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**A Case of INI1-deficient Tumor in the Forearm Successfully Diagnosed as Epithelioid
Malignant Peripheral Nerve Sheath Tumor: Intratumoral Nerve Fibers with Wallerian
Degeneration as a Diagnostic Aid**

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23 **Running head:**

24 INI1-deficient tumor in the forearm

25

26 **Key words:**

27 Epithelioid malignant peripheral nerve sheath tumor

28 INI1

29 Schwannoma

30

31 **Abbreviations:**

32 Malignant peripheral nerve sheath tumor (MPNST)

33 **To the Editor (1199 words):**

34 Malignant peripheral nerve sheath tumor (MPNST) is a spindle cell sarcoma with features
35 suggesting Schwannian differentiation and is often associated with neurofibromatosis type 1
36 (NF1) or irradiation. The epithelioid variant, epithelioid MPNST, is not related to such
37 clinical situations, however, and also exhibits distinct pathological and genetic features from
38 conventional MPNST^{1,2}. Thus, the diagnosis of epithelioid MPNST can be difficult without
39 knowledgeable and careful pathological evaluation. Here, we report a case of epithelioid
40 MPNST in which the degenerated nerve fibers within the tumor contributed to the correct
41 diagnosis.

42 A woman in her forties without significant hereditary background consulted a
43 physician for a 1 cm subcutaneous nodule on her right forearm. The patient had noticed the
44 tumor approximately three years earlier, and it had gradually grown. Upon physical
45 examination, the patient exhibited a positive Tinel's sign, suggesting peripheral nerve
46 irritation, and a diagnosis of Schwannoma was suspected. The tumor was subsequently
47 excised and submitted for pathological evaluation.

48 Histologically, the tumor was well circumscribed, with variegated cellular densities
49 vaguely giving a multilobular appearance, and it consisted of spindle to pleomorphic cells on
50 a myxoid background (Figure S1A). In the area of dense cellularity, neoplastic cells exhibited
51 epithelioid aggregations with a squamoid-like appearance (Figure 1A), and there were many

multinucleated tumor cells (Figure 1B). Mitotic figures were occasionally detected (1/10 high-power fields [HPFs]) (Figure 1B), and no necrosis was evident. At the periphery of the tumor, nerve fibers with Wallerian degeneration (i.e., fragmented axons, some of which formed myelin ovoids) were observed (Figure 1C-D and Figure S1B-D), suggesting the association of the tumor with the peripheral nervous system. Numerous macrophages were also observed within the tumor (Figure S1E).

Immunohistochemically, the tumor cells were diffusely and strongly positive for S-100 protein (Figure 1E), and focally positive for EMA and GFAP; they were negative for alpha-SMA, CD34, cytokeratin, desmin, HMB-45, Melan A, and p63 (not shown). The tumor cells were negative for INI1 (Figure 1F), H3K27me3 expression was retained, and the Ki-67 labeling index was 13% (not shown). With these morphological and immunohistochemical features, a diagnosis of epithelioid MPNST was made. The patient has been carefully followed without any postoperative therapies and has remained disease-free for about 44 months.

Epithelioid MPNST is a rare variant of MPNST (<5%). Contrary to conventional MPNST, the characteristic features of this tumor include almost no association with NF1, diffuse and strong positivity for S-100 protein in immunohistochemistry, and INI1-deficiency^{1, 2}. According to the largest case series of epithelioid MPNST², the tumor can occur at almost every age, with a peak in middle-aged adults. Some cases are associated with nerve

tissue and arise in pre-existing Schwannoma, and only 1 case among 63 cases occurred in an NF1 patient. The most common sites of involvement are the subcutis of the extremities. The size of the tumor is variable (average: 3.0 cm, range: 0.4–20 cm). Most cases are well circumscribed, and occasionally have hemorrhage and necrosis. Tumors are often multilobulated and consist of round, polygonal, or ovoid neoplastic cells, which in most cases exhibit marked cytologic atypia with irregular vesicular nuclei and prominent nucleoli. Mitotic rates are variable in each case (from 1–46/10 HPFs), and necrosis can be seen. Diffuse and strong positivity for S-100 protein is a constant feature, and keratins and melanocytic markers are generally negative.

Epithelioid MPNST frequently exhibits a loss of INI1 expression resulting from the loss of the *INI1* gene, which is not observed in conventional MPNST³. In contrast, global loss of H3K27me3 expression, a feature of conventional MPNST, is not observed. These genetic features, as well as the clinicopathological findings, highlight the unique characteristics of this variant.

Based on the epithelioid morphology, the differential diagnoses in our case included various diseases, such as epithelioid myxofibrosarcoma, epithelioid sarcoma, and metastasis of carcinoma or melanoma. However, one of the most important differential diagnoses is myoepithelial carcinoma of soft tissue, which frequently exhibits morphological and immunohistochemical features similar to epithelioid MPNST¹. This tumor is the soft tissue

counterpart of that arising in the salivary gland, and is composed of atypical cells with myoepithelial differentiation. It can occur in a wide age range, with a peak in young to middle-aged adults. The majority of tumors develop in the limbs, usually in subcutaneous tissue. Macroscopically, the tumor is often well circumscribed and sometimes infiltrative, and it varies in size. The tumor exhibits variable histological patterns with myxoid stroma and is composed of epithelioid to spindle cells. The tumor cells exhibit nuclear atypia, often with a high mitotic rate and necrosis. Almost every case is positive for cytokeratin, S-100 protein, and calponin, and loss of INI1 expression can be observed in myoepithelial carcinoma, although it is usually limited in pediatric cases³. Half of the myoepithelial carcinomas of soft tissue involve *EWSR1* rearrangement.

In summary, it can be challenging to differentiate epithelioid MPNST from myoepithelial carcinoma of soft tissue through morphological and immunohistochemical evaluation of the neoplastic cells. Therefore, the presence of neuronal fibers with Wallerian degeneration at the periphery of the tumor, as observed in the current case, is key to the correct diagnosis. Through the invasion of surrounding tissues, peripheral nerve tissues can be involved, even in non-neurogenic tumors. The observation of neuronal fibers with Wallerian degeneration appears to be rare, however. A recent review put forth the importance of the de- and regeneration processes of peripheral nerve tissues involving multiple cell types, including axons and macrophages, for Schwannoma development⁴. Thus, we think that the

109 presence of degenerated nerve fibers strongly suggests the possibility of Schwannian tumors
110 with the relevance of their tumorigenesis.

111 Another important differential diagnosis is epithelioid Schwannoma, because the
112 morphological architecture and immunophenotype are almost identical to those of epithelioid
113 MPNST, including the loss of INI1 expression⁵. Degenerated neuronal fibers, of course,
114 could be observed. The nuclear atypia and pleomorphism in our case would be beyond that
115 which could be observed in epithelioid Schwannoma. The small size, low mitotic activity,
116 and seemingly benign clinical behavior so far may suggest its low-grade malignant potential,
117 however. In addition to the common pathological findings, epithelioid Schwannoma can
118 transform into epithelioid MPNST, which is unlikely in conventional Schwannoma^{1,5}. Thus,
119 epithelioid MPNST and epithelioid Schwannoma might be distinct from each conventional
120 non-epithelioid counterpart and might form a spectrum of one disease entity as an
121 INI1-deficient Schwannian tumor. Our case may be an example of this.

122 INI1-deficient tumor, the prototype would be malignant rhabdoid tumor, currently
123 encompasses a large number of diseases with different sites, histologies, and clinical
124 behaviors. This speaks to the broad and various impacts of dysfunction of the SWI/SNF
125 complex in neoplastic transformation in diverse cellular lineages. Updating the knowledge of
126 this expanding tumor family would be necessary and helpful for pathologists to keep up with
127 the current molecular biology of cancer and its possible therapeutics.

128 In summary, our case suggests that careful morphological observation of both the
129 tumor cells themselves and the microenvironmental elements of the tumor (the degenerated
130 nerves in this case) is of value in reaching a correct diagnosis. The case of epithelioid
131 MPNST described herein as part of the INI1-deficient tumor group may contribute to a better
132 understanding of this particular group of tumors.

133

134 **Disclosure Statement**

135 The authors have no conflicts of interest to declare.

136

137 **Author Contributions**

138 YY was responsible for drafting the manuscript and figures. All authors handled the
139 correction and approval of the manuscript.

140 **Figure legends**

141 **Figure 1. Morphological and immunohistochemical features of the tumor**

142 (A-D) Hematoxylin and eosin (H&E) staining of the tumor. Spindle to pleomorphic cells on a
143 myxoid background in a hypocellular area (A-D). Tumor cells with an epithelioid appearance
144 and squamoid-like aggregation (A). Pleomorphic tumor cells with bizarre nuclei (B) and
145 multinucleated cells (arrow), with occasional mitotic figures (inset). At the periphery of the
146 tumor, nerve fibers with Wallerian degeneration (i.e., fragmented axons, some of which
147 formed myelin ovoids) are evident (some degenerated axon are depicted by the arrow) (C, D).
148 (E, F) Immunohistochemically, the tumor cells are diffusely and strongly positive for S-100
149 protein (E) and negative for INI-1 (F).

150

151 **Supplementary information**

152 **Figure S1. Morphological and immunohistochemical features of the tumor**

153 (A) Hematoxylin and eosin (H&E) staining of the tumor. The tumor was well circumscribed
154 and vaguely lobulated, and consisted of spindle to pleomorphic cells on a myxoid background.
155 (B, C) Immunohistochemistry for neurofilament detects linear but partially discontinuous
156 neuronal fibers within the tumor (arrow, B). Additionally, fragmented axons, some of which
157 formed myelin ovoids, are observed (B, C. some degenerated axons are depicted by the
158 arrows). (D) Bodian staining also shows myelin ovoids (some degenerated axons are depicted
159 by the arrows). (E) Immunohistochemistry for PU.1 shows that numerous macrophages
160 infiltrated the tumor.

161

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Figure 1

Figure S1