Special Types of Breast Cancer and Non-epithelial Tumors

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13.1 Introduction and Historical Perspective

Since the early twenties of the past century, when according to Dr. Borst only five breast tumor subtypes had been identified, the histopathological classification of breast carcinomas has been profoundly modified, in order to refine its diagnostic efficiency and to embody the results flourishing from basic science [1, 48]. Histopathology has been therefore relentlessly evolving for the accomplishment of two main tasks: providing prognostic information and predicting the response to surgical and medical treatments. In the early seventies, Dr. Haagensen pointed out in his book entitled *Diseases of the Breast* his "…hope to sort out from among them (breast tumors)…, additional characteristic types of breast carcinomas," in an attempt to ascertain their clinical-pathological correlation. He emphasized the need to consider in situ lesions as "fully malignant," recommending the same "drastic" surgical cure usually applied to invasive tumors [2]. This attitude clearly illustrates how physicians have been tailoring the treatment of breast cancer to histopathological features since the beginning of modern oncology.

Pathologists have been deeply involved into breast cancer care by then, developing the concept of invasive breast cancer of special type, which carries obvious "useful clinical correlates and prognostic implications" [3]. Along this line, Japanese authors developed a morphological classification dissecting tubule-papillary, solid-tubular, and scirrhous patterns according to their private risk of relapse [4]. The painstaking evaluation of tumor histology allowed the recognition of different coexisting patterns [5]. In particular, combined features of special type carcinomas have been described in up to 30% of breast carcinomas of NST (no special type). The frequent occurrence of morphological tumor heterogeneity prompted pathologists to recognize mixed types of breast tumors, which may hinder the clinical relevance of histological classification. The overall percentage of the special component has been described according to different series and authors, ranging from over 50% to at least 90% [3]. Actually, the lack of agreement in the cutoff by which a specific histological subtype should be considered as predominant has weakened the clinical impact of subgrouping breast carcinomas [6, 7].

13.2 Mucinous Carcinoma

Mucinous carcinomas have pushing margins with typical gelatinous, soft cut surface.

The neoplastic cells have intracellular mucin with solid, micropapillary, cribriform, and tubular formations, floating in pools of extracellular mucin. "Signet ring" cells may also be present, rarely being the predominant feature [46]. Multiple sections are required in paucicellular form to detect the neoplastic cells to establish the diagnosis. Delicate bands of fibrovascular connective tissue can be observed within the mucous lakes. This characteristic histology should be present in at least 90% of the tumor. Almost all tumors express strong ER and PgR and rarely overexpress HER-2/neu oncoprotein. According to different series, the frequency is up to 2%. They have excellent prognosis with a 10-year overall survival up to 80–100% [8, 9] (Fig. 13.1a).

13.3 Tubular Carcinomas

They are ill-defined, usually small neoplasm with stellate appearance. They are characterized by an irregular haphazard collection of angulated, oval, or elongated well-formed tubules, with a central lumen; typically, they have a single

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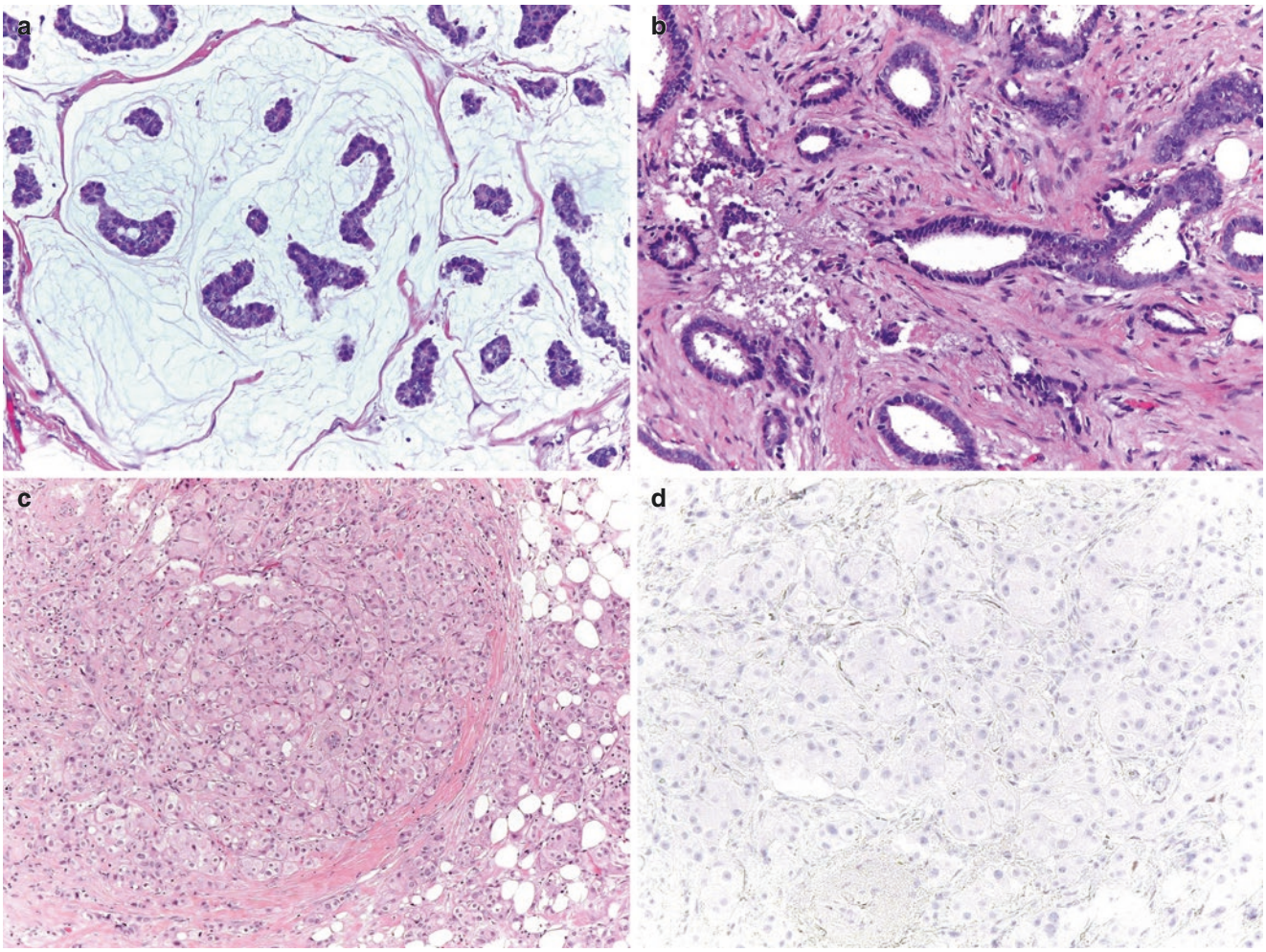

Fig. 13.1 (**a**) Mucinous carcinoma shows neoplastic cells floating in mucous lake. (**b**) Tubular carcinoma with angulated single layer glands in desmoplastic stroma. (**c**) Apocrine carcinoma with eosinophilic large cytoplasm. (**d**) Negative estrogen receptor immunohistology in the very same apocrine carcinoma depicted in (**c**)

layer of small, monomorphic epithelial cells often showing apical "snouts." They show desmoplastic changes and/or stromal elastosis. Tubular carcinoma shows low cytologic atypia with rare mitoses. Calcifications are often present. These features should be present in more than 90% of the lesion. Conventional types of ductal intraepithelial neoplasia (DIN) may be present, and coexistent columnar cell lesions including flat epithelial atypia and lobular neoplasia are common in the proximity of tubular carcinoma. They extensively express ER and PgR and they do not overexpress HER-2/neu oncoprotein. They account of less than 2% of carcinomas, and the survival at 10 years is up to 99–100% [6, 10] (Fig. 13.1b).

13.4 Apocrine Carcinoma

They may show a brownish-tan cut surface. They have cytological features of apocrine cells, and two types of cells could be observed: type A cells (large, with abundant eosinophilic granular cytoplasm with enlarged rounded hyperchromatic nuclei and prominent nucleoli) or type B cells with foamy cytoplasm containing lipid droplets resembling histiocytes or sebaceous differentiation. Tumor cells with bizarre, multilobulated nuclei may be present. The apocrine morphology needs to be seen in more than 90% of the cancer cells. An intraepithelial apocrine component (DIN) with high nuclear grade is often present. They typically express androgen recep-

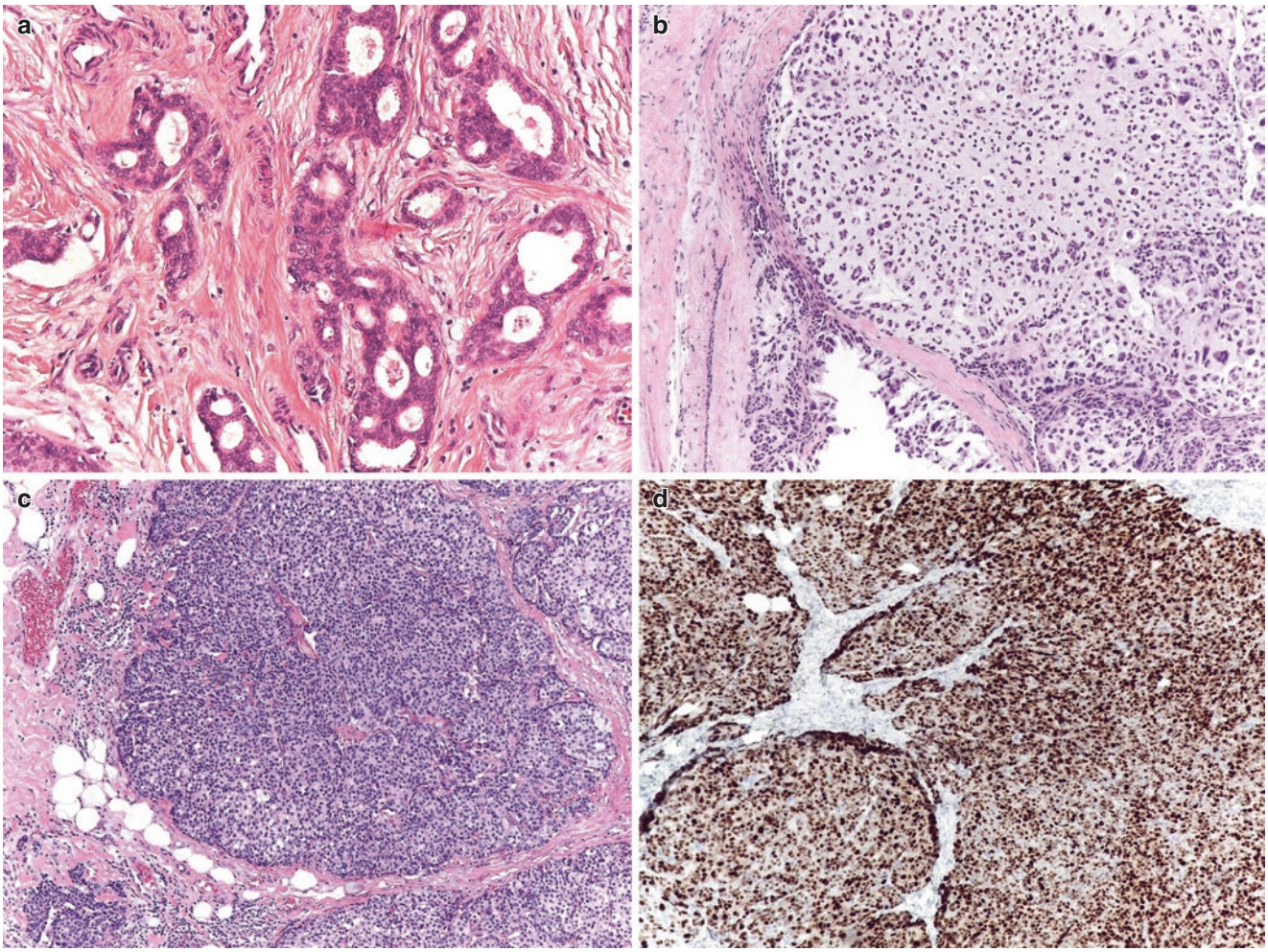

Fig. 13.2 (**a**) Cribriform carcinoma with typical fenestrated glands. (**b**) Metaplastic carcinoma with direct transition from epithelial cells to mesenchymal component (matrix-producing). (**c**) Papillary carcinoma showing solid pattern with fibrovascular core. (**d**) Positive estrogen receptor immunohistology in the very same papillary carcinoma depicted in (**c**)

tors and are triple negative, even though sometimes they may overexpress HER-2/neu oncoprotein. According to different series, they account to 1–4% of the carcinomas. The pure form has a 10-year survival >95% [11, 12] (Fig. 13.1c, d).

13.5 Cribriform Carcinoma

They show angulated and fenestrated cribriform glands as in ductal intraepithelial neoplasia (DIN) of cribriform type with low or intermediate nuclear grade cellularity. Osteoclastic-like giant cells have been reported in some cases. Mitosis is rare. In the mixed cribriform carcinoma form, more than 50% show a cribriform pattern, but areas (10–49%) of non-tubular less differentiated type are also present. In the vast majority of cases, adjacent DIN with cribriform and micropapillary growth pattern is present. They express ER and PgR but usually do not overexpress HER-2/neu oncoprotein. In the pure form, they represent up to 4% of breast carcinomas, with a 10-year survival of 90–100% [6, 13] (Fig. 13.2a).

13.6 Medullary Carcinomas

They are well circumscribed, with a soft, gray/tan cut surface. Medullary carcinomas have histologic circumscription with pushing, expansive margins (smooth, rounded contour). They grow in a syncytial pattern of solid clusters of tumor cells forming anastomosing cords and sheets. Neoplastic cells have severe nuclear atypia, prominent nucleoli, and

indistinct cell borders with high mitotic count. The lymphoplasmacytic infiltration (composed almost entirely of either lymphocytes or plasma cells) is often present throughout the tumor. They are triple-negative carcinomas with a good prognosis if strict histologic criteria are accomplished (up to 95% survival) [14, 15].

13.7 Metaplastic Carcinomas

They are carcinomas with a variable percentage of mesenchymal differentiation. They could be subdivided in two categories: carcinomas with squamous and/or spindle cell metaplasia (low-grade adenosquamous carcinoma, fibromatosis-like metaplastic carcinoma, squamous cell carcinoma, and spindle cell carcinoma) and carcinomas with heterologous metaplasia.

Carcinomas with heterologous metaplasia are poorly differentiated duct carcinomas associated with mesenchymal elements, most commonly chondroid, osseous, and rhabdomyoid, but also lipomatous and angiomatous. The heterologous elements can be either well differentiated with minimal atypia or sarcomatous as for tumors originating in soft tissues. If there is a direct transition from epithelial to the mesenchymal components without an intervening spindle cell component, the term "matrix-producing carcinoma" has been used (Fig. 13.2b).

Metaplastic carcinomas are triple negative, although occasional tumors with focal positivity for ER and/or HER-2/neu are encountered in the mesenchymal component. The frequency is up to 5% of the carcinomas, and the overall survival at 5 years is 18–81% according to stage at the presentation [16, 17].

13.8 Squamous Cell Carcinomas

Squamous cell carcinomas arising in the breast parenchyma are exceedingly rare and usually represent metastatic squamous carcinoma. In their pure form, they often appear as cystic lesion with keratin debris, simulating necrosis. Intercellular bridges and keratin pearls are observed and spindle or acantholytic in appearance as well. They are triple-negative carcinomas with a survival at 5 years ranging from 81 to 46.9% if metastases (both regional and distant) are absent or present at the time of diagnosis [18].

13.9 Papillary Carcinoma

Papillary carcinomas have a predominantly papillary morphology (>90%) harboring papillae formed by malignant epithelial cells and fibrovascular cores. If the individual papillary fronds become crowded and are not separated by spaces, the term solid papillary carcinoma is used (Fig. 13.2c, d). An intraepithelial component (DIN), often also demonstrating a papillary architecture, is usually present. Neuroendocrine features have been consistently reported. ER and PgR positivity and HER-2/neu negativity is the most frequent phenotype. The prevalence varies according to different series from 0.04 to 2.7% with an overall survival of >90% at 5 years [19].

13.10 Micropapillary Carcinoma

Micropapillary carcinomas are arranged in micropapillary, tubuloalveolar, or morular clusters and lie within optical clear stromal spaces (shrinkage artifact), simulating lymphatic/vascular spaces. They lack fibrovascular cores, sometimes containing mucinous material. Typically, the cells have the apical surface polarized to the outside, finely granular or dense eosinophilic cytoplasm, and intermediate-to-high-grade nuclei with frequent mitoses. The majority of tumors are associated with an intraductal component of micropapillary and cribriform patterns and show extensive peritumoral vascular invasion paralleled by a prevalence of axillary lymph node metastasis significantly higher than ductal carcinoma NST. They variably express ER, PgR, and HER-2/neu [20].

13.11 Salivary Gland-Type Carcinomas

The most common subtype of salivary gland-type carcinomas is represented by adenoid cystic carcinoma. These tumors are usually well circumscribed with small cystic areas. They are formed by adenoid and basaloid cells forming true glandular spaces and pseudo-lumina. Sebaceous cells and squamous metaplasia of luminal cells may be present. They grow with an irregular, infiltrating pattern showing solid, cribriform, and trabecular-tubular arrangements, even if a mixture pattern may often be observed. As for their salivary gland counterpart, high-grade carcinomas have >30% of solid growth, while well-differentiated forms show exclusively a cyst and glandular appearance. Tumors with an intermediate differentiation show <30% of solid pattern. Mitotic count is usually low [21]. They are triple-negative carcinomas with an excellent prognosis when well differentiated (up to 90%) at 10 years. The remaining subtypes of salivary gland-type carcinomas, i.e., mucoepidermoid and acinic cell carcinomas, are exceedingly rare and resemble morphologically their salivary gland counterpart.

13.12 Rare Types of Breast Carcinoma

Few cases of tubulo-lobular carcinoma have been reported. These tumors are classic type of lobular carcinomas intermingled with well-formed single layer glands. Other very uncommon breast cancer subtypes are represented by lipid-

rich carcinoma, which shows extensive foamy appearance due to intracytoplasmic lipid accumulation, glycogen-rich carcinoma, secretory and hypersecretory carcinoma, and osteoclast-like giant cell carcinoma. Neuroendocrine small cell carcinomas have morphological features similar to their lung counterpart.

13.13 Non-epithelial Tumors

Primary mesenchymal tumor of the breast represents a heterogeneous group of neoplasm by far less frequent than pure epithelial neoplasm. Non-epithelial neoplasm could be subdivided in mixed (fibroepithelial neoplasms) and in pure mesenchymal form [22]. The most relevant entities of the first group are fibroadenomas and phyllode tumors. Fibroadenoma is a well-circumscribed biphasic (fibroepithelial) neoplasm showing stromal proliferation around glands (pericanalicular pattern) or compressing cleft-like ducts (intracanalicular pattern). The ducts are lined by two cell layers of luminal epithelial cells and myoepithelial cells. Fibroadenomas and phyllode tumors could be considered a continuum degree of progressive malignancy of the stromal component, which in the high-grade phyllode tumors is definitely sarcomatous (so-called cystosarcoma phyllodes). The stroma is loosely cellular, with regular spindled cells and collagen, and it may sometimes exhibit multinucleated giant cells, extensive myxoid changes, or hyalinization [23].

Areas of stromal hypercellularity may be seen within a fibroadenoma, leading to a diagnosis of cellular fibroadenomas because the typical leaflike architecture of phyllode tumors is absent or focal. Mitotic figures are uncommon. The epithelial component of fibroadenoma can show varying degrees of epithelial hyperplasia, particularly in young women. Squamous or apocrine metaplasia may also occasionally be observed. Whenever papillary apocrine changes, cysts, epithelial calcifications, and sclerosing adenosis occur, these tumors have been classified as complex fibroadenomas. Rarely, atypical ductal hyperplasia, lobular neoplasia, ductal intraepithelial neoplasia (DIN), or carcinoma may occur within fibroadenomas [24].

Benign phyllode tumors resemble intracanalicular fibroadenomas, and the hallmark of the tumor is the formation of stromal leaflike processes protruding into cystic spaces. Phyllode tumors are classified as benign, borderline, and malignant. In benign tumors, the mitotic count should not exceed 2 × 10 HPF. Borderline and malignant phyllode tumors are distinguished on the basis of the degree of stromal cellularity, stromal atypia, stromal overgrowth, tumor borders, and mitotic activity (3–9 × 10 HPF in borderline and >9 in malignant phyllode tumors). Local recurrences can occur in all types of phyllode tumors, with the highest prevalence for the malignant type, and distant metastases have been reported almost exclusively in malignant tumors [25, 26].

The second group of pure mesenchymal tumors mirrors the morphological features of their counterparts primarily arising in soft tissues [27]. Breast sarcomas must be differentiated from metaplastic carcinoma, due to their different surgical and clinical management. As a matter of fact, the sarcomatous component of a triple-negative carcinoma with extensive metaplastic features may outgrow the epithelial component, thus leading to a misdiagnosis of primary pure sarcoma. Therefore, focal remnants of carcinoma should be scrutinized in tumors showing prominent mesenchymal differentiation.

Vascular lesions include benign hemangioma and angiomatosis, atypical vascular proliferations, and angiosarcomas. Angiosarcomas may develop following radiation therapy for breast cancer or, less commonly, as primary neoplasms arising in patients with no prior history of radiation [28–31].

Tumors showing adipocyte differentiation include lipoma, a benign tumor composed of mature adipocytes without atypia, sometimes incorporating small vessels (angiolipoma), and liposarcoma that represents its malignant counterpart [32].

Schwannoma and neurofibroma of the breast derive from the sheath of peripheral nerves; most of them arise in the mammary subcutaneous tissue, even if parenchymal lesions have also been described [33].

Primary granular cell tumor of the breast is a benign neoplasm derived from Schwann cells of peripheral nerves and composed of compact nests of cells with prominent eosinophilic cytoplasmic granules, which are PAS positive and strongly immunoreactive for CD68 and S100 protein [34].

Myofibroblastoma is a benign, well circumscribed, pseudoencapsulated mammary stromal spindle cell tumor with prominent myofibroblastic differentiation, immunoreactive for desmin, smooth muscle actin, and CD34. They show broad bands of hyalinized collagen in the absence of any mammary duct and lobules [35].

Desmoid-type fibromatosis of the breast is a locally infiltrative, histologically low-grade proliferation of spindle cells and collagen. It rarely occurs within the breast parenchyma, frequently arising from the pectoral fascia [36].

Nodular fasciitis is a self-limiting, mass-forming fibroblastic/myofibroblastic proliferation. Inflammatory myofibroblastic tumor is a usually low-grade neoplasm composed of myofibroblastic spindle cells with prominent admixed inflammatory cells, most commonly plasma cells [37].

Pseudoangiomatous stromal hyperplasia is a benign disease in which the stromal cells form a complex pattern of anastomosing empty spaces in a dense collagenous stroma coexisting with duct and lobular epithelium. The spaces rarely contain a few red blood cells. Myofibroblasts (usually CD34 and calponin immunoreactive) line the slit-like spaces, resembling endothelial cells [38].

Leiomyoma and leiomyosarcoma of the breast show distinct smooth muscle differentiation [39, 40].

Pure rhabdomyosarcoma and osteosarcoma of the breast are composed of cells showing varying degrees of skeletal muscle differentiation or osteoid formation [41, 42].

Periductal stromal tumor is a rare lesion of low-grade sarcoma behavior [43].

The most frequent subtypes of primary lymphomas of the breast are diffuse large B-cell non-Hodgkin lymphomas, not otherwise specified (DLBCL), extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) type, and follicular lymphoma. Rare cases of Burkitt lymphoma, lymphoblastic lymphoma of either B-cell or T-cell type, and peripheral T-cell lymphomas have also been reported. Hodgkin and non-Hodgkin lymphomas originating from nodal sites may secondarily involve the breast [44].

Metastasis to the breast represents up to 1.3% of all mammary malignant tumors, including melanoma and carcinomas of the lung, ovary, prostate, kidney, and stomach [45].

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