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Overdiagnosis of breast malignancy: Azzopardi's *Problems in Breast Pathology* revisited, Part I

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ABSTRACT

Dr. John G. Azzopardi's textbook *Problems in Breast Pathology* is a critical work for breast pathologists. His observations on over- and underdiagnosis of breast malignancy are summarized in two chapters which are highly educational for everyday practice to reach an accurate diagnosis. Almost five decades later, his observations are still valid, and the same problems persist. In two separate reviews, we revisit these chapters and discuss these diagnostic challenges with an updated perspective and include developments (most importantly immunohistochemistry) in the field since then. In part I, lesions which may be overdiagnosed as malignancy are discussed, including those that were covered in Dr. Azzopardi's textbook (mainly sclerosing adenosis and radial scar) and some others that exert challenges on the pathologist. In part II, we will cover underdiagnosis of breast malignancy.

Accurate diagnosis is critical in surgical pathology for appropriate patient management. Breast pathology is one of the subspecialties where the pathologist shoulders a great weight of responsibility as the diagnoses, especially on biopsy specimens, have major management implications. Despite having relatively fewer numbers of lesions, diseases of the breast show extensive morphologic variability, and as Dr. Pierre Masson noted in *Human Tumors* "they constitute a picture chaotic enough to discourage all attempts at description" generating a wide range of diagnostic issues for breast pathologists.[1]

Dr. John G. Azzopardi (1929-2013), besides making many contributions to breast pathology literature, authored *Problems in Breast Pathology* (Fig. 1), a unique textbook with astute observations and invaluable opinions on the challenges the breast pathologist faces.[2] Among many highly educational chapters, IX and X stand out: "*Overdiagnosis of Malignancy*" and "*Underdiagnosis of Malignancy*". These chapters focus on challenging lesions of the breast which may lead to mistakes in diagnosis and subsequent error in patient management.

Despite having been published almost five decades ago, the same diagnostic problems remain to date, and some new ones have emerged. However, within this time frame our understanding of some of these lesions have changed with more accurate diagnostic criteria and common usage of ancillary tools, i.e., immunohistochemistry, for work-up have made it easier to address some of the diagnostic dilemmas. Herein, we aim to revisit one of the two great chapters of *Problems in Breast Pathology* and discuss problems in overdiagnosis of breast malignancy with an updated perspective focusing on diagnostic challenges; a separate review on underdiagnosis of breast malignancy will follow. The readers should note that this review series is by no means a comprehensive review of all problematic breast lesions as there are many areas in breast pathology which may create diagnostic challenges. Our aim is to present our reflections on the common problems in light of Dr. Azzopardi's views.

Adenosis/sclerosing adenosis

Sclerosing adenosis (SA) is a relatively common entity, more likely to be identified incidentally except for when it forms a mass ("adenosis tumor"; Fig. 2A).[3] SA may be misdiagnosed as a malignancy both clinically and by mammography.[4] Microscopically, SA has long been recognized as a lesion most likely to be misinterpreted as invasive carcinoma (IDC), and thus it comprises a rather long section in Dr. Azzopardi's chapter.[2]

The key to diagnosis of SA is low-power identification of the nodular, lobulocentric and often multifocal appearance of sclerosing adenosis. Within the nodules, one appreciates zonal architecture comprised of compressed, tight acini in the center gradually dilating towards the periphery (Fig. 2B, C). Myoepithelial cells are easily identified and may occasionally undergo myoid change. In challenging cases,

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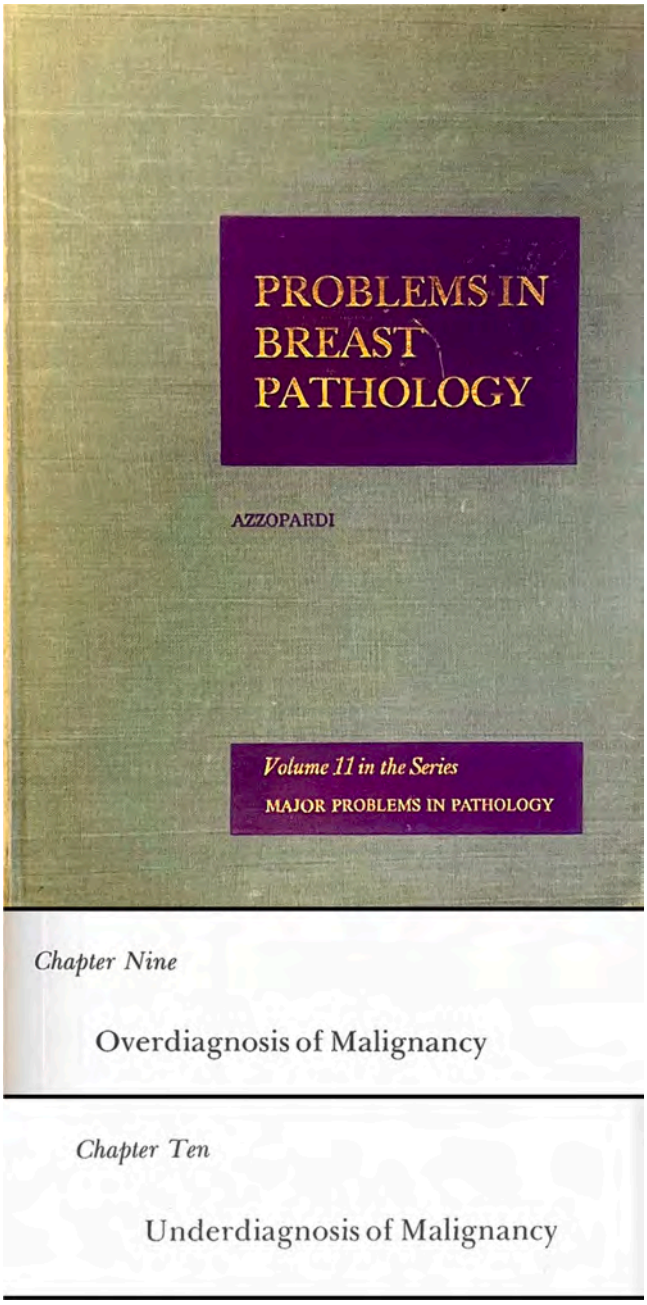

Fig. 1. Cover of Dr. Azzopardi's *Problems in Breast Pathology* (top) and the title pages from chapters 9 and 10 (middle and bottom) (Reprinted with permission).

immunohistochemistry (IHC) can be useful in highlighting the two-cell layer of the acini. IHC has been the most major advancement since Dr. Azzopardi wrote on this diagnostic difficulty.

Well-differentiated IDC is in the differential diagnosis of SA; however, low-power appearance is often not as nodular, and the glands typically show irregular, angulated shapes (Fig. 3). *In situ* carcinoma involving sclerosing adenosis remains a challenging diagnosis and may be mistaken for invasive carcinoma and in such cases liberal use of myoepithelial markers would be helpful (Fig. 4).[5] Compressed cells within the center of SA, especially when atrophic, may be confused with invasive lobular carcinoma (ILC) (Fig. 5A); however, the latter often have irregular contours with invasion into fat or native breast glandular tissue. SA is often multifocal which may provide a clue and detailed examination of cytologic features would also help the pathologist to

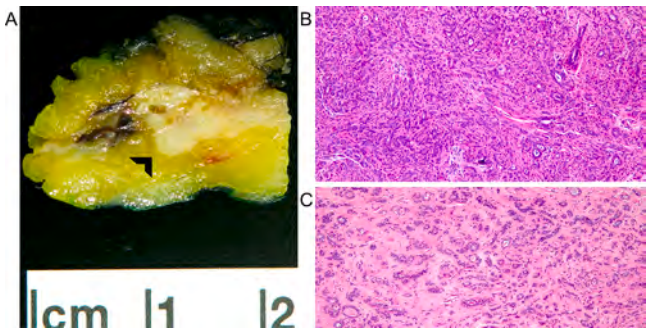

Fig. 2. Nodular sclerosing adenosis may rarely form a mass raising concern for a neoplasm; note the relatively well-circumscribed borders (arrowhead) (A). The glands in sclerosing adenosis show a variety of morphological features ranging from extremely tight architecture (B) to sclerosis separating them (C).

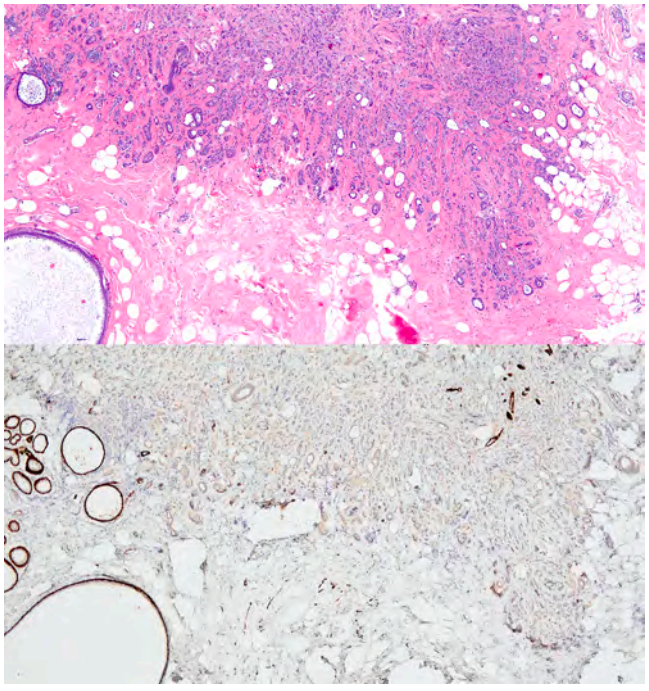

Fig. 3. Invasive ductal carcinoma may occasionally have a low-power appearance similar to that seen in sclerosing adenosis (top); however, the edges are irregular and the glands within the lesion have more complex shapes than seen in sclerosing adenosis. Myosin immunostain confirms a diagnosis of invasive carcinoma (bottom).

identify the two-cell population in sclerosing adenosis as opposed to the monotonous cell population in ILC; IHC would solve the problem (Fig. 5B).

Another major challenge is nerve or vessel involvement by SA (Fig. 6).[6,7] Since these phenomena are commonly associated with malignant processes, identification of such foci may lead to overdiagnosis; however, it should be noted that nerve involvement has been identified up to 2 % of SA.[7]

SA with apocrine metaplasia, i.e., apocrine adenosis, may also pose diagnostic challenges. Apocrine metaplasia is commonly partial within the lesion (Fig. 7A); however, it may sometimes involve it completely. Apocrine cells typically show large nuclei and prominent nucleoli. These two features may be mistaken for true cytologic atypia; in such cases, the dense eosinophilic and vacuolated cytoplasm should guide the pathologist to recognize the apocrine nature of the cells. Rarely apocrine cells may show atypia with cytoplasmic pallor, nuclear pleomorphism, necrosis, mitotic activity - in these cases the term "atypical apocrine

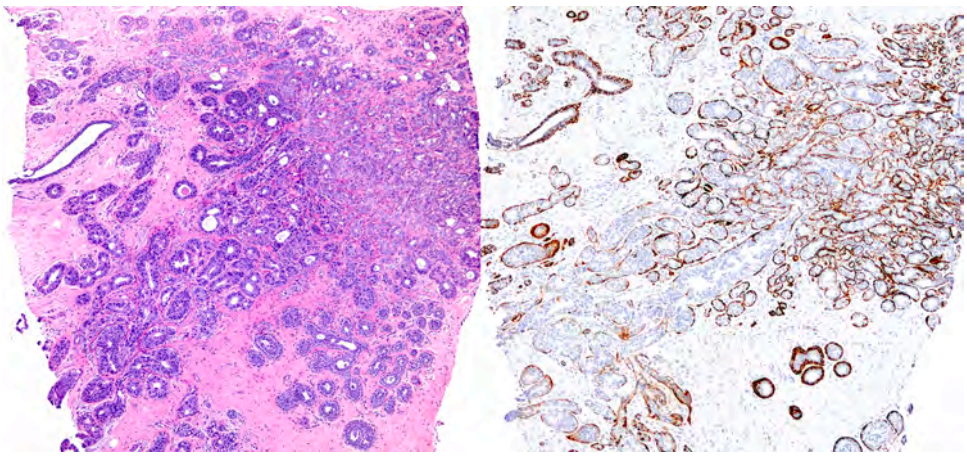

Fig. 4. DCIS involving sclerosing adenosis may be confused with stromal invasion (left). Myosin immunostain highlights myoepithelial cells (right).

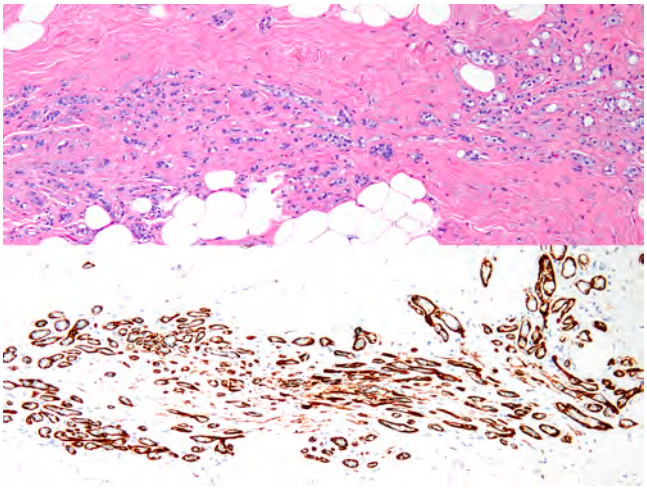

Fig. 5. Sclerosing adenosis with atrophic changes may resemble invasive lobular carcinoma (top); the diagnostic challenge can be resolved by myosin immunostain (bottom) or another myoepithelial marker.

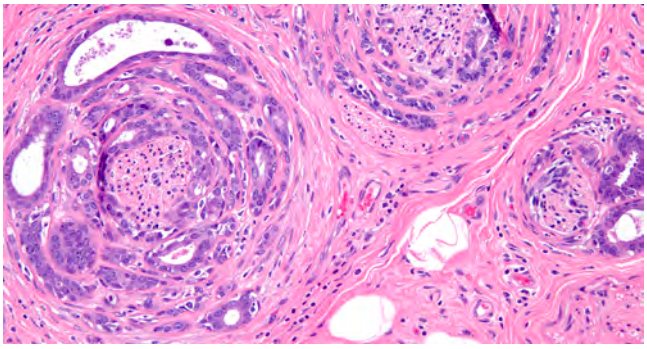

Fig. 6. Perineural involvement by sclerosing adenosis.

adenosis" is used (Fig. 7B). It is critical not to overdiagnose such cases as carcinoma *in situ*.[8]

Radial scar (RS)/Complex sclerosing lesion (CSL)/ infiltrating epitheliosis (IE)

Dr. Azzopardi noted that despite being relatively common, infiltrating epitheliosis (the term he used for RS/CSL in the chapter), had not

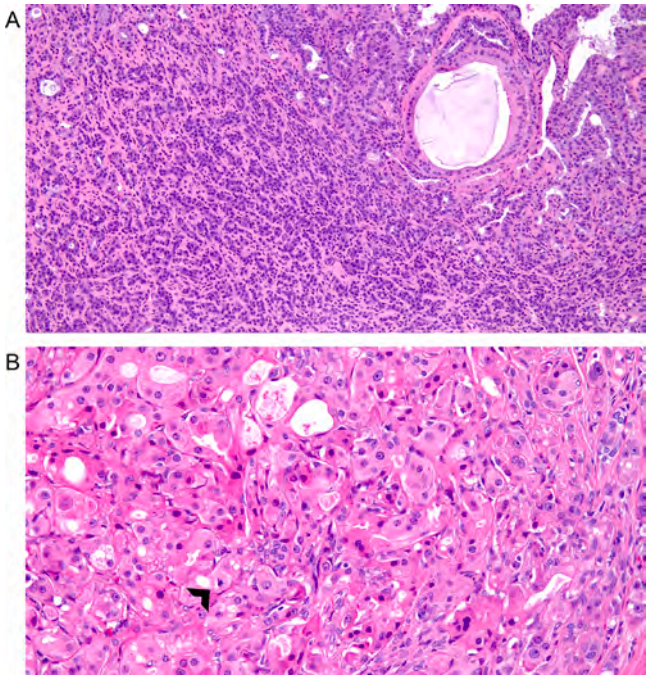

Fig. 7. Focal apocrine metaplasia (top right) is common in sclerosing adenosis (A). Atypical apocrine adenosis shows architectural and cytologic atypia, as well as mitotic activity (arrowhead) (B).

received adequate recognition until then. Various alternate terms have been suggested for IE and the current preferred nomenclature for this (now well-studied) lesion is radial scar (RS) and complex sclerosing lesion (CSL).[9-11] The latter term is used for larger (typically >1 cm) and more disorganized lesions.

The imaging and gross appearance of RS may be indistinguishable from a small invasive carcinoma as both are typically spiculated (Fig. 8A). RS has a zonal architecture (Fig. 8B) with central scarring (nidus) and fibroelastosis associated with distorted, small tubules, and a periphery (corona) with fibrocystic changes, adenosis, usual ductal hyperplasia (UDH), and other benign proliferative changes.

Both zones of RS (nidus and corona) exert distinct diagnostic challenges on the pathologist. The distorted, small glands in the nidus, especially when it is the only focus sampled in a needle core biopsy (NCB), may mimic those seen in well-differentiated IDC (Fig. 9); however, these glands are limited to the center as opposed to a more irregular distribution in invasive carcinoma and one can highlight the two-

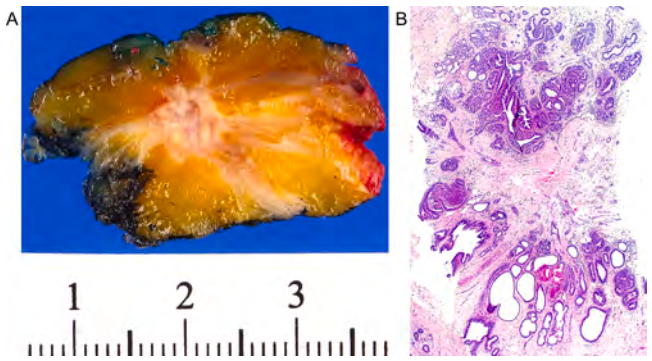

Fig. 8. Gross appearance of radial scar (A) is highly similar to that of invasive ductal carcinoma causing radiological and clinical concern. Typical appearance of a radial scar with zonal architecture (B).

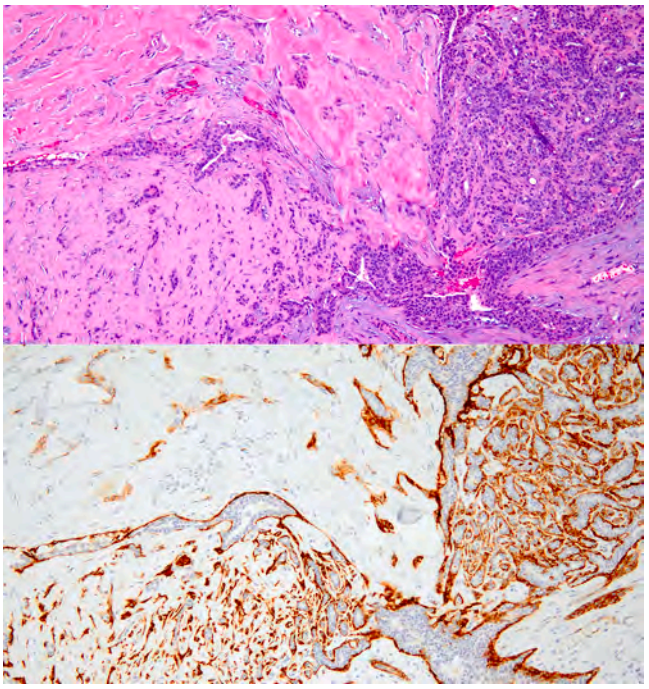

Fig. 9. Nidus of radial scar shows distorted, small glands within extensive sclerosis causing concern for invasive ductal carcinoma (top); myosin immunostain solves the diagnostic challenge (bottom).

cell layer using IHC. RSs which are early in their evolution may have a more myxoid and inflammatory nidus while longstanding ones may be extensively sclerotic. The latter process may attenuate the myoepithelial cells limiting their detection with IHC.[12] Multiple IHC markers are recommended for such lesions.

The corona may show florid UDH with reactive atypia and rarely foci of necrosis (Fig. 10). These areas often merge with typical foci of UDH and apocrine metaplasia, they lack architectural atypia and are confined to the proliferative zone. Identification of necrosis should not dissuade the pathologist from a diagnosis of UDH within a RS. This finding is also emphasized in Dr. Azzopardi's chapter as a separate part, "*Severe Epitheliosis*", and it is stated that if the overall architecture and cytology correspond to those seen in UDH, the additional changes should not lead to overdiagnosis.[2] Use of IHC [particularly cytokeratin 5/6 and estrogen receptor (ER)] may also be helpful in challenging cases.[13, 14]

Larger and disorganized RSs, i.e., CSLs, may create diagnostic challenges as the typical zonal architecture is distorted. In such cases, the pathologist should focus on investigation of stroma around the small,

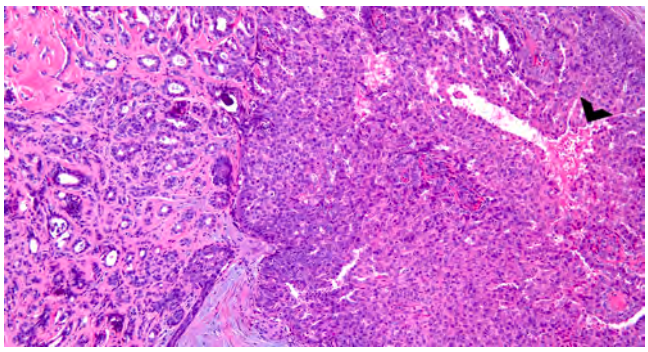

Fig. 10. Corona of radial scar may show extensive benign proliferative changes and may even rarely have foci of necrosis (arrowhead).

distorted glands as it would typically be sclerotic/fibroelastotic in CSLs while the glands would invade the fat and native breast stroma in invasive carcinomas. This is another area where use of IHC has mitigated the diagnostic challenge.

As seen in many other breast lesions, invasive and *in situ* carcinoma may involve RSs (Fig. 11) and, in such cases, identification of a distinct population of neoplastic cells which does not merge with hyperplastic cells, and extension of carcinomatous ducts beyond the lesion is helpful in diagnosis. IHC to confirm atypia/carcinoma (keratin 5/6 and ER to distinguish from UDH) is often useful. Multiple myoepithelial cell markers can help exclude invasive carcinoma. Lobular carcinoma *in situ* (LCIS) may also occasionally involve RS/CSL; e-cadherin IHC is helpful in this regard.

Microglandular adenosis

The uncommon lesion of microglandular adenosis (MGA) was not fully described until 1983, half a decade after Dr. Azzopardi published *Problems in Breast Pathology*.[15, 16] Unsurprisingly, MGA was not described in the chapter; however, it is a rare, benign entity which may easily be overdiagnosed as a well-differentiated IDC.

MGA exhibits a haphazard distribution of small, rounded tubules within fibrous or fatty stroma (Fig. 12A). The glands are devoid of myoepithelial cells and the luminal cells typically have pale cytoplasm. The glandular lumens contain characteristic eosinophilic dense secretions. The distribution of glands and lack of myoepithelial cells are concerning features for the pathologist; however, the rounded shape and luminal secretions are important clues for diagnosis.

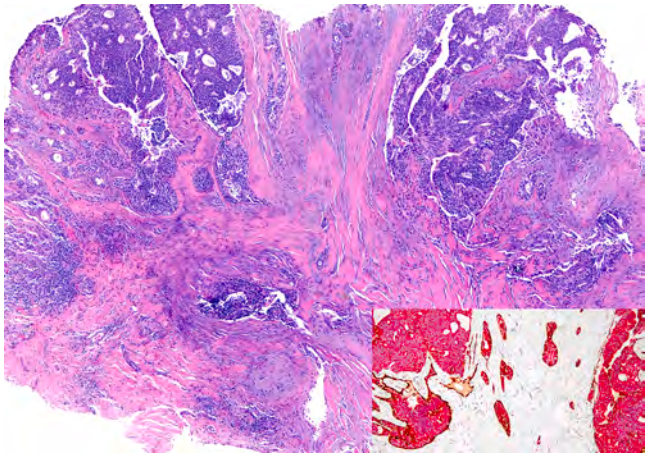

Fig. 11. DCIS involving radial scar may show irregular gland shapes concerning for invasion; a combined immunostain (epithelium-red, myoepithelium-brown) highlights myoepithelial cells around nests (inset).

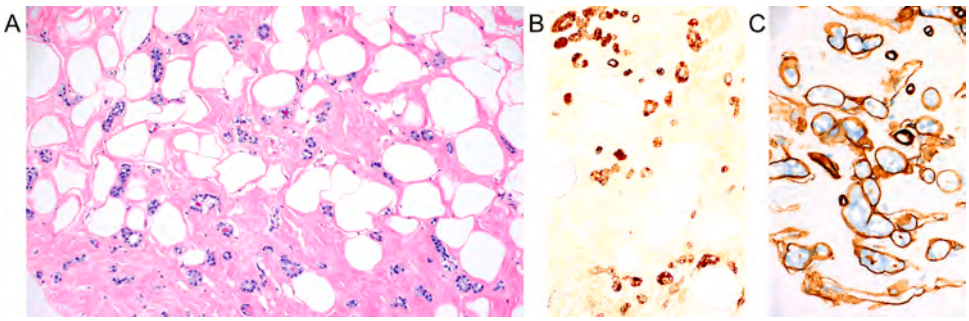

Fig. 12. Small, rounded tubules of microglandular adenosis showing haphazard distribution; note dense luminal secretions (A). S100 is typically positive in microglandular adenosis (B) and the glands show retained basement membrane with Collagen IV immunostain (C).

IHC is helpful in this challenging diagnosis as MGA is negative for ER and progesterone receptor (PR), results which would be highly unusual for a well-differentiated IDC, and S100 is typically positive in MGA (Fig. 12B). Additionally, MGA retains basement membrane around the glands highlighted by Collagen IV IHC (Fig. 12C). Exceedingly rarely MGA may show crowding, glandular complexity, cytologic atypia and mitotic activity and in such cases, the term atypical MGA is used. With increasing degree of cytological and architectural atypia, the designation of carcinoma arising in MGA should be considered.[17]

Procedure-related changes

Procedure-related changes including NCB procedures and needle localization have disruptive effects on breast tissue resulting in diagnostic challenges. Displacement of neoplastic epithelium in a case of ductal carcinoma *in situ* may be interpreted as IDC (Fig. 13A).[18, 19] Similarly, displaced benign epithelium may mimic invasive carcinoma. In such cases, low power examination and identification of carcinomatous nests within the healing fibrous biopsy tract is critical to avoid overdiagnosis.

Similarly, biopsy procedures can displace neoplastic epithelium in an encapsulated papillary carcinoma (Fig. 13B). Typically, frank invasion is diagnosed by identification of irregular geographic, jigsaw puzzle-like edges of cellular nests permeating beyond the fibrous capsule. The pathologist should be cautious when diagnosing invasive carcinoma in this clinicopathological context.

Fat necrosis (FN) can also be seen following NCB procedures and excisions. FN can be worrisome clinically, radiologically, and grossly. Histological features vary depending on the time interval from the procedure: earlier lesions show extensive neutrophilic and lymphohistiocytic inflammatory cell infiltrate while the later stage is characterized by cystic change, fibrosis, and dystrophic calcifications (Fig. 13C). Marked inflammation may either mimic or obscure neoplastic cells and broad-spectrum keratin IHC can be helpful in these cases.[20]

Radiation-related changes

Radiation therapy may cause marked alteration of both glandular tissue and stromal elements.[21, 22] These changes do not affect the breast tissue uniformly and can persist long after the radiation. The alterations in glandular tissue are characterized by cytologic atypia and lobular atrophy. Irradiated luminal epithelium may show cellular enlargement with preserved nucleus-to-cytoplasm ratio, pale eosinophilic cytoplasm with vacuoles, and enlarged, irregular, pale nuclei with variably prominent nucleoli. These changes occur in a spotty manner and the background lobular atrophy further exaggerates the atypia of these cells. In this context, it is critical to obtain clinical history. Relatively preserved nucleus-to-cytoplasm ratio, haphazard distribution of atypical cells rather than crowding, and background lobular atrophy with thickened basement membrane are important clues not to overdiagnose

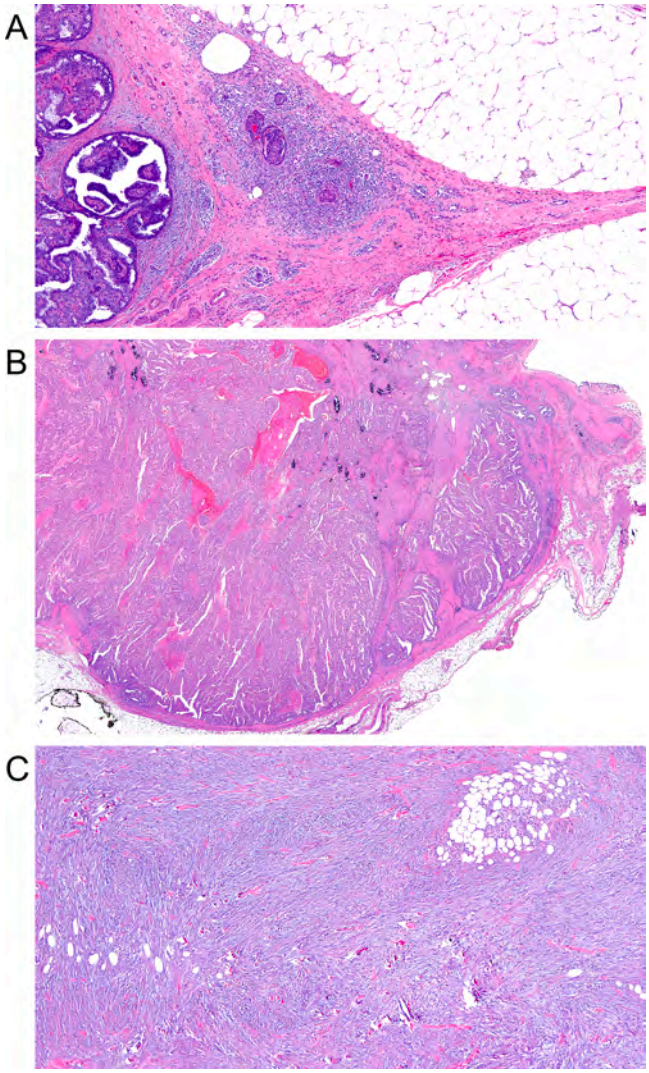

Fig. 13. Nests around DCIS after needle core biopsy procedure may be concerning for invasion; note inflammation and neovascularization of the focus, as well as the linear fibrous biopsy tract (A). Encapsulated papillary carcinoma after needle core biopsy procedure may show irregular borders (B, right). Fat necrosis may rarely be associated with extensive fibrohistocytic proliferation causing diagnostic challenge; note a typical focus of fat necrosis on top right (C).

such cytologic atypia as carcinoma *in situ* (Fig. 14). In challenging cases, identification of low Ki-67 proliferation index may be helpful in this differential diagnosis.[23] Other radiation-related changes include

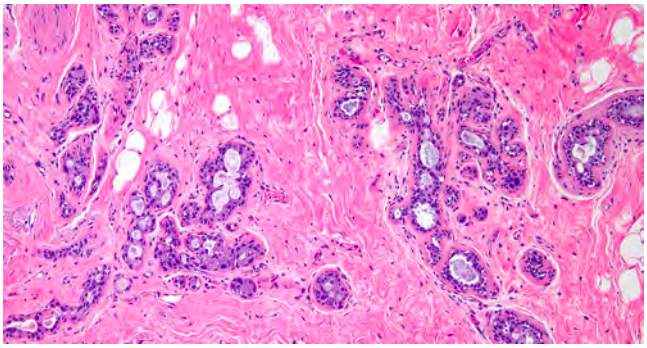

Fig. 14. Irradiated luminal epithelium showing cytologic atypia with scattered, rare, large, irregular nuclei; note background lobular atrophy and thickened basement membranes.

endothelial atypia/intimal thickening of blood vessels and stromal fibrosis with atypical fibroblasts. The latter may be worrisome for invasive carcinoma; however, keratin IHC would easily resolve the problem.

Multinucleated stromal giant cells

Multinucleated stromal giant cells (MSGC) are focal, typically incidental findings which may concern the pathologist.[24] They can be usually identified with low-power magnification, show a haphazard distribution in stroma and are remarkable for multiple, hyperchromatic, florette-like nuclei and scant cytoplasm (Fig. 15). MSGCs are also identified in the stroma of fibroadenomas and phyllodes tumors; and are similar to stromal cells occasionally seen in organs such as vagina, cervix and bladder. These cells may be concerning for an invasive carcinoma, especially in the setting of post-neoadjuvant treatment; however, the IHC profile of MSGCs (keratin negative, vimentin positive) helps in this differential diagnosis.

Lymph node lesions

Sentinel lymph node evaluation is standard of care in invasive breast carcinoma. The pathologist should be aware of rare lesions involving lymph nodes which may be overdiagnosed as metastatic carcinoma. These lesions primarily include benign heterotopic epithelial inclusions (Fig. 16A),[25,26] presence of megakaryocytes as a part of extramedullary hematopoiesis (Fig. 16B)[27] and nevus cell aggregates (Fig. 17).[28] In addition to comparing the morphologic features with the primary carcinoma, appropriate IHC for the lesions described would be helpful; however, it should be noted that metastatic carcinoma may co-exist with these lesions.

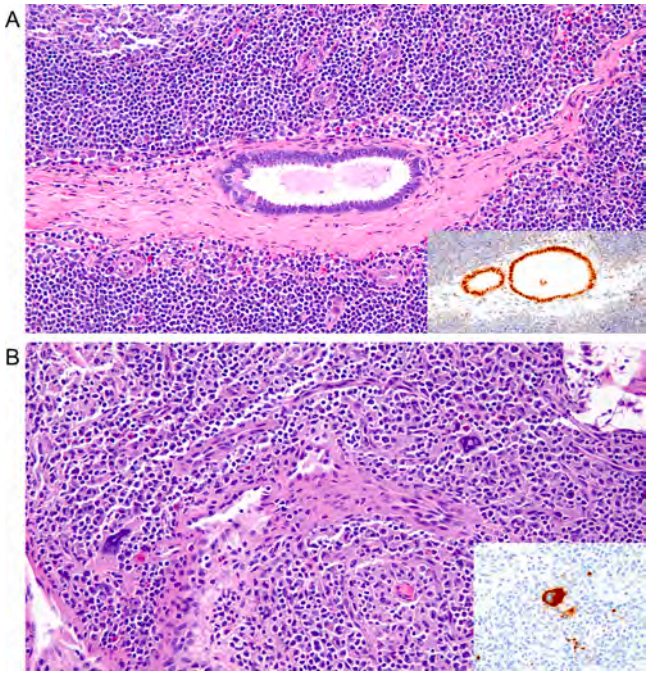

Fig. 16. Müllerian inclusion within lymph node (A) with ciliated, tubal-type epithelium, confirmed with PAX8 IHC (inset). Megakaryocytes in lymph node (B) may be confused with metastatic carcinoma; CD61 IHC highlights these cells (inset).

Conclusions

Many of the problems regarding overdiagnosis of breast malignancy highlighted by Dr. Azzopardi remain to date. Herein we briefly discussed the entities in the initial publication and added a few additional such lesions. Our understanding of these lesions has changed with evolving literature and the ancillary techniques developed since the publication of *Problems in Breast Pathology*. Part II of this review series will focus on underdiagnosis of breast malignancy.

CRediT authorship contribution statement

Baris Boyraz: Writing – review & editing, Writing – original draft, Conceptualization. **Syed A. Hoda:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

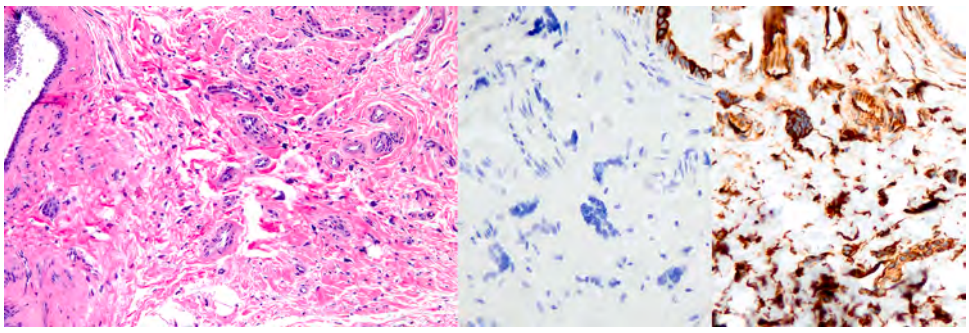

Fig. 15. Multinucleated stromal giant cells with multiple, hyperchromatic nuclei can be identified even on low-power (left); these cells are negative for cytokeratin (middle) and positive for vimentin (right) making it easier to differentiate from invasive carcinoma.

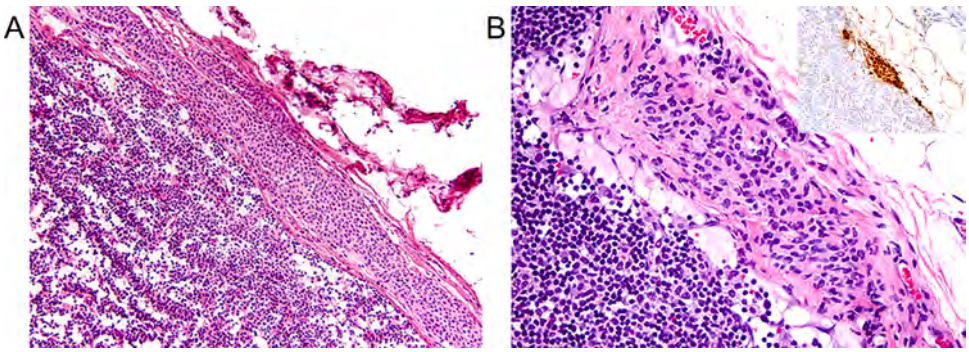

Fig. 17. Benign nevus cell aggregate in a lymph node from a patient with invasive lobular carcinoma misdiagnosed as metastasis on frozen section (A). Permanent sections show nuclear pseudoinclusions and pale cytoplasm; S100 immunostain confirms their melanocytic origin.

the work reported in this paper.

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