

Undifferentiated sarcoma

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Definition

Undifferentiated soft tissue sarcoma (USTS) shows no identifiable line of differentiation when analysed by presently available technology. At present, this is a heterogeneous group and a diagnosis of exclusion, although genetic subgroups (particularly in the round cell group) have emerged. Not included are dedifferentiated types of specific soft tissue sarcomas (e.g. dedifferentiated liposarcoma), in which the high-grade component is commonly undifferentiated.

ICD-O coding

8805/3 Undifferentiated sarcoma

ICD-11 coding

2B5F.2 & XH73J4 Sarcoma, not elsewhere classified of other specified sites & Giant cell sarcoma

2B5F.2 & XH0947 Sarcoma, not elsewhere classified of other specified sites & Malignant fibrous histiocytoma

2B5F.2 & XH6HY6 Sarcoma, not elsewhere classified of other specified sites & Undifferentiated sarcoma

2B5F.2 & XH85G7 Sarcoma, not elsewhere classified of other specified sites & Small cell sarcoma

Related terminology

None

Subtype(s)

Spindle cell sarcoma, undifferentiated; pleomorphic sarcoma, undifferentiated; round cell sarcoma, undifferentiated

Localization

USTS may be found at any location. Published data are limited, but overall it seems that these lesions are most common in somatic soft tissue.

Clinical features

USTS has no characteristic clinical features that distinguish it from other types of sarcoma, other than a frequently rapid growth rate.

Epidemiology

USTSs are uncommon mesenchymal neoplasms that are anatomically ubiquitous and occur at all ages and with no difference between the sexes. USTSs account for as many as 20% of all soft tissue sarcomas. Those with round cell morphology are most frequent in young patients and are currently in large part labelled according to their main driving genetic anomaly, if known (see Chapter 2: *Undifferentiated small round cell sarcomas of bone and soft tissue*, p. 321). Those that are pleomorphic (often known as pleomorphic malignant fibrous histiocytomas in the past) occur mostly in older adults.



Fig. 1.400 Undifferentiated pleomorphic sarcoma. Grossly, undifferentiated pleomorphic sarcomas most often feature a fleshy appearance with areas of necrosis and haemorrhage.

Etiology

The etiology of most USTSs is unknown. However, at least 25% of radiation-associated soft tissue sarcomas are undifferentiated [1163,1761].

Pathogenesis

Undifferentiated pleomorphic sarcomas (UPSs) typically display extensive genomic rearrangements. Cytogenetic data from > 100 cases have, with few exceptions, revealed complex karyotypes with chromosome numbers ranging from near-haploid to hyperoctaploid [1021,1390]. The extensive reshuffling of chromosomal material indicated by tumour karyotypes is corroborated by array-based genomic studies, showing structural rearrangements and copy-number shifts involving most if not all chromosomes [482,1699], as well as by massively parallel sequencing studies [472,2935]. UPSs demonstrate substantial copy-number heterogeneity compared with other sarcoma subtypes and do not form distinct methylation subgroups [472,2935]. Whole-genome sequencing has revealed that punctuated evolutionary events such as whole-genome duplications and chromothripsis accompanied by telomere dysfunction underpin the genomic complexity of UPS [2935]. The aberrations in telomere biology are achieved either through activation of telomerase through deregulation of *TERT* or through the alternative lengthening of telomeres pathway [472,2935]. There are no tumour-specific amplicons, but some 10–15% of cases show amplification of *VGLL3* or *YAP1*, and 10% have amplification of *CCNE1* [1344,472]. Targets of frequent deletions and disruptive rearrangements include *CDKN2A* and *CDKN2B* in 9p, *PTEN* in 10q, *RB1* in 13q, and *TP53* in 17p, each affected in 10–20% of cases [2865,576,2492,1150,472,2935]. *RB1* and *TP53*, as

well as *ATRX*, are among the few genes that recurrently show pathogenetic variants at the nucleotide level [472]. At the transcriptomic level, UPS cannot be distinguished from high-grade myxofibrosarcoma, and it is possible that these two entities may lie on a spectrum of differentiation [472]. A small subset of UPSs with low mitotic counts show gene fusions involving the *PRDM10* gene, with either *MED12* or *CITED2* as the 5' partner [1390]. Otherwise, driver gene fusions have not been found in UPS [472].

Macroscopic appearance

USTs are a heterogeneous group and thus have no distinctive macroscopic features, other than the frequent presence of necrosis and haemorrhage.

Histopathology

USTs may be broadly divided into pleomorphic, spindle cell, round cell, and epithelioid subsets, but none have specific defining features other than their lack of an identifiable line of differentiation [1018]. Pleomorphic USTs, which represent the largest group, closely resemble other specific types of pleomorphic sarcomas and are often patternless, with frequent bizarre multinucleated tumour giant cells. Spindle cell USTs most often show a fascicular architecture with variably amphophilic or pale eosinophilic cytoplasm and tapering nuclei. Round cell USTs consist of relatively uniform rounded or ovoid cells with a high N:C ratio, and they most often closely resemble

other specific types of round cell sarcomas, especially Ewing sarcoma. However, many cases can now probably be more precisely classified within specific molecular subsets, such as *CIC*-rearranged and *BCOR*-rearranged sarcomas, as well as within the group of round cell sarcomas associated with *EWSR1* fusions involving partners unrelated to the ETS family of genes (e.g. *PATZ1*, *NFATC2*, *SP3*, *SMARCA5*, and *POU5F1*) – see Chapter 2: *Undifferentiated small round cell sarcomas of bone and soft tissue* (p. 321). USTs with epithelioid morphology have been little studied as yet [2716], but they are probably not rare. Morphologically, these lesions closely resemble metastatic carcinoma or melanoma, but they generally lack nesting and have amphophilic or pale eosinophilic cytoplasm and large vesicular nuclei. Some appear to show *SMARCA4* inactivation [1789,2493]. Importantly, genomic profiling may reveal that some seemingly undifferentiated sarcomas can be classified more specifically [482,639,641,2150].

Cytology

Not clinically relevant

Diagnostic molecular pathology

Undifferentiated pleomorphic and epithelioid sarcomas are characterized by complex genetic aberrations not suitable for diagnostic purposes. However, molecular genetics plays a major role in excluding specific molecular entities, particularly when dealing with undifferentiated round cell sarcomas. UPS must be

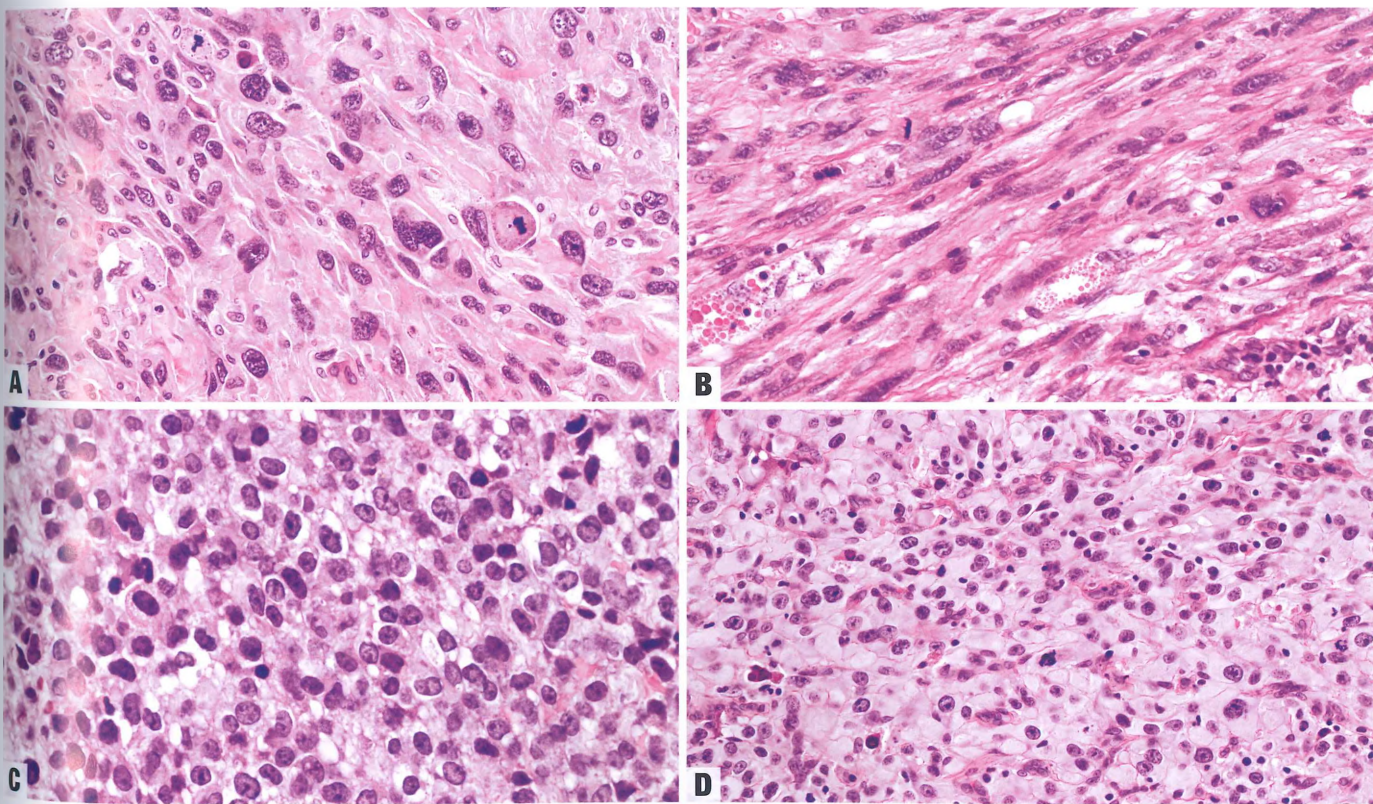


Fig. 1.40 Undifferentiated sarcoma. **A** Undifferentiated pleomorphic sarcoma is composed of a spindle cell and pleomorphic cell population most often characterized by high mitotic activity. Atypical mitoses are very common. **B** Undifferentiated spindle cell sarcoma features a highly atypical spindle cell proliferation. Mitotic activity is most often high. **C** Currently, undifferentiated round cell sarcoma can be diagnosed only if distinctive gene fusions have been ruled out. **D** Undifferentiated epithelioid sarcoma is most often composed of a high-grade epithelioid cell population lacking any specific line of differentiation.

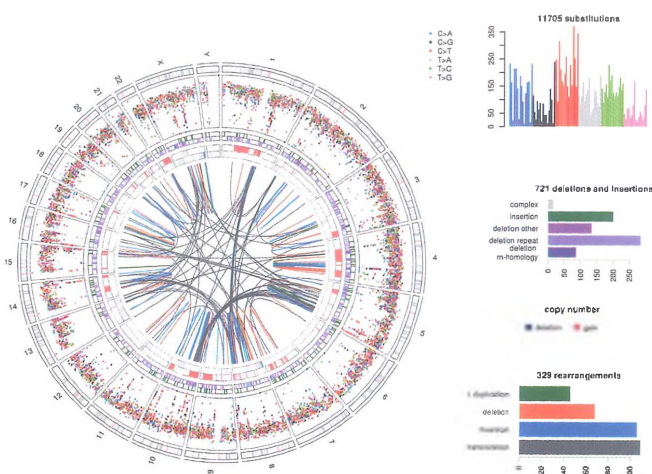


Fig. 1.402 Undifferentiated pleomorphic sarcoma. Circos plot illustrating the complex copy-number and rearrangement patterns seen in a typical undifferentiated pleomorphic sarcoma genome. The outer ring denotes chromosomal location, with subsequent rings representing single-nucleotide variants, insertions, deletions, and copy-number gains and losses. The arcs represent interchromosomal and intrachromosomal rearrangements.

separated from dedifferentiated liposarcoma, a lesion characterized molecularly by *MDM2* and *CDK4* gene amplification [57, 641].

Essential and desirable diagnostic criteria

Essential: spindle, pleomorphic, epithelioid, and round cell (rarely often high-grade) morphology; absence of any morphological or immunohistochemical feature of specific differentiation; demonstrated absence of distinctive molecular aberration

Staging

The American Joint Committee on Cancer (AJCC) or Union for International Cancer Control (UICC) TNM system may be used.

Prognosis and prediction

Because of the lack of substantive studies, data are limited. The majority of USTSs are morphologically high-grade. Among pleomorphic sarcomas in adults, those that are undifferentiated and arise in the limbs or trunk have a reported 5-year metastasis-free survival rate of 83% [1023]. USTS with epithelioid morphology seems to be more aggressive [2716]. In children, reported survival rates for USTS, whether of round cell or spindle cell / pleomorphic type, are 70–75% [59,2468,2905].