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Underdiagnosis of breast malignancy: Azzopardi's *Problems in Breast Pathology* revisited, part II

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ABSTRACT

In the second part of this two-part review series, we revisit Chapter X of the seminal textbook *Problems in Breast Pathology* written by Dr. John G. Azzopardi and discuss breast malignancies which may be underdiagnosed. We include the two major lesions covered in Dr. Azzopardi's textbook: ductal carcinoma *in situ* and lobular carcinoma *in situ*. Furthermore, we discuss microinvasive carcinoma, residual invasive carcinoma status-post neoadjuvant treatment and carcinomas with certain morphologic features which may lead to underdiagnosis. While discussing these lesions, we highlight problems raised by Dr. Azzopardi and discuss both their morphologic features as well as ancillary tools developed since then to aid reaching the diagnosis.

In the first part of this two-part review series, we revisited Chapter IX of *Problems in Breast Pathology* by Dr. John G. Azzopardi and discussed breast lesions which may be overdiagnosed as malignancy.[1] Herein, we will review Chapter X and focus on malignant lesions which may be underdiagnosed.

The main lesions discussed in Azzopardi's chapter X were ductal carcinoma *in situ*, lobular carcinoma *in situ* and various morphologic variations of these entities, including clinging carcinoma, cancerization of lobules and Pagetoid spread. We will revisit these lesions with an updated diagnostic approach and discuss related developments.

Azzopardi's chapter includes the statement that "in general, invasive carcinomas larger than 5 mm will not be misdiagnosed by competent and reasonably experienced pathologists". Smaller lesions ("minimal breast cancer" at the time), most importantly microinvasion ($\leq$ 1 mm in the current AJCC Cancer Staging Manual) is challenging for the pathologist. Although "minimal breast cancer" was not discussed by Dr. Azzopardi, we will comment on diagnostic challenges regarding microinvasive carcinomas.

It is also stated in the chapter that "certain cancers are prone to be underdiagnosed because of their morphology" and in that respect, we will comment on invasive ductal carcinomas with extensive sclerosis, invasive cribriform carcinoma, histiocytoid invasive lobular carcinoma, low-grade adenosquamous carcinoma and single cell/small nest pattern of residual invasion seen after neoadjuvant treatment.

"Borderline" lesions (atypical ductal or lobular hyperplasia) were also discussed by Dr. Azzopardi; however, our understanding of these lesions has advanced significantly, and currently they do not fall under the term "malignancy". Therefore, they will not be included in this review.

Ductal carcinoma *in situ* (DCIS)

Common forms of DCIS are easily recognized by the pathologist and do not cause major diagnostic challenges. A particular form, *i.e.* clinging/flat-micropapillary DCIS, discussed extensively by Dr. Azzopardi, remains a diagnostic challenge. The pathologist may overlook these lesions at scanning magnification as their low-power appearance does not differ appreciably from microcysts (Fig. 1A). However, the lumina of the cysts are usually filled with necrotic debris which is a clue for further high-power magnification. This would help the pathologist appreciate the prominent epithelium with pleomorphic cells showing high-grade cytologic atypia (Fig. 1B and C). Identification of more common architectural patterns of DCIS, such as solid and cribriform types, in the vicinity would also be helpful in diagnosis.

Certain morphological variations of DCIS may cause diagnostic challenges. One such finding is involvement ("cancerization") of lobules (Fig. 2A) and of sclerosing adenosis. In these cases, especially when a typical focus is not present in a needle core biopsy (NCB) specimen, the pathologist may underdiagnose malignancy by overlooking malignant cells as the low-power magnification of terminal duct-lobular unit may

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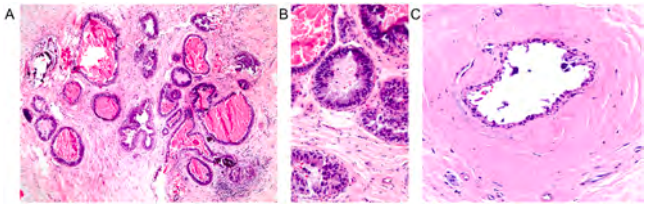

Fig. 1. Despite its similarity to microcysts on low power examination, clinging DCIS shows prominent epithelium, luminal debris and calcifications, making it easy to spot (A). High-power examination of the same case reveals cytological atypia and necrotic debris (B). Another case with a highly challenging area as there are only rare, highly atypical cells in the focus (C).

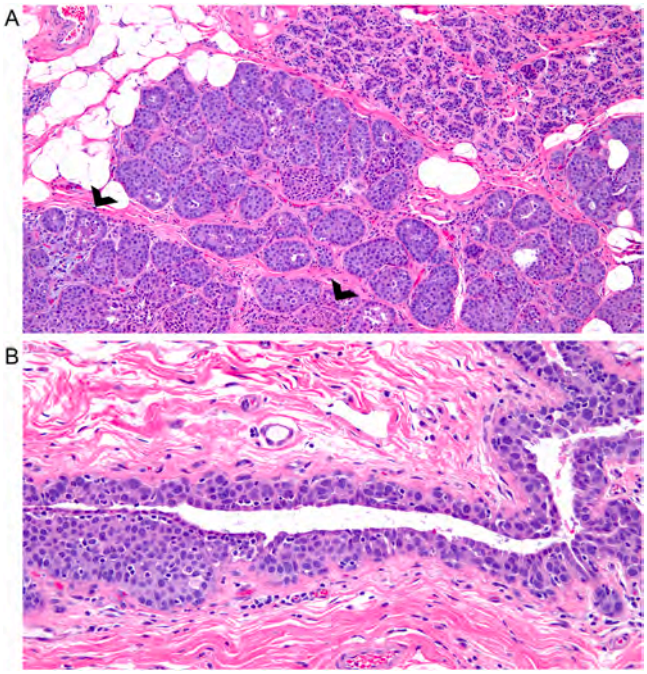

Fig. 2. Despite retaining the normal lobular architecture, foci with lobule involvement by DCIS show enlarged cells (please compare to the uninvolved lobule, top right) and lumina may contain necrotic debris (arrowheads) (A). Carcinoma cells lifting up and underlying normal luminal epithelium; left side with clustering of carcinoma cells makes it easier to diagnose Pagetoid spread by DCIS (B).

not be appreciably altered. However, similar to that seen in clinging DCIS, the cells are larger than those in background lobules, and one appreciates cytologic atypia and, rarely, necrotic luminal debris. These foci are also prone to overdiagnosis as the pathologist may interpret DCIS involving adenosis as an invasive focus, a challenge we discussed in the prior part. Pagetoid spread of DCIS (Fig. 2B) may also cause a diagnostic problem, especially in the setting of NCB specimens if conventional foci of DCIS are not present. The pathologist should focus on the ducts with prominent epithelium and identify the distinct population of carcinoma cells underlining the native luminal epithelium.

Low- and high-grade DCIS are easily recognized by the pathologist without difficulty; however, intermediate-grade DCIS may be occasionally difficult to distinguish from usual ductal hyperplasia (UDH). Architectural atypia may not be well-defined in intermediate-grade DCIS and may overlap with the "pseudo-cribriform" spaces seen in UDH. Identification of a rather monotonous cell population with enlarged nuclei is often helpful as UDH will typically have a mixed population of cells. In challenging cases, cytokeratin 5/6 and estrogen receptor may also aid in this differential diagnosis.[2, 3]

While discussing flat proliferations, Dr. Azzopardi included lesions with both high and low-grade cytologic atypia. The current understanding supports distinct pathogenesis for these lesions with the former being "clinging DCIS" while the latter is now recognized as "flat epithelial atypia (FEA)" instead of carcinoma.[4] Both lesions may appear as dilated cysts on scanning magnification; however, FEA shows monotonous, cuboidal to low-columnar cells with low-grade cytologic atypia and apical snouting (Fig. 3). The luminal contents also differ. FEA typically shows proteinacous debris with calcifications as opposed to the necrotic debris seen in DCIS. FEA is now recognized as a non-obligate precursor to ADH and is commonly associated with other low-grade pathway lesions such as lobular carcinoma *in situ* and tubular carcinoma (also known as Rosen's triad) .[5]

One longstanding problematic area is the distinction between atypical ductal hyperplasia (ADH) and low-grade DCIS. In such cases, there are guidelines with quantitative (0.2 cm extent or involvement of 2 duct spaces) criteria[6]; however, one should note that despite being practical, relying solely on quantitative findings to diagnose malignancy is rather too simplistic and the pathologist should use all available morphological evidence to neither underdiagnose DCIS or overdiagnose ADH.

Lobular carcinoma *in situ* (LCIS)

Dr. Azzopardi wrote *Problems in Breast Pathology* at a time when there was emerging interest in lobular lesions; hence, there is extensive discussion on the clinical and pathologic characteristics of LCIS. Multiple studies since then have increased our understanding of LCIS including their immunohistochemical and molecular features; however, two recently described, aggressive variants may be underdiagnosed.

Non-classic LCIS include florid variant (Fig. 4A), diagnosed with a linear cut-off of ~40–50 cells across in an acinus and pleomorphic variant (Fig. 4B), diagnosed by high-grade cytologic atypia of tumor cells (which may also show apocrine features).[7-9] Both variants may show central necrosis and calcifications. They are important to recognize as they show a higher prevalence of associated invasive carcinoma. Identification of non-classic LCIS should prompt careful search for (micro)invasive carcinoma. Furthermore, management regarding classic LCIS is controversial with imaging correlation typically recommended for excision while non-classical LCIS should be excised with negative margins.

Rarely, classic LCIS with type B cells (with relatively larger nuclei with mild variability in nuclear size and shape, and micronucleoli; Fig. 4C) may be confused with pleomorphic LCIS leading to overdiagnosis. In such cases, identification of higher-grade atypia, mitotic figures and necrosis would support the latter.

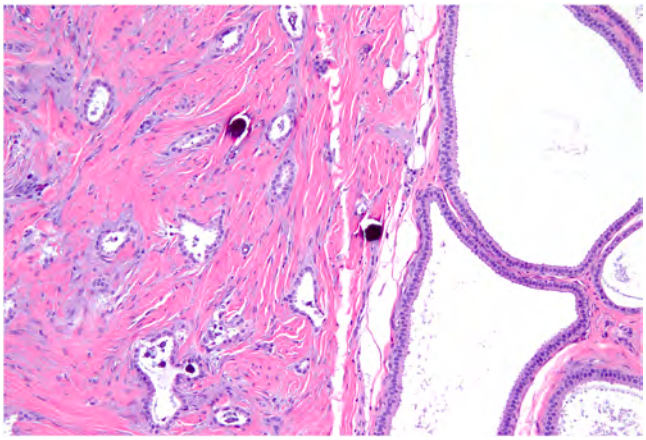

Fig. 3. Invasive tubular carcinoma (left) associated with flat epithelial atypia (right).

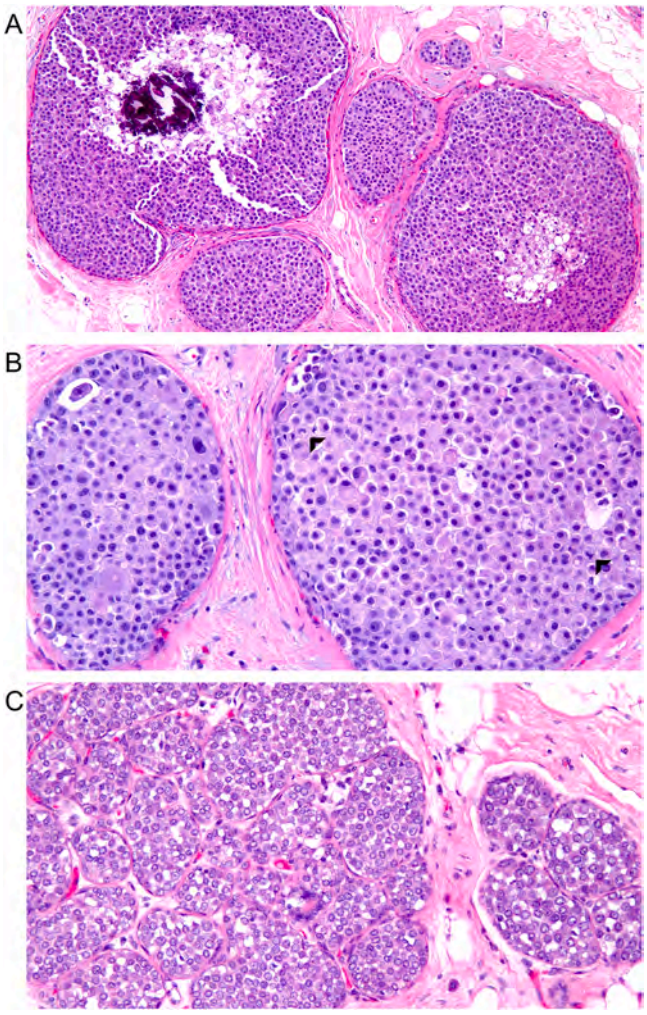

Fig. 4. Florid LCIS with highly expanded acini, central necrosis and calcifications (A). Pleomorphic LCIS showing high grade cytologic atypia, pleomorphism and mitotic activity (arrowheads) (B). LCIS with type B cells with relatively enlarged nuclei with variable micronucleoli; compare cytological features with pleomorphic LCIS above (C).

Microinvasive carcinoma

Identification of high-grade DCIS should prompt search for microinvasion as this is the typical scenario of potential underdiagnosis wherein an invasive focus may be missed. Presence of fibrosis with marked inflammatory infiltrate (predominantly lymphocytic) around DCIS and irregular outline of the ducts are typically suggestive features for microinvasion (Fig. 5A) .[10] The carcinoma cells typically invade as single cells and small nests making it difficult to identify them. The surrounding inflammatory infiltrate and endothelial cells may either obscure or mimic tumor cells. In these cases, the pathologist should carefully investigate foci around DCIS and identify areas where the duct has an irregular outline, and the basement membrane appears to be discontinuous. IHC is also extremely helpful in this setting either as separate broad-spectrum cytokeratin and myoepithelial cell markers, and if possible, as a combined immunostain (Fig. 5B) .[11]

Similarly, microinvasive lobular carcinoma may be identified around LCIS, typically of the pleomorphic type. Double immunostaining (cytokeratin and myoepithelial cell marker) is helpful in these cases. Identification of microinvasive lobular carcinoma without contiguous *in situ* carcinoma is extremely rare and it is an especially challenging scenario since invasive lobular carcinoma typically does not cause stromal alteration (Fig. 6). Moreover, microinvasive lobular carcinoma with small, dyscohesive carcinoma cells may be easily mistaken for lymphocytes. The authors can recommend that the pathologist maintain alertness, especially if the patient has a history of lobular neoplasia and use IHC whenever needed.

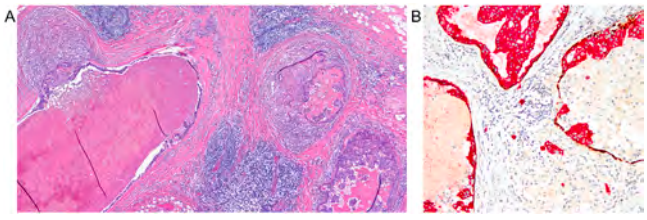

Fig. 5. High-grade DCIS with adjacent fibrosis, extensive inflammation and irregular duct outline (top left); these features are highly suspicious for potential microinvasion (A). A combined IHC (epithelium-red, myoepithelium-brown) highlights invasive carcinoma cells in the "chaotic" background (B).

Invasive ductal carcinoma with sclerosis

Invasive ductal carcinoma (IDC) typically elicits a desmoplastic reaction composed of fibroblastic proliferation within a myxoid matrix; however, occasionally the stroma may be densely fibrotic/sclerotic making it challenging to differentiate from the nidus of a radial scar, especially in the setting of NCB. Well-differentiated IDCs often have a stellate shape similar to radial scar (Fig. 7); however, they lack the zonal architecture of the latter, and glands show an irregular distribution throughout the lesion. Periphery of a radial scar typically shows proliferative changes with pushing borders while extension of invasive glands to the periphery of the mass with overt invasion of the surrounding tissue is expected in IDC. Furthermore, identification of DCIS is helpful in such cases. IHC for myoepithelial cell markers is useful in this setting; however, use of multiple immunostains is recommended as myoepithelial cells may also get attenuated in radial scars.[12]

Rarely, the sclerosis may be so extensive that it could be hard to identify invasive glands in NCB specimens (Fig. 8). In such cases, upon encountering irregularly shaped tubules with disorganized distribution, the pathologist should have a low threshold to perform IHC for myoepithelial cell markers.

Residual invasive carcinoma status-post neoadjuvant treatment

Assessment of residual invasive carcinoma may be challenging in the setting of neoadjuvant chemotherapy. Tumor cells typically undergo

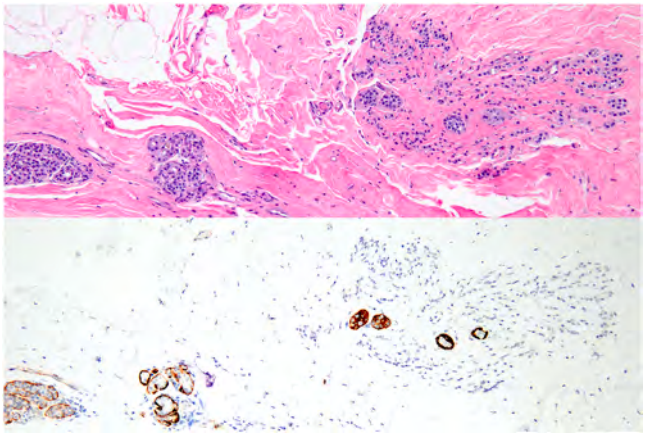

Fig. 6. A subtle focus of microinvasive lobular carcinoma (right, top panel) without stromal reaction; note associated atypical lobular hyperplasia (bottom left, top panel). Myosin IHC confirms microinvasion in the bottom panel.

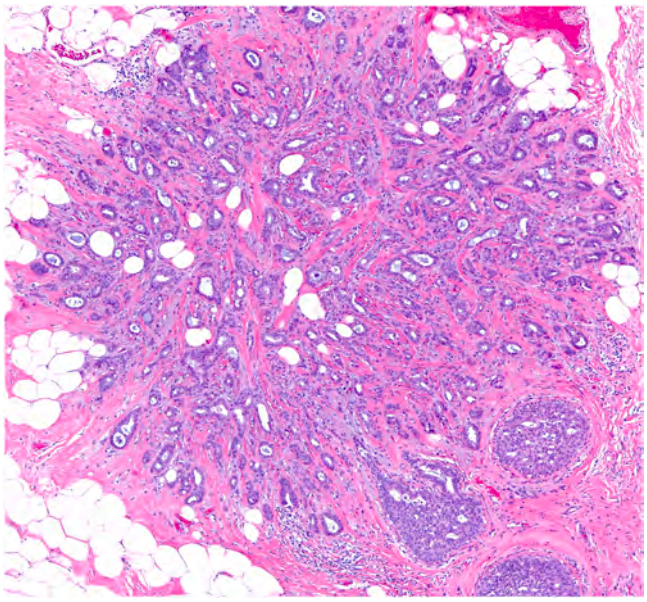

Fig. 7. Well-differentiated invasive ductal carcinoma with a low-power appearance similar to radial scar; note DCIS at bottom right.

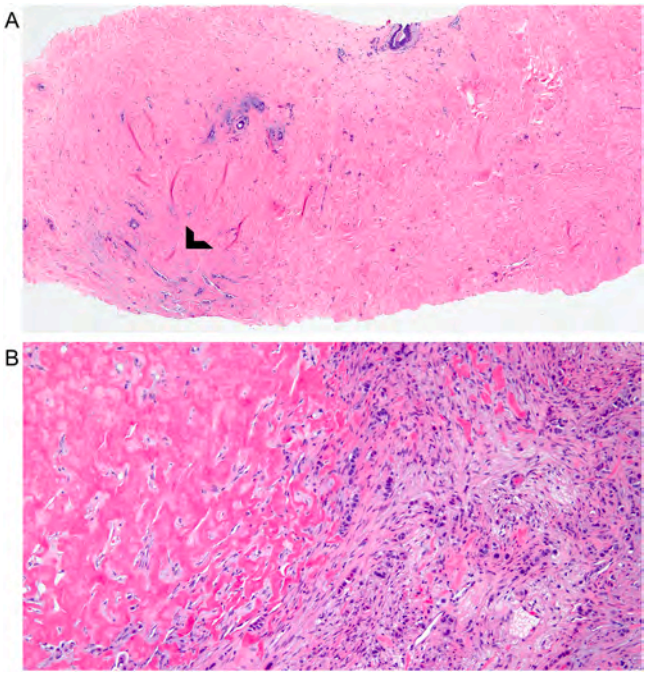

Fig. 8. Extensive sclerosis obscures invasive glands with irregular shapes (arrowhead) (A). Carcinoma cells at the edge of sclerosis makes the diagnosis easier in another case (B).

cytologic changes after chemotherapy and become enlarged with abundant, often vacuolated, cytoplasm; and large, hyperchromatic, and pleomorphic nuclei (Fig. 9A). Rarely, the carcinoma cells may become smaller after treatment. There are often also background changes including fibrosis, edema, vessel proliferation and chronic inflammation.[13] Residual invasive carcinoma, when present as single cells or small nests, may result in diagnostic challenges as it may be difficult to identify small foci in the "busy" background and sometimes the inflammatory cells may mimic invasive carcinoma and *vice versa*. In this context, especially when no residual invasive carcinoma is identified, liberal use of cytokeratin IHC is suggested as the pathologist may be

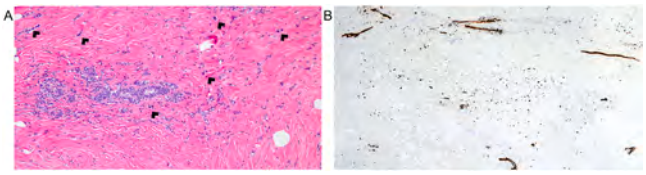

Fig. 9. Scattered atypical cells with enlarged, hyperchromatic nuclei, suspicious for residual invasive carcinoma in post-neoadjuvant treatment setting (A). Cytokeratin IHC in the same slide shows many more carcinoma cells than those readily identified on H&E-stained slide (B).

unpleasantly surprised to detect foci of invasion overlooked on H&E-stained sections (Fig. 9B).

Rare types of invasive carcinoma

Certain rare types of invasive carcinoma may be underdiagnosed due to their morphologic overlap with other lesions. Two variants of ILC are in this category: histiocytoid and alveolar. Histiocytoid ILC (Fig. 10A) is composed of tumor cells with low to intermediate grade nuclei and abundant, foamy cytoplasm resembling histiocytes.[14] The invasive carcinoma cells may be overlooked as inflammatory cells; however, accompanying chronic inflammatory cells are typically absent. Alveolar ILC (Fig. 10B) shows invasion as grouped clusters which may be mistaken for LCIS. In both variants, classic LCIS is often present resolving the diagnostic challenge. In difficult cases, cytokeratin IHC would reveal the epithelial nature of tumor cells in histiocytoid ILC and myoepithelial markers would highlight the invasive nests in alveolar ILC.

Similar to alveolar ILC, IDC may also rarely show "blunt" invasion, one such variant being invasive cribriform carcinoma (Fig. 11) .[15] There is often associated more conventional patterns of invasion; however, when only present in the NCB specimen, the foci of blunt invasion may be underdiagnosed as DCIS. In these cases, the distribution of clustered invasive carcinoma cells does not resemble that seen in breast ducts/lobules involved by DCIS and the abundance of back-to-back masses should raise the possibility of invasion. IHC is helpful in this differential diagnosis; however, it should be noted that ducts with extensive DCIS may also have attenuated myoepithelial cells; thus, use of multiple

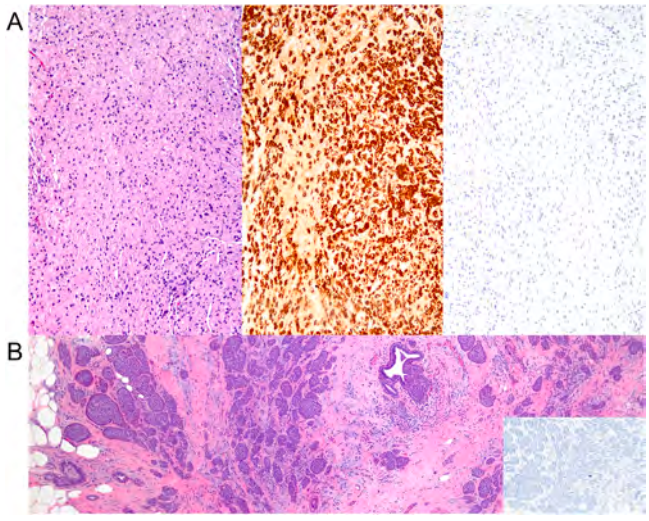

Fig. 10. Histiocytoid ILC forming sheets of cells with abundant, foamy cytoplasm (A, left). Cytokeratin IHC confirm the epithelial origin (A, middle) and E-cadherin is negative supporting lobular differentiation (A, right). Alveolar ILC with rounded nests may be mistaken for LCIS; however, the distribution of nests is different from normal breast architecture (B). Myosin IHC confirms invasive nature of nests (B, inset).

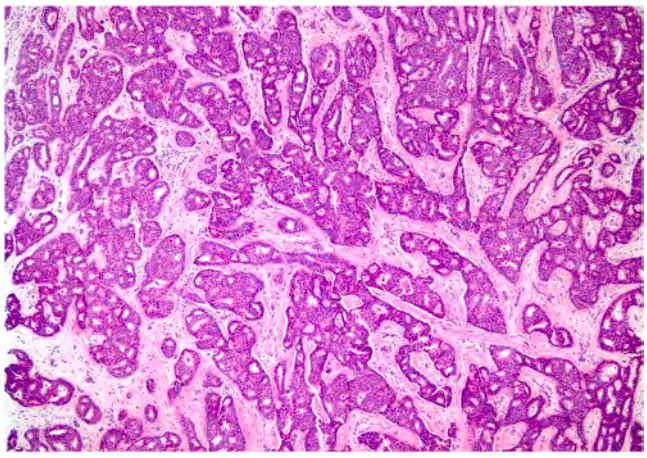

Fig. 11. Invasive cribriform carcinoma may be underdiagnosed as DCIS; however, the distribution of invasive carcinoma nests differs from the latter.

immunostains is recommended.

Low-grade adenosquamous carcinoma (LGASC) is a metaplastic carcinoma prone to underdiagnosis. LGASC frequently arises in a background radial scar/complex sclerosing lesion and in NCB specimens, it may be extremely challenging to draw the line between carcinoma and sclerosing lesion[16, 17]: the glandular component of LGASC may be similar to those seen in radial scars; and squamous metaplasia is often seen in sclerosing lesions. IHC profile is "consistently inconsistent" which may be a clue for diagnosis; however, it may also confuse the pathologist. The pathologist should be cautious upon encountering a sclerosing lesion with irregular nodules and squamous metaplasia (Fig. 12A). In such cases, the possibility of an associated LGASC should be mentioned. In excision specimens, the pathologist should try to identify infiltrative growth pattern and associated lymphocytic aggregates, which could help in reaching the diagnosis (Fig. 12B).

Conclusions

Breast pathology has many areas with diagnostic challenges for the pathologist. Dr. Azzopardi reported his observations on problems regarding over- and under-diagnosis of breast malignancy in his seminal textbook *Problems in Breast Pathology*. In this two-part review approximately fifty years after the publication, we revisited the problems brought to attention by Dr. Azzopardi and approached them with an updated perspective. We also discussed additional relatively common lesions that may lead to over- or under-diagnosis of malignancy.

Knowledge of these problems do not eliminate the diagnostic difficulties; however, we would hope these reflections will be helpful to the practicing pathologist in dealing with such cases. One should always be alert as "anything can turn up", stated by Dr. Paul P. Rosen, the legendary breast pathologist.[18] Furthermore, to cite Dr. Robert E. Scully, "anything can look like anything" .[19] Therefore, diagnostic problems are infinite and will remain so.

CRediT authorship contribution statement

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

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

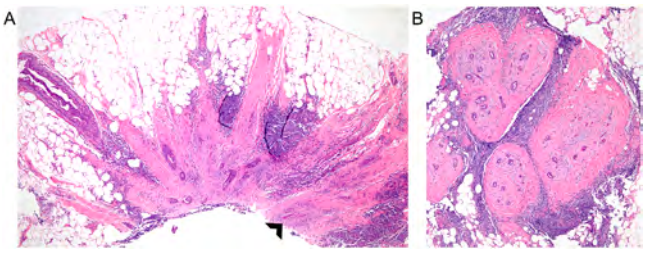

Fig. 12. Radial scar with squamous metaplasia (arrowhead) and lymphoid aggregates raised concern for low-grade adenosqaumous carcinoma in the NCB specimen (A) and the excision confirmed low-grade adenosquamous carcinoma (B) arising in the former.

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