

Immunohistochemistry in the Differential Diagnosis of Breast Spindle Cell and Sarcomatoid Lesions: A Narrative Review



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¹Ahmed J. Alfahdawi, ²Ali M. Sameen, ³Ibraheem A. Shabeeb

¹Department of Pathological Analysis, University of Fallujah, Anbar, Iraq.

^{2,3}Department of Biology, College of Science, University of Anbar, Anbar, Iraq.

Abstract:

Breast pathology encompasses a wide spectrum of lesions that are often difficult to diagnose, particularly spindle cell and sarcomatoid lesions. Although hematoxylin and eosin (H&E) examination remains the cornerstone of diagnosis, immunohistochemistry (IHC) is an essential adjunct in diagnostically challenging cases. However, inappropriate selection or interpretation of immunohistochemical markers may also lead to diagnostic pitfalls. This narrative review summarizes the current role of immunohistochemistry in the differential diagnosis of breast spindle cell and sarcomatoid lesions. The review focuses on the practical application of immunohistochemical markers alongside histomorphological features and clinical findings to distinguish metaplastic spindle cell carcinoma from benign spindle cell lesions, phyllodes tumors, primary breast sarcomas, and metastatic tumors. However, there is no single immunohistochemical marker provides absolute sensitivity and specificity in breast spindle cell pathology. Diagnostic accuracy relies on selecting an appropriate panel of markers according to the differential diagnosis and interpreting the findings together with the histomorphological features. Myoepithelial markers remain important for assessing stromal invasion, whereas lineage-associated markers, including GATA3, SOX10, and the recently introduced TRPS1, improve the identification of breast epithelial differentiation, particularly in triple-negative and metaplastic carcinomas. TRPS1 has also shown advantages over conventional breast markers in selected diagnostic settings. Immunohistochemistry remains an indispensable tool in the evaluation of breast spindle cell and sarcomatoid lesions. Reliable diagnosis requires careful correlation of immunohistochemical findings with histomorphological features and relevant clinical information, while the choice of antibody panel should always be guided by the specific diagnostic question.

Keywords: Immunohistochemistry, Breast Pathology, Spindle Cell Lesions, Sarcomatoid Neoplasms, Differential Diagnosis.

1. Introduction

Breast lesions are known to represent a wide range of heterogeneous pathological conditions, wherein benign and

malignant processes are often seen to show overlapping features. This continues to pose significant challenges in terms of diagnosis. While conventional histopathological examination with hematoxylin and eosin (H&E) sections is essential in breast pathology, there are circumstances where, apart from conventional morphology, additional modalities might be required, especially in cases showing unusual architectural features, limited tissue sampling, and significant cytological atypia (Brogi, 2004; Magro, 2018; Rakha et al., 2016; Rakha et

al., 2022; E Yoon et al., 2022). It is in these circumstances that immunohistochemistry (IHC) has been recognized as playing an essential role in the characterization of tumor types, lineage, and invasive potential.

Immunohistochemistry in breast pathology covers a wide spectrum of diagnostic possibilities. Immunohistochemistry can be used to distinguish ductal from lobular carcinomas, to investigate spindle cell and sarcomatous lesions, to assess stromal invasion, and to distinguish primary breast cancers from metastases (Canas-Marques & Schnitt, 2016; Dabbs et al., 2013; Rakha et al., 2016; E Yoon et al., 2022). Such diagnostic possibilities assume great clinical importance because they have a direct impact on the management of patients with breast carcinoma (Tan et al., 2020; Obeng-Gyasi et al., 2016; Pramod et al., 2021; Wilson et al., 2021). However, there are certain limitations to immunohistochemical results. No marker can be said to have absolute sensitivity or specificity. Furthermore, abnormal staining results have been recognized as a problem, particularly in high-grade poorly differentiated carcinomas with a high degree of metaplasia (Canas-Marques & Schnitt, 2016; Da Silva et al., 2008; Rakha et al., 2010).

One of the more challenging groups of lesions to diagnose in breast pathology is the spindle cell and sarcomatoid lesions. The range of this group of lesions varies from reactive processes and benign mesenchymal lesions to locally aggressive processes and malignant lesions, both primary and metastatic (Magro, 2018; E Yoon et al., 2022). There is considerable overlap among these lesions, and this is made worse when the specimen for examination is limited, as it is with biopsy material, and when the immunohistochemical panel used for evaluation is narrow (Rakha et al., 2016; Rakha et al., 2022). Similarly, to other sclerosing or architecturally complex breast lesions, accurate assessment of stromal invasion often requires the integration of morphologic features with myoepithelial cell marker expression, both of which have associated diagnostic pitfalls (Ginter et al., 2016; Hoda et al., 2022; Kővári et al., 2015; Lee, 2013; Mukai et al., 1981). In addition, differentiation of primary breast carcinoma from metastatic malignancy can be particularly problematic in high-grade triple-negative carcinomas and sarcomatoid carcinomas in the absence of an identifiable in situ component (Mahrous et al.,

2012; Sibartie et al., 2011). Although several immunohistochemical markers have been identified that have associations with breast pathology, no immunohistochemical markers have been identified that are exclusively associated with breast tissue. In addition, expression of immunohistochemical markers in non-mammary malignancies has been well documented (Huo et al., 2015; Sangoi et al., 2016; Wendroth et al., 2015). Consequently, immunohistochemical findings must always be interpreted alongside histomorphology and relevant clinical information.

This narrative review article aims to highlight the major immunohistochemical markers for diagnostically difficult breast lesions. Emphasis is placed on their practical application, limitations, and pitfalls, especially with regard to differentiating ductal from lobular carcinoma, spindle cell and sarcomatoid lesions, invasion, and primary from metastatic disease. Immunohistochemistry is highlighted as an important ancillary tool for breast pathology, but it is emphasized that it should always be used appropriately and as part of a holistic approach to breast pathology. Accordingly, this article was identified through PubMed, Scopus, and Web of Science searches up to March 2026. Studies were selected for their relevance to the diagnostic use of immunohistochemistry in breast pathology.

2. Diagnostic Considerations in Spindle Cell Lesions of the Breast

Breast spindle cell lesions range from reactive and tumor-like disorders to benign mesenchymal tumors, as well as low- and high-grade malignant tumors (Brogi, 2004; Magro, 2018; Rakha et al., 2016; Rakha et al., 2022; E Yoon et al., 2022). Though rare, the malignant types often show considerable histological overlap, and the small tissue samples obtained with a core needle biopsy may pose considerable challenges in the histopathological diagnosis of the tumor types. For this reason, the precise histopathological classification of the tumor is important, as the treatment approaches and clinical outcomes vary substantially from one tumor to another. In this context, immunohistochemical staining plays an important role in the histopathological diagnosis of the tumor types, and the representative tumor types are discussed in the sections below.

3. Fibromatosis of the Desmoid Type

Desmoid-type fibromatosis is an infiltrative spindle cell tumor characterized by local aggressiveness and a high propensity for local recurrence, but without any metastatic potential (Boland et al., 2021; Wargotz et al., 1987). The most common sites from which this tumor arises are the deep tissues, such as the fascia of the pectoralis major muscle or Cooper's ligaments, and then spreads to the adjacent breast tissue. The radiological features reveal the presence of fibromatosis, which is detectable by mammography and appears as an ill-defined mass in ultrasonography, often mimicking invasive breast cancer. The histological features reveal relatively uniform spindle cells arranged in long, sweeping fascicles or in parallel bundles in a sometimes collagen-rich background. The growth pattern is infiltrative, and the tumor extends into the adjacent adipose tissue, often entrapping adjacent structures. The presence of a

peripheral lymphocytic cuff is common and can also be helpful in diagnosis. The cytological atypia is minimal, and the mitotic rate is low. The immunohistochemical features reveal myofibroblastic differentiation, as indicated by the presence of α -smooth muscle actin (SMA) in most cases. The presence of nuclear accumulation of β -catenin is also observed in most cases, in more than 80% of cases, and is helpful in diagnosis in the appropriate context. The absence of cytokeratins, p63, CD34, desmin, S-100 protein, and hormone receptors is also observed in fibromatosis, as depicted in Figure 1A, B. It is, however, important to note that nuclear accumulation of β -catenin is not entirely specific and can also be observed in other breast lesions such as phyllodes tumors and fibromatosis-like metaplastic carcinomas. Hence, the immunohistochemical results should always be interpreted in conjunction with the underlying histological features to avoid misclassification (Lacroix-Triki et al., 2010).

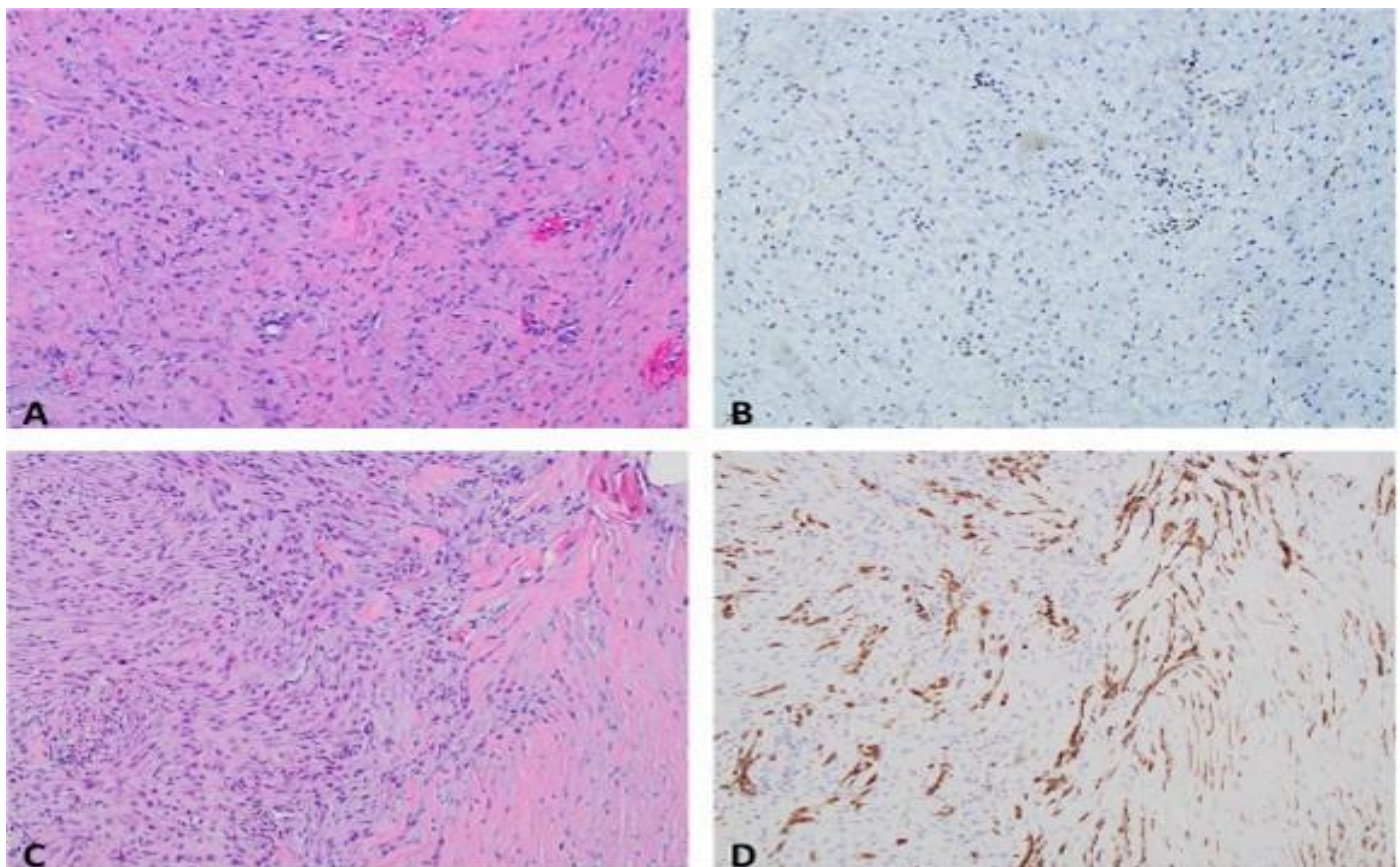


Figure 1 Comparative assessment of a benign desmoid-type fibrous proliferation and a low-grade spindle cell carcinoma with a fibromatosis-like pattern in the breast.

Case 1: Desmoid-type fibromatosis, as evidenced by the presence of a bland spindle cell population on hematoxylin and

eosin staining (A) and the absence of pancytokeratin positivity on immunohistochemical staining (B). Case 2: Low-grade

spindle cell carcinoma with a fibromatosis-like pattern, as evidenced by the presence of corresponding histological features on hematoxylin and eosin staining (C) and positivity for pancytokeratin in tumor cells on immunohistochemical staining (D). Original magnification $\times 200$ (A-D).

4. Fibromatosis-Like Metaplastic Carcinoma of the Breast

Fibromatosis-like Metaplastic Carcinoma (MBC) is a low-grade spindle cell tumor that has the potential to resemble desmoid-type fibromatosis under routine histological examination. It is considered to be one of the most deceptive bland spindle cell tumors that may be encountered in the breast, because of its close resemblance to desmoid-type fibromatosis. Despite its relatively indolent appearance, fibromatosis-like MBC carries a recognised risk of local recurrence, and a small subset of patients may also develop metastatic disease (Gobbi et al., 1999).

Histologically, the tumour is composed predominantly of spindle cells with low-grade cytological features; however, careful examination often reveals focal areas that are diagnostically informative. In particular, the presence of cytological atypia and foci of epithelioid differentiation supports a diagnosis of fibromatosis-like metaplastic carcinoma. The epithelioid component is defined by tumour cells with well-circumscribed borders, eosinophilic cytoplasm and evenly contoured nuclei, forming tight nests or grouped aggregates instead of the long, sweeping fascicles seen elsewhere (Dwyer & Clark, 2015; Sneige et al., 2001). Although not invariably present, inflammatory infiltrates may be identified, particularly at the tumour periphery, and typically consist of scattered lymphocytes and plasma cells, occasionally forming germinal centres.

In a proportion of cases, confirmation of malignancy relies largely on immunohistochemical demonstration of epithelial differentiation. In most cases, the neoplastic cells show immunoreactivity for cytokeratins and/or p63 (Fig. 1C, D), a feature that, when interpreted alongside the histological findings, provides strong evidence in support of the diagnosis. Expression of α -smooth muscle actin (SMA) is also commonly observed, whereas CD34, oestrogen receptor (ER),

progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) are typically negative. When interpreted alongside the histological features and clinical setting, this immunophenotypic profile is essential for distinguishing fibromatosis-like metaplastic carcinoma from desmoid-type fibromatosis and other benign spindle cell mimics of the breast.

5. High-Grade Malignant Spindle Cell Tumours of the Breast

High-grade spindle cell malignancies of the breast are most commonly represented by metaplastic spindle cell carcinoma (SpCC) and malignant phyllodes tumour (MPT). Together, these two entities account for the majority of aggressive spindle cell tumours encountered at this site. This differential diagnosis extends further and can include fewer common conditions like primary breast sarcomas showing spindle cell features and metastatic high-grade spindle cell malignancies involving the breast. This differential diagnosis becomes particularly pertinent when the spindle cell tumor does not show convincing evidence of epithelial differentiation on histological and immunophenotypic grounds, nor does it show the characteristic leaf-like pattern seen in phyllodes tumors. It becomes essential, under these circumstances, to evaluate the clinical context, especially with respect to the presence of recent or past history of soft tissue sarcoma or metastatic sarcomatoid malignancy. Thus, the accurate classification of these high-grade spindle cell malignancies becomes the result of an integrated evaluation of histological, immunophenotypic, and clinical features.

6. Metaplastic Spindle Cell Carcinoma of the Breast

Metaplastic spindle cell carcinoma (SpCC), a high-grade variant of metaplastic breast cancer, often manifests clinically as a hard, large breast mass (Moten et al., 2016). Histopathologically, the tumor may consist entirely of spindle cells or may display a mixed phenotype in which spindle cells co-exist with benign and/or malignant epithelial cells (Wargotz et al., 1989). The spindle cell component is often architecturally varied and may form short or long fascicles, storiform patterns, or even a patternless growth in some areas

of the tumor. The cytological atypia is often marked, and mitotic activity is easily discernible. Tumor necrosis is also occasionally seen. In the mixed forms of metaplastic SpCCs, easily recognizable areas of invasive breast carcinoma and/or squamous cell carcinoma with cutaneous adnexal differentiation are often present, especially at the periphery of the tumor. The spindle cell component is also seen in metaplastic carcinomas with heterologous mesenchymal differentiation, such as chondroid, osseous, rhabdomyoblastic, and occasionally neuroglial differentiation. While the presence of overt malignant epithelial components generally facilitates diagnosis, cases composed purely of spindle cells pose a greater diagnostic challenge. In such situations, confirmation of epithelial or myoepithelial lineage through immunohistochemistry is essential for establishing the correct diagnosis (Carter et al., 2006; Wargotz et al., 1989). To aid in this distinction, the use of a broad cytokeratin immunohistochemical panel is recommended. This typically includes pancytokeratin antibodies such as AE1/AE3 and

MNF116, high-molecular-weight cytokeratins (CK903, CK5/6, CK14 and CK17), as well as low-molecular-weight cytokeratins including CAM5.2, CK7 and CK19 (Adem et al., 2002). The myoepithelial marker p63 is frequently expressed in metaplastic spindle cell carcinoma and provides a valuable additional diagnostic clue. SOX10 expression has also been reported in a subset of cases and is identified in approximately 46% of spindle cell components, including those arising in metaplastic breast carcinomas (Cimino-Mathews et al., 2013). GATA-binding protein 3 (GATA3) shows a higher frequency of expression in metaplastic spindle cell carcinoma compared with other spindle cell lesions arising in the breast (Jin et al., 2021). More recently, trichorhinophalangeal syndrome type 1 (TRPS1) has been recognised as a highly sensitive and specific marker of breast carcinoma and has been shown to remain expressed in metaplastic breast carcinomas, including cases in which GATA3 immunoreactivity is absent (Ai et al., 2021; Parkinson et al., 2022) as shown in (Fig. 2A–C).

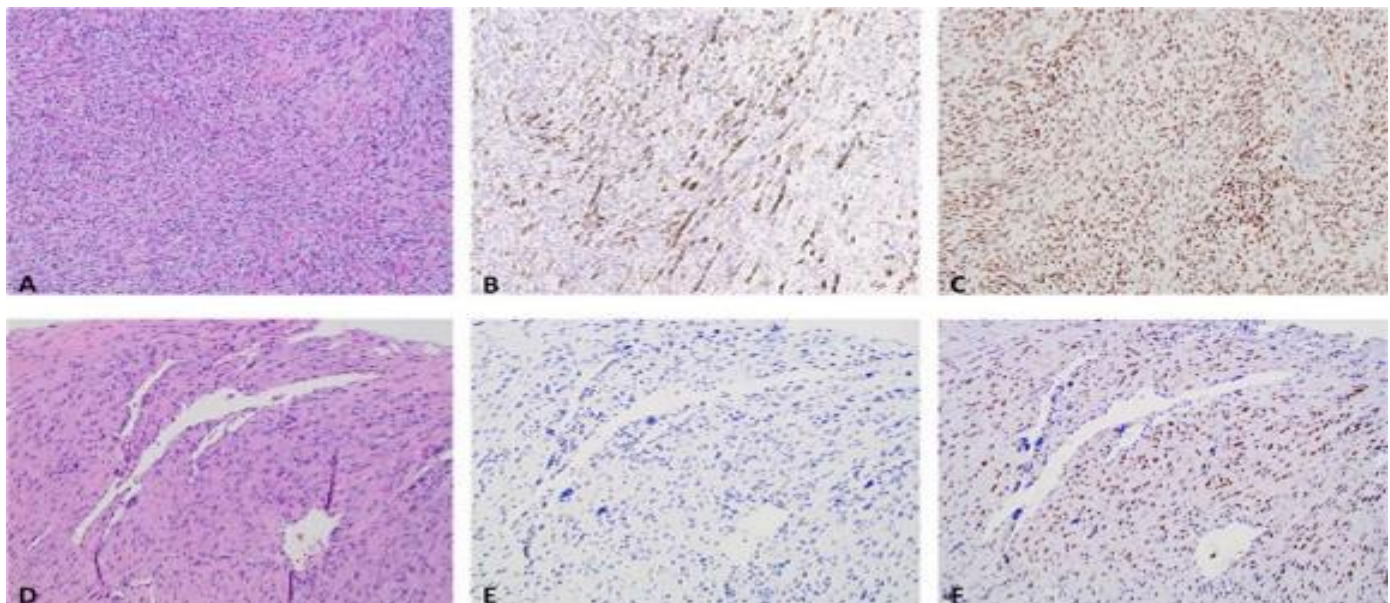


Figure 2. Histological features and immunohistochemical profiles of high-grade spindle cell tumours of the breast.

Case 1 depicts metaplastic spindle cell carcinoma, showing its characteristic morphology on hematoxylin–eosin–stained sections (A), accompanied by diffuse pancytokeratin immunoreactivity within tumour cells (B) and nuclear positivity for trichorhinophalangeal syndrome type 1 (TRPS1) (C). Case 2 illustrates malignant phyllodes tumour, with representative histological findings on H&E (D), lack of

pancytokeratin expression on immunohistochemistry (E), and retained nuclear TRPS1 staining (F). Original magnification $\times 200$ (A–F).

7. Malignant Phyllodes Tumour of the Breast

The stroma-dominant MPT is one of the most important differential diagnoses for metaplastic SpCC (Tan et al., 2016).

While the presence of epithelial lined clefts creating a leaf like morphology is diagnostic of phyllodes tumours (PT), MPT may, in rare cases, be indistinguishable from an appearance of pure spindle cell lesion. This situation occurs most frequently in core needle biopsies, where only the stromal component may have been sampled. In diagnostically challenging cases, immunohistochemical evaluation using a panel that includes cytokeratins and Bcl-2 can assist in distinguishing malignant phyllodes tumour from metaplastic spindle cell carcinoma. Among these markers, CD34 is particularly informative, as most malignant phyllodes tumours retain at least focal CD34 expression, although staining is typically weaker or more heterogeneous than that observed in benign or borderline phyllodes tumours. By contrast, CD34 expression is generally absent in metaplastic spindle cell carcinoma (Dunne et al., 2003; Moore & Lee, 2001). On the contrary, CD117 and Bcl-2 expressions are more likely to be detected in higher-grade phyllodes tumours and MPTs rather than benign or borderline ones (Dunne et al., 2003; Noronha et al., 2011). The possibility of diagnostic pitfalls should be noted for interpretation of epithelial markers. However, CKs and p63 are known to be expressed in most metaplastic breast carcinomas, although they may be downregulated in high-grade lesions. In addition, focal positivity for these markers has been described in the stromal component of a subset of malignant phyllodes tumours which could potentially confuse interpretation (Fig. 2D–F) (Chia et al., 2012; Cimino-Mathews et al., 2014). The frequent overexpression of TRPS1 in malignant phyllodes tumour diminishes its ability to serve as a distinguishing marker between this lesion and metaplastic spindle cell carcinoma of the breast (Wang et al., 2022). In problematic cases, extensive sampling of excision specimens is imperative. Diagnosis of a diagnostic leaf-like stromal–epithelial architecture is indicative of MPT, whereas finding an unequivocal carcinoma component which in turn favours metaplastic spindle cell carcinoma permits proper categorization and clinical management.

8. Primary Spindle Cell Sarcoma of the Breast

Primary sarcomas arising within the breast are exceptionally uncommon (Bousquet et al., 2007; Lee et al., 2021). In principle, virtually all recognised histological subtypes of soft

tissue sarcoma may occur at this site, and when they do, their morphological and immunohistochemical features closely resemble those of morphologically identical tumours arising in extra-mammary soft tissues. Radiation-induced angiosarcoma constitutes the most prevalent form of primary breast sarcoma encountered in clinical practice (Lee et al., 2021). Radiation-induced angiosarcomas typically present as high-grade malignant neoplasms. Histologically, they are composed predominantly of sheets of malignant spindle-shaped or epithelioid cells and often show irregular, poorly formed vascular channels. Marked mitotic activity is common, and areas of tumour necrosis, haemorrhage, and blood-filled spaces or so-called “blood lakes” are frequently identified. Clinically, secondary angiosarcoma of the breast follows an aggressive course and is associated with an unfavourable prognosis (Bonito et al., 2020; Gutkin et al., 2020). Given these implications, a high index of diagnostic suspicion is required, and confirmation using vascular immunohistochemical markers such as CD31, CD34, D2-40 and ERG is essential. Most angiosarcomas arising in previously irradiated breast tissue show marked amplification of the MYC gene located at chromosome 8q24, a molecular finding that assists in separating these tumours from atypical vascular proliferations and from angiosarcomas that develop in the absence of prior radiation exposure (Fraga-Guedes et al., 2015). Excluding angiosarcoma, undifferentiated pleomorphic sarcoma is considered the most common histological subtype of primary breast sarcoma (Lee et al., 2021). From a practical diagnostic standpoint, however, precise subtyping of primary breast sarcoma is often of secondary importance. The critical task for the pathologist is to rigorously exclude the far more common mimics, particularly metaplastic spindle cell carcinoma and malignant phyllodes tumour, before rendering a diagnosis of primary spindle cell sarcoma of the breast.

9. Metastatic High-Grade Spindle Cell Tumours Involving the Breast

Metastatic involvement of the breast by extramammary malignancies is distinctly uncommon, accounting for only a small proportion of breast cancers, estimated at approximately 0.2–1.1%. Importantly, in nearly one-quarter to one-third of cases, breast metastasis may represent the first clinical

presentation of an otherwise occult primary malignancy (Tan et al., 2020). A number of clinical and pathological features should prompt consideration of a metastatic process. These include a known history of malignancy, unusual or non-specific morphological features, lack of an in-situ carcinoma component, a triple-negative immunophenotype, multifocal disease, or bilateral breast involvement. Among non-epithelial metastases to the breast, melanoma is by far the most frequently encountered tumour (DeLair et al., 2013). Melanoma may assume a spindle cell morphology, and careful histological evaluation for features such as intranuclear cytoplasmic inclusions, brisk mitotic activity and the presence of melanin pigment is therefore essential when this diagnosis is considered. Other high-grade spindle cell malignancies reported to metastasise to the breast (Ding et al., 2007; Hsiao et al., 2008; Mahrous et al., 2012; Sibartie et al., 2011). In these settings, immunohistochemistry plays a central role in establishing tumour origin and excluding a primary breast

lesion. Table 1 summarises a selection of immunohistochemical markers that are useful in differentiating frequently encountered metastatic spindle cell tumours involving the breast from primary breast lesions, including metaplastic spindle cell carcinoma and malignant phyllodes tumour. In routine diagnostic practice, a targeted immunohistochemical panel is typically applied, incorporating markers expected to yield both positive and negative results across the relevant differential diagnoses. Awareness of potential immunohistochemical pitfalls is crucial to avoid diagnostic error. In particular, expression of SOX10 and S-100 protein may be seen in both triple-negative breast carcinomas, including metaplastic spindle cell carcinoma, and metastatic melanoma, representing a well-recognised diagnostic challenge in breast pathology. Careful integration of immunophenotypic findings with morphological features and clinical information therefore remains essential for accurate diagnosis (Cimino-Mathews, 2021).

Table 1. Immunohistochemical markers useful for distinguishing primary from metastatic high-grade sarcomatoid tumours of the breast.

Markers	Metaplastic Spindle Cell Carcinoma	Malignant Phyllodes Tumor	Melanoma	Leiomyosarcoma	Rhabdomyosarcoma	Most Useful Marker(S)
CKs	+/-	-/+	-	-	-	Pan-cytokeratin (AE1/AE3)
p63	+/-	-/+	-	-	-	p63
GATA3	-/+	-	-	-	-	GATA3
SOX10	-/+	-	+	-	-	SOX10 (with S-100/Melan-A)
TRPS1	+/-	+/-	-	-	-	TRPS1
CD34	-	+/-	-	-	-	CD34
S-100, HMB45, Melan-A, MITF	-	-	+	-	-	S-100, SOX10, Melan-A, HMB45
SMA	-	-	-	+	+	SMA
Desmin	-	-	-	+	+	Desmin
Caldesmon	-	-	-	+	-	Caldesmon
Myogenin, MyoD1	-	-	-	-	+	Myogenin and MyoD1

10. Assessment of Stromal Invasion in Breast Carcinoma

Within the context of breast pathology, a diagnosis of invasion is made when epithelial tumour cells escape the confines of pre-existing ducts or lobules by crossing the basement membrane and its surrounding myoepithelial cell layer to involve the adjacent stroma (Tan et al., 2020). Consequently, recognition of a preserved, circumferential myoepithelial layer around epithelial proliferations remains one of the most robust indicators of non-invasive disease, aiding in the distinction between benign lesions with complex growth patterns and invasive carcinoma, as well as between in situ and invasive carcinoma.

Within this diagnostic context, immunohistochemistry is most commonly employed for two principal purposes: first, to aid in the distinction between sclerosing benign lesions and invasive carcinoma, and second, to clarify whether a carcinoma should be classified as in situ or invasive (Hicks, 2011; Hoda et al., 2022; Lee, 2013; Li & Dabbs, 2022).

In this context, the presence of a continuous layer of myoepithelial cells is usually taken as suggestive of the absence of stromal invasion. In general, under routine conditions, myoepithelial cells are readily identifiable in normal structures of the duct and acinar epithelium in sections stained with hematoxylin and eosin. However, this evaluation becomes problematic in cases in which there is some degree of distortion and reactive changes in the stroma, such as fibrosis, desmoplastic reaction, and inflammatory infiltrates, which can make the evaluation of gland structures and the recognition of the layer of myoepithelial cells more problematic. In this context, immunohistochemical staining for myoepithelial cells can play an important role as an aid in the evaluation of the tumor.

11. Sclerosing Adenosis Of the Breast

Sclerosing adenosis represents the most common type of adenosis and has been well recognized as a mimicker of invasive breast cancer, with the diagnostic pitfall particularly

evident from limited specimens such as core biopsy specimens (Ginter et al., 2016; Hicks, 2011; Hilson et al., 2010; Lee, 2013). The lesion can be associated with both radiological and histopathological features that can be deceptive and require careful evaluation to exclude the possibility of overdiagnosis. Microscopically, the lesion is defined by the presence of crowded small glandular structures associated with a conspicuous population of spindled myoepithelial cells and stromal sclerosis. The stromal response can be associated with the glands being compressed, distorted, and/or irregular in shape. The radiological features of sclerosing adenosis can be varied and include the presence of microcalcifications, architectural distortion, and/or a discrete mass on the mammogram. Microscopically, the lesion typically involves the terminal duct-lobular units and can be associated with a lobulocentric growth pattern. The lesion can have a rounded and well-defined appearance at low magnification. However, the lobular pattern can be less evident, and the proliferated glands can extend into the adjacent adipose tissue, producing an infiltrative pattern that can mimic invasive cancer. Significantly, sclerosing adenosis does not display malignant cytological features such as marked nuclear atypia, increased mitotic activity, and desmoplasia as seen in invasive carcinoma. Apocrine cell cytological atypia is also observed in sclerosing adenosis; however, this does not suggest malignant change. The identification of the myoepithelial cell layer is often straightforward but can be difficult in some cases, especially when sclerosis of the stroma is marked. In such situations, immunohistochemical techniques are often required to demonstrate the presence of a myoepithelial cell layer (Figure 3A-D). Other histological features that are occasionally observed in sclerosing adenosis include the presence of secretions in the lumina of glands, calcification within glands, and variable hyalinisation or fibrosis of the stroma. In some instances of sclerosing adenosis, irregular invasion into adipose tissue and growth along nerve fibres is observed; such appearances could be mistaken for perineural invasion. In such situations, demonstration of a continuous layer of myoepithelial cells around the involved glands is crucial for establishing a correct diagnosis of benign disease (Hilson et al., 2010).

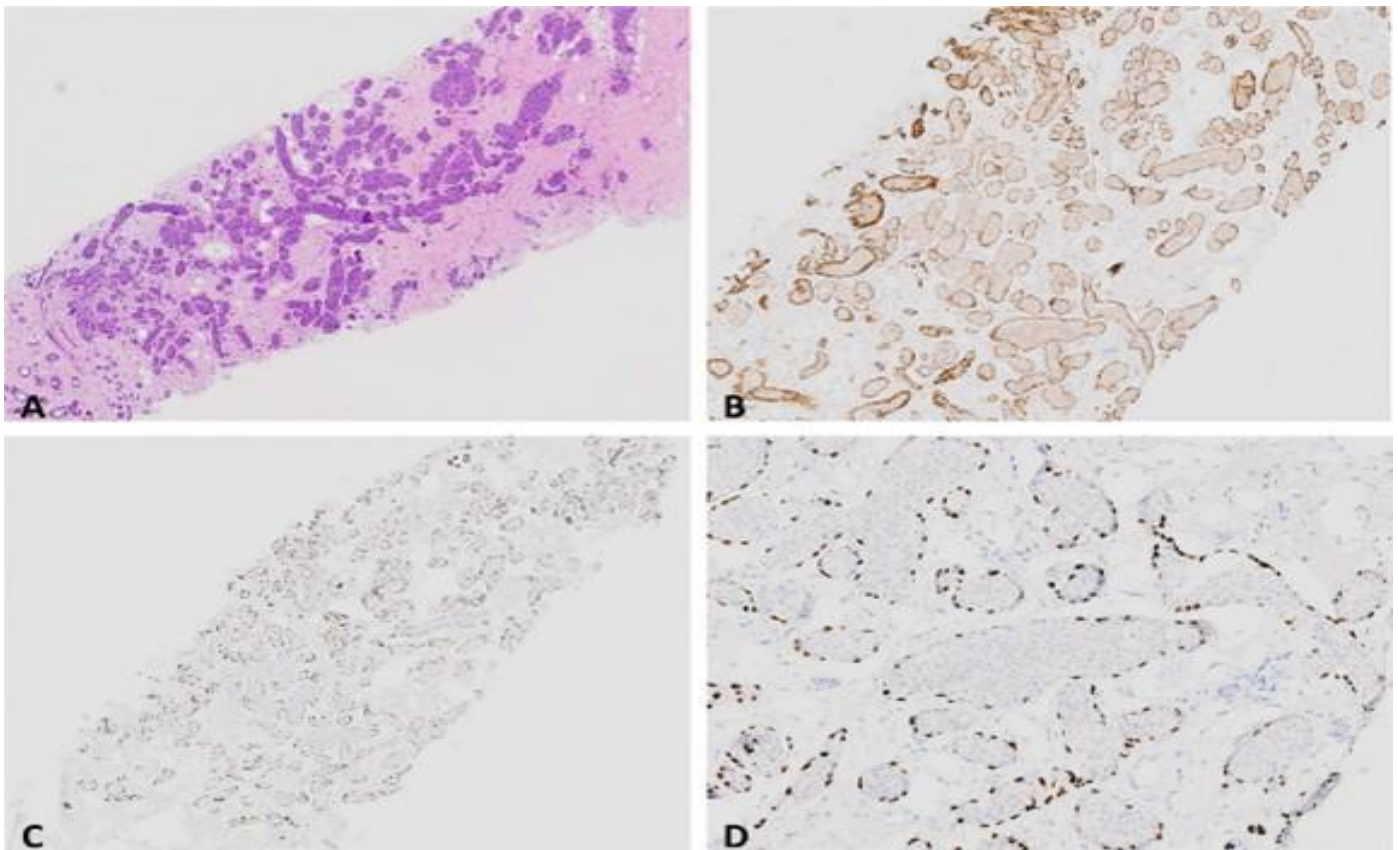


Figure 3. Ductal carcinoma in situ in sclerosing adenosis in a core needle biopsy specimen.

In hematoxylin and eosin sections, there is marked enlargement of glandular structures with a compact epithelial cell proliferation that results in the near-total obliteration of luminal space (A). In this background, the disorganized groupings of epithelial cells can be mistaken for stromal invasion. Immunohistochemical studies show that there remains a continuous layer of myoepithelial cells surrounding the gland (B-D), thus confirming the absence of invasive growth. Original magnification $\times 40$ (A-C), $\times 100$ (D).

12. Distinguishing Ductal Carcinoma in Situ from Invasive Ductal Carcinoma

Ductal carcinoma in situ (DCIS) is regarded as a non-obligate precursor of invasive breast carcinoma and is defined by a malignant epithelial proliferation that remains confined to pre-existing ducts and lobules of the breast (Tan et al., 2020). Stromal invasion, by contrast, is established when tumour cells breach the basement membrane and extend into the surrounding stroma. In most cases, this distinction can be made confidently on routine hematoxylin–eosin (H&E)–stained sections. Nevertheless, diagnostic difficulty may arise in

a subset of cases where architectural features blur the boundary between in situ and invasive disease. Certain invasive breast carcinomas, including cribriform, papillary and adenoid cystic subtypes, may grow in architectural patterns that closely imitate those typically associated with ductal carcinoma in situ. By contrast, ductal carcinoma in situ involving lobular units can trigger a pronounced stromal response, producing architectural distortion that may be mistaken for invasive growth. In these diagnostically complex settings, immunohistochemical assessment with myoepithelial markers is particularly helpful, as it allows evaluation of the integrity of the myoepithelial cell layer and thereby aids in distinguishing in situ disease from true stromal invasion (Figure 4A–C).

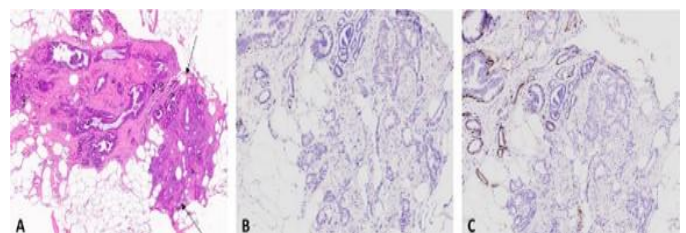


Figure 4. Limited invasive ductal carcinoma occurring in association with widespread high-grade ductal carcinoma in situ.

Hematoxylin–eosin–stained sections reveal small, irregularly shaped glands extending into the adjacent stromal tissue (A, arrows). Immunohistochemical analysis using the myoepithelial markers p63 (B) and smooth muscle myosin heavy chain (C) demonstrates loss of the myoepithelial cell layer around these glands, providing evidence of stromal invasion. Original magnification $\times 40$ (A) and $\times 100$ (B, C).

Despite the availability of numerous immunohistochemical

markers for the identification of myoepithelial cells in routine diagnostic practice, none demonstrates absolute sensitivity and specificity. Consequently, no single marker can be relied upon in isolation for definitive assessment. In current practice, the markers most frequently employed to highlight myoepithelial differentiation include p63, p40, α -smooth muscle actin (SMA), smooth muscle myosin heavy chain (SMM-HC), and calponin (Table 2) (Kawaguchi & Shin, 2012; Kővári et al., 2015; Mukai et al., 1981; Tramm et al., 2011).

Table 2. Myoepithelial immunohistochemical markers used to assess stromal invasion.

Markers	Staining Pattern	Luminal Cells	Myofibroblast	Vascular Smooth Muscle Cells
SMA	C	-/+	+/+	+
SMM-HC	C	-	-/+	+
Calponin	C	-	+	+
p63	N	-/+	-	-
p40	N	-/+	-	-

p63 and p40 are members of the p53 family of transcription factors, with p40 representing a truncated isoform of p63. In normal breast tissue, both markers show nuclear expression in myoepithelial cells and are therefore widely used to highlight the myoepithelial layer. In ductal carcinomas, however, staining for p63 and p40 may be discontinuous, with focal areas of loss or so-called “holes,” a phenomenon that does not, in itself, indicate stromal invasion. In addition, expression of p63 and p40 is not entirely restricted to myoepithelial cells. Expression can also be observed in a subset of invasive breast carcinomas exhibiting squamous or basal-type differentiation, such as low-grade adenosquamous carcinoma, squamous cell carcinoma, metaplastic breast carcinoma with sebaceous differentiation (Kawaguchi & Shin, 2012), and TNBC breast cancer (Kővári et al., 2015).

Additional immunohistochemical markers, including S-100 protein, selected cytokeratins such as CK5/6 and CK14, as well as maspin and CD10, may also highlight myoepithelial cells. However, variable sensitivity and limited specificity reduce their reliability when used in isolation. In routine diagnostic practice, myoepithelial cells should therefore be demonstrated

using a panel of antibodies rather than reliance on a single marker. The combined use of two markers is generally recommended, with p63 together with either SMM-HC or α -SMA providing a practical balance of sensitivity, specificity and interpretative robustness.

13. Immunohistochemical Markers for Identifying Primary and Metastatic Breast Carcinoma

In the diagnostic practice, a newly diagnosed breast carcinoma ER- and/or PR-positive or exhibiting HER2 overexpression or amplification is considered a primary breast tumour unless clinical history suggests an alternative location as the primary site (e.g. ovarian serous carcinoma). Among such scenarios, there is usually no need for additional diagnostic markers to determine the breast lineage in these habitats. In contrast, high-grade TNBCs lacking an associated in situ component may evoke the possibility of metastatic carcinoma, and further investigations with ancillary immunohistochemical studies are needed to rule out other potential primaries.

By contrast, when metastatic carcinoma is detected in the liver, lung or other distant sites (with the exception of bone) in a woman and no prior history of breast malignancy exists, a primary breast site frequently falls under consideration for men. This represents both a high frequency of breast carcinoma and the known ability of occult primary tumours to occur within the breast. In these clinicopathological situations, the provision of a sensitive and specific breast-related immunohistochemical profile is necessary in order to make or dispel the diagnosis of mammary origin because such a diagnosis affects directly and profoundly upon patient management and treatment. Recently trichorhinophalangeal syndrome type 1 (TRPS1) has also been introduced as yet another potential marker in this group. These markers yield different sensitivities in subsites of invasive breast carcinoma, and can be grossly divided into three groups according to their expression patterns and diagnostic values.

14. TRPS1 as a Shared Diagnostic Marker for Luminal and Basal Invasive Breast Carcinomas

Trichorhinophalangeal syndrome type 1 (TRPS1) has emerged as one of the most informative immunohistochemical markers for breast carcinoma, demonstrating both high sensitivity and high specificity across molecular subtypes, with particularly strong performance in triple-negative breast cancer (TNBC) (Ai et al., 2021). Since its introduction into diagnostic pathology, TRPS1 has been rapidly incorporated into routine practice in the United States and internationally. Biologically, TRPS1 belongs to the GATA family of zinc finger transcription factors and plays an essential role in chondrogenesis, skeletal development and hair morphogenesis. Germline loss of TRPS1 underlies trichorhinophalangeal syndrome, an autosomal dominant disorder characterised by distinctive craniofacial and skeletal abnormalities (Fantauzzo et al., 2008; Izumi et al., 2010; Radvanyi et al., 2005; Wuelling et al., 2009).

Recent studies on large numbers of cases have helped to elucidate the diagnostic potential of TRPS1 in different subtypes of breast cancer. In a study by Ai et al., who analyzed the data using the Cancer Genome Atlas, it was shown that TRPS1 overexpression was not limited to luminal breast cancer

but was also observed in HER2 and basal-like breast cancer (Ai et al., 2021; Alfahdawi et al., 2026). TRPS1 and GATA3 have shown comparable sensitivities in ER-positive (98% vs. 95%) and HER2-positive (87% vs. 88%) invasive breast carcinomas, while in the case of TNBC, TRPS1 has shown a significant diagnostic advantage compared to GATA3. In metaplastic TNBC, TRPS1 was positive in 86%, while in the case of GATA3, positivity was significantly low at 21%. Similar observations were made in non-metaplastic TNBC, with 86% positivity with TRPS1 and ~51% positivity with GATA3.

Although TRPS1 is expressed in the vast majority of TNBCs, rare exceptions have been documented. Both TRPS1 and GATA3 are consistently negative in acinic cell carcinoma, most cribriform adenoid cystic carcinomas and neuroendocrine carcinoma of the breast (EC Yoon et al., 2022). Despite its more recent introduction into routine testing, the diagnostic performance of TRPS1 consistently exceeds that of GATA3 and SOX10. Importantly, TRPS1 is positive in virtually all GATA3-positive and SOX10-positive invasive breast carcinomas, supporting its role as a unifying marker across both luminal-differentiated and basal-differentiated breast cancers (Figures 5). Although TRPS1 is expressed in the vast majority of TNBCs, rare exceptions have been documented. Both TRPS1 and GATA3 are consistently negative in acinic cell carcinoma, most cribriform adenoid cystic carcinomas and neuroendocrine carcinoma of the breast (Zhang et al., 2023), as presented in (Fig. 5A–H).

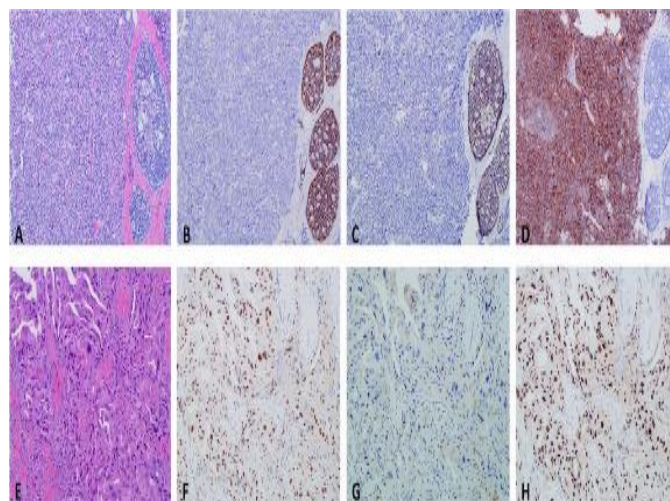


Figure 5. Histological and Immunophenotypic Features of Neuroendocrine and Apocrine Carcinoma of the Breast.

Case 1 shows neuroendocrine (small cell) carcinoma with characteristic morphology on hematoxylin–eosin staining (A), loss of GATA3 (B) and trichorhinophalangeal syndrome type 1 (TRPS1) expression (C), and diffuse synaptophysin positivity (D). An adjacent ductal carcinoma in situ component is present and, in contrast, retains GATA3 and TRPS1 expression while lacking synaptophysin staining. Case 2 illustrates apocrine carcinoma, displaying typical apocrine morphology on H&E (E), preserved nuclear GATA3 expression (F), absence of TRPS1 staining (G), and strong androgen receptor immunoreactivity (H). Original magnification $\times 200$ (A–H).

15. Conclusion

Spindle cell and sarcomatoid lesions of the breast are among the most puzzling lesions a breast pathologist is likely to encounter. Some of these lesions have overlapping morphologic characteristics and require detailed evaluation for an accurate diagnosis.

Routine evaluation of sections stained with hematoxylin and eosin is considered essential for evaluation of these lesions. Immunohistochemistry is considered helpful for differentiation of fibromatosis from fibromatosis-like metaplastic carcinoma, for differentiation of metaplastic carcinoma from malignant phyllodes tumor, and for determining the mammary origin of these lesions.

However, there is no single immunohistochemical marker available for a definitive diagnosis. However, accurate evaluation of these lesions is possible only with a judicious integration of morphological evaluation and immunohistochemistry. Myoepithelial markers are considered useful for evaluation of stromal invasion. TRPS1 is highly sensitive for all subtypes of breast carcinoma, including triple-negative breast carcinoma.

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