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Original Article

Epithelioid sarcoma of the scalp: a case report and literature review

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Abstract: Epithelioid sarcoma (ES) is an aggressive mesenchymal tumor exhibiting bi-directional phenotypes. According to its proclivity for different sites, ES can be subdivided into two categories: distal and proximal variants. Proximal ES often affects the truncal tissue, thighs, head, and neck. Accumulating evidence indicates that several locations in the head, including the orbital, gingival, and nasal cavities, are involved in ES. However, the underlying mechanisms of ES carcinogenesis and progression are largely unknown, including and especially the reason why the tumor cells are positive for both epithelial and mesenchymal classical markers. Thus, we wish to share a rare case of ES in the scalp and its clinical and molecular features. Only 9 cases to date have been reported. An 80-years-old man had sustained a painful swollen mass in his scalp for three months. A diagnosis of epithelioid sarcoma was established based on the combination of the histopathological and immunohistochemical findings. The tumor cells were positive for both mesenchymal (vimentin and S100) and epithelial markers (pan-cytokeratin). This case suggests that ES can be derived from the soft tissue of the scalp. The tumor cells co-expressed biomarkers of epithelial and mesenchymal cells, suggesting the mesenchymal-epithelial transition (MET) may be involved.

Keywords: Epithelioid sarcoma, scalp, mesenchymal-epithelial transition, head, diagnosis

Introduction

ES is a rare and aggressive soft tissue sarcoma first named by Enzinger [1]. The 5-year rate of local recurrence is 35% [2]. Up to 50% of cases develop metastatic lesions, especially in the lung and regional lymph nodes [3]. Adverse prognostic factors include male sex, older age, and proximal/axial location [4]. Proximal ES is distinct from the distal variant by its location [5]. It has a slight predilection for male gender. Jawad et al. identified 441 cases, and the male-to-female ratio was 1.309:1 (250:191) with the major peak incidence in the 17- to 60-years age range [6]. ES has a high propensity for local recurrence, lymphatic invasion, and distant metastasis, especially when it involves the lungs [6-9]. The disease-specific survival for patients under 16 years of age is better [6].

Tumor nodules are composed of spindle-shaped cells and large ovoid or polygonal epithelioid cells with plenty of cytoplasms and prominent nucleoli [5, 10]. In the setting of bi-directional morphology, ES should be distinguished from other sarcomas and undifferentiated carcinomas. Immunohistochemistry may facilitate the establishment of the final diagnosis and the exploration of the underlying mechanisms. Consistent with its morphological characteristics, both subtypes of ES express classical epithelial and mesenchymal markers, including cytokeratins and vimentin, suggesting a possibility that these tumor cells are undergoing a mesenchymal-epithelial transition (MET).

The tumor nodules always slowly increase in size and involve superficial subcutis or deeper soft tissue of the fingers and proximal upper extremities, rather than the trunk, neck, and perineum [11]. Only 9 primary cases have been reported in the scalp to date. We did a retrospective analysis and reviewed all the reported cases.

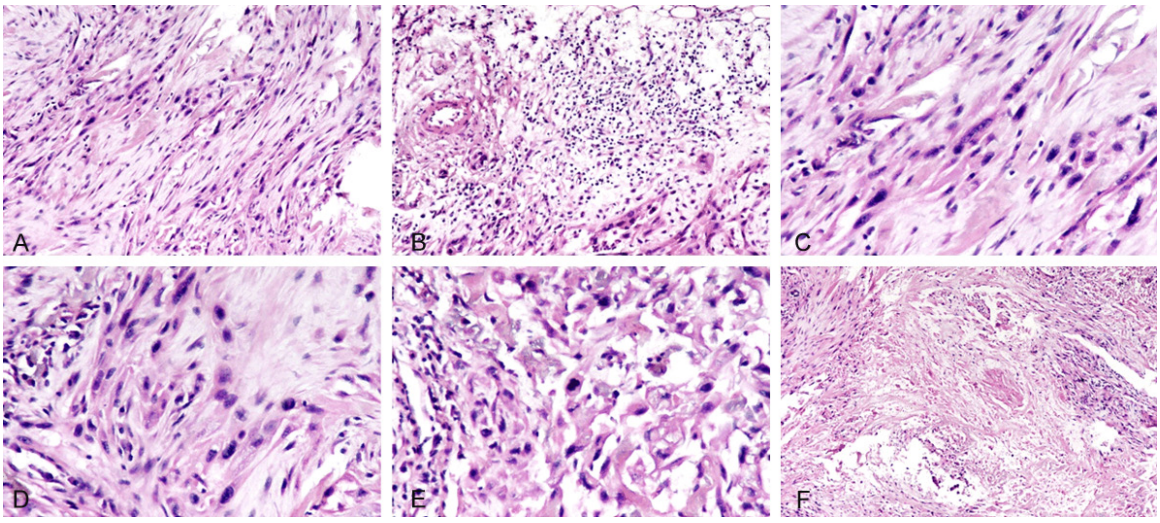

Figure 1. Histological features of scalp ES. A. The tumor cells arranged in fascicular, fluvial, or herringbone patterns; (H&E, original magnification ×200). B. Small and mature immune cells infiltrated and formed clusters; (H&E, original magnification ×200). C. The epithelioid or spindled tumor cells contained small nucleoli; (H&E, original magnification ×400). D. Abundant eosinophilic cytoplasms were observed in the tumor cells; (H&E, original magnification ×400). E. Occasional mitoses were found; (H&E, original magnification ×400). F. Coagulation necrosis was evident (H&E, original magnification ×200).

Case presentation

An 80-years-old man with a painful swollen mass in his scalp for 3 months visited our hospital. Except for chronic bronchitis, his past medical history was silent. The lesion exhibited a rapid growth pattern and appeared as a protuberant nodule with a surface ulcer beneath the stratified squamous epithelium. His laboratory results were within the normal limits. A pathological evaluation confirmed a bi-directional differentiation characterized by epithelial and mesenchymal features. Like spindled cells, the epithelioid cells organized into fascicular and sheet-like pattern and expressed both epithelial and mesenchymal markers such as cytokeratin and vimentin. The final diagnosis of the presented case was PES of the scalp. An extended resection was performed without chemotherapy and radiation.

Histopathology

The tumor underwent a resection and showed an infiltrative growth pattern in the dermis and subcutaneous tissue with an unclear boundary. The tumor cells exhibited epithelioid and spindled morphological features arranged in a fascicular, fluvial, or herringbone pattern (**Figure 1A**). Scattered throughout the tumor cell infiltrate were some small clusters of mature lymphocytes (**Figure 1B**). The epithelioid cells contained large vacuolated nuclei and inconspicuous nucleoli (**Figure 1C**). Both the epithelioid and spindled cells showed moderate amounts of eosinophilic cytoplasm and cytologic atypia (**Figure 1D**). Occasional mitoses and tumor giant cells were noticed (**Figure 1E**). The fusion of the necrosis nodules resulted in a central geographic necrosis and a granuloma-like structure (**Figure 1F**).

Immunohistochemistry

Immunohistochemistry was used to explore the phenotype of the tumor cells in serial sections. Diffuse and strong cytoplasmic reactivities for pan-cytokeratin (CKpan) and vimentin suggested its uncertain histologic origin and MET possibility (**Figure 2A**, **2B**). CK decorated both epithelioid and spindled tumor cells, but vimentin positivity was only observed in the latter. Both cytoplasmic and nuclear positivity indicated that these cells expressed S-100 (**Figure 2C**). The Ki-67 positive ratio was about 15% (**Figure 2D**). The malignant cells were negative for smooth muscle actin (SMA) (**Figure 2E**), CD34 (**Figure 2F**), pan-actin, desmin, Melan-A, melanoma, and factor VIII (data not shown).

Discussion

Several hypotheses emerge regarding the origin and tumorigenesis of ES. It has been pro-

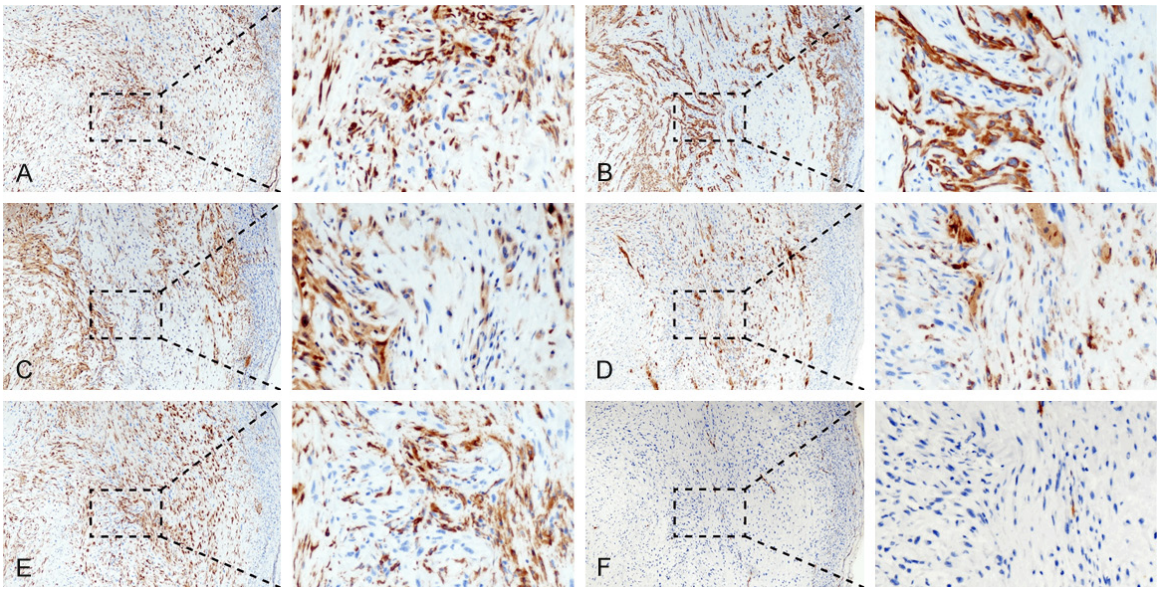

Figure 2. Immunohistochemical staining in scalp ES. A Rhabdoid tumor cells showed cytoplasmic positivity for vimentin. B. The cytoplasms of the spindled and epithelioid tumor cells were positive for CKpan. C. S-100 immunoreactivity was observed in both the cytoplasms and nuclei of the tumor cells. D. Few tumor cells expressed Ki67. E. The loss of the SAM protein in tumor cells, rather than in the smooth muscle cells. F. Malignant cells exhibited CD34 negativity (IHC staining, left: original magnification ×200; right: magnification ×400).

posed that ES is a mesenchymal tumor derived from primitive mesenchymal or myofibroblastic cells [1, 12]. Ultrastructure evidence that the tumor cells contain cell-cell junctions, microvilli, and tonofilaments further supports this idea [13]. Another hypothesis argues that ES originates from naive synovial cells and represents a variant of synovial sarcoma [14]. Modena et al. showed that, analogous to malignant rhabdoid tumors, PES exhibits an allele deletion of the tumor suppressor gene SMARCB1/INI1, suggesting the possibility that ES belongs to the rhabdoid tumor family [15]. Previous studies, including this case, found that epithelioid cells arrange in a fascicular and sheet-like pattern, similar to the patterns of mesenchymal cell-derived tumors (**Table 1**). Meanwhile, the positivity for the epithelial markers cytokeratin and epithelial membrane antigen (EMA) reflects their epithelial phenotype. As described above, we propose that ES derives from mesenchymal stem or progenitor cells, followed by the malignant transformation through the mesenchymal-epithelial transition (MET). The transitioning tumor cells are capable of co-expressing epithelial and mesenchymal markers [16].

Accumulating evidence suggests that epithelium-derived malignant cells gain mesenchymal-like phenotypes and enhanced invasiveness through the epithelial-mesenchymal transition (EMT) [17]. Sarcoma cells can reverse the EMT cascade by a counterbalanced process, MET. The overexpression of the miR-200 family and GRHL2 endows malignant mesenchymal cells with an epithelioid morphology [17, 18]. The changes of gene expression during MET contribute to the tumor dedifferentiation and transdifferentiation, resulting in phenotypic plasticity, poor prognosis, and a high propensity for metastasis [18]. Complicated signaling networks have been studied and demonstrate that the expression of E-cadherin during the MET cascade of ES is associated with SYT-SSX fusion [19]. Down expression of E-cadherin influenced by dysadherin is observed which may be an important factor for prognosis and has a higher positive rate in PES compared with distal epithelioid sarcoma [20].

Both subtypes of ES affect patients of a wide age range. PES has a marked predilection for the older population [7, 8]. PES presents obvious malignant histologic features, including a high mitotic index, necrosis, and invasiveness. The age at the diagnosis of scalp ES ranges from 3-months to 80-years, and the average age is 27.7-years. The propensity for local recur-

Table 1. The clinical and pathological data of 10 cases of PES derived from the scalp

Case No.	Age/sex	Position	Tumor size (cm)	Symptoms	Histological	Stage	Prognosis	Reference
1	34/F	Temporal space	3.0×2.5×1.5	Lobulated growing mass	EC; CN; pseudo granulomatous	Local	FD, 18 mo	Kim et al. [27]
2	18/M	Occipital region	2.7×2×1.5	NM	EC; hemorrhage; necrosis	LNM	-	Gurwale et al. [28]
3	32/M	Parietal bone	-	Mass; ulcers; BE; high serum calcium level	EC; CN	Local	-	Tocco et al. [29]
4	21/F	Supra-auricular	2×4	NM; BE	EC; CN; thin fibrous septa; inflammation	LNM	Recur in 10th year	Hanna et al. [30]
5	7/M	Scalp	2.2×2.5	NM; hemorrhage	SC; CN; thin fibrosis; inflammation	Local	FD, 72 mo	Hanna et al. [30]
6	30/F	Parietooccipital scalp	6×5	NM; BE; hemorrhage	EC	Recurred	Recur in 3th year	Chaichoompol et al. [31]
7	47/M	Scalp	-	Ulcer	SC; high grade	Local	-	Skoog et al. [32]
8	7/M	Scalp	-	Not specific	Central degeneration or CN	Local	FD, 15 mo	Gross et al. [33]
9	1/F	Forehead	-	-	-		FD, 24 mo	Kodet et al. [34]
10	80/M	scalp	1.5×1×0.8	Mass; ulcer	SC; CN; collagen deposition; inflammation; pseudo granulomatous	Local	FD, 12 mo	Present study

M: male; F: female; NM: nodular mass; BE: bony erosion; CN: central necrosis; EC: dominated epithelioid tumor cells with abundant eosinophilic cytoplasms, vesicular nuclei and small prominent nucleoli; SC: dominated spindle or rhabdoid tumor cells with an apparent fascicular, fluvial or herringbone arrangement; LNM: Lymph node metastases; FD: free of disease.

rence and distal metastasis is higher in PES of the scalp and is usually correlated with bone invasion, indicating its distinction from PES of other locations. PES occurring in the head and neck are supposed to be differentiated from other epithelioid tumors by INI stains [21].

ES is expected to be distinguished from other bi-directional malignant tumors such as synovial sarcoma, epithelioid angiosarcoma, and malignant rhabdoid tumors of the kidney. Nodular granuloma-like morphology of ES may be confused with that of granuloma annulare, rheumatoid nodules, and progressive necrotizing granuloma. Immunopositivity for CKpan, vimentin, and EMA may facilitate the differential diagnosis. Synovial sarcoma, also characterized by its bi-directional morphological features, is usually CD99, CKpan, and EMA positive [22]. However, synovial sarcoma is prone to affect the joints, but ES often involves superficial subcutis or deeper soft tissue of extremities. Negativity for factor VIII, CD31, and CD34 can rule out epithelioid angiosarcoma. Nodular lesions with central necrosis are rarely observed in epithelioid angiosarcoma. Another mimic of ES is malignant rhabdoid tumor (MRT), which always occurs in children under 10-years-old and shows rhabdomyoid characteristics without epithelioid and spindled cells. One hypothesis argues that PES should be considered a variant of MRT because of their similar morphological characteristics and the lack of SMARCB1 expression [15]. However, several issues need to be addressed. First, tumor cells are negative for desmin and CD34. Second, the prognosis of PES is much better than that of MRT, and the involved molecular mechanisms are different [15, 21].

Poorly differentiated squamous cell carcinoma (SCC) with spindled features must be added to the differential diagnosis panel of ES. Intercellular bridges and keratinization can be found in SCC, rather than ES. Cytokeratin positivity and vimentin negativity favors the diagnosis of SCC. Fibrosarcoma, malignant peripheral schwannoma, and leiomyosarcoma can contain spindled cells, but they rarely exhibit a granulomatous structure and CK or EMA positivity. Potential mimics of ES also include malignant melanoma, which typically expresses synaptophysin, S-100, HMB45, and Melan-A.

The clinical and pathological features of published cases and our present case are summarized (**Table 1**). The male-to-female ratio is approximately 1.5:1. The 10 cases of scalp ES including the present study predominated by epithelioid tumor cell morphology account for the majority (60%). Scalp ES is correlated with a poor prognosis and all relapsed cases exhibited bone erosion. Necrosis exists in up to 70% of the cases and is usually associated with central degeneration. Most cases exhibit a dominated epithelioid morphology in the dermis and subcutaneous tissue with ulcer and lymphatic vascular invasion. Granuloma-like features, calcification and bone formation occasionally occur.

Comparative genomic hybridization in ES reveals several aberration patterns including gains of 22q [23]. Fluorescence in situ hybridization (FISH) further confirms that the 22q11 breakpoints contain the INI1 gene, which encodes an invariant subunit of SWI/SNF chromatin remodeling complex and shows a homozygous deletion in ES [15]. ES rarely express the SMARCB1/INI1 gene, a tumor suppressor gene for rhabdoid sarcoma, but there are cases of an “INI preserved” pattern [24]. The loss of the conserved core subunit of the SWI/SNF complex, consisting of the BRG1, INI, and BAF170 proteins, contributes to the tumorigenesis of PES [24]. INI loss appears to correlate with rhabdoid features, but some cases exhibit morphological heterogeneity [25], suggesting the involvement of the MET possess. The loss of INI can activate the PI3K/AKT/mTOR pathway, which is frequently upregulated in ES and promotes cell proliferation [26]. More studies are needed to gain more insights into the mechanisms underlying the MET process of ES.

Conclusion

Primary ES of the scalp is extremely rare, and only few cases have been reported. Distinguishing ES from other mesenchymal tumors and undifferentiated cancers has been the focus of clinical efforts. The combination of morphological evaluation and immunohistochemistry can provide substantial evidence to establish a final diagnosis. We report a case of scalp ES, which was composed of atypical epithelioid and spindled cells co-expressing cytokeratin and vimentin. Further work is required

to explore the underlying molecular mechanisms.

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Disclosure of conflict of interest

None.

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