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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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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Running head:

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INI1

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Abbreviations:

Malignant peripheral nerve sheath tumor (MPNST)

To the Editor (1199 words):

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

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

Histologically, the tumor was well circumscribed, with variegated cellular densities vaguely giving a multilobular appearance, and it consisted of spindle to pleomorphic cells on a myxoid background (Figure S1A). In the area of dense cellularity, neoplastic cells exhibited 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 MPNST [2], 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 MPNST [3]. 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 MPNST [1]. 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 cases [3]. 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 development [4]. Thus, we think that the

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

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

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

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

Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contributions

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

Figure legends

Figure 1. Morphological and immunohistochemical features of the tumor

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

Supplementary information

Figure S1. Morphological and immunohistochemical features of the tumor

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

References

1. World Health Organization Classification of Tumours Editorial Board. Soft Tissue and Bone Tumours. 5th ed. Lyon (France): IARC; 2020.
2. Jo VY, Fletcher CD. Epithelioid malignant peripheral nerve sheath tumor: clinicopathologic analysis of 63 cases. Am J Surg Pathol. 2015;**39**:673-82.
3. Hornick JL, Dal Cin P, Fletcher CD. Loss of INI1 expression is characteristic of both conventional and proximal-type epithelioid sarcoma. Am J Surg Pathol. 2009;**33**:542-50.
4. Helbing DL, Schulz A, Morrison H. Pathomechanisms in schwannoma development and progression. Oncogene. 2020;**39**:5421-9.
5. Jo VY, Fletcher CDM. SMARCB1/INI1 loss in epithelioid Schwannoma: a clinicopathologic and immunohistochemical study of 65 cases. Am J Surg Pathol. 2017;**41**:1013-22.

Figure 1

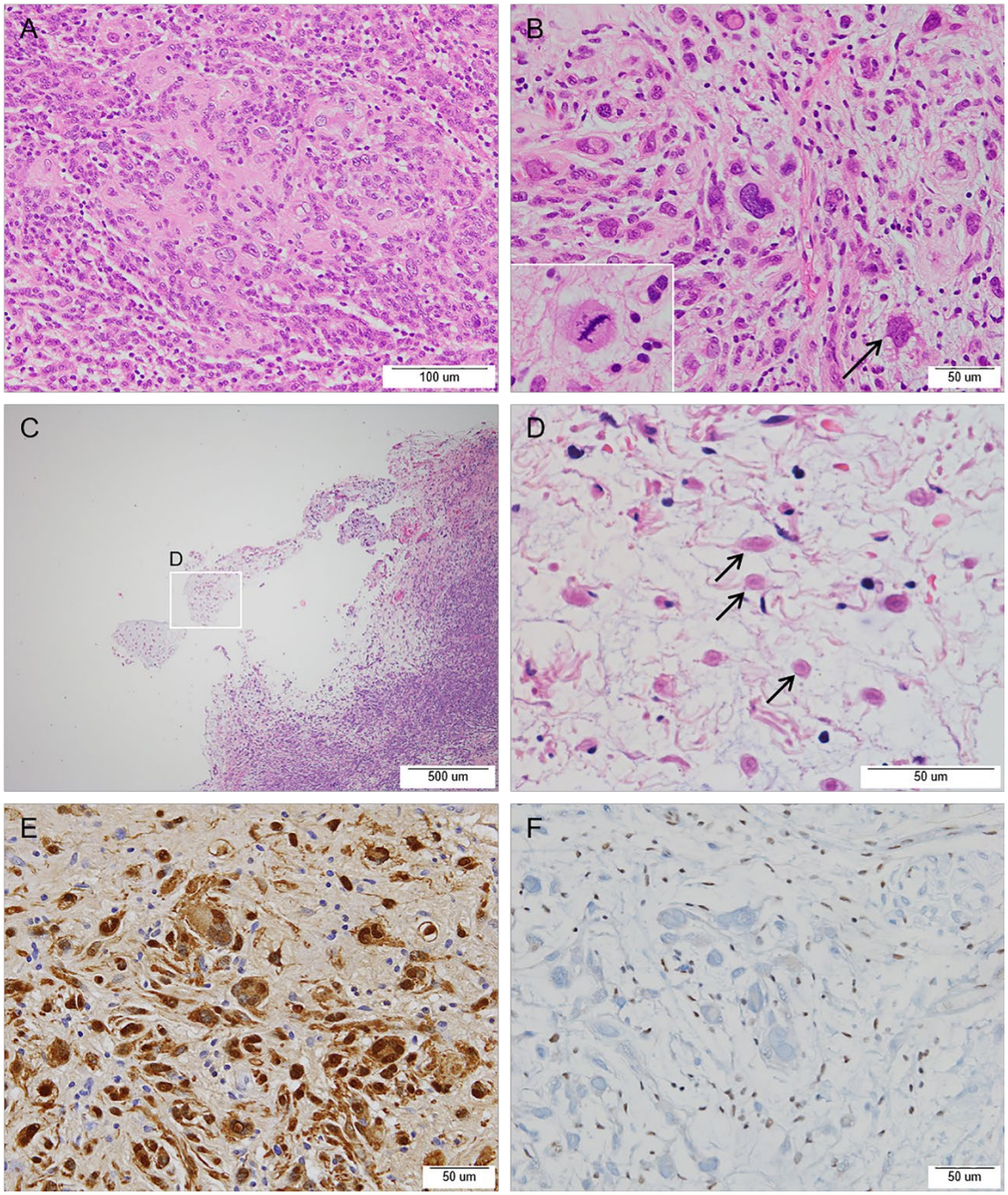

Figure S1