Myogenic tumors in children and adolescents

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Myogenic Tumors in Children and Adolescents

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ABSTRACT

Neoplasms of striated and smooth muscle in children are a diverse group of neoplasms that have some unique aspects in contrast to these tumors in adults. Rhabdomyosarcoma is the most common soft tissue sarcoma of infancy and childhood and is relatively common in adolescents. In contrast, smooth muscle tumors are relatively rare, and the various types of rhabdomyoma and smooth and skeletal muscle hamartomas are very uncommon. In recent years, the understanding of the pathologic and genetic aspects of rhabdomyosarcoma has been enhanced by adjunct techniques, such as immunohistochemistry and cytogenetic or molecular genetic analysis. The current classification of rhabdomyosarcoma emphasizes the histologic-prognostic correlations. This article reviews the clinicopathologic features of striated and smooth muscle tumors with an emphasis on the unique aspects of these neoplasms in children and adolescents and the differential diagnosis.

Key words: leiomyoma, leiomyosarcoma, muscle tumors, rhabdomyoma, rhabdomyosarcoma

INTRODUCTION

In this chapter, we discuss neoplasms that have the appearance of skeletal and smooth muscle. As an operative term, one may consider these as ''muscle tumors,'' but it must be remembered that they often arise from sites devoid of muscle and so appear to be mesenchymal stem cell neoplasms. Of this group, by far the most common tumors to arise in children are rhabdomyosarcomas, which make up the predominant form of pediatric soft tissue sarcoma, the 5th largest category of childhood malignancy. Although smooth muscle neoplasms occur relatively commonly in adults, they are unusual in children. Finally, in contrast to the relative commonality of rhabdomyosarcomas, benign neoplasms of striated muscle origin are quite rare and may be syndromic in nature.

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SKELETAL MUSCLE TUMORS

Rhabdomyosarcoma

Roughly defined, rhabdomyosarcoma is a malignant tumor of primitive mesenchyme with a proclivity for incomplete myogenesis. To be sure, many examples arise within the skeletal musculature of the extremity, but the definition of ''tumor of skeletal muscle'' does not account for the propensity of these lesions to arise in such sites as the urinary tract [1] and bile ducts [2]. The more precise definition allows for the origin of rhabdomyosarcoma in areas devoid of skeletal muscle, and it explains the marked differences in the degree of myogenesis and the stage to which it has progressed. Thus, to understand rhabdomyosarcoma, one must study myogenesis, the process that defines it [3].

The biologic signals that initiate muscle formation begin at the somite stage, when signals from the notochord lead to delineation of the myotome and sclerotome. These mesodermal derivatives subsequently migrate according to axial signals and begin the process of early muscle formation. In the developing embryonic limbs, loose, stellate primitive mesenchymal cells, initially separated by interstitial mucin, begin to aggregate in the sites of the definitive muscles. As these muscles develop, the myoblasts acquire elongate, eosinophilic cytoplasm with a nascent filamentous framework. This framework undergoes progressive structural transformation into thick and thin filaments aligned by Z-bands and anchored to the plasma membrane and surrounding tissue. Adjacent myocytes fuse to form multinucleate giant cells. These continue to elongate as their nuclei migrate peripherally and form fully developed myocytes.

Key molecular events orchestrate the process of myogenesis [4]. At the somite level, expression of such genes as *SHH* by the notochord modulates the axial positioning and formation of the somite and myotome. These in turn induce expression of *PAX3* by the primitive mesenchyme. *PAX3*, 1 of a class of segmentation genes characterized by paired box and homeodomain motifs, in turn initiates myogenesis via induction of *MyoD* and *myogenin*, which encode DNA-binding transcription factors with a helix-loop-helix configuration [5]. A

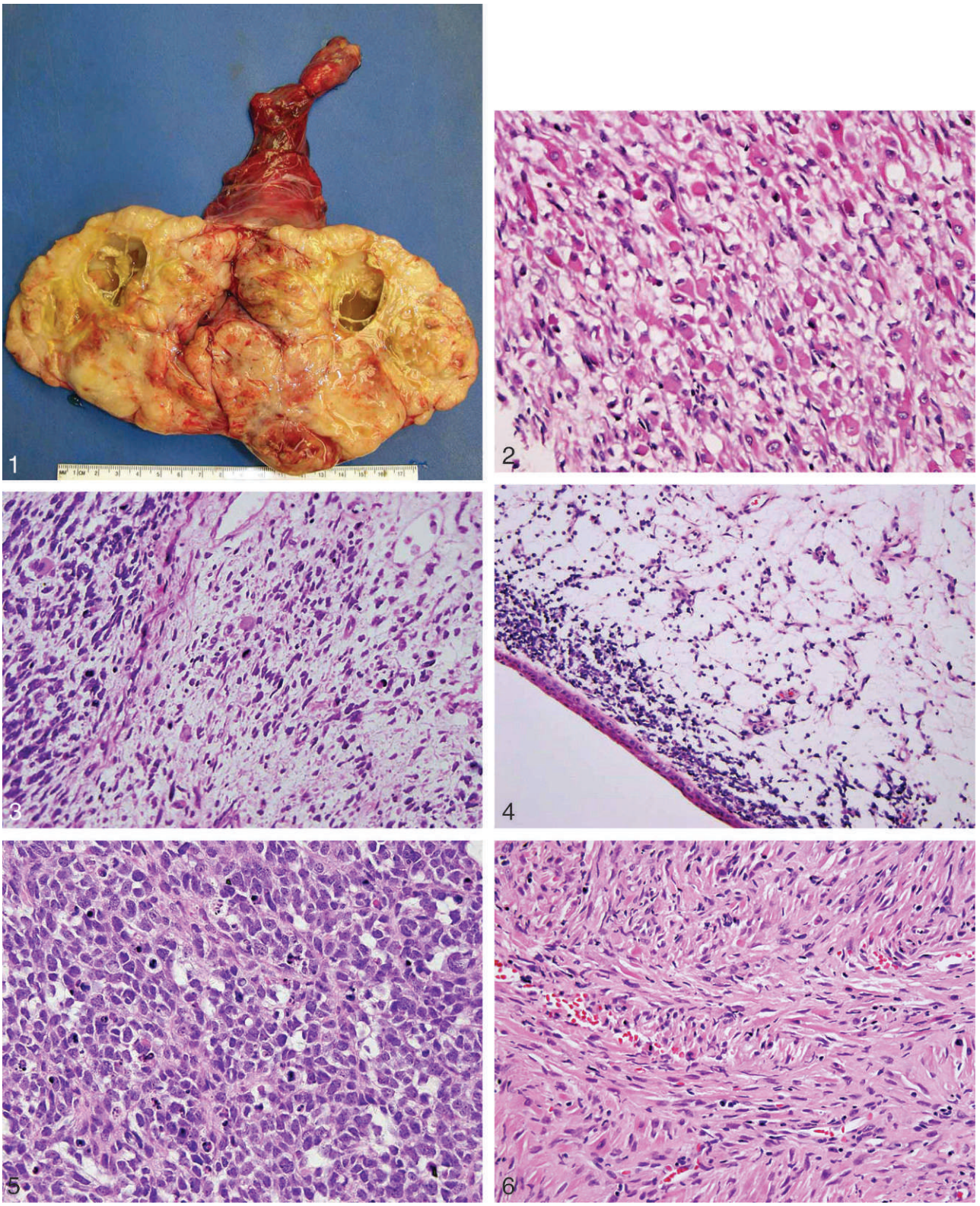

Figure 1. Paratesticular rhabdomyosarcoma. The cut surface of the lesion shows a fleshy tumor with areas of cystic degeneration and necrosis. Photograph courtesy of Dr Carlos Galliani, Cook Children's Hospital, Fort Worth, TX.
Figure 2. Embryonal rhabdomyosarcoma with extensive myogenesis. The lesion contains abundant rhabdomyoblasts with prominent, brightly eosinophilic cytoplasm, eccentric nuclei, and fusiform outlines (hematoxylin and eosin [H&E], ×100).
Figure 3. Embryonal rhabdomyosarcoma. The typical pattern makes up areas of variable cell condensation, imparting a ''loose'' and ''dense'' appearance. The constituent cells have fusiform outlines and hyperchromatic nuclei. Occasional rhabdomyoblasts are present (H&E, ×100).
Figure 4. Embryonal rhabdomyosarcoma (botryoid variant). A loose, watery stromal makes up the bulk of this lesion. Note the cambium layer, a subepithelial zone of condensation (H&E, ×50).

Table 1. The International Classification of Rhabdomyosarcomas [16]

Superior prognosis
Botryoid rhabdomyosarcoma
Spindle cell rhabdomyosarcoma
Intermediate prognosis
Embryonal rhabdomyosarcoma
Poor prognosis
Alveolar rhabdomyosarcoma
Undifferentiated sarcoma[a]

[a]No longer classified with rhabdomyosarcoma by the Children's Oncology Group.

related gene, *PAX7*, appears to initiate muscle regeneration in stem cells known as ''satellite cells'' [6]. Either *MyoD* or *MYF5* can function as alternate limbs of the pathway, but myogenin protein constitutes a critical element; *myogenin* knockout mice die in early fetal life with undeveloped musculature [7,8]. These proteins subsequently nestle into the DNA helix in upstream promoter regions of myogenic proteins, such as desmin, myoglobin, and creatine kinase [5]. Expression of myogenic proteins proceeds via polymerization of prefilamentous subunits produced via mRNA translation. At the ultrastructural level, one observes myosin-ribosome complexes indicative of this process, constituting the earliest morphologically recognizable step in myogenesis [9]. Myogenic factor transcription is enhanced by interaction with myocyte enhancer factors [10]. As differentiation proceeds, transcription factors are downregulated, particularly after innervation [11]. Innervation appears to be critical for terminal differentiation [12]. Except for innervation and terminal differentiation, all of the above processes are variably observed in rhabdomyosarcoma [13].

Clinically, rhabdomyosarcomas cause a wide range of symptoms related to their origin in widely separate anatomic sites [14]. Key areas include the head and neck, genitourinary tract, paraspinal region, biliary tree, and musculature of the trunk and limbs. Orbital tumors make up 1 of the most common head and neck sites and cause such symptoms as diplopia and proptosis. Within this general region, tumors also show a propensity for origin in the sinonasal tracts, external and middle ear, temporal fossa, parapharygeal region, masseter muscle, and cheek. Genitourinary tumors most commonly arise from the urinary bladder, prostate, vagina, and uterine cervix and particularly from the paratesticular soft tissue. Paraspinal tumors typically abut the meninges and make up a high-risk group that often invades the central nervous system. Biliary tumors may arise from the extrahepatic bile ducts, causing biliary obstruction, or they can originate from intrahepatic foci. Rhadomyosarcomas of the trunk may involve the thorax, abdomen, or perianal region, and those of the extremities involve arms, legs, hands, or feet.

Grossly, rhabdomyosarcomas form fleshy, infiltrating masses that vary from soft and myxoid with some embryonal rhabdomyosarcomas to firm and fibrous with sclerosing and spindle cell variants (Fig. 1). After therapy, dense fibrosis and foci of hemorrhage and necrosis commonly occur.

Formation of rhabdomyoblasts makes up the key diagnostic feature of rhabdomyosarcoma at the microscopic level. Traditionally, identification of rhabdomyoblasts has required a search for differentiated cells with cross-striations, an exercise fraught with uncertainty and impatience. Modern practice has become less stringent, and finding isolated cells with brightly eosinophilic cytoplasm and oval nuclei seems sufficient (Fig. 2). However, many primitive lesions lack even this finding; happily, immunohistochemical stains have supplanted the absolute requirement for histologic evidence of myogenesis. One must beware overcalling eosinophilic cells, because cellular necrosis induces a similar appearance. Also, cells with epithelial differentiation may appear eosinophilic; again, immunohistochemistry usually resolves this dilemma.

Rhabdomyoblasts assume a variety of histologic appearances that have immensely helped pathologists with their identification efforts since the earliest descriptions. Elongated cells with cytoplasmic extensions may resemble tadpoles or razor straps; these have been termed ''tadpole cells'' or ''strap cells.'' At times these assume peculiar bent shapes referred to as the ''broken straw'' sign [15]. Particularly in cardiac rhabdomyoma and similar tumors, myofibrils may accumulate in a perinuclear striated pattern. Similar to developing muscle, tumor cells can fuse to produce multinucleated giant cells, and peripheralization of tandem nuclei occurs in more differentiated cells. One must beware of confusing tumoral rhabdomyoblasts with entrapped, atrophic muscle, an ever-present danger in extremity lesions. Generally, the latter cells seem too easily identifiable and starkly contrast with the primitive tumor cells that surround them. This danger extends to overinterpretation of immunostains, which requires careful attention to the cellular contour and nuclear features of positive cells.

Once the diagnosis of rhabdomyosarcoma has been established, the lesion must be subclassified as in Table 1, which shows the International Classification of Rhabdo-

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Figure 5. Embryonal rhabdomyosarcoma, dense variant. This lesion contains tightly packed aggregates of stellate to oval cells, with no loose areas (H&E, ×200).

Figure 6. Embryonal rhabdomyosarcoma, spindle cell variant. Bundles of spindle cells, many with bright cytoplasm, make up this lesion, which otherwise resembles neoplasms, such as fibrosarcoma and leiomyosarcoma (H&E, ×100).

Table 2. Comparative features of rhabdomyosarcoma subtypes [22]

	Embryonal rhabdomyosarcoma	Alveolar rhabdomyosarcoma
Age of patient	Usually less than 5 years; patients with spindle cell variants are often adolescents	Affects all ages; more likely to be alveolar if occurring in patients age 5 years and older
Site of origin	Head and neck: orbit, cheek, mouth, pharynx, ear, temporal fossa, parotid region Abdomen: abdominal soft tissues, bile ducts (intrahepatic and extrahepatic), gall bladder Genitourinary tract: urinary bladder, prostate, vagina, cervix, uterus Scrotum: paratesticular soft tissues	Extremities: upper, particularly hand; lower, including thigh, calf, and foot Trunk: gluteal musculature, perianal region, chest wall, abdominal wall, paraspinal musculature Head: paranasal sinuses and base of skull
Genetic features	Loss of heterozygosity of short arm of chromosome 11 Imprinting abnormalities Heterogeneous expression pattern on gene expression array	*PAX3-FOXO1* fusion *PAX7-FOXO1* fusion Gene amplification Homogeneous expression pattern on gene expression array (for fusion-positive tumors)
Cytogenetic features	Gains of chromosomes 2, 7, 8, 11, 12, 13q21, and 20 Losses of 1p35–36.3, 6, 9q22, 14q21–32, and 17 Diploid or hyperdiploid	t(1;13)(p36;q14) t(2;13)(q35;q14) Diploid or near-tetraploid
Myogenin expression	Patchy expression: rare to 80% of nuclei	Strong diffuse nuclear reactivity in 80–100% of tumor cells

Table 3. Genetic disorders associated with rhabdomyosarcoma

Disorder	Genetic aberration
Beckwith-Weidemann syndrome [23]	Deletions and loss of heterozygosity at chromosome 11p15, particularly affecting *IGF2, CDKA1C, H19,* and/or *LIT1*
Gorlin syndrome (basal cell nevus syndrome) [24]	*PTCH* gene mutation
Costello syndrome [25]	*H-RAS* mutation
Neurofibromatosis 1 [26]	*NF1* mutation
Li-Fraumeni syndrome [27]	*TP53* mutation
Mosaic variegated aneuploidy syndrome [28]	*BUB1B* mutation
Nijmegen breakage syndrome (ataxia-telangectasis syndrome variant 1) [29]	*NBS* mutation
Rubinstein-Taybi syndrome [30]	*CREBBP* mutation
Constitutional mismatch-repair/deficiency syndrome [32]	*PSM2* mutation
Adenomatous polyposis coli [33]	*APC* mutation
Hereditary retinoblastoma [34]	*RBI* mutation
Familial pleuropulmonary blastoma syndrome [31]	*DICER* mutation
Noonan syndrome [35]	*PTPN11* mutation
Werner syndrome [36]	*RECOL2* mutation

myosarcoma, as established by Newton and colleagues [16]. This subcategorization is required for patient management and tumor prognostication [17]. These lesions are subdivided into prognostic groups analogous to those of the Lymphoma Working Group [18]; however, in practice, tumors with the superior risk subclassification diagnoses do not receive treatment different from the intermediate risk embryonal rhabdomyosarcomas. This classification has been challenged by current molecular studies [19]. Recent new subtypes, such as sclerosing rhabdomyosarcoma [20] and anaplastic rhabdomyosarcoma [21], are not yet included, but the classification remains in effect for current Children's Oncology Group protocols.

In addition to the histologic differences listed below, a number of clinical and genetic features appear to distinguish subtypes of rhabdomyosarcoma (Table 2) [22]. A variety of genetic disorders predispose patients to rhabdomyosarcoma (Table 3) [23–36]. Many of these lesions represent tumor susceptibility syndromes, generally caused by loss of autosomal dominant genes and associated with increased risk for other neoplasms. Of note, mutations of *PAX3* do not predispose to rhabdomyosarcoma but instead cause Waardenburg syndrome, a neurologic disorder with hereditary deafness [37]. Rhabdomyosarcoma can also occur in patients with private syndromes [38] and birth defects [39] and as a 2nd malignant neoplasm [40].

Embryonal rhabdomyosarcoma

As the name implies, embryonal rhabdomyosarcomas closely recapitulate the morphologic and biologic features of embryo fetal muscle. Their basic pattern consists of alternating zones of loose, myxoid, paucicellular stroma and dense, richly populated aggregates of primitive cells (Fig. 3). This feature calls to mind the early stages of cellular aggregation that define nascent muscles, and the myxoid stroma has features of embryonic connective tissue. Similarly, the cellular aggregates contain cells with variable cytologic features of myogenesis, as described in the preceding section. Of note, embryonal rhabdomyosarcomas vary from being predominately loose, myxoid, hypocellular lesions (Fig. 4) to densely cellular, small round cell lesions that recall alveolar rhabdomyosarcomas (Fig. 5), as described in the following section. This variability in appearance can be accentuated by small biopsies containing a limited sample of tumor. Myogenin stains typically show a weak or heterogenous pattern of staining (see below for immunohistochemical information).

In many embryonal rhabdomyosarcomas, there is little to no differentiation apparent at the light microscopic level, as might be expected from a primitive neoplasm. The number of cells with rhabdomyoblastic features varies in other tumors, and some possess an amazing content of differentiated cells that closely resemble rhabdomyoma [41]. Differentiation can be accentuated after chemotherapy, both in patients [42] and in laboratory models [43].

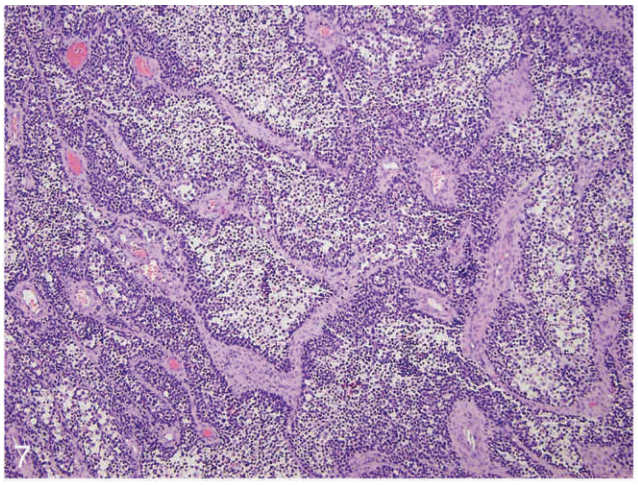
Botryoid and spindle cell rhabdomyosarcoma are currently considered to be variants of embryonal rhabdomyosarcoma. Botryoid rhabdomyosarcomas constitute a special class of rhabdomyosarcoma because of their unique appearance and superior outcome [44]. They arise from hollow viscera, such as the vagina, urinary bladder, and biliary tract, and are thus partially covered by epithelium that may be ulcerated. Botryoid rhabdomyosarcomas form grape-like, polypoid excrescences that may create an unusual radiographic appearance. The histologic requirement for diagnosis is the cambium layer, a subepithelial density of cells that resembles those in the outer rings of a growing plant (Fig. 4). Because of their defining characteristics, botryoid rhabdomyosarcomas only arise from sites that have been defined as ''low stage'' by the Children's Oncology Group [45]. This factor may account for their good outcome.

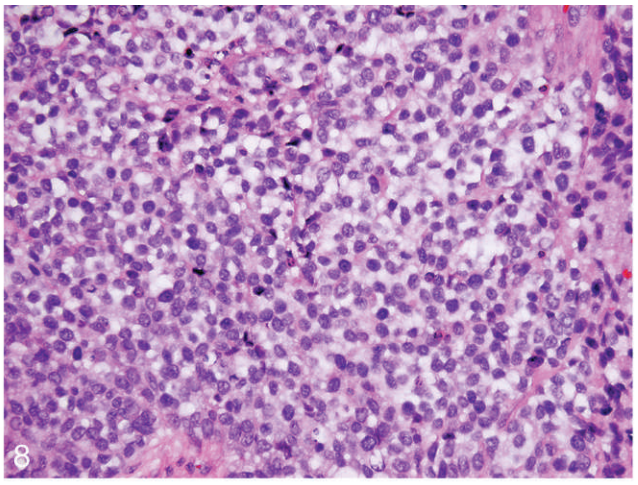
Like botryoid lesions, spindle cell rhabdomyosarcomas tend to arise in specific sites; the overwhelming majority occurs in the paratesticular region, followed by the orbital soft tissues. As the name implies, they contain fascicles of spindle cells similar to fibrosarcomas and leiomyosarcomas (Fig. 6) [46,47]. Grossly, these impart a firm, fibrous, gray-tan consistency to the tumors, rather than the usual soft fleshiness of the other subtypes. At times they contain a moderate to prominent amount of intercellular collagen that accentuates these features. Minor foci of typical embryonal rhabdomyosarcoma may be present. Spindle cell rhabdomyosarcoma may have a whorled, storiform pattern similar to pleomorphic sarcoma, and they often contain scattered enlarged cells that impart ''nuclear unrest.'' These cells vary in size and display nuclear atypia and enlargement but lack the 3-fold nuclear enlargement and atypical mitoses of classic anaplasia as defined for Wilms tumor [48]. Paratesticular lesions may metastasize to regional lymph nodes.

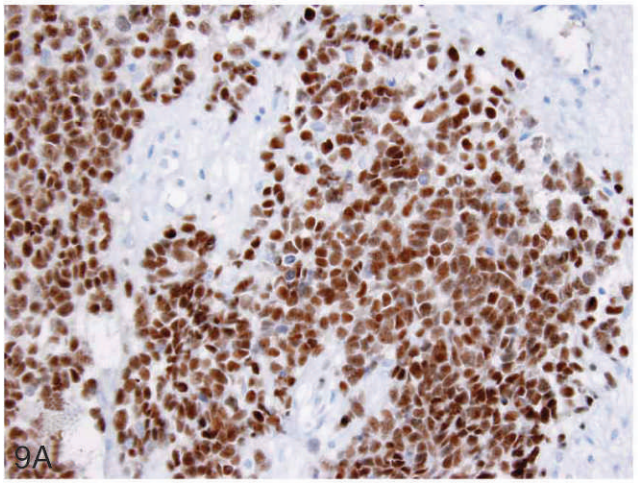
Biologically, embryonal rhabdomyosarcomas share many features with developing skeletal muscle. Like fetal myoblasts, they show partial demethylation of the *MyoD1* gene [49], and like satellite cells, they express *PAX7* [6]. They show no single characteristic aberration, but comparative genomic hydridization reveals recurring chromosome losses and gains [50–52]. However, alveolar rhabdomyosarcoma may show similar losses and gains [53], so the value of comparative genomic hydridization in classification is debatable. On the other hand, embryonal rhabdomyosarcomas contain a distinctive loss of heterozygosity for chromosome 11p15.5 [54,55]. This region is highly imprinted, indicating that epigenetic imbalance plays a role in tumorigenesis [56]. *MyoD1* is located in the 11p15 region. Loss of heterozygosity at 11p15 commonly occurs within several embryonal neoplasms [57], suggesting a link between disparate lesions, such as hepatoblastoma, rhabdomyosarcoma, and Wilms tumor, all of which occur with increased frequency in Beckwith-Wiedemann syndrome [58]. Beckwith-Wiedemann syndrome, an overgrowth genetic lesion characterized by organomegaly, macroglossia, omphalocele, adrenal cytomegaly, and other features, is caused by mutations, deletions, and epigenetic lesions of the same region [59–61]. Particularly affected in Beckwith-Wiedemann syndrome are the *IGF1* and *CDKN1C* genes, so it should come as no surprise that alterations of *IGF1* function commonly occur in embryonal rhabdomyosarcoma [62]. The protein product of *CDKN1C*, p57, does not appear to be directly involved in tumorigenesis [62], but its function appears critical for rhabdomyosarcoma differentiation [63].

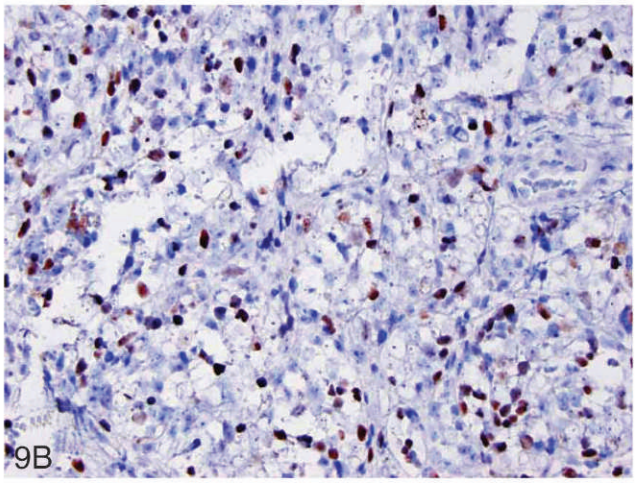
Alveolar rhabdomyosarcoma

Alveolar rhabdomyosarcoma is a distinct subtype of rhabdomyosarcoma that is characterized by unique morphologic and genetic features associated with aggressive behavior. Initial descriptions focused on its classical histologic features, which simulate fetal lung [64]. It is a highly cellular lesion resembling Ewing sarcoma or lymphoma, but the classical pattern was distinguished by nests of cells separated by fibrous septa that tended to peripheral discohesion (Fig. 7). This feature, likely caused by artefactual tissue shrinkage, makes the cells appear to float in alveolar spaces. A separate layer of tumor cells adheres to the fibrous septa in picket fence fashion. Multinucleated tumor giant cells with eosinophilic cytoplasm may be seen in some cases, but most lack obvious myogenesis prior to therapy. Later studies of









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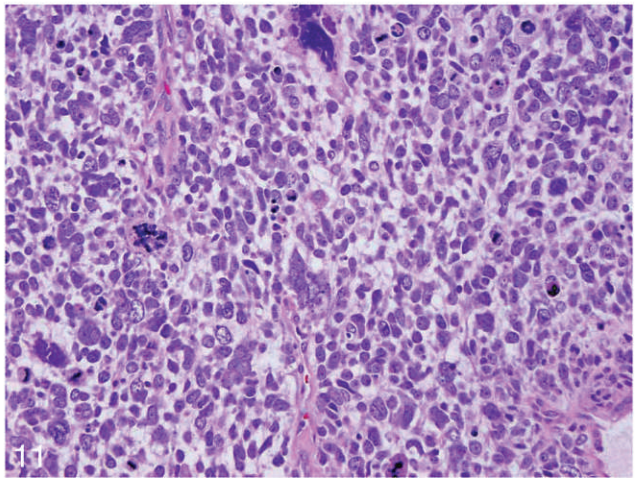


Figure 7. Alveolar rhabdomyosarcoma, classical pattern. This tumor contains nests of small round cells, subtended by fibrous septa. Note the peripheral condensation of the cell nests and relative looseness of their central portions (hematoxylin and eosin [H&E], ×50).

Figure 8. Alveolar rhabdomyosarcoma, solid pattern. Like this example, solid alveolar tumors contain patternless sheets of small round blue cells with no intervening fibrous septa. They thus resemble lymphoma or Ewing sarcoma and often contain little apparent cytoplasm (H&E, ×50).

Figure 9. Myogenin immunostains. **A.** Alveolar rhabdomyosarcoma, showing strong, diffuse nuclear positivity from virtually every tumor cell (immunohistochemistry, ×100). **B.** In contrast, this embryonal rhabdomyosarcoma shows staining in only scattered tumor cell nuclei (immunohistochemistry, ×100).

Figure 10. Alveolar rhabdomyosarcoma karyotype, showing balanced translocation between chromosomes 1 and 13. The normal chromosomes are on the left, and rearranged chromosomes are on the right side of this composite photograph. Photograph courtesy of Dr Ji-Yun Lee, University of Oklahoma Health Sciences Center, Oklahoma City, OK.

Figure 11. Anaplastic rhabdomyosarcoma. This embryonal rhabdomyosarcoma has a dense pattern and contains prominent cells with enlarged, hyperchromatic nuclei. Note the multipolar mitosis (H&E, ×100).

alveolar rhabdomyosarcoma focused on a ''solid variant,'' which has similar even, round, lymphoma-like cells but lacks fibrous septa (Fig. 8) [65]. Without ancillary immunohistochemistry and/or genetic studies, this type of rhabdomyosarcoma is often impossible to distinguish from other round cell neoplasms. One clue to classification of alveolar rhabdomyosarcoma is its strong, diffuse nuclear myogenin expression, with up to 80–100% of tumor cells positive, unlike the patchy, heterogeneous pattern often seen with embryonal rhabdomyosarcoma, with few to 80% of tumor cells positive (Fig. 9) [66–68]. Of note, aberrant staining for neural, lymphoid, and epithelial markers has been described [69]. Strong myogenin expression may be an independent predictor of outcome in rhabdomyosarcoma [70].

Recent studies have concentrated on the genetic features of alveolar rhabdomyosarcoma, which is characterized by fusions of the *FOXO1* gene on chromosome 13 with either the *PAX3* gene on chromosome 2 or the *PAX7* gene on chromosome 1. These result from reciprocal translocations t(2;13)(q35;q13.1) or t(1;13)(p36;q13.1) (Fig. 10) [54]. Variant translocations involving the breakpoint regions are described [71]. *PAX3-FOXO1* fusions account for approximately one half of alveolar rhabdomyosarcomas, *PAX7-FOXO1* fusions account for approximately one quarter, and no *PAX* fusions have been identified in the remainder of cases. *PAX/FOXO1* fusions create a distinctive biologic signature on expression arrays [19], and fusion-negative alveolar rhabdomyosarcomas appear to be clinically, prognostically, and biologically similar to embryonal rhabdomyosarcoma [72]. As a result, some are calling for *PAX* fusion confirmation before regarding any rhabdomyosarcoma as ''alveolar,'' regardless of histology [73]. Of note, *PAX7-FOXO1* fusions have also been linked to better outcome [74], but this phenomenon has not been addressed in recent biologic studies. *PAX/FOXO1* fusion-negative tumors may at times be due to ''low expressors,'' if only RNA analysis is used for testing [75], or they rarely occur because of an alternate *PAX* fusion partner, such as *AFX* [75] or *NCOA1* [76,77].

Anaplastic rhabdomyosarcoma

Anaplastic rhabdomyosarcomas are forms of embryonal and alveolar rhabdomyosarcoma containing large, irregular, hyperchromatic nuclei and atypical, multipolar mitoses (Fig. 11) [78]. Embryonal rhabdomyosarcomas with anaplasia show chemoresistance that leads to relatively poor clinical outcomes, compared with nonanaplastic lesions [21]. Whether the anaplasia is focal or diffuse does not seem to have further prognostic significance for embryonal rhabdomyosarcoma. The effect of anaplasia is more pronounced in univariate statistical analysis than in multivariate calculations, so it is not currently used for treatment stratification. Alveolar rhabdomyosarcomas show no differences in biologic potential based on the presence or absence of anaplasia [21].

Genetic studies show that anaplastic embryonal rhabdomyosarcomas, like some alveolar tumors, exhibit foci of genomic amplification, particularly involving chromosome 15q25–26 [53]. Of note, adult pleomorphic rhabdomyosarcoma also shows genomic amplification but involving different regions [79].

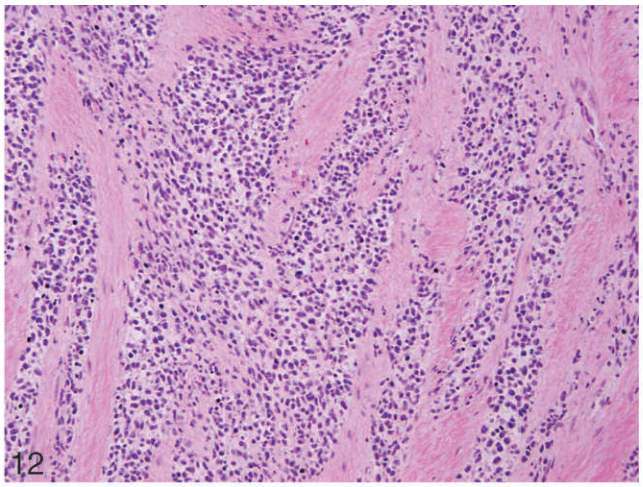
Sclerosing rhabdomyosarcoma

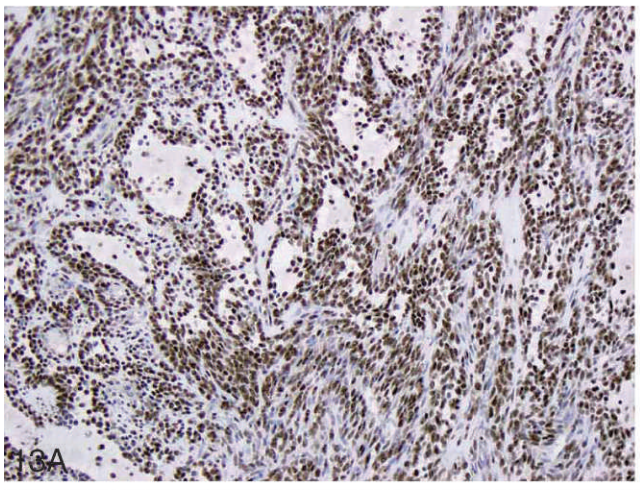
In 2000, a new variant of rhabdomyosarcoma joined the list of subtypes seen in this tumor [80]. Called ''sclerosing rhabdomyosarcoma,'' this neoplasm contains an abundant, densely collagenous stroma that separates tumor cells into nests and strongly resembles that of scirrhous carcinoma (Fig. 12). These lesions resemble alveolar rhabdomyosarcoma but without the ''floating clusters,'' picket fence arrangement, or well-defined septa. They occur in children as well as adults [20] and were originally described as ''carcinoma-like'' in a review by Bale in 1975 [81]. Characteristic features include absence of *PAX* fusions [82], relatively weak myogenin expression, and comparatively strong MyoD staining (Fig. 13) [83]. These lesions likely account for some examples of fusion-negative alveolar rhabdomyosarcoma. Similar to anaplastic rhabdomyosarcoma, gene amplification may be present [84], and chromosomal analyses reveal gains and losses similar to embryonal rhabdomyosarcoma [82].

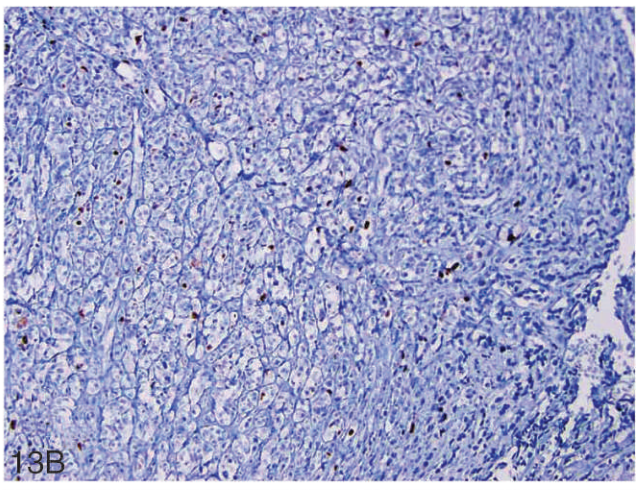
Unusual variants of rhabdomyosarcoma

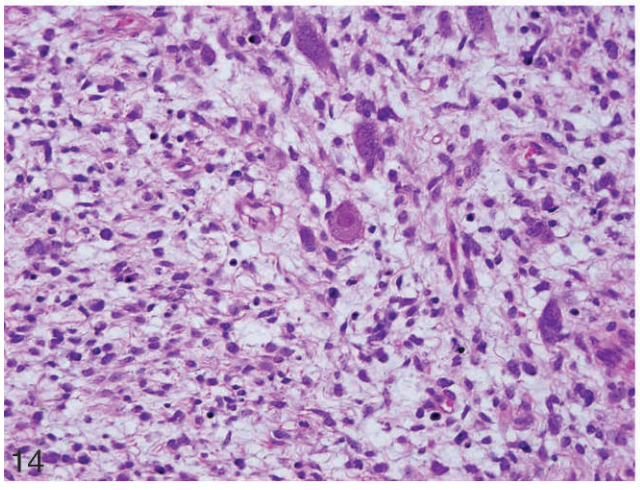
Unusual mixed histologies may be seen in embryonal rhabdomyosarcomas, possibly because of the plastic nature of the mesenchymal stem cells from which they arise. Lipidized [85] or clear cell [86] variants that contain lipid droplets by electron microscopy have been described. One peculiar neoplasm, the so-called ''infantile rhabdomyofibrosarcoma,'' contains evidence of both myofibroblastic and rhabdomyoblastic differentiation [87,88]. Rare botryoid embryonal rhabdomyosarcomas, particularly those arising in the female genital tract, contain foci of hyaline cartilage [89].

Malignant ectomesenchymomas (also called ''biphenotypic sarcomas'') are tumors with rhabdomyoblastic and neural differentiation [90]. The nature of these lesions is uncertain. Some appear to represent forms of primitive neuroectodermal tumor, as judged by cytogenetic analysis [91,92]. However, other cytogenetic studies show features of embryonal rhabdomyosarcoma [93], and we have seen 1 case with a *FOXO1* rearrangement typical of alveolar rhabdomyosarcoma. Of interest is that extensive ganglioneuromatous differentiation may be seen before or after therapy [94]. Regardless of nosologic considerations, ectomesenchymomas are currently treated as rhabdomyosarcomas by the Children's Oncology Group [90]. Diagnosis should be based on clear-cut morphologic evidence of ganglionic or neuroblastic differentiation (Fig. 14), because aberrant neural marker positivity may be seen in alveolar rhabdomyosarcoma [69].









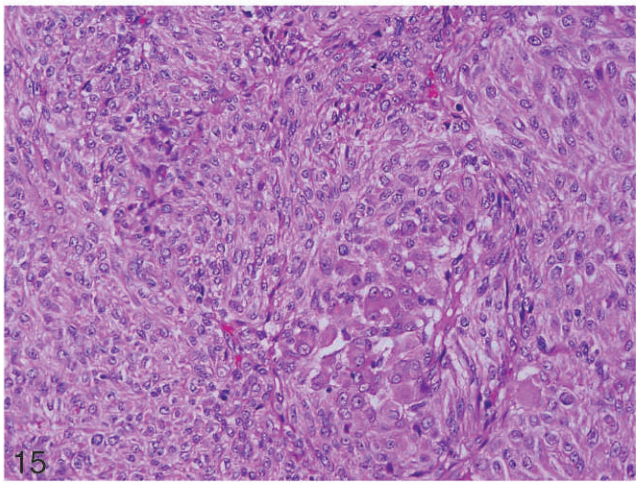
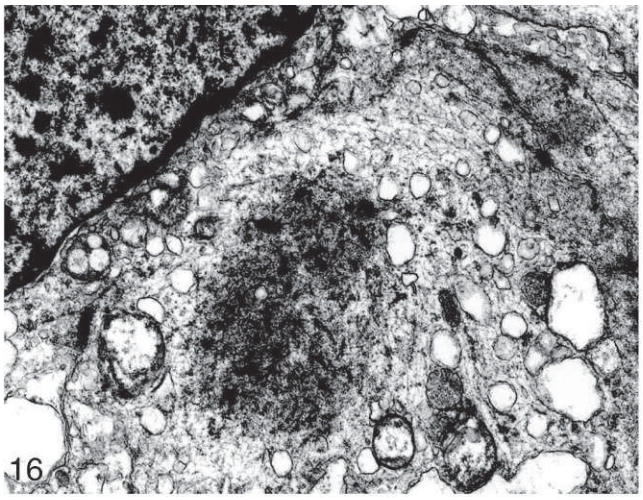
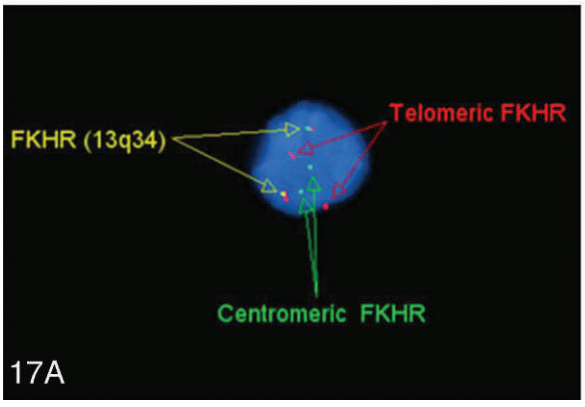


Figure 12. Sclerosing rhabdomyosarcoma. This lesion contains round to spindle cells separated by abundant, dense, collagenous stroma (hematoxylin and eosin [H&E], ×50).
Figure 13. Sclerosing rhabdomyosarcoma. Immunostains reveal strong, diffuse MyoD positivity (**A**) and weak, focal myogenin positivity (**B**) (immunohistochemistry, ×50).
Figure 14. Ectomesenchymoma. This lesion contains both neural and myogenous elements. It primarily contains embryonal rhabdomyosarcoma with primitive spindle cells, but a mature neuron punctuates the central portion of the field (H&E, ×200).
Figure 15. Pleomorphic rhabdomyosarcoma. This adult sarcoma was an extremity lesion from a middle-aged man. It contains variably sized cells with moderately pleomorphic nuclei. A focal nest of cells shows myogenesis (H&E, ×200).





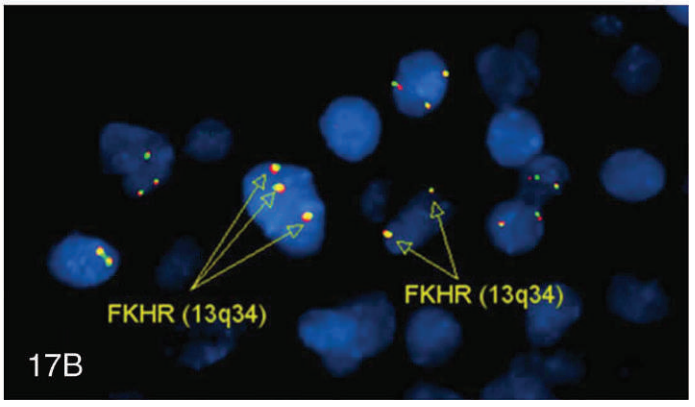


Figure 16. Electron photomicrograph of rhabdomyosarcoma, showing central cytoplasmic cluster of filaments and electron dense Z band material (×5000).
Figure 17. *FOXO1 (FKHR)* fluorescence in situ hybridization, rhabdomyosarcoma. **A.** An alveolar rhabdomyosarcoma shows rearrangement of the *FKHR* gene, indicating the presence of a t(2;13) or t(1;13). There is 1 intact *FKHR* gene, indicated by the yellow probe (mixed red and green) and 3 rearranged genes, indicated by separate telomeric (red) and centromeric (green) portion. This suggests tetraploidy, a frequent event in alveolar rhabdomyosarcoma. **B.** An embryonal rhabdomyosarcoma contains 3 intact *FKHR* genes, as evidenced by 3 yellow signals. Gain of chromosome 13 is not uncommon in embryonal rhabdomyosarcoma, but there is no evidence here of translocation. Photographs courtesy of Dr Ji-Yun Lee, University of Oklahoma Health Sciences Center, Oklahoma City, OK (×1000).

Pleomorphic rhabdomyosarcoma primarily arises in adults and is not included in the current classification system for childhood sarcomas [16]. It contains whorls and bundles of irregular spindle cells with large, atypical nuclei showing foci of myogenic differentiation (Fig. 15) [95]. MyoD1 and/or myogenin may be used to highlight myogenesis in these tumors [96,97]. Spindle cell rhabdomyosarcoma, akin to the lesions described above as variants of embryonal rhabdomyosarcoma, also occurs in adults and behaves aggressively, in contrast to its childhood counterpart [98]. When these lesions contain anaplastic cells, there is overlap with anaplastic rhabdomyosarcomas of children [21].

Ancillary diagnosis of rhabdomyosarcoma

Because of the primitive, undifferentiated nature of rhabdomyosarcomas, ancillary techniques have been extensively used for diagnostic confirmation. Periodic acid–Schiff stains show cytoplasmic glycogen, and phosphotungstic acid-hematoxylin accentuates cross-striations, but the former technique is utterly nonspecific in embryonal neoplasms, and the latter is relatively insensitive. The earliest technique with reasonable specificity and sensitivity for rhabdomyosarcoma diagnosis was electron microscopy, which was often employed in the latter decades of the 20th century. Ultrastructural analysis of rhabdomyosarcomas demonstrates organelles indicative of myogenesis in differentiating cells. These include bundles of ''thick'' 15-myosin filaments (measuring 15 nm in diameter) and ''thin'' actin filaments (measuring 5 nm in diameter). Dense linear material representing abortive Z-discs punctuates the filament bundles (Fig. 16). These features are typically present in cells having eosinophilic cytoplasm by light microscopy, but visible striations may be absent on histopathologic examination. Myosin-ribosome complexes represent polymers of myosin moieties forming in active translation from cytoplasmic mRNA. These organelles offer a more sensitive feature for ultrastruc-

tural diagnosis of myogenesis and are said to be the earliest recognizable feature of rhabdomyosarcoma [9].

In modern practice, immunohistochemistry has largely supplanted electron microscopy for ancillary diagnosis of electron microscopy, although the latter technique still has its proponents [99]. Expression of myogenic transcription factors, such as myogenin and MyoD, offers a means of detecting the earliest stage of myogenesis, which is not recognizable by ultrastructural means (Fig. 9A). These proteins are expressed strongly by even the most primitive of alveolar rhabdomyosarcomas, indicative of a block in terminal differentiation caused by *PAX* fusion gene-induced molecular dysfunction [100]. Embryonal rhabdomyosarcomas show less expression of myogenin (Fig. 9B) and may even lack myogenin reactivity [66], so it is wise to add MyoD and/or desmin to the diagnostic panel of immunostains. However, MyoD shows frequent nonspecific cytoplasmic staining in a variety of tumors, so that only nuclear staining should be used for diagnosis [101]. Of note, some reports suggest that myogenin and MyoD are frequently negative in pleomorphic rhabdomyosarcoma [102]. Rhabdomyosarcomas typically express desmin, a cytoplasmic filament found primarily in the Z-bands of mature muscle. However, it is comparatively nonspecific, staining a variety of spindle cell and round cell neoplasms, so that myogenin and/or MyoD have become the antigens of choice for staining [103]. EGFR2 and AP2-beta are promising immunohistochemical markers in the distinction between translocation-associated alveolar rhabdomyosarcoma, which demonstrates strong, diffuse nuclear staining for AP2-beta and lacks EGFR2 reactivity, versus embryonal rhabdomyosarcoma, which displays strong, diffuse membranous EGFR2 reactivity and is nonreactive for AP2-beta [104].

In addition to immunohistochemistry, genetic testing for *PAX/FOXO1* fusions is becoming standard practice for diagnosis of alveolar rhabdomyosarcoma and has been advocated as essential by some [73]. Detection of a *FOXO1* rearrangement may be detected in paraffin sections by fluorescence in situ hybridization (Fig. 17) [105]. Alternatively, reverse transcriptase polymerase chain reaction can be performed on paraffin sections and offers distinction between *PAX7* and *PAX3* fusions [106]. This information may have prognostic significance in patients with metastatic disease [74]. Fluorescence in situ hybridization testing, however, may suggest the presence of *PAX7* fusions, which are frequently amplified (Fig. 18) [107]. Of note, amplification of other gene regions, particularly *MYCN*, occurs frequently in alveolar rhabdomyosarcoma. Amplification of 12q13–14 occurs in about 10% of cases and appears to signal more aggressive behavior [108].

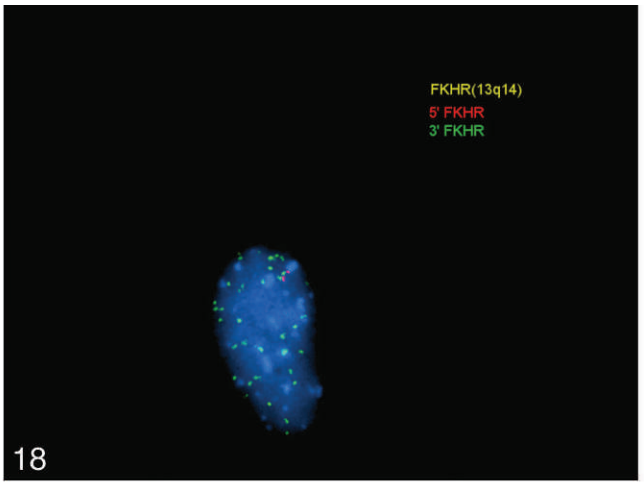
Differential diagnosis of rhabdomyosarcoma

The list of diagnoses that must be considered prior to diagnosing rhabdomyosarcomas contains a large number of diverse entities, as seen in Table 4 [109]. However, one can conveniently subdivide them into 3 major categories: small round cell malignancies, neoplasms with muscle differentiation, and spindle cell tumors. Some neoplasms freely overlap between these divisions. Use of the ancillary techniques as listed above should serve to clarify possible confusion. However, it must be noted that no single immunostain has absolute specificity. For example, myogenin staining may be seen in melanotic neuroectodermal tumor [110] and in occasional examples of myofibroma [67]. Desmin staining occurs in a number of lesions, including desmoplastic small round cell tumor [111], leiomyosarcoma, myofibroblastic tumors of various types, giant cell tumor of tendon sheath [112], occasional peripheral neuroectodermal tumors [113], and angiomatoid fibrous histiocytoma [114]. All lesions with myogenic potential will show similar staining. Conversely, rhabdomyosarcomas may show unexpected staining with such markers as ALK1 [115], cytokeratin [69,116], and S100 [116]. Therefore, it is important to be familiar with the clinical and histologic features of these neoplasms in order to confidently exclude them. In particular, a high index of suspicion is critical for neoplasms that lack myogenin or MyoD positivity; conversely, in lesions showing positivity but having atypical features, it is wise to consider alternate diagnoses. Rhabdoid tumors of various types may resemble rhabdomyosarcoma [117,118] but lack INI1 staining, which is preserved in true myogenic tumors [119].

Of particular note are neoplasms with myogenic differentiation (Fig. 19). This is a common feature in embryonal tumors, such as Wilms tumor (Fig. 19A) [120] and pleuropulmonary blastoma (Fig. 19B) [121], in which the rhabdomyosarcomatous element may overgrow the blastemal component. Among sarcomas, myogenesis defines the malignant Triton tumor, which makes up the malignant peripheral nerve sheath tumor with rhabdomyosarcoma [122], and it also occurs in dedifferentiated chondrosarcoma and liposarcoma (Fig. 19C) [123,124]. Rhabdomyosarcomatous elements also occur in some forms of Sertoli-Leydig cell tumors (Fig. 19D) [125], and in our experience, the myogenic element may persist after therapy. Finally, adult tumors, such as carcinosarcoma, may contain muscle [126], and myogenesis has even been reported in melanocytic nevi and melanomas [127]. Benign myogenic lesions are discussed in subsequent sections.

Treatment and outcome

Thanks to modern multidisciplinary approaches to therapy, the outcome of intermediate-risk rhabdomyosarcoma and embryonal rhabdomyosarcoma has steadily improved over several decades [45,128]. The mainstays of therapy have been preoperative chemotherapy based on a combination of vincristine, adriamycyin, and cyclophosphamide, followed by surgery and consolidation therapy. Radiation therapy has been a major factor in



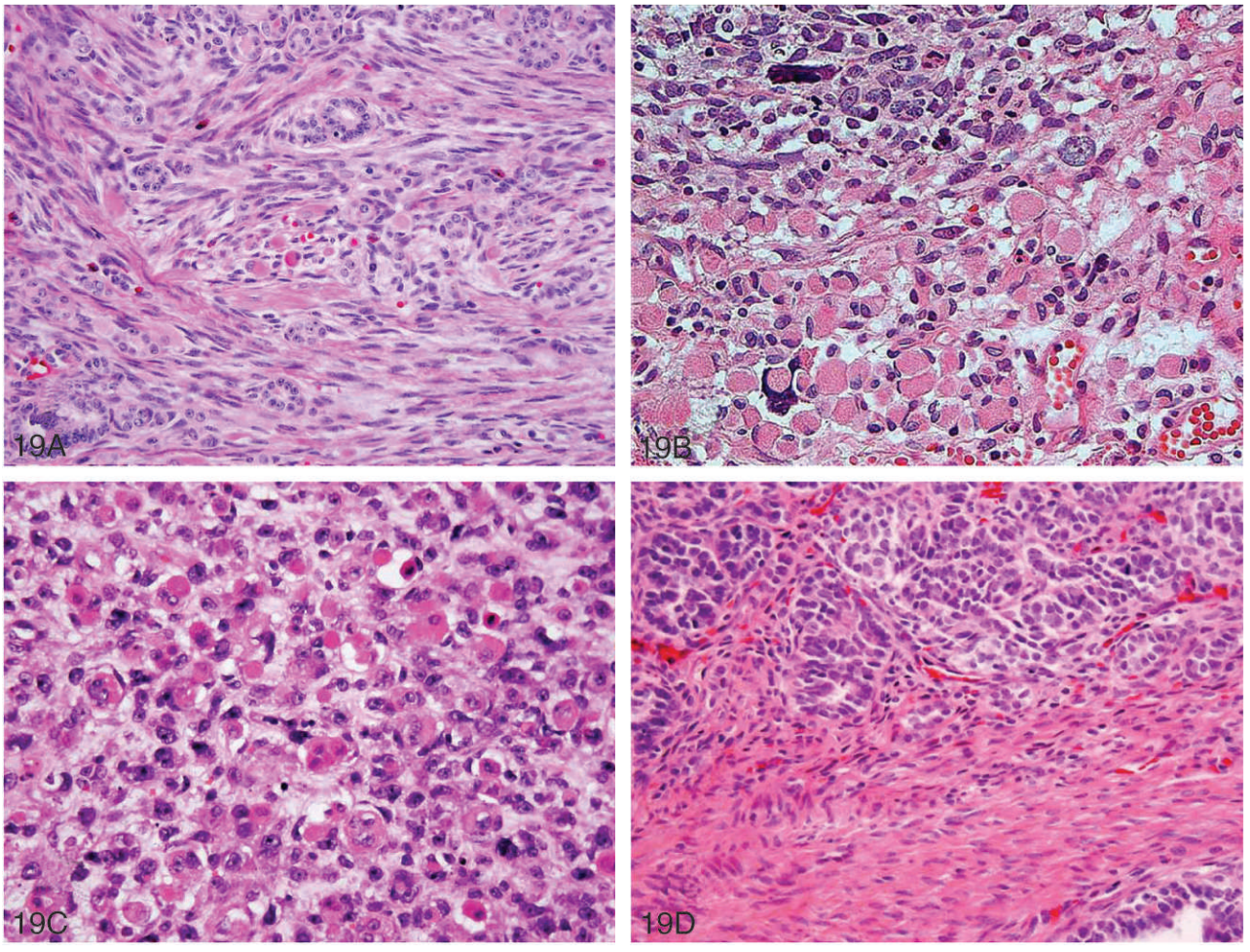


Figure 18. *FOXO1 (FKHR)* fusion amplication, alveolar rhabdomyosarcoma. This tumor contained a t(1;13), which frequently shows fusion gene amplication. In this fluorescence in situ hybridization photomicrograph, a nucleus contains numerous green signals, indicating multiple copies of a rearranged *FKHR* gene. Two intact genes (adjacent red and green signals) are also present. Photograph courtesy of Dr Ji-Yun Lee, University of Oklahoma Health Sciences Center, Oklahoma City, OK (×1000).

Figure 19. Myogenic differentiation may be seen in diverse neoplasms. Pictured herein are Wilms tumor (**A**) (hematoxylin and eosin [H&E], ×100), pleuropulmonary blastoma (**B**) (H&E, ×200), dedifferentiated liposarcoma (**C**) (H&E, ×100), and Sertoli-Leydig cell tumor (**D**) (H&E, ×100). All show foci of residual tumor with usual histology, such as tubules (**A**), blastema (**B**), lipoblasts (**C**), and retiform elements (**D**).

Table 4. Differential diagnosis of rhabdomyosarcoma [109]

Small round cell neoplasms
Ewing sarcoma family of tumors (Ewing sarcoma, primitive neuroectodermal tumor, Askin tumor)
Neuroblastoma
Non-Hodgkin lymphoma (particularly B-cell lymphomas)
Extramedullary leukemia
Langerhan cell histiocytoses
Localized giant cell tumor of soft tissue (giant cell tumor of tendon sheath)
Malignant rhabdoid tumor
Epithelioid sarcoma
Primitive carcinomas, such as *NUT* translocation carcinoma
Desmoplastic small round cell tumor
Melanotic neuroectodermal tumor
Myogenic neoplasms
Rhabdomyoma, infantile and genital types
Rhabdomyomatous hamartoma
Neuromuscular choristoma
Malignant Triton tumor (malignant peripheral nerve sheath tumor with heterologous myogenic differentiation)
Wilms tumor (rhabdomyomatous nephroblastoma)
Hepatoblastoma, with heterologous differentiation
Pleuropulmonary blastoma
Sertoli-Leydig cell tumor
Mixed Mullerian tumor
Carcinosarcoma
Melanoma with myogenic differentiation
Medullomyoblastoma
Spindle cell neoplasms
Inflammatory myofibroblastic tumor
Low-grade myofibroblastic sarcoma
Leiomyosarcoma
Myofibroma
Fibrosarcoma
Malignant peripheral nerve sheath tumor
Low-grade fibromyxoid sarcoma
Pleomorphic sarcoma (‘‘malignant fibrous histiocytoma’’)
Dendritic cell neoplasms

preventing recurrence of localized tumors [129]. A variety of factors have been used to stratify therapy into low-risk, intermediate-risk, and high-risk groups [128]. Improving the outcome of high-risk patients remains challenging, although newer agents, such as irinotecan, have offered some hope [130].

The appropriate therapy for fusion-negative alveolar rhabdomyosarcomas has been the source of recent controversy. Due to clinical and genetic indications that fusion-negative alveolar rhabdomyosarcomas have an outcome similar to embryonal rhabdomyosarcomas, some have called for therapeutic decisions based on fusion status alone, without consideration of histology [73]. However, the Children's Oncology Group Soft Tissue Sarcoma Committee has suggested that this approach is premature for a number of reasons, including the lack of any targeted therapy for fusion-positive alveolar rhabdomyosarcoma and the relatively low proportion of patients who would be affected by this approach, estimated at 7–22% of cases of alveolar rhabdomyosarcoma in previous studies [131].

One particularly challenging aspect of rhabdomyosarcomas is the evaluation and interpretation of excised tumors after therapy. Successfully treated rhabdomyosarcomas typically contain a mixture of necrotic tumor and terminally differentiated myoblasts [42], reflecting diversion of actively dividing cells into either apoptosis or a G0 phase. Identification of differentiated cells is particularly challenging in areas with skeletal muscle, for they are identical to regenerative myoblasts. Another conundrum is the appropriate therapy for tumors with residual microscopic disease limited to differentiated cells, although some reports suggest that these have outcomes no different from completely excised lesions [132,133].

Considerations for the future

Future prospects for rhabdomyosarcoma include further dissection of molecular mechanisms responsible for tumorigenesis and chemosensitivity and the identification of biologic agents that can improve upon current therapy. Several groups of investigators have accrued much data from expression arrays that map virtually the entire transcriptome [134–136], and information gained from these assays will be probed for new diagnostic markers [19] and potential bioactive agents [137]. High-risk rhabdomyosarcoma continues to offer a therapeutic challenge and constitutes a major focus for new studies [138]. Recent improvements in patient survival with low-risk tumors conversely call for reduction of treatment toxicity while maintaining current survival levels [1,139,140].

RHABDOMYOMAS

Benign tumors containing skeletal muscle make up a rare subgroup of myogenous tumors and have distinct clinicopathologic properties (Table 5). Rhabdomyomas account for less than 2% of all tumors of striated muscle and are divided into 2 major categories: cardiac and extracardiac. Extracardiac rhabdomyomas include 3 distinct histologic groups: adult, fetal, and genital [141,142]. Cardiac and fetal are the principal rhabdomyoma types in infants or young children. Genital rhabdomyoma may occasionally be encountered in older children and adolescents [143,144].

Cardiac rhabdomyoma

Cardiac rhabdomyoma is the most frequent benign rhabdomyogenic lesion and accounts for more than 60% of all cardiac tumors during the fetal life and childhood [145]. Multiple or, less frequently, single cardiac rhabdomyomas may represent the 1st clinical manifestation in about 50% of patients with tuberous sclerosis, in

Table 5. Clinicopathologic features of benign lesions of skeletal muscle in children

	Cardiac rhabdomyoma	Fetal rhabdomyoma	Rhabdomyomatous hamartoma
Age	Infant	Child, adult	Child, adult
Site	Ventricles, interventricular septum	Head, neck (86%) perianal, stomach, parotid abdominal wall (14%)	Face, neck, oral cavity (rare)
Size	Small	1.5–12.5 cm	<2 cm
Male:female ratio	1:1	7:1	Male
Histologic key features	Mature myocytes, spider cells	Well circumscribed Immature skeletal muscle Absent cytologic atypia	Polypoid Mature skeletal muscle Other mature tissues
Follow up	Spontaneous regression	Very rare recurrence	No recurrences
Associated condition	Tuberous sclerosis	Nevoid basal cell carcinoma	Ectodermal/mesodermal malformations, oculocerebrocutaneous syndrome

absence of other signs [145–147]. Association of cardiac rhabdomyoma with trisomy 13 or 21 has been also documented [146]. The prenatal diagnosis is often made after the 20th week of gestational age. Tumors may be incidentally found during routine obstetrical ultrasonography or evaluation for fetal cardiac arrhythmia [145,148–150]. Hydrops fetalis, intrauterine death, or sudden death immediately after birth may rarely occur [151–154]. After birth, the symptoms are related to the inflow or outflow tract obstruction and depend on the number, position, and size of tumors. Right-sided tumors may cause cyanosis or features that suggest tetralogy of Fallot or pulmonary stenosis; left-sided lesions may present as subaortic obstruction or hypoplastic left heart syndrome. Atrial or ventricular arrhythmias, including Wolff-Parkinson-White syndrome, occur in 16–47% of patients and may be related to the creation from tumor cells of an accessory pathway between atrial and ventricular myocardium [155–158]. Structural cardiac defects may be associated with cardiac rhabdomyoma; examples include hypoplastic left heart syndrome, transposition of the great arteries, ventricular septal defect, endocardial fibroelastosis, subaortic stenosis, Ebstein anomaly, hypoplastic tricuspid valve, double outlet right ventricle, and pulmonary atresia [159]. The diagnosis can be established with echocardiography or cardiac magnetic resonance imaging [150,160]. Grossly, rhabdomyomas are white-yellow, firm, circumscribed, nonencapsulated intramyocardial nodules located in the ventricles or interventricular septum, with intracavitary growth in about 50% of cases. Occasional isolated tumors may be localized to the atria or in the subepicardial region.

Rhabdomyomas are considered hamartomatous lesions. They are characterized by overgrowth of cardiac myocytes, which are arranged in solid nodules or form small groups. Myocytes show small central nuclei and enlarged clear cytoplasm containing glycogen-filled vacuoles and sparse myofilaments. In some cells, delicate strands of eosinophilic cytoplasm radiate from nucleus to the cell membrane and give rise to the so-called spider cells, which are considered pathognomonic of cardiac rhabdomyoma. Mitoses are absent, and there is only mild cellular atypia. Periodic acid–Schiff stains are strongly positive and highlight the abundant glycogen [150,160–163]. Rhabdomyomas show positive immunostaining for muscle cell markers, including myoglobin, desmin, actin, and vimentin. Hamartin, tuberin, and HMB45 may be expressed [150,161,164].

Ultrastructurally, cardiac rhabdomyoma cells display abundant glycogen and cross-striations. Cellular junctions resembling intercalated disks surround the cell periphery. Cardiac rhabdomyomas increase in size until 32 weeks of gestation (probably under the influence of maternal hormones), followed by progressive spontaneous regression [165,166]. According to the model proposed by Wu and colleagues [167], the vacuolization of cytoplasm results in spider cell formation with activation of the ubiquitin pathway, degradation of myofilaments and apoptosis, myxoid degeneration, and regression. Surgery should be reserved for patients with severe hemodynamic compromise or arrhythmia not controlled by drugs [168].

Cardiac rhabdomyoma is easily distinguished from histiocytoid cardiomyopathy, a rare, arrhythmogenic disorder characterized by multiple microscopic hamartomatous nodules of polygonal cells with foamy to granular cytoplasm, generally located within the subendocardial region. These oncocytic cells, probably representing abnormal Purkinje cells, are immunoreactive for muscular markers and ultrastructurally show numerous abnormal mitochondria and scattered myofibrils with absence of the t-tubule system. Histiocytoid cardiomyopathy is probably an X-linked disorder and mostly affects girls younger than 2 years, often causing sudden death [169].

Fetal rhabdomyoma

Fetal rhabdomyomas are rare and may occur at any age, although most are diagnosed within the 1st 3 years of life. They have a predilection for the head and neck, but a wide range of anatomic sites, such as the trunk, anal

region, and parotid gland, may be involved [170–173]. They may be associated with the nevoid basal cell carcinoma syndrome (Gorlin-Goltz syndrome) [174–176].

Grossly, fetal rhabdomyomas are circumscribed, soft masses, generally measuring less than 3 cm, but larger lesions up to 12.5 cm may occur. The cut surface has a glistening, mucoid appearance. Mucosal tumors are generally polypoid. Rare cases are multifocal.

Histologically, fetal rhabdomyomas display skeletal muscle cells in varying stages of maturation (Fig. 20). Two different histologic subtypes have been recognized: the myxoid or classic type [177–179] and the cellular type, also called juvenile or intermediate rhabdomyoma [178,180]. Classic fetal rhabdomyomas are mild to moderately cellular tumors composed of oval-spindled undifferentiated mesenchymal cells and immature muscle fibers, haphazardly arranged within a loose myxoid stroma. Myofibrils and cross-striations may be identified in scattered larger ''strap'' cells [177–179].

Cellular fetal rhabdomyomas show a predominance of less immature-appearing spindle rhabdomyoblasts with variable degrees of differentiation towards skeletal muscle, arranged in interlacing bundles and minimal intervening myxoid stroma (Fig. 20). Focally infiltrative growth, increased mitoses (up to 14 mitoses per 50 high-power field), focal necrosis, and mild to moderate nuclear hyperchromatism and pleomorphism have been reported in both subtypes [177–179].

Immunohistochemical analysis reveals diffuse reactivity for desmin, myoglobin, and muscle-specific actin and focal staining for smooth muscle actin. In one series, positive staining for S-100 and/or glial fibrillary acidic protein was reported in 50% of cases, suggesting multipotential primitive mesenchymal cells or a possible relation to Triton tumor [178,181]. Electron microscopy shows thick and thin myofilaments with Z-bands and glycogen within the cytoplasm of rhabdomyoblasts [178].

The differential diagnosis of fetal rhabdomyoma includes embryonal and spindle cell rhabdomyosarcomas and benign conditions, such as the neuromuscular hamartoma (benign Triton tumor) [182] and the rhabdomyomatous mesenchymal hamartoma of the skin. The distinction from rhabdomyosarcoma can be challenging in lesions with higher cellularity, mitoses, or foci of necrosis. Circumscription, superficial location, cellular maturation, and lack of striking nuclear atypia support a diagnosis of fetal rhabdomyoma [178]. Although the occurrence of a mixed embryonal/alveolar rhabdomyosarcoma has been reported in 1 case, the possibility of malignant transformation is questionable [41].

Complete excision is an effective treatment. Rare local recurrences are related to incomplete excision.

RHABDOMYOMATOUS MESNCHYMAL HAMARTOMAS

Rhabdomyomatous mesenchymal hamartomas are rare lesions, with fewer than 35 cases reported in literature, mostly occurring in infants and small children as solitary polypoid masses or a dome-shaped papule in the skin or submucosa of the head and neck (especially the nose, chin, and periorbital regions) [183–187]. Multiple lesions have been reported in 3 cases [188].

Rhabdomyomatous hamartomas may be associated with cleft lip, bilateral sclerocorneas, retinal dysplasia, amniotic band syndrome, oculocerebrocutaneous syndrome [189,190], and bilateral microtia with aural atresia [191]. Lentiginous melanocytic hyperplasia has been described in the affected area of the skin in 1 case [192].

Cutaneous rhabdomyomatous hamartomas are polypoid lesions covered by epithelium and composed of mature skeletal muscle fibers intermingled with adipose tissue and other different components (including sebaceous, apocrine, eccrine, seromucinous, and salivary glands) and with neural tissues. In the oral cavity, salivary or seromucinous glands may be found (Fig. 21). The etiology of rhabdomyomatous mesenchymal hamartoma is still unclear, but aberrant embryologic development or migration of mesoderm may play a pathogenetic role [185,187,191].

The differential diagnosis of rhabdomyomatous hamartoma includes fetal rhabdomyoma and embryonal rhabdomyosarcoma. Rhabdomyomatous hamartomas show additional mature tissue components as integral parts of the lesion and lack the immature skeletal muscle cells present in rhabdomyosarcoma and fetal rhabdomyoma. The elective treatment is complete excision.

SMOOTH MUSCLE TUMORS

Smooth muscle tumors are rare in children and adolescents [142,193–195]. The pathologic spectrum encompasses hamartomas, benign conditions (eg angioleiomyoma, leiomyoma, leiomyomatosis, leiomyosarcoma), and smooth muscle tumors of uncertain malignant potential in immunocompromised individuals. Smooth muscle tumors in children differ from those in adults by an absence of gynecologic leiomyomas and leiomyosarcomas, relatively low-grade morphology, and a more favorable prognosis, even for leiomyosarcoma. Immunohistochemical markers for smooth muscle include smooth muscle actin, muscle-specific actin, desmin, calponin, and h-caldesmon, which is particularly useful in the distinction from fibroblastic-myofibroblastic and myoepithelial neoplasms [196–201]. Ultrastructurally smooth muscle tumors display external lamina, abundant pinocytotic vesicles, intermediate filaments, and skeins of cytoplasmic microfilaments that insert into cytoplasmic dense bodies [202,203].

Smooth muscle hamartoma

Smooth muscle hamartoma is a congenital or acquired cutaneous or submucosal proliferation [204–206]. In the skin, smooth muscle hamartoma consists of nodular or

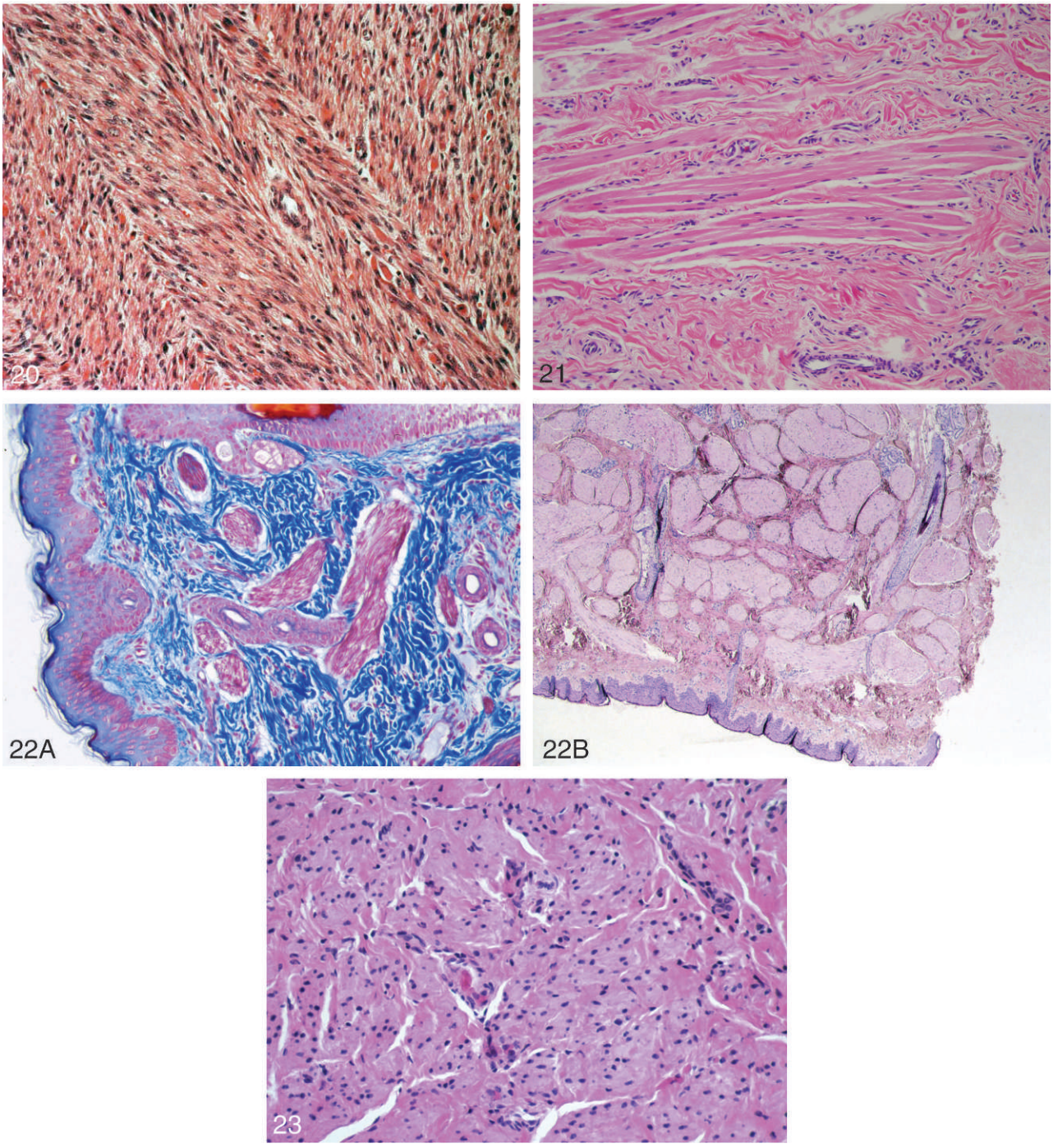


Figure 20. Fetal rhabdomyoma consists of interlacing bundles of differentiating spindled myoid cells with abundant cytoplasm (hematoxylin and eosin [H&E], ×200).
Figure 21. Rhadomyomatous mesenchymal hamartoma. Mature striated muscle fibers infiltrate between dermal structures (H&E, ×200).
Figure 22. Smooth muscle hamartoma. **A.** The dermis contains enlarged fascicles of smooth muscle clustered around adnexal structures (trichrome, ×100). **B.** Abundant disorganized fascicles of mature smooth muscle create a mass (H&E, ×40).
Figure 23. Leiomyoma. The lesion consists of interlacing bundles of smooth muscle cells with small bland nuclei and abundant eosinophilic cytoplasm (H&E, ×200).

plaque-like disorganized dermal fascicles of mature smooth muscle, originating from erector pili and oriented around hair follicles (Fig. 22). Although most are solitary, rare multiple familial examples have been reported [205]. Hypertrichosis, follicular dimpling, increased skinfolds, Becker melanosis, or a congenital pattern melanocytic nevus may be present in the affected area of the skin [204,205,207,208].

Leiomyoma

Leiomyomas in children are relatively uncommon, and the anatomic distribution differs from adults, with 15% originating in soft tissue and 9% in the skin and subcutaneous tissue [193–195]. Other sites that may be affected include the gastrointestinal tract, bladder, head and neck, and lung [209]. Gynecologic leiomyomas in children and adolescents are very rare. Benign leiomyomas occur throughout childhood, with peaks in the 1st 5 years and in the 2nd decade of life. There is a slight female predominance. The mass may be tender, and site-specific symptoms due to obstruction occur in the gastrointestinal or respiratory tract. Most leiomyomas are solitary, except in Carney's triad with gastric epithelioid leiomyoma, pulmonary chondroma, and extraadrenal paraganglioma [210–213]. Other conditions associated with multiple leiomyomas in children include Alport syndrome and immunodeficiency [214,215]. Pathologically, size ranges widely, but leiomyomas are generally smaller than leiomyosarcomas [195]. The circumscribed pink or tan rubbery nodule has a whorled cut surface. Dystrophic calcification in deep leiomyoma may mimic osseous and chondroid tumors [216–218]. Histologically, bundles and whorls of mature smooth muscle cells are accompanied by variable stromal collagen (Fig. 23). The tumor cells have elongated nuclei with rounded edges and paranuclear cytoplasmic vacuoles. The epithelioid leiomyoma is unusual in childhood, except in the setting of Carney's triad, and consists of round or polygonal cells with round nuclei and clear or vacuolated cytoplasm intermingled with a more characteristic spindle cell leiomyoma [194,195,219]. Leiomyomas lack mitoses, atypia, and necrosis.

The treatment is simple excision.

The differential diagnosis of leiomyoma includes fibroblastic-myofibroblastic tumors (eg nodular fascitis, fibromatoses, myofibromatosis), infantile fibrosarcoma, cellular schwannoma, granular cell tumor, and leiomyosarcoma.

Leiomyomatosis

Leiomyomatosis is a diffuse mature smooth muscle proliferation that involves the esophagus, tracheobronchial tree, perirectal region, and female external genitalia, including the vulva, clitoris, and urethra [195,220–226]. It is associated with Alport syndrome, which consists of hereditary nephropathy, sensorineural deafness, and eye abnormalities. Alport syndrome has an X-linked inheritance pattern due to deletions of the *COL4A5* and *COL4A6* genes [214,215,227–232]. Leiomyomatosis is histologically identical to benign leiomyoma, except that it is a diffuse infiltrative process (Fig. 24).

Angioleiomyoma

Vascular leiomyoma, or angioleiomyoma, is rare in children and is a benign, frequently painful, subcutaneous or deep dermal tumor [194,195,233]. The mature smooth muscle bundles surround and dissect between blood vessels and form a morphologic continuum with myofibroma and myopericytoma [142]. Some cases reported in the past as vascular leiomyoma are now categorized among smooth muscle tumors of uncertain malignant potential associated with immunodeficiency. Histologically, the bundles of smooth muscle blend with the vascular smooth muscle of venous walls or cavernous dilated vascular channels. Alternatively, the mass may consist of compact solid and intersecting fascicles of spindle cells near a blood vessel. Histologically, degenerative nuclear atypia, hyalinization, calcification, hemorrhage, and small aggregates of mature adipocytes may be seen as variations.

Leiomyosarcoma

Malignant smooth muscle tumors are infrequent in children and adolescents, and only a few series have been published in the literature (Table 6) [194,195,203,234–237]. According to information from St. Jude Children's Hospital and the Kiel Pediatric Tumor Registry, approximately 4% of childhood soft tissue sarcomas are leiomyosarcomas [238,239].

The clinicopathologic features of leiomyosarcomas in children and adolescents are shown in Table 6. Some of the older series may have included tumors that are now classified as gastrointestinal stromal tumors. Sites include the skin, superficial and deep soft tissue, bone, and viscera, such as the lung and gastrointestinal tract, including the oral cavity [235–237,240–247]. There is a slight male predominance. Age at diagnosis ranges from infancy to 18 years, with a mean of 8–11 years in the pediatric series. Leiomyosarcoma has been reported as a 2nd malignant neoplasm after radiation therapy for retinoblastoma and other tumors [248–251].

Pathologically, leiomyosarcoma is a large, fleshy pink-gray nodular mass that is circumscribed but not encapsulated and may display hemorrhage and necrosis. Diameter ranges from 1 cm to 13 cm. Some tumors may be multinodular, and mucosal tumors may show bosselation and ulceration. Histologically, characteristic interlacing bundles of packed spindle cells with elongated, round-ended nuclei are present (Fig. 25). Variants include myxoid, hyalinized, palisaded, pleomorphic, and epithelioid morphology [142,252–254]. Immunohistochemistry is useful for confirming the smooth muscle phenotype, with reactivity for smooth muscle actin, muscle-specific actin, desmin, and h-caldesmon (Fig. 26) [198,236]. In contrast to uterine leiomyosarcomas, soft tissue and visceral leiomyosarcomas in children and adolescents lack estrogen receptors [255]. Ultrastructural analysis reveals features of smooth muscle.

The inflammatory variant of leiomyosarcoma is a spindle cell neoplasm with fascicular areas occupying 5–80% of the tumor and a prominent inflammatory infiltrate

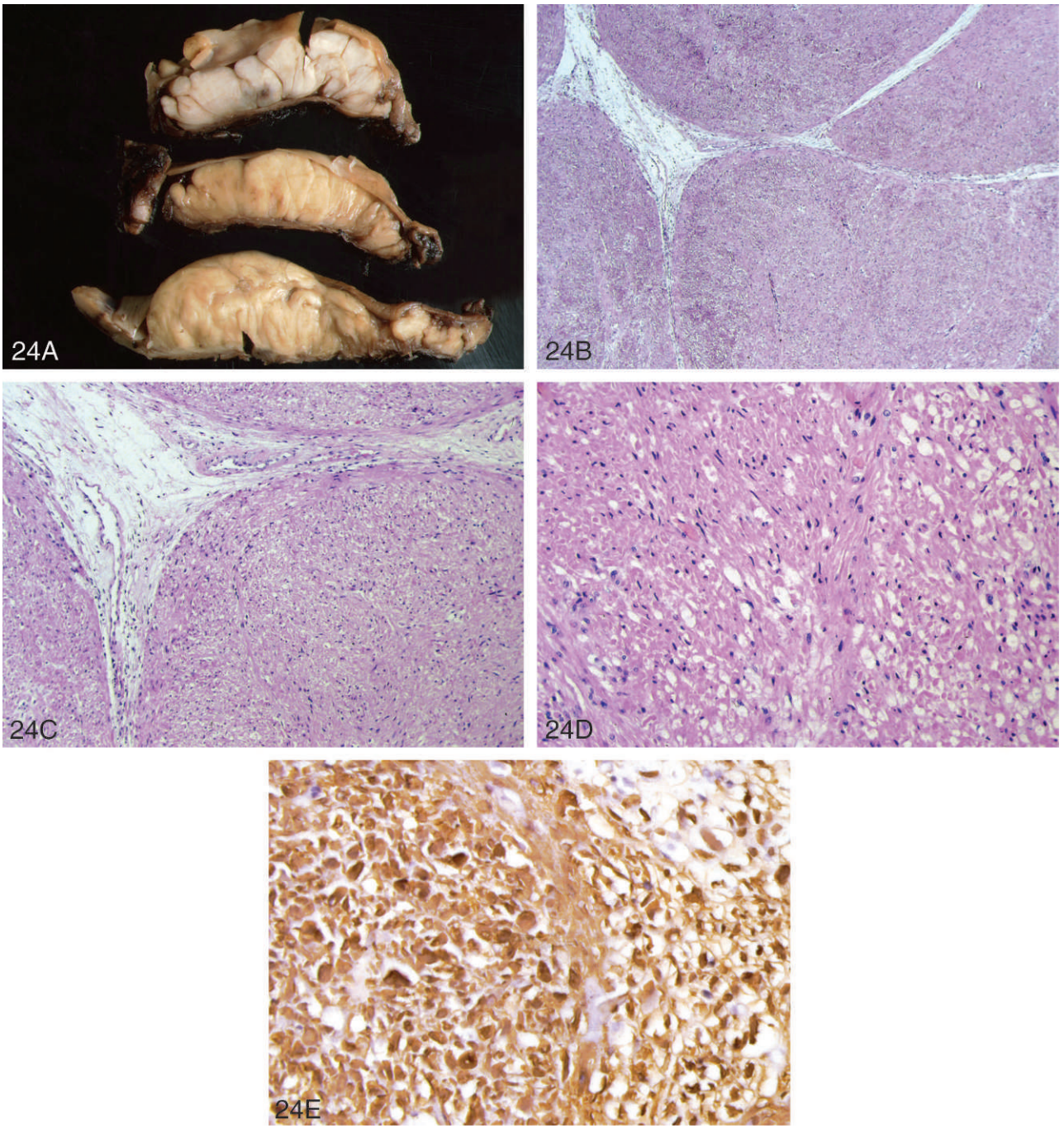


Figure 24. Leiomyomatosis. **A.** Sections of esophageal leiomyomatosis reveal an infiltrative fasciculated firm mass in the submucosa muscle and adjacent soft tissue. **B.** Bundles of bland smooth muscle are separated by sparse connective tissue (hematoxylin and eosin [H&E], ×40). **C.** The smooth muscle cells resemble leiomyoma, are uniform, and lack atypia (H&E, ×100). **D.** The smooth muscle cells have small bland nuclei and clear cytoplasmic vacuoles (H&E, ×200). **E.** Immunohistochemistry for smooth muscle actin reveals diffuse cytoplasmic positivity (H&E, ×200).

of histocytes with variable lymphocytes, neutrophils, and foamy macrophages (Fig. 27) [256]. The inflammatory infiltrate may be so dense that it masks the underlying neoplastic smooth muscle cells. Karyotypically, inflammatory leiomyosarcoma harbors extra copies of chromosomes 5, 18, 20, 21, and 22, which are distinct from the nonspecific but complex structural and numerical cytogenetic changes of other types of leiomyosarcoma [257–259].

Myxoid leiomyosarcoma is a gelatinous mass with a myxoid stroma occupying greater than 50% of the tumor [253]. The predominantly spindle cells have 3 major architectural patterns: fascicular, reticular/microcystic, and myxofibrosarcoma like. Myxoid leiomyosarcoma is a low-grade variant of leiomyosarcoma with a tendency for local recurrence but only rare metastases. Young adults may be affected, and females predominate.

Table 6. Clinicopathologic features of leiomyosarcoma in 7 pediatric series

	Yannopoulos and Stout [194]	Botting and colleagues [195]	Lack [234]	Swanson and colleagues [203]	Hwang and colleagues [235]	De Saint Aubain-Somerhausen and colleagues [236]	Ferrari and colleagues [237]
No. of patients	10	10	10	6	21	20	16
Male: female ratio	4.0	1.5	1.0	2.0	0.9	0.8	0.9
Site							
Head/neck	2	4	1	3	5	5	5
Gastrointestinal tract	4	3	6	NS	5	0	4
Genitourinary tract	2	NS	3	NS	0	0	0
Extremities	2	2	NS	1	7	9	2
Other	NS	1	NS	2	4	6	5
Age							
Range	4 months–14 years	3–16 years	2–15 years	8 months–18 years	21 years	4–15 years	2–21 years
Mean	8.6 years	11.1 years	10.4 years	9.7 years	14.2 years	10 years	12 years
Survival rate	80–90%	40%	60%	66%	79%	100%	73%

NS indicates not specified.

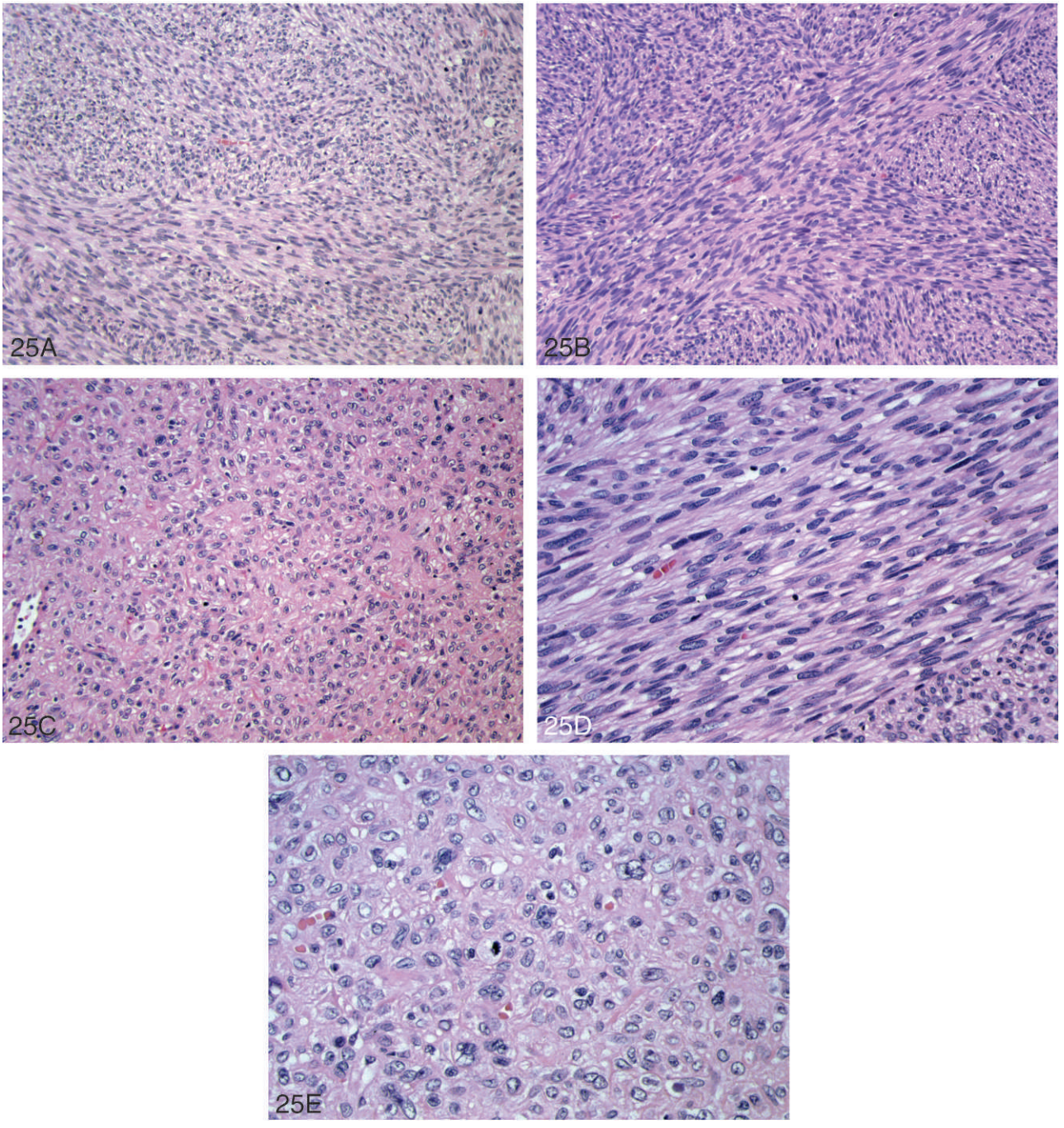
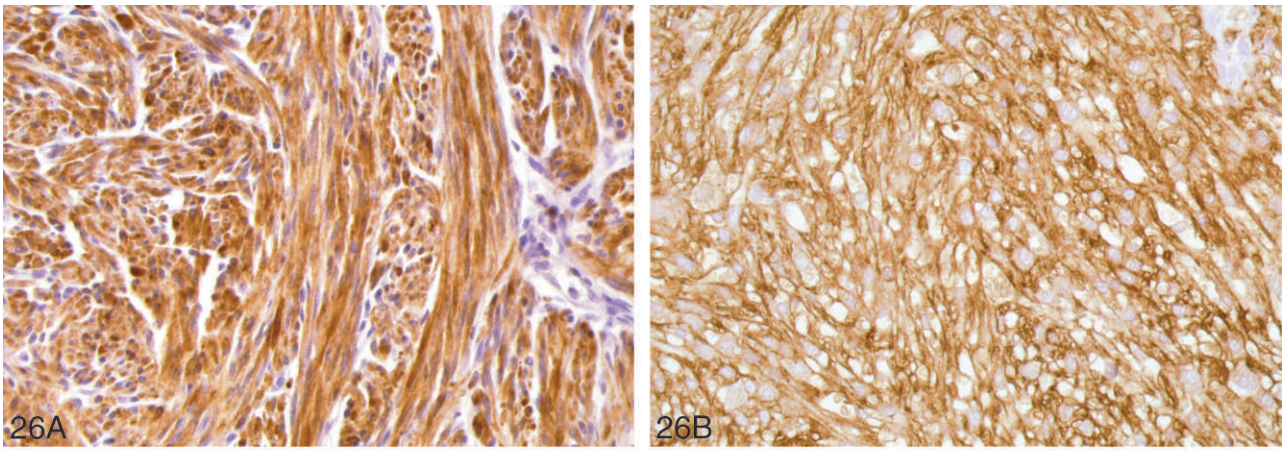


Figure 25. Leiomyosarcoma. **A.** Large interlacing fascicles of spindle cells have a more cellular architecture than leiomyoma or leiomyomatosis (hematoxylin and eosin [H&E], ×100). **B.** The tumor cells have elongated nuclei, perinuclear cytoplasmic vacuoles, variation in nuclear size, and a fascicular architecture (H&E, ×200). **C.** In some areas, the tumor cells are plump and polygonal with an epithelioid appearance (H&E, ×200). **D.** The nuclei are elongated and have oval tips with perinuclear cytoplasmic vacuoles and occasional mitoses (H&E, ×400). **E.** Nuclear atypia, pleomorphism, and mitotic activity are histologic findings in leiomyosarcoma with an epithelioid appearance (H&E, ×400).

Complete surgical excision is the treatment of choice, and the role of chemotherapy and radiation therapy is not fully defined [237]. Survival rates have ranged from 79% to 100% and the data indicate that the prognosis for leiomyosarcoma is better in children and adolescents than in adults [203,235–237]. Metastases to unusual sites, such as the peritoneum, may be seen [260]. Late metastases can occur. Survival rates progressively decrease over long periods [235].

The differential diagnosis of leiomyosarcoma includes smooth muscle tumor of uncertain malignant potential, myofibrosarcoma, low-grade fibromyxoid sarcoma, cellular schwannoma, synovial sarcoma, inflammatory myofibroblastic tumor, and spindle cell rhabdo-



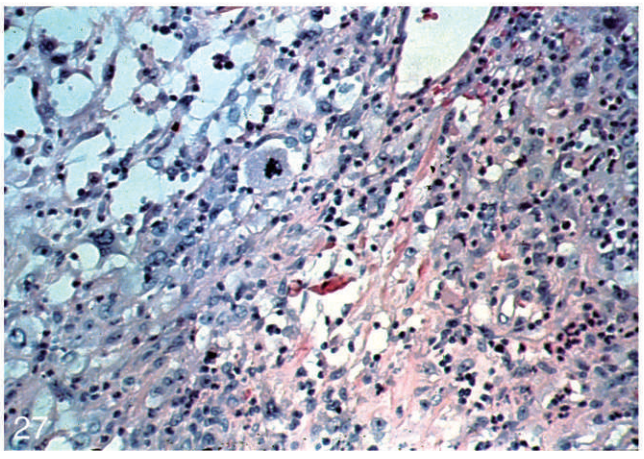


Figure 26. Leiomyosarcoma immunohistochemistry. **A.** h-Caldesmon is reactive in the cytoplasm of nearly all tumor cells (immunohistochemistry, ×200). **B.** Smooth muscle actin shows diffuse reactivity (immunohistochemistry, ×200).
Figure 27. Inflammatory leiomyosarcoma. The lesion displays atypical plump, polygonal, and spindle cells accompanied by an inflammatory infiltrate of histiocytes and lymphocytes (hematoxylin and eosin, ×200).

myosarcoma. These are distinguishable by careful attention to clinicopathologic features and use of diagnostic adjuncts.

Smooth muscle tumors in immunocompromised patients

Smooth muscle tumors of uncertain malignant potential are associated with human immunodeficiency virus infection [202,261–266]; immunosuppression due to steroid treatment or organ transplantation [267–269]; and primary immunodeficiencies, such as common variable immunodeficiency and ataxia-telangiectasia [270–272]. Infection with Epstein-Barr virus is thought to be causal, and some patients have both smooth muscle tumors of uncertain malignant potential and post-transplant lymphoproliferative disorder [202,263,269, 274–275]. These smooth muscle tumors are often multifocal and occur in unusual sites, most commonly the viscera, lungs, spleen, soft tissue, skin, gastrointestinal tract, brain, and bones [142,202,261,269,270,274,276–278]. Histologically, the tumor cells are well differentiated, with only low or moderate atypia, variable mitotic activity ranging from none to 18 mitoses per 10 high-power field (average of 3 per 10 high-power field), variable myxoid change, and variable primitive round cell areas (Fig. 28A,B). Intratumoral lymphocytes may be prominent, and a perivascular growth pattern is often seen. Multifocal tumors in an individual patient are clonally distinct and are thought to originate from multiple infection events. Epstein-Barr virus type 2 is present, and some tumors have a deletion of the *LMP1* gene [142,269]. In situ hybridization for Epstein-Barr virus–encoded small RNA is reliable to detect the presence of Epstein-Barr virus (Fig. 28C). Immunohistochemically, smooth muscle actin, muscle-specific actin, and h-caldesmon are expressed (Fig. 28D).

Smooth muscle tumors of uncertain malignant potential are less aggressive than sporadic leiomyosarcomas, although they can recur. Treatment options include resection with or without chemotherapy and cessation of pharmacologic immunosuppression. The differential diagnosis includes other spindle cell neoplasms, Kaposi sarcoma, gastrointestinal stromal tumor, and atypical mycobacterial infection with a spindle cell proliferation.

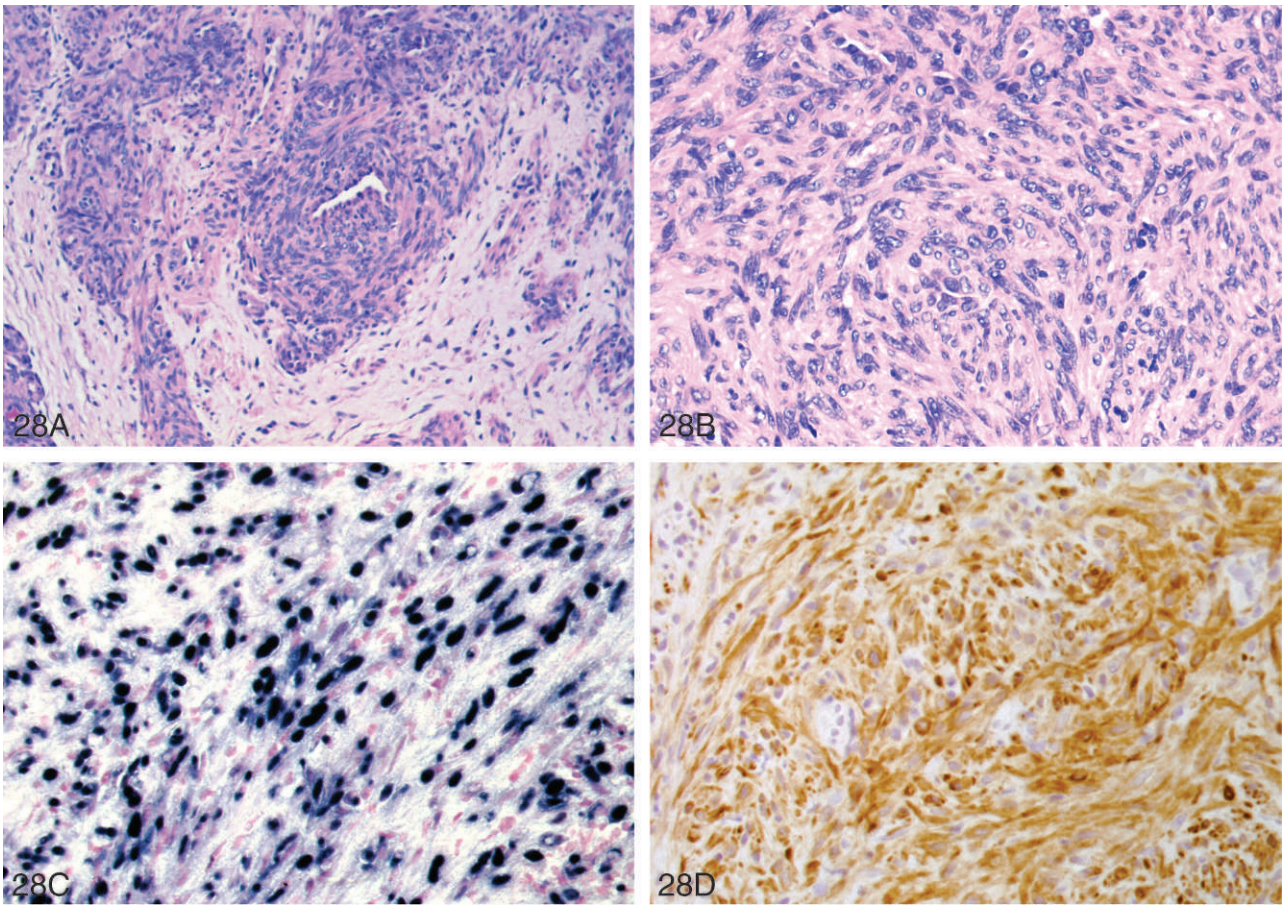


Figure 28. Smooth muscle tumor of uncertain malignant potential. **A.** Smooth muscle cells form multiple nodules with a perivascular architectural pattern (hematoxylin and eosin [H&E], ×100). **B.** The smooth muscle cells are arranged in fascicles and short whorls and have nuclear variability and occasional mitoses (H&E, ×400). **C.** In situ hybridization for Epstein-Barr virus is positive (in situ hybridization, ×400). **D.** Immunohistochemistry for h-caldesmon is positive (immunohistochemistry, ×200).

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