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Original Article

Clinicopathologic features of epithelioid sarcoma: report of seventeen cases and review of literature

Yijie Li[1,3*], Gaoxiang Cao[2*], Xiaoying Tao[1,3], Jiannan Guo[1,3], Shiwu Wu[1,3], Yisheng Tao[1,3]

Departments of [1]Pathology, [2]Gastrointestinal Surgery, The First Affiliated Hospital of Bengbu Medical College, Bengbu, Anhui Province, China; [3]Department of Pathology, Bengbu Medical College, Bengbu, Anhui Province, China. [*]Equal contributors.

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Abstract: Epithelioid sarcoma (ES) is a rare malignant soft tissue tumor, which is characterized by nodular aggregates of epithelioid cells and immunoreactivity of cytokeratin (CK) as well as epithelial membrane antigen (EMA) and often with CD34. It can be divided into proximal and distal subtypes. Classic ES has a microscopic nodular appearance that is composed of large polygonal epithelioid cells combined with central necrosis, and presents as a subcutaneous or deep dermal mass in the distal extremities of young adults. The proximal variant preferentially occurs in proximal limbs and limb girdles and the midline of the trunk, and is composed of more atypical cells with variable rhabdoid morphology. In this study we investigated the clinicopathologic features of 17 patients diagnosed with ES. In addition, we reviewed relevant literature and discussed some diagnostic and differential diagnostic points of this disease.

Keywords: Epithelioid sarcoma, immunohistochemistry, pathology

Introduction

Epithelioid Sarcoma (ES) is an aggressive malignant soft tissue neoplasm, which has been classified as a tumor of uncertain differentiation by WHO in 2013 [1]. The name "epithelioid sarcoma" was first named by Enzinger in 1970 [2]. There are two histologic variations: classic or distal type and proximal type.

Classic ES has a predilection for the superficial dermis or subcutaneous of the distal limbs of adolescence and young adults. Histologically, classic ES commonly characterized by multiple granulomatous nodules. In the center of the nodules, necrosis, hemorrhage and cystic changes commonly appear. In addition, infiltration of chronic inflammatory cells can also be found. The nodules are surrounded by large epithelioid cells, which are polygonal, round, or ovoid. The neoplastic nuclei tend to be circular or ovoid, and the atypia is relatively mild. Apart from that, small nucleoli can be noted. Occasionally, neoplasms grow along the tendon sheath, fascia, blood vessels, or nerves. The shape of neoplastic cells is variable. Some tumor cell cytoplasm is abundant and eosinophilic, resembling rhabdomyosarcoma cells or rhabdomyoblastoma cells, and some of them are spindle shaped, similar to fibrosarcoma cells. Spindled cells may be present focally and are often peripherally located, merging with the epithelioid cells without demarcation [3].

Proximal ES (PES) commonly affects middle-aged people and often presents a as deep soft tissue mass of proximal limbs, external genitalia, and the midline of the trunk [3]. Histologically, PES is similar to classic type, but the neoplastic cells are more aggressive with prominent nucleoli. Tumor necrosis can occur in PES, which is different from granuloma-like structures in classic ES [4, 5]. Immunohistochemical study commonly shows strong expression of both epithelioid markers and mesenchymal markers [6, 7].

In addition, ESs are rare, and accounts for less than 1% of adult soft tissue sarcomas and for about 4%~8% of children's non-rhabdomyosarcomas [6], so ESs are easily confused with

Table 1. Results of immunohistochemistry

Case	CK	EMA	Vim	S100	HMB45	CD31	CD34	SMA	Des	Mel-A	Ki-67
1	+	++	+	-	-	-					30%
2	-		+	-	-	-	-				
3			+	-		-	+	+	-		40
4	+		+	-	-	-	-	-	-		20
5	+	-	+++	-	-		-	-	-		40
6	++	+	++	-	-	-	-	-	-	-	80
7	++	+/-	+	-/+			-	-			60
8	+	+	+	-		-	+	-			10
9	++		++	-	-	-	-	-		-	80
10	++		++	-		-	+++		-		20
11	++	±	++	-					-	-	
12	++	-	+	less+	-	-	-			-	20
13	++	-	++	-		-	-	-	-		
14	-	+	++	-	-			-	+		
15	+		+	-	-		-		-		20
16	+		+	-			+	-	-	-	30
17	++	++	++	-	-		-				30

Empty cell means relative immunohistochemical markers were not performed.

Table 2. Clinical features

Case	Depth	Sex	Age (y)	Site	Size (cm)	Metastatic site	Therapy	Pain	Survival (months)	Type
1	Deep	Male	71	Hypogastrium	6.5	M0	Excision	N	35	C
2	Deep	Female	20	Thigh	2.5	M0	Excision	N	40	C
3	Superficial	Female	34	Forearm	4.5	M0	Excision	N	48	C
4	Deep	Female	60	Thumb	3	M0	Wide excision + amputation	Pain	45	C
5	Superficial	Male	51	Instep	0.5	Lymph node	Excision	Pain	29	C
6	Deep	Male	48	Thigh	6.0	Lymph node	Amputation	N	38	P
7	Deep	Female	40	Chest wall	7.0	Bone	Excision	Pain	6	P
8	Superficial	Female	26	Tongue	0.5	M0	Excision	Pain	23	P
9	Superficial	Male	54	Inguinal region	10	Lymph node	-	Pain	15	P
10	Superficial	Male	47	Forearm	0.8	Lymph node, lung	chemotherapy	N	42	C
11	Deep	Male	59	Thigh	10	M0	Chemotherapy	N	12	C
12	Deep	Female	63	Centrum	2	Shank	-	Pain	14	P
13	Superficial	Female	33	Thigh	8	M0	Amputation + chemotherapy	Pain	41	C
14	Deep	Male	39	Lung	2	Lymph node	Chemotherapy	N	20	P
15	Superficial	Female	78	Forearm	3	M0	-	N	60	C
16	Deep	Male	47	Thigh	3	Lung, liver, kidney	Chemotherapy	Pain	30	P
17	Deep	Male	74	Lung	15	Lymph node	Pneumonectomy	N	12	P

P: PES; C: classic ES; M0: not metastasis; "-": refused treatment; N: no pain and tenderness.

granuloma, and with epithelioid and rhabdomyoid tumors, which may lead to misdiagnosis.

In this study, we analyze diagnosis features of 17 ESs, present relative differential diagnosis, and review the literature to distinguish Epithelioid sarcoma from other diseases with similar characteristics.

Materials and methods

Materials

We collected 17 ES cases and clinical data diagnosed in The First Affiliated Hospital of Bengbu Medical College from 2012 to 2018. The clinicopathologic data are listed in **Table 2**.

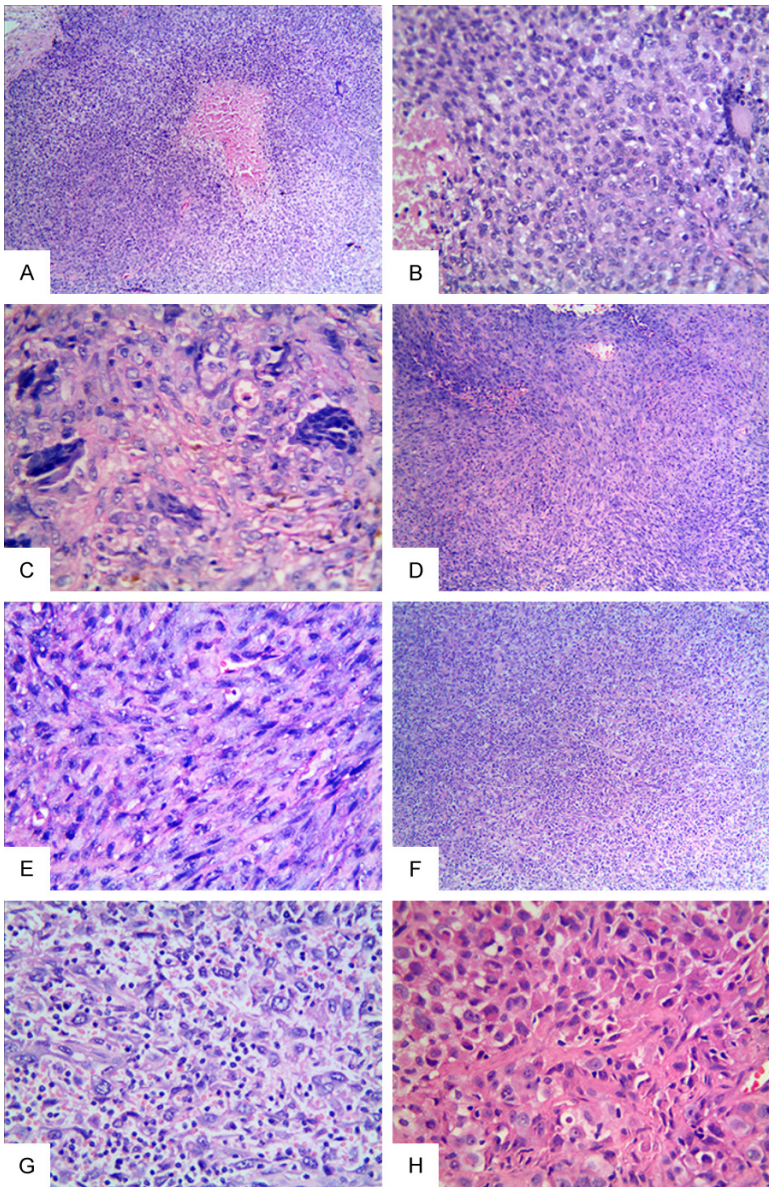

Figure 1. Classic epithelioid sarcoma (ES): A. Granulomatous appearance with central necrosis and polynuclear giant cells; B. Round or ovoid epithelioid cells around necrosis; C. Many polynuclear giant cells in neoplasm cells; D and E. The neoplasm consisted of spindle cells with small nucleoli; F and G. Large polygonal cells are the major composition; H. Tumor cellular cytoplasm is eosinophilic.

Among all patients, 9 cases were diagnosed as classic ES and 8 were PES. The median age of 9 male and 8 female patients who were first confirmed was 50 (range 20 to 78). The follow-up rate was 100%, and the follow-up time was 6 to 60 months with a median follow-up time of 30 months. All patients were followed from the date of diagnosis to the most recent follow-up or death. Only one patient is still alive (case 16).

Methods

All of the specimens were fixed in 10% neutral formalin and embedded in paraffin. H&E and immunohistochemical stain were performed and examined. Immunohistochemistry was conducted according to the guideline of Elivision™. All of reagents were purchased by Fuzhou Maixin company.

In our study, tumor located at distal extremities was defined as “distal”, and located in proximal extremities or the middle of the trunk defined as “proximal”.

All data in this study were analyzed by SPSS 25.0 statistical software. The X^2 test was employed to determine any statistical difference between clinicopathologic parameters and proximal ES. $P < 0.05$ was considered significant.

Results

Pathology

Histologically, 9 cases were diagnosed as classic type, and 8 were diagnosed as proximal type. Classic ES showed characteristic of multiple granulomatous nodules (**Figure 1A**). The nodule was surrounded by round and ovoid epithelioid cells (**Figure 1B**). Hemorrhage was noted in 3 of our cases. In addition, the infiltration of chronic inflammatory cells can be present. In one case, many polynuclear giant cells were found in tumor tissue (**Figure 1C**). The tumor can be composed of spindle cells with small nucleoli (**Figure 1D** and **1E**). It is more likely to be misdiagnosed when the neoplasm consists of spindle cells with mild cellular atypia. In addition, the nodule was made up of large polygonal epithelioid cells with atypical

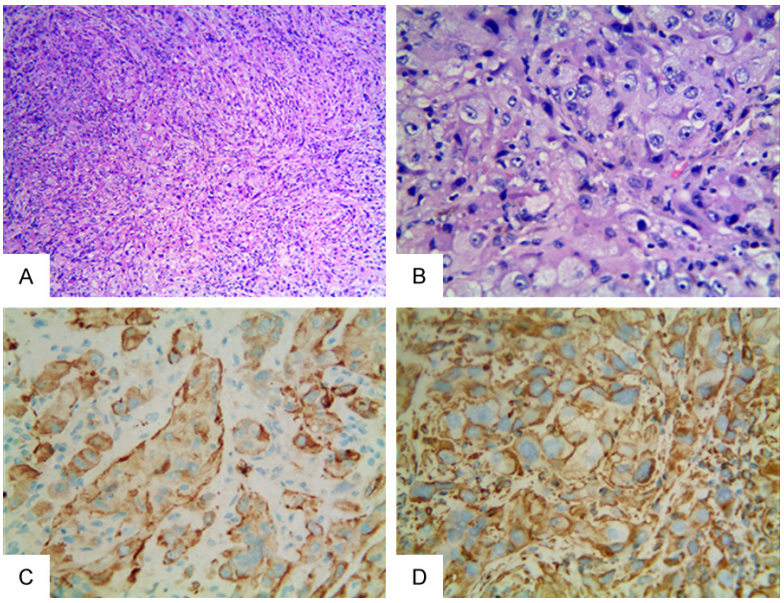

Figure 2. (A and B) PES is composed of comparatively large epithelioid cells with vesicular nuclei and prominent nucleoli; (C) cytokeratin (CK) and (D) vimentin are positive in almost all ES.

nuclei and inflammatory cells (**Figure 1F** and **1G**), and some tumor cellular cytoplasm is abundant and eosinophilic (**Figure 1H**).

PES was similar to classic type, but PESs were composed of comparatively large epithelioid cells which frequently had significant atypia with vesicular nuclei and prominent nucleoli. (**Figure 2A** and **2B**). Also, the degree of nuclear atypia was significant.

Immunohistochemistry

Immunohistochemical results are shown in the Table *. Vimentin reactivity is present in all 17 cases (**Figure 2C**). CK is expressed in 15 of 17 cases. (88.2%) (**Figure 2D**). EMA is positive in 7 (70%) of 10 cases that were examined. CD34 is minimally positive in 4 (28.6%) of 14 cases. Loss of expression of S-100 protein (100%) was shown in all cases. SMA and desmin were both negative in 8 (88.9%) of 9 cases. 10 cases expressed neither CD31 nor HMB45 (**Table 1**).

Clinical features

There were 17 ES patients diagnosed in The First Affiliated Hospital of Bengbu Medical College; 9 were male and 8 were female (1.13:1). As we can see, ES may occur at any age, and in this study the age ranged from 20 to 78 with a median age of 50. Additionally, 13 patients noticed a nodule, 1 patient had an ulcer in the middle of the lesion and 5 patients came to the hospital for treatment because of pain. One of the cases (case 5) occurred on the instep and manifested as a 0.5 cm lesion with ulcer on the surface, but the patient did not get concerned until the inguinal lymph node enlarged with pain. The size of tumors was 0.5 cm to 15 cm (median size, 3 cm). Five patients presented with subcutaneous or deep soft tissue masses in the thigh, the forearm in three, the lung in two, and one each in tongue, hypogastrium, inguinal region, chest wall, instep, centrum, and thumb. 9 masses were located at the deep of the tissue, and 8 were located at superficial aspects. Metastases were noted in 10 (58.9%) cases. Lymph node metastases were found in 6 cases, and lung metastases occurred in 2 cases. Multiple metastases were noted in lung, liver, and kidney in only one of the 17 cases.

As for the treatment of these patients, 6 patients got surgical excision (1 of 6 got extended resection), with amputation in 3 patients, and pneumonectomy in one patient. Because of tumors noted in multiple places (**Table 2**) 5 patients accepted chemotherapy and three patients refused treatment.

The result of X^2 test revealed that proximal type of ES has a significant relationship with the proximal or axial location (P=0.008) and metastasis (P=0.007). Proximal-type ES was also found to have a higher rate of deep lesions, although statistically not significant (P=0.086) (**Table 3**).

Discussion

ES is a rare malignant soft tissue tumor with a predominance in males [3], that has two subtypes: classic type and proximal type. These types are similar both histologically and pathologically. Also, it is reported that these two subtypes are a continuum of disease [8]. PES comprises less than 1/3 of ES [9].

Table 3. Clinicopathologic variables in cases of classic- and proximal-type epithelioid sarcoma

Variable	Total (n)	Classic Type (n)	Proximal Type (n)	*P* Value
Sex				0.457
Male	9	4	5	
Female	8	5	3	
Age at presentation (years)				0.457
≤50	9	4	5	
>50	8	5	3	
Location				0.008
Distal	10	8	2	
Proximal	7	1	6	
Depth				0.086
Superficial	8	6	2	
Deep	9	3	6	
Tumor size				0.819
≤3.0	9	5	4	
>3.0	8	4	4	
Metastasis				0.007
No	8	7	1	
Yes	9	2	7	

Classic type ES usually presents as slow growing painless firm nodules in the superficial dermis or subcutaneous of the distal limbs of young patients [4]. However, PES is considered as a more aggressive type of ES [4, 7, 10], which tends to occur in the deep soft tissue of proximal limbs of older patients. In our study, 13 patients noticed a nodule, 1 patient had an ulcer in the middle of the lesion, and 5 patients came to the hospital for examination because of pain. After reviewing the literature, ES seems to be able to develop in the superficial dermis, subcutaneously, which was easily noticed. In addition, ES can also affect deep soft tissue, which rarely manifest as pain or tenderness. Patients are difficult to notice these lesions, unless the mass suddenly gets bigger or painful (maybe large nerves are affected [11]), or has hemorrhaging, or ulcers. The large size and deep location predict a poor prognosis [12]. However, patients, and sometimes even doctors do not easily not pay attention to the mass because of its nonspecific identity.

Histologically, the mass of classic type is composed of central granulomas with necrosis and large polygonal cells with eosinophilic cytoplasm. PES is composed of large epithelioid cells with vesicular nuclei and prominent nucleoli. The cells of PES show greater atypia. Diagnoses cannot be established just by histology. Histology and immunohistochemistry are complementary means of diagnosing this disease.

IHC studies are typically positive for epithelial markers, include cytokeratin (CK), epithelioid membrane antigen (EMA) and vimentin. Furthermore, about half of ES express CD34 [3]. However, HMB45 is negative in ES, and this is useful to distinguish malignant melanoma from ES. S-100, smooth muscle antigen (SMA), and desmin are commonly negative.

To date, there is no consensus about ES and the research of its origin is a hot topic. Some scholars believe that ES stems from mesenchymal tissue, and some believe that it originates from epithelium, and some believe the ES has the same source as meningioma [13]. So far the etiology is unknown [14]. Some reports indicated that the neoplasm happened after old scars, or it had something to do with trauma. Because of the small sample sizes, further studies are needed.

Differentiation

ES occasionally gets confused with many benign and malignant conditions, both clinically and histologically. The lesion resembles a number of non-neoplastic lesions as well as malignant neoplasms of skin and soft tissue [15, 16].

Granuloma

Clinically, ES has a high rate of recurrence and metastasis whether treated or not. In contrast, granuloma fails to recur at the site of treatment. Pathologically, ES and granuloma both show central necrosis surrounded by epithelioid cells and lymphocytes. However, in granuloma, epithelioid cells have abundant and amphophilic cytoplasm and do not show cytologic atypia [16]. Most importantly, one must separate these two diseases with immunohistochemistry since granuloma is negative for CK and EMA while ES is positive for both.

Epithelioid angiosarcoma

Epithelioid angiosarcoma expresses factor-VIII related antigen, CD31, [17] but EMA is not

detected [18]. These factors express in opposite ways in ES [8]. In addition, ES occasionally has central necrosis, which is not found in epithelioid angiosarcoma.

Malignant melanoma

Malignant melanoma, especially amelanotic melanoma is easy confused with ES. Malignant melanoma expresses S-100 [19] and HMB-45, which are not found in ES. However, CK positivity is very rare in malignant melanoma, but it is commonly seen in ES.

Synovial sarcoma

Synovial sarcoma usually occurs near the joints, and rarely involves skin. Biphasic synovial sarcoma has both spindle and epithelioid cells, which is similar to ES, but synovial sarcoma expresses CD99 and bcl-2 [20]; CD34 is negative [7].

Malignant Extrarenal Rhabdomyoid Tumor (MRT)

Malignant extrarenal rhabdomyoid tumor (MRT) has a predilection for the kidney of infants or young children, which is different from ES. They both have vesicular nuclei, but ES has a characteristic of multiple nodules and central necrosis. By these features, it is not difficult to distinguish malignant extrarenal rhabdomyoid tumor and ES. ES often exhibits positive expression of CD34 and β-catenin, while extrarenal MRT typically lacks immunoreactivity to these markers [21].

Therapy and prognosis

ES is a malignant neoplasm, which etiology is unclear and has high rate of local recurrence and metastasis, commonly with metastasis to lung [22]. Furthermore, there is no curative treatment and consensus with the treatment. At present, when the mass is localized, surgical resection (amputation or wide resection) with or without radiotherapy and chemotherapy is usually accepted. On account of the plain appearance of ES, the entity is likely to be designated as a benign mass, which may lead to a positive margin and affect the prognosis [16, 23]. Nonetheless, its characteristics of recurrence and metastasis means the disease is inoperable [22], so neo-adjuvant or adjuvant radiation therapy and chemotherapy are often administered [8]. Although lymphatic metastasis is frequent, it is not associated with survival [7, 24].

Literature reports that lymph node metastasis is the signature of poor prognosis [7]. Lymph node resection is not helpful to prolong life time. However, studies are insufficient to draw an exact conclusion. It is reported by Linch [22] and Jones [24] that cytotoxic therapy that usually consists of doxorubicin and ifosfamide has been the mainstay of treatment for many years. Two variants of ES respond to radio- and chemotherapy differently, and PES usually benefits more [10], but, due to the lack of relevant reports and the immature of research in this area, the role of adjuvant radio- and chemotherapy is unclear [25-27].

Despite multimodal therapy of ES, the recurrence rate is still high [8], and metastasis occurs in about 50% of patients. Tumor size and early metastasis are independently associated with poor prognosis, but these two are not related [25]. Generally, small size tumor (smaller than 10 cm), single lesion, and metastasis-freedom has relation with better prognosis [26]. PES is more aggressive.

Conclusion

ES is a rare and poor prognostic malignant tumor, which is found in a majority of males. Because of its uncharacteristic clinical features, it is easy to misdiagnose. As the number of reports and studies is gradually increasing, diagnosis based on pathologic and immunohistochemical features is becoming clearer, and the rate of misdiagnosis may decrease. The therapy is still controversial. To date, surgical resection with or without (radio-) chemotherapy is the most acceptable and effective method. In order to improve survival time, more and more scholars did research on target therapy, which is hopeful to become the special treatment.

Disclosure of conflict of interest

None.

Address correspondence to: Yisheng Tao, Department of Pathology, Bengbu Medical College, 287 Changhuai Road, Bengbu, Anhui Province, China. Tel: +86-15255299986; E-mail: 2532219709@qq.com

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