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Epithelioid Malignant Peripheral Nerve Sheath Tumor: Case Report and Review of the Literature

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Abstract

Malignant peripheral nerve sheath tumor (MPNST) is an uncommon soft tissue tumor originating from peripheral nerve cells, including Schwann cells, perineural cells, and fibroblasts. Epithelioid MPNST (EMPNST) is a rarer variant showing epithelioid morphological features and a distinctive immunohistochemical profile. EMPNST can arise in association with a pre-existing neurofibroma or any peripheral nerve and typically have a relatively long period of slow growth followed by a sudden growth acceleration. This tumor can be confused with other tumors such as malignant melanoma or epithelioid tumors due to similar histology; however, its unique immunohistochemistry and genetic profile allow for precise differentiation. Treatment for both MPNSTs and EMPNSTs is equal, involving a combination of complete resection with negative margins and cytotoxic chemotherapy. To add to the limited literature on EMPNST, we present a case of this rare flank tumor with metastasis to the lungs and review the literature.

Introduction:

Malignant peripheral nerve sheath tumors (MPNSTs) are derived from peripheral nerve cells and account for approximately 3 to 10 % of malignant soft tissue tumors.[1] Epithelioid malignant peripheral nerve sheath tumors (EMPNSTs), an exceedingly rare subtype of (MPNSTs), are defined as the presence of greater than 50 percent of epithelioid polygonal tumor cells in sheets or nodules. These tumors have distinct immunophenotypical characteristics accounting for approximately 11% of MPNSTs.[2,3]

In contrast to conventional MPNST, occurrence from or within a pre-existing benign peripheral nerve sheath tumor is uncommon in the epithelioid variant. There is also only an infrequent association with neurofibromatosis (NF1).[3] Although uncommon, some investigators report that these tumors could arise in association with a pre-existing neurofibroma, schwannomas, or a peripheral nerve and are characterized by a relatively long period of slow growth followed by a sudden growth acceleration.[4] Clinically, EMPNST is most commonly present as an enlarging palpable mass in the upper and lower extremities or trunk region, with or without tenderness.[5] is generally poor, with high relapse rates following multimodality therapy in early disease, low response rates to cytotoxic chemotherapy in advanced disease, propensity for rapid disease progression and systemic involvement, and high mortality.[6] Here we report a case of a 44-year-old man with no history of neurofibroma who presented with a painful flank mass recently enlarging in size diagnosed as EMPNST and present a brief review of the literature on this rare tumor.

Case Presentation:

A 62-year-old man presented with a painful right flank mass recently enlarging in size. There was no history of neurofibroma, but the patient gave an account of localized prostatic carcinoma treated with radiation therapy three years before the current presentation. There was no other significant medical history. Imaging studies showed a well-defined deep-seated right flank mass measuring approximately 11 x 8.5 cm with multinodular appearance and hypointensity on T2-weighted magnetic resonance imaging (MRI). Gadolinium-enhanced T1-weighted MRI image with fat suppression showed heterogeneous enhancement but isointense to the surrounding muscles. In addition, CT studies showed two well-defined right lung masses, the larger measuring 5.5x3.5 cm and the smaller measuring 3x2 cm. Microscopic examination of tissue core biopsies taken from the right flank mass and the larger lung mass showed similar histomorphological

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findings. The tumor was characterized by an overall multilobulated growth pattern of clustered nodules of tumor cells (Figure 1A). The tumor cells showed epithelioid cell features with prominent nucleoli, eosinophilic cytoplasm, and dense fibromyxoid stroma (Figure 1B). The examined core tissue material showed extensive hemorrhage, significant areas of tumor necrosis, and abundant mitotic figures of more than 16/10HPF, indicating a high-grade tumor. Cellular epithelioid features were identified in more than 80% of the examined tumor.

Histomorphological features were diagnostic of a high-grade malignant tumor, but the differential diagnosis was varied, including carcinoma, melanoma, and epithelioid sarcoma. Immunohistochemistry (IHC) studies were essential to identify definitive tumor differentiation. The tumor cells were strongly positive for CD56 (Figure 1C), S100 (Figure 1D), glial fibrillary acidic protein (GFAP), vimentin, and weakly positive for EMA. The IHC studies were negative for p63, cytokeratin AE1/AE3, melan-A, HMB-45, CD34, desmin, and carcinoembryonic antigen (CEA). The mass showed that 20 percent of cells were positive for Ki-67. A radiological body scan showed no evidence of other metastatic sites. IHC studies also showed SMARCB1/INI1 immunohistochemical loss. Molecular studies on the core tissue material revealed tumor suppressor gene SMARCB1/INI1 inactivating mutations. The histomorphological features and IHC profile were diagnostic of high-grade Epithelioid malignant peripheral nerve sheath tumor with metastasis to the lung.

Following the recommendation of a multidisciplinary tumor board presentation, neoadjuvant chemotherapy using anthracycline and ifosfamide was initiated, followed by complete resection of the flank mass and the two lung masses. A wide safe surgical margin was obtained with the resection of lung masses; however, the flank mass showed multifocal margins involvement by the tumor. Treatment effect in the form of tumor necrosis and fibrosis was noted only in 40% of the examined tumor mass. The patient received adjuvant radiation therapy and was followed for six months with no evidence of recurrence or metastasis. Unfortunately, he expired due to widespread lung, bone, and liver metastases.

Discussion:

Epithelioid malignant peripheral nerve sheath tumor (EMPNST) is a rare sarcoma first described in 1954 by McCormack et al. and is considered a variant of malignant peripheral nerve sheath tumor (MPNST).[7] Peripheral nerve sheath tumors are a broad group of abnormal cell growths with well-defined clinicopathological features. They range from benign schwannomas and perineuromas to malignant peripheral nerve sheath tumors, often resistant to conventional chemotherapeutic treatments.[8] The different components of the peripheral nerve structure include the endoneurium, the perineurium, and the epineurium. The nerve cell is populated by various cell types, including fibroblasts, Schwann cells, and specialized perineural cells, all spindle cells with elongated nuclei and tapered ends.[9] Malignant peripheral nerve sheath tumors (MPNSTs) are derived from peripheral nerve cells and account for approximately 3 to 10 % of malignant soft tissue tumors.[1] Most MPNSTs are spindle cells, following a trend of recapitulating the normal cell morphology of peripheral nerve components. Epithelioid MPNST (EMPNST), accounting for approximately 11% of MPNSTs, presents predominant epithelioid cell morphological features. MPNSTs can create diagnostic challenges by being confused with other epithelial and melanocytic entities.[2,9] Tumors can present as a slowly enlarging mass lodged in the deep soft tissue compartment. The most common site of origin is the lower extremity, followed by the upper extremity, trunk, and more rarely in subfascial locations such as the ileum, prostate, pleura, mediastinum, and retroperitoneum.[5] EMPNST has an equal sex distribution and presents most commonly in the third or fourth decade of life with a broad age range from 6 to 80 years old, with a median age of 44.[10,11]

Currently, the diagnosis of EMPNST rests on cell morphology and immunohistochemical findings. However, unlike conventional MPNSTs, which tend

to show only focal immunoreactivity for S100 and Sox10, EMPNSTs commonly show diffuse and robust expression of S100 and Sox10.[5] In addition, Glial fibrillary acidic protein (GFAP) is also expressed in 60% of cases, yet EMPNSTs do not tend to express melanoma-associated antigens such as Melan A and HMB45.[12]

Immunohistochemical distinctions between MPNSTs and EMPNSTs include cytokeratin, which is rare in EMPNSTs. Tumor suppressor gene SMARCB1/INI1 inactivating mutations is reported in the majority (75%) of EMPNST correlating with SMARCB1/INI1 immunohistochemical loss with IHC study.[5,13,14]

Histologically, EMPNST is characterized by a largely epithelioid cytomorphology and an overall multilobulated growth pattern.[14] The tumor displays key morphologic characteristics, including a circumscribed solid sheet-like growth pattern, prominent fibromyxoid stroma, multinucleated giant cells, clear cell morphology, nuclear inclusions, perivascular whorling, and heterologous/metaplastic elements such as cartilage or bone.[14] Higher power examination reveals large epithelioid cells with abundant eosinophilic cytoplasm, large nuclei with strikingly vesicular chromatin, and often eosinophilic nucleoli.[9] Mitoses and necrosis have also been frequently documented.[15] In an analysis of 63 cases of EMPNST, Jo VY et al. found the median tumor size to be 3 cm, though some cases were reported to be up to 20 cm.[5]

Treatment for both MPNSTs and EMPNSTs largely remains the same, involving a complete resection with negative margins with or without radiation therapy.[16]

Prognosis is generally poor, though highly variable and dependent on the location of the tumor, with high rates of relapse following multimodality therapy in early disease, low response rates to cytotoxic chemotherapy in advanced disease, and propensity for rapid disease progression and increased mortality.[6]

Due to EMPNST's varying histopathological findings and features, differential diagnosis is critically important, especially in the case of malignant melanoma. This differential diagnosis is necessary to consider when, in an adult, a tumor is localized in the lower extremities, is dermal-based without an intraepidermal component, if the patient has no previous history of malignant melanoma, and if it expresses S-100 protein.[17] Even though both melanoma and EPMNST can show histomorphologic and immunohistochemical overlap, the presence of marked atypical cytology and pleomorphism together with the expression of melanocytic specific antigens (Melan A/Mart-1, HMB45, and MiTF) in addition to the normal INI1/SMARCB1, all favor the diagnosis of melanoma over EMPNST.[5,18] In addition, a subset of melanomas was found to harbor SMARCB1 gene variations, yet, in contrast to EMPNST, all tested lesions displayed INI/SMARCB1 expression in immunohistochemistry.[18]

MRI features of malignant nerve sheath tumors were studied and showed that certain features help to distinguish malignant peripheral nerve sheath tumors from neurofibromas. These features include an increased largest dimension of the mass, the presence of an enhanced peripheral pattern, the presence of a perilesional edema-like zone, and the presence of intra-tumoral cystic lesions.[19]

The differential diagnosis of epithelioid MPNST also includes clear cell sarcoma, epithelioid sarcoma (ES), epithelioid schwannoma (ESch), and carcinoma. Lack of expression of melanocytic markers (e.g., Melan A, HMB45, MITF) helps distinguish epithelioid MPNST from melanoma and clear cell sarcoma.[12,20] Absent cytokeratin expression distinguishes EMPNST from carcinoma and epithelioid sarcoma.[21]

Regarding distinguishing proximal-type ES from EMPNST, both show histomorphologic features common to SMARCB1-deficient malignancies, particularly the abundant eosinophilic, sometimes rhabdoid-like cytoplasm a vesicular chromatin pattern with "eye-like" prominent eosinophilic nucleoli.[9] Immunohistochemical differentiation is possible, however, as ES lesions are consistently negative for S100/Sox10 and characteristically express cytokeratin.[22,33]

Differentiation of EMPNST from epithelioid schwannoma can be problematic due to documented cases of EMPNST arising from ESch.[5,24] Nevertheless, malignant features, including sheet-like and infiltrative growth patterns, diffuse nuclear atypia, and atypical mitoses and necrosis, indicate a diagnosis of EMPNST over ESch.[25]

Treatment options for MPNSTs and their epithelioid variant are minimal, relying mainly on surgical resection and cytotoxic chemotherapy.[26] The 5-year survival rate of patients with MPNST who received surgical treatment with and without negative margins were 67% and 22%, respectively.[27] Despite advances in our understanding of the pathophysiology of MPNST, including loss of the tumor suppressor gene neurofibromin and subsequent activation of the Ras pathway, targeted therapy to modify the poor prognosis seen in MPNST patients has thus far been without success. Correspondingly, MPNST patients are treated as per soft tissue sarcoma treatment algorithms with anthracycline-based therapy as the front-line therapy for patients with unresectable, locally advanced, or metastatic MPNST.[28] Beyond first-line anthracycline-based therapy, other standard cytotoxic chemotherapy agents used in advanced MPNST include the alkylating agent ifosfamide and the topoisomerase II inhibitor etoposide.[28]

There are no targetable therapies currently known to be of benefit in patients with EMPNST.[10] However, the recent discovery of the molecular biology of EMPNST demonstrating tumor suppressor gene SMARCB1/INI1 inactivating mutations present in the majority (75%) of EMPNST may show promise for a new method of treatment.[15] Uninhibited EZH2 methyltransferase overactivity results from loss of antagonism by SMARCB1/INI1. Studies utilizing EZH2 inhibitors in patients with epithelioid sarcoma, which is also SMARCB1/INI1 deficient and SMARCB1/INI1-deficient rhabdoid tumor, have shown improved survival.[15] Therefore, EZH2 inhibitors may benefit EMPNST but will require testing to ascertain their benefit in EMPNST patients.

Despite extensive clinicopathological studies of malignant peripheral nerve sheath tumors (MPNST), rendering an accurate diagnosis can be challenging due to histological similarity to other epithelioid tumors. Therefore. IHC studies and possibly molecular testing should be utilized for the definitive diagnosis. Our understanding of the pathophysiology of MPNST and its variants, including loss of the tumor suppressor gene neurofibromin and subsequent activation of the RAS pathway, prompted targeted therapy to modify the poor prognosis in MPNST patients, but unfortunately, thus far has been without success. However, progress has been made to distinguish MPNST from its common mimickers. The ongoing investigation has made great strides in finding additional biomarkers for this rare type of neoplasm. We hope by providing other cases of this tumor to the limited literature, we raise the awareness of clinicians and pathologists to include it in the differential diagnosis of a flank mass.

Figures:

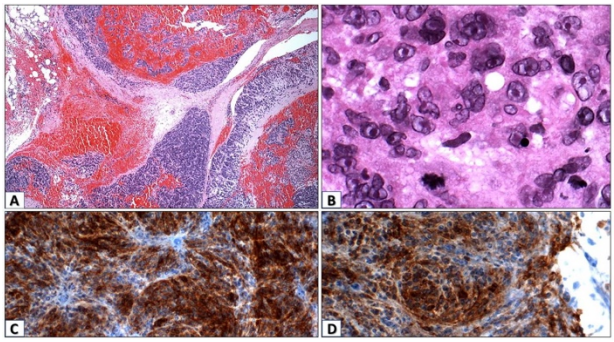

Figure-1: Microscopic examination of the excised MPNST.
1A: Low power view showing tumor characterized by an overall multilobulated growth pattern of clustered nodules of epithelioid tumor cells associated with hemorrhage and necrosis (H&E stain X20).
1B: High power view showing epithelioid cell features with prominent nucleoli, eosinophilic cytoplasm, and increased mitotic activity (H&E stain x 40).
1C: Tumor cells positive for CD56.
1D: Tumor cells positive for S-100

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