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THE MENACE IN BREAST PATHOLOGY

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Introduction

Diagnosis by non-operative procedures has of late become the standard of care. This helps the pathologist to make far reaching decisions on small tissue samples. Haematoxylin and eosin (H&E)-stained sections estimation with analytical thinking assisted by the significant use of immunohistochemistry (IHC) and other tests, resume to be the bulwark of histological diagnosis. This review aims to accentuate the hidden difficulty in the interpretation of breast lesions that could diversely guide to under diagnosis, over diagnosis, or incorrect categorization of malignancy, with possible dire after effects to the patients. The review focusses on interpretation of H&E and IHC in breast pathology and aims to complement existing literature on the subject. 1,2,3,4

Entities that may result in over diagnosis of malignancy:

In general, some breast lesions show pervading crop up that mimics incursion which may be misread as invasive carcinoma (IC). These include nipple adenoma, benign syringomatous tumour of the nipple, radial scar / complex sclerosing lesion, sclerosing adenosis, and micro glandular adenosis. Benign intraduct papilloma may probably decipher flushed ductal hyperplasia (UDH), sensitised epithelial alterations which may be misled for a malignant tumour.

Some lesions like core needle biopsy (CNB) specimens that lack the typical epithelial-myoepithelial glandular bi-layer, e.g. pleomorphic adenoma and sclerosed adeno myoepithelioma that may be incorrectly diagnosed as metaplastic breast carcinoma (MBC), the epithelioid variant of myofibroblastoma, comprised of incoherent oestrogen receptor (ER)-positive epithelioid cells resembling invasive lobular carcinoma (ILC), fat necrosis with a florid histiocytic response that may be misguided for apocrine ILC, and Toker cell hyperplasia of the nipple that may be misled as Paget's disease of the nipple. Here we report studies that may result in over diagnosis of malignancy based on the histological findings. 6,7,8

Glandular, Sclerosing and Papillary lesions

Nipple adenoma

Erosive papillomatosis or Nipple adenoma which develop superficially presented as an ulceration clinically mimic Paget's disease mainly when long lasting. Intense clinical assessment illustrates a dermal nodule and the intuitive clinician will identify finely. Occurrence is reported in both the gender, women being most common. Ultrasound may signify a mass but generally non-specific. By histological protocols, nipple adenoma may be mistaken for IC due to the irregular outline of the glandular proliferation, often involved by ruddy UDH with center of necrosis, mocking ductal carcinoma in situ (DCIS) (Figure 1). Emergence of virulence in nipple adenoma has been uncommonly reported. Recognition of the state and the classical clinical appearance normally direct to the exact diagnosis. In skeptical cases, myoepithelial cell (MEC) IHC may be applied to signify the benign nature of the glands and to distinguish the supplementing epithelial cell growth. In some lesions, the MEC the MEC sheet may appear to be absent principally and it is preferable to use relatively two MEC markers in tough cases. 9,10

Syringomatous tumour of the nipple

Syringomatous tumour of the nipple is accounted as a slow, permeable lesion which is commonly small and significant for confined recurrence but do not become carcinogenic. This show morphological lap over with low-grade adeno squamous carcinoma. Core needle biopsy may not be helpful. Accurate anatomical position will be helpful. This tumour is usually spotted apparently pervade the smooth muscle of the areola which infrequently expands to the dermis. Discrete cells are mild and mitoses are rare. Comparatively low-grade adeno squamous sarcoma emerges in depth the interstitial tissue of the breast. This may reach large size which is rare. In contrast, low-grade adeno squamous carcinoma arises deeper in the interstitial tissue of the breast, may reach a large size. The principal cell type of syringomatous tumour is myoepithelial with detection of p63, high molecular weight (HMW) cytokeratin (CKs), and other MEC markers. 11,12,13

Radial scar/complex sclerosing lesion

These sclerosing lesions hardly become symptomatic and are usually diagnosed at screening mammography. Their symmetrical arrangement feature IC on imaging though appearance of a radiolucent core is outlined actively resemble radial scar. Most of the lesions are classified as level 4 (sceptical for malignancy) using the Breast Imaging Reporting and Data System (BIRADS). Rapid increase of glandular form with the characteristic radial presentation may generate an perception of invasive tubular carcinoma, especially at low power or on CNB. Rise of the central fibro-elastotic nidus, the lack of add on of tubules into peripheral fat, the desertion of cytological atypia, and the existence of two cell class should direct to the precise diagnosis. Since the nature of the tubules are fragmented the identification of the peripheral MEC layer by H&E probably be difficult. IHC is normally applicable (Figure 2) but MECs may also be hard to view due to cellular attenuation, mainly on p63 nuclear stain. Along with benign change, the epithelial hyperplasia, cyst formation, papillomatosis, and sclerosing adenosis, is regular. About one third of cases are identified significantly with flat epithelial atypia, atypical ductal hyperplasia, DCIS, or invasive breast carcinoma (IBC). Radial scar/complex sclerosing lesion identified by CNB, need to be analysed on conformity by gold standards. The progressive phase of radial scar/complex sclerosing lesions may exhibit adeno squamous multiplication which is when glitzy may give rise to the doubt of low grade adeno squamous sarcoma. In similar cases surgical extirpation is reposed to allow investigation of the surrounding breast tissue, which is regularly involved by the infiltrating adeno squamous nests in low-grade adeno squamous carcinoma. 14,15,16,17

Sclerosing adenosis

Sclerosing adenosis is a benignant lesion state which is often seen as a secondary inference in breast biopsies and extirpations conducted for other breast state and as a feature of radial scar/complex sclerosing lesion. Numerous sections complicated by sclerosing adenosis can

merge leading to a mass lesion, indicated as 'nodular adenosis'. Normally these affected lobules are intense with additional numbers of glandular pattern which are squeezed, widened and warped because of the mass of stromal collagen. Early ulcers lead to be cellular and may generate a spindle cell characters. Calcification is frequent. The pronounced glandular deformation may lead to an uneven shape with a modification of a cord-like development motif with advancement into fat. This manifestation may be false guided for centre of ILC, distinctly when exist in samples which also contain ILC, possibly focussing to magnification of disease measures and incorrect evaluation of extremity level (Figure3A). Association of sclerosing adenosis by apocrine alterations and in situ carcinoma may mimic IC. Expansion of sclerosing adenosis by lobular carcinoma in situ (LCIS) may lead to integration of the affected sections masking the linked myoepithelium, interposing stroma, and acinar architecture, passing to a low-magnification appearance of a solid sheet of IC cells. 18,19,20

Association of sclerosing adenosis by DCIS may also be misconstrued as IC. 5 This is distinctly complicated in cases of broad DCIS with extension of sclerotic portions and the complementing periglandular lymphocytes, mimicking high-grade IC (Figure 3B). Perineural percolation may also be noticed in sclerosing adenosis which may lead to mis interpretation if the pathologist is not aware of this difficulty. Sclerosing adenosis is the non-malignant breast lesion mostly incorrectly diagnosed as malignant. The most beneficial indication to the exact diagnosis are the presence of lobulo-centric manner of the damaged lobules on H&E at low power, and that although glands may extend into fat, they do not distort it. (Figure 3A). IHC illustration of the peripheral MEC is effective, notably in excluding the identification of IC. IHC expression of the peripheral MEC is productive in ruling out diagnosis of IC in cases of sclerosing adenosis involved by in situ carcinoma, considering the pitfall which may be experienced due to cell attenuation. 21-24

Microglandular adenosis

Microglandular adenosis is an uncommon infiltrative breast lesion which may activate tubular carcinoma of the breast. The tubules of microglandular adenosis are generally circular enclosed by the basement membrane, and aligned by a single layer of epithelial cells which are S100-positive (Figure 4) and negative for ER, progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). Absence of the peripheral MEC layer. The tubules will lie free in the stroma and fat with no additional stromal response. Microglandular adenosis is now considered as a possible precursor lesion of triple-negative breast carcinoma (TNBC) initially assessed to be an entirely benign lesion. Significance from tubular sarcoma is critical to warrant applicable treatment. Microglandular adenosis is normally controlled by surgical obliteration without adjuvant therapy. Microglandular adenosis, together with the unusual structures share the morphological and molecular characteristics with acinic cell carcinoma of the breast.

Either entities dearth peripheral MECs and in the factors of acinic cell carcinoma, untypical solid group similar to atypical microglandular adenosis need to be evaluated part of the acinic cell sarcoma range. 25-27

Intraduct papilloma

Benign intraduct papilloma, without existing UDH at times muddled with encapsulated or solid papillary carcinoma, due to its protected framework, matured fibro vascular connective tissue foci shielded by epithelial and MECs, and peripheral MEC sheath. UDH innards the intraduct papilloma is a usual hypothesis but commonly principal, frequently with apocrine metaplasia, and seldom produce diagnostic struggle. We have observed few cases of intraduct papilloma presented with prolific UDH with mitotic activity, inhabiting the entire lesion with destruction of the well-developed papillae to build a solid appearance which may mimic solid papillary carcinoma or DCIS simulating a papilloma (Figure 5). Organized drive to diagnosis

which involves determining the features of the basal lesion and valuing the diverse nature of the epithelial cell increase on H&E, assisted by IHC, will typically guide to the right diagnosis. 28 Intraduct papillomas may be restricted following CNB and a lead of squamous metaplasia which may generate a representation of metaplastic carcinoma or infrequently, mucoepidermoid sarcoma. Misinterpretation of excess viable ductal epithelium by fibrosis at the margin of the lesion may also reproduce IC. The low power physiognomy of the lesion, the lack of cytologic characteristics of malignancy and the existence of peripheral MECs are functional standard other than diagnosis of IC. The shift of epithelial cells together with the needle zone may appear following CNB and should not be misinterpreted for sarcoma. 29,30

Benign Breast lesions with Myxoid Matrix

Fibroadenoma is a regular and generally upright interpretation on CNB. Rare cases fibroadenomas with a distinguished myxoid stroma and infrequent glandular elements may make an influence of matrix causing carcinoma. Knowledge of this potential complications and radiology-pathology association should rule out diagnostic misinterpretation. Pleomorphic adenoma is an infrequent manifestation in the breast that may exhibit a puzzling presence on CNB due to the leading myxoid stroma comprising lesser atypical epithelial cells that may illustrate pricipally CKs and are hormone receptor-negative. 3,6

Spindle Cell/Mesenchymal Lesions

Benign spindle cell lesions (SCLs) of the breast comprises a variety of complications, few may present a significant and important picture histologically, with a probability for misinterpretation as virulent, particularly on CNB. Adding on to assessment of the H&E and IHC detections, analysis of the clinical history, duration of symptoms, radiological investigations and the accurate anatomical position of the lesion would be crucial in all breast lesions and will help to evade incorrect readings. We recommend clustering of SCLs into ‘benign presence’ and ‘malignant presence’, which support a wide differential diagnosis and factor of a bland interpretation when show malignant lesion and vice versa as discussed below (Malignant conditions that may be interpreted as benign). 31

Even though infrequent, the benign breast SCLs with probability for misinterpretation as virulent that are more commonly observed are scar, fibromatosis, nodular fasciitis, myofibroblastoma, and cellular pseudo angiomatous stromal hyperplasia. Uncommon benign SCLs are inflammatory myofibroblastic tumour, solitary fibrous tumour, spindle cell lipoma, benign smooth muscle, and neural tumours, the spindle cell modification of adenomyoepithelioma, cellular sclerosing adenosis, and myoid hamartoma. 32

Scar

Scar tissue is mostly experienced on CNB, frequently implemented for assessment of calcification or a stacked lesion. Few patients have a history of ipsilateral prior breast surgery or breast trauma. Others may not have any noted history and scar need to be in mind while assessing breast SCL. Currently present scar may be a growth of very active fibroblasts with mitotic activity phase, identified as a postoperative spindle cell nodule. Information on clinical history and the concordant changes e.g. hemosiderin displacement, foamy macrophages, fat necrosis, and foreign body giant cells aid diagnosis (Figure 6). Scar tissue may demonstrate smooth muscle actin. CKs, p63, CD34, and b-catenin are negative. 33

Fibromatosis

Fibromatosis is an infrequent breast lesion that display clear morphological affinity to fibromatosis-like MBC (discussed below). Both lesions favour to have an infiltrative form with involvement of peripheral fat and lymphocytic inflammation. The cells of fibromatosis lack cytological atypia and mitoses considered hard to identify (Figure 7A). The lesion might reoccur narrowly but is generally governed by supervision. B-catenin nuclear staining (Figure

7B) and smooth muscle actin (SMA) cytoplasmic staining are the typical IHC findings. CKs, p63, and CD34 are typically negative. 34,35

Nodular fasciitis

Nodular fasciitis is also an unusual benign breast SCL which may mount with a history of accelerated advancement and is normally self-limiting. The section fibroblasts generally have a stellate presentation with moderately bland manifestation and a plumed developed pattern. The matrix may be myxoid or collagenous and hold exuded red blood cells (Figure 8). Some lesions are extremely cellular, with recurrent mitoses which may lead in over diagnosis as malignant. Recognition of the entity, clinical history details, notice of devoid of uncommon mitoses will be useful to avoid diagnostic misinterpretation. The cells of nodular fasciitis may be smooth muscle actin-positive. They are CK and p63 negative. 36

Cellular pseudoangiomatous stromal hyperplasia (PASH)

Cellular pseudoangiomatous stromal hyperplasia (PASH), probably be falsely understood for angiosarcoma because of the conjoining order of the pseudovascular channels. They are grooved by comparatively bland developing spindle shaped myofibroblasts and do not involve red blood cells (Figure 9) which should alert the pathologist to the exact diagnosis. The lining cells are CD34 and PR-positive and may demonstrate actin and desmin. Other vascular markers are negative. 37

Myofibroblastoma

Myofibroblastoma of the breast may mock spindle cell MBC. The common well-confined class of lesion on radiology and the finding of amianthoid fibres and arbitrating adipocytes on H&E might be useful the pathologist to make the accurate diagnosis. In addition to ER, myofibroblastoma cells are commonly CD34, SMA, and desmin-positive. CKs and p63 are negative. As stated prior the epithelioid mutant of myofibroblastoma may feature ILC, with additional ability for a false-positive interpretation due to ER positivity (Figure 10). 38

Eosinophilic Granular lesion

The distinguishing diagnosis of eosinophilic lesions of the breast, such as histiocytic inflammation and granular cell tumour, comprises carcinoma with oncocytic modifications and apocrine carcinoma. 39

Histiocytic inflammation

Florid histiocytic inflammation may effect from a cleaved duct or extend secondary to a prior breast procedure. Histologically, this may resemble apocrine carcinoma, specifically on CNB where supplementing adaptations which promote exact diagnosis, e.g. elements of a duct/cyst or a fibrous reaction, may not be exhibited (Figure 11). Histiocytes are CD68- positive and CK-negative.

Granular cell tumour

Granular cell tumour is an uncommon, routinely benign, breast tumour that generally appear in women. It has a penetrating progress scale and may simulate IC both clinically and histologically. The tumour is comprised of round to polygonal cells with profuse, eosinophilic,
granular cytoplasm, due to cumulation of lysosomes, which may mimic apocrine carcinoma. Perineural and perivascular association may be seen and lesions settled in the dermis may be integrated with surrounded pseudo epitheliomatous hyperplasia, with advanced potentiality for misdiagnosis. Clues to the valid diagnosis lead to the concrete diagnosis involve recognition of tiny, located in the centre, hyperchromatic, nuclei, scanty mitoses and undefined cell margin. Lesional cells are completely S100-positive and are also CD68 - and

NSE- positive. CKs, melan-A and HMB45 are negative, differentiating this tumour from carcinoma and melanoma (Figure 12). 40,41,42

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Epithelial cell displacement following needling procedures

Epithelial cell exclusion in breast tissue may appear after diagnostic needling protocols and generate investigative complications resulting abscission samples which have been produced at a lesser time interval. This occurrence is observed usually in link with papillary lesions, but has also been outlined on account of liposuction for gynaecomastia and after biopsy of radial scar, DCIS, and IC. The dislocated epithelial cells are reviewed as trivial, their existence in breast tissue devoid of a MEC layer at the epithelial stromal contacts or within vascular passages may lead to over diagnosis of IC. The occurrence **of** epithelial exclusion in malignant tumours may influence the estimation of tumour/lesion size and perimeter level and guide to over diagnosis of lympho-vascular invasion and IC, especially in DCIS, with prospective management associations. IHC will not help in differentiating the shifted epithelial cells from focal point of IC, since they are particularly devoid of a MEC layer. The exact diagnosis of replaced epithelial cells aided by recognition of an initial needling protocol and valuing of the following post protocol histological alterations involving haemorrhage, granulation tissue, acute and chronic inflammation, and fat necrosis with assembly of vacuolated and haemosiderin-laden macrophages. The time line between the needling procedure and the surgical excision need to be considered. 43-50

In difference, timely virulent centre in compact papillary carcinoma may be followed by rigid stromal transformations, generating the impact of epithelial replacement. Discriminating attributes involve the multiform character of initial capture with sensitive stromal modifications. The second are examined to be due to recapitulated small cracks of the cystic papillary structure than the secondary to a diagnostic needling technique in which the alterations are significantly localised and frequently linear.

Artefactual displacement of DCIS (‘toothpaste effect’)

Artefactual replacement of DCIS (ADDCIS) not integrated with needling protocols may arise to alternative to mechanical contraction of breast specimens directing to over-diagnosis of IC, as recently reported. Shabihkhani et al reported 16 cases of ADDCIS not related to needle section changes raised for estimation with a positive diagnosis, of IC. Lumpectomy specimens show high incidence, the foci size from <1 to 5 mm and include the breast stroma in a non-lobular spread. The centre >4 mm exhibited a continuous basis of replacement, this is a significant diagnostic indication. Smeared chromatin and the absence of a stromal reflection are supportive properties. Equivalent to replaced epithelium successive needling protocol MEC IHC is negative. The patients in follow up did not advanced metastases, sustaining the view that ADDCIS does not show IC. 51

Collagenous spherulosis

Collagenous spherulosis is a comparatively rare, benign, lesion indicated by accumulation of acellular, eosinophilic, or basophilic, network bounded by basement membrane, myoepithelial, and ductal epithelial cells. It is generally secondary microscopic detection. Collagenous spherulosis may be involved by LCIS yielding a ‘collision’ lesion with a cribriform impression which may be falsely understood for low-grade cribriform DCIS. Both lesions are marked by the merge of small cells with consistent nuclei and circular punched-out arrangements. Recognizing eosinophilic basement membrane or basophilic mucoid material internally in the spaces, distinguishing the lack of polarised epithelial cells throughout the cribriform spaces, and considering that the increase is possessed with discontinuous epithelial cells with intracytoplasmic vacuoles may guide the pathologist to review the diagnosis. Knowledge of this system may persuade the pathologist to use IHC to

additionally examine the biopsy results and to elude a misdiagnosis of low-grade DCIS. 52-54

LCIS cells are generally E-cadherin-negative, those of DCIS are E-cadherin-positive. MEC IHC will illustrate MECs in the region of the position of collagenous spherulosis, but the cribriform zone of DCIS is not lined by MECs (Figure 13). Collagenous spherulosis also mimic adenoid cystic carcinoma due to the presence of basement membrane-like material. Collagenous spherulosis infrequently form a lump and is typically c-kit (CD117)-negative, in comparison to adenoid cystic carcinoma. 55,56

Lactactional change

Lactational alterations may be roseate and with important nuclear modifications involving nucleomegaly, pleomorphism, and a hobnail occurrence that may head to identification of flat or hypersecretory type DCIS (Figure 14). The determination of DCIS need to be confined to patients showing constructive atypia involving cribriform, solid or micropapillary extension motif and positive primary necrosis or HER2 IHC positiveness (IHC score 3+). Appearance of p53 and/or a high Ki67 also offer identification of DCIS. 57,58

Hypersecretory thyroid-like adenosis

Hypersecretory thyroid-like adenosis is a newly reported atypical unit which comprises of several dilated glands of varied sizes, with a conserved lobular design involving heavy eosinophilic diastase PAS-positive colloid-like secretions. The glands are coated by ER-negative epithelial cells and are encircled by a thick basement membrane. Peripheral MECs are not present. The epithelial cells do not exhibit cytological atypia or mitotic activity, if detected show high conclusion of IC. Hypersecretory thyroid like adenosis is more suitably noted as a secondary inference than exposing as a clinical or radiological malformations. 59

Ectopic breast tissue in lymph nodes

The appearance of ectopic breast tissue in axillary lymph nodes may be misunderstood as nodal metastases, distinctly if the breast tissue shows hyperplastic transformations.

Malignant conditions that may be misinterpreted as benign:

Few malignant breast lesions may emerge falsely mild, leading to under-diagnosis as alternatively, benign, hyperplastic, or locally infiltrative. Few invasive malignancies are also properly classified as in situ lesions due to their idle biological operations.

Spindle Cell DCIS

DCIS associated with spindle cell morphology is an infrequent presence which may be wrongly understood for UDH, mainly if it is the only pattern without any supplementing conventional type DCIS. This shape of DCIS is comprised particularly or mainly of spindle cells determined in fascicles, whorls, and solid sheets. The fascicular presentation of the spindle cells may reproduce the ‘streaming’ design of UDH. Indication to the exact diagnosis involve the development arrangement with intercellular and peripheral gaps. The cells occur constant with low- to intermediate-level nuclear atypia. In comparison of structures of DCIS, the cells are negative for HMW CKs 5/6 and 14. Maximum cases are ER-positive and decipher neuroendocrine disparity. 60,61

LOW-GRADE SOLID DCIS

The differentiation of low-grade solid DCIS from typical LCIS is clinically prime due to the recent distinct control measures. The common LCIS is usually controlled by mammographic surveillance with factors of risk-reducing endocrine therapy. In comparison, DCIS is generally governed as a direct breast cancer precursor with total surgical removal, frequent follow up by radiation therapy. The diagnosis may be hard, notably on CNB. Both comprise of minor consistent cells with monomorphic nuclei. Characters indicative of ductal difference involve cellular bonding, precise cell margin and main columnar shape of the neoplastic cells. The recognition of microacini with polarisation of cells surrounding lumina present a

diagnosis of DCIS. Aspects in favour of a lobular phenotype comprise lack of cellular unity and the appearance of intracytoplasmic vacuoles. E-cadherin IHC is useful when appeared with this differential diagnosis, directing in mind with some of the troubles related with interpretation of this IHC, as discussed further. 62

ENCAPSULATED PAPILLARY CARCINOMA

Though intraduct papilloma is hardly misdiagnosed as malignant, encapsulated papillary carcinoma may show a 'benign' development initially because of its completely confined outline, extensive rise design and notable papillary framework. A major clue at lesser power is the disintegrated and distorted kind of the lesion in contrast to the conserved, complete nature of intraduct papilloma (Figure 15). Further investigation, surrounding papillary carcinoma normally lack a peripheral MEC layer and the fibrovascular cores within the lesion are enclosed by epithelial cells only that are cytologically atypical with mitotic activity. 63,64 It is significant to recognise that the fibrovascular cores are outlined by a single cell type, frequently with multiple cell layers, in comparison to the cores of intraduct papilloma which are demarcated by two cell types. IHC may be used to elucidate the nature of the cells in doubtful cases.

SOLID PAPILLARY CARCINOMA

Solid papillary carcinoma is comprised of an amplification of constant epithelial cells punctuated by delicate fibrovascular cores. Tumours with a circular contour and a propelling perimeter are classified as in situ with or without marginal MEC layer. Tumours are classified as intruding if the border is spiked with stromal desmoplasia and/or the cytology of the epithelial cells is increased nuclear grade. 63,67 These tumours may decipher neuroendocrine divergence and are sometimes linked with mucinous carcinoma. 68,69 Well demarcated tumours where the epithelial cells show less to moderate nuclear class with spindling impact may show a bland impression on H&E and the lesion may be misguided for intraduct papilloma with florid UDH, the other state to that described earlier. 70,71 The exact investigation is enabled by identification of the uniform nature of the epithelial cells, the fragile fibrovascular network, and the lack of MECs within and usually at the perimeter of the nodules. In difficult cases, IHC is useful in illustrating the absence of MECs and the clonal nature of the epithelial cell expansion which is diffusely ER-positive and HMW CK-negative 72

FIBROMATOSIS LIKE METAPLASTIC CARCINOMA (FLMBC)

The most crucial differential diagnosis for a bland-appearing breast SCL32 is fibromatosis-like metaplastic carcinoma (FLMBC), which is easily confused with fibromatosis or a different benign lesion, especially on CNB (Figure 16). Spindle cells with little nuclear pleomorphism, little mitotic activity, and no in situ component often make up this type of cell (24, 73). The stroma may be collagenized or sclerotic. Some tumors exhibit a peripheral inflammatory cell infiltration with lymphoid follicles. The risk of under diagnosis is increased further by the combination of FLMBC with benign sclerosing lesions, especially in early lesions. When compared to other MBCs, FLMBC has an excellent prognosis; yet, it may recur locally, and there have been sporadic instances of metastases. Given that these tumors are being handled using the low-grade IBC approach, recognition is obviously crucial. Most tumors show CKs and p63 expression. Since CK positivity might be focal and no single antibody can stain all MBCs, a panel of antibodies against epithelial markers is advised because CK positivity can be focal. In FLMBC, 24 b-catenin nuclear staining, a sign of fibromatosis, is not frequently observed. Focal faint nuclear staining, however, may rarely be present and shouldn't prevent the pathologist from identifying FLMBC. CD34 is unfavourable. On CNB, a definitive diagnosis might not be achievable; in this situation, diagnostic excision is advised (74,75).

LOW GRADE ANGIOSARCOMA

Angiosarcoma is a rare, but usually aggressive, breast tumour that accounts for ~25% of primary breast sarcomas.76 Angiosarcoma of the breast may be primary or develop secondary to the effects of radiation therapy and shows varied morphology, ranging from a predominantly vasoformative lesion to a tumour with a predominantly solid growth pattern. Primary angiosarcoma is more frequently composed of anastomosing, well-formed, small to medium sized vascular channels that dissect through adipose tissue compared with secondary angiosarcoma (Figure 19). Low-grade angiosarcoma is composed of well-formed vascular channels, lined by endothelial cells with minimal atypia, with potential for misdiagnosis as a benign haemangioma. Unlike haemangioma, the vascular proliferation of angiosarcoma does not display a lobulated configuration, the vessels intercommunicate and traverse normal lobules and adipose tissue. 77

MALIGNANT CONDITIONS THAT MAY BE INCORRECTLY DIAGNOSED AS PRIMARY BREAST CARCINOMA

METASTASES TO THE BREAST

Between 0.2% and 1.1% of breast cancers are classified as malignant tumors, and in up to one-third of instances, the first symptom of malignancy is breast metastases from extra mammary original malignancies.78 The incidence seems to be rising, which 79, 80 is probably because histological analyses and radiographic investigations are becoming more in-depth. Melanoma, lung, gastric, and colorectal adenocarcinomas, renal cell carcinoma, sarcoma, and prostatic carcinoma in males are the most frequent causes of metastases to the breast. Breast involvement is possible with malignant mesothelioma, neuroendocrine tumors, and uterine cervix squamous cell carcinoma. The clinical presentation, which may be symptomatic or picked up on a screen, may be strikingly similar to that of primary BC. Accurate diagnosis is crucial for directing proper care, which includes avoiding unnecessary surgery. The clinical, radiological, or patient's prior medical history may alert the pathologist to the risk of metastases. Although multifocal and/or bilateral lesions are prevalent in primary BC, the pathologist should take metastases into account if they are present. Although not all primary BCs exhibit an in situ component at diagnosis, the absence of DCIS may be a clue that the index lesion is a metastasis. Other microscopic indicators of extra mammary metastases include unusual morphology, such as melanoma's melanin pigment, colorectal carcinoma's classic "garland-like" necrosis, or renal cell carcinoma's clear cytoplasm, as well as a biomarker profile that is inconsistent with the histological features, such as a triple-negative low-grade carcinoma. The diagnosis can be clarified greatly by comparison with prior histology and IHC workup, including breast markers ER, GATA3, GCDFP-15, SOX10, and other antibodies based on morphology and clinical history. Although breast metastases are typically triple-negative, ER expression is widespread in Gynaecological malignancies and is not limited to breast cancer. Similar to this, GATA3 is expressed in several tumors, such as malignant mesothelioma, squamous cell carcinoma of the skin, and urothelial carcinoma. Despite a comprehensive examination, some high-grade malignancies, such as those of the lung and ovary, may not be morphologically identifiable from high-grade primary BC. It may also be challenging to discern between synchronous original tumours and metastatic illness. 81,82

LYMPHOMA

2% of extranodal lymphomas and up to 0.5% of all breast cancers are lymphomas that include the breast.83 Patients typically have symptoms, although screening mammography can also identify breast lymphoma. The most frequent subtype in patients with localized disease is diffuse large B cell lymphoma, which is followed by extranodal marginal zone lymphoma of mucosal associated lymphoid tissue (MALT lymphoma), which typically

presents as a single breast mass. Patients with disseminated illness are more likely to develop follicular lymphoma, mantle cell lymphoma, and small lymphocytic lymphoma, which can manifest as multifocal breast tumors.84 Breast lymphoma and primary BC look quite similar clinically and radiologically, yet a recent study suggests that lymphoma can be discriminated on imaging because of bigger lesion size. Due to the uniform, dyscohesive character of the cell population and the presence of thick collagen, particularly in follicular lymphoma, which may result in a single cell pattern of infiltration, low-grade breast lymphomas may histologically resemble ILC (Figure 20). When evaluating a diagnosis of ILC on CNB, being aware of this potential pitfalls and noting the absence of atypical lobular hyperplasia/LCIS and unexpected hormone receptor negative could help avoid misdiagnosis and pointless surgery. It is possible to confuse triple-negative IBC, no special type (NST), grade 3 with high-grade lymphoma. Accurate detection is aided by careful consideration of cytological and architectural detail, the lack of DCIS, and a low threshold for additional IHC investigation of triple-negative BCs. It is usually important to take lymphoma or other cancerous conditions into consideration when assessing multifocal or bilateral breast tumors. 83,84,85

HIGH GRADE ANGIOSARCOMA

High-grade angiosarcoma is made up of solid sheets of spindle and epithelioid cells with varying degrees of vasoformation, as opposed to the low-grade angiosarcoma that was previously addressed. Blood lakes, necrosis, and mitotic activity are frequently observed. Angiosarcomas that mostly have an epithelioid appearance and occasionally display epithelial markers might be misinterpreted for IBC NST, grade 3 on H&E. CD31 and ERG are two endothelium markers expressed by angiosarcoma. These tumors exhibit variable degrees of CD34, D2- 40, and FLi1 antibody positivity. Any previous clinical history should be taken into account, and any distinctive clinical manifestations should be recognized. Most breast pathologists will come across a few of these tumors over their careers, despite the fact that they are rather uncommon in the breast, and they should include angiosarcoma in in the differential diagnosis of high grade triple-negative breast tumours. 86,87, 88

OTHERS

Some uncommon BCs could look like benign lesions or be misdiagnosed as a primary invasive illness. Well-differentiated adenoid cystic carcinomas can be mistaken for breast cylindromas and mucoepidermoid carcinomas with a bland appearance for intraduct papillary lesions with metaplasia. Due to the duct-like features of the infiltrative papillary clusters, some instances of invasive papillary carcinoma may be mistaken for papillary DCIS. Some high-grade ICs may resemble encapsulated papillary carcinoma by having a well-circumscribed pushing border and papillary-like centers.89 Failure to recognize low grade lymphoma in lymph nodes excised for the detection of metastatic cancer is another error we have made in clinical practice. 89

IMMUNOHISTOCHEMISTRY PITFALLS

E – CADHERIN

ILC correctly diagnosed is clinically relevant. When ILC is identified through a biopsy, a breast magnetic resonance imaging (MRI) examination may be ordered to establish the extent of the disease, rule out the potential of multifocal and bilateral tumors, and assess the patient's eligibility for breast-conserving surgery. Neoadjuvant chemotherapy generally results in a worse response in ILCs than in IBC NST,90 which may have an impact on future clinical recommendations and therapeutic choices. ILC and LCIS diagnoses are frequently made using morphological characteristics.39 The underlying loss of E-cadherin-mediated cell adhesion causes the dyscohesive look that distinguishes lobular lesions. Due to this, E-cadherin is not expressed in the membrane, which may be shown using IHC and is frequently utilized to help with diagnosis in morphologically ambiguous instances (Figure 21A, B). The majority of ILCs and LCIS (including florid and pleomorphic varieties) do not express E-

cadherin on their membranes, although IBC NST, DCIS, and healthy breast epithelium do. However, the presence of E-cadherin does not rule out the diagnosis of lobular disease. It may not express E-cadherin in some high-grade IBC NSTs and up to 16% of ILCs 91, LCIS 91-93.

There is a growing understanding of "aberrant" E cadherin staining patterns that could be challenging to decipher. 62,92,94 ILC and LCIS frequently have weak or decreased and fragmented membrane expression rather than being totally E cadherin-negative (Figure 21C, D). The pattern's "aberrant" nature and support for a lobular phenotype can be confirmed by comparison with the significant diffuse membranous staining in nearby normal breast tissue. E-cadherin's cytoplasmic expression is also discussed. 92

Some cases with the characteristic morphology of an ILC or LCIS have widespread strong membranous staining, which may be caused by inactivated E-cadherin that is still present on the cell surface as an abnormal protein. 92 In these circumstances, the use of p120 and b-catenin, if available, may offer proof of lobular differentiation. Reassessing morphology in light of the E-cadherin results is also beneficial. LCIS with mixed benign epithelial cells that are E-cadherin positive may be challenging to interpret. LCIS can undermine pre-existing benign epithelium in a pagetoid pattern or partially include ducts or acini. Strong E-cadherin expression is present in the remnant benign native epithelium, which could cause LCIS to go undetected or be mistaken for DCIS. MECs may coexist with LCIS cells in the acinar and ductal areas covered by LCIS. It is possible to mistake the granular staining of MECs and their cytoplasmic processes (Figure 21E, F) for that of LCIS cells.

When combined with UDH, LCIS cells can mimic atypical ductal hyperplasia or DCIS. The pathologist can identify E-cadherin positivity in hyperplastic ductal epithelium by comparison with H&E, which is typically seen at the center of the proliferation with a streaming or syncytial look. At the duct's outermost part, the uniform population of small, rounded, dyscohesive LCIS cells is most prominent. Diagnoses in complex situations may also benefit from the use of CK5/6 and ER. When the diagnosis is simple to make on the basis of morphology, E-cadherin IHC is not advised. If the histological traits are usual, unexpected or abnormal staining patterns shouldn't prevent the pathologist from identifying a lesion as lobular.

BREAST MARKERS

IHC panels with "breast lineage" markers (discussed below) and the biomarkers ER, PR, and HER2 may be used in conjunction with organ/site specific markers, such as CDX2 (digestive system), TTF1 (lung), and PAX8 (gynecological tract), in addition to morphological assessment, to identify the origin of a tumour. When trying to detect whether a tumour is a metastasis from a breast primary, the pathologists' choice of IHC markers will be influenced by the clinical context and tumour location. 96-98

- **GCDFP-15 and mammaglobin**

Mammaglobin and the fluid protein associated with gross cystic disease 15 (GCDFP-15) are cytoplasmic stains. The majority of ER+ and HER2+ BCs contain these markers, however expression might vary and is frequently focal96, 98. GCDFP-15.99,100 is less sensitive than mammaglobin as a stain. These stains are less helpful in TNBC, as sensitivities for GCDFP-15 and mammaglobin are reported to vary from 12 to 16% and 16 to 32%, respectively.96,97,101 When evaluating potential cutaneous recurrences, pathologists should keep in mind that skin adnexal carcinomas may also show these markers. 99-101

- **GATA3**

Nuclear transcription factor GATA3 is connected to the ER signaling pathway in BC and is involved in the development of breast luminal epithelial cells.102 GATA3 sensitivity and ER

status are closely related. Over 90% of ER+ BCs express it, and it typically exhibits robust, diffuse staining.99 Compared to GCDFP-15 or mammaglobin, it is a more accurate indicator of ER+ BC, and the nuclear staining pattern of GATA3 is also simpler to understand. Additionally, expressing GATA3, lymphocytes frequently serve as an effective internal positive control. 99,102 With reported expression rates of 66%, 67%, and 82% in the literature, GATA3 is less sensitive in TNBC. A useful marker in the examination of possible metastatic BC is GATA3. GATA3 expression is highly correlated with both primary breast tumours and metastases. Even with reduced ER expression, concordance remains high. While GATA3 is a sensitive marker for both breast and urothelial carcinomas, increasing experience with this marker has shown that it stains additional epithelial tumours, such as chorio carcinoma, chromophobe renal cell carcinoma, salivary gland, and pancreatic ductal adenocarcinomas. It is also expressed less frequently (<10%) in a range of carcinomas, such as adenocarcinomas with lung, gastrointestinal, and gynecological origins, Miettinen et al. have demonstrated. 99-104

- **SOX10**

The IHC examination of melanocytic and neural tumours was the first application of SOX10, a transcription factor that participates in the formation of neural crest cells, melanocytes, and Schwann cells105. Additionally, expressed in breast and salivary gland MECs106, SOX10 also highlights the distinction of MECs and basal cells in a collection of breast and salivary gland tumours. As it stains a subgroup of BCs that do not express GCDFP-15, mammaglobin, or GATA3, SOX10 is a useful IHC marker. Unlike GATA3, SOX10 expression is uncommon in ER+ BC, but it has been found in 31 to 69% of TNBCs, particularly in GATA3-negative TNBCs, with reported expression rates of 30-74% in that subgroup. 94-110
As they appear to preferentially stain different subsets, GATA3 staining and SOX10 are complementary and may help to clarify a primary breast origin in suspected TNBC metastases. GATA3 staining is seen in metastatic BC from a non-TNBC primary tumour with loss of biomarker expression, while SOX10 labels metastases from primary TNBC.104 According to reports, SOX10 expression is consistent between primary and metastatic tumours, just like GATA3 expression.104-110
In addition to the expression of breast markers by tumours other than breast tumours, it is interesting that BC may express markers that are commonly expressed by other tumours, such as CDX2 and PAX8, as was recently observed. This serves as a reminder to consider IHC findings alongside H&E morphology as well as in a clinical and radiological context. 111

MYOEPITHELIAL CELL IMMUNOHISTOCHEMISTRY

In the diagnostic process and classification of benign and malignant glandular, papillary, and intraductal proliferative lesions, the identification of MECs, both on H&E and on IHC, is crucial. The lack of MECs near the edge of a lesion may support the diagnosis of invasive malignancy, but it must be read carefully and in light of the surrounding circumstances. As previously mentioned, despite the lack of a peripheral MEC layer, encapsulated and solid papillary carcinoma may be categorized as in situ lesions.
When demonstrating MECs is necessary for categorization, it is advised to utilize a minimum of two MEC markers, typically a mix of a nuclear and cytoplasmic stain. 24
Nuclear stain p63 has a high sensitivity and specificity for MECs and does not express in myofibroblasts or blood vessels. SMA, calponin, smooth muscle myosin heavy chain (SMMHC), and CD10 are typical cytoplasmic MEC markers with various degrees of sensitivity and specificity. The main drawback of cytoplasmic MEC markers is their propensity to stain blood vessels and myofibroblasts, which can make them difficult to interpret. Because myofibroblasts are aligned at the edges of the invasive foci, simulating a

MEC layer on cytoplasmic MEC IHC, it can be difficult to distinguish deformed ducts affected by DCIS from foci of IC in this situation (Figure 17).

MECs can also be stained with antibodies to HMW CKs, but this method may produce varying staining intensities and false-negative results. In addition to myofibroblasts, CD10 may react in an unintended manner with epithelial cells. In comparison to high-grade DCIS, it is said to be a more precise marker for the identification of MECs in LCIS and low-grade DCIS. Sclerosing adenosis, DCIS, and apocrine lesions have been associated with decreased p63 nuclear staining intensity, which may make diagnosis more challenging. 113-115 This could be attributed to MEC hypertrophy, which causes cell elongation and increased inter-nuclear distance, making the nuclear staining difficult to see. However, decreased expression of cytoplasmic MEC markers has also been observed in benign and non-invasive breast lesions113–115, leading to the hypothesis that immune-phenotypic changes may be to blame for decreased or even absent MECs, especially in apocrine lesions—the so-called "missing MECs."115 All cytological and architectural characteristics should be considered when evaluating apocrine lesions in particular, and classification should not be based primarily on the presence or absence of MECs. The expression of p63 in cells that have undergone squamous or basal differentiation is another possible problem.2 Some low-grade TNBCs may be difficult to diagnose because of this, such as low-grade adeno squamous carcinoma (Figure 23), in which the epithelial cells of tiny glandular formations exhibit p63 staining and could be mistaken for MECs. Additionally, MECs may exhibit lympho-vascular markers, such as D2-40. In order to differentiate between DCIS with retraction, in which the peripheral MECs express both markers, and lympho-vascular invasion (p63-negative and D2-40-positive), a unique MEC marker will be used. 112-115

Conclusion

The breast pathologist's skill set must include knowledge of the potential pitfalls in the evaluation of H&E-stained sections and IHC preparations as well as the capacity to keep an open mind during the diagnostic work-up of operative and non-operative breast specimens in order to prevent interpretative error and guarantee safe and proper patient management.

Figure1: Nipple adenoma and DCIS (High grade with comedo necrosis) 10x magnification

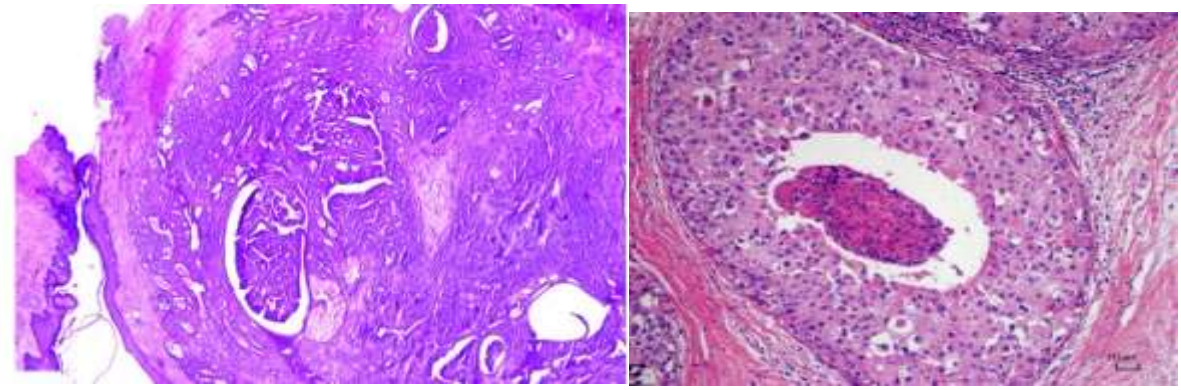

Figure2: Attenuated p63 expression in radial scar

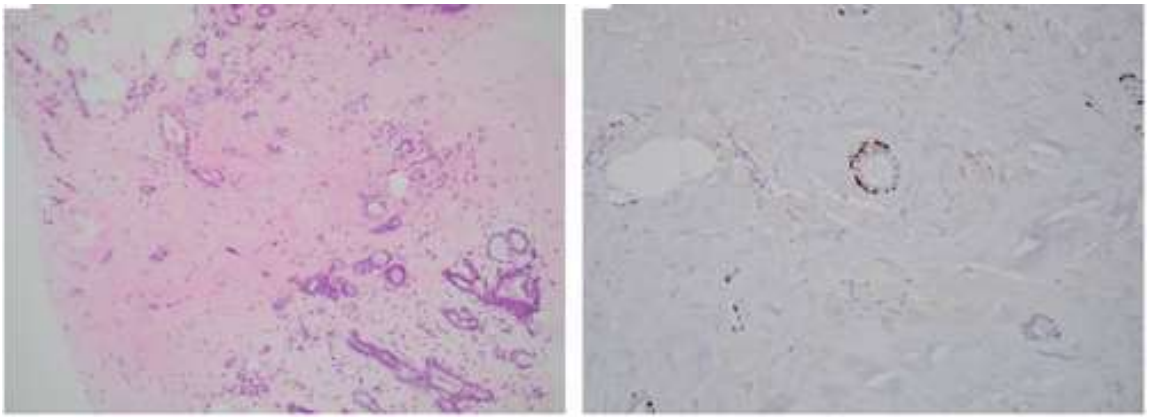

Figure3A: Sclerosing adenosis with periglandular lymphocytes
Figure3B: Sclerosing adenosis extending into the fat mimicking Invasive Carcinoma (IC)

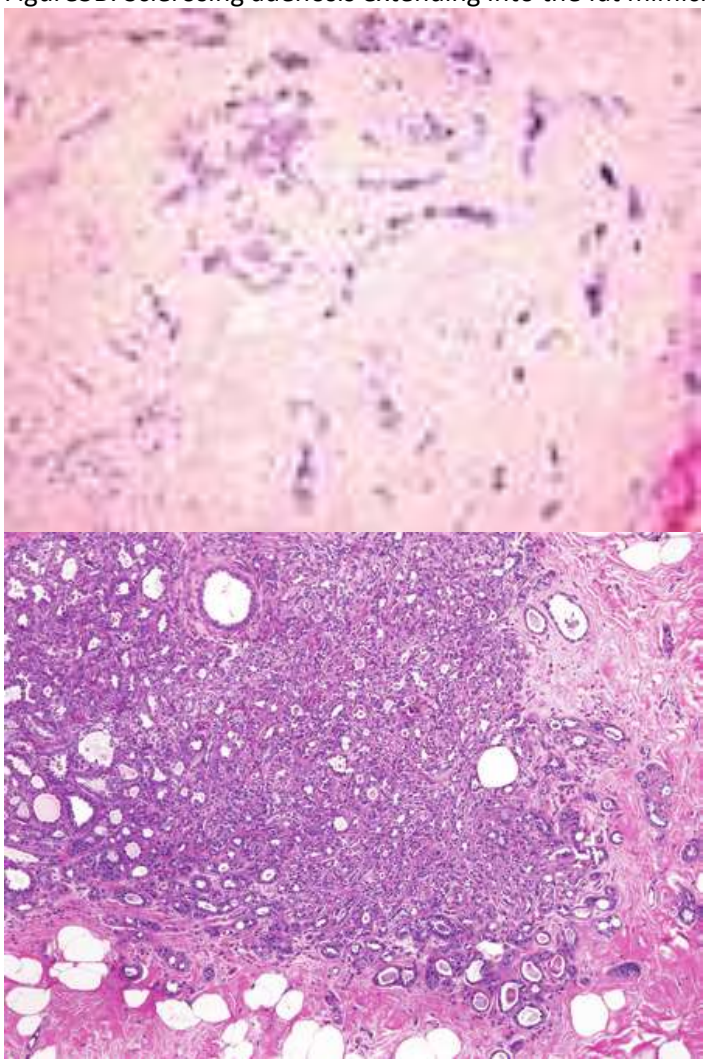

Figure4: Microglandular adenosis – Immunohistochemistry S-100

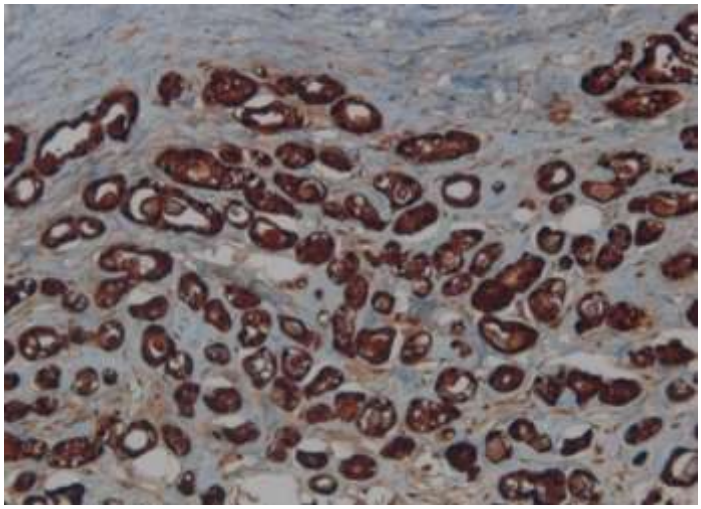

Figure5: Intraductal Papilloma with Ductal Carcinoma in Situ

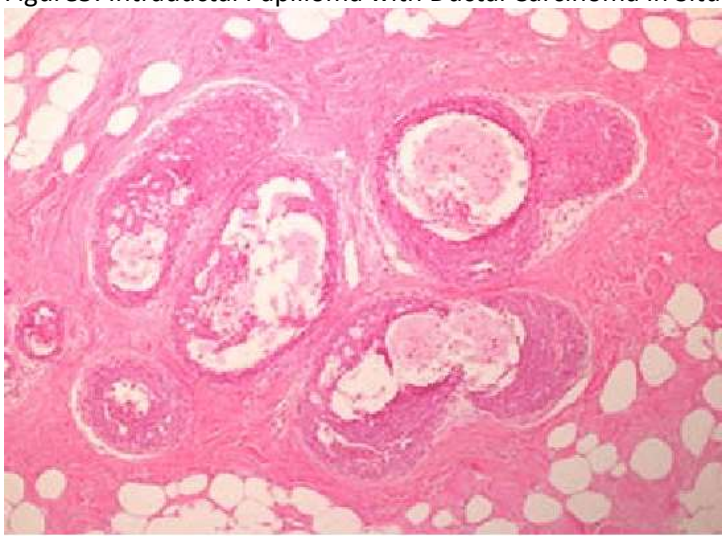

Figure6: Scar tissue in Breast with chronic inflammatory cells and Hemosiderin laden macrophages

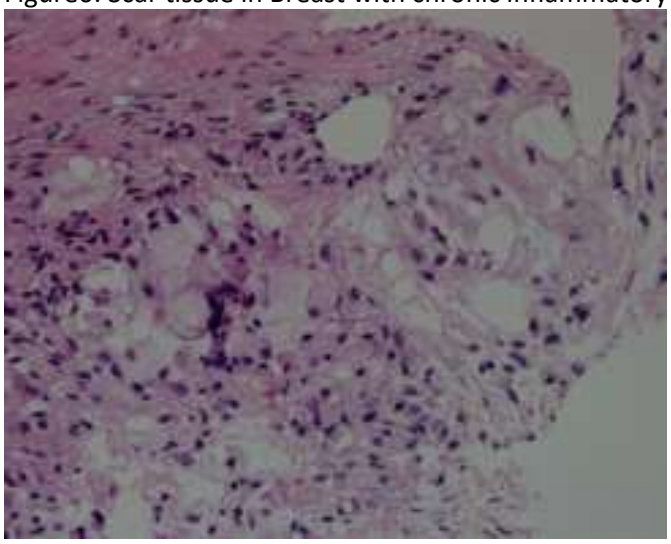

Figure7A: Fibromatosis of Breast

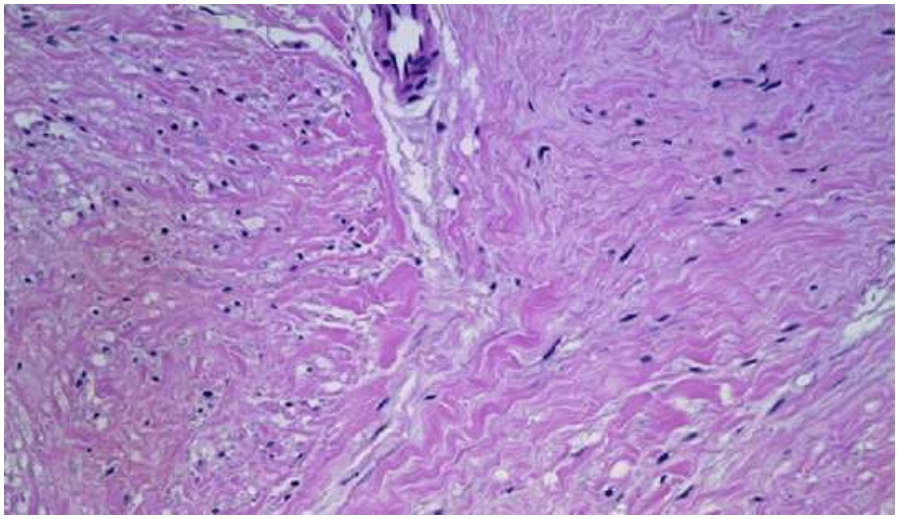

Figure7B: β catenin nuclear staining in Fibromatosis Breast

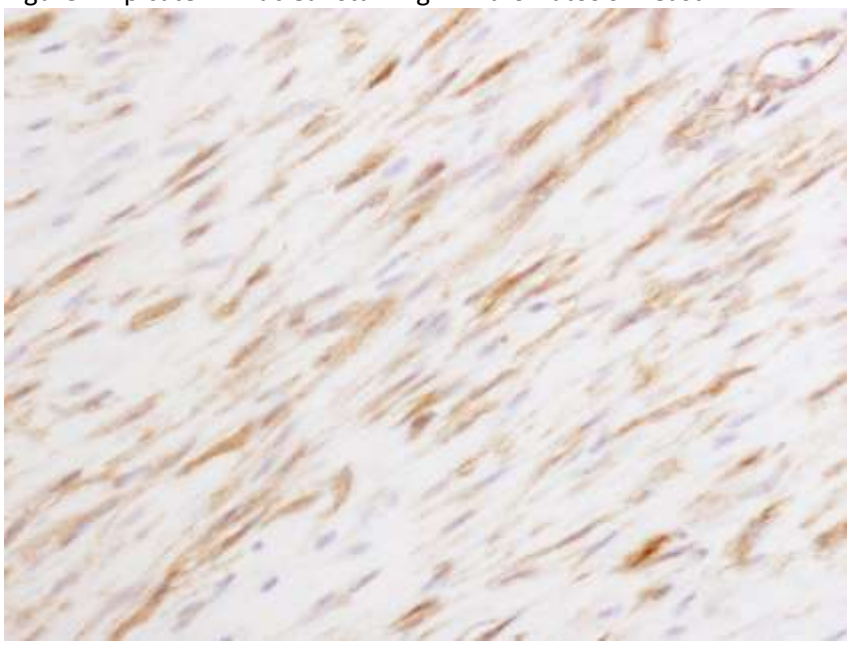

Figure 8: Nodular Fasciitis in Breast with extravasated red blood cells

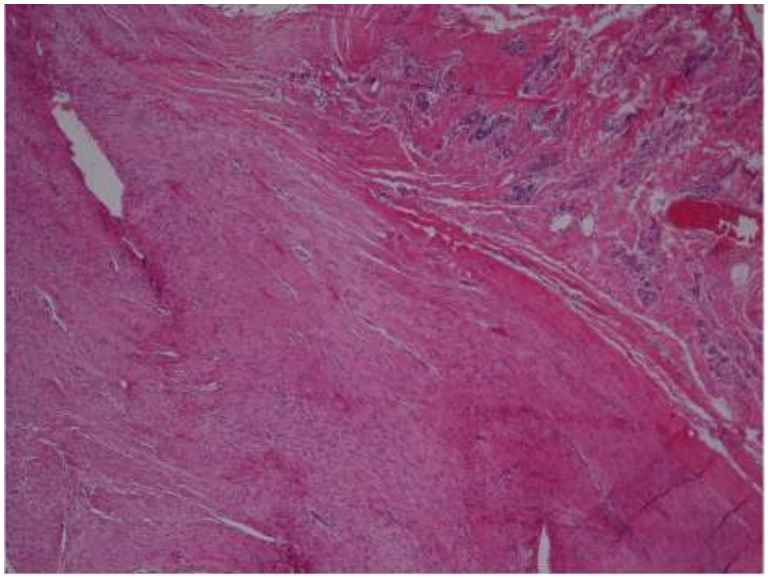

Figure 9: Cellular pseudoangiomatous stromal hyperplasia (PASH)

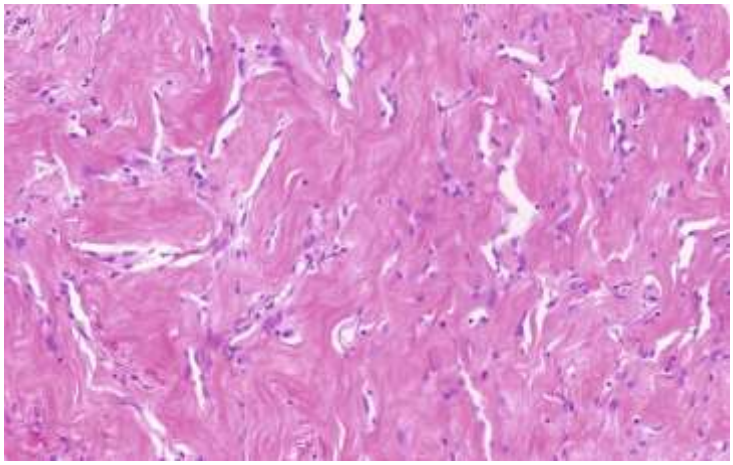

Figure10: Myofibroblastoma with ER Positivity mimicking invasive lobular carcinoma

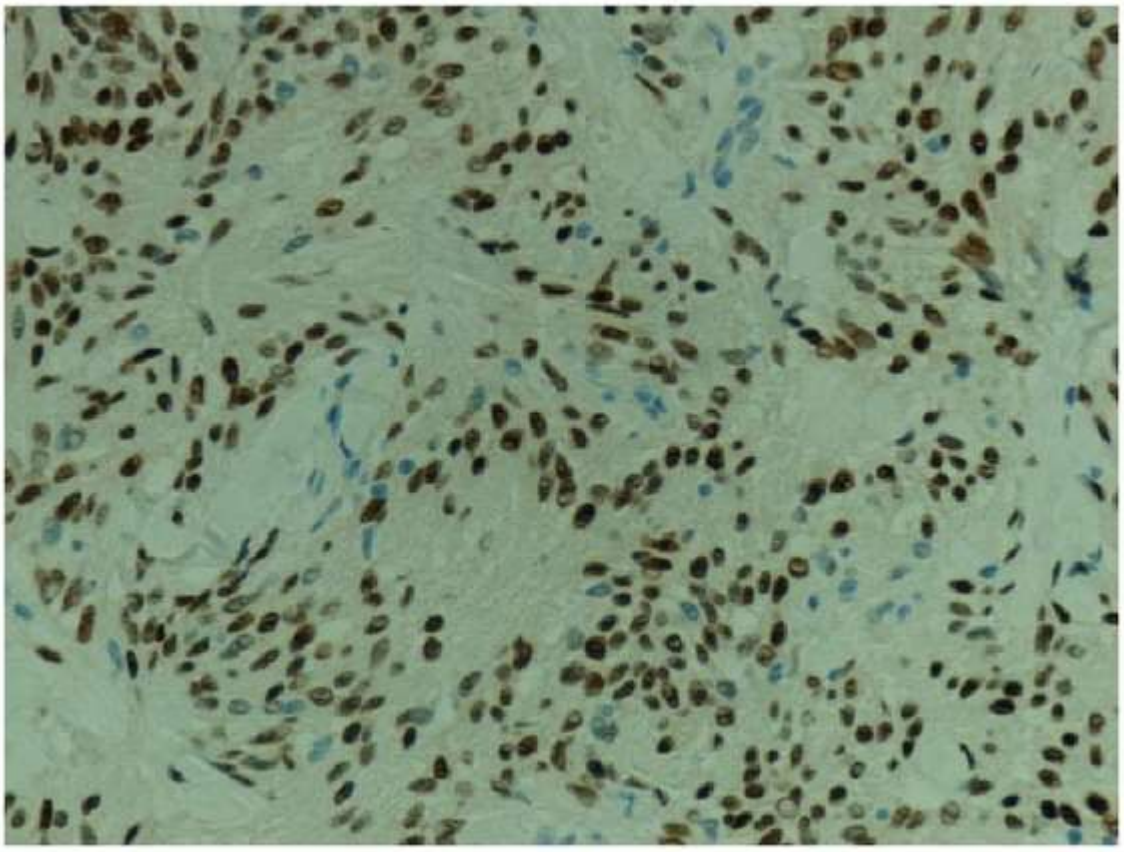

Figure11: Florid Histiocytic reaction with giant cells

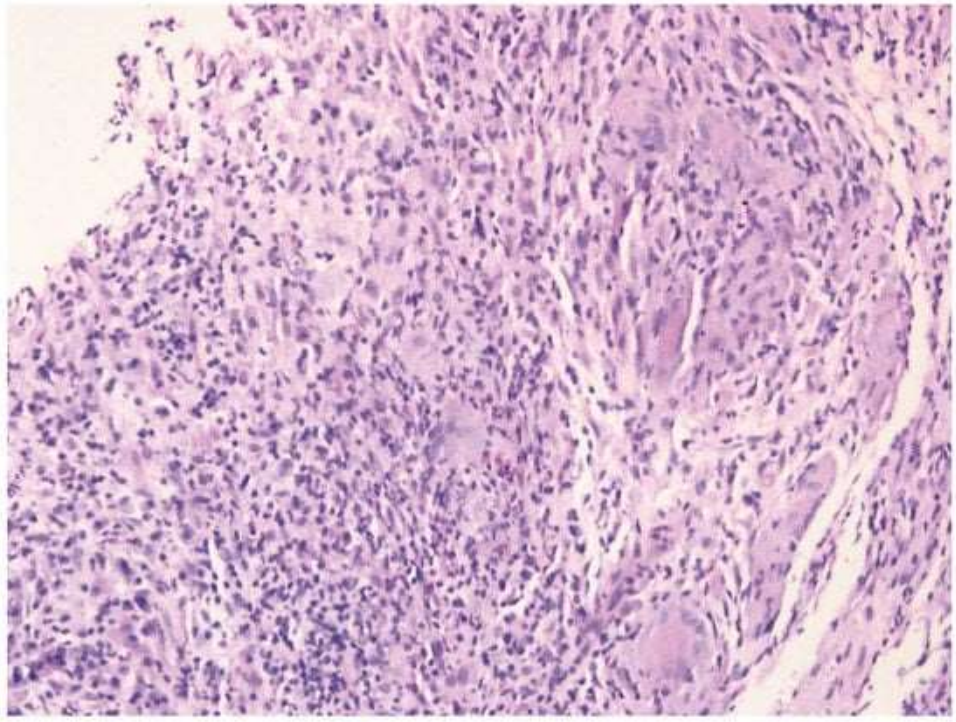

Figure12: Granular cell Tumor

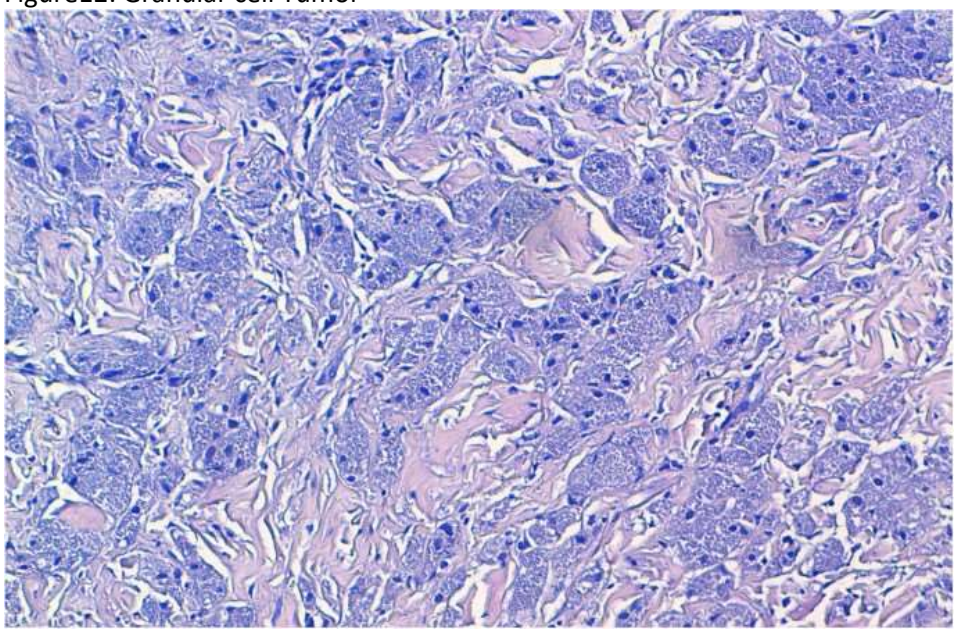

Figure 13: Collagenous spherules with myoepithelial marker positive in IHC p63

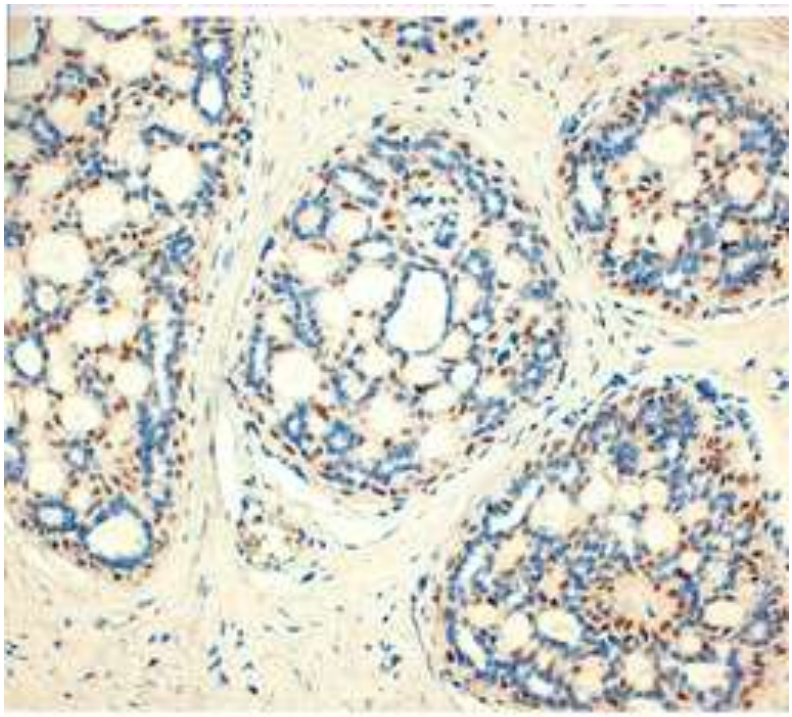

Figure 14: Lactational change with nuclear pleomorphism mimicking ductal carcinoma in situ

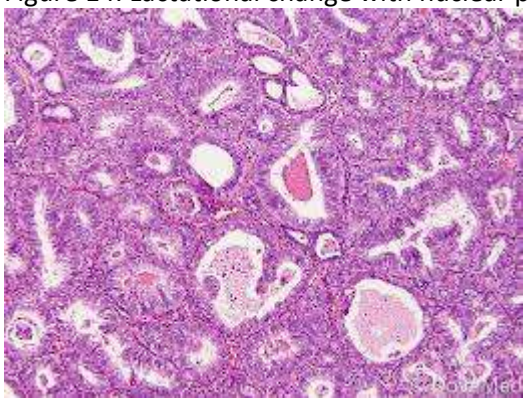

Figure 15: Encapsulated papillary carcinoma with disintegrated and distorted morphology

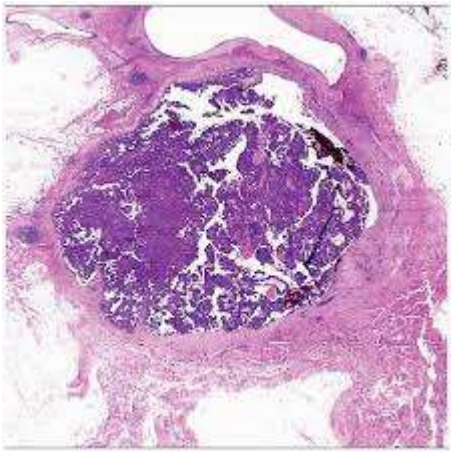

Figure 16: Fibromatosis like metaplastic carcinoma

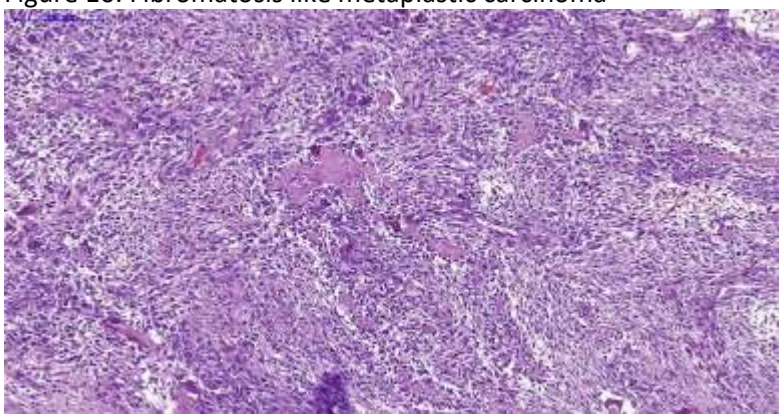

Figure 17: p63 showing positivity in papillary Carcinoma breast

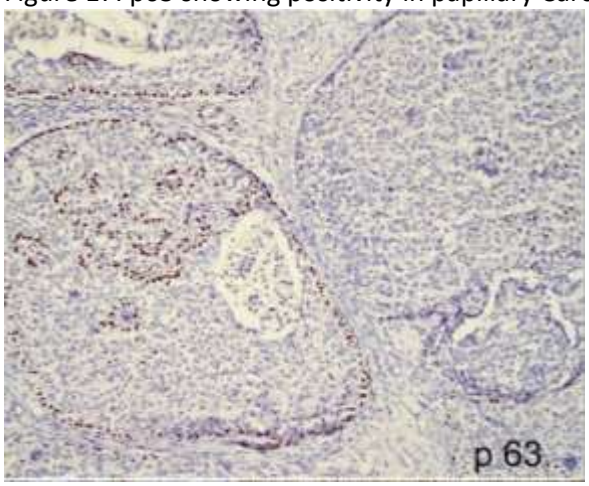

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Figure1: Nipple adenoma and DCIS (High grade with comedo necrosis) 10x magnification

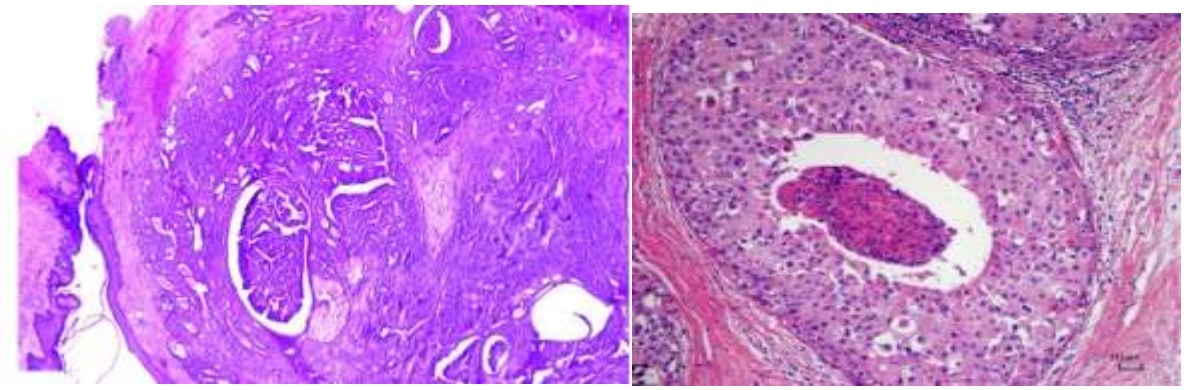

Figure2: Attenuated p63 expression in radial scar

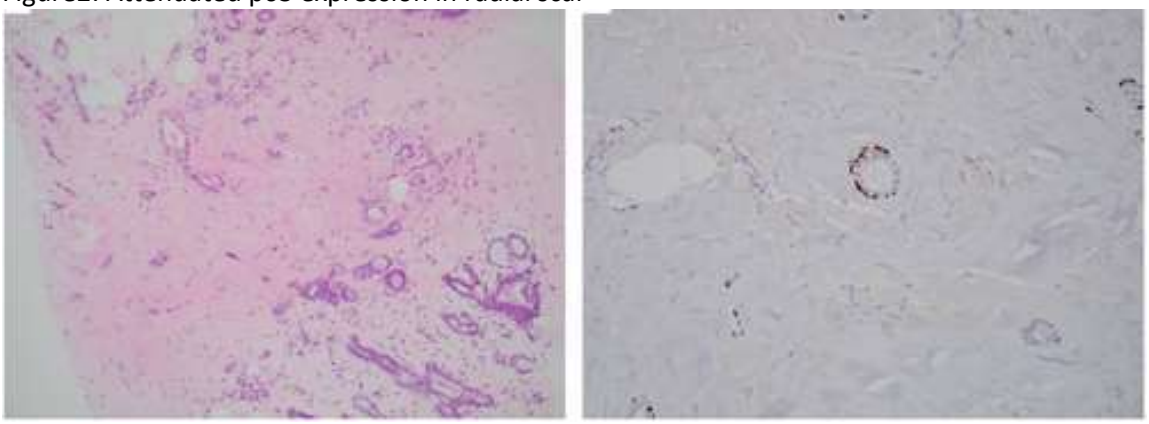

Figure3A: Sclerosing adenosis with periglandular lymphocytes
Figure3B: Sclerosing adenosis extending into the fat mimicking Invasive Carcinoma (IC)

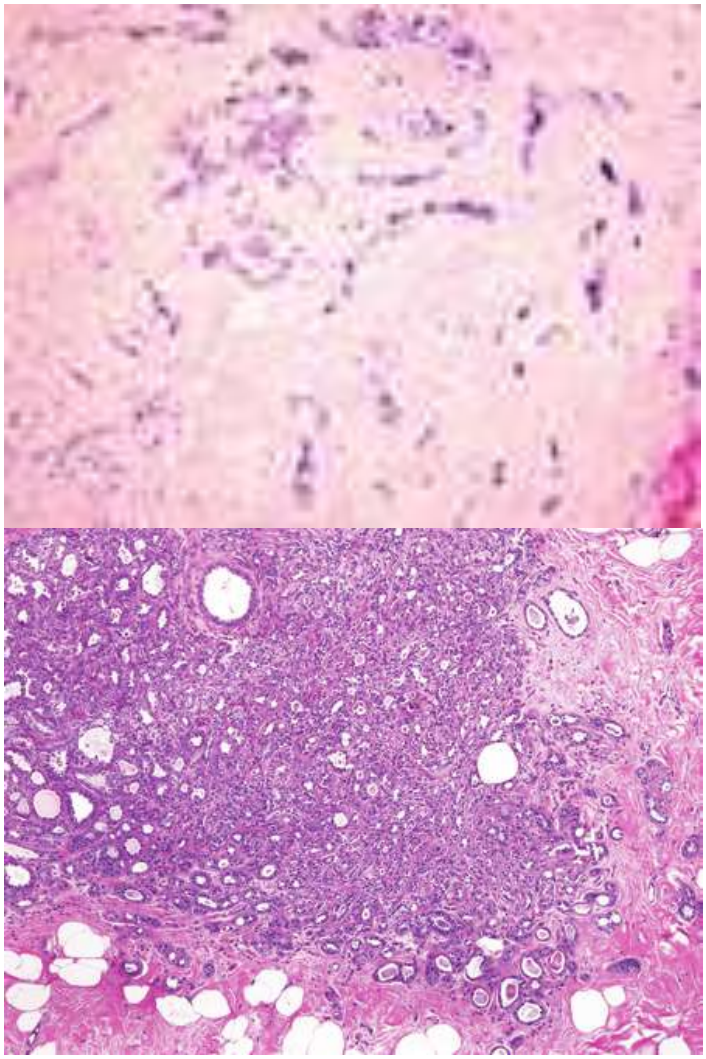

Figure4: Microglandular adenosis – Immunohistochemistry S-100

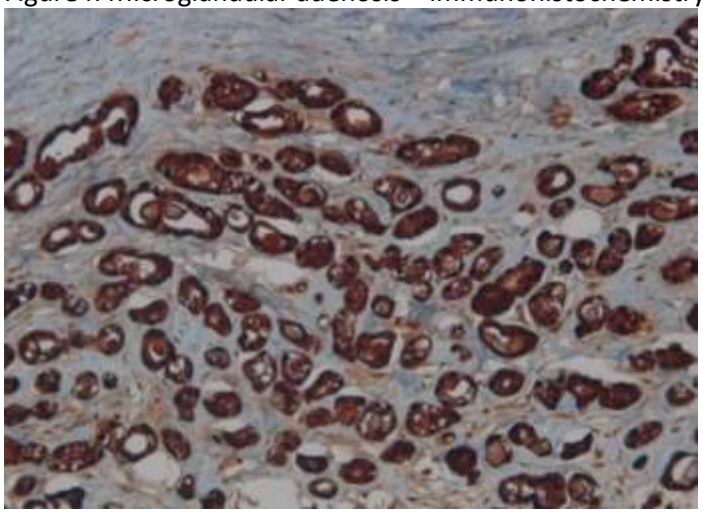

Figure5: Intraductal Papilloma with Ductal Carcinoma in Situ

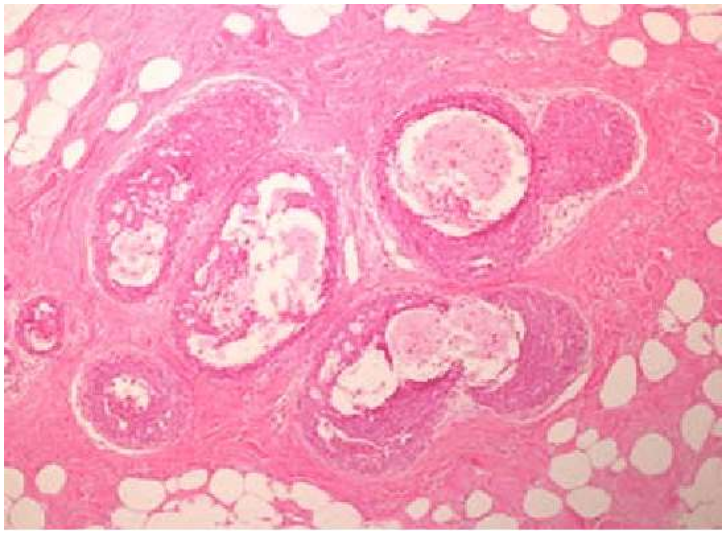

Figure6: Scar tissue in Breast with chronic inflammatory cells and Hemosiderin laden macrophages

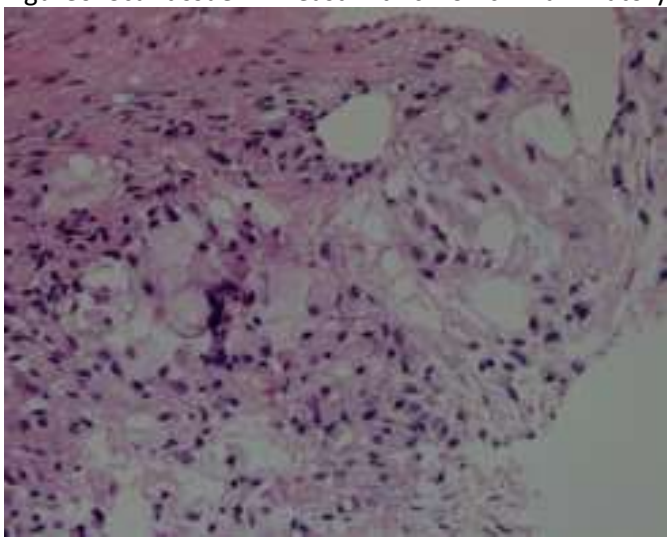

Figure7A: Fibromatosis of Breast

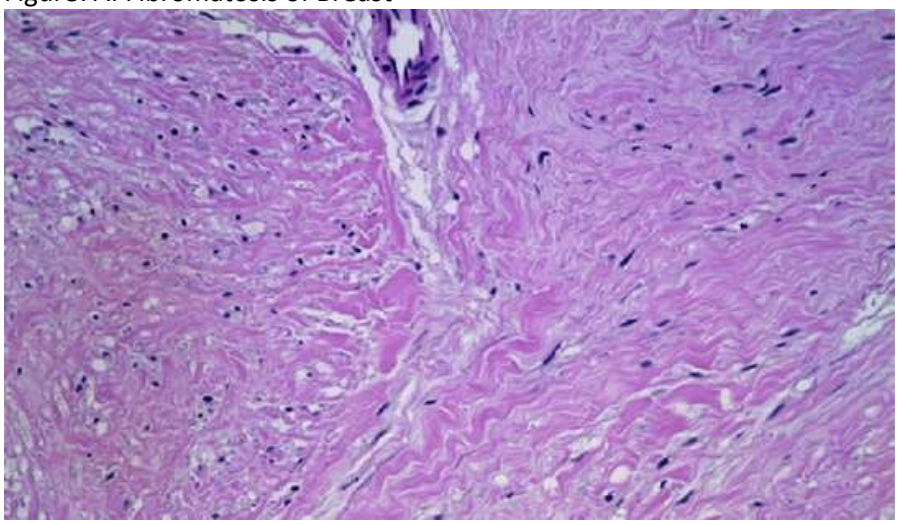

Figure7B: β catenin nuclear staining in Fibromatosis Breast

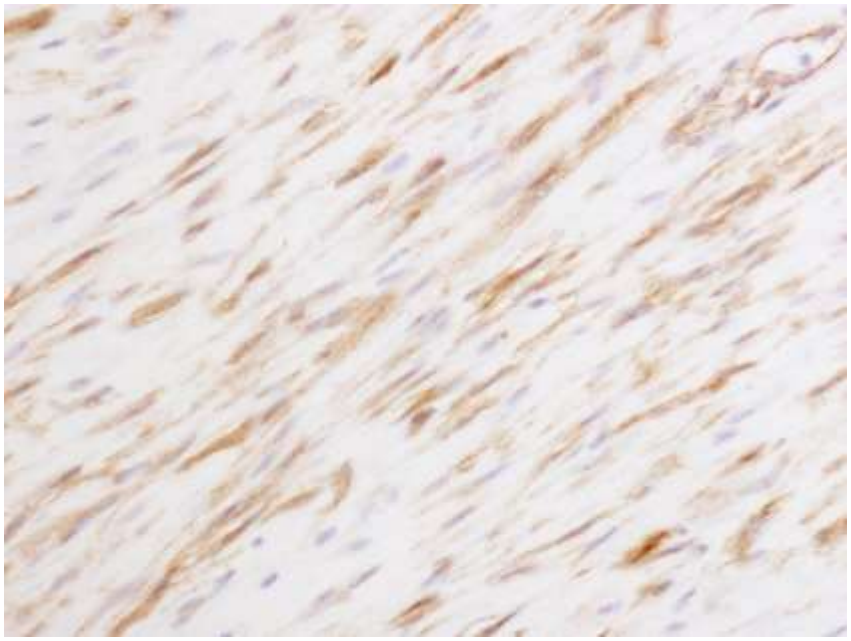

Figure 8: Nodular Fasciitis in Breast with extravasated red blood cells

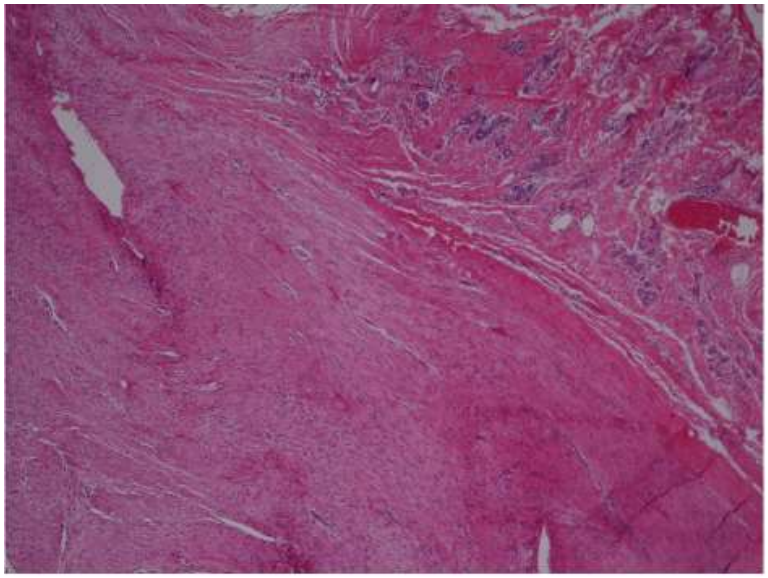

Figure 9: Cellular pseudoangiomatous stromal hyperplasia (PASH)

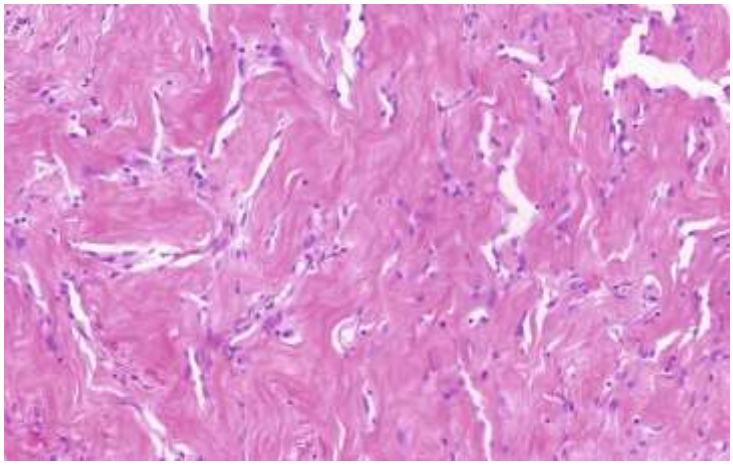

Figure10: Myofibroblastoma with ER Positivity mimicking invasive lobular carcinoma

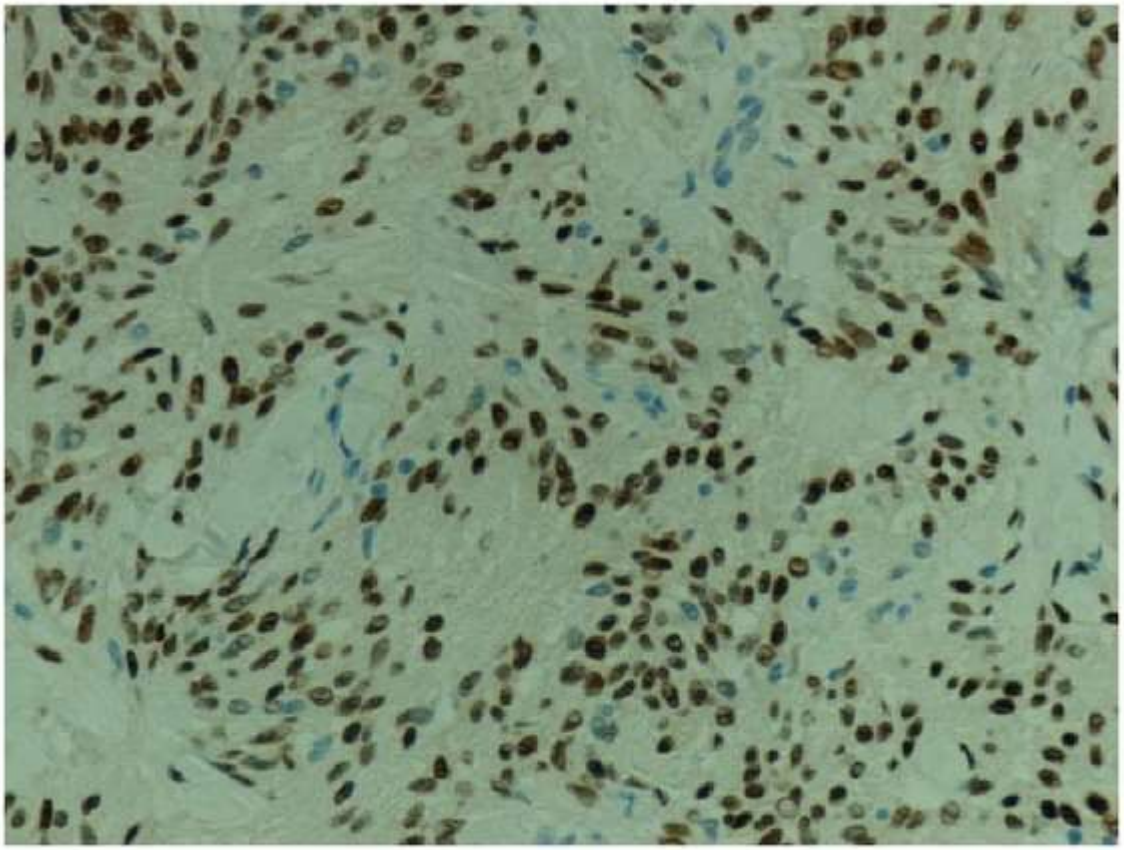

Figure11: Florid Histiocytic reaction with giant cells

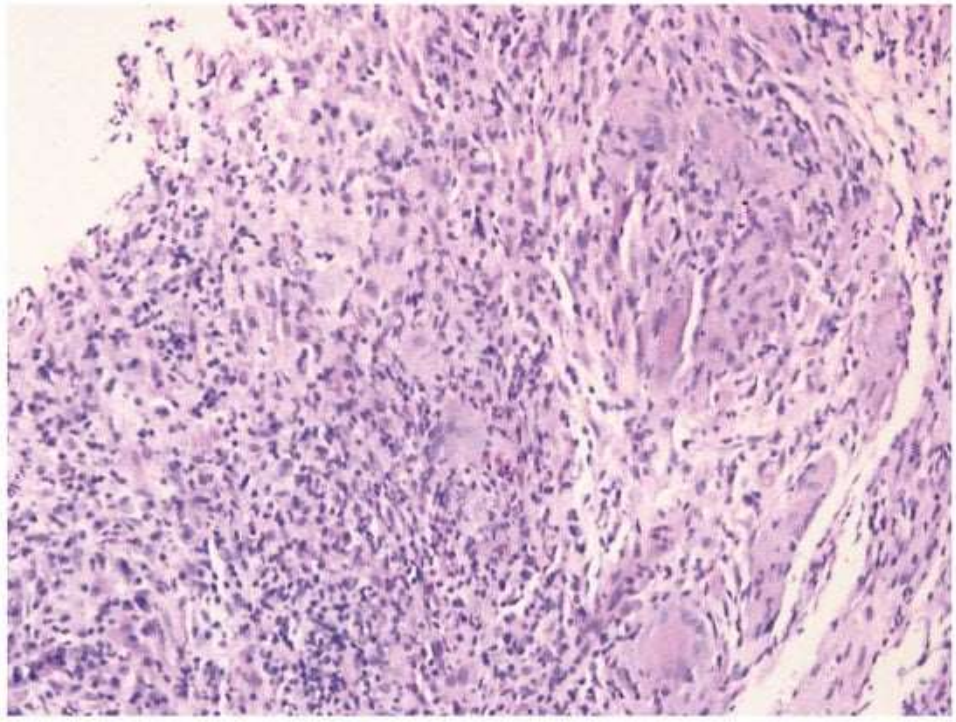

Figure12: Granular cell Tumor

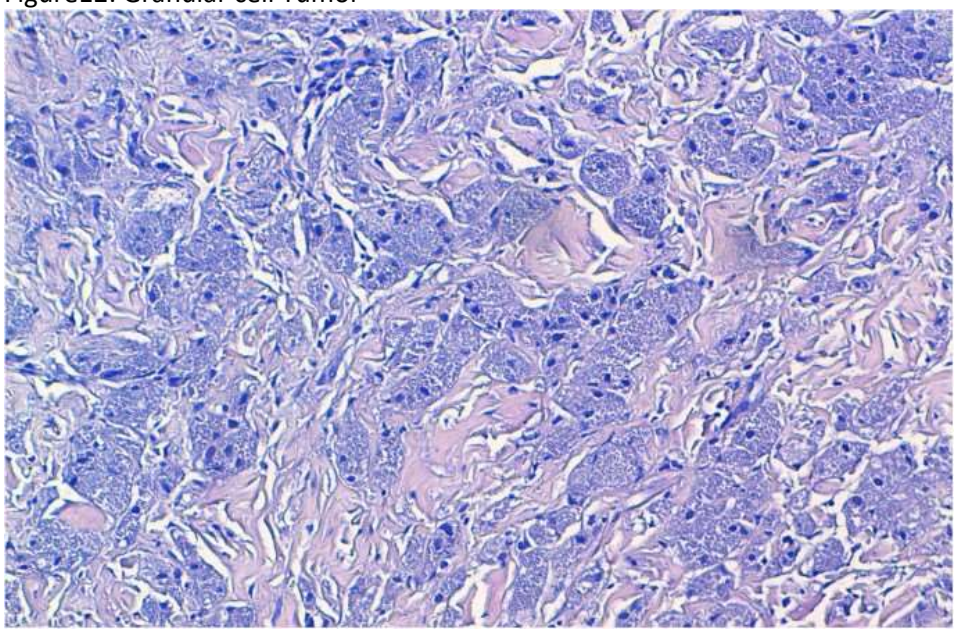

Figure 13: Collagenous spherules with myoepithelial marker positive in IHC p63

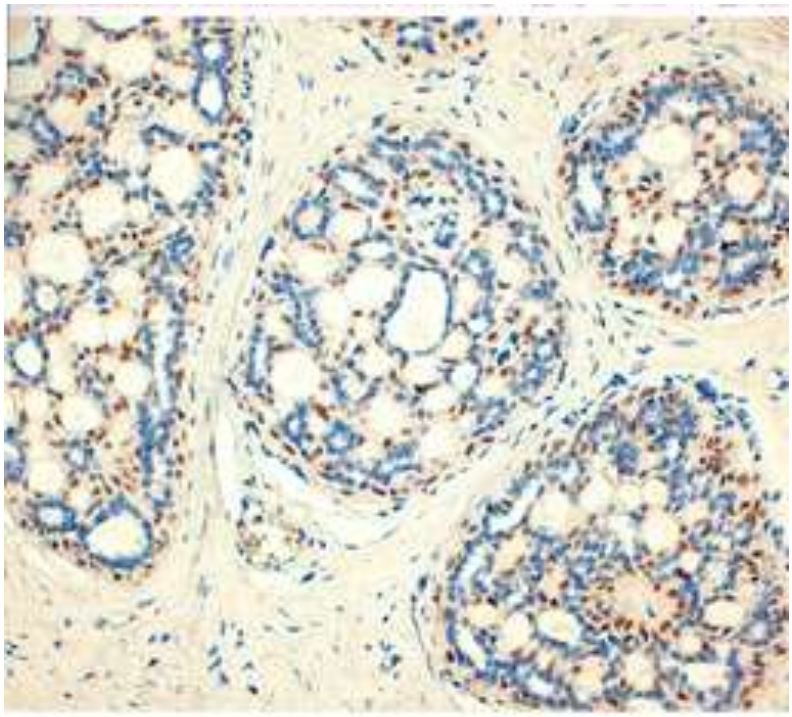

Figure 14: Lactational change with nuclear pleomorphism mimicking ductal carcinoma in situ

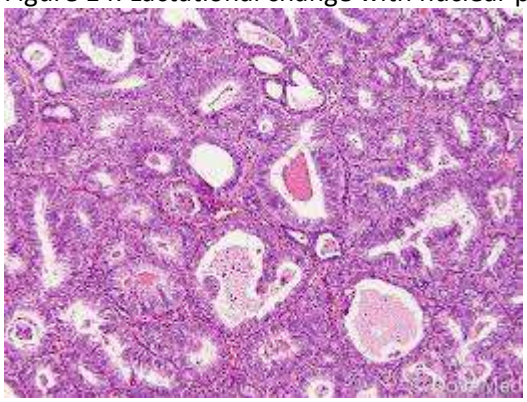

Figure 15: Encapsulated papillary carcinoma with disintegrated and distorted morphology

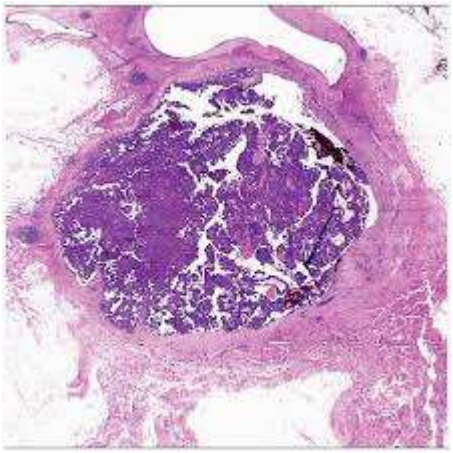

Figure 16: Fibromatosis like metaplastic carcinoma

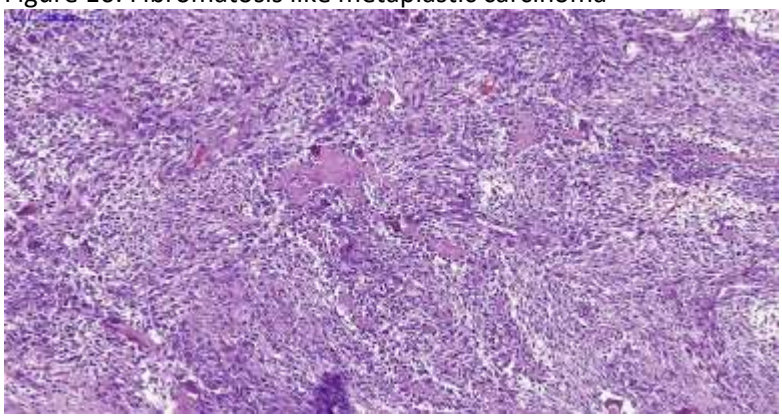

Figure 17: p63 showing positivity in papillary Carcinoma breast