Pediatric Surgical Pathology of Sarcomas of the Head and Neck

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Introduction

One third of pediatric sarcomas occurs in the head and neck region. They represent about 12% of all pediatric malignancies in this site and are occasionally associated with genetic syndromes or previous radiation exposures. Males and females are equally affected, with a more frequent occurrence in the first decade of life [1]. The sites commonly involved include skin and soft tissues, followed by bones of the skull and face and, less frequently, oral cavity, larynx, and upper airways (Table 31.1) [1]. A correct histological classification is crucial in planning adequate therapeutic strategies. Rhabdomyosarcomas are the most frequent histotype, accounting for about 35–50% of all sarcomas in this region (Table 31.2) [1]. According to SEER (Surveillance, Epidemiology, and End Results) data, less than 30% of patients present with a stage I disease [1]. Most of the patients receive a pre-therapy biopsy or a radical excision according to international guidelines for pediatric sarcomas and are enrolled in the specific therapeutic protocols active in Europe and the USA. The histologic diagnosis may be particularly challenging in head and neck because of the anatomic characteristics of this region that can represent an obstacle to the adequate sampling or may predispose to artifacts [2, 3]. The prognosis of head and neck sarcomas, like in other sites, is influenced by the histotype, tumor stage, and patient's age, although the anatomy of the region may be associated with a more aggressive behavior related to the proximity with vital structures and the difficulty to obtain a radical excision in case of limited response to chemotherapy. An adequate histologic sampling and an appropriate triage of the biopsy is important to define and fully characterize the majority of pediatric sarcomas, thus limiting the number of unclassifiable tumors. Apart from the material for histologic diagnosis, touch imprints for fluorescence in situ hybridization (FISH) and freezing of a tumor fragment should be available for biological studies [4].

Table 31.1 Distribution of malignant soft tissue tumors in head and neck region (modified from SEER)

Site	%
Skin soft tissue	46
Bones of skull	21
Nasal cavity, sinuses, and middle ear	13
Nasopharynx	8
Oral cavity	4
Oropharynx	3
Others	5

Table 31.2 Distribution of histotypes of soft tissue tumors in head and neck region (modified from SEER)

Histotype	%
Rhabdomyosarcoma	48
Malignant peripheral nerve sheath tumors	4
Synovial sarcoma	2
High-grade undifferentiated sarcoma (ex malignant fibrous histiocytoma)	11
Bone tumors and others[a]	15

[a]Chordomas; osteosarcoma; chondrosarcoma

Rhabdomyosarcomas

Definition Rhabdomyosarcomas are aggressive tumors showing morphological, immunohistochemical, and ultrastructural features of skeletal muscle differentiation [5]. They are one of the most common solid tumors in children

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and adolescents. Approximately 35% of rhabdomyosarcomas occur in the head and neck [6], where they account for 35–40% of all sarcomas. About 20% involve the nasal cavity, nasopharynx, and nasal sinuses [6–8].

Clinical Presentation Although rhabdomyosarcomas tend to occur more often in males than in females, this difference is lacking in the head and neck region [7]. According to the tumor site, rhabdomyosarcomas of the head and neck region are traditionally divided into parameningeal tumors [9], localized in proximity to meninges, nasal cavities, nasopharynx, paranasal sinuses, middle ear, infratemporal and pterygopalatine fossae, and non-parameningeal tumors, equally distributed in the soft tissues of head and neck, including orbit, face, nose, skull base, external ear, oropharynx, and oral cavity [7, 10–12]. The early signs may be non-specific, including sinonasal or auricular duct congestions sinusitis, epistaxis, facial pain, swelling, and ear pain [10]. Neurologic symptoms (cranial nerve deficits, hearing loss) should prompt to the possibility of a malignant tumor involving the skull base or the central nervous system. Rhabdomyosarcomas arising from soft tissues present as deep-located masses, while rhabdomyosarcomas located in oral, pharyngeal, or nasal cavities present as painless submucosal polypoid masses, sometimes with a grape-like appearance.

Classification/Subtypes Based on morphological and molecular features, the following subtypes of rhabdomyosarcomas are recognized by the last edition of WHO: (1) embryonal rhabdomyosarcoma (conventional and anaplastic) [13]; (2) alveolar rhabdomyosarcoma [14]; (3) spindle cell/sclerosing rhabdomyosarcoma [15]; (4) pleomorphic rhabdomyosarcoma [16]. Embryonal rhabdomyosarcoma is the most common (50–70% of cases) subtype of rhabdomyosarcoma in the head and neck region, mainly in the orbit, nasopharynx, middle ear, and oral cavity (Table 31.3) [12, 23–25] (Fig. 31.1). As in other sites, most patients are children with an age ranging from 3 to 10 years (mean age 6.2 years). The alveolar subtype accounts for approximately 20–30% of the cases (Table 31.3) [12, 23, 25]. Spindle cell/sclerosing rhabdomyosarcomas are relatively rare (3–5%) and affect both children and adults with the tendency to arise in children mostly in paratesticular and head and neck region where they can represent up to 52% of all rhabdomyosarcomas [24, 26, 27]. There is a predilection for males, with a male to female ratio of up to 6:1. Pleomorphic rhabdomyosarcoma is extremely rare in the head and neck region in children [28].

Macroscopic Features Grossly, rhabdomyosarcomas present as poorly circumscribed, fleshy, pale to tan masses. A subset of rhabdomyosarcomas occurring in cavities like oral cavity or in the ear may show a botryoid morphology with a grape-like, polypoid endoluminal growth covered by mucosa. In alveolar rhabdomyosarcoma necrotic and/or hemorrhagic areas are often seen. Unlike the other subtypes of rhabdomyosarcomas, spindle cell/sclerosing rhabdomyosarcoma has a fibrous appearance, often with a white to tan and whorled cut surface.

Microscopic Features Embryonal rhabdomyosarcoma partially recapitulates the morphological, immunohistochemical, and ultrastructural features of the different stages of embryonal and fetal development of the skeletal muscle. Conventional-type embryonal rhabdomyosarcoma is composed of small- to medium-sized stellate/round/ovoid cells with little amphophilic cytoplasm and hyperchromatic nuclei without prominent nucleoli. A variable number of these cells show features of skeletal muscle differentiation, such as larger size, spindle or round/polygonal/epithelioid shape, as well as more deeply eosinophilic cytoplasm. These cells, labeled *"rhabdomyoblasts,"* are usually large cells with abundant deeply eosinophilic fibrillar cytoplasm and eccentric nuclei (Fig. 31.2). Occasionally they may be spindle-shaped and contain intracytoplasmic cross striations. Multinucleated rhabdomyoblasts, closely reminiscent of secondary fetal myotubes, can also be seen. Neoplastic cells are haphazardly arranged and characteristically set in loose, myxoid, usually paucicellular stroma alternating with more dense, highly cellular zones.

Table 31.3 Clinicopathologic features of head and neck rhabdomyosarcoma: review of the literature

Reference	Histotype			Age Range (median)	Sex		Site	
	ERMS	ARMS	SRMS		M	F	Parameningeal	Non-parameningeal
Reilly et al. [10]	11	6	/	0,7–19,2 (6,9 y)	7	10	13	4
Simon et al. [12]	40	9	/	1–72 (6,2 y)	–	–	25	12
Andrade et al. [17]	564	227	/	1,5-72y (14,3 y)	–	–	11	16
Buwalda et al. [18]	20	2	/	0,5–12,4 (4,8 y)	–	–	16	6
Chigurupati et al. [19]	1	3	/	0–7 (3,5 y)	2	2	1	3
Kraus et al. [20]	61	5	/	0, 3–19, 9 (7,7 y)	42	27	31	38
Sercarz et al. [21]	22	10	/	1–18 (7 y)	16	16	4	28
Ahmed and Tsokos [22]	/	6	/	9–16 (8y)	2	4	3	3

OS overall survival, *ERMS* embryonal rhabdomyosarcoma, *ARMS* alveolar rhabdomyosarcoma, *SRMS* spindle cell/sclerosing rhabdomyosarcoma

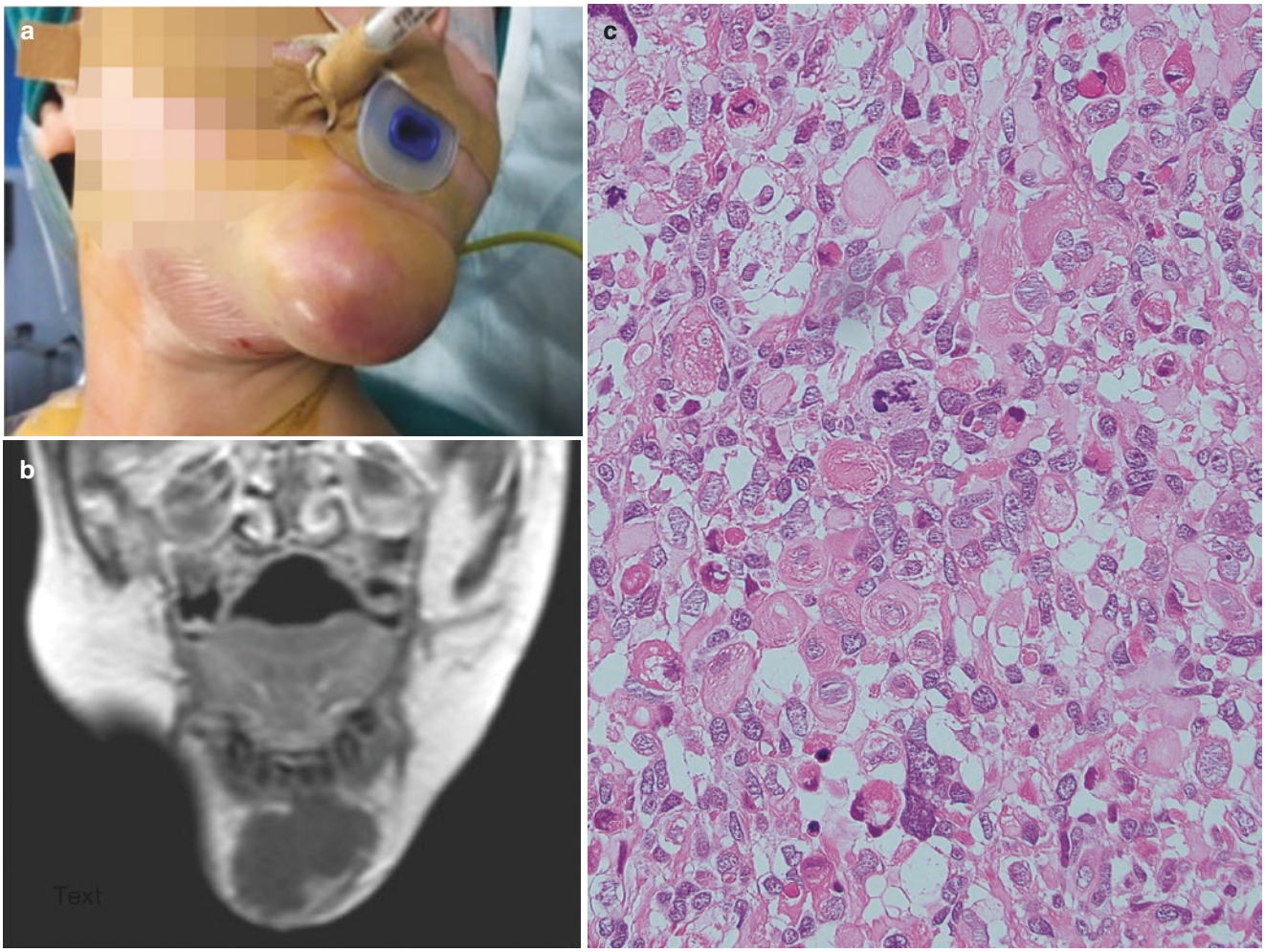

Fig. 31.1 (**a**) A 4-yr-old female with a mass of soft tissues of the chin (MRN) and its radiological appearance (**b**). (**c**) H&E: Rhabdomyosarcoma with anaplasia and extensive rhabdomyoblastic differentiation

The extension of these areas may vary greatly in the context of the same tumor or among the different tumors. Embryonal rhabdomyosarcomas with a predominant rhabdomyoblastic component, closely resembling rhabdomyomas, may occasionally occur in the head and neck region. However, rhabdomyoma-like features are more frequently related to therapy-induced changes [29]. Occasional foci of immature cartilaginous or osseous tissue can be found in embryonal rhabdomyosarcoma occurring in the nasal region. Embryonal rhabdomyosarcoma may contain focal or diffuse areas of anaplasia, consisting of large cells with hyperchromatic, pleomorphic nuclei and atypical mitoses (anaplastic variant of rhabdomyosarcoma) (Fig. 31.1) [13]. The prognostic significance of anaplastic component is so far unknown. Botryoid rhabdomyosarcoma is now included in the embryonal rhabdomyosarcoma subtype. It is characterized by a "*cambium layer,*" i.e. a subepithelial zone condensation of undifferentiated, stellate to round neoplastic cells variably admixed with rhabdomyoblasts, which form a distinct linear (continuous or discontinuous) band beneath the overlying epithelium (Fig. 31.3).

Alveolar RMS consists of ill-defined nests of undifferentiated, small to medium-sized round/oval cells, separated by fibro-vascular septa. The most striking feature is the cellular discohesion seen in the center zones of the nests, which makes neoplastic cells free of floating in empty spaces, while the neoplastic cells at the edge form a layer which adheres to the fibrous septa. This overall appearance imparts to the tumor an alveolar growth pattern. A solid growth pattern with closely placked neoplastic cellular nests and rare interspersed fibro-vascular septa can be usually observed at the periphery of most alveolar rhabdomyosarcomas (Fig. 31.4). However, in "*alveolar rhabdomyosarcoma, solid variant*" this pattern predominates. Most neoplastic cells show little eosinophilic cytoplasm, indistinct borders, and relatively large round to oval hyperchromatic nuclei. Mitoses, cellular degeneration, and/or necrosis are common features.

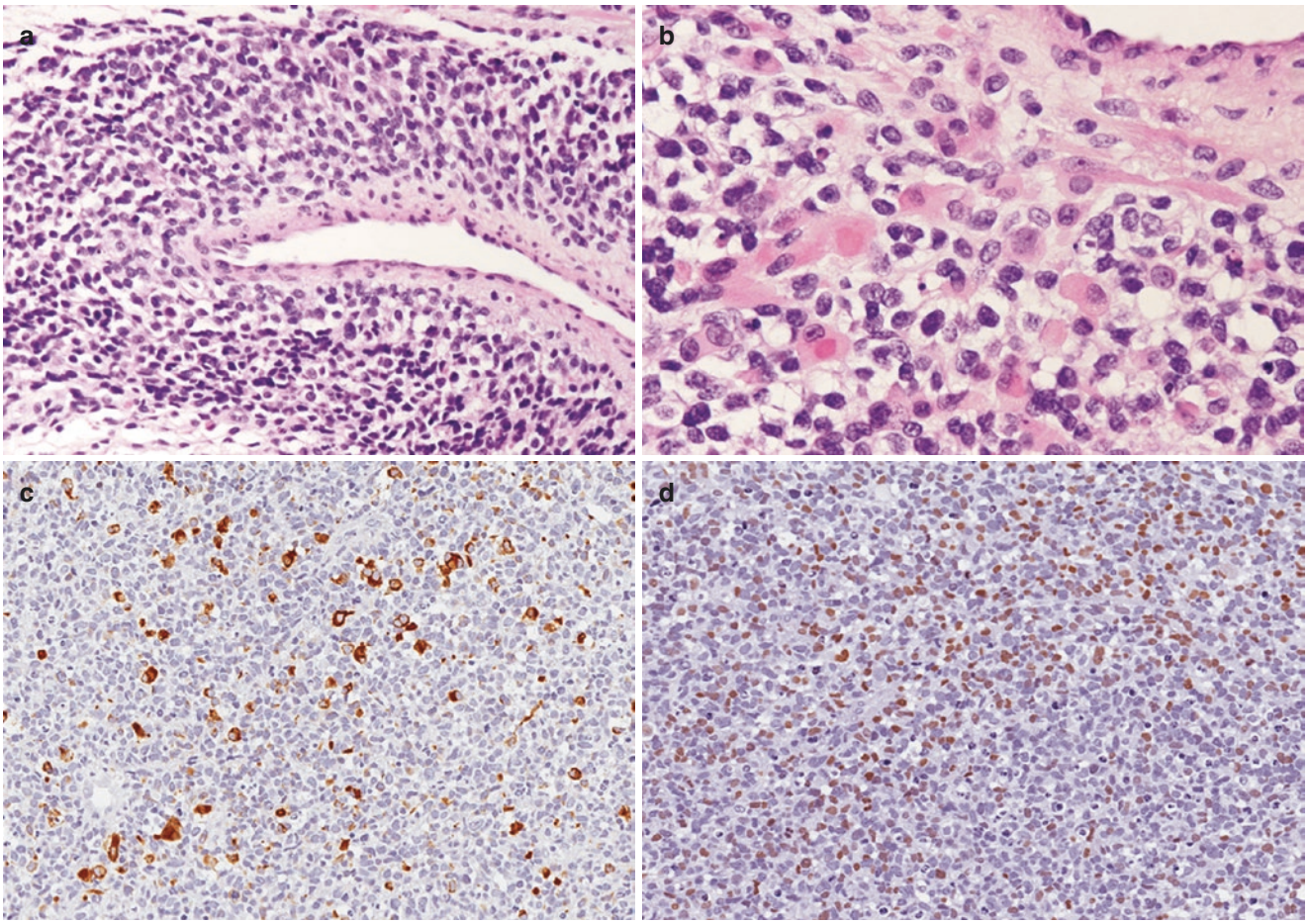

Fig. 31.2 Embryonal rhabdomyosarcoma of the face. (**a**) Small round blue cell tumor with neoplastic cells showing hyperchromatic nuclei and scant cytoplasm with scattered rhabdomyoblasts showing abundant eosinophilic cytoplasm (**b**). Neoplastic cells show heterogeneous staining for desmin (**c**) and (**d**) myogenin

Rhabdomyoblasts can be scattered among the undifferentiated cells or identified as single floating cells within the pseudo-alveolar spaces. Wreath-like multinucleated giant cells showing pale to weakly eosinophilic cytoplasm can be identified in the alveolar spaces (Fig. 31.5).

Spindle cell and sclerosing rhabdomyosarcomas, originally interpreted as variants of embryonal rhabdomyosarcoma, are currently recognized by the last edition of WHO as a single subtype [15]. Spindle cell/sclerosing rhabdomyosarcoma is composed of uniform, compact, elongated spindle cells arranged in long intersecting fascicles with an overall appearance closely reminiscent of fibrosarcoma and/or leiomyosarcoma. Focal whorled or storiform growth pattern can be encountered. The neoplastic cells show palely eosinophilic cytoplasm, distinct cellular borders, and spindle-shaped nuclei with small nucleoli (Fig. 31.6). A mild to moderate degree of nuclear pleomorphism and a significant mitotic activity, including atypical mitoses, can be documented in the majority of cases. A variable amount of collagen fibers is frequently seen intermingling among the spindle cells. Unlike embryonal rhabdomyosarcoma, spindle cell/sclerosing rhabdomyosarcoma contains only a few rhabdomyoblasts, while loose myxoid stroma or pleomorphism are lacking. In some tumors stromal sclerosis can obscure the spindle cell component, entrapping the neoplastic cells into pseudo-alveolar, pseudo-vascular, trabecular, or cord-like structures (Fig. 31.6). Similarly to conventional embryonal rhabdomyosarcoma, spindle cell/sclerosing rhabdomyosarcoma may contain areas of anaplasia.

Immunohistochemistry/Molecular Diagnostic Features
Although diagnosis of embryonal rhabdomyosarcoma is suspected on histological examination, immunohistochemical confirmation is strongly recommended, especially for tumors with undifferentiated morphology. The neoplastic cells express desmin, myogenin (Myf4), and MyoD1. Although their expression varies in the different subtypes, they are considered the most reliable diagnostic immunomarkers. Alveolar rhabdomyosarcomas typically show a strong and diffuse myogenin staining. Unlike alve-

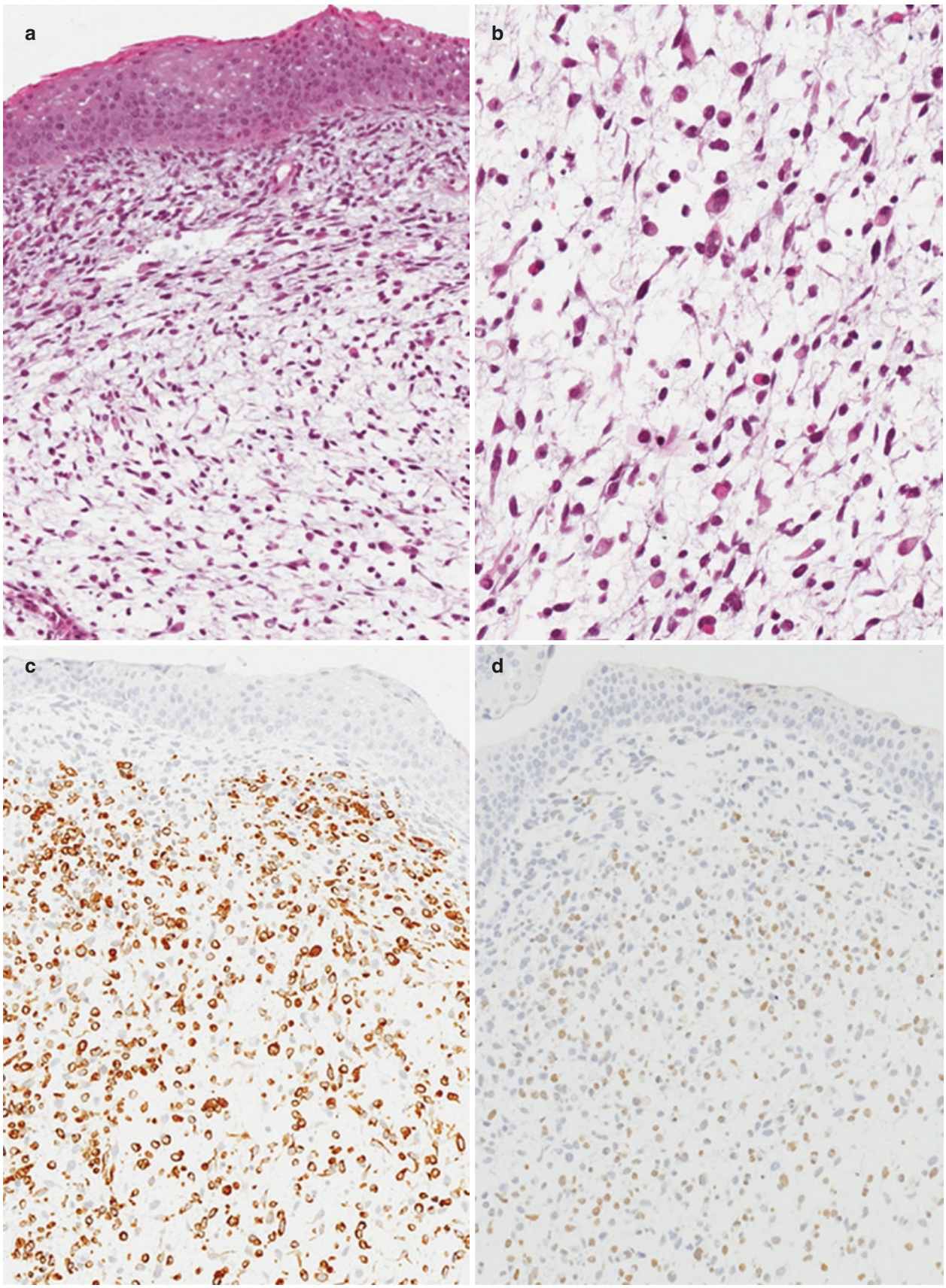

Fig. 31.3 Embryonal rhabdomyosarcoma (botryoid variant) of the external auditory canal. (**a**) Proliferation of neoplastic cells with subepithelial condensation (cambium layer). At higher magnification round to spindle neoplastic cells sometimes with skeletal muscle differentiation are embedded in a myxoid stroma (**b**). Most neoplastic cells are stained with desmin (**c**) and myogenin (**d**)

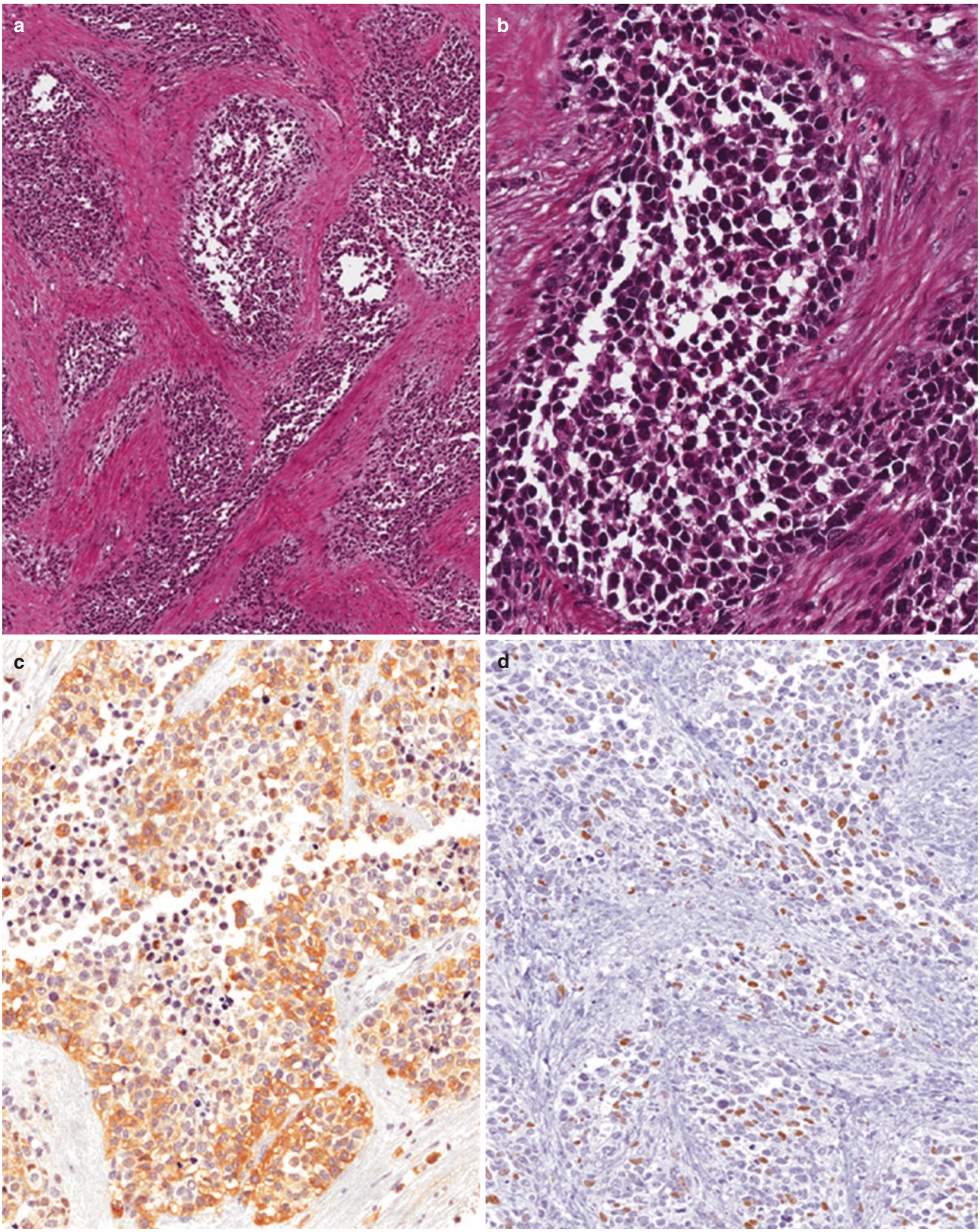

Fig. 31.4 Alveolar rhabdomyosarcoma of the soft tissues of the neck. Neoplastic lobules separated by fibrous septa (**a**). At higher magnification neoplastic cells are poorly cohesive in the center of the lobule (**b**). Desmin (**c**) and myogenin (**d**) immunostainings

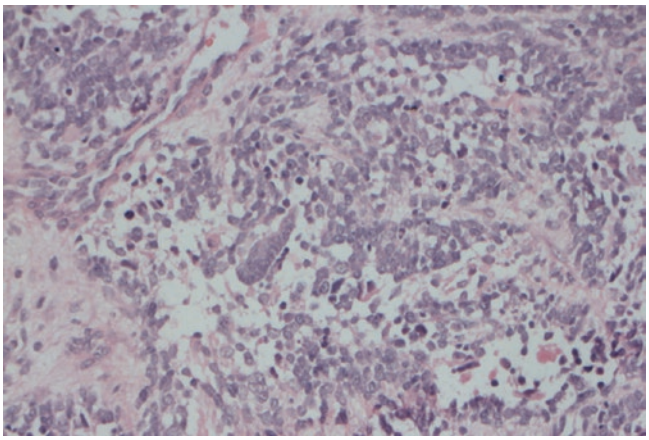

Fig. 31.5 Alveolar rhabdomyosarcoma: Wreath-like cells projecting into alveolar spaces

olar and spindle cell/sclerosing rhabdomyosarcoma, currently there are no available molecular diagnostic tests that can be used to confirm the diagnosis of embryonal rhabdomyosarcoma [5].

Alveolar rhabdomyosarcoma is associated with recurrent translocations involving *PAX* and *FOXO1 (FKHR)* family genes [14, 30, 31] with 70–80% showing a t(2;13)(q35;q14) leading to *PAX3-FOXO1* gene fusion, 10–20% have a t(1;13)(p36;q14) resulting in a *PAX7-FOXO1* gene fusion [32]. Other less common translocations, such as *PAX3–NCOA1*, *PAX3–NCOA2*, *PAX3–FOXO4*, have also been identified [33]. These molecular abnormalities can be detected by reverse transcriptase-polymerase chain reaction (RT-PCR) or FISH using frozen or paraffin-embedded tissues [34–40].

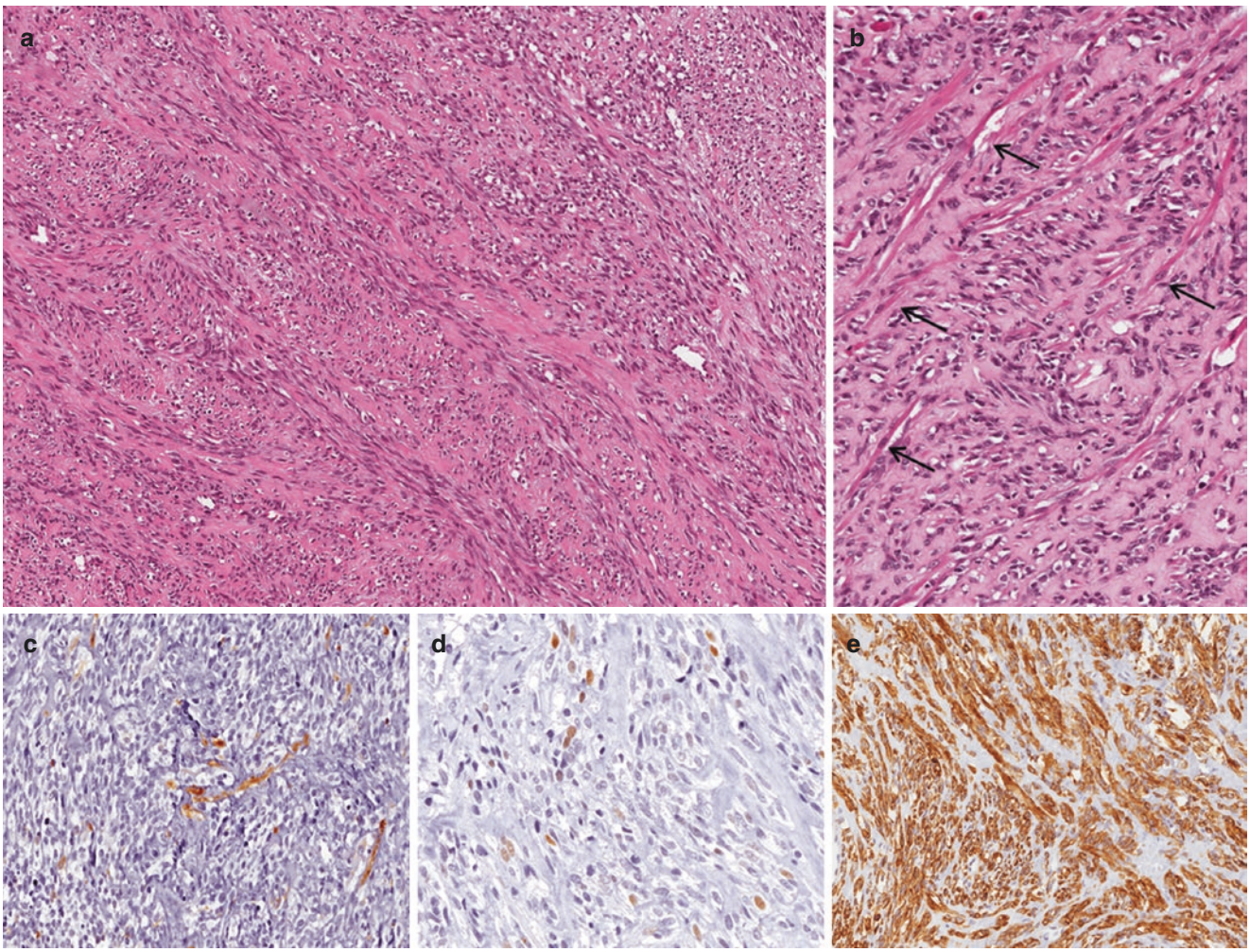

Fig. 31.6 Spindle cell/sclerosing rhabdomyosarcoma of the soft palate, with MyoD1 mutation. Bland-looking spindle cells are arranged in long fascicles (**a**). Rhabdomyoblastic differentiation is evident in some deeply eosinophilic spindle-shaped cells (arrows) (**b**). Desmin and myogenin are focally positive (**c**, **d**) while WT1 (**e**) shows diffuse cytoplasmic staining (C-terminus antibody)

Spindle cell/sclerosing rhabdomyosarcomas are a heterogeneous category, including a subset of tumors harboring *MYOD1* (L122R) mutations in 41–56% of cases analyzed [41, 42], often co-existing with *PIK3CA*. Interestingly in a series of spindle cell/sclerosing rhabdomyosarcomas analyzed for activating mutations in MyoD1, the majority of tumors occurred in the head and neck region of both children and adults [43]. Notably the cases with MYOD1 mutations usually exhibit a diffuse immunostaining for MYOD1, which, however, was lacking in 20% of wild-type *MYOD1* tumors. [43–45]. The subset of spindle cell rhabdomyosarcomas characterized by *VGLL2-CITED2* of *TEAD1-NCOA2* and *SRF-NCOA2* transcripts has been reported exclusively in infants in the lower neck and back region. They have an extremely bland morphology resembling infantile fibrosarcoma and a favorable prognosis [46].

Differential Diagnosis Differential diagnosis of rhabdomyosarcoma can be quite challenging, especially in case of small biopsies containing undifferentiated small round/ovoid blue cells without evidence of rhabdomyoblasts. It is crucial the distinction of embryonal from alveolar rhabdomyosarcoma as these subtypes have a different prognosis. Undifferentiated, hyperchromatic, small round/ovoid cells with high mitotic activity may be the predominant component in the so-called dense cellular variant of embryonal rhabdomyosarcoma [47], making the distinction from alveolar rhabdomyosarcoma particularly challenging. Dense cellular embryonal rhabdomyosarcomas are especially frequent in the orbit. Moreover the head and neck embryonal rhabdomyosarcomas may show a frequent solid pattern of growth with thick collagen or highly vascular septa that can simulate an alveolar rhabdomyosarcoma (Fig. 31.7). The presence of small round to stellate to spindle cells set in a myxoid matrix is an important clue to the diagnosis of embryonal rhabdomyosarcoma. The final distinction of embryonal versus alveolar rhabdomyosarcoma is based on the demonstration of the typical translocations in alveolar rhabdomyosarcoma. Rarely a benign small round cell tumor with fibroblastic/myofibroblastic profile arising in the oral cavity of children may be a mimicker of embryonal rhabdomyosarcoma [48]. This tumor is composed of desmin-positive, small round/ovoid cells embedded in a myxo-edematous stroma. However, unlike embryonal rhabdomyosarcoma, it shows neither nuclear atypia nor rhabdomyoblasts, while a striking feature is the presence of thick keloid-like collagen bands, variably interspersed with neoplastic cells. Although neoplastic cells are stained with desmin, there is no expression of myogenin and MyoD1 [48]. Distinction of alveolar rhabdomyosarcoma from Ewing's sarcoma is based on negative staining for myogenic markers in the latter, while immunostaining with CD99 may be found in both lesions [49]. Cytokeratins and neural/neuroendocrine markers can also be occasionally expressed in both [49]. Cyclin D1 is negative in alveolar rhabdomyosarcoma and diffusely expressed in Ewing sarcoma [50, 51]. Olfactory neuroblastoma, lymphoblastic lymphoma, and small cell neuroendocrine carcinoma can be differentiated by alveolar rhabdomyosarcoma on the basis of the lack of the expression of myogenic markers.

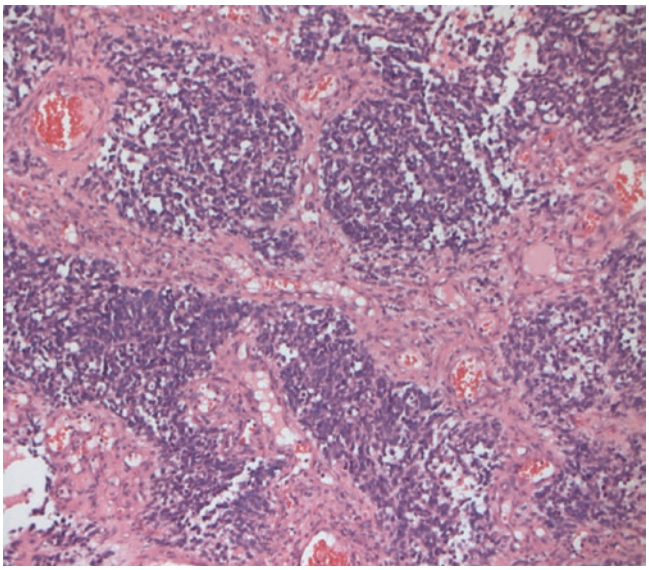

Fig. 31.7 Embryonal rhabdomyosarcoma in the maxillary region. Fibrovascular septa define pseudo-alveolar spaces containing primitive cells with absent rhabdomyoblastic differentiation

Spindle cell/sclerosing rhabdomyosarcoma should be distinguished from spindle cell tumors showing relatively bland elongated cells with fascicular, storiform, or whorled growth pattern, such as desmoid-type fibromatosis, cellular schwannoma, infantile/adult-type fibrosarcoma, low-grade myofibroblastic sarcoma/myofibrosarcoma, low-grade leiomyosarcoma, and low-grade malignant peripheral nerve sheath tumor. The diagnosis is based on the identification of both morphological and immunohistochemical features of skeletal muscle cell differentiation.

The prognosis of rhabdomyosarcoma is influenced by site, histotype, and tumor stage. Based on these factors and on the residual disease after therapy, different risk groups have been identified for therapeutic stratification. In the past the prognosis of rhabdomyosarcomas of the head and neck region was poor. Currently the combination of multi-drug chemotherapy, radiation therapy, and surgery has improved the outcome of head and neck rhabdomyosarcomas [52, 53]. However, parameningeal rhabdomyosarcomas have a more aggressive clinical course for their tendency to intracranial extension, with a 5-year survival rate less than 34% versus 43.6% non-parameningeal tumors, excluding the orbital lesions (Table 31.4) [7, 20]. These latter tumors have a favorable prognosis with an overall survival of 92% at 5 years [10,

Table 31.4 Prognosis of patients with head and neck rhabdomyosarcoma: tumor histotype and site. Review of the literature

Authors/reference	Follow-up		
	OS	OS Param vs Non-Param	OS ERMS vs ARMS
Reilly et al. [10]	75%	66,67% vs 100%	90% vs 50%
Simon et al. [12]	60%	/	/
Andrade et al. [17]	28,7	20,4 vs 41,7	23,8 vs 0,0
Chigurupati et al. [19]	75%	0 vs 100%	100% vs 33%
Kraus et al. [20]	64%	N.A.	N.A.
Sercarz et al. [21]	59%	N.A.	N.A.

OS overall survival, *Param* parameningeal tumors, *Non-Param* non-parameningeal tumors, *ERMS* embryonal rhabdomyosarcoma, *ARMS* alveolar rhabdomyosarcoma

23]. However, head and neck alveolar rhabdomyosarcomas have still an aggressive behavior, with a 5-year overall survival of 44% compared to 72% of embryonal rhabdomyosarcoma (Table 31.4) [7].

PAX3-FOXO1-positive alveolar rhabdomyosarcomas tend to be more aggressive than those with *PAX7-FOXO1* fusion with a 5-year overall survival in metastatic patients of 8% and 75%, respectively, [37–40]. In intermediate-risk patients *PAX3-FOXO1*-positive tumors have a 5-year survival rate of 54% versus 77% of embryonal rhabdomyosarcoma [37, 38]. Fusion-negative alveolar rhabdomyosarcomas have a clinical course similar to that of embryonal rhabdomyosarcoma [40].

Spindle cell/sclerosing rhabdomyosarcomas have a variable prognosis related to their molecular characteristics. Those carrying MyoD1 mutation may be highly aggressive with death occurring in the majority of cases [46]. Regardless of histotype, the prognosis of children (approximately 15% of cases) with distant metastases at diagnosis still remains poor with only 20–30% survival rate at 5 years [54–56].

Ewing Sarcoma

Definition Ewing sarcoma is a high-grade sarcoma usually affecting bones and soft tissues in children and young adults [57]. Primary Ewing sarcomas of the head and neck are extremely rare, comprising less than 9% of all Ewing sarcomas [58–63]. The distinction between Ewing sarcomas primary of bones in this region and those arising in soft tissue is sometimes difficult and the data from the literature are inclusive of both groups.

Clinical Presentation Head and neck Ewing sarcomas have a peak incidence in the first two decades of life and are commonly reported in mandible, skull base, orbital and nasal cavities. Male/female ratio is 1.2:1, like in Ewing sarcoma at any other anatomical sites [64]. Superficial tumors present as enlarging masses, while deep-seated lesions cause non-specific symptoms (pain, swelling, cranial nerve deficits). Tumors arising from cavities may result into nasal obstruction, rhinorrhea, or recurrent otitis media, according to the site [65–67].

Macroscopic Features Tumors appear as circumscribed or infiltrating mass of varying size, often larger than 10 cm, with multinodular and lobulated appearance and occasionally surrounded by a pseudocapsule. The cut section reveals a tan-gray, friable mass, frequently with necrotic, hemorrhagic, and cystic areas.

Microscopic Features Histologically, head and neck Ewing sarcomas do not differ from those in other sites. They are composed of uniform, small, round, primitive-appearing blue cells arranged in sheets or in a vaguely alveolar pattern, with thick fibro-vascular septa (Figs. 31.8 and 31.9). Head tumors, especially those in the sinonasal region, show a prominent nested pattern that can simulate an epithelial tumor [68]. Some tumors may contain fluid- or blood-filled lakes. Neoplastic cells have scanty clear to amphophilic cytoplasm, indistinct borders and round to ovoid nuclei with finely dispersed chromatin and 1–3 small nucleoli. Frequently these cells are admixed with a minority of darker staining neoplastic cells. Given the intracytoplasmic accumulation of glycogen, neoplastic cells are often PAS-positive. Mitoses are easily appreciated, but their number is usually low. Tumor necrosis is common and, when diffuse, only neoplastic cells around blood vessels can remain viable. Homer-Wright rosettes, containing a central core of neurofibrillary material can be identified. "*Adamantinoma-like Ewing sarcoma*" is a variant of Ewing sarcoma frequently located in head and neck, characterized by a nested/lobular growth pattern with peripheral nuclear palisading, prominent fibrosis, and squamous pearls [69–73] (Fig. 31.10). The former category of atypical/large cell Ewing sarcomas showing a peculiar cytology with larger cells, vesicular nuclei and prominent nucleoli, may be part of the group of Ewing-like sarcomas carrying recently recognized translocations (see below).

Immunohistochemistry/Molecular Diagnostic Features Immunohistochemically, Ewing sarcoma expresses CD99 and FLI-1, while desmin, α-smooth muscle actin, S100 protein, synaptophysin, chromogranin A, and WT1 (both cytoplasmic and nuclear staining) are variably expressed [5, 74]. Cyclin D1 is helpful as a diagnostic adjunct to these conventional markers, being diffusely expressed in the majority of Ewing sarcomas [50, 51]. Low-molecular-weight cytokeratins are expressed in 20% of Ewing sarcomas; however, the adamantinoma-like variant expresses high molecular weight cytokeratins (34-beta-E12). Cytogenetic testing and/or

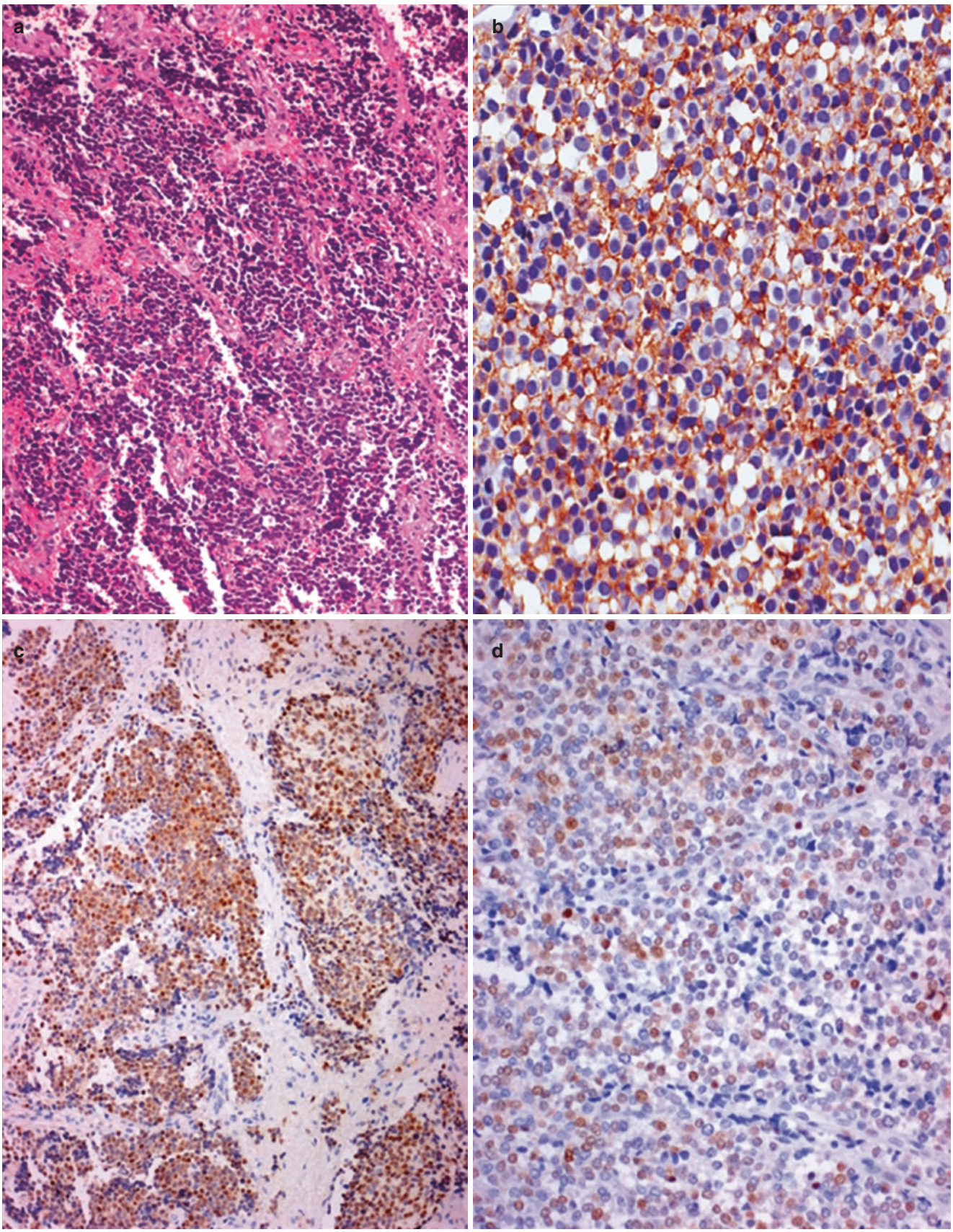

Fig. 31.8 Ewing sarcoma of the maxilla, involving oral cavity. The tumor is composed of small round cells in lobular and diffuse growth, infiltrating the overlying mucosa (**a**), with positive immunostaining for CD99 (membrane, **b**) FLI1 (nuclear, **c**) and cyclin D1 (nuclear, **d**)

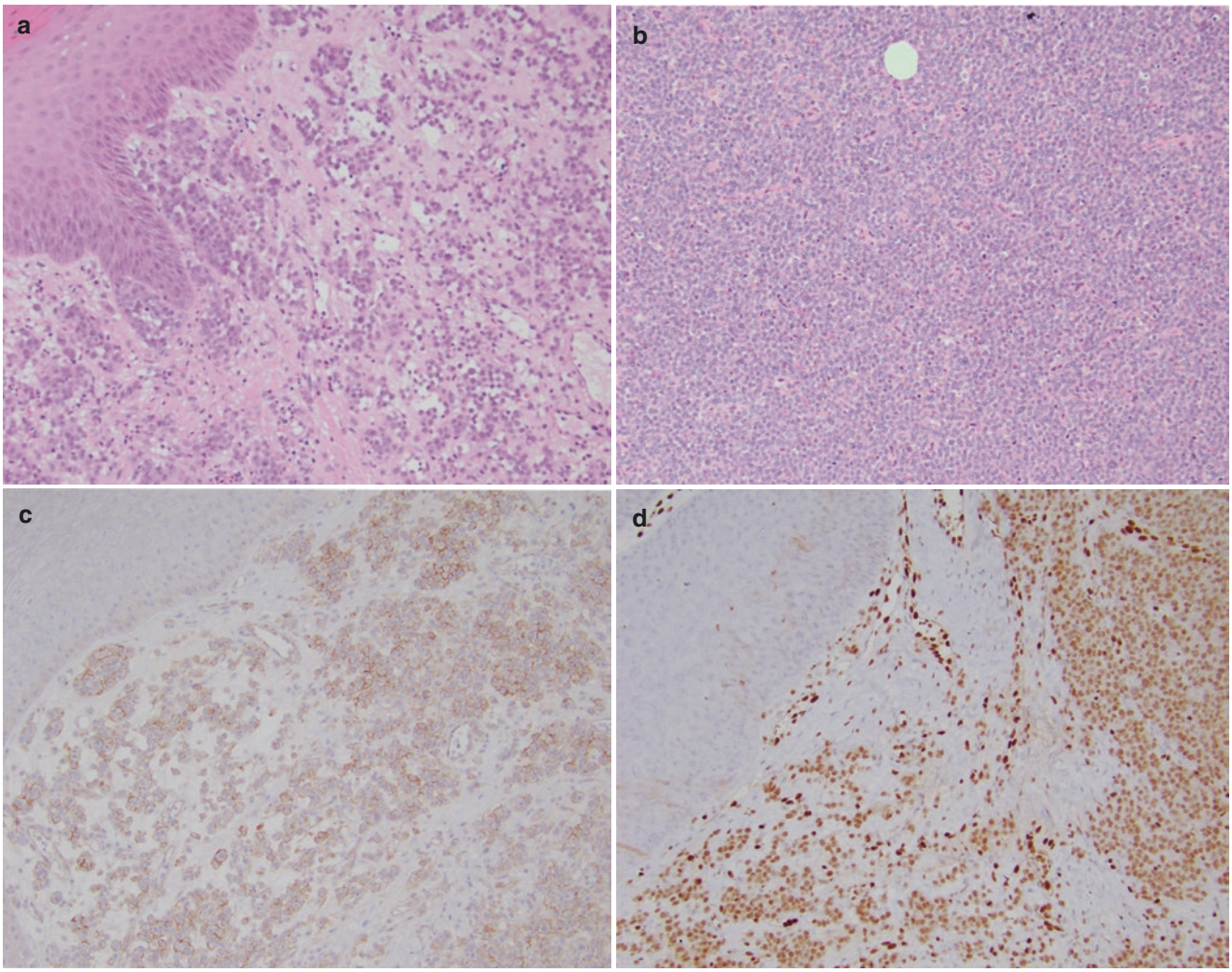

Fig. 31.9 Ewing sarcoma of the orbit. Vaguely lobular and solid architecture mimicking alveolar rhabdomyosarcoma (**a**, **b**). Positive staining for CD99 (**c**) and FLI-1 (**d**)

molecular biology are required for the diagnosis. In the largest series of head and neck Ewing sarcomas, with molecular characterization or cytogenetic analysis, *EWS* rearrangement was found in a percentage variable from less than 50% to 100% [68, 73, 75]. Independently from the site, *EWS–FLI1* from the translocation t(11;22)(q24;q12) is the most frequent rearrangement found in about 85–90% of Ewing sarcomas. The *ESW–ERG* rearrangement from the t(21;22)(q22;q12) is found in 5–10%, while the remaining 5% of Ewing sarcoma may carry a rearrangement of *EWS* with *ETV1* from the translocation t(7;22)(p22;q12), *E1AF* from the translocation t(17;22)(q12;q21) or *FEV* from the translocation t(2;22)(q33;q12), respectively [5, 76]. Rare cases can show *FUS* rearrangements from either translocation t(16;21)(p11;q22) or translocation t(2;16)(q35;p11) instead of *EWS* with *ERG* or *FEV*, respectively. [5, 76].

Differential Diagnosis The differential diagnosis of Ewing sarcoma in head/neck includes other malignancies typical of pediatric age, such as alveolar rhabdomyosarcoma, olfactory neuroblastoma, mesenchymal chondrosarcoma, lymphoblastic lymphoma, poorly differentiated synovial sarcoma, and desmoplastic small round cell tumor. Immunohistochemical staining for CD99, FLI-1, and cyclin D1, along with negativity for desmin, myogenin, and MyoD1 exclude alveolar rhabdomyosarcoma [50, 51]. The olfactory neuroblastoma arises exclusively in the olfactory neuroepithelium and thus involves nasal cavities and paranasal sinuses [77]. Both neuroblastoma and Ewing sarcoma may express neural/neuroendocrine markers (S-100 protein, CD56, CD57, synaptophysin, neurofilament protein), NB84 (20–64% of cases) and cyclin D1 [49]. However olfactory neuroblastoma lacks

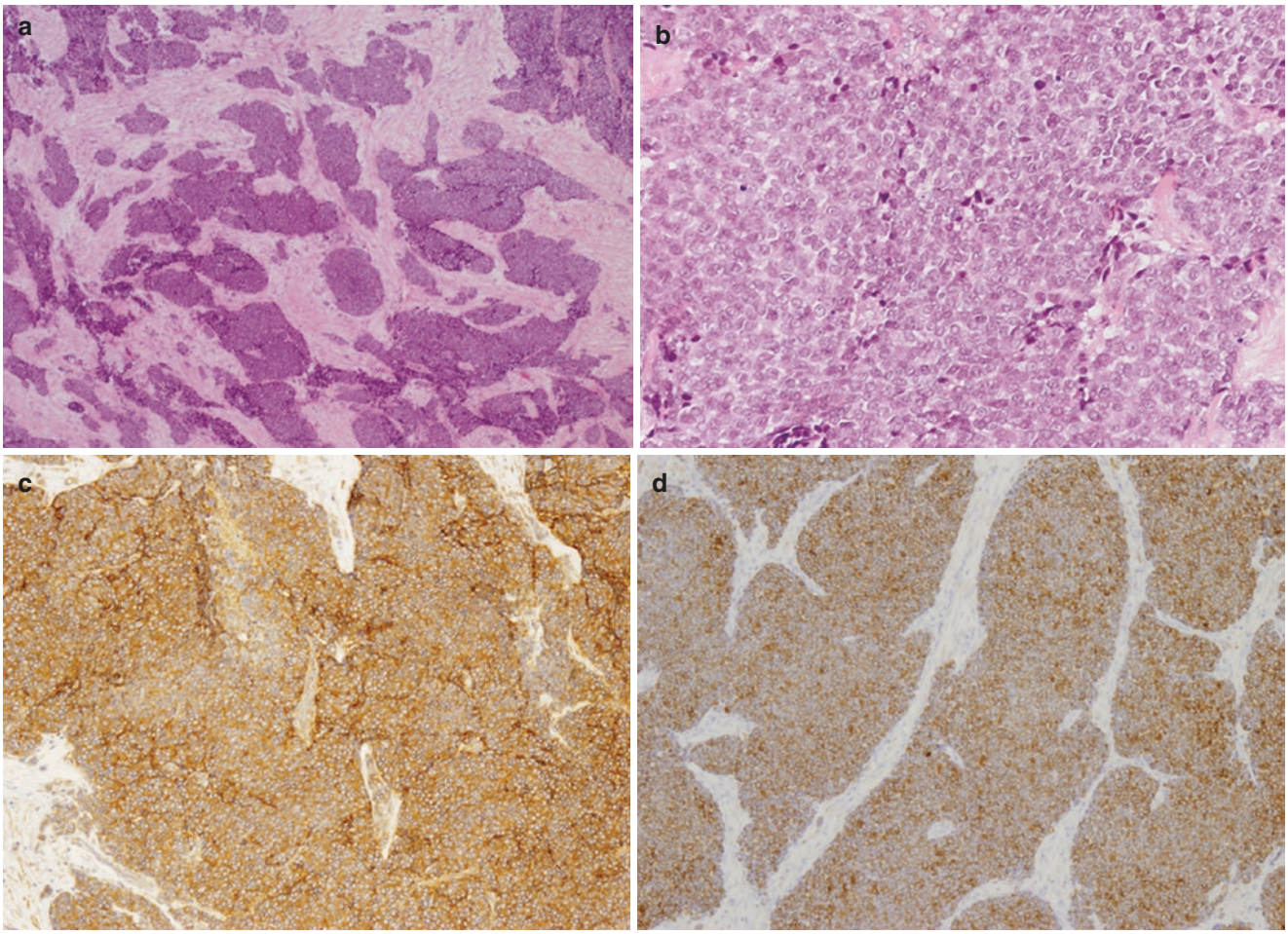

Fig. 31.10 Adamantinoma-like Ewing sarcoma. Tumor showing a nested growth pattern with prominent stromal sclerosis (**a**). Higher magnification shows round cells with scant cytoplasm and round nuclei with fine chromatin and small nucleoli (**b**). Diffuse cell membrane staining for CD99 (**c**), and pancytokeratin (**d**)

strong membrane staining for CD99 [5, 49]. The diagnosis of mesenchymal chondrosarcoma is challenging in absence of the typical cartilage component. Furthermore, it shows also strong positivity for CD99 [78, 79]. However S0X9 is selectively expressed by mesenchymal chondrosarcoma [79, 80]. Lymphoblastic lymphoma can be ruled out by the absence of staining for terminal-deoxynucleotidyl-transferase (TdT), along with B or T cell markers. A poorly differentiated component with Ewing sarcoma-like round cell morphology in a synovial sarcoma may simulate Ewing sarcoma, also in view of the CD99 and cytokeratins positive immunostaining in both [81–84]. Detection of t(X;18)(p11;q11) in synovial sarcoma by conventional cytogenetics or the resultant *SSX1-SS18* or *SSX2-SS18* fusion by RT-PCR may be needed. Adamantinoma-like Ewing sarcoma may diffusely express epithelial (cytokeratins and EMA) and neuroendocrine markers (synaptophysin and chromogranin A) [49], mimicking a myoepithelial carcinoma or a small cell neuroendocrine carcinoma. Myoepithelial carcinomas can show an Ewing sarcoma gene rearrangement, but the partner genes are different from those found in Ewing sarcoma. Small cell neuroendocrine carcinoma, extremely rare in children, is more diffusely positive for these markers than does Ewing sarcoma and lacks CD99 immunoreactivity. Ewing sarcomas are highly aggressive with an overall survival of 70% for localized disease and 30% for metastatic disease. Head and neck tumors seem to have a slightly better prognosis with a 3-year event free survival of 87% in patients with localized disease, after treatment by a combination of surgery, radiotherapy, and chemotherapy [64, 85]. This favorable survival rate may be related to earlier diagnosis, in absence of distant metastasis in about 30% of cases [86]. Metastatic tumors, however, have a significantly worse outcome with 29% overall survival.

Soft Tissue Sarcomas other than Rhabdomyosarcoma and Ewing Sarcoma

Fibroblastic/Myofibroblastic Tumors

Introduction The term fibrosarcoma identifies a group of fibroblastic/myofibroblastic lesions including congenital/infantile fibrosarcoma, typical of small children, and a subset of adult fibrosarcoma that have been redefined in the last decades, thanks to the widespread use of immunohistochemical, cytogenetic, and molecular techniques. The classic adult-type fibrosarcoma has almost disappeared, while well-defined categories of fibrosarcoma with recurrent genetic alterations and specific clinicopathologic features have been identified. These include: low-grade fibromyxoid sarcoma, sclerosing epithelioid fibrosarcoma, the myxoinflammatory fibroblastic sarcoma, and the myofibroblastic sarcoma. Low-grade fibromyxoid sarcoma, myofibroblastic sarcoma, and myxoinflammatory sarcoma are frequently located in the head and neck region.

Congenital/Infantile Fibrosarcoma

Congenital/infantile fibrosarcoma is a relatively uncommon, intermediate (rarely metastasizing) tumor that occurs in the first years of life, at birth or antenatally [87]. Although it typically arises as a painless rapidly growing large mass of the extremities, less than 1% occurs in head and neck region, especially in the oral cavity (tongue), followed by scalp, neck, maxilla, and ethmoid sinus [88–91].

Clinical Presentation Infantile fibrosarcomas may present as rapidly or slowly growing mass that later enlarges rapidly; in the scalp, they may extend to the underlying bone [88]. The high vascularization may simulate a hemangioma on magnetic resonance.

Macroscopic Features Grossly, congenital/infantile fibrosarcoma presents as solid masses measuring 3–10 cm in diameter, with poorly circumscribed margins. The cut surface is gray-white, fleshy, often with foci of necrosis and hemorrhage, especially in large tumors.

Microscopic Features Histologically, congenital/infantile fibrosarcoma is composed of uniform spindle cells arranged in intersecting fascicles or bundles, often exhibiting a herringbone pattern. Neoplastic cells are relatively bland-looking, with mild to focally moderate nuclear pleomorphism. Mitoses are frequent, but atypical forms are lacking. Cellularity varies from hypocellular fibrous areas to highly cellular ones. Frequently the neoplastic cells may show a more rounded and immature looking appearance. A typical hemangiopericytoma-like vascular pattern may be seen, especially in the center of the lesion (Fig. 31.11). A common feature is the presence of scattered inflammatory cells, particularly lymphocytes, among neoplastic cells. Foci of necrosis, as well as of extramedullary hematopoiesis can be found.

Immunohistochemistry/Molecular Diagnostic Features Congenital/infantile fibrosarcoma is diffusely positive for vimentin and variably expresses α-smooth muscle actin or muscle-specific actin, desmin, h-caldesmon, and occasionally cytokeratins and S100 protein. A diffuse cytoplasmic staining for WT1 is also seen [92]. Congenital/infantile fibrosarcoma bears a recurrent translocation t(12;15)(p13;q25) with *ETV6-NTRK3* gene fusion [93]. Although several spindle cell lesions should be distinguished from congenital/infantile fibrosarcoma, the most challenging diagnosis is desmoid-type fibromatosis. A significant number of cases (up to 30%) of the latter may occur in the first years of life, and congenital cases have also been reported [94]. Unlike desmoid-type fibromatosis, the neoplastic cells of congenital/infantile fibrosarcoma are more atypical, closely packed and overlapping, with a more prominent fascicular growth pattern and often a significant mitotic count (>1 per 10 high power fields). Congenital/infantile fibrosarcoma and desmoid-type fibromatosis share the expression of α-smooth muscle actin and less frequently desmin. The lack of immunostaining with β-catenin, along with a diffuse WT1 cytoplasmic staining, favors the diagnosis of congenital/infantile fibrosarcoma [92]. The identification of the *ETV6-NTRK3* gene fusion is helpful in confirming the diagnosis of congenital/infantile fibrosarcoma. Like in other sites, congenital/infantile fibrosarcoma of head and neck has a favorable clinical course. Although local recurrence may develop, distant metastases are very rare [5, 94]. Surgery is the best treatment for resectable tumors. Conversely, unresectable or very large tumors are treated with chemotherapy [5]. Recently a congenital case of fibrosarcoma involving the neck and face, refractory to chemotherapy, was successfully treated with TRK (tropomyosin-related kinase) inhibitor LOXO-101, suggesting the potential clinical use of similar targeted therapies [95].

Low-Grade Myofibroblastic Sarcoma

Definition Low-grade myofibroblastic sarcoma is a fibroblastic/myofibroblastic tumor with propensity to recur locally, but with a low metastatic potential [96–98]. The extremities and the head and neck region are the most commonly involved sites, especially in pediatric age [99–101].

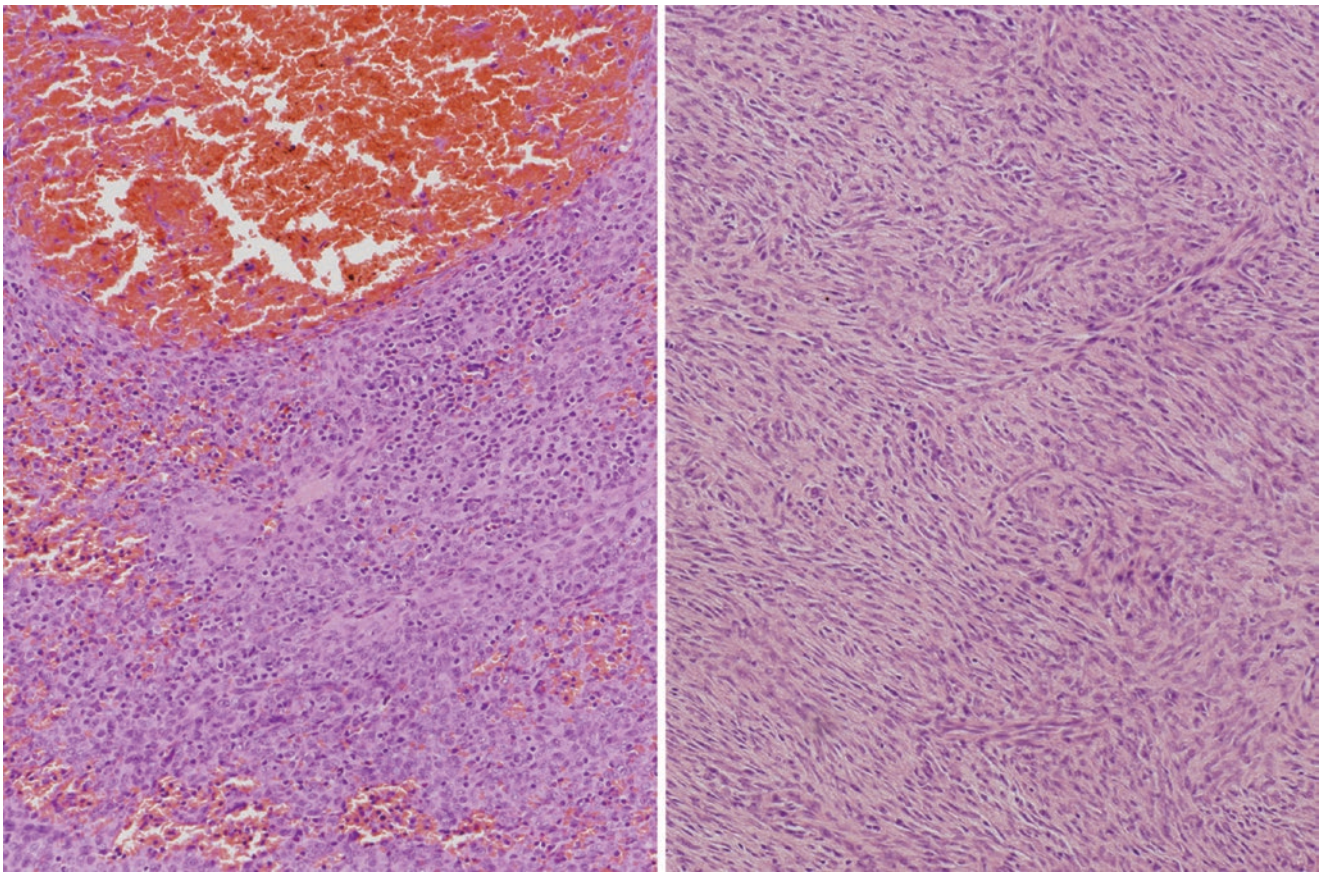

Fig. 31.11 Infantile fibrosarcoma: Spindle cells in short fascicles with minimal cytologic atypia. Sometimes large vascular channels can simulate a vascular neoplasm (left)

Clinical Presentation About 40% of head and neck lesions arise in the oral cavity, especially tongue [97, 102, 103] or, more rarely, in maxilla [104], jaw [100], parotid gland [105], larynx, paranasal sinus [103], or mandibular canal [106]. Tumors present as enlarging masses, often with clinical symptoms related to the site of origin such as hoarseness, dysphonia, and paresthesia.

Macroscopic Features Grossly, head and neck low-grade myofibroblastic sarcoma presents as circumscribed or infiltrative mass, ranging in size from 1 to 7 cm (mean size 3.2 cm). Head and neck low-grade myofibroblastic sarcomas tend to be larger than 4 cm [103]. The cut surface usually shows a homogeneous, fibrous mass, firm in consistency.

Microscopic Features Histologically, low-grade myofibroblastic sarcoma is composed of spindled- to stellate-shaped cells arranged into intersecting long or short fascicles, with focal storiform, whorled or herringbone growth patterns. Tumor margins are at least focally infiltrative. Neoplastic cells have pale eosinophilic cytoplasm with ill-defined borders. Their nuclei are usually fusiform and wavy, but may be tapered, vesicular with indentations and small nucleoli. Isolated cells with mild to moderate atypia or in small aggregates are, at least focally, present. Mitotic activity is variable, but the majority of tumors contain 1–3 mitoses/10 high power field. Atypical mitoses and necrosis are usually absent. Neoplastic cells are usually set in a fibrous to sclerotic stroma, although focal myxoid changes are not uncommon. Osteoclast-like giant cells have been occasionally reported (Fig. 31.12). Scattered inflammatory cells are also found.

Immunohistochemistry/Molecular Diagnostic Features Immunohistochemical analyses reveal the myofibroblastic nature of the neoplastic cells. In the majority of the cases neoplastic cells exhibit α-smooth muscle actin-positive/desmin-negative profile, while in a minority of cases desmin can be focally expressed, alone or in combination, with α-smooth muscle actin [97, 102, 105, 107]. Calponin can be variably expressed, while h-caldesmon is absent or only focally positive [107]. The most frequent but non-specific unbalanced chromosomal aberrations include changes in Xp and 11q, deletions of 15q and gains at 1p11, 12p12.2, 5p13.2, and loss at 15q25 [108, 109].

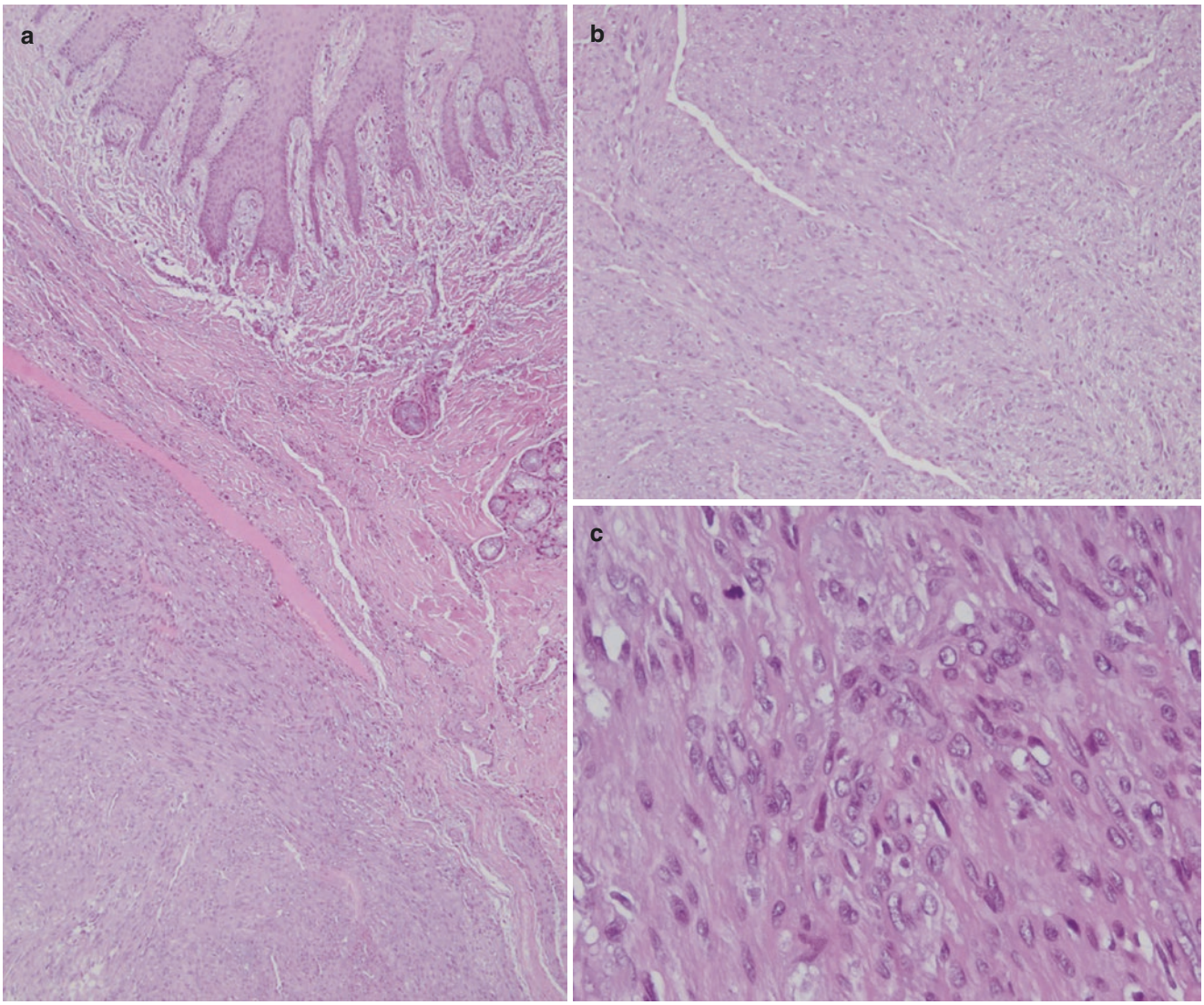

Fig. 31.12 Myofibroblastic sarcoma (low-grade myofibrosarcoma): oral mucosa with underlying myofibroblastic proliferation (**a**) with a fascicular arrangement, hemangiopericytoma like vascular pattern (**b**), mild cytologic atypia and mitoses (**c**)

Differential Diagnosis The main differential diagnosis includes nodular fasciitis. The latter is characterized by a zonation pattern and lacks cytologic atypia, a feature always seen, at least focally, in low-grade myofibroblastic sarcoma. The best treatment should be the wide surgical resection with tumor-free margins, while the role of both radiotherapy and chemotherapy remains to be established. The overall survival rate at 5 years is 71.6% [103].

Low-Grade Fibromyxoid Sarcoma

Definition Low-grade fibromyxoid sarcoma is an unusual variant of fibrosarcoma with deceptively bland morphology, capable of local recurrence and distant metastases [110]. It occurs more frequently in young adult males, as a slowly growing mass located in deep soft tissue of the lower extremities and trunk [111–113]; however in children, it typically arises in the superficial soft tissues [111–113].

Clinical Presentation Less than ten cases have been reported in the head and neck region, mostly in the maxilla and cheeks. Patients' age ranges from 1 to 9 years and tumors have been reported to occur in jaw, cheek, neck, and posterior cervical spine [114–117].

Macroscopic Features Grossly, low-grade fibromyxoid sarcoma is a well-circumscribed, sometimes lobulated, mass ranging from 2 to 18 cm, with a firm, homogenous white to tan cut surface.

Microscopic Features Histologically, it shows low to moderate cellularity with an abrupt transition from myxoid hypocellular to highly collagenized areas. At the periphery the lesions tend to be infiltrative. The myxoid areas contain delicate curvilinear or branching blood vessels. Tumor cells vary from bland-looking spindle to stellate cells with pale eosinophilic cytoplasm and ovoid to tapered nuclei with small nucleoli. In more densely cellular areas they may be arranged in swirling, storiform, or fascicular pattern. Mitoses are rare and necrosis is absent. Nuclear pleomorphism and increased cellularity are more frequent in relapses. Some tumors, reported in the past with the term of "*hyalinizing spindle cell tumor with giant rosettes*" [112], may contain collagen rosettes, consisting of a central area of eosinophilic collagen surrounded by concentrically arranged round/epithelioid cells. Tumor areas indistinguishable from intermediate-grade adult-type fibrosarcoma can be seen in 15–20% of cases [5, 94, 112]. Low-grade fibromyxoid sarcoma containing areas resembling sclerosing epithelioid fibrosarcoma may occur, suggesting a close relation between the two tumors [5, 94, 118]. Foci of bone or calcifications, scattered multinucleated giant cells, cystic change, and tumor necrosis can be rarely encountered.

Immunohistochemistry/Molecular Diagnostic Features Immunohistochemically, low-grade fibromyxoid sarcoma displays diffuse staining for MUC4 (mucin 4), a highly sensitive and specific marker for the diagnosis [119]. Apart from vimentin, a variable staining for epithelial membrane antigen (EMA), CD34, CD99, claudin, BCL2, and p63 can be observed [5, 94]. All the low-grade fibromyxoid sarcomas reported in the head and neck region showed one of the recurrent translocations t(7;16)(q33;p11) involving the *FUS* gene on chromosome 7 and the *CREB3L2* gene on chromosome 16 [120, 121]. The *FUS-CREB3L2* gene fusion can be detected in up to 90–95% of cases and it seems not only highly sensitive but also specific, as none of the other spindle cell mimickers harbors this genetic alteration [122]. A transcript *EWSR1-CREB3L1* from translocation t(11;22)(p11;q12) is detected in a subset of low-grade fibromyxoid sarcoma [123].

Differential Diagnosis The differential diagnosis includes benign tumors such as neurofibroma and perineurioma. Perineurioma, like low-grade fibromyxoid sarcoma, shows variable immunoreactivity for EMA and claudin [94]. However, unlike low-grade fibromyxoid sarcoma, both neurofibroma and perineurioma lack the curvilinear vascular pattern and are MUC4-negative. In addition neurofibroma is S100-protein positive. Desmoid-type fibromatosis displays a more prominent fascicular growth pattern, with only focal myxoid areas, and nuclear staining for β-catenin along with the loss of MUC4 immunoreactivity. Low-grade fibromyxoid sarcoma has a good prognosis (5-year overall survival: 95%) if radically excised. Despite its deceptively bland morphology, however, low-grade fibromyxoid sarcoma has a recurrence rate of 10%, with a metastatic potential in 5–10% of patients [5, 94]. Metastases, mainly to the lung, pleura, and bones, can occur even 10–25 years after diagnosis. Superficial tumors have a better prognosis [94]. Head and neck tumors do not differ in their clinical behavior, with relapses and metastasis. A review of the literature, including 11 patients with follow-up from 3 months to 43 years, showed that four patients developed local recurrence, with two of them dead of lung metastatic disease [115].

Sclerosing Epithelioid Fibrosarcoma

Definition Sclerosing epithelioid fibrosarcoma is an entity strictly related to low-grade fibromyxoid sarcoma, mostly occurring in the deep soft tissues of the lower extremities/limb of elderly, and characterized by an aggressive behavior with tendency to local recurrence and distant metastases [124].

Clinical Presentation Sclerosing epithelioid fibrosarcoma in the head and neck region of adults and adolescents is extremely rare, with less than 20 cases reported [125–130], almost exclusively in adults. Only two 19-year-old patients with mandibular and zygomatic-temporal area tumors have been reported [128, 129].

Macroscopic Features Grossly, the tumor presents as a well-circumscribed firm mass, often with a lobulated external surface, ranging in size from 1 to 5 cm in greatest diameter.

Microscopic Features Histologically, sclerosing epithelioid fibrosarcoma is a fibrosclerotic tumor with variable cellularity, showing a nodular pattern, often with infiltration of the surrounding tissues. It is composed of small- to medium-sized epithelioid to fusiform cells with a clear to pale eosinophilic cytoplasm, and relatively bland round/oval angulated nuclei containing small nucleoli. Mitoses are rare, but >5 mitoses/10 high power field can be occasionally encountered. The neoplastic cells are typically arranged in cords, nests, strands, sheets, or pseudo-alveoli, and are embedded in a fibrosclerotic stroma with foci of calcifications and/or chondroid/osseous metaplasia. Necrosis can be observed. Areas reminiscent of low-grade fibromyxoid sarcoma may be seen in a subset of sclerosing fibrosarcomas [5, 124].

Immunohistochemistry/Molecular Diagnostic Features Neoplastic cells are immunoreactive for MUC-4, vimentin, BCL-2 protein, and EMA (epithelial membrane antigen) (50% of cases). S100 protein, cytokeratins, and p53 can be expressed in a small number of cases. Desmin and α-smooth muscle actin are negative. Most of the molecular studies come from sclerosing epithelioid fibrosarcoma outside head and neck. However the majority of pure sclerosing epithelioid fibrosarcoma shows frequent *EWSR1-CREB3L1* gene rearrangements, from translocation t(11;22)(p11;q12) while *FUS-CREB3L2* gene rearrangements from translocation t(7;16)(q33;p11) are observed in hybrid low-grade fibromyxoid sarcoma/sclerosing epithelioid fibrosarcoma [118, 131].

Differential Diagnosis The differential diagnosis includes several tumors with epithelioid morphology, especially invasive lobular carcinoma, signet ring cell carcinoma, clear cell sarcoma, poorly differentiated synovial sarcoma, and spindle cell/sclerosing rhabdomyosarcoma. Clinicopathologic correlation, an extensive immunohistochemical panel and molecular characterization are helpful to achieve the correct diagnosis. Sclerosing epithelioid fibrosarcoma is an aggressive tumor, with local recurrence rate in more than 50% of cases, a metastatic rate of 40–80% and an overall 5-year survival rate of 70% [94]. All the patients affected by sclerosing epithelioid fibrosarcoma in the head and neck region died of disease after local relapses and distant metastases [129].

Malignant Adipose Tumors: Liposarcomas

Definition Liposarcomas are a heterogeneous group of malignant soft tissue tumors with adipocytic differentiation, typically occurring in adults. They are extremely rare in children, comprising less than 3% of all pediatric sarcomas [132]. In adults 2–8% of all liposarcomas occur in the head and neck region [133, 134].

Clinical Presentation Apart from a large series of pediatric liposarcomas, that included five tumors arising in the head and neck region (6% of all cases), there are only a few cases reported in children, occurring in the orbit, oral cavity (tongue), maxillary region, nasopharynx, and neck (Table 31.5) [132–134, 142–145]. Tumors present as painful masses, sometimes producing asymmetry in the patient's facial appearance [134].

Classification The following histotypes can be diagnosed in children: (1) myxoid (low- and high-grade) liposarcoma; (2) atypical lipomatous tumor/well-differentiated liposarcoma; (3) pleomorphic liposarcoma. While myxoid liposarcoma is the most common subtype, both well-differentiated [154] and pleomorphic liposarcomas [155] are exceptional in children. Dedifferentiated liposarcomas are exclusive tumors of adults. In head and neck region, especially orbit, there is a higher incidence of the pleomorphic/myxoid subtype [132], whereas in the oral cavity and other sites the clas-

Table 31.5 Clinicopathologic features of sarcomas other than rhabdomyosarcomas: review of the literature

Histotype (number of cases)	Age (median)	M:F	Site	Follow-up
Synovial sarcoma (n. 14) *Monophasic* (n. 5) *Biphasic* (n. 4) *Poorly differentiated* (n. 1) *Not specified* (n. 4) [135–141]	4–17 year (5.5)	1:1	Nasolabial (1) Mandibular(1) Mastoid/infratemporal/cervical(3) Parotid (1) Soft tissue head(2) Parapharyngeal (4) Not specified (2)	4 ANED 4 DOD 2 died of other causes 4 not specified
Liposarcoma (*LPS*) (n. 14) *WD-LPS* (n. 3) *Pleomorphic LPS* (n. 5) *Pleomorphic M-LPS* (n. 1) *MLPS/RCLPS* (n. 4) *Na* (n. 1) [132–134, 142–145]	8–18 year (12,5)	1:1.5	Orbit (2) Oral cavity (4) Soft tissue head neck(5) Nasopharyngeal (1) Maxillary sinus/maxilla (2)	2DOD 1LFU Local relapse 1 Progression 1 1ANED
Undifferentiated sarcoma High-grade pleomorphic sarcoma (12) [146–151] BCOR-fusion*transcripts (2) [152] BCOR-ITD** (5) [153]	2–9 year 5–6 year <1 year	1:7*** 1:1	Dura (2) Gum (1) Parotid (1) Nasal cavity (1) Orbit (1) Scalp (1) Neck (4) Head nos (1) Base of skull neck	8ANED 1AWD 1MTS (LFU) 1Died of toxicity 1DOD 1ANED 1NA

[] = references; *ANED* alive without disease; *DOD* died of disease; *NA* not available; *LFU* lost to the follow-up; *MTS* metastasis; * excluded cerebral tumors; **not included tumors of possible origin from salivary gland; ***data not available in all cases

sic histopathologic features of myxoid liposarcomas are more frequent.

Macroscopic Features Liposarcomas are soft, partially capsulated masses of small to medium size in the head and neck region, with a yellow-grayish, gelatinous, cut surface. White nodules, sometimes with fleshy cut surface may be seen.

Microscopic Features Atypical lipomatous tumor/well-differentiated liposarcoma is usually divided into three subtypes: lipoma-like, sclerosing, and inflammatory. The common basic theme is the presence of a variable mixture of adipose and fibrous tissues. Adipocytes vary in size and show at least focal nuclear atypia. Similarly, spindle and multipolar atypical stromal cells are set in the fibrous component (which can be prominent) and among adipocytes. A variable number of uni- or multi-vacuolated lipoblasts are variably present. Well-differentiated liposarcomas are extremely rare in children; however, the sclerosing variant is more frequently seen in head and neck region. Pure myxoid (low-grade) liposarcoma is characterized by an abundant myxoid matrix, delicately arborizing capillary-sized vasculature, and a variable amount of bland-looking uniform, round to short spindle cells admixed with univacuolated lipoblasts [5]. Progressive transition into hypercellular areas composed of primitive-appearing round cells tightly packed and without intervening extracellular matrix defines the "*myxoid/round cell (high-grade) liposarcoma.*" The round cells show high nuclear/cytoplasmic ratio and overlapping hyperchromatic nuclei with prominent nucleoli (Fig. 31.13). The round cell component, usually representing from 5% to 80% of the entire neoplasm, is associated with a poor prognosis [5] but it is rare in children. The pleomorphic myxoid variant of liposarcoma consists of an otherwise typical myxoid liposarcoma admixed with areas containing pleomorphic lipoblasts [132]. It can occur also in head and neck [132].

Immunohistochemistry Regardless of the histotypes, the diagnosis of liposarcoma is based on morphology. However liposarcomas show variable positive staining for S100 protein. Nuclear staining with p16 may be helpful in the differential diagnosis from lipomas and lipoblastomas [156]. Lipoblastomas show selective PLAG 1 nuclear expression.

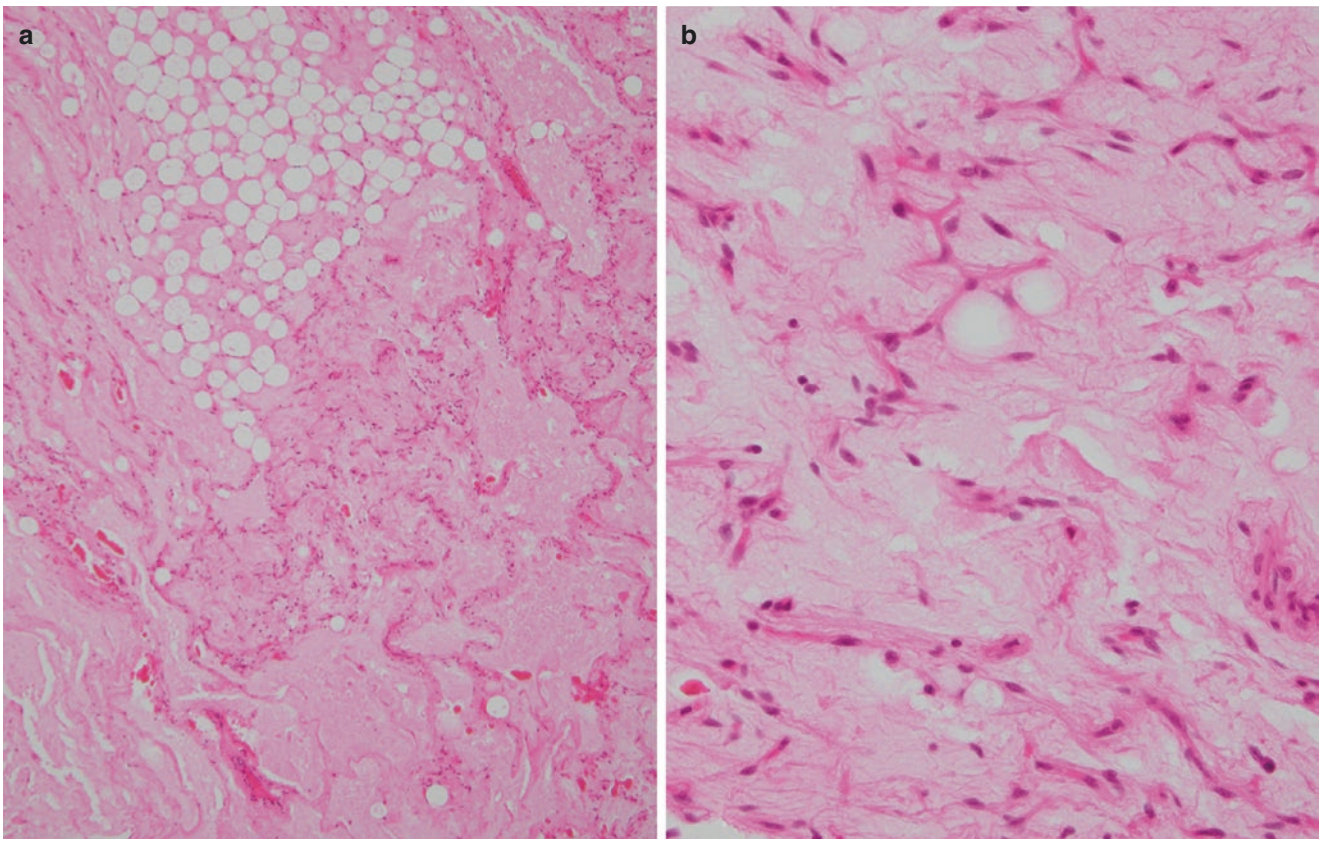

Fig. 31.13 Myxoid liposarcoma (9-yr-old girl, cheek). Alveolar like spaces contain pool of mucin in continuity with a group of bland-looking uniform univacuolated lipoblasts embedded in a myxoid matrix (**a**). Higher power highlights the typical arborizing vasculature (**b**)

Expression of MDM2 is found in well-differentiated liposarcomas; however, their rarity in children does not allow defining the percentage of positive cases and their relationship with the gene amplification reported in adults.

Differential Diagnosis Many of the cases of well-differentiated liposarcomas reported in infants and small children in head and neck region in the past might actually represent lipoblastomas. Lipoblastoma can mimic either a well-differentiated liposarcoma or a myxoid liposarcoma. The rarity of well-differentiated liposarcoma and even of myxoid liposarcoma in the first years of life should suggest a molecular analysis of PLAG1 to exclude a lipoblastoma before giving a diagnosis of liposarcoma. The molecular characteristics of pediatric myxoid liposarcomas have been investigated in few cases, however search for the *FUS-CHOP* from t(12;16)(q13;p11) and *EWSR1-CHOP* rearrangements from t(12;22)(q13;q12) may be a helpful diagnostic tool [132, 157]. The overall prognosis of liposarcomas in head and neck region in adults is likely better than in other sites, probably for the younger age of patients and the smaller size of the tumor. In children, in general, liposarcomas have a favorable prognosis. However myxoid liposarcomas with pleomorphism may behave aggressively [132].

Malignant Neurogenic Tumors

Definition Malignant peripheral nerve sheath tumors are neoplasms arising from peripheral nerve or preexisting benign nerve sheath tumor (usually neurofibroma; very rarely schwannoma) or in patients with neurofibromatosis-type 1 (NF1) [158]. Outside this context, the diagnosis should be made only if a malignant tumor exhibits morphological, immunohistochemical, and ultrastructural features suggesting Schwann-cell differentiation. Malignant peripheral nerve sheath tumors are one of the more frequent non-rhabdomyosarcoma pediatric soft tissue sarcomas, accounting in some series for 5–7% and 17% of soft tissue sarcomas and pediatric neurogenic tumors, respectively [159]. Most malignant peripheral nerve sheath tumors occur after 10 years of age, while a minority of cases (10–20%) are diagnosed in the first 2 decades of life. Only rarely these tumors are congenital [159]. Although they can occur sporadically or following radiotherapy, there is a relative risk for patients affected by NF1 greater than 100 times that of the general population. The lifetime risk of malignant peripheral nerve sheath tumors for these patients is between 2% and 10% [159]. Unlike adults, about half of malignant peripheral nerve sheath tumors in children and adolescents arise in the context of NF1, with the majority of cases occurring before 30 years of age [159]. Malignant peripheral nerve sheath tumors tend to occur more frequently in the extremities and limb girdles, followed by the trunk and retroperitoneum. Approximately 10% of all these tumors arise in the head and neck region [160–162], where they account approximately for only 2–6% of all sarcomas [1, 163].

Clinical Presentation In the largest series of pediatric malignant peripheral nerve sheath tumors, 21% of cases involved head and neck region, with approximately 17% arising in the context of NF1-patients [164]. The most common clinical presentation in children is an enlarging soft tissue mass with or without pain, dysesthesia, or other neurologic symptoms [159].

Classification/Subtypes These tumors are classified as conventional and epithelioid MPNST. The latter variant occurs rarely (<5% of all MPNSTs). There is no general agreement about the grading system useful to classify conventional MPNST. Based on a 2-tiered grading system, conventional MPNST is divided into low-grade and high-grade MPNST [165]. The former tumor exhibits a neurofibroma-like appearance, being composed of a cellular proliferation of bland, back-to-back spindle cells in continuity with the so-called atypical neurofibroma; the latter, high-grade, tumors are characterized by intersecting fascicles of spindle cells with hyperchromatic nuclei, very high mitotic counts, geographic areas of necrosis and limited, if any, evidence of schwannian differentiation at immunohistochemistry. Some authors prefer to classify conventional MPNST as low-grade, intermediate-grade, and high-grade according to FNCLCC grading system [166].

Macroscopic Features Grossly, a malignant peripheral nerve sheath tumor may be attached to a nerve. A residual preexisting neurofibroma (often plexiform type) may be seen. Malignant peripheral nerve sheath tumors present as a large (>5 cm in greatest diameter) and firm fusiform/oval eccentric mass with a fleshy, white-tan cut surface. Areas of hemorrhage, necrosis, and pseudocystic degeneration are seen.

Microscopic Features Histologically, conventional malignant peripheral nerve sheath tumors exhibit a wide spectrum, ranging from neoplasms resembling a neurofibroma to highly pleomorphic sarcomas. However the majority of malignant peripheral nerve sheath tumors have an overall appearance closely reminiscent of fibrosarcomas, being composed of tightly packed spindle-shaped cells mainly arranged in long interlacing fascicles, often exhibiting herringbone, storiform, and whorled growth patterns. Neoplastic cells have pale and indistinct cytoplasm with hyperchromatic, tapered, often wavy nuclei. Most tumors show variation in cellularity, with alternating hypercellular and more myxoid hypocellular areas, resulting in a "mar-

bled pattern." In a significant number of cases, perivascular cellular condensation can be identified [159]. Mitoses (at least 1 mitosis per 10 high power field) and necrosis are common. The latter is frequently seen as geographic necrosis, often rimmed by palisading nuclei. In areas with diffuse necrosis, perivascular tumor cells often survive (Fig. 31.14). Additional morphological features are represented by the herniation of tumor cells into blood vessel lumens, often in association with vaguely glomeruloid small vessels proliferation, whirling and/or curlicue arrangement of neoplastic cells, suggesting tactoid differentiation, hyalinized cords, or nodules. A recent consensus overview on MPNST arising from NF1 suggests to divide these tumors into "low or high grade." High-grade tumors are more frequent and are characterized by a sarcomatous growth pattern, often fibrosarcoma-like pattern, nuclear atypia, and $\geq$ 10 mitoses/10 HPF. Tumor necrosis, often present, is not required. Conversely tumors with the above-mentioned features but with a mitotic rate of 3–9 mitoses/10 HPF can be classified as "high-grade" or "low-grade" if tumor necrosis is present or absent, respectively [165]. Low-grade tumors usually arise in the context of NF1 from a preexisting neurofibroma [165]. Heterologous components (mesenchymal or epithelial) can be observed in about 10–15% of malignant peripheral nerve sheath tumors, mostly in the context of NF1 [5, 158]. The most common heterologous component is represented by rhabdomyoblasts like in embryonal rhabdomyosarcoma (the so-called "*malignant Triton tumor*"). A chondrosarcomatous or osteosarcomatous component may be also seen alone or variably admixed with other heterologous components [5, 158, 159]. Benign or malignant epithelial components and/or angiosarcomatous component can be occasionally identified. A small round blue cell component with primitive neuroepithelial differentiation is seen in up to 15% of pediatric malignant peripheral nerve sheath tumors [5, 158, 159].

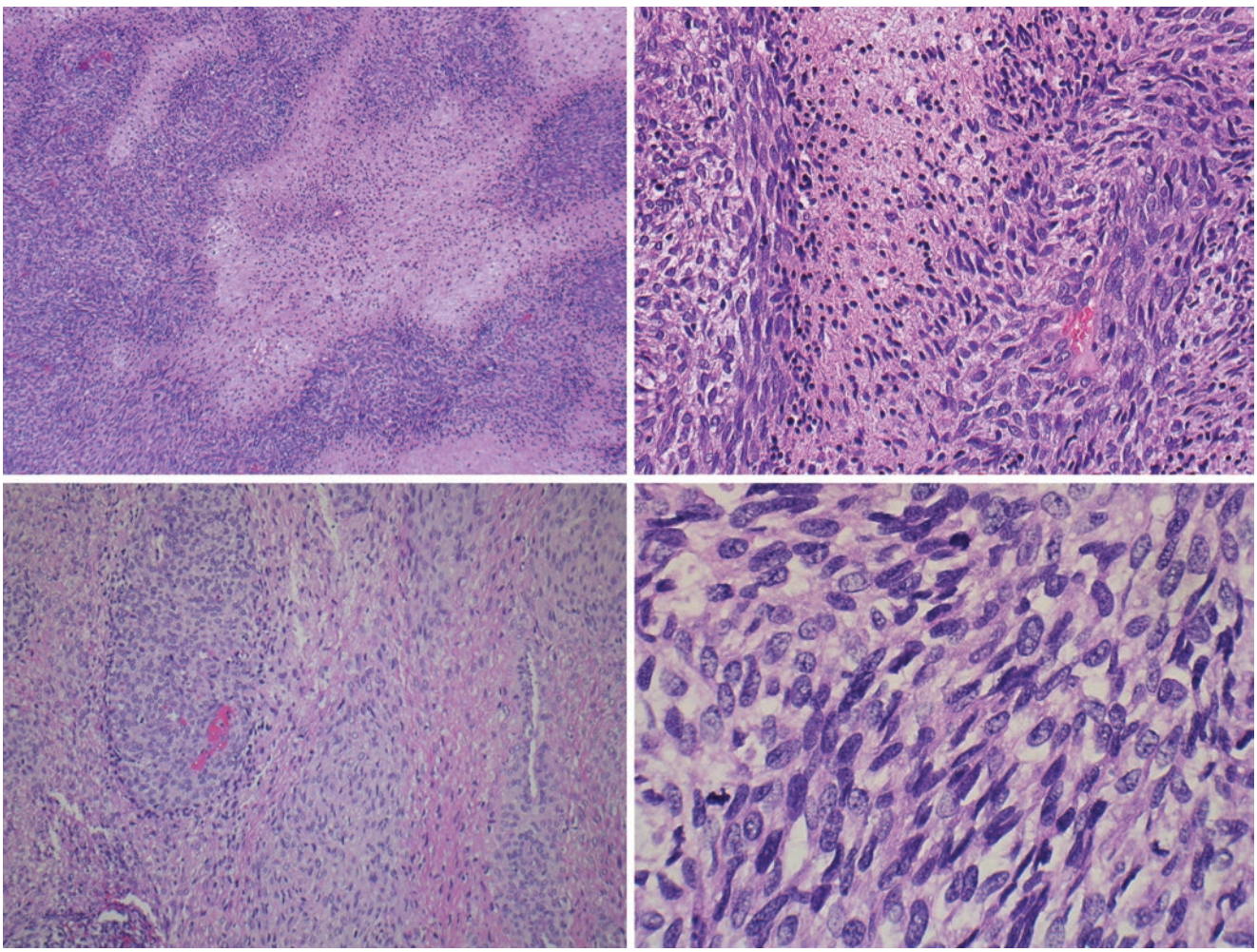

Fig. 31.14 Malignant Peripheral Nerve Sheath Tumor arising in a neurofibroma of the neck with a characteristic geographic necrosis (**a**). The neoplastic cells exhibit a spindle cell morphology and are arranged in fascicles (**b**). Residual areas of neurofibroma are seen (**c**). (**d**) The cells are elongated with hyperchromatic nuclei

Immunohistochemistry/Molecular Diagnostic Features Unfortunately there are no specific markers for diagnosis of conventional malignant peripheral nerve sheath tumors. S-100 protein (focal staining), GFAP, CD56, CD57, and CD34 are usually expressed in about 30–50% of the cases. The expression of SOX10, a neural crest transcription factor, has been reported to have better sensitivity and specificity than S-100 protein [167]. Epithelioid malignant peripheral nerve sheath tumors are generally diffusely and strongly stained with S100 protein, but are negative for cytokeratins and melanoma-associated antigens (HMB-45, Melan-A). INI1 nuclear immunoreactivity is negative in about 40–50% of cases [5, 168, 169]. Recently a homozygous inactivation of the polycomb repressive complex 2 (PRC2), derived from inactivating mutations of its constituents *SUZ12* or *EED1*, has been identified in 70–90% of malignant peripheral nerve sheath tumors [170]. PRC2 inactivation promotes tumor progression with loss of histone H3K27 trimethylation (H3K27me3). The loss of immunohistochemical expression of H3K27me3 has been found to be a useful marker, especially for sporadic malignant peripheral nerve sheath tumors, being it retained in most spindle cell mimickers [165, 166]. Epithelioid malignant peripheral nerve sheath tumors, by contrast, retain the expression of H3K27me3 [165].

Differential Diagnosis The main differential diagnosis includes a variety of spindle cell sarcomas, especially synovial sarcoma. Synovial sarcomas may occur even in the context of NF1 [166]. It exhibits a more uniform fascicular growth pattern and the neoplastic cells, with a fibroblastic-like morphology, lack features of neural differentiation. Immunoreactivity for epithelial markers (cytokeratins and EMA) in the neoplastic spindle cells favors the diagnosis of synovial sarcoma. About 30–40% of synovial sarcoma may express S100 protein. The demonstration of *SS18-SSX1* or *SS18-SSX2* gene fusions is crucial for confirming the diagnosis of synovial sarcoma.

As in other sites, the strongest predictor of survival for malignant peripheral nerve sheath tumors in the head and neck region is its complete surgical resection [159, 164, 171]. However a complete en bloc resection is often not feasible for most tumors, given the anatomic complexity and the presence of vital structures. Some authors have reported a 5-year overall survival of 47% for pediatric malignant peripheral nerve sheath tumors of the head and neck [164]. Negative prognostic factors are: large tumor size (>5 cm) and the presence of regional or distant metastases [164]. Malignant peripheral nerve sheath tumors in the context of NF1 have an invariably aggressive clinical course.

Soft Tissue Sarcomas with Uncertain Type

Synovial Sarcoma

Definition Synovial sarcoma is a malignant mesenchymal tumor occurring in the extremities and in proximity of articular spaces [172]. The head and neck region is its second most common site of origin, representing up to 10% of all cases in adults [5, 173]. Less than 3% of pediatric synovial sarcomas arise in the head and neck region, mostly in the peripharyngeal soft tissue or in maxillary/submaxillary regions. The other involved sites are: oral cavity, sinonasal tract, submandibular area, parotid gland, temporal/infratemporal regions, cheek, scalp, mandible, nasolabial regions, and pharynx [1, 135–141, 173–175] (Table 31.5). Occasionally, synovial sarcoma may arise in the context of *NF1* [135].

Clinical Presentation The tumors are generally asymptomatic and clinical manifestations are related to the site of origin and its growth with entrapment of anatomic structures. High resolution multiplanar CT and MRI contribute to define the extension of the lesion and the involvement of the adjacent structures [174, 175].

Classification/Subtypes Like in other sites, conventional synovial sarcoma, with all its histological variants (monophasic, biphasic, and poorly differentiated) is represented in the head and neck region [140].

Macroscopic Features Grossly, tumors may present as well or poorly circumscribed masses, usually firm in consistency with a yellow to whitish cut surface. Some tumors may contain areas of hemorrhage, necrosis, and pseudocystic formations, resembling a vascular tumor.

Microscopic Features Monophasic synovial sarcoma (70% of all synovial sarcoma) is characterized by solid sheets and fascicles of overlapping, uniform fibroblastic-like cells with oval to elongated, hyperchromatic nuclei and finely dispersed chromatin. Mitoses are usually scarce. Alternating hypercellular and hypocellular areas can be seen. Abundant thick collagen bands, often plaque-like, a ~~A~~ hemangiopericytoma-like vascular pattern and stromal calcifications are typical of synovial sarcoma (Fig. 31.15). Foci of osseous metaplasia can also occur. In biphasic synovial sarcoma there is a variable mixture of spindle cells with epithelioid cells arranged in solid nests or cords, and/or true glands usually containing intraluminal eosinophilic secretions. A focal squamous differentiation can be occasionally observed. Poorly differentiated synovial sar-

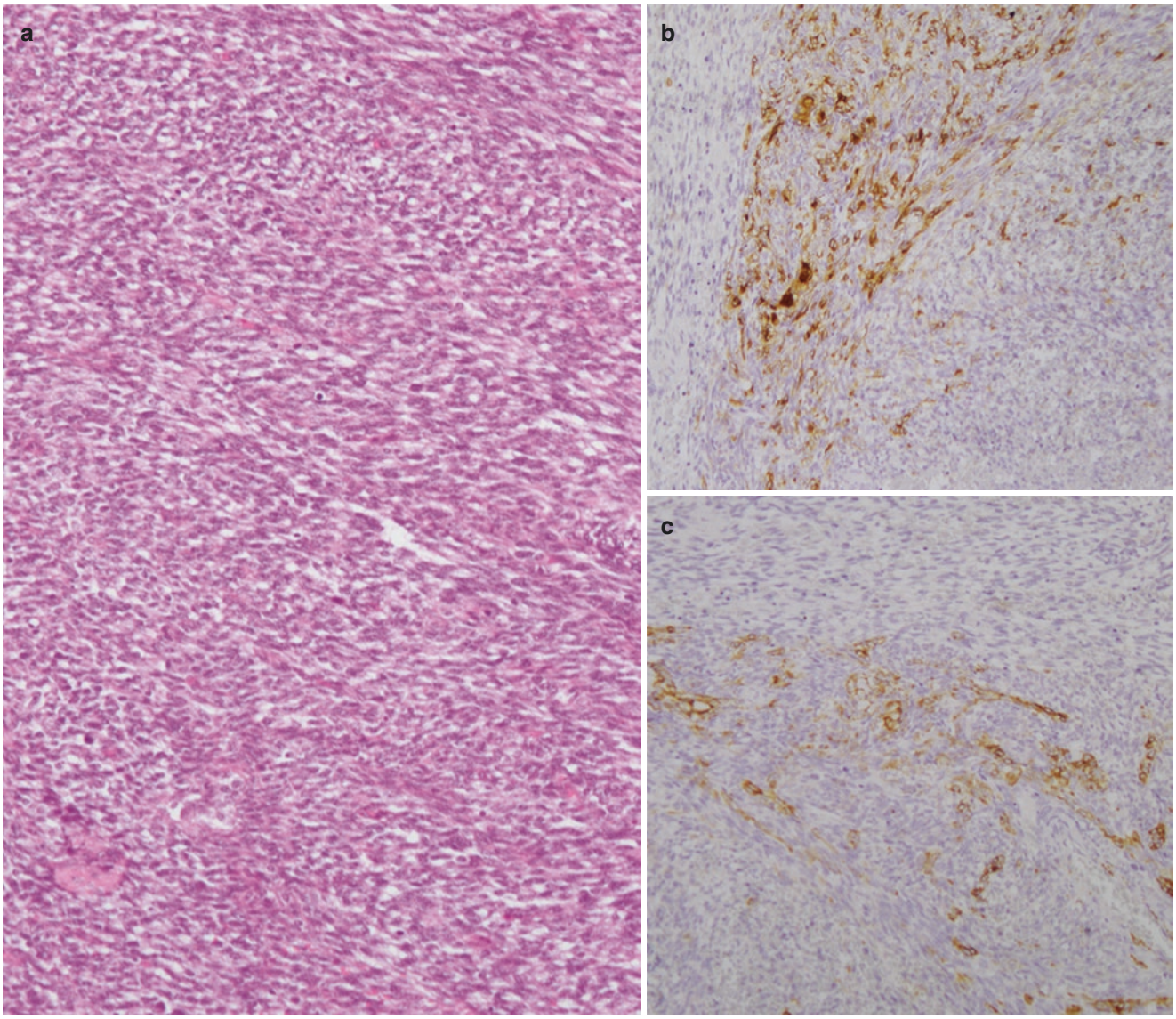

Fig. 31.15 Fibrous monophasic synovial sarcoma of the larynx, in a 7-year-old boy. Elongated cells arranged in intersecting fascicles. Nuclei show uniform dark chromatin (**a**). Immunophenotype of synovial sarcoma with scattered positive cells for Cytokeratin 7 (**b**) and EMA (**c**)

coma is viewed as the morphologic result of tumor progression. It consists of small- to medium-sized round cells with hyperchromatic nuclei, as well as frequent mitoses and foci of necrosis.

Immunohistochemistry/Molecular Diagnostic Features Synovial sarcomas show positive immunostaining for vimentin and, at least focally, for cytokeratins (especially cytokeratins 7 and 19), epithelial membrane antigen (EMA), TLE1, CD99, and BCL2. S100 protein immunoreactivity can be occasionally found (Fig. 31.15). Almost all synovial sarcomas show strong nuclear expression of TLE1 [176, 177]. Interestingly a decreased, but not the complete loss of INI1 expression has been found in most cases of synovial sarcomas [178, 179]. A recurrent chromosomal translocation t(X;18)(p11.2;q11.2) with fusion of *SYT* gene on chromosome 18 with *SSX1*, *SSX2,* or *SSX4* is found in the vast majority of synovial sarcomas. *SYT-SSX1* transcript is associated with biphasic histology [140, 172].

Differential Diagnosis The diagnosis of synovial sarcoma in the head and neck region may be challenging, especially in children. The differential diagnosis in monophasic fibrous synovial sarcoma, which is more frequent in head and neck, includes rhabdomyosarcoma and malignant peripheral nerve sheath tumor. Lack of immunohistochemical markers of myogenic differentiation is useful in excluding rhabdomyosarcoma. Malignant peripheral nerve sheath tumors and synovial sarcoma share the fascicular pattern and the cytologic features may be misleading. The expression of epithe-

lial markers and TLE1, along with lack of S100 protein, favors the diagnosis of synovial sarcoma. In addition poorly differentiated synovial sarcoma needs to be distinguished from many other small round cell tumors. The detection of the translocation by conventional cytogenetics or the resultant *SSX1-SS18* or *SSX2-SS18* fusion transcripts by molecular techniques are important diagnostic tools [5, 172]. The mainstay of treatment includes radical surgical excision, being synovial sarcoma poorly responsive to chemotherapy. Radiotherapy is important to obtain the local control in cases of incomplete or marginal excision [180]. The prognosis is related to age, tumor size, and radical excision. Tumors less than 5 cm with negative resection margins have a more favorable prognosis [181]. Prognostic significance of tumor grade or molecular status is still debated.

Alveolar Soft Part Sarcoma

Definition Alveolar soft part sarcomas represent 0.2–0.9% of all soft tissue sarcomas. They are aggressive tumors with an overall poor prognosis due to a high rate of metastases [182]. In children approximately 25% of cases arise in the head and neck region, especially oral cavity (tongue), nasal cavity, orbit, and pharynx/larynx (Table 31.6) [183, 216–218]. The mean age of patients is 5 years and there is no sex predominance.

Clinical Presentation Tumors present as slowly growing masses, often without clinical symptoms. Orbital tumors cause proptosis and lid swelling.

Macroscopic Features Head and neck alveolar soft part sarcomas tend to be very small, varying from 1 to 5 cm and poorly circumscribed with a gray, focally hemorrhagic, and often necrotic cut surface. They have a soft consistency.

Microscopic Features Histologically, they are composed of epithelioid cells with abundant eosinophilic cytoplasm, eccentric nuclei, and single prominent nucleoli, arranged in a nested pattern. Vascular invasion is frequent in the tongue but does not have prognostic significance [216, 219–223]. Occasionally solid sheets or nests of tumor cells are present, especially in lingual alveolar soft part sarcomas occurring in young patients [216] (Fig. 31.16). Typical cytoplasmic rhomboid, polygonal, or spiked crystals are found in 25–80% of alveolar soft part sarcomas [216, 221, 223].

Immunohistochemistry/Molecular Diagnostic Features The diagnosis of alveolar soft part sarcoma is based on morphology, in fact there are no lineage specific immunohistochemical markers [224]. However nuclear positive immunostaining for TFE3 may suggest the presence of the *ASPL-TFE3*-fusion transcript, deriving from the t(X,17)(p11;q25) typical of alveolar soft part sarcoma [224, 225].

Differential Diagnosis The differential diagnosis includes a variety of other epithelioid cell neoplasms, especially clear cell sarcoma of soft part and epithelioid sarcoma, both extremely rare in head and neck region. Alveolar soft part sarcoma is a slowly growing neoplasm, with an indolent clinical course. Metastases affecting lungs, bone, and liver may occur after many years. Overall survival of head and neck alveolar soft part sarcomas in children and adolescents is superior to 75%. The better prognosis compared to other sites may be related to the smaller size of the tumors and early diagnosis [216, 222]. Surgery is the elective treatment for alveolar soft part sarcoma. Radiotherapy may be helpful in achieving local control in incompletely resected tumors [226]. Response to chemotherapy is obtained in less than 10% of patients. The new agents targeting tyrosine kinase receptors or the mammalian target of rapamycin (mTOR) are a promising therapeutic alternative, being mTOR a downstream effector in the MAP kinase and PI3K/Akt pathway via interaction with MET/hepatocyte growth factor [227, 228].

Clear Cell Sarcoma of Soft Parts

Definition Clear cell sarcomas of soft parts are aggressive soft tissue tumors showing melanocytic differentiation, frequently arising in association with tenosynovial structures of extremities [229]. They represent less than 2% of soft tissue sarcomas in head and neck region in adults, while in children they are a rarity, with only a few cases reported in the last three decades [192–195] (Table 31.6).

Clinical Presentation Clear cell sarcomas of soft parts generally present as small lesions and, when occurring in oral cavity, may be misinterpreted for a mucocele or dental abscess [194, 195].

Macroscopic Features Most of the head and neck clear cell sarcomas are small (1–5 cm), circumscribed lesions with a lobulated gray-white cut surface. Necrotic and/or pseudocystic degeneration can occur.

Microscopic Features Histologically, clear cell sarcomas are composed of nests or fascicles of epithelioid to spindled cells with clear or eosinophilic cytoplasm and nuclei with single prominent nucleoli. Occasionally multinucleated giant cells are seen (Fig. 31.17).

Immunohistochemistry/Molecular Diagnostic Features Positive immunostaining for S100 protein and HMB45 supports the melanocytic nature of the tumor, differentiating

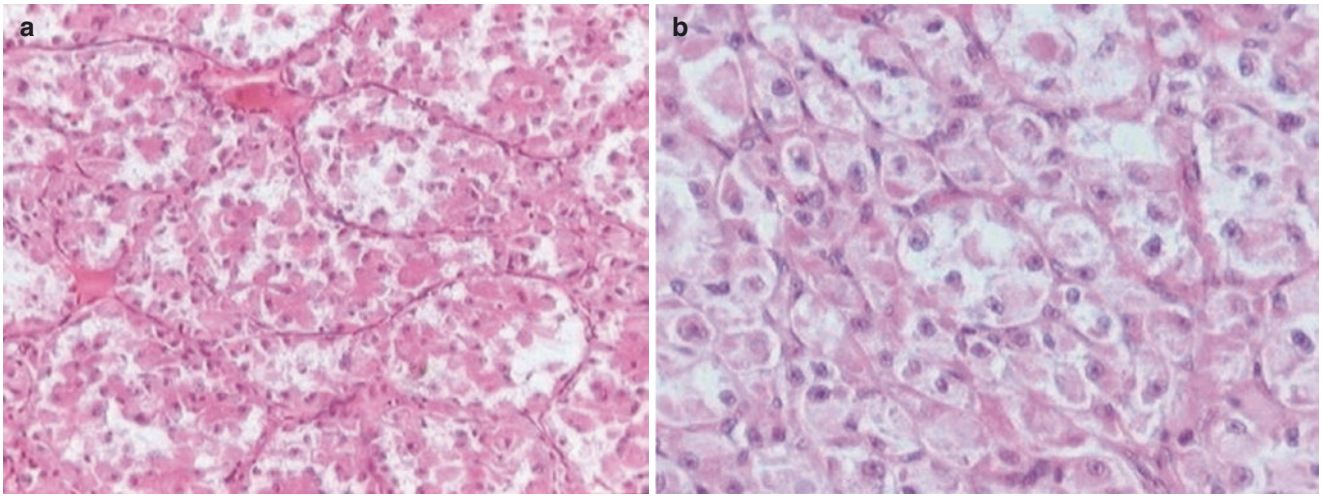

Fig. 31.16 Alveolar soft part sarcoma. Nests (**a**) or solid sheets (**b**) of epithelioid cells with abundant eosinophilic cytoplasm, eccentric nuclei. Immunostains help to exclude other diagnoses (see text)

Table 31.6 Clinical features of sarcomas with predominant epithelioid morphology in children: review of the literature

Histotype (#)	Age (median)	M:F	Site	Follow-up
Alveolar soft part sarcoma (59) [183–191]	2–18 year (6)	2:3	Oral cavity (52) Nasal cavity (3) Pharynx/larynx (2) Orbit (3) Other (3)	45 ANED 6 DOD 2 AWD 6 NA
Clear cell sarcoma soft parts (4) [192–195]	13–17 year (15)	3:1	Oral mucosa, mandibular(1) Skin (lip, cheek, cervical) (3)	2ANED 1DOD 1NA
Myoepithelial carcinoma (9)** [196–200]	0–18 year (6.2)	1:1	Infratemporal/parietotemporal/craniofacial (4) Neck (2) Nuchal (1) Orbit (1) Retroauricular (1)	ANED (5) DOD (2) 2NA
Angiosarcoma (11) [201–207]	4 month–17 year (15.5)	2:1	Tongue, oral mucosa, lip (3) Orbit (1) Middle ear (1) Nose (1) Submandibular (1) Skin scalp (1) Neck (1) Head NOS (2)	5 ANED 2 DOD 2 AWD 2 NA
Epithelioid hemangioendothelioma (16*) [208–215]	4–18 year (9)	1:1	Oral cavity (11) Orbit (1) Nose, forehead, ear (skin or cavity) (5)	1 relapse 1MTS/ANED 14 ANED

[] = references; *ANED*: alive without disease; *DOD*: died of disease; *NA*: not available; *NOS*: not otherwise specified; *MTS*: metastasis; * excluded cerebral tumors; **not included tumors of possible origin from salivary gland

clear cell sarcoma from alveolar soft part sarcoma and epithelioid sarcoma. Melan-A may be negative in mucosal lesions. *EWSR1-ATF1* fusion transcript from t(12;22)(q13;q12) has been detected in all clear cell sarcomas of head and neck.

Differential Diagnosis Distinction of clear cell sarcoma from melanoma, epithelioid malignant peripheral nerve sheath tumors, and cellular blue nevus may require molecular testing [230].

Epithelioid Sarcoma

Definition Epithelioid sarcoma is a rare and aggressive soft tissue sarcoma with a high risk for local recurrence and metastasis [231]. It occurs more frequently in adolescents and young adults (median age 26 years), while it is rare in children. There is a preponderance of males over females with a reported ratio of 2.0. The most common involved sites are distal extremities, while less than 1% of tumors arise in head and neck region, especially in the scalp [5]. The largest

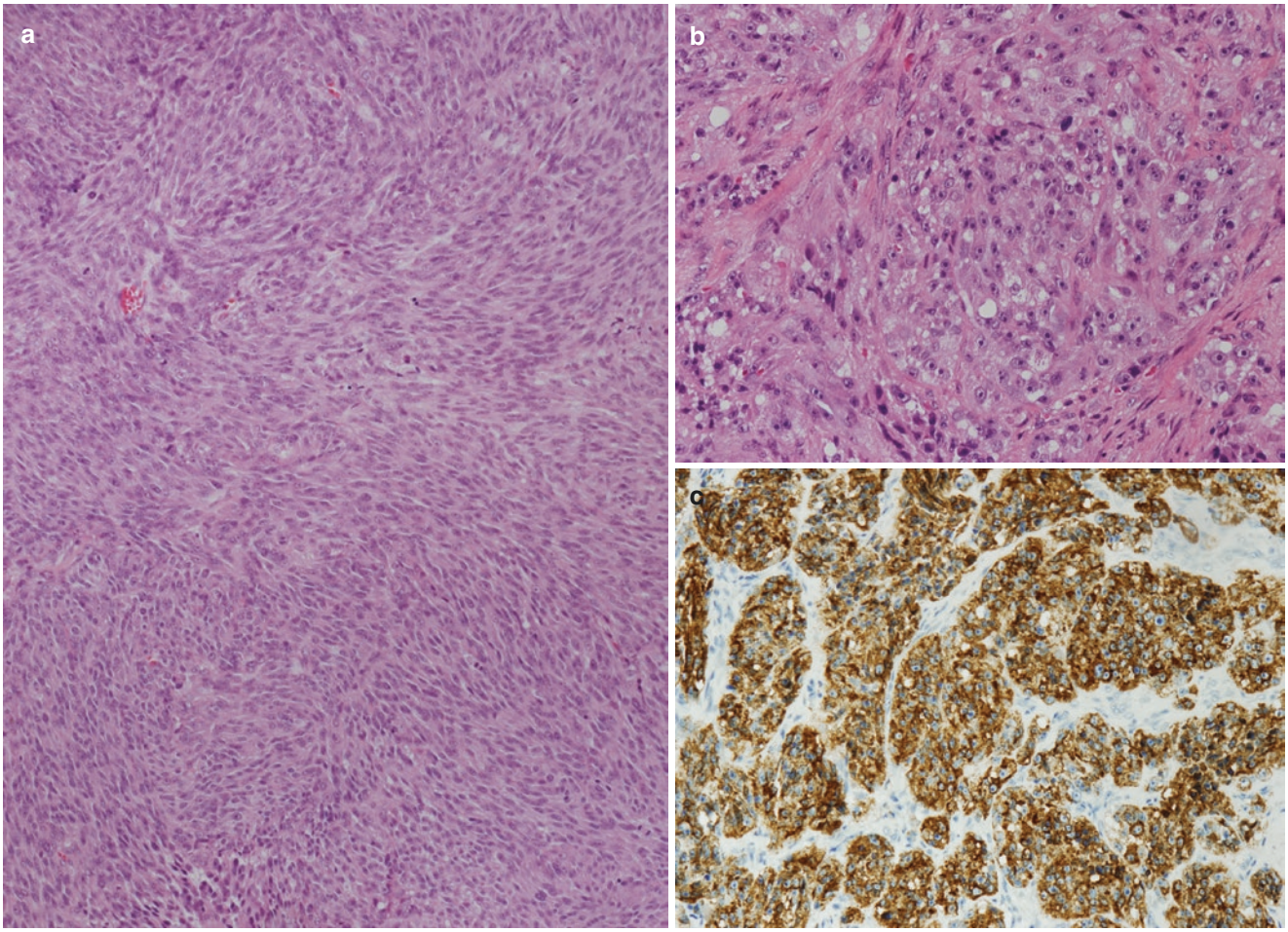

Fig. 31.17 Clear cell sarcoma of soft parts (non-head neck site): The tumor shows elongated cells in fascicles (**a**) with focal nesting (**b**). Cells show eosinophilic to clear cytoplasm and nuclei with prominent nucleoli (**b**). Cytologic features and positive immunostaining for HMB45 (**c**) are useful to differentiate this tumor, that is rare in head and neck, from other tumors more frequent in this site (see text)

series of pediatric epithelioid sarcomas included three cases occurring in the head, mostly oral cavity and tongue [232, 233], while isolated case reports have been described in the parotid gland [234].

Clinical Presentation Tumor presentation largely depends on the superficial or deep localization. The superficial lesions present as slowly growing and painless, solitary (sometimes multiples nodules) nodules, with the tendency to undergo ulceration in a few weeks or months. Given this deceptive appearance, there is often confusion with an ulcer, or infected wart. Deep-seated tumors are usually larger in size (up to 15 cm) and present as areas of induration or multinodular masses (Fig. 31.18).

Classification Two histologically variants of epithelioid sarcoma are recognized: conventional-type and proximal-type epithelioid sarcoma, with the latter typically arising in the pelvis, perineum, and genital tract.

Macroscopic Features Grossly, most superficial epithelioid sarcomas present as one or more ulcerated nodules, ranging in size from 0.5 to 5 cm. Deep-seated tumors are larger in size and tend to present as firm multinodular masses with irregular borders. The cut surface shows a gray-white or gray-tan nodule with foci of necrosis and/or hemorrhage.

Microscopic Features Conventional epithelioid sarcoma shows epithelioid to polygonal and, less frequently, spindle cells with abundant eosinophilic cytoplasm, and uniform hyperchromatic nuclei, arranged in a solid, often nodular, pattern with frequent central geographic necrosis. Accordingly, epithelioid sarcoma, at low magnification, may mimic a granulomatous process. Nuclear pleomorphism is minimal or absent. Mitoses are rare. Occasionally neoplastic cells are variously arranged in sheets, pseudo-alveoli or pseudo-vascular spaces (Fig. 31.19). Proximal-type epithelioid sarcoma is composed of large atypical epithelioid to rhabdoid cells, with large and vesicular nuclei containing

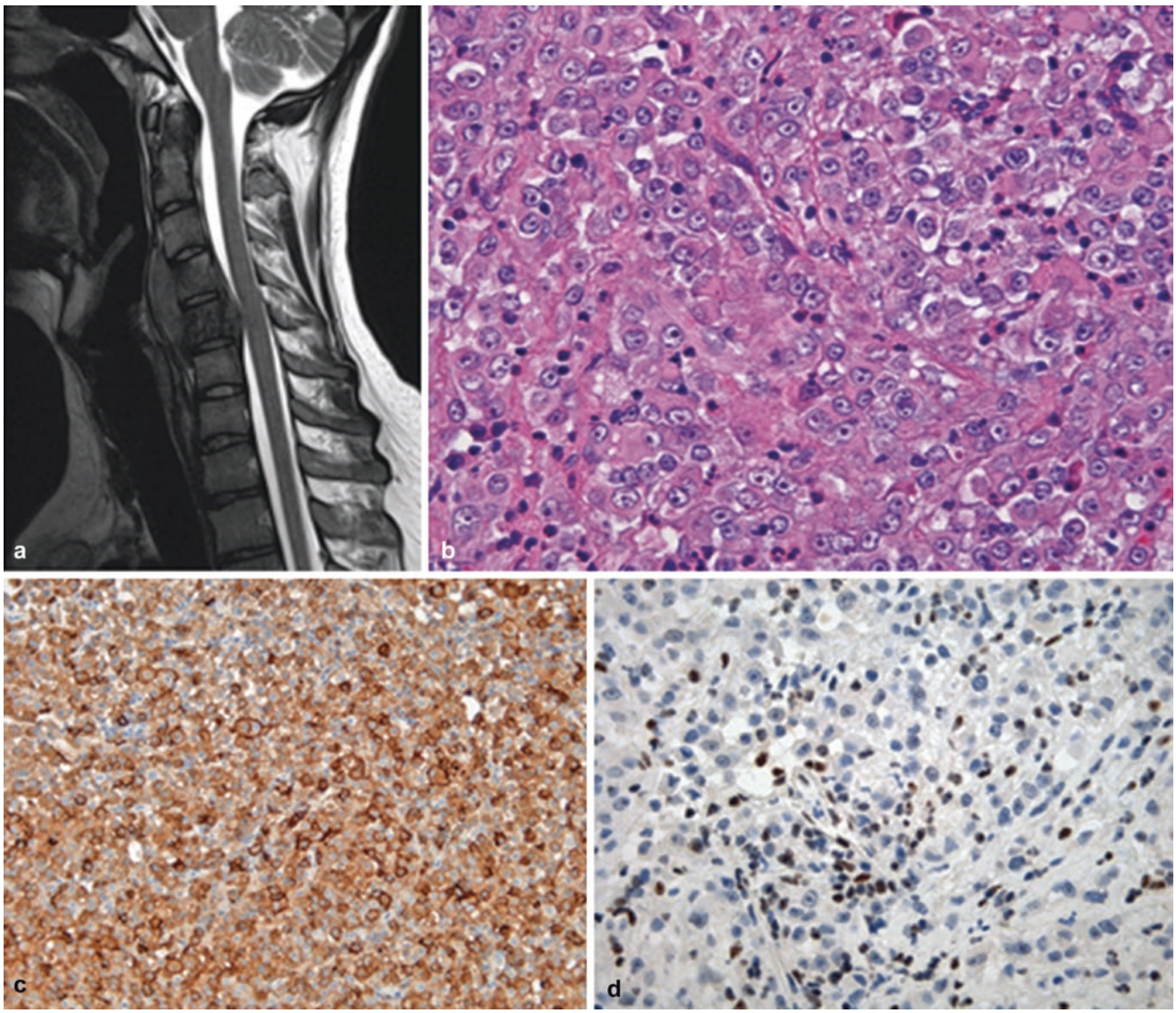

Fig. 31.18 Epithelioid sarcoma, proximal-type in an 18-year-old boy (neck region, paravertebral space) (**a**). Sheets of large epithelioid cells with vesicular nuclei and prominent nucleoli (**b**), with diffuse EMA positive staining (**c**). INI-1 highlights isolated lymphocytes interspersed among the tumor cells, which are negative (**d**)

prominent nucleoli (Fig. 31.18). Rhabdoid cells show typical paranuclear eosinophilic inclusions. Necrosis is commonly found.

Immunohistochemistry/Molecular Diagnostic Features Regardless of the histologic subtype, epithelioid sarcoma shows immunoreactivity for epithelial markers (cytokeratins, epithelial membrane antigen) and vimentin. The absence, in more than 90% of cases, of INI1 nuclear expression, related to a loss of expression of *SMARCB1* gene located on chromosome 22q11.2, is a very helpful diagnostic tool. CD34 is variably positive (45–60%) [235]. Epithelioid sarcoma is a high-grade tumor characterized by multiple local recurrences and late distant metastasis. However, the prognosis is influenced by tumor size, site, and the adequacy of surgical excision [5]. Proximal-type epithelioid sarcoma has an overall survival of 35% compared to 55% for conventional type [5].

Rhabdoid Tumor

Definition Rhabdoid tumors are highly aggressive tumors typically occurring in infants [236]. About 12% of rhabdoid tumors occur as primary cutaneous lesions located in the dermis or in deep soft tissue of the head and neck [237].

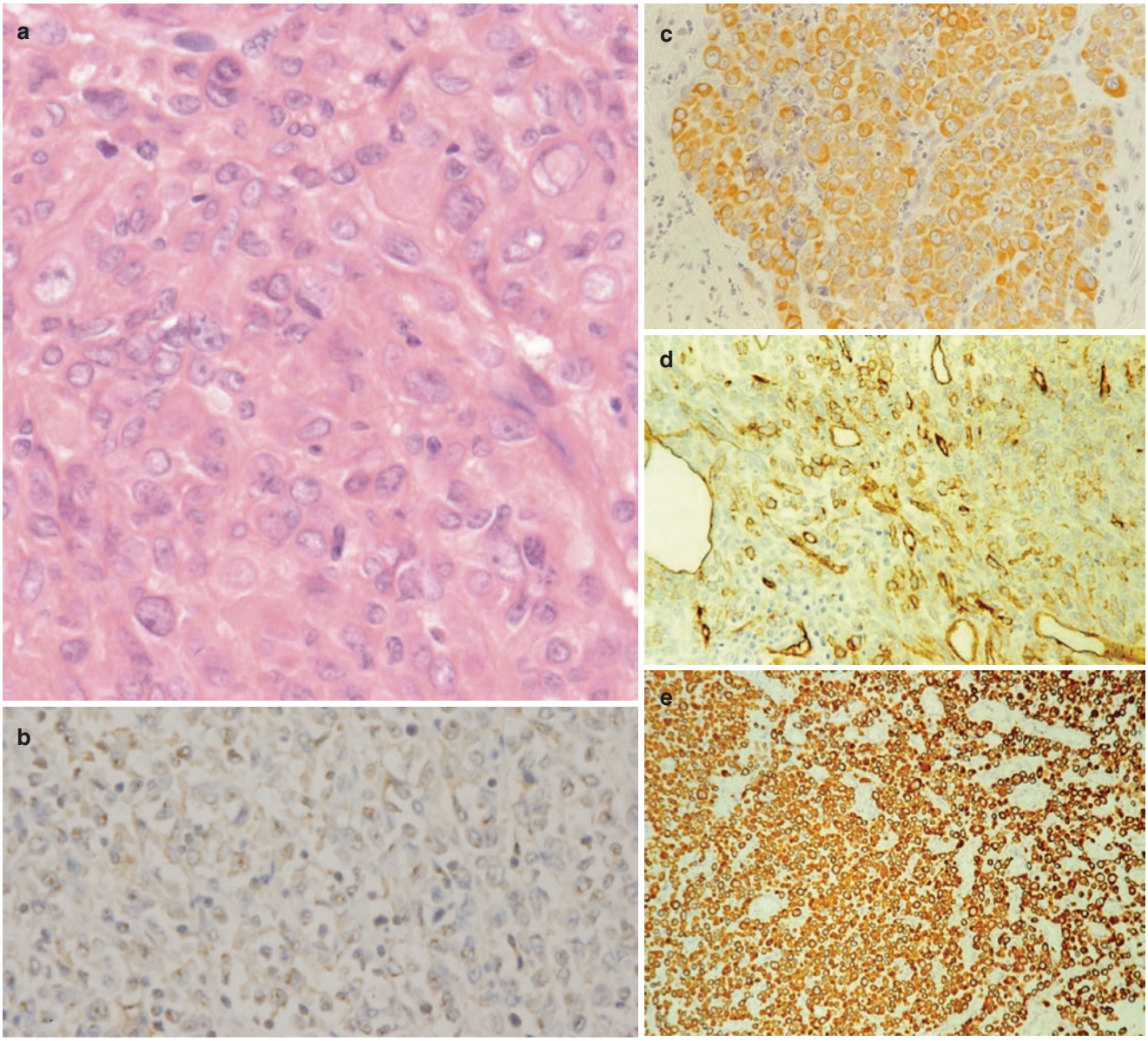

Fig. 31.19 Epithelioid sarcoma, classic type (**a**) with diffuse EMA and vimentin staining (**c**, **e**), focal positivity for CD34 (**d**) and INI-1 loss (**b**)

Clinical Presentation A recent review collected 14 cases of head and neck rhabdoid tumors, mostly affecting newborns and infants. The age ranges from 1 day to 11 years [238]. The most commonly involved sites were tongue, gingiva, orbit, oropharynx, parapharyngeal space, scalp, thyroid, and face [238].

Macroscopic Features Grossly, head and neck rhabdoid tumors are usually less than 5 cm in greatest dimension. They present as soft masses with a fleshy, and gray to tan in color, cut surface. Hemorrhage and necrosis are common.

Microscopic Features Histologically, they are composed of sheets or nests of rhabdoid cells, i.e. large and epithelioid to polygonal in shape, with abundant eosinophilic cytoplasm containing juxtanuclear eosinophilic, PAS-positive hyaline inclusions, and eccentric vesicular nuclei with macronucleoli (Fig. 31.20).

Immunohistochemistry/Molecular Diagnostic Features Rhabdoid tumors show positive immunostaining for vimentin, cytokeratins, and EMA, while desmin and α-smooth muscle actin are variably expressed. Negative immunostainings for myogenic and endothelial markers exclude rhabdomyosarcomas with epithelioid features and epithelioid vascular tumors, respectively. A negative nuclear immunostaining for INI-1, related to a loss of expression of *SMARCB1* gene, located on chromosome 22q11.2, is an important diag-

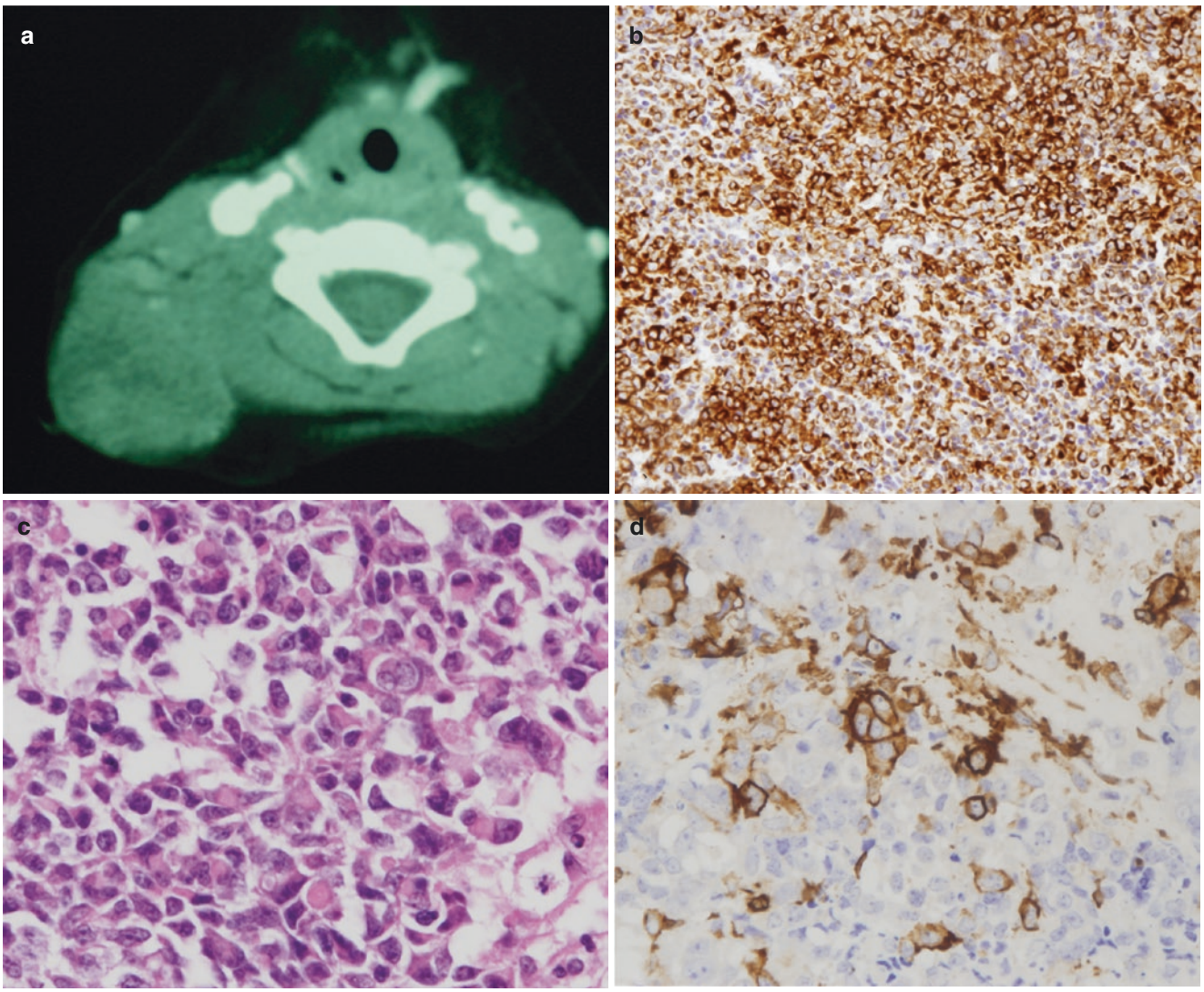

Fig. 31.20 Rhabdoid tumor: CT scan from a deep neck mass with cystic areas in a 9-month-old girl (**a**) Sheets of large epithelioid cells with vesicular nuclei, prominent nucleoli and intracytoplasmic paranuclear eosinophilic inclusions (**b**). EMA is focally positive (**c**). Vimentin is positive in 100% of rhabdoid tumors (**d**). INI -1 expression is lost

nostic tool [239]. Negative INI-1 immunostaining is useful in excluding alveolar soft part sarcomas and clear cell sarcomas. However other soft tissue tumors may lack INI expression, included synovial sarcomas and myoepithelial carcinomas [240].

Differential Diagnosis The most challenging differential diagnosis is between rhabdoid tumor and proximal-type epithelioid sarcoma. These tumors may be morphologically similar and share the loss of INI1 expression. Despite this common molecular features, their genomic profile is different with a highly complex genome in epithelioid sarcoma compared to rhabdoid tumors, and this diversity may influence the different clinical course [241]. Distinction from chordomas may be challenging especially in tumors arising in the clivus region. Physaliferous cells can show marked vacuolation of cytoplasms and express S100 protein and brachyury, both absent in rhabdoid tumors. Rhabdoid tumors have a highly aggressive clinical course, independently from the site, with a 3-year overall survival of 38.4% [237, 242].

Malignant Vascular Tumors

Epithelioid Hemangioendothelioma

Definition Epithelioid hemangioendothelioma is a low- to intermediate-grade malignant vascular tumor [243].

Clinical Presentation In children less than 20 cases has been reported, mostly in the oral cavity, in the nose and

orbital region (Table 31.6) [208–215, 244–247]. It usually presents as a solitary (occasional multifocal), painful mass, which can be associated (50% of cases) with the wall of a vein.

Macroscopic Features Epithelioid hemangioendotheliomas usually present as bloody soft masses, sometimes with infiltrative margins. Lesions arising from vessels have a white-red color surface, resembling organizing thrombi attached to the surrounding tissues. Tumors without association with vessels appear as white-gray masses.

Microscopic Features Histologically, epithelioid hemangioendothelioma is characterized by the proliferation of epithelioid, eosinophilic endothelial cells with frequent cytoplasmic vacuolization, around a central vein in the context of a myxohyaline stroma. A mitotic activity >3 mitoses/10 high power fields and tumor size >3 cm may be associated with an aggressive clinical behavior [243, 245].

Immunohistochemistry/Molecular Diagnostic Features Neoplastic cells are immunoreactive for endothelial markers, such as ERG, CD31, and CD34. As other sarcomas with epithelioid morphology, epithelioid hemangioendothelioma variably expresses pan-cytokeratins and EMA. A *WWTR1-CAMTA1* fusion gene from t(1;3)(p36;q25) has been recently demonstrated in epithelioid hemangioendothelioma [246]. A subset of tumors with vasoformative features and nests of epithelioid eosinophilic cells shows the *YAP1-TFE3* transcript from t(11;X)(q13;p11) [247].

Differential Diagnosis The distinction from epithelioid angiosarcoma in based on the absence of vase formation in epithelioid hemangioendothelioma. However the molecular characterization may be required. [247]. A preserved INI-1 staining excludes epithelioid sarcoma.

Pseudomyogenic Hemangioendothelioma

Definition Pseudomyogenic hemangioendothelioma is a low-intermediate grade vascular tumor that can morphologically mimic epithelioid sarcoma [248].

Clinical Features About 3% of tumors arise in the head and neck region and are frequently multifocal [249]. There is a predilection for young males. The clinical course is indolent [249].

Macroscopic Features Tumor typically presents as a superficial or deep nodule with gross features similar to those of epithelioid sarcoma.

Microscopic Features Histologically it consists of epithelioid to spindle cells with abundant brightly eosinophilic cytoplasm, mild to moderate nuclear atypia and low mitotic count (<5 mitoses/10 high power field). Frequently a transition of epithelioid into spindle cells can be seen (Fig. 31.21). Neoplastic cells are arranged in sheets or fascicles, and set in a fibrous stroma. There is no evidence of vascular channels or cytoplasmic vacuoles.

Immunohistochemistry/Molecular Diagnostic Features The immunoprofile is characterized by positive staining for cytokeratins and variably for CD31 and CD34 (Fig. 31.21). Recently a t(7;19)(q22;q13), resulting in a fusion *SERPINE1-FOSB*, has been identified with a positive immunostaining for FOSB [250, 251].

Differential Diagnosis As pseudomyogenic hemangioendothelioma does not form either vascular channels or cytoplasmic vacuoles, the recognition as vascular tumor may be challenging and is often misdiagnosed as epithelioid sarcoma. However, the lack of EMA staining and the retained INI-1 immunoreactivity are important in the distinction from epithelioid sarcoma. The clinical course is indolent with only rare lymph node or distant metastases.

Angiosarcomas

Definition Angiosarcomas are high-grade, malignant vascular tumors representing less than 2% of vascular tumors in children and adolescents and 0.3% of all pediatric sarcomas [201, 202, 252, 253].

Clinical Features Compared to adult angiosarcoma, that arises in head and neck region in 50% of cases, pediatric tumors are rare in this region, with less than 15 cases reported mostly in the skin, and less frequently in mucosal sites (oral cavity, lip and tongue) or salivary gland (submandibular region [202–207] (Table 31.6). The age at diagnosis ranges from infants to 15 years. There is a male predilection (female to male ratio: 2:1) [20]. Association with xeroderma pigmentosum is 20% of cases [201, 202].

Macroscopic Features Grossly, angiosarcomas arising in the skin and in the mucosa are polypoid, friable, and dark red with hemorrhagic and necrotic areas.

Microscopic Features Histologically, angiosarcomas do not differ from their adult counterpart and from those occurring in other sites, although the epithelioid morphology is much more prominent. The histological picture consists of tortuous, irregular spaces dissecting the stroma, with forma-

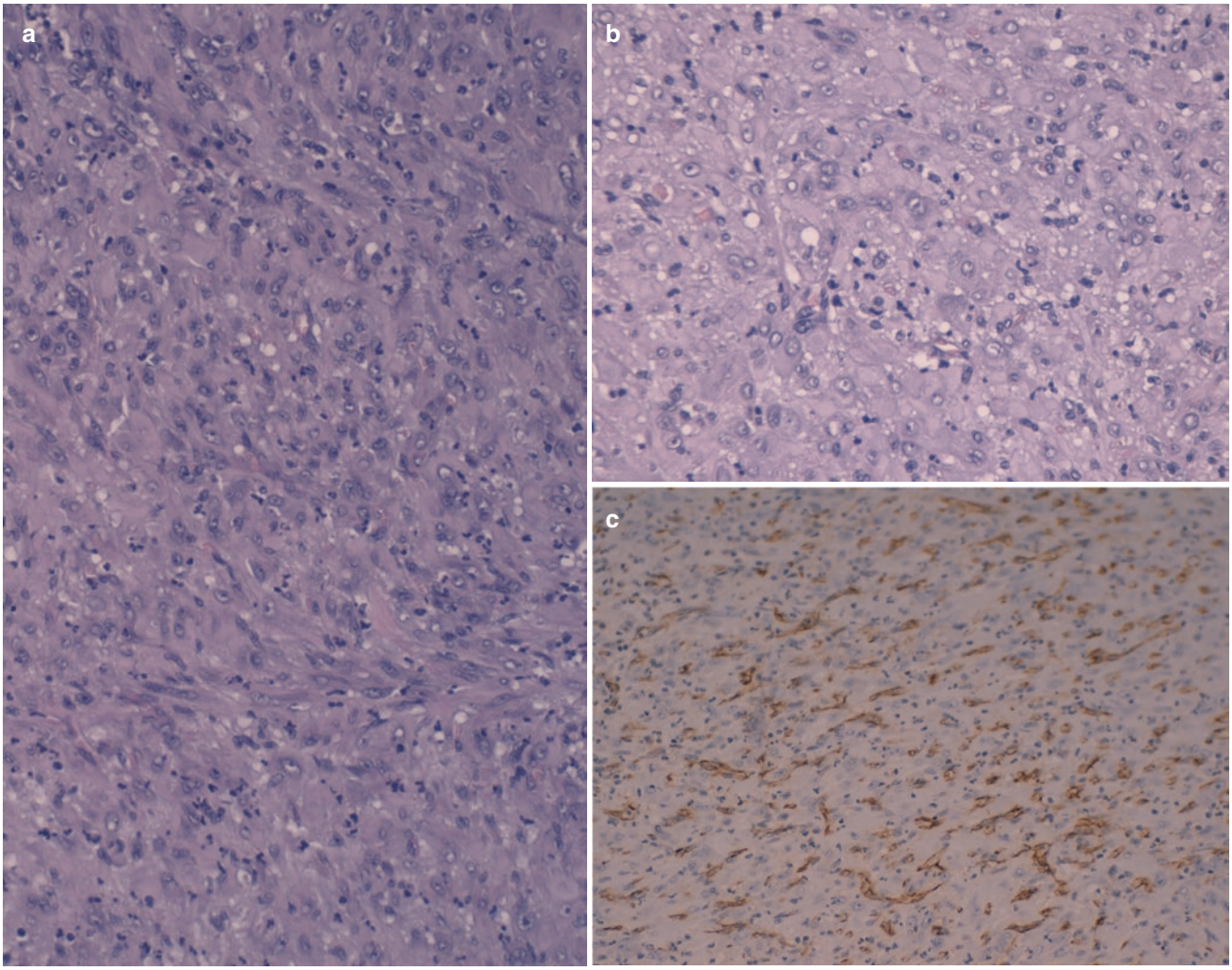

Fig. 31.21 Pseudomyogenic hemangioendothelioma: epithelioid to spindle cells with abundant cytoplasm (**a**) or rhabdomyoblastic-like features and moderate nuclear atypia (**b**) arranged in sheets and intermingled with granulocytes (**a**). Negative immunostaining for CD 31 (**c**)

tion of primitive-appearing vessels. The more enlarged vascular spaces are lined by multiple layers of plump, atypical, epithelioid to spindle endothelial cells abutting into the lumina. Cells with a more epithelioid appearance may contain intracytoplasmic lumina containing red cells. Cytologic atypia may be prominent. Mitotic rate is variable, with possible atypical mitoses. Some tumors may show spindle cell areas and, more rarely, the spindle cell morphology may be predominant (Fig. 31.22).

Immunohistochemistry Positive immunostaining for ERG, CD34, CD31, and Factor VIII are important to confirm the vascular nature of the tumor [201, 252, 253]. Focal reactivity for cytokeratins or epithelial membrane antigen may raise the suspicion of epithelioid sarcoma that can be also focally CD31-positive. The preserved INI-1 expression supports the diagnosis of angiosarcoma [201, 252, 253].

Differential Diagnosis The most challenging distinction is with epithelioid hemangioendothelioma (see previous section). In general angiosarcomas in children are highly aggressive tumors and the role of tumor grading is still debated [254, 255].

Malignant Tumors of Myoepithelial Cells

Definition Myoepithelial carcinomas are rare soft tissue malignancies of unknown histogenesis, with 20% of cases occurring in children [196, 256].

Clinical Features In children myoepithelial carcinomas are more frequent in the extremities; however, their incidence in head and neck varies from 15% to 50%. In the few reported

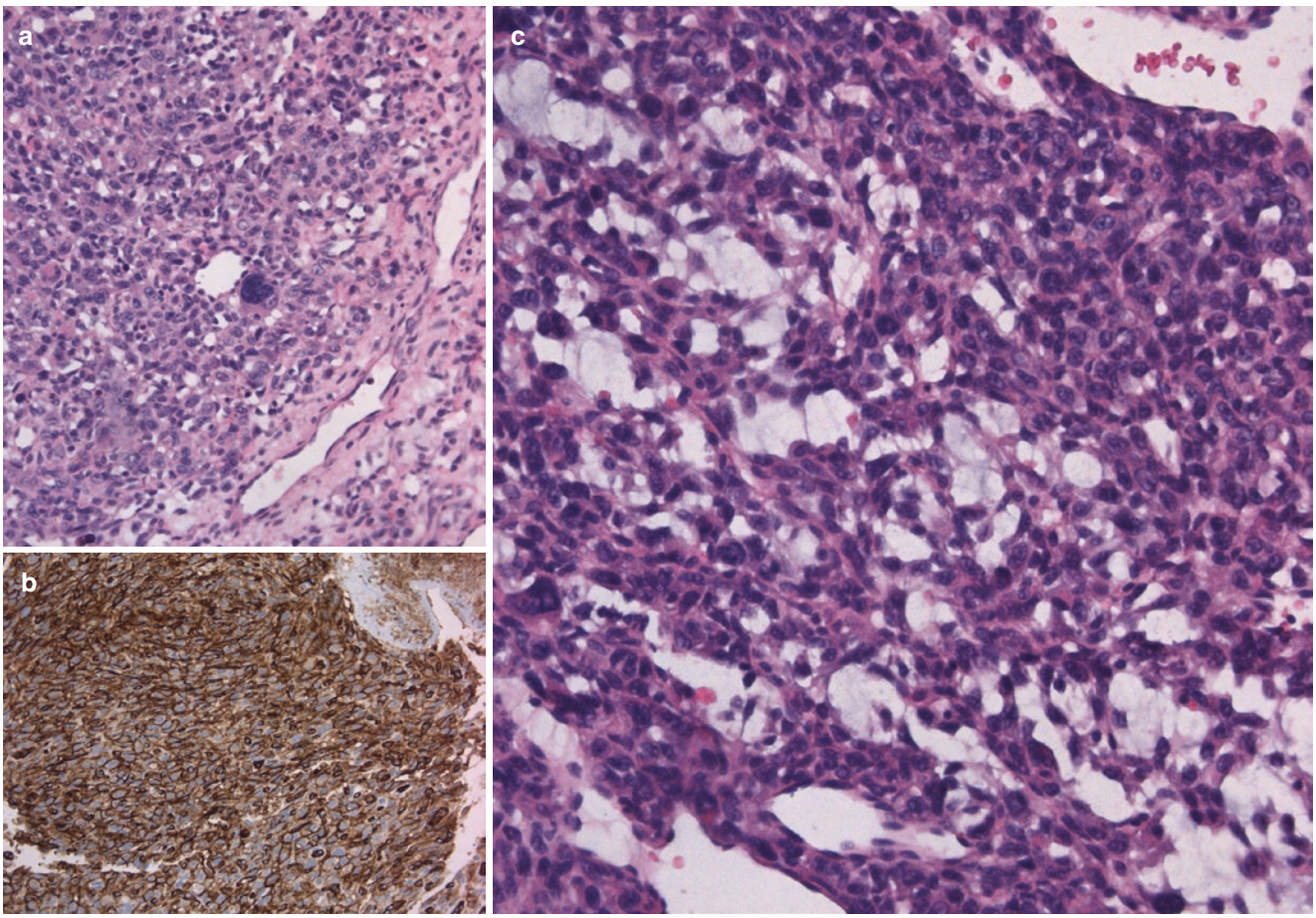

Fig. 31.22 High-grade angiosarcoma in the maxillary sinus in an adolescent. Epithelioid cells are arranged in sheets containing irregular spaces with formation of primitive vessels (**a**, **c**). Multiple layers of plump, atypical cells line some vascular spaces cells abutting into the lumina (**c**). Markedly atypical cells are seen (**a**). CD31 is diffusely positive (**b**)

series, there is an almost identical incidence in males and females. There is a wide age range from newborns to 18-year-old patients [197–200] (Table 31.6). The tumor size varies from 2 cm to more than 5 cm.

Macroscopic Features On gross examination, these tumors are un-encapsulated, with infiltrative margins and show variable consistency, from soft to hard, according to the stromal component. The cut surface is white to yellow-tan with mucoid and myxoid areas. Microcysts, calcifications, and necrosis may be seen.

Microscopic Features Histologically, they are composed of spindle, plasmacytoid, epithelioid or clear cells variably embedded in a myxoid stroma or growing in a solid or reticular pattern (Fig. 31.23).

Immunohistochemistry/Molecular Diagnostic Features Immunostains show reactivity for EMA and S-100 protein, variably combined with cytokeratins, GFAP, p63 and myogenic markers (calponin, α-smooth muscle actin) [200] (Fig. 31.24). *EWSR1* gene rearrangements are detected in more than 50% of myoepithelial carcinomas [200]. *EWSR1-POU5F1* fusion from t(6;22)(p21;q12) is associated with tumors characterized by clear cell morphology. Other partner genes identified include *PBX1, PBX3, ZNF444* from t(1;22)(q23;q12), t(9;22)(q33;q12), t(19;22)(q13;q12) respectively and *FUS-POU5F1* fusion from t(6;16)(p21;p11)[200, 257, 258].

Differential Diagnosis The cellular heterogeneity, the myxoid background, and the typical immunoprofile EMA/S100-positive are helpful in the distinction from clear cell sarcoma and alveolar soft part sarcoma. The main differential diagnosis is with adamantinoma-like Ewing sarcoma. The distinction may be challenging as both tumors show *EWS* rearrangements, epithelioid morphology, and expression of cytokeratins, included high weight keratins and EMA, simulating a myoepithelial carcinoma [259]. Nuclear INI-1 loss, detected in about 40% of myoepithelial tumors of children, along with positive immunostaining for cytokeratins and EMA, may mimic an epithelioid sarcoma. However immunoreactivity for S100 protein is not typical of epithelioid sarcoma [260]. Myoepithelial carcinomas in children are

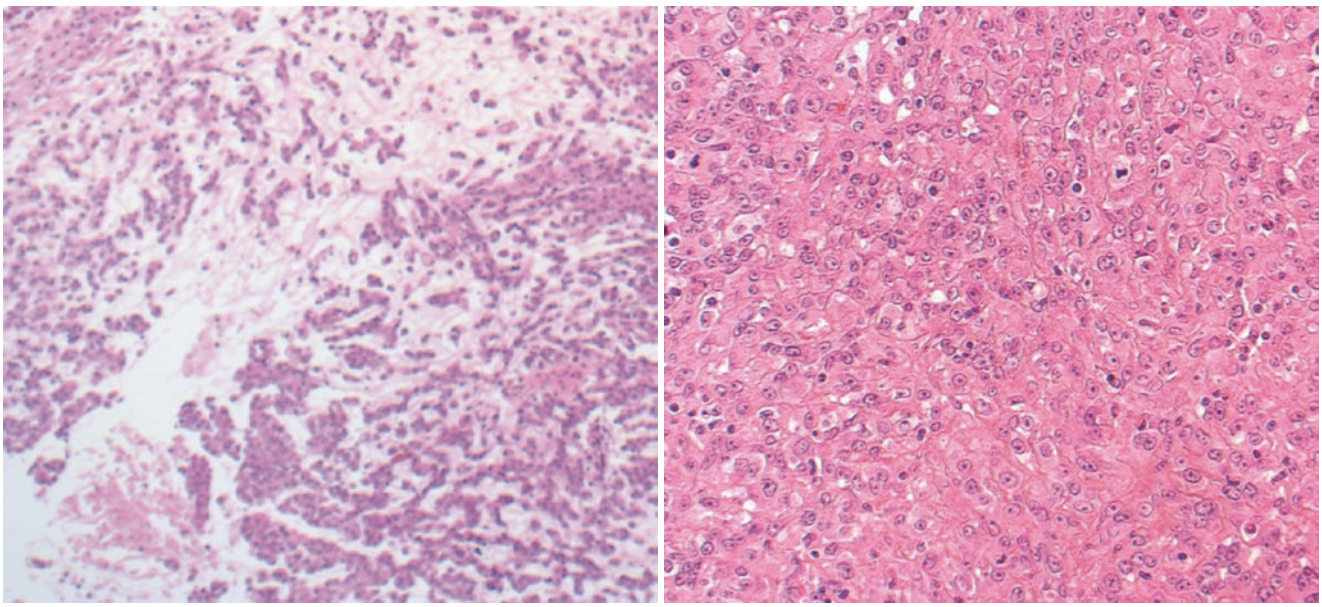

Fig. 31.23 Myoepithelial carcinoma, cords and aggregates of epithelioid cells with abundant eosinophilic cytoplasm are embedded in a myxoid stroma

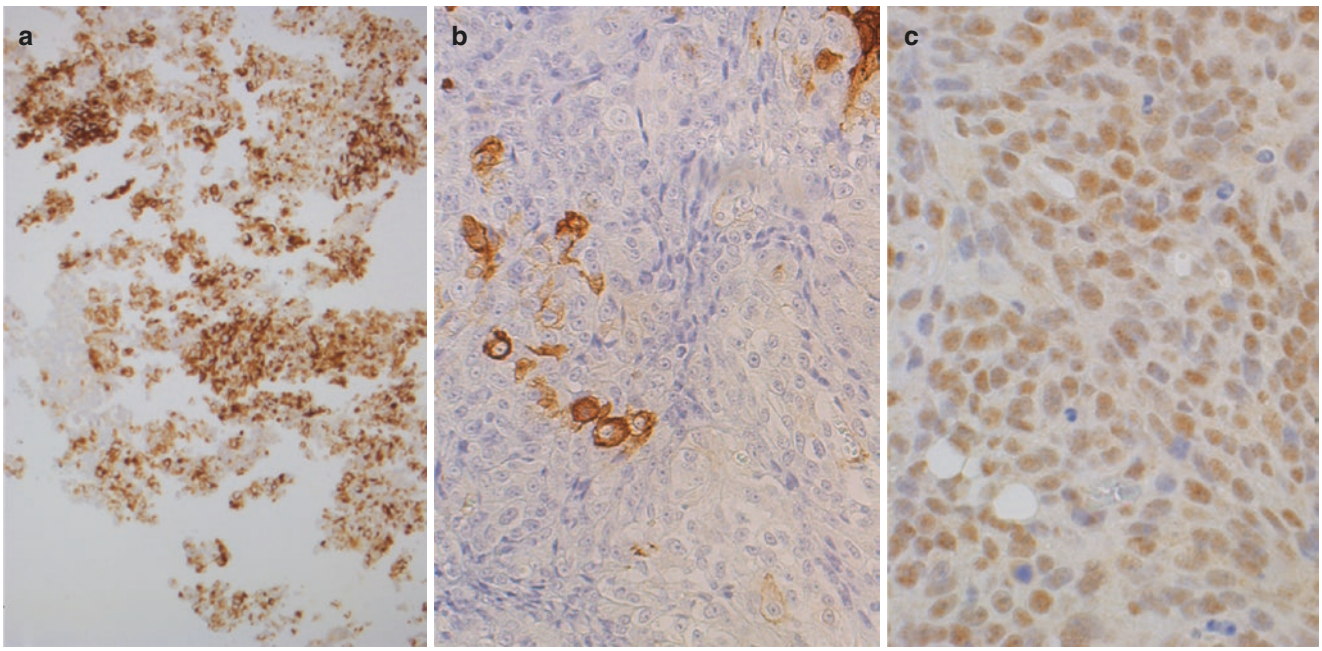

Fig. 31.24 Cytokeratin and S100 protein are typically co-expressed in myoepithelial carcinoma (**a**, **b**). INI-1 is preserved (**c**)

highly aggressive independently from the site, with local recurrence in 39%, distant metastases in 52%, and death in 43% [200].

Undifferentiated Sarcomas

Definition The category of undifferentiated sarcomas has been introduced for the first time in the WHO classification of 2013, as a diagnosis of exclusion [146–151, 261]. Their incidence has progressively decreased with the progress in the immunohistochemical and molecular techniques. (Table 31.5).

Clinical Features Undifferentiated sarcoma occurs in children with two age peaks: one in the first year of life, the other in the second decade of life, with differences in site, prognosis, and histology. In older children, high-grade pleomorphic undifferentiated sarcomas are the more frequent undifferentiated sarcomas, with 40% occurring in head and neck region,

especially the dura, gum, nose, parotid gland [147, 148]. An association with previous radiotherapy has been reported, with 4 out of 7 tumors occurring in children with history of treated retinoblastoma in two different series [148–150]. In infants the undifferentiated sarcomas occur both in the lower extremities and in head and neck region. The clinical presentation is related to the site and the extension of disease. Most of the superficial tumors are asymptomatic.

Classification In WHO 2013 classification, undifferentiated sarcomas have been classified into round, spindle, epithelioid, and pleomorphic cell tumors. Among the small cell/spindle cell undifferentiated sarcomas, recently identified groups include those carrying the *BCOR-CCNB3* transcript from para-centric inversion of a region within Chromosome X, those carrying *CIC-DUX4* transcript from t(4;19)(q35;q13.1) or t(10;19)(q26.3;q13), and those with *BCOR* internal tandem duplication (ITD). *BCOR-CCNB3* sarcomas are typical of young patients and occur in extremities or axial sites; however, two cases have been reported in the skull of a 5-year-old child and in the neck of a 6-year-old girl, respectively [152, 262]. By contrast *CIC-DUX4* sarcomas seem to be typical of young adults. *BCOR-ITD* undifferentiated sarcomas occur in infants and children in the first year of life and 3 out of 5 tumors reported were located in the head and neck region (one each in orbit, larynx and jaw and 2 in the neck) [153].

Microscopic Features/Molecular Diagnostic Features Undifferentiated sarcomas occurring in infants vary from spindle cell tumors in a myxoid background with typical curvilinear vessels (spindle cell undifferentiated) to others with a prominent round cell component and collagen rosette formation (small round cell undifferentiated). The small round and/or short spindle cells are uniform, with nuclei with finely dispersed chromatin, variable amount of cytoplasm and occasional lipoblast-like features. They are variably arranged in sheets or in short fascicles with a frequent hemangiopericytoma-like pattern. The cytologic characteristics are bland. Mitoses are frequent (Fig. 31.25).

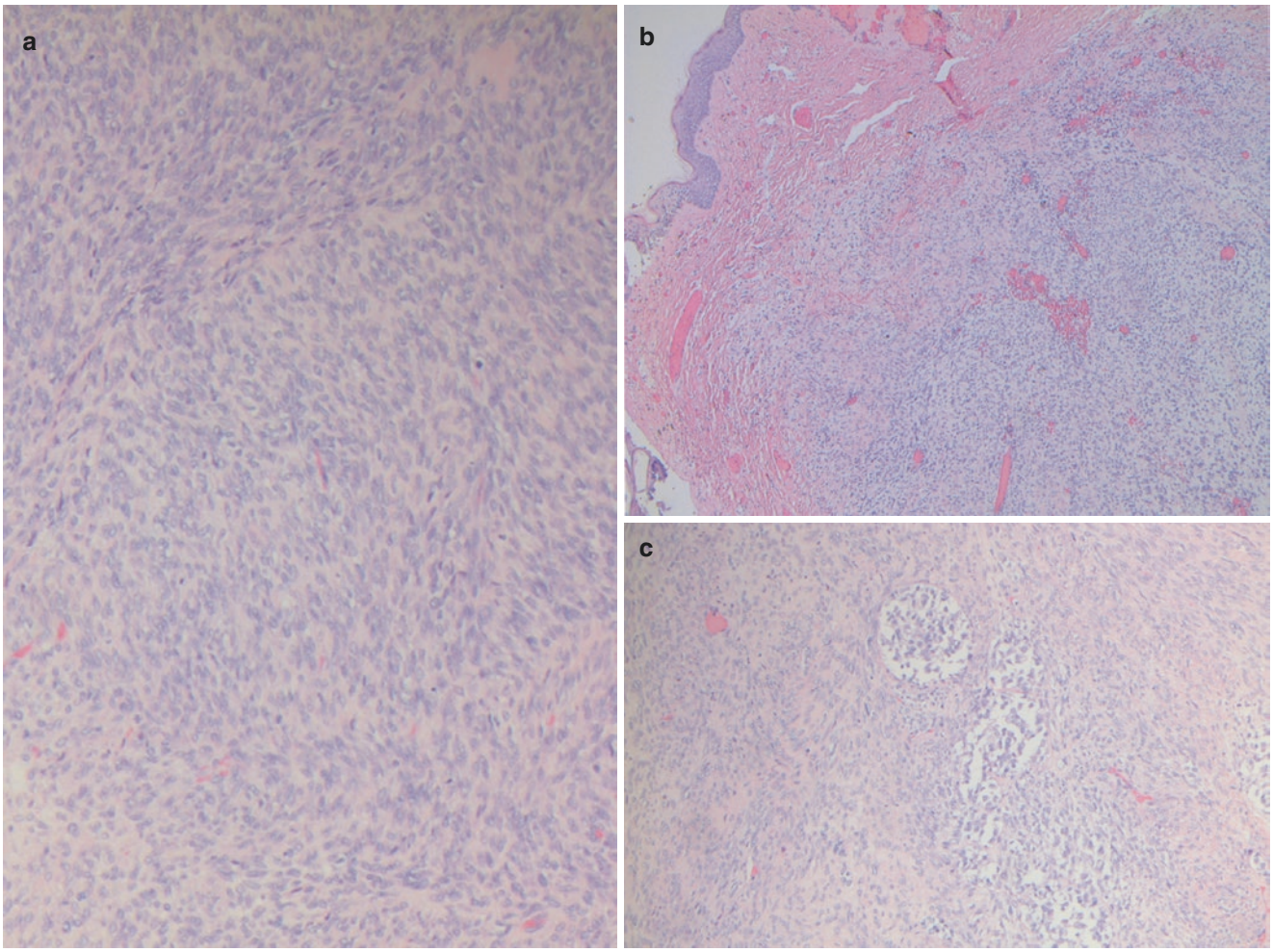

Fig. 31.25 Undifferentiated sarcoma of larynx in a newborn with a spindle morphology mimicking an infantile fibrosarcoma (**a**). The local relapses (**b**, **c**) involved also the skin (**b**) and progressively acquired predominantly small cell morphology. The tumor showed *BCOR ITD*

These tumors have been reported to carry the *BCOR-ITD* recurrent genetic alteration, found also in clear cell sarcoma of kidney [256]. *BCOR-CCNB3* undifferentiated sarcomas show a morphology resembling an Ewing sarcoma with atypical features and spindle cell areas. Curvilinear blood vessels are seen in the context of the myxoid background.

Undifferentiated sarcomas with epithelioid cell morphology are extremely rare and the diagnosis is of exclusion, ruling out all the other sarcomas with epithelioid morphology. High-grade pleomorphic sarcomas are characterized by spindle cells arranged in fascicles with a focal or diffuse storiform pattern or polygonal/epithelioid cells in sheets. Scattered cells with hyperchromatic pleomorphic nuclei and multinucleated cells are seen. Focal necrosis, frequent mitoses, atypical mitoses vascular invasion are present.

Immunohistochemistry Immunostains show lack of specific markers, with variable positivity for CD68, α-smooth muscle actin, and desmin. PAX8 and CyclinD1 are positive in the group of *BCOR*- undifferentiated sarcomas.

Differential Diagnosis The tumors with round cell or spindle cell morphology should be distinguished from Ewing sarcoma or congenital/infantile fibrosarcoma, respectively. Molecular tests to identify the specific transcripts of both these tumors are mandatory.

Pleomorphic undifferentiated sarcomas in children have a better prognosis, probably for their superficial location. However those located intracranially have a poor prognosis. Undifferentiated sarcomas with BCOR ITD may behave very aggressively, especially if showing round cell morphology. BCOR-CCNB3 seems to have a better prognosis than Ewing sarcoma [153, 262].

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