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Soft Tissue Special Issue: Fibroblastic and Myofibroblastic Neoplasms of the Head and Neck

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Abstract

Fibroblastic and myofibroblastic neoplasms of the head and neck encompass a group of rare tumor types with often overlapping clinicopathologic features that range in biologic potential from benign to overtly malignant. Even neoplasms with no metastatic potential may provide significant therapeutic challenges in this region due to the unique anatomy of the head and neck. This review will cover the following entities, highlighting important clinical aspects of each neoplasm and then focusing on their characteristic histomorphology, immunophenotype, and molecular alterations: nodular and cranial fasciitis, fibrous hamartoma of infancy, nasopharyngeal angiofibroma, nuchal-type and Gardner fibromas, desmoid fibromatosis, dermatofibrosarcoma protuberans and giant cell fibroblastoma, solitary fibrous tumor, inflammatory myofibroblastic tumor, low-grade myofibroblastic sarcoma, infantile fibrosarcoma, low-grade fibromyxoid sarcoma, and sclerosing epithelioid fibrosarcoma. While some of these neoplasms characteristically arise in the head and neck, others are rarely described in this anatomic region and may therefore be particularly difficult to recognize. Distinction between these entities, however, is crucial, particularly as the molecular pathogenetic basis for these neoplasms are being rapidly elucidated, in some instances allowing for targeted therapeutic approaches.

Keywords Soft tissue tumors · Beta-catenin · STAT6 · MUC4 · NTRK · Translocation

Introduction

This review provides an overview of fibroblastic and myofibroblastic neoplasms that may arise in the head and neck, beginning with benign entities (some of which have only recently been recognized to be neoplastic), and ending with clinically aggressive fibroblastic sarcomas. While some of these neoplasms occur frequently (even exclusively) in the head and neck, others are rarely reported at these sites and require awareness of the possibility of such tumor types in order to arrive at the correct diagnosis. Several neoplasms discussed herein have recently described or well-known recurrent molecular alterations, while other neoplasms are yet genetically uncharacterized (Table 1). Special attention to recent immunophenotypic and/or molecular findings has been paid throughout this review in order to highlight diagnostically or clinically relevant updates for these neoplasms.

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Nodular and Cranial Fasciitis

Nodular fasciitis (NOF) is a benign myofibroblastic neoplasm that presents as a solitary subcutaneous mass on the upper extremities, trunk, or head and neck (up to 25% in some series) [1–4]. In the head and neck, NOF most commonly arises on the face or neck, but has also been reported in the oral cavity, orbit, parotid and ear [4–6]. While the age range at presentation is wide, the peak incidence is in the third and fourth decades [1, 2]. Tumors grow rapidly, typically with a preoperative duration of less than 3 months, may be tender or painless, and often measure less than 3 cm on excision [1–4]. Spontaneous regression prior to surgical resection is characteristic, with "recurrences" only occurring after incomplete surgical excision [1, 7].

Cranial fasciitis (CF) is a rare variant of NOF that arises on the scalp, most commonly in the temporal and parietal regions, with 80 reported cases since its original description in 1980 [8, 9]. In contrast to NOF, CF typically presents

Table 1 Summary of molecular findings in fibroblastic/myofibroblastic neoplasms

Tumor type	Molecular alteration
Nodular fasciitis	*USP6* rearrangements (70% *MYH9-USP6*)
Cranial fasciitis	*USP6* rearrangements
Fibrous hamartoma of infancy	*EGFR* exon 20 insertion/duplication mutations
Nasopharyngeal angiofibroma	*CTNNB1* exon 3 mutations
Nuchal-type fibroma	Unknown
Gardner fibroma	*APC* inactivation
Desmoid fibromatosis	*CTNNB1* exon 3 mutations in most sporadic cases *APC* inactivation in syndromic cases
Dermatofibrosarcoma protuberans	*COL1A1-PDGFB* fusion
Giant cell fibroblastoma	*COL1A1-PDGFB* fusion
Solitary fibrous tumors	*NAB2-STAT6* fusion
Inflammatory myofibroblastic tumor	*ALK* rearrangements (many fusion partners)
Low-grade myofibroblastic sarcoma	Unknown
Infantile fibrosarcoma	*NTRK* rearrangements in most cases (90% *ETV6-NTRK3)*
Low-grade fibromyxoid sarcoma	*FUS* rearrangements (90% *FUS-CREB3L2)*
Sclerosing epithelioid fibrosarcoma	*EWSR1* or *FUS* rearrangements

in infants prior to two years of age (with a male predominance), including some congenital tumors [8–10]. Lesions often cause a "saucer-like" erosion of the outer table of the skull, occasionally eroding through the inner table as well [8]. Although trauma has often been invoked for the etiology of both CF and NOF, evidence for this association is weak [4, 9].

On gross examination, NOF and CF are rubbery, fibrous or myxoid, focally cystic masses, which can appear circumscribed or somewhat infiltrative [1, 8]. Histologically, both are cellular lesions comprised of plump, spindled-to-stellate cells with bland ovoid nuclei arranged in loose fascicles (Fig. 1) [2, 3, 8]. More cellular lesions appear vaguely storiform or whorled. The stroma may be predominantly myxoid or collagenous, including areas of keloidal collagen (see Fig. 1c); prominent admixed capillaries are reminiscent of granulation tissue [1–3]. The cells notably lack nuclear atypia, hyperchromasia, or pleomorphism, but often display a high mitotic rate (10 per 10 HPF or higher) without atypical forms. Extravasated erythrocytes and chronic inflammation are common findings; more rarely, osteoclast-like giant cells may be prominent (see Fig. 1d) [3]. Immunohistochemistry (IHC) is not particularly helpful; smooth muscle actin (SMA) is characteristically diffusely positive, and focal desmin expression is sometimes seen [3].

Though NOF has been widely regarded to be reactive in nature, recent studies have identified recurrent *USP6* gene rearrangements in most cases, often with *MYH9* as the fusion partner (~70%), reclassifying these lesions as benign neoplasms [11–13]. *USP6* gene rearrangements have also been documented in CF [14]. Given that these tumors are self-limited, the concept of "transient neoplasia" has been proposed [12].

Fibrous Hamartoma of Infancy

Fibrous hamartoma of infancy (FHI) is a rare benign neoplasm that presents as a painless, solitary, subcutaneous mass in the axilla, trunk, or proximal extremities, though up to 10% occur in the head and neck region, including the cheek, scalp, and orbit [15–18]. FHI typically arises in infants less than 2 years of age (20% of cases are congenital), with a male predominance [17, 18]. FHI recurs locally in 15% of cases, without aggressive behavior or metastases [16–18]. Grossly, FHIs are poorly circumscribed, containing variable amounts of adipose and fibrous tissue, and measure between 3 and 5 cm [15].

Histologically, FHI displays a distinctive triphasic organoid architecture: (1) intersecting fascicles of bland spindle cells within a collagenous stroma, (2) mature adipose tissue, and (3) nodules of primitive mesenchyme composed of spindled to stellate cells within a loose basophilic or myxoid stroma (Fig. 2) [15, 19]. The proportions of these components are highly variable; when one predominates, diagnosis can be challenging, especially on biopsy. Around a quarter of cases contain prominent areas of hyalinized collagenous stroma with pseudoangiomatous slit-like spaces, mimicking giant cell fibroblastoma (see Fig. 2b) [17]. IHC reveals SMA expression in fibroblastic fascicles and CD34 in primitive mesenchyme as well as hyalinized collagenous areas [17, 19]. Interestingly, recent studies have revealed recurrent somatic *EGFR* exon 20 insertion/duplication mutations in FHI, supporting a neoplastic rather than hamartomatous etiology for this lesion [20, 21].

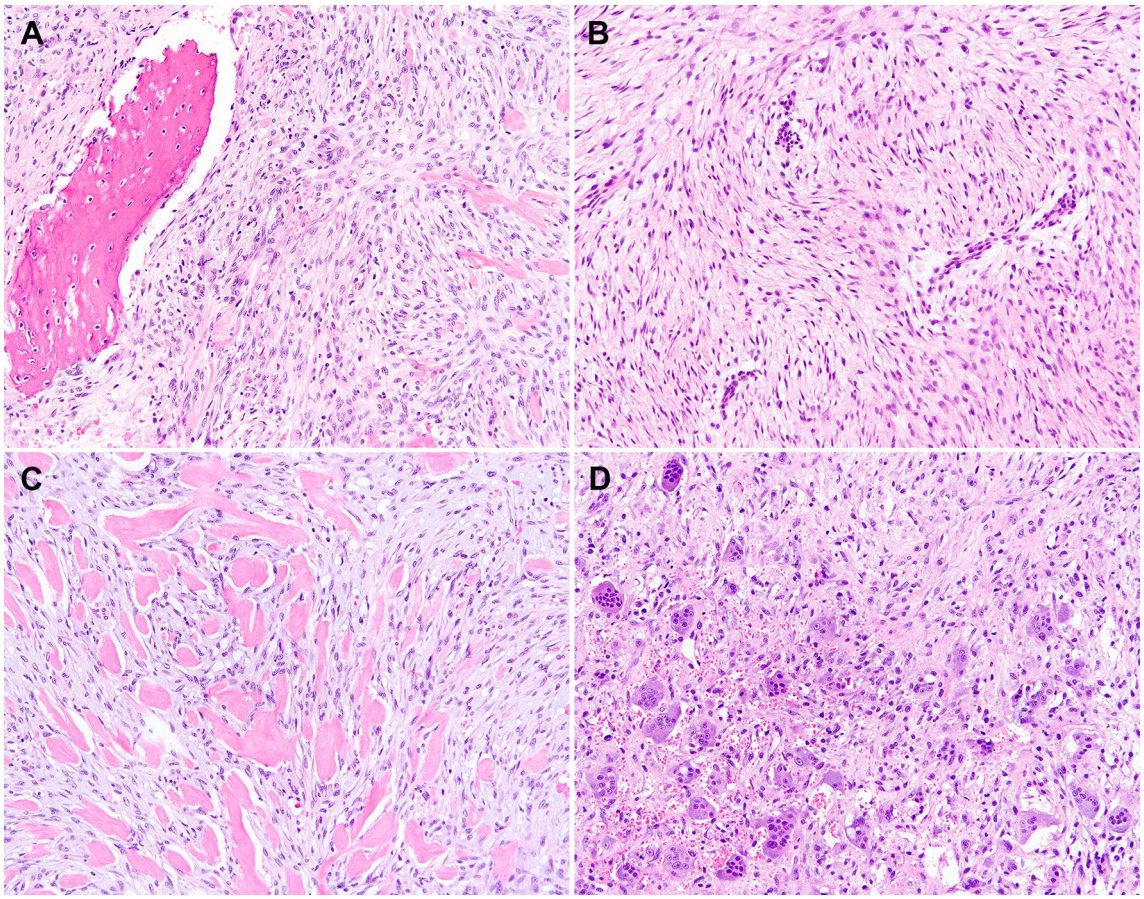

Fig. 1 **a** Cranial fasciitis infiltrating the outer table of the skull. **b** Cranial fasciitis composed of loose fascicles of myofibroblastic spindle cells with pale eosinophilic cytoplasm in a scant myxoid stroma. **c** An example of cranial fasciitis with prominent keloidal collagen bundles. **d** Nodular fasciitis with prominent osteoclast-like giant cells

Nasopharyngeal Angiofibroma

Nasopharyngeal angiofibroma (NA) is a rare fibrovascular neoplasm that arises in the posterolateral nasal wall almost exclusively in adolescent males [22–25]. NA classically presents with the triad of nasal obstruction, recurrent epistaxis, and a nasopharyngeal mass; this tumor may be locally aggressive, causing destruction of the paranasal sinuses, orbit, and skull base with intracranial extension in occasional cases [24, 25]. NA is associated with familial adenomatous polyposis (FAP) in some cases [26], and these lesions are thought to be hormonally driven given their predilection for adolescent males, although the etiology remains unclear [27]. Imaging is often diagnostic, obviating preoperative biopsy, and recurrence despite surgical resection may occur in up to a quarter of cases [22–25].

Macroscopically, NAs typically measure around 4 cm and appear polypoid or lobulated [23]. Histologically, they are composed of numerous variably-sized vascular spaces within a fibrous stroma containing plump spindled to stellate stromal cells (see Fig. 2c) [28]. Vascular spaces range from slit-like capillaries to dilated, branching vessels of varying thickness. Stroma may be loose and edematous or densely collagenous, often containing prominent mast cells [28]. By IHC, stromal cells are often positive for androgen receptor (AR) [29, 30] and show strong diffuse nuclear staining for β-catenin (see Fig. 2d) [31]. Studies have shown X chromosome gains, with associated gains in a copy of AR [27], as well as somatic mutations in exon 3 of *CTNNB1* (encoding β-catenin) in up to 75% of cases [31, 32].

Nuchal-Type and Gardner Fibromas

Nuchal-type fibroma (NTF) and Gardner fibroma (GAF) are two histologically similar yet distinct benign fibroblastic tumors that arise within different age groups and at different body sites, allowing for distinction in most cases. Unlike GAF, which affects males and females equally, NTF has a strong male predominance (4.5:1) [33–35]. Notably, NTF occurs most commonly in the 5th decade of life, while GAF is more common in young children, although age ranges are wide for both tumor types [34, 35]. While 70% of NTF arise

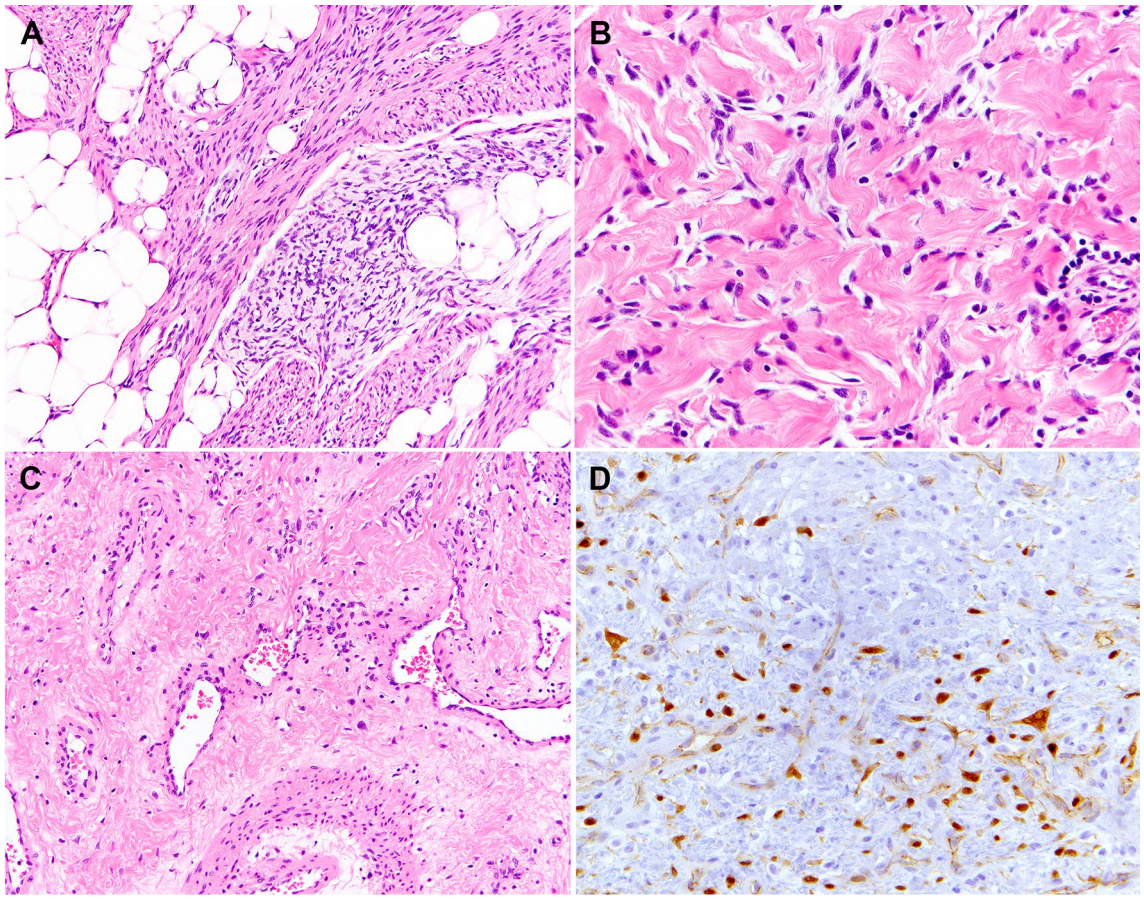

Fig. 2 **a** Fibrous hamartoma of infancy (FHI) showing the characteristic components: fascicles of spindle cells with eosinophilic cytoplasm, adipocytes, and nodules of stellate-to-spindle cells in a basophilic, myxoid stroma. **b** Areas of FHI often contain prominent stromal collagen and pseudoangiomatous slit-like spaces, mimicking giant-cell fibroblastoma. **c** Nasopharyngeal angiofibroma containing vessels of varying caliber within a hyalinized collagenous stroma with stellate fibroblasts. **d** Stromal cells in nasopharyngeal angiofibroma show aberrant nuclear beta-catenin

in the posterior neck, they may occur at extra-nuchal sites, including the face and upper back [33, 35]. In contrast, only 15% of GAF occur in the head and neck, with the majority arising on the trunk, especially the paraspinal region [34]. The vast majority of GAF are associated with FAP and *APC* germline mutations, making GAF a sentinel lesion for FAP; all patients diagnosed with GAF should undergo genetic counseling, along with their parents [36, 37]. Up to 50% of patients with NTF have diabetes mellitus [35]. Recurrence following surgical excision of either lesion is not uncommon [33–35]. Importantly, desmoid fibromatosis arises at the same site of up to half of surgically excised GAF [34].

Both lesions are poorly circumscribed, subcutaneous to dermal, hypocellular proliferations of nondescript, bland stromal fibroblasts admixed with collagen bundles (Fig. 3). Entrapped adipose tissue or skeletal muscle is seen in both lesions; entrapped nerves are common in NTF often with peripheral traumatic neuroma-like areas [34, 35]. IHC for CD34 is positive in the stromal cells of both lesions, with nuclear β-catenin seen in two-thirds of GAF [34–36]. Biallelic *APC* inactivation has been reported in FAP-associated GAF [37].

Desmoid Fibromatosis

Desmoid fibromatosis (DF) is a locally aggressive fibroblastic neoplasm, which occurs in the head and neck in up to 15% of cases, and in a greater percentage of cases in the pediatric population [38–40]. In this region, the neck is most commonly affected; tumors of the face, mandible, paranasal sinuses, larynx, orbit, and oral cavity are also reported [38–41]. Children and young adults are most commonly affected by head and neck DF, although the age range is wide [39–41]. Patients typically present with a painless, rapidly growing, deep-seated mass, though pain and neurological deficits have been reported for DF of this region [39, 41]. As in other locations, DF of the head and neck is associated with prior trauma or surgery, and more rarely with *APC*

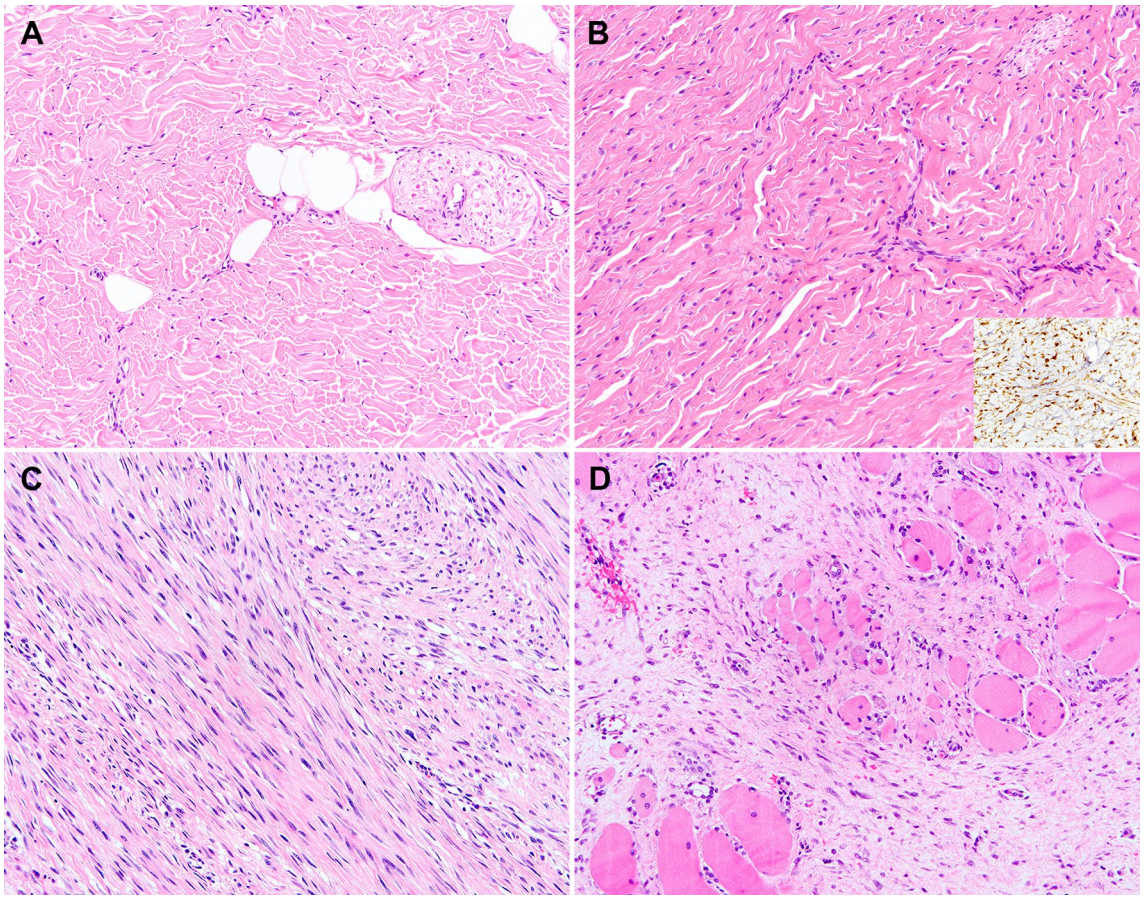

Fig. 3 **a** Nuchal-type fibroma entrapping fat and nerves. **b** Gardner fibroma with dense collagen, slit-like spaces, and aberrant nuclear beta-catenin (inset). **c** Desmoid fibromatosis composed of long, sweeping fascicles of uniform spindle cells with tapering nuclei. **d** Desmoid fibromatosis infiltrating through adjacent skeletal muscle

germline mutations, highlighting the likely multifactorial pathogenesis of DF [39, 42]. Head and neck DF presents unique therapeutic challenges given the unpredictable tumor behavior and proximity to vital anatomic structures, with rare fatalities reported due to airway or vascular involvement and high morbidity with attempts to achieve negative margins [39, 41]. Though DF is often locally aggressive, with a recurrence rate of up to 30% following surgical excision, stable disease without treatment is common, and spontaneous regression also occurs [39–42]. Treatment typically involves surgery, but given the complexities of operating at this site, may also include radiotherapy, chemotherapy, tamoxifen, and tyrosine kinase inhibitors such as imatinib and sorafenib; a conservative "watchful waiting" approach has become more common in recent years [39, 41].

Grossly, DF appears white-tan, whorled, and fibrous, with ill-defined borders [42, 43]. Histologically, the lesions are comprised of bland spindled to stellate fibroblasts arranged in long sweeping fascicles within a collagenous stroma, irregularly infiltrating through surrounding adipose tissue or skeletal muscle (see Fig. 3c and d) [42–44]. Stroma may contain areas of dense keloidal collagen or loose myxoid change, as well as prominent vasculature with perivascular edema. Tumor cells are uniform, lacking nuclear atypia or hyperchromasia. By IHC, SMA is usually positive, and up to 80% of DF show nuclear staining for β-catenin [42]; importantly, nuclear β-catenin is also observed in superficial fibromatoses and some sarcomas and is therefore not specific, nor entirely sensitive, for DF [45]. Somatic mutations in exon 3 of *CTNNB1* are found in up to 90% of sporadic DF, with the S45F mutation predicting a higher risk of local recurrence [46–48]; rarely, somatic *APC* mutations are identified instead [49].

Dermatofibrosarcoma Protuberans and Giant Cell Fibroblastoma

Dermatofibrosarcoma protuberans (DFSP) and giant cell fibroblastoma (GCF) are two cutaneous fibroblastic neoplasms that share clinicopathologic and genetic features. GCF predominantly affects pediatric patients and DFSP arises most often in young to middle-aged adults, although

both tumor types can affect newborns to elderly individuals [50–52]. Both have a male predilection and present with a slow-growing, painless, often protuberant, multinodular or polypoid cutaneous mass or plaque [50–52]. While they both most commonly arise on the trunk and proximal extremities, rare GCF and up to 15% of DFSP occur in the head and neck [50–53]. GCF and DFSP are associated with local recurrence in up to 50% of cases, especially if incompletely excised. Neither GCF nor conventional DFSP metastasize; however, the fibrosarcomatous variant of DFSP is associated with metastatic potential (up to 15%), typically to the lungs [54, 55]. Excision with wide surgical margins is the treatment of choice, although tyrosine kinase inhibitors such as imatinib may be administered to patients with tumors at sites where surgery would be morbid or disfiguring [52].

Grossly, both DFSP and GCF are ill-defined, infiltrative, predominantly dermal and subcutaneous lesions; DFSP arising on the scalp may invade periosteum or the skull [50, 52]. Histologically, both neoplasms display honeycomb infiltration through subcutaneous fat (Fig. 4), often with sparing of entrapped skin adnexal structures. DFSP is characterized by uniform, cytologically bland, hyperchromatic spindle cells arranged in a monotonous storiform pattern with low mitotic activity [52]. Occasional tumors contain distinctive myoid nodules (see Fig. 4b). GCF is relatively hypocellular, composed of a haphazard arrangement of bland spindle cells embedded in a myxoid to collagenous stroma, containing distinctive angiectoid spaces lined by floret-like giant cells (see Fig. 4d) [50]. Interestingly, hybrid tumors with areas of both DFSP and GCF can be seen; pure GCF may recur as hybrid tumors or as DFSP and vice versa, highlighting the close relationship between these tumor types [51]. Mitotic activity is not prominent in either neoplasm but is often high in the fibrosarcomatous variant of DFSP, which is characterized by a fascicular growth pattern and enlarged, vesicular nuclei with increased nuclear atypia (see Fig. 4c). Approximately 5% of DFSP (and rarely GCF) may display melanin pigment-containing tumor cells, known as Bednar tumors [52]. By IHC, both tumors are characteristically positive for CD34, though, notably, there is loss of CD34 staining in half of fibrosarcomatous DFSP [54]. Genetically, both DFSP and GCF are associated with rearrangements of 17q21 and

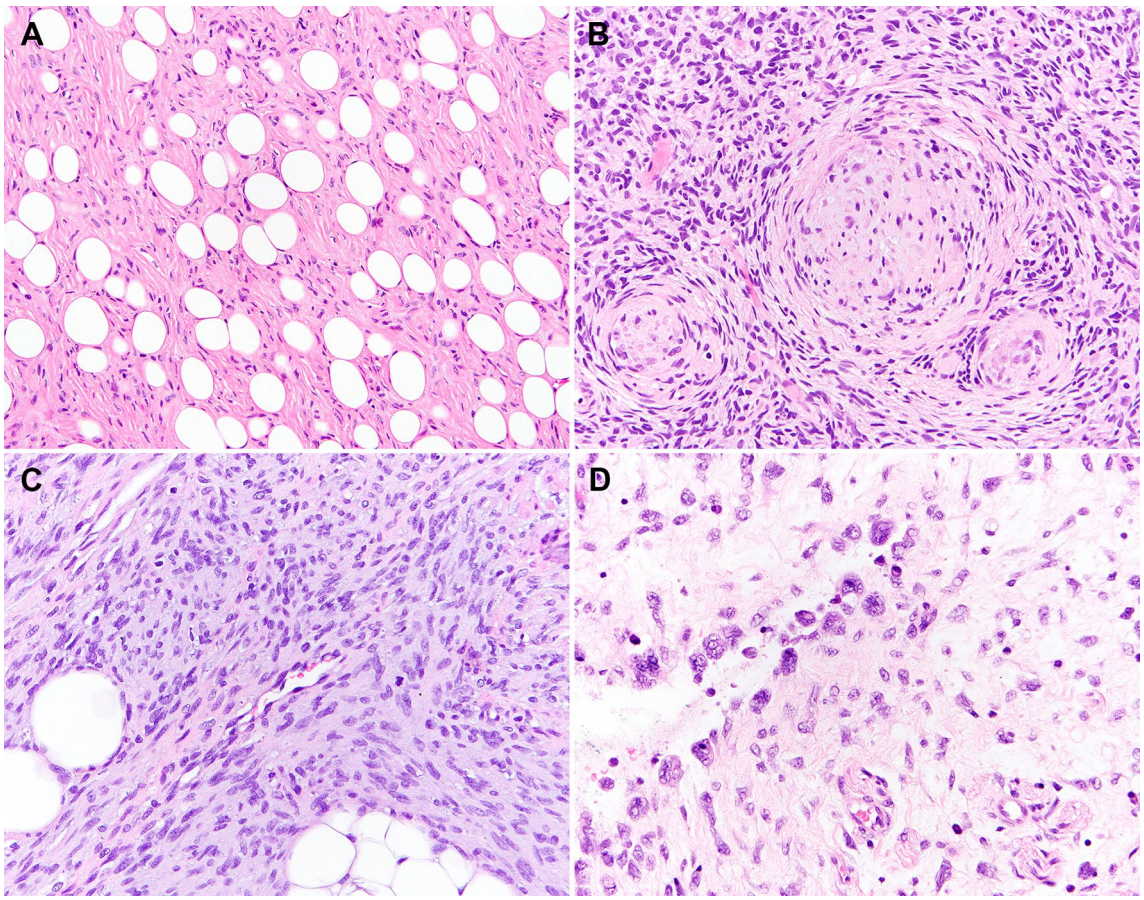

Fig. 4 **a** Hyalinized dermatofibrosarcoma protuberans (DFSP) showing the characteristic honeycomb growth pattern through subcutaneous adipose tissue. **b** DFSP with myoid nodules. **c** Fibrosarcomatous DFSP with fascicular architecture, plump nuclei, and increased mitotic activity. **d** Giant-cell fibroblastoma containing floret-like giant cells lining angiectoid spaces

22q13, resulting in a *COL1A1-PDGFB* gene fusion, further supporting the close relationship between these tumor types [56]. DSFP contains this fusion within supernumerary ring chromosomes, whereas GCF usually harbors a balanced t(17;22) translocation [50, 56]. Interestingly, studies in hybrid GCF-DFSP tumors have shown multiple copy gains of *COL1A1-PDGFB* in DFSP areas compared to GCF areas, as well as progressive copy number gains of the fusion gene in tumors progressing from GCF to hybrid GCF-DFSP to fibrosarcomatous DFSP [57, 58]. Recent studies have identified alternate *COL6A3-PDGFD* and *EMILIN2-PDGFD* fusion genes in DFSP [59, 60].

Solitary Fibrous Tumor

Solitary fibrous tumors (SFTs) are fibroblastic neoplasms of intermediate biologic potential with a peak incidence in middle-aged adults and no sex predilection [61, 62]. Although SFTs display a wide anatomic distribution, 10–15% occur in the head and neck, with the sinonasal tract, orbit, oral cavity and salivary glands most frequently involved [62–64]. Head and neck SFTs typically present as slow-growing painless masses, with site-related compressive symptoms and at smaller sizes (often 5 cm or less) than at other anatomic locations [62, 64]. Rates of positive surgical resection margins and local recurrences (up to 35%) are higher in SFTs of the head and neck, although rates of distant metastases are lower than at other sites [61–64]. Recurrences may occur greater than 15 years after primary excision [61]. Recent studies have demonstrated that clinicopathologic features associated with increased risk of metastasis and death from disease include older age, larger tumor size, increased mitotic activity, and presence of tumor necrosis, leading to the creation of a 3-tiered risk stratification model including these factors [61, 65].

Grossly, head and neck SFTs are often circumscribed, solid, white-tan and fibrous, with infiltrative growth and bony invasion occasionally seen [62, 66]. Histologically, SFTs are morphologically heterogenous, characterized by cytologically bland ovoid to spindle cells arranged in a paternless architecture within a hypocellular to densely cellular collagenous stroma, associated with prominent thin-walled, dilated, branching hemangiopericytoma-like ("staghorn") vessels (see Fig. 5) [66]. Stromal and perivascular hyalinization as well as keloidal-type collagen is common. Less common SFT morphologic variants include myxoid (with prominent myxoid stroma) (see Fig. 5c), epithelioid (with predominantly rounded cells with pale to eosinophilic cytoplasm), lipomatous or fat-forming (with interspersed mature adipocytes, formerly known as "lipomatous hemangiopericytoma"), and giant cell-rich (with scattered multinucleated giant cells, often lining dilated pseudovascular spaces, formerly known as "giant cell angiofibroma") (see Fig. 5d), all of which are seen in the head and neck [62, 63, 66]. Mitotic activity ranges from absent to brisk, with a greater risk for metastasis associated with mitotic activity equal to or greater than 4 per 10 HPF [61, 65]. Rarely, "dedifferentiation", or high-grade sarcomatous transformation with overt pleomorphism and necrosis, may be identified, and is associated with poor outcomes [67]. Characteristically, SFTs are diffusely positive for CD34 [66]. Importantly, recent studies have identified recurrent *NAB2-STAT6* gene fusions in nearly all SFTs [68–70]; subsequent studies revealed that nuclear expression of STAT6 by IHC is highly sensitive and specific for SFT (see Fig. 5a) [71]. More recent studies have revealed *TERT* promoter mutations in 20–30% of SFTs, which are associated with worse prognosis [72, 73].

Inflammatory Myofibroblastic Tumor

Previously termed "inflammatory pseudotumor" (among many other names), inflammatory myofibroblastic tumor (IMT) is a myofibroblastic neoplasm of intermediate biologic potential that arises predominantly in children, adolescents, and young adults in the lungs, abdomen, and pelvis [74, 75]. However, up to 15% of IMTs arise in the head and neck, where they are more common in adults [76–79]. Laryngeal IMTs present with hoarseness and dysphonia [77, 78], while sinonasal IMTs typically present with nasal obstruction and pain [76]. Systemic symptoms and laboratory abnormalities described in up to 30% of IMTs overall [75] are not typically reported in sinonasal or laryngeal IMTs [76, 77]. Laryngeal IMTs generally arise in the glottis and follow a benign clinical course following excision [77, 78], while sinonasal and oral cavity IMTs are clinically more aggressive, with higher rates of recurrence, metastasis and mortality despite treatment [79, 80]. Other reported sites include pharynx, neck, skull base, salivary glands, trachea, and orbit [74, 79].

Grossly, IMTs appear polypoid or nodular, with fibrous or fleshy, white-tan cut surfaces [75], typically less than 3 cm in the larynx and less than 7 cm elsewhere in the head and neck [78, 79]. Histologically, IMTs display three histologic patterns, sometimes all within the same lesion: a myxoid fasciitis-like pattern, a cellular spindle cell pattern, and a hypocellular fibromatosis-like pattern (Fig. 6) [74, 75]. The myxoid pattern is characterized by plump or stellate cells loosely arranged in a myxoid matrix with prominent vasculature and an associated inflammatory infiltrate of eosinophils, neutrophils and lymphocytes. The cellular spindle cell pattern is composed of uniform elongated spindle cells with vesicular chromatin within a collagenous stroma arranged compactly in a fascicular or storiform architecture, often with numerous admixed plasma cells and lymphocytes. The hypocellular fibrous pattern mimics DF, with relatively sparse elongated spindle cells arranged within fascicles of dense collagenous

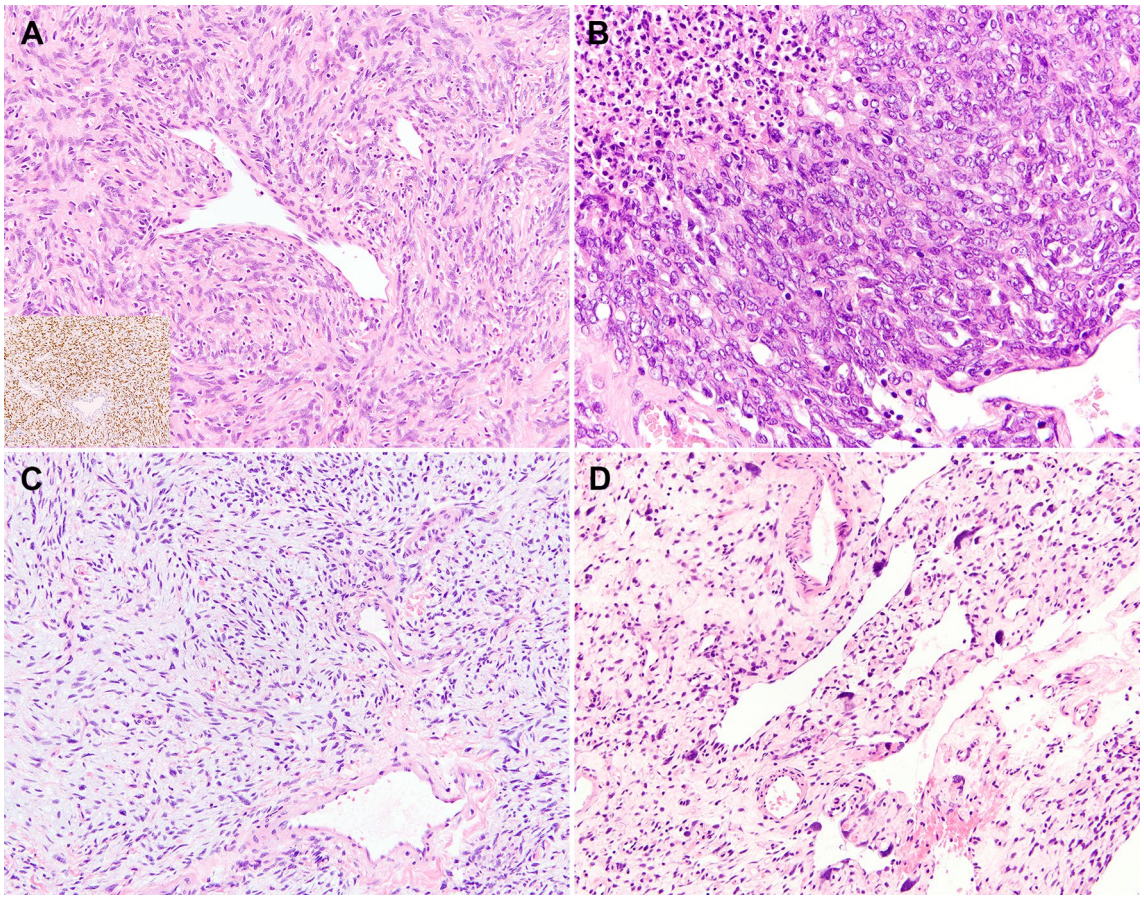

Fig. 5 **a** Solitary fibrous tumor (SFT) composed of short spindle cells with a patternless architecture within a collagenous stroma containing a branching hemangiopericytoma-like vessel; STAT6 is positive (inset). **b** High-risk SFT with high cellularity, nuclear atypia, and focal tumor necrosis (upper left corner). **c** Myxoid SFT can be challenging to recognize. Note the dilated, thin-walled blood vessels. **d** Giant cell-rich SFT with a hyalinized stroma

stroma containing scattered lymphocytes, plasma cells, and eosinophils. Nuclei typically display mild atypia and low mitotic activity, without atypical mitoses or hyperchromasia [81]. Some IMTs display scattered large polygonal "ganglion-like" cells with vesicular nuclei, prominent nucleoli, and abundant amphophilic cytoplasm [75, 81]. IHC for SMA and desmin is at least focally present in the vast majority of IMTs [75]. Recurrent chromosomal rearrangements of 2p23 resulting in *ALK* gene fusions are documented in approximately 60% of IMTs, with a wide range of fusion partners [82, 83]. Cytoplasmic ALK staining by IHC is observed in up to 60% of IMTs (see Fig. 6c), which correlates with *ALK* gene rearrangement by FISH [84–86]. IMTs lacking ALK expression are associated with older patient age and a more aggressive clinical course [76, 81].

Low-Grade Myofibroblastic Sarcoma

Low-grade myofibroblastic sarcoma is a rare, relatively indolent myofibroblastic neoplasm with low metastatic potential and a predilection for the extremities and head and neck [87, 88]. The oral cavity, especially the tongue, is a preferred site, although cases have been reported in the mandible, paranasal sinuses, larynx, neck, and skull base [88–90]. While low-grade myofibroblastic sarcoma can occur in pediatric and elderly patients, the majority arise during the 4th and 5th decades of life, commonly presenting as a painless, slowly enlarging mass or swelling, which may be submucosal, subcutaneous, intramuscular or rarely intraosseous [87–90]. Following complete wide surgical excision, local recurrence is uncommon and distant metastasis rare, although complete excision of head and neck tumors may be challenging [90, 91].

Grossly, tumors appear white-tan and fibrous, with ill-defined margins, and are often less than 5 cm in size within the head and neck [88, 91]. Histologically, tumors are composed of cellular fascicles (occasionally with a herringbone or storiform architecture) of atypical spindle cells within a collagenous and variably hyalinized stroma (Fig. 7) [87, 92]. The nuclei are tapering and wavy or plump and stellate, with

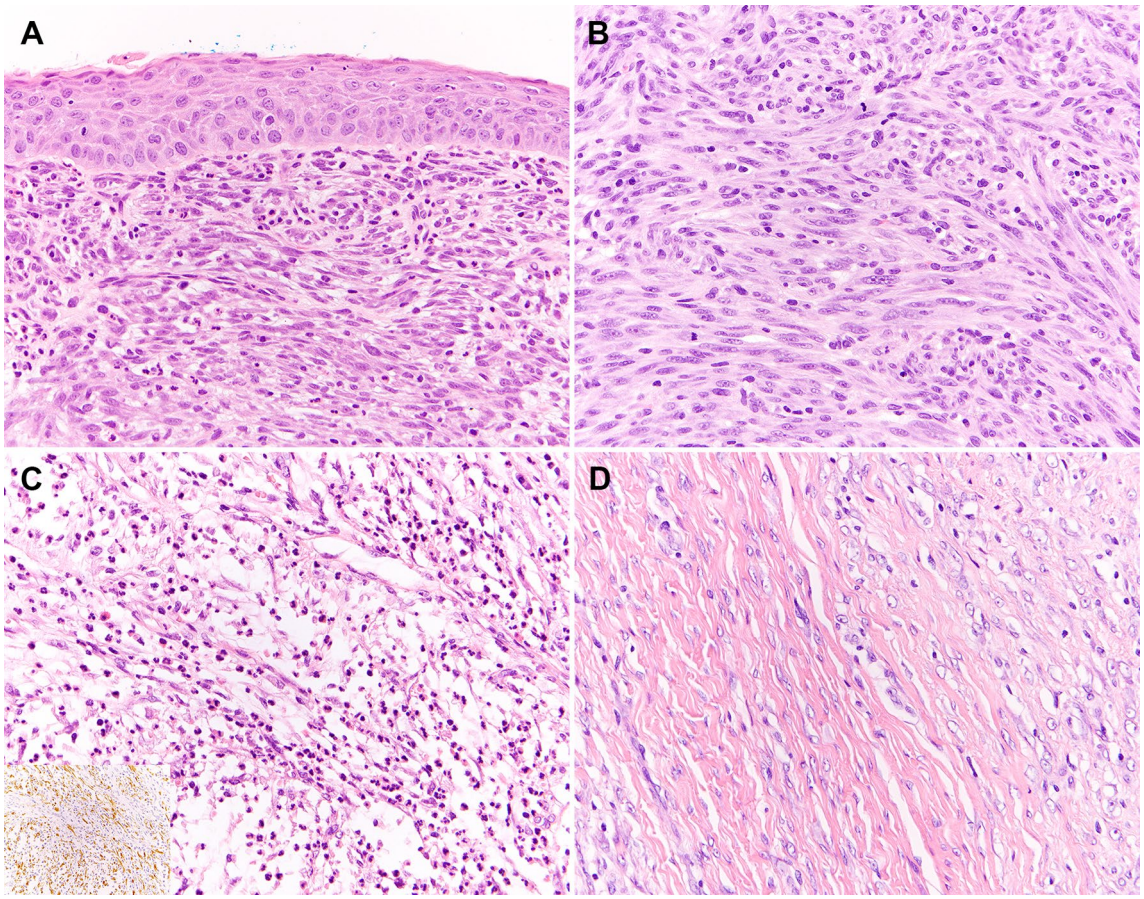

Fig. 6 **a** Inflammatory myofibroblastic tumor (IMT) of the trachea composed of uniform spindle cells. **b** A cellular IMT showing a fascicular growth pattern and scattered lymphocytes. **c** Myxoid IMT with abundant neutrophils and diffuse expression of ALK (inset). **d** Hypocellular IMT with dense stromal collagen mimicking desmoid fibromatosis

mild to moderate nuclear atypia and low mitotic activity (typically < 6 per 10 HPF) [92]. When intramuscular, low-grade myofibroblastic sarcoma displays diffuse infiltration among individual muscle fibers creating a characteristic "checkerboard" pattern, mimicking proliferative myositis (see Fig. 7a) [87]. Unlike IMT, lymphocytes and plasma cells are not prominent [92]. Low-grade myofibroblastic sarcoma displays a variable immunophenotype with some tumors positive for both desmin and SMA, and others positive for only one or the other [91, 92]. Importantly, up to a third of tumors show nuclear β-catenin by IHC, leading to potential confusion with DF [45]. No recurrent cytogenetic or molecular genetic alterations have been described thus far [90, 93].

Infantile Fibrosarcoma

Infantile fibrosarcoma (IFS), also known as congenital fibrosarcoma, is a rare malignant fibroblastic neoplasm with a male predilection, which arises predominantly in the limbs of infants [94–96]. Over a third of IFS are present at birth, with the majority diagnosed prior to 12 months [96–98]. Up to 15% of IFS occur in the head and neck, with reported sites including scalp, tongue, parotid, and orbit [94–97]. IFS typically presents as a rapidly enlarging painless mass with erythematous, often ulcerated, overlying skin, mimicking a vascular tumor [94, 95]. Local recurrence following surgical excision is common (25–40%), with metastases and mortality at around 10% [98–100]. While surgical excision is often curative, even with microscopically positive margins [98, 99], outcomes for tumors in the head and neck may be worse due to challenging surgery at this site [96]. Chemotherapy, and more recently targeted therapy with tyrosine kinase (NTRK) inhibitors, has been shown to be effective in surgically challenging or aggressive cases [97–99, 101].

Grossly, IFS are poorly circumscribed and lobulated, with a mean size of 5–6 cm (sometimes > 15 cm), and display fibrous or more often fleshy tan-gray cut surfaces with focal necrosis, hemorrhage or cystic degeneration [94]. Histologically, IFS are densely cellular lesions characterized by monomorphic primitive hyperchromatic ovoid to spindle cells arranged in tight fascicles (see Fig. 7c),

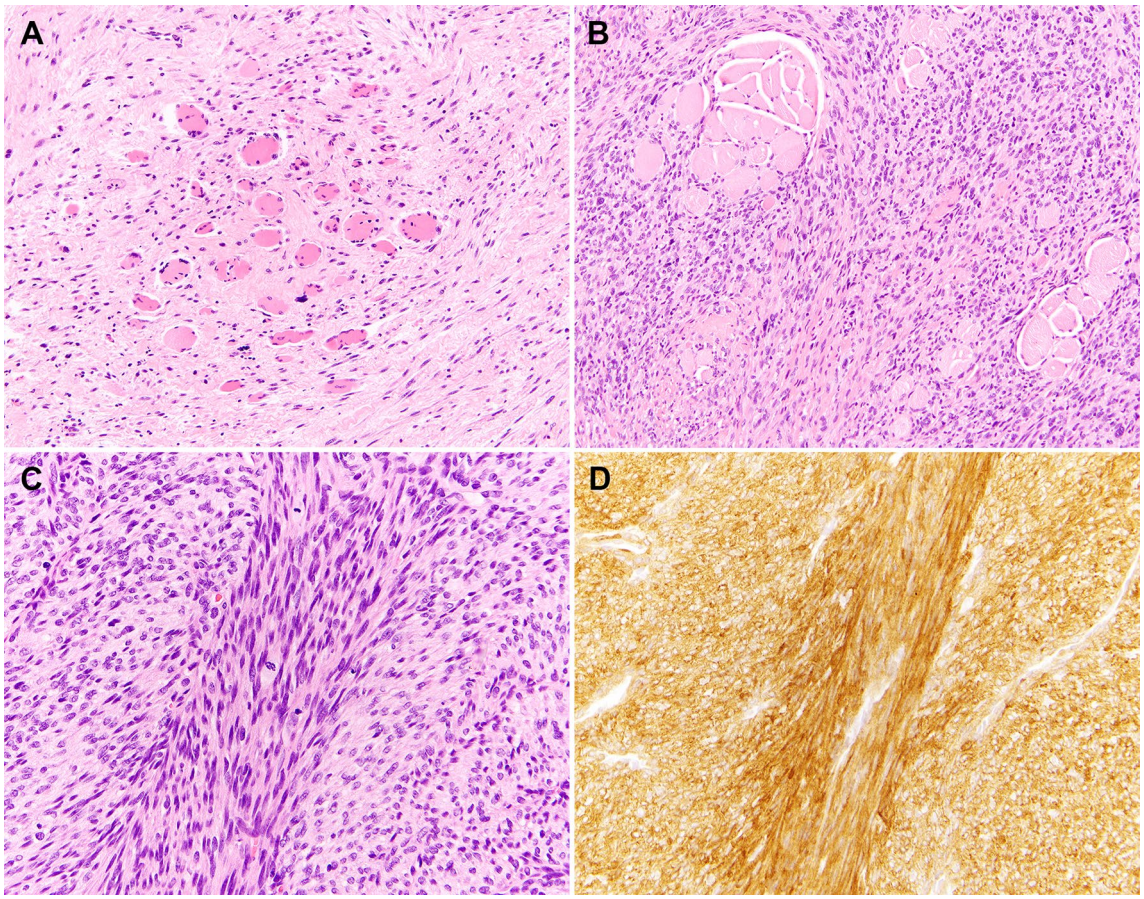

Fig. 7 **a** A relatively hypocellular low-grade myofibroblastic sarcoma showing a checkerboard pattern of infiltration through muscle fibers. **b** Low-grade myofibroblastic sarcoma displaying greater cellularity and nuclear atypia and characteristic infiltration through muscle fibers. **c** Infantile fibrosarcoma showing highly cellular, fascicular growth and a high mitotic rate. **d** Diffuse staining with a pan-TRK antibody in an infantile fibrosarcoma

within a variably collagenous stroma [94–96, 102]. Tumors are diffusely infiltrative and may display prominent dilated hemangiopericytoma-like vasculature, focal necrosis and hemorrhage, or an associated chronic inflammatory infiltrate and focally myxoid stroma (mimicking IMT) [102]. Mitotic activity is often conspicuous (> 10 per 10 HPF), but is not prognostically significant [94, 102]. The immunophenotype for IFS is non-specific, with variable expression of desmin, SMA, CD34 and S100 protein [102, 103]. Genetically, IFS harbor a t(12;15) translocation resulting in the oncogenic *ETV6-NTRK3* gene fusion in up to 90% of cases [104, 105], with alternate *EML4-NTRK3* fusions in a minority of cases [106]. IHC using a pan-TRK antibody is highly sensitive and specific for IFS with *NTRK* fusions (see Fig. 7D), typically with diffuse nuclear and cytoplasmic staining; of note, patchy staining can also be seen in a subset of FHI, DFSP, and low-grade myofibroblastic sarcoma [103, 107]. Recent studies have identified *NTRK1*, *NTRK2*, *BRAF*, and *MET* gene rearrangements in a small subset of cases [108–111].

Low-Grade Fibromyxoid Sarcoma

Low-grade fibromyxoid sarcoma (LGFMS) is a deceptively bland and relatively indolent malignant fibroblastic neoplasm with a propensity for late local recurrences and metastases [112–115]. LGFMS predominantly affects young adults in the 3rd and 4th decades of life, typically presenting as a painless slow-growing deep-seated mass of the trunk or proximal extremities [113], though superficial cases have been reported [116], as well as rare cases in the head and neck [117]. In studies with long-term follow up (greater than 10 years), LGFMS follows a protracted clinical course, with local recurrence in more than half and metastases in almost half of cases, often decades after primary excision [112–115].

Grossly, tumors are circumscribed and fibrous, with a wide size range [112]. Histologically, LGFMS is characterized by bland spindle cells with a whorled growth pattern within sharply alternating collagenous and myxoid areas (Fig. 8), the latter associated with arcades of delicate

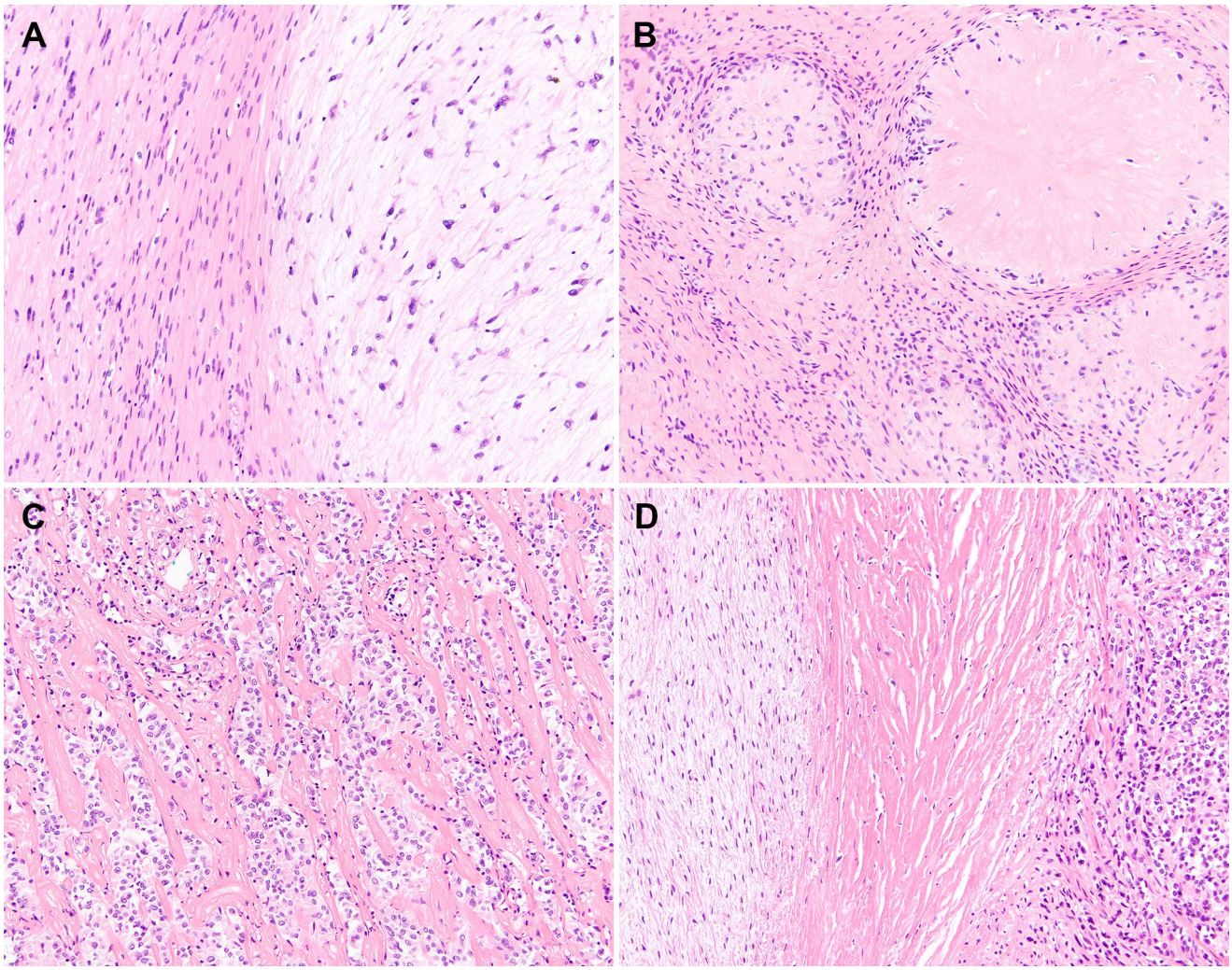

Fig. 8 **a** Low-grade fibromyxoid sarcoma (LGFMS) showing abrupt demarcation between collagenous and myxoid areas. **b** LGFMS with giant collagen rosettes. **c** Sclerosing epithelioid fibrosarcoma (SEF) composed of epithelioid cells arranged in trabeculae within a dense collagenous stroma. **d** Hybrid LGFMS-SEF showing classic LGFMS morphology with alternating collagenous and myxoid areas (left), and SEF morphology with cords of rounded cells with scant clear cytoplasm within a sclerotic matrix (right)

thin-walled blood vessels [112–114]. Some tumors, previously thought to be clinically distinct and designated "hyalinizing spindle cell tumor with giant rosettes", display prominent collagen rosettes consisting of nodules of acellular hyalinized collagen surrounded by palisading epithelioid fibroblasts (see Fig. 8b) [114]. Mitotic activity is generally low (< 1 per 10 HPF), and a subset of tumors may display foci of hypercellularity, hyperchromasia and moderate nuclear pleomorphism, or epithelioid cell morphology (resembling sclerosing epithelioid fibrosarcoma) [113]. By IHC, MUC4 is highly sensitive (> 99%) and specific for LGFMS [118]; EMA is also often positive (60–80%), and focal SMA expression is observed in around 30% of cases [117]. Genetically, LGFMS harbors recurrent t(7;16), and less frequently t(11;16), chromosomal translocations [119], resulting in the *FUS-CREB3L2* (over 90%) and *FUS-CREB3L1* gene fusions [120, 121], respectively, with rare reports of *EWSR1-CREB3L1* gene fusions in non-*FUS* rearranged tumors [122].

Sclerosing Epithelioid Fibrosarcoma

Sclerosing epithelioid fibrosarcoma (SEF) is a rare, aggressive malignant fibroblastic neoplasm that typically arises in young to middle-aged adults as a slowly growing, painless deep-seated mass on the trunk or extremities, and less commonly in the head and neck [123–127]. SEF may present as an intraosseous neoplasm [128], including sites such as the skull, mandible, and palate, with particularly aggressive clinical behavior due to local intracranial spread and challenges in surgical resection [124–126]. High rates of local

recurrence (> 50%), metastasis (40–50%), and tumor-related mortality are reported [123–125].

SEFs are generally large (> 5 cm), lobulated, grossly circumscribed masses displaying firm, gray-white, whorled cut surfaces [123, 124]. Histologically, SEFs are composed of monomorphic epithelioid cells with clear to eosinophilic cytoplasm arranged in cords, strands, and nests within a densely hyalinized sclerotic matrix (see Fig. 8c) [123]. Peripheral infiltration of surrounding muscle, fascia, or periosteum is frequently seen, with a subset of SEF showing focal necrosis or fibromyxoid regions closely resembling LGFMS [124, 129]. By IHC, 80–90% of SEFs are strongly and diffusely positive for MUC4 [129], with EMA positive in around 40% and keratins typically negative, which is helpful to distinguish SEF from metastatic carcinoma. Recurrent gene fusions of *EWSR1-CREB3L1* are found in the majority of SEFs, with *EWSR1-CREB3L2* or *FUS-CREB3L2* more rarely reported [125, 130, 131]. Given their overlapping clinicopathologic, immunophenotypic, and molecular features, in addition to reports of tumors presenting as one and recurring as the other, as well as hybrid tumors (see Fig. 8d), LGFMS and SEF are considered to be related neoplasms [129, 131]. A recent study reported *KMT2A* gene rearrangements (some with a *YAP1* fusion partner) in a subset of MUC4-negative SEFs [132].

Summary

Fibroblastic and myofibroblastic neoplasms of the head and neck include rare tumor types that pose significant diagnostic and therapeutic challenges. While some entities have characteristic histologic features, others show significant morphologic overlap (particularly on biopsy specimens) and require IHC or ancillary molecular testing for accurate diagnosis. Awareness of these entities in the head and neck and knowledge of their clinical behavior can help avoid unnecessarily aggressive treatment for benign tumors and ensure adequate surgery, systemic therapy (when relevant), and appropriate follow-up for intermediate and malignant neoplasms.

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