiles.

The myoepithelial-type cells are located at the periphery of the dilated ductules (Fig. 7a). They show a round to oval nucleus with an indented profile. The cytoplasm contains scattered cisternae of RER, mitochondria, rare lysosomes and sometimes few secretory granules like those found in the epithelial-type cells (Fig. 7a–b). Pinocytotic vesicles are numerous near the basal portion of the cells. The hyaloplasm is filled with microfilaments forming parallel bundles sometimes featuring dense zones. On the basal side the myoepithelial-type cells form club-like projections protruding into the surrounding stroma and containing microfilaments that converge toward the hemidesmosomes capping the cytoplasmic processes. The myoepithelial-type cells are covered by a tortuous basal lamina, often reduplicated and showing focal thickening opposite the hemidesmosomes.

## Discussion

Primary endocrine neoplasms of the breast are rare. Up to data, only a few cases have been described (Feyrter and Hartmann 1963; Cubilla and Woodruff 1977; Kaneko et al. 1978; Fisher et al. 1979; Capella et al. 1980; Gould and Chejfec 1980).

Recently four examples of lobular endocrine neoplasia within fibroadenoma of the breast have been reported (Eusebi and Azzopardi 1980). Microscopically they showed analogy with the carcinoids type A (solid) and C (tubular), according to the Soga and Tazawa classification (1971). At ultrastructural examination, three of these cases demonstrated granules with a dense core separated by a pale halo from a limiting membrane. Moreover, one of them (case 4) showing alcianophilic vacuoles and casein in rare tumor cells, represented a hybrid tumor with both endocrine and exocrine differentiation. The authors think that “the endocrine elements arise from the same stem cells which give rise to the epithelial and myoepithelial cells in a fibroadenoma”.

Our case, with similar light microscopic appearance, positive argyrophilic reaction and electron microscopic demonstration of secretory granules, showed structural resemblance to the tumors described by Eusebi and Azzopardi, and especially to the hybrid one. However there were some peculiar features which expanded the spectrum of the previous observations.

Clinically, the age of the patient was higher than in three of the cases reported by Eusebi and Azzopardi and corresponded to the peak-incidence of lobular carcinoma in situ in fibroadenoma (40–45 years: Goldman and Friedman 1969). Histologically, the lobular endocrine proliferation was associated with a fibroadenoma “variant” (Azzopardi 1979). At electron microscopic examination, two types of cells, epithelial and myoepithelial-type, were observed. The former often contained either secretory granules or intracytoplasmic lumena lined by microvilli, and filaments inserted on well-defined desmosomes. Only a few cells showed both endocrine and exocrine secretory products (amphicrine cells). The myoepithelial-type cells were present at the periphery of the neoplastic ductules and sometimes also contained secretory granules. These findings, except for the observation of secretory granules in both epithelial and myoepithelial-type cells, fitted those described as typical of lobular carcinoma in situ (Fisher 1976; Ozzello 1979) and differed from the report of Eusebi and Azzopardi

because of the presence of amphicrine and myoepithelial-type cells and in some submicroscopic characteristics of the secretory-type cells, such as intracytoplasmic lumina, microfilaments and desmosomes. Another unusual finding, never seen before in lobular neoplasia of any sort, was the "hyaline"-like material within the solid and pagetoid clumps. From its histochemical characteristics this material might be related to an over-production of intercellular matrix similar to the basal lamina.

From the ultrastructural and clinical findings we think that our case could be regarded as a special variant of LCIS showing evidence of endocrine differentiation. Nevertheless, in agreement with Eusebi and Azzopardi, it seems more suitable to define also this endocrine tumor with the non-committal term of "lobular endocrine neoplasia".

With regard to the histogenesis of endocrine tumors of the breast, we think that the simultaneous presence in our case of epithelial-type and myoepithelial-type cells with or without dense core granules and of amphicrine cells, strengthens the hypothesis that all these elements have a common origin from the same stem cell (Eusebi and Azzopardi 1980).

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