Invasive Breast Cancers

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5.1 Introduction

There are many different histological subtypes of breast cancer. Approximately 60–70% of breast cancers are invasive ductal carcinoma (invasive carcinoma of no special type), and the second most common is invasive lobular carcinoma (8–10%). Other histological types are less common. Prognostic factors that are routinely evaluated in the practice of pathology are of great importance in order to make the prediction of prognosis correctly in breast cancer. These prognostic factors are histological type of tumour, tumour size, degree of tumour differentiation (histological grade), lymphovascular space invasion, oestrogen/progesterone receptors, proliferation index, HER-2 expression status and axillary node involvement.

The modified Bloom-Richardson grading system is often used to determine the histological grade of breast tumours. In this scoring system, tubule formation rate, nuclear atypia and mitotic counts are evaluated. A numerical scoring system of 1–3 is used to ensure that each factor is assessed independently (see Table 5.1).

The three values are added together to produce final scores of 3–9, which the grade is assigned as follows:

- **Grade 1** tumour (**well-differentiated**), if the final score is **3–5**.
- **Grade 2** tumour (**moderately differentiated**), if the final score is **6–7**.
- **Grade 3** tumour (**poorly differentiated**), if the final score is **8–9**.

Prognosis worsens as grade increases.

In the following sections, the most common breast carcinomas, as well as breast carcinomas with distinct features, are described.

Table 5.1 Modified Bloom-Richardson grading system

Features		Points
	In more than 75% of the tumour	1
Tubule formation	In 10–75% of the tumour	2
	In less than 10% of the tumour	3
	Nuclei with minimal or mild variation in size and shape	1
Nuclear features	Nuclei with moderate variation in size and shape	2
	Nuclei with marked variation in size and shape and prominent nucleoli	3
Mitotic count	0–9	1
Per 10 high-power fields (for 0.27 mm2 area)	10–19	2
	>19	3

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M. Rezai et al. (eds.), *Breast Cancer Essentials*, https://doi.org/10.1007/978-3-030-73147-2_5

5.2 Invasive Carcinoma of no Special Type (NST) (Invasive Ductal Carcinoma)

About 47–75% of all invasive breast carcinomas are invasive ductal carcinoma [1]. Most cases occur in people around the age of 50. These tumours are also known as scirrhous carcinoma, or infiltrating ductal carcinoma with productive fibrosis, or carcinoma simplex. Following the discovery that some breast cancers showing the macroscopic and microscopic characteristics of scirrhous carcinoma were invasive lobular carcinoma, the term 'infiltrating ductal carcinoma' has been deemed more appropriate to describe these tumours.

These tumours are on average 2 cm in diameter. They sometimes reach 4–5 cm or even greater diameters and are fairly hard in consistency, with clearly defined margins. During palpation, 2/3 of tumours are perceived as having irregular borders due to infiltrating development [2, 3]. Retracted nipple, 'peau d'orange', Paget's disease or large masses may be present. They infiltrate the chest wall and invade the skin of the breasts, causing nipple retraction. Cross sections are hard, with a cartilage-like consistency in reaction to desmoplastic stromal response, and give out an audible friction rub when cut with blade. Central part of the tumour is less firm, of a chalk-like consistency, and may contain necrotic tumour areas.

Histologically, the tumour is composed of anaplastic ductus epithelium cells showing alignments comprising cordons, solid cellular nests, tubular and gland structures and groups of anastomoses. In some cases, intraductal components may be observed quite clearly [4]. Infiltrating tumour cells also spread to the fibrous stroma. Some of the cells forming a tumour are moderately hyperchromatic, small cells with regular nuclei (nuclear grade I), while some other cells comprise irregular large cells with hyperchromatic nuclei (nuclear grade III) [5, 6]. Most of the time, the nuclei are of surprisingly uniform volume and shape, forming very few mitoses. Tumour cells are observed to have infiltrated into the stroma and the surrounding fat tissues in parts matching the periphery of the tumoral mass. Additionally, lymphatic vein, perivascular and perineural invasion is frequently observed (Fig. 5.1). In some cases, the granulomatous reaction may be observed around the tumour or lymph nodes as an immune response to the tumour. There are numerous ongoing researches about the importance of many prognostic and predictive factors in breast cancers including hormone receptor status, c-erbB-2 oncoprotein overexpression and gene amplification (Fig. 5.2), angiogenesis, Ki-67 proliferative index, lymph vascular space invasion and lymph node metastases [7–9].

Today, breast cancers are classified based on hormone receptor and c-erbB-2 oncoprotein overexpression statuses as luminal A, luminal B, Her-2 positive and basal-like [10, 11].

5.3 Invasive Lobular Carcinoma

Characterised as the linear growth pattern of small cells, invasive lobular carcinoma (ILC) make up 0.7–14% of all invasive breast cancers [12]. ILC can affect people aged 26–86, mean age group being 45–57. Two per cent of breast cancers affecting women aged under 35 and 11% of breast cancers affecting women aged over 75 are invasive lobular carcinoma. As is the case for other types of breast cancers, majority of women present with palpable masses. Larger tumours may infiltrate the skin over them or retract the nipples. It is interesting that ILC does not coexist with Paget's disease. Identifying some lobular carcinoma may be difficult because the tumour does not form a mass with clear margins due to diffuse growth pattern of the cellular infiltrate. In some cases, lesions may be palpated as areas with clinical density; however, they may not show up on mammographic images. Problems encountered in the interpretation of mammograms are lack of calcification, indistinct margins and multifocality. 6–28% of all cases are bilateral. 9–14% of cases subsequently develop contralateral breast cancer, 50% of which are invasive [13].

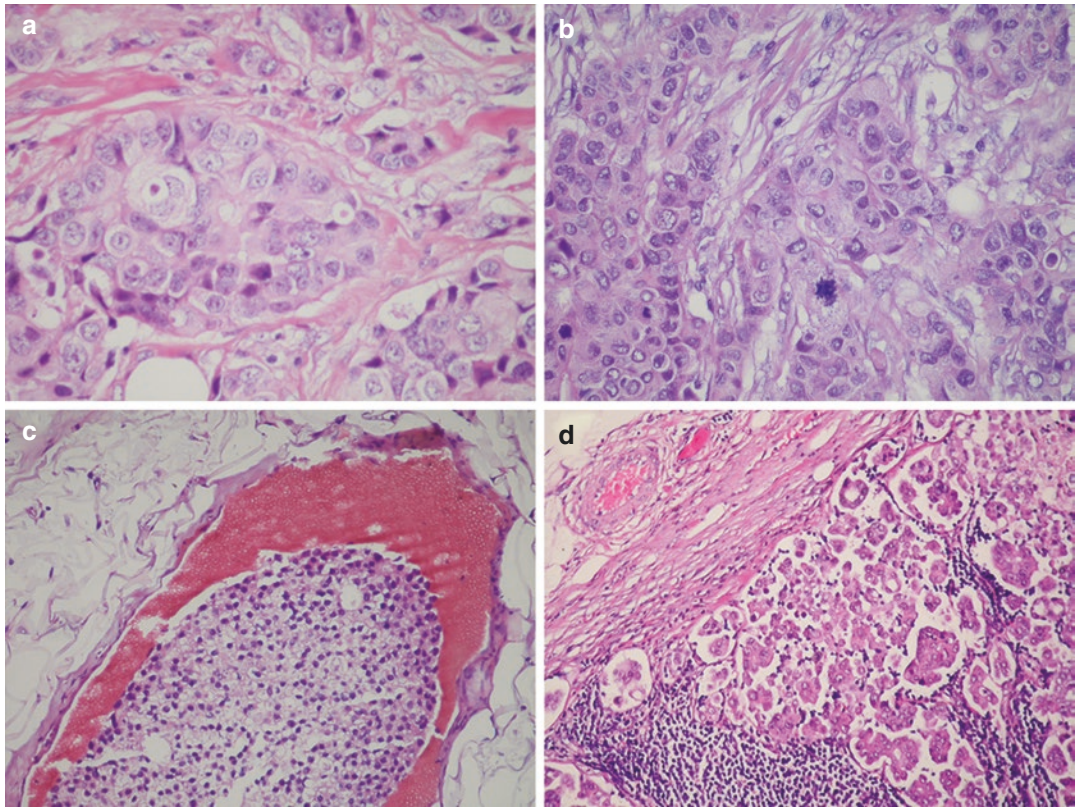

Fig. 5.1 Invasive ductal carcinoma infiltrating into adjacent tissues (**a**) and with atypical mitosis (**b**) and with vascular space invasion (**c**). Lymph node metastasis of invasive micropapillary carcinoma (**d**)

Lesions may be visible macroscopically as an irregular, infiltrating or well-delineated mass, or it may not be visible to the naked eye.

Microscopically, the classic pattern is characterised by diffuse infiltration of stroma by cohesive and generally small cells (Fig. 5.3). Tumour cells have round, notched or ovoid nuclei and a thin rim of cytoplasm which may contain intracytoplasmic lumen. Tumour cells infiltrate breast stroma in a diffuse manner, destroying normal structures and growing in a bull's eye (targetoid) pattern around ducts [14]. Other patterns of ILC that were defined afterwards are the solid, the alveolar, the pleomorphic patterns as well as the mixed pattern, which comprises the previous three. 40–60% of co-occurrence with lymph node metastasis have been identified for these patterns. The pleomorphic pattern is characterised by pleomorphic nucleus and distinct nuclear atypia assessed as nuclear grade III [15, 16]. Negative hormone receptor status, c-erbB-2 overexpression and positive e-cadherin status can be shown in this group with a poorer prognosis [17, 18]. In tubulolobular pattern, there are cell cords in 'Indian file' formation along with adjacent and dense tubular structures around it. Most researchers do not recognise tumours showing tubular formation as a variant of lobular carcinoma [19]. Tumour can be thought of as both ductal and lobular carcinoma invasion [20].

In ILC, oestrogen receptor is 60–90% positive, while progesterone receptor is positive in slightly lower percentages. Compared to ductal carcinoma in situ, c-erbB-2 and p53, which have a poor prognosis in breast cancer, are rarely expressed in lobular carcinoma in situ. Although E-cadherin, a molecule of epithelial adhesion, is prominent in ductal carcinoma in situ and invasive ductal carcinoma, it is rarely positive in atypical lobular hyperplasia, LCIS and ILC [21] (Fig. 5.4).

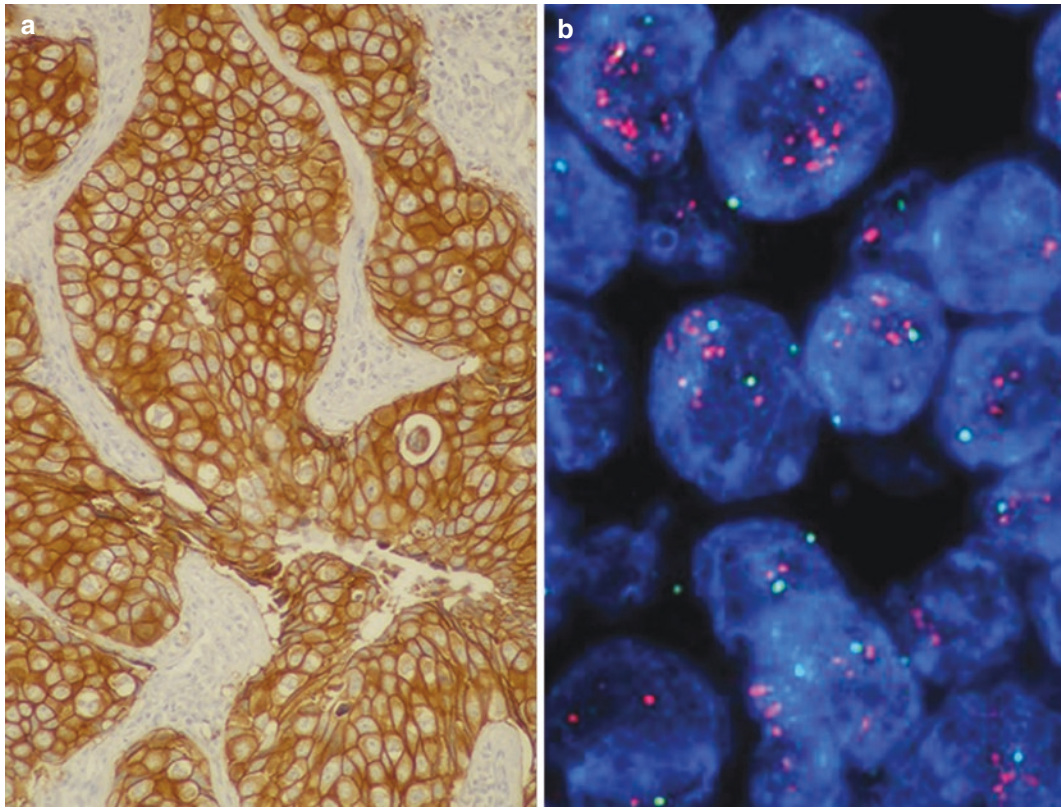

Fig. 5.2 Immunohistochemical stain in invasive ductal carcinoma for c-erbB-2 displays diffuse positive membranous staining (**a**) and HER-2/neu oncogene amplification with fluorescence in situ hybridization (**b**)

ILC cannot be distinguished with histiocytes in metastatic focus when concentrated in subcapsular or medullar sinus. Concentration of tumour cells in a layer formation and distortion of lymph node structure facilitate accurate diagnosis. When differential is difficult, mucin or cytokeratin may resolve the problem.

Metastatic pattern of ILC is different from skeletal, visceral, serosal and retroperitoneal metastases of invasive ductal carcinoma. Invasive ductal carcinoma metastasizes in the form of parenchymal deposits, while metastasis of ILC in the central nervous system has meninx involvement [22, 23]. Breast cancers most commonly metastasize to the bone marrow. Metastases to ovaries and uterus have the same characteristic. Metastases in the endometrium cause haemorrhage. However, it may easily be overlooked due to small size and diffuse infiltration pattern of cells.

5.4 Tubular Carcinoma

It is a very well-differentiated model of breast cancer. It has been defined separately from other invasive carcinomas because of the excellent prognosis of the tumour. Tumour usually takes the form of small nodules radial infiltrating the surrounding tissue. Tumour is made up of elongated, oval or angular-looking tubular structures, and these structures are inlaid with uniserial ductal cells, not showing pleomorphism (Fig. 5.5a). Mitotic activity is rare. Tubule lumens appear empty and generally open and dilated. Most ductal carcinoma in situ cases are of non-necrotic cribriform or micropapillary type. There are usually elastosis areas where elastic fibres are concentrated around tubules. When the entire lesion is made up of tubules, it is called pure tubular carcinoma. On the other hand, when the minor component of the lesion is made up of other

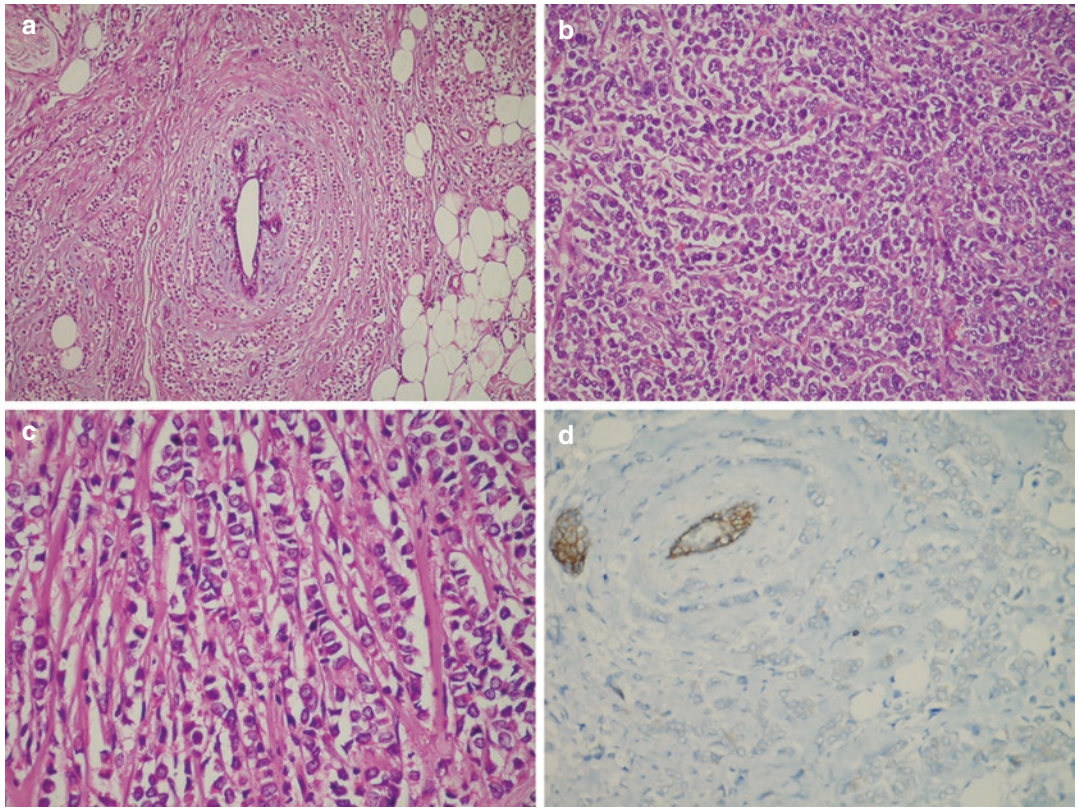

Fig. 5.3 Invasive lobular carcinoma showing targetoid pattern around the non-neoplastic duct (**a**). Invasive lobular carcinoma with solid pattern (**b**). Pleomorphic invasive lobular carcinoma with 'Indian file' pattern (**c**). Negative tumour cells for e-cadherin in invasive lobular carcinoma (**d**)

infiltrating carcinomas, then it is called mixed tubular carcinoma. Tubular carcinoma should be differentiated from sclerosing adenosis. Differential of sclerosing adenosis with its infiltrating type is difficult. In sclerosing adenosis, periphery of glandular structures is regular, inlaid with double layer of epithelium containing epithelial and myoepithelial cells [24]. Besides, tubular structure is intact. On the other hand, tubular carcinoma exhibits a radial development.

5.5 Invasive Cribriform Carcinoma

It is one of the breast cancer tumours with very good prognosis. It constitutes approximately 0.6–3.5% of all breast carcinoma. The cribriform pattern that is characteristic to the intraductal cribriform carcinoma is present in invasive areas with the same characteristics (Fig. 5.5b, c). Invasive areas may be accompanied with tubular carcinoma areas [25–27].

5.6 Invasive Micropapillary Carcinoma

This tumour has one of the worst prognoses among invasive breast cancer types [28, 29]. It usually exhibits tumour cell groups forming inverse glandular structures or morula like aggregates in the clear empty spaces within the loose stroma (Fig. 5.5d). Tumour cells are shaped like low columnar or cubes, while their cytoplasmic extensions lie toward the periphery. It may exhibit extensive lymphatic emboli [29–31]. It may mostly be present with invasive duc-

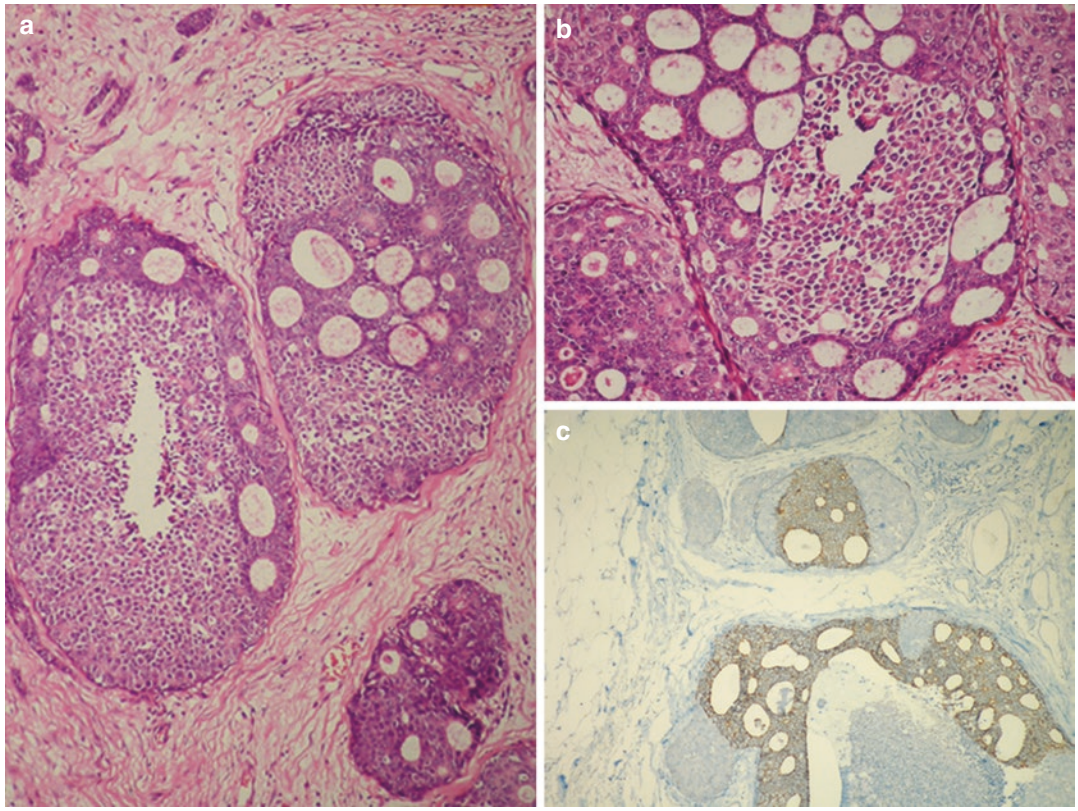

Fig. 5.4 Coexistence of lobular carcinoma in situ and ductal carcinoma in situ (**a**, **b**). Ductal carcinoma in situ component positive and lobular carcinoma in situ component negative for e-cadherin (**c**)

tal carcinoma. Although it may not be identified in some primary tumours of breast cancer that are large in diameter, presence of invasive micropapillary carcinoma may be identified in axillary metastases (Fig. 5.1d). Investigating Wilms tumour-1 and Ca 125 expression when differentiating primary invasive micropapillary carcinoma of the breast from ovarian serous papillary carcinoma metastasized to the breast may prove useful [32].

5.7 Medullary Carcinoma

Accounting for 5–7% of all cases of breast cancer, medullary carcinoma is a soft, fleshy tumour that may grow up to 5–10 cm in diameter. Cut surface is raised in comparison to the surrounding tissue. These tumours exhibit a centrifugal development and are clearly distinguished from the surrounding normal tissue with well-defined margins. Its margins are so clearly defined that imaging methods and clinical examination may be suggestive of fibroadenoma. Necrosis and haemorrhage are commonly observed in these considerably soft tumours [33, 34].

Histologically, syncytial growth pattern composed of large cells with vesicular, pleomorphic nuclei containing distinct nucleoli, solid nests with little fibrous stroma and numerous atypical mitoses are observed in medullary carcinoma (Fig. 5.6a, b). Gland formation is not present. Syncytial growth pattern is seen in at least 75% of the cross section. Furthermore, this tumour has moderately distinct lymphocytic infiltration among cell nests characteristically [35, 36]. Granulomatous reaction may rarely be observed in stroma. The following are microscopic features of a typical medullary carcinoma [37]:

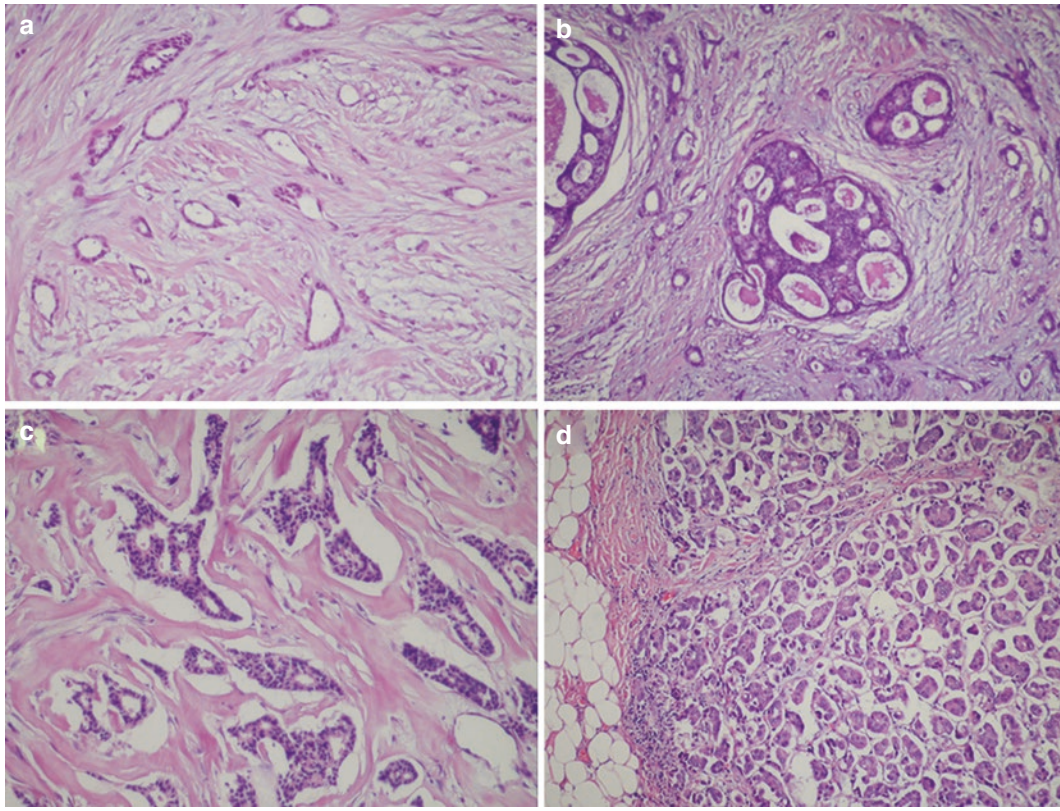

Fig. 5.5 Tubular carcinoma (**a**). Invasive cribriform carcinoma and cribriform carcinoma in situ with necrosis (**b**). Invasive cribriform carcinoma (**c**). Invasive micropapillary carcinoma (**d**)

- Syncytial growth pattern (>75%).
- Regular margin.
- Moderately diffuse lymphoplasmositic infiltration.
- Lack of glandular structures.
- Up to moderate level nuclear polymorphism (nuclear grade 1–2).
- Lack of ductal carcinoma in situ.

5.8 Adenoid Cystic Carcinoma

Very rarely seen in the breast, this tumour accounts for 0.1–0.2% of all cases of breast cancer. It is a specific breast tumour with distinguished histological outlook and fairly good prognosis. It is very similar to the tumour often found in the salivary glands. Contrary to aggressive behaviour defined in the salivary gland, it has an excellent prognosis in the breast [38]. It has macroscopically well-defined edges and may grow up to 1–5 cm in diameter. Cross section is greyish yellow; cystic areas are sometimes visible, but not common. It is an invasive carcinoma of the breast in characteristic cribriform appearance. These tumour looks like adenoid cystic carcinoma found in salivary gland and cylindroma. Its prognosis is better than that of invasive ductal carcinoma. It should be differentiated from cribriform carcinoma. There are two types of cells in its histology, namely, myoepithelial and epithelial. Predominant basaloid cells and cells with less bright eosinophilic cytoplasm are observed. Tumour cells exhibit well-defined nests, islands and chord-like alignments. These cells also form cribriform, tubular, trabecular and solid patterns (Fig. 5.7a, b). About 15% of all cases of adenoid cystic carcinoma contain sebaceous cells as a third cell type. Basophilic cells are actin, p63 and S100 positive, while eosinophilic cells are cytokeratin positive [39].

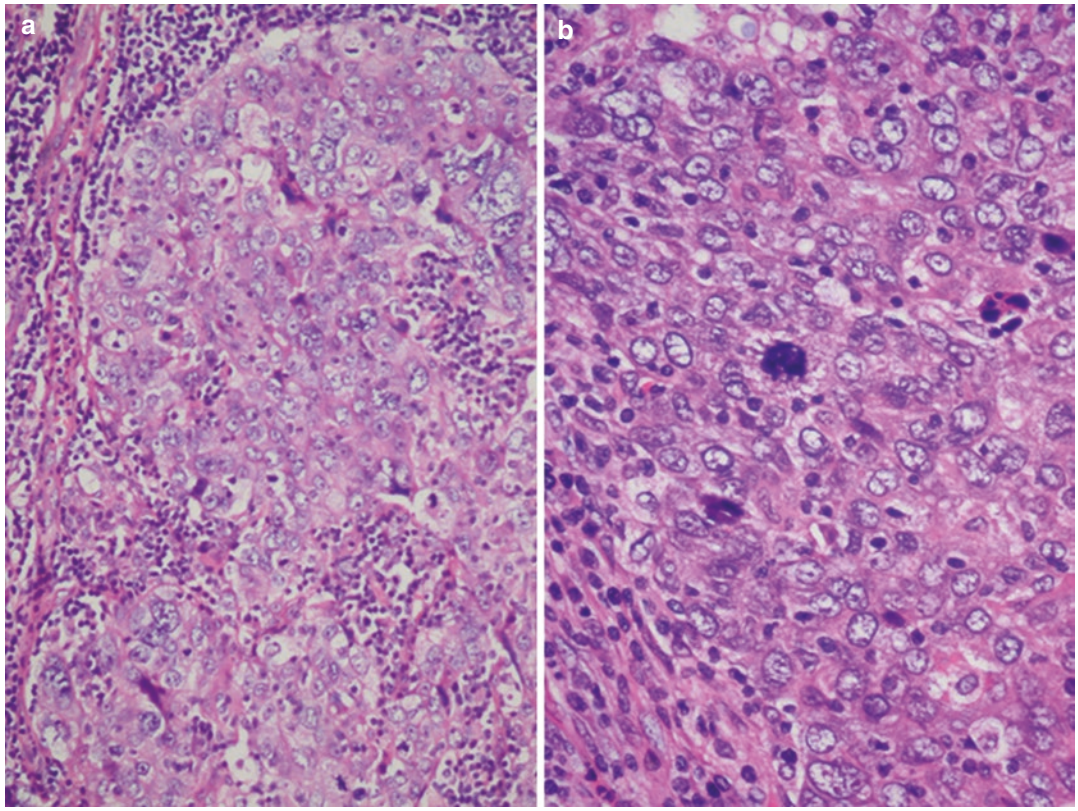

Fig. 5.6 Medullary carcinoma with lymphoplasmocytic stroma (**a**). Atypical medullary carcinoma with solid tumour island and atypical mitosis (**b**)

5.9 Inflammatory Breast Cancer

Inflammatory breast cancer accounts for 1–2% of all cases of breast cancer [40]. Most of the patients are postmenopausal and over the age of 50. Lymphatic obstruction resulting from invasion of derma lymphatics by tumour cells leads to extensive skin oedema associated with insufficient lymphatic drainage. Clinically, it translates into an orange peel appearance (peau d'orange) on the skin of the breast. There is rash and tightness on the breast as well as thickening of the skin of the breast [41]. Clinical characteristics are compatible with pathological findings such as retention of derma lymphatics in most cases. Definitive pathological diagnosis for inflammatory carcinoma is retention of derma lymphatics by tumour cells (Fig. 5.8a, c) [42, 43].

5.10 Metaplastic Carcinoma

Metaplastic carcinoma is a heterogeneous tumour group characterised by a mix of spindle-cell, squamous, chondroid or osseous areas and adenocarcinoma areas [44–46].

- Squamous carcinoma.
- Adenosquamous carcinoma.
- Spindle-cell metaplastic adenocarcinoma.
- Carcinoma with chondroid differentiation (Fig. 5.8b).
- Carcinoma with osseous differentiation.

Primary squamous carcinoma is fairly rare, accounting for less than 1% of all breast carcinomas. Tumours are usually cystic and well-defined, while sometimes they may have irregular margins. Microscopic appearance may be in

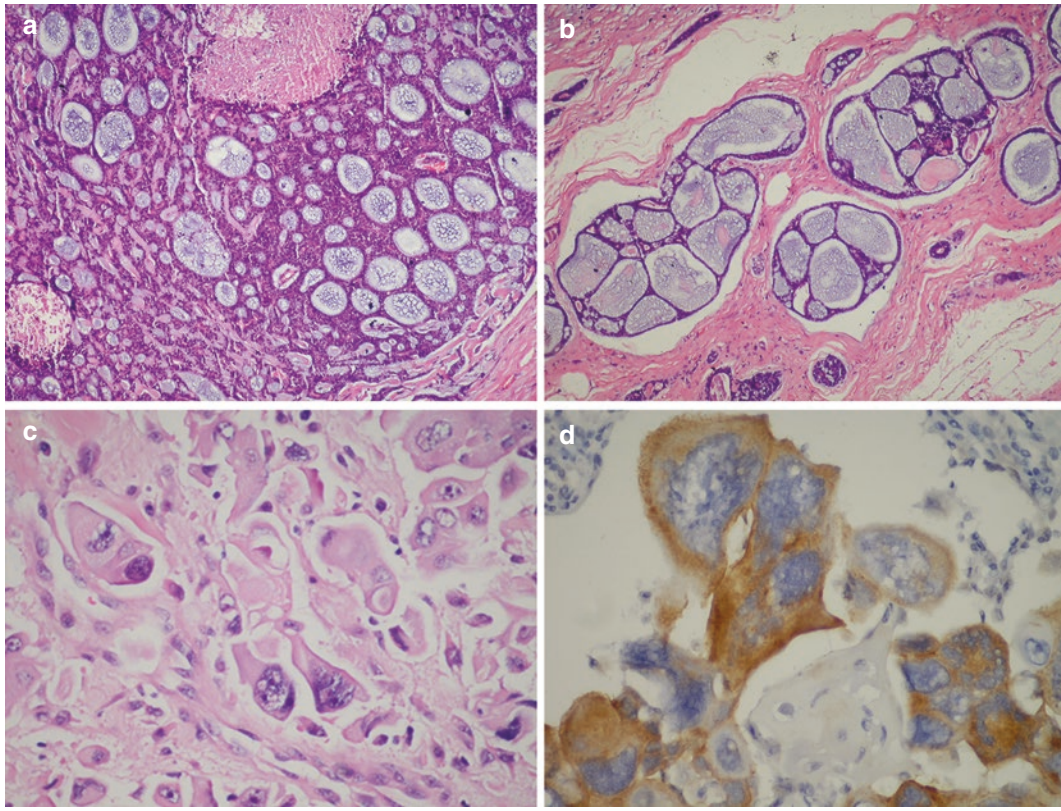

Fig. 5.7 Adenoid cystic carcinoma with microcysts and tumour necrosis (**a**). Adenoid cystic carcinoma with intraluminal secretion (**b**). Carcinoma with choriocarcinomatous features displays nuclear pleomorphism (**c**). Positive staining for human chorionic gonadotropin in carcinoma with choriocarcinomatous features (**d**)

the form of squamous cells, keratinised large cells, acantholytic spindle cells or a combination of these cells. Intercellular bridges, keratin pearls, keratohyalin granules and extensive necrosis areas may be observed [47–49].

5.11 Clear Cell Carcinoma (Glycogen-Rich Carcinoma)

It accounts for 1–3% of all cases of breast cancer. On average, it is seen at the age of around 57. These tumours are characterised either by solid tubulocystic or by papillary growth pattern. The cells have an abundance of transparent cytoplasm and are columnar or polygonal. Nuclei are usually centrally placed (Fig. 5.8d). About 90% of tumours are shown to have PAS-positive (+) material that is non-resistant to diastase in the large granular cytoplasm [50]. Women with palpable masses in the breast may suffer from retractions in the skin of the breast and nipple. Tumour may be 1–8 cm in diameter.

Microscopically, the tumour is usually characterised with solid or chord-forming cell proliferation. However, it may sometimes involve papillary structures and rarely tubular growth pattern.

Tumour cells either form clusters of varying volumes with well-defined margins or exhibit typical infiltration pattern. Transparent cytoplasm of neoplastic cells contain glycogen, not mucin and lipid. Nuclei with hyperchromatic features may be oval, round or irregularly shaped. It exhibits central or eccentric localisation [51, 52]. Its prognosis is as aggressive as that of invasive ductal carcinoma, even more so in some cases. Five-year survival is 33% in cases with glycogen-rich carcinoma and 56% in other invasive breast cancer cases.

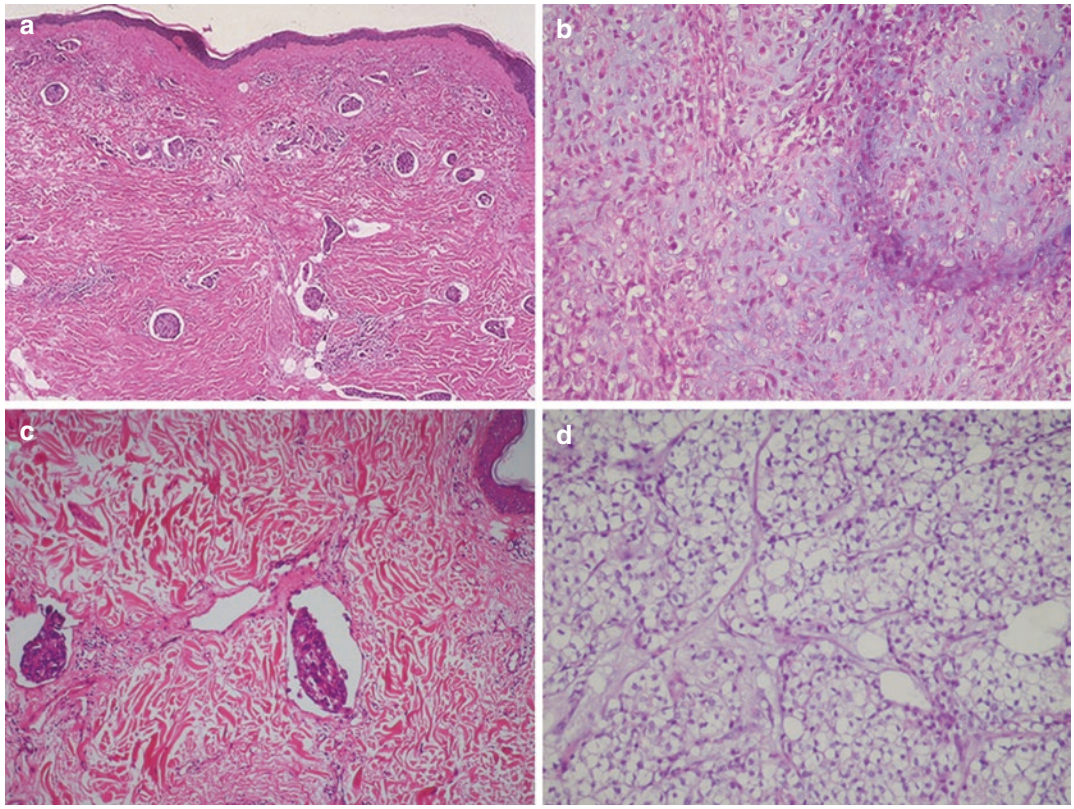

Fig. 5.8 Inflammatory breast carcinoma displays tumour embolus in dermal lymphatics (**a**, **c**). Metaplastic breast carcinoma with chondroid differentiation (**b**). Glycogen-rich breast carcinoma (**d**)

5.12 Carcinoma with Choriocarcinomatous Features

Breast carcinoma can produce various hormones including human chorionic gonadotropin (hCG), adrenocorticotropic hormone (ACTH), placental lactogen and norepinephrine. It has areas that are macroscopically like choriocarcinoma. There may be an abundance of syncytiotrophoblastic giant cells (Fig. 5.7c). Tumour cells are hCG and cytokeratin positive (Fig. 5.7d) [53].

5.13 Conclusion

Breast carcinomas exhibit quite colourful and unique histopathological features under a light microscope. Therefore, the diagnosis is usually made under a light microscope and supported by immunohistochemical examinations. Furthermore, immunohistochemical studies uncover molecular properties (e.g., oestrogen, progesterone and C-erbB2) that provide information about tumour biology that guides the treatment of the patient.

As in all cancer types, the prognosis in breast cancers is directly related to the stage and histopathological features of the tumour. In addition to conventional prognostic features such as tumour size, histological grade, lymph node involvement, and lymphovascular space invasion, molecular and genetic features rendering tumour biology have become important for determining the prognosis of breast carcinomas. All these features should be included in pathology reports in routine practice. These data are frequently used in patient follow-up.

The importance of patient-specific treatments is increasing day by day, which reveals the value of the multidisciplinary approach in breast cancer cases.

Tips and Tricks

- Approximately 60–70% of breast cancers are invasive ductal carcinoma (invasive carcinoma of no special type), and the second most common is invasive lobular carcinoma (8–10%).
- The modified Bloom-Richardson grading system in which tubule formation, nuclear features of tumour cells and mitotic activity are evaluated is used to determine the degree of differentiation of breast cancers (see Table 5.1).
- Tumours with a low modified Bloom-Richardson score have better prognosis.
- Survival expectations are higher in low-grade tumours such as invasive cribriform carcinoma, tubular carcinoma, tubulolobular carcinoma and mucinous carcinoma.
- The prognosis is worse in aggressive subtypes such as invasive micropapillary carcinoma and glycogen-rich breast carcinoma.
- Breast cancers are grouped mainly according to their molecular expression status as luminal A, luminal B, HER-2 positive and basal-like (triple negative).
- The molecular classification of breast cancers plays an important role in the selection of treatment protocols.
- HER-2 overexpression is observed in approximately 20% of all breast cancers.

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