

Review

Mammary myofibroblastoma: an update with emphasis on the most diagnostically challenging variants

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Summary. Myofibroblastoma (MFB) is a rare benign mesenchymal tumor which usually occurs in the breast parenchyma of both females and males. Although this tumor is typically composed of bland-looking spindle-shaped cells arranged in short fascicles interrupted by keloidal-like collagen fibers, several variations on this basic morphological theme do exist. With the advent of mammographic screening, an increased number of mammary MFBs are being detected and pathologists should be aware of the wide morphological and immunohistochemical spectrum exhibited by this unusual tumor. This review focuses on the most diagnostically challenging variants of mammary MFB, which could represent potential diagnostic pitfalls of malignancy, especially when evaluating needle core biopsies. In this regard the following variants of MFB, including the most recently recognized, will be presented: myxoid MFB, lipomatous MFB, epithelioid cell MFB, deciduoid cell MFB, epithelioid cell MFB with multinodular growth pattern, palisaded/schwannian-like MFB and MFB with extensive myxoedematous stromal changes. Histological illustrations along with differential diagnostic problems for each single variant of MFB will be provided to offer helpful suggestions for a correct diagnostic approach in daily practice.

Key words: Myofibroblastoma, Breast, Morphological variants, Diagnosis, Immunohistochemistry

Introduction

Benign stromal tumors of the breast encompass a wide morphological spectrum of lesions ranging from spindly fibroblast-like cells to plump myofibroblasts (Magro et al., 1998, 2001, 2002a; Dragoumis et al., 2010). Immunohistochemical and ultrastructural studies have shown that most of these tumors are mainly composed of cells showing fibroblastic, myofibroblastic and, only focally, leiomyomatous differentiation (Toker et al., 1981; Boger, 1984; Chan et al., 1984; Wargotz et al., 1987a; Begin, 1991; Magro et al., 1998, 2001, 2002a, 2003). Myofibroblastoma (MFB) is the prototypic myofibroblastic tumor of the benign stromal tumors of the breast, first recognized as a distinct clinico-pathologic entity by Wargotz et al. (1987a). However it is likely that the first cases of mammary MFB were reported by Toker et al. who described morphologically similar tumors with the term "benign spindle cell breast tumor" (Toker et al., 1981). The term "myofibroblastoma" seems to be appropriate for such a tumor as it shows myofibroblastic differentiation at morphological, immunohistochemical and ultrastructural level (Wargotz et al., 1987a; Magro et al., 2001, 2002a, 2003; Corradi et al., 2008; Magro, 2008). Tumors with similar morphological and immunohistochemical features have been occasionally described at extra-mammary sites, especially in soft tissues of vagina, inguinal, perianal and paratesticular regions, seminal vesical and oral cavity, with the descriptive term "mammary-type MFB" or other terms (McMenamin and

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Fletcher, 2001; Mukonoweshuro et al., 2007; Magro, 2007; Magro et al., 2008a, 2012b; Zhang et al., 2010; Kojima et al., 2012).

Although diagnosis of classic-type MFB is usually straightforward, serious diagnostic problems may arise when pathologists are dealing with unusual morphological variants which may mimic malignant tumors. The present paper reviews the current status of mammary MFB, with special emphasis on the recently recognized and most diagnostically challenging variants. Differential diagnostic clues and illustrations of the more unusual variants are provided to aid in the recognition and distinction of mammary MFB from its mimics.

Classic-type MFB

Although mammary MFB can occur at any age, including in adolescents (Alam et al., 2002), it has been mainly documented in older men and postmenopausal women (Wargotz et al., 1987a; Julien et al., 1994; Hamele-Bena et al., 1996; Magro et al., 2001, 2002a, 2012a; Magro, 2008). MFB occurs sporadically, rarely in association with gynecomastia (Yoo et al., 1998; Reis-Filho et al., 2001; Gurzu and Jung, 2012; Solak et al., 2013). Clinically the tumor usually presents as a solitary, painless nodule, ranging from few millimeters to 15 cm in size (Ali et al., 1994; Abeysekara et al., 2008; Corradi et al., 2008; Magro, 2008). MFB can be occasionally detected as a non-palpable mass on a routine screening mammogram (Greenberg et al., 1998). The imaging characteristics of MFB are not specific. Sonography usually reveals a well-circumscribed, homogeneously or heterogeneously, hypoechoic mass without associated microcalcifications, suggestive of fibroadenoma (Pina et al., 1997; Greenberg et al., 1998; Dockery et al., 2001; Yoo et al., 2010; Mele et al., 2011; Solak et al., 2013). Mammography usually reveals a circumscribed, lobulated, hyperdense mass without calcifications (Pina et al., 1997; Yoo et al., 2010; Mele et al., 2011). Magnetic resonance imaging (MRI) shows a homogeneous enhancing mass with internal septations (Vourtsi et al., 1999; Yoo et al., 2010). In rare cases, computed tomography (CT) scan reveals a circumscribed, ovoid, non-enhancing, solid mass (Solak et al., 2013).

With the advent of ultrasonography-guided fine-needle aspiration cytology (FNAC) or needle core biopsy, there is an increasingly pre-operative diagnosis of MFB (Simsir et al., 2001; Desrosiers et al., 2007; Solak et al., 2013; Shivali et al., 2013). In this regard, cytological, histological and immunohistochemical findings should be evaluated in conjunction with the clinical and radiologic data to achieve a correct diagnosis (Negri et al., 1995; Lopez-Rios et al., 2001; Desrosiers et al., 2007; Magro, 2008, 2009). MFB can be suspected on cytology on the basis of the presence of randomly arranged, spindle-shaped cells (Ordi et al., 1992; Odashiro et al., 2004; Yoo et al., 2010), occasionally showing nuclear pleomorphism (Amin et

al., 1994; Negri et al., 1995). However, the possibility of a misdiagnosis is relatively frequent (Amin et al., 1994; Simsir et al., 2001), including confusion with malignant lesions (Powari et al., 2002; Álvarez-Rodríguez et al., 2012). Ultrasonographically-guided core biopsy increases the chance of a correct diagnosis of MFB (Miller et al., 1997; Dockery et al., 2001; Desrosiers et al., 2007; Magro, 2008; Yoo et al., 2010; Solak et al., 2013). However, it should be emphasized that some variants, especially epithelioid/deciduoid cell or lipomatous variants, may be diagnostically challenging (Magro, 2008, 2009; Mele et al., 2011; Bakula-Zalewska et al., 2012; Ibrahim and Shousha, 2013).

Grossly, MFB presents as a well-circumscribed, round to oval mass, with smooth, frequently, lobulated external surface and usually firm in consistency. The cut surface usually reveals a solid lesion, pale white to grayish in color, with occasional whorling appearance (Wargotz et al., 1987a; Magro et al., 2001; Magro, 2008). Neither necrosis nor hemorrhage are seen. Histological examination of the classic-type MFB shows an unencapsulated tumor with pushing, lobulated borders (Fig. 1A), composed of bland-looking spindle-shaped cells arranged in short, straight, haphazardly intersecting fascicles or nests interrupted by keloid-like, brightly eosinophilic collagen fibers (Fig. 1B-C) (Wargotz et al., 1987a; Magro et al., 2001, 2002a; Magro, 2008). Only focally neoplastic cells are arranged in a storiform growth pattern. The cells exhibit a relatively abundant, pale to deeply eosinophilic cytoplasm with distinct cell borders and a centrally located oval to round nucleus containing one or two small nucleoli (Fig. 1D). In some tumors, nuclei may have grooves or pseudoinclusions (Wargotz et al., 1987a; Ordi et al., 1992; Ali et al., 1994). Tumor stroma is predominantly fibrous, but focal myxoid changes usually do occur. The mitotic count is low, ranging from 0 to 2 mitoses per 10 high-power fields. Atypical mitoses, necrosis, or nuclear pleomorphism are absent. The vascular component is represented by small- to medium-sized blood vessels, often with hyalinization and foamy histiocytes in their walls (Magro et al., 1999, 2001, 2002a; Magro, 2008). A hemangiopericytoma-like pattern can be occasionally observed in MFB (Magro et al., 1999). Numerous mast cells are found in most cases. Small islands of mature adipose tissue can be found, mainly at the periphery of the tumor. Mammary ducts or lobules are usually not entrapped within the tumor. Distinction of MFB from other mesenchymal lesions is crucial because local excision of tumor is curative, with no evidence of recurrence or distant metastasis after a long follow-up period of 15 years (Magro, 2008).

Differential diagnosis of classic-type MFB includes tumor- and tumor-like spindle cell lesions which can arise primarily in the breast parenchyma. Among benign lesions, MFB should be distinguished from: i) nodular fasciitis (Squillaci et al., 2007; Hayashi et al., 2007); ii) leiomyoma (Jones et al., 1994; Vecchio et al., 2013); iii) spindle cell lipoma (Chan et al., 1984; Magro et al.,

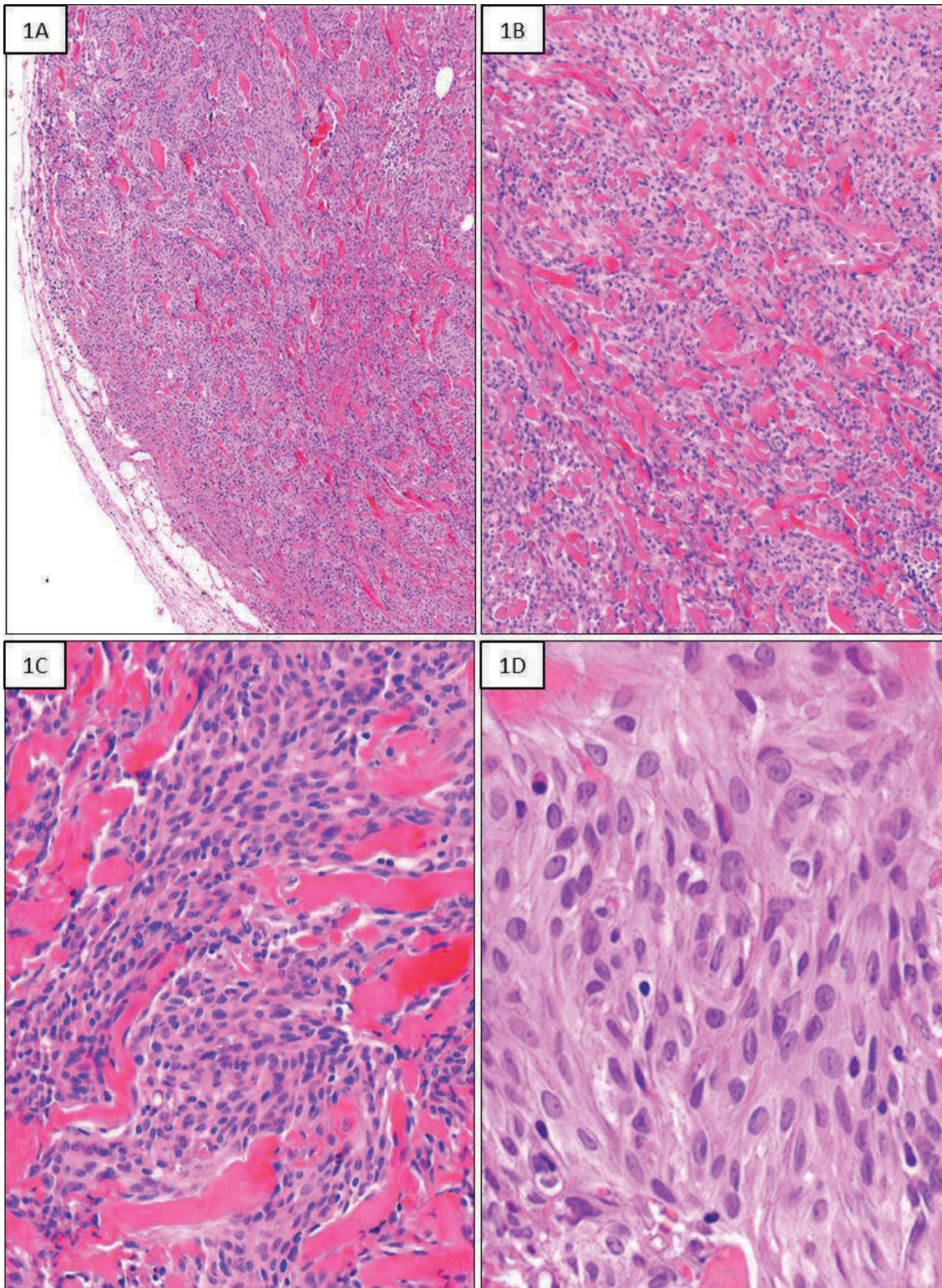


Fig. 1. Classic-type MFB. **A.** Low magnification showing a tumor with pushing borders, containing numerous thick, eosinophilic collagen fibers. **B.** Tumor area rich in keloidal-like, brightly eosinophilic collagen fibers. **C.** Tumor is composed of bland-looking spindle-shaped cells with eosinophilic cytoplasm, arranged in short fascicles interrupted by keloidal-like collagen fibers. **D.** Higher magnification showing cells with round to ovoid nuclei containing one or two small nucleoli.

1998; Mulvany et al., 1999); iv) fascicular variant of pseudoangiomatous stromal hyperplasia (Magro and Bisceglia, 2005; Rosen, 2009; Virk et al., 2010); v) benign fibrohistiocytoma (Friedman et al., 1994); vi) solitary fibrous tumor (Magro et al., 2000c; Salomao et al., 2001; Falconieri et al., 2004); vii) inflammatory myofibroblastic tumor/pseudotumor (Vecchio et al., 2011; Bosse et al., 2014); viii) muscular/myoid hamartoma (Magro and Bisceglia, 1998; Kajo et al., 2010; Makiguchi et al., 2014). The main low- or high-grade malignant spindle cell tumors which should be included in the differential diagnosis with classic-type MFB are: i) desmoid-type fibromatosis (Wargotz et al., 1987b; Magro and Mesiti, 1998; Devouassoux-Shisheboran et al., 2000; Magro et al., 2002b); ii) low-grade fibromatosis-like spindle cell carcinoma (Sneige et al., 2001; Dwyer et al., 2015); iii) low-grade myofibroblastic sarcoma (Morgan et al., 2005;); iv) low-grade fibrosarcoma (Jones et al., 1992; Adem et al., 2004; Lee et al., 2011); v) spindle cell myoepithelial carcinoma (malignant myoepithelioma) (Abd el-All, 2006; Ohtake et al., 2013); vi) leiomyosarcomas (Jones et al., 1994; Szekely et al., 2001; Lee et al., 2004; Rane et al., 2012); vii) dermatofibrosarcoma protuberans (Sandberg et al., 2003; Tsang et al., 2005; Ahmed et al., 2010); viii) follicular dendritic cell sarcoma (Pruneri et al., 2002; Kapucuoglu et al., 2009); ix) low-grade malignant peripheral nerve sheath tumors (Dhingra et al., 2007; Woo et al., 2007). Differential diagnosis between MFB with each of the above mentioned tumor-like and tumor lesions are described in detail elsewhere (Magro, 2008). Nevertheless, the following morphological and immunohistochemical features favor the diagnosis of classic-type MFB: i) unencapsulated mesenchymal tumor with circumscribed borders; ii) bland-looking, pale to eosinophilic spindle-shaped cells; iii) interspersed keloidal-like, brightly eosinophilic collagen fibers; iv) absent or low mitotic count (up 2 mitoses per 10 high-power fields); v) immunoreactivity for desmin and CD34. Conversely, the following features are not consistent with diagnosis of classic-type MFB: i) diffusely infiltrating margins with entrapment of adipose tissue and mammary glandular structures; ii) mitotic activity: >2 mitoses per 10 high-power fields; iii) atypical mitoses; iv) tumor necrosis ; v) absence of immunostaining with desmin and CD34.

Unusual morphological features in an otherwise classic-type myofibroblastoma

In the context of an otherwise classic-type MFB, the following unusual and alarming morphological features can be encountered: i) focally infiltrative margins (Fig. 2A); tumors with these features, designated as “infiltrating MFB”, may be potential diagnostic pitfalls of malignancy (Begin et al., 1989; Hamele-Bena et al., 1996; Schmitt and Mera, 1998; Teng and You, 2005); ii) high cellularity (Fig. 2B); tumors with these features, designated as “cellular MFB” (Fig. 2B), tend to have

cellular overlapping, mild nuclear pleomorphism, focal storiform or herringbone pattern, infiltrative borders and thin, rather than thick, collagen fibers; they can be potentially confused with malignant tumors (Schmitt and Mera, 1998; Gocht et al., 1999; Rosen, 2009; Gurzu and Jung, 2012); iii) mono- or multi-nucleated cells with variable degree (mild to moderate to severe) of nuclear pleomorphism (Fig. 2C) (Amin et al., 1994; Fukunaga et al., 1996; Lázaro-Santander et al., 1999; Magro et al., 2001, 2002a; Magro, 2008); iv) multinucleated floret-like cells (Fig. 2D) (Nucci and Fletcher, 1999; Magro et al., 2001, 2002a; Magro, 2008); these cells are similar, if not identical, to those more commonly observed in spindle/pleomorphic lipoma (Weiss and Goldblum, 2008).

Moreover the following additional histological findings, which represent merely histological curiosities, have been occasionally reported in an otherwise classic-type MFB: i) predominant fibrous stroma; these tumors have also been designated as “fibrous MFB” (Magro, 2008; Rosen, 2009); ii) intra-cytoplasmic and extracellular hyaline globules, strongly reacting with desmin, h-caldesmon and smooth muscle myosin heavy chain (Ozerdem et al., 2015); the intracellular globules are strongly reminiscent of eosinophilic inclusion bodies as seen in some phylloides tumors or digital fibromatosis (digital fibroma) (Weiss and Goldblum, 2008); iii) heterologous mesenchymal components, including mature lipomatous, leiomyomatous (Fukunaga et al., 1996; Fukunaga and Ushigome, 1997; Thomas et al., 1997; Mnif et al., 2013), osseous (Kobayashi et al., 1996), or cartilaginous (Wargotz et al., 1987a; Kobayashi et al., 1996; Fukunaga and Ushigome, 1997; Lopez-Rios et al., 2001; D'Alfonso and Scognamiglio, 2013) components; these tissues, usually in the form of small foci, are regarded as the result of metaplastic changes or divergent differentiation from the common precursor mesenchymal cell (Magro, 2008).

Immunohistochemical markers of classic-type MFB

Apart from vimentin, the most common markers of classic-type MFB are desmin and CD34, being reported, at least focally, in the majority of cases (Julien et al., 1994; Hamele-Bena et al., 1996; Gocht et al., 1999; Magro et al., 2001, 2002a; Magro, 2008; Huang and Chen, 2012) (Fig. 3A,B). Immunostaining for alpha-smooth muscle actin, bcl-2, CD99, CD10, and estrogen/progesterone/androgen receptors (Fig. 3C-E) is frequently obtained, but with variable intra-lesional and inter-lesional extension (Magro et al., 2000a, 2001, 2007a; Magro, 2008). A focal expression of h-caldesmon can be identified, suggesting the possibility that a minority of neoplastic cells undergo leiomyomatous differentiation (Magro et al., 2003). CD68 and factor XIIIa immunoreactivity has also been occasionally documented (Silverman et al., 1998; Gocht et al., 1999). Based on these findings, it is commonly believed that neoplastic cells of MFB are fibroblastic and

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myofibroblastic in nature (Wargotz et al., 1987a; Magro, 2008). Conversely, cytokeratins, EMA (epithelial membrane antigen), S100 protein, HMB-45, and c-Kit (CD117) are consistently negative (Magro et al., 2001, 2002a; Magro, 2008).

Ultrastructural features

Electron microscopy studies have shown that mammary MFB is usually composed of a variable admixture of undifferentiated mesenchymal cells,

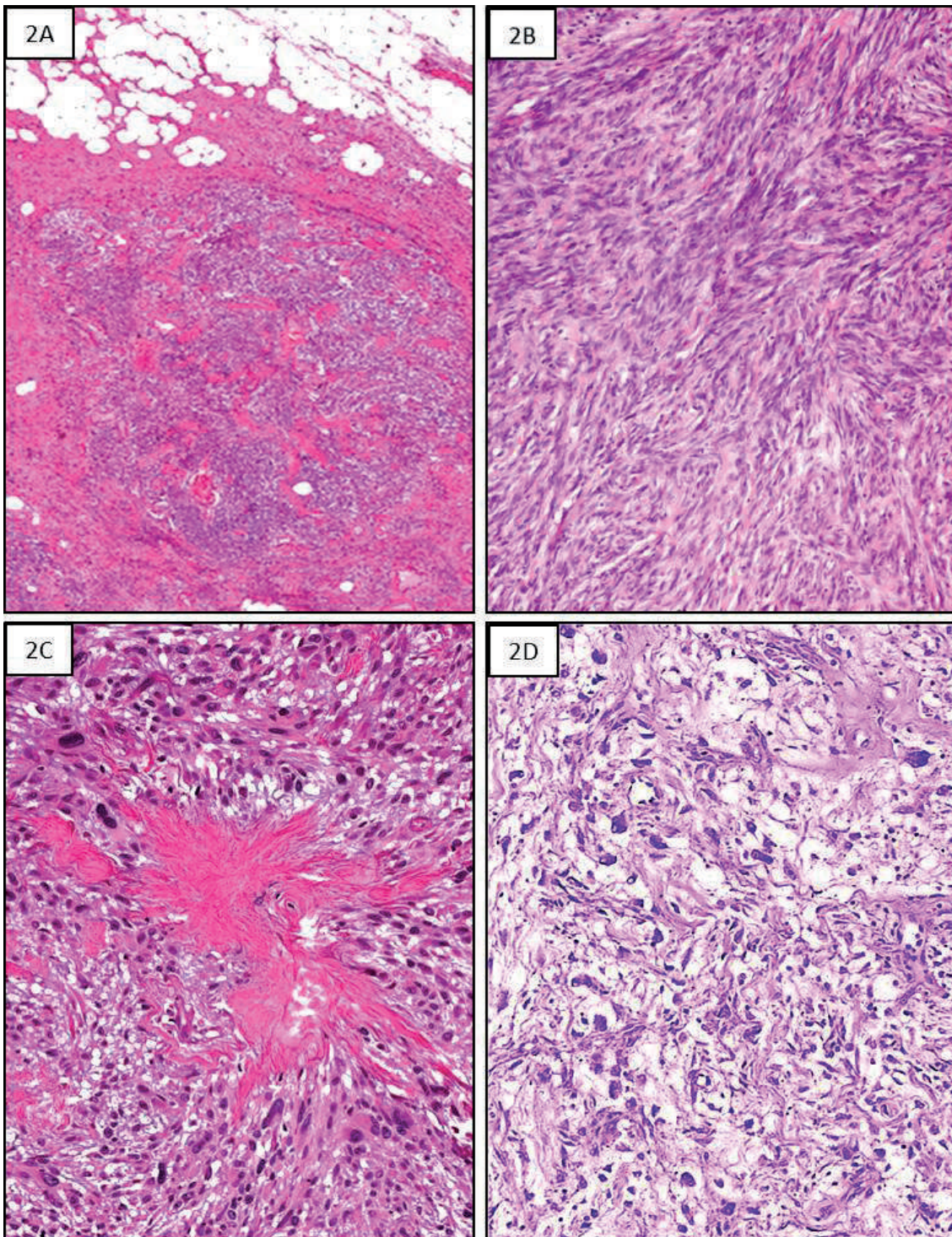


Fig. 2. Unusual morphological features in classic-type MFB. **A.** MFB exhibiting focal infiltrating borders into surrounding adipose tissue. **B.** A case of MFB showing high cellularity, cellular overlapping and thin collagen fibers (so-called “cellular MFB”). **C.** Atypical cells with severe nuclear pleomorphism can be seen around an amianthoid-like collagen fiber. **D.** Occasionally, tumor areas with multinucleated floret-like cells can be observed.

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fibroblasts, myofibroblasts, and smooth muscle cells. Myofibroblasts contain organelles (rough endoplasmatic reticulum, Golgi complexes), bundles of myofilaments forming focal densities and, focally, basal lamina-like material associated with the cell surface (Toker et al., 1981; Ghadially et al., 1983; Wargotz et al., 1987a; Begin, 1991; Amin et al., 1994; Eyden et al., 1999; Gocht et al., 1999). Only focally, fibronectin fibrils (so-called microtendons) and/or fibronexus junctions can be seen (Gocht et al., 1999; Corradi et al., 2008).

Genetics

Cytogenetic studies have shown that MFB is

associated with the loss of material from chromosome 13 and more rarely from chromosome 16 (Pauwels et al., 2000). There is increasing evidence that most cases of mammary MFB exhibit the loss of the 13q14 region, which can be shown by the losses of *RB*/13q14 and/or *FOXO1(FKHR)*/13q14 loci in tumor cells by FISH analyses (Fig. 3F) (Magro et al., 2012c; Trepant et al., 2014). Notably, similar results have also been obtained in spindle cell lipoma (Dal Cin et al., 1997), mammary-type soft tissue MFB (Maggiani et al., 2006), vulvo-vaginal MFB (Magro et al., 2012c) and cellular angiofibroma (Maggiani et al., 2007; Flucke et al., 2011), suggesting the possibility of a genetic link among these entities (Magro, 2007; Magro et al., 2012c). Given

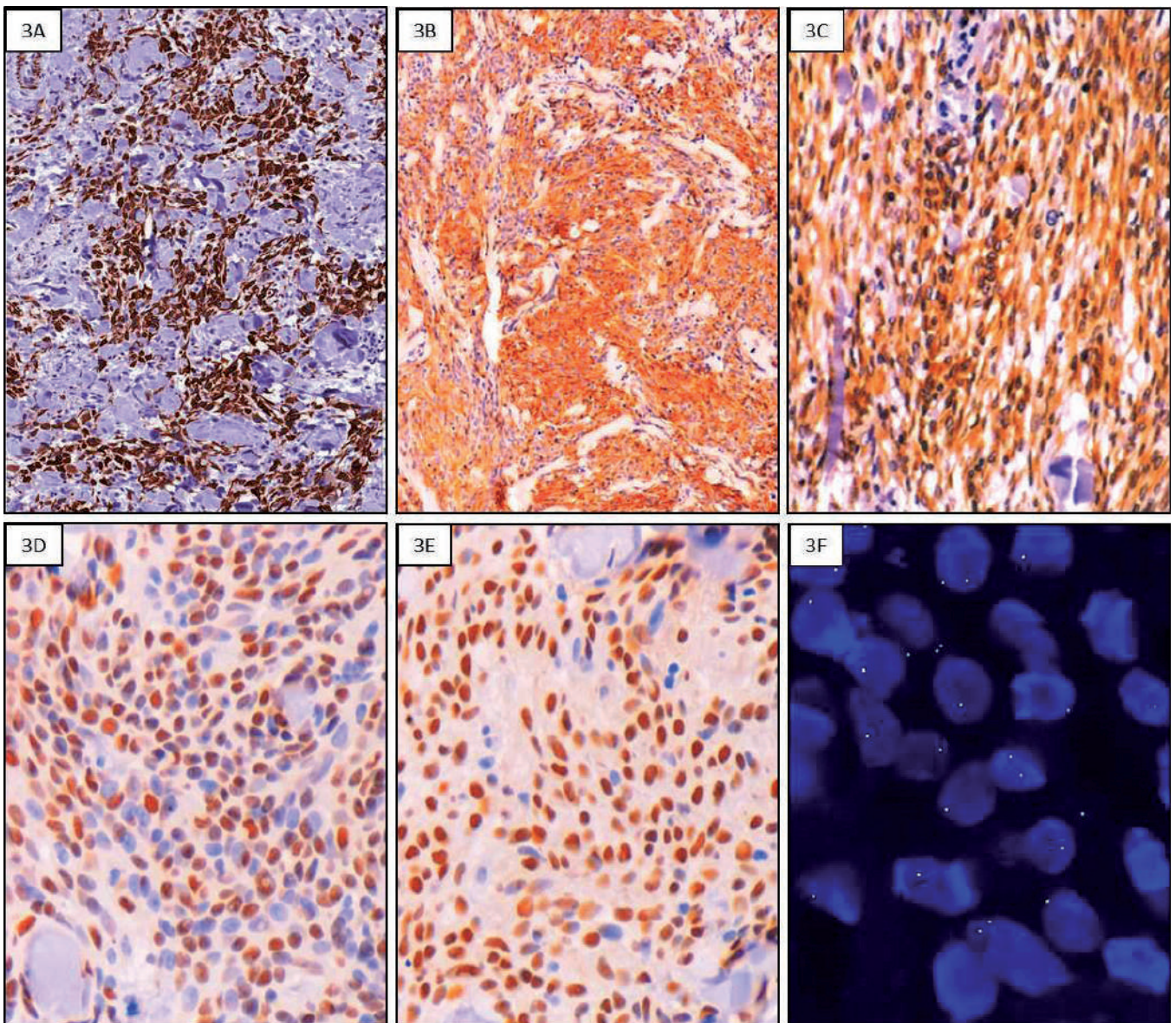


Fig. 3. Immunomarkers and cytogenetics of MFB. Neoplastic cells of mammary MFB are typically stained with desmin (A) and CD34 (B), and variably with alpha-smooth muscle actin (C), estrogen (D) and progesterone (E) receptors. (F) FISH analysis showing monoallelic loss of FOXO1/13q14 loci as indicated by the presence of 1 fusion red/green signal in most tumor cells.

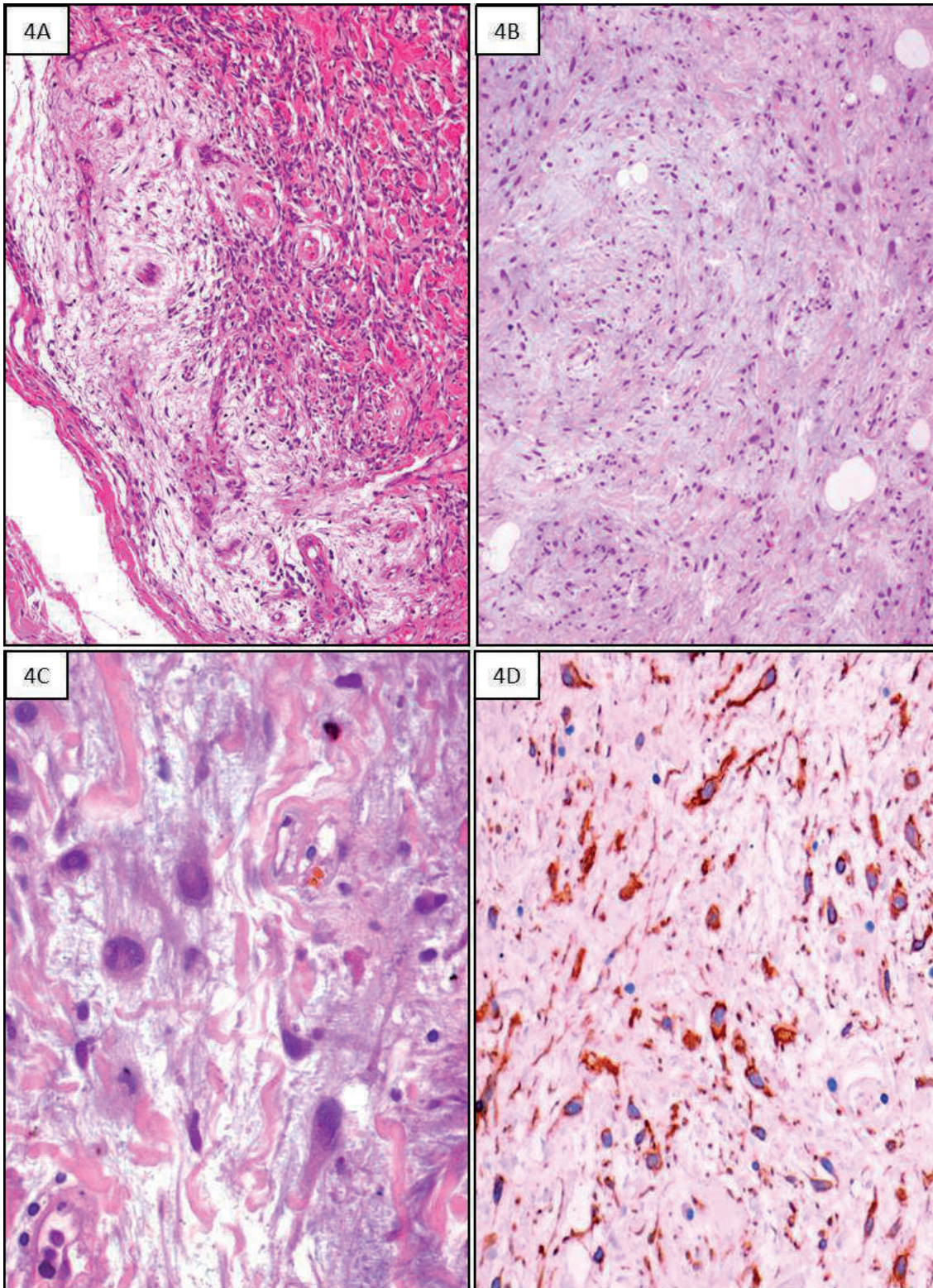


Fig. 4. Myxoid MFB. **A.** Classic-type MFB with focal myxoid area. **B-D.** True myxoid MFB showing extensive myxoid stromal changes with interspersed spindle-shaped cells (**B**); focally neoplastic cells may exhibit severe nuclear pleomorphism (**C**). Immunohistochemical analyses, showing diffuse expression of desmin by neoplastic cells (**D**), are mandatory in confirming the diagnosis.

the morphological, immunohistochemical and genetic overlapping among MFB, spindle cell lipoma and cellular angiofibroma, it has been postulated that these lesions belong to the same tumor entity, likely arising from a common precursor cell, and their differences may merely represent morphological and immunohistochemical variations on a common basic theme (Magro, 2007; Magro et al., 2012c).

Morphological variants of mammary MFB

Currently it is accepted that mammary MFB encompasses a wide morphological spectrum which reflects the capability of precursor stromal cells, not only to differentiate toward various mesenchymal cell lineages, but also to adopt different sizes and shapes (Magro et al., 2001, 2002a; Magro, 2008). This can explain the marked intra-lesional and inter-lesional variability in morphology, as well as the different morphological variants. Rarely, two different morphological variants may coexist in the same tumor (Rosen, 2009; Magro et al., 2001, 2002a; Wahbah et al., 2011). Recognition of MFB variants is not of merely academic interest, but it is crucial to prevent an overdiagnosis of malignancy, especially when dealing with cytological material or small biopsies.

Myxoid MFB

Although MFB may contain focal myxoid stromal changes (Fig. 4A), only rarely does this tumor exhibit prominent myxoid stroma. The term “myxoid myofibroblastoma” designates those rare cases entirely or predominantly consisting of myxoid stroma in which neoplastic cells are variably interspersed (Magro et al., 2007b; Magro, 2008; Corradi et al., 2008; Rosen, 2009).

Grossly, the tumor presents as a well circumscribed, unencapsulated nodular to oval-shaped mass, with a variable size (from 3 to 12 cm in greatest dimension). On cut section, the mass is whitish in color and gelatinous in appearance. Histological examination reveals, at low magnification, a hypocellular myxoid tumor mass with pushing borders, closely reminiscent of myxoma. The tumor consists of an abundant myxoid extracellular matrix stained positively with Alcian blue at pH 2.5 and negative for periodic acid-Schiff, in which spindle, and less frequently, epithelioid to stellate cells are embedded (Fig. 4B). Isolated keloid-like collagen fibers are usually identified within myxoid stroma. Neoplastic cells have pale to deeply eosinophilic cytoplasm and round to oval nuclei containing one or two small nucleoli. Some cells are bi- or multinucleated. Notably, a mild to moderate degree of nuclear pleomorphism can be focally observed (Fig. 4C). A minor mature fatty component can be found throughout the tumor. Mitoses are usually absent or rare (up to 2 mitoses x10 high power field). Atypical mitoses, necrosis or haemorrhage are lacking. Mammary ducts or lobules are not entrapped within the tumor.

Immunohistochemically, neoplastic cells show a profile similar to that seen in classic-type MFB (Fig. 4D) (Magro et al., 2007b).

Differential diagnosis includes benign and malignant breast lesions with abundant myxoid stroma. Among benign lesions, myxoid MFB needs to be distinguished mainly from: i) myxoma; ii) nodular mucinosis (first reported as nerve sheath myxoma); iii) nodular fasciitis (myxoid variant); iv) neurofibroma (myxoid variant). Primary myxoma of the breast parenchyma is rare, with only a few cases reported in the literature so far (Tyler, 1915; Chan, 1986; Balci et al., 2007; Magro et al., 2010). Although myxoma may share with myxoid MFB some morphological features, the former lacks the expression of desmin, alpha-smooth muscle actin, CD34 and estrogen/progesterone receptors (Magro et al., 2010). Unlike myxoid MFB, nodular mucinosis is usually located under the nipple, and it consists of small-sized myxoid nodules containing spindled cells and entrapped mammary ducts/lobules, as well as sweat glands (Michal et al., 1998). Nodular fasciitis may be composed predominantly of myxoid extracellular matrix. However it usually shows, at least focally, infiltrative margins and a variable number of inflammatory cells, including extravasated red blood cells. The myofibroblasts of nodular fasciitis express alpha-smooth muscle actin, but they are not usually stained with desmin, CD34 and estrogen/progesterone receptors (Hayashi et al., 2007). Neurofibroma, which can rarely occur in the breast parenchyma with abundant myxoid matrix (Gokalp et al., 2007), expresses S100 protein, while myxoid MFB does not. Malignant tumors with myxoid extracellular matrix, which should be distinguished from myxoid MFB, are myxofibrosarcoma (Klopcic et al., 2009), myxoid liposarcoma (Pant et al., 2008) and mucocele-like tumors (Rosen, 2009). The former is easily ruled out for the absence of significant nuclear pleomorphism, mitotic activity and curvilinear vasculature (Klopcic et al., 2009). Unlike myxoid MFB, myxoid liposarcoma contains lipoblasts and characteristic plexiform vasculature (Pant et al., 2008). Lastly, mucocele-like lesions include both benign and malignant lesions characterized by mucin-containing cysts in which benign (normal or hyperplastic) or in situ/invasive mucinous carcinomas can be identified (Rosen, 2009). Unlike myxoid MFB, the extra-cellular matrix stains positively with PAS and contains epithelial elements which can be highlighted by pancytokeratin and EMA (Rosen, 2009).

Lipomatous MFB

Although islands of mature adipocytes can be variably found interspersed throughout MFB, only rarely does this tumor contain a significant (>50% of the entire tumour) mature fatty component (Magro et al., 2000b; Baxendine-Jones et al., 2001; Wahbah et al., 2011; Magro et al., 2014a). The term “*lipomatous myofibroblastoma*” has been first coined by Magro et al. (2000b).

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to designate such rare cases, emphasizing that they may represent potential diagnostic pitfalls of malignancy.

Grossly, lipomatous MFB presents as a well-circumscribed, incompletely encapsulated lipomatous

mass, of variable size (1.5 to 3 cm). The cut surface shows a yellow tumor mass with some interspersed whitish areas. Calcifications, haemorrhage and necrosis are not seen. Histological examination reveals, at low

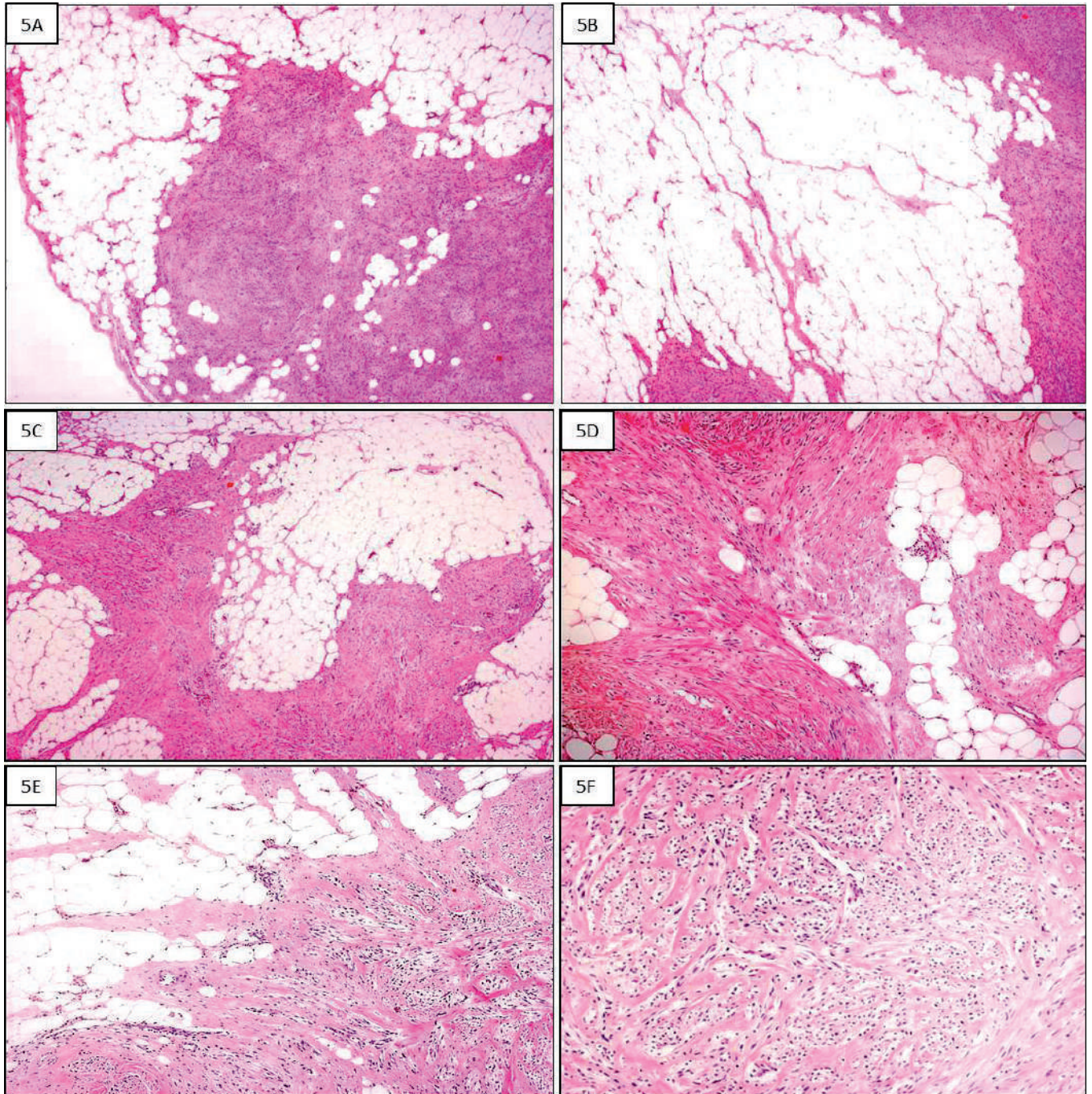


Fig. 5. Lipomatous MFB. **A.** Low magnification showing a fibro-lipomatous tumor with pushing borders. **B.** Tumor area composed predominantly of mature fatty tissue. **C.** Fibrous tumor component showing infiltrating-like pattern into fatty component. **D.** Higher magnification showing spindle-shaped cells embedded in a fibrous stromal component with fibromatosis-like growth pattern. **E.** The spindle cells, set in a fibrous stroma, showing a finger-like growth pattern into adjacent tumor fatty component. **F.** Tumor area with features of classic-type MFB.

magnification, a lipomatous tumor with pushing borders, closely reminiscent of a fibro-lipoma or spindle cell lipoma (Fig. 5A). The tumor consists of a dominant fatty component (Fig. 5B) which contains dispersed, vaguely nodular or irregularly shaped spindled cellular areas and fibrous septa (Fig. 5C-E). The fatty component is represented by mature adipocytes, uniform in size and shape, without nuclear pleomorphism. The non-adipocytic component consists of spindle-shaped cells usually arranged in short, haphazardly intersecting fascicles interrupted by keloid-like collagen fibers (Fig. 5D-F). These cells show pale to eosinophilic cytoplasm, with ill-defined borders and an oval nucleus with occasional small nucleoli. A mild to moderate degree of nuclear pleomorphism can be focally seen. Like in classic-type MFB, mitoses are absent or rare (up to 2 mitoses x10 high power field). Atypical mitoses and necrosis are not features of lipomatous MFB. Interestingly, spindle-shaped cells which exhibit intracytoplasmic accumulation of lipids, in the form of single large non-membrane-bound droplet or multiple small droplets, are lacking. Adipocytes and the spindled cells are variably admixed, often resulting in a finger-like pseudo-infiltrative growth pattern (Fig. 5C,E). Mammary ducts or lobules are usually not trapped within the tumour. Immunohistochemically, the spindled cells show a myofibroblastic profile, and they express all the markers which can be typically found in the classic-type MFB (Magro et al., 2000b). The cellular mechanisms responsible for fat accumulation in mammary MFB are still to be established. The absence of neoplastic cells with hybrid features between myofibroblasts and adipocytes argues against the possibility that the fatty component is the result of a metaplastic process from the former into the latter cells. Conversely, it is likely that the fatty component arises “ex novo”, reflecting the capability of the stromal precursor cells to undergo multidirectional differentiation, including myofibroblastic and lipomatous differentiation (Magro, 2008; Magro et al., 2014a). Based on this hypothesis, lipomatous MFB should be viewed as a bimorphic tumor with the lipomatous component overwhelming the myofibroblastic one (Magro et al., 2000b). A similar histogenetic hypothesis has been proposed for lipomatous angiomyo-fibroblastoma of the vulvo-vaginal area (Magro et al., 2014b), which although it lacks the deletion of 13q14 region (Magro et al., 2014c), morphologically is partially reminiscent of a lipomatous MFB, especially with epithelioid cell component (Magro et al., 2014b).

Awareness by pathologists of the possibility that mammary MFB may contain a dominant fatty component is crucial to avoid misdiagnosis with other spindle cell tumors containing or infiltrating fat. In this regard, differential diagnosis mainly revolves around spindle cell lipoma, lipoma-like well-differentiated liposarcoma, spindle cell liposarcoma, desmoid-type fibromatosis, low-grade myofibroblastic sarcoma and

low-grade fibromatosis-like spindle cell metaplastic carcinoma. CD34-positive tumors with morphology similar, if not identical, to spindle cell lipoma of soft tissue have been rarely described in the breast parenchyma (Magro et al., 1998, 2002a). In addition, it is likely that some tumors of the breast labeled as “benign spindle cell tumors” (Toker et al., 1981; Boger, 1994; Chan et al., 1984) do represent low- or fat-free spindle cell lipomas (Magro, 2015). Unlike spindle cell lipoma, lipomatous MFB shows a short fascicular arrangement of neoplastic spindled cells, and it exhibits significant expression of myogenic markers, such as desmin and alpha-smooth muscle actin (Magro et al., 2000b). However, it should be emphasized that both spindle cell lipoma and MFB are currently viewed as belonging to the same category of the benign mesenchymal tumours with deletion of the 13q14 region (Magro, 2008, 2015; Magro et al., 2012c). Accordingly, both tumors can be better regarded as two distinct phenotypes of the same disease rather than two distinct entities. Liposarcoma only rarely occurs in the breast (Austin and Dupree, 1986). Lipoma-like well-differentiated liposarcoma contains both atypical adipocytes and atypical stromal cells in the fibrous septa which intersect the adipocytic component (Al-Rikabi et al., 2013). In addition a variable amount of lipoblasts can be found in most tumors. Lipoblasts and atypical adipocytes are not features of lipomatous MFB. Another lipomatous tumor which can be confused with lipomatous MFB is spindle cell liposarcoma, a distinctive clinicopathological entity occurring in soft tissues (Dei Tos et al., 1994; Deyrup et al., 2013). The latter can be distinguished from the former for the presence, even if only focally, of lipoblasts which are closely reminiscent of human embryonic fat (Deyrup et al., 2013). Desmoid-type fibromatosis is a locally recurring tumor that rarely involves the breast parenchyma (Wargotz et al., 1987b; Magro and Mesiti 1998; Devouassoux-Shisheboran et al., 2000; Magro et al., 2002b). Unlike lipomatous MFB, desmoid-type fibromatosis exhibits infiltrating borders with entrapment of both fat and mammary glandular tissue. It is composed of long, sweeping cellular fascicles of spindle-shaped cells embedded in a fibrous stroma rather than of short fascicles as seen in MFB. Immunohistochemically, desmoid-type fibromatosis and lipomatous MFB share the expression of alpha-smooth muscle actin. However desmin, CD34 and estrogen/progesterone receptors, diffusely expressed in the majority of MFB, are absent or only focally detected in desmoid-type fibromatosis (Magro et al., 2002b). Conversely, desmoid-type fibromatosis usually shows beta-catenin expression (80% of cases) (Abraham et al., 2002), while MFB does not. Given the bland cytology, low-grade fibromatosis-like spindle cell metaplastic carcinoma may mimic lipomatous MFB (Sneige et al., 2001; Carter et al., 2006). Although spindle cells of this carcinoma may express alpha-smooth muscle actin, they are also positive for epithelial (cytokeratins, EMA) and

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myoepithelial markers (Sneige et al., 2001; Carter et al., 2006). In addition they do not express desmin and CD34, markers typically found in MFB.

Epithelioid cell MFB

The diagnosis of epithelioid cell MFB is often challenging, with the possibility of confusion with a malignant tumor, especially when dealing with small

biopsies. Making a correct diagnosis is primarily dependent on awareness by the pathologist of this unusual variant of MFB (Magro, 2009). Occasionally, an otherwise classic-type MFB may contain a minority of epithelioid cells (Magro, 2008), but the term “*epithelioid cell MFB*” should be restricted to those tumors composed, exclusively or predominantly (>50% of the entire tumor), of cells with epithelioid morphology (Reis-Filho et al., 2001; Magro et al., 2002a; Magro,

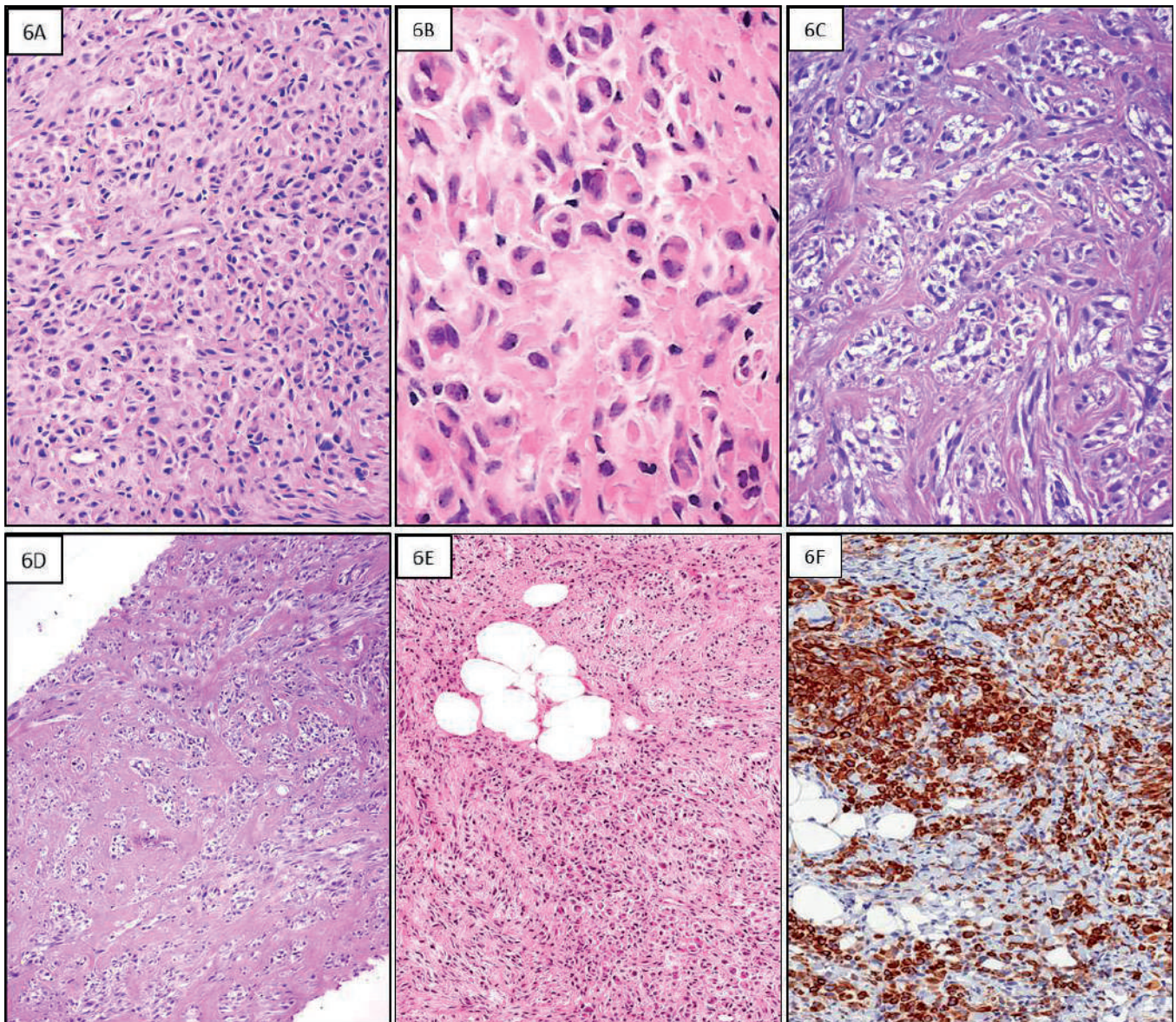


Fig. 6. Epithelioid cell MFB. **A.** Tumor is composed predominantly of medium-sized epithelioid cells haphazardly arranged in a fibrous stroma. **B.** Higher magnification showing mono- or multi-nucleated epithelioid cells with mild to moderate nuclear pleomorphism but without mitotic figures. **C.** Neoplastic cells may adopt a pseudo-alveolar growth pattern. **D.** Core biopsy showing nests of epithelioid, and less frequently, spindle-shaped cells embedded in a fibrous stroma. **E.** In some tumor areas neoplastic cells, showing a single-file arrangement, are closely intermingling with intra-tumoral adipocytes, mimicking an invasive lobular carcinoma. **F.** Neoplastic cells exhibit a diffuse cytoplasmic staining for WT1 (antibodies anti-N-terminus of WT1 protein; clone WT 6F-H2).

2008, 2009, 2012; Rosen, 2009). If these strict criteria are applied, epithelioid cell MFB is relatively rare, with only a few cases reported so far (Magro, 2009, 2012). Recognition of epithelioid cell MFB is crucial because this variant, showing a pseudo-infiltrative growth pattern, may result in a false diagnosis of invasive lobular carcinoma, especially on core needle biopsy (Magro, 2009, 2012; Bakuła-Zalewska et al., 2012; Arafah et al., 2015).

Grossly, the tumor, ranging in size from 15 to 30 mm. in largest diameter, presents as round to ovoid in shape, with well-circumscribed borders and smooth external surface. Cut section shows a firm, pale white to grayish solid tissue. Necrosis, cystic spaces, or hemorrhage are absent. Histological examination reveals a tumor with pushing borders, composed of medium-sized, epithelioid mono- or bi-nucleated cells containing pale to deeply eosinophilic cytoplasm and round to oval, eccentrically placed nuclei with small evident nucleoli (Fig. 6A). A mild to moderate degree of nuclear pleomorphism is often seen (Fig. 6B) (Magro, 2009, 2012). There is significant intra-lesional and inter-lesional variability in cellularity, with tumors homogeneously highly cellular and others showing alternating hypercellular and hypocellular fibrotic areas. Mitotic activity is absent to low (up to 2 mitoses per 10 high-power fields) and neither atypical mitoses nor necrosis are features of epithelioid cell MFB. Interestingly, neoplastic cells, set in a predominant fibrous stroma, usually adopt various architectural growth patterns, even within the same tumor. They are usually arranged in single cells, single cell files, nests, pseudo-alveolar, solid, or trabecular growth patterns (Fig. 6A-E). Keloid-like collagen fibers are frequently observed among neoplastic cells, but they can completely encase alveolar nests, resulting in the formation of neural-like structures, closely reminiscent of small peripheral nerves (Magro, 2009). While some cases of epithelioid cell MFB contain dispersed islands of mature adipose tissue throughout the tumor (Fig. 6E), a few cases may exhibit a prominent fatty component, accounting for approximately 40% of the entire tumor (Magro, 2009). Vascularization is represented by small-to medium-sized blood vessels with focal hyalinization of their walls. Immunohistochemistry, showing a diffuse expression of desmin and a variable immunoreactivity for alpha-smooth muscle actin, reveals the myofibroblastic nature of the neoplastic cells. Other markers of classic-type MFB, such as CD34, bcl-2 protein, CD99, CD10 and estrogen/progesterone receptors are variably expressed (Magro, 2009). Recently, it has been shown that, by using antibodies against the N-terminus of WT1 protein (clone WT 6F-H2), neoplastic cells of epithelioid cell MFB show a diffuse cytoplasmic staining (Fig. 6F) when compared with the other MFB variants (Magro et al., 2014e). Accordingly, WT1 may be considered as an additional marker of epithelioid cell MFB, which can be exploitable in daily diagnostic practice. Even with lower

percentage, epithelioid cell MFB shows chromosome abnormalities associated with the loss of the 13q14 region by FISH analyses (Magro et al., 2012c, 2013a).

Histogenesis of epithelioid cell MFB is still to be elucidated. It is possible to hypothesize that this variant reflects the plasticity of the precursor stromal cells to give rise to cells exclusively or predominantly with epithelioid morphology (Magro, 2008, 2009). Although epithelioid cell MFB should be viewed as a result of a variation within a morphologically continuous spectrum, this tumor poses serious diagnostic problems in daily practice. These difficulties are the result of the variable degree of nuclear pleomorphism and the wide variety of growth patterns (single cell, single cell files, pseudo-alveolar, solid or trabecular patterns) adopted by neoplastic cells (Magro, 2009). It is the single cell or single cell file arrangement that results in a striking resemblance to invasive lobular carcinoma (Fig. 6A-E), especially if the pathologist is dealing with an epithelioid cell component as the only cytotype seen in small biopsies (Fig. 6D). Malignancy is also suspected if neoplastic cells, closely intermingling with intra-tumoral adipocytes, exhibit a pseudo-infiltrative growth pattern (Fig. 6E). The suspicion of malignancy is also high if epithelioid cell MFB is associated with foci of in situ lobular carcinoma (Arafah et al., 2015). Accordingly, the distinction of epithelioid cell MFB from invasive lobular carcinoma is crucial. In this regard, it should be emphasized that, unlike MFB, invasive lobular carcinoma shows infiltrating margins and expresses epithelial markers, such as cytokeratins and EMA. Apart from invasive lobular carcinoma, epithelioid cell MFB needs to be distinguished from both benign or malignant tumors with epithelioid morphology. In this regard, primary leiomyomas and leiomyosarcomas of the breast may be predominantly composed of epithelioid cells (Roncaroli et al., 1993; Wei et al., 1993). These smooth muscle tumors differ from MFB in that they express, albeit with variable extension, h-caldesmon and they usually lack immunostaining for CD34, bcl-2, CD99 and CD10. In addition, leiomyosarcoma has infiltrating margins, nuclear pleomorphism, high mitotic activity, atypical mitoses, and necrosis. Among malignant tumors with epithelioid cell morphology, the possibility of a metastatic melanoma should also be considered. This malignant tumor can be easily diagnosed for its diffuse expression of S100 protein, variably associated with immunoreactivity of other melanocytic markers (HMB45, Melan A, MART-1 and Tyrosinase).

Although diagnosis of epithelioid cell MFB is difficult, not only on core biopsy but also in surgically resected specimens, it can be confidently rendered if morphological features are correlated with clinical and radiological information. In this regard, this unusual variant of MFB is suspected if the tumor has pushing borders, absent to low mitotic activity, and mild to moderate nuclear pleomorphism. Awareness of the possibility that an epithelioid cell tumor, especially in small biopsies, can be a MFB should prompt the

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pathologist to perform an immunohistochemical panel which includes appropriate markers for such a tumor.

Epithelioid cell MFB with multinodular growth pattern

The epithelioid cell variant of MFB may rarely be

composed of numerous, medium- to large-sized neoplastic cells showing mild to moderate/severe nuclear pleomorphism and a multinodular growth pattern (Magro et al., 2013a). This recently described variant should be recognized by pathologists because it does represent a potential diagnostic pitfall of malignancy

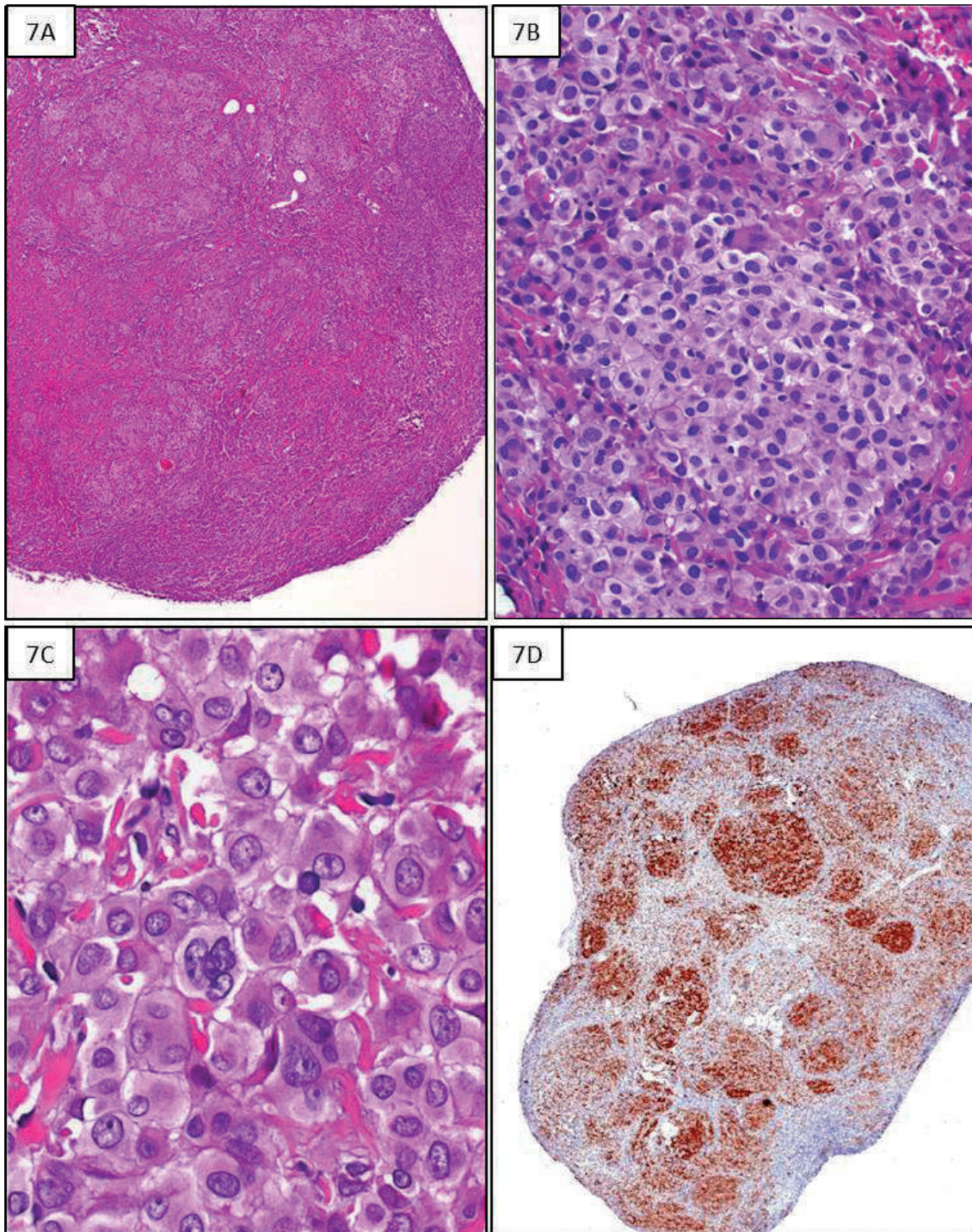


Fig. 7. Epithelioid cell MFB with multinodular growth pattern. **A.** Low magnification showing cellular tumor with well circumscribed borders and multinodular growth pattern. **B.** Neoplastic cells, with abundant eosinophilic cytoplasm and well delineated cellular borders, are tightly packed in a puzzle-like arrangement. **C.** Mono- or multi-nucleated cells contain vesicular nuclei with one or more prominent nucleoli. **D.** Immunostaining for desmin is helpful in highlighting the multinodular growth pattern of neoplastic cells.

(Magro et al., 2013a).

Grossly, the tumor presents as a well circumscribed, unencapsulated mass, measuring a few centimeters in its greatest diameter. On cut section, the tumor mass is whitish in color and firm in consistency. Histological examination, at low magnification, reveals a cellular lesion with multiple variable-sized nodules, vaguely reminiscent of a reactive lymph node with numerous follicles (Fig. 7A). Higher magnification shows tightly packed medium- to large-sized cells arranged in a multinodular growth pattern (Fig. 7B). Neoplastic cells exhibit abundant eosinophilic cytoplasm, well defined cellular borders and large, frequently pleomorphic, vesicular nuclei containing one or more prominent nucleoli (Fig. 7C). Some cells are bi- or multi-nucleated (Fig. 7C). Interestingly, keloid-like collagen fibers can be seen among neoplastic cells or around cellular nodules. Mitoses are rare (<1 mitosis x 10 high power field). Atypical mitoses and necrosis are absent. Mammary ducts or lobules are not seen within the tumor. Tumor areas outside the nodules are composed of neoplastic cells dispersed in the fibrous stroma as single cells, single cell files or nests, giving a close resemblance to invasive carcinoma (apocrine, oncocytic, pleomorphic lobular carcinoma).

Due to atypical cell component and unusual multinodular architecture, this tumor poses serious diagnostic problems in daily practice. The main differential diagnoses are invasive apocrine, oncocytic and pleomorphic lobular carcinomas (Eusebi et al., 1992, 2012). This is due to the fact that all these carcinomas are characterized by cells with abundant eosinophilic cytoplasm and large pleomorphic nuclei. Diagnosis of MFB is supported by the absence of infiltrative margins, high mitotic index, atypical mitoses, and necrosis. In addition, immunohistochemistry, revealing the expression of desmin (Fig. 7D), CD34 and alpha-smooth muscle actin, is crucial in confirming the myofibroblastic nature of the neoplastic cells. All carcinoma subtypes can be ruled out for the absence of epithelial markers expression. Other malignant tumors, such as metastatic melanoma, pleomorphic rhabdomyosarcoma or epithelioid sarcoma, can be more rarely considered in the differential diagnosis. In this regard, melanoma is excluded due to the absence of immunoreactivity to S100 protein and HMB-45. Although adult-type pleomorphic rhabdomyosarcoma shares desmin expression with this rare variant of MFB, the former is also variably stained with myogenin and Myo-D1. Unlike MFB, epithelioid sarcoma is stained with EMA and cytokeratins, and it usually lacks INI-1 expression (Hornick et al., 2009). Among benign tumors, epithelioid leiomyoma, angiomyolipoma and epithelioid schwannoma are needed to be distinguished. Unlike MFB, the former is diffusely positive for h-caldesmon, whereas CD34, CD99, and CD10 are usually negative. The absence of immunoreactivity to HMB-45 and S100 protein is extremely helpful in ruling out epithelioid angiomyolipoma and epithelioid

schwannoma, respectively.

Deciduoid cell MFB

Although in the context of an epithelioid cell MFB, a minority of cells may be larger in size with vesicular nuclei, only rarely they can adopt exclusively or predominantly a deciduoid-like morphology (Magro et al., 2008b). This morphological variant, labeled as “*deciduoid-like MFB*” differs from epithelioid cell MFB in that neoplastic cells are larger and closely packed, with more abundant eosinophilic cytoplasm and large and vesicular nuclei with prominent nucleoli. However, it is likely that epithelioid cell and deciduoid-like MFB represent a continuous morphological spectrum and the term “*epithelioid/deciduoid cell MFB*” seems to be more appropriate. Deciduoid cell MFB should be kept in mind by pathologists because its worrisome morphological features make difficult its recognition as MFB, representing a potential diagnostic pitfall of malignancy (Magro et al., 2008b).

Grossly, the tumor presents as a well circumscribed, unencapsulated mass, measuring 2 cm in its greatest diameter. On cut section, the nodular mass is whitish in color and firm in consistency. Histological examination shows a well-circumscribed tumor composed exclusively or predominantly of closely packed, large-sized, round to polygonal cells with a solid or trabecular growth pattern, focally arranged in nests (Fig. 8A). The cells, with well distinct borders, contain abundant eosinophilic glassy cytoplasm and large round nuclei with vesicular chromatin and single or multiple prominent nucleoli (Fig. 8B). The cytological appearance of this tumor is closely reminiscent of decidua. Interestingly, some neoplastic cells are binucleated, or may show eccentric nuclei with occasional eosinophilic intracytoplasmic inclusions, resembling rhabdoid cells. As in classic-type MFB, keloidal-like collagen fibers, sometimes with an amianthoid-like appearance, can be easily observed among cells or around cellular nests (Fig. 8B). Mitoses are rare (1 mitoses x10 high-power fields). Atypical mitoses, necrosis or haemorrhage are lacking. Mammary ducts or lobules are not entrapped within the tumor. Immunohistochemically, neoplastic cells show a profile similar to that seen in classic-type MFB (Magro et al., 2008b). The histogenesis of this unusual morphological variant of MFB can be explained if we assume that the stromal precursor cells, from which MFB arises, has the capability of adopting a wide cytological appearance, including a deciduoid-like morphology. The possibility that mammary stroma may undergo similar deciduoid-like changes in the setting of gynecomastia in diabetic patients supports this hypothesis (Magro et al., 2004).

Differential diagnosis includes both benign and malignant tumors, such as epithelioid leiomyoma, epithelioid schwannoma, epithelioid angiomyolipoma, invasive apocrine carcinoma, metastatic pleomorphic rhabdomyosarcoma, melanoma or malignant rhabdoid

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tumor (Magro et al., 2008b). Unlike deciduoid-like MFB, leiomyoma is positive for h-caldesmon, whereas CD34, bcl2-protein and CD99 are usually negative.

Angiomyolipoma and schwannoma can be easily ruled out because they are positive, respectively, for HMB-45 and S100 protein. Among the malignant tumors, due to

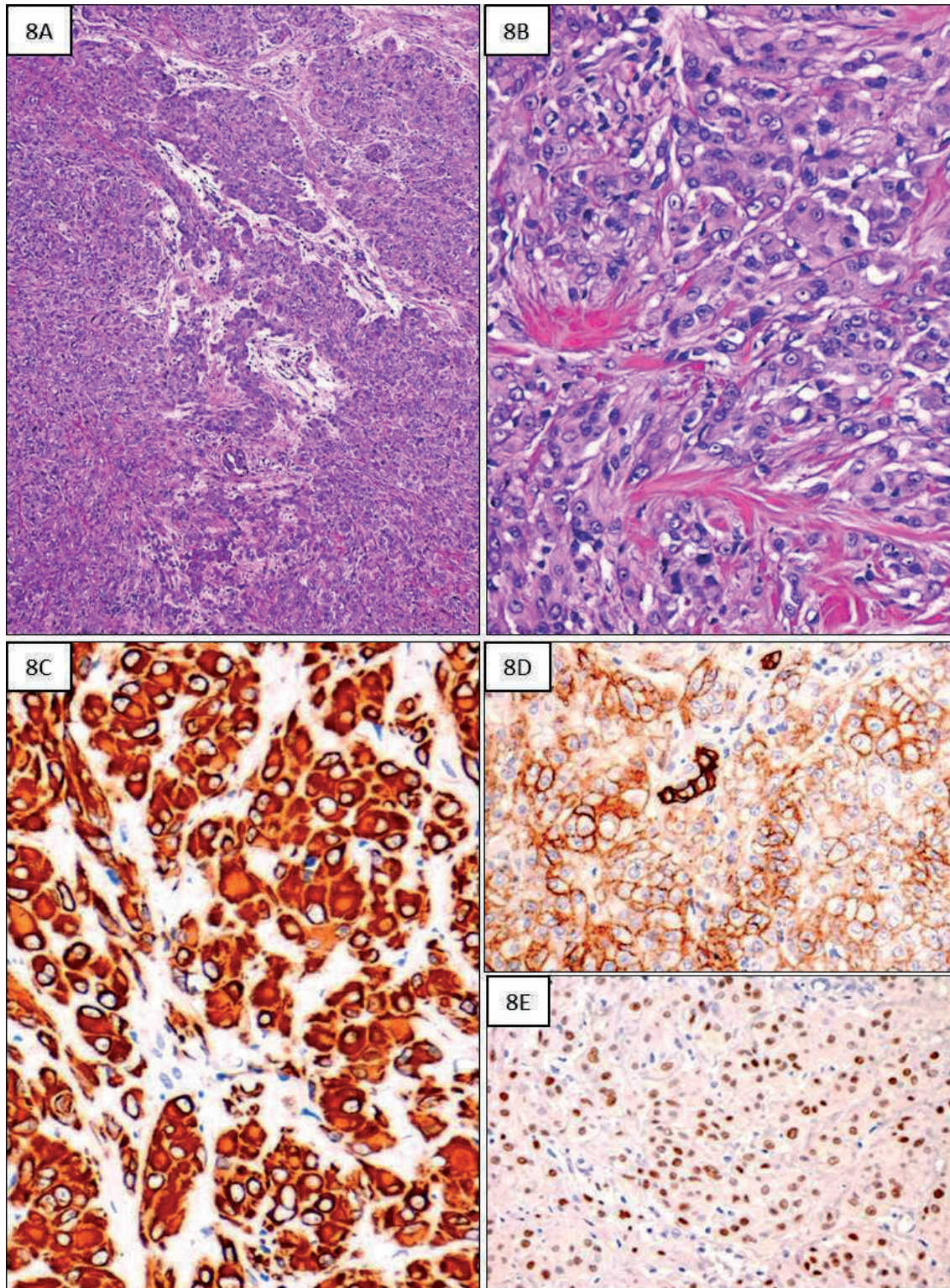


Fig. 8. Deciduoid cell MFB. **A.** Low magnification showing a cellular tumor with solid and trabecular growth pattern. **B.** Tumor is composed of large-sized neoplastic cells with deeply eosinophilic cytoplasm and vesicular nuclei, reminiscent of decidual cells. Keloidal-like eosinophilic collagen fibers are interspersed among neoplastic cells. **C.** Neoplastic cells show diffuse and strong cytoplasmic staining for desmin. They also show cell membrane staining for CD10 (**D**) and nuclear staining for estrogen receptors (**E**).

site of origin (breast), differential diagnosis mainly revolves around invasive apocrine carcinoma. This tumor, like deciduoid-like MFB, is composed of large-sized neoplastic cells with abundant eosinophilic cytoplasm and large vesicular nuclei containing prominent nucleoli (O'Malley et al., 2012). However, the absence of high mitotic activity, atypical mitoses, necrosis, and infiltrative margins argues against malignancy. Immunohistochemistry is mandatory for a correct diagnosis in that neoplastic cells of deciduoid cell MFB exhibit a profile similar to that seen in classic-type MFB (Fig. 8C-E), while they lack any staining for epithelial markers. Pleomorphic rhabdomyosarcoma, albeit desmin-positive, expresses myogenin and Myo-D1, markers which are absent in MFB. Melanoma and malignant rhabdoid tumor can be excluded for the absence of immunoreactivity to S100 protein or INI1 protein, respectively.

Palisaded/schwannoma-like MFB

Apart from schwannoma, other spindle cell tumors that may show nuclear palisading are “*intranodal palisaded myofibroblastoma*”, and occasionally “*uterine or soft tissue leiomyomas*”, “*angioleiomyomas*”, and “*GISTs (gastro-intestinal stromal tumors)*” (Weiss and Goldblum, 2008). Recently two cases of mammary MFB with remarkable features of nuclear palisading and Verocay-like bodies formation have been reported (Magro et al., 2013b). Due to this morphology, tumors were labeled as “*palisading or schwannian-like myofibroblastoma*”, emphasizing that they represent an uncommon morphological variant within the spectrum of mammary MFB (Magro et al., 2013b). Awareness of the possibility that mammary MFB may adopt a morphology similar to schwannoma is important to avoid diagnostic confusion.

Grossly, tumors, measuring 1.5 to 2 cm in their greatest dimension, show well-circumscribed and lobulated borders. The cut surface is whitish in color, with focal gelatinous appearance. Histological examination, at low magnification, reveals well-circumscribed, unencapsulated tumors, closely reminiscent of schwannoma (Fig. 9A). Entrapped fat tissue or mammary lobules/ducts are not observed. The tumor is composed of bland-looking, spindle-shaped cells which exhibit diffuse (>90% of the entire tumor) nuclear palisading with formation of numerous Verocay-like bodies (Fig. 9A,B). Neoplastic cells, with pale to eosinophilic cytoplasm and oval nuclei containing one small nucleolus, are set in an Alcian blue-positive myxoid stroma. As in classic-type MFB, keloid-like collagen fibers can be detected throughout the myxoid stroma or less frequently among neoplastic cells. A minor component (5-10% of the entire tumor) of an otherwise classic-type MFB can be usually found. Nuclear pleomorphism, mitoses, and/or necrosis are absent. Immunohistochemistry reveals the fibroblastic/

myofibroblastic nature of the neoplastic cells, showing a diffuse staining for desmin (Fig. 9C), CD34 and alpha-smooth muscle actin. Other markers of classic-type MFB, such estrogen and progesterone receptors, bcl-2 protein, CD99 and CD10, are variably expressed.

The most important differential diagnosis of palisading MFB includes schwannoma, a tumor that may rarely occur in the breast parenchyma (Jones et al., 1994). However, unlike MFB, schwannoma is typically encapsulated and it shows alternating Antoni A and B areas (Weiss and Goldblum, 2008). Immunohistochemistry, revealing the myofibroblastic nature of the neoplastic cells, along with no expression of S-100 protein (Fig. 9D), is mandatory for a correct diagnosis. Although benign tumors, the distinction of MFB from schwannoma is important because the latter may be part of familial or sporadic syndromes, such as type II neurofibromatosis or schwannomatosis, in which multiple schwannomas may arise from different sites of the body (Magro et al., 2013b). Apart from schwannoma, malignant spindle cell tumors that may exhibit nuclear palisading are mainly malignant peripheral nerve sheath tumors and leiomyosarcomas (Jones et al., 1994). However, unlike palisaded MFB, these malignant tumors commonly show infiltrating margins, cellular atypia, typical and/or atypical mitoses, as well and necrosis.

MFB with extensive myxo-edematous stromal changes

Rarely mammary MFB may undergo such extensive myxo-oedematous stromal changes that obscure the underlying neoplastic cells, rendering difficult its recognition as MFB (Magro et al., 2014d). Awareness of this possibility is important for pathologists when evaluating myxo-edematous lesions of the breast parenchyma, especially on small biopsies.

Grossly, the tumor presents as a well-circumscribed, unencapsulated nodular mass, measuring 2 cm across and soft in consistency. The cut surface shows a myxoid lesion, whitish in color. Histologically, at low magnification, a hypocellular, myxo-edematous lesion containing numerous blood vessels with fibrinoid material and foamy histiocytes in their walls, can be appreciated. The tumor, vaguely reminiscent of myxoma, is composed of abundant myxo-edematous extracellular matrix, only focally stained positively with Alcian blue (at pH 2.5), in which bland-looking spindled, stellate and, less frequently, multi-nucleated floret-like cells are dispersed (Fig. 10A-C). A variable amount of thin- to- thick eosinophilic collagen fibers, inflammatory cells, including mast cells, can be observed interspersed throughout the tumor. Mitoses, nuclear pleomorphism and necrosis are absent. Mammary ducts and/or lobules are not entrapped within the tumor. Notably, recognition of such a lesion as MFB is based on the identification of small-sized, residual cellular areas consistent with classic-type MFB (Fig.

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10D). These areas are composed of spindle-shaped cells haphazardly arranged in short fascicles interrupted by thick collagen fibers. Immunohistochemically, neoplastic

cells of the area consistent with classic-type MFB, as well as those set in the myxo-edematous stroma, show a myofibroblastic profile with expression of desmin,

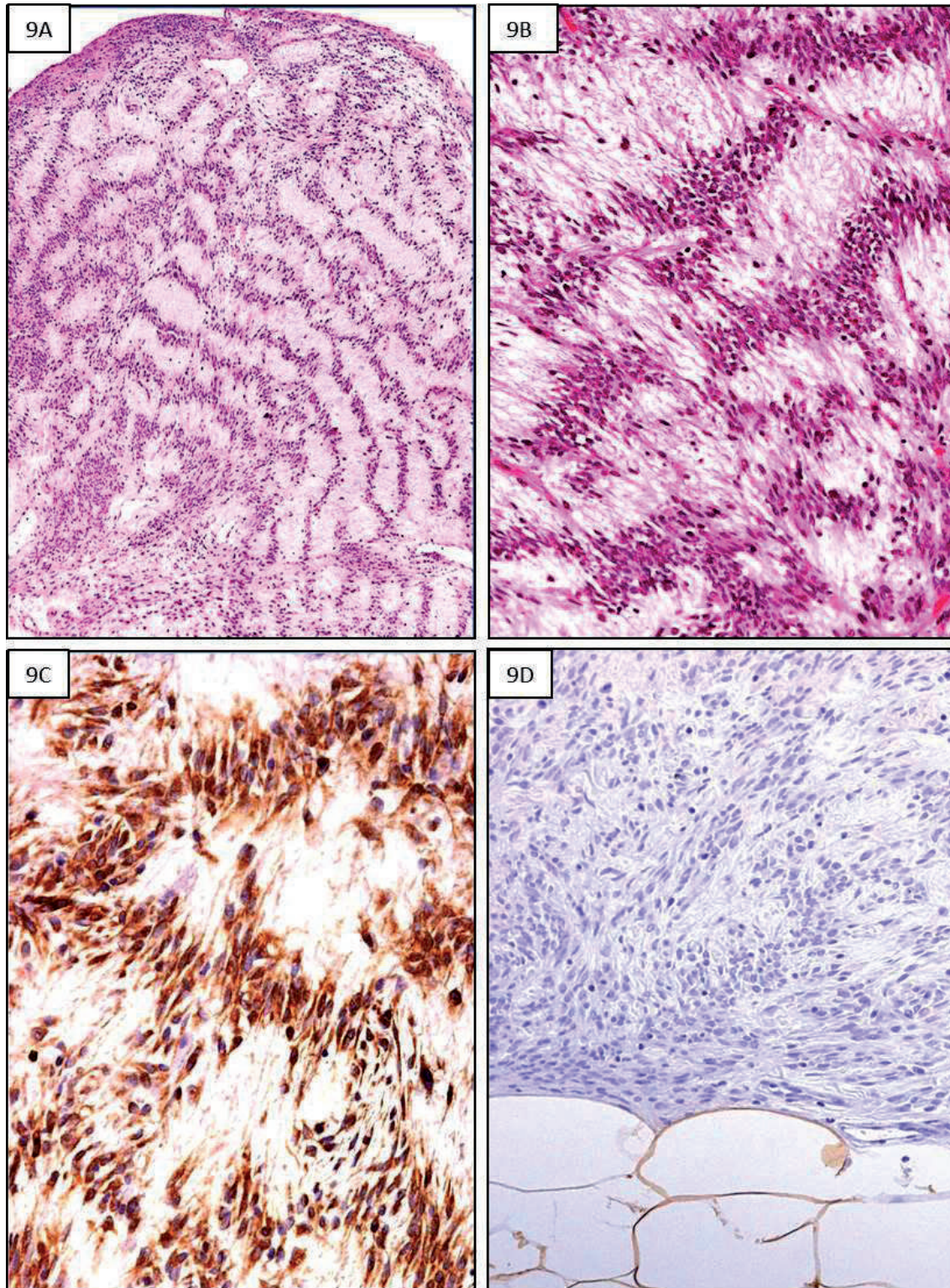


Fig. 9. Palisaded/schwannian-like MFB. **A.** Low magnification showing a tumor with pushing borders and Verocay-like bodies, closely reminiscent of schwannoma. **B.** At higher magnification spindle-shaped cells are arranged in rows of well aligned nuclei, separated by abundant myxoid matrix, with formation of Verocay-like bodies. **C.** Neoplastic cells are stained with desmin, revealing their myofibroblastic nature. **D.** They do not express S-100 protein as schwannoma does. Adipocytes at tumor periphery are stained with S100 protein and served as internal control.

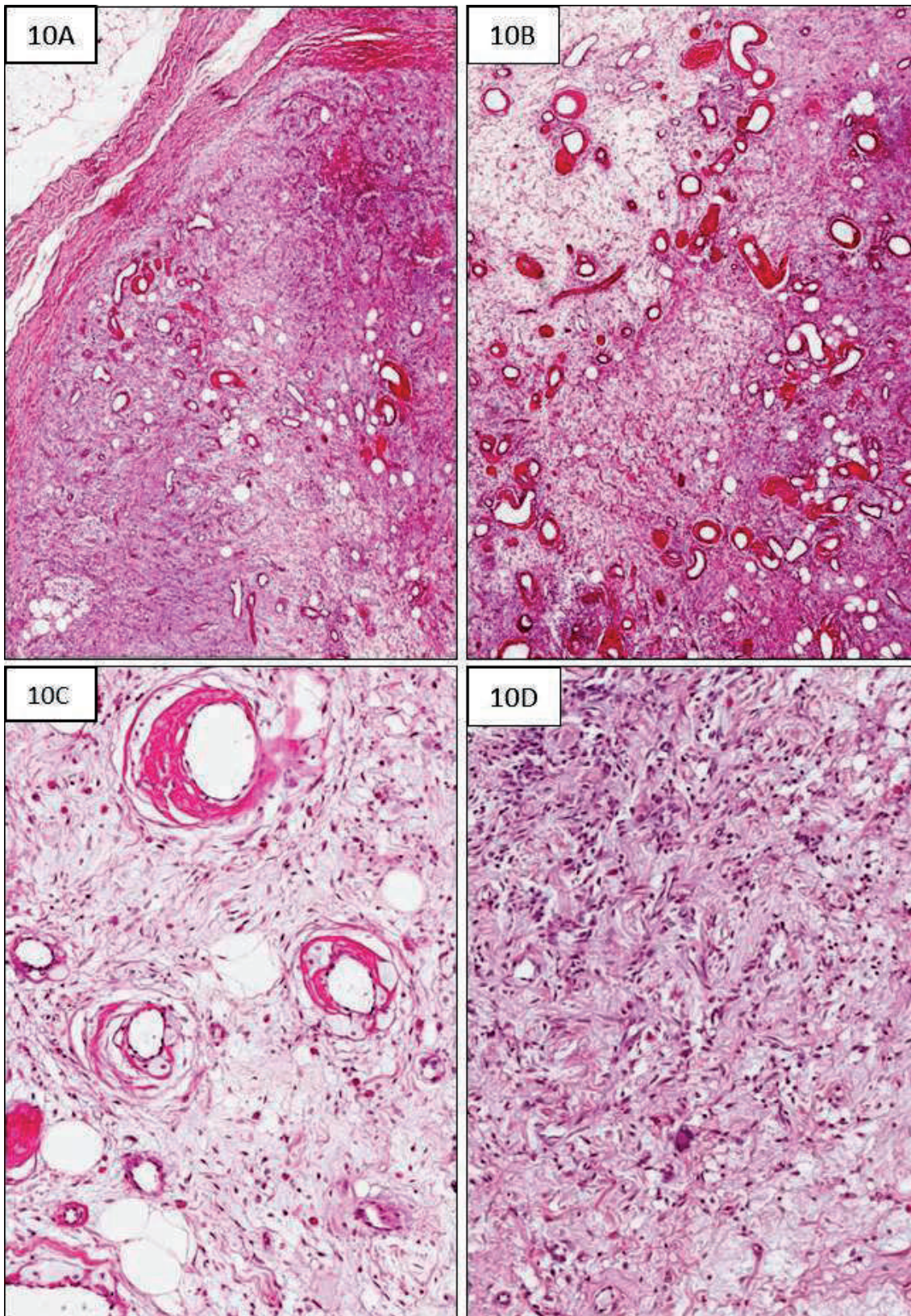
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Fig. 10. MFB with extensive myxo-edematous stromal changes. **A.** Low magnification showing a nodular, myxo-edematous lesion with pushing borders. **B.** Numerous blood vessels containing fibrinoid material in their walls are seen. **C.** Higher magnification showing blood vessels with accumulation of fibrinoid material and foamy histiocytes in their walls. **D.** Only focally a tumor area reminiscent of mammary MFB can be observed. Notably a multinucleated floret-like cell is evident (below).

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CD34 and alpha-smooth muscle actin (Magro et al., 2014b). Other markers of classic-type MFB, including bcl-2 protein, CD99, CD10 and estrogen/progesterone receptors, are variably expressed (Magro et al., 2014b). Pathologists should be aware of the possibility that long-standing mammary MFBs may undergo regressive myxo-edematous stromal changes, likely the result of local ischemic, traumatic or inflammatory stimuli. This is crucial to avoid confusion with other myxoid benign or malignant breast lesions. In this regard, tumor and tumor-like lesions which enter in the differential diagnosis are similar to those previously discussed for myxoid MFB. Before diagnosing a myxoid lesion of the breast parenchyma, a careful search for small residual areas of classic-type MFB is crucial for a correct diagnostic interpretation. As MFB with extensive myxo-edematous stromal changes contains blood vessels with sub-endothelial fibrin deposition, differential diagnostic problems may arise with pleomorphic hyalinizing angiectatic tumor. Although this tumor of intermediate malignant potential usually occurs as a painless subcutaneous lesion in the lower extremities, rare cases have been reported in the breast parenchyma (Tallarigo et al., 2009). Unlike myxoid MFB, pleomorphic hyalinizing angiectatic tumor contains numerous pleomorphic cells and it does not express desmin and/or alpha-smooth muscle actin (Tallarigo et al., 2009).

Mesenchymal hybrid tumors with MFB component

Rare cases of mammary benign stromal tumors composed of apparently distinct histotypes have been reported (Magro et al., 2001, 2002a). In this regard, MFB has been described to be admixed with a minor tumor component which resembles solitary fibrous tumor (Magro et al., 2002a) or spindle cell/pleomorphic lipoma (Magro et al., 1999; Ibrahim and Shousha, 2013). Actually, mammary MFB and solitary fibrous tumor are viewed as two distinct entities (Magro et al., 2000c; Falconieri et al., 2004; Fritchie et al., 2012). The former differs from the latter for significant desmin/alpha-smooth muscle actin expression and for the loss of genetic material from the 13q14 region (Magro et al., 2012b; Fritchie et al., 2012). Conversely, unlike MFB, solitary fibrous tumor exhibits a strong and diffuse nuclear STAT-6 immunoreactivity as the result of NAB2-STAT6 fusion gene, which is detectable in the majority of solitary fibrous tumors (Doyle et al., 2014). The coexistence of MFB with areas of classic-type spindle cell lipoma is not at all surprising. Both tumors share CD34 and CD10 expression and the loss of genetic material from the 13q14 region, suggesting a close histogenetic link between MFB and spindle cell lipoma (Magro et al., 2001, 2002a, 2007a, 2012b,c; McMenamin, et al., 2001). In addition, there is evidence that desmin, typically expressed by MFB, may be detected in a subset of spindle cell lipomas (Tardio et al., 2004), reinforcing a possible unifying histogenetic concept for these two tumors (Magro et al., 2002a).

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