

AN OVERVIEW AND UPDATE on SOFT TISSUE LESIONS OF THE HEAD AND NECK

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ABSTRACT

Soft tissue lesions of the head and neck encompass a broad range of pathological entities associated with different prognoses and requiring different treatments. All pathologists will encounter a wide range of soft tissue tumours in whatever specialist area they practice. Getting the diagnosis 'right the first time' is critical for patients to be offered optimal treatment. Molecular testing can help reach the correct diagnoses and this arena is developing fast. However, pathologists should not rely unquestioningly on special tests, whether it is immunohistochemistry or whole genome sequencing as no test is entirely specific or sensitive. Pathologists should provide a diagnosis in the context of all tests including the histology along with medical imaging and the patient's symptoms, signs and family history. This article reviews key clinical, pathological and histologic features of tumours most commonly presenting in the head and neck region, including those most recently described.

Key words: Sarcoma, genetics, soft tissue, head, neck

GENERAL INTRODUCTION

Soft tissue sarcomas represent no more than 1% of all cancers but are relatively common in the head and neck region, accounting for 5–15% of all soft tissue sarcomas. Head and neck soft tissue tumours can be classified as benign, intermediate (locally aggressive), intermediate (rarely metastasising) and malignant (sarcoma). The French grading system employed for grading sarcomas, a three tier system based on differentiation, mitotic activity and necrosis. Grade 1 represents low grade disease and Grades 2 and 3 are high grade.

Patients present with painful or painless mass which may be symmetric or asymmetric. Specific symptoms depend on the site of the tumour such as neurological symptoms such as sinusitis, and nasal discharge secondary to nasal or paranasal sinus obstruction, and diplopia. The treatment of choice of any lesion discussed, unless otherwise stated, involves surgical excision with wide margins if feasible with or without adjuvant radiotherapy and chemotherapy.

Whereas CT and magnetic resonance is the main form of imaging used to assess soft tissue lesions, it does not provide sufficient detail on which to base a diagnosis; its value is largely in assessing the extend of local disease which helps to plan surgery, and delivery of radiotherapy, as well as staging disease, and surveillance.

All patients diagnosed with sarcomas should be treated in a specialist centre by a multidisciplinary team. However, as the tumours may present at any site of the body, it is not uncommon for non-specialist pathologists to see the first biopsy, and therefore a general knowledge of these tumours and how to reach a diagnosis is important.

More detailed and comprehensive information on soft tissue sarcoma can be found in the WHO Classification of soft tissue and bone tumours ¹ and Enzinger and Weiss's book on soft tissue tumors ².

MYOFIBROBLASTIC TUMOURS

The features of the myofibroblastic tumours described here below share histological features and may be difficult to distinguish. Also included in the differential diagnosis are other myo/fibroblastic lesions such as scar tissue, Gardner fibroma, giant cell fibroblastoma, inflammatory myofibroblastic tumour, dermatofibrosarcoma protuberans, and nerve sheath tumours. Consider site – superficial or deep as this can help and see Table 1 for supplementary tests ³.

FIBROMATOSIS OR DEEP FIBROMATOSIS

Definition

A locally aggressive infiltrative, non-metastasising spindle cell, myofibroblastic tumour with approximately 10% occurring in the head and neck region. It may be associated with ulceration in the oral cavity. Typically, fibromatosis presents between 15-60 years more commonly in females. There is no bias towards any geographical location, race or ethnicity.

Aetiology and pathogenesis

The cause of fibromatosis is unknown but there is evidence that hormonal changes during pregnancy, as well as when using the oral contraceptive pill may act as risk factors. The majority of cases are sporadic, but about 5-10% are associated with Familial Adenomatous Polyposis, occurring on the background of germline alterations in the tumour suppressor gene *APC*. A variant of familial adenomatous is Gardner syndrome in which osteomas and epidermoid cysts also manifest. Fibromatosis in the head and neck region is more likely to occur sporadically.

Activating mutations in the *CTNNB1* gene and alterations in the tumour suppressor *APC* gene cause excessive β -catenin levels due to reduced degradation of the protein, persistent activation of the Wnt signalling pathway and ultimately uncontrolled cellular proliferation.

Macroscopic and microscopic description

Fibromatosis is a poorly circumscribed pale white lesion which is hard when palpated. It rarely presents less than 20mm. The histological features are shown and described in Figure 1.

Diagnostic markers and differential diagnosis

Mutations in *CTNNB1* are present in virtually all sporadic cases of desmoid fibromatosis and can be extremely valuable when making a diagnosis on a small biopsy. These are mutually exclusive of *APC* mutations which are found in the familial form of the disease.

Immunoreactivity for beta-catenin is not specific.

Treatment and prognosis

Treatment is determined by the size, site and symptoms; options include ‘a watch and wait’ approach, surgical excision, radiotherapy and anti-oestrogen therapy. Patients should be treated in specialist units.

Recurrence is associated with surgery hence a ‘watch and wait’ approach is advocated in asymptomatic individuals. The condition generally has a good prognosis with the major prognostic factors being: age, tumour size and location. Younger patients tend to have the worst prognosis.

LOW GRADE MYOFIBROBLASTIC TUMOUR

Definition

A myofibroblastic tumour with an infiltrative growth pattern, of unknown cause, which rarely metastasises. It most commonly occurs in the head and neck region, with a predilection for the tongue and oral cavity regions, rarely in the salivary glands, and paranasal spaces. It occurs more commonly above the age of 60 but affects all ages with a slight bias towards males.

Pathological features, diagnostic markers and differential diagnoses

The tumour is a firm pale mass sited deep to fascia with infiltrative borders. Necrosis is not a feature. The tumour exhibits an infiltrative growth of spindle shaped myofibroblastic cells (Figure 2). The tumours can erode bone. There is no specific diagnostic marker for this tumour; it expresses smooth muscle actin; desmin is generally not expressed but occasionally may be weak and focal. Many of the tumours which share histological features with low grade myofibroblastic sarcoma can be excluded through immunohistochemistry and characteristic genetic alterations. For a list of the differential diagnoses refer to the differential diagnoses listed in the desmoid fibromatosis section.

Prognosis

A poorer prognosis is generally associated with older patients. A wide excision reduces the risk of recurrence, along with small tumour size. Metastases are rare and generally occur after a long history of the disease.

NODULAR FASCIITIS

Definition

Nodular fasciitis is a benign non-metastasising, self-limiting fibroblastic/myofibroblastic tumour. The term ‘pseudosarcomatous’ should not be used. It is characterised by a genomic structural rearrangement involving fusion of *USP6* in nearly all cases. It occurs most commonly between 20-40 years, and typically presents as a mass <3cm in diameter, with non-specific soreness. It may occur after trauma.

Pathological features, diagnostic markers and differential diagnoses

The histological features are variable and reflect the time at which the lesion is biopsied (Figure 3).

Virtually all cases of nodular fasciitis harbour a *USP6* fusion gene which can be detected by FISH. The lesional cells express smooth muscle actin which is not specific, nevertheless, immunohistochemistry plays a key role in excluding differential diagnoses - See Table 1.

Treatment and Prognosis

In many cases, nodular fasciitis can be managed conservatively and a ‘watch and wait’ approach taken as the tumour may recede fully. However, if there is any concern about a definitive diagnosis excision is advised. Metastases do not occur. Malignant transformation is exceptional.

TUMOURS OF UNCERTAIN LINEAGE WITH RECURRENT GENETIC ALTERATIONS

PLEOMORPHIC DERMAL SARCOMA

Definition

Pleomorphic dermal sarcoma is a malignant spindle cell tumour arising in the dermis. It typically occurs in the head and neck, however, it can occur in other locations such-as the trunk, shoulders and upper limbs. Typically, it presents as a well circumscribed red nodule >2cm in diameter, with overlying skin often appearing crusty or ulcerated. Mostly in the over 60 age group and in white males.

Aetiology and pathogenesis

Exposure to UV-radiation leads its formation, explaining the anatomical location. Risk factors include predisposing genetic conditions such as Li Fraumeni (germline *TP53* mutations); immunosuppression and previous radiotherapy. The common UV-induced *TP53* mutations and UV-light mutational signature can be detected in these tumours. High frequency of *TERT* promotor mutations are also a feature which allow cells to avoid senescence. Other commonly detected mutations are found in *HRAS* and *KRAS*, *CDKN2A*, *KNSTRN* and *PIK3CA* genes.

Pathological features, diagnostic markers and differential diagnoses

The microscopic features are described in Figure 4. There is no specific diagnostic marker (Table 1). The main consideration are other UV light-associated tumours including melanoma, carcinoma and angiosarcoma. The features of atypical fibroxanthoma (AFX), a dermal-based tumour, are very similar to dermal sarcoma but is less aggressive and does not invade into subcutaneous invasion, around lymphatics or nerves, and does not exhibit necrosis. Furthermore, AFX does not metastasise (Table 1).

Prognosis

The recurrence rate is around 20-30%, occurring in patients with incomplete excisions. Distant metastases occur in around 20% of cases, between 12-24 months after initial surgical treatment. Common metastasis locations include the skin, lungs and lymph nodes.

BIPHENOTYPIC SINONASAL SARCOMA

Definition

A recently defined malignant tumour exhibiting myogenic and neural features, harbouring recurrent structural alterations in the *PAX-3* gene, fusions with *MAML3*, *FOXO1* or *NCOA1*. Biphenotypic sinonasal sarcoma arises in the sinonasal tract, with a predilection for the superior aspect of the nasal cavity ethmoid air cells and the sphenoid sinus. Patients present with symptoms of sinonasal obstruction, and the lesion appears pink and polyploid, with papillary excrescences. Ages of presentation have been reported between 24-87 years, with a predilection for females in the ratio 2:1. There is no reported ethnic predilection.

Pathological features, diagnosis marker and differential diagnoses

Histological features are shown in Figure 5. Microscopic invasion of bone occurs in 20% of cases. There is focal expression of S100 and some cases express desmin and myogenin. Although there is no entirely specific immunoprofile, the absence of cytokeratin and *SOX10* largely excludes synovial sarcoma and schwannoma and MPNST. Absence of *STAT6* excludes solitary fibrous tumour (Table 1).

Prognosis

Recurrence is common, with disease recurrence-free periods ranging from less than 12 months to over 9 years. There are no reports of metastases.

SYNOVIAL SARCOMA

Definition

A malignant tumour of uncertain lineage and cause unknown characterised by fusion of *SS18* to *SSX1* or *SSX2*; *SSX4* with *SS18* has also been implicated. 3-10% occurs in the head and neck but they have been reported at almost all sites. Most common age of presentation is 15-40 years, with no gender, geographical or ethnic bias.

Pathological features, diagnostic markers and differential diagnoses

The histological features and immunohistochemistry are represented in Figure 6 and Table 1. The differential diagnosis includes many spindle-cell lesions, particularly MPNST and the poorly differentiated variant can have shares features with the more classical 'round cell tumours' such as Ewing sarcoma. Epithelial glands and less commonly squamous differentiation characterise the biphasic variant. In view of the expression of cytokeratins, it is important to exclude a carcinoma and epithelioid sarcoma (loss of INI1 expression).

Prognosis

Metastases and local recurrences are common. The most common metastatic site is the lungs but spread also occurs to bone and lymph node. Tumours containing >20% poorly differentiated areas have a worse prognosis.

LINEAGE-SPECIFIC TUMOURS

ANGIOSARCOMA

Definition

Angiosarcoma is a malignant neoplasm of endothelial cells, most commonly sited in the dermis in the sun-exposed areas of the head and neck region, and may ulcerate. The diagnosis is frequently delayed as the features can mimic infection or injury. It may be associated with anaemia and bleeding diathesis. It typically affects 50-70-year old.

Aetiology and pathogenesis

Angiosarcoma is often associated with UV-light exposure, particularly in elderly men. Radiotherapy can lead to secondary angiosarcoma, generally presenting at least 5 years after treatment of the primary malignancy. This is more common if a patient has a germline disorder predisposing to cancer, such as Retinoblastoma.

Most angiosarcomas exhibit complex genomic changes but unlike most other sarcomas do not harbour *TP53* mutations. An array of vascular-specific receptor tyrosine kinases is up-regulated in secondary angiosarcoma, such-as *KDR*, *TIE1*, *TEK*, and *FLT*. Approximately 40% of angiosarcomas carry recurrent alterations including *KDR*, *PLCG1* and *FLT4*.

Angiosarcoma secondary to radiation and chronic lymphoedema generally display high levels of *MYC* amplification. Amplification of the *FLT4* gene, which codes for VEGF3, occur most commonly in *MYC*-amplified tumours. *PLCG1* and *KDR* (VEGFR2) mutations occur in a mutually exclusive manner and can be found irrespective of *MYC* amplification. *FLT4*-amplified angiosarcomas do not harbour *KDR* and *PLCG1* mutations.

Pathological features, diagnostic markers and differential diagnoses

Small lesions are soft and red, whereas larger lesions are fleshy, often with necrosis and haemorrhage. The histology of angiosarcoma varies from well-formed vascular structures which are difficult to distinguish from haemangiomas to poorly differentiated. They often exhibit a spindle and/or epithelioid appearance and are difficult to distinguish from a spindle

cell sarcoma or carcinoma. Features include extravasated blood cells, blood lakes and necrosis, as well as haemosiderin deposition. An inflammatory infiltrate may be present and occasionally reactive bone is present (Figure 7).

Immunohistochemistry is valuable for reaching a diagnosis particularly in poorly differentiated tumours. CD31 and *ERG* are usually positive. CD34 and factor VIII-related antigen expression are less commonly expressed. Tumours exhibiting an epithelioid morphology frequently express cytokeratins.

Prognosis

Local recurrence is common. Metastases occur to lymph nodes, lung, bones and liver. Overall survival ranges from 6-16 months. Well differentiated tumours may behave aggressively, therefore the value of grading is debated.

LEIOMYOSARCOMA

Definition

Leiomyosarcoma is a malignant tumour showing smooth muscle differentiation, representing 5-10% of all soft tissue sarcomas.

Aetiology and pathogenesis

Hereditary genetic conditions such as *TP53* mutations and Retinoblastoma are thought to predispose for leiomyosarcoma, along with radiation exposure.

Pathological features, diagnosis marker and differential diagnoses

Figure 8 shows typical features. High grade tumours may have the appearance of an undifferentiated sarcoma and can only be classified using immunohistochemistry. The expression of at least two muscle markers (SMA, caldesmon and desmin) are required for classifying as a leiomyosarcoma although these may only be focally positive.

Leiomyosarcomas can also be focally positive for cytokeratins.

Prognosis

The outcome depends on tumour grade. Leiomyosarcoma has a high recurrence and metastatic rate. Recurrence rate is around 55%. Metastasis usually occurs in the lungs and liver.

EBV-ASSOCIATED SMOOTH MUSCLE TUMOUR

This smooth muscle tumour occurs in immunosuppressed individuals including those with HIV or post-transplant patients and may be multicentric. These are classified as tumours of uncertain malignant potential. They rarely metastasise and the clinical outcome is related to the underlying condition. They express smooth muscle markers and EBV (Figure 9).

MALIGNANT PERIPHERAL NERVE SHEATH TUMOURS

Definition

Malignant Peripheral Nerve Sheath Tumours (MPNST) are spindle cell sarcomas which arise from peripheral nerve branches. Patients present with painful masses, sometimes with weakness and paraesthesia. Around half of MPNSTs develop in conjunction with the autosomal dominant condition Neurofibromatosis Type 1 (NF1) caused by the recessive gene *NF1* and is the leading cause of death in this population, with patients having an 8-13% chance of developing MPNST during their lifetime. The average age of presentation in patients with NF1 is 30 years, compared to 50-60 years in the sporadic disease.

Aetiology and pathogenesis

MPNST is a genetically complex condition driven by genetic alterations in the tumour suppressor *NF1* gene. The cause of the sporadic disease is not known but it appears that the same range of genetic alterations occur in both setting. *NF1* mutations lead to an activation of the *RAS* pathway which results in activation of several mitogenic pathways, including *mTOR*, *MAPK* and *AKT*. Loss of *CDKN2A* and mutations in *TP53*, *EGFR* and *SUZ12* genes have all been commonly found in genomic analysis ^{4,5}.

Pathological features, diagnostic markers and differential diagnoses

The histological appearance of high grade MPNSTs are highly variable and there are no specific markers to ‘clinch’ the diagnosis. Hence it is one of the most challenging soft tissue sarcoma diagnoses (Figure 10). Knowledge that the patient has *NF1* and or the presence of a benign neurofibroma, or a low-grade component helps reach a diagnosis. However as most sporadic MPNSTs are high grade such information does not help.

NF1 genetic changes occur in cancers other than MPNST but when they occur in combination with alterations in *PRC2* core components, *SUZ12* or *EED1*, they are highly suggestive of the diagnosis of MPNST. Loss of H3K27me3 on immunohistochemistry is seen in the majority of such genomically classified cases. Hence, loss of the protein is largely specific but not sensitive with up to 60% of cases, proven by genomic analysis, retaining expression of H3K27me3 ⁶. The differential diagnosis is wide including synovial sarcoma, dermatofibrosarcoma protuberans, rhabdomyosarcoma and undifferentiated sarcoma amongst others. Many of such diagnoses can be excluded on the basis that they harbour their own characteristic molecular alterations and/or immunoprofile (Table 1).

Diffuse expression of S100 can be seen in neurofibroma and Grade 1 MPNST but in high grade tumour only focal expression is present and even this is only seen in about 50% of cases. Hence extensive S100 expression in a sarcoma should largely exclude a high grade MPNST. However you might consider epithelioid MPNST which is a different disease and characterised by loss of *INI1* expression. *SOX10* may also be present focally but this is not specific for this tumour. Loss of H3K27me3 is largely, but not entirely specific for MPNST as the expression is retained in up to 60% of cases ^{6,7}. Loss of expression is more commonly associated with the classical variant of the tumour ⁶.

Figure 10 and Table 1 show histological and immunohistochemical features.

RHABDOMYOSARCOMA

Rhabdomyosarcoma is a malignant tumour showing skeletal muscle differentiation of unknown cause. It is the most common soft tissue sarcoma found in children. It is classified into 4 major variants: alveolar (25%), embryonal, sclerosing/spindle cell and pleomorphic (see undifferentiated sarcoma below).

ALVEOLAR RHABDOMYOSARCOMA

Definition

An aggressive rapidly sarcoma showing skeletal muscle differentiation of unknown cause and characterised by recurrent fusion genes involving *PAX3* or *PAX7* genes with *FOXO1*. Alveolar rhabdomyosarcoma (ARMS) represents 20% of all rhabdomyosarcomas. Peak

presentation occurs between 10-25 years but a subset occurs over 40 years old. Although more common in the extremities it also presents in the head and neck region.

Pathological features, diagnostic markers and differential diagnoses

ARMS exhibit a primitive round cell morphology which is arranged in nests which give the tumour its name (Figure 11). The differential diagnoses include other 'round cell tumours', such as but not exclusively Ewing sarcoma, sarcoma with BCOR genetic alterations which may occur in the head and neck region and CIC-re-arranged sarcomas which rarely occur in the head and neck location.

Prognosis

ARMS has significant potential to metastasise, with 25-30% of patients presenting with metastases which spread by lymphatics and blood. Prognosis for patients with a PAX3-FOXO1 ARMS is worse than those with PAX7-FOXO1 ARMS. It has a less favourable outcome than embryonal rhabdomyosarcoma and fusion negative rhabdomyosarcoma.

EMBRYONAL RHABDOMYOSARCOMA

Definition

A skeletal muscle tumour that is the most common sarcoma in children with 30% in children under the age of 5. It is common in the head and neck region particularly around the orbit.

Pathogenesis

The cause of the tumour is unknown. It is associated with syndromes where there is activation of RAS signalling such as in neurofibromatosis type 1, Noonan syndrome and Costello syndrome. It exhibits complex genomic changes.

Pathological features, diagnostic markers and differential diagnoses

Figure 12 and Table 1 present the pathology and immunohistochemistry for ERMS.

Prognosis

Prognosis is better in paediatric cases presenting up to 9 years of age. Overall survival rate for those presenting with metastatic disease is <25%.

SCLEROSING/ SPINDLE CELL RHABDOMYOSARCOMA

Definition

A rapidly growing skeletal muscle tumour with spindle cell morphology and genetic recurrent alterations. The head and neck region is the most common site for this tumour.

Pathogenesis

Sclerosing rhabdomyosarcoma in paediatric patients frequently carry recurrent gene fusions involving *VGLL2*, *SRF*, *TEAD1*, or *NCOA2*. A second more common variant occurs in adolescence and adults and harbours a *MYOD1* pLeu122arg mutation. A third group does not show any recurrent alterations to date.

Pathological features, diagnostic markers and differential diagnoses

Figure 13 and Table show the histological and immunohistochemical features ³.

Prognosis

Tumours presenting in infants have a favourable prognosis with gene fusions. MYOD1-mutant tumours have a poor outcome.

UNDIFFERENTIATED SARCOMA

A tumour which fails to show a specific line of differentiation employing current technologies and does not exhibit a recurrent alteration, for example, *SSX18-SYX*. When considering making this diagnosis ensure that you have considered poorly differentiated lymphoma, carcinoma, germ cell tumours and a melanoma. Immunohistochemistry, although may be focal, demonstrates specific lineages such as desmin and caldesmon for leiomyosarcoma and myogenin, MYOD1 for rhabdomyosarcoma. Also consider pleomorphic liposarcoma – look for lipoblasts (Figure 14).

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MULTIPLE CHOICE QUESTIONS:

1. Which genetic condition predisposes to malignant peripheral nerve sheath tumour?
 - a. Li Fraumeni syndrome
 - b. Retinoblastoma
 - c. Familial Adenomatous Polyposis
 - d. Neurofibromatosis Type 1

Answer: D - Neurofibromatosis Type 1

2. Which anatomical location does angiosarcoma have a predilection for?
 - a. Trunk
 - b. Scalp
 - c. Orbit
 - d. Upper limb

Answer: B – Scalp

3. Which of these risk factors are **not** implicated in aetiology of Fibromatosis/Deep Fibromatosis?
 - a. UV light exposure
 - b. Pregnancy
 - c. Oral contraceptive pill
 - d. Familial Adenomatous Polyposis

Answer: A – UV light exposure

Table 1: Summary of recurrent genetic alterations and characteristic immunoprofiles useful in reaching diagnoses in head and neck soft tissue sarcomas

Tumour type	Recurrent genetic alteration used for diagnostic purposes	Characteristic immunoreactivity	Negative immunoreactivity
Alveolar rhabdomyosarcoma	<i>PAX3/PAX7-FOXO1</i> ,	Desmin, Myogenin,-, MyoD1	
Angiosarcoma	<i>KDR, PLCG1, FLT4</i>	CD31, ERG,	
Biphenotypic sinonasal sarcoma	<i>PAX3</i> rearrangement	S100, SMA,	Cytokeratins, CD34, STAT6
Pleomorphic dermal sarcoma	<i>TP53</i>	CD10, SMA	Melanocytic, epithelial, endothelial and myogenic markers,
Dermatofibrosarcoma protuberans	<i>COALIA1, PDGFB</i> fusion gene	CD34	S100, Desmin
Desmoid fibromatosis	<i>CTNNB1</i> mutations	Beta-catenin	
Embryonal rhabdomyosarcoma	Unknown	Desmin, myogenin,	EMA
Inflammatory myofibroblastic tumour	<i>ALK, ROS</i>	SMA, ALK	S100
Leiomyosarcoma	Unknown	SMA, Desmin, Caldesmon	S100
Low grade myofibroblastic sarcoma	Unknown	SMA	MUC4
Malignant peripheral nerve sheath tumour	<i>NF1</i> alterations in combination with mutations in PRC2 core components	Focal S100, SOX10, Loss of H3K27me3 – sensitive but not specific	
Neurofibroma	<i>NF1</i> mutation	S100 diffuse, CD34	
Nodular fasciitis	<i>USP6</i> fusion gene	SMA	Desmin
Synovial sarcoma	<i>SS18-SSX1, SSX2</i> , rarely <i>SSX4</i>	Cytokeratins, EMA	CD34, Desmin, Myogenin, MyoD1 and <i>SOX10</i>

SMA – alpha smooth muscle actin

Figure Legends

Figure 1. Desmoid fibromatosis. This diagnosis is made largely on low power magnification Eosinophilic monomorphic spindle cells organised in long fascicles containing widely dispersed compressed vessels (a) running in parallel (b). c. The cells have indistinct cytoplasm, tapered nuclei, and mitotic figures are scarce. The amount of collagen matrix can be variable.

Figure 2. Low grade myofibroblastic sarcoma have variable amounts of collagen; the cells form fascicles but also a storiform pattern with wavy nuclei, pale eosinophilic cytoplasm and indistinct cell borders (a). The atypia may be subtle, but the cells are larger than reactive or benign myo/fibroblasts. Mitoses are infrequent and necrosis is not a feature. Smooth muscle actin decorates the spindle cells highlighting the 'tram-tracking' pattern characteristic of this tumour (b).

Figure 3. Nodular fasciitis a benign myo/fibroblastic vascularised spindle cell lesion showing characteristic features. Note the absence of atypia and necrosis (a). Mitotic activity can be marked. With time the lesion is more fibrotic and less proliferative (b).

Figure 4. Pleomorphic dermal sarcoma. A subcutaneous invading subcutaneous fat (inset) composed of proliferative atypical spindle cell lesion (a). The tumour cells are large polygonal tumour cells with strongly eosinophilic cytoplasm (b). Also characterised by areas of necrosis, mitotic activity and lymphatic and perineural involvement (not shown).

Figure 5. Biphenotypic sinonasal sarcoma. A subepithelial highly cellular lesion of medium-long fascicles of uniform spindle cells. Necrosis is not a feature and very few mitotic figures are seen (a). Respiratory glandular epithelium may be entrapped within the tumour (inset a). There is patchy distribution of S100 (b).

Figure 6. Synovial sarcoma is composed of fascicles of monomorphic plump spindle cells and the extent of collagen deposition is variable and can be extensive (a) and the biphasic variant also exhibits epithelial glandular (b) or squamoid structures (less commonly, not shown). The poorly differentiated variant contains a round cell pattern (c). Areas of calcification can occur (not shown). Cytokeratin is expressed variable amounts (d).

Figure 7. Angiosarcoma may mimic a spindle cell sarcoma but is distinguished by areas of haemorrhage (arrow), the dilated vascular channels lined by atypical cells (star), and vacuolated cells (blob) (a). Solid areas of severely atypical mitotically active cells with fibrin deposition and vascular channels with hobnailed cells (b). Nuclear immunoreactivity for ERG (c). Tumours exhibiting an epithelioid morphology frequently express cytokeratins and EMA (not shown).

Figure 8. Leiomyosarcoma is characterised by elongated blunt-ended spindle cells sharply defined intersecting fascicles (a). The cells exhibit indistinct margins (b). Inflammatory cells, myxoid matrix can be seen in some cases (not shown). The degree of nuclear atypia, necrosis and mitotic activity varies.

Figure 9. EBV-associated smooth muscle tumour is a cellular lesion with a monomorphic smooth muscle cell appearance. Mitotic activity is low (a). Tumour cells expressing EBV (b).

Figure 10. Most MPNSTs are high-grade tumours classically exhibiting interlacing fascicles of hyper and less cellular fascicle composed of a largely uniform cell population (a) with geographic necrosis (not shown). Others exhibit heterologous elements, the most common being rhabdomyosarcoma (Triton tumour) – scattered myogenin immunoreactivity (b), but osteosarcoma, chondrosarcoma and angiosarcoma differentiation can also occur. This pleomorphic sarcoma is classified as a MPNST because it has arisen in a patient with NF1 (c).

Figure 11. Alveolar rhabdomyosarcoma is a round cell sarcoma classically described as having a pseudoalveolar pattern – nests of tumour cells surrounded by fibrous bands - (arrows), but solid areas are also frequent (a). Although many cells exhibit primitive features some (arrows) rhabdomyoblastic differentiation as demonstrated by the eosinophilic cytoplasm (b). Strong diffuse nuclear expression of myogenin distinguishes alveolar rhabdomyosarcoma from other subtypes where this protein is expressed focally (c).

Figure 12. Embryology rhabdomyosarcoma exhibits the features of mesenchymal cells at different stages of skeletal muscle differentiation. Primitive small spindle cells in a myxoid matrix (a) and the high power magnification showing scattered rhabdomyoblasts characterised by the abundant eosinophilic cytoplasm representing greater differentiation (b). However, ERMS may be largely composed of these rhabdomyoblasts (not shown). Only scattered cells in ERMS are immunoreactive myogenin in contrast to the extensive expression seen in alveolar rhabdomyosarcoma (c).

Figure 13. Sclerosing / spindle cell rhabdomyosarcoma is spindle cell sarcoma. The sclerosing variant shows conspicuous hyalinisation and the compressed tumour cells, round or spindled, exhibit cords and nests of cells and may show a pseudoalveolar pattern (a). The spindle cell variant contains cellular fascicles of eosinophilic cells (b). Necrosis, haemorrhage and an inflammatory infiltration may also be evident. Both variants are diffusely positive for desmin (c) but reveal only scattered myogenin (MYF4)-immunoreactivity. Sparse numbers of MYOD1-positive cells may be present in the spindle cell variant (d) and diffusely positive in the sclerosing variant (not shown).

Figure 14. Undifferentiated sarcoma. A cellular pleomorphic neoplasm. Others may exhibit less pleomorphism.