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Review Article

Immunohistochemistry in the Diagnosis of Spindle Cell Lesions of the Breast: A Review

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Abstract

Breast spindle cell lesions (BCSLs) are a highly heterogenous group of diseases that frequently challenge the diagnostic skills of even specialist breast pathologists. While a systematic morphological assessment remains central to narrowing the differential diagnosis, immunohistochemistry (IHC) is a valuable ancillary test that can help to either further narrow or confirm a diagnosis. However, BSCLs can also show a remarkable degree of intra-tumoural morphological and immunohistochemical heterogeneity, meaning that IHC is rarely either specific or sensitive for a particular lesion and that care must be taken when interpreting diagnostic core biopsies. IHC results must, therefore, always be interpreted with caution and in the context of the morphological features and wider clinicopathological findings.

Key Points / Clinical Take-Home Messages

- Immunohistochemistry is a useful ancillary test to narrow the differential diagnosis of breast spindle cell lesions, particularly pure spindle cell lesions with bland morphology
- Immunohistochemistry must always be interpreted with caution, recognising that no antibody target is fully sensitive nor specific for a particular entity
- Definitive categorization may be impossible on core needle biopsies and the final diagnosis may only be possible on excisional biopsy
- Spindle cell metaplastic carcinoma must always be considered in the differential diagnosis.

INTRODUCTION

Although rare, breast spindle cell lesions (BSCLs) together represent a large and heterogeneous collection of conditions ranging from reactive to benign and malignant neoplasms [1]. The histopathological diagnosis is further challenged by the presence of the usual hallmarks of malignant neoplasms appearing across the spectrum of disease, including cytological atypia and mitoses, and conversely some malignant neoplasms appearing remarkably bland. The diagnosis must often be made on limited core biopsy material which may not be representative of the lesion as a whole, especially with biphasic tumours. While clinicopathological correlation is of course important, the radiological and clinical findings are often unhelpful [1]. It is self-evident that the correct diagnosis, particularly discriminating benign and reactive conditions from malignant ones, is mandatory.

Although the use of immunohistochemistry (IHC) in diagnosing BSLCs also suffers from a relative lack of sensitivity and specificity, it nevertheless plays an important role as an ancillary test for confirming or securing the final diagnosis. Here we focus on the role of IHC in the diagnosis of BSCLs, but refer readers interested in the morphological diagnosis of BSCLs to several excellent recent reviews [2-4].

Breast Spindle Cell Lesions: The Differential Diagnosis

While the diagnosis of BSCLs should rightly be regarded as a multidisciplinary and multimodality effort, the morphological diagnosis lies at the core of the process. In their algorithmic approach to diagnosing BSCLs, Varma and Shin [4] suggested evaluating four key components: (i) the composition of cellular proliferation; (ii) cytomorphological atypia; (iii) mitotic activity; and (iv) adjacent or admixed cells/tissue. In addition, they recommend integrating the clinico-radiological features. This useful algorithm is shown in Figure-1, the aim being to either come to a final

diagnosis or, in the case of limited core needle biopsy material, narrow the differential (i.e., report the biopsy as B3) until definitive diagnosis is possible on excisional biopsy.

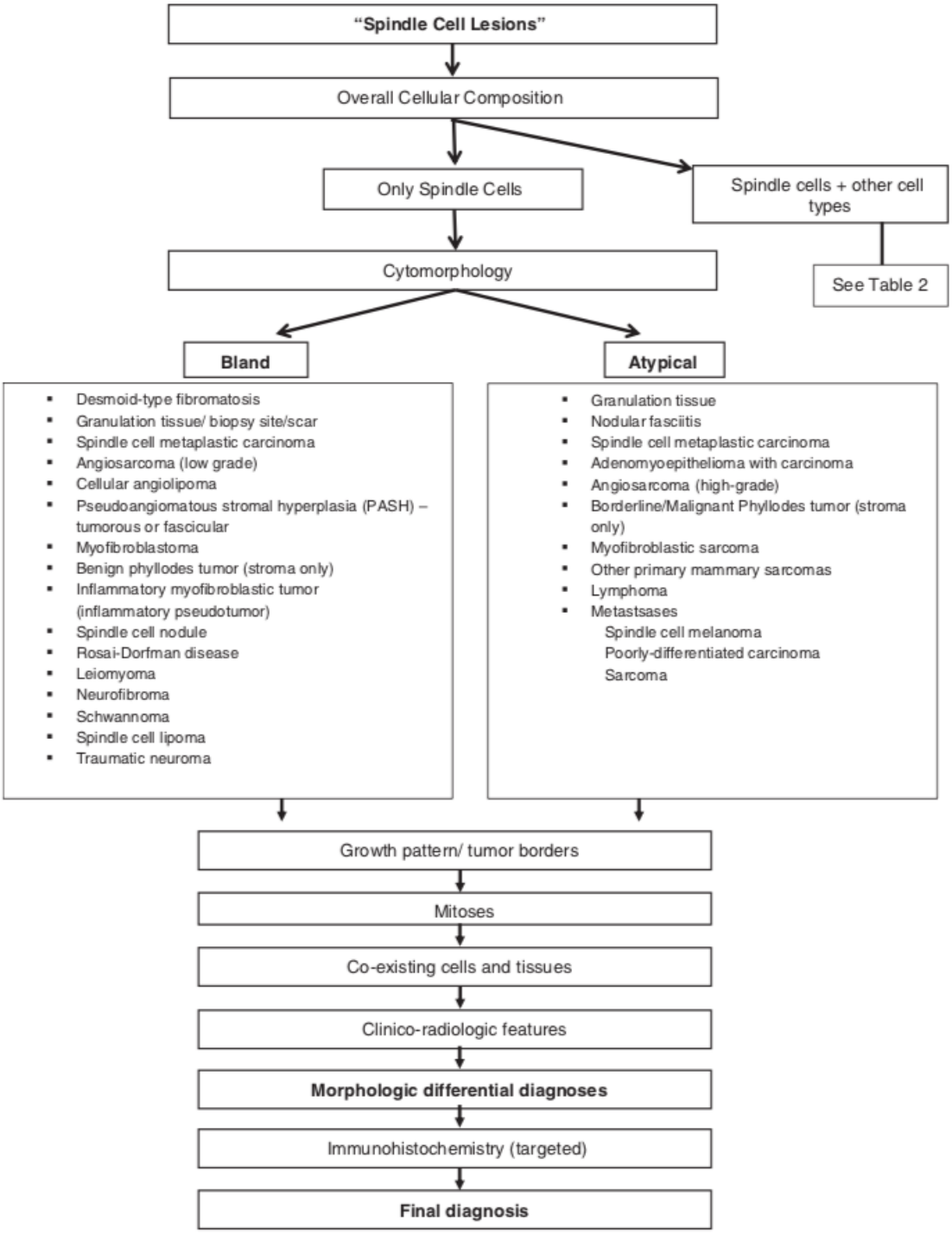

Fig-1: The Varma and Shin [4] algorithm for the histopathological diagnosis of BSCLs

Cellular Composition

The first step is to assess the overall composition of the lesion, in particular noting whether the lesion is composed entirely of spindle cells or a mixture of spindle and epithelial cells. If the latter, the arrangement of the two components should be assessed (i.e., whether they are admixed or separate), since admixed spindle and epithelial cells raises the possibility of spindle cell metaplastic carcinoma, while separate components might favour fibroepithelial lesions, mixed ductal and metaplastic carcinoma, or perhaps epithelium displaced into the needle tract [5]. The diagnostic algorithm for mixed spindle cell and epithelioid lesions is shown in Figure-2.

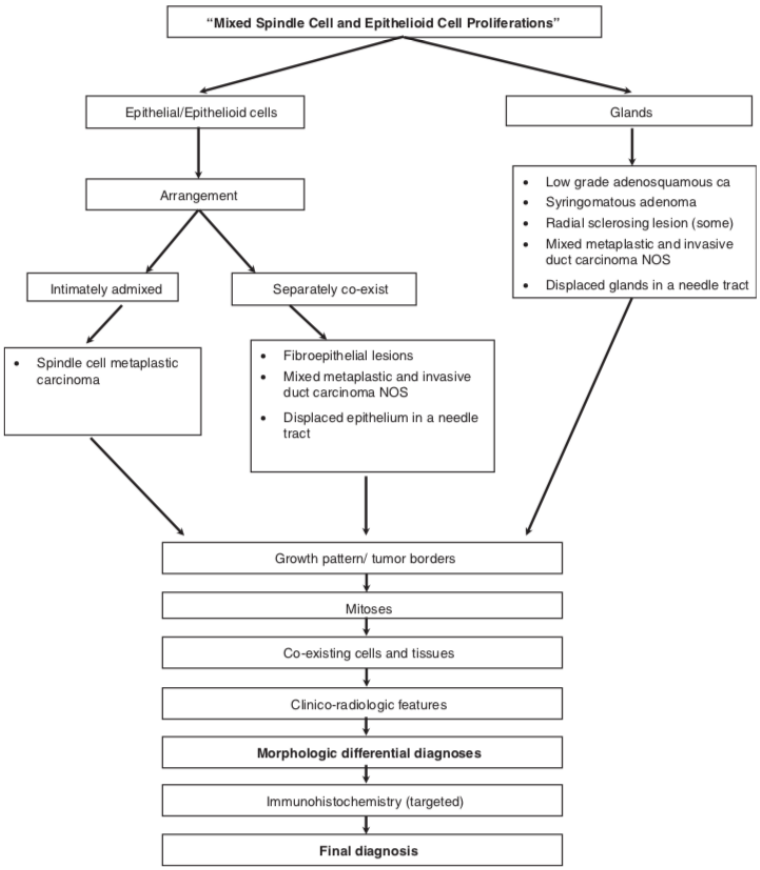

Fig-2: The Varma and Shin [4] algorithm for the histopathological diagnosis of BSCLs with mixed epithelial and spindle cell components

Cytomorphological Atypia

In pure spindle cell lesions, the first feature to note is whether the cytology is "bland" or "atypical", remembering that these categories are not synonymous with "benign" and "malignant"; for instance, low-grade angiosarcoma can have a bland cytological appearance and granulation tissue can show marked cytological atypia. The full differential diagnosis under these headings is shown in Figure-1. Pure populations of bland spindle cell proliferations are the most challenging with the broadest differential diagnosis; where representative, the growth pattern and tumour border may provide clues to the diagnosis, for example long, collagenised bands in fibromatosis and well-healed scars, or capillary like vessels in low-grade angiosarcoma (although also seen in pseudoangiomatous stromal hyperplasia (PASH), angiolipoma, and granulation tissue).

Mitoses

Mitoses, even in cytologically bland pure spindle cell lesions, raise the index of suspicion for malignancy, with the notable exceptions of those seen in exuberant granulation tissue and myofibroblastoma. Conversely, low-grade angiosarcomas rarely contain mitoses, so their absence does not exclude a malignant diagnosis.

Adjacent or Admixed Cells/Tissue

In addition to establishing whether the lesion is biphasic or a pure population of spindle cells, the adjacent cell population can be informative. For instance, the absence of glandular breast tissue might favour a subcutical location and therefore nodular fasciitis, while overlying skin might suggest a dermal spindle cell lesion such as dermatofibrosarcoma protuberans. Inflammatory infiltrates and their distribution favour certain diagnoses (e.g., peripheral aggregates in fibromatosis and low-grade adenosquamous carcinoma; dispersed among spindle cells in other entities such as spindle cell metaplastic carcinoma, granulation tissue, inflammatory myofibroblastic tumour, and nodular fasciitis).

Clinico-Radiological Features

Clinical correlation, as with all areas of pathology, is necessary but often lacking. This is especially true of BSCLs: for instance, a history of trauma or recent biopsy will favour reactive diagnoses. Likewise, although not specific, imaging can be helpful; for instance, the infiltrative tumour border of fibromatosis is not seen in the better circumscribed lesions of PASH tumour or myofibroblastoma [6].

Applying immunohistochemistry to BSCLs

Having narrowed the differential diagnosis of a BSCL based on the morphology, IHC is very useful

for narrowing the differential further or for confirming the morphological diagnosis. Since no marker is entirely sensitive or specific, a panel of antibodies should be used. There are two main considerations when using IHC in diagnosing BSCLs: (i) the antibodies to be used and (ii) pitfalls in interpretation. These are considered separately below.

The main antibodies used in the diagnosis of BSCLs

Given that BSCLs can contain a mixture of native breast tissue cells (mesenchymal cells, myoepithelial cells, and glandular epithelial cells with variable hormone receptor expression) and their aberrant counterparts, these represent the main antibody targets. The "typical" IHC profiles of the more common BSCLs are shown in Table-1.

Table-1: IHC profiles for some common BSCLs (adapted from) [4]

Pure spindle cell lesions with bland cytological features	
Spindle cell metaplastic carcinoma	CK14±, CK5/6±, 34βE12±, CAM5.2±, CK7±, MNF116±, AE1/AE3±, p63±, β-catenin±, CD34-, ER-, PR-, HER2-
Fibromatosis	β-catenin+; actin±, desmin±, Bcl-2-, CD34-, ER-, PR-
PASH tumour	CD34+, PR>ER, Bcl-2+, CD99+; SMA±, desmin±
Myofibroblastoma	CD34+, SMA± , desmin± , vimentin+, Bcl-2+, CD99+, S100-, HMB45-, β-catenin-, EMA-, CK- , ER±, PR±, AR±
Low-grade angiosarcoma	CD31+, CD34+, factor VIII+; FLI1+, CK-
Cellular angiolipoma	CD31+, CD34+, factor VIII+; CK-
Biopsy site changes	CD68±, β-catenin±
Inflammatory myofibroblastic tumour	ALK-1+ (50%), CD68+, β-catenin-
Mixed spindle cell/epithelial lesions	
Spindle cell metaplastic carcinoma	CK14±, CK5/6±, 34βE12±, CAM5.2±, CK7±, MNF116±, AE1/AE3±, p63±, β-catenin±, CD34-, ER-, PR-, HER2-
Phyllodes tumour (in the stroma)	No specific markers, CD34+, Bcl2+, CK±
Low-grade adenosquamous carcinoma	Circumferential myosin± and p63±; CK± "core" staining (see [14])
Epithelial displacement in biopsy site	Myoepithelial markers (p63, SMM)± around epithelial cells
Pure spindle cell lesions with atypical/malignant cytological features	
Spindle cell metaplastic carcinoma	CK14±, CK5/6±, 34βE12±, CAM5.2±, CK7±, MNF116±, AE1/AE3±, p63±, β-catenin±, CD34-, ER-, PR-, HER2-
Phyllodes tumour (in the stroma)	No specific markers, CD34+, Bcl2+, CK±
Angiosarcoma	CD31+, CD34+, factor VIII+; FLI1+, CK-
Other sarcomas	As per histogenesis (see [15])
Spindle cell melanoma	S100+, A103+, HMB45+, CK-

Abbreviations: CK, cytokeratin; ER, estrogen receptor; PASH, pseudoangiomatous stromal hyperplasia; PR, progesterone receptor; SMM, smooth muscle myosin

The key mesenchymal antibody targets include smooth muscle actin (SMA), desmin, vimentin, actin, and CD31. With respect to epithelial cytokeratins, it is important to use both low- and high-molecular weight cytokeratins (CKs), since their expression is variable in metaplastic carcinomas and no individual CK antibody is specific [7]. Furthermore, some phyllodes tumours can focally express cytokeratins [8]. The main myoepithelial marker is p63, while estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor-2 receptor (HER2) assessment may be useful in some specific diagnoses and also to assess whether the suspected malignant epithelium shares a common phenotype with surrounding *in situ* carcinoma.

Finally, the expression of several antibody targets are associated with some specific lesions and will be included in a panel in which a particular diagnosis is suspected, for instance CD34, Bcl-2, and CD99 in myofibroblastoma; MDM2 and CDK4 in liposarcomas; nuclear β-catenin expression in fibromatosis (with the caveat that about a quarter of spindle cell metaplastic breast cancers can express it too [9]; and Melan-A, S100, and HMB-45 in spindle cell melanoma.

Pitfalls in interpretation of IHC in BSCLs

Therefore, the selection of the most appropriate antibodies will be guided by the morphological differential diagnosis. While antibody target selection is of course important, perhaps even more important is an understanding of the commonly encountered pitfalls when interpreting the IHC. As with all IHC interpretation, it is first important to establish that the technique has worked by looking at internal and external controls. Specific to BSCLs, patchy expression and non-specificity are two important considerations, as discussed below.

Patchy Expression

A pathologist encountering any BSCL will, at the back of their mind, want to exclude spindle cell

metaplastic carcinoma, which can be deceptively benign looking and low grade. Since they are thought to arise from transdifferentiation – or epithelial-to-mesenchymal transition – they show and intermediate phenotype between (myo)epithelial cells and pure mesenchymal cells [10]. Therefore, both myoepithelial and cytokeratin expression can be weak and patchy. As noted above, both low- and high-molecular weight CKs should be used. A useful panel includes CK14, CK5/6, 34βE12 (basal), CAM5.2, CK7 (luminal), MNF116 and AE1/AE3 (broad spectrum) [11] together with p63, which can be similarly patchy.

Non-Specificity

No IHC antibody is pathognomonic for a particular entity (Table-1). For instance, nuclear β-catenin is usually positive in fibromatosis (in 80% of cases [12], but it is also expressed in quarter of spindle cell metaplastic breast cancers and a high proportion of phyllodes tumours [9] as well as benign proliferations such as scar tissue. In another example, CD34 is useful for confirming the diagnosis of myofibroblastoma but it is also positive in angiosarcoma, PASH tumours, spindle cell lipomas, and phyllodes tumours [13], which then become diagnoses of exclusion with CD31 and S-100 useful for excluding angiosarcoma and spindle cell lipoma, respectively.

CONCLUSIONS

In conclusion, BCSLs are a heterogenous group of lesions that can frequently challenge even specialist breast pathologists. While morphology remains the cornerstone of narrowing the differential diagnosis, IHC is a valuable ancillary test that can help to either narrow or confirm the morphological diagnosis. However, BSCLs can also show a remarkable degree of intra-tumoural morphological and immunohistochemical heterogeneity, with two important implications: first, that core biopsies may not be representative of the lesion as whole, therefore prompting only a tentative (B3, uncertain malignant potential) diagnosis on core biopsy and the need for definitive excisional biopsy; and second that IHC is rarely either specific or sensitive for a particular lesion. Care must be taken not to fall into common pitfalls when interpreting IHC in the diagnosis of BSCLs.

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