1353

CALIFORNIA
TUMOR TISSUE REGISTRY

"Tumors of the Breast"

118th Semi-annual cancer slide seminar

Case Histories

Speaker:

F. A. Tavassoli, M.D.
Yale University School of Medicine
Newhaven, Connecticut

June 5, 2005
Westin South Coast Plaza
Costa Mesa, California
8:30 a.m. – 4:30 p.m.

Case 1 - Acc 28814

Contributed by E. Holburt, M.D. Fallbrook, CA

Clinical History: A 55-year-old female was found to have a cluster of what appeared to be microcalcifications of the left breast on routine mammogram. She'd had an abnormal mammogram two years previously, revealing a 7 mm cyst in the right breast. A left breast biopsy was performed. The specimen consisted of three portions of breast tissue, with the largest one measuring 2.0 cm in diameter.

Case 2 - Acc 28758

Contributed by R. Sambhi, M.D. El Centro, CA

Clinical History: A 42-year-old female presented with a mass in the left breast. An excisional biopsy was performed.

Case 3 - Acc 29921

Contributed by U. Garg, M.D. Camarillo, CA

Clinical History: An 80-year-old female noted a mass in her left breast. An excisional biopsy was performed. The specimen consisted of an ovoid, nodular, indurated fragment of grayish-yellow tissue which measured 2.5 x 2.4 x 2.4 cm.

Case 4 - Acc 28093

Contributed by M. Janssen, M.D. Anaheim, CA

Clinical History: During the course of a routine physical examination, a mass was identified in the right breast of a 17-year-old female. The patient stated that she had been aware of the mass for years, but thought it was normal. The mass was excised and consisted of a 29.6 gram, 7.0 x 6.0 x 1.0 cm portion of fibroadipose tissue with a cut surface composed of numerous cysts ranging from 1 to 3 mm. The gross appearance was that of a sponge containing mucoid material

Case 5 - Acc 28949

Contributed by P. Robinson, M.D. Boynton Beach, FL

Clinical History: A 78-year-old female presented with a mass in the right breast. An excisional biopsy was performed consisting of a firm fragment of yellow to white tissue which measured 6.5 x 4.2 x 2.7 cm. Sectioning revealed a firm white area containing mucoid material.

Case 6 - Acc 29962

Contributed by K. Frankel, M.D. Glendale, CA

Clinical History: A 78-year-old female noted a mass in her breast which was excised. The cut surface of the 6.5 x 4.0 x 3.5 cm tissue fragment was vaguely nodular, and tan-pink. There was an area up to 3.0 cm in diameter which corresponded to the grossly noted nodule immediately beneath the skin.

Case 7 - Acc 19635

Contributed by A. Garib, M.D. Denton, TX

Clinical History: During routine physical examination of a 46-year-old female, an area of nodularity was palpated in the medial aspect of the right breast. Approximately one year later, the patient returned with complaints of nipple discharge. Re-examination of the breast revealed a significant increase in size of the nodule. A biopsy produced a 5.0 x 2.0 cm tissue fragment with multiple small foci of tan, soft, bulging, discrete nodules up to 1.0 cm in diameter.

Case 8 - Acc 24791

Contributed by J. Craig, M.D. Pasadena, CA

Clinical History: An 11-year-old female had bilateral breast lumps removed. The specimen consisted of two masses of gray-tan tissue. The smaller specimen, from the left breast, measured 18 x 17 x 11mm with a nodule of light tan tissue, 10 mm in diameter, seen to one side. The larger specimen, reportedly from the right breast, consisted of a 23 x 10 mm wedge of skin and underlying light tan tissue measuring 32 x 20 x 12 mm containing a 13 mm encapsulated mass.

Case 9 - Acc 29270

Contributed by J. Kollin, M.D. Lakewood, CA

Clinical History: A 32-year-old female sought treatment for a lump in her breast that she stated had been present for approximately ten years. Mammogram and ultrasound revealed a solid lesion approximately 3.0 cm in diameter. The 3.2 cm biopsy revealed a nodular encapsulated grayish-tan tissue fragment with streaks of white, fibrous and adipose tissue.

Case 10 - Acc 29229

Contributed by R. Terry, M.D. San Gabriel, CA

Clinical History: A 65-year-old female presented with a right breast mass of 3-4 month duration, accompanied by occasional pain. The patient had undergone a breast biopsy 27 years previously for a benign lesion. The excised mass consisted of a portion of fatty tissue measuring 6.1 x 5.2 x 3.2 cm. Sectioning showed a 2.3 cm poorly demarcated whitish-yellow region.

Case 11 - Acc 29548

Contributed by X. Wang, M.D. Pasadena, CA

Clinical History: A 49-year-old female presented with a palpable breast mass which had been present for approximately one year. FNA was performed, revealing dysplastic cells suspicious for malignancy. Chemotherapy was begun based on the high suspicion of metastatic disease. The patient received a modified mastectectomy with the specimen measuring 12.0 x 11.5 x 4.5 cm. The central deep portion of the breast parenchyma was involved by a somewhat well-defined tan, firm mass which measured 6.0 x 5.5 x 2.0 cm. The cut surface of the lesion was solid with a mucinous and fine granular texture.

Case 12 - Acc 28979

Contributed by X. Wang, M.D. Pasadena, CA

Clinical History: A simple mastectomy was performed on a 64-year-old female for a large left breast mass. A well-circumscribed, variegated red and tan, firm neoplasm measuring 16.5 x 13.0 x 6.5 cm involved the majority of the breast parenchyma. The neoplasm was focally hemorrhagic, and the cut surface was solid with a slightly gelatinous appearance.

Case 13 - Acc 30163

Contributed by K. Frankel, M.D. Glendale, CA

Clinical History: A 72-year-old female underwent an excisional biopsy for a mass in her right breast. A 3.0 x 3.0 x 2.5 cm, poorly-circumscribed, gray-tan mass which extended grossly close to the lower margin was present in the 8.0 x 6.0 x 3.0 cm excised specimen.

Case 14 - Acc 29456
Contributed by F. Ali, M.D. Ventura, CA
Clinical History: A 53-year-old female who apparently had breast implants for more than a decade without problems, presented five months ago with a cystic mass in her left breast. Exploration of the cyst cavity revealed serosanguineous fluid which was negative for bacterial organisms on Gram's stain and culture. There was firm white tissue in the wall of the cavity, extending to the subcutis. A biopsy was taken.

Case 15 - Acc 29133
Contributed by X. Wang, M.D. Pasadena, CA
Clinical History: An 89-year-old female noted a mass in her left breast. A simple mastectomy was performed showing a well-circumscribed, dense, fibrous and bulging red-purple mass which measured 5.5 x 5.0 x 4.5 cm. There were also tan-grey regions.

Case 16 - Acc 29327
Contributed by X. Wang, M.D. Pasadena, CA
Clinical History: A 64-year-old African-American female presented with indeterminate clusters of calcifications medially in the right breast. There was no palpable mass on examination. An excisional biopsy of the right breast calcifications following x-ray localization was performed. The specimen measured 9.0 x 7.0 x 6.0 cm and contained an ovoid, partially cystic neoplasm which measured 4.0 x 2.5 x 2.0 cm. The cyst contained friable fragments of yellow and pink, lobulated, partially necrotic soft tissue.

Case 17 - Acc 28599
Contributed by F. Ali, M.D. Ventura, CA
Clinical History: A 43-year old Hispanic female on oral contraceptives developed a rapidly enlarging, 5 cm mass over 5 months in the right breast. The excisional biopsy contained translucent pink-white, friable, soft myxoid "leaf-like"/papillary-appearing tissue measuring 4.3 x 4.0 x 3.0 cm. .

Case 18 - Acc 29521
Contributed by H. Otto, M.D. Cheboygan, MI
Clinical History: A 60-year-old female presented with a lump in her right breast, identified during a monthly breast exam. There was accompanying pain and tenderness in the breast. The pain also extended to the front of the chest and radiated into the left arm. Bilateral mammograms revealed an 8.0 cm mass within the right breast. The nearly 11cm excisional biopsy contained a gray-tan lobulated tumor measuring 7.0 x 7.0 cm and contiguous with smaller nodules. At least one nodule extended to the margins of resection.

Case 19 - Acc 29772
Contributed by W. Chick, M.D. Loma Linda, CA
Clinical History: A 55-year old female noted a right breast mass. On physical examination, the mass measured 3.0 cm, and was firm, smooth and round. A lumpectomy was performed. The cut surface of the specimen revealed a 4.0 x 3.2 x 2.5 cm pale tan, yellow-tan, soft and fibrous, well-circumscribed nodule.

Case 20 - Image only
Contributed by F. Tavassoli, M.D. New Haven, CT
Clinical History: A 57-year-old female presented with new microcalcifications on her mammogram. A core biopsy was performed. The image represents the most advanced lesion in the core biopsy.

Case 21 - Image only

Contributed by F. Tavassoli, M.D. New Haven, CT

Clinical History: A 52-year-old woman was found to have extensive microcalcifications on her first screening mammogram. A core biopsy was followed by lumpectomy.

Case 22 - Image only

Contributed by F. Tavassoli, M.D. New Haven, CT

Clinical History: A 48-year-old woman with a family history of breast cancer was found to have an irregular density with a few microcalcifications in her left breast. A core biopsy was performed.

CALIFORNIA
TUMOR TISSUE REGISTRY

118TH SEMI-ANNUAL CANCER SEMINAR

"Tumors of the Breast"

Fattaneh A. Tavassoli, M.D.

Yale University School of Medicine
New Haven, Connecticut

Sunday, June 5, 2005
8:30 a.m. - 4:30 p.m.

Westin Hotel, South Coast Plaza
Costa Mesa, California

Dr. Fattaneh ("Tanya") A. Tavassoli, is currently Professor of Pathology and Director of the Women's Health Program/Gynecologic & Breast Pathology at Yale University School of Medicine. Until recently, she was Chair of the Department of Gyn & Breast Pathology at the Armed Forces Institute of Pathology, Washington D.C. She serves on numerous editorial boards, including International Journal of Gyn Pathology, International Journal of Surgical Pathology, and others. Her book Pathology of the Breast (2nd ed), is largely viewed as the definitive text of the topic. She was also an editor of the WHO Classification of Tumors of the Breast and Female Genital Tract, and is editing the upcoming 3rd series fascicle on Tumors of the Breast. Her professorships, slide seminars, and invited lectureships are myriad. We are pleased that she has decided to follow-up her 1998 CTTR seminar on Gyn Tumors with this seminar on breast tumors.

118TH CTTR Semi-annual Cancer Seminar:

"Tumors of the Breast"

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CASE 1

Clinical History (CTTR Acc 28814): A 55-year-old female was found to have a cluster of what appeared to be microcalcifications of the left breast on routine mammogram. She'd had an abnormal mammogram two years previously, revealing a 7 mm cyst in the right breast. A left breast biopsy was performed. The specimen consisted of three segments of breast tissue with the largest fragment measuring 2.0 cm in diameter.

Diagnosis: ***Extensive lobular intraepithelial neoplasia (lobular carcinoma in situ)***

DISCUSSION

Lobular Intraepithelial Neoplasia

Definition

Characterized by a proliferation of generally small and often loosely cohesive cells, the term lobular intraepithelial neoplasia (LIN) refers to the entire spectrum of atypical epithelial proliferations originating in the terminal duct-lobular unit (TDLU) with or without pagetoid involvement of terminal ducts. LIN constitutes a risk factor and is a non-obligate precursor for the subsequent development of invasive carcinoma of either ductal or lobular type.

Historical Background and Clinical Features

The designations of atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS) have been widely used for variable degrees of the lesion. Two series published in 1978 {Haagensen et al, 1978; Rosen et al., 1978} concluded that the features generally used to subdivide the lobular changes into LCIS and ALH were not of prognostic significance. While Rosen continued to use the terms ALH and LCIS, Haagensen suggested the designation of lobular neoplasia for these lesions. To emphasize the non-invasive nature of this lesion, the term *lobular intraepithelial neoplasia* (LIN) is used.

The **frequency** of LIN (LCIS) ranges from less than **1% to 3.8 %** of all breast carcinomas. LIN is found in 0.5% to 4% of otherwise benign breast biopsies. Between 1978 and 1998, there has been a continuous increase in the incidence of LCIS among women 50 to 59 years of age (Li 2002). Overall, the incidence increased four-fold from 0.90/100,000 person-years in 1978-1980 to 2.83/100,000 person-years in 1987-1989, but then increased modestly up to an incidence rate of 3.19/100,000 person-years in 1996-98 (Li 2002). It is possible that the widespread use of hormone replacement therapy and obesity may account for some of this increase, but this has not been substantiated. Women with LIN range in age from 15 to over 90 years but most are premenopausal. The lesion is multicentric in as many as 85% of patients and bilateral in 30% to 67% of women who had been treated by bilateral mastectomy. No mammographic abnormalities are recognized, except in the occasional variant of LIN characterized by calcification developing with or without central necrosis.

Gross Features
LIN is not associated with any grossly recognizable features.

Histopathology
The lesion is located within the terminal duct-lobular unit {Wellings et al., 1975} with pagetoid involvement of the terminal ducts evident in as many as 75% of cases. On low power examination, while lobular architecture is maintained, the acini are expanded to varying degrees by a monomorphic proliferation of loosely cohesive, usually small cells, with uniform round nuclei, indistinct nucleoli, uniform chromatin and rather indistinct cell margins with sparse cytoplasm. Necrosis and calcification are uncommon and mitoses are infrequent. Intracytoplasmic lumens are often present but are not specific to LIN. In some lesions, however, the proliferating cells are larger and more pleomorphic or of signet ring type. Apocrine metaplasia also occurs and an endocrine variant of LIN has been described.

When composed of pleomorphic or signet-ring cells, the terms **pleomorphic or signet-ring cell LIN** (LCIS) would be appropriate. The neoplastic cells either replace or displace the native epithelial cells in the TDLU. The myoepithelial cells may remain in their original basal location or they may be dislodged and admixed with the neoplastic cells. The basement membrane is generally intact although this is not always visible in all sections. Solid obliteration of acini may occur, sometimes with massive distension and central necrosis. LIN may involve a variety of lesions including sclerosing adenosis, radial scars, papillary lesions, fibroadenomas and collagenous spherulosis.

Grading. A three-tiered grading system has been based on the extent and degree of proliferation and/or cytological features (Table 1). However, a vast majority of LIN lesions encountered in general practice fall in the LIN 2 category. Furthermore, it is only the LIN 3 lesions that we are more concerned about as reflecting a more advanced stage of the disease that would require re-excision if present at or close to the margin. Those lesions with distended acini and/or central necrosis (LIN3), those with signet ring cells (LIN3) or severely pleomorphic cells (LIN3) with or without acinar distension are more often seen in association with invasive carcinomas rather than in pure form. For routine diagnosis and practical purposes, the term LIN is all that is necessary with qualification of those that have necrosis, massive distension, pure signet-ring cells and nuclear pleomorphism in the following manner:

- LIN, necrotic type
- LIN, signet-ring cell type
- LIN, pleomorphic type
- LIN, macro-acinar type

Immunoprofile. LIN is positive for oestrogen receptor (ER) in 60-90% of cases and in a slightly lower percentage for progesterone receptor (PR); the classic variety of LIN is more likely to be positive than the pleomorphic variant. E-Cadherin, commonly identified in ductal lesions, is generally absent in both LIN and invasive lobular carcinoma, while the neoplastic cells show a polarized cytoplasmic positivity with high molecular weight CK903 (34betaE12).

Differential Diagnosis

Note: Poor tissue preservation may give a false impression of loosely cohesive cells leading to over-diagnosis of LIN.

Distinction of LIN from a solid DCIS can be difficult on morphological grounds alone. The presence of secondary lumens or rosette-like arrangement of cells indicates a ductal lesion. In problematic cases, the immunoprofile may be helpful. LIN is typically E-Cadherin and CK 5,6 negative, but HMW CK34BE12 positive {Bratthauer et al.,2001}. Ductal lesions, on the other hand, are typically E-Cadherin positive. Occasional lesions are negative or positive for both HMW CK34BE12 and E-Cadherin markers. Since, at present, it is uncertain how these morphological and immunohistochemical hybrid lesions should be designated, it is important that they are recognised so that more can be learned about their nature in the future.

When LIN involves sclerosing adenosis or other sclerosing lesions, it can be confused with an invasive carcinoma. The presence of a myoepithelial cell layer around the neoplastic cell clusters excludes the possibility of an invasive carcinoma; immunostaining for actin can unmask the myoepithelial cells, thus facilitating the distinction.

Presence of isolated cells invading the stroma around a focus of LIN can cause diagnostic problems. Absence of myoepithelial cells around the individual cells and their haphazard distribution accentuated with any of the epithelial markers - optimally with double immunostaining techniques - can help establish the presence of stromal invasion by individual or small clusters of neoplastic cells.

Molecular Genetics

Loss of Heterozygosity (LOH) at loci frequently observed in invasive carcinoma has also been reported in LCIS (LIN), ranging from 8% on chromosome 17p to 50% on 17q. LOH on chromosome 16q, the site of the E-Cadherin gene, was found in approximately 30%. LOH was identified in LCIS (LIN) associated with invasive carcinoma and in pure LCIS (LIN), suggesting that LCIS may be a direct precursor of invasive lobular cancer. Further support for this hypothesis has come from a report that showed LOH in 50% of LCIS associated with invasive carcinoma at markers on chromosome 11q13. Using comparative genomic hybridization (CGH), loss of chromosomal material from 16p, 16q, 17p and 22q and gain of material to 6q was identified in equal frequency in 14 ALH and 31 LCIS lesions, suggesting that both are 'neoplastic' and at a similar stage of genetic evolution. In one study, 27 of 48 (56%) of invasive lobular carcinomas had mutation in the E-Cadherin gene, while none of 50 breast cancers of other types showed any alteration. It was subsequently demonstrated that truncating mutations identified in invasive lobular carcinoma were also present in the adjacent LIN, providing direct proof that LIN was a precursor lesion.

Prognosis and predictive features

The relative risk (RR) for subsequent development of invasive carcinoma among patients with LIN (ALH/LCIS) ranges from 6.9 to about 12 times that expected in women without LIN. Among 1174 women in 18 separate retrospective studies, diagnosed as having either LCIS or LN and treated by biopsy alone, 181 (15.4%) eventually developed invasive carcinoma. Of these, 102 (8.7%) developed carcinoma in the ipsilateral breast, and 79 (6.7%) in the contralateral breast, demonstrating an almost equal risk for either breast.

With extended follow-up, the risk continues to increase to 35% for those women who survive 35 years after their initial diagnosis of LIN. Furthermore, the RR increases substantially from 4.9 (95% CI: 3.7 -6.4) after one biopsy with LIN to 16.1 (95% CI:6.9 -31.8) after a second biopsy with LIN/LN {Bodian et al.,1996}.

A more recent study using the three-tiered grading system and with a comparatively short follow up of 5 years (Table 2), found that LIN 3 and, to a lesser extent LIN 2,were associated with an increased risk {Fisher et al.,1996/58}. Also, 86% of invasive carcinomas associated with LIN3 were lobular in type in contrasting to 47% of those associated with LIN2 and only 11% of those associated with LIN1 (Bratthauer and Tavassoli 2002).

Management of LIN has evolved with increased understanding of the disease. The current consensus is that LIN (LCIS or ALH) constitutes a risk factor and a non-obligate precursor for subsequent development of invasive carcinoma in either breast, of either ductal or lobular type, but only in a minority of women after long-term follow-up. The current recommended management for LIN (diagnosed on excisional biopsy) is, therefore, life long follow-up with or without tamoxifen treatment. Re-excision should be considered after an excisional biopsy in cases of palpable mass, nipple discharge, imaging abnormality, massive acinar distension, or when pleomorphic or necrotic variants (any of the LIN3 subtypes) are identified at or close to the margin. Breast conserving surgery with radiotherapy has been used in a small number of patients (n=25) (Cutuli et al, 2005).

When LIN is the only lesion present **in a core biopsy**, correlation with mammographic findings is mandatory. In my opinion, an excisional biopsy is prudent for all cases with pure LIN3 or those presenting as a mass lesion. Shin and Rosen (2002) have shown that 21% of patients with a primary diagnosis of LCIS on needle core biopsies have either DCIS or an invasive carcinoma in the subsequent excision. There are those who believe follow-up is sufficient for patients with pure LCIS in core biopsies (Renshaw et al 2002). After excluding the necrotic and pleomorphic variants of LIN, Middleton et al recommended excisional biopsy of LCIS and atypical lobular hyperplasia only when it is associated with a synchronous mass lesion (2002). Obviously, opinions vary about the significance of LIN in a core biopsy and the best approach to its management. After ascertaining that the lesion of mammographic concern has been sampled in the core, follow-up is sufficient for LIN1.

TABLE 1: Grading of LIN based on extent of lobular involvement as used for investigational purposes.

- **LIN1.** There is partial or complete replacement of the normal epithelial cells of the acini within one or more lobules by a proliferation of generally uniform cells with poorly defined margins which may fill, but do not distend, the acinar lumens (in comparison to adjacent uninvolved acini).

- **LIN2.** There is more abundant proliferation of similar cells as in LIN1 that fill and actually distend some or all acini, but the acinar outlines remain distinct and separate from one another with persistence of intervening lobular stroma. Residual lumens may persist in some acini.

- **LIN3.** There is proliferation of cells similar to those of LIN1 or LIN2, but there is a massive degree of acinar distension to the point that the acini appear almost confluent; the interacinar stroma is barely evident. When the proliferating cells are completely of the pleomorphic or signet-ring cell type, significant acinar distension is not required.

** Note: The myoepithelial cells may remain in their usual location or may be dislodged in any of these variants. In a small number of LIN3 lesions, the myoepithelial cell layer is hardly visible on H&E stained slides; however an immunostain for actin usually shows widening of the intermyoepithelial cell gaps.

FOR PRACTICAL PURPOSES:

1. In general practice, 95%+ of all LIN qualify as LIN 2, therefore LIN requires no further qualification in most cases.

2. Rather than using grade 3 for the LIN with necrosis, etc., they can be specifically designated as:

- **LIN, necrotic type**
- **LIN, pleomorphic type**
- **LIN, signet-ring cell type**

Note: Re-excision would be prudent if any of these LIN variants are detected on a core biopsy.

Table 2a: Relation of grade of LIN to recurrences. (1996 Data NSABP)

Grade	No of Patients	% of Patients	No of IBTR	Avg. An. Rate /100
1	63	34.6	0	0
2	81	44.5	3	0.84
3	38	20.9	4	2.36

Table 2b: Relation of grade of LIN to recurrences. (2004 Data NSABP)

Grade	No of Patients	% of Patients	No of IBTR	Avg. An. Rate /100
1	63	34.6	4 (6.3)	0.55
2	80	44.4	15 (18.7)	1.83
3	37	37	7 (18.9)	1.85

Table 3: Relationship of grade of LIN to type of associated invasive carcinoma

Grade of LIN	Number (%)	Total Inv CA	Inv DCA	Inf LCA
LIN1	65 (8%)	9 (14%)	8 (89%)	1 (11%)
LIN2	618 (80%)	110 (18%)	58 (53%)	52 (47%)
LIN3	92 (12%)	21 (23%)	3 (14%)	18 (86%)

Table 4: Intraepithelial neoplasia: Immunoexpression of E - cadherin and CK 34BetaE1

	E-K+	E+K-	E+K+	E-K-
Classic LIN1-3	40	0	0	0
Classic DIN 1c-DIN3	0	20	0	0
MIN by H&E (n=50)	17	6	16	11
Ultimate LIN	16			
Ultimate DIN		6		
Positive hybrid MIN			16	
Negative hybrid MIN				11

Adapted from Reference #3

FIGURES

(see page 15)

Fig. 1a. Lobular intraepithelial neoplasia (lobular carcinoma in situ). Two TDLU's show solid occlusive proliferation of uniform cells in all acini.

Fig. 1b. Lobular intraepithelial neoplasia (lobular carcinoma in situ). The acini in the TDLU are distended by solid proliferation of loosely cohesive, uniform small cells.

Fig. 1c. Lobular intraepithelial neoplasia (lobular carcinoma in situ). Immunostain for E-cadherin shows total lack of immunoreactivity in the neoplastic cells.

CASE 2

Clinical History (CTTR Acc 28758): A 42-year-old female presented with a mass in the left breast. An excisional biopsy was performed.

Diagnosis: ***Infiltrating lobular carcinoma***

DISCUSSION

Invasive lobular carcinomas constitute 1 to 15% of invasive breast cancers in different series, obviously reflecting different criteria used in these studies. For pure lobular carcinomas, the incidence rates have increased 1.53 fold, while that for mixed ductal/lobular carcinomas increased 1.96 fold; the proportion of breast cancers with a lobular component has increased from 9.5% in 1987 to 15.6% in 1999 (Li et al 2003).

Either the classic cytology (small, 8 - 12 micron uniform cells with or without intracytoplasmic lumens) and/or one of the recognized growth patterns (**single cell file, solid, or alveolar**) of invasive lobular carcinoma should be present for this diagnosis. If anywhere in the lesion there is evidence of clear-cut tubular arrangements, then I would regard the lesions as a mixed ductal and lobular carcinoma. *Therefore, I regard the so-called tubulolobular variant of invasive lobular carcinoma as a mixed ductal and lobular carcinoma on morphologic basis alone.* The immunoprofile of tubulo-lobular carcinoma is positive for both E-Cadherin and CK903 indicating a hybrid lesion with combined ductal and lobular features (Wheeler et al, 2004).

A **pleomorphic variant** of infiltrating duct carcinoma has been defined relatively recently. In this variant, the growth pattern in cords and single cells is typical, but the cells are quite atypical with grade 2 to 3 nuclei and relatively abundant cytoplasm. Nuclear pleomorphism is characteristic of this variant and mitotic activity is easily identifiable in contrast to the typical infiltrating lobular carcinoma. The pleomorphic variant of lobular carcinoma shows overexpression of Her2 protein in 53% of the cases. The typical invasive lobular carcinoma rarely, if ever, shows overexpression of Her2 (Frolik 2003).

Apocrine differentiation has been described in both the intraepithelial and infiltrating lobular carcinomas.

Finally, **signet-ring cell differentiation** also occurs in invasive lobular carcinomas and is associated with a more aggressive behavior even if it constitutes only 10% of the tumor. It should be emphasized that signet ring cell differentiation also occurs in unequivocal ductal carcinomas.

GRADING OF INVASIVE LOBULAR CARCINOMA

Grading infiltrating lobular carcinomas on the basis of the modified Bloom-Richardson system is acceptable and encouraged. In the Nottingham series, using this grading approach, 13% of the lesions qualified as grade 1, 75% as grade 2, and 12% as grade 3. Invasive lobular carcinoma

will always get a score of 3 for tubules, and almost always receive a score of 1 for mitotic activity. It is the *cytologic features* that account for the variations in the grading. The typical uniform small cells get a score of 1, qualifying the lesion as grade 1, while the pleomorphic variant would get a nuclear grade of 3, qualifying the lesion as a grade II invasive carcinoma.

PROGNOSIS

The prognosis of invasive lobular carcinoma is generally comparable to a grade II invasive carcinoma. The survival rates for the classic invasive lobular carcinoma have varied from 30%-77%. It is generally agreed that the pleomorphic variant is more aggressive, but opinions regarding the significance of the alveolar variant have varied; some have claimed a better prognosis, others have suggested a worse prognosis.

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Invasive Lobular Carcinoma

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FIGURES

Fig. 2a. Infiltrating lobular carcinoma. The dense subcutaneous stroma is permeated by a cellular infiltrate.

Fig. 2b, c. Infiltrating lobular carcinoma. The invasive tumor cells forming short cords permeate the stroma.

CASE 3

Clinical History (CTTR Acc 29921): An 80-year-old female noted a mass in her left breast. An excisional biopsy was performed. The specimen consisted of an ovoid, nodular, indurated fragment of grayish-yellow tissue which measured 2.5x2.4x2.4 cm.

Diagnosis: ***Histiocytoid (myoblastomatoid) carcinoma***

DISCUSSION

Histiocytoid (myoblastomatoid) carcinoma. The term histiocytoid carcinoma was coined by Hood et al (1973), referring to metastatic mammary carcinomas (to the eyelid region) characterized by cells with foamy clear cytoplasm that resembled histiocytes. Subsequently, these lesions were interpreted as apocrine variants of lobular carcinoma characterized by large clear vesicles that store secretory material. Foamy apocrine epithelial cells as such are "nonspecific" in the sense that they can be seen in any type of carcinoma of either ductal or lobular type. Interestingly, lobular neoplasms that display apocrine differentiation are E-cadherin negative, whereas ductal lesions with apocrine differentiation are E-cadherin positive. As expected, in either setting, apocrine differentiation is associated with androgen receptor (AR) positivity (Augros, et al).

The term "histiocytoid" relates to the foaminess of the cytoplasm, sufficient to render a histiocytic appearance at low magnification as well as on FNA - the tumor can be mistaken for an inflammatory reaction (Walford and Ten Velden). When the cells display abundant granular eosinophilic cytoplasm reminiscent of a granular cell tumor (myoblastoma), the term "myoblastomatoid carcinoma" has been used.

Another lesion with overlapping features is primary acinic cell carcinoma of the breast, a lesion first described by Roncaroli et al in 1996. About 10 examples of this lesion have been described in patients who have ranged in age from 35 to 80 years. The tumors vary in size from 2 to 5 cm. Some of these cases have a microglandular growth pattern in pure form or admixed with more solid areas. Others have a more diffuse growth pattern. If carcinomas arising in microglandular adenosis are included among these, the number of cases of acinic cell carcinoma will increase significantly. The interpretation is very much dependent on the immunoprofile of the tumor. Acinic cell carcinomas of the breast have been positive for S-100, amylase, lysozyme, alpha-1-antichymotrypsin and EMA, but negative for ER, PR, AR and HER-2. Axillary node metastases have been reported in 3 of 7 patients who had axillary node dissection. Local recurrence (1 case), liver (1 case) and lung metastasis (1 case) have been reported. The follow-up of generally less than 5 years available on most reported cases is too short and with longer follow-up the true long term behaviour of this lesion will be clarified in the future.

It is important to keep in mind that with the availability of a tremendous variety of antibodies and markers, we will undoubtedly define more precise categories of hopefully clinically relevant lesions as these markers are applied to our routine assessment of usual and uncommon lesions.

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FIGURES

(see page 25)

Fig. 3a. Histiocytoid/apocrine carcinoma. A solid proliferation composed of cells with abundant granular, amphophilic cytoplasm and round nuclei.

Fig. 3b. Histiocytoid/apocrine carcinoma. The cytoplasm is granular and vacuolated; there are prominent nucleoli.

Fig. 3c. Histiocytoid/apocrine carcinoma. E-Cadherin immunostain shows diffuse membranous positivity pointing against a lobular carcinoma.

CASE 4

Clinical History (CTTR Acc 28093): During the course of a routine physical examination, a mass was identified in the right breast of a 17-year-old female. The patient stated that she had been aware of the mass for years, but thought it was normal. The mass was excised. The specimen consisted of a 29.6 gram, 7.0 x 6.0 x 1.0 cm fibroadipose tissue with a cut surface composed of numerous cysts ranging from 1 to 3 mm. The gross appearance was that of a sponge containing mucoid material

Diagnosis: ***Florid low risk ductal intraepithelial neoplasia (intraductal hyperplasia). A nice example of "juvenile papillomatosis"***

FIGURES

(see pages 25-27)

Case 4 a,b,c,d. Papillomatosis and low risk DIN (IDH)/Juvenile papillomatosis.

Fig. 4a. Distended ducts show variable epithelial proliferation, apocrine metaplasia or secretory content.

Fig. 4b and c. Intraductal papillary proliferation with diffuse epithelial hyperplasia.

Fig. 4c. Fibrovascular cores are apparent.

Fig. 4d. Classic low risk DIN with peripheral fenestration and irregular, overlapping distribution of proliferation cells.

For Discussion: See cases 20-22.

CASES 5 and 6

CASE 5. Clinical History (CTTR Acc 28949): A 78-year-old female presented with a mass in the right breast. An excisional biopsy was performed. The specimen consisted of a firm fragment of yellow to white tissue which measured 6.5x4.2x2.7 cm. Sectioning revealed a firm white area containing mucoid material; the firm area measured 3.5 x 3x 1.5 cm and extended to the lateral margin.

Diagnosis: ***Ductal intraepithelial neoplasia, grade 2, apocrine type, micropapillary and cribriform patterns***
(Ductal carcinoma in situ, grade 2, apocrine type)

CASE 6. Clinical History (CTTR Acc 28758): A 78-year-old female noted a mass in her breast. An excisional biopsy was performed.

Diagnosis: ***Invasive apocrine carcinoma***

DISCUSSION

Definition: Apocrine carcinoma of the breast is an intraepithelial or invasive carcinoma characterized by cytologic and immunohistochemical (abundant granular eosinophilic cytoplasm, prominent nucleoli and AR+/ER-/PR- immunoprofile) features of apocrine cell differentiation (present in >90% of tumor cells in the invasive tumors).

Background: The precise frequency of pure apocrine DIN (DCIS) is not well known, but it is relatively uncommon. More frequently, it is found admixed with the more common non-apocrine intraepithelial neoplasias/carcinomas. Most patients present with mammographic calcifications, although, rarely, presentation as a palpable mass still occurs. The incidence of invasive apocrine carcinoma varies between 0.3 to 4% due to highly varied criteria used in the past (Frable 1968, WHO 2003). Diagnosis of apocrine carcinoma based only on GCDFP-15 immunoreactivity is not appropriate since this marker is identifiable in many variants of breast carcinoma and is not exclusive to apocrine cells. Furthermore, focal areas of apocrine differentiation are not uncommon in a variety of infiltrating ductal and lobular carcinomas and this feature is insufficient for diagnosis of apocrine carcinoma.

The clinical, mammographic and gross presentation of apocrine carcinoma is not different from non-apocrine carcinomas (Gilles, 1994).

Histopathology: Nearly all variants of breast carcinoma may exhibit apocrine differentiation whether ductal or lobular in type, invasive or intraepithelial (in situ). The most widely recognized variant of apocrine cell is the type with abundant granular, intensely eosinophilic cytoplasm, round nuclei with prominent nucleoli. This variant has also been referred to as myoblastomatoid (Eusebi 1995) because of its resemblance to granular cell tumors. Less frequently the apocrine cells whether metaplastic or neoplastic have foamy (histiocytoid) to

finely vacuolated (sebocrine) cytoplasm; some neoplasms are composed nearly purely of one or both of these cell types.

A vast majority of **apocrine "DCIS"** are high grade with significant nuclear pleomorphism and necrosis. There are, however, those that display a very monotonous uniform population of cells proliferating in cribriform, micropapillary or solid patterns with or without necrosis. Once epithelial bridges form across the lumen by apocrine cells, the proliferation is atypical.

> *To qualify as "DCIS," the duct(s) cross sections involved by cribriform and/or micropapillary patterns composed of uniform cells should exceed 2 mm in aggregate maximum diameter. When there is necrosis present in this setting, the 2 mm size is no longer required. Nor is there a size requirement for those lesions with high grade cytology.*

Case 5 shows predominantly micropapillary and cribriform patterns of proliferation with cells that have either uniform or slightly variable nuclear contours qualifying as grade 2. The cells were ER and PR negative, but AR positive. The lesion was extensive, involving numerous duct cross sections in multiple blocks assessed.

Case 6 shows invasive clusters and nests of cells composed of cells with abundant granular eosinophilic cytoplasm, round nuclei, prominent nucleoli, somewhat distinct cell margins and occasional attempt at acinus formation. The tumor cells were ER negative, PR negative and AR positive by immunohistochemistry.

Differential Diagnosis: I distinguish between apocrine and sebaceous carcinomas. Sebaceous carcinomas are grossly yellow and microscopically contain cells with multiple large rounded vacuoles and may be admixed with cells that display squamous differentiation; in contrast to apocrine carcinomas that are ER and PR negative even when cytologically well differentiated, sebaceous carcinomas can be ER positive. While some apocrine cells, whether metaplastic or neoplastic may develop hybrid features of sebaceous and apocrine cells (sebocrine cells), these cells are generally admixed with typical apocrine cells. Histiocytoid carcinoma is a term initially used for a variant of lobular carcinoma and has often been used in tumors with intracytoplasmic mucin droplets with cells that are generally ER positive. Others have used the terms histiocytoid (Eusebi 1995), myoblastomatoid and apocrine carcinomas almost interchangeably and/or consider histiocytoid carcinoma an apocrine variant of lobular carcinoma.

When apocrine metaplasia involves sclerosing lesions of the breast (Carter 1991), it can be easily confused with invasive carcinoma because of the large cell size that fills the compressed tubules of sclerosing lesions and due to the compact aggregation of tubules in these lesions. Identification of myoepithelial cells (ME) around the tubules on H&E stained sections or using a variety of immunostains for ME cells helps unmask the true nature of the lesion. This problem is further accentuated in the presence of atypical apocrine metaplasia.

Immunophenotype: Apocrine cells, whether neoplastic or metaplastic are typically GCDFP-15 positive (Mazoujian, 1989), BCL2, ER, and PR negative (Tavassoli 1996). Interestingly, many ER negative apocrine carcinomas do have the ER mRNA, but fail to produce the protein

(Bratthauer 2002). An important feature of apocrine cells is their frequent positivity for androgen receptors (AR, Tavassoli 1996) noted in 81-97% of intraepithelial lesions and 22 to 62% of invasive carcinomas (Miller 1985;Selim1999). In my personal experience, negativity for AR is a rare occurrence whether the lesion is in situ or invasive. If a case is positive for ER, PR and negative for AR, the diagnosis of apocrine carcinoma should be reconsidered.

Molecular Features: Assessment of the molecular features of apocrine metaplasias and neoplasias basically parallel those of non-apocrine carcinomas. (Lininger et al 1999; Jones et al 2001).

Prognosis and Management: The survival of patients with invasive or intraepithelial apocrine carcinomas is not significantly different from that of non-apocrine counterpart. It should be kept in mind that these patients are being treated in the same fashion as ER, PR negative tumors since these markers became available and are now a routine component of work-up. With the knowledge that apocrine carcinomas are often AR positive, incorporation of this information in the management of the patients could potentially provide a more effective therapy for the patient.

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FIGURES

Fig. 5a. Apocrine DIN2 (Apocrine DCIS, gr 2). Multiple ducts show proliferation of mildly to moderately atypical apocrine cells forming arcades or micropapillae.

Fig. 5b. Apocrine DIN2 (Apocrine DCIS, gr 2). Rigid arcades and micropapillae are formed by neoplastic apocrine cells with granular eosinophilic cytoplasm and round nuclei with prominent nucleoli.

Fig. 5c. Apocrine DIN2 (Apocrine DCIS, gr 2). There is nuclear size variation and a mitotic figure evident.

Fig. 5d. Apocrine DIN2 (Apocrine DCIS, gr 2). The neoplastic cells show androgen receptor (AR) positivity.

Fig. 6a. Invasive apocrine carcinoma. The invasive tumor forms clusters (a) and is composed of neoplastic cells with abundant granular eosinophilic cytoplasm, round nuclei and nucleoli.

Fig. 6b. Invasive apocrine carcinoma. Immunostain for androgen receptor (AR) is diffusely positive in the invasive tumor cells.

CASES 7 AND 8

CASE 7. Clinical History (CTTR Acc 19635): During routine physical examination of a 46-year-old female, an area of nodularity was palpated in the medial aspect of the right breast. Approximately one year later, the patient returned with complaints of nipple discharge. Re-examination of the breast revealed a significant increase in size of the nodule. A biopsy was performed. On sectioning the 5.0 x 2.0 cm tissue specimen, there were multiple small foci of tan, soft, bulging, discrete nodules measuring up to 1.0 cm in diameter.

Diagnosis: ***Papillary intraductal carcinoma***

CASE 8. Clinical History (CTTR Acc 24791): An 11-year-old female had bilateral breast lumps removed. The specimens consisted of two masses of gray-tan tissue. The smaller specimen, from the left breast, measured 1.8 x 1.7 x 1.1 cm with a nodule of light tan tissue, 1.0 cm in diameter, seen to one side. The larger specimen, reportedly from the right breast, consisted of a 2.3 x 1.0 cm wedge of skin and underlying light tan tissue measuring 3.2 x 2.0 x 1.2 cm containing a 1.3 cm encapsulated mass.

Diagnosis: ***Intraductal papilloma with adenomyoepithelial hyperplasia and squamous metaplasia***

DISCUSSION

CLASSIFICATION OF PAPILLARY LESIONS OF THE BREAST

I. Benign

1. ***Papilloma*:** Central, solitary
2. ***Papillomatosis*:** Peripheral, multiple, arises **in TDLU**

II. Atypical Papillary Lesions

1. ***Atypical Papilloma*:** Central, solitary or complex
2. ***Atypical Papillomatosis*:** Peripheral, multiple

III. Malignant

1. **Noninvasive Papillary Carcinoma (Intraductal Papillary Carcinoma)**
   a. Central, solitary, palpable
   b. Peripheral, multiple, nonpalpable (malignant counterpart of papillomatosis)
2. **Invasive Papillary Carcinoma**
   a. Either of the above (a or b) generally, the former, with areas of regular infiltrating **duct** carcinoma
   b. Invasive micropapillary carcinoma

Definition: A papillary lesion should have papillary processes supported by a fibrovascular stalk whether benign or malignant. The fibrovascular stalk may be inconspicuous due to the extent of the epithelial proliferation particularly in some carcinomas or it may be quite prominent and sclerotic in some benign papillary lesions. Papillary lesions of the breast occur in a wide age range. Benign papillary lesions have been described even in children and adolescent females. However, the malignant papillary lesions are quite rare prior to the age 30 years.

Among women, papillary carcinomas account for 1-2% of breast carcinomas and often occur in an older age group with a mean age ranging between 63 - 67. Papillary carcinomas are more common in the male breast accounting for up to 5% of male breast carcinomas.

Papillary lesions of the breast may assume a variety of appearances and presentations. They may be solitary, visible to the naked eye, centrally located beneath the nipple or they may be multiple, microscopic-only, and located in the smaller peripheral ducts. The latter originate in the terminal duct-lobular unit (TDLU). Furthermore, a papillary lesion may be benign or malignant regardless of its size or location. Included among these are:

- solitary papilloma
- papillomatosis
- sclerosing papilloma, and
- papillary carcinoma.

Whether benign or malignant, a solitary (or multiple large) centrally located papilloma(s) may be associated with nipple discharge. The most important, and actually *the only feature that invariably indicates a malignant process is the absence of a myoepithelial cell layer in the papillary processes*. This rule holds regardless of the size, number, or locations of the papillary lesions. In larger lesions (those solitary or complex centrally located lesions), the presence of a myoepithelial (ME) cell layer does not invariably exclude a diagnosis of papillary carcinoma, however.

It has also been suggested that CD44 could be helpful in distinguishing benign papillomas from papillary carcinoma. Normal breast epithelial cells and intraductal papillomas express CD44 in more than 70% of the cells, whereas papillary carcinomas express CD44 in less than 10% of the epithelial cells (Saddik and Lai, 1999). More experience with this marker would be valuable before its routine application.

Variants of Papillary Lesions:

Papillomas are generally centrally located lesions and associated with nipple discharge in a good proportion of the cases. They may develop sclerosis (sclerosing papilloma), atypia or infarction. The infarction is usually hemorrhagic in nature and secondary to torsion of one or more papillary processes. Clonal analysis of solitary intraductal papilloma has shown that it is monoclonal in origin suggesting that the lesion originates from a common precursor cell capable of differentiating into epithelial and myoepithelial cells (Noguchi).

When multiple and located in the small peripheral ducts, the term **papillomatosis** would be appropriate for the benign lesions. The association of multiple papillomas (MP) with AIDH,

ALH/LCIS, malignant lesions, and bilaterality suggests that MP may represent a marker of constitutionally increased breast cancer risk (Ali-Fehmi et al 2003).

Sclerosing papilloma undergoes various degrees of sclerosis leading to extensive hyalinization, distortion and pseudoinvasive patterns that are easily mistaken for carcinoma. None of the thirty sclerosing papillomas reported by Fenoglio and Lattes (1979) developed recurrences after a median follow-up of 6 years, however. Some papillomas appear as a relatively solid proliferation of tubules occluding the lumen of the involved duct in some planes of section.

The term **"intraductal adenoma"** has been used for this presentation. Generally, the papillary nature of the process becomes apparent when additional levels or sections are assessed.

Papilloma with myoepithelial hyperplasia (papillary adenomyoepithelioma). Myoepithelial cell prominence is common among papillomas. Less frequently, diffuse or prominent patches of myoepithelial hyperplasia develop in papillomas. When this feature exceeds one or two foci of 2-3 mm each, the term papillary adenomyoepithelioma would be appropriate. If mitotic figures are noted among the proliferating myoepithelial cells and the number is $\geq$ 3 mf per high power fields, it is prudent to check the lung fields and continue to do so as part of the patient's follow-up. Adenomyoepitheliomas with 3 or more mf/10hpf have the potential (though not always realized) for local recurrence and distant metastases.

Atypical papilloma is characterized by

- areas of stratification of epithelial cells with loss of myoepithelial cell layer or
- areas of cribriform or micropapillary proliferation of uniform atypical cells with or without loss of the myoepithelial cell layer confined to less than one third of the papillary lesions.

If such areas occupy at least a third of the lesion and up to 90%, then the term carcinoma arising in a papilloma would be appropriate.

The background papillary lesion for atypia or in situ carcinoma arising in a papilloma may be a regular solitary papilloma, a complex papilloma, or a sclerosing papilloma. **Atypical papillomatosis** rarely occurs and is most often of the type with stratified spindle cell showing at most partial loss of the myoepithelial cell layer and often admixed with micropapillae.

In a recent review of a variety of papillomas (those florid epithelial hyperplasia, atypical hyperplasia or carcinoma arising in papilloma), the quantity of these proliferations made no impact on the final outcome for the patient. When the atypia or even "in situ carcinomas" were confined to the papillary lesion, the patients did well. It was the presence of DIN, low risk or atypical proliferations of ductal or lobular type and infarction within the papillary lesion that appeared associated with risks of progression to carcinoma (MacGrogan and Tavassoli).

Papillary carcinomas may be solitary and centrally located or multiple and peripheral in distribution. A majority of papillary carcinomas are noninvasive and therefore associated with an excellent prognosis; they are basically intraductal carcinomas with a papillary growth pattern. The involved duct may become cystically dilated (intracystic carcinoma). The chances for recurrence of a solitary (cystic) papillary carcinoma after lumpectomy are increased when it

displays high grade cytologic features or when there is intraductal carcinoma in the adjacent breast tissue.

Papillary carcinomas with more solid growth and/or spindle cell composition generally display neuroendocrine differentiation.

The multifocal, microscopic and peripherally located papillary carcinoma is generally referred to as **intraductal carcinoma, stratified, spindle cell, or papillary variant.** This pattern is often admixed with other patterns of non-necrotic intraductal carcinoma. The so called micropapillary intraductal carcinoma is composed of epithelial tufts lacking fibrovascular support and does not qualify as a true papillary lesion since we require the presence of fibrovascular support for a papillary lesion by definition.

A rare variant of papillary carcinoma with transitional cell differentiation has also been described (Mooney & Tavassoli). This variant generally presents as a solitary, nodular papillary lesion. Microscopically, it shows a solid proliferation of numerous layers of epithelial cells overlying a fibrovascular core with flattening of the superficial cells. Microinvasion was evident in one case. The behavior of the small number of reported cases parallels that of papillary carcinoma, NOS.

When a papillary carcinoma invades or metastasizes, it generally assumes the pattern of an infiltrating duct carcinoma. Metastases to lymph nodes rarely, if ever, retain classic papillary configuration if the invasive component is pure ductal NOS type. Early invasion may be found around the main duct in which the papillary carcinoma is proliferating. **Entrapment of the in situ component into a sclerotic duct wall should not be confused with true invasion; distinction can be difficult. Also, when the papilloma has been aspirated, dislodged tumor cells may mimic invasive carcinoma.** As a general rule, if I have any doubt about the possibility of entrapment or dislodgement, I would not call the lesion invasive since early invasion of less than 1 to 2 mm is probably unlikely to change the prognosis significantly. Immunostains for actin or any other markers of myoepithelial cells could be helpful if it identifies ME cells around the dislodged clusters; most dislodged clusters lack a ME cell layer, however.

In 1993, the term **invasive micropapillary carcinoma** was coined for an unusual variant of invasive papillary carcinoma that shows retention of papillary or micropapillary configurations in the areas of invasion. The small invasive papillae appear to float in empty stromal spaces or within vascular channels. The associated non-invasive component is generally DIN1 (atypical hyperplasia or low grade DCIS of the micropapillary or cribriform types). When a non-invasive component is absent, the possibility of a metastatic ovarian carcinoma (serous papillary) should be considered and excluded. It occurs either in pure form or admixed with regular infiltrating duct carcinoma. Metastases and recurrences retain the micropapillary configuration.

Cytologically, micropapillary carcinoma is characterized by a "dual" pattern formed by round or angulated, three-dimensional, cohesive clusters of neoplastic cells with pseudopapillary configuration and two-dimensional, dyscohesive aggregates and single cells with high grade nuclei and intact cytoplasm (Pettinato et al 2002).

Four subsequent reports, two from the same group in Spain, have further elaborated on the characteristics of this lesion. The group from Spain who have reported on these lesions have suggested that these tumors have a high incidence of axillary node metastases and a poor clinical outcome compared to regular infiltrating duct carcinomas. A report on 14 cases of MPC from NIH also suggested that MPC is an aggressive tumor with an unfavorable prognosis (Middleton et al). In another study of 21 such lesions, however, invasive micropapillary carcinoma was found to have survival rates similar to those of other patients with equivalent numbers of lymph node metastases (Paterakos et al). A larger series of 80 invasive micropapillary carcinomas included a substantial number of tumors combined with other types of invasive carcinoma (Walsh 2001).

Molecular alterations

Clonal analysis of solitary intraductal papilloma has shown that it is monoclonal in origin suggesting that the lesion originates from a common precursor cell capable of differentiating into epithelial and myoepithelial cells (Noguchi). Sixty to 63% of benign papillomas and papillary lesions harboring carcinoma have LOH on chromosome 16p13, respectively. Chromosome 16p may contain a tumor suppressing gene that is mutated in papillary lesions (Lininger & Tavassoli). In one study, 4 out of 5 informative cases of invasive micropapillary carcinoma had LOH on locus 17p13.1 (p53) (Middleton et al). Numerical and structural alterations at chromosomes 16q and 1q with fusion of chromosomes 16 and 1 [der(1;16)] have been described (Tsuda et al 1997). Papillary lesions are highly complex and the current molecular studies have barely touched on many of the possible variations that occur in this group of lesions.

Papillary Lesions on Core Biopsy

Core biopsies showing papillary lesions should be interpreted cautiously. This is due to the heterogeneity within papillary lesions that may contain benign and malignant areas simultaneously. If the sampled fragments show benign papillae, it is quite possible that the remaining lesions may have atypical or in situ carcinoma within it. On the other hand, if a small sample is morphologically identical to a papillary carcinoma, the lesion may prove to be an atypical papilloma if the changes are limited to a small portion of the papillary structures.

Because different areas of a papillary lesion may have variable morphologic appearances, complete excision would be prudent if papillary fragments of any type are detected on needle core biopsy.

Behavior

Intracystic papillary carcinoma in the absence of either concomitant DCIS or invasive carcinoma in the surrounding breast tissue has a very favorable prognosis with *no reported lymph node metastases or disease-related deaths.*

Management of Papillary lesions

Solitary papillary carcinomas should be excised with a rim of uninvolved mammary tissue to assess the alterations in the surrounding breast tissue. The likelihood of recurrence increases when either atypical intraductal hyperplasia or DCIS is present in the surrounding ducts.

Multifocal peripheral intraductal papillary carcinoma should be approached and managed as DCIS whether diagnosed on either core or excisional biopsy. Management of patients with papillomatosis diagnosed on core biopsies requires a cautious approach and consideration of family history and mammographic findings. If the lesion is localized in its distribution and small enough to have been removed by the biopsy, no more than follow-up would be required for women who have other risk factors. If there is widespread calcification, however, management would depend on the degree of clinical suspicion for malignancy, definitive guidelines for this issue are difficult to establish. About 20% of in situ ductal carcinomas, in my experience, have papillomatosis in the surrounding area somewhat complicating recommendation for management of papillomatosis based entirely on a core biopsy.

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FIGURES

Fig. 7a. Papillary intraductal carcinoma. Multiple adjacent cystically dilated ducts contain a branching papillary proliferation

Fig. 7b,c. A stratified spindle cell epithelial proliferation is apparent overlying the fibrovascular cores with no intervening myoepithelial cells.

Fig. 7d. Immunostain for calponin confirms absence of myoepithelial cells.

Fig. 8a. Papilloma with myoepithelial cell hyperplasia and squamous metaplasia. (Papillary adenomyoepithelioma). Papillary processes show a thickening of the epithelial surface lining.

Fig. 8b. Papilloma with myoepithelial cell hyperplasia and squamous metaplasia (Papillary adenomyoepithelioma). The myoepithelial cells are hyperplastic beneath the epithelial cell layer.

Fig. 8c. Papilloma with myoepithelial cell hyperplasia and squamous metaplasia (Papillary adenomyoepithelioma). Focally, the cells show a squamous differentiation.

Fig. 8d. Papilloma with myoepithelial hyperplasia and squamous metaplasia (Papillary adenomyoepithelioma). In at least two foci, chondroid differentiation was evident in the papillary stalk.

CASES 9 AND 10

CASE 9. Clinical History (CTTR Acc 29270): A 32-year-old female sought treatment for a lump in her breast that she stated had been present for approximately ten years. Mammogram and ultrasound revealed a solid lesion approximately 3.0 cm in diameter. The 3.2 cm biopsy revealed a nodular encapsulated grayish-tan tissue fragment with streaks of white fibrous and adipose tissue within it.

Diagnosis: ***Hamartoma***

CASE 10. Clinical History (CTTR Acc 29229): A 65-year-old female presented with a right breast mass of 3-4 month duration, accompanied by occasional pain. The patient had undergone a breast biopsy 27 years previously for a benign lesion. The mass was excised. The specimen consisted of a segment of fatty tissue measuring 6.1x5.2x3.2 cm. Sectioning showed a poorly demarcated whitish-yellow tissue measuring approximately 2.3 cm in greatest diameter.

Diagnosis: ***Myoid Hamartoma***

DISCUSSION

Definition: A hamartoma is a nodule composed of a variable aggregation of mature cells and tissues that normally occurs in the breast but is devoid of normal mammary structural organization or any of the patterns associated with recognized entities found in the breast.

First described in 1968 by Hogeman and Ostberg (14), the designation of hamartoma was first applied to these lesions by Arigoni et al who described 10 examples of this lesion mimicking fibroadenomas in 1971. Occurring in a wide age range, hamartomas occur most often in premenopausal women. A possible relationship to Cowden's disease has been proposed for some cases (Gatti et al 2005). Hamartomas present most often as a solitary mass or a discrete mammographically detected lesion. The development of hamartomas appears to be independent of hormonal stimulation of pregnancy or lactation. Mammographically, the lesion is characterized by a well-delineated electron-dense mass with a rim of radiolucency. Occasionally the mass may be tender.

Grossly, the tumor is round to ovoid and ranges in size from 2 to over 21 cm and rarely weighs over 1 kilogram (8). Softer than fibroadenomas and gray white to yellow on cut surface, they are generally solid though a cystic papillary variant rarely occurs. (10).

The microscopic appearance of hamartomas varies depending on the proportion of fibroadipose and glandular elements in the lesion. The lesion consists of a partially to completely encapsulated nodule of sequestered normal to minimally altered mammary tissue; adipose tissue comprises anywhere between 5 and 90% of the lesion (2,14). Some cases show a dominant proliferation of smooth muscle admixed with adipose tissue and variably dispersed ductules; these cases have been referred to as myoid hamartoma. Fibrocystic changes, sclerosing adenosis

and pseudoangiomatous stromal changes may develop (4,5,14); even rare examples of carcinoma arising in hamartomas have been reported (1,14).

When the typical mammographic features are present, the possibility of a hamartoma can be noted on aspiration cytology and core biopsies.

In case 9, there is focal ductal intraepithelial neoplasia 1 (atypical intraductal hyperplasia) at one edge of the lesion beneath the capsule.

Several **variants of hamartoma** occur; the most common are **adenolipomas** that are composed of substantially more adipose tissue and **chondrolipomas** that contain hyaline cartilage in addition to other components. The lesion now best recognized as **myoid hamartoma** is thought to reflect a variant of nodular sclerosing adenosis with prominent proliferation of spindled myoid myoepithelial cells assuming nodular smooth muscle configuration. The adipose tissue component is limited in myoid hamartomas; cystically dilated ducts occur occasionally. Myoid hamartomas occur in a wide age range, vary in size from 2 to over 10 cm, are often located in the upper outer quadrant and appear as well delineated nodules of variable density on mammograms; cystic areas are suggested on imaging studies.

As with other lesion that have a sclerosing adenosis component, core biopsy of the pseudoinfiltrative areas of myoid hamartoma can pose significant diagnostic difficulties. Only by considering these possibilities in the differential diagnosis of sclerotic lesions sampled on cores can we avoid overdiagnosis of invasive carcinoma in such cases. Immunostains for several ME markers may be necessary for diagnostic purposes.

Hamartomas including the variants and myoid hamartomas are benign, but "recurrences" have been noted in 8% of patients – particularly among those with the more typical hamartomas (3). These most probably reflect multifocal disease rather than a true recurrence. Because of the encapsulated nature of the nodules, they are easily enucleated.

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FIGURES

Fig. 9a. Hamartoma. An encapsulated mass composed of irregularly dispersed ductules in a fibroadipose stroma.

Fig. 9b. Hamartoma. Benign tubules with occasional microcalcification dominate.

Fig. 9c. Hamartoma. At one pole of the mass, an aggregate of ducts show intraluminal proliferation of uniform cells forming arcades, and a cribriform growth qualifying as DIN 1.

Fig. 10a. Myoid hamartoma. A well delineated mass, the lesion is composed of adipose tissue, variably distributed sclerotic tubular ducts and a prominent smooth muscle component.

Fig. 10b. Myoid hamartoma. Small sclerotic tubules proliferate between larger ducts.

Fig 10c. Myoid hamartoma. The sclerotic tubules often mimic an invasive carcinoma.

CASES 11 AND 12

CASE 11. Clinical History (CTTR Acc 29548): A 49-year-old female presented with a palpable breast mass which had been present for approximately one year. A FNA revealed dysplastic cells suspicious for malignancy and chemotherapy was begun due to a high suspicion of metastatic disease. The patient then had a modified mastectomy. It measured 12.0 x 11.5 x 4.5 cm and centrally had a well-defined tan, firm mass which measured 6.0 x 5.5 x 2.0 cm. The cut surface of the lesion was solid with a mucinous and fine granular texture.

Diagnosis: ***Mucinous carcinoma, Hypocellular variant***

CASE 12. Clinical History (CTTR Acc 28979): A simple mastectomy was performed on a 64-year-old female for a large left breast mass. A well-circumscribed, variegated red and tan, firm neoplasm measuring 16.5 x 13.0 x 6.5 cm involved the majority of the breast parenchyma. The neoplasm was focally hemorrhagic, and the cut surface was solid with a slightly gelatinous appearance.

Diagnosis: ***Mucinous Carcinoma, Hypercellular variant***

Pathologic Findings: The tumor was composed of solid sheets of densely packed uniform cells with mucoid material in between the nests of tumor cell. Some cells had a more eosinophilic granular cytoplasm.

DISCUSSION

Definition: Mucinous Carcinoma is an invasive duct carcinoma of low malignant potential, characterized by neoplastic cells floating within extracellular mucins (Synonyms: Colloid carcinoma, gelatinous carcinoma, mucoid carcinoma).

Pure mucinous carcinomas account for about 2% (range 0.8 to 5.3%) of all breast carcinomas. While it occurs in a wide age range, a high proportion of the women affected are post-menopausal and over 60 years of age (reported median age: 62 to 68 years). Presentation as a solitary mass is common. The lesions varies from <1 cm to over 20 cm, with an average size of 2.8 to 3 cm. The cut surface of the lesion is typically gelatinous and easily recognizable.

The classic mucinous (colloid) carcinoma of the breast is characterized by large amounts of extracellular mucin forming lakes populated by clusters of tumor cells. The neoplastic cells are surrounded by mucus and have no direct contact with the fibrous stroma. Variable degrees of cellularity and neuroendocrine differentiation may occur in the tumor. The cells generally form small clusters, appear uniform with rounded nuclei and display no evidence of intracellular mucin. Occasionally papillary and even signet-ring type cells are observed. Case 11 is an example of hypocellular while Case 12 is an example of hypercellular mucinous carcinoma.

Traditionally, mucinous carcinoma has been classified into **pure and mixed forms**. In the latter, at least 10% of the tumor should have typical mucinous carcinoma appearance. The pure form

has an excellent prognosis, particularly when there is abundant mucin and minimal amounts of tumor cells. The prognosis for the mixed form is not as favorable. Recent studies suggest that it may be possible to distinguish the pure and mixed forms using mammographic and sonographic echo pattern (ultrasound) studies (Memis et al 2000). The pure tumor is characterized by a mammographically well-defined mass lesion, and it is isoechogenic relative to fat on US. The mixed form has poorly defined or spiculated margins mammographically and all were hypoechogenic relative to subcutaneous fat. The MRI findings include dynamic curves of the gradually enhancing type and a very high signal intensity on T2 weighted images (Kawashima M 2002).

The pure form has been further subdivided into **hypocellular and cellular** variants depending on the degree of cellularity of the lesion; the cellular variant is more likely to develop local recurrences. The use of special stains for argyrophilic granules has been suggested as a simple method for separating the two variants of the pure mucinous carcinoma, since the cellular group has argyrophilic granules in a high proportion of cases. It is important to emphasize that even the cellular variant with argyrophilic granules has an excellent prognosis and a far more favorable prognosis than the mixed variant. Furthermore, a recent review of 61 pure and mixed variants of mucinous carcinoma suggests that these tumors as a whole are neuroendocrine-programmed lesions.

Microcalcifications are rare among mucinous carcinomas and when present (in 30% of cases) are often confined to the intraepithelial component.

While mucinous carcinomas can be reliably interpreted on core biopsies, it is important to be cautious since the hypocellular variant may be misinterpreted as a mucocele due to insufficient sampling; also, the needle sampling may miss the infiltrating duct carcinoma component of a mixed type tumor.

A high proportion of colloid carcinomas are ER positive; PR positivity has been reported in less than 70% of the cases. Compared to regular infiltrating duct carcinomas, mucinous carcinomas have increased expression of MUC2 (intestinal type) and MUC6 (gel forming mucus) but do not express MUC1/CORE and MUC1/HMFG-1; the latter two are associated with poor prognosis in gastric and colorectal carcinomas (Matsukita S 2003). Less than 5% will show immunoreactivity with HER2/neu (Diab et al 1999).

An unusual variant of mucinous carcinoma characterized by the presence of large macroscopic cysts filled with mucoid material and tall columnar epithelial cell lining the cyst wall occurs. We have designated this lesion "**mucinous cystadenocarcinoma**" due to its practically identical morphology to ovarian mucinous cystadenocarcinomas (Koenig 1998). These may become massive in size and do metastasize to axillary nodes. The behavior of this tumor is not as low grade as the more classic mucinous carcinomas. There is another variant that is also composed of columnar mucinous epithelial cells forming cords or lining irregular spaces, but does not form large cysts.

At the molecular level, the mucinous phenotype is associated with the expression of immunostimulatory and inhibitory genes and expression of enzymes involved with mucin production; also mucinous carcinomas have a different panel of metalloproteinases compared to infiltrating duct carcinomas (Pusztai L, et al 2003).

Differential Diagnosis

The hypocellular variant of mucinous carcinoma may be confused with a mucocele and a myxoid fibroadenoma. A **mucocele** generally contains no tumor cells, but can have foamy cytokeratin negative, histiocytes in the mucus lakes; occasionally, a fragment of detached ductal lining cells (epithelial and myoepithelial) are found floating in the mucus. Even a hypocellular mucinous carcinoma should contain some clusters of neoplastic cells. A **myxoid fibroadenoma** will invariably contain at least a rare focus of epithelial/myoepithelial lined slit-like spaces; it will also have mast cells in the myxoid stroma. In almost all of these cases, the correct diagnosis can be established by cutting deeper levels or additional sampling of the tumor.

Survival and Prognostic Features

Axillary node metastasis occurs with a much lower frequency among pure mucinous carcinomas. In one report, 26% of the pure mucinous carcinomas had nodal metastases compared to 65% of the mixed type. By multivariate analysis, the single most important factor for predicting recurrence free survival is lymph node metastases. The 20 year survival of patients with the pure variant is 75-87% compared to 45-54%% for those with the mixed variant in one study (Scopsi et al; Andre et al). After mastectomy, a ten year survival of 90% has been reported for pure mucinous carcinoma (Komaki K et al 1988). Among 16 women treated by conservative surgery and radiation therapy, there were no breast recurrences after a median follow-up of 11.2 years; one patient did develop systemic recurrence 11 years after surgery (Haffty BG et al 1997). The survival of pure MC at 5 years FU is similar to that of the general population. On the contrary no difference in survival is seen between mixed MC and ordinary invasive carcinomas (Toikkanen 1989). The favorable prognosis associated with this carcinoma has been recognized for a long time; follow-up of over 10 to 15 years has been lacking in most published reports, however. Nonetheless, mucinous carcinoma has retained its position among low grade mammary carcinomas.

Although it has been suggested that increased cellularity and the presence of neuroendocrine differentiation may be associated with increased likelihood of aggressive behavior, a recently published study concluded that **the only statistically significant predictors of favorable behavior are histologic (pure) type and the absence of axillary node metastases.**

Mucin producing carcinomas of the breast

Histological Type	Location of Mucin	In situ Component	Behavior
Mucinous (Colloid)	Extracellular	Ductal	Low grade
Cystadeno-adenocarcinoma	Intra- & Extra cellular	Ductal	Intermediate
Columnar cell	Intracellular	Ductal	Intermediate
Signet ring cell	Intracellular	Ductal or Lobular	Aggressive

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FIGURES

(see page 53)

Fig. 11a. Mucinous carcinoma, hypocellular variant. A lake of mucinous material dissects the mammary stroma in between benign structures. A few cell clusters are visible at this magnification.

Fig. 11b. Mucinous carcinoma, hypocellular variant. Fibrous septa divide the mucinous material into irregular compartments with only rare cells visible in some.

Fig. 11c. Mucinous carcinoma, hypocellular variant. A few small aggregates of tumor cells with mild to moderate nuclear atypia float in the mucinous lake.

Fig. 12a. Mucinous carcinoma, hypercellular variant. The tumor is far more cellular than case 11 with abundant mucinous material; one of the blocks used had a particularly hypercellular region of the tumor with more limited mucinous material.

Fig. 12b. Mucinous carcinoma, hypercellular variant. Some tumor cell clusters form multiple secondary lumens.

Fig. 12c. Mucinous carcinoma, hypercellular variant. Two distinctly different cell populations are evident: a relatively uniform smaller cell population is evident at the lower half of the field, while those in the upper half are larger and show pleomorphic nuclei.

CASE 13

Clinical History (CTTR Acc 20163): A 72-year-old female underwent an excisional biopsy for a mass in her right breast. A 3.0 x 3.0 x 2.5 cm, poorly-circumscribed, gray-tan mass which extended grossly close to the lower margin was present in the 8.0 x 6.0 x 3.0 cm excised tissue sample.

Diagnosis: ***Adenoid Cystic Carcinoma (ACC)***

DISCUSSION

Definition: ACC is a low malignant potential tumor which is histologically similar to its salivary gland counterpart (synonyms: carcinoma adenoides cysticum; adenocystic basal cell carcinoma; cylindromatous carcinoma).

Unlike its salivary gland counterpart, adenoid cystic carcinoma (ACC) of the breast is associated with an excellent prognosis. This tumor accounts for about 0.1% of mammary carcinomas, but its distinctive morphology and unexpectedly low grade behavior make its recognition most important. The age at presentation for this tumor is not significantly different from that of ordinary ductal carcinomas. It occurs mainly in female breast, though rare examples have been reported in male breast. Patients range in age from 38 to over 80 years and a majority present with a discrete nodule; about 50% are subareolar in location and are occasionally associated with pain or tenderness. Grossly, the tumor appears well-circumscribed, tan to gray and occasionally microcystic; the size varies from <1 cm to over 10 cm, with an average size of 3 cm.

On mammography and ultrasonography, ACC may simply show density or well defined nodules with heterogeneous echogenicity without features of a malignant lesion (Sheen-Chen et al).

Typically they are well-demarcated and around 2 cm. **Histologically**, mammary ACC is identical to those that occur in the salivary glands, trachea, etc. Despite its grossly circumscribed margins, the tumor displays an invasive proliferation of circumscribed nests and clusters of cells forming solid, cribriform, tubular and trabecular arrangements. Several of these patterns coexist in a given tumor, though one may dominate. *The presence of two cell types somewhere within these proliferating cells is required for a diagnosis of ACC, and is quite helpful in distinguishing some variants of this tumor from invasive cribriform carcinoma.* A small basaloid cell population dominates in all cases and often constitutes the more solid areas of the cell nests. The second cell type often has a fibrillar, elongated cytoplasm that is intensely eosinophilic and surrounds spaces lined by fibrillar whorls or granular material. The tumor cells characteristically grow in a spiral fashion engulfing portions of the surrounding stroma or around nerve fibers. A third population of cells, sebaceous cells, are present in 15% of ACC. The lumens within the cell clusters variably contain myxoid acidic alcian blue-positive mucosubstances, basement membrane-like material (hyaline collagen) or eosinophilic granular secretory material (neutral mucosubstances) that are PAS positive after diastase digestion.

Positivity for ER and PR is uncommon in ACC, but has been reported. Positivity for actin, calponin, CD10, p63 and S-100 protein is expected considering the origin of this tumor from myoepithelial cells; the degree of positivity is highly variable for these two markers, however.

Fine needle aspiration usually yields abundant material in which uniform round to oval cells with regular nuclei are seen. Chromatin is finely granular and small nucleoli are evident. Sheets, small aggregates or tubule- like structures are intermingled with dissociated cells. Giemsa stain shows pink to red homogeneous or fibrillar globules, cylinders or straps of interstitial material. These are surrounded by cells in a fashion reminiscent of stromal spaces. All these features have been regarded as characteristic of ACC in cytology smears (Stanley et al).

The **differential diagnosis** of ACC includes collagenous spherulosis, cribriform IDCA and invasive cribriform carcinoma (ICC). Both of the latter tumors are composed of a single cell type. The **invasive cribriform carcinoma** has the sieve-like pattern typical of cribriform IDCA. Instead of the rounded outline of the ducts typically seen in the IDCA, the sieve-like nests are often elongated, angulated and highly irregular in size and shape. Fortunately, distinction from the classic invasive cribriform carcinomas may not be very significant, since ICC is also considered a low grade carcinoma with little likelihood of axillary node metastases; rare recurrent disease has been reported, however. **Collagenous spherulosis** is a benign proliferation with a growth pattern that simulates ACC. Myoepithelial cells proliferate around the pink globules admixed with epithelial cells within the ducts affected by collagenous spherulosis.

Adenoid cystic carcinoma is among the least aggressive of mammary carcinomas. Nonetheless, it rarely metastasizes to axillary nodes (2 cases reported), it may recur and it may also develop distant metastases many years after the initial diagnosis. Metastases to the lungs within even 6 years of initial diagnosis has occurred. Grading mammary ACC has been suggested to help predict those that are more likely to cause subsequent problems. Two recent studies have found expression of p53 in recurrent or metastatic ACC despite either the absence or only limited expression of p53 in the primary lesion (Papadaki et al ; Pastolero et al).

Despite the reputation of ACC as a low grade carcinoma, long term follow-up of the patient is necessary. Metastases occur in about 10% of cases with the lungs as the favored site. Local recurrences do develop. ACC responds well to conservative management at presentation, with good outcome even following local recurrence (Millar et al).

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FIGURES

Fig. 13a,b. Adenoid cystic carcinoma. Variably sized aggregates of invasive tumor cells with an admixture of two cell types suggested.

Fig. 13c. Adenoid cystic carcinoma. The small nest of tumor cells shows two types of secretory material (mucinous and eosinophilic floccular material) and two cell types.

Fig. 13d. Adenoid cystic carcinoma. Immunostain for p63 shows positivity in the neoplastic cells supporting ME cell derivation of the tumor.

CASES 14, 15, 16

CASE 14. Clinical History (CTTR Acc 29456): A 53-year-old female who apparently had breast implants for more than a decade without problems, with a five month history of a cystic mass in her left breast. Exploration of the cyst cavity by a surgeon revealed serosanguineous fluid which was negative for bacterial organisms on Gram stain and culture as well as firm white tissue in the wall of the cavity, extending to the subcutis. A biopsy was taken from this area.

Diagnosis: ***Squamous Carcinoma with minor adenocarcinoma component***

CASE 15. Clinical History (CTTR Acc 29133): An 89-year-old female noted a mass in her left breast. A simple mastectomy was performed. A well-circumscribed, bulging red-purple mass measuring 5.5 x 5.0 x 4.5 cm was present in the mastectomy specimen. The cut surface of the lesion was pale tan-grey, dense and fibrous.

Diagnosis: ***Spindle cell adenocarcinoma***

CASE 16. Clinical History (CTTR Acc 29327): A 64-year-old African-American female presented with indeterminate clusters of calcifications medially in the right breast. There was no palpable mass on examination. An excisional biopsy of the right breast calcifications following x-ray localization was performed. The specimen measured 9.0 x 7.0 x 6.0 cm and contained an ovoid, partially cystic neoplasm which measured 4.0 x 2.5 x 2.0 cm. The cyst contained friable fragments of yellow and pink, lobulated, partially necrotic soft tissue.

Diagnosis: ***Carcinosarcoma***

DISCUSSION

Definition: Metaplastic carcinoma refers to a heterogeneous group of neoplasms generally characterized by an intimate admixture of adenocarcinoma with areas of spindle, squamous, chondroid, and osseous differentiation; the metaplastic spindle and squamous carcinomas may present in pure form without any admixture with a recognizable adenocarcinoma. Metaplastic carcinomas should be classified into distinctive subtypes according to the phenotypic appearance of the tumor. Immunohistochemical confirmation is required for the spindle cell tumors.

Background and Clinical Features

First described by Huvos et al (13), the average age of the patients in that series, the clinical presentation, and the overall 5-year survival of 55% were not considerably different from that of regular infiltrating duct carcinoma. When tumors with spindle and squamous differentiation were combined in one group, 56% of the women had axillary node metastases and they had a 63% 5 - year survival. Only 19% of neoplasms showing osseous and chondroid metaplasia had axillary node metastases and their 5 -year survival was 28%. Classification according to the apparent phenotype of the tumor is now required. If the tumor shows pure squamous differentiation, it is designated as squamous carcinoma. If the adenocarcinoma shows osseous differentiation, it should be designated as such. Interestingly, a case of carcinoma with

chondroid differentiation that metastasized to the uterus closely mimicked a primary uterine mixed mesodermal tumor (23).

The classification of metaplastic carcinomas into specific variants is illustrated in Table 1.

Table 1. 2003 WHO Classification of Metaplastic Carcinomas

PURE EPITHELIAL

Squamous Carcinoma

a. Large cell type, keratinizing or nonkeratinizing
b. Squamous carcinoma with spindle cell metaplasia (with or without acantholytic changes)

Adenosquamous Carcinoma, including mucoepidermoid variant

a. High grade
b. Low Grade

Adenocarcinoma with spindle cell metaplasia

MIXED EPITHELIAL/MESENCHYMAL

Carcinoma with Chondroid differentiation

a. Regular infiltrating duct or other type of carcinoma with focal chondroid differentiation
b. Chondroid carcinoma

Carcinoma with Osseous Differentiation

Carcinosarcoma (Specify components)

PURE EPITHELIAL

Squamous Carcinoma

Definition: A breast carcinoma entirely composed of metaplastic squamous cells that may be keratinizing, non-keratinizing or spindled and clearly not derived from the overlying skin or from other sites.

Clinical Features: Squamous carcinomas are rare accounting for significantly less than 1% of all invasive breast carcinomas. The patients range in age from late 20's to mid 80s with an average age of around 54 years. They present with a palpable mass that may get large enough to ulcerate through the skin. Origin from the overlying skin should be excluded.

This can be difficult in cases where large tumors become fixated to the skin. Mammographic presentation is with a mass lesion as calcifications rarely occur, but there are no specific mammographic findings (22).

Cytologic Features: It is possible to establish or at least suggest the possibility of a squamous carcinoma when atypical squamous cells are present in the cytology preparation, but metaplastic carcinomas can be a source of diagnostic problems on aspiration cytology (4,5,14). When only well differentiated squamous cells are identified, it is important to rule out the possibility of reactive squamous metaplasia around a prior biopsy or aspiration site.

Macroscopic Features: With a median size of 3 to 4 cm, more than half of these well-circumscribed tumors are over 5 cm with multiple and generally small cysts apparent in the larger tumors.

Microscopic Features: Squamous carcinomas assume several phenotypes including large cell keratinizing, poorly differentiated, and less frequently spindle cell and acantholytic types; some show a combination of patterns. The tumor cells often proliferate around irregularly shaped, small cystic spaces. The most bland appearing and well differentiated cells often line the cystic spaces; as the tumor cells emanate out infiltrating the surrounding stroma, they spindle out and lose their squamous features. A pronounced stromal reaction is often admixed with the spindled squamous carcinoma. The squamous differentiation is retained in the metastatic foci.

Special Studies: The spindle cell and acantholytic variants require immunohistochemical confirmation of their epithelial nature. The tumor cells are positive with kermix and CK903, CK5, EGFR but negative for Factor VIII or CD34. Nearly all squamous carcinomas are negative for ER and PR (27, 34). Common genetic aberrations in the acantholytic variant include loss at 3p11-p25, 5q21-p25, 8p, 9, 13p13-q21, 16q12-q21, and 17p while gains are noted at 1q31-qter, 7p, 18q12-qter, 19q and 20 by CGH (Aulmann et all 2005). The acantholytic variant has reduced E-Cadherin staining (Aulmann et al 2005).

Prognostic factors and Behavior: Given the tumor size of over 5 cm in many cases, metastases to axillary nodes are relatively uncommon; approximately 10% to 15% of pure squamous carcinomas have axillary node metastases (34). Advanced stage and lymph node involvement are associated with a more aggressive course as anticipated. Among squamous carcinomas, the acantholytic variant may exhibit a more aggressive behavior (7) and may be confused with angiosarcoma. The positive reaction of the tumor cells with keratin and negative reaction with Factor VIII or CD34 rules out the possibility of an angiosarcoma.

Adenosquamous Carcinoma: While focal squamous differentiation has been observed in 3.7% of infiltrating duct carcinomas (6), a prominent admixture of invasive ductal and squamous carcinoma is not common. The gross appearance of these generally ill-defined lesions varies depending on the amount of squamous differentiation which manifests as pearly white nodules. The squamous component is often keratinizing and ranges from very well differentiated keratinizing areas to poorly differentiated non-keratinizing foci. The few reported cases have been aggressive, but behavior is generally a reflection of the degree of differentiation of the two components of the lesion. Some have included infiltrating syringomatous adenoma as a low grade variant of adenosquamous carcinoma (4, 21, 30); infiltrating syringomatous adenomas have a tendency to recur because their infiltrative nature makes complete excision difficult, but they do not metastasize.

Hormone Receptors: The squamous component is negative for both ER and PR, while the positivity of the ductal carcinoma component for ER and PR depends on its degree of differentiation.

Mucoepidermoid Carcinoma: Eight tumors have been described as examples of low grade mucoepidermoid carcinoma comparable to those occurring in the salivary glands.

Adenocarcinoma with spindle cell differentiation: Spindle cell differentiation also occurs in adenocarcinomas, albeit rarely. The intraepithelial component of this lesion may also have prominent spindle cell morphology. Spindle adenocarcinoma is more readily recognized as a glandular process when it presents as a papillary lesion or when the spindle cells are in continuity with cribriform arrangements. To qualify as a spindle cell carcinoma (adeno or squamous), the spindle cells should be cytokeratin positive whether the cells appear bland or anaplastic. Spindled adenocarcinoma is negative for CK903, while spindle cell squamous carcinoma is positive for CK903.

MIXED EPITHELIAL/ MESENCHYMAL

Adenocarcinoma with chondroid differentiation: Generally reported together with adenocarcinoma showing osseous differentiation under the umbrella term of "matrix producing carcinomas," not much is known about either as a separate entity. Chondroid and osseous differentiation occur focally in 0.2% of breast carcinomas (15). The tumors are generally well circumscribed nodular masses that may become massive (up to 20 cm) resulting in nipple displacement and ulceration through the skin. Macroscopically, the tumors are generally well-defined and firm. The cut surface has glistening areas corresponding to the foci of chondroid differentiation. Microscopically, some show an infiltrating duct carcinoma admixed with areas of bland chondroid differentiation. Others appear as a predominantly chondroid mass with a rim of peripheral cellularity composed of cells with overlapping epithelial and chondroid features; some of these cells show clustered to tubular arrangements. The metaplastic tumor cells are S-100 positive and simultaneously express kermix, but are negative for actin. Axillary node metastases may or may not have the chondroid differentiation

Ultrastructural Features: The tumor cells range from those rich in tonofilaments and desmosomal attachments to more rounded cells with short microvilli, abundant rough endoplasmic reticulum, prominent Golgi apparatus and rare lipid droplets. The latter reflect the chondrocytic cells and are surrounded by a territorial matrix (25).

Adenocarcinoma with osseous differentiation: These tumors are characterized by an admixture of adenocarcinomas (most often ductal type) with areas of benign osseous differentiation some of which may be through enchondral ossification.

Hormone Receptors: Many of these matrix producing carcinomas are negative for ER and PR both in the adenocarcinoma as well as the chondroid or osseous areas.

Carcinosarcoma

Neoplasms with a true sarcomatous component admixed with carcinoma are essentially biphasic should be referred to as carcinosarcomas regardless of their mode of origin (25, 26). Any or both components of carcinosarcoma may metastasize. The sarcomatous component in these tumors does not display epithelial features immunohistochemically or ultrastructurally. Molecular analysis of a small number suggests derivation of the sarcomatous component through cumulative alterations beyond those present in the carcinomatous elements; these findings support the conversion hypothesis as a multi-step mechanism for the histogenesis of carcinosarcomas (36).

Prognostic Factors and Behavior: About 19% to 25% of cases have axillary node metastases (15,31), and 21% have distant metastases. Axillary node metastases are not as common as one might anticipate from the large size of many of these tumors. When metaplastic carcinomas metastasize to the axillary nodes or beyond, they retain and often manifest their metaplastic potential. In studies combining carcinomas with chondroid and osseous metaplasia, the five year survival has ranged from 28% to 68% (13,15,33).

There is not much information available on the efficacy of current therapies in the management of metaplastic carcinomas. A recent review of 27 such cases from Mayo Clinic concluded that patients with metaplastic carcinoma, particularly those with metastatic disease, could be appropriate candidates for innovative therapeutic regimens since systemic therapy appeared to be less effective in their management (20).

Table 2. Immunohistochemical profile of various spindle cell carcinomas.

Marker	Squamous	Adenocarcinoma	Myoepithelial
CK34BE12	+	-	+
ER, PR	-	+	-
Tonofilaments	++	rare	rare
Pinocytotic Vesicles	-	-	+

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FIGURES

Fig. 14a. Squamous carcinoma. Irregular nests of well to moderately differentiated squamous carcinoma proliferate in a prominent fibroblastic stroma.

Fig. 14b. Squamous carcinoma. Well differentiated squamous epithelium is at the center, while less differentiated cells at the periphery extend into the surrounding stroma.

Fig. 14c. The well differentiated squamous cells have distinct and often thickened cell membranes.

Fig. 14d. Squamous carcinoma. The squamous cells show intense positivity with CK5/6.

Fig. 15a,b. Spindle cell adenocarcinoma. The tumor is composed of sheets of epithelial spindle cells (a) and (b) clear cut adenocarcinoma.

Fig. 15c. Spindle cell adenocarcinoma. The spindle cells show significant atypia and abundant eosinophilic to amphophilic cytoplasm.

Fig. 16a. Carcinosarcoma. Invasive epithelial cell aggregates are intimately admixed with a spindle cell sarcoma.

Fig. 16b. Carcinosarcoma. The mesenchymal component contains atypical cells, and patches of osteoclastic multinucleated giant cells.

Fig. 16c. Carcinosarcoma. Immunostain for AE1/AE3 decorates the epithelial component while the mesenchymal elements fail to immunoreact.

Fig. 16d. Carcinosarcoma. DIN 2 (DCIS, grade 2) was present in multiple ducts around the tumor.

CASES 17 AND 18

CASE 17. Clinical History (CTTR Acc 28599): A 43-year old Hispanic female on oral contraceptives developed a mass rapidly enlarging over 5 months in the right breast with an estimated size of 5.0cm on physical exam. The excisional biopsy contained a translucent pink-white, friable, soft myxoid "leaf-like"/papillary-appearing tissue measuring 4.3 x 4.0 x 3.0 cm.

Diagnosis: ***Myxoid fibroadenoma with focal leaf-like processes***

CASE 18. Clinical History (CTTR Acc 29521): A 60-year-old female presented with a lump in her right breast, identified during a monthly breast exam. There was accompanying pain and tenderness in the breast. The pain also extended to the front of the chest and radiated into the left arm. Bilateral mammograms revealed an 8.0 cm mass within the right breast. The nearly 11 cm excisional biopsy contained a gray-tan lobulated tumor measuring 7.0 x 7.0 cm and contiguous with smaller nodules. At least one nodule extended to the margins of resection.

Diagnosis: ***Phyllodes Tumor***

DISCUSSION

Biphasic Tumors of the Breast

Definition: Biphasic tumors of the breast constitute a distinctive group of lesions that are characterized by a simultaneous proliferation of both epithelial and mesenchymal elements. Depending on the presence of benign or malignant morphologic features within either the mesenchymal or the epithelial component, various combinations may occur. Best known among these, are fibroadenoma and phyllodes tumors.

Fibroadenoma (FA)

Distinguished by proliferation of a relatively hypocellular but dominant stroma around epithelial/myoepithelial lined spaces, the dominant and most conspicuous abnormality in fibroadenomas is the stromal proliferation.

The third most common mammary lesions, fibroadenomas originate in the terminal duct-lobular unit (lobules) and appear to develop from coalescence of adjacent fibroadenomatous nodules. It is not uncommon to find fibroadenomatous hyperplasia around fully developed fibroadenomas. This is why sometimes excision of a FA is followed by development of one or more new tumors.

Fibroadenomas present as a generally painless solitary, well-circumscribed and freely moveable mass. The average age of women with FA ranges between 20 and 33. The juvenile variant of FA is the most common mammary lesion in the adolescent female. It may display rapid growth and massive size.

The frequent occurrence of FA during the reproductive age and its lower prevalence in an involuted form (small, sclerotic, hyalinized) in postmenopausal women who are not on hormone replacement therapy supports the role of estrogenic hormones in development and maintenance of fibroadenomas. Myxoid mammary fibroadenomas have been observed in some patients suffering from Carney's syndrome, a complex of cardiac and cutaneous myxomas, spotty pigmentation, and endocrine overactivity.

It has been suggested that fibroadenomas are associated with a relative risk of 2.17 for subsequent development of invasive breast carcinoma; this risk is relative to that of women without fibroadenomas for subsequent development of invasive breast carcinoma. The risk is generally associated with those that contain epithelial proliferations or sclerosing adenosis.

Pathologic Features

Well-circumscribed, oval to round, the typical fibroadenoma is 2-3 cm and has a gray-white, bulging cut surface. Those occurring during adolescence may have a more fleshy consistency, while those with myxoid stromal change display a gelatinous appearance. Hyalinized fibroadenomas have a rock-hard consistency. Massive tumors of about 20 cm may occur in adolescent females.

Microscopically, fibroadenomas most often display an intracanalicular growth pattern they may also show a pericanalicular pattern when occurring in adolescent females. It is not uncommon to find focal intracanalicular growth in many juvenile fibroadenomas (JFA) where the pericanalicular pattern dominates. When rarely an otherwise typical fibroadenomas displays focal leaf-like processes (phyllodes architecture) the term fibroadenoma phyllodes would be appropriate.

A gynecomastoid pattern of ductal intraepithelial epithelial proliferation of the low risk DIN type (IDH) characterized by formation of irregular tufts overlying a stratified epithelium is not uncommon in JFA. Other patterns of DIN may also occur less frequently. Lobular neoplasia also occurs in fibroadenomas. A variety of metaplastic changes may develop in the epithelial (apocrine, squamous) and stromal (myxoid, mucinous, adipose) components of FA. Less commonly, atypical and bizarre multinucleated giant cells are identified focally or diffusely in the stroma; they are benign and have no prognostic significance.

Spontaneous infarction rarely occurs (in significantly less than 1% of cases) particularly during pregnancy and lactation. Hemorrhagic infarction may occur following fine-needle aspiration.

Core Biopsy: Fibroadenomas are easily recognizable on core biopsies. The classic biphasic pattern is evident.

Fine-Needle Aspiration: The typical FA aspirate appears far more cellular than one anticipates from a fibroadenoma. Characteristic are fenestrated sheets of evenly spaced, polygonal, or multilayered epithelial cells in branching formations (antler horn clusters) with myoepithelial cells adherent to the clusters or loose in the background and often appearing as bipolar naked nuclei.

Treatment

Ordinary fibroadenomas are generally shelled out without any further complications or recurrences. A small proportion of lesions are associated with significant fibroadenomatous hyperplasia around the main tumor mass. These may lead to development of additional lesions that are generally interpreted as recurrences because of their proximity to the previous lesion. Full understanding of these recurrences is not clear at this time. Management of carcinoma arising in fibroadenoma should follow treatment recommendations for carcinoma in the breast proper.

Phyllodes Tumor (PT)

Described by Johannes Mueller in 1838, phyllodes tumor accounts for 0.3% of malignant breast lesions and about 2.5% of all fibroepithelial lesions of the breast.

PT is observed most frequently among women 45-49 years of age - that is about 15 to 20 years older than the age of women with fibroadenoma. Women with aggressive phyllodes tumors are even older by approximately 7 years compared to all patients with phyllodes are tumor.

The clinical presentation is that of a painless, lobulated and freely movable breast mass. Large tumors, whether benign or malignant, may cause stretching and ulceration of the overlying skin with distension of the superficial vein.

Axillary node enlargement, observed in nearly 20% of cases, is generally due to reactive changes; actual lymph node involvement occurs rarely by contiguous growth.

Pathologic Features

Phyllodes tumors have a median size of around 6 cm, but may exceed 20 cm. The typical phyllodes tumor is solitary, well-circumscribed, solid with cystic areas. Fleshy leaf-like processes protrude into the cystic spaces. In some lesions, however, cysts may be barely visible.

Microscopically, PT consists of a benign epithelial component and a cellular, spindle cell stroma, forming leaf-like processes that protrude into cystic spaces. The cellular, hyperplastic stroma of phyllodes tumor is in sharp contrast to the hypocellular appearance of fibroadenomas. The benign epithelium lining the ducts and slit-like spaces and covering the leaf-like processes consists of the two cell layers: epithelial cells along the luminal aspect and the myoepithelial cells beneath them.

The stromal cells are spindle-shaped and either fibroblastic or myofibroblastic in nature. A variety of mesenchymal metaplastic changes may occur including osseous, chondroid, lipoid, rhabdomyoblastic and smooth muscle change. A multinucleated floret-type stromal giant cell of no prognostic significance is present in some cases. When morphologically malignant, the stromal component generally assumes a fibrosarcomatous appearance, but liposarcoma, chondrosarcoma, osteosarcoma, rhabdomyosarcoma hemangiopericytoma, and malignant fibrous histiocytoma can also develop in PT. In a significant proportion of cases, the sarcomatous component defies classification as a distinct soft tissue sarcoma.

Core Biopsy: Phyllodes can be easily recognizable on core biopsies when a hypercellular, or malignant stroma is evident in the biphasic tumor. Since the appearance of PT is variable in different areas, it is possible that the biopsied sample may lack diagnostic features.

Fine-Needle Aspiration: There is significant overlap in the appearance of PT and FA in cytology preparations making accurate diagnosis of PT difficult on cytology. The presence of low epithelial/stromal ratio, epithelial atypia, 'columnar' stromal cells with visible cytoplasm and stromal giant cells favor a diagnosis of PT (Tse et al 2002). Of course the presence of obvious sarcoma in a biphasic tumor would also indicate a PT.

Grading and Correlation of Histologic Features with Clinical Behavior

Phyllodes tumors manifest their aggressive potential mainly in the form of local recurrences sometimes with progression to a more aggressive morphologic appearance and far less frequently in the form of metastases. It is, however, extremely difficult to reliably predict the behavior of PT on the basis of its histologic features.

A fairly good prediction of the behavior of phyllodes tumors can be made, however, by evaluating several pathologic features, including tumor size, contour, stromal atypia, mitotic activity and sarcomatous overgrowth. Opinions vary regarding the prognostic significance of various gross and histologic parameters, however. Based on a composite evaluation of the number of mitotic figures, atypia, and tumor contour, numerous investigators have proposed subdivision of phyllodes tumors into benign, intermediate (borderline), and malignant groups. The criteria proposed by various investigators for this subdivision are different, however. The difference is primarily in the number of mitotic figures allowed for each subgroup and the weight accorded to stromal cellularity and atypia as factors influencing the subdivision. Although addition of a borderline category may appear useful, the criteria advanced so far seem more helpful in creating an arbitrary histologic separation than in providing clinical predictive values.

It is important to keep in mind that even benign PT may recur. Stromal overgrowth is another factor with prognostic significance; this feature has been quantified relatively recently. Defined as an overgrowth of the sarcomatous component to the point that epithelial elements are absent in at least 1 low-power field (4X magnification), stromal overgrowth was found in 6 of 7 women who died of tumor in a review of 26 cystosarcomas by Ward and Evans.

No single histologic feature can reliably predict the behavior of PT; a combination of tumor size, margin, atypia, and mitotic activity are helpful as a guide in predicting the behavior of these

lesions, but clearly not in an absolute way. In the 1967 study from AFIP (Norris & Taylor), none of the 15 tumors that proved fatal was smaller than 4 cm, but did recur in 11% of cases. More than a third (38%) of tumors with infiltrating margins recurred and 35% of the patients died of their tumor. Of those with "pushing" margins, 15% recurred and the tumor was lethal in only 3%. Of the 15 tumors that proved fatal, only 5 (33%) had 3+ atypia (scale of 1 to 3), whereas of the 30 lesions with 1+ atypia, 27% recurred and 7% proved fatal. Tumors with 5 or more mitotic figures/10 hpf accounted for 11 of the 15 deaths. Of tumors with 0 - 2 mitotic figures/10 hpf, 17% developed recurrence, and 18% of those with only 3 - 4 mitotic figures/10 hpf died from the tumors, despite radical mastectomy in one case. Of course, if a specific sarcoma is identified, then it is included in the diagnosis; for example liposarcoma arising in a phyllodes tumor. Most tumors with intermediate features, are currently designated as borderline PT (WHO 2003). The importance of clear/negative margins were significantly associated with reduced recurrence hazard by 51.7% (Tan et al).

The presence of **tumor at the resection margin** is a major determinant of local recurrence and should be noted in assessment of these lesions. Kocova and colleagues have found a good correlation between conventional grading of PT based on histologic criteria and MIB1 indices (MIB1 monoclonal antibody directed against cell proliferation-associated Ki-67 antigen; the MIB1 index expresses the percentage of MIB1 positive proliferating stromal cells). In another study, the stromal cells in 89% of high grade PTs expressed Ki-67, compared to 43% of low grade PTs; the epithelial cells of high grade PT had Ki-67 expression in 33% of the cases, compared to 14% in the low grade lesions (Dacic S et al 2002). Increased p53 expression has been noted among malignant phyllodes tumors, but not in lower grade PT or fibroadenomas; also a distinctive pattern of p53 immunostaining was observed among high grade PT by Millar, et al (1999). This expression is associated with known negative prognostic factors (overgrowth, nuclear pleomorphism, mitotic count of the stromal cells, an infiltrative tumor margin and high grade of the tumor), but is not a useful determinant of tumor recurrence or long-term survival (Feakins, 1999).

Differential Diagnosis

When sarcomatous overgrowth is pronounced, a pure sarcoma becomes an important alternative. In such cases, adequate sampling of the tumor (one tissue section per each centimeter of maximum tumor diameter) is necessary to identify the epithelial elements. Furthermore, since the recurrence of some phyllodes tumors may be in the form of a pure sarcoma, availability of a thorough history concerning any previous biopsies is essential.

The distinction from cellular fibroadenomas is made predominantly on the basis of absent phyllodes structures in FA.

Recurrence and Metastases

In general, approximately 30% of phyllodes tumors develop recurrences, and a majority does so within 2 years after the diagnosis; some recur in excess of 10 times over a 20 year period. Recurrences generally retain the histologic features of the original neoplasm, but may develop more aggressive phenotype. Metastases are preceded by local recurrences develop in about 50% of patients.

Metastases through the bloodstream occur in less than 10% of cases; a majority of the tumors (66%) metastasize to the lungs. Metastases have been reported to almost all organ sites, however. Lymph node metastases are generally absent, but have been described in about 15% of metastatic neoplasms. With rare exceptions, the metastatic tumors have been devoid of epithelial elements.

Treatment

The current treatment of choice is wide local excision to achieve complete excision of the tumor. Simple mastectomy is reserved for massive tumors, lesions with infiltrating margins, those with aggressive histologic features that would defy total excision with a clear margin by a lesser procedure, and for local recurrences of borderline and malignant lesions. Given the rarity of axillary node metastases by PT, axillary node dissection is not necessary. While pulmonary metastases may be resectable, surgical management for metastatic disease has proven discouraging. The efficacy of chemotherapy has not been established. Cure and survival over 10 years are rare after metastases, but they have occurred.

Periductal Stromal Sarcoma

The term "cellular periductal stromal tumor" has been applied to conventional phyllodes tumors by some pathologists. I prefer to use the term "periductal stromal sarcoma" for a specific and rare biphasic neoplasm. Characterized by a cellular, sarcomatous, spindle cell proliferation forming cuffs around tubules with open lumens, these lesions lack the leaf-like processes of typical PT and invariably dissect irregularly into the adjacent breast tissue. The tumor generally presents as a palpable mass in women between ages of 44 and 62.

Pathologic Features

A delineated firm nodular or lobulated mass characterizes most tumors. Microscopically PSS is often partially circumscribed, one or multiple nodules show periductal proliferation of spindle cells (Fig. 1). The ducts and lobules around which the spindle cells proliferate retain their configuration with either no or only minimal distortion. Mitotic figures (> 3/10 high power fields) and/or atypia are invariably present. Adipose tissue separates the sarcomatous cuffs in some cases. While the tumor is at least partially circumscribed, it lacks a phyllodes pattern and invariably infiltrates the surrounding mammary adipose tissue. The morphologic differences between these tumors and typical phyllodes tumors may be a reflection of the origin of PT in the TDLU, while PSS originates from the stroma around larger ducts.

While long term follow-up is not available on too many of these tumors, they appear to behave as low grade PT unless an aggressive sarcoma develops within them. Recurrences may develop and the lesion may evolve into a typical PT when it recurs.

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Periductal stromal sarcoma

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FIGURES

(see page 81)

Fig. 17a. Fibroadenoma with myxoid change and leaf-like processes.

Fig. 17b. Focal leaf-like appearance.

Fig. 17c. The compressed ducts have epithelial and myoepithelial lining classic and leaf-like processes and hypercellular stroma.

Fig. 18a. Phyllodes tumor. Classic leaf-like processes and hypercellular stroma.

Fig. 18b,c. A periductal stromal sarcoma pattern (b) with osteoid (c) and atypical hypercellular stroma.

CASE 19

Clinical History (CTTR Acc 29772): A 55-year old female noted a right breast mass. On physical examination, the mass measured 3.0 cm, and appeared firm, smooth and round. A lumpectomy was performed. The cut surface of the specimen revealed a 4.0 x 3.2 x 2.5 cm pale tan, yellow-tan, soft and fibrous, well-circumscribed nodule.

Diagnosis: ***Myofibroblastoma***

DISCUSSION

In 1987, Wargotz et al. described 16 cases of a tumor that was composed predominantly of "cells having features of both fibroblasts and smooth muscle cells". The neoplastic cells were regarded as myofibroblasts with cytoplasmic stress fibers, cells junctions and basal/laminar-like material evident at the ultrastructural level, meeting the criteria for a myofibroblastoma.

Myofibroblastoma is a benign and rare mesenchymal neoplasm that occurs in the breast over a wide age range (25-85 years), with an average age of 63. It is important to recognize myofibroblastomas in order to avoid misinterpretation of the lesion as a spindle cell carcinoma. Although originally reported to be more frequent in men, at present they are considered to arise with equal frequency in both sexes. The lesion is most frequently unilateral and solitary with only one case of synchronous bilateral lesions described. Clinically, it appears as a mobile nodule not adherent to the skin usually present for several months duration. The neoplasm ranges in size from 1.0 to 4.0 cm, with a mean diameter of 2.3 cm, but rarely exceeds 10 cm. The lesion displays well-circumscribed margins and the gray-pink cut surface has a vague lobulated appearance.

Microscopically the lesion is bound by a pseudocapsule and generally does not contain glandular epithelium. Rarely, the margins appear irregular. The cellularity of the lesions is variable. Some tumors contain hypercellular areas, others show a loose edematous to occasionally myxoid stroma. In some cases the cellularity varies from area to area within the same tumor creating a multilobulated appearance to the lesion. The proliferating cells are arranged in short fascicles and are spindle shaped. The cytoplasm is eosinophilic and the nuclei are round to ovoid, with an irregular nuclear membrane, dispersed chromatin and distinct small nucleoli. Multinucleated floret-like giant cells are not uncommon. Mast cells are always present, but mitotic figures are infrequent. The short cellular fascicles are separated by generally thick bands of hyalinized collagen. Most tumors have variable amounts of adipose tissue; some consider this a true component of the lesion, while others believe it reflects entrapped adipose tissue.

Rarely, the cells appear epithelioid and the nuclei may be pleomorphic and irregular; giving rise to the term "atypical myofibroblastomas". These cases do not differ significantly in prognosis from the more conventional forms. Occasional cases containing foci of mature cartilage or areas with smooth muscle differentiation have been reported.

Myofibroblastoma (MFB) and solitary fibrous tumors (SFT) of the breast have significant overlapping features which has led Damiani et al to consider them as identical lesions. Both show proliferations of bland-appearing spindle cells intermixed with variable amounts of collagen. Immunoreactivity for vimentin and negativity for cytokeratin and S100 protein has been documented in both tumors. While intense CD34 positivity is observed in solitary fibrous tumors, positivity has also been observed in myofibroblastomas. Expressed in normal mammary stromal cells, CD 34, the human progenitor cell antigen, may be involved in the pathogenesis of many mesenchymal tumors of the breast. Variability in the distribution of cellular areas (more haphazard admixture of hypercellular and hypocellular areas in SFT in contrast to the organized distribution resulting in a multilobulated appearance in MFB), slightly older age of patients with SFT and presence of a range of fibroblasts and myofibroblasts along with occasional cartilage and smooth muscle in MFB have been used by some (Salamao et al) who insist on separating the two lesions. Possibly more significantly, Salamao et al have used immunoprofile of the 2 lesions to retain them in separate groups (Table 1); the four SFT lesions in their study did not express actin, SMA, or desmin, while the 9 MFB tumors in their study expressed desmin and most also expressed actin and/or SMA. It is noteworthy that only one desmin antibody was used and 5 of the MFB had only 1+ positivity with desmin.

In our experience, using more than one antibody for desmin often results in more positive cases. This controversy appears to have no clinical significance since both lesions are benign, but we need to assess a larger number of mammary SFT before this issue can be resolved definitively.

Malignant variants of myofibroblastoma are characterized by numerous mitotic figures, areas of atypia and infiltrating margins (Gocht et al, 1999).

Cytogenetically, partial monosomy 13q and partial monosomy 16q have been reported.

The typical lesion never recurs and excision of the lump is the optimal treatment.

Table 1. Immunoprofile of Myofibroblastoma and solitary fibrous tumor

	AE1/AE3	Desmin	Actin	Sm. Muscle Actin	CD 34
Myofibroblastoma	-	+	±	±	±
Solitary Fibrous Tumor	-	-	-	-	+

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FIGURES

Fig. 19a. Myofibroblastoma. The lesion is well delineated and composed of spindle cells

Fig. 19b. Myofibroblastoma. Thick collagen bands are a common finding.

Fig. 19c. Myofibroblastoma. Focally, the cells assume an epithelial configuration.

CASES 4, 20, 21 and 22

CASE 4. Clinical History (CTTR Acc 28093): During the course of a routine physical examination, a mass was identified in the right breast of a 17-year-old female. The patient stated that she had been aware of the mass for years, but thought it was normal. The mass was excised. The specimen consisted of a 29.6 gram, 7.0 x 6.0 x 1.0 cm fibroadipose tissue with a cut surface composed of numerous cysts ranging from 1 to 3 mm. The gross appearance was that of a sponge containing mucoid material

Diagnosis: ***Florid low risk ductal intraepithelial neoplasia (intraductal hyperplasia).*** (A nice example of "juvenile papillomatosis").

CASE 20. Clinical History: A 57-year-old female presented with new microcalcifications on her mammogram. A core biopsy was performed. The image represents the most advanced lesion in the core biopsy.

Diagnosis: ***Flat DIN1 (Flat epithelial atypia)***

CASE 21. Clinical History: A 52-year-old woman was found to have extensive microcalcifications on her first screening mammogram. A core biopsy was followed by lumpectomy.

Diagnosis: ***DIN2 (Ductal carcinoma in situ, grade 2)***

CASE 22. Clinical History: A 48-year-old woman with a family history of breast cancer was found to have an irregular density with a few microcalcifications in her left breast; a core biopsy was performed.

Diagnosis: ***DIN2 (Ductal carcinoma in situ, grade 2)***

DISCUSSION

Ductal Intraepithelial Neoplasia (Intraductal hyperplasia, atypical intraductal hyperplasia, ductal carcinoma in situ)

Definition:
Ductal intraepithelial neoplasias are a group of cytologically and architecturally diverse lesions confined to the mammary duct-lobular system and associated with an increased risk, albeit of different magnitudes, for subsequent development of invasive carcinoma.

Site of Origin, Distribution of Lesion, and Route of Lesion Progression
A vast majority of ductal intraepithelial proliferations originate in the terminal duct-lobular unit (TDLU). A substantially smaller proportion originates in larger and lactiferous ducts.

Clinical Features and Epidemiology

The age range of women with DIN lesions is wide, spanning 7 to 8 decades post adolescence. All these lesions are extremely rare prior to puberty and when they do occur among infants and children, they generally a reflection of exogenous or abnormal endogenous hormonal stimulation. The mean age for DCIS is between 50 to 59 years. An increasing number of these lesions are detected mammographically.

Proliferative changes are present in nearly 60% of breast biopsies. The reported frequency of atypical proliferations ranges from 1.7% to 19% of breast biopsies. The precise frequency of atypia is difficult to determine, however. In an autopsy study of young and middle-aged (20 to 54 years) Danish women, atypical ductal proliferations were noted in 7% of the women, while DCIS was noted in another 13% of the women {Nielsen et al.,1987}. Among 207 consecutive autopsies of Australian women over 15 years of age, AIDH was found in 12.6% and DCIS in 12.6% {Bhathal et al.,1985}.

A striking increase in the detection of DCIS has been noted with the introduction of widespread screening mammography and increasing awareness of breast cancer in the general population since 1983. The average annual increase in the incidence rate of DCIS in the decade of 1973 to 1983 was 3.9% compared to 17.5% annually in the decade between 1983 to 1992, increasing from 2.4 per 100,000 women in 1973 to 15.8 per 100,000 in 1992 for women of all races, an overall increase of 557% (Ernster et al, 2001). In the US, data from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program noted that the proportion of breast carcinomas diagnosed as DCIS increased from 2.8% in 1973 to 14.4% in 1995 {Dupont et al.,1993}. While close to 90% of pre-mammography DCIS were of the high-grade comedo type, nearly 60% of mammographically detected lesions are non-comedo and this percentage is increasing.

Mammographic Features

Microcalcifications are the more common mammographic abnormality among women younger than 50 years of age, whereas densities and asymmetric soft tissue alterations are more common among those over 50 years of age.

The mammographic calcifications in DCIS either form linear casts, granularity with either a crushed stone or a powdery appearance, or a combination of the two and present in a clustered or dispersed arrangement that may outline the distribution of one or more branching involved ducts. The linear casts are more frequently encountered among comedo (necrotic) variant of DCIS, whereas a granular, snake-skin pattern is more common among the lower grade non-necrotic lesions. The mammographically based extent of DCIS may underestimate the actual extent by as much as 2 cm in 12% to 50% of lesions depending on their subtype {Holland et al.,1990}. The proportion of palpable tumours decreased from 54% in the premammographic era (1969-1985) to 12% in the post-mammographic period (1986-1990) in one study, while the mammographically detected DCIS increased from 19% to 80% {Pandya et al.,1998}.

Pathologic Features
A vast majority of intraductal proliferative lesions, particularly those detected mammographically, are not evident on macroscopic inspection of the specimen. Criteria for diagnosis of various subtypes of intraductal epithelial proliferation are listed in Tables 3-5 below. Proper assessment of these proliferative lesions requires evaluation of both architectural features at low magnification and cytological features at higher magnification. Grading relies on assessment of cytological features and to a lesser extent, presence or absence of intraluminal necrosis. A range of intraductal proliferative lesions is often present in a given biopsy.

Low risk DIN1 (Intraductal Hyperplasia)
IDH is characterized irregularly shaped and sized secondary lumens, often peripherally distributed, and streaming of the central bolus of proliferating cells. Epithelial bridges are thin and stretched and nuclei are unevenly distributed. Cytologically, the lesion is composed of cells with indistinct cell margins, variation in the tinctorial features of the cytoplasm and variation in shape and size of nuclei (Table 2). Admixture of epithelial, myoepithelial or metaplastic apocrine cells is not uncommon. The presence or absence of either microcalcifications or necrosis does not impact the diagnosis.

Flat DIN 1 /Flat epithelial atypia (atypical columnar cell change/hyperplasia)
A flat type of epithelial atypia, this change is characterized by replacement of the native epithelial cells by one or more layers of mildly atypical cells often with apical snouts, with occasional mounding, but no arcades or micropapillary formations. The TDLUs involved are often variably distended and often contains secretory mucoid or floccular material and less frequently, microcalcifications (Table 3).

At the molecular level, flat DIN1 shows loss of heterozygosity at loci similar to those found in DCIS and infiltrating duct carcinoma, whether they occur in pure form or in association with in situ and/or invasive carcinomas (Moinfar et al 2000).

Detection on Core Bx: If flat DIN1 is the only lesion on the core biopsy and it diminishes on deeper levels of the blocks, we do not recommend re-excision. If it persists on deeper levels, an additional set of 3 recuts are evaluated to determine if the lesion advances to show more clear cut intraluminal proliferation. Only if it advances to at least AIDH, would we recommend re-excision. Flat epithelial atypia is often multifocal.

Flat DIN1 at or close to the inked margin in cases with more advanced lesions including invasive carcinoma. There is no need for re-excision.

Follow-up studies on this lesion are few. In a review of 9000 breast biopsies initially interpreted as benign, Eusebi et al found 25 cases of flat DIN1 which they designated as "clinging carcinoma, monomorphic type." With an average follow-up of 19.2 years, only one of the 25 women developed local recurrence which was morphologically identical to the original lesion. This indicates lack of progression even if the new focus were residual disease left behind. In another study (EORTC 10853), a randomized clinical trial comparing lumpectomy with or without radiation for DCIS, no local recurrences were noted among 59 women with the monomorphous variant of clinging DCIS (flat DIN1) with a median follow-up of 5.4 years.

DIN 1, ≤ 2mm (AIDH)

The most distinctive feature of this lesion is the proliferation of evenly distributed monomorphic cells with generally ovoid to rounded nuclei. The cells may grow in micropapillae, tufts, fronds, arcades, rigid bridges, solid and cribriform patterns (Table 4). Assessment of the size of the smaller lesions is currently based on measurement of duct cross sections completely involved by one of these patterns. Since the current definition depends on a size measurement, adequate sampling is required to rule out a more advanced process. Microcalcifications of the psammomatous type may be absent, focal or extensive within the lumen of involved ducts; its presence does not impact diagnosis.

DIN 1, >2mm (Low grade or grade 1 DCIS)

Low grade DCIS is composed of cells morphologically identical to those in AIDH growing in arcades, micropapillae, cribriform or solid patterns. Microcalcifications are generally of the psammomatous type. The presence of necrosis is unacceptable within low grade DCIS in most current classification systems. The micropapillary DCIS appears to be associated with a more extensive distribution in multiple quadrants of the breast compared to other variants.

DIN 2 (Intermediate grade or grade 2 DCIS)

Grade2 DCIS is generally composed of cells cytologically similar to those of low grade DCIS, but some ducts contain intraluminal necrosis. Or the cells may display minor size and shape variation with or without intraluminal necrosis. The distribution of microcalcifications is generally similar to that of low grade DCIS.

DIN 3 (High grade or grade 3 DCIS)

High grade DCIS is composed of highly atypical cells proliferating as one layer, forming micropapillae, cribriform or solid patterns with or without intraluminal necrosis and microcalcifications. The former is also designated as the comedo type. Mitotic figures are a common feature, but their presence is not required.

Unusual Variants of DCIS

A minority of the DCIS lesions are composed of spindled {Farshid et al.,2001}, apocrine {Tavassoli et al.,1994}, signet ring, neuroendocrine, squamous or clear cells. There is no consensus or uniform approach to the grading of these unusual variants. Assessment of nuclear features and necrosis can be applied to grading of the unusual variants as well. Using this approach, many apocrine DCIS lesions qualify as high grade, while a minority would qualify as grade 2 or grade 1 DCIS. The clear and spindle cell variants of DCIS are sometimes found coexistent and continuous with typical low grade DCIS, but often the nuclei are moderately atypical qualifying the lesions as grade 2 DCIS. High nuclear grade spindle or clear cell DCIS is extremely rare. A vast majority of apocrine carcinomas are ER, PR and bcl2 negative, but androgen receptor positive {Tavassoli et al.,1996}.

Distribution and Progression of DCIS

Segmentally distributed, ductal carcinoma in situ (DCIS) progression within the duct system is from its origin in a TDLU toward the nipple and into adjacent branches of a given segment of the duct system {Ohtake et al.,1995;Ohuchi et al.,1994;Ohuchi,1999}. The rare lesions that develop

within the lactiferous ducts may progress toward the nipple resulting in Paget's or to the adjacent branches of the reference duct. Progression beyond the duct system and into the surrounding stroma may occur at any point in the intraductal route in higher grade DIN lesions (AIDH/DCIS).

Differential Diagnosis

The solid variant of low grade DCIS may and is often misinterpreted as lobular intraepithelial neoplasia (LIN). Immunohistochemistry for E-cadherin and CK34BetaE12 are helpful in separating the two. DINs of all grades are E-cadherin positive in nearly 100% of cases {Bratthauer et al.,2001;Gupta et al.,1997} and 34BetaE12 negative in 92% of cases {Bratthauer et al.,2001;Moinfar et al.,1999}, whereas LIN is E-cadherin negative {Bratthauer et al.,2001;Goldstein et al.,2001} and 34BetaE12 positive in nearly all cases.

IDH with necrosis, a rare event, is often mistaken for grade 2 DCIS; the diagnosis is based on the cytological features and not the presence of necrotic debris. IDH generally displays either diffuse or a mosaic pattern of positivity with CK34betaE12; it is also positive for E-cadherin.

The presence of individual or clusters of cells invading the stroma (microinvasion) around a duct with DCIS is a frequent source of diagnostic problems. The difficulty is compounded by the frequent presence of dense lymphoplasmacytic infiltrate around the involved ducts. Immunostains for an epithelial and myoepithelial marker are helpful optimally in the form of double immunostaining; the epithelial cell marker can unmask the haphazard distribution of the cells, while the absence of a myoepithelial cell layer would ascertain the invasive nature of the cells in question. Despite all these added studies, the distinction can remain impossible in some cases.

An unknown but relatively small proportion of intraepithelial neoplasias cannot be easily separated into ductal or lobular subtypes on the basis of pure H&E morphology. Using immunostains for E-cadherin and 34βE12, some of these will qualify as ductal (E-cadherin +, 34BetaE12-), some as lobular (E-cadherin-, 34βE12+), while others referred to as mammary intraepithelial neoplasia (MIN) are either negative for both markers (negative hybrid) or positive for both (positive hybrid){Bratthauer et al.,2001}. This group of lesions requires further evaluation as it may reflect a neoplasm of mammary stem cells or the immediate post-stem cells with plasticity and potential to evolve into either ductal or lobular lesion.

Markers and Special studies

There are no markers or special studies that can consistently, accurately or independently separate the various intraductal proliferations (Table 5).

Rationale for Adoption of DIN Classification (Tavassoli, 2005)

Intraductal proliferative lesions of the breast have **traditionally** been **divided into** three categories: **intraductal ductal hyperplasia (IDH), atypical intraductal hyperplasia (AIDH) and ductal carcinoma in situ (DCIS).** Clinical follow-up studies have indicated that these lesions are associated with different levels of risk for subsequent invasive breast cancer, ranging from approximately 1.5 times that of the reference population for IDH, to 4-5-fold (range, 2.4-

13.0-fold) for AIDH, to 8-10-fold for DCIS. It should be noted, however, that the term "DCIS" encompasses a highly heterogeneous group of lesions which differ with regard to their mode of presentation, histopathologic features, biological markers, molecular alterations, and risk for progression to invasive cancer. In many cases, the histopathologic distinction between different types of intraductal proliferation can usually be made on morphologic grounds alone, particularly with standardization of histopathologic criteria. However, even with the use of standardized criteria, the distinction between some of the lesions (particularly between AIDH and low grade forms of DCIS) remains problematic. In addition, the widespread use of screening mammography has resulted in increased detection of lesions that show cytologic atypia but do not fulfill the diagnostic criteria for any of the existing categories. Such lesions have been described in the past as clinging carcinoma and more recently referred to under a variety of names including flat epithelial atypia, atypical cystic lobules, atypical columnar alteration with prominent apical snouts and secretions.

Recent immunophenotypic and molecular genetic studies indicate that the long-held notion of a linear progression from normal epithelium to hyperplasia to atypical hyperplasia to carcinoma in situ and finally to invasive cancer is overly simplistic and that the relationship among these various intraductal proliferative lesions and to invasive breast cancer is far more complex.

These emerging genetic data have raised important questions about the manner in which intraductal proliferative lesions are currently classified. Given the trend toward the use of the term "intraepithelial neoplasia" in many other organ systems and to avoid the term "carcinoma" for non-invasive neoplastic lesions, the new concept of ductal intraepithelial neoplasia (DIN) has been introduced. Although this could be construed as a unifying concept, it is not meant to imply that the multi-step process of carcinogenesis in the breast is identical to that in other organ systems or that there is necessarily a progression of one intraductal lesion to the next.

A translation of traditional terms to the DIN system is provided in Table 1. For purposes of clinical management and tumor registry coding, when the DIN terminology is used, the traditional terminology should be used as well.

Reproducibility: A Major Problem of Traditional Classification

Multiple studies have assessed reproducibility in diagnosing the range of intraductal proliferative lesions, some with emphasis on the borderline lesions {Palli et al 19916;Palazzo et al.,1998;Rosai,1991;Schnitt et al.,1992;Sloane et al.,1998;Sloane et al.,1999}. The results have ranged from lack of a unanimous diagnosis on any case by expert breast pathologists when no standardized criteria are used {Rosai,1991} to a poor kappa value of agreement of 0.33 for atypical hyperplasias {Palli et al.,1996}. When a single set of criteria was used with intensive training in its application, disagreement in diagnosis of AIDH vs. DCIS occurred in 33% of cases {Schnitt et al.,1992}. It has been concluded that there are sufficient problems with reproducibility of the criteria that risk estimates for specific features of borderline conditions, particularly at the individual level, would be ill-advised {Bodian et al.,1993}.

SUBSEQUENT INVASIVE CANCER RISK

Absolute

About 2.2% of women with proliferative breast lesions develop an invasive carcinoma {Kodlin et al.,1977} to 10% {Bodian et al.,1993;Dupont et al.,1987}. Among those with IDH, 2.6% develop subsequent invasive carcinoma {Tavassoli et al.,1990}. Following a breast biopsy diagnosis of AIDH, 3.7% to 22% of the women develop invasive carcinomas {Bodian et al.,1993;Dupont et al.,1987;Tavassoli et al.,1990}. The average interval to the subsequent development of invasive carcinoma is over 14.3 years for women with IDH compared to 8.3 years for those with AIDH {Tavassoli et al.,1990}.

Relative

Using the same set of criteria, drastically different relative risk (RR) figures ranging from a low of 2.4 to a high of 13 have been reported for AIDH {Carter,1988; Dupont,1985; London,1992; Marshall, 1997; McDivitt, 1992; Palazzo1998; Pall,1991}. The higher values are even higher than the RR of 8-10 and 11 suggested for DCIS {Dupont,1985;Fitzgibbons.,1998}. On the other hand, the RR of 2.4 for AIDH reported in one study is much closer to the RR of 1.9 associated with IDH {Marshall,1997}.

RR for IDH is about 1.5-2.0 for subsequent development of invasive carcinoma, while the RR reported for AIDH approximates 2.4-5.0 for subsequent development of invasive carcinoma {Fitzgibbons,1998}.

Trends in Behaviour of DCIS

Interestingly, despite the more limited surgical excisions, mortality from "DCIS" has declined. While 3.4% of women with a diagnosis of DCIS diagnosed between 1978 and 1983 (pre-mammographic era) died of breast cancer at 10 years even though a majority of these women had mastectomy for treatment of their lesion, only 1.9% of women diagnosed with DCIS between 1984 and 1989 died of breast cancer at 10 years despite the increasing trend toward lumpectomy {Ernster et al.,2000}. Judging from the 10-year follow-up period currently available for these women, it appears as if "*DCIS per se is not a life threatening disease* {Ernster et al.,2000}." The deaths that do occur are probably related to an undetected invasive carcinoma present at the time of the initial diagnosis of DCIS, progression of residual incompletely excised DCIS to invasive carcinoma, or development of a de novo invasive carcinoma elsewhere in the breast {Ernster et al.,2000}.

Molecular Alterations (Loss of heterozygosity, LOH) - See Table 6

LOH has been identified frequently in AIDH lesions on chromosomes 16q, 17p, and 11q13 {Lakhani et al.,1995;Lakhani,1999}. Shared LOH patterns among IDH, AIDH, and associated invasive carcinomas strongly supporting a precursor relationship between these lesions and the cancers they accompany {Lakhani,1999; Jones et al, 2003}.

A majority of recurrent DCIS has the same morphology as the original lesion. When more than one grade or cell type is present, any one may be present in the recurrence. While less than 25 paired lesions have been evaluated at the molecular level by either assessment of loss of heterozygosity (LOH) {Lininger et al.,1998} or comparative genomic hybridization (CGH),

recurrences most often have alterations similar to the original lesion but may gain additional ones {Lininger et al.,1998;Waldman et al.,2000}. By LOH assessment, recurrent disease (2-15 years following initial diagnosis) had all the allelic losses seen in the original tumour with at least one additional LOH suggesting same derivation with further genetic progression with time {Lininger et al.,1998}. The losses involved chromosomes 3p, 8p, 11q, 16q, 17p. The acquired molecular changes of the recurrent lesions are not always reflected in morphological alterations. By CGH, the most common findings in the paired specimen (primary and recurrent DCIS) were gains involving chromosome 17q and losses involving chromosomes 8p and 17p. In one case, the recurrent lesions had the same LOH as that found in an area of ADH within the original biopsy rather than the LOH profile of the original DCIS {Lininger et al.,1998}. These findings support focusing on total eradication of the primary lesion (DCIS and ADH) by requiring excision of wide margins and /or postoperative radiation therapy.

Assessment of Size/Extent/Distribution of various intraductal proliferations

The extent or size of UDH does not impact outcome or therapy, whereas the size and/or extent of DCIS does influence management of the lesion. Assessment of size is difficult with many unresolved and problematic issues. Correlation of mammogram, specimen mammogram, and histologic findings are important, but the ultimate decision on many cases is based on the findings in the slides. The mammographically determined size based on microcalcifications underestimates the size in 23% of DCIS lesions when compared to pathologically determined size {Coombs et al., 1997}.

When the entire biopsy sample has been sequentially processed, small localized lesions present on one slide can be measured directly on the microscopic slide. When larger lesions are present in multiple consecutive tissue blocks, the number of involved blocks is multiplied by the thickness of tissue section to obtain the extent of the disease (i.e. lesion present in 3 consecutive blocks of 2.5 mm thickness indicates a size of 7.5 mm). Sometimes the extent on a single block may be 3.5 cm, but the size on consecutive blocks may be only 2.4 cm; in such cases it is important to provide size on a single slide as well as extent distribution on multiple consecutive or discontinuous blocks. When there is involvement of ducts at opposing poles on a tissue block with normal intervening breast tissue, either the extent of lesion distribution is assessed or individual foci are measured with distance between them noted. When the entire sample has not been processed, the volume of lesions could be conveyed by providing the proportion of slides containing the lesion; the volume of lesion appears to influence the chances of recurrence {Goldstein et al.,2000}. Assessment of whole mounts would provide the optimal approach to determination of size, extent and margin status of DCIS.

Factors Influencing Recurrence and Prognosis of DCIS (DIN)

The most important factor influencing the possibility of recurrence is persistence of neoplastic cells post-excision (persistence of residual disease). The significance of margins is mainly to ascertain complete excision. In randomized clinical trials, comedo-type necrosis was found to be an important predictor of local recurrence in the NSABP-B17 trial, while solid and cribriform growth patterns along with involved margin of excision were found to be predictive of local recurrence in EORTC-10853 trial. In retrospective trials, on the other hand, high nuclear grade, larger lesion size, comedo necrosis and involved margins of excision were all found to be predictive of local recurrence following breast conservative treatment for DCIS.

Treatment of DIN

Depending on the extent and grade of the DIN, an awareness of the slightly increased risk and follow-up is all that is necessary for low risk DIN, while mastectomy, breast conserving therapy with radiation therapy for DCIS lesions, or breast conserving therapy with tamoxifen therapy for the very small low grade DCIS are alternatives that have been used. Radiation therapy and tamoxifen have significantly reduced the chances of recurrence {Fisher et al.,1999;Fisher et al.,1995}.

The optimal management is evolving as data accumulates from a variety of prospective studies.

Table1. Translational Table of Traditional and DIN Terminology

Traditional Terminology	Ductal Intraepithelial Neoplasia (DIN) Terminology
Intraductal hyperplasia (IDH)	Low risk DIN
Flat epithelial atypia	Flat DIN 1
Atypical ductal hyperplasia (ADH)	DIN 1 (≤2mm)
Ductal carcinoma in situ, low grade (grade 1)	DIN 1 (>2mm)
Ductal carcinoma in situ, intermediate grade (grade 2)	DIN 2
Ductal carcinoma in situ, high grade (grade 3)	DIN 3

Table 2. Low risk DIN 1/Intraductal Hyperplasia

Architectural features of DIN1a:

1. Irregular fenestrations
2. Peripheral fenestrations
3. Stretched or twisted epithelial bridges
4. Streaming
5. Uneven distribution of nuclei and overlapped nuclei

Cellular features of DIN1a:

1. Multiple cell types*
2. Variation in appearance of epithelial cells
3. Indistinct cell margins and deviation from a round contour
4. Variation in the appearance of nuclei

* an admixture of 2 or more cell types (epithelial, myoepithelial and metaplastic apocrine cells)

Table 3. DIN 1 - Flat type / Flat epithelial atypia

DIN1 - Flat type is characterized by proliferation of a monotonous atypical cell population that replaces the native epithelial cell layer and may show occasional mounding or uniform stratification generally up to 3 - 5 cell layers. The ducts involved are often variably distended and may contain secretory material and less frequently microcalcifications. This pattern is referred as "clinging carcinoma, monomorphous type" by some of our European colleagues.

Table 4. Cytologic Features of both AIDH and low grade DCIS

1. **Monotonous, uniform rounded cell population**
2. **Subtle increase in nuclear-cytoplasmic ratio**
3. **Equidistant or highly organized nuclear distribution**
4. **Round nuclei**
5. **Hyperchromasia may or may not be present**

Architectural features - Of AIDH (DIN1, ≤ 2mm)

Arcades, solid, cribriform and/or micropapillary proliferation of above cells involving anywhere from part of a single duct to multiple ducts or ductules. The completely involved ducts should measure ≤ 2mm.

Architectural features - Of Low Grade DCIS (DIN1, >2mm)

One or more adjacent ducts/ductules completely involved by cribriform, micropapillary, arcades or solid proliferation of the above cells exceeding 2mm in maximum diameter.

Table 5. Immunohistochemical expression of various markers in DIN

- **P53 -** Expression of p53 is noted mainly in DIN3 and may be associated with an increased risk for subsequent invasive carcinoma.
- **bcl-2 -** Expression of bcl-2 is diminished with increasing grade
- **Estrogen receptor (ER) -** Expression of ER and PR diminishes in higher grades of DIN. Apocrine DIN of all grades generally lacks expression of ER.
- **Progesterone (PR) receptors -** Expression of ER and PR diminishes in higher grades of DIN. Apocrine DIN of all grades generally lacks expression of PR.
- **Cytokeratin 34BetaE12 (CK1,5,10,14) -** Expression of this marker diminishes significantly or is completely absent in 87% of AIDH and 92% of DCIS.
- **E-Cadherin -** Expression of this adhesion molecule is characteristic of all variants of DIN, but it may be slightly diminished in some high grade DIN lesions

Table 6. Extent of loss of heterozygosity (LOH) in various grades of DIN

Grade of DIN	LOH at any one locus	Overall LOH at multiple loci	Total number of cases evaluated (# of loci)
IDH (- CA)	1-12%	37% (15)	163
IDH (+ CA)	0-20%	40% (15)	48
Flat atypia (- CA)	0-50%	78% (8)	9
Flat atypia (+ CA)	25-57%	77% (8)	13
AIDH (-CA)	0-15%	42% (15)	26
AIDH (+CA)	0-38%	44% (15)	25
nc DCIS (-CA)	2-35%	70% (15)	67
nc DCIS (+CA)*	0-75%	93% (15)	14
cDCIS (-CA)	0-39%	79% (15)	42
cDCIS (+CA)*	0-44%	79% (15)	14

Adapted from JNCI 1998;90:697-703 (assessed all lesions but flat epithelial atypia) and Cancer 2000;88:2072-2081

-CA= unassociated with in situ or invasive carcinoma
+CA= associated with both in situ and invasive carcinoma
(+CA)* associated with invasive carcinoma
nc= non-comedo
c= comedo

Table 7. Advantages of the DIN classification

1. It diminishes the impact of having two drastically different designations of cancer and non-cancer applied to the same lesion by different observers.

2. It incorporates the flat epithelial atypias ("atypical columnar metaplasia") that have been proven to have molecular alterations similar to those of cells in low-grade DCIS and tubular carcinoma in the classification system as DIN1, flat type, while the high-grade polymorphous flat lesions are categorized as DIN3.

3. It allows for management approaches based on the size /extent of distribution of either the low- or higher-grade lesions.

4. It diminishes the anxiety and emotional stress associated with a diagnosis of cancer for the patient and her family while allowing for an individualized approach to managing the disease.

5. It eliminates the term cancer and the likelihood of mastectomy -a possibility that persists due to geographic variations in practice standards even for small low-grade DCIS.

6. It applies the unifying concept of intraepithelial neoplasia as it is already used in many other organs including vagina, vulva, prostate, pancreas, and colo-rectum.

7. Modifications can be made easily as we learn more about distinctive subgroups within the system.

Table 8: Essential Information to be included in the Report on all DIN (DCIS) lesions

- Type
- Size/Extent
- Grade (include proportion of various grades when heterogeneity is noted)
- Nuclear Grade
- Necrosis
- Microcalcifications
- Margins: Positive (state which);
- Distance to closest margin
- ER/PR

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FIGURES

Figures for Case 4: see page 25)

Case 4 a,b,c,d. Papillomatosis and low risk DIN (IDH)/Juvenile papillomatosis.

Fig. 4a. Distended ducts show variable epithelial proliferation, apocrine metaplasia or secretory content.

Fig. 4b and c. Intraductal papillary proliferation with diffuse epithelial hyperplasia.

Fig. 4c. Fibrovascular cores are apparent.

Fig. 4d. Classic low risk DIN with peripheral fenestration and irregular, overlapping distribution of proliferation cells.

Figures for Cases 20-22: see pages 103-105

Fig. 20a. Flat Ductal intraepithelial neoplasia 1 (Flat epithelial atypia). Several distended acini in a lobule are contain microcalcifications and are lined by multiple layers of mildly atypical cells.

Fig. 20b. Flat ductal intraepithelial neoplasia 1 (Flat epithelial atypia). A single duct shows stratification in the epithelial lining with subtle atypia, but no tufts or arcades.

Fig. 20c. Ductal intraepithelial neoplasia 2 (DCIS, grade 2). While two of the ducts show a flat epithelial atypia, the atypia is more pronounced with intraluminal necrosis and an actual epithelial bridge in one of the ducts (upper right side) qualifying the changes as grade 2.

Fig. 21a. Ductal intraepithelial neoplasia, grade 2 (DCIS, grade 2). A branching duct shows solid proliferation of epithelial cells and contains necrotic debris.

Fig. 21b. Ductal intraepithelial neoplasia, grade 2 (DCIS, grade 2). A collision of two cell types is evident in the duct. A smaller cell population with hyperchromatic nuclei and hardly any cytoplasm shows a fenestrated, cribriform pattern of proliferation in the duct segment in the upper half of the field, while cells with abundant eosinophilic cytoplasm proliferate in a solid fashion in the lower half. Necrotic debris is present in both areas.

Fig. 22a. Ductal intraepithelial neoplasia, grade 2 (DCIS, grade 2). A duct is distended with a solid proliferation of cell associated with intraluminal necrosis.

Fig. 22b. Ductal intraepithelial neoplasia, grade 2 (DCIS, grade 2). Higher magnification shows relatively uniform cells with mild nuclear size variation, rare secondary lumens and intraluminal necrosis.

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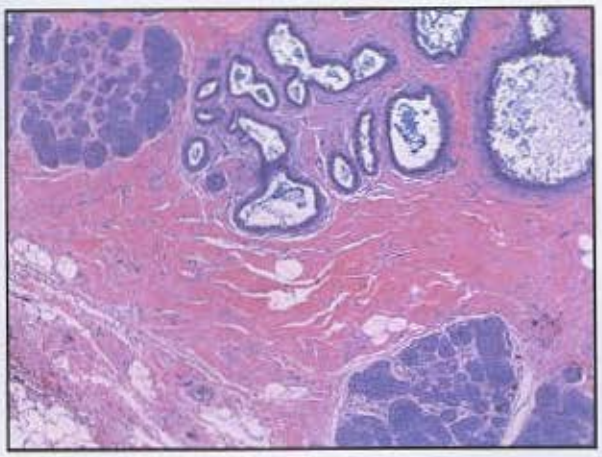
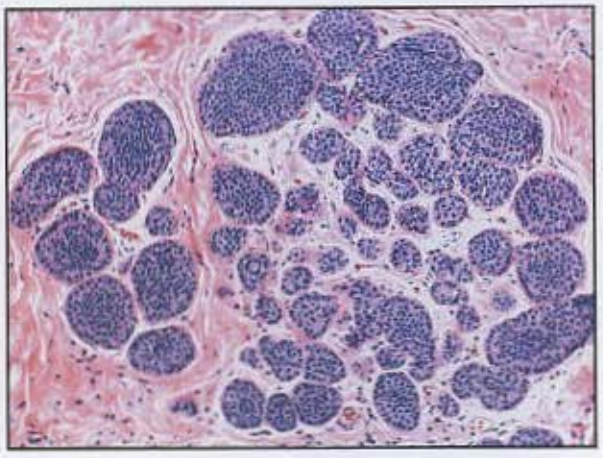
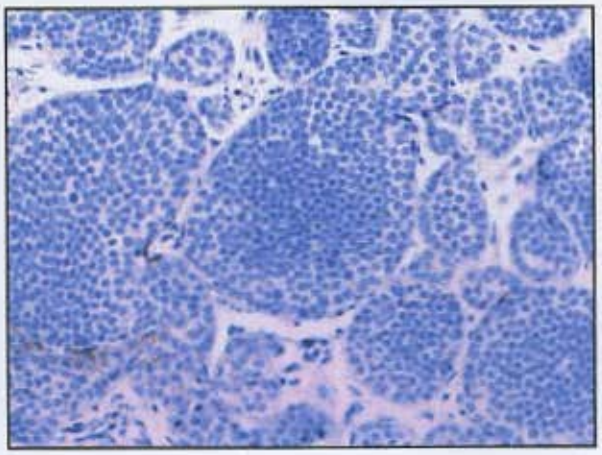


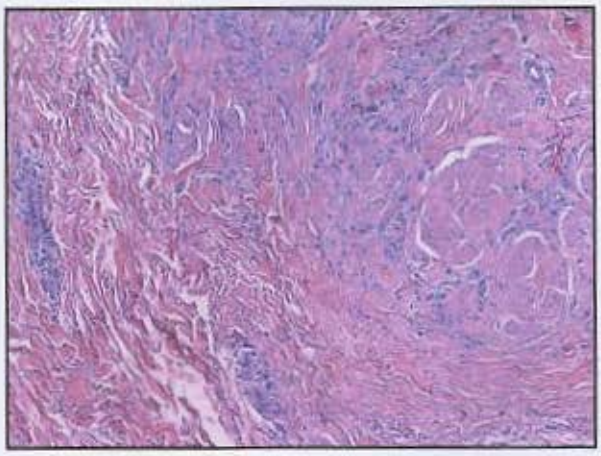
Case 1a



Case 1b



Case 1c



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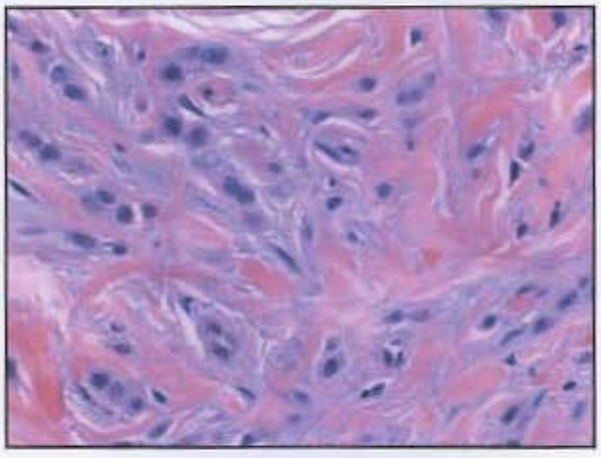
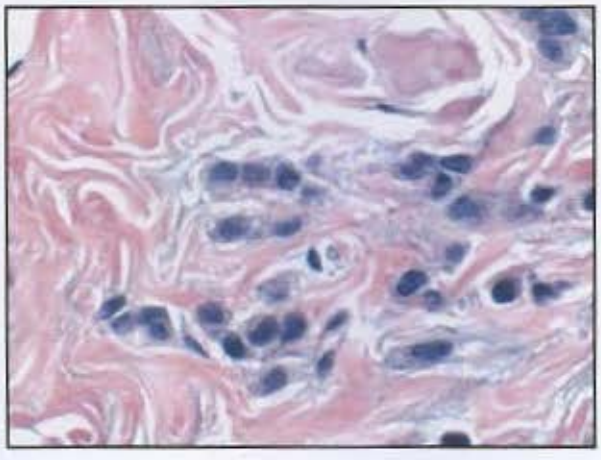
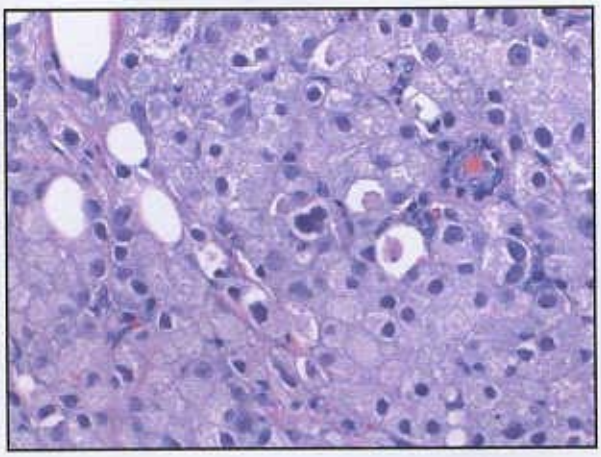


Case 2b



Case 2c



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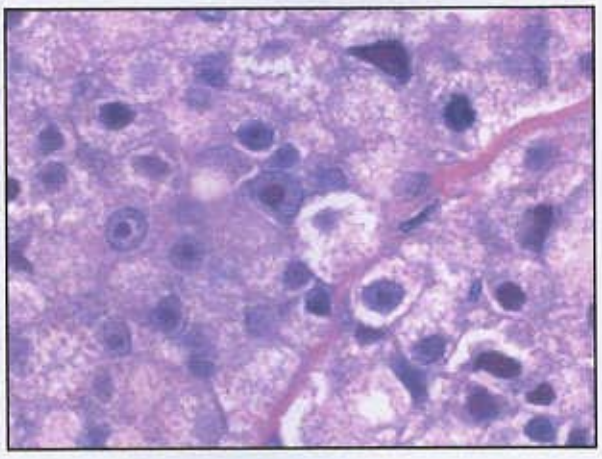
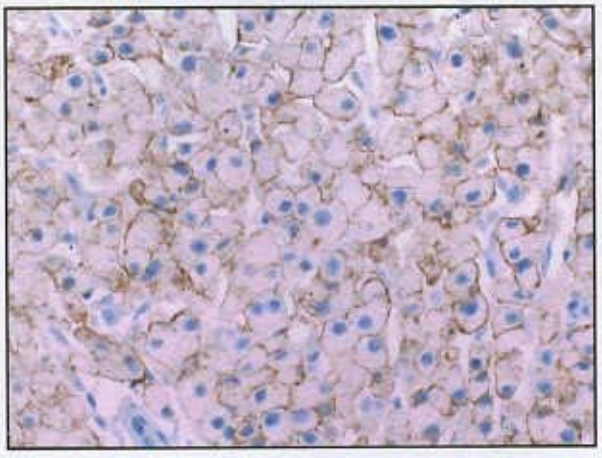
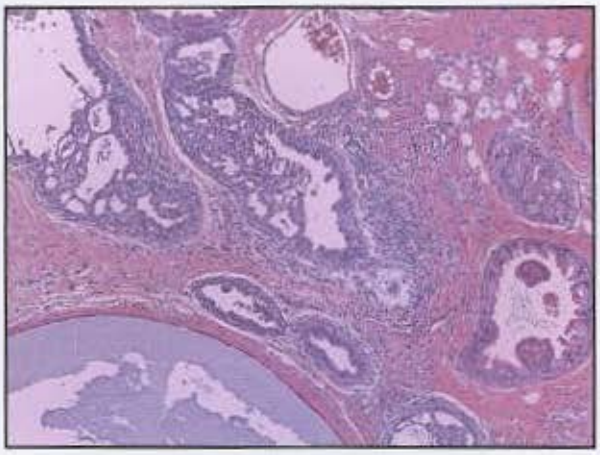


Case 3b



Case 3c

4a



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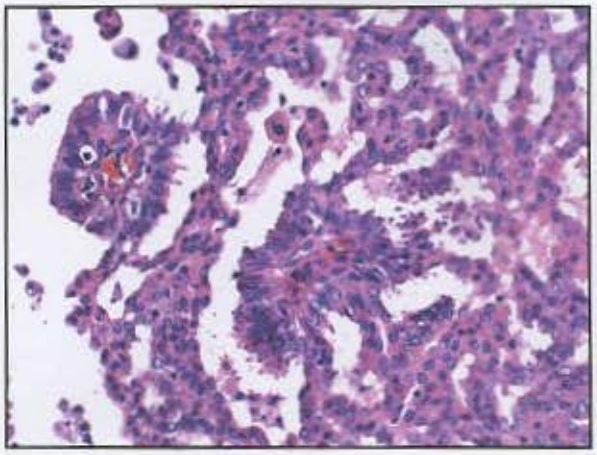

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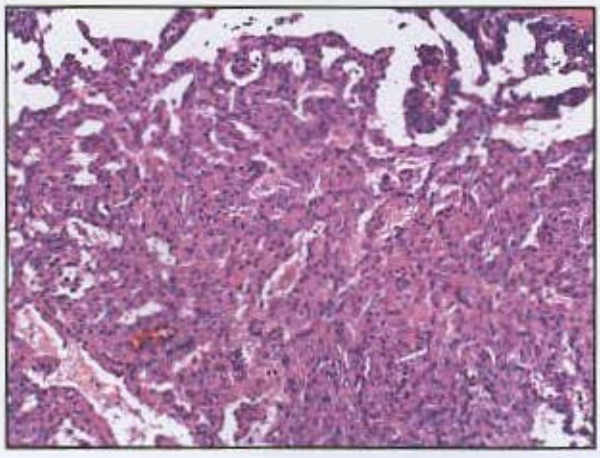

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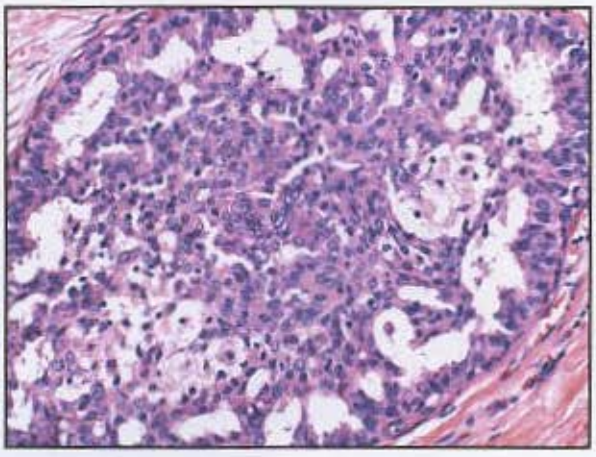

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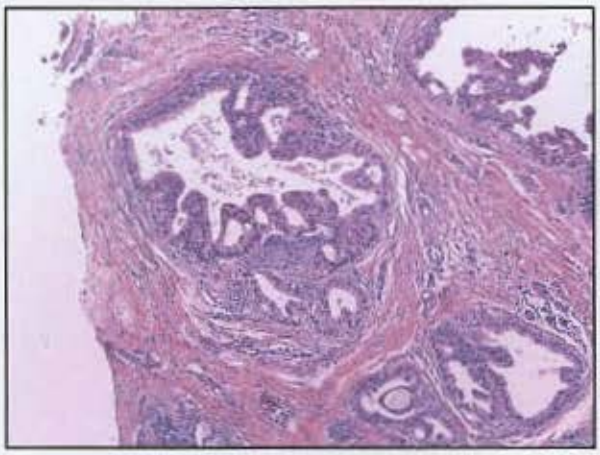

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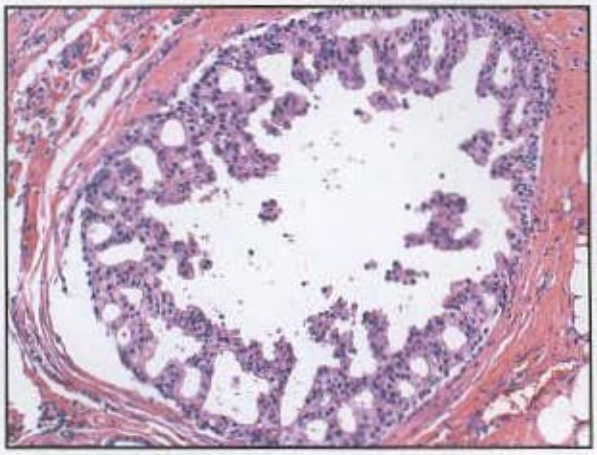

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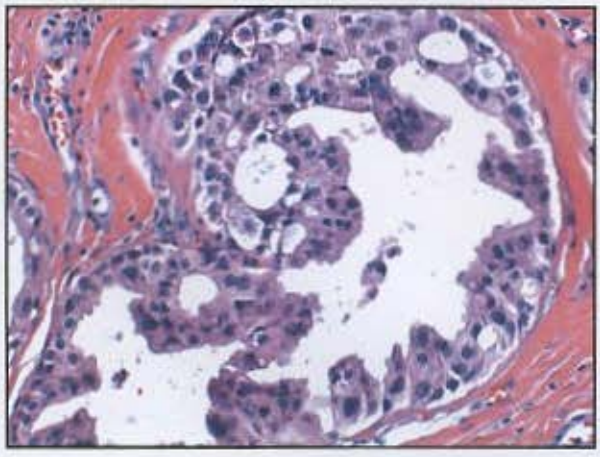

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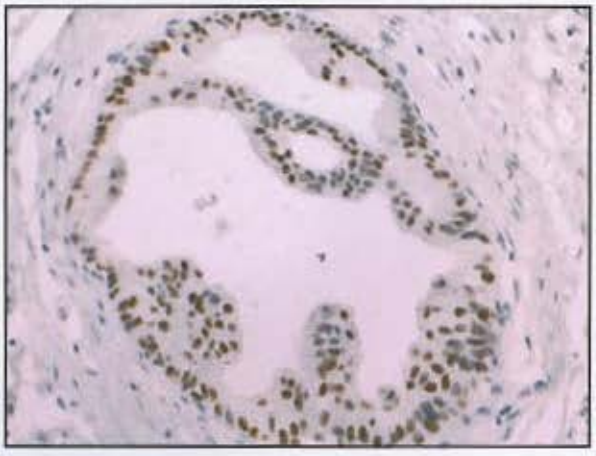

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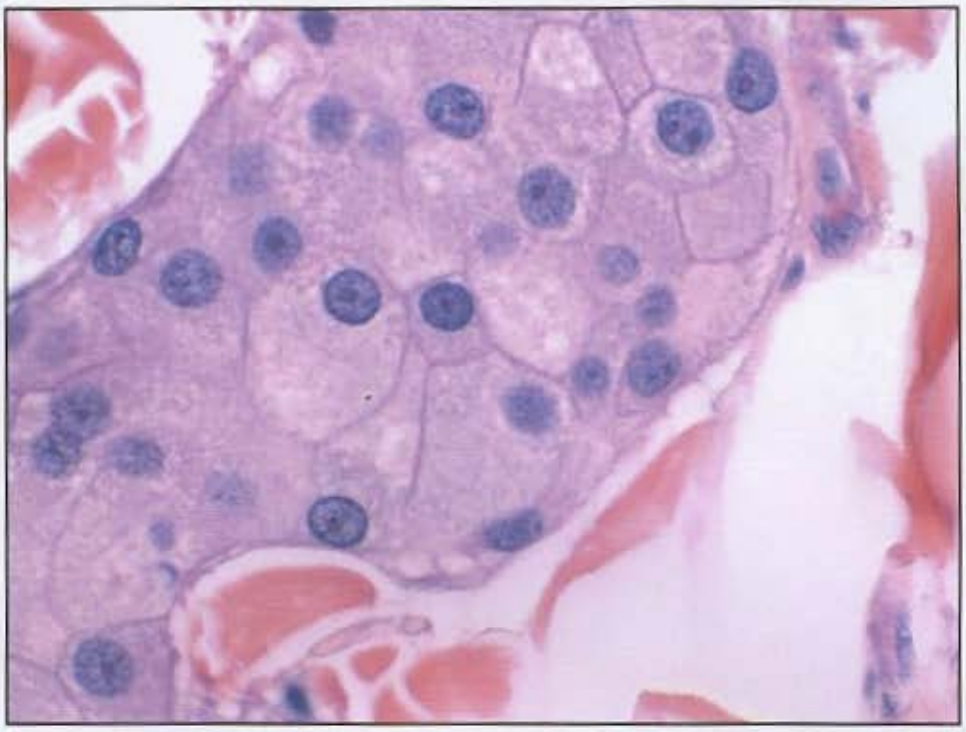

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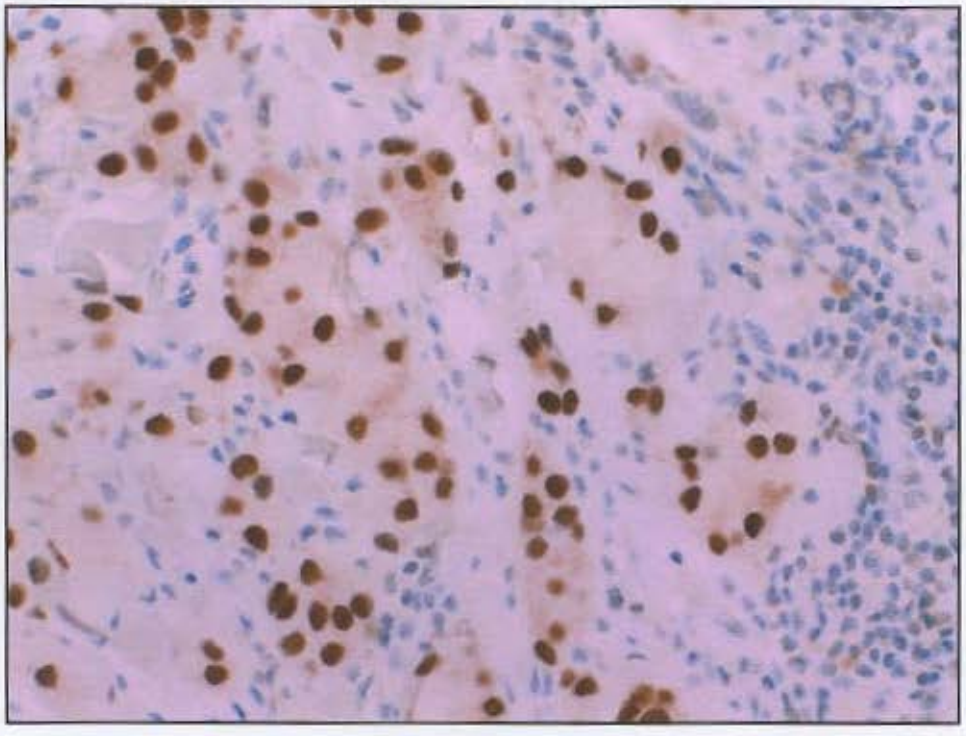

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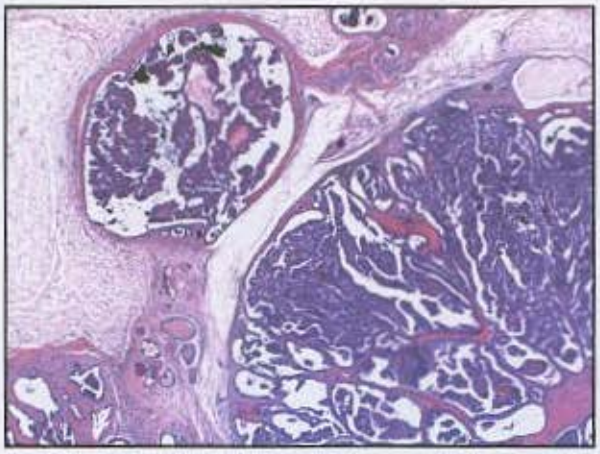

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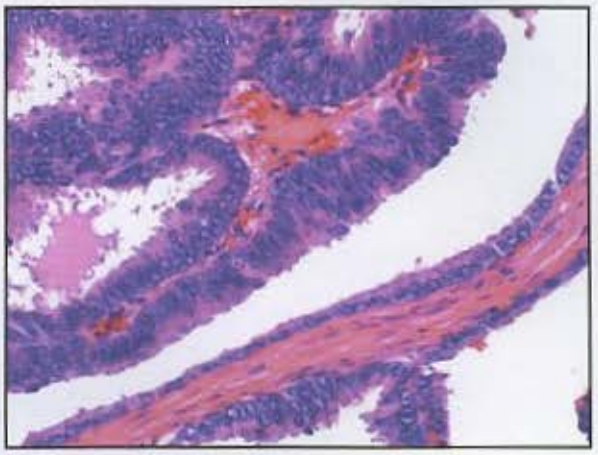

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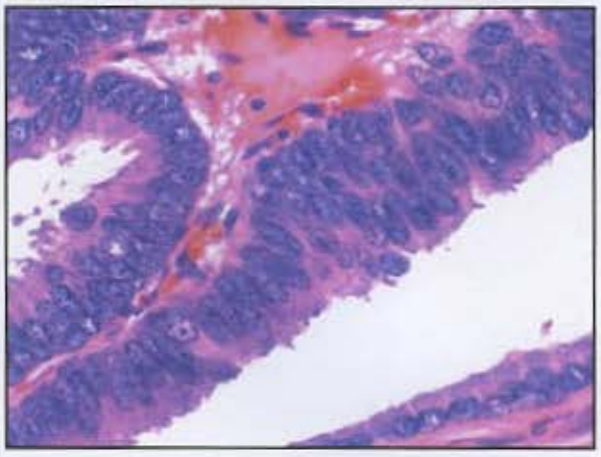

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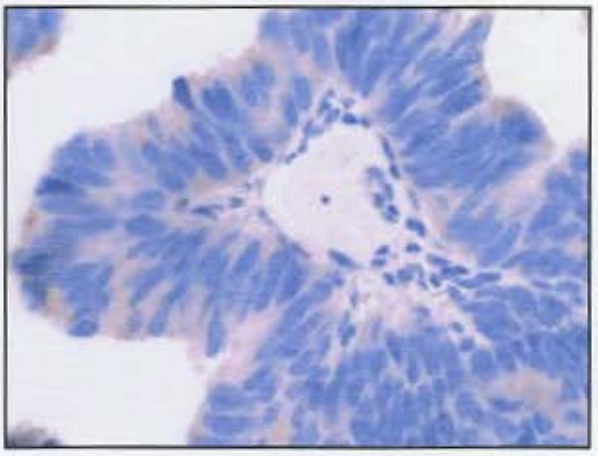

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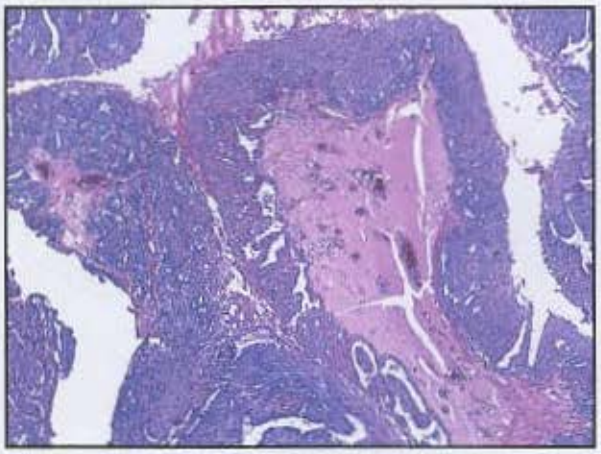

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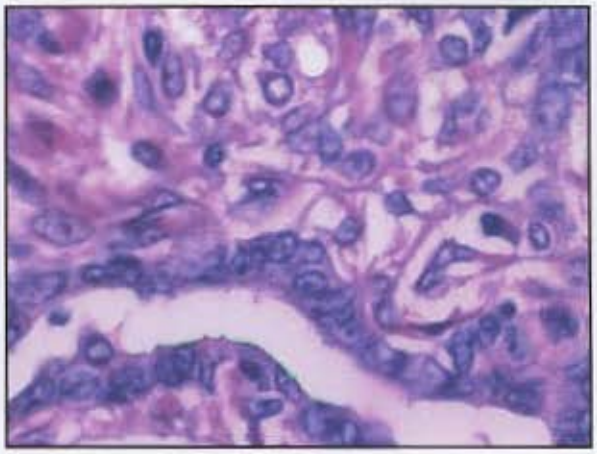

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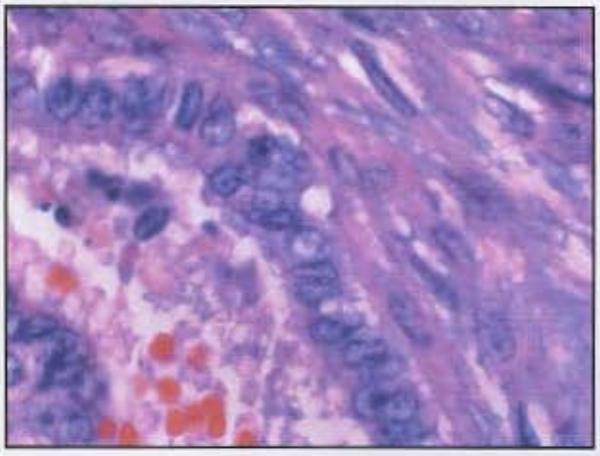

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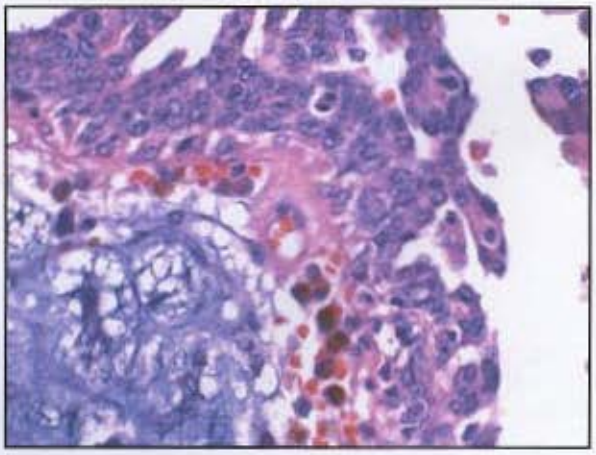

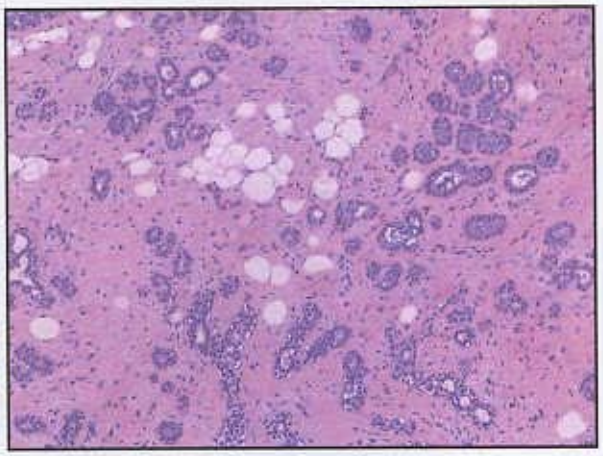

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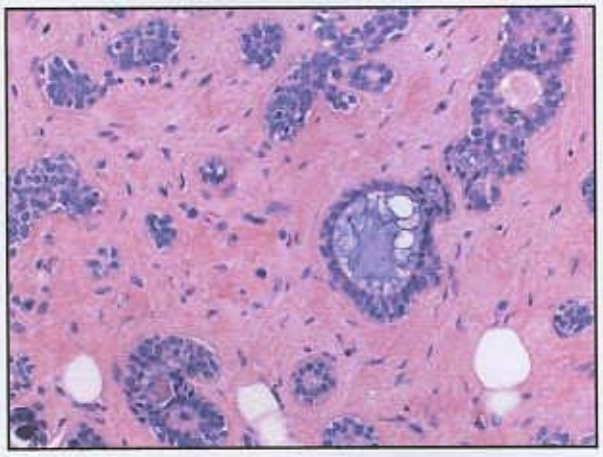

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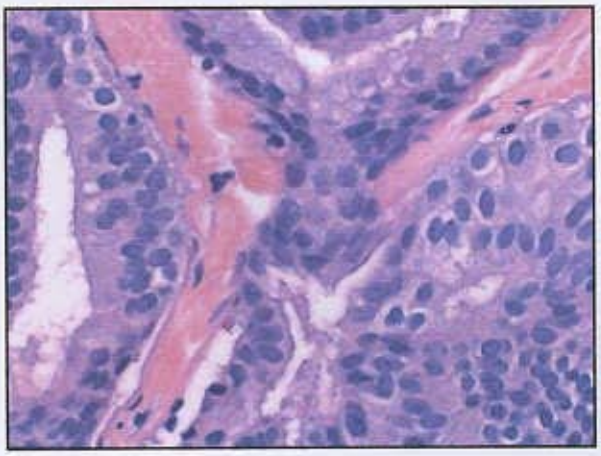

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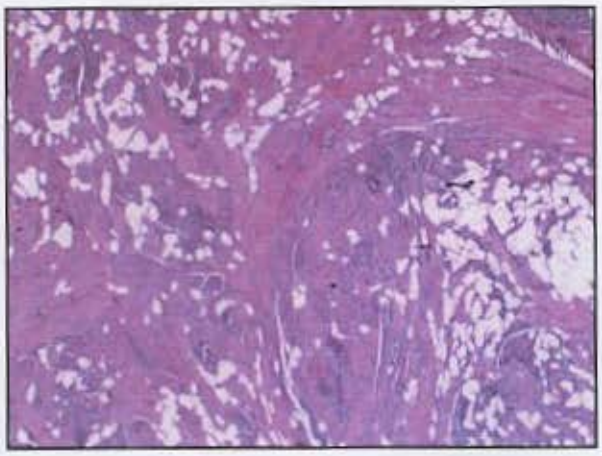

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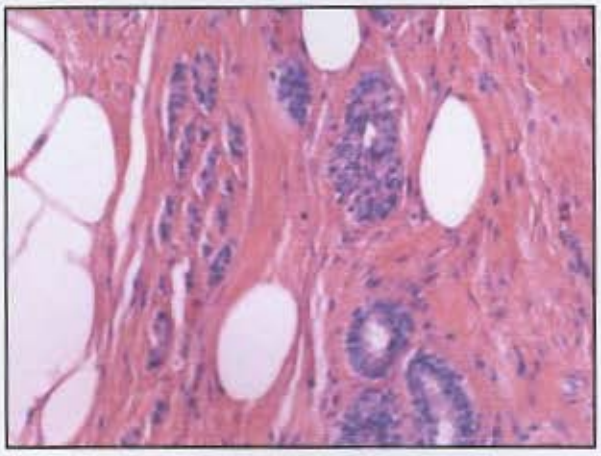

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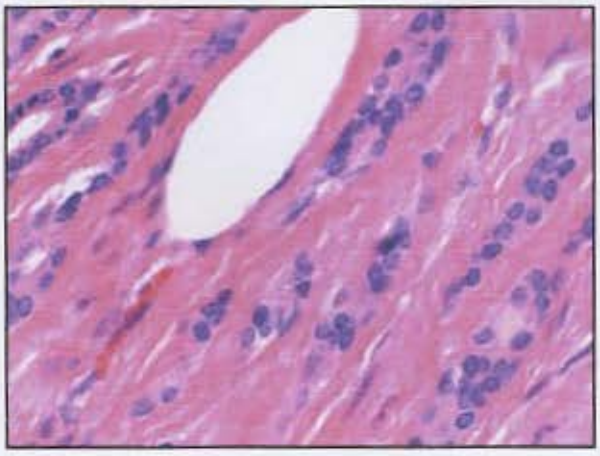

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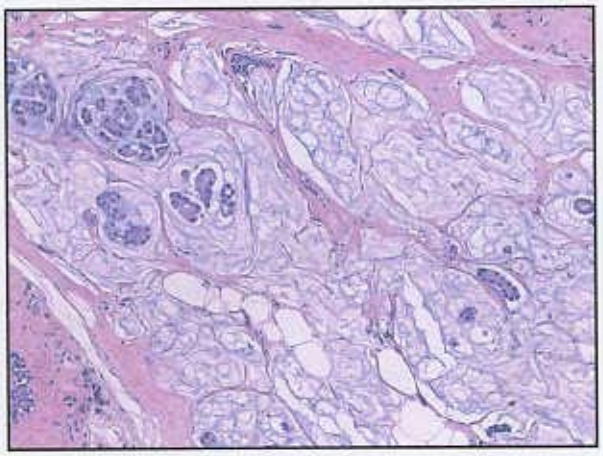

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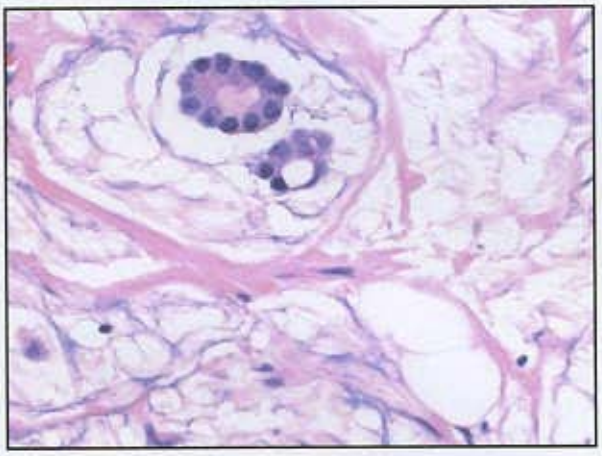

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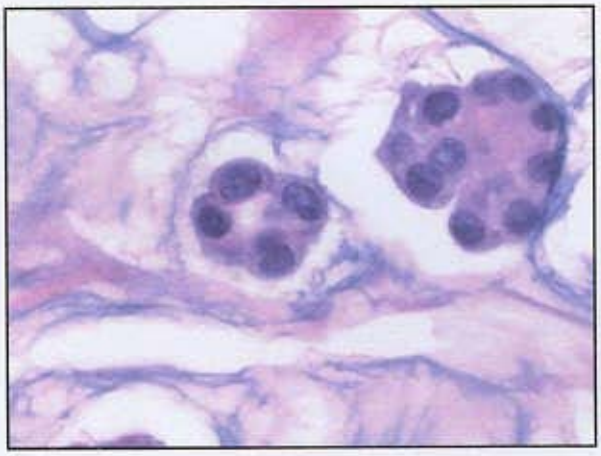

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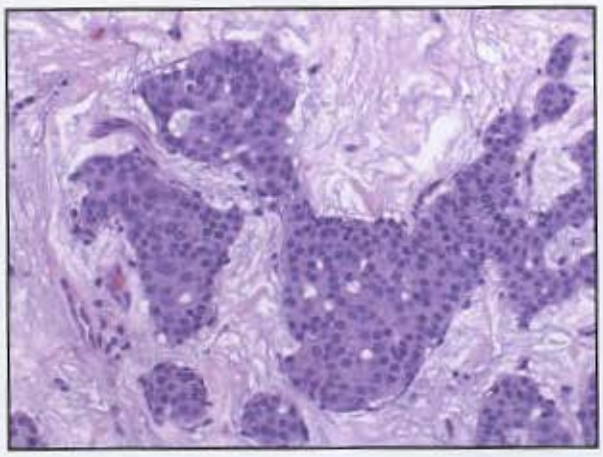

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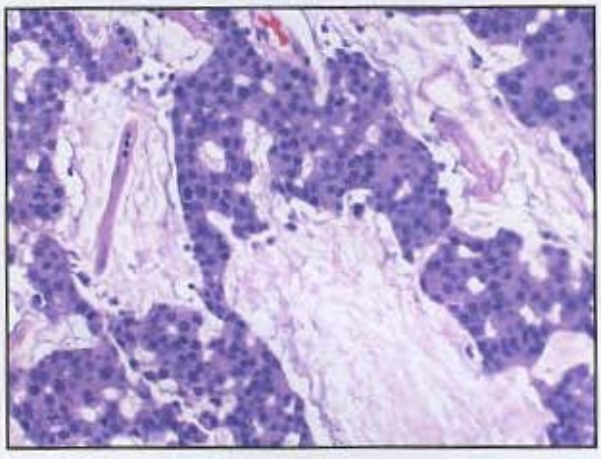

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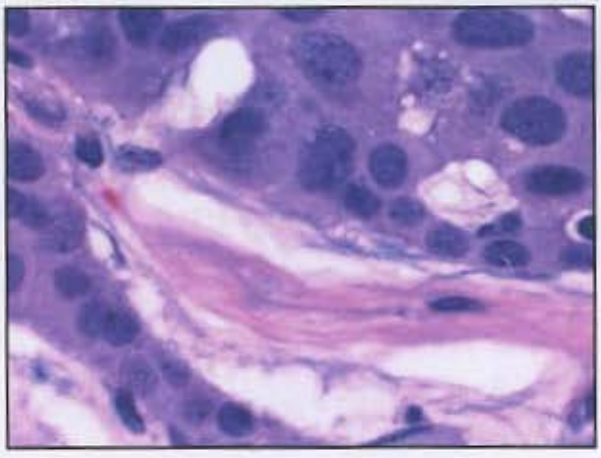

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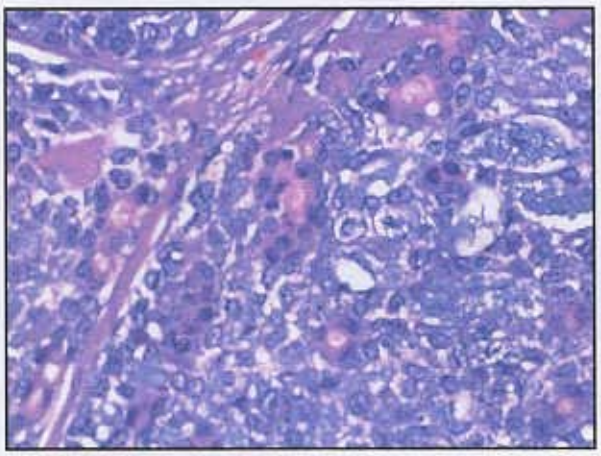

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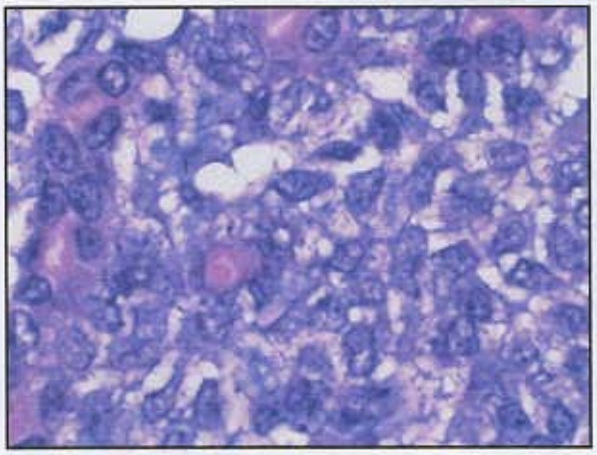

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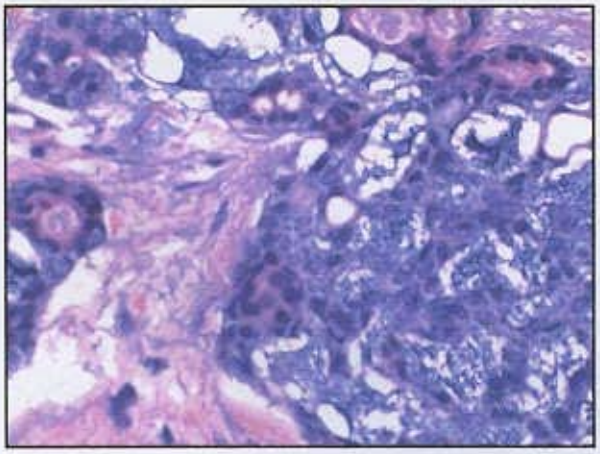

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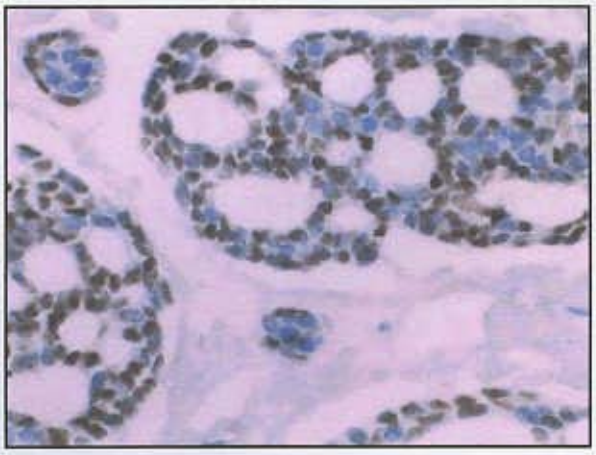

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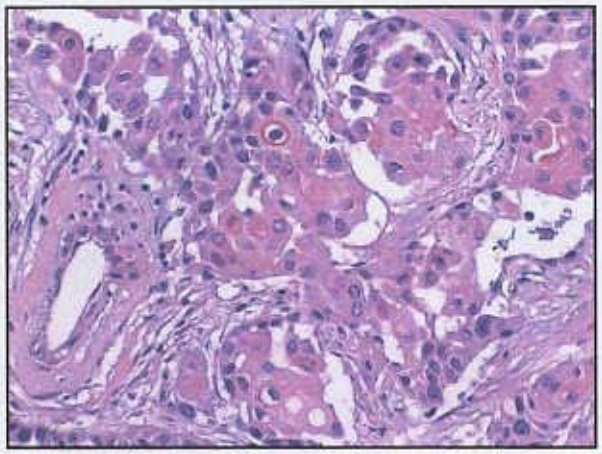

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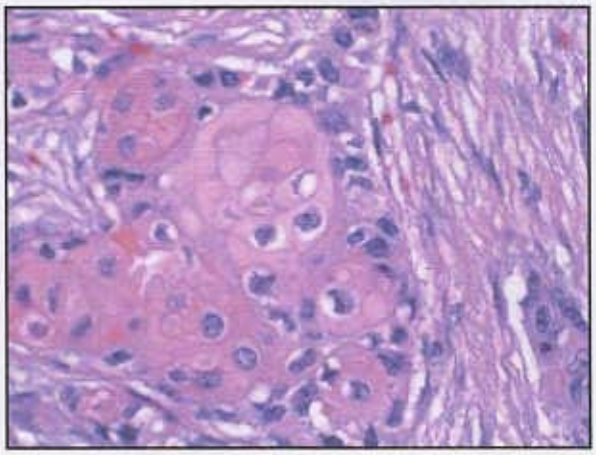

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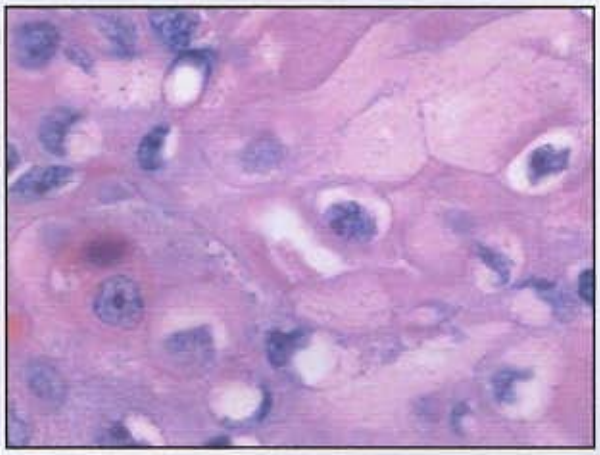

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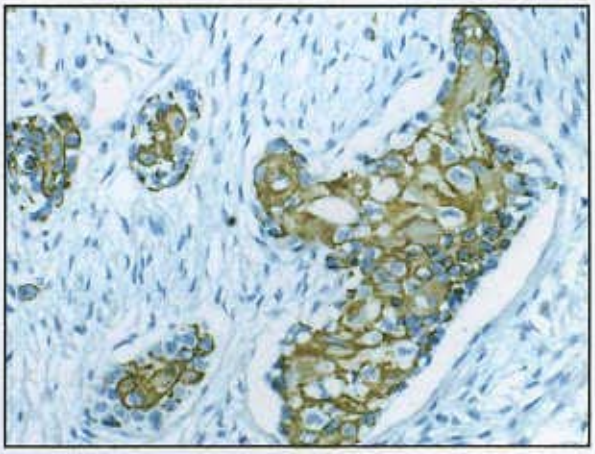

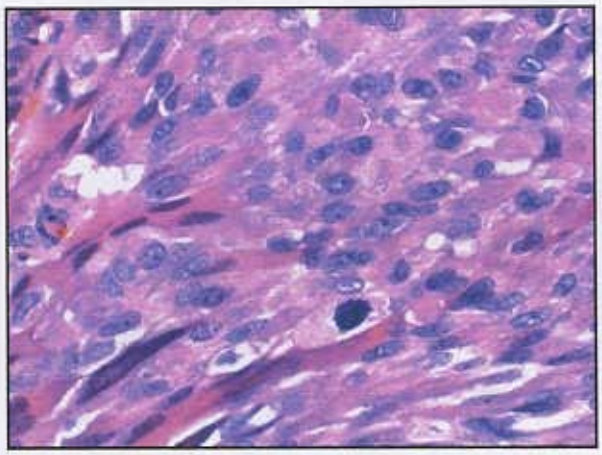

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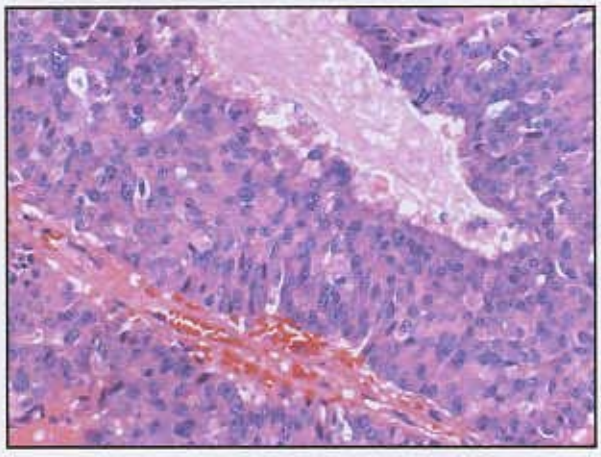

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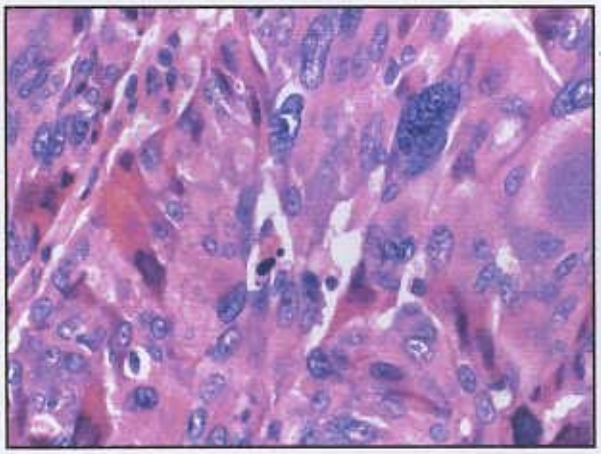

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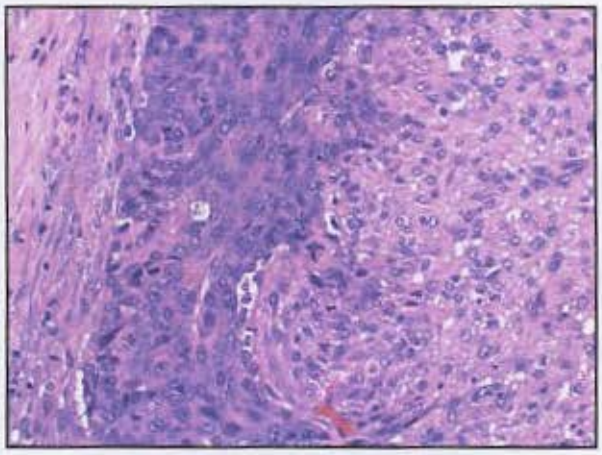

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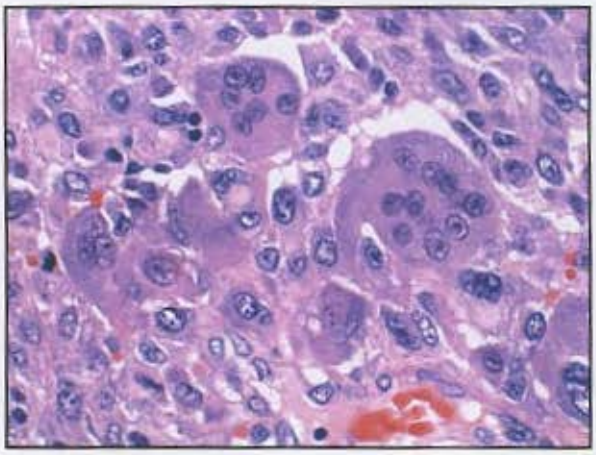

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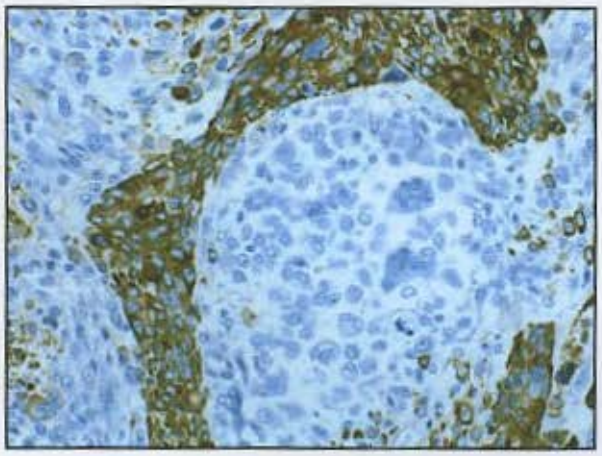

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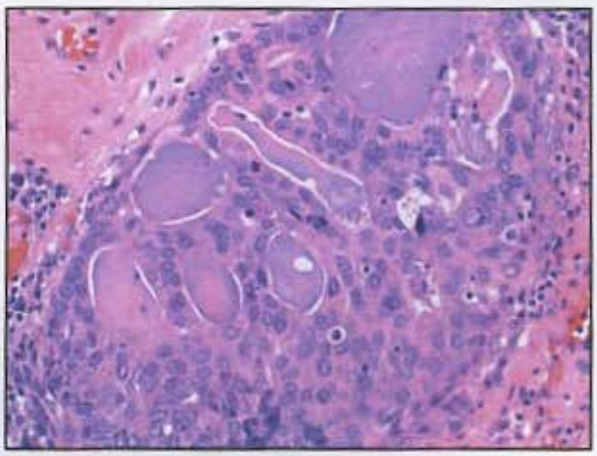

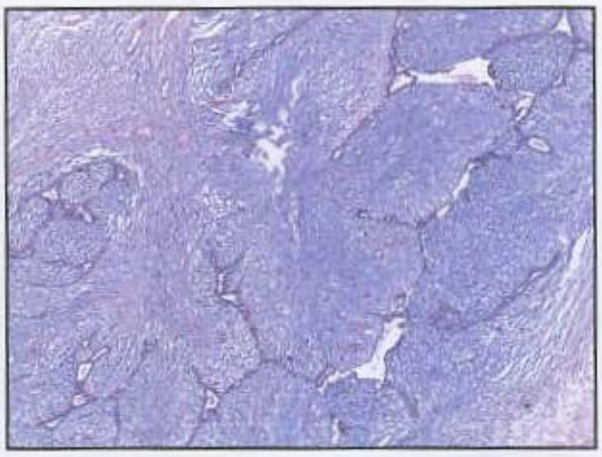

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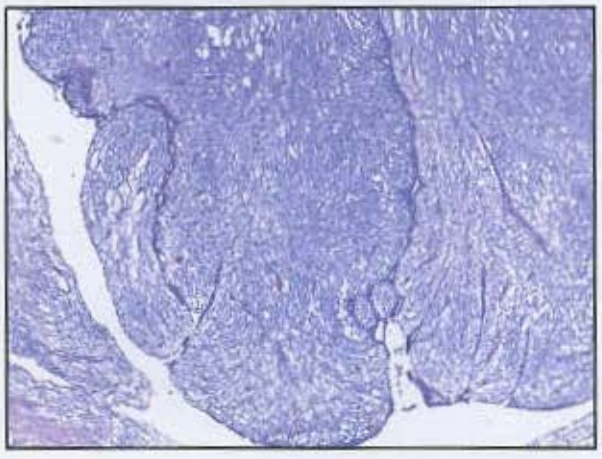

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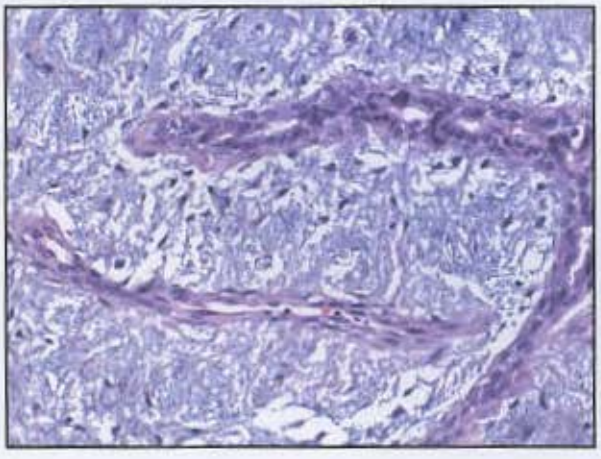

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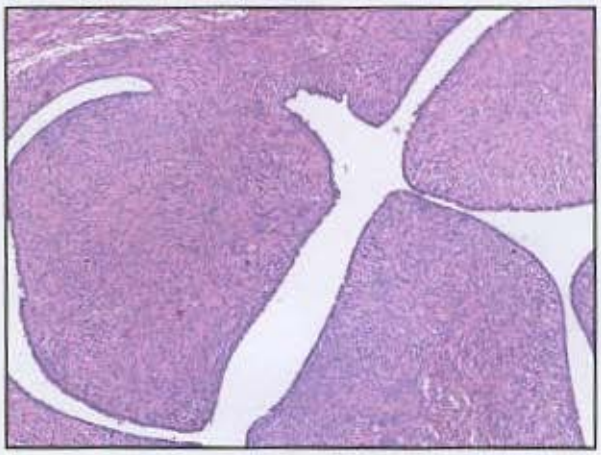

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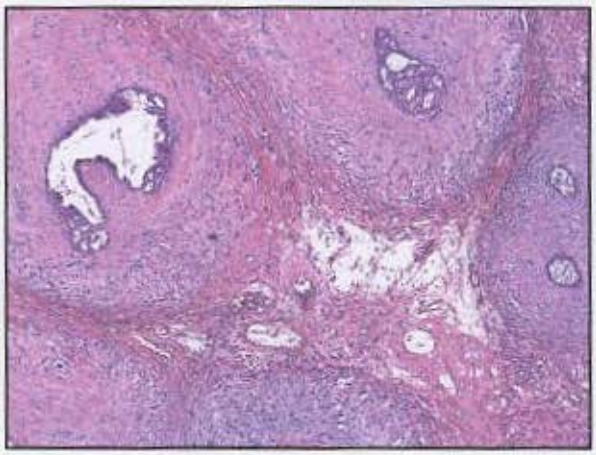

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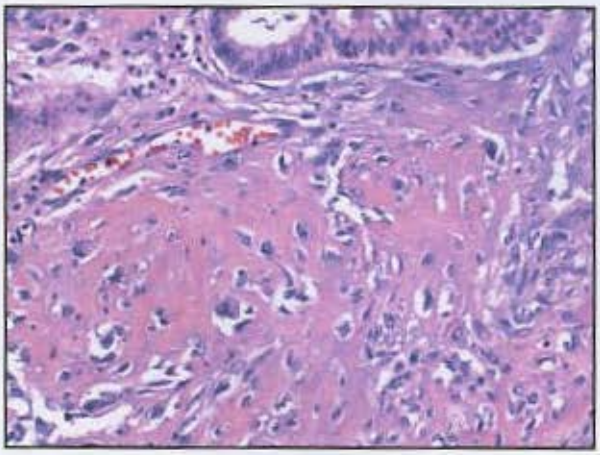

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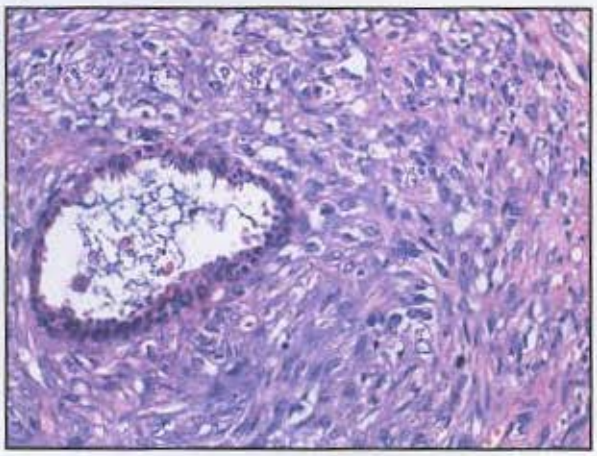

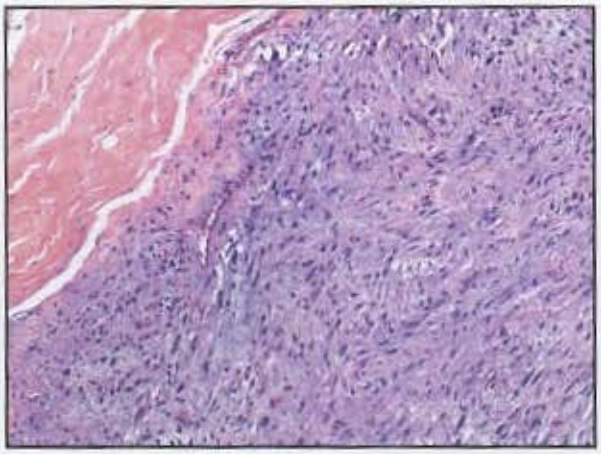

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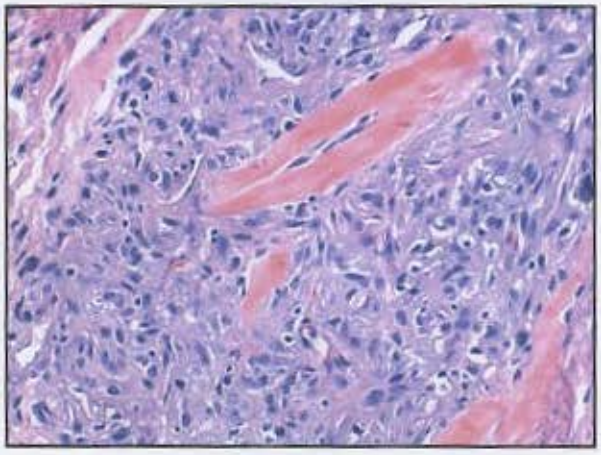

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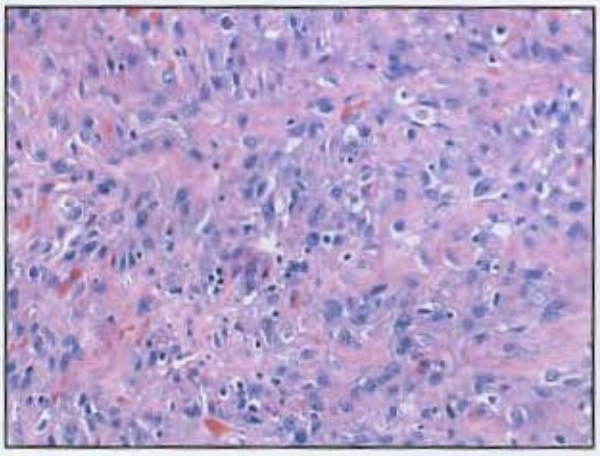

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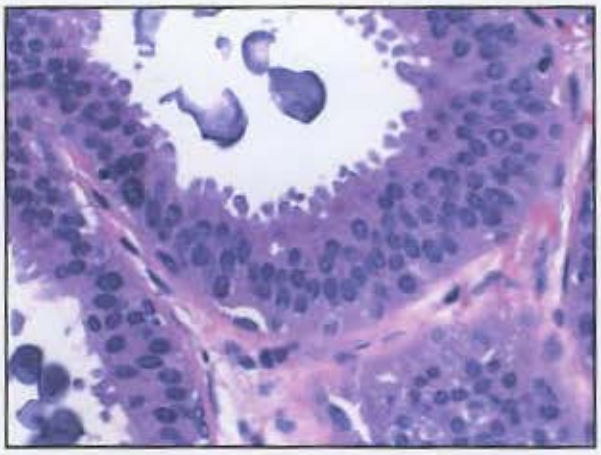

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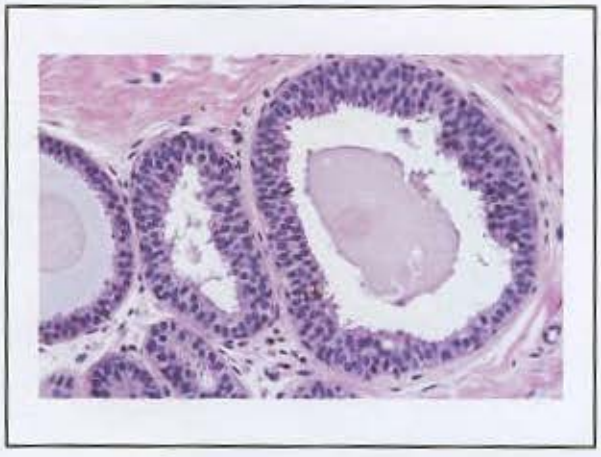

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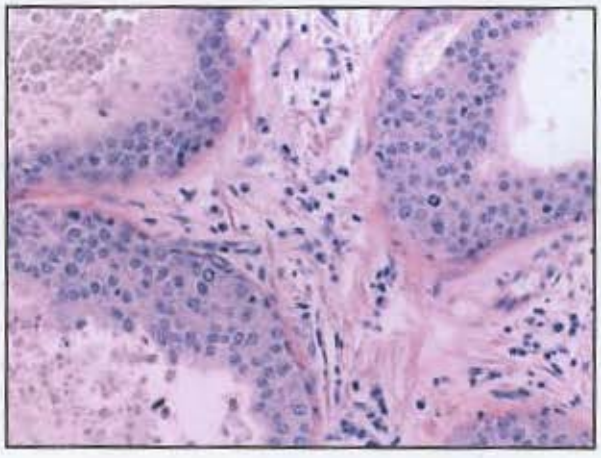

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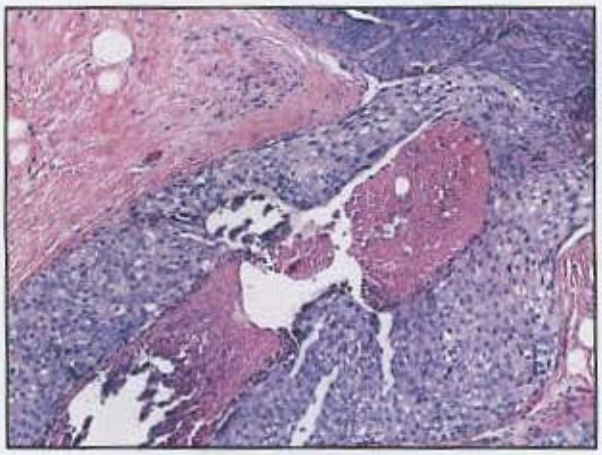

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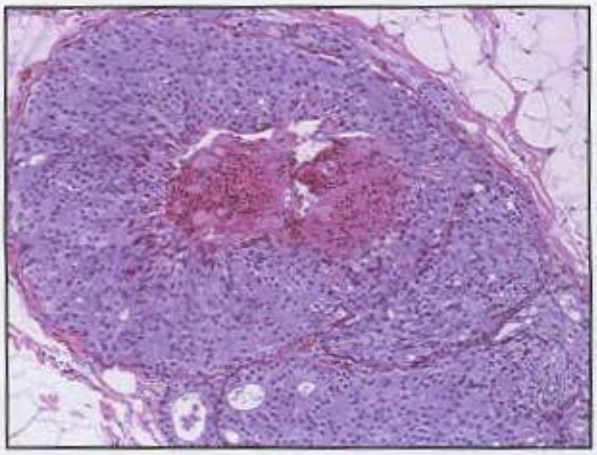

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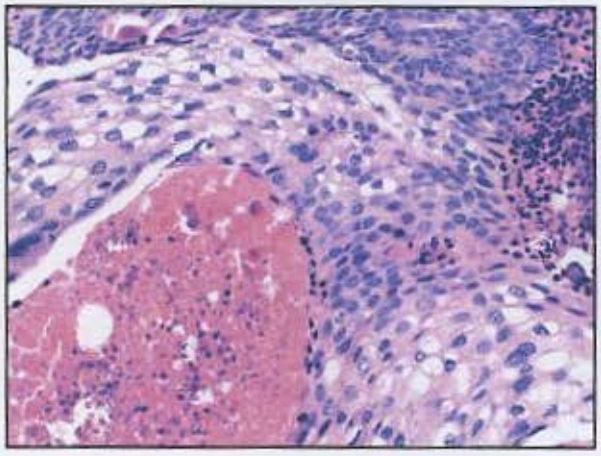

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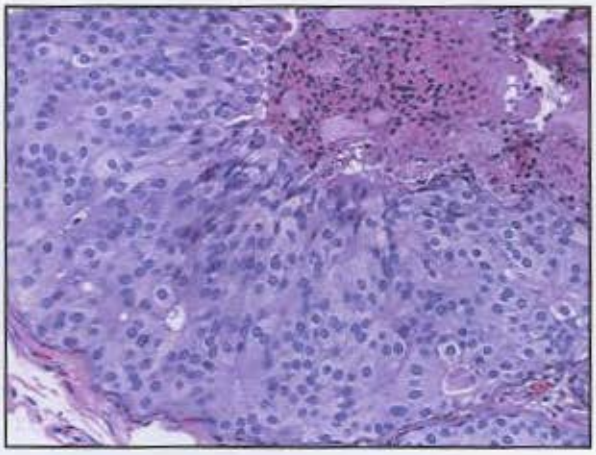

FLAT. DIN 12