Special Subtypes of Breast Carcinoma:

Tubular Carcinoma

Low Grade Adenosquamous Carcinoma

Invasive Micropapillary Carcinoma

Mucinous Carcinoma

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TUBULAR CARCINOMA

This outline is extracted from chapter 13 - Tubular carcinoma, 4th Edition of Rosen’s Breast Pathology Textbook (1). Tubular carcinoma (TC) is a special subtype of mammary carcinoma. It consists of simple neoplastic glands lined by a single layer of neoplastic cells with low to intermediate nuclear grade. Pure tubular carcinoma constitutes less than 2% of all breast carcinomas. Most TCs are smaller than 1 cm. In one series, 5% of 382 T1N0M0 breast carcinomas were TC (2). When stratified by size, TC represented 9% of lesions 1.0 cm or smaller (2). In a series by Rakha et al. (3), 59% of 102 tubular carcinomas were smaller that 1 cm and only 4% were larger than 2 cm.

Clinical Presentation
TC is often nonpalpable, and it is usually detected mammographically as irregular or calcified spiculated lesion. Louwman et al. (4) reported that TC constituted 8% of 9259 screen-detected carcinomas, but only 2% of 5413 interval carcinomas. TC can be an incidental finding in a surgical excision specimen for another lesion. The radiologic differential diagnosis of TC includes benign sclerosing lesions such as radial scar or sclerosing adenosis, and invasive duct carcinoma. TC can occasionally arise in association with a radial scar. TC can occur at any age, but is more common in postmenopausal women. A study based on SEER data reported that 73.6% of 4,477 TC diagnosed in the US between 1992 and 2007 occurred in women 50 to 79 years old (5). Ninety percent of women with TC were non-Hispanic white (5). TC has also rarely been reported in males. Paget’s disease is very rarely associated with TC. In one study, 90.5% of women with TC presented at Stage I disease (5). Axillary lymph node metastases occur in approximately 10% of cases (2, 6-16). TC constituted only 1.5% of all carcinomas in a series of 142 patients with T1N1M0 disease (17). Affected lymph nodes are usually in level I (8). Fedko et al. (18) found lymph node metastases in five (5.4%) of 93 patients with pure TC and known lymph node status: two patients had macrometastases, and the other three had micrometastases. Two-additional patients had lymph nodes with isolated tumor cells (N0(i+)) (18). The size of the primary tumor ranged from 0.9 cm to 1.5 cm. In a French study (19), 2.5% patients with TC had lymph node macrometastases, 6.4% micrometastases and 0.8% had isolated tumor cells (N0(i+)). All patients with macrometastatic carcinoma had a tumor greater than 1 cm. On multivariate analysis, pathological tumor size >10 mm was the only parameter significantly associated with lymph node involvement.

*Microscopic pathology*
TC consists of haphazardly arranged small glands and tubules lined by monolayered polarized epithelial cells with low to intermediate nuclear grade. The diagnosis of pure TC requires that at least 90% of the tumor be composed of monolayered, simple neoplastic tubules with low grade atypia. Features incompatible with the diagnosis of TC include complex architecture, multiple layers of cells, significant nuclear pleomorphism and frequent mitoses.

The glands of TC are angular and have irregular shape, with widely patent lumen. The cytoplasm usually is amphophilic. Cytoplasmic “snouts” are often present at the apical cell border. Mitoses are rarely seen and necrosis is always absent. The stroma between the glands of TC tends to be more abundant than in non-tubular well differentiated ductal carcinomas. Stromal elastosis is also common, but it is not present in all cases. Stromal elastosis is also common in ER-positive non-tubular carcinomas and in some benign lesions, such as radial scars. Calcifications in the glandular lumen or in the stroma are present in at least 50% of TC. DCIS, ADH and columnar cell change associated with TC can also harbor calcifications.

DCIS associated with TC typically has papillary, micropapillary, or cribriform pattern. In a significant number of cases, only ADH or columnar cell change with or without atypia are present. TC may arise in association with a radial scar. High grade DCIS is only rarely associated with TC. In a study by Aulman et al. (55), columnar cell change was associated with 24 (89%) of 27 TC and showed atypia in 22/24 cases. Low grade DCIS was present in 37% of cases and foci of lobular neoplasia in 11%. Coexistent classical LCIS has been described in 0.7% to 40% of patients with TC.

**Differential diagnosis**

*Microglandular adenosis:* Small TC measuring less than 1 cm may closely resemble microglandular adenosis (MGA). The glands of MGA tend to be smaller than those of TC, and
round or oval throughout, with no angular contours. The epithelium of MGA is typically cuboidal, with uniform height and pale to clear cytoplasm, whereas the epithelium of TC ranges from columnar to more cuboidal or flattened, and cells of different height may coexist in the same gland. The lumen of the MGA glands is open, but not overtly patent and often contains dense homogenous eosinophilic secretion that may undergo calcification. TC and MGA are both devoid of myoepithelium, but the glands of MGA are completely surrounded by basement membrane. Some investigators however, have detected attenuated or focally discontinuous basement membrane in association with some well differentiated invasive carcinomas. The distinction between TC and MGA should be based on the results of immunoperoxidase studies for S100 protein (positive in MGA but not in TC) and ER and PR (strongly positive in TC and negative in MGA) (20).

Sclerosing lesions: Sclerosing adenosis has a lobulocentric proliferative pattern not seen in TC. The glands of sclerosing adenosis are compressed, not patent, and they are surrounded by myoepithelium. Stromal elastosis is a common feature of radial sclerosing lesions. The myoepithelial cells in a radial scar can be markedly attenuated but they can be demonstrated with immunoperoxidase stains, such as calponin and p63. Some of the cytoplasmic myoepithelial antigens have variable cross-reactivity with myofibroblasts. It is recommended to use a panel of myoepithelial antigens inclusive of p63 and calponin and/or SMA, because some of the other myoepithelial markers may be markedly attenuated in sclerosing lesions (21). This is especially important when dealing with a needle core biopsy sample.

Well differentiated invasive ductal carcinoma: In well-differentiated non-tubular ductal carcinoma glands lined by two or more cell layers or showing complex bridging patterns represent more than 10% of the lesion. The glands also show greater cytologic atypia than in TC.
**Tubulo-lobular carcinoma**: A carcinoma with areas of invasive lobular and glandular carcinoma is referred to as *tubulo-lobular carcinoma*. The relative proportion of the two components tends to vary and this type of tumors is quite heterogenous, and also shows mixed reactivity for E-cadherin. Axillary lymph node metastases are more frequent in tubulo-lobular carcinoma than in TC.

**Tubular Carcinoma and CBX**

The diagnosis of pure TC can be difficult in this material, especially when only a small portion of the lesion is present. Pure tubular morphology in a CBX sample does not guarantee that the same morphology is present in the rest of the lesion. It is good practice to indicate in the CBX report that the final classification of the carcinoma will depend on the findings in the core and excisional biopsies.

**Immunohistochemistry**

Most TCs are strongly positive for ER and PR. AR is positive in 80% of cases (22). All TCs studied by Rakha et al. (3) were negative for HER2/neu. KI67 proliferation index is usually low (<10%) (14). TC is positive for EMA and negative for S100.

**Genetics**

Loss of 16q is the most frequent chromosomal abnormality in TC and is also found in other low grade mammary epithelial neoplastic lesions, including columnar cell change with atypia, ADH, low grade DCIS, ALH, classical LCIS, well differentiated invasive ductal carcinoma, tubulo-lobular carcinoma, and invasive cribriform carcinoma (23). Aulmann et al. (24) documented LOH involving the long arm of chromosome 16 as well as chromosome 8p21, 3p14, 1p36 and 11q14 in TC, and a high degree of homology with columnar cell changes with atypia and low grade DCIS. Riener et al. (25) found loss of the *CDH13* locus on chromosome 16q in 86% of 23.
TC. The \textit{CDH13} gene encodes a cell surface glycoprotein, member of the cadherin family (25). TC and well differentiated invasive ductal carcinoma share some genetic alterations, including ER-driven signaling pathways, and phosphatidylinositol signaling (26).

\textbf{Treatment and prognosis}

TC carries very good prognosis. Patients with unifocal pure TC are usually treated with breast conservation therapy. According to SEER data, about two thirds (64.3\%) of patients received adjuvant radiation treatment (5). Patients with TC treated with breast conservation therapy had a low rate of distant metastases (1\%) and of breast cancer specific death (1\%) (27). Livi et al. (28) reported a series of 307 patients with TC and median follow-up time of 8.4 years. Most (80\%) patients who underwent breast conserving surgery received adjuvant radiotherapy and 35\% had tamoxifen treatment. Only 21 women (7\%) received chemotherapy, including 15 with lymph node metastases. Twelve patients had recurrence of carcinoma after a median time of 4.1 years, one patient recurred in the supraclavicular fossa (28). Rakha et al. (3) compared the outcomes of 102 TC and 212 grade 1 invasive ductal carcinoma. The median F/U time was 127 months. Local recurrences developed in only 6.9\% patients with TC initially treated by wide local excision. Recurrences occurred in 25.1\% of patients with grade 1 invasive ductal carcinoma and 9\% of patients died of disease. Disease free survival and breast cancer specific survival were significantly longer for patients with TC than patients with grade 1 invasive ductal carcinoma, even when analysis was limited to sub-centimeter tumors (3), confirming the good prognosis of TC diagnosed based on strict morphologic criteria. Radiotherapy is usually administered to patients treated with breast conserving surgery. Adjuvant hormonal therapy is also a mainstay of treatment for patients with TC.
REFERENCES

LOW-GRADE ADENOSQUAMOUS CARCINOMA

This outline is in part extracted from chapter 16 – Carcinoma with metaplasia, 4th Edition of Rosen’s Breast Pathology Textbook (1). Low-grade adenosquamous (LG-AdSq) carcinoma is an unusual variant of metaplastic mammary carcinoma morphologically similar to adenosquamous carcinoma of the skin. It was first described in 1987 by Rosen and Ernsberger (2), and more than one hundred examples have since been reported in few small series and case reports. A case of LG-AdSq has been described in a BRCA1 germline mutation carrier (3).
CLINICAL PRESENTATION

All reported cases of LG-AdSq have occurred in women, usually of peri- or post-menopausal age. The clinical presentation is usually as a palpable mass or a mammographic abnormality. LG-AdSq carcinoma has no distinctive imaging findings. The tumor arises in the breast parenchyma, including in the retroareolar region.

MICROSCOPIC PATHOLOGY

Some tumors have a stellate growth pattern, while others appear relatively more circumscribed. The tumor tends to infiltrate peripherally in the form of small glands and/or squamous nests surrounded by desmoplastic stroma that at least focally grow between normal and undistorted lobules. This infiltrative pattern helps to differentiate LG-AdSq carcinoma from non-neoplastic complex sclerosing lesions. This differential diagnosis can be challenging, as LG-AdSq carcinoma often arises in association with sclerosing lesions such as a papilloma, an adenomyoepithelioma, a radial scar, or even sclerosing adenosis. The glands of LG-AdSq carcinoma are lined by neoplastic epithelium and myoepithelium (biphasic carcinoma). Squamous nests of various size and shape, and even scattered single squamous cells are also part of the carcinoma. Small cysts containing keratotic debris with calcification are sometimes present. The tissue immediately around squamous foci often has a distinctive lamellar arrangement of spindle cells that merges with the epithelium. Very rarely, LG-AdSq carcinoma can shows transition to conventional high-grade spindle cell and squamous sarcomatoid metaplastic carcinoma. DCIS can be present, and sometimes shows apocrine features, but it may be difficult to distinguish from infiltrative areas.

Syringomatous adenoma of the nipple is a skin-based lesion morphologically and immunophenotypically indistinguishable from LG-AdSq carcinoma, and differs from it because
of its superficial location. The distinction between these two entities can be very challenging, and few case reports have documented local recurrence requiring surgical management by mastectomy for tumors initially misdiagnosed as syringomatous adenoma of the nipple (3).

**CBX Diagnosis**

The diagnosis of LG-AdSq carcinoma in CBX is very challenging. Disorganized syringomatous squamous nests and duct-like structures surrounded by desmoplastic stromal cells may suggest LG-AdSq carcinoma. The differential diagnosis usually includes a complex sclerosing lesion. One should entertain the differential diagnosis of LG-AdSq carcinoma when the CBX material shows a sclerosing lesion with unusual morphologic features.

**IMMUNOREACTIVITY**

The cells of LG-AdSq carcinoma show immunoreactivity for AE1:3, CK5/6, 34 beta E12 and CAM5.2. In one study (4) some of the epithelial clusters in each tumor were negative for some cytokeratins, although no single keratin was consistently negative in all the epithelial clusters of a case. Another group found strong reactivity for the basal cytokeratins CK5/6, CK14 and CK17 in five tumors (5). The spindle stromal cells of LG-AdSq carcinoma usually show no staining for cytokeratins. Due to the biphasic nature of the tumor, that shows a myoepithelial component, staining for myoepithelial markers can yield different patterns. Most importantly, one needs to entertain the differential diagnosis of LG-AdSq carcinoma when a sclerosing lesion shows an inconsistent staining pattern for myoepithelial markers. Complete circumferential (4) staining for p63, SMM-HC, SMA, CD10 and calponin around all epithelial nests was present in only 11% of cases. About a third (36%) of cases showed a pattern of complete, discontinuous and absent circumferential staining for myoepithelial markers in the same tumor. Glandular luminal staining was seen 74% of the tumors evaluated for p63, suggesting that p63 positivity highlights areas of
squamous (not myoepithelial) differentiation. LG-AdSq carcinoma is negative for ER, PR and
HER2. Familiarity with the morphologic features of this tumor and with its different staining
patterns is required for accurate diagnosis of this carcinoma.

PROGNOSIS AND TREATMENT

Lymph node involvement by LG-AdSq carcinoma is extremely rare, with only one documented
case (6). In the study by Kawaguchi and Shin (4), one of two patients with SLN biopsy had
dispersed epithelial clusters in four lymph nodes that were interpreted as secondary to artifactual
displacement; the other patient had no SLN involvement.

A 33 years old woman with a 8.0 cm tumor metastatic to the lung at presentation constitutes the
only documented case of distant metastases of LG-AdSq carcinoma (6). LG-AdSq carcinoma,
however, tends to recur locally, and management of the local recurrence can require mastectomy
(6). It is unclear whether local recurrence occurs only if the index tumor has been incompletely
excised. The current management of LG-AdSq carcinoma is similar to that of other types of
invasive breast carcinomas. Radiotherapy is used in patients treated with breast-conserving
surgery. Although LG-AdSq carcinoma is a metaplastic triple negative carcinoma, chemotherapy
does not appear to be indicated given the low propensity of this tumor to develop distant
metastases.

REFERENCES

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3. Noel JC, Buxant F, Engohan-Aloghe C. Low-grade adenosquamous carcinoma of the breast--A case


INVASIVE MICROPAPILLARY CARCINOMA

This outline is extracted from chapter 29 – Invasive micropapillary carcinoma, 4th Edition of Rosen’s Breast Pathology Textbook (1).

Invasive micropapillary (MP) carcinoma is a morphologically distinctive form of mammary carcinoma in which the neoplastic cells are arranged in morule-like clusters devoid of fibrovascular cores and located within empty stromal spaces. Pure invasive MP carcinoma has MP morphology in 90% or more of the tumor mass. A carcinoma with less of 90% MP admixed with invasive ductal carcinoma NST is referred as mixed invasive MP carcinoma.

CLINICAL PRESENTATION

The median age at diagnosis ranged from 46 (2) to 62 (3) years. Rare cases of invasive MP carcinoma have been described in male patients. Most tumors present as a palpable breast mass, but occasional lesions are detected mammographically as a density or because of associated calcifications. The median tumor size in few different series ranges from 1.5 cm to 3.9 cm. Tumors with more extensive MP component tend to be larger.

MICROSCOPIC PATHOLOGY

Invasive MP carcinoma consists of small clusters of neoplastic epithelial cells with serrated outer border and suspended in tight clear spaces. The clusters have no fibrovascular cores and display reverse polarity with the luminal aspect of the cell present on the outer surface of the cluster. This growth pattern closely mimics lymphovascular invasion. Nuclear grade is usually intermediate to high (4) and mitotic activity is easily detected. Pure invasive MP carcinoma is
rare and constitutes less than 2% of all breast carcinomas. Invasive MP carcinomas are significantly more likely to show lymphovascular invasion (68.1% vs 38.2%; p<0.0001) and lymph node metastases with extracapsular extension (40.3% vs 28.9%; p=0.001) than control tumors matched for age, size and stage (52.8% vs 37.5%; p=0.0387) (2).

IMMUNOHISTOCHEMISTRY

Most invasive MP carcinomas are positive for ER and PR. HER2 gene amplification was found in 8.3% pure invasive MP tumors. Some invasive MP carcinomas could be HER2-gene amplified even if they are HER2 (1+) by immunohistochemistry. For this reason, the 2013 ASCO/CAP guidelines (5) recommend that HER2 FISH testing be performed for invasive MP carcinomas that have focal complete HER2 (1+) staining intensity. Forty-six percent of invasive MP carcinomas in one study showed Ki67 staining in more than 30% of cells (6). No expression of basal markers (EGFR, CK5/6 and CK14) and c-kit has been detected. EMA staining yields continuous reactivity on the outer surface of the MP clusters (7, 8); MUC1 staining has similar results. These findings support reversed cell polarity in the MP clusters.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of invasive MP carcinoma includes mucinous carcinoma of the breast with areas of MP growth, as well extramammary carcinomas with MP pattern metastatic from other primary sites, such as ovary (9), bladder, colon or lung. Serous ovarian carcinoma is usually reactive for WT-1, while this marker is only rarely and focally positive in invasive MP breast carcinoma. PAX8 is also negative in invasive MP carcinoma of the breast. CA125 stains 21% of invasive MP carcinomas (10), but is strongly and diffusely positive in over 90% of serous papillary ovarian carcinomas.

TREATMENT AND PROGNOSIS
Lymphovascular invasion is present in 50%-90% of invasive MP carcinomas, and 70-77% of patients have axillary lymph node metastases at the time of diagnosis. Metastases to more than three lymph nodes are common, as well as extranodal extension. Most studies report that breast carcinomas with MP features tend to be more aggressive and carry a worse prognosis than non-MP tumors. Small invasive MP carcinomas are currently treated with breast conserving surgery and whole-breast irradiation; larger and multifocal tumors often require mastectomy. Some patients with large tumors developed chest wall recurrence after a mean time of two years (11). Yu et al. (2) compared the clinical F/U of 72 patients with invasive MP carcinomas and 144 patients matched for age, size, stage and treatment. Sixty-five percent of patients with MP carcinoma had been treated by mastectomy; 35% had breast conserving surgery and whole-breast irradiation. After a median F/U of 26 months a total of 21% of patients with invasive MP carcinoma recurred, including 15.3% with local and/or regional recurrence, and 14% with distant metastases. In this study the 5-years OS for patients with invasive MP carcinomas was 86.0%, and the 5-years RFS was 68.2%. Loco-regional RFS was significantly lower in patients with MP carcinomas than in patients with non-MP tumors.

REFERENCES

MUCINOUS CARCINOMA

This outline is extracted from chapter 18 - Mucinous carcinoma, 4th Edition of Rosen’s Breast Pathology Textbook (1).

Pure mucinous carcinoma (MC) consists of clusters of carcinoma admixed with extracellular mucin in at least 90% of the tumor mass. The term mixed mucinous carcinoma is used for tumors in which the mucinous component represents between 50% and 90% of the lesion.

CLINICAL PRESENTATION

Pure MC constitute 1% to 2% of all breast carcinomas. In a SEER data based study (2) the median age at diagnosis was 71 years and 66% of patients were 65 years or older. Most patients with mucinous carcinoma are postmenopausal (3-5). MC is most frequent among Caucasian women and can occur in men.
The initial symptom of a pure MC is usually a soft breast mass or a non-palpable mammographic abnormality. Tumors with abundant mucin production are mammographically and sonographically lobulated or circumscribed, in contrast to most mixed mucinous carcinomas. Mammographically detected calcifications occur in up to 40% of MC and/or in the associated DCIS. On ultrasound, myxoid fibroadenoma, benign cystic lesions, high-grade matrix-producing carcinoma and high-grade carcinoma with central acellular zone sometimes may resemble pure mucinous carcinoma (6). In a large population based study (2), MC had a mean size 2.2 cm, with 83.2% of tumors measuring 3.0 cm or less. In another series (7), the average size of pure MC with no lymph node metastases was 1.5 cm versus 2.6 cm for tumors with nodal involvement.

**MICROSCOPIC PATHOLOGY**

MC consists of carcinoma clusters admixed with abundant extracellular mucin. In a pure MC more of 90% of the invasive component is admixed with stromal mucin. Carcinomas with less than 90% mucinous component are referred as mixed mucinous. Multiple sections may be required to detect carcinoma cells in an extremely hypocellular MC. The majority of pure mucinous carcinomas are well or moderately differentiated. The presence of unusual morphologic features, such as necrosis, high mitotic activity, high grade nuclear atypia, extensive micropapillary morphology or goblet cells should be noted in the diagnosis. MC with these morphologic features may have more aggressive clinical behavior.

Capella et al. (8) classified MC based on epithelial growth pattern and some associated features. MC Type A has abundant mucin and the epithelium is distributed in large trabeculae and ribbons. MC Type B is more cellular and intracytoplasmic mucin is more common. Some MCs with type AB morphology were also noted. Type B MCs often show neuroendocrine differentiation. The morphologic distinction between type A and B MCs has no clinical significance. Ranade et al.
(9) have reported that type A MCs may have more favorable characteristics than type B tumors, but this finding needs confirmation in larger studies.

When assessing margin status of a MC it is important to look for transected protrusions that may be obscured by cautery artifact or blend with fat. In a patient with known MC the presence of mucin at ink is interpreted as tumor at margin, even if no tumor clusters are identified in the transected mucin in deeper level sections, provided that artifactual displacement is excluded.

**Micropapillary variant of pure mucinous carcinoma:** A micropapillary (MP) variant of pure MC has been described (9-11). The micropapillae are arranged in small tightly cohesive clusters or have ring-like configuration. EMA decorates the outer surface of the micropapillae, confirming reverse polarity of the epithelium, akin to invasive MP carcinoma. A MP component was present in 20% to 66.6% of pure MC in three different series (9, 11, 12). Ranade et al. (9) reported that pure MCs with MP component tended to occur in younger patients. In another series (13), lymphovascular invasion was detected in 60% of MC with MP component, and 33% had lymph node metastases. One of 13 patients with F/U developed a chest wall recurrence 9 months after mastectomy.

**Signet ring variant of pure mucinous carcinoma:** Carcinomas with abundant extracellular mucin rarely also have signet ring cell morphology. Signet ring cells admixed with mucin are commonly found in pure MC with neuroendocrine features (type B).

**Mucinous carcinoma associated with solid and papillary carcinoma:** MC may also arise from solid and papillary carcinoma. It often has type B morphology and shows neuroendocrine differentiation or neuroendocrine features. Genetic evidence supports a close relationship between these two entities (14, 15).

**DCIS and Mucinous Carcinoma**
DCIS associated with MC is usually cribriform, papillary, micropapillary, or solid. Abundant mucin can be present in the lumen of DCIS. In one series (16) 70% of DCIS associated with MC showed neovascularization of the intraluminal mucin. In the absence of overt invasion neovascularization of the mucin present in the lumen of ducts with DCIS should not be interpreted as evidence of tumor invasion.

**STROMAL MUCIN AND THE ASSESSMENT OF STROMAL INVASION**

A diagnostic problem arises in patients who have DCIS and extravasated mucin in the adjacent stroma. Extravasation of mucin from DCIS may be secondary to a prior procedure, trauma, handling of the tissue or it might occur spontaneously and does not necessarily always represent evidence of MC. In these cases, deeper level sections should be obtained. The mucin associated with stromal invasion usually shows a rounded to bulbous outline, neovascularization, and admixed inflammatory cells and fibroblasts (so called “dirty mucin”).

**Mucocele-like lesions:** A mucocele-like lesion (MLL), first described by Rosen in 1986 (17), consists of mucin-containing cysts that tend to rupture and discharge the mucin into the adjacent stroma. MLLs are usually detected by mammography because of associated calcifications. The term MLL is descriptive and should be further qualified indicating if epithelial atypia is present. The epithelium lining the ducts is often attenuated or low cuboidal, but can show a spectrum of changes ranging from columnar cells to ADH to DCIS (17-19). Verschuur-Maes and Van Diest (20) described a mucinous variant of columnar cell lesions with acini variably dilated and filled with mucin. Stromal mucin was detected in 18/20 (90%) of these 20 cases. No evidence of carcinoma was found at surgical excision of 3/20 lesions (2 with ADH and one without atypia).

**Mucocele-like lesions and CBX** (see Table I): Benign and malignant mucinous lesions of the breast can usually be reliably diagnosed by CBX, but distinguishing between pure and mixed
mucinous carcinoma requires evaluation of the entire tumor. In some cases deeper level sections are required to distinguish between a hypocellular MC and artifactual displacement of mucin into the stroma. If stromal mucin devoid of cells is present in a surgical excision specimen, the entire specimen (or at least some additional tissue) should be examined microscopically, and deeper level sections of the areas with stromal mucin and/or ADH should be obtained.

Stromal mucin devoid of cells is a very rare finding in a CBX specimen, representing only 0.32% of cases in a large retrospective series (21). The risk of upgrade to DCIS or invasive carcinoma for a MLL with atypia at CBX is consistent with the upgrade rate of ADH diagnosed in a CBX, whereas the excision of a MLL without atypia in a CBX can be safely spared provided that the radiologic and pathologic findings are concordant (21-25). Excisional biopsy is recommended if a MLL yields epithelial atypia at CBX and/or the radiologic and pathologic findings of the target lesion are discordant (22-27).

**DIFFERENTIAL DIAGNOSIS OF MAMMARY MUCINOUS LESIONS**

Cystic hypersecretory lesions of the breast can resemble MLLs, but do not contain mucin. The dense hypersecretory material often shows the characteristic “Venetian blinds” shattering effect. Secretory carcinoma is a rare and distinct variant of breast carcinoma containing luminal and sometimes intracellular secretion (28, 29), that is amphophilic or pale to eosinophilic, and often bubbly in appearance. Other breast lesions to consider in the differential diagnosis of mucinous carcinoma include myxoid fibroadenoma, myxoma and neurofibroma with prominent myxoid change. Mucoid stroma can also be present in a phyllodes tumor, pleomorphic adenoma, adenoid cystic carcinoma and metaplastic carcinoma. Metastatic mucinous carcinoma from an extra-mammary site has been reported. Foreign material may also occasionally closely resemble
extracellular mucin. In all these cases, in addition to evaluating the characteristics of the mucin, it is very important to obtain an accurate clinical history.

**IMMUNOREACTIVITY OF MUCINOUS CARCINOMA**

Most MC are positive for ER and PR, and negative for HER2. AR is positive in 80% of pure MC (30). Less than 5-10% of MC (9) overexpress HER2 and are likely to be more aggressive than usual MC. In a study by Lacroix-Triki et al. (14) Ki67 was low (<10%) in 91.4% of cases. Nuclear staining for WT1 is present in 65% mammary MC and 33% of mixed mucinous carcinoma (14, 31).

**GENETICS**

Lacroix-Triki et al. (14) found that pure and mixed mucinous carcinomas of the breast have genetic aberrations distinct from those of grade- and ER-matched invasive ductal carcinoma NST. Gains of 1q and losses of 16q, commonly seen in invasive ductal carcinomas NST, are uncommon in MC. Weigelt et al. (15) found that all mucinous and neuroendocrine carcinomas cluster together and separately from invasive ductal carcinomas NST. In particular, type B MCs and neuroendocrine carcinomas are closely associated.

**TREATMENT AND PROGNOSIS**

The relatively favorable prognosis of MC is supported by numerous studies (2, 7, 32-46). The rate of lymph node metastases for small (<1 cm) MC was 2.9% in one series (47), with no lymph node metastases for T1a MC and only 3.5% in T1b MC. Larger tumor size correlates significantly with lymph node involvement (2, 7). Neoadjuvant chemotherapy is rarely used for MC and yields only minimal, if any response (48). In a series of 61 patients treated by lumpectomy (43), 90% received radiotherapy, 41% hormonal therapy and 13% chemotherapy.
Local and loco-regional recurrence rates were both 5%, significantly lower than for invasive ductal carcinoma NST. The DFS was 91.6% at 5 years and 75.3% at 10 years. The OS rate was 91.8% at 5 years and 74.5% at 10 years. In this study, the authors found no benefit of chemotherapy in patients with mucinous carcinoma.

Prognostic factors that are relevant for most types of breast carcinoma are prognostic also for pure MC (34, 35). Nodal status was the most significant prognostic factor by multivariate analysis in one study (2). Other significant features include patient age, tumor size, PR status, and nuclear grade. Late systemic recurrences have been described after mastectomy in patients with mucinous carcinoma (32, 37, 38, 49-51). Some of the longest intervals to recurrence have been 25 (52) and 30 years (53). Late recurrence (54, 55) or late death due to disease (34) does not seem to occur in women with small, pure MC.

**Cystic Papillary Mucinous Carcinoma (Mucinous Cystadenocarcinoma) (CP-MAC)**

CP-MAC is a unique and extremely rare form of primary mucin-producing carcinoma of the breast. It consists of multiple cysts filled by mucin and lined by micropapillary, papillary, and cribriform carcinoma. The nuclei of the neoplastic mucinous epithelium usually show low grade atypia; areas with higher nuclear atypia are associated with intracytoplasmic mucin depletion (56-64). All reported cases have occurred in women (age range 41 to 96 years). Lack of myoepithelial lining around the mucin filled cysts of CP-MAC supports an invasive process. Rarely, areas of invasive ductal carcinoma NOS (58, 60) or foci of sarcomatoid metaplasia (56) have been observed admixed with these tumors, but the usual morphology of pure MC has not been identified. Focal DCIS is often present. CP-MAC is typically **ER and PR negative** (56-60,
62, 63, 65, 66). HER2 is also negative, except for one reported case (63). CP-MAC is also negative for neuroendocrine markers, CDX2, CK20, PAX8, WT1 and TTF1.

CP-MAC appears to have a relatively good prognosis, and only few patients presented lymph node metastases (56, 57, 66), that were morphologically similar to the primary tumor. Focal squamoid differentiation was reported in one case (57). The differential diagnosis of CP-MAC, an ER-negative and PR-negative mucinous carcinoma (56-60, 62, 63, 65, 66), includes metastasis from an extramammary mucinous carcinoma, such as from ovary, pancreatobiliary or GI tract.
**Table 1**

Findings at surgical excision of rad-path concordant lesions yielding stromal mucin and with or without epithelial atypia at core needle biopsy

<table>
<thead>
<tr>
<th>Study</th>
<th>Total CBX cases</th>
<th>CBX without atypia</th>
<th>CBX with atypia</th>
<th>Total patients with carcinoma or ADH</th>
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<td>with EXC cases</td>
<td>ADH at EXC/total CBX cases (%)</td>
<td>Carcinoma at EXC/total CBX cases (%)</td>
<td>Carcinoma at EXC/total CBX cases (%)</td>
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<td>Renshaw 2002 (21)</td>
<td>8</td>
<td>3</td>
<td>1/3 (33%)</td>
<td>0/3</td>
</tr>
<tr>
<td>Wang 2007 (22)</td>
<td>11</td>
<td>7</td>
<td>0/7</td>
<td>0/7</td>
</tr>
<tr>
<td>Begum 2009 (23)</td>
<td>23</td>
<td>10</td>
<td>0/10</td>
<td>1* /10 (*10%)</td>
</tr>
<tr>
<td>Sutton 2012 (24)</td>
<td>38</td>
<td>22</td>
<td>not specified</td>
<td>0/22</td>
</tr>
<tr>
<td>Edelweiss 2013 (25)</td>
<td>28</td>
<td>10</td>
<td>4/10 (40%)</td>
<td>0/10</td>
</tr>
<tr>
<td>TOTAL</td>
<td>108</td>
<td>52</td>
<td>5/30 (17%)</td>
<td>1* /52 (2%)</td>
</tr>
</tbody>
</table>

a= one case with discordant radiologic-pathologic findings

CBX= Core biopsy; EXC= surgical excision; ADH= atypical ductal ductal hyperplasia
REFERENCES


