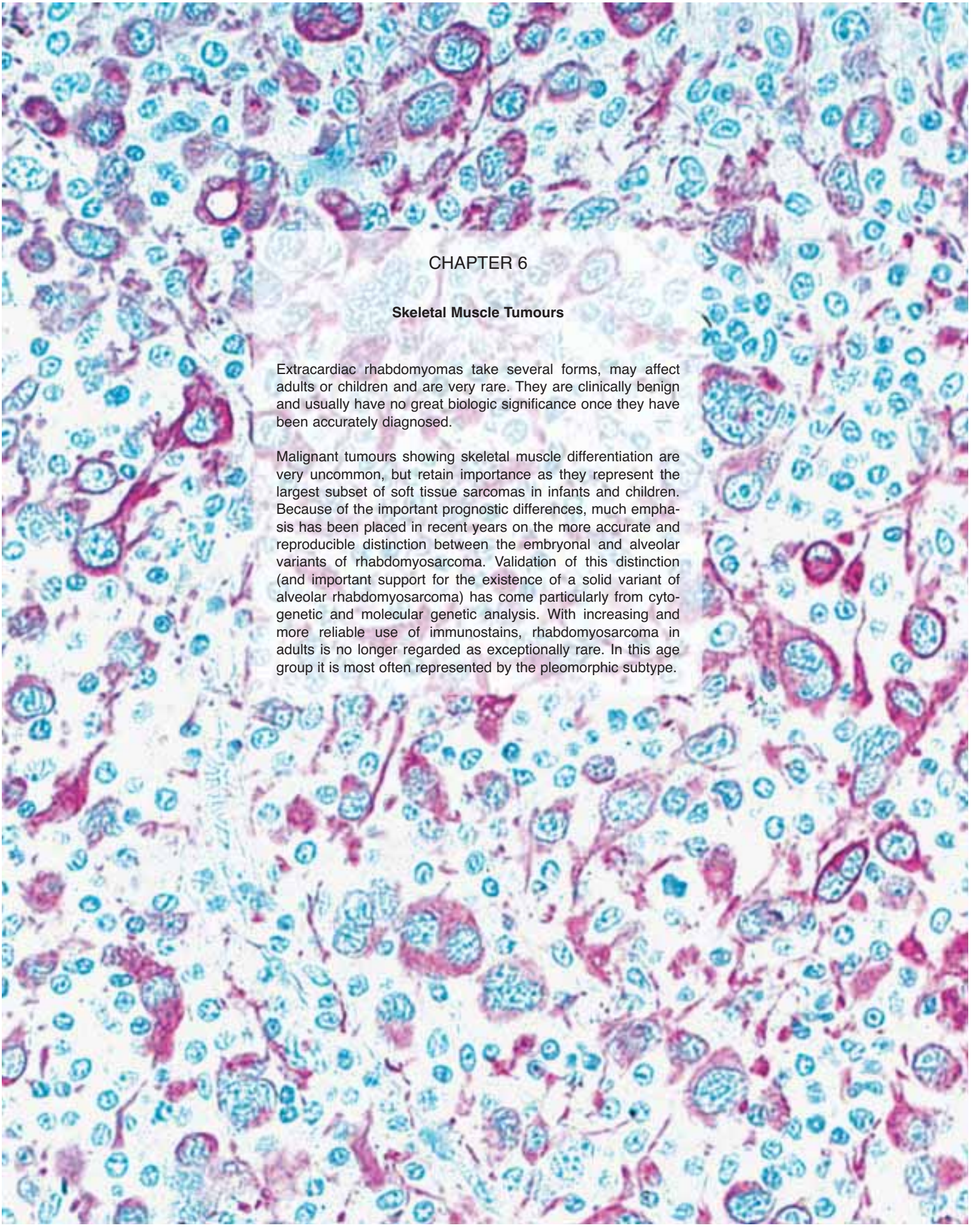

CHAPTER 6

Skeletal Muscle Tumours

Extracardiac rhabdomyomas take several forms, may affect adults or children and are very rare. They are clinically benign and usually have no great biologic significance once they have been accurately diagnosed.

Malignant tumours showing skeletal muscle differentiation are very uncommon, but retain importance as they represent the largest subset of soft tissue sarcomas in infants and children. Because of the important prognostic differences, much emphasis has been placed in recent years on the more accurate and reproducible distinction between the embryonal and alveolar variants of rhabdomyosarcoma. Validation of this distinction (and important support for the existence of a solid variant of alveolar rhabdomyosarcoma) has come particularly from cytogenetic and molecular genetic analysis. With increasing and more reliable use of immunostains, rhabdomyosarcoma in adults is no longer regarded as exceptionally rare. In this age group it is most often represented by the pleomorphic subtype.

Rhabdomyoma

S.B. Kapadia
F.G. Barr

Rhabdomyoma (RM) is a benign mesenchymal tumour with skeletal muscle differentiation that is classified into cardiac and extracardiac types based on location {1978}. Cardiac RM will be dealt with in the WHO classification of heart tumours. Extracardiac RM is further classified into adult and fetal types, depending on the degree of differentiation, and has a predilection for the head and neck {515,1063,1065,1155,2274}. Rarely, RM may occur in the genital tract (genital RM). Unlike cardiac RM, there is no association with tuberous sclerosis {1065,1978,2274}.

ICD-O code 8900/0

Adult rhabdomyoma

Definition
Adult rhabdomyoma (A-RM) is a rare benign mesenchymal tumour with mature skeletal muscle differentiation and a predilection for the head and neck region.

ICD-O code 8904/0

Sites of involvement
The head and neck region (90%) is the most common site, mainly the upper aerodigestive mucosa (pharynx, oral cavity, and larynx) and soft tissue of neck {1065}.

Clinical features
The median age is 60 years (range 33 to 80 years) with a 3:1 male predominance {1065}. Symptoms include upper airway obstruction and mucosal or soft tissue mass (median duration 2 years, range 2 weeks to 3 years); in 10% the mass is asymptomatic {1065}. A-RM is often solitary (70%), but may be multinodular (26%) with discrete nodules in the same anatomic area or, rarely, multicentric (4%) {1065}.

Macroscopy
The mass (median size 3 cm, range 1.5 to 7.5 cm) is circumscribed deep tan to red-brown, soft, and nodular or lobulated {1065}.

Histopathology
A-RM is well circumscribed but unencapsulated and composed of lobules of closely packed uniform large polygonal cells in a scant stroma {1065}. The cells have abundant, eosinophilic, granular or vacuolated cytoplasm ("spider" cells) with well defined borders, and vesicular, small, round, centrally or peripherally located nuclei, at times with prominent nucleoli. Haphazardly arranged rod-like cytoplasmic inclusions and cross striations are seen focally. The glycogen-rich cytoplasm is periodic acid-Schiff (PAS)-positive, diastase sensitive. Phosphotungstic acid-hematoxylin, Masson trichrome or immunohistochemical stains highlight the cytoplasmic cross striations as well as the crystalline or rod-like inclusions {1065}.

Immunophenotype
The skeletal muscle differentiation is easily demonstrated on immunohistochemical stains with cytoplasmic positivity for MSA, desmin and myoglobin in all cases {368,616,880,933,1063,1065,2274}. Focal or rare positivity may be seen for vimentin, SMA and S100 protein. GFAP, cytokeratin, EMA, and CD68 stains are negative {1065}.

Ultrastructure
Electron microscopy demonstrates cytoplasmic myofilaments, Z-bands and glycogen granules {142,368,933,1155}.

Prognostic factors
Complete excision is the recommended treatment. In one study, follow-up showed local recurrence (42%) in the same anatomic site, from 2-11 years after diagnosis, often after incomplete

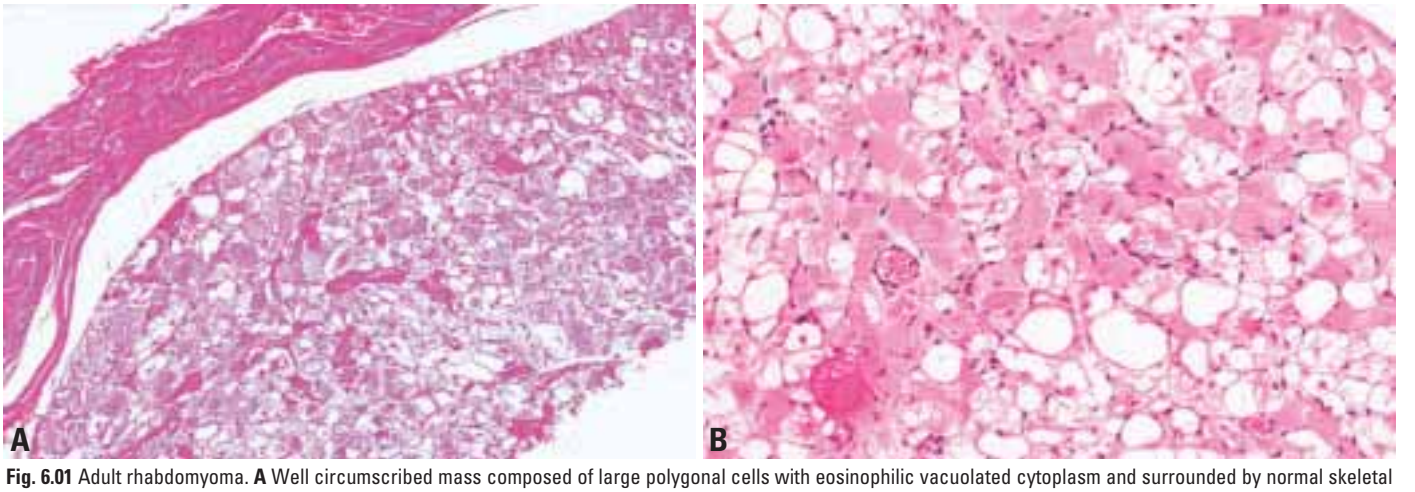

Fig. 6.01 Adult rhabdomyoma. **A** Well circumscribed mass composed of large polygonal cells with eosinophilic vacuolated cytoplasm and surrounded by normal skeletal muscle. **B** Higher magnification shows large, polygonal cells with abundant granular and vacuolated cytoplasm.

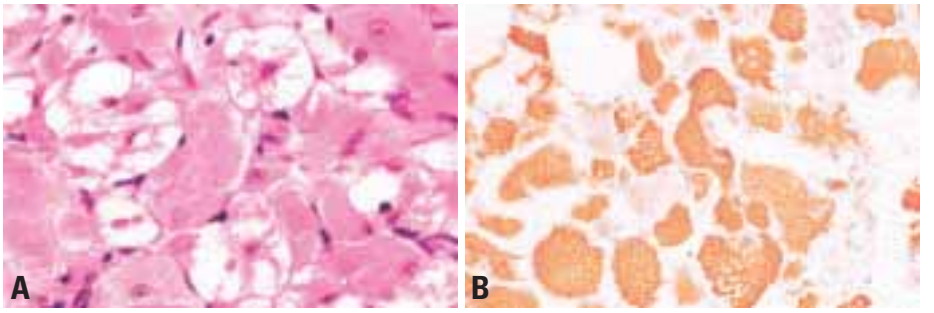

Fig. 6.02 Adult rhabdomyoma. **A** Vesicular nuclei and prominent round nucleoli are the hallmark of "spider" cells. **B** Cytoplasmic immunopositivity for myoglobin.

excision {1065}. A-RM may recur after many years or on more than one occasion, but lacks aggressive behaviour or malignant potential.

Fetal rhabdomyoma

Definition

Fetal rhabdomyoma (F-RM) is a rare benign mesenchymal tumour that exhibits immature skeletal muscle differentiation and a predilection for the head and neck.

ICD-O code 8903/0

Sites of involvement

More than 90% of F-RM occur in the soft tissue or mucosal sites of the head and neck although, rarely, other sites may be involved {409,485,1064,1620}. "Classic" F-RM has a predilection for the postauricular soft tissue {485,1064}, and those with "intermediate" differentiation tend to occur in soft tissue of face or in mucosal sites, but both subtypes may occur at any site in head and neck {1064}.

Clinical features

The median age is 4 years (range, 3 days-58 years) with a 2.4:1 male predominance {1064}. In one study, 10/24 cases (42%) were <1 year old, 6 (25%) were congenital, and 11 (46%) occurred in patients >15 years of age.

The median size is 3.0 cm (range 1-12.5 cm). F-RM presents as a well defined solitary mass involving soft tissue or mucosa (median duration 8 months, range 3 days to 19 years) {1064}. Some cases are associated with naevoid basal cell syndrome.

Macroscopy

F-RM presents as a solitary, circumscribed, soft, gray-white to tan-pink mass with a glistening cut surface. In mucosal sites F-RM is polypoid.

Histopathology

F-RM is circumscribed but unencapsulated. "Classic" immature F-RM is composed of bland primitive spindled cells associated with delicate fetal myotubules haphazardly arranged in abundant myxoid stroma. "Intermediate" F-RM (also referred to as "juvenile" or "cellular") displays a wider spectrum of differentiation or more advanced maturation between that of the "classic" F-RM and A-RM {485, 515, 1064, 1155, 1620}. Interlacing large strap-like striated muscle cells, broad fascicles of delicate spindled rhabdomyoblasts simulating a smooth muscle tumour, or ganglion-like rhabdomyoblasts may be seen {1064}. Nuclear atypia and necrosis are absent in F-RM. Mitoses are usually absent, but in one study 5/24 F-RM had had 1-14 mitoses/50HPF {1064}. The relationship of the latter cases to well differentiated embryonal rhabdomyosarcoma is unclear. Lack of prominent nuclear atypia is the most important criterion separating F-RM from rhabdomyosarcoma {1064}.

Immunophenotype

A skeletal muscle immunophenotype is demonstrated in all cases, with strong positivity for MSA, myoglobin and

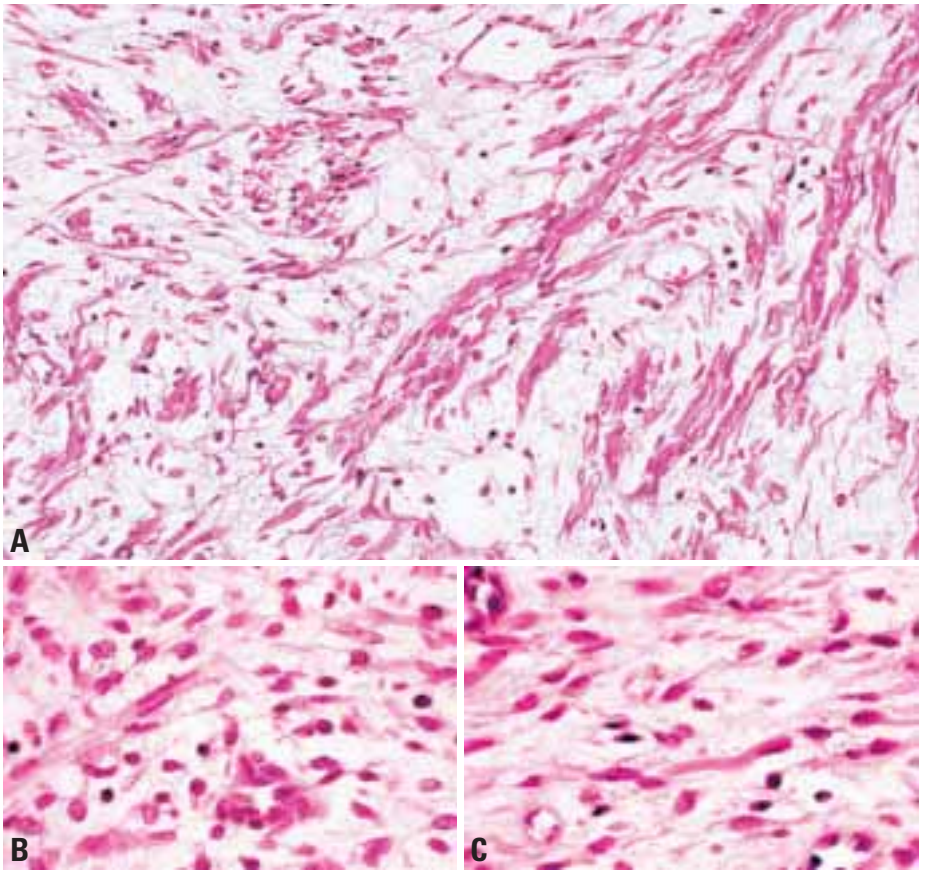

Fig. 6.03 Classic fetal rhabdomyoma. **A** Tumour is composed of cytologically bland, delicate fetal myotubules. **B** Primitive spindle cells in a myxoid stroma. **C** Occasional delicate rhabdomyoblasts display cross striations.

desmin {1064}. Focal reactivity may also be noted for SMA, S100 protein, GFAP, and vimentin {1064}. Vimentin staining is variable and often weak. Cytokeratin, CD68, and EMA are negative {1064}.

Ultrastructure
Electron microscopy demonstrates thick and thin myofilaments with Z-bands and glycogen within cytoplasm of immature rhabdomyoblasts {485}.

Genetic susceptibility
Multiple cases of fetal rhabdomyoma have been reported in patients with nevoid basal cell carcinoma syndrome {818}. This syndrome is caused by mutations in the tumour suppressor gene *PTCH* {524,866,1043}. *PTCH* encodes an inhibitory receptor in the sonic hedgehog signaling pathway, and germline mutations often lead to protein truncation and functional inactivation {2264}. Though rhabdomyomas have not been specifically examined, the wild-type allele is often eliminated by an allelic loss mechanism in other tumours found in this syndrome {755}.

Prognostic factors
Complete excision of the mass is the recommended treatment. In one study, follow-up available in 15 cases (median duration 49 months, range 2 months-52 years) showed local recurrence in only 1 case, at 3 months after excision, probably due to incomplete excision {1064}. None of the tumours metastasized.

Genital rhabdomyoma

Definition
Genital rhabdomyoma (G-RM) is a rare benign mesenchymal tumour with an advanced degree of skeletal muscle differentiation and a predilection for the vagina, almost exclusively in middle-aged women.

ICD-O code 8905/0

Sites of involvement
Most cases present as polyps in the vagina, vulva or cervix {322,750,803, 1066,1240,1283,2049}. Rare G-RM have been described in males in the paratesticular region or epididymis {2085, 2225}.

Clinical features
The mean age is 42 years (range 30-48 years) {1066}. The mass may be asymptomatic or known to be present for 4-5 years {1066}. Vaginal RM is a well defined, solitary mass with the clinical appearance of a benign vaginal polyp.

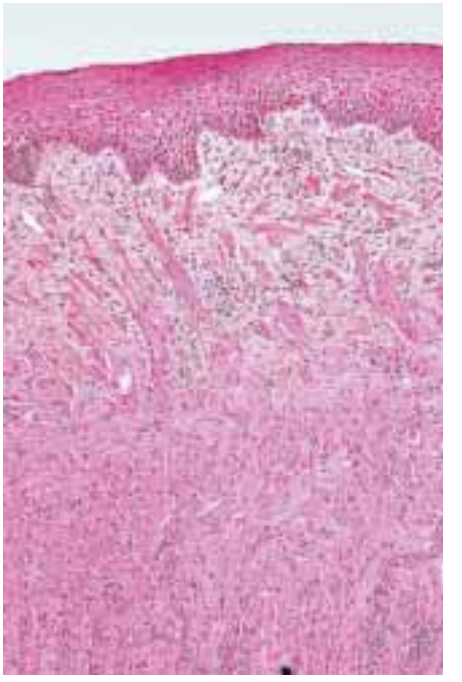

Fig. 6.05 Intermediate fetal rhabdomyoma. Submucosal mass shows broad strap-like rhabdomyoblasts with abundant eosinophilic cytoplasm.

Macroscopy
The polypoid vaginal mass (median size 2 cm, range 1-3 cm) is covered by smooth mucosa. A pedicle (0.6-1.5 cm long) is seen in some cases.

Histopathology
The polypoid unencapsulated mass is composed of a haphazard arrangement of bland, interlacing, broad strap-like or round striated muscle cells embedded in a fibrous stroma containing dilated vascular channels {1066}. The cells have abundant eosinophilic glycogen-rich cytoplasm that displays uniform advanced maturation with cross striations and longitudinal myofibrils seen in many cells. One (or more) uniform, centrally located round vesicular nucleus contains prominent round nucleoli. Vaginal RM lacks the vacuolated "spider" cells seen in A-RM, and the prominent myxoid stroma and primitive spindle cells or delicate fetal-type rhabdomyoblasts seen in "classic" F-RM. They show more rhabdomyoblastic maturation than the "classic" F-RM and are analogous to some "intermediate" mucosal F-

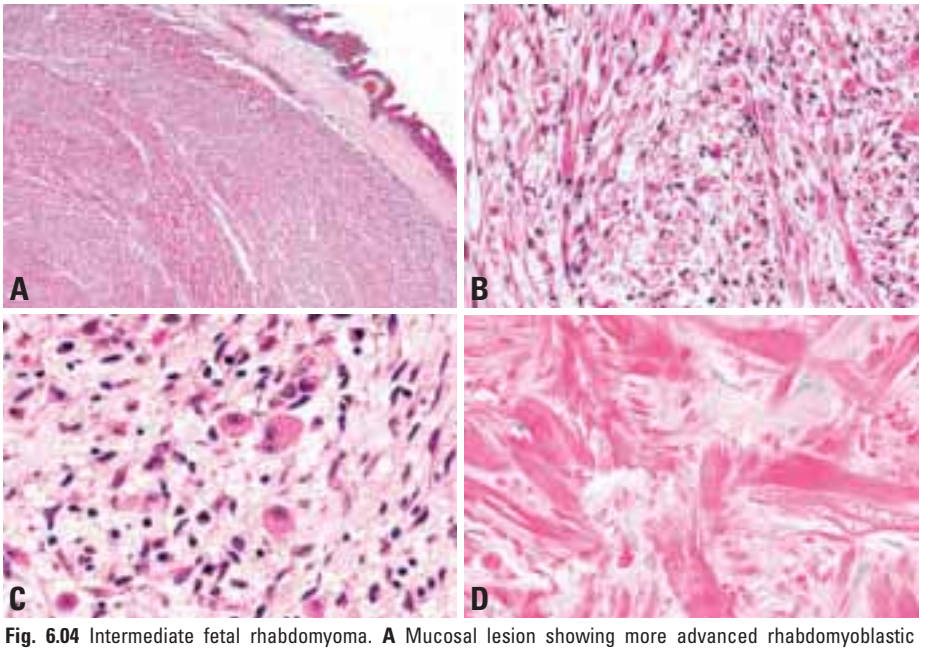

Fig. 6.04 Intermediate fetal rhabdomyoma. **A** Mucosal lesion showing more advanced rhabdomyoblastic maturation than the "classic" type. **B** Fascicles of spindled rhabdomyoblasts simulating smooth muscle cells. **C** Note round ganglion cell-like rhabdomyoblasts. **D** Cytoplasmic cross striations are highlighted by Masson trichrome stain.

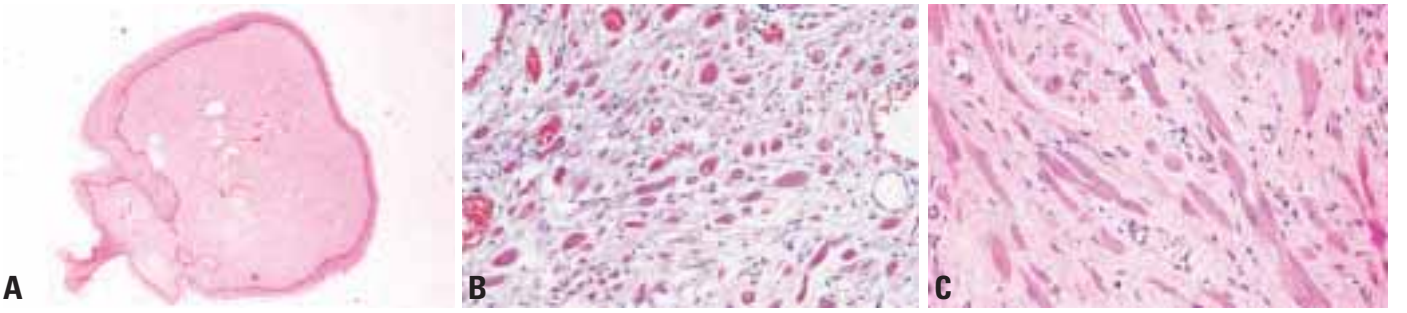

Fig. 6.06 Vaginal rhabdomyoma. **A** Whole mount shows a polypoid configuration and a fibrous stroma. **B** Medium magnification displays fibrous stroma with dilated vessels and round or strap-like rhabdomyoblasts with abundant eosinophilic cytoplasm. **C** Cellular details of rhabdomyoblasts.

RM of the head and neck. However, they lack the more variable cellular morphology and architecture of head and neck "intermediate" F-RM {1066}.

Immunophenotype

The skeletal muscle differentiation of G-RM is confirmed in all cases on immunohistochemical stains which show diffuse cytoplasmic positivity for MSA, myoglobin and desmin {1066, 1283, 2049, 2085, 2225}. The SMA, vimentin, cytokeratin, S-100, GFAP, Leu 7, EMA and CD 68 stains are negative {1066}.

Ultrastructure

Electron microscopy confirms the striated muscle origin of the striated rhabdomyoblasts in G-RM {803,1240, 2085}.

Prognostic factors

Local excision is adequate treatment. Follow-up available in four vaginal RM in one study (median duration 11 years, range 2 to 20 years) revealed no recurrence after excision and no evidence of tumour at other sites {1066}. G-RM lacks aggressive behaviour or any malignant potential.

Embryonal rhabdomyosarcoma

D.M. Parham
F.G. Barr

Definition

A primitive, malignant soft tissue sarcoma that recapitulates the phenotypic and biological features of embryonic skeletal muscle. The term embryonal rhabdomyosarcoma encompasses the spindle cell, botryoid, and anaplastic variants.

ICD-O codes

Embryonal rhabdomyosarcoma	8910/3
Spindle cell rhabdomyosarcoma	8912/3
Botryoid rhabdomyosarcoma	8910/3
Anaplastic rhabdomyosarcoma	8910/3

Synonyms

Myosarcoma, malignant rhabdomyoma, rhabdomyosarcoma, rhabdopoietic sarcoma, rhabdosarcoma, embryonal sarcoma.

Epidemiology

Rhabdomyosarcomas comprise the single largest category of soft tissue sarcomas in children and adolescents, occurring in 4.6/million U.S. children <15 years of age {860}. Embryonal rhabdomyosarcomas constitute the most common subtype of rhabdomyosarcoma, occurring in 3.0/million U.S. children <15 years of age {860}. Children less than ten years of ages are typically affected; among patients <15 years of age, only 17% of embryonal rhabdomyosarcoma arise in adolescents {860}. The greatest proportion (46%) of embryonal rhabdomyosarcomas occur in children less than 5 years of age. Five per cent of rhabdomyosarcomas affect infants {1746}, and a few are congenital {1011}. Embryonal rhabdomyosarcoma also constitutes important histological variant in adults {610, 910}, albeit such cases are rare.

In the U.S., embryonal rhabdomyosarcomas show a slight male:female predominance (1.2:1) {860}. Seventy per cent of U.S. rhabdomyosarcomas occur in non-Hispanic whites, compared to 14% in African-Americans, 10% in Hispanics, and 4.5% in Asians {846}, and incidence rates are higher in whites {1664}. Incidence figures in Europe resemble those in the U.S., with a similar male excess, whereas incidence rates appear somewhat lower in eastern and southern Asia {1664}.

Sites of involvement

Although embryonal rhabdomyosarcomas contain cells that are histologically identical to developing striated muscle, less than 9% arise within the skeletal musculature of the extremities. The greatest proportion occur within head and neck (about 47%), followed by the genitourinary system (about 28%) {1550}. Common locations in the genitourinary tract include the urinary bladder, prostate, and paratesticular soft tissues. Typical sites of origin in the head and neck include the soft tissues intrinsic to or surrounding the orbit and eyelid, oropharynx, parotid, auditory canal and middle ear, pterygoid fossa, nasopharynx, nasal passages and paranasal sinuses, tongue, and cheek. Besides these two general regions, embryonal rhabdomyosarcomas occur in the biliary tract, retroperitoneum, pelvis, perineum, and abdomen and have been reported in various visceral organs, such as the liver, kidney, heart, and lungs. Embryonal rhabdomyosarcomas may involve the soft tissues of the trunk and appendicular skeleton but much less frequently than alveolar rhabdomyosarcomas (see below). Primary origin in the skin also rarely occurs.

Spindle cell and botryoid variants of rhabdomyosarcoma involve a relatively limited repertoire of organs. Spindle cell rhabdomyosarcomas most commonly arise in the scrotal soft tissues, with the remainder mostly involving head and neck regions {316}. Spindle cell rhabdomyosarcoma also occurs in adults, usually in non-paratesticular locations {1818}. By definition, botryoid rhabdomyosarcomas must arise beneath a mucosal epithelial surface, limiting it to organs such as the urinary bladder, biliary tract, pharynx, conjunctiva, or auditory canal.

Clinical features

Coincident with the diversity of their anatomic origins, embryonal rhabdomyosarcomas produce a variety of clinical symptoms, generally related to mass effects and obstruction {1829}.

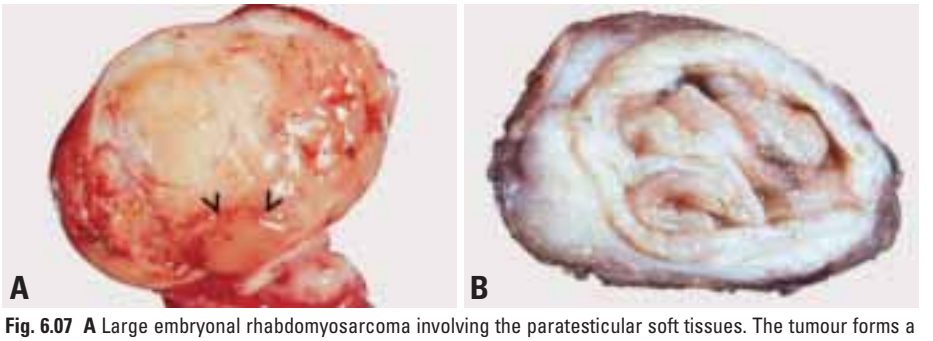

Fig. 6.07 **A** Large embryonal rhabdomyosarcoma involving the paratesticular soft tissues. The tumour forms a fleshy, pale tan mass with compression of the adjacent testis (arrows). **B** Botryoid rhabdomyosarcoma presenting as polypoid mucosal excrescences, obliterating the lumen of the gall bladder.

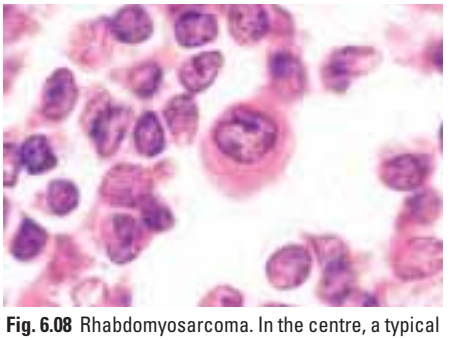

Fig. 6.08 Rhabdomyosarcoma. In the centre, a typical rhabdomyoblast, with an eccentric oval nucleus, central nucleolus, and eosinophilic cytoplasm.

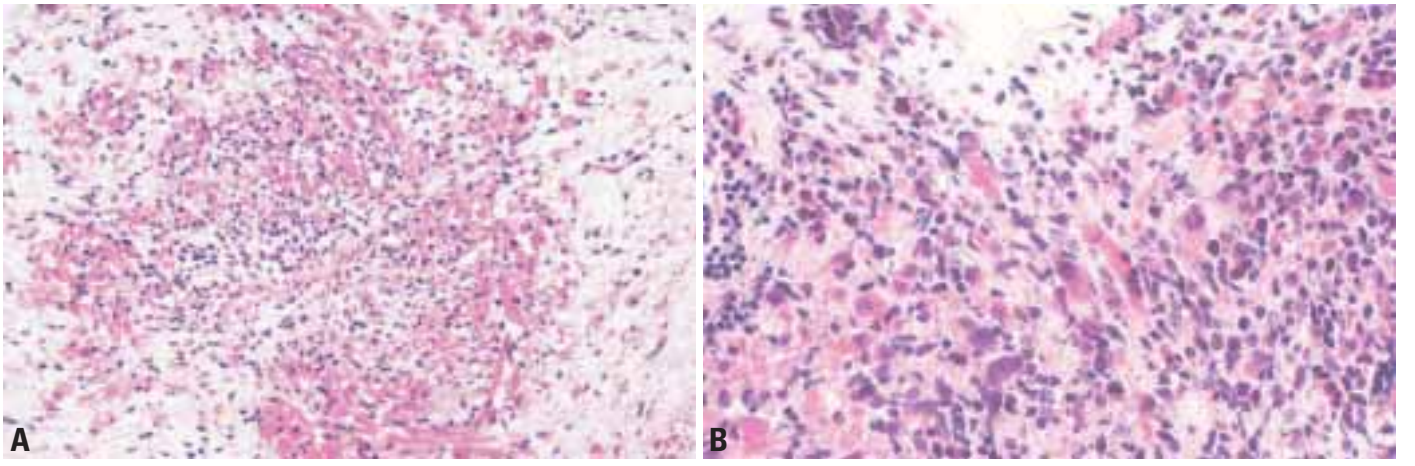

Fig. 6.09 Embryonal rhabdomyosarcoma. **A** Numerous rhabdomyoblasts with brightly eosinophilic cytoplasm and occasional multinucleated strap cells. **B** A compact area with rhabdomyoblastic differentiation adjacent to an area with loose, mucoid stroma.

Hence, head and neck lesions can cause proptosis, diplopia, sinusitis, or unilateral deafness, depending on their location. Similarly, genitourinary lesions may produce a scrotal mass or urinary retention, and biliary tumours may cause jaundice. Otherwise, the symptoms are generally those of a rapidly growing soft tissue mass.

Imaging studies are primarily used in delineating the extent of lesions for staging and prior to definitive surgery. Computed tomography and magnetic resonance imaging are most useful for these purposes, although ultrasonography can be used as a screening modality. Images generally recapitulate those of an expansile soft tissue mass in various organs, with heterogenous signals reflecting the variable vascularity, myxoid stroma, and necrosis. Of particular note is the striking appearance of botryoid lesions, which create a cluster of tumour nodules of variable size, typically within hollow viscera such as the urinary bladder or gall bladder.

Aetiology

Embryonal rhabdomyosarcomas may result from sporadic or inherited mutations, as discussed below. Generally this occurs as a variation of the Knudson-Strong two-hit hypothesis, which theoretically may involve loss of heterozygosity or aberrant gene methylation as well as DNA mutations. Malignant transformation of rhabdomyomas very rarely causes rhabdomyosarcoma. Carcinogens causing rhabdomyosarcomas in humans have not been identified but have been found in studies of mice {2124} and zebrafish {2012}.

Macroscopy

Like most primitive pediatric neoplasms, embryonal rhabdomyosarcomas form poorly circumscribed, fleshy, pale tan masses that directly impinge upon neighbouring structures. Spindle cell and botryoid variants display additional distinctive features. Spindle cell rhabdomyosarcomas, like other spindle cell lesions, form firm, fibrous tumours with tan-yellow, whorled cut surfaces. Botryoid tumours, as the name implies, have a characteristic polypoid appearance with clusters of small, sessile or pendunculated nodules that abut an epithelial surface.

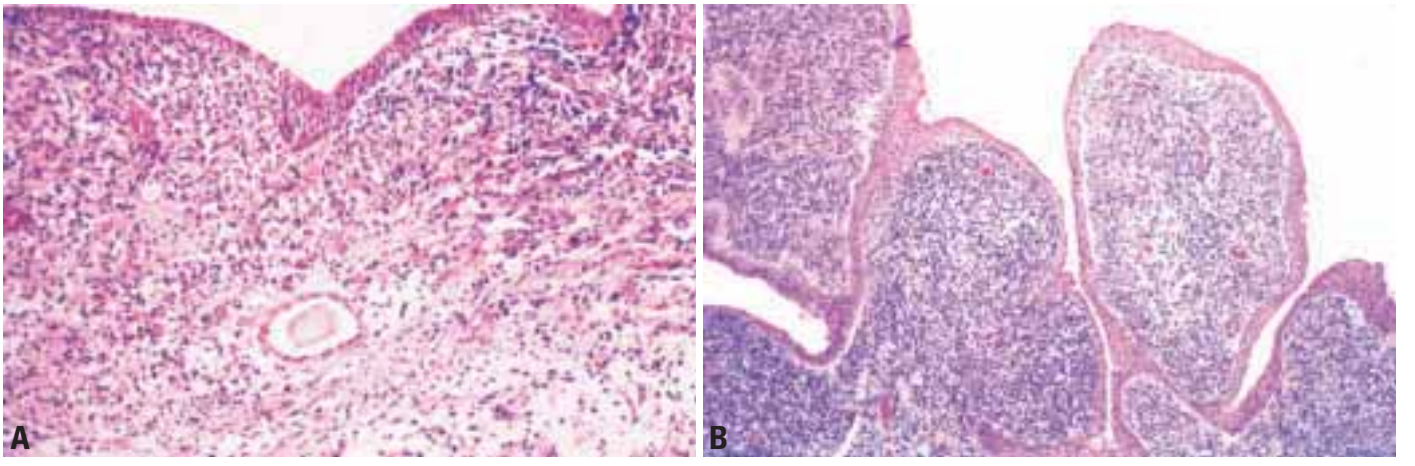

Fig. 6.10 Botryoid rhabdomyosarcoma. **A** A dense layer of tumour cells abuts an epithelial surface and forms a cambium layer. **B** Squamous epithelium outlines polypoid masses of tumour cells.

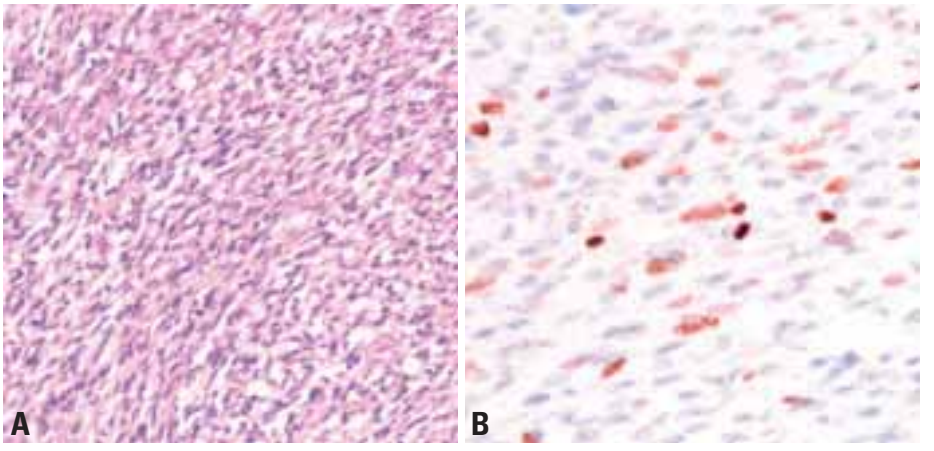

Fig. 6.11 Spindle cell rhabdomyosarcoma. **A** The fascicular architecture of this paratesticular tumour may readily be mistaken for other forms of spindle cell sarcoma. **B** Some tumour cells show nuclear immunopositivity for myf-4 (myogenin).

Histopathology

Analogous to embryonic skeletal muscle, embryonal rhabdomyosarcomas are composed of primitive mesenchymal cells in various stages of myogenesis, i.e. rhabdomyoblasts. Stellate cells with lightly amphophilic cytoplasm and central, oval nuclei represent the most primitive end of this spectrum. As these cells differentiate, they progressively acquire more cytoplasmic eosinophilia and elongate shapes, manifested in descriptive terms such as "tadpole", "strap", and "spider" cell. Bright eosinophilia, cytoplasmic cross striations, and multinucleation indicate terminal differentiation, and myotube forms may be evident. Differentiation tends to be more evident following chemotherapy, as differentiated elements become the predominant cell population, separated by therapy-induced necrosis and fibrosis {379}.

The histological architecture of embryonal rhabdomyosarcoma also resembles embryonic muscle, which forms aggregates of myoblasts amid loose, myxoid mesodermal tissues {1549}. Similarly, alternating areas of dense, compact cellularity and loose, myxoid tissues constitute embryonal rhabdomyosarcomas. The amount of loose and dense cellularity varies from case to case: an abundant, mucoid stroma containing scattered rhabdomyoblasts and resembling myxomas predominates in some examples, and compact aggregates of densely arrayed spindle cells form other tumours.

The botryoid variant of embryonal rhabdomyosarcoma contains linear aggregates of tumour cells that tightly abut an epithelial surface. This feature, known as a "cambium layer", typifies these tumours. Botryoid rhabdomyosarcomas also contain variable numbers of polypoid nodules, often with an abundant, loose, myxoid stroma that can appear deceptively benign.

Densely arrayed whorls or fascicles of spindle cells constitute the spindle cell variant of embryonal rhabdomyosarcoma. These spindle cells often resemble smooth muscle cells, with blunted central nuclei and tapered ends, but cytoplasmic cross striations, if present, and/or bright eosinophilia indicate striated muscle differentiation, which should be confirmed by immunohistochemistry. Spindle cell rhabdomyosarcomas may have a storiform architecture similar to fibrous histiocytoma or a wavy character like neurofibroma.

The presence of enlarged, atypical cells with hyperchromatic nuclei defines the anaplastic variant of rhabdomyosarcoma {1149}. This feature may be seen in both embryonal and alveolar tumours but is more prevalent in the former. Bizarre, multipolar mitoses are also often present. Anaplastic features can be focal or diffuse. Focal anaplasia indicates the presence of only single, dispersed anaplastic cells, whereas diffuse anaplasia indicates the presence of clone-like clusters of anaplastic cells.

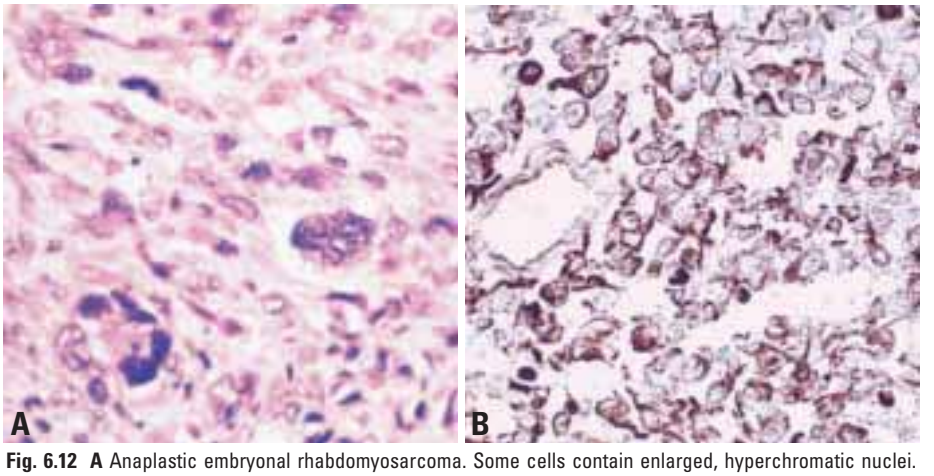

Fig. 6.12 **A** Anaplastic embryonal rhabdomyosarcoma. Some cells contain enlarged, hyperchromatic nuclei. **B** Desmin stain of rhabdomyosarcoma. Scattered tumour cells contain strongly positive cytoplasmic tails.

Immunophenotype

Markers of skeletal muscle differentiation typify embryonal rhabdomyosarcomas {1653}. The presence of these markers correlates with the degree of tumour cell differentiation, as it does in embryogenesis. Thus, only vimentin is present in the cytoplasm of the most primitive cells, and desmin and actin are acquired by developing rhabdomyoblasts. Differentiated cells exhibit myoglobin, myosin, and creatine kinase M, markers that correspond to terminal differentiation. A variety of less commonly used muscle markers, such as titin, dystrophin, and acetylcholine receptor antigens alsocharacterize rhabdomyosarcomas. Muscle markers such as desmin and muscle-specific actin (HHF-35) are shared by cells with a myogenic phenotype, including smooth muscle, cardiac muscle, myofibroblasts, myoepithelial cells, pericytes, and some mesothelial cells.

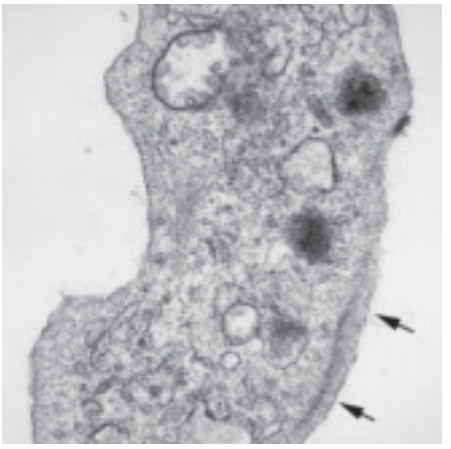

Fig. 6.13 Electron micrograph of an uncommitted mesenchymal cell in rhabdomyosarcoma. There are no features of myoblastic differentiation. Note the subplasmalemmal microfilaments (arrows).

Antibodies against MyoD1 and myogenin are highly specific and sensitive for rhabdomyosarcoma and are currently used as standard antibodies for diagnosis {321}. However, one must note that only nuclear staining is specific and that non-specific cytoplasmic MyoD positivity is common in heat-retrieved, paraffin-embedded tissues {2214}.

Occasional aberrant staining with a variety of immunohistochemical markers has been noted. Aberrantly expressed markers include cytokeratin, S100 protein, neurofilaments, and B cell proteins such as CD20 and immunoglobulins {384, 1450, 1709}. Smooth muscle actin and neuron-specific enolase staining occurs more frequently (in 10% and 30% of rhabdomyosarcomas, respectively) {1652, 1653}.

Ultrastructure

Rhabdomyosarcomas exhibit a range of ultrastructural characteristics corresponding to those of developing striated muscle, primarily bundles of 5 and 15 nm thick and thin filaments punctuated by abortive Z-bands. Parallel arrays of 15 nm filaments and ribosomes (myosin-ribosome complexes) comprise the earliest diagnostic stage {609}. Earlier cells show non-specific features of primitive mesenchyme, such as discontinuous basal lamina, phagocytosed collagen, and ergastoplasm {520}. These uncommitted cells may contain lipid or subplasmalemmal microfilaments. Leptomeric fibrils may be seen on occasion.

Genetics

Molecular analyses of polymorphic loci revealed allelic loss in chromosomal region 11p15 in most embryonal rhabdomyosarcomas {1160,1915}. The finding of growth suppression when chromosomal fragments containing the 11p15 region were introduced into embryonal rhabdomyosarcoma cells further supports the premise that there is a tumour suppressor gene within this region {1152,1278}. Furthermore, inherited alterations of the 11p15 region occur in Beckwith-Wiedemann syndrome {1251}, a heterogeneous overgrowth syndrome with an increased risk for development of several cancers, including embryonal rhabdomyosarcoma. Expression studies have indicated that several 11p15 genes, such as *IGF2*, *H19*, and *CDKN1C*, are expressed from one of the two alleles in a parent-of-origin specific process termed imprinting. These combined findings suggest a model in which an imprinted tumour suppressor gene is inactivated during embryonal rhabdomyosarcoma tumourigenesis by allelic loss of the active allele and retention of the inactive allele.

Cytogenetic studies of embryonal rhabdomyosarcoma have found complex structural and numerical chromosomal changes, often including extra copies of chromosomes 2, 8, and 13 {816, 2210}. Rearrangements of the 1p11-q11 and 12q13 regions have also been noted in a fraction of cases. Subsequent comparative genomic hybridization analyses of genome-wide copy number changes confirmed chromosomal gains and identified several regions of loss, such as chromosome 16, in embryonal rhabdomyosarcoma subsets {260, 2223}. These analyses also indicated that genomic amplification was generally rare in embryonal rhabdomyosarcoma, except for its subset with anaplastic features {259}. Finally, directed analyses of known oncogenes and suppressor genes identified inactivating mutations of *TP53* {648} and *CDKN2A* {1009} and activating mutations of *RAS* family genes in subsets of embryonal rhabdomyosarcoma {2041}. These various genetic alterations may indicate variable collaborating events that occur during embryonal rhabdomyosarcoma tumourigenesis.

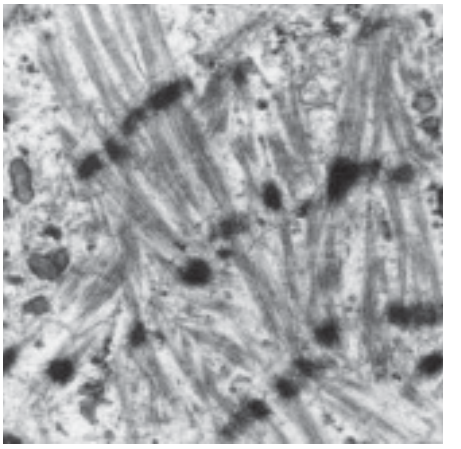

Fig. 6.14 Electron microscopic appearance of embryonal rhabdomyosarcoma showing well-formed Z-bands.

Prognostic factors

Prognosis can be determined by stage, histological classification, age, and site of origin. Staging is accomplished by clinical evaluation (IRSG Stage) or surgicopathological evaluation (IRSG Group) {1755}. Younger patients tend to have a more favourable prognosis. Histological classification in paediatric patients predicts outcome independent of age, stage, and location, with embryonal tumours having a better prognosis than alveolar tumours {1755}. Spindle cell and botryoid variants have a superior outcome as a group. However, the rare spindle cell lesions in adults are more aggressive {1818} and, in fact, histological subtype in adults with rhabdomyosarcoma appears to have no prognostic relevance. Embryonal rhabdomyosarcomas with diffuse anaplasia may have a worse outcome than the other subsets of embryonal rhabdomyosarcoma {1149}. Parameningeal and extremity tumours tend to have a bad outcome compared to other locations, whereas orbital and paratesticular tumours tend to have a better one.

Tumour cell ploidy predicts outcome in some reports, with hyperdiploid embryonal rhabdomyosarcomas having a better outcome. However, this phenomenon has not been universally confirmed and does not appear to be an independent variable {478,1107,1928}.

Alveolar rhabdomyosarcoma

D.M. Parham
F.G. Barr

Definition
Alveolar rhabdomyosarcoma is a primitive, malignant, round cell neoplasm that cytologically resembles lymphoma and which shows partial skeletal muscle differentiation.

ICD-O code 8920/3

Synonyms
Rhabdomyoblastoma, rhabdomyopoietic sarcoma, monomorphous round cell rhabdomyosarcoma.

Epidemiology
Alveolar rhabdomyosarcomas occur at all ages, but they do not show a predilection for younger children and more often occur in adolescents and young adults; very rare cases may be congenital. The median ages of affected patients was 6.8 and 9.0 years in reports from the International Society of Pediatric Oncology (SIOP) {291}, and the Intergroup Rhabdomyosarcoma Study (IRS) {1550}. They occur less frequently than embryonal rhabdomyosarcomas (21% of rhabdomyosarcomas in the IRS report; 19% in the SIOP report). The male:female ratio is approximately even. No geographic or racial predilection is reported.

Sites of involvement
Alveolar rhabdomyosarcomas commonly arise in the extremities, where 39% were reported in the the Kiel Paediatric Tumour registry {887}. The Armed Forces Institute of Pathology series indicates that there is no favoured site of origin {596}. Additional sites of involvement include the paraspinal and the perineal regions and the paranasal sinuses. Mixed embryonal/alveolar tumours may arise in areas favoured by embryonal rhabdomyosarcomas, such as the urogenital tract and orbit, but generally these are unusual sites of origin {887}.

Clinical features
Alveolar rhabdomyosarcomas typically present as rapidly growing extremity masses. Paranasal lesions may present with proptosis or cranial nerve deficits. Perirectal tumours can cause constipation. Paraspinal lesions can cause nerve root abnormalities, such as paresthesia, hypesthesia, or paresis. Imaging is best accomplished by nuclear magnetic resonance, which reveals an infiltrative, expansile, soft tissue mass. Rare tumours present as disseminated lesions with no obvious primary and resemble leukaemia {613}.
Alveolar rhabdomyosarcomas tend to be high stage lesions at presentation {1158, 1756}.

Fig. 6.15 Nuclear magnetic image of a cranial alveolar rhabdomyosarcoma. The expansile lesion destroys the nasal and paranasal bone and extends into the orbit and parameningeal tissues (arrows).

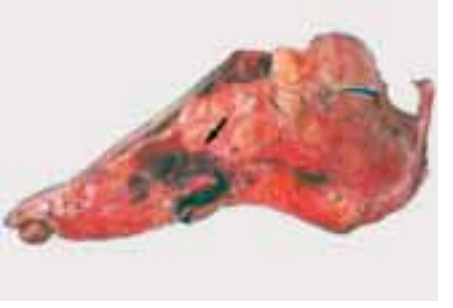

Fig. 6.16 Sagittal section of foot containing alveolar rhabdomyoasarcoma. An infiltrative, haemorrhagic mass arises in the soft tissue of the plantar and metatarsal soft tissues (arrows).

Macroscopy
Alveolar rhabdomyosarcomas form expansile, rapidly growing soft tissue tumours with a fleshy, grey tan quality. They contain variable amounts of fibrous tissue.

Histopathology
Three major histological subtypes comprise alveolar rhabdomyosarcoma: those with typical features, those with a solid pattern, and those with mixed embryonal and alveolar features {1549}. All alveolar rhabdomyosarcomas exhibit round cell cytological features reminiscent of lymphomas but with primitive myoblastic differentiation. Morphologic features vary, depending on the presence or absence of fibrous stroma and embryonal histology. Typical alveolar rhabdomyosarcomas produce fibrovascular septa that separate the tumour cells into discrete nests. These nests contain central clusters of cells with loss of cohesion around the periphery. Tumour cells align the septa in a picket fence pattern. Giant cells with rhabdomyoblastic differentiation are common. Occasional cases show clear cell morphology and may mimic clear cell carcinoma or liposarcoma.
Solid variant alveolar rhabdomyosarcomas lack the fibrovascular stroma and form sheets of round cells with variable rhabdomyoblastic differentiation (often little). Occasional small nests may be seen, particularly with larger samples. The cytologic features do not differ from typical lesions {2138}.
Mixed embryonal / alveolar rhadomyosarcomas contain foci with embryonal histology, i.e., myxoid stroma and spindle cell myoblasts as well as areas with alveolar histology. The alveolar foci usually contain nests with fibrous stroma, although highly cellular solid foci resembling lymphoma may occur.

Immunophenotype
Alveolar rhabdomyosarcomas stain with antibodies against muscle proteins, as described under "Embryonal rhab-

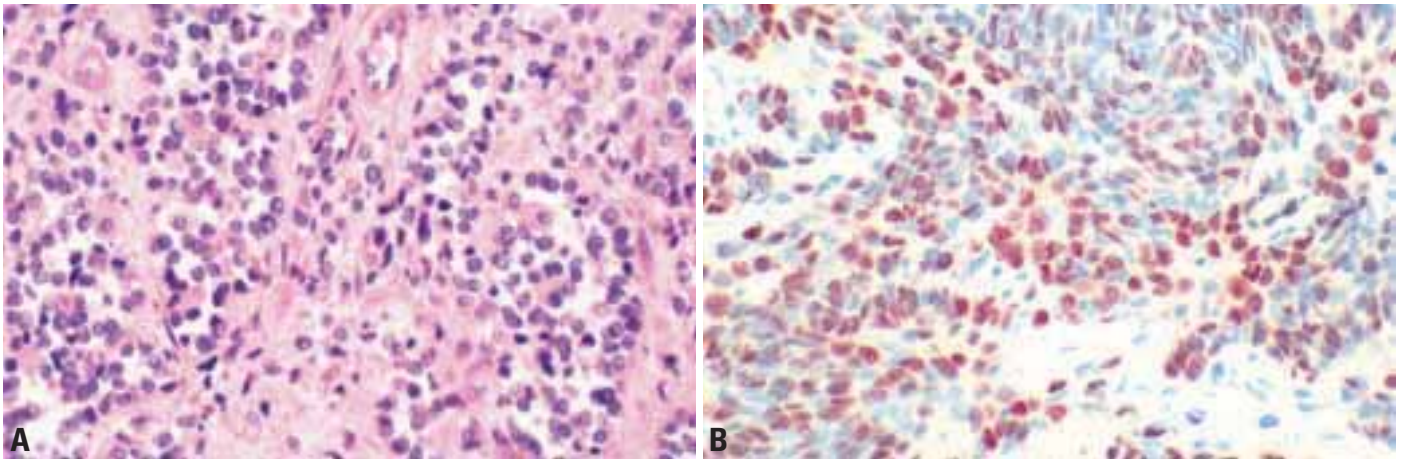

Fig. 6.17 **A** Typical alveolar rhabdomyosarcoma. Collagenous fibrovascular septa divide mixtures of undifferentiated tumour cells and rhabdomyoblasts into discrete nests. **B** Myogenin stain of alveolar rhabdomyosarcoma. Many tumour cell nuclei show strong immunopositivity.

domyosarcoma" (see above), although primitive tumours may have focal or lack positivity. MyoD-related stains, especially myogenin, typically show a diffuse, strong nuclear staining pattern {516}.

Genetics

Cytogenetic analyses demonstrated recurrent translocations that are consistently and specifically associated with alveolar rhabdomyosarcoma. A t(2;13)(q35;q14) was found in the majority of alveolar rhabdomyosarcoma cases and a t(1;13)(p36;q14) was noted in a smaller subset of cases {125}. These translocations juxtapose the *PAX3* or *PAX7* genes on chromosomes 2 and 1, respectively, with the *FKHR* gene on chromosome 13, to generate chimeric genes which encode PAX3/FKHR and PAX7/FKHR fusion proteins {127,456, 759}. PAX3 and PAX7 are related members of the paired box family of transcription factors whereas FKHR is a member of the forkhead transcription factor family. The PAX3/FKHR and PAX7/FKHR fusion products contain the PAX3/PAX7 DNA binding domain and the FKHR transcriptional activation domain, and function as potent transcriptional activators {162, 163}. In addition to this functional change, the translocations also alter the expression and subcellular localization of regulatory pathways to generate high levels of these chimeric proteins that are constitutively present in the nucleus {455, 495}. These changes maximize the ability of these chimeric proteins to activate downstream transcriptional targets, and are postulated to exert oncogenic effects by altering control of proliferation, apoptosis, and differentiation {170,605,1097,1211}

As part of an effort to find other genetic alterations that collaborate with the gene fusion events in alveolar rhabdomyosarcoma tumourigenesis, comparative genomic hybridization studies of ARMS cases identified a variety of amplification events {814}. The most frequent amplification events in alveolar rhabdomyosarcoma, each occurring in roughly one-third of cases, involve chromosomal regions 12q13-15 and 2p24. The 12q13-15 region contains many growth-related genes such as the *GLI*, *CDK4*, and *MDM2*, whereas the 2p24 region harbours the *MYCN* oncogene, which is amplified in several tumour categories, such as neuroblastoma. Other less frequent amplicons occur at chromosomal regions 13q31, 2q34-qter, 15q24-26, and 1p36. The *PAX7/FKHR* fusion gene is

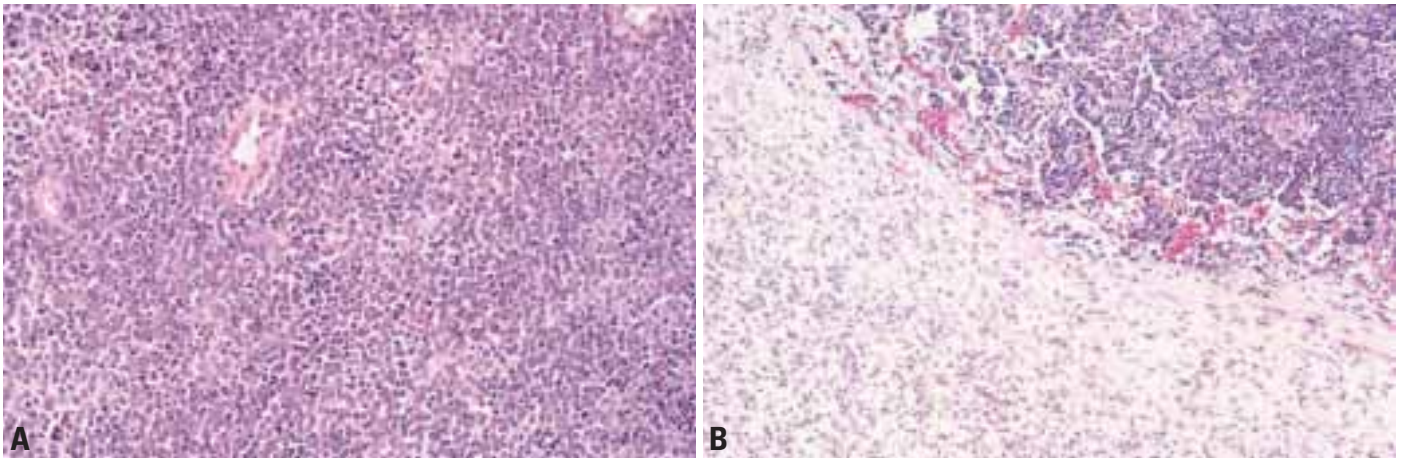

Fig. 6.18 **A** Solid variant alveolar rhabdomyosarcoma. Sheets of undifferentiated rhabdomyosarcoma cells without fibrovascular septa. Cytogenetic analysis revealed a t(2;13) translocation, characteristic of alveolar rhabdomyosarcoma. **B** Mixed alveolar-embryonal rhabdomyosarcoma. A discrete, highly cellular focus of alveolar rhabdomyosarcoma contrasts with the adjacent loose embryonal histology.

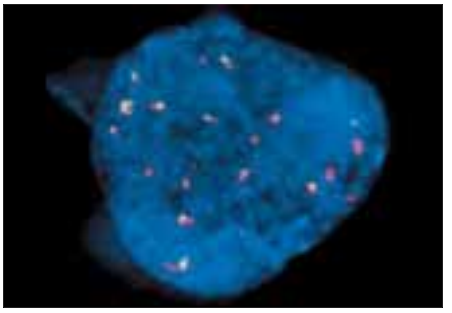

Fig. 6.19 1460 Alveolar rhabdomyosarcoma. Interphase fluorescence in situ hybridization (FISH) analysis showing amplification of the *PAX7/FKHR* fusion gene (juxtaposed red and green signals) by 1;13 translocation breakpoint-flanking probes.

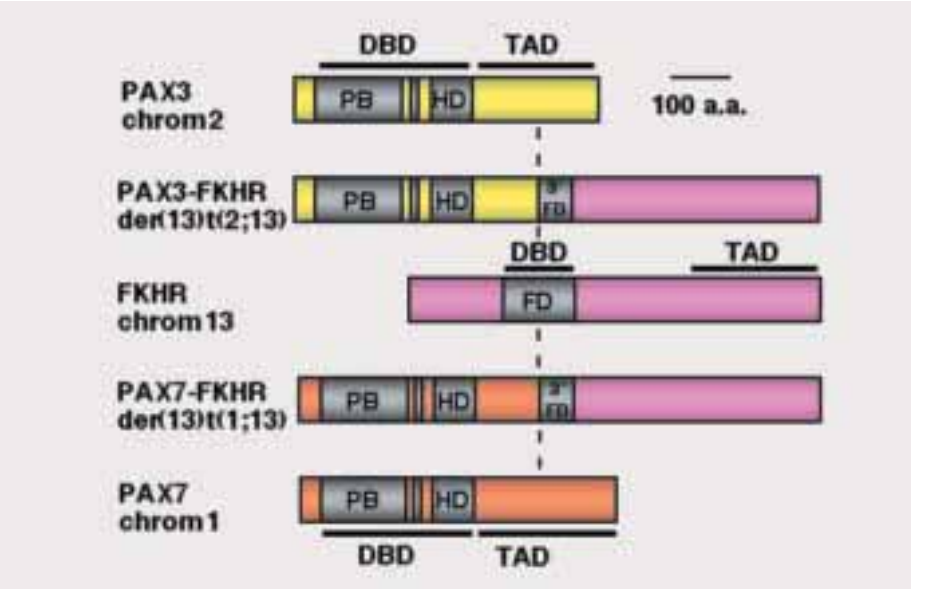

Fig. 6.20 Wild-type and fusion products associated with the 2;13 and 1;13 translocations. The paired box, octapeptide, homeobox and fork head domain are shown as grey boxes. Transcriptional domains (DNA binding domain - DBD, transcriptional activiation domain - TAD) are indicated as solid horizontal bars. The translocation fusion point is shown as a vertical dashed line.

amplified in the majority of ARMS cases with the 1;13 translocation in contrast to the less frequent amplification of the *PAX3/FKHR* fusion in alveolar rhabdomyosarcoma with the 2;13 translocation {128}.

The subset of alveolar rhabdomyosarcomas not displaying a typical *PAX/FKHR* gene fusion is genetically heterogeneous, with some cases showing alternative fusions with other genes or unusual fusion products and some possibly being true fusion-negative cases {129}.

Prognostic factors

Alveolar rhabdomyosarcomas are high grade neoplasms that are inherently more aggressive than embryonal rhabdomyosarcomas {1755}. Surgicopathological staging (IRS grouping) is predictive of outcome. With mixed embryonal / alveolar tumours, site may also be predictive, as described under "Embryonal rhabdomyosarcoma", although, in general these mixed lesions behave the same as the alveolar subtype. Age predicts outcome of rhabdomyosarcomas in general {1200}. Preliminary data indicate that genetic fusions predict outcome, with *PAX7/FKHR* positive tumours behaving in a more benign fashion than *PAX3/FKHR* positive ones {1085}.

Pleomorphic rhabdomyosarcoma

E. Montgomery
F.G. Barr

Definition
Pleomorphic rhabdomyosarcoma is a high grade sarcoma occurring almost exclusively in adults and consisting of bizarre polygonal, round, and spindle cells which display evidence of skeletal muscle differentiation. No embryonal or alveolar component should be identified.

ICD-O code 8901/3

Epidemiology
These lesions occur almost exclusively in adults, are more common in men and present at a median age in the 6th decade {675,746,748,753,1897}.
Exceptional cases may be seen in children but their existence has been disputed {1550}.

Sites of involvement
These tumours usually occur in the deep soft tissues of the lower extremities but have been reported in a wide variety of other locations {37,389,675,746,748, 753,1149,1897}.

Clinical features
Most patients present with a rapidly-growing painful swelling {748}. On imaging, lesions are isointense to skeletal muscle on T1 weighted images and heterogeneous on T2 images. Necrotic foci are readily identifiable in many cases.

Macroscopy
Tumours are well circumscribed, usually large (5-15 cm), and often surrounded by a pseudocapsule. The cut surface is whitish and firm with variable haemorrhage and necrosis.

Histopathology
These are pleomorphic sarcomas composed of undifferentiated round to spindle cells and an admixture of polygonal cells with densely eosinophilic cytoplasm in spindle, tadpole, and racquet-like contours. Some observers have classified adult lesions into "classic" (pleomorphic rhabdomyoblasts in sheets), "round cell", and "spindle cell" patterns {748}. Cross striations are vanishingly rare. The presence of pleomorphic polygonal rhabdomyoblasts on routine hematoxylin and eosin stains coupled with immunohistochemical evidence of at least one skeletal muscle-specific marker by immunohistochemistry is required for diagnosis {675,748,753}.

Immunophenotype
Pleomorphic rhabdomyosarcomas, like other rhabdomyosarcoma types, express myoglobin, MyoD1, skeletal muscle myogenin, fast (skeletal muscle) myosin, and desmin. They variably express muscle specific actin, smooth muscle actin, and myogenin {517, 675, 746, 748, 753, 1149, 1897, 2251}. Interestingly, myoD1 and myogenin seem to show more limited positivity than in paediatric rhabdomyosarcomas. They lack epithelial markers and S100 protein.

Ultrastructure
By ultrastructure, rudimentary sarcomere formation is the key criterion. Such sarcomeres consist of Z-bands or irregular masses of Z-band material with converging thick (16nm) and thin (8nm) filaments {748, 1897}.

Genetics
Only six pleomorphic rhabdomyosarcomas with chromosome aberrations have been reported. All had highly complex karyotypes, and in none of them could a t(1;13) or t(2;13) translocation be detected {1477}.

Prognostic factors
The prognosis for these tumours is poor and reliable prognostic factors have yet to be developed. In two series with follow-up, 28/38 patients (74%) died of disease {748, 753}.

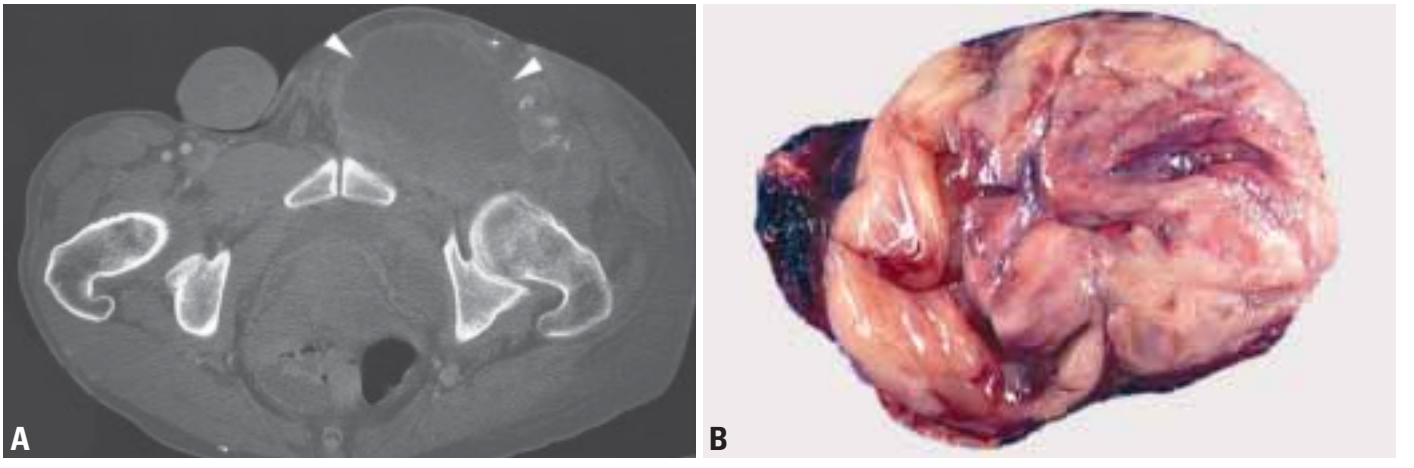

Fig. 6.21 **A** CT without contrast enhancement of a recurrent pleomorphic rhabdomyosarcoma. The tumour is similar in consistency to the adjacent skeletal muscles. **B** This mass, which displays zones of necrosis, was excised from the thigh of a 56-year-old man. The lesion extended into the pelvis and recurred quickly following the initial resection.

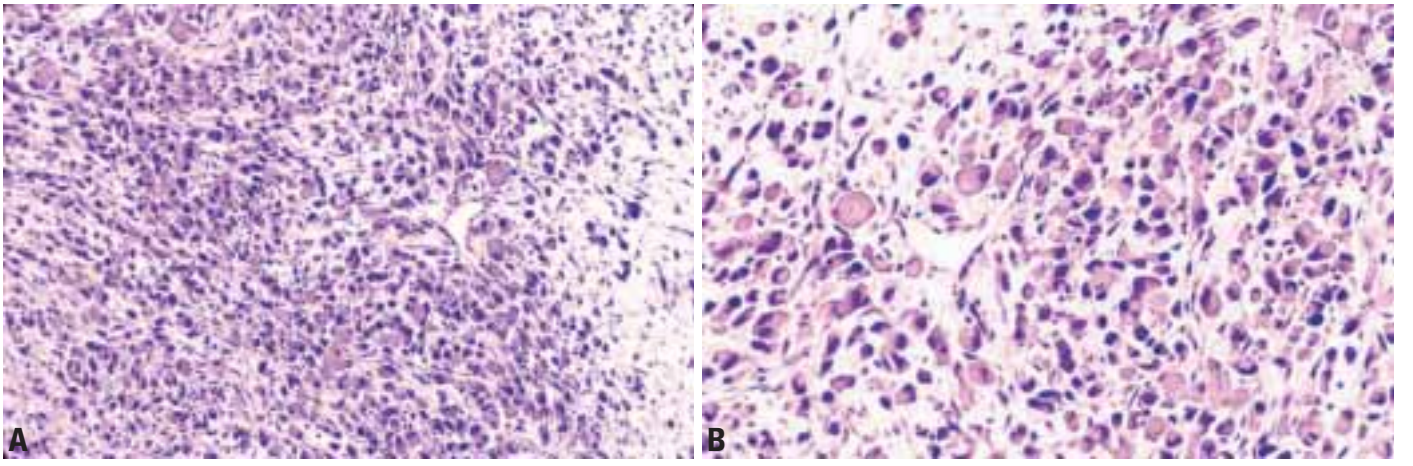

Fig. 6.22 **A** Pleomorphic rhabdomyosarcoma composed of intensely eosinophilic polygonal cells. **B** Note the wide range of cell shapes from round to tadpole-like.

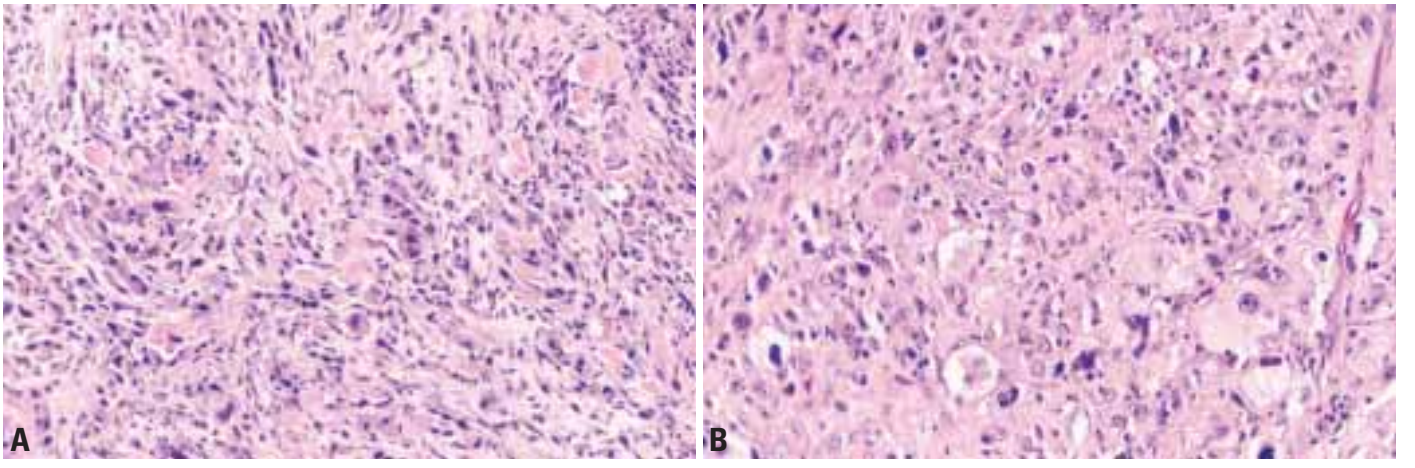

Fig. 6.23 **A** Pleomorphic rhabdomyosarcoma composed of spindled and polygonal cells. **B** Bizarre nuclei and abundant cytoplasm are seen in this example of pleomorphic rhabdomyosarcoma.

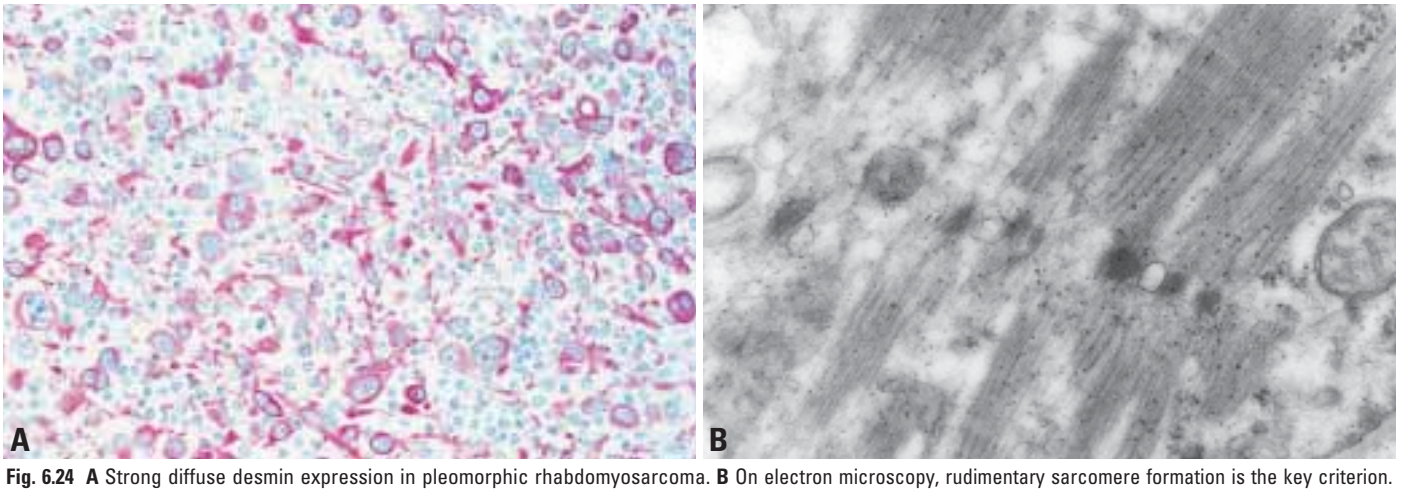

Fig. 6.24 **A** Strong diffuse desmin expression in pleomorphic rhabdomyosarcoma. **B** On electron microscopy, rudimentary sarcomere formation is the key criterion. Such sarcomeres consist of Z-bands or irregular masses of Z-band material with converging thick (16 nm) and thin (8 nm) filaments.