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Epithelioid sarcoma: one institution's experience with a rare sarcoma

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Abstract

Background—Epithelioid sarcomas (ES) are extremely rare soft tissue sarcomas. As such, their clinical behavior and response to treatment are poorly described in the literature.

Methods—We queried the centralized cancer registry and pathology archives at the Johns Hopkins Medical Institution and identified 22 patients with a diagnosis of ES. We excluded two patients because of inadequate data. A pathologist reviewed patient charts and reexamined available histological slides. This study was performed with institutional review board approval.

Results—The median age at diagnosis was 27.8 y; most patients (75%) were male. Regional lymph node metastases were present in 10% of patients at presentation. The majority of tumors (57.9%) recurred and 35% recurred more than once, although the number of recurrences did not affect survival ($P = 0.48$). Patients did not experience a decrease in time to recurrence with increasing number of resections. The median time between resection and recurrence was 1.23 y and the maximum was 18.8 y. Median overall survival was 56.2 mo and 5-y survival was 92%.

Conclusions—Our study reveals that ES is an extremely rare tumor with a protracted and recurrent course, but overall survival may be more favorable than in the past. Patients benefit from aggressive and repeated resection. Epithelioid sarcoma is unique because it metastasizes to regional nodal basins. Extended surveillance is indicated, because recurrences can appear after decades of quiescence.

Keywords

Epithelioid sarcoma; Proximal-type sarcoma; Sarcoma; Rhabdoid epithelioid sarcoma; Lymph node metastasis; Outcomes

1. Introduction

Bliss and Reed [1] first described epithelioid sarcomas (ES) as a variant of synovial sarcoma in 1968. It was not until 1970, when Enzinger [2] published a series of 62 patients, that this tumor was recognized as a unique entity and given its current name. Reports of these tumors continue to be uncommon in the literature, which raises uncertainties regarding their clinical behavior and response to treatment. For this reason, there is a need to report even small series of cases.

Patients have been described as presenting with either a superficial lesion or deep lesions, usually of the extremities. The superficial lesions are described as a “hard woody knot” [3]. These rarely limit function but often ulcerate later in their course. They are frequently mistaken for ulcers, abscesses, or infected warts that fail medical management [4]. Deeper lesions are often larger at presentation; findings include an area of firmness or localized pain [2].

Part of the diagnostic dilemma is the “deceptively harmless appearance during the initial period of the disease.” Patients are often young at presentation and a presumed benign diagnosis is frequently pursued for an extended period of time [3]. Diagnostic delays longer than 6 mo are typical [5].

Histologic identification of ES is similarly challenging [6]. It is believed to be mesenchymal, but it displays epithelial differentiation. Microscopically, it manifests a characteristic nodular growth pattern and is composed of a mixed proliferation of eosinophilic epithelioid and spindle cells exhibiting slight nuclear atypia, vesicular nuclei, and small nucleoli [7]. Co-expression of vimentin and epithelial markers such as cytokeratin, keratin, and epithelial membrane antigen are characteristic of ES and, more recently, loss of INI1 [8–11]. A subtype of ES, called proximal-type ES, has rhabdoid features and is associated with worse outcomes [7,12].

Recommendations for treatment of ES have mainly been extrapolated from the treatment of other types of sarcomas. Surgery with wide negative margins is indicated. A unique feature of ES is its tendency to mimic epithelial malignancies and spread to the lymph nodes. For this reason, an examination of regional lymph nodes radiographically, by sentinel lymph node biopsy, or by lymphadenectomy has been recommended [3]. Radiation is frequently given, although its efficacy has not clearly been described [13]. Chemotherapy is similarly of unknown benefit, but regimens generally include doxorubicin alone or in combination with ifosfamide [14].

Epithelioid sarcoma appears to behave similarly to other sarcomas in its recurrence pattern. Recurrences, both local and distant, are frequent, and the time between recurrences can be as long as 2 decades [15]. This protracted course, in addition to the inherent difficulties of prolonged patient follow-up, adds to the clinical uncertainty of this rare disease. We present a single institution’s experience with ES, to provide current information on the clinical behavior of these rare tumors.

2. Materials and methods

We prospectively entered all patients diagnosed with ES between 1980 and 2010 into the Pathology Archives Database, as well as the Oncology Database at our institution. At the time of this study, we retrospectively reviewed the outcomes with the approval of the institutional review board.

A total of 22 patients were diagnosed with ES during the period mentioned. Two were excluded owing to a lack of adequate information for analysis. Overall survival was measured as actuarial survival from time of diagnosis to date of last follow-up or date of death. Surgical margins were declared R0 if the margins were negative, R1 if the margins were microscopically positive or <1 mm, and R2 if gross tumor was left behind. Recurrence was defined as reappearance of the tumor, either locoregionally or as distant metastasis. Time to recurrence was the time from which patient was declared disease-free to the time of discovery of any new lesions.

2.1. Pathologic evaluation

A single pathologist with expertise in sarcomas re-reviewed all locally available pathologic specimens at the time of this study, using World Health Organization criteria [7]. We noted the histologic variant known as proximal-type ES, which demonstrates rhabdoid features, when it was present; otherwise, the tumor was described as typical-type variant.

2.2. Statistics

The study end points included disease-free interval (DFI) and overall survival (OS). We calculated them using the Kaplan-Meier method with R/Bioconductor software packages (R Foundation for Statistical Computing; Vienna, Austria) [16]. We performed univariate analysis of DFI and OS using the log-rank test. We performed multivariate analysis using the Cox proportional hazard model. Patients whose disease progressed without response to any treatment were considered to have a DFI of 0. Any *P* values <0.05 were deemed significant.

3. Results

3.1. Presentation

A total of 20 patients had adequate available follow-up information. Table 1 summarizes patient, tumor, and treatment characteristics. Table 2 details the clinical profiles of each patient. Fifteen patients (75%) were male. Age at presentation ranged from 7.3 to 75.4 y. The median age at presentation was 27.8 y. Of patients presenting to our institution with primary disease (13; 65%), only two had spread to locoregional lymph nodes. The remainder had disease confined to the primary site. Among the patients who first presented to our hospital with recurrent disease (seven; 35%), four (57.1%) presented with a local recurrence and the rest (three; 42.9%) presented with distant metastases.

The most common site of ES in this cohort was the extremities. The proximal upper extremity (shoulder to wrist) accounted for 25%; distal upper extremity, 15%; proximal lower extremity (hip to ankle), 15%; and distal lower extremity, 10%. Non-extremity tumors, also referred to as axial tumors, occurred in the anus (5%), inguinal region (10%), genitalia (10%), and cervical spine (10%).

3.2. Histologic type

Two patients were diagnosed with the proximal-type histologic variant of ES. The remainder of patients had the typical-type histologic variant. All extremity tumors were the typical type variant. However, 29% of axial tumors were the proximal type histologic variant.

3.3. Treatment

After presentation with primary disease, surgery was offered to all 20 patients. One patient underwent radiation and refused further treatment. He was lost to follow-up a year later. All other patients underwent surgery. Margins after initial resection were negative in nine

patients (R0 resection) (47.4%), microscopically positive in four (R1 resection) (21.05%), and grossly positive in two (R2 resection) (10.5%). Margin status was unavailable for four cases (21.05%). Tumor size after initial resection ranged from 1.2 to 8 cm. Median tumor size was 4.5 cm (Table 1). A correct histologic diagnosis was made in 78.9% of patients after the first surgery. Three patients who had the initial procedure at an outside hospital were given a histologic diagnosis of benign fibrohistiocytoma (5.3%), liposarcoma (5.3%), and sarcoma (5.3%). These patients were not given a diagnosis of ES until they were treated at our institution for recurrences.

Most patients received radiation therapy at some point during the disease course (14; 70%); 71% of these remained disease-free. Of the nine patients who never had a recurrence, six (66%) received radiation. Half the patients (10; 50%) received chemotherapy, for a total of 14 occurrences of their tumor. Chemotherapy regimens included doxorubicin (28.6%), doxorubicin and ifosfamide (28.6%), and a combination of taxol, Taxotere, and carboplatin (14.3%), or were undocumented (28.6%). Recurrence of the tumor was observed in 50% of patients after chemotherapy.

3.4. Recurrences

Over half (11; 57.9%) of the patients had recurrences after the initial operations. Of these, four (36%) only had one recurrence, three (27.2%) had a second recurrence, three (27%) had a total of three recurrences, and one (9%) had five recurrences, for a total of 33 recurrences in 11 patients (mean of 2.09 recurrences). Recurrences were local in 45%, locoregional in 12%, and distant in 43%. Distant metastasis included lung (seven; 21%), distant soft tissue (four; 12%), bone (one; 3%), liver (one; 3%), and brain (one; 3%). Margin status upon initial operation did not appear to correlate with recurrence ($P > 0.05$). Fifteen patients had margin status of the primary resection documented. Of these, nine had R0 resections and four (44%) recurred. Four patients had an R1 resection and two (50%) recurred; two had an R2 status and one (50%) recurred.

A total of 16 episodes of recurrence (48.4%) were treated by surgery with curative intent. Ten of these operations (30.3%) resulted in negative margins (R0 resection) and three (9%) in microscopically positive margins (R1 resection), and three (9%) did not have documentation of margin status. Patients received radiation in nine instances of recurrence (27.2%), and chemotherapy in seven (21.2%).

3.5. DFI

The DFI after primary resection ranged from 1 mo to 11.4 y, with a median of 1.9 y and a mean of 3.25 y (Fig. 1). The DFI after second surgery ranged from 1 mo to 3.9 y, with a median of 1.5 y and a mean of 1.60 y. Disease free interval after third surgery ranged from 5 mo to 18.8 y, with a median of 1.2 y and a mean of 5.42 y. Only one patient recurred for the fourth and fifth time, and the DFI was 1.14 y and 0.58 y, respectively, for these recurrences. The overall median DFI was 1.23 y, the mean was 2.99 y, the minimum was 0.08 y, and the maximum was 18 y.

Univariate analysis by log-rank demonstrated combined negative (R0 resection) with microscopically positive margins (R1 resection) to have improved DFI, as did the typical histologic variant ($P = 0.005$ for both). Location of the tumor on the extremity also demonstrated trending DFI, but was not statistically significant ($P = 0.055$) (Table 3). No variable was significant on multivariate analysis.

3.6. OS

The OS ranged from 0.11 to 22.6 y. The median OS was 4.68 y and the mean was 6.25 y. Median overall 5-y survival was 92% (Fig. 2). No variable was significant on univariate or multivariate analysis (Table 3).

4. Discussion

4.1. Presentation

The results of this study compare favorably with previous reports suggesting that although small, our patient population accurately reflects the disease as a whole. We observed a 3:1 male predominance, which is well within the range of other reports [3,17]. We observed that most ES arose in the upper extremity; the next most frequent location was the lower extremity. Non-extremity or axial tumors were the least common site.

The delay in diagnosis observed in several other studies was not seen at this institution [15]. The median diagnostic delay was 1.9 mo and greatest delay was 9.5 mo. This could result from the lower threshold for operation, greater suspicion prompting biopsy, or a recording bias, but it appears to be consistent among patients. This also highlights our relatively high incidence of isolated local presentations, suggesting that earlier presentation is associated with fewer metastases.

4.2. Treatment

Surgical resection with negative margins is necessary for these patients, but the need for surgical evaluation of the lymph nodes remains strongly debated [18]. Epithelioid sarcoma, like synovial sarcoma, clear cell sarcoma, and some angiosarcomas, is one of the few adult types of sarcomas to metastasize to the lymph nodes. The rate of lymph node metastasis in ES ranges from 20% to 45% in the literature [3,17]. Our rate of lymph node metastasis was lower, at 10%–17% for primary and recurrent presentations, respectively.

Lymphadenectomy most definitively addresses the risk of lymph node metastasis, but is associated with significant morbidity. Some authors have advocated performing sentinel lymph node biopsy as a less morbid procedure. The efficacy of this is unknown, but may hold promise [19]. Radiographic imaging has markedly improved over the past decade and may be another option. Regardless, the regional lymph nodes of all patients with ES should be evaluated using at least one of these modalities.

The small number of patients in this study makes assessing the efficacy of radiation difficult; nevertheless, there appears to be some benefit. Most patients received radiation therapy, as per our general institutional guidelines for management of sarcomas. Most of our patients (71%) remained disease-free after radiation, which suggests some benefit. Other studies supporting radiation for ES have been small, like ours, but the general consensus seems to be that radiation confers some protection from local recurrence [13,20,21].

Chemotherapy does not appear to confer benefit, because the rate of recurrence was 50% after chemotherapy, compared with 55% in the entire group.

4.3. Recurrences

This tumor, much like other sarcomas, has a propensity to recur multiple times. At our institution, 45% of patients never had a recurrence, 20% of patients had one, 15% had two, and 20% had three or more. This is comparable to the series by Chase et al [3], in which 31% of tumors recurred only once, 27% recurred twice, and 18% recurred three or more times. The DFI is another factor that must be considered, especially when deciding whether operative re-intervention would be beneficial. In our series, the median DFI did not

drastically differ between recurrences. This suggests that patients with multiply recurrent tumors benefit from aggressive surgical control.

Completeness of surgical resection was not significant for risk of recurrence ($P > 0.05$). A total of 44% of patients with an R0 resection recurred and 22.2% of these had distant metastasis. In addition, 50% of patients with R1 and 50% of patients with R2 resections recurred after primary resection and none of these were distant metastasis. In our series, patients received R1 and R2 resections without re-excision owing to involvement of tumors with critical structures, including the cervical spine, groin, and distal extremity. Whitworth *et al* [22] examined the use of amputation in ES and found no advantage of amputation at any stage *versus* wide local excision. This may reflect an aspect of the biology of ES that is not yet fully understood.

4.4. DFI

Several factors appear to be related to decreased DFI. This includes surgical margins, histologic type, and location. Patients with positive surgical margins, proximal-type histologic variant, and axial tumor location may benefit from the addition of radiation therapy early in the course, to prevent recurrence.

Another notable feature of ES is its long latency before recurrence and the frequency of recurrences. Over half of our patients (55%) recurred; the longest time to recurrence was 18.8 y. Median time between first resection and recurrence in the literature is often described as <1 y but can be delayed as long as 20 y [3,15,23]. In studies with extended follow-up, 85% of patients have been reported to develop either local or distant recurrence during their lifetime [3,22].

4.5. OS

Median survival in this study was 4.68 y and overall 5-y survival was 92%. Reported 5-y survival rates in the literature for ES range from 66% to 74% [15,23]. In our univariate analysis, no single factor was significantly associated with improved survival. This is likely a result of our small cohort size. Several factors appeared to trend with survival. Patients with axial tumors had a median overall survival of 1.3 y, compared with patients with extremity tumors with a median survival of 6.6 y.

Our study also suggests that men have a better overall survival than do women, and fewer recurrences. Women had a median overall survival of 2.67 y after diagnosis, compared with men, who had a median overall survival of 8.4 y. Women recurred a mean of 1.6 times, compared with men, who recurred a mean of 1.07 times. There has been some suggestion of hormonal influences upon this tumor, because prepubescent and postmenopausal women have equal incidents of ES and similar outcomes, but our data did not support that finding [3].

Epithelioid sarcoma also manifests in children. This cohort included three children under the age of 13, and all were male. To date, one child is alive after 4.8 y with no evidence of disease; another is alive after 10.9 y with no evidence of disease. The final patient lived with the disease for 9.8 y and had five recurrences, including distant metastasis. This would suggest that children have a relatively long survival after successful treatment. Chase *et al* [3] reported that whereas children under 10 y of age have frequent recurrences, they had no metastasis and no deaths resulting from disease.

The results of this study contribute to the limited knowledge of this rare tumor. Patients benefit from a complete surgical resection with negative margins. Clinicians should be cognizant of the risk of lymphatic spread and address this accordingly. Patients with axial

location and the proximal variant have a diminished time to recurrence and may require closer surveillance. Patients with ES appear to benefit from multiple surgical resections; recurrence is not by itself a contraindication to re-excision.

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Fig. 1.
Kaplan-Meier curve of first DFI.

Fig. 2.
Kaplan-Meier curve of OS.

Table 1

Patient, tumor, and treatment characteristics.

Characteristic	
Median age (y)	27.8 (range, 7–75)
Sex	
Male	15 (75%)
Female	5 (25%)
Median tumor size (cm)	4.5 (range, 1.2–8)
Location	
Extremity	
Distal upper extremity	3 (15%)
Proximal upper extremity	5 (25%)
Distal lower extremity	2 (10%)
Proximal lower extremity	3 (15%)
Axial	
Anus	1 (5%)
Inguinal region	2 (10%)
Genitalia	2 (10%)
Cervical spine	2 (10%)
Primary presentation	
Localized	18 (90%)
Lymph node	2 (10%)
Distant metastasis	0
Surgery	
Yes	19 (95%)
No	1 (5%)
Surgical margins	
R0	9 (47.4%)
R1	4 (21.05%)
R2	2 (10.5%)
Undocumented	4 (21.05%)
Chemotherapy	
Yes	7 (35%)
No	13 (65%)
Radiation	
Yes	9 (55%)
No	11 (45%)

Table 2

Clinical profile details.

Case	Age at diagnosis (y)	Gender	Primary site	Diagnostic delay (mo)	Presentation	Recurrences (n)	Location of recurrences	Time to recurrence (mo)	Length of follow-up (y)	Status at last visit
1	37.1	F	PUE	3.25	Recurrent	3	Local/local/unknown	11.4/0.41/18.8	22.6	AWD
2	33.1	M	DLE	1.02	Recurrent	2	Soft tissue/lung, paravertebral tissue	1.91/0.59	3.78	DOD
3	35.5	M	PLE	4.40	Primary	3	Lung/lung/bone, lung/liver	9.60/3/39/1.21	16.3	AWD
4	12.0	M	PUE	0.03	Recurrent	5	Local/local, distal site subcutaneous nodules/local/local, lungs, lymph node/brain	3.08/2.75/1.23/1.14/0.58	9.86	DOD
5	29.5	M	DUE	1.77	Primary	0			1.52	NED
6	22.8	M	PUE	1.25	Primary	0			9.80	NED
7	22.8	M	PUE	1.02	Recurrent	3	Local/local/local, lymph node	0.91/2.37/0.44	4.58	NED
8	13.3	M	Penis	0.59	Primary	1	Lymph node	3.62	11.0	NED
9	36.5	F	Vulva	2.07	Primary	1	Lung, skin	1.2	1.37	AWD
10	75.4	M	DUE	3.98	Primary	0			8.55	NED
11	24.7	F	PLE	3.38	Primary	0			8.45	NED
12	26.1	M	DLE	0	Recurrent	1	Local	2.48	4.86	NED
13	56.5	F	Inguinal region	9.46	Recurrent	2	Local, lymph nodes	0.13/0.088	1.15	AWD
14	17.3	M	Cervical spine	3.55	Primary	0			1.11	NED
15	20.8	M	Cervical spine	1.93	Primary	0			0.22	NED
16	41.3	F	Inguinal region	8.08	Recurrent	2	Local/local, lung	0.080	2.74	AWD
17	7.3	M	DUE	0.95	Primary	0			4.77	NED
18	53.1	M	Anus	0	Primary	0			3.42	NED
19	42.0	M	PUE	3.02	Primary	0			0.97	NED
20	19.7	M	PLE	1.94	Primary	1	Local	1.30	8.04	NED

DUE = distal upper extremity; PUE = proximal upper extremity; DLE = distal lower extremity; PLE = proximal lower extremity; AWD = alive with disease; NED = no evidence of disease; DOD = dead of disease.

Table 3

Univariate analysis of OS and DFI.

	DFI*	OS*
	<i>P</i> value	<i>P</i> value
Gender (male <i>versus</i> female)	0.79	0.47
Age (≤ 18 <i>versus</i> >18)	0.74	0.71
Presentation (primary <i>versus</i> recurrent)	0.16	0.12
Location (extremity <i>versus</i> axial)	0.055	0.52
Diagnosis (correct <i>versus</i> incorrect initial diagnosis)	0.20	0.16
Histologic variant (typical <i>versus</i> proximal)	<0.005	1
Metastasis at presentation (yes <i>versus</i> no)	0.86	0.52
Tumor size (≤ 5 cm <i>versus</i> >5 cm)	0.926	†
Surgery (yes <i>versus</i> no)	0.81	1
Margins (R0/R1 <i>versus</i> R2)	0.001	†
Radiation (yes <i>versus</i> no)	0.65	0.56
Chemotherapy (yes <i>versus</i> no)	0.46	0.41
Recurrence (<1 <i>versus</i> ≥ 1)	0.79	0.48

* Values calculated by log-rank test.

† Insufficient data for analysis.