Epithelioid Sarcoma

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• Epithelioid sarcomas are rare, mesenchymal tumors of unknown histogenesis and display multidirectional differentiation, which is predominantly epithelial. They have no normal cellular counterpart and differ from both synovial sarcoma and carcinoma. They account for less than 1% of all soft tissue sarcomas and are usually slow growing, with peak incidence in young adult men and occur predominantly in extremities. Histologically, they form nodules, with central necrosis surrounded by bland, polygonal cells with eosinophilic cytoplasm and peripheral spindling. They regularly express vimentin, cytokeratins, epithelial membrane antigen, and CD34, whereas staining is usually negative with S100, desmin, and FLI-1. Ultrastructurally, they display epithelial and mesenchymal features, including myofibroblastic differentiation. They manifest no specific cytogenetic findings, but several cases have displayed chromosomal abnormalities in 22q region. Clinically, they have a high recurrence rate, and up to 50% of epithelioid sarcomas metastasize. Proximal, fibroma-like, and angiomatoid variants have been described. The proximal variant (with larger cells, prominent nucleoli, and rhabdoid changes) is clinically more aggressive.

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Epithelioid sarcoma (ES) is a soft-tissue tumor, composed of large, polygonal cells resembling carcinomas. Epithelioid sarcoma was first characterized as a distinct clinicopathologic entity by Enzinger in 1970,[1] after being described as aponeurotic sarcoma in 1961 by Laskowski[2] and as large-cell sarcoma of the tendon shealth in 1968 by Bliss and Reed.[3] It is a relatively rare, soft-tissue sarcoma (accounting for <1% of all soft-tissue sarcomas) of unknown histogenesis, usually slow-growing throughout a period of years, with a seemingly benign pathomorphologic appearance and is, therefore, often misdiagnosed on first encounter.[4] Epithelioid sarcoma is a mesenchymal tumor with a predominant epithelial differentiation, showing reactivity for both epithelial and mesenchymal markers, such as cytokeratin, epithelial membrane antigen, vimentin and CD34.[4–7] Unlike most soft tissue sarcomas, ES characteristically spreads via lymphatics to noncontiguous areas of skin, deep soft tissue, fascia, and bone, as well as by direct extension.[6,8,9]

In its conventional or classic form, it is usually a solitary or multifocal tumor involving the dermis, subcutis, or deeper soft tissues in the distal extremities of young adults in 55% to 60% of cases[4,6] and is frequently associated with ulceration of the overlying skin. The classic-type ES is rare in children and older individuals, and occurs more commonly in men than in women. Epithelioid sarcoma has a tendency to develop local recurrences and metastasis thereafter to regional lymph nodes, lung, bone, brain, and other locations, including the scalp, which has been noted in 40% to 50% of cases and can be reduced by adequate surgery.[4–6] The recognized adverse prognostic factors include male sex, older age, large size, multifocality, proximal or axial location, depth of invasion, mitotic activity, necrosis, vascular invasion, tumor hemorrhage, nodal involvement, rhabdoid cytomorphology, and inadequate excision.[4–6,10]

Microscopically, ES is usually multinodular with a central necrosis surrounded by bland polygonal cells with eosinophilic cytoplasm and peripheral spindling. The classic-type ES has cells with only mild atypia, although they can appear more pleomorphic in recurrences or metastases. Therefore, it has a wide differential diagnosis from numerous benign and malignant conditions, including granuloma annulare, melanoma, and epithelioid vascular neoplasms.[4–6] Hence, ES is characterized by diagnostic difficulties, both clinically and histopathologically, which result in a high frequency of initial misdiagnosis and the loss of crucial treatment time.

Apart from the more common, classic-type of ES (granuloma-like), angiomatoid or angiosarcoma-like and fibrous histiocytoma-like or fibroma-like subtypes were first noted in 1991 and 1992, respectively.[11,12] Lately, an aggressive subtype of ES has been identified, known as the proximal type or axial type.[13] The proximal subtype was first described as a distinct subtype of ES in 1997.[13] Histologically, the proximal subtype differs from the classic type by its larger epithelioid cells, with vesicular nuclei, and prominent nucleoli; copious, eccentric cytoplasm; marked cytologic atypia; and frequent rhabdoid features.[13] Tumoral necrosis is also a common finding in the proximal subtype, but it is usually without the granuloma-like appearance of the classic type.[13,14] Clinically, the proximal subtype differs from the classic type by its multinodular growth pattern, more frequent occurrence in older patients, more proximal/axial distribution (mainly, but not exclusively, involving the pelvic, perineal, and genital areas), more deep-seated location, and more aggressive clinical behavior from the outset (with more frequent recur-

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rence, earlier development of metastasis, and a higher incidence of tumor-related deaths).[13,14] However, it is not yet certain whether the reduced survival associated with the proximal subtype is due to its different histomorphology or to its lesser surgical resectability because of its deeper location, more proximal distribution, and/or larger size at diagnosis.

CLINICAL PRESENTATION

Clinically, ES usually presents as painless, slow-growing, firm nodules in deep soft tissue (less frequently, in skin or subcutis), often accompanied by superficial ulceration, hemorrhage, necrosis, and plaques. It can attain a large size, up to 20 cm in diameter. Epithelioid sarcoma occurs at any age, with a peak in young adults, and is more frequent in men. Ulcerating ES lesions have raised margins and are nonhealing, clinically resembling granuloma annulare. Deeper ES lesions can extend along tendon sheaths or aponeuroses.[4–10] The proximal subtype occurs predominantly in adults (age range, 13 to 80; median, 40), with a slight predominance in men, and mainly in axial or proximal regions, including limb girdles, pelvis, perineum, or genitalia, mediastinum, and trunk.[13,14] However, the classic and proximal types can each occur in either proximal or distal locations. A higher than usual proportion of cases (up to 27%)[4,9] has been associated with antecedent trauma, including origin in scar tissue,[15,16] although any causal relationship is unsubstantiated.

PATHOLOGIC FEATURES

Gross Features

Grossly, ES is a predominantly solid, multinodular mass, with an ill-defined, diffusely infiltrative, glistening, gray-tan appearance and multiple areas of hemorrhage and necrosis.[4–6,8]

Microscopic Features

Histologically, ES is characterized by irregular nodules composed of a proliferation of relatively uniform, polygonal or epithelioid cells (Figure 1), often with loss of cohesion, which merge peripherally into spindle cells embedded in desmoplastic fibrous stroma without a clear demarcation. The cells usually have relatively abundant, deeply eosinophilic cytoplasm and minimal pleomorphic nuclei (Figure 1, inset) with occasional mitoses (often less than 5 per 10 high-power fields). The tumor is often associated with lymphocytic infiltration, mucin deposition, hemorrhage, hemosiderin deposition, and vascular invasion. Ulceration and necrosis are typical, with the frequent central necrosis (Figure 2), resulting in a pseudogranulomatous appearance, which can mimic benign necrobiotic granulomatous lesions. Stromal changes include desmoplasia, focal calcification, or metaplastic ossification, and rarely, myxoid change.[4–6,8]

Less commonly, ES can exhibit a prominent cord of bland spindle cells with a collagen-rich storiform pattern (the fibroma-like variant[7,12] with an affinity for bone involvement), a vascular proliferation with red blood cells in the tumor area (the angiomatoid or angiosarcoma-like variant[7,17]; Figure 3), or a solid growth pattern with larger cells with vesicular pleomorphic nuclei, prominent nucleoli, and focal or prominent rhabdoid features (proximal type or rhabdomyosarcoma-like variant[13,14]; Figure 4). These rhabdoid features include intracytoplasmic, paranuclear, spheroid, hyaline-like globules compressing and displacing the nucleus eccentrically (Figure 4, inset). Additionally, the proximal variant is characterized by marked cytologic atypia, frequent mitosis, vascular invasion, and absence of a granulomatous appearance.[13,14] Rarely, a tumor has features of both the classic and proximal variants.[18] Although the concept of proximal-type ES is not yet universally accepted, Sur and Nayler[18] described the hybrid form, showing transitions from the morphologically classic-type ES to the high-grade morphology typical of proximal-type ES and suggested that proximal-type ES is a distinct entity.

Immunohistochemical Features

Although there are several reported immunohistochemical studies on ES, a specific tumor marker for the diagnosis of this tumor has not yet been established. Virtually all cases of ES are positive for cytokeratins (Figure 5) and epithelial membrane antigen (Figure 6).[4–7] Among the cytokeratins, the reported percentage of expression in ES is as follows: CK8, 94%; CK14, 48%; and CK19, 72%, but rarely, CK7, 22%; CK20, 15%; or CK5/6, 30%, focal.[7] Most cases co-express vimentin (Figure 7) and cytokeratin, but a few are vimentin-negative.[19] CD34 staining is positive in more than half of ESs.[4–7] The other endothelial markers, CD31[20] and FLI-1[21], are usually negative. Smooth muscle actin and neurofilament are often positive, especially in the spindle cells.[4–7] Desmin was positive in several cases in one study,[13] but negative in all variants of ES examined in a larger series.[7] Most cases are negative for S100, although HMB-45 was found in a minority of cells in 3 cases of proximal-type ES.[13]

However, no single marker was able to distinguish the 4 main histologic subtypes of ES.[4–7] More recent studies[22–24] have suggested that CA 125 (Figure 8) immunoreactivity, with an elevated serum CA 125 level, could be a useful tumor marker for diagnosing ES and monitoring its clinical course. Ten (91%) of 11 ESs (comprising 10 classic types and 1 proximal type) were positive for CA 125, but other soft-tissue tumors, including 6 synovial sarcomas, 6 clear cell sarcomas, 8 leiomyosarcomas, 6 rhabdomyosarcomas, 14 liposarcomas, 5 malignant peripheral nerve sheath tumors, 10 malignant fibrous histiocytomas, 17 desmoid tumors, 6 squamous cell carcinomas (cutaneous squamous cell carcinoma of the distal extremities), 2 rheumatoid nodules, and 7 foreign body granulomas used as controls were negative for CA 125.[23]

Electron Microscopic Features

Ultrastructurally, ES displays a spectrum of appearances from undifferentiated cells, and carcinoma-like epithelial differentiation to mesenchymal features, including myofibroblastic differentiation.[5,13,25,26] These features include desmosome-like intercellular junctions, surface microprocesses or filopodia, and interdigitating cell membranes indicating epithelial differentiation.[5,25,26] Other features are dilated, rough endoplasmic reticulum; intermediate filaments; and peripheral myofilament bundles, especially in the spindle cells at the periphery of the nodules, indicating fibrohistiocytic, fibroblastic, or myofibroblastic differentiation.[5,25,26] The rhabdoid cells in the proximal subtype show abundant paranuclear, cytoplasmic, well-delineated aggregates of intermediate filaments, indenting the nucleus eccentrically.[13]

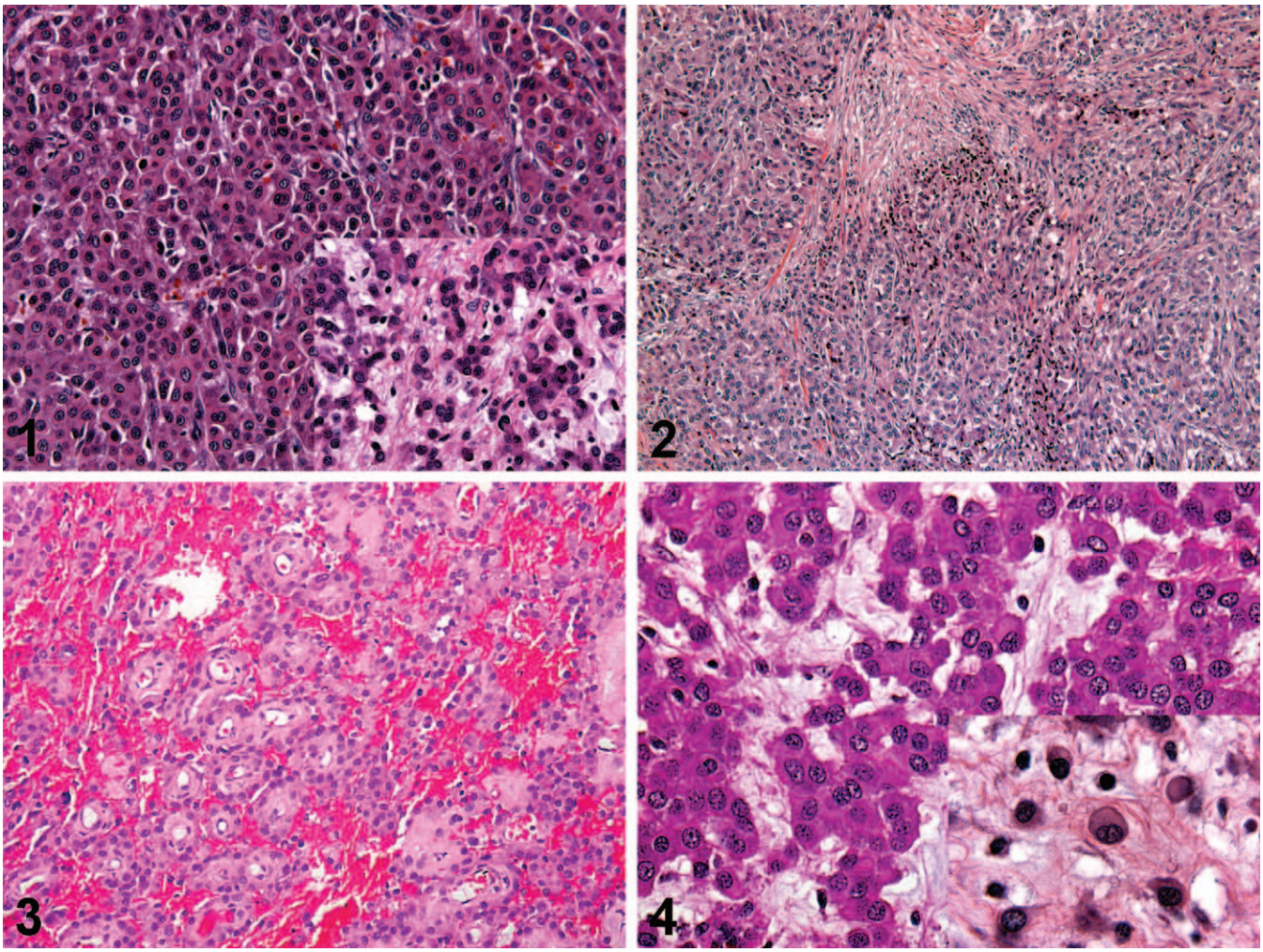

Figure 1. *Polygonal or epithelioid cells with minimal pleomorphism and abundant deeply eosinophilic cytoplasm (hematoxylin-eosin, original magnification ×200, ×400 [inset]).*

Figure 2. *Multinodular growth pattern with characteristic central necrosis in the classic-type epithelioid sarcoma (hematoxylin-eosin, original magnification ×100).*

Figure 3. *Vascular proliferation with red blood cells in the tumor area of the angiomatoid or angiosarcoma-like subtype of epithelioid sarcoma (hematoxylin-eosin, original magnification ×200).*

Figure 4. *Larger cells with vesicular pleomorphic nuclei, prominent nucleoli, and focal rhabdoid features in the proximal-type epithelioid sarcoma (hematoxylin-eosin, original magnification ×600, ×1000 [inset]).*

Cytogenetic and Molecular Features

There are no consistent or specific cytogenetic findings in ES, but several cases display chromosomal abnormalities in the 22q region.[27,28] Additionally, inactivation of a tumor-suppressor gene *SMARCB1/INI1*, located at band 22q11, has been found in proximal, but not classic type, ES.[29]

DIFFERENTIAL DIAGNOSIS

Epithelioid sarcoma has many histopathologic mimics, including benign and malignant conditions, such as granuloma annulare, necrobiosis lipoidica, chronic granulomatous inflammation (especially rheumatoid nodules), fibrous histocytoma, nodular fasciitis, fibromatosis, giant cell tumor of tendon sheath, melanoma, clear-cell sarcoma of the tendon and aponeurosis (amelanotic melanoma of soft part), schwannoma, metastatic squamous cell carcinoma, metastatic adenocarcinoma (especially renal cell carcinoma), synovial sarcoma, epithelioid hemangioendothelioma, epithelioid leiomyosarcoma, and malignant extrarenal rhabdoid tumors of the soft tissue.[1,4–8,13,14,18,22–24,30]

The bland cytology and pseudogranulomatous appearance of classic-type ES in the dermis can lead to misinterpretation as granuloma annulare, chronic granulomatous inflammation (especially rheumatoid nodules), or other necrotizing granuloma (especially necrobiosis lipoidica).[1,4–8] However, the presence of mitotic activity should raise the index of suspicion for ES, and the presence of diffuse epithelial marker positivity indicates the correct diagnosis.

Epithelioid sarcomas are sometimes composed of spindle-shaped cells, and they may be confused with other malignant spindle-cell neoplasms, such as synovial sarcomas, fibrosarcomas, angiosarcomas, malignant fibrous histiocytomas, malignant extrarenal rhabdoid tumor, ep-

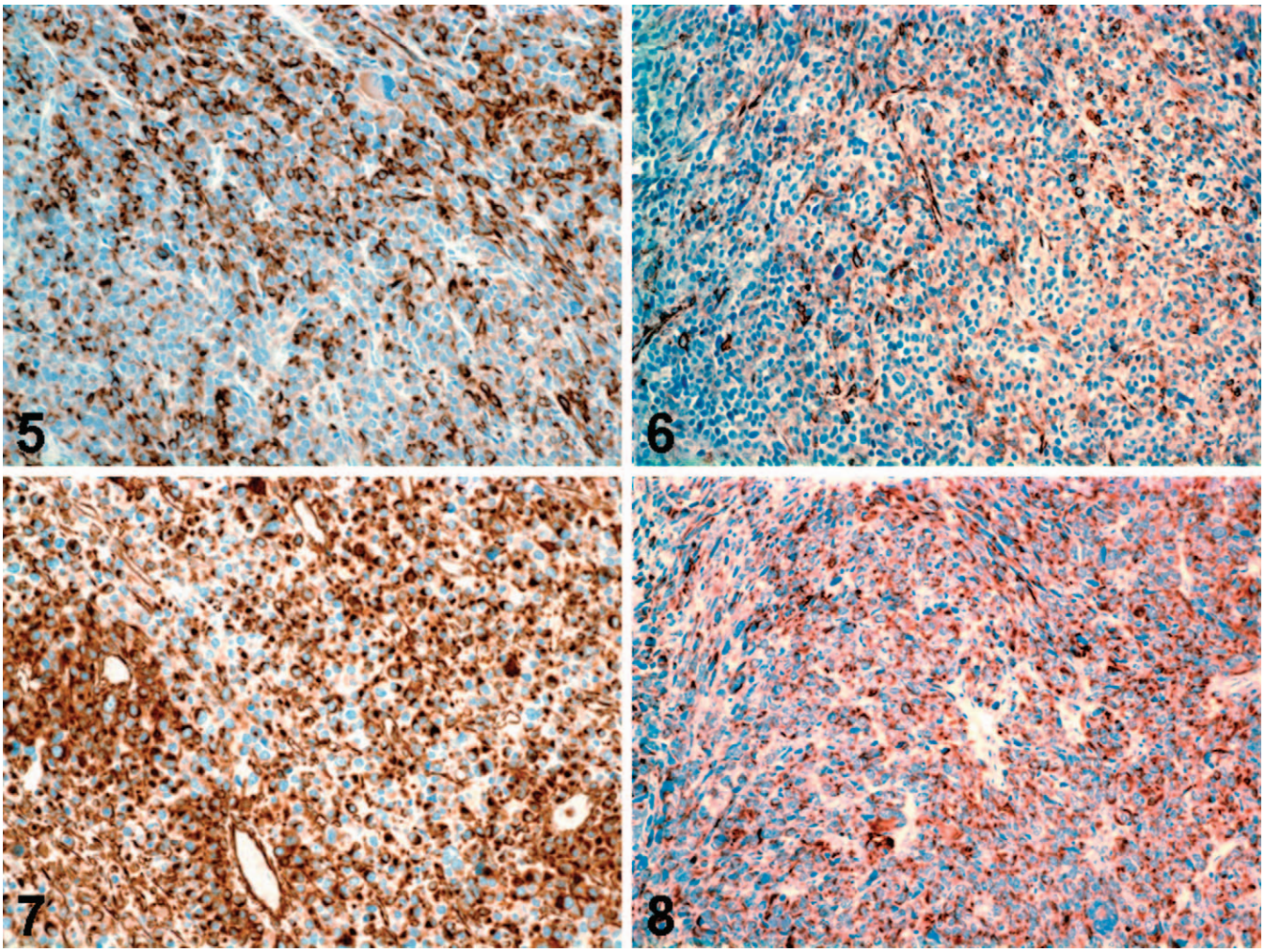

Figure 5. *CAM 5.2 staining shows strong and diffusely positive cytoplasmic and membranous reactivity in tumor cells (immunoperoxidase, original magnification ×200).*

Figure 6. *Epithelial membrane antigen staining shows focal positive cytoplasmic and membranous reactivity in tumor cells (immunoperoxidase, original magnification ×200).*

Figure 7. *Vimentin staining shows strong and diffusely positive cytoplasmic and membranous reactivity in tumor cells (immunoperoxidase, original magnification ×200).*

Figure 8. *CA 125 staining shows strong and diffusely positive cytoplasmic and membranous reactivity in tumor cells (immunoperoxidase, original magnification ×200).*

ithelioid hemangioendothelioma, and amelanotic melanoma. However, ESs are the only one of these to possess the combination of cytokeratin and vimentin positivity and a pseudogranulomatous pattern.[1,4–8]

Proximal-type ES should also be distinguished from other neoplasms with epithelioid and/or rhabdoid features, such as malignant extrarenal rhabdoid tumor, epithelioid rhabdomyosarcoma, melanoma, malignant peripheral nerve sheath tumor, and undifferentiated carcinoma.[13,14,22]

Appropriate immunohistochemical studies showing positivity for vimentin, cytokeratins, CD34, epithelial membrane antigen, and CA 125, and negativity for the S100 protein, HMB-45, FLI-1, and desmin, are helpful to exclude most of these other mentioned tumors from the differential diagnosis. Coexpression of vimentin and keratin is thought to be characteristic of ES.[1,4–8,13,14,18,22–24,30]

Carcinomas, both primary (especially those of adnexal origin) and metastatic, can have a presentation similar to ES. Carcinomas are nearly always CD34 negative, and although CD34 is only expressed in about 50% to 60% of ESs, this marker is particularly useful for diagnosing the deep-seated, proximal-type ES, which can be misdiagnosed as metastatic carcinoma of an unknown primary site.[4,7] Additionally, metastatic renal cell carcinoma may be delineated by virtue of its glandular and papillary pattern, despite the similarity in cell morphology.

Synovial sarcomas may have cytokeratin and vimentin positivity; however, the tumor cells are usually less pleomorphic, are oval to spindled, and often show areas of glandular differentiation, unlike ES. Synovial sarcoma can have plump epithelioid and even rhabdoid cells on occasion. The immunoprofile of the synovial sarcoma and ES can overlap, but synovial sarcoma is often positive for S100 protein and only very rarely CD34 positive. Finally, the specific t(X;18) of synovial sarcoma is not found in ES.[4,7]

Epithelioid angiosarcomas and hemangioendotheliomas may be cytokeratin positive, but they have areas sugges-

tive of vascular channel formation or intracytoplasmic lumen, and they are usually positive for endothelial markers, such as CD34, CD31, or factor VIII, whereas ES is rarely positive for CD34, but it is negative for these latter markers.[4,7] Epithelioid vascular tumors can resemble ES, and additionally, some express CK. However, they differ from ES in being positive for CD31, factor VIIIa, and FLI-1 but negative for CD34.[4,7]

Rhabdomyosarcoma is readily excluded by immunohistochemistry, showing positive epithelial markers and an absence of desmin, myogenin, MyoD1.[4,7] It might not be possible to distinguish S100 protein–negative rhabdoid melanoma from proximal-type ES, especially as some of the latter have been reported to be HMB-45 positive.[5,13] Many tumors formerly diagnosed as malignant rhabdoid tumor are now classified as proximal-type ES. Fanburg-Smith et al[30] reported that all extrarenal rhabdoid tumors are negative for CD34 and have distinctive findings at chromosome 22, findings that are not observed in ES. Therefore, ES and extrarenal rhabdoid tumor are considered separate entities.

HISTOGENESIS

Epithelioid sarcoma is a tumor of uncertain differentiation and is described as being of unknown lineage.[4–7] However, the reported histomorphology, immunophenotype, and ultrastructure of ES suggest a mesenchymal neoplasm with multidirectional differentiation, including epithelial, histiocytic, fibroblastic, myofibroblastic, endothelial, and perineural.[4–7] Epithelioid sarcoma has no normal cellular counterpart and differs from both synovial sarcoma and carcinoma.[4] Notwithstanding its epithelial differentiation, ES differs from synovial sarcoma and carcinoma in many respects. It has been suggested that ES might represent a carcinoma of soft parts, but the absence of an in situ carcinoma component and the absence of a primary site of carcinoma elsewhere in the reported cases of ES, in addition to the immunophenotype of ES, especially the CK profile and the expression of CD34, differ from those of carcinomas, making this suggestion untenable.[4–7] Clinically, ES is often dermal and usually located in the extremities, features that would be exceptional for synovial sarcoma. Unlike synovial sarcoma, ES is not truly biphasic, but the spindle cells emerge at the edge of the tumor nodules with continuous transition from the polygonal cells and have no glandular formation, morphologically or ultrastructurally, and no external lamina. Additionally, synovial sarcomas display epithelial markers more focally, express CK7, which is infrequent in ES, and are almost always CD34-negative.[4–7] Cytogenetically, the t(X;18) with *SYT-SSX* fusion genes, which is characteristic of synovial sarcoma, is never found in ES, which has variable abnormalities, including, most commonly, those of the 22q region.[27,28]

CURRENT TREATMENT AND PROGNOSIS

Epithelioid sarcoma is an aggressive neoplasm, and local recurrence is the rule. It recurs persistently, often with successive lesions appearing more proximally, and eventually metastasizes.[4–6,10] Wide, total surgical excision with clear margins (amputation or wide en bloc excision) and high-dose chemoradiotherapy represent optimum treatment and achieve low rates of local recurrence. However, even this regimen is associated with a recurrence rate of between 34% and 77% (depending on the adequacy of initial excision), metastases in about 40% of the patients (primarily involving the lungs, regional nodes, scalp, bone, and brain), and a median overall survival of about 88 months for patients without distant metastases and just 8 months for those with distant metastases.[4–6,10] In the largest series of 202 cases of ES with follow-up, 77% recurred, and 45% metastasized predominantly to lungs (51%), local lymph nodes (34%), scalp and other skin areas (22%), bone, brain, liver, and pleura.[4] Metastases developed in 36% of patients without local recurrence. Adverse prognostic factors included proximal location (71% metastasized vs 38% of distal cases), amount of necrosis and vascular invasion, and inadequate excision.[4] Proximal-type ES is even more aggressive. In the series of Guillou et al,[13] 6 (43%) of 14 patients, with up to 8 years follow-up, developed metastases, and 5 patients (36%) died of the tumor. However, 6 patients (43%) were alive and well at last follow-up, including 1 patient (7%) with local recurrence at 2 months, who was disease-free at 8 years.[13] In a second series of 20 cases of proximal-type ES, 65% (13/20) developed local recurrence, and 75% (15/20) developed metastases, with 65% (13/20) dead of the disease.[14]

Unlike most soft-tissue sarcomas, metastases affecting the lymph nodes are common in ES.[4–6,8–10] However, the lungs are the most common site of distant metastases in ES. A prognostically ominous sign is lymph node involvement, although sex and tumor size are the most important determinants of outcome.[4–6,8–10] Women have a better prognosis, with up to 80% 5-year survival rate, whereas the survival rate for men at 5 years is 40%.[4–6,8–10] Favorable factors are young age at first diagnosis, female sex (78% survival rate vs 64% for men),[4] and small size of tumor (less than 5 cm).[4,8] Additionally, older age, multifocal local disease, initial proximal limb or axial location, depth of invasion, high mitotic activity, necrosis, vascular invasion, tumor hemorrhage, rhabdoid cytomorphology, and inadequate excision predict a poor survival free from distant metastasis.[4–6,10] Spillane et al[8] found a 5-year survival of 70% and a 10-year survival of 42%, in a series with a metastatic rate of 40%. Because of the relatively indolent behavior, the incidence of late recurrence, and the continuing death rate, long-term follow-up is indicated in ES.[4]

CONCLUSIONS

Almost 40 years after Enzinger's first characterization of ES as a distinct clinicopathologic entity, ES is still of uncertain histogenesis (without a normal counterpart cell and a characteristic cytogenetic finding). However, it remains a distinct clinicopathologic entity with characteristic histomorphology, immunophenotype, and ultrastructure. The correct diagnosis of ES is essential because it can easily be misdiagnosed as another benign and less-aggressive malignant epithelioid lesions. Generally, the presence of large polygonal cells with prominent nucleoli and abundant necrosis on histology warrants the consideration of ES in the differential diagnosis. However, an immunohistochemical confirmation is a must for definitive diagnosis.

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