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Epithelioid schwannoma of soft tissue: unusual morphological variant causing a diagnostic dilemma

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Abstract Epithelioid variant of peripheral nerve sheath tumors is a rare but, at the same time, a well-known entity especially in the malignant counterpart. However, peculiar epithelioid morphology in soft tissue schwannomas is unusual and has been defined recently. These tumors may cause diagnostic errors owing to their increased cellularity and epithelioid morphology. Typical histologic features of classic schwannoma such as Antoni A and B areas, Verocay bodies, and hyalinized vessels are either absent or only present in focal areas. Furthermore, strong and diffuse S-100 protein expression is seen in both benign and malignant counterparts of epithelioid schwannoma. The findings that are suggestive of the benign nature of the lesion are long-term clinical history, small size, superficial localization, encapsulation, bland morphology, lack of mitosis and necrosis, and a benign clinical course after complete excision. Pathologists should be aware of the epithelioid variant of schwannoma to avoid false diagnosis of malignancy. We hereby report 3 cases of unusual benign epithelioid schwannoma of the soft tissue with special regard to problems in differential diagnosis.

Keywords: Schwannoma; Epithelioid; Soft tissue

1. Introduction

Benign peripheral nerve sheath tumors (PNSTs) are heterogeneous group of tumors composed of schwannoma, neurofibroma, and perineuroma. Schwannomas from this group have different morphological types; however, histologic diagnosis can be made easily on classic type with typical histologic features, that is, Antoni A and B areas, Verocay bodies, hyalinized vessels, and presence of hemosiderin pigment. On the contrary, the other morphological variants of schwannoma, such as ancient, melanocytic, and granular cell, may cause diagnostic difficulty. In addition to these subtypes, epithelioid morphology is a well-defined feature in malignant PNSTs rather than the benign counterpart [1]. Epithelioid morphology in benign PNSTs is unusual, with only limited number of cases reported in the literature [2,3]. These tumors may cause diagnostic errors owing to their increased cellularity and epithelioid morphology.

We hereby report 3 cases of unusual benign epithelioid schwannoma (ES) of soft tissue with special regard to problems in differential diagnosis.

1.1. Case 1

A 64-year-old female patient with a thigh mass was referred to our institution for consultation. Material was composed of only 6 paraffin blocks without macroscopic material. The mass was reported to be 7 × 6 × 5 cm in diameter, well circumscribed, solid, and gray-white. The case was diagnosed as "suggestive of rhabdoid tumor" by the first examiner pathologist without any immunohistochemical studies. Microscobic examination revealed that the tumor was separated with fibrous capsule from surrounding subcutaneous tissue. The tumor was highly cellular and composed of spindle and epithelioid cell groups (Fig. 1). Cystic degeneration and intracapsular and pericapsular lymphocytic infiltration were observed in some areas (Fig. 1). We also noticed highly cellular

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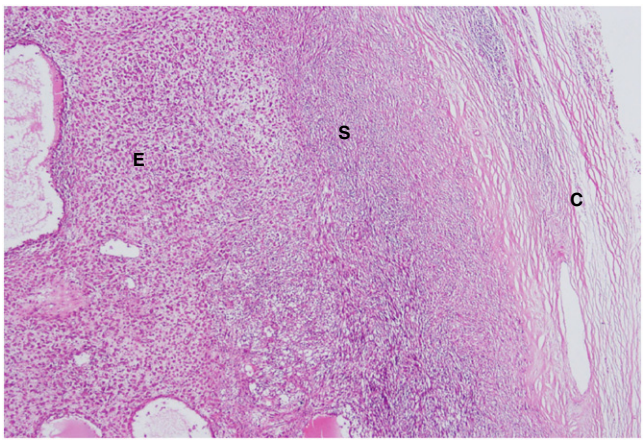

Fig. 1. Tumor is composed of spindle (S) and epithelioid (E) cell groups surrounded by a fibrous capsule (C). Cystic degeneration and intracapsular and pericapsular lymphocytic infiltration were observed in some areas (case 1).

areas with spindle cell bundles that resemble cellular schwannoma, which made up approximately 20% of the tumor. The rest of the tumor was composed of epithelioid cell groups with nesting pattern in myxoid stroma (Fig. 2). Areas with spindle cell and epithelioid cells had a distinct demarcation. Epithelioid component was composed of cells with large eosinophilic cytoplasm, rounded nuclei, and distinct cell borders. Occasional multinuclear cells were also seen. Lipid-laden histiocytes and mast cells were present in both spindle and epithelioid components. We did not observe Antoni A and B areas and Verocay bodies. Necrosis was not evident. Mitotic activity was less than 1 in 10 high-power fields. Immunohistochemically, both epithelioid and spindle cell areas diffusely expressed vimentin and S-100 protein (Fig. 2). Desmin, smooth muscle actin, pancytokeratin, EMA, HMB-45, and CD34 were all negative. Ki-67 index was less than 1%. No recurrence was seen at 5 years of follow-up.

1.2. Case 2

A 47-year-old male patient was admitted to our hospital for a mass of 1 year duration in the lumbar region. Macroscopically, the mass was whitish-gray in appearance, well circumscribed, focally encapsulated, and 10 × 6 × 5 cm in diameter. The cut surface has a nodular and myxoid appearance in some areas. Microscopic examination revealed that the tumor was composed of hypocellular and

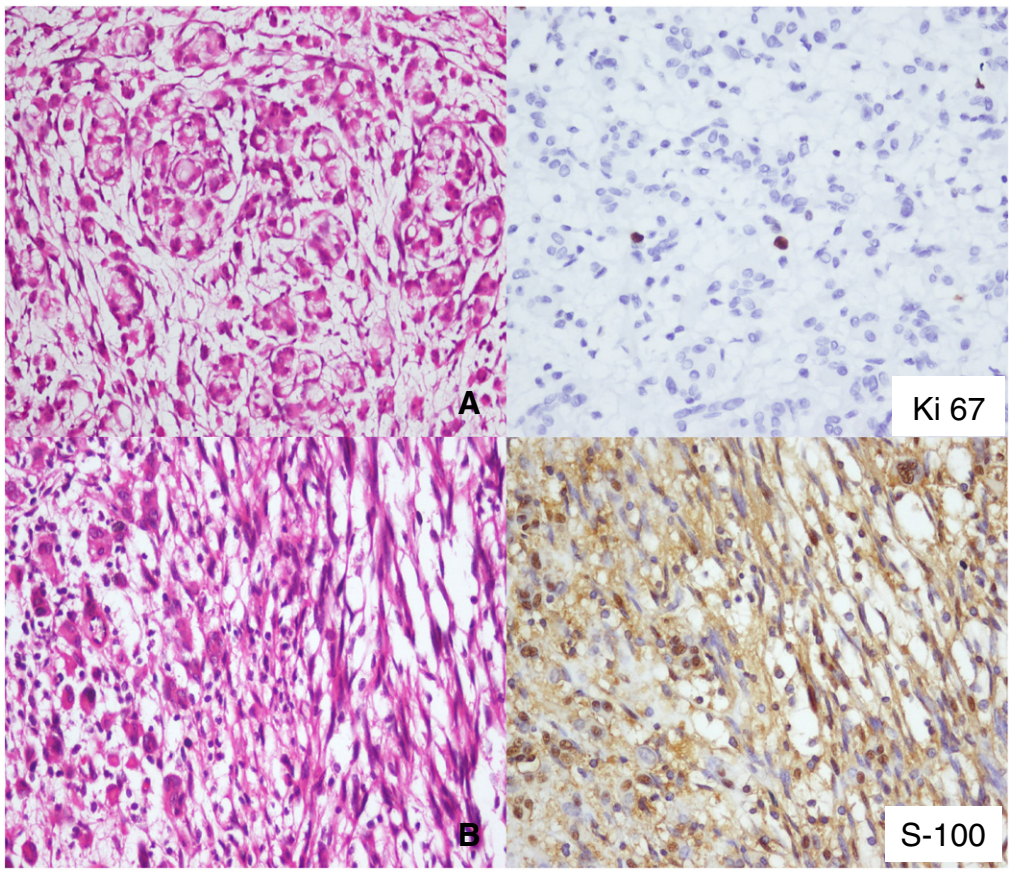

Fig. 2. Groups of epithelioid cells with nesting pattern in a myxoid stroma (A). Transition of spindle cells into epithelial component. Some of the epithelioid cells have multiple nuclei (B). Ki-67 proliferation index is 1%. Diffuse expression of S-100 protein in spindle and epithelioid cells (case 1).

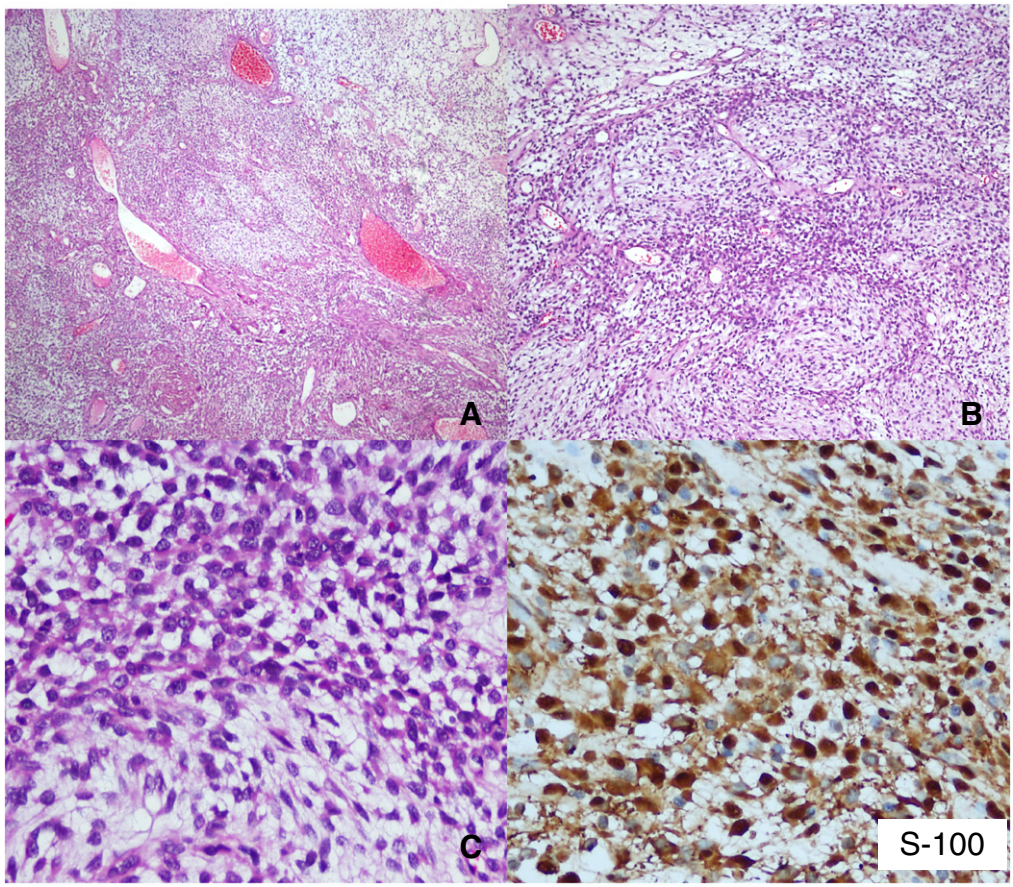

Fig. 3. Hypocellular and hypercellular areas separated by a myxoid and loose edematous stroma with numerous thick-walled, hyalinized blood vessels (A and B). The epithelioid cells and a small number of spindle cell in myxoid background (C). Diffuse nuclear and/or cytoplasmic staining with S-100 protein (case 2).

hypercellular areas with spindle and epithelioid cells. Bundles of spindle cell with myxoid ground and large hyalinizing walled vessels were also present (Fig. 3). The epithelioid cells with large eosinophilic cytoplasm, which contain central nucleoli, were observed in hypercellular areas mostly (Fig. 3). Necrosis was not evident. Mitotic activity was less than 1 in 10 high-power fields. Immunohistochemically, the tumor cells strongly and diffusely expressed S-100 protein (Fig. 3). Smooth muscle actin, HMB-45, and melan A were not expressed in tumor cells. Ki-67 proliferation index was 1%. At 2 years of follow-up, there was no recurrence.

1.3. Case 3

A 67-year-old woman presented with a thigh mass of 3 years duration. Magnetic resonance imaging revealed a homogeneous contrast-enhanced, well-defined intramuscular mass measuring 5 × 4 cm in the left thigh. Microscopic examination of the specimen obtained by percutaneous needle core biopsy revealed a pure population of epithelioid cells with large eosinophilic cytoplasm. The nuclei of the epithelioid cells were centrally or eccentrically located and mainly round. Nuclear atypia, including variability in nuclear size and shape, and intranuclear inclusions were observed in some cells (Fig. 4). Necrosis and mitosis were not evident. On immunohistochemistry, the tumor was strongly positive for S-100 protein and was negative for smooth muscle actin, HHF-35. Ki-67 proliferation index was 1% (Fig. 5). With these findings, the case was diagnosed as benign ES, and the mass was excised totally. Histopathologic examination revealed similar features with the core biopsy. With 3 years of follow-up, no recurrences have been detected.

2. Discussion

Epithelioid morphology is a peculiar feature, which was defined in both benign and malignant PNSTs. Epithelioid PNSTs do not have true epithelial elements such as glandular or squamous differentiation. Epithelioid variant is a well-known entity especially in malignant PNSTs [1]. However, epithelioid morphology in schwannoma is unusual and rare with limited number of cases reported in the literature. Taxy and Battifora [4] documented the first 2 cases in 1981. These 2 epithelioid tumors, which do not express clinical, macroscopic, and microscopic features of conventional

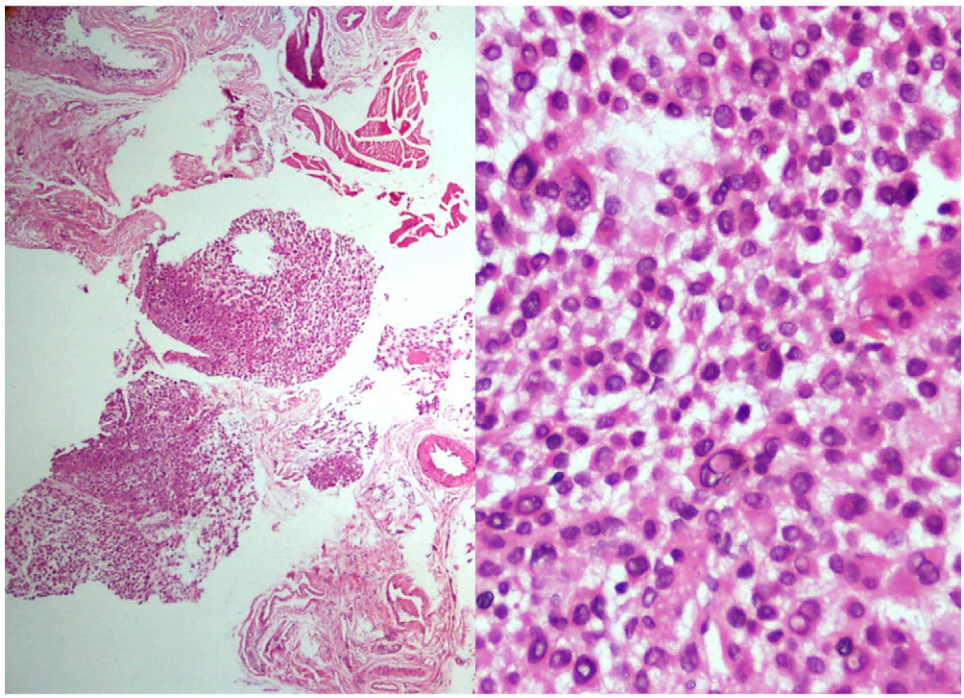

Fig. 4. Core biopsy material in case 3. Epithelioid cells with intranuclear inclusions and ancient atypia.

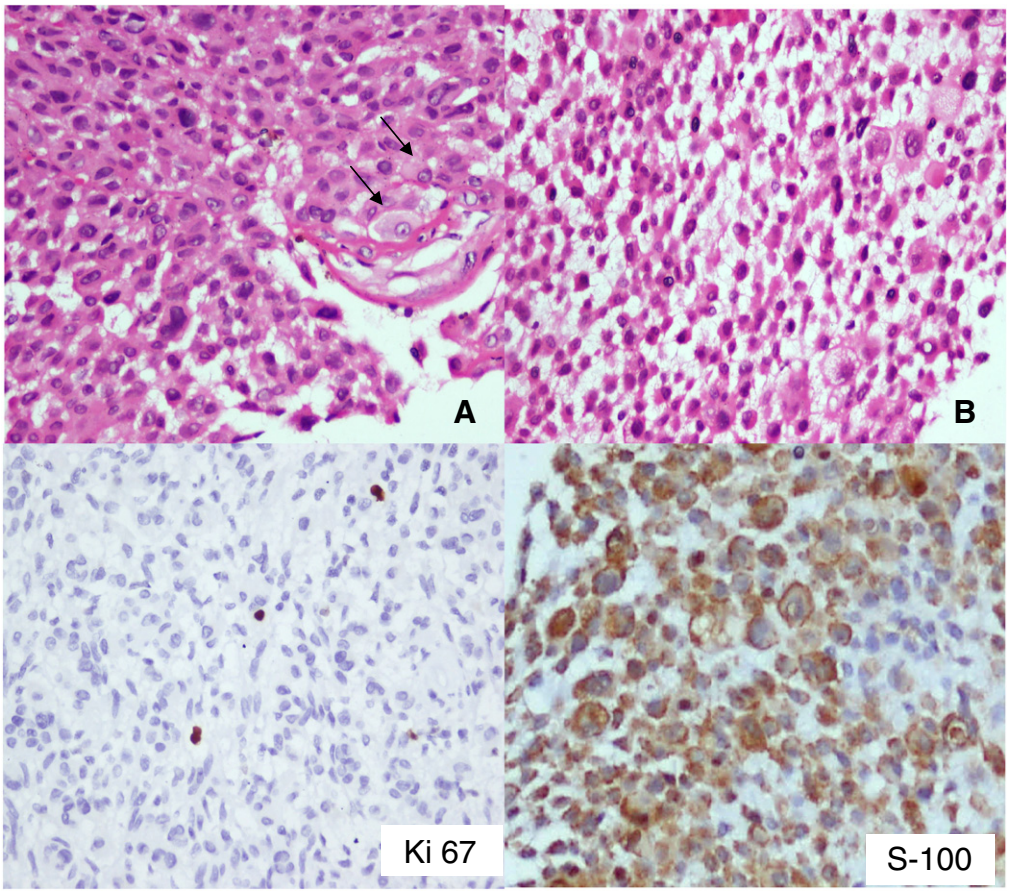

Fig. 5. Epithelioid cells with central nucleoli and eccentric nuclear localization reminiscent of a rhabdoid cell (arrows) and nuclear atypia in some of these cells (A and B). Low proliferation index (Ki-67: 1%-2%): diffuse nuclear and/or cytoplasmic staining with S-100 (case 3).

type of benign and malignant schwannoma, displayed benign schwannoma features in electron microscopy. Franks [5] reported a case of an epithelioid neurilemmoma of the trigeminal nerve in 1985 and observed the absence of S-100 expression in epithelioid component. However, the author also reported that ultrastructurally, epithelioid cells were of schwannian nature and proposed that these cells were less well differentiated and derived from a Schwann cell precursor. The first series regarding this entity is limited and belongs to Kindbloom et al [2] (5 cases) and Laskin et al [3] (4 cases). Afterwards only a few case originating from the soft tissue have been reported so far [7-9]. In addition to soft tissue, intracranial and mucosal cases have also been reported [10,11]. In recent years, Ples et al [12] reported 2 cases in the colon, and Chan et al [13] reported a case of benign ES derived from intraparotid facial nerve.

Laskin et al reported the largest series with 33 cases in predominantly dermal/subcutaneous location [3]. He reviewed AFIP archival cases, which were diagnosed between 1970 and 2000, and reassessed the benign PNSTs, which consisted more than 50% of epithelioid differentiation. They were able to identify 18 cases of epithelioid neurofibroma. The remaining 15 cases showed some histologic features suggestive of schwannoma. Among these, 5 cases were classified as "benign epithelioid PNSTs of indeterminate histogenesis" owing to the uniform cellularity, absence of nuclear palisading, and presence of a significant CD34-positive spindled cell population [3].

Identification of the classic schwannoma areas is helpful in differential diagnosis [2,3]. However, it might not be possible to demonstrate these areas in each case. Tumor may completely be formed of epithelioid component, and also, spindle cells may constitute part of the tumor [6,7]. Furthermore, typical schwannoma areas may be absent (Antoni A and B, Verocay bodies) as in our cases. We interpreted all 3 cases as benign and as ES because of the capsule formation, absence of striking nuclear atypia (except for third case, with atypia in the form of ancient change), lack of necrosis and mitosis, the presence of degeneration findings (thick-walled vessels, cystic degeneration, hemosiderin pigment), presence of spindle cells that resemble cellular schwannoma, strong S-100 expression in both cell types, and low proliferation index (Ki-67 $\leq$1%).

Epithelioid neurofibroma might display similar histologic features to ES. The presence of nerves in tumoral tissue, classic neurofibroma areas, and neurofibromatosis type1 association are helpful in distinguishing these 2 entities. Distinction between these tumors is important because the malignant transformation in schwannomas is very rare. The best ways to demonstrate the Schwann cell differentiation in ESs are electron microscopy and strong S-100 expression [2,4,5]. Laskin et al [3] object to use the term *neurofibroma* or *schwannoma* without performing ultrastructural and molecular studies. They prefer the term *benign epithelioid peripheral nerve sheath tumor*, particularly "indeterminate histogenesis" category [3].

The main differential diagnostic problem is malignant epithelioid PNSTs. Increased cellularity, epithelioid morphology, and the absence of typical schwannoma component may be misleading to malignant diagnosis. Moreover, malignant epithelioid PNSTs also show strong and diffuse S-100 protein expression [1]. However, superficial location, low mitotic activity, encapsulation or well demarcation from surrounding tissue, low Ki-67 index, absence of necrosis, and striking nuclear atypia are features of benign ES [2,3]. The presence of typical schwannoma component is also helpful in differential diagnosis.

Cellular neurothekeoma, myoepithelial tumors, melanocytic tumors, and epithelioid-type fibrous histiocytoma should be considered in differential diagnosis albeit less likely. As in our first case, large eosinophilic cytoplasm and eccentric localization of the nuclei might lead to a misdiagnosis of rhabdoid tumor. In addition to the distinguishing morphological characteristics of benign ES, the ultrastructural and immunohistochemical studies help in the differential diagnosis.

Simple total excision is sufficient for treatment of benign ES. Development of malignant epithelioid PNST from benign schwannoma is extremely rare [14,15].

Metastases have not been reported in literature [2,3,7,8]. Laskin et al [3] observed recurrence or persistence in 3 of 33 cases; however, they did not report destructive recurrence, metastasis, or death related to disease. There is no evidence that the ES has a worse prognosis than classic schwannoma. However, there are a limited number of well-examined cases in this regard. Therefore, close follow-up, especially for the cases with cytologic atypia, is being advised [3]. The follow-up period of our cases was between 2 and 5 years. During this period, no recurrence or metastasis was observed.

In conclusion, epithelioid morphology, although rare, may be encountered in schwannomas. To be aware of epithelioid variant of schwannoma is important because it might be misdiagnosed as a malignant epithelioid PNST especially in core biopsy. Furthermore, histopathologic features of ES may overlap with those of other epithelioid soft tissue tumors and melanocytic tumors.

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