

Review Article

Unraveling Round Cell Sarcomas: A Contemporary Diagnostic Guide Beyond Ewing Sarcoma

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ABSTRACT

Round cell sarcomas represent a continuously evolving category of malignant mesenchymal tumors, currently encompassing 5 main tumor subtypes: Ewing sarcoma, *Capicua Transcriptional Repressor* (CIC)-rearranged sarcoma, sarcomas with *BCL6-corepressor* (BCOR)-genetic abnormalities, *POZ/BTB and AT hook containing zinc finger 1* (PATZ1)-rearranged sarcoma, and *nuclear factor of activated T cells 2* (NFATC2)-rearranged sarcoma. These tumors show some degree of histomorphologic overlap, which, coupled with their infrequency, may render their diagnosis challenging for the pathologist. Furthermore, although ancillary techniques like immunohistochemistry and molecular tests can be of diagnostic aid, they are still limited by inherent sensitivity and specificity issues and cannot replace meticulous integration of clinical and radiologic findings. This review is focused on (1) providing a guide for tackling the diagnosis of round cell sarcomas and their mimics using an integrative approach combining demographics, clinicoradiologic data, histomorphology, and ancillary techniques and (2) detailing the most recent information on round cell sarcomas from the latest World Health Organization classification of Bone and Soft Tissue Tumors (fifth edition).

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Introduction

In recent decades, advances in multiomics techniques have greatly improved the classification of round cell sarcomas by helping to identify tumor subsets with distinct clinicopathologic features. Although this has greatly expanded our understanding of human disease, it has also introduced new layers of complexity

into routine diagnostic pathology. This is due to the diversity of tumor subtypes, the presence of common molecular alterations in tumors with divergent prognoses, the constant description of potential new entities, and the lack of widespread access to molecular techniques in many parts of the world.

Fortunately, important efforts have also resulted in the development of an increasing arsenal of immunohistochemical markers with high sensitivity and specificity for most round cell sarcoma subtypes. These markers offer the advantages of shorter turnaround times, broader availability, and lower cost compared with most molecular techniques. However, as every ancillary technique, immunohistochemistry does not provide perfect sensitivity or specificity. Therefore, meticulous histomorphologic assessment and careful correlation with clinical, radiologic, and, in some cases, molecular findings remain essential for reaching an accurate diagnosis.

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In anticipation of the forthcoming World Health Organization (WHO) Classification of Bone and Soft Tissue Tumors, which will attempt to further refine tumor categories, this review seeks to provide a practical and hopefully enduring resource for navigating this challenging field of pathology.

The article is structured into 2 main parts:

The first part provides a general guide for the diagnosis and classification of round cell sarcomas, highlighting the importance of an integrative approach combining demographics, clinicoradiologic data, histomorphology, and ancillary techniques.

The second part focuses on the current state of the art of the round cell sarcoma subtypes acknowledged in the current WHO Classification of Bone and Soft Tissue Tumors (fifth edition).¹

First Part: Integrative Approach

Current Classification and Incidence of Round Cell Sarcomas

The most recent WHO classification of Bone and Soft Tissue Tumors (fifth edition) recognizes 5 main subtypes of round cell sarcomas under the “Undifferentiated small round cell sarcomas of bone and soft tissue” category: Ewing sarcoma, *Capicua Transcriptional Repressor* (CIC)-rearranged sarcoma (CIC-sarcoma), sarcomas with *BCL6-corepressor* (BCOR)-genetic abnormalities (BCOR-sarcoma), and round cell sarcomas with *EWS RNA binding protein 1* (EWSR1)-non-ETS fusions, which include *POZ/BTB* and *AT hook containing zinc finger 1* (PATZ1)-rearranged sarcoma (PATZ1-sarcoma) and *nuclear factor of activated T cells 2* (NFATC2)-rearranged sarcoma (NFATC2-sarcoma).¹

Among these, Ewing sarcoma remains by far the most common subtype of round cell sarcoma (Supplementary Fig. S1). Hence, integrating the full range of features of Ewing sarcoma is crucial to confidently rule it out before considering other diagnostic possibilities.

Demographics and Clinicoradiologic Data: What Is Important to Consider?

Although numerous clues can aid in the diagnostic approach to round cell sarcomas, the author has summarized the main features evaluated in his current practice. These include age group, patient sex (biological sex), primary tumor origin, tumor anatomical location, radiologic characteristics, presence of adenopathies, and, in selected cases, blood chemistry and urinalysis. A detailed summary of these features in round cell sarcomas and their differential diagnosis is provided in the included Table.²⁻⁷⁶

Brief examples for their practical application are provided below.

- Age group: the incidence of round cell sarcoma subtypes varies significantly with patient age. For example, Ewing sarcoma and BCOR-sarcoma occur predominantly in children and adolescents <20 years old. Conversely, CIC-sarcoma (particularly those with *CIC::Double Homebox 4* [DUX4] fusions), NFATC2-sarcoma, and PATZ1-sarcoma occur more frequently in young- to middle-aged adults (<50 years). In older adults, a tumor displaying rhabdomyosarcomatous features (particularly those resembling embryonal rhabdomyosarcoma) should incite the pathologist to consider the possibility of a tumor with heterologous

rhabdomyosarcomatous differentiation (melanoma, carcinoma, mesothelioma, and rarely, germ cell tumors). Importantly, for some entities in the differential diagnosis of round cell sarcomas, patient age alone can almost entirely exclude certain considerations; eg, neuroblastomas and nephroblastomas occur almost exclusively in children <5 years.

- Patient sex: most round cell sarcomas show an almost equal sex distribution or a slight male predominance. However, certain entities, such as BCOR-sarcoma (particularly those with *BCOR::Cyclin B3* [CCNB3] fusions) and desmoplastic round cell tumor, show a striking male predilection.
- Primary tumor origin: sarcomas typically originate in soft tissue or bone and rarely in viscera. Among well-defined round cell sarcoma subtypes, Ewing sarcoma, sarcomas with *BCOR::CCNB3* fusions, and NFATC2-sarcomas predominantly arise in bone and less frequently in soft tissue or visceral sites. Conversely, primary skeletal CIC-sarcomas are extremely rare, and PATZ1-sarcomas have never been reported in skeletal locations. Similarly, with the exception of rhabdomyosarcomas with *TFCP2* and *MEIS1* fusions,^{77,78} most rhabdomyosarcomas do not originate in bone. In fact, the presence of rhabdomyoblastic differentiation in a primary bone tumor should prompt consideration of a tumor with heterologous elements, such as a metastatic carcinoma or a melanoma, particularly in older adults.
- Tumor anatomical location: some round cell sarcomas show striking predilections for specific anatomical sites. Desmoplastic small round cell tumor occurs almost exclusively in mesothelial-lined cavities. Embryonal rhabdomyosarcoma most commonly affects the head and neck region (particularly the orbit) and the genitourinary tract in infants. Mesenchymal chondrosarcoma frequently arises in the jaw. Tumors located in intraabdominal or pelvic regions should encourage consideration of a genital origin and highlight the need for specific ancillary techniques (eg, immunohistochemistry for hormone receptors for ruling out low-grade endometrial stromal sarcoma or SALL4 for germ cell tumors).
- Radiologic characteristics: a basic understanding of radiologic interpretation is important for both general pathologists and bone pathologists. On radiographs and computed tomography (CT) scans, the following features are useful when assessing a primary bone tumor: *patient age group* (mature or immature skeleton based on the presence of growth plates), *type of bone involved* (long, flat, axial, and appendicular), *osseous location* (epiphysis, metaphysis, diaphysis, central, and surface), *tumor margins* (well defined or ill defined, with or without peripheral sclerosis), *tumor size and focality* (unifocal or multifocal), *signs of rapid growth* (eg, prominent periosteal reaction, Codman triangle, extraosseous extension), *signs of slow growth* (eg, expansive remodeling), *tumor texture* (osteolytic, sclerotic, mixed, and other), *patterns of matrix production* (cumulus cloud>osteogenic, irregular calcifications>chondrogenic, and ground glass>fibrogenic), and *tumor growth dynamics* (when serial imaging studies are available). Most round cell sarcomas arising in skeletal locations are generally homogeneously osteolytic. However, matrix production (bone and cartilage) can be seen in small cell osteosarcoma, mesenchymal chondrosarcoma, and rare cases of BCOR-sarcoma, which can lead to misdiagnosis as small cell osteosarcoma. NFATC2-sarcoma may also occasionally demonstrate a distinctive radiologic pattern (see second part).

For additional information on the basic interpretation of bone tumor radiology, refer to Bush CH.⁷⁹

Table

Main clinicopathological and immunohistochemical features of round cell sarcomas and mimics

Entity	Peak age (y) of onset	M:F ratio	Primary origin	Main anatomical locations	Diagnostic clues	Immunohistochemistry	
						Positive	Negative
Ewing sarcoma ²⁻¹¹	Children and adolescents (<20 y)	M>F (~1.5:1)	Bone (~90%) Extra skeletal (~30%)	Flat and long bones (diaphysis or metadiaphysis)	- Sheets of very monotonous round cells with cytoplasmic clearing - Rosettes (subset)	<u>Most:</u> CD99 (diffuse membranous), PAX7, FLI-1 (most), NKX2-2, PKC β II <u>FUS/EWSR1::ERG</u> subset: ERG <u>Variable:</u> PRAME, S100, CK	Desmin, CD34, AGGRECAN ^a , SATB2, ETV4, WT1 (N-ter), SOX10, DUX4 (C-ter)
<i>CIC</i> -rearranged sarcoma ¹²⁻²¹	<u><i>CIC::DUX4</i></u> : Young adults (25-35 y)	M>F (~1.2:1)	Soft tissue >viscera>bone	Trunk and extremities	- Multinodular architecture - Round to spindle cell morphology, sometimes epithelioid (including rhabdoid cells) - Irregular nuclei with prominent nucleoli - Myxoid stroma	<u>Most:</u> CD99 (patchy, rarely diffuse), FLI-1, WT1 (nuclear, N-ter or C-ter), ETV4, DUX4 (C-ter), MUC5AC (scattered cells), PRAME, NUTM1 (nongranular, <i>CIC::NUTM1</i> subset) <u>Rare:</u> BCOR	Desmin ^a , CK ^a , CD34, S100, NKX2-2 ^a , PKC β II, AGGRECAN ^a
	<u><i>CIC::NUTM1</i></u> : Variable (infants to adults)	M>F (~2:1)	Soft tissue and CNS>viscera	CNS and paravertebral tissue			
Sarcomas with BCOR-genetic abnormalities ²²⁻²⁸	<u><i>BCOR::CCNB3</i></u>: children and adolescents (<20 y)	M>F (~3.7:1)	Bone>Soft tissue>Viscera	Long and pelvic bones>Trunk and extremities	- Myxoid stroma - Collagen strands - Rich capillary network - Round to spindle cell morphology - Monotonous nuclei with inconspicuous nucleoli	<u>Most:</u> CD99 (focal to diffuse), SATB2, BCOR, CCNB3 (<i>BCOR::CCNB3</i> subset) <u>Variable:</u> pan-TRK, PRAME <u>Rare:</u> OLIG2	S100, CK, EMA ^a , CD34, Desmin, NKX2-2, WT1 (N-ter), ETV4, DUX4 (C-ter), AGGRECAN, PKC β II
	<i>BCOR ITD</i> and <i>YWHAE::NUTM2B/E</i>: infants (<1 y)	M>F (1.3:1)	Soft tissue>Bone	Axial soft tissue and abdominopelvic region			
<i>PATZ1</i> -rearranged sarcoma ^{29,30}	Adults (40-50 y)	M>F (1.8:1)	Soft tissue	Thoracoabdominal	- Well-circumscribed lesion +/- pseudocapsule - Microcystic change - Sclerosis/fibrous bands - Perivascular hyalinization - Round to spindle cell morphology (sometimes epithelioid) - Polymorphous tumors (variable histological grade)	<u>Most:</u> S100, GFAP, Desmin, MYOD1, PAX7 <u>Variable:</u> CD99, SOX10 (focal), Myogenin (focal) CK (focal) <u>Rare:</u> SOX10 (focal) and Myogenin (focal)	BCOR, NKX2-2, NKX3-1, PKC β II, DUX4 (C-ter), CD34 ^a
<i>NFATC2</i> -rearranged sarcoma ³¹⁻³⁶	Young adults (25-40 y)	M>F (~2.2:1)	Bone>Soft tissue	Long bones	<u>Radiology:</u> expansive intraosseous lesion with massive extraosseous component - Fibrous to myxoid stroma - Nested and trabecular architecture - Round/epithelioid/spindled cells - Polymorphous tumors (variable histological grade) <u>FISH:</u> <i>EWSR1</i> amplification pattern with FISH break-apart probes (<i>EWSR1::NFATC2</i> subset)	<u>Most:</u> CD99 (cytoplasmic or membranous), AGGRECAN <u><i>EWSR1</i> variants only:</u> PAX7, NKX2-2, NKX3-1 <u>Variable:</u> BCOR, WT1 (nuclear), ETV4, CK	Desmin, S100, CD34, SATB2, PKC β II, DUX4 (C-ter)

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Entity	Peak age (y) of onset	M:F ratio	Primary origin	Main anatomical locations	Diagnostic clues	Immunohistochemistry	
						Positive	Negative
Synovial Sarcoma ^{19,37-39}	Adolescents and young adults (15-39 y)	F=M (~1:1)	Soft tissue >viscera>bone	Lower and upper extremity	- Collagen strands - High cellularity with «school of fish» pattern - Round to spindle cells +/- true epithelial differentiation (including glandular structures) - Poorly differentiated: prominent nucleoli, high mitotic activity and rhabdoid morphology - Calcifications and cystic change	<u>Most:</u> EMA and CK (patchy), TLE1, PRAME, NY-ESO-1, SS18, SS18-SSX, INI1 (reduced expression/mosaic) <u>Variable:</u> BCOR <u>Rare:</u> SATB2	CD34, S100 ^a , Desmin, WT1 (N-ter), PKC β II ^a , NKX2-2 ^a , ETV4, DUX4 (C-ter), PAX7 ^a
Myxoid liposarcoma (high grade/round cell) ⁴⁰⁻⁴²	Adolescents to adults (<50 y)	F=M (~1:1)	Soft tissue very rarely viscera	Thigh	- Lobulated architecture - Round to ovoid cells with scant cytoplasm - Adipocytic component (including lipoblasts) - Branching capillaries - Myxoid stroma and myxoid pools	<u>Most:</u> S100 (patchy and weak), DDIT3, PRAME, NY-ESO-1	CD34, Desmin, CK, WT1 (N-ter), PKC β II ^a , PAX7, ETV4
Mesenchymal chondrosarcoma ^{7,33,43,44}	Young adults (20-30 y)	M>F (~1.2:1)	Soft tissue and bone > viscera	Craniofacial region (jaw ++) but ubiquitous	- Radiology: intralesional irregular calcifications - Prominent staghorn-like vasculature - Abrupt transition from round cell component to cartilage islands	<u>Most:</u> SOX9, CD99, NKX2-2, NKX3-1, SATB2, AGGRECAN <u>Variable:</u> WT1 (N-ter)	CK, Desmin ^a MYOD1 ^a , Myogenin ^a , EMA ^a , PKC β II, PAX7, ETV4, CD34, FLI-1, S100 (round cells)
Rhabdomyosarcoma (Embryonal) ⁴⁵⁻⁴⁷	Children (median age: 8 y)	M>F (1.4:1)	Soft tissue > viscera	Head and neck (orbit ++), genitourinary tract and pelvis	- Mildly pleomorphic round to spindle cells - Rhabdomyoblastic differentiation (strap cells +/- striations) - Variable myxoid stroma with zonation (cambium layer)	<u>Most:</u> Desmin (focal), MYOD1 and myogenin (focal, <50% cells), HMGA2, PAX7, PRAME <u>Variable:</u> CK, S100, WT1 (N-ter)	AP-2 beta, FOXO1, MUC4, OLIG2a, CD34, PKC β IIa, NKX2-2, ETV4, DUX4 (C-ter)
Rhabdomyosarcoma (alveolar) ⁴⁵⁻⁴⁹	Children and adolescents (10-25 y)	M=F (~1:1)	Soft tissue > viscera	Head and neck and Extremities	- Primitive monotonous round cells - Multinucleated tumor giant cells - Rhabdomyoblastic differentiation rare and subtle - Alveolar to solid architecture	<u>All:</u> Desmin, MYOD1 and Myogenin (diffuse, >50%) <u>Most:</u> MUC4, OLIG2, FOXO1, AP-2 beta, PAX7 <u>Variable:</u> CK, PRAME, WT1 (N-ter)	CD34, S100, HMGA2, PKC β II, NKX2-2, ETV4, DUX4 (C-ter)

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Entity	Peak age (y) of onset	M:F ratio	Primary origin	Main anatomical locations	Diagnostic clues	Immunohistochemistry	
						Positive	Negative
Extrarenal rhabdoid tumor ⁵⁰	Infants and children (<18 y)	M=F (~1:1)	Soft tissue > viscera	Deep axial locations and liver	• Rapidly evolving and generally disseminated at onset • Frequent lymph node metastasis • Sheets of rhabdoid cells (abundant, brightly eosinophilic cytoplasm, and large, eccentric nuclei with vesicular chromatin and prominent nucleoli) • Small subset composed of primitive round cells	<u>Most</u> : INI1 (<i>SMARCB1</i>) loss (>95% of cases), CK and EMA (focal to diffuse), CD99. <u>Subset</u> : BRG1 (<i>SMARCA4</i>) loss <u>Variable</u> : SALL4, CD34, S100 (focal)	Desmin, Brachyury
Extra skeletal myxoid chondrosarcoma ⁵¹	Adults (50–60 y)	M>F (1.6:1)	Soft tissue > viscera	Lower extremity (thigh)	• Nodular/multinodular • Variable amounts of cellularity and myxoid stroma • Prominent hemorrhagic areas • Small spindle-to-ovoid cells with uniform nuclei with fine chromatin and inconspicuous nucleoli • Variable component of epithelioid cells with brightly eosinophilic cytoplasm and conspicuous nucleoli • Architecture: rounded clusters, cords or rarely sheets	<u>Variable</u> : S100 (focal), KIT, Synaptophysin, INSM1 (focal)	CK, EMA ^a , Desmin, CD34, SOX10, PRAME, DDIT3, NKX2-2, PAX7
Osteosarcoma (small cell) ⁵²	Adolescents and young adults (<30y)	M=F (~1:1)	Bone	Metaphysis and/or Diaphysis of long bones (femur and tibia)	• <u>Radiology</u>: aggressive osteolytic lesions with frequent soft tissue extension and variable mineralization • Small round cells with mild pleomorphism and variable amounts of bone matrix	<u>Most</u> : SATB2 <u>Variable</u> : BCOR	CD99 ^a
Adamantinoma-like Ewing sarcoma ^{53,54}	Young adults (Median 41 y)	M>F (2.4:1)	Soft tissue > viscera > bone	Head and neck	• Lobulated and basaloid proliferation of cohesive round cells arranged in cords or nests with palisading rimming • Desmoplastic stroma • Focal keratinization (subset)	<u>Most</u> : CD99 (diffuse membranous), EMA, CK, CK5/6, p40, p63, NKX2-2, FLI-1, Synaptophysin	Desmin, CD34, WT1, NUT, BCOR, S100a

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Entity	Peak age (y) of onset	M:F ratio	Primary origin	Main anatomical locations	Diagnostic clues	Immunohistochemistry	
						Positive	Negative
Desmoplastic small round cell tumor ^{55,56}	Young adults (20–30 y)	M>F (~3.6:1)	Soft tissue > viscera	Abdominopelvic cavity	• Multinodular lesions in mesothelial-lined surfaces • Variably sized nests in abundant desmoplastic stroma • Round to epithelioid cells (rarely spindle) • Can present rosettes or glandular like structures	<u>Most:</u> WT1 (C-ter, nuclear), Desmin (cytoplasmic dot-like), CK, EMA <u>Variable:</u> CD99, NKX2-2, ETV4	WT1 (N-ter), CD99, S100, Myogenin, MYOD1, Chromogranin A, PKC β II ^a , PAX7, BCOR, DUX4 (C-ter)
Solitary fibrous tumor ^{7,16,17,57}	Adults (40–70 y)	M=F (~1:1)	Soft tissue > viscera > bone	Extremities and pleura, but ubiquitous	• Well-circumscribed lesion • Prominent branching (staghorn-like) vessels +/- hyalinized walls • Collagen strands or bands • Haphazardly arranged spindle-to-round cells • Prominent round cell morphology (subset)	<u>Most:</u> CD34 (~90%), STAT6 (diffuse and strong nuclear expression) <u>Variable:</u> BCOR, CD99	S100 ^a , CK, Desmin, h-caldesmon, NKX2-2, DUX4 (C-ter), PRAME, PKC β II, MDM2, PAX7
GLI1-altered mesenchymal tumor ^{58,59}	• <u>GLI1-rearranged:</u> adults (median 40 y)	M>F (~1.5:1)	Soft tissue > viscera	Trunk, extremities, stomach and head and neck	• Lobular architecture • Nested arrangement of tumor cells	<u>Most:</u> CD56, CD10, GLI1 <u>Variable:</u> SMA, S100 and CK	MDM2, CDK4, STAT6, Desmin, SOX10, CD34, EMAs, CD99a
	• <u>GLI1-amplified:</u> adults (median 39 y)	M=F (~1:1)	Soft tissue > Viscera	Lower extremities (acral++)	• Prominent vasculature • Spindle-to-round cells with uniform nuclei with small nucleoli • Rarely epithelioid cells with vesicular nuclei • Perivascular/intravascular growth	<u>Most:</u> CD56, CD10, GLI1, CDK4, MDM2 <u>Variable:</u> STAT6 (nuclear and cytoplasmic) and DDIT3, S100, SMA <u>Rare:</u> CK	Desmin, CD34, EMA, SOX10, CD99a
Glomus tumor ⁶⁰	Adults (median 50 y)	M=F (~1:1)	Soft tissue > viscera > bone	Distal extremities (subungual region) and stomach	• Painful tumor • Small nodular lesion (<2 cm) • Small rounded cells with uniform round nuclei and distinct cell borders • Rich vascular component (variably ectatic capillaries)	SMA, h-caldesmon, Collagen type IV (pericellular), BRAF V600E (small subset)	S100, Desmin, CD34a, CK, EMA, PAX7

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Entity	Peak age (y) of onset	M:F ratio	Primary origin	Main anatomical locations	Diagnostic clues	Immunohistochemistry	
						Positive	Negative
Lymphoma/leukemia (lymphoblastic) ⁶¹	<u>B-lymphoblastic leukemia/lymphoma</u> : Children (<6y) <u>T-lymphoblastic leukemia/lymphoma NOS</u> : adolescents and young children	M>F M>F	Bone marrow and/or lymph nodes	Bone marrow and/or lymph nodes, rarely soft tissue and CNS involvement	• <u>Clinical</u>: Lymphadenopathies, hepatosplenomegaly, mediastinal/retroperitoneal mass • Sheets of poorly cohesive small to medium-sized round cells • Round to convoluted nuclei with variably distinct nucleoli and variably degree of pleomorphism • Massive and irregular infiltration of normal tissues	<u>Most (both T and B-ALL/LBL)</u> : CD99, TdT, CD34, PKC β II <u>B-ALL/LBL</u> : CD10, CD19, CD22, CD79a and PAX5 <u>T-ALL/LBL</u> : CD3, CD5, CD7, CD1a and KIT	CK, Desmin, S100, NKX2-2, ETV4, CD20 and CD45 (low to negative), MPO and Lysozyme
Lymphoma (Burkitt) ⁶²	Children to adults (variable depending on Burkitt-lymphoma subtype)	M>F (2-4:1)	Extranodal sites	<u>Endemic subtype</u> : mandible and maxilla <u>Sporadic subtype</u> : abdomen and soft tissue of the orbit	• Diffuse growth of medium-sized monomorphic cells with round nuclei and multiple nucleoli • High mitotic activity and abundant apoptotic debris • Interspersed tingible-body macrophages giving a "Starry-sky" pattern	CD20, PAX5, CD10, BCL6, CD38, MYC, Ki67 (~100%)	CK, S100, Desmin, CD34, TdT, Cyclin D1
Myeloid sarcoma ⁶³	Adults (46-59 y)	M>F (~1.2:1)	Nodal and extranodal sites	Skin and soft tissue, but ubiquitous	• Previous history of acute myeloid leukemia • Cytopenia's • Single mass effacing normal tissue architecture • Diffuse sheets of small to medium-sized cells with round to oval nuclei and variable amounts of cytoplasm • Vesicular chromatin with prominent nucleoli • High mitotic activity and abundant apoptotic debris	<u>Most</u> : CD43, Myeloperoxidase, CD33, CD68 <u>Variable</u> : KIT, CD34, CD99, CD45	CK, S100, Desmin, EMA

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Entity	Peak age (y) of onset	M:F ratio	Primary origin	Main anatomical locations	Diagnostic clues	Immunohistochemistry	
						Positive	Negative
Neuroblastoma ^{14,64,65}	Children (<5 y)	M>F (~1.2:1)	Soft tissue and viscera (neural crest migration sites)	Abdomen and retroperitoneum (adrenal glands and sympathetic ganglia)	• Clinical: elevated urinary catecholamine metabolites, associated paraneoplastic syndromes (diarrhea, hypertension, Horner syndrome) • Sheets and nests of small round cells • Variably abundant neuropil and rosettes • Granular chromatin (salt and pepper)	Most: CD56, NSE, NB84, Synaptophysin, Chromogranin A, TH, PHOX2B, PKC β II. Variable: ALK, S100 (Schwan cells)	CD99, EMA, CK, Desmin, WT1 (N-ter), NKX2-2 ^a , PAX7, ETV4, DUX4 (C-ter)
Carcinoma (lung small cell)	Adults (>60 y)	M>F	Viscera	Lung	• Clinical: smoking history • Radiology: mediastinal/perihilar lymphadenopathies • Sheets of small round cells with granular chromatin • Nuclear molding • Abundant necrosis and apoptotic debris • Azzopardi effect	CK, EMA, CD56, INSM1, Synaptophysin, Chromogranin A, TTF1	Desmin, S100, SOX10, CD34, PKC β II ^a
Carcinoma (Merkel)	Adults (>50 y)	M>F	Skin	Head and neck (sun exposed skin)	• Clinical: adenopathies • Nodules, sheets, nests or rarely trabeculae of round cells with high N:C ratio • Round uniform nuclei with granular chromatin • Nuclear molding • Abundant necrosis and apoptotic debris	Most: CK20 (perinuclear dot-like), CK, CD56, INSM1, Synaptophysin, Chromogranin A, SATB2, Variable: CD99, PKC β II, MCPyV large T-antigen (subset)	TTF1a, Desmin, S100, CD34, NKX2-2, ETV4, WT1 (N-ter) ^a
Melanoma	Adults	M>F	Skin > Other	Head and neck (sun exposed skin)	• Clinical: location in sun damaged skin, lymphadenopathies, primary soft tissue mass in axilla, groin or neck, previous history of melanoma • Nested architecture • Poorly cohesive tumor cells • Areas with epithelioid to rhabdoid morphology • Nuclear pleomorphism and prominent nucleoli	Most: S100, SOX10, MiTF, MelanA, HMB45, PRAME Variable: BRAF V600E, NRAS Q61R, WT1 (N-ter)	CD34, CK ^a , Desmin ^a , myogenin ^a , PKC β II ^a , NKX2-2, ETV4 ^a

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Entity	Peak age (y) of onset	M:F ratio	Primary origin	Main anatomical locations	Diagnostic clues	Immunohistochemistry	
						Positive	Negative
Thymoma	Adults (50-60y)	F>M	Viscera	Thymus	• <u>Clinical</u>: associated myasthenia gravis • <u>Radiology</u>: well-circumscribed anterior mediastinal mass • Lobules separated by fibrous septa • Small round to ovoid cells with very uniform nuclei and variably conspicuous nucleoli • Interspersed lymphocytes and/or Hassall corpuscles • Generally low mitotic activity and no necrosis	<u>Most</u> : CK, p63, p40, PAX8, TdT and CD99 (in interspersed thymocytes)	Desmin, S100, CD34, STAT6
Embryonic-type neuroectodermal tumor of the testis and gynecologic tract ^{66,67}	Young adults (<40 y)	-	Viscera	Testis and Gynecologic tract	• <u>Clinical</u>: previous history of gonadal tumor, pelvic or retroperitoneal mass and/or lymphadenopathies • Tumors resemble CNS embryonal tumors • Presence of teratomatous or germ cell tumor component • Neuroectodermal tubules and rosettes	<u>Most</u> : SOX2, S100, GFAP, SOX11 <u>Variable</u> : SALL4, WT1 (nuclear), AFP, OLIG2, NeuN, Desmin, CD99 (focal to membranous expression)	CK, CD34, NKX2-2
Nephroblastoma (Wilms tumor) ⁶⁸	Children (<5 y)	M<F	Viscera	Kidney	• <u>Clinical</u>: kidney mass in an infant, hypertension • Heterogeneous morphology with 3 components: blastemal (primitive round cells), epithelial and stromal • Rosettes, tubules and trabecular arrangement of cells	<u>Most</u> : WT1 (N-ter, nuclear) and PAX8 <u>Variable</u> : Desmin, myogenin, S100, CD34 (stromal component), CK and EMA (epithelial component), CD99 (focal), PKC β II, ETV4	NKX2-2
Small cell carcinoma of the ovary hypercalcemic type ⁶⁹	Young adults (median 25 y)	F	Viscera	Ovary/Pelvis	<u>Clinical</u>: Hypercalcemia • Sheets of poorly cohesive small round to rhabdoid cells with vesicular chromatin and conspicuous nucleoli • Nested or corded cell arrangement • High mitotic activity and frequent necrosis • Microcystic change (follicle-like spaces)	<u>Loss of expression</u> : BRG1 (SMARCA4) and BRM (SMARCA2) <u>Most</u> : WT1 (nuclear), CD10, EMA <u>Variable</u> : SALL4, CK, Calretinin, Inhibin	Desmin, S100, CD99, FOXL2

(continued on next page)

Table (continued)

Entity	Peak age (y) of onset	M:F ratio	Primary origin	Main anatomical locations	Diagnostic clues	Immunohistochemistry	
						Positive	Negative
Low-grade endometrial stromal sarcoma ⁷⁰	Wide age range (median age ~50 y)	F	Viscera and soft tissues	Uterus/abdominopelvic cavity	• Difficult to classify round cell tumor in the abdominopelvic cavity of females • Very monotonous and bland cells with round to ovoid nuclei, low mitotic activity and generally no necrosis • Arrangement in sheets and storiform fascicles • Prominent arterioles and collagen bundles	<u>Most:</u> ER, PR, CD10, IFITM1 <u>Variable:</u> CK, smooth muscle actin, Desmin, h-caldesmon, CD99, WT1, calretinin, inhibin	S100, SOX10, CD34, FOXL1, BCOR
Emerging entities							
Superficial Neurocristic FET:: ETS fusion tumor ⁷¹	Children and young adults (<20 y)	M=F (~1:1)	Soft tissue	Lower extremity and trunk	• Superficial location (skin and subcutis) • Triphasic pattern: nests of tumor cells + bland spindle cells and fibroblasts + adipocytes • Ewing sarcoma-like cytological features with unusual architectural patterns (nested and corded arrangement) + diffuse expression of S100 and SOX10	<u>All described cases:</u> S100 and SOX10 (diffuse and strong), NKX2-2, CD56 <u>Variable:</u> CD99 (negative to diffuse membranous), FLI-1, CD34, EMA	CK, Desmin, myogenin, MYOD1, WT1
NUT-sarcoma ⁷²	Children to adults	M<F (1:2.3)	Soft tissue and viscera	Intraabdominal (including gastrointestinal tract)	• Multifocal and rapidly disseminating disease at presentation • Polymorphous morphology: variable proportions of sheets of poorly cohesive epithelioid/rhabdoid cells to spindle or round cells • Amianthoid-like fibers • Prominent nucleoli • Generally high mitotic activity and frequent necrosis	<u>Most:</u> NUTM1 (homogeneous staining, nongranular) <u>Variable:</u> SMA, Desmin, S100, CK, CD34, CD99 (membranous)	P63, SOX10

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Table (continued)

Entity	Peak age (y) of onset	M:F ratio	Primary origin	Main anatomical locations	Diagnostic clues	Immunohistochemistry	
						Positive	Negative
Pseudoendocrine sarcoma ⁷³	Adults (median 65 y)	M>F (1.3:1)	Soft tissue	Paravertebral soft tissue	- Discordance between neuroendocrine morphology and lack of expression of neuroendocrine markers (INSM1, Synaptophysin, Chromogranin A) - Close resemblance to solid pseudopapillary neoplasm of the pancreas - Sheets, nests or cords of small epithelioid to ovoid cells with uniform round to ovoid nuclei with speckled chromatin - Extracellular hyaline globules and fibrovascular cords/septa	<u>Most:</u> Beta-catenin (nuclear), CD56, S100 <u>Variable:</u> Desmin, Brachyury, HuD, CD99, CD34, GLUT1	CK, EMA, SOX10, Synaptophysin, Chromogranin A, INSM1, GFAP
<i>CRTC1::SS18</i> sarcoma ⁷⁴	Young adults (median 34 y)	M<F (1:2)	Soft tissue	Lower extremity	- Prominent desmoplastic stroma - Nested architectural pattern - Round to epithelioid/rhabdoid cells - Nuclear pseudoinclusions	<u>Most:</u> CD99 (patchy), ALK, PAX8 <u>Variable:</u> CK, CD34, pan-TRK	Desmin, myogenin, MYOD1, WT1, EMA, S100
<i>SS18::POU5F1</i> sarcoma ⁷⁵	Adolescents and young adults (median 22y)	M=F (~1:1)	Soft tissue and Viscera	Variable	- Sheets, trabeculae or nests of cohesive round to epithelioid/rhabdoid cells - High mitotic activity and frequent necrosis	<u>All described cases:</u> EMA, CK, S100 (all markers generally focally positive) <u>Variable:</u> CD99, PAX8	Desmin, SOX10, NKX2-2, WT1
<i>EWSR1::POU2AF3</i> sarcoma ⁷⁶	Adults (median 49y)	M=F (~1 :1)	Soft tissue and bone	Head and neck	Polymorphous tumors with 2 main patterns: “Low-grade”: variable cellular components, including spindle cells with mild to moderate atypia in a fibromyxoid stroma with low mitotic activity and no necrosis +/- round cells foci “High-”: densely cellular tumors composed of highly atypical round and spindle cells - Synovial sarcoma-like morphology (bi-phasic pattern) - Heterologous components (including glands, bone and striated muscle)	<u>Most:</u> CD56 <u>Variable:</u> CK, EMA, S100, SATB2, CD99 (including membranous staining) <u>Heterologous components:</u> Desmin, myogenin, MYOD1, SATB2	CD34, SOX10, SS18-SSX, PKC β II

F, female; M, male; NOS, not otherwise specified.

^a Rare cases ($\leq 10\%$) have been reported as positive (generally focally).

adenopathies: Metastatic spread to lymph nodes is uncommon in sarcomas overall. When it does occur, it is most frequently seen in rhabdomyosarcoma, angiosarcoma, SWI-/SNF-deficient tumors, clear cell sarcoma, and, less commonly, Ewing sarcoma and synovial sarcoma.⁸⁰ Accordingly, the presence and distribution of lymphadenopathy may sometimes serve as a clue, suggesting a tumor of nonsarcomatous origin, such as undifferentiated/dedifferentiated melanoma or carcinoma.

- Blood chemistry and urinalysis: evaluation of serum tumor markers such as alpha-fetoprotein and beta-human chorionic gonadotropin can be a useful clue in favor of a germ cell tumor. Similarly, elevated levels of catecholamine metabolites in an infant support the possibility of neuroblastoma.

Histomorphology: What to Look for?

Round cell sarcomas are typically composed of small- to medium-sized round cells with monotonous nuclei and a high nuclear-to-cytoplasmic ratio, which imparts a “blue color” to the tumor at low-power microscopy. As a general rule, prominent nuclear pleomorphism argues against a diagnosis of a fusion-driven round cell sarcoma.

Importantly, round cell morphology can occur in a wide range of tumors (including nonsarcomatous neoplasms) either focally or, more rarely, diffusely. This can complicate diagnosis, especially in small biopsies or when clinical, radiologic, and ancillary data are not adequately integrated.

Within the WHO classification category of “Undifferentiated small round cell sarcomas of bone and soft tissue,” tumors can be roughly divided into those with Ewing and “Ewing-like” morphology (CIC-sarcoma, PATZ1-sarcoma, BCOR-sarcoma, and NFATC2-sarcoma). This distinction can be guided by evaluating *cell morphology* (uniformly round vs round to spindle or epithelioid), *nuclear features* (round nuclei with inconspicuous nucleoli vs ovoid/irregular nuclei with variable degrees of pleomorphism and prominence of nucleoli), *cell arrangement* (sheets and rosettes vs nested, corded, trabecular, and sheet patterns), and *stroma* (scant vs myxoid, fibrous, or richly vascularized) ([Supplementary Fig. S2](#)).

This morphologic approach offers a useful framework to guide further ancillary testing. However, it is not entirely reliable, as rare cases of Ewing sarcoma may display features of Ewing-like sarcomas (so-called “atypical Ewing sarcoma”) and vice versa.

Immunohistochemistry: What to Order?

As the morphological spectrum of round cell sarcomas encompasses a wide range of entities, immunohistochemistry plays a pivotal role in their diagnostic workup. When the morphologic differential is broad, a step-by-step approach is favored, prioritizing sensitive markers over specific ones to initially narrow the differential diagnosis. Subsequently, more specific markers can be used to arrive at the correct diagnosis ([Supplementary Figs. S3 and S4](#)).

A useful immunohistochemical panel of sensitive markers includes pan-keratin (eg, AE1/AE3), EMA, S100, CD99, Desmin, and CD34. In addition, if there is concern about the possibility of hematolymphoid malignancy, a germ cell tumor, or if none of the initial markers are clearly expressed, the following markers should also be considered: CD20, CD3, CD30, CD43, MUM1, TdT, myeloperoxidase, KIT, and SALL4. As a rule of thumb, the marker that is the most strongly and diffusely expressed generally

provides the most reliable indication of the tumor’s line of differentiation.

In some situations, due to the presence of characteristic morphologic features, a single marker or a small panel may be sufficient, thanks to the near-perfect specificity of certain antibodies (eg, SS18-SSX for synovial sarcoma^{37,38}). However, the use of reduced panels depends on multiple factors, including the experience of the interpreting pathologist and the availability of modern immunohistochemical markers, among others. In any case, no immunohistochemical marker is perfect, underscoring the need for careful correlation with the clinical context.

Detailed information on the immunohistochemical profiles of round cell sarcomas and mimics, including both sensitive and specific markers, is provided in the included [Table](#).

Molecular Genetics

The impact of molecular genetics on tumor classification is profound and indisputable. For certain pathologies, it has also laid the foundation for the development of novel treatment strategies that significantly influence patient prognosis.

Currently, the most frequently employed molecular techniques for diagnostic pathology include karyotyping, fluorescence in situ hybridization (FISH), single nucleotide polymorphism array, reverse-transcription PCR (RT-PCR) and derivatives, next-generation sequencing (NGS)-based techniques (RNA or DNA, targeted or comprehensive), and methylation profiling. As with all ancillary techniques, these methods come with advantages and limitations that must be carefully considered, including cost, turnaround time, specificity, sensitivity, technical complexity, and personnel requirements.⁸¹ Importantly, molecular findings need to be meticulously integrated into the clinicopathologic context to arrive at an accurate diagnosis. This has become increasingly evident with growing recognition that molecular aberrations, including gene fusions, are not always specific to a single entity.⁸²

An important question remains: in which situations should molecular analysis be pursued? In the author’s opinion, for diagnostic purposes, when highly specific immunohistochemical markers are available, systematic molecular analysis should not be mandatory for confirmation. Instead, its use should be reserved for cases in which significant diagnostic uncertainty persists after careful assessment of all available clinicopathologic data. However, this decision often depends on the pathologist’s experience with bone and soft tissue neoplasms, which are rare and diverse, thereby increasing the risk of misdiagnosis.

In France, the establishment of bone and soft tissue pathology review networks, where every sarcoma is confirmed by a specialized pathologist, has improved diagnostic accuracy, positively impacting patient survival and reducing health care costs.^{83,84} Expertise in the field enables more accurate judgment in specific scenarios. As a practical example, a diagnosis of small cell osteosarcoma should only be rendered after molecular analysis has excluded specific translocations, as several round cell sarcomas (including BCOR- and NFATC2-sarcomas) can mimic osteosarcoma and may lead to misdiagnosis even by expert pathologists.^{22,31} Conversely, for the diagnosis of Ewing sarcoma and CIC-sarcoma, sufficiently specific and validated immunohistochemical markers are available, allowing molecular testing to be omitted in most cases.

Second Part: State of the Art of Round Cell Sarcomas

Ewing Sarcoma

Historical Context and Nomenclature

Initially described in the literature by James Ewing in 1921 as “diffuse endothelioma of bone,” Ewing sarcoma represents the prototype of round cell sarcomas. In his seminal article, the tumor was noted to occur predominantly in young patients, exhibit distinctive radiologic and histological features, and be radiosensitive. Several terminologies, initially considered to represent distinct entities, have been used in the past but are now encompassed under the term *Ewing sarcoma*, and their use is discouraged. These include primitive neuroectodermal tumor, Askin tumor, and the original designation of diffuse endothelioma of bone.

Clinical Features

The vast majority of cases occur in young patients (<20 years) with a peak incidence at 15 years old and a slight male predominance. Ewing sarcoma is much more frequent in patients of European descent than in those of African and Asian descent. Most tumors occur in intraosseous locations, particularly flat and long bones, whereas ~30% are extraosseous. The latter more frequently occur in older patients.^{2,85} Clinical symptoms are largely unspecific and include pain (frequently increasing at night), visible lump/swelling, and difficulty walking. A pathologic fracture is sometimes present, particularly in advanced tumors.^{86,87}

Radiology

Ewing sarcoma typically arises in the diaphysis or metadiaphysis of long bones and less frequently in flat bones. These tumors are usually homogeneously osteolytic, with poorly defined margins, and show frequent extension into surrounding soft tissues (Figs. 1A and 2A, B). Additional features (suggestive of a highly aggressive lesion) include a prominent periosteal reaction and subperiosteal growth with formation of a “Codman triangle.”

Macroscopic and Histopathologic Features

Macroscopic images of Ewing sarcoma have become rare due to the widespread use of neoadjuvant chemotherapy, which often results in significant tumor shrinkage. When available, tumors typically appear fleshy with a white cut surface and may exhibit variable areas of necrosis and hemorrhage (Fig. 1B).

Histologically, the striking majority of cases show conventional features, characterized by densely packed sheets of small round cells with scant cytoplasm that often appears clear due to glycogen accumulation. The nuclei are round, very uniform in size and shape, and contain inconspicuous nucleoli. Mitotic activity and necrosis are variably seen but, when present, do not appear to have prognostic significance. The stroma is scant, sometimes showing thin fibrous septa and small capillaries (Fig. 1C, D).

Unconventional features include pseudoalveolar and nested architecture, rosette-like structures, and spindle tumor cell morphology (Fig. 2B-E). Rare cases may show larger cell size, mild nuclear pleomorphism, and 1 or multiple nucleoli (so-called large cell Ewing sarcoma).

Following neoadjuvant chemotherapy, most cases show varying degrees of fibrosis and necrosis. In rare instances, post-

therapeutic histologic maturation toward neural tissue can be observed (Supplementary Fig. S5).

Immunohistochemical Profile

Among sensitive markers, Ewing sarcoma shows diffuse membranous expression of CD99 in practically all cases (Fig. 1E). Negative, cytoplasmic dot-like, or heterogeneous staining strongly argues against the possibility of Ewing sarcoma. Desmin, CD34, S100, and keratins are typically negative. However, some series have reported focal keratin expression in up to 30% of cases and S100 expression in 20% to 40% of cases.^{3,4}

FLI-1 immunohistochemistry has been reported to be a sensitive and specific marker of Ewing sarcoma, but contemporary studies including novel round cell sarcoma subtypes are lacking.⁸⁸ Cases harboring *FET:ERG* fusions show diffuse immunohistochemical expression of ERG.⁵ Notably, both FLI-1 and ERG expression have been reported in CIC-sarcomas, representing a potential diagnostic pitfall.

More specific immunohistochemical markers include NKX2-2 and PKC β (Fig. 1F, G).^{6,7} Expression of these proteins is directly regulated by the *EWSR1-FLI1* chimeric protein (and likely also by rare fusion variants), which accounts for their increased specificity for Ewing sarcoma. Importantly, some tumors in the morphologic differential diagnosis of Ewing sarcoma may rarely express these markers (Table).

Molecular Pathology and Genetic Alterations

Ewing sarcoma is characterized by gene translocations resulting in the fusion of a *FET* family gene (typically *EWSR1* and rarely *FUS* or *TAF15*) with an *ETS* family transcription factor gene (most commonly *FLI1* but also *ERG*, *ETV1*, *ETV4*, *ETV5*, or *FEV*). These gene fusions occur at varying frequencies: *EWSR1::FLI1* (~85%-90% of cases), *EWSR1::ERG* (5%-10%), and other rare fusions (<1%).⁸⁶

The canonical gene fusions can be deduced using various methods, including FISH, RT-PCR, or NGS-based techniques. Importantly, *EWSR1* break-apart FISH is frequently falsely negative in *EWSR1::ERG* fusion variants.⁵

Additional recurrent mutations are infrequently detected, but when present, they often involve *STAG2* and *TP53*, both of which have been associated with adverse clinical outcomes.⁸⁹

Recurrent copy number variations described in Ewing sarcoma include gains of chromosomes 8, 2, 1q, and 20 and losses of 16q and 9p. Specifically, gain of 1q and 16q loss has been correlated with poor outcomes.^{90,91}

Prognosis

Patients with localized disease are generally treated with neoadjuvant chemotherapy (vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide) followed by complete surgical excision of the tumor. This approach leads to a 5-year survival rate of ~70%. Radiotherapy may be used in selected cases.

The most significant adverse prognostic factor in Ewing sarcoma is the presence of metastatic disease, which is associated with a 5-year survival rate of <30%. Additional factors linked to poor outcomes include primary tumor location in the pelvic bones and older age at diagnosis (>18 years old).

Interestingly, primary cutaneous and subcutaneous Ewing sarcoma have a significantly better prognosis, with a reported 5-year survival rate of 93%.⁹² This finding has raised the question of whether a shorter and less intensive chemotherapy regimen may be appropriate in such cases.

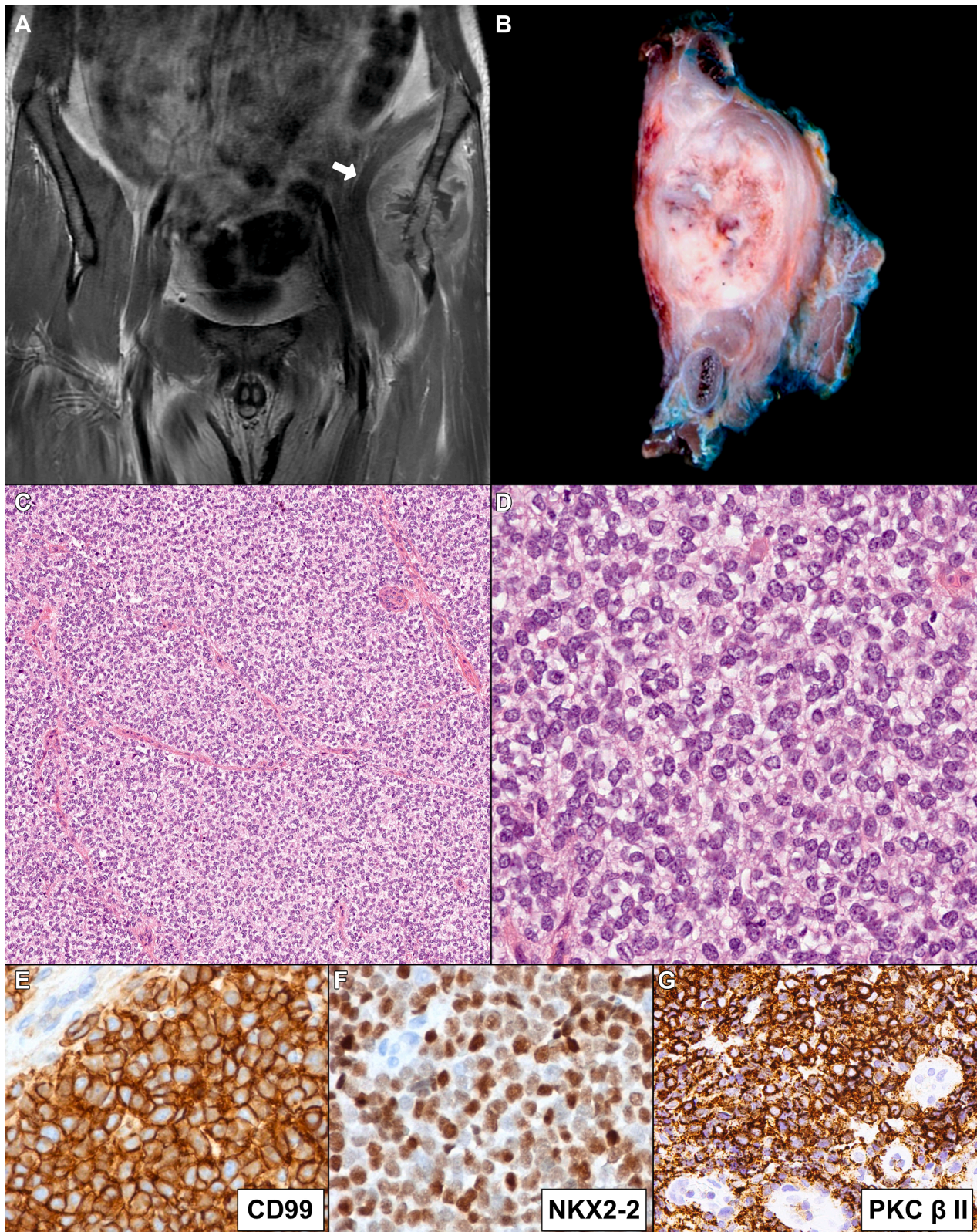


Figure 1.

Ewing sarcoma. (A) Coronal T1-weighted contrast-enhanced magnetic resonance imaging (MRI) showing a large, heterogeneously enhancing mass in the iliac bone. (B) Gross photograph of a relatively well-circumscribed rib tumor with a white cut surface and areas of hemorrhage. (C) Histology showing solid sheets of round cells in a scant stroma, associated with longilneal capillaries. (D) The tumor cells have a poorly abundant clear cytoplasm and round, monotonous nuclei, with inconspicuous nucleoli. (E) CD99 shows diffuse and strong membranous staining, a pattern present in >99% of Ewing sarcoma cases. Similarly, most cases show nuclear expression of NKX2-2 (F) and cytoplasmic expression of PKCβII (G, photomicrograph courtesy of Dr. Jerzy Lasota).

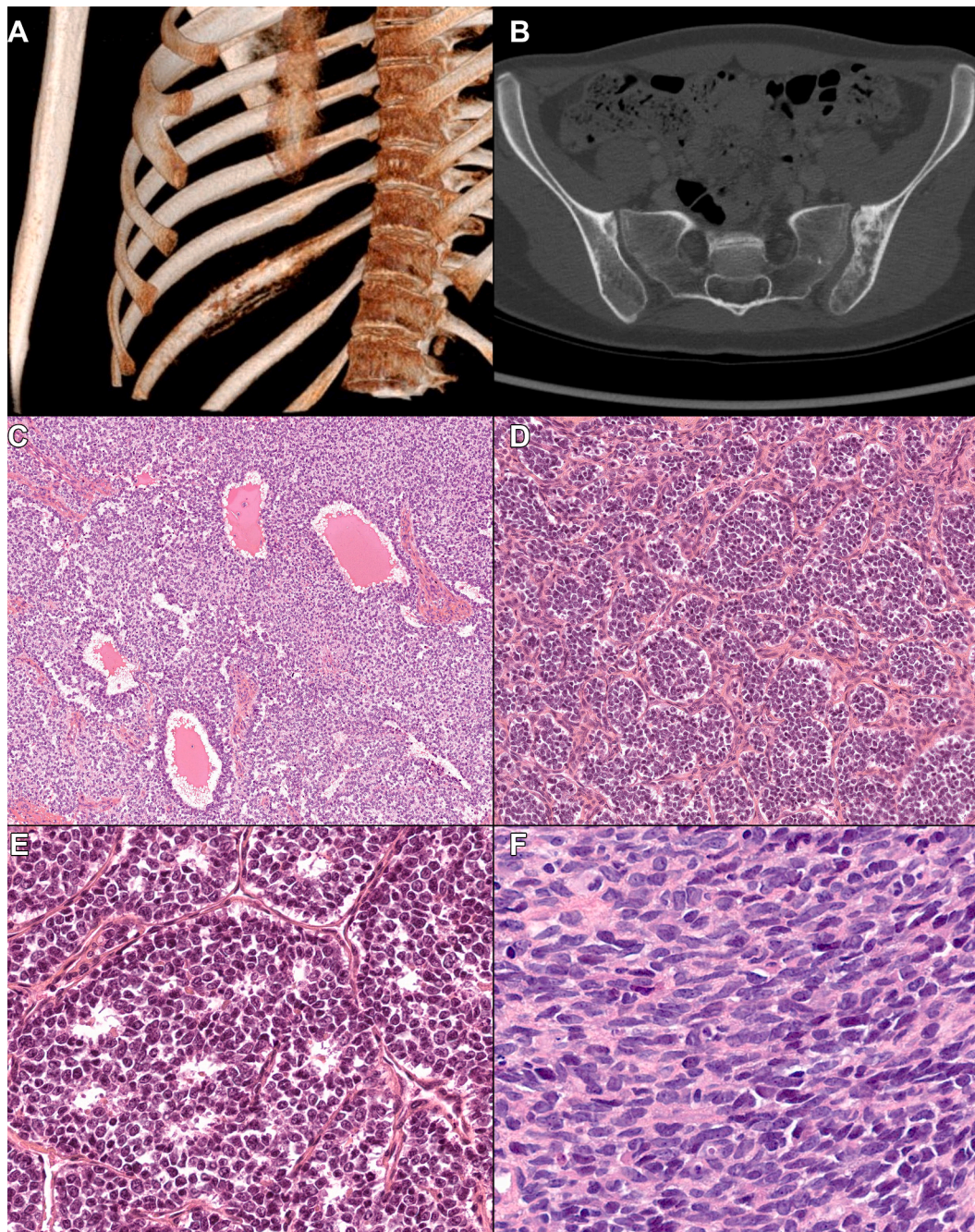


Figure 2.

Ewing sarcoma. (A) 3-Dimensional volume-rendered computed tomography (CT) scan of the thoracic cage showing a rib tumor with prominent periosteal reaction. (B) Axial CT scan showing a mixed lytic and sclerotic iliac bone tumor. (C) Histological images showing rare features seen in Ewing sarcoma, including microcysts (C), nested architecture (D), rosettes (E), and spindle cell morphology (F).

Emerging Entities With Controversial Relationships With Ewing Sarcoma

Two entities harboring the same canonical *FET::ETS* fusions seen in Ewing sarcoma have been recently described: superficial neurocristic *FET::ETS* fusion tumor and adamantinoma-like Ewing sarcoma.

Superficial neurocristic *FET::ETS* fusion tumors typically occur in superficial locations (skin or subcutis) of young adults. Morphologically, the tumor generally consists of monotonous round cells that may be cytologically indistinguishable from

those in Ewing sarcoma. The tumor frequently shows a multi-nodular architecture, with cells arranged in nests, cords, or single files within the nodules. Additional features may include rosettes, entrapped fatty tissue, and hemorrhage. Mitotic activity is variable, and necrosis has been occasionally reported. Immunohistochemically, the tumors are variably positive for CD99 (including diffuse membranous staining) and NKX2-2. However, in contrast to Ewing sarcoma, reported cases have consistently shown strong and diffuse expression of S100 and SOX10. Notably, the tumors appear to have an indolent clinical course and exhibit

epigenetic differences with conventional Ewing sarcoma. Nevertheless, the limited number of reported cases ($n = 11$) and the short median follow-up time (24 months) warrant caution and highlight the need for additional larger series.⁷¹ Figure 3 shows representative images of a case that meets the criteria for superficial neurocristic *FET::ETS* fusion tumor.

Adamantinoma-like Ewing sarcoma shows striking predilection for the head and neck of young adults. Morphologically, it is typically composed of small round cells with cytological features similar to Ewing sarcoma. However, the tumor frequently shows a lobulated architecture, sometimes with palisading, and is typically accompanied by a desmoplastic stroma. True epithelial differentiation, including abrupt formation of keratin pearls, may also be observed. Immunohistochemically, these tumors share immunophenotypic features with conventional Ewing sarcoma (CD99 and NKX2-2) but are distinguished by consistent and generally diffuse expression of epithelial and squamous markers, such as keratins, p63, and p40. A recent methylation study has shown epigenetic differences between adamantinoma-like and conventional Ewing sarcoma. Regarding prognosis, adamantinoma-like Ewing sarcoma is a malignant tumor with metastatic potential. The most adequate treatment strategy and whether it should differ from that for conventional Ewing sarcoma remain unclear.^{93,53} Representative images of a case of adamantinoma-like Ewing sarcoma are provided in Figure 4.

CIC-Rearranged Sarcoma

Clinical Features

CIC-sarcoma shows a similar sex distribution and a wide age range at presentation, with a peak onset between 25 and 35 years. Most tumors arise in the deep soft tissues, with a predilection for the trunk and extremities. Rarely, tumors may originate in visceral organs and, exceptionally, in bone. A small subset of tumors harbor *CIC::NUTM1* gene fusions and have been frequently reported in the central nervous system (CNS).

Radiology

The radiologic features of CIC-sarcoma are not extensively documented in the literature. In 1 series, the tumors were large (>5 cm) and necrotic. Magnetic resonance imaging (MRI) revealed well-defined masses, most of which exhibited heterogeneous contrast enhancement and flow voids. Additional findings included fluid-fluid levels and hemorrhage. On CT scans, tumors were isodense or hypodense relative to muscle, with heterogeneous enhancement and no evidence of calcification, including in a case originating in the rib.⁹⁴ A representative MRI sequence of a CIC-sarcoma is provided in Figure 5A.

Macroscopic and Histopathologic Features

Tumors are generally large and well circumscribed, with a white, fleshy cut surface. Hemorrhagic and necrotic areas are frequent (Fig. 5B).

Histologically, at low power, tumors show a solid, nodular, or multinodular architecture, with varying proportions of myxoid stromal change and hemorrhage. At high magnification, tumor cells are generally round to ovoid or spindle shaped, with at least some degree of nuclear pleomorphism (a feature that contrasts with Ewing sarcoma). The cells are arranged in sheets or short fascicles and, occasionally, in single files or reticular patterns, particularly in areas with prominent myxoid change. Some cases show focal to diffuse epithelioid or rhabdoid morphology, typically associated with moderately to marked nuclear

pleomorphism. Nuclear features vary between cases: tumors with mild pleomorphism and homogeneous, hyperchromatic nuclei are sometimes observed, but most cases demonstrate vesicular chromatin with ≥ 1 prominent nucleoli. Mitotic activity is generally brisk, and large areas of necrosis are common. Additional rare findings include multinucleated tumor cells and cartilaginous metaplasia. Representative histological features of CIC-sarcoma are shown in Figures 5 and 6.

In the author's experience, some of the most important and challenging differential diagnoses of CIC-sarcoma include extra-skeletal myxoid chondrosarcoma, myoepithelial tumors, and malignant neoplasms with rhabdoid morphology.

Immunohistochemical Profile

CIC-sarcoma generally shows focal to multifocal CD99 immunoreactivity (Fig. 5E), with $\sim 25\%$ of cases showing diffuse expression, based on the largest series to date.¹² Keratins, S100, Desmin, SOX10, and CD34 are typically negative, like more specific Ewing sarcoma markers such as NKX2-2 and PKC β II.

Notably, proteins from the ETS family, FLI-1 and ERG, are commonly expressed in CIC-sarcoma, often with diffuse nuclear staining. Furthermore, coexpression of ERG and patchy CD31 has been reported in a subset of cases, raising diagnostic difficulty with epithelioid angiosarcoma.⁹⁵ However, true vasof ormation is not observed in CIC-sarcoma, and CD31 is not diffusely expressed as in angiosarcomas.

Most CIC-sarcomas show nuclear expression of WT1 (both N-terminal and C-terminal clones; Fig. 5F) and preferentially expressed antigen of melanoma, although these markers are nonspecific. More diagnostically useful markers include ETV4 and DUX4, which are highly sensitive and specific for CIC-sarcoma (Fig. 5G, H). Importantly, CIC-sarcomas with *CIC::NUTM1* gene fusions show homogeneous (nongranular) nuclear immunoreactivity with NUTM1.

Molecular Pathology and Genetic Alterations

In $\sim 95\%$ of cases, CIC-sarcomas harbor fusions involving the *CIC* gene and the *DUX4* gene. Rare alternative fusion partners of *CIC* include *NUTM1*, *NUTM2*, *LEUTX*, *FOXO4*, *AXL*, *CITED1*, *DUX4L*, and *SYK*, among others.

The oncogenic mechanism of the fusion seems to be primarily related to the disruption of *CIC*'s normal structure. Under physiological conditions, *CIC* functions as a transcriptional repressor, particularly of the PEA3 group of ETS family genes, such as *ETV1*, *ETV4*, and *ETV5*. However, when the fusion results in the loss of *CIC*'s C-terminal domain, this repressive function is lost. The resulting *CIC* chimeric protein instead acquires transcriptional activity. In line with this, CIC-sarcomas show protein expression of ETV4, which, as previously mentioned, is exploited for diagnostic purposes.^{13,14,96}

Interestingly, rare CNS tumors that overlap morphologically, transcriptomically, and epigenetically with CIC-sarcomas have been shown to harbor fusions involving *ATXN1* or its ortholog *ATXN1L*, with various other genes, including *DUX4*, *NUTM1*, *NUTM2A*, *LEUTX*, and *EWSR1*. As *ATXN1* and *ATXN1L* closely interact with *CIC* and play roles in its degradation and stability, this finding supports the idea that tumors with *ATXN1* and *ATXN1L* fusions fall within the broader spectrum of CIC-sarcoma. Of note, a group of so-called high-grade neuroepithelial tumors with *CIC* fusions has been described in the CNS as unrelated neoplasms to CIC-sarcomas; however, these lesions show significant clinical, radiologic, immunohistochemical, and molecular overlap, calling into question their designation as unrelated entities.^{97,98}

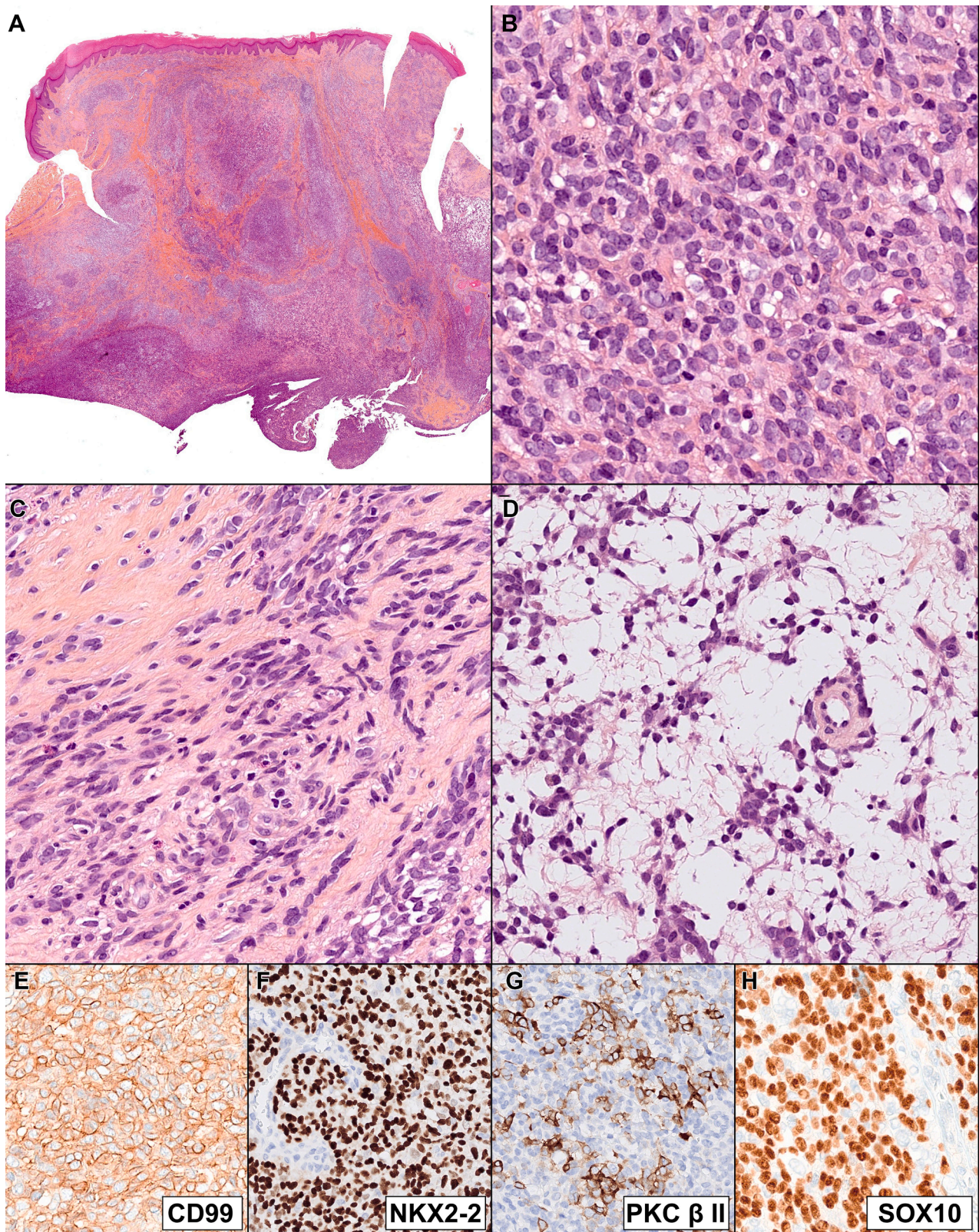


Figure 3.

A case of so-called “superficial Neurocristic *FET::ETS* fusion tumor.” (A) The tumor was located in the dermis and subcutis and showed both lobulated and infiltrative areas. (B) On high power, the tumor cells were round and uniform. (C) Focally the tumor cells exhibited a spindle cell morphology. (D) One area showed myxoid stroma with a somewhat reticular arrangement of cells. Immunohistochemical analysis demonstrated strong and diffuse membranous expression of CD99 (E), diffuse nuclear expression of NKX2-2 (F), patchy cytoplasmic expression of PKCβII (G), and diffuse nuclear expression of SOX10 (H) and S100 (not shown).

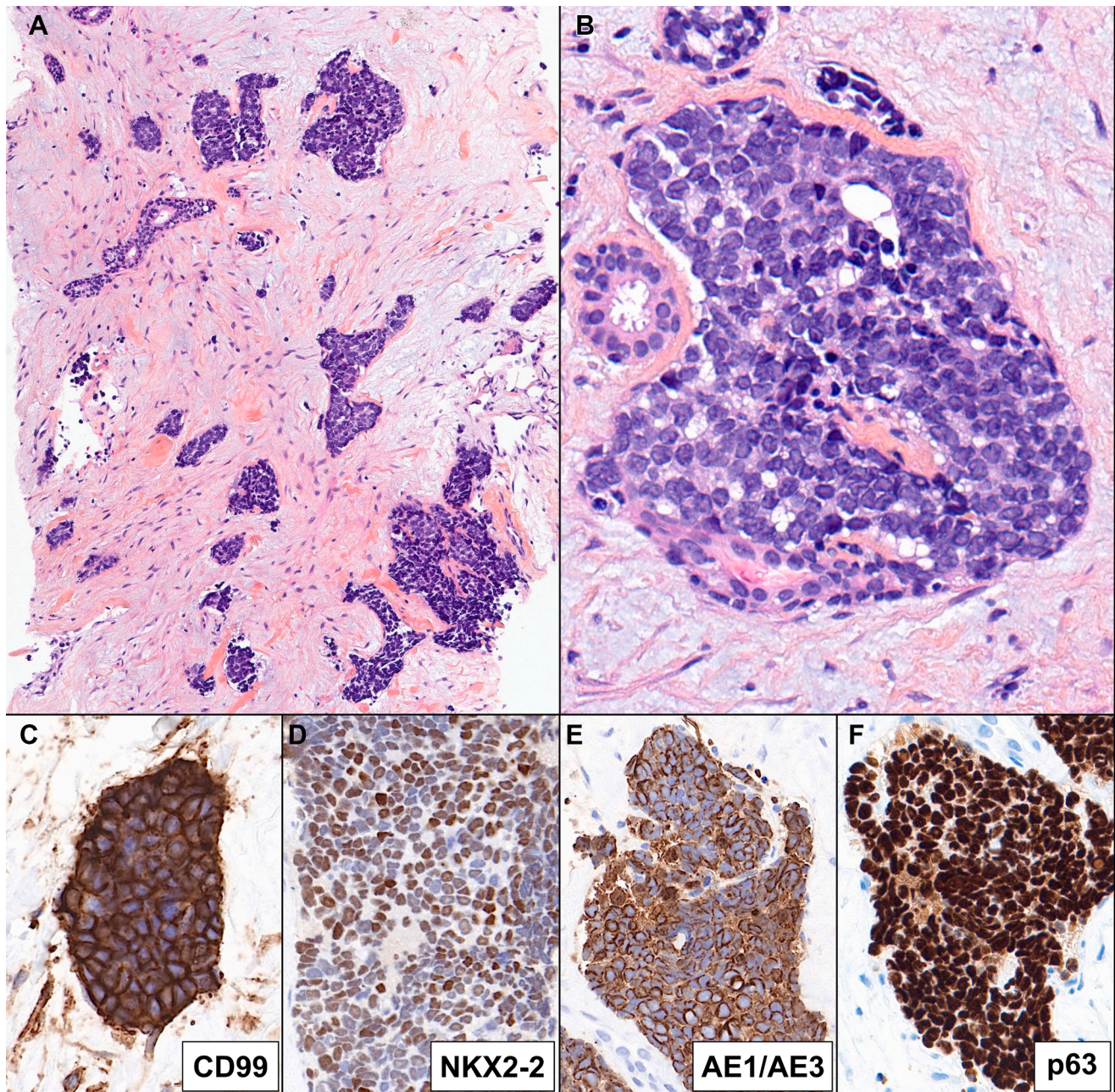


Figure 4.

A case of adamantinoma-like Ewing sarcoma. (A) Histological images show a basaloid proliferation composed of nests within a desmoplastic stroma. (B) The tumor cells are round with monotonous nuclei and inconspicuous nucleoli. Immunohistochemical analysis showed diffuse and strong membranous expression of CD99 (C), heterogeneous nuclear expression of NKX2-2 (D), diffuse cytoplasmic expression of PKC β II (not shown), diffuse cytoplasmic expression of pan-keratin (E) and diffuse nuclear expression of p63 (F).

Rare but recurrent copy number variations described in CIC-sarcoma include *MYC* amplification, 1p loss, and trisomy 8.^{99,100}

From a diagnostic standpoint, CIC aberrations can be detected using various techniques, including CIC break-apart FISH or NGS-based methods. However, it must be noted that there are significant false-negative rates associated with both techniques (up to 25% of cases with FISH).¹⁰¹ False-negative cases can often be accurately classified using gene expression profiling, methylation profiling, or, in some cases, by multiplying fusion gene detection algorithms. Nevertheless, in the author's experience, the use of modern immunohistochemistry techniques allows for accurate

classification of CIC-sarcomas without the need for molecular techniques in most cases.

Prognosis

CIC-sarcomas are aggressive neoplasms, with a 5-year survival rate of 34% to 43%.^{12,102} There is no consensus regarding the optimal management of CIC-sarcoma, but patients generally receive multimodal treatment, with most documented cases receiving Ewing sarcoma protocols. However, tumors have shown poor response to these regimens. Management based on high-grade soft tissue sarcoma protocols, following European guidelines, does not appear to significantly improve overall survival.¹⁰³

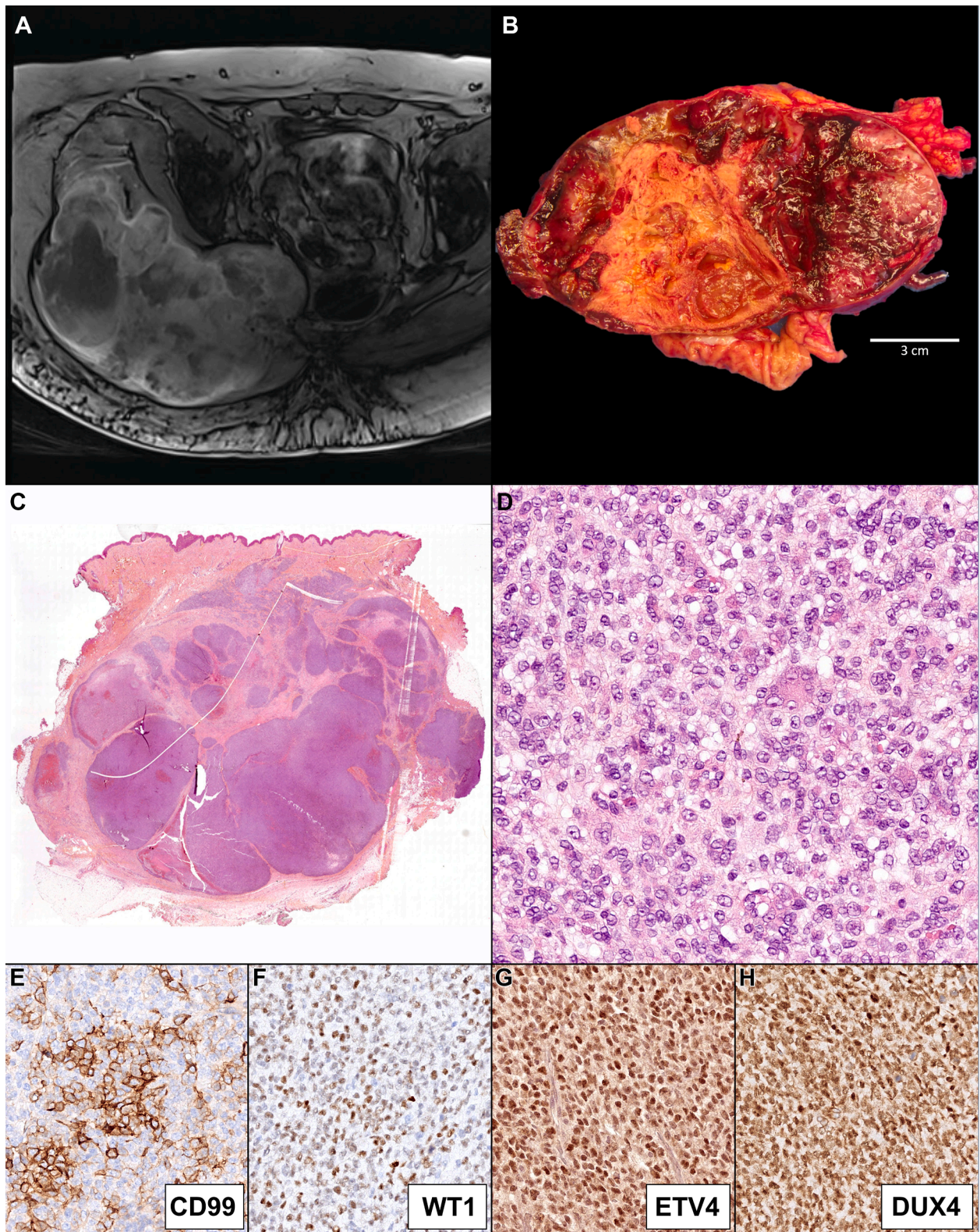


Figure 5.

CIC-sarcoma. (A) Axial T1-weighted Dixon contrast-enhanced magnetic resonance imaging (MRI) showing a large, lobulated, heterogeneous mass in the gluteal area. (B) Gross photograph of a gastric CIC-sarcoma with a variegated, tan, fleshy and hemorrhagic cut surface; the tumor also shows areas of fibrosis and necrosis related to neo-adjuvant treatment (wedge-shaped yellowish area on the left tumor side). (C) Low-power view showing a cutaneous lesion with a characteristic lobulated/multinodular silhouette. (D) High-power view shows sheets of small to intermediate-sized round cells with pale eosinophilic cytoplasm and irregular round nuclei with vesicular chromatin and conspicuous nucleoli; multinucleated tumor cells are also present. On immunohistochemistry, CIC-Sarcomas generally show patchy membranous staining of CD99 (E) and nuclear expression of WT1 (F) and ETV4 (G). In addition, cases with *CIC::DUX4* fusions (~95% of cases) show nuclear expression of DUX4 (H).

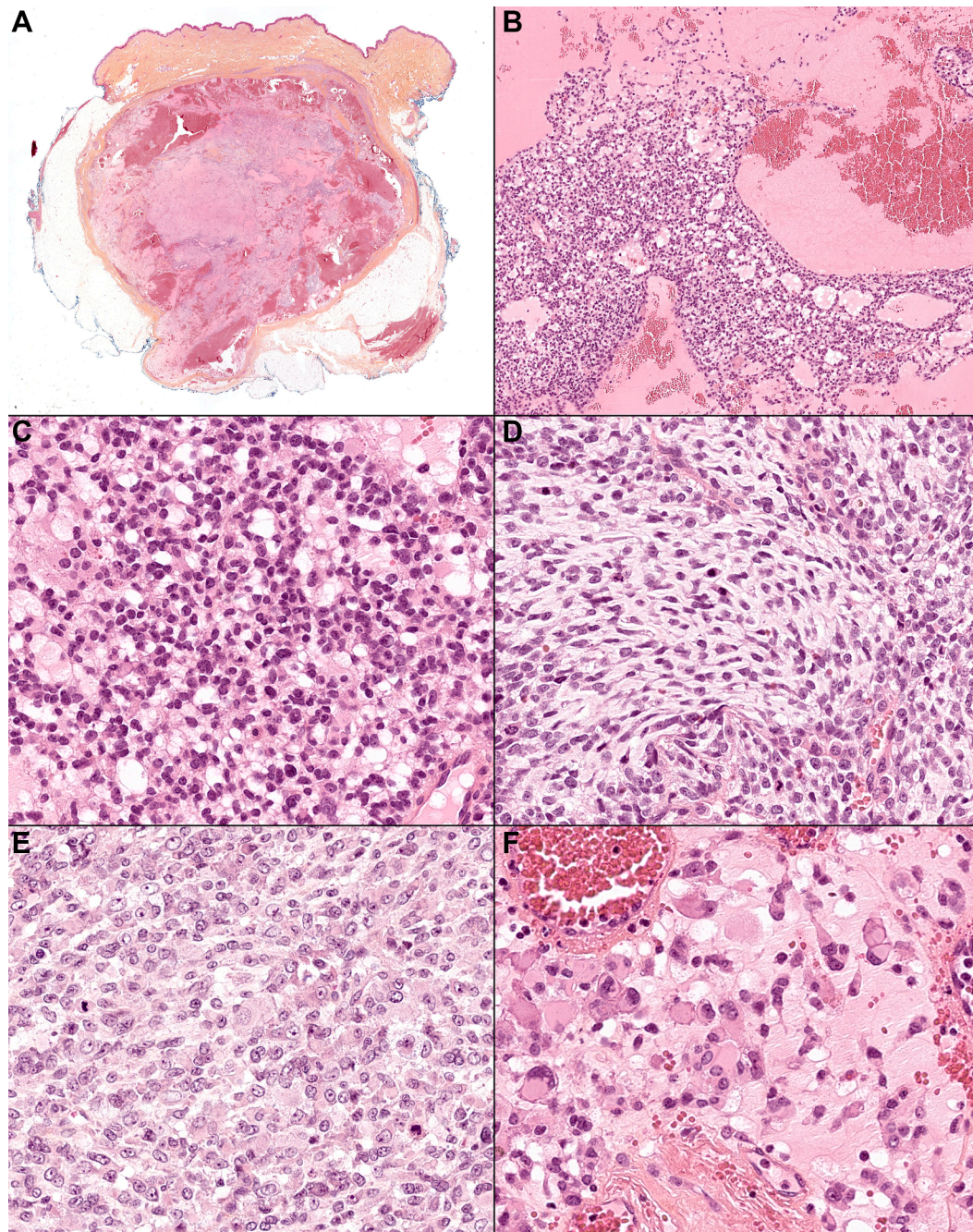


Figure 6.

CIC-sarcoma. (A) A cutaneous nodular tumor with prominent myxoid stroma. (B) Cystic change, hemorrhage, and prominent myxoid areas are seen in some CIC-sarcomas and can closely mimic myoepithelial tumors or extra skeletal myxoid chondrosarcoma (B). The cytological features of CIC-sarcoma are broad, varying from uniform small round cells (C), spindle cells (D), epithelioid cells with vesicular nuclei and prominent nucleoli mimicking SWI/SNF-deficient tumors (E), to rhabdoid cells (F).

A recent study has identified upregulation of *POLE* and DNA repair pathways as potential mechanisms contributing to the chemoresistance observed in CIC-sarcoma.¹⁰⁴

Of note, cutaneous and subcutaneous CIC-sarcomas appear to behave as aggressively as their deep soft tissue counterparts.¹⁰⁵

Sarcoma With *BCOR*-Genetic Alterations

Clinical Features

Sarcomas with *BCOR*-genetic alterations primarily occur in bone and soft tissue and only rarely in visceral organs. These

tumors can be broadly subclassified based on the underlying molecular alteration into 2 groups: those with *BCOR* gene fusions and those with *BCOR*-internal tandem duplications (ITDs).

Sarcomas with *BCOR* gene fusions (particularly, *BCOR::CNNB3*) show a marked male predilection, with the majority of cases occurring in children and adolescents (<20 years old).^{22,23} These tumors more frequently arise in bone than in the soft tissues. Rare visceral locations include the lung and kidney.^{24,106}

Sarcomas with *BCOR* ITD tend to occur more frequently in infants (<1 year old), with a slight male predilection. The tumors predominantly involve the soft tissue, especially in axial

locations, and only rarely arise in bone. Interestingly, rare soft tissue tumors with *YWHAE::NUTM2B/E* gene fusions have shown clinicopathologic similarities with *BCOR* ITD tumors.

It is important to note that molecular alterations involving the *BCOR* gene are found in several entities that demonstrate varying degrees of morphologic, immunohistochemical, and molecular overlap with *BCOR*-sarcomas. However, due to differences in clinical settings and, in some cases, prognosis, these entities are classified separately from *BCOR*-sarcomas and are seen as part of the “*BCOR* family of tumors.” These include clear cell sarcoma of the kidney, CNS tumor with *BCOR* ITD, and a subset of high-grade endometrial stromal sarcomas.¹⁰⁷

Radiology

Skeletal sarcomas with *BCOR* fusions occur more frequently in the pelvic bones and the metadiaphysis of long bones. On plain radiographs, they appear as well defined to poorly circumscribed lesions and are generally lytic, rarely showing mixed lytic or predominantly sclerotic appearances (Fig. 7A). Aggressive radiologic features, including permeative patterns, a moth-eaten appearance, and periosteal reactions, are common. On CT scans, tumors have been described as well defined to poorly marginated, often showing cortical destruction and heterogeneous enhancement (Fig. 7B). On MRI, tumors are typically large, frequently demonstrating cortical destruction and extraosseous extension. They usually show intermediate signal intensity on T1-weighted images and heterogeneous hyperintensity on T2-weighted images, likely reflecting their variable myxoid content. Notably, calcifications have been reported in *BCOR*-sarcomas, and primary soft tissue tumors seem to show similar MRI features to those of bone lesions. Information regarding the radiographic findings of sarcomas with *BCOR* ITD is currently limited. For a detailed review of the radiologic features of *BCOR*-sarcomas and their differential diagnoses, refer to the study by Sirisena et al.¹⁰⁸

Histopathologic Features

Tumors are composed of primitive round to spindle cells, with some cases showing a predominance of one of the cell components. The cells have scant cytoplasm and monotonous round to ovoid nuclei, which may be mildly anisocaryotic, and display homogeneous chromatin with inconspicuous nucleoli (Fig. 7C). The tumor cells are typically arranged in sheets and intersecting fascicles. Mitotic activity is variable, and necrosis can be present and may be extensive. Most tumors are richly vascularized by thin capillaries and show variable proportions of myxoid stroma, ranging from absent or scant to abundant (Fig. 7D). Other findings include multinodular, nested, palisading, or single-cell arrangements, collagenous strands, a rich sclerotic stroma, and bone and cartilaginous differentiation (Fig. 7E, F).^{22,23-26}

The “primitive myxoid mesenchymal tumor of infancy” is a descriptive term that falls within the spectrum of *BCOR*-sarcomas. These tumors generally show an abundant myxoid stroma and predominantly arise in the soft tissues of the trunk in infants. This variant significantly overlaps with clear cell sarcoma of the kidney and, like the latter, commonly harbors *BCOR* ITDs or *YWHAE::NUTM2B/E* gene fusions.²⁷

From a morphologic differential diagnosis standpoint, *BCOR*-sarcomas should be distinguished from synovial sarcoma, malignant peripheral nerve sheath tumor, solitary fibrous tumor, low-grade myxofibrosarcoma, and, in the context of primary bone tumors, small cell osteosarcoma.

Immunohistochemical Profile

The tumors show focal to diffuse membranous expression of CD99 and are negative for pan-keratin, S100, CD34, and Desmin. Similarly, the following markers, used to distinguish *BCOR*-sarcomas from other round cell sarcomas, are negative: NKX2-2, PKC β II, WT1, DUX4, ETV4, and AGGRECAN (Fig. 7G, H).

BCOR immunohistochemistry is typically diffusely and strongly positive in most cases; however, this marker lacks specificity and can also be strongly expressed in synovial sarcoma, solitary fibrous tumor, and other entities.^{28,109} Similarly, SATB2 is frequently expressed in *BCOR*-sarcomas but is nonspecific (Fig. 7I, J).

A more specific marker is *CCNB3*, but it is only expressed in tumors with *BCOR::CCNB3* gene fusions.²³ Notably, pan-TRK expression is frequently observed and is likely associated with *NTRK3* upregulation.¹¹⁰

Molecular Pathology and Genetic Alterations

BCOR-sarcomas present molecular aberrations involving the BCL6 corepressor (*BCOR*) gene, located in the Xp11.4 locus. Under physiological situations, 2 main functions of *BCOR* are known: (1) enhancing transcriptional repression of BCL-6 target genes through interaction with BCL-6 and (2) mediating epigenetic transcriptional repression as part of the Polycomb Repressive Complex 1.1 (PRC1.1). Through these functions, *BCOR* plays roles in cell differentiation, fate determination, and maintenance of stemness.

The most common *BCOR* gene fusion involves the Cyclin B3 gene (*CCNB3*), resulting from a paracentric inversion on the X chromosome. This rearrangement typically fuses the 5' end of *BCOR* to the 3' end of *CCNB3* and likely contributes to oncogenesis through cell cycle promotion via overexpression of Cyclin B3.²³ In addition, *BCOR::CCNB3* fusions are associated with *BCOR* and *NTRK3* overexpression, both of which likely contribute to tumor pathogenesis.^{22,110} Other *BCOR* fusion partners include *CIITA*, *MAML3*, *CHD9*, *KMT2D*, *ZC3H7B*, among others.^{110,111,112} Interestingly, in some fusions, *BCOR* is located in the 3'. For example, *ZC3H7B::BCOR* gene fusions have been identified in *BCOR*-sarcomas, high-grade endometrial stromal sarcomas, and rare tumors classified as malignant ossifying fibromyxoid tumors.¹¹³⁻¹¹⁵

As previously noted, other anomalies within the *BCOR*-sarcomas include *BCOR* ITD, most commonly involving exon 15. These duplications affect the C-terminal PCGF Ubiquitin-like fold discriminator domain of *BCOR*, which may impact the assembly and function of the PRC1.1.¹¹⁶ Notably, tumors harboring *BCOR* ITDs, *YWHAE::NUTM2B/E* fusions, and *BCOR* gene fusions show similar gene expression profiles, including upregulation of *BCOR* itself.¹¹⁷

BCOR fusions can be detected using NGS-based methods and FISH *BCOR* break-apart probes. Tumors with *BCOR* ITD and *YWHAE::NUTM2B/E* gene fusions can be detected using targeted RNA-sequencing panels.

Prognosis

Sarcomas with *BCOR::CCNB3* have shown a 5-year overall survival rate of 72% to 76%, which is comparable to that of Ewing sarcoma. Although treatment schemes are not standardized, most cases have been managed with Ewing sarcoma protocols and have shown histological signs of response to treatment.^{22,118}

In contrast, sarcomas with *BCOR* ITD or *YWHAE::NUTM2B/E* gene fusions have been associated with a more aggressive clinical course, with a reported 5-year overall survival rate of 34% in 1 series.²⁷ In the same study, intraabdominal or retroperitoneal locations were associated with a poorer prognosis compared

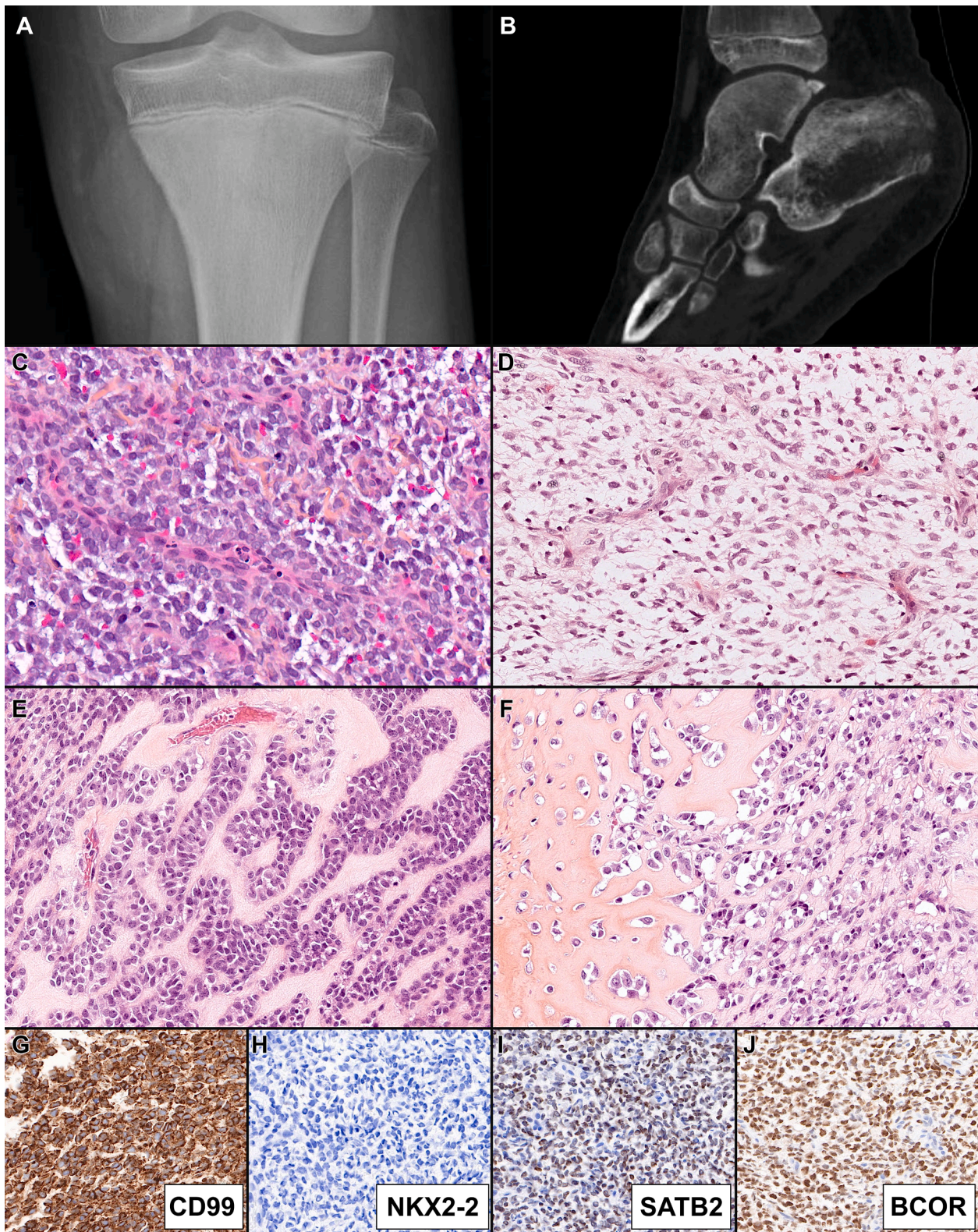


Figure 7.

BCOR-sarcoma. (A) Anteroposterior radiography showing a lytic lesion developing in the metaphysis of the tibia with infiltration into the surrounding soft tissues; note the ill-defined cortex in the tumor region. (B) Sagittal computed tomography-scan showing an ill-defined lytic lesion of the calcaneus. (C) A densely cellular tumor composed of sheets of round to ovoid cells with fine chromatin and inconspicuous nucleoli. (D) A case with prominent myxoid change and a rich capillary network. (E) A tumor with a trabecular arrangement of cells in a hyalinized stroma. (F) A tumor with osteogenic areas. On immunohistochemistry, BCOR-Sarcomas frequently express CD99 (G), but in contrast to Ewing sarcoma, they are negative for NKX2-2 (H). In addition, tumors typically express SATB2 (I) and BCOR (J).

with trunk locations. Treatment schemes for this molecular subset of BCOR-sarcomas are not standardized. Histological response to treatment was reported in 2 cases, 1 treated with neoadjuvant chemotherapy using a vincristine, actinomycin-D, cyclophosphamide, and adriamycin regimen and the other with vincristine, actinomycin-D, and cyclophosphamide alternating with ifosfamide and etoposide, combined with surgery and brachytherapy.²⁷

Emerging Entities in the Spectrum of BCOR-Sarcoma

A recent study has described a small subset of sarcomas with *KDM2B* gene rearrangements showing epigenetic and morphologic overlap with BCOR-sarcomas.¹¹⁹ Like BCOR, *KDM2B* is a key component of the PRC1.1; therefore, gene aberrations affecting *KDM2B* could disrupt the complex and affect the regulation of its target genes. Although reported cases remain limited, these findings suggest that *KDM2B*-rearranged sarcomas could represent an additional member of the BCOR-sarcoma family.

Round Cell Sarcomas With *EWSR1*-Non-ETS Fusions

PATZ1-Rearranged Sarcoma

Clinical Features

PATZ1-sarcomas are rare, with <50 cases reported in the literature to date. These tumors exhibit a male predilection, wide age distribution, and a peak incidence among middle-aged adults (40–50 years). Tumors most commonly arise in the soft tissues of the thoracoabdominal regions and have been infrequently reported in the head and neck, extremities, lung, and pelvis. No primary skeletal locations have been documented.^{30,29} Clinical symptoms are largely nonspecific and include a palpable mass and tenderness.

Radiology

Data on the radiologic features of PATZ1-sarcomas are very limited. MRI findings reported in 3 cases from 2 recent studies described intermediate to hyperintense soft tissue masses on T2-weighted images with variable contrast enhancement.^{29,120}

Macroscopic and Histopathologic Features

The rare documented cases with macroscopical descriptions consisted of well circumscribed to infiltrative masses with tan-yellow to gray-white cut surfaces and variable areas of necrosis.³⁰

Histologically, at low power, PATZ1-sarcomas are generally well circumscribed, variably lobulated and septated, and often surrounded by a fibrous pseudocapsule. In some cases, tumors are infiltrative or show invasion into the surrounding tissues with tongue-like projections. Lymphoid aggregates may be observed at the tumor periphery. A common and diagnostically useful finding is the presence of pseudocysts containing proteinaceous material, which, when numerous, may impart a follicular-like pattern reminiscent of the thyroid tissue (Fig. 8A).

At higher magnification, the tumors are typically polymorphous, composed of spindle-to-round or ovoid cells, and in some cases, epithelioid cells. The cellular composition is variable; most tumors predominantly contain spindle-to-ovoid cells (Fig. 8B), although rare cases are composed predominantly or exclusively of round or epithelioid cells. Tumor cell nuclei are generally bland and monotonous, with homogeneous chromatin and inconspicuous nucleoli; however, examples with more pronounced pleomorphism have been reported. Mitotic activity is

variable, and some tumors show necrosis. Interestingly, a subset of cases may show abrupt rhabdomyoblastic differentiation (Fig. 8C).

Tumor cellularity ranges from low to high, depending on the amount of stroma, which may be predominantly sclerotic or fibromyxoid (Fig. 8D, E). Within the stroma, tumor cells may be arranged in solid sheets, trabecular, reticular, and occasionally whorled patterns. Additional findings include the presence of small capillaries with thickened, hyalinized walls. Rarely, degenerative-type nuclear atypia and marked nuclear pleomorphism are observed.

Entities in the differential diagnosis of PATZ1-sarcomas include solitary fibrous tumor, myoepithelioma, rhabdomyosarcoma, and malignant peripheral nerve sheath tumor with rhabdomyoblastic differentiation (malignant triton tumor).

Immunohistochemical Profile

PATZ1-sarcomas exhibit a “polyphenotypic” or “neuromuscular” immunohistochemical profile, characterized by a near-constant coexpression of S100, Desmin, PAX7, and MYOD1 (Fig. 8G, I). Myogenin and SOX10 are expressed in a smaller proportion of cases and typically in a more focal pattern than the aforementioned markers (Fig. 8J). Most tumors express GFAP, and a significant proportion shows keratin positivity, usually in a focal, weak, or nonspecific dot-like pattern. Variable expression of CD99 has been reported, ranging from absent to diffuse cytoplasmic or membranous. CD34 and OLIG2 may be rarely expressed. The following markers commonly used in round cell sarcoma workups have been reported as negative: BCOR, NKX2-2, NKX3-1, PKC β II, and DUX4 (C-terminal).

Molecular Pathology and Genetic Alterations

All PATZ1-sarcomas reported to date have harbored *EWSR1::PATZ1* gene fusions, likely resulting from an intrachromosomal paracentric inversion. A subset of cases also harbored copy number loss of *CDKN2A/B*.

PATZ1 encodes a structural transcriptional regulator, which plays roles in stemness, neurogenesis, adipogenesis, and cell proliferation.^{121–123} Due to its diverse functions, *PATZ1* has been associated with oncogenesis in various cancer types.^{124,125} Most fusions involving *PATZ1* affect exon 1, where the BTB (Broad-complex, Tramtrack, and Bric-à-brac) domain is located. This likely leads to disruption of the BTB domain, which is essential for *PATZ1* dimerization, interaction with corepressors, and regulation of p53 activity.^{126,127} As a result, disruption of the BTB domain may impair *PATZ1*'s tumor-suppressive functions, thereby promoting oncogenic transformation.

It is noteworthy that identical *EWSR1::PATZ1* fusions have also been recently described in a subset of neuroepithelial tumors from the CNS and thyroid-like renal cell carcinomas. These entities display phenotypes distinct from PATZ1-sarcomas.^{128,129}

From a diagnostic perspective, as *EWSR1* and *PATZ1* are located in close proximity on chromosome 22 (~2 Mb apart), break-apart FISH techniques are frequently negative. Therefore, NGS-based methods or RT-PCR should be preferred for confirming the fusion event.

Prognosis

Currently, among 31 reported cases with known disease status, 11 had metastatic disease (35%).^{29,30,120,130–133} However, cases with long-term follow-up (>24 months) remain scarce. The most frequent site of metastasis was the lung, and a subset of cases presented with multimetastatic disease at presentation.

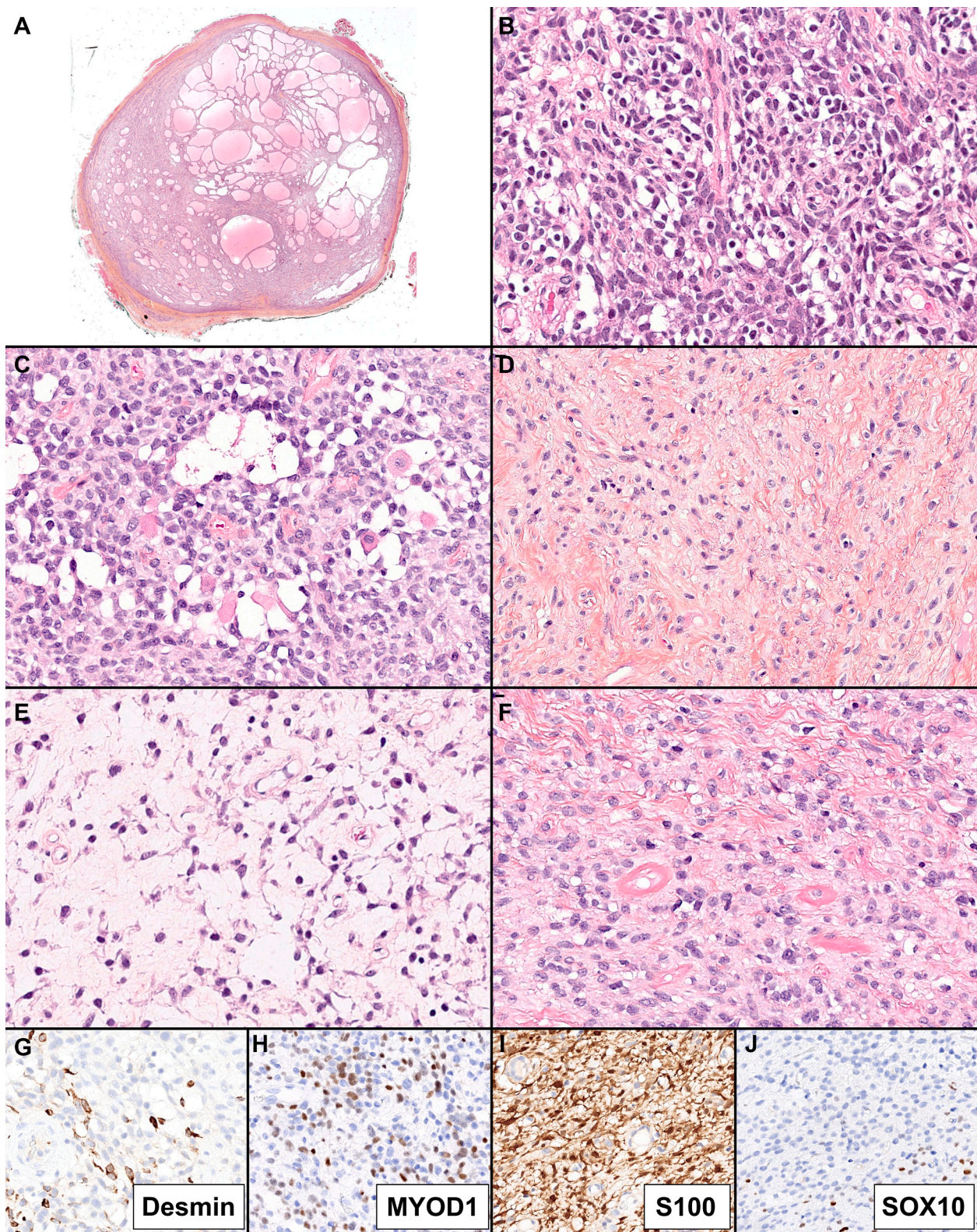


Figure 8.

PATZ1-sarcoma. (A) Ultra-low-power view showing an encapsulated nodular lesion with prominent microcystic change, simulating thyroid tissue. (B) Densely cellular areas composed of spindle-to-round cells with mild to moderate nuclear pleomorphism. (C) Areas showing abrupt rhabdomyoblastic differentiation. (D) A tumor composed of bland spindle cells in an abundant fibrous stroma. (E) Areas rich in myxoid stroma and single-file arrangement of cells. (F) Small capillaries with thick, hyalinized walls are frequently seen in PATZ1-sarcomas. These tumors are characterized by a neuromuscular phenotype, with frequent coexpression of Desmin (G), MYOD1 (H), S100 (I) and, in a smaller proportion of cases, SOX10 (J).

There is no standardized treatment for NFATC2-sarcomas. Most cases have been managed with a combination of surgery, radiotherapy, and chemotherapy.

NFATC2-Rearranged Sarcoma

Clinical Features

NFATC2-sarcomas encompass tumors with either *EWSR1::NFATC2* or *FUS::NFATC2* gene fusions. Among the <80 cases reported in literature with significant clinical data, NFATC2-sarcomas have shown a marked predilection for males and a peak age of onset in young adults (25–40 years). Tumors can develop in both skeletal and extraskelatal sites, but most cases occur in bone, particularly the femur and the tibia. Notably, tumors with *FUS::NFATC2* fusions have been reported exclusively in bone. Extraskelatal tumors have been documented in various locations, including intraabdominal and retroperitoneal regions. Reported clinical symptoms are nonspecific and include pain and a mass-forming lesion. A long duration of symptoms before consultation has been documented, ranging from several months to years.^{31–36,134–139}

Radiology

Studies specifically focusing on the radiologic features of NFATC2-sarcoma are currently unavailable. Reported primary tumor sizes range from 2 to 15 cm (median, 8 cm). Skeletal tumors are typically lytic, well circumscribed to poorly defined, and located in the metaphysis or diaphysis of long bones. Aggressive radiologic features, including cortical destruction and infiltration into the surrounding soft tissues, can be seen. Interestingly, NFATC2-sarcomas may exhibit a particular radiologic pattern, suggestive of slow tumor growth. This is characterized by an intramedullary lytic lesion with expansile remodeling, variably accompanied by an extraosseous component (Fig. 9A, B). In some cases, overt cortical destruction is absent, and the surface extension induces cortical thickening and scalloped erosion of the subjacent cortex.¹⁴⁰

Macroscopic and Histopathologic Features

Macroscopically, NFATC2-sarcomas are generally large, lobulated to infiltrative, and show a whitish to tan, fleshy cut surface, with variably myxoid areas (Fig. 9C).

Microscopically, NFATC2-sarcomas are characterized by a wide morphologic spectrum.^{31,32,34,138} At low power, tumors may appear nodular, multinodular, or infiltrative, and in bone, they often show entrapment of bone trabeculae. Tumor cells exhibit epithelioid, primitive round cell, or spindle cell morphology in varying proportions; in some cases, only 1 cell type is present. When epithelioid or round, the cells are often arranged in small nests, trabeculae, or cords (Fig. 9D, E), although solid sheet arrangement is also possible (Fig. 9F). On the other hand, spindle cells generally arrange in short, sweeping fascicles (Fig. 9G).

Nuclear features are variable. Atypia ranges from mildly pleomorphic nuclei with hyperchromasia to moderately pleomorphic nuclei with variably conspicuous nucleoli. Similarly, mitotic activity can range from low to brisk, and necrosis is variably present. In the author's experience, cases with predominantly spindle cell morphology tend to have mild atypia, low mitotic activity, and no necrosis, suggesting a low-grade lesion. In contrast, tumors with a primitive round cell morphology can overlap significantly with Ewing sarcoma and may represent a higher-grade variant within the NFATC2-sarcoma spectrum.

The tumor stroma can be fibrous, fibromyxoid, sclerotic, or hyalinized. The latter may closely simulate osteoid when individual cells are embedded in the matrix, potentially leading to an incorrect diagnosis of osteosarcoma (see Fig. 3E from the study by Perret et al³¹). Similarly, the matrix can be myxochondroid or can show true cartilaginous metaplasia. Rare cases have shown highly pleomorphic nuclei, typically in a focal distribution.

Due to their extremely polymorphous appearance, the morphologic differential diagnosis of NFATC2-sarcoma is broad. These tumors show significant overlap with myoepithelioma. Other important considerations include ossifying fibromyxoid tumor, sclerosing epithelioid fibrosarcoma, extraskelatal myxoid chondrosarcoma, mesenchymal chondrosarcoma, osteoblastoma, osteosarcoma, and other round cell sarcomas.

Immunohistochemical Profile

Most reported cases of NFATC2-sarcomas have shown CD99 expression, which ranges from focal to diffuse and may be membranous, cytoplasmic, or display dot-like patterns (Fig. 9H). Focal expression of keratins has been reported in a subset of cases. S100 is typically negative, except for areas with cartilaginous differentiation. CD34, Desmin, and SOX10 are consistently negative.

Irrespective of the fusion variant, all tested cases in a series showed cytoplasmic expression of AGGRECAN (Fig. 9I), which demonstrates higher specificity than CD99.³¹ However, this marker was also expressed in a significant proportion of myoepitheliomas. Nuclear positivity for NKX3-1, NKX2-2, and PAX7 has been reported in cases with *EWSR1::NFATC2* fusions but not in *FUS::NFATC2* variants. Importantly, expression of NKX3-1 and NKX2-2 can also be seen in mesenchymal chondrosarcoma, whereas NKX2-2 and PAX7 are commonly positive in Ewing sarcoma.^{6,8,33} A subset of cases has shown nuclear expression of BCOR, WT1, and ETV4.³¹

Molecular Pathology and Genetic Alterations

These tumors are characterized by fusions involving *EWSR1* (22q12.2) or *FUS* (16p11.2) genes with *NFATC2* (20q13.2). The nuclear factor of activated T cells (NFAT) family of transcription factors is composed of 5 members (*NFATc1–4* and *NFAT5*), which have roles in immune response through regulation of T-cell activity, differentiation of various cell lineages, and oncogenesis.^{141–143}

In cases with *EWSR1::NFATC2* fusion, the rearrangements are complex, leading to a derivative ring chromosome, and are commonly associated with amplifications encompassing the *EWSR1* and *NFATC2* loci. Cases with *FUS::NFATC2* fusions may show copy number gain of the *FUS* and *NFATC2* loci³¹ but do not seem to be associated with amplifications (high-level copy number gains).

At the methylation and transcriptomic levels, NFATC2-sarcomas have been shown to form a distinct cluster, independent from other round cell sarcomas, supporting their designation as a unique entity. Interestingly, both *FUS* and *EWSR1* variants are generally fused to exon 3 of *NFATC2*, likely resulting in the disruption of the N-terminal regulatory domain of NFATc2. However, significant transcriptomic differences have been observed between the 2 variants,³⁶ a phenomenon that contrasts with other tumors in which alternative *FUS*/*EWSR1* fusions do not significantly affect gene expression (eg, Ewing sarcoma and myxoid liposarcoma). One possible explanation is the presence of different structural chromosomal alterations and copy number variants between the fusion types, as shown in a small cohort of cases.³¹ Whether *FUS* and *EWSR1* variants of NFATC2-sarcomas

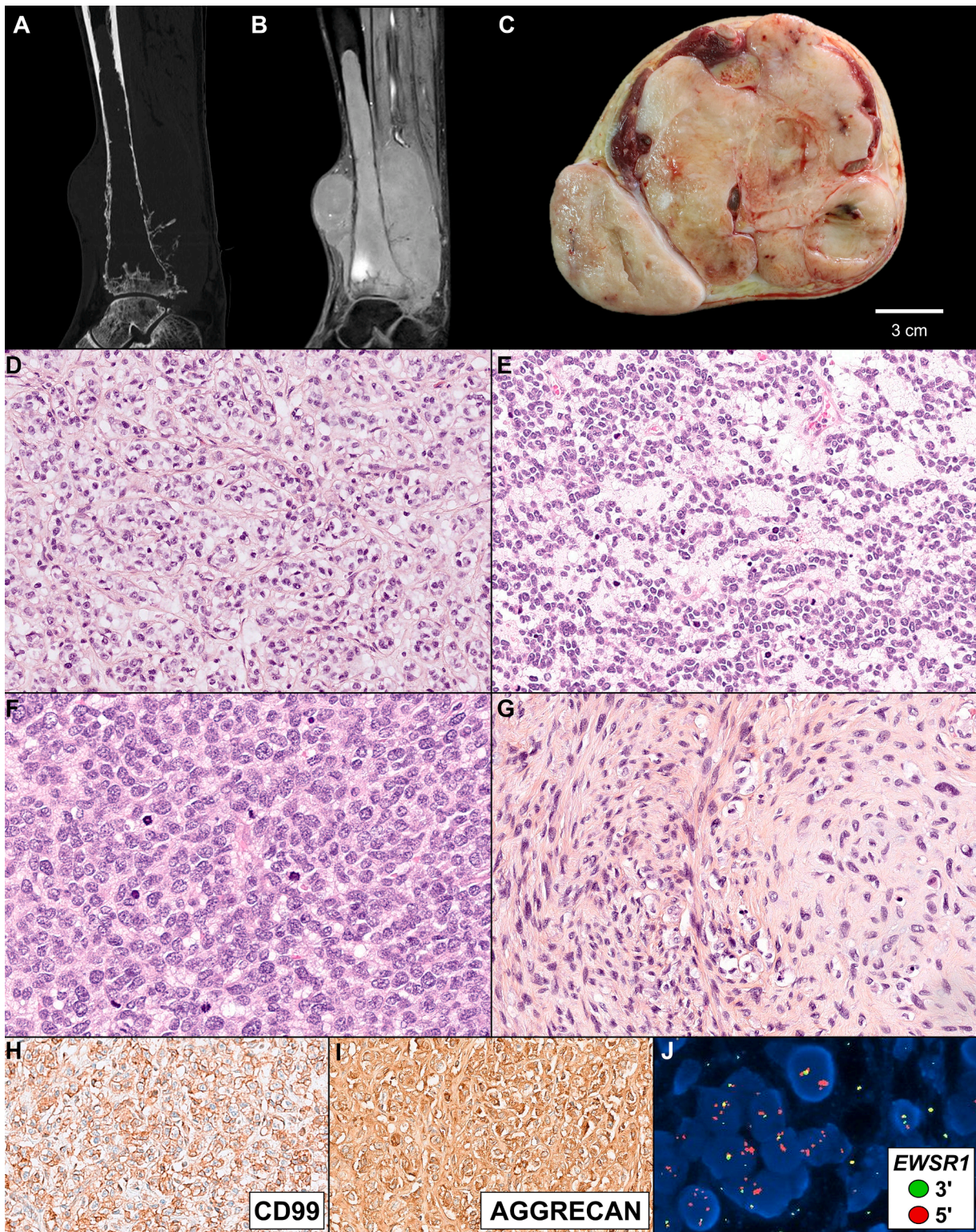


Figure 9.

NFATC2-sarcoma. (A) Sagittal computed tomography-scan of a *FUS::NFATC2* sarcoma, showing a large lytic lesion of the tibia with endosteal scalloping and a massive extraosseous component with periosteal reaction. The lesion had been present for 4 years and was managed conservatively before recurring and ultimately leading to amputation. (B) Sagittal T1-weighted Dixon MRI image of the same lesion. (C) Macroscopic photograph, showing a large, multilobulated tumor with a whitish cut surface, massively infiltrating the tibia and surrounding soft tissues. NFATC2-sarcomas have a polymorphous histological appearance, but most tumors show at least focal areas composed of nests and cords of round to epithelioid cells with variably abundant pale cytoplasm (D and E). Less frequently, tumors may be composed of sheets of primitive round cells, overlapping morphologically with Ewing sarcoma (F), or a fascicles of bland spindle cells (G). On immunohistochemistry, NFATC2-sarcomas are generally positive with CD99 (H) and diffusely positive with AGGRECAN (I). *EWSR1::NFATC2* variants have also been reported to commonly express NKX3-1 (not shown). A characteristic FISH pattern can be seen in most *EWSR1::NFATC2* variants, consisting of gain/amplification of the 5' probe of *EWSR1* (J).

show distinct morphologic features and prognostic differences should be addressed in future studies.

EWSR1/FUS::NFATC2 fusions can be evidenced using RT-PCR or NGS-based methods. In addition, *EWSR1* variants can be suspected using commercially available *EWSR1* break-apart FISH probes, which reveal a distinctive signal pattern consisting of amplification of the 5' end probe (Fig. 9J). It should be noted that *EWSR1/FUS::NFATC2* fusions have also been described in bone cysts and hemangiomas.^{144,145} However, unlike in sarcomas, these tumors do not show amplification of the involved genes.

Prognosis

Data regarding the prognosis of NFATC2-sarcomas are limited to ~38 cases with follow-up.^{31,32,34,35,135,137–140,146–152} Among these, 10 cases (28%) showed confirmed metastatic spread and 9 cases (23%) experienced local recurrences. These include only 5 *FUS::NFATC2*-fused cases, of which 3 (60%) developed metastasis and 2 (40%) local recurrences.

There are currently no standardized treatment schemes for NFATC2-sarcomas. A significant proportion of cases have been managed following Ewing-sarcoma protocols. Tumors have generally shown poor response to neoadjuvant chemotherapy.

Concluding Remarks

The classification of round cell sarcomas is becoming increasingly complex, often leading to diagnostic challenges. Although ancillary techniques will continue to support more accurate and refined diagnoses, a methodical assessment of histomorphologic features and the rational integration of clinical and radiologic data remain the cornerstone of a precise diagnosis.

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Author Contributions

R.E.P. conceptualized and wrote the review.

Data Availability

The data sets used during the current study are available from the corresponding author on reasonable request.

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Declaration of Competing Interest

None.

Ethics Approval and Consent to Participate

Not required.

Supplementary Material

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