# Infiltrating Carcinoma of No Special Type

# 14

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Infiltrating breast carcinoma is a category of malignant epithelial tumors characterized by adjacent tissue invasion and distance metastasis. This category includes several microscopic types that differ from one another from morphological, immunohistochemical, molecular, and prognostic points of view. It is currently known that all these microscopic types have their origin in the terminal duct/lobular unit. The WHO 2012 classification categorized both invasive carcinomas of no special type (NST), previously termed as ductal carcinomas, and lobular and other special and rare subtypes of carcinomas, as infiltrating epithelial tumors, only distinguishing between these types in terms of morphological appearance, but disregarding the origin of proliferation [1].

## 14.1 NST Infiltrating Carcinoma

The NST infiltrating carcinoma, also called ductal, classic, or not otherwise specified (NOS), is the most common form, accounting for 40–75% of invasive breast carcinomas [1]. Its origin is in the epithelium of ducts and acini. By definition, it describes a heterogeneous group in which the microscopic appearance is uncharacteristic of any of the specific microscopic variants of breast carcinoma (like tubular, medullary carcinoma, etc.). Grossly, the tumor size is highly variable, from a few millimeters (Fig. 14.1) to more than 10 cm (Fig. 14.2) with infiltrating edges, while its shape may be stellate or nodular (Figs. 14.3, 14.4, and 14.5) but usually solid, and rarely with cystic changes determined by tumor necrosis (Fig. 14.6). Tumor consistency is high and sometimes the tumor is so hard that its hardness is comparable to that of wood. It is rare, however, due to the minor stromal component, that the tumor consistency is soft. The color varies between white and gray with yellow striations (confirming the presence of elastosis in the tumor) but sometimes has a yellow color (Fig. 14.7) or red color due to intratumor hemorrhage (Figs. 14.8 and 14.9). When the tumor is high-stage, it invades the skin and can produce skin ulceration (Figs. 14.10, 14.11, and 14.12).

The microscopic diagnosis of NST type is based on the growth pattern of the tumor. Microscopic appearance is highly variable and can be challenging for an inexperienced pathologist because the tumor cells may be present in clusters, nests, cords, tubules (with evident central lumen), or isolated in a more or less abundant stroma (Figs. 14.13, 14.14, 14.15, 14.16, and 14.17). These structures are comprised of only epithelial tumor cells and are not accompanied by myoepithelial cells or basement membrane (Fig. 14.18). Tumor cells are sometimes arranged in a "single file" or a targetoid pattern, as in infiltrating lobular carcinoma, but they have a completely different morphologic appearance and they are cohesive (Fig. 14.19). Some pathologists, however, indicate that the presence of the lumina itself is in favor of NST (ductal) differentiation, because lobular in situ carcinomas or invasive carcinomas lack lumina [2]. Tumor cells are typically round or polygonal, with abundant and eosinophilic cytoplasm, and sometimes with vacuolated cytoplasm or signet-ring appearance, and have nuclei with variable pleomorphism and with one or more evident nucleoli (Figs. 14.20, 14.21, and 14.22). Mitotic activity varies from one tumor to another or from one microscopic field to another within the same tumor (Fig. 14.23). Tumor stroma is highly variable in quantity, and in some tumors, it is cellular and fibroblastic, while in others it may be hypocellular with extensive hyalinization. The stroma may have stromal elastosis (periductal and perivascular), necrosis, as well as inflammatory lymphoplasmacytic infiltrate, sometimes with a granulomatous character and microcalcifications (Figs. 14.24, 14.25, 14.26, and 14.27). Rarely, the tumor may present minor or sometimes extensive hemorrhage, which may obstruct the tumor cells and may lead to difficulty in microscopic interpretation (Fig. 14.28). Some tumors may be associated with perineural invasion. The presence of

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vascular tumor emboli can be better appreciated at the periphery of the tumor. The tumor cells, however, must be detected within vascular channels lined by endothelial cells and not within artifactual spaces that have been caused by tissue shrinkage occurring during the processing of the tissue (Fig. 14.29).

Also, areas of in situ carcinoma (ductal or lobular or both, with identical microscopic grade as in the infiltrating component) can be detected at the periphery of the tumor in more than 80% of cases (Figs. 14.30 and 14.31). Immunohistochemically, the tumor cells have a variable positivity for the ER, PR, HER2. E-cadherin is typically positive, but positivity may be low in some cases (Fig. 14.32). Also, E-cadherin-positivity does not equal ductal differentiation in the context of appropriate histologic features, and one should be aware of the limitation in the use of E-cadherin immunostaining. The Ki67 index is highly variable and it correlates with the tumor microscopic grade.

Regarding differential diagnosis, it should be emphasized that the diagnosis of NST infiltrating ductal carcinoma is a diagnosis of exclusion. It is a form of carcinoma that does not meet classic criteria for other microscopic types. As a rule, it is advisable that in difficult situations, a diagnosis of NST infiltrating ductal carcinoma be preferred, especially when the tumor reveals tubular structures, because most authors consider that NST infiltrating ductal carcinoma is the most common form of breast cancer. The most important differential diagnosis is with infiltrating lobular carcinoma. The appearance of the latter carcinoma is characterized by the presence of small and uniform dyscohesive cells arranged in "single file" in its classic form. Sometimes, NST infiltrating carcinoma may also present a linear "single file" arrangement, where the abundant fibrous stroma compresses the trabeculae of tumor cells (Fig. 14.33). NST infiltrating ductal carcinoma cells are more uneven and more pleomorphic, but especially more cohesive than, those of infiltrating lobular carcinoma. Immunohistochemical stains (with E-cadherin and p120 catenin) can help differentiate between the two lesions, but with some limitations (Fig. 14.34). The solid subtype of infiltrating lobular carcinoma must be distinguished from poorly differentiated NST infiltrating ductal carcinoma in which the tumor cells are arranged in large nests and glandular lumen formation is rarely seen (Fig. 14.35). In this case, however, differential diagnosis is favored by the fact that tumor cells of NST infiltrating ductal carcinoma are more pleomorphic. If the cells are small, uniform, and arranged predominantly in nests, the question of alveolar subtype of infiltrating lobular carcinoma arises (in the alveolar subtype of infiltrating lobular carcinoma, however, cells have more eosinophilic cytoplasm and lack cohesiveness). A clue in recognizing the lobular infiltrating carcinoma is the presence of intracytoplasmic lumina with eosinophilic material, but one must be aware of the fact that rare NST carcinomas can display similar features (Figs. 14.36 and 14.37). The increased amount of intracytoplasmic mucin must be differentiated by using special stains for the presence of glycogen (PAS-positive) or lipids (Sudan III-positive), characteristic of breast carcinoma variants containing abundant lipids and of clear cell carcinoma abundant in glycogen. If the cells appear uniform with low and elongated cytoplasm arranged in nests, NST carcinoma must be differentiated by a carcinoma with neuroendocrine differentiation (the latter is positive for neuroendocrine markers such as chromogranin, synaptophysin, etc.) (Fig. 14.38). The occasional presence of extracellular mucin must be differentiated from a mucinous carcinoma, and the presence of an abundant inflammatory infiltrate of lymphoplasmacytic type in the stroma should not be confused with the similar appearance of medullary carcinoma, especially when the tumor has "pushing" margins. Finally, NST infiltrating carcinoma should not be confused with adenosis, a benign lesion that can sometimes mimic an infiltrating carcinoma (but in which epithelial cells do not have atypia and myoepithelial cells can be distinguished in most of the cases).

The prognosis of NST invasive carcinoma of the breast is variable and depends on several prognostic parameters, which will be discussed in detail in another chapter.

**Fig. 14.1** Invasive carcinoma of NST subtype with small size (10 mm of diameter)

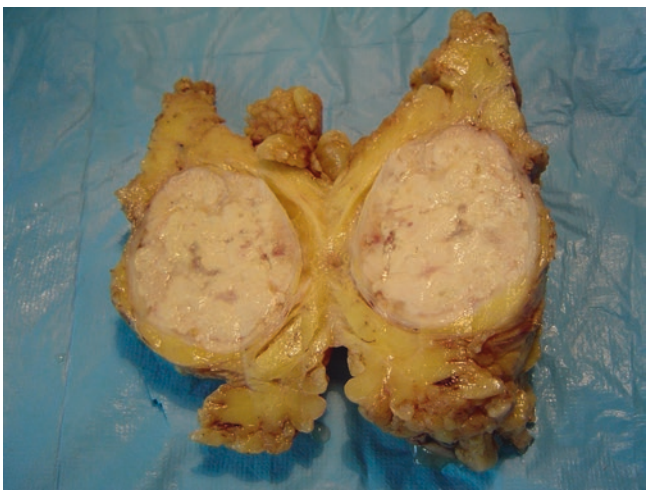

**Fig. 14.2** Invasive carcinoma of NST subtype with large size (locally advanced tumor)

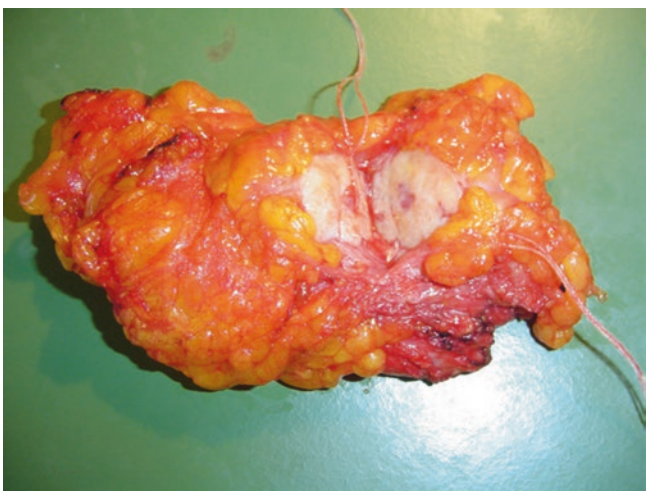

**Fig. 14.3** Invasive carcinoma of NST subtype with lobulated margins

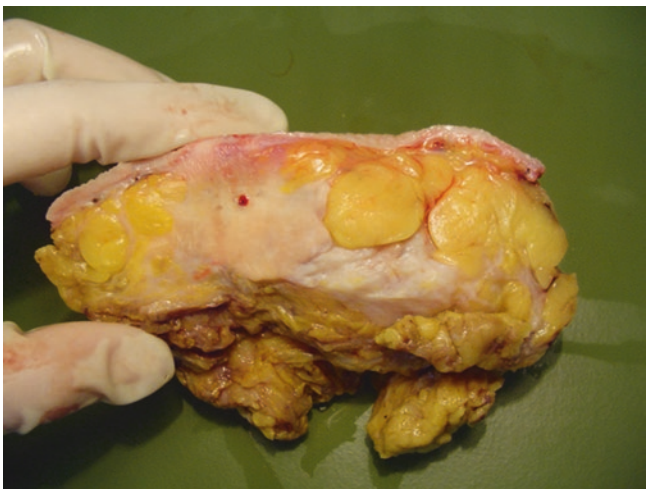

**Fig. 14.4** Invasive carcinoma of NST subtype with infiltrating margins

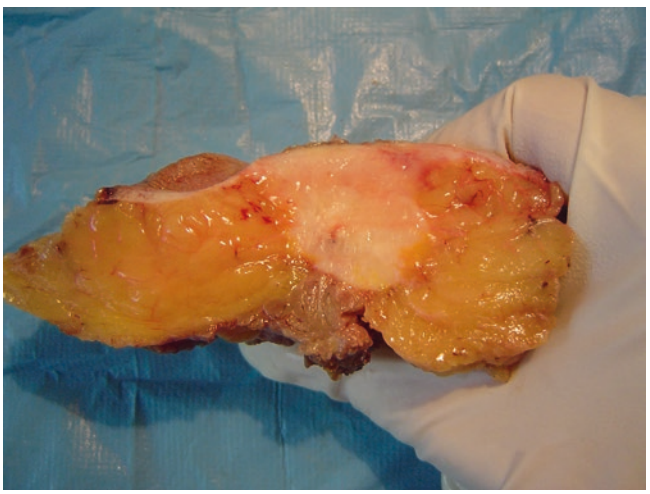

**Fig. 14.5** Invasive carcinoma of NST subtype with partially infiltrating margins

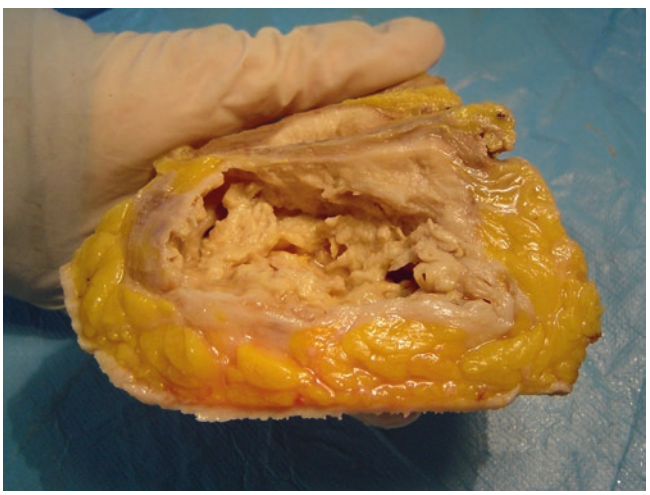

**Fig. 14.6** Invasive carcinoma of NST subtype with cystic changes determined by central tumor necrosis

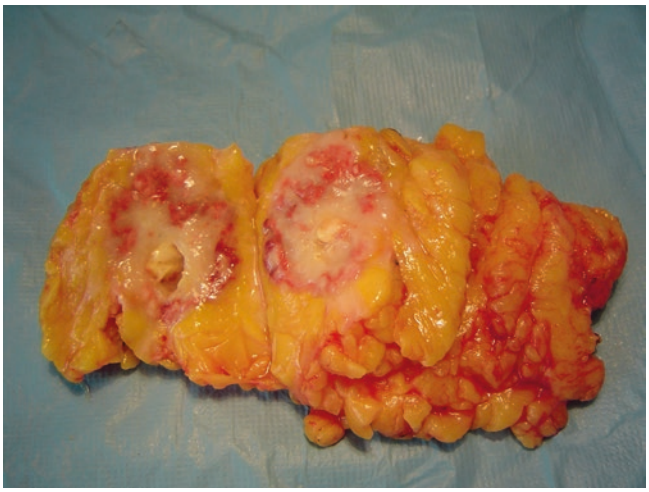

**Fig. 14.7** Invasive carcinoma of NST subtype with cystic changes and yellow color on the section surface

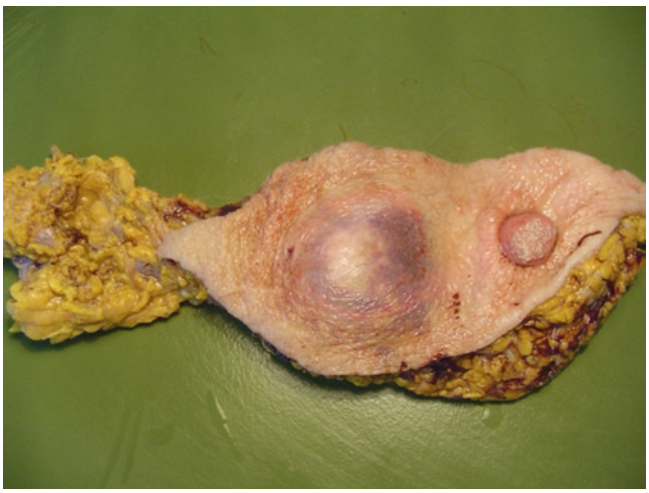

**Fig. 14.10** High stage Invasive carcinoma of NST subtype infiltrating the skin

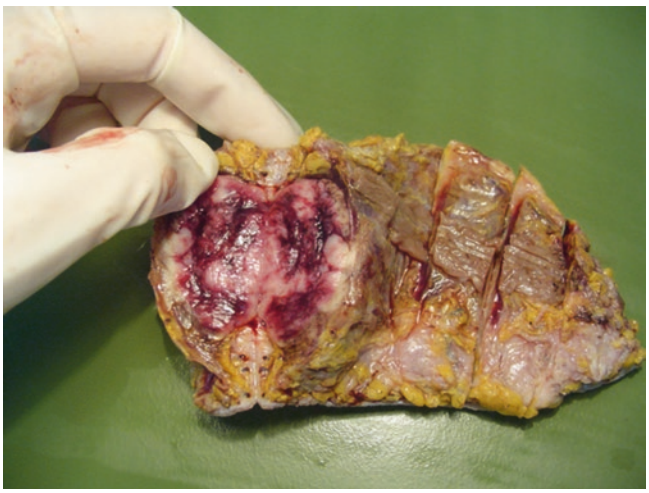

**Fig. 14.8** Invasive carcinoma of NST subtype with red color due to intratumor focus of hemorrhage

**Fig. 14.11** Invasive carcinoma of NST subtype infiltrating the skin and the nipple

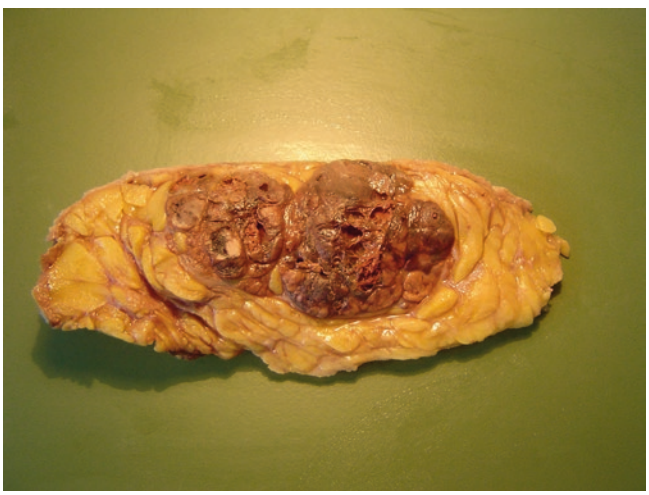

**Fig. 14.9** Invasive carcinoma of NST subtype with red color and cystic spaces due to intratumor hemorrhage

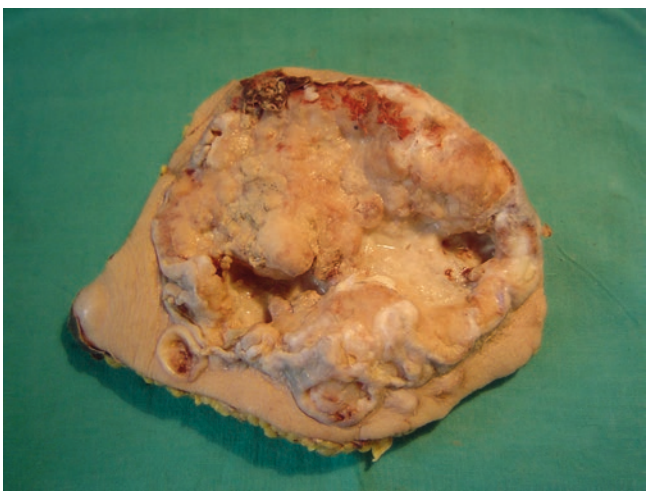

**Fig. 14.12** Invasive carcinoma of NST subtype with massive skin ulceration

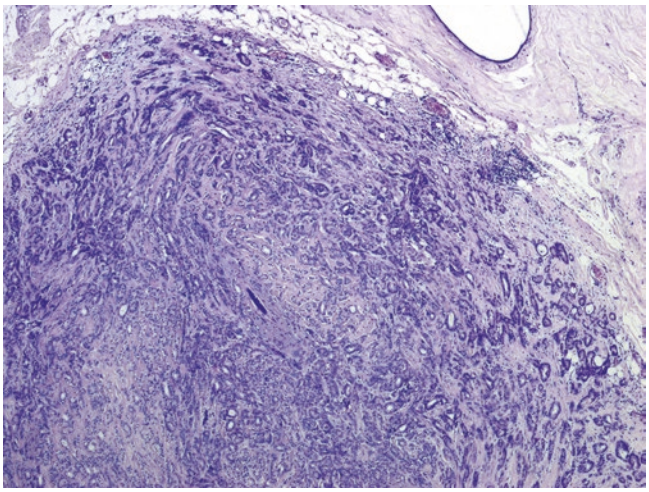

**Fig. 14.13** Invasive carcinoma of NST subtype: microscopic architectural and cellular appearance is highly variable

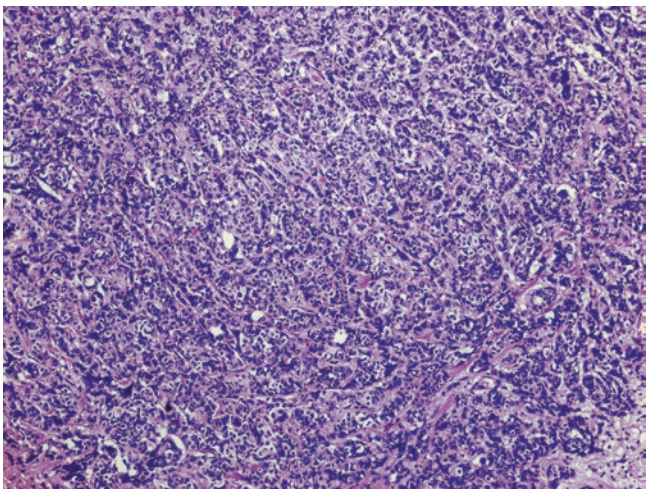

**Fig. 14.16** Invasive carcinoma of NST subtype: trabecular and alveolar arrangement

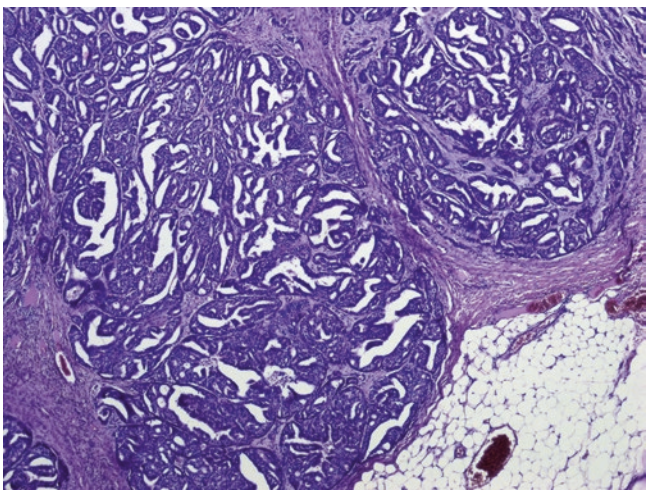

**Fig. 14.14** Invasive carcinoma of NST subtype: in this case, the tumor cells are mostly arranged in tubules

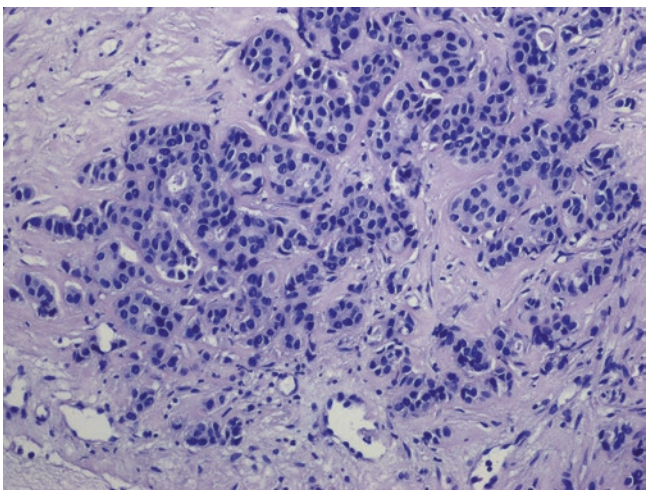

**Fig. 14.17** Invasive carcinoma of NST subtype: alveolar arrangement of the tumor cells

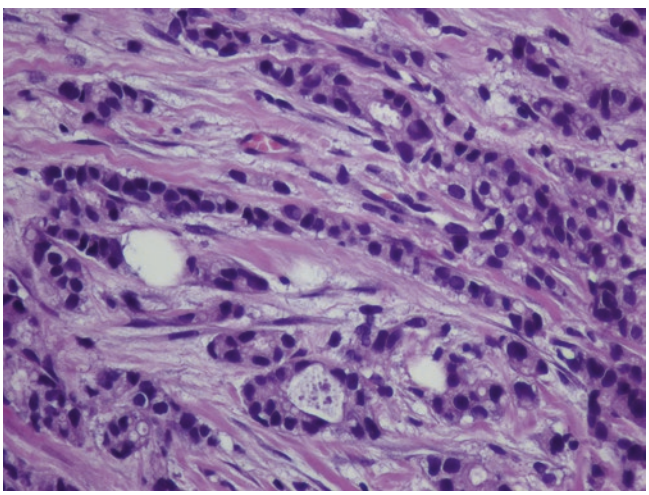

**Fig. 14.15** Invasive carcinoma of NST subtype: in this case, the tumor cells are mostly arranged in cords

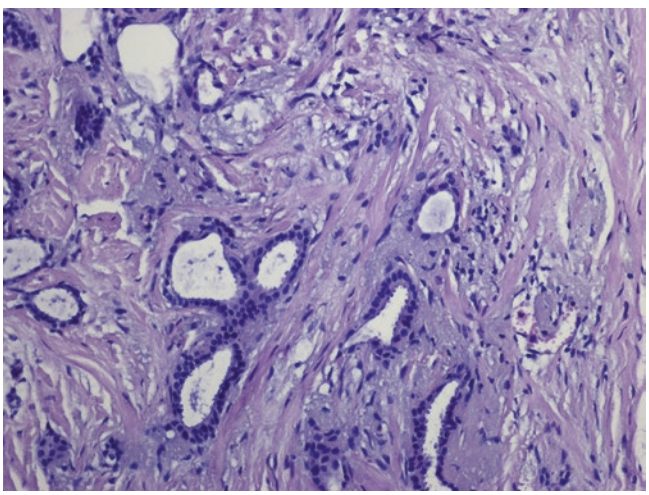

**Fig. 14.18** Invasive carcinoma of NST subtype: tubular structures are composed of only epithelial tumor cells, which are not accompanied by myoepithelial cells or basement membrane

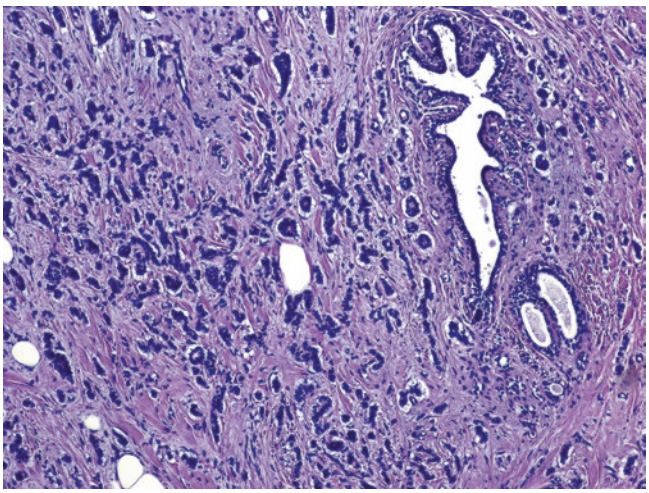

**Fig. 14.19** Invasive carcinoma of NST subtype: in this case, the tumor cells are arranged in a targetoid pattern around a normal duct, mimicking an infiltrating lobular carcinoma; however, they have a completely different morphologic appearance and are associated with tubular formation

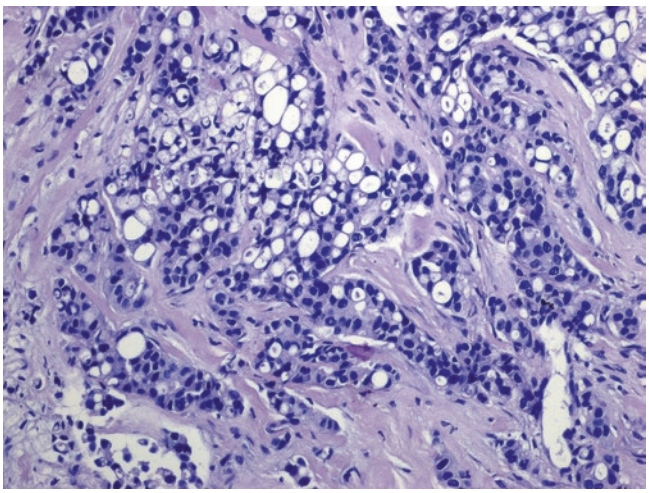

**Fig. 14.22** Invasive carcinoma of NST subtype: most of the tumor cells have a signet-ring appearance; in this case, however, E-cadherin was positive, differentiating from an invasive lobular carcinoma with signet-ring cells (not shown here)

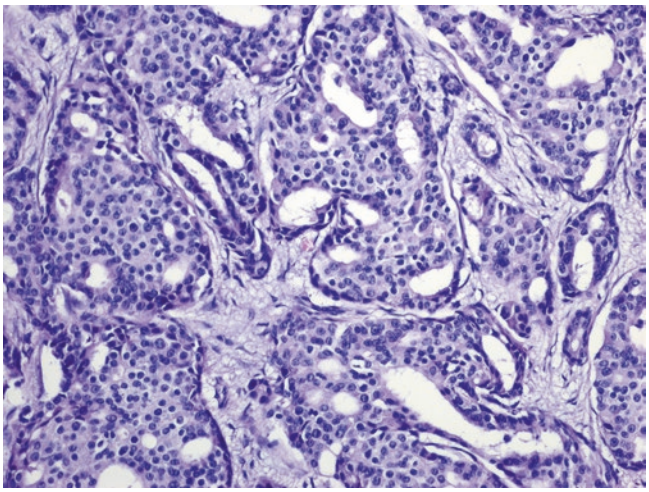

**Fig. 14.20** Invasive carcinoma of NST subtype: the tumor cells are typically round or polygonal, with abundant and eosinophilic cytoplasm

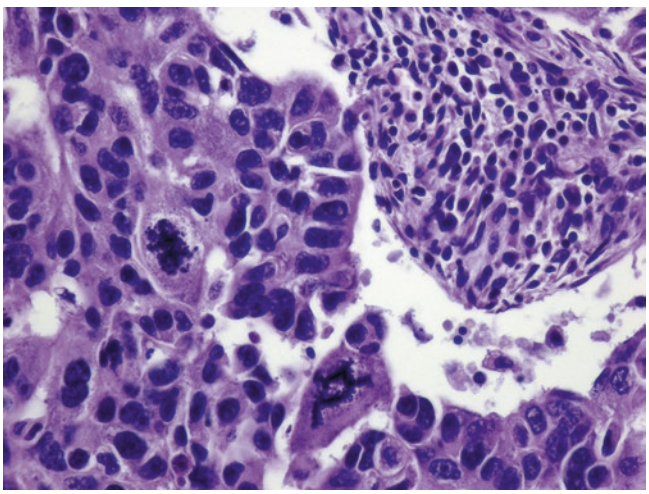

**Fig. 14.23** Invasive carcinoma of NST subtype: high-grade tumor with numerous atypical mitotic figures

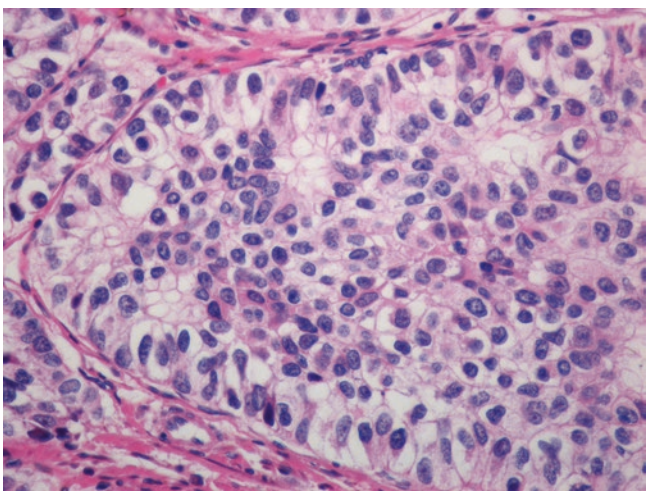

**Fig. 14.21** Invasive carcinoma of NST subtype: sometimes the tumor cells have a vacuolated cytoplasm

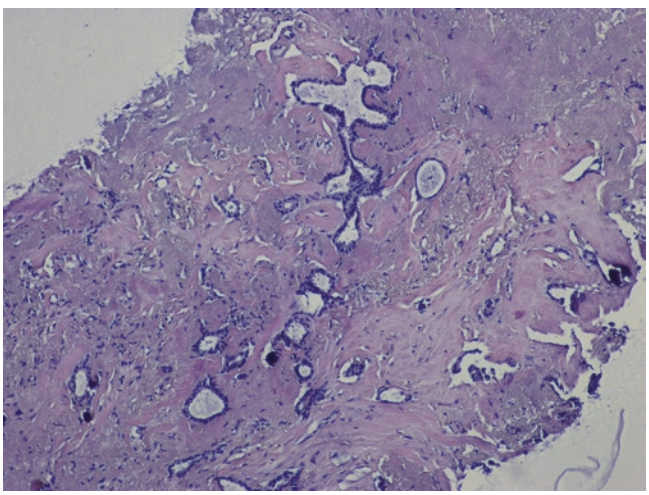

**Fig. 14.24** Invasive carcinoma of NST subtype: the stroma displays abundant stromal elastosis

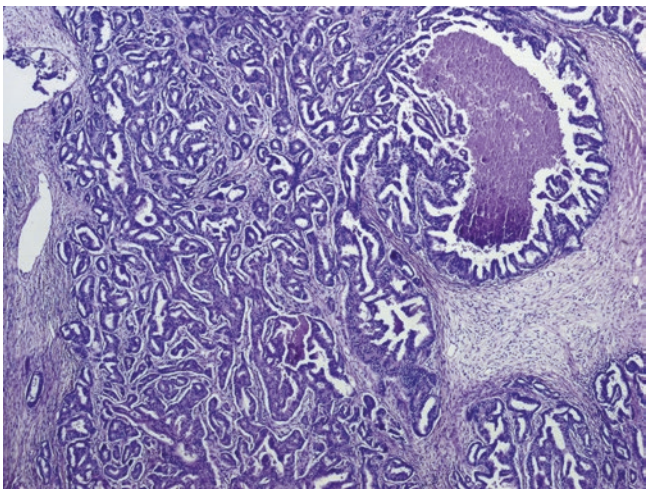

**Fig. 14.25** Invasive carcinoma of NST subtype with focal necrosis

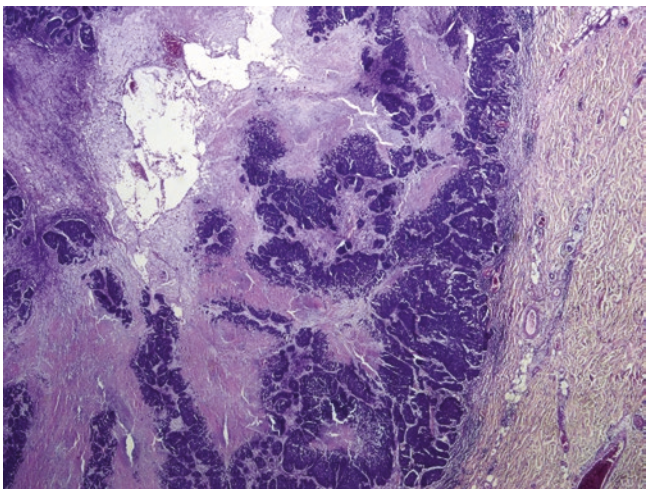

**Fig. 14.26** Invasive carcinoma of NST subtype with extensive geographic-type necrosis (typically associated with basal-like invasive carcinomas)

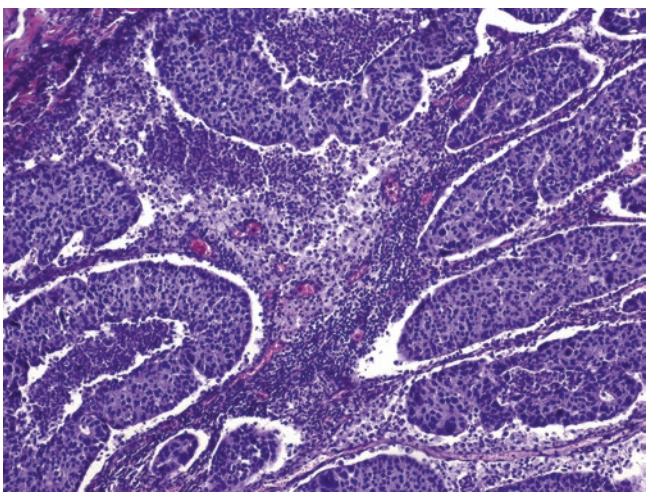

**Fig. 14.27** Invasive carcinoma of NST subtype presenting an inflammatory lymphoplasmacytic infiltrate, with numerous macrophages within the tumor stroma

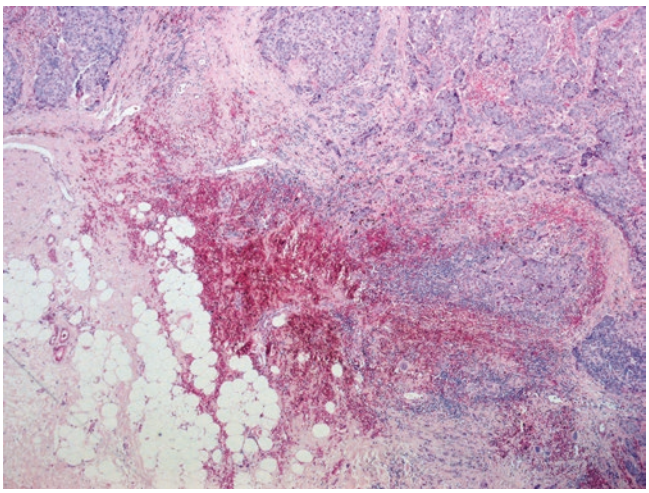

**Fig. 14.28** Invasive carcinoma of NST subtype: the tumor presents minor hemorrhagic area

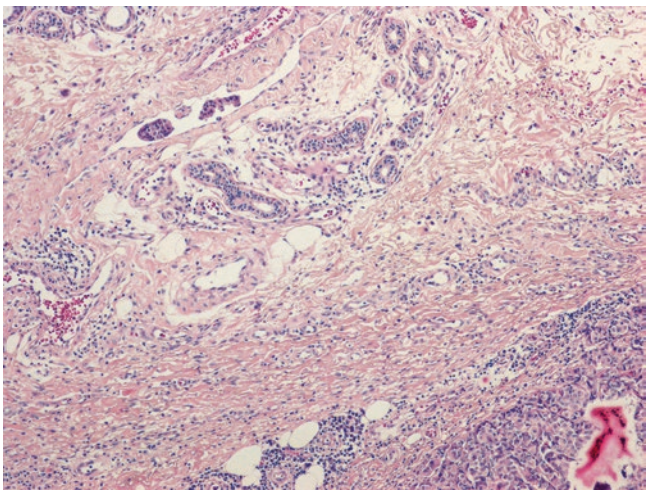

**Fig. 14.29** Invasive carcinoma of NST subtype: at the periphery and outside of the tumor border, the presence of vascular tumor emboli can be better appreciated

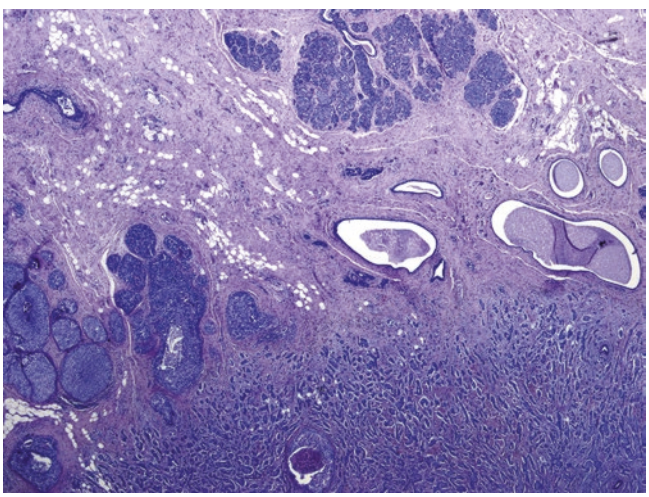

**Fig. 14.30** Invasive carcinoma of NST subtype: areas of both in situ ductal and lobular carcinoma are detected at the periphery of this tumor

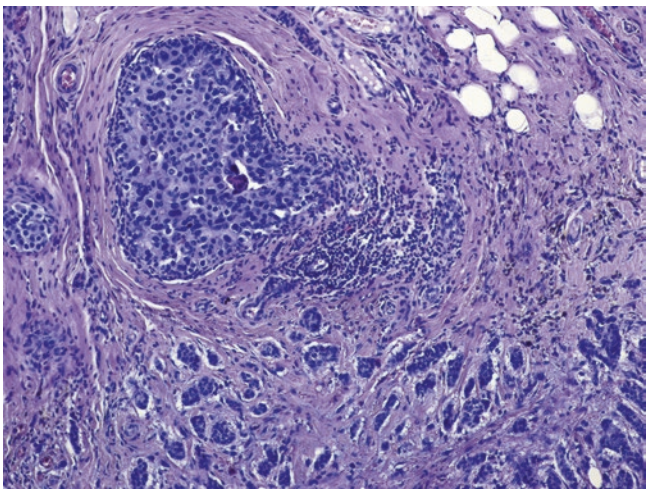

**Fig. 14.31** Invasive carcinoma of NST subtype: identical morphological appearance of the tumor cells is present in both in situ and infiltrating component

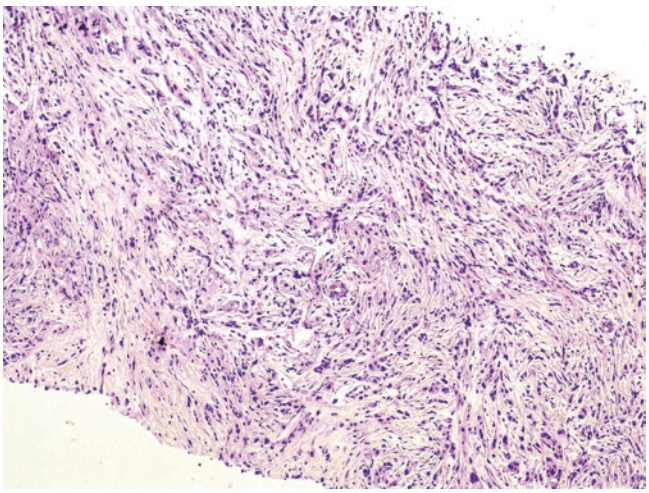

**Fig. 14.33** Invasive carcinoma of NST subtype: tumor cells are arranged predominantly in trabeculae, mimicking an invasive lobular carcinoma

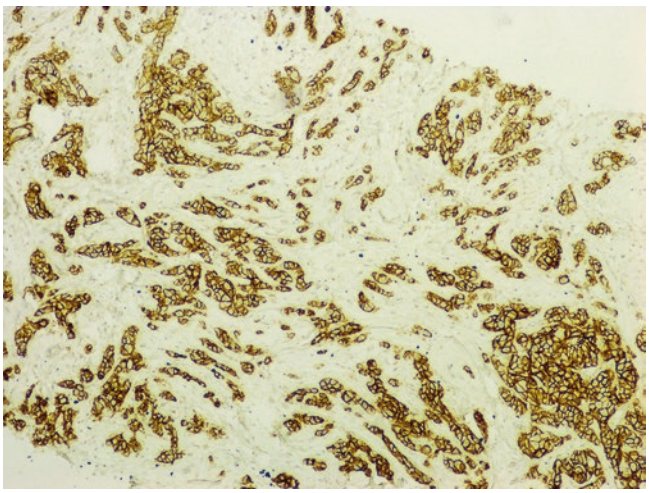

**Fig. 14.32** Invasive carcinoma of NST subtype: the tumor cells are positive for E-cadherin

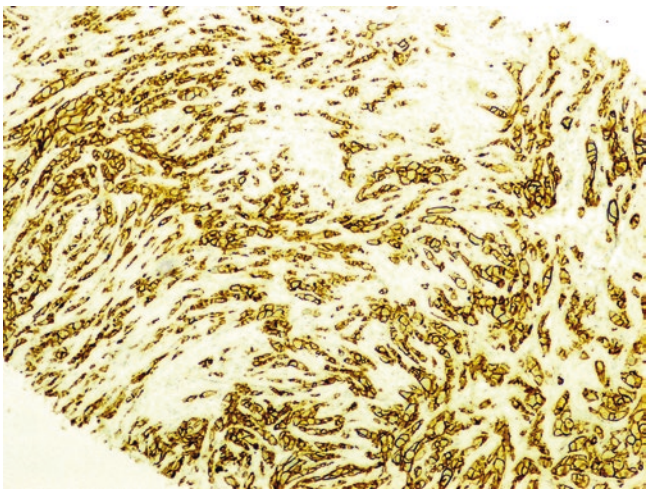

**Fig. 14.34** Invasive carcinoma of NST subtype with tumor cells are arranged in trabeculae, mimicking invasive lobular carcinoma; however, the E-cadherin is positive helping in differentiating the two entities

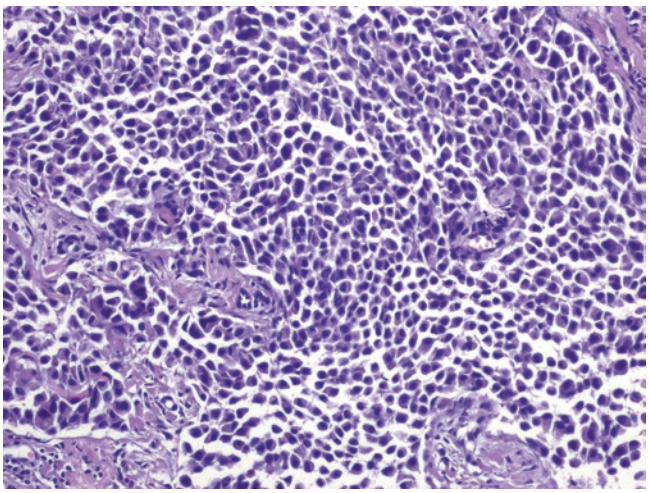

**Fig. 14.35** The solid subtype of infiltrating lobular carcinoma must be distinguished from poorly differentiated NST infiltrating ductal carcinoma; however, in the lobular invasive carcinoma the cells are dyscohesive (as shown in this picture)

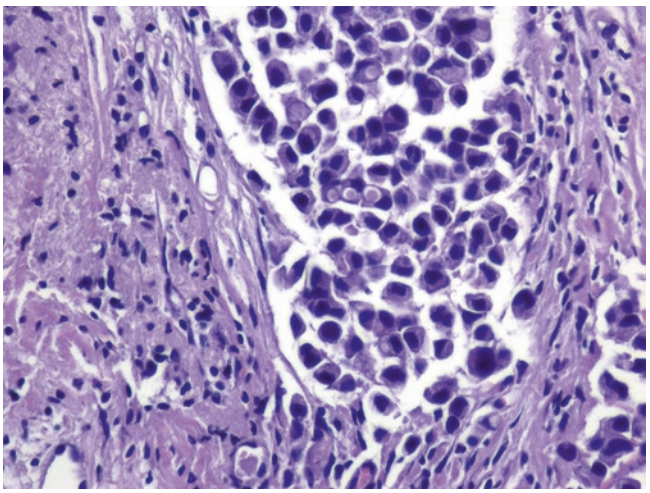

**Fig. 14.36** Invasive lobular carcinoma: high-power examination reveals the presence of intracytoplasmatic lumina with eosinophilic material, a very characteristic feature of this tumor, besides the fact that the tumor cells are dyscohesive

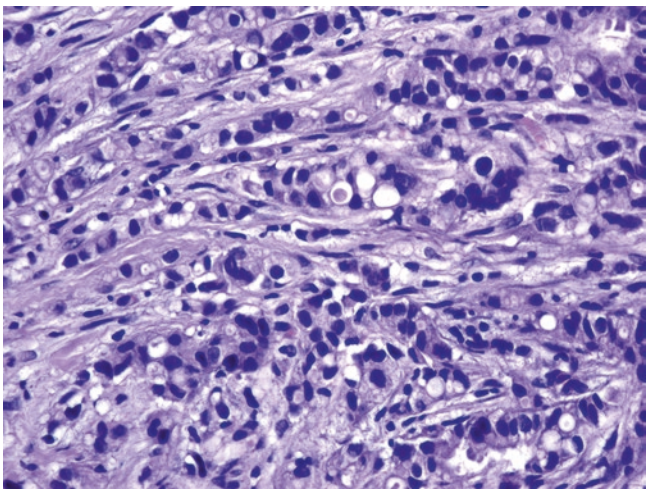

**Fig. 14.37** Invasive carcinoma of NST subtype: some tumor cells may also display intracitoplasmic lumina with eosinophilic content, similar to lobular invasive carcinoma. But the cells are more cohesive

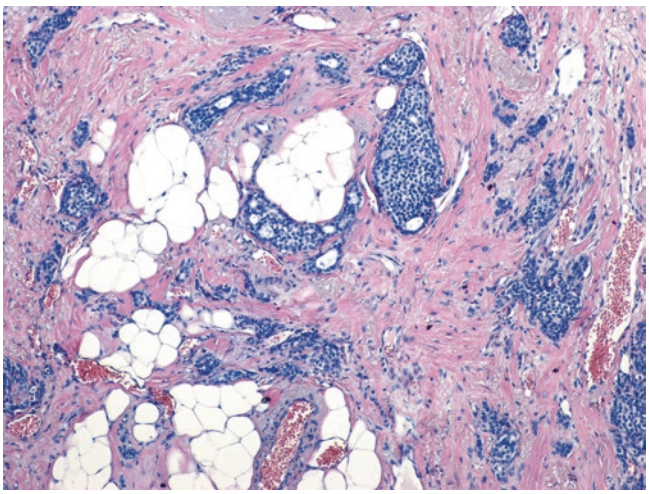

**Fig. 14.38** Invasive carcinoma with neuroendocrine differentiation: of note, the cells are uniform and arranged in nests, a finding that can also occur in the infiltrating NSY subtype

## 14.2 Mixed Carcinoma

To qualify as NST type, this pattern must be present in more than 90% of the tumor. Mixed carcinoma is a microscopic variant in which NST infiltrating carcinoma features should represent 10–49% of the tumor, while other microscopic subtypes represent the rest. Both components should be reported and microscopically graded (Figs. 14.39 and 14.40).

The 2012 WHO classification distinguishes four subtypes of NST infiltrating ductal carcinoma: pleomorphic carcinoma, carcinoma with osteoclast-like stromal giant cells, carcinoma with choriocarcinomatous features, and carcinoma with melanotic features [1].

**Fig. 14.39** Mixed infiltrating carcinoma: macroscopic examination of the tumor cut surface demonstrates a solid infiltrating NST component with hard consistency (left side) associated with a larger, more gelatinous and softer mucinous component (right side)

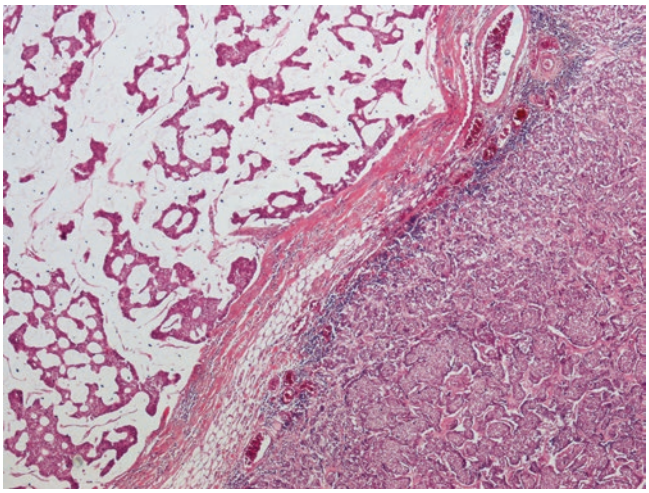

**Fig. 14.40** Mixed infiltrating carcinoma with a mucinous hypercellular component (left side) and a second component of NST subtype (right side)

## 14.3 Pleomorphic Carcinoma

Pleomorphic carcinoma is a rare variant, characterized by a proliferation of large, pleomorphic, and bizarre tumor cells, which comprise over 50% of the tumor. The remaining tumor is usually represented by an NST infiltrating carcinoma (rarely by a metaplastic, squamous cell or spindle-cell carcinoma, in which case the lesion should be diagnosed as metaplastic carcinoma). Macroscopically, the tumor resembles an NST infiltrating carcinoma often accompanied by central necrosis. Microscopically, tumor cells are large, bizarre, with abundant eosinophilic cytoplasm, have a nucleus with marked pleomorphism, and the cells are frequently multinucleated and have numerous mitotic figures (this tumor is always of high-grade of malignancy). Sometimes the cells are spindle, resembling a sarcomatous component (Figs. 14.41 and 14.42). An intraductal carcinoma can be noticed at the margin of the tumor, as well as numerous vascular tumor emboli. Most of these tumors are either triple negative or ER and PR-negative, while the HER2 is positive. Tumor cells are diffusely positive for pan-Cytokeratin. Differential diagnosis should be done with various forms of sarcoma (immunohistochemical tests are useful for this purpose). It is important to bear in mind that primary breast sarcomas are very rare, and by combining a good sample of the tumor with ancillary stains (it is advisable to use a panel of markers for the epithelial differentiation as well as for the exclusion of the mesenchymal differentiation), one can almost always recognize a pleomorphic carcinoma [3]. Of note, some sarcomas can be pan-CK positive, while other carcinomas can show positivity for Vimentin. Also, a differential diagnosis with metaplastic (also called sarcomatous carcinoma or myoepithelial carcinoma, as the two lesions represent the same entity) needs to be considered in cases in which a malignant mesenchymal-looking carcinoma is present. In metaplastic carcinoma, however, the NST component is not identified. Of interest, several publications demonstrated positivity for myoepithelial markers in metaplastic (sarcomatoid) carcinomas (such as p63, CD 10, SMA, S100), as well as for basal cell markers (CK5/6, CK14, CK34betaE12) [4].

This pleomorphic carcinoma has a very aggressive behavior and is very rarely associated with axillary lymph node metastases, being characterized by a behavior more like that of a sarcoma.

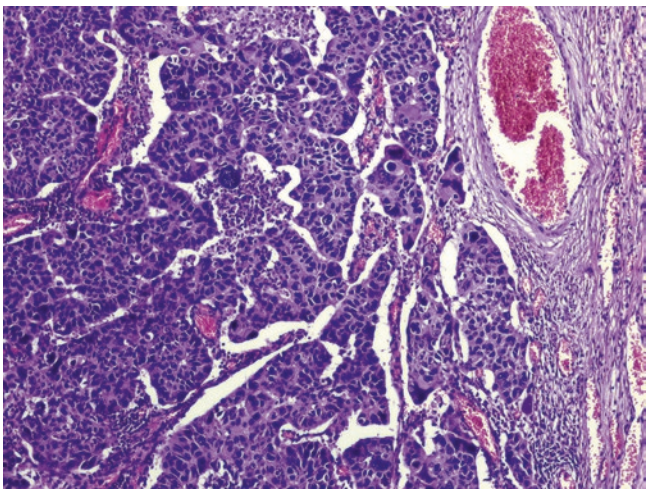

**Fig. 14.41** Pleomorphic carcinoma with solid architecture and composed of very pleomorphic tumor cells, some of them with large and bizarre nuclei

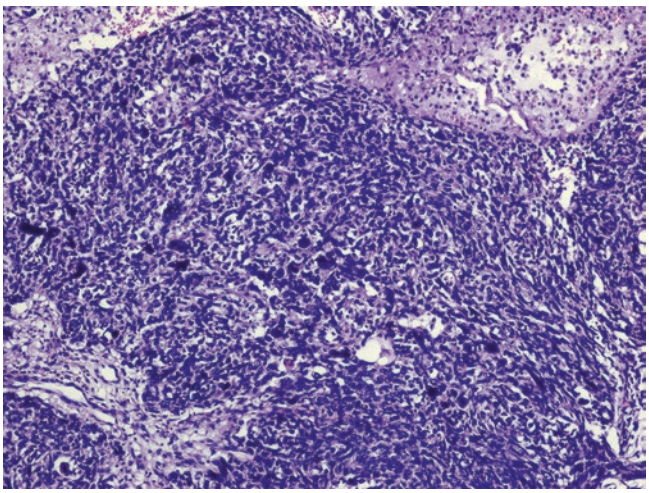

**Fig. 14.42** Pleomorphic carcinoma: another example of tumor composed of spindle- shaped tumor cells, resembling a sarcomatous component

## 14.4 Carcinoma with Osteoclast-Like Stromal Giant Cells

This microscopic subtype is a rare form of infiltrating carcinoma. Macroscopically, it has a soft consistency, brownish color due to bleeding foci, and may have clearly defined or infiltrating margins. Microscopically, the tumor is characterized by the presence of giant multinucleated stromal cells that are similar to osteoclasts [5]. Inflammatory infiltrate can be found in the stroma, as well as numerous blood vessels, extravasated erythrocytes, and histiocytes with intracytoplasmic hemosiderin. Giant stromal cells vary in shape and are located in the stroma, arranged around nests of tumor cells (usually of NST type, well or moderately differentiated), or even inside the lumens formed by the tumor cells. They have an abundant eosinophilic cytoplasm and numerous non-atypical round nuclei, usually arranged in the center of the cell, resembling osteoclasts. Immunohistochemically, multinucleated giant stromal cells are positive for CD-68, acid phosphatase, non-specific esterase, and lysozyme, and are negative for alkaline phosphatase, S-100 protein, actin, Cytokeratin, EMA, ER, and PR. Immunohistochemical and ultrastructural studies have confirmed the histiocytic origin of these cells. The invasive carcinoma component is represented by an NST infiltrating ductal carcinoma. Prognosis depends on the characteristics of the invasive NST carcinoma component and is not influenced by the presence of multinucleated giant stromal cells. The prognosis is driven by the NST component and does not appear to be influenced by the presence of the giant stromal cells.

## 14.5 Carcinoma with Choriocarcinomatous Features

An extremely rare variant of infiltrating breast carcinoma, this type is associated with increased ß-HCG (β-Human chorionic gonadotropin) serum [6–8]. The microscopic appearance of NST infiltrating ductal carcinoma is associated with choriocarcinomatous areas of differentiation, formed by multinucleated giant cells with eosinophilic cytoplasm and syncytial appearance (syncytiotrophoblast-type of differentiation), together with groups of small, uniform, mononuclear cells, with cytotrophoblastic differentiation. The tumor must be differentiated from metastatic choriocarcinoma originating in the uterus (associated with evidence of primary uterine tumor). A large number of NST cases may have HCG-positive cells without morphological identification of these cells as having trophoblast appearance. Prognosis is difficult to establish because there are very few cases of this microscopic subtype reported in the literature.

## 14.6 Carcinoma with Melanotic Features

This is a very rare breast carcinoma, which likely appears as the result of a process of metaplasia to a melanocytic component of an infiltrating breast carcinoma. Grossly, the tumor has a brownish color, while microscopically it is composed of areas with an NST infiltrating ductal carcinoma appearance and areas of malignant melanoma (with spindle cell or epithelioid tumor cells). Immunohistochemically, areas of NST infiltrating carcinoma type are positive for Cytokeratin and negative for HMB-45, Melan A, and S-100 protein. The melanocytic-appearing differentiations are negative for Cytokeratin and positive for HMB-45, Melan A, and S-100 protein. Differential diagnosis must include infiltrating breast carcinomas that may have melanin pigment (due to its phagocytosis by tumor cells), and breast carcinomas infiltrating the skin (without areas with melanocytic differentiation). Also, the tumor must be distinguished from infiltrating breast tumors, which sometimes may contain lipofuscin deposits (special stains differentiate the two pigments). Another differential diagnosis is made with metastasis of malignant melanoma with an extramammary origin (clinical evidence of another primary tumor) and intramammary metastasis of malignant cutaneous melanoma, which starts in the skin of the mammary gland or another location (without areas appearing as NST infiltrating ductal carcinoma). Sometimes an NST carcinoma may have Melan A positive cells lacking an association with a component with melanocytic features. This tumor usually has an aggressive behavior.

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