Annals of Clinical Case Reports

Clinical Presentation
Published: 17 Jun, 2019

Lower Back Epithelioid Malignant Peripheral Nerve Sheath Tumor: A Case Presentation and Review of Literature

Kelly Shortridge, Andrew Fraser, Hugo Araujolino and Raul Lopez*

Department of General Surgery, Mountain Vista Medical Center, USA

Abstract

Epithelioid Malignant Peripheral Nerve Sheath Tumor (EMPNST) is a rare variant of an already rare sarcoma, Malignant Peripheral Nerve Sheath Tumor (MPNST). Approximately 5% of MPNSTs are EMPNSTs. EMPNST is similar to MPNST in that they are both of neural origin. Histologically, EMPNST differs in that its cells are epithelioid in nature. EMPNST has a specific histologic marker profile which is diffusely positive for S100 & SOX-10 with a lack of expression of INI-1. In this study, we present the case of a 30-year-old female with a non-locally invasive EMPNST who underwent wide local surgical excision. Research is limited in this disease process and management of these neoplasms is not structured or standardized. Wide local excision currently remains the mainstay of treatment and chemoradiation is an option for advanced or metastatic disease.

Keywords: Epithelioid Malignant Peripheral Nerve Sheath Tumor; Malignant Peripheral Nerve Sheath Tumor; Excision

Introduction

Malignant Peripheral Nerve Sheath Tumors (MPNST) are considered a rare form of sarcoma which originate from peripheral nerves or from cells associated with the nerve sheath, such as Schwann cells or fibroblasts [1]. Also known as malignant schwannomas, the incidence of MPNSTs is approximately 3% to 10% of malignant soft tissue tumors [2,3]. MPNST is considered to be an aggressive soft tissue tumor [4]. MPNSTs are, for the most part, bulky, deep-seated tumors, which often form in the neck, extremities or buttocks [5]. Generally speaking, half of MPNSTs present de novo and half are related to Neurofibromatosis type I (NF-1) [6].

Prognosis of patients with these MPNST nerve sheath tumors is decreased in certain circumstances including the presence of neurofibromatosis, tumor size, excisional margins, site and depth of tumor location. In patients with a tumor size >5 cm it seems that tumor recurrence and metastases is increased [2,7]. On the other hand, there seems to be no difference in prognosis on the basis of male to female [2,8-10].

EMPNST differs from conventional MPNST in that it shows diffuse positivity for S-100 staining and is rarely associated with NF1. Loss of expression for INI-1 marker is found in up to two thirds of patients diagnosed with EMPNST [11]. These tumors can stain positively for neuron-specific enolase but will lack melanoma-associated antigen and cytokeratin [12]. For an unknown reason, most EMPNST will arise within a pre-existing schwannoma. The differential diagnosis of EMPNST includes melanoma, clear cell sarcoma, epithelioid sarcoma and carcinoma [11].

Histologically speaking, EMPNST will show an epithelioid pattern consistent with large epithelioid cells [11]. They will have rhabdoid cytology and will simulate carcinoma or a melanoma. Many are seen to have a characteristic nodularity with cords and strands with rounded epithelioid cells with prominent nucleoli [12].

Case Presentation

We present the case of a 30-year-old black female with no significant past medical history other than 2 C-sections, who presented to our clinic with complaints of a protruding mass on her lower back. The mass had grown slowly over time at the site of her last epidural which was 3 years prior. The mass itself was non tender, irritation was present with certain clothing but due to its location and increasing size, the patient requested surgical removal. The patient had no history of cancer

OPEN ACCESS

Correspondence:
Kelly Shortridge, Department of General Surgery, Mountain Vista Medical Center, 1301 S Crismon Rd Mesa, USA, Tel: 16025616696; E-mail: Kellyshortridge1@gmail.com

Received Date: *03 May 2019*
Accepted Date: *12 Jun 2019*
Published Date: *17 Jun 2019*

Citation:
Shortridge K, Fraser A, Araujolino H, Lopez R. Lower Back Epithelioid Malignant Peripheral Nerve Sheath Tumor: A Case Presentation and Review of Literature. Ann Clin Case Rep. 2019; 4: 1670.

ISSN: 2474-1655

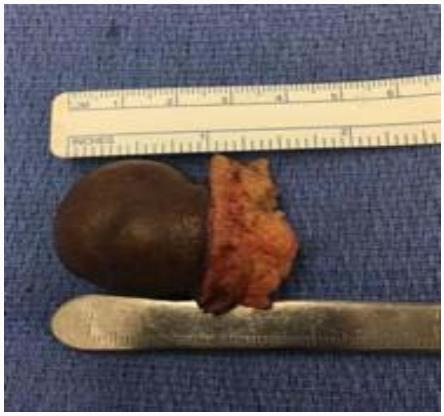

Figure 1: Lower back mass after ellipse excision showing pedunculated appearance.

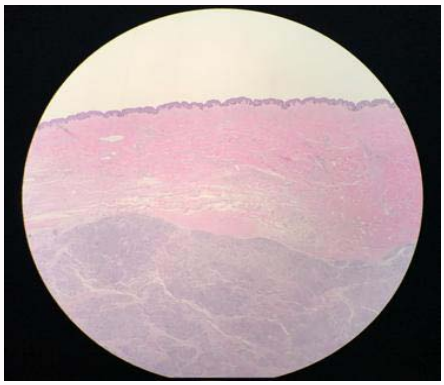

Figure 2: EMPNST: 20x view of skin edge.

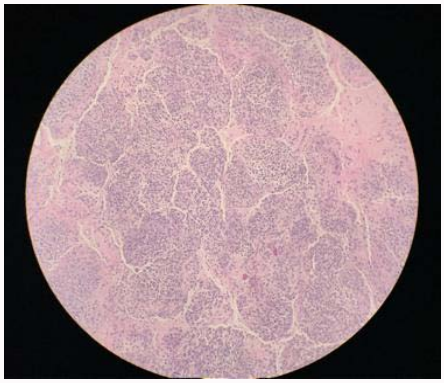

Figure 3: EMPNST: 40x view.

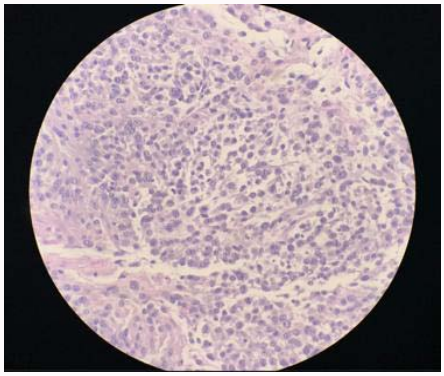

Figure 4: EMPNST: 100x view.

or radiation exposure. Family history was positive for cancer on her father's side, but was unaware of any specific details regarding that history. Physical exam revealed a large 3 cm × 4 cm × 1 cm pedunculated exophytic mass roughly at the level of L4. The mass was non-tender with a firm and rubbery texture on palpation. There was no erythema, induration, or other signs of infection. The patient had no similar masses or skin lesions elsewhere. The initial differential diagnosis was lipoma *vs.* acrochordon. The patient was scheduled for elective surgical excision. In the operating room, a wide elliptical incision was made along the vertical axis of the spine using a 15 blade scalpel. The soft tissue was dissected using electrocautery until normal appearing subcutaneous adipose tissue was encountered. The mass was then excised en bloc. The subcutaneous tissue was approximated using a simple interrupted stitch with 3-0 Vicryl suture and the epidermis was closed using an interrupted horizontal mattress stitch with 2-0 nylon. Post operatively, the excision site healed well without any complications. Gross pathology revealed a 4.0 cm × 3.0 cm × 1.8 cm mass weighing 16.0 grams (Figure 1). Located centrally within the specimen is a 3.5 cm × 2.5 cm × 2.5 cm subcutaneous lobulated mass with the nearest margin being 0.2 cm. Immunohistochemical stains were performed with the results shown in Table 1 [13-18], which also highlights a description and some of the common uses of each stain.

With this initial stain pattern, the diagnosis was indeterminate. The pathologist recommended an outside pathology consultation with the Cleveland Clinic for further evaluation and confirmation. At the Cleveland Clinic, additional immunostains included smooth muscle actin, EMA, BRAF and INI-1. The mass showed weak immuno-activity against EMA, as well as loss of nuclear expression of INI-1. No significant activity was seen for the other tumor markers. Based on their evaluation, the diagnosis of epithelioid MPNST was made with the following features: mitotic rate of 3/10 HPF, no necrosis noted, histologic grade 2 with negative margins, and no lymphovascular identified.

With the diagnosis of EMPNST, the patient was referred to an oncologist for recommendations on chemotherapy and/or radiation therapy. A CT scan of the chest, abdomen and pelvis was done for staging purposes. The scans did not reveal any evidence of metastasis or lymphadenopathy and therefore, no adjuvant therapy was indicated. With the narrow margin of 0.2 cm, a discussion was had regarding re-excision, however, the patient elected for close clinical follow up with the oncologist and surgeon.

Discussion

The reason for presentation to a surgical clinic for an EMPNST will either be for cosmetic reasons or because there is associated pain. Generally, a patient will present with a new onset mass. The patient in our case presented with a mass that caused irritation while wearing certain types of clothing.

Diagnosis of an EMPNST is generally done via a tissue biopsy. There are several reports in the literature of cases that successfully diagnosed EMPNST with fine needle aspiration. Whether it is better to arrive at a diagnosis through wide local excision or FNA is not clear. Many of these neoplasms will most likely be diagnosed through wide local excision. Treatment of EMPNST has generally been carried out by wide local excision. Surgical excision is the mainstay of treatment for non-locally invasive or metastatic disease. Several papers have

Table 1: Results, description and common uses of initial immunochemical stains used.

Stain	Result	Description	Use
S100	Positive	Multigenic group of non ubiquitous cytoplasmic EF-hand Ca^{2+} - binding proteins.	S100 is commonly used as a marker of neural tissue and melanomas [13].
SOX-10	Positive	Transcription factor known to be crucial in the specification of the neural crest and maintenance of Schwann cells and melanocytes	Melanoma marker. SOX10 shows an increased specificity for soft tissue tumors of neural crest origin compared with S100 [14].
Melan-A	Negative	Melan-A stands for melanoma antigen. Melanocyte specific cytoplasmic protein involved in the formation of stage II melanosomes.	Melanocyte lineage specific marker, more sensitive than HMB45 in the diagnosis of metastatic melanoma [15].
HMB45	Negative	Human melanoma black is a common marker to confirm melanoma. Not necessary for a standard panel.	Useful for confirmation of melanoma after Melan-A/Marta1 and S100 are positive [15].
CD34	Negative	Also called hematopoietic progenitor cell antigen CD34. Commonly used marker of hematopoietic progenitor cells and endothelial cells	Distinguish CD34+ dermal neoplasms such as Kaposi's sarcoma, dermatofibrosarcoma protuberans / DSFP (both CD34+) and epithelioid sarcoma (often CD34+) from dermatofibroma (CD34-) [15].
NSE	Negative	NSE is a cytoplasmic enzyme expressed by neuroendocrine cells and tumors. It is also commonly found in clear cell renal cell carcinomas.	NSE is not always expressed in neuroendocrine tumors, but almost all tumors that express NSE are of neuroendocrine origin [16].
CD-45	Negative	CD-45 mutations result in abnormalities of B and T cell development.	Pathologists use this test to test for hematopoietic nature of tumors and may assist in classification of lymphomas and leukemias [17].
Desmin:	Negative	Desmin is a common stain used for diagnosis of myogenic tumors.	Pathologists will use this stain to differentiate between smooth muscle tumors which are Desmin positive from gastrointestinal stromal tumors (GIST) [18].

outlined their treatments of similar lesions. Tomohiro et al. presented a case of a 62 year old male without neurofibromatosis with advanced EMPNST showing complete response with combination of wide local excision and chemotherapy [12]. Their patient presented initially with a large fungating foot lesion. Ten weeks after initial excision the patient presented with lung nodules on computed tomography. The patient was treated with systemic adjuvant chemotherapy using doxorubicin (60 mg/m^2) and ifosfamide (7.5 g/m^2). The patient received two doses as well as surgical resection of remaining lesions in lower lung fields. The lesions were confirmed metastatic EMPNST. Complete response was noted after the patient had completed four rounds of chemotherapy in combination with resection of the pulmonary lesions [12]. This case highlights the effectiveness of adjuvant chemotherapy for highly aggressive metastatic EMPNST. Since EMPNST is an aggressive lesion with metastasis commonly, chemotherapy should be a considered to provide complete response. Considering that MPNST is a rare tumor and EMPNST is only 5% of these tumors, there is little standardization of treatment [11]. The optimal excision margins have not been standardized as of yet. With our patient, the margins were 0.2 cm. Efficacy of radiation therapy and chemotherapy have yet to be determined as well. It seems that further research and standardization needs to be achieved for this rare condition.

In a review of 63 patients with EMPNST by Jo VY et al. [19], half of the patients had a median follow-up of 36 months after primary resection. Thirteen of the patients received chemotherapy and/or radiation. Twenty-two patients had no evidence of disease at time of follow-up. Nine patients developed local recurrence. Five patients developed distant metastases and four patients died of the disease [20]. This review emphasizes the aggressive behavior of this neoplasm. Distant metastasis is common and the treating team should be aware. Post-op surveillance should be mandatory. This brings up an important question which tries to identify what screening interval should be used. Also, considering distant metastasis is common, would these patients benefit from interval computed tomography or other imaging modality?

In an article by Kar M et al. [20], twenty-four cases of MPNST were reviewed. Ten cases had relapsed. Eight out of the ten cases showed relapse within the first two years of their treatment. Also, the overall survival and disease-free survivals were 58% and 38%, respectively, with median disease-free period of 17 months. EMPNST and MPNST are closely related, and this paper points out that many cases of metastases occurred within two years. Considering the disease tends to metastasize to lungs and other distant organs, it would be pertinent to perform aggressive surveillance early on in both MPNST and EMPNST with computed tomography for screening of recurrence. Regular physical exams at intervals of 3, 6 and 12 months of the surgical site as well as lymph node examination of draining sites would be prudent. History including symptoms of new onset shortness of breath or other respiratory symptoms should be performed. New onset abdominal pain would raise suspicions for abdominal metastases. History and physical examinations could be increased to 1-year intervals, and it should be stressed to the patient that loss of follow up could be detrimental. 5-year disease free survival of MPNST is 38% in certain studies and emphasizes the importance of follow-up and surveillance [20]. CT scan of the chest, abdomen and pelvis could also be completed at regular intervals. Whether this should be done at yearly intervals or more frequent is uncertain. In a study by Kim A et al. [21] the importance of whole-body MRI as surveillance for high grade MPNST is emphasized. Another article by Reilly KM et al. [22] emphasizes a similar concept of whole-body MRI for surveillance of MPNST recurrences. Would whole body MRI be a useful modality for surveillance in EMPNST as well? A review of the literature found very little information, if any, on the matter. Considering the close relationship between the two entities it could be of importance.

Considering the diagnosis and size of our patient's tumor size and the malignant nature of these neoplasms, follow up would be highly recommended as emphasized above including history and physical exams at increasing intervals. The patient could also benefit from more frequent imaging at 6 months, 12 months, and yearly thereafter. This would be beneficial as most metastases seem to occur before 2 years and the 5 year overall disease free survival is low in high risk patients.

Prognosis of patients with these nerve sheath tumors is worse in certain circumstances including patient with concomitant neurofibromatosis, increased tumor size, positive excisional margins, site and increased depth of tumor location [2]. In patients with tumor size >5 cm it seems that tumor recurrence and metastases is increased [2,7]. There seems to be no difference in prognosis on the basis of male to female [7-10]. Having said all this, biological behavior and prognosis of EMPNST is less clear than that of MPNST. Malignant

peripheral nerve sheath tumors are prone to locally recur, are highly malignant and commonly metastasize.

EMPNST will stain diffusely positive for S100 and will generally stain negative for INI-1 [23]. This is in contrast to the much more studied MPNST which will stain positive for CD99/013 (86%), S100, and CD57. MPNST will also stain negative for EMA, Keratin and CD19 in most cases. Histologically, EMPNST will differ in appearance from MPNST. MPNST will show monomorphic serpentine cells, palisading, large gaping vascular spaces, and geographic necrosis with tumor palisading at edges which resembles a glioblastoma multiforme. These will also have glandular differentiation and melanin in the tumor cells [5].

Conclusion

MPNST and EPMNST differ in terms of their origin as well as their histologic and immunochemical staining properties. They are closely related, but the latter is a rarer presentation. EMPNST will stain diffusely positive for S-100 protein and will show loss of INI-1 expression. More research needs to be done on this neoplasm as there is no standardization of management and follow up long term. Generally, they can be treated with wide local excision. However, advanced cases should be treated with a combination of chemotherapy and/or radiation therapy. If the disease is large preoperatively, neoadjuvant chemo-radiation can be beneficial. Postoperatively, patients should undergo regular follow-up with history, physical exam and imaging studies. Imaging modalities such as computed tomography and whole-body MRI are possible modalities of benefit. Distant metastasis is of concern for EMPNST and tends to present within 2 years of initial treatment. Intervals should be regular and more frequent early on. Very little research has been done on the rare entity of EMPNST. Much standardization needs to be achieved in terms of treatment including minimal margins, indications for chemotherapy and radiation, dosing and timing. Further research and standardization for postoperative surveillance including exact modality and timing would improve the management of this rare condition.

References

1. Jiwani S, Gokden M, Lindberg M, Ali S, Jeffus S. Fine-needle aspiration cytology of epithelioid malignant peripheral nerve sheath tumor: A case report and review of the literature. Diagn Cytopathol. 2016;44(3):226-31.
2. Ducatman BS, Scheithauer BW, Piepgras DG, Reiman HM, Ilstrup DM. Malignant peripheral nerve sheath tumors. A clinicopathologic study of 120 cases. Cancer. 1986;57(10):2006-21.
3. Gupta G, Maniker A. Malignant peripheral nerve sheath tumors. Neurosurg Focus. 2007;22(6):E12.
4. Shankar V. Malignant peripheral nerve sheath tumor (MPNST). 2012.
5. Leroy K, Dumas V, Martin-Garcia N. Malignant Peripheral Nerve Sheath Tumour in Neurofibromatosis Type 1. Internet J Surg. 2012;28(3).
6. Fletcher CDM, Bridge JA, Pancreas CW. Hogendoorn. WHO classification of tumors of soft tissue and bone. 4th ed. 2013.p.187-9.
7. Uenotsuchi T, Okuda Y, Imafuku S, Urabe K, Furue M. Solitary malignant peripheral nerve sheath tumor not associated with neurofibromatosis. Jpn J Dermatol. 2001;111(7):1091-7.
8. Hruban RH, Shiu MH, Senie RT, Woodruff JM. Malignant peripheral nerve sheath tumors of the buttock and lower extremity. A study of 43 cases. Cancer. 1990;66(6):1253-65.
9. Laskin WB, Weiss SW, Bratthauer GL. Epithelioid variant of malignant peripheral nerve sheath tumor (malignant epithelioid schwannoma). Am J Surg Pathol. 1991;15(12):1136-45.
10. Rodriguez FJ, Folpe AL, Giannini C, Perry A. Pathology of peripheral nerve sheath tumors: Diagnostic overview and update on selected diagnostic problems. Acta Neuropathol. 2012;123(3):295-319.
11. Seno N, Koizumi T, Sano K, Fukushima T, Gomi D, Kobayashi T, et al. Successful treatment with doxorubicin and ifosfamide for mediastinal malignant peripheral nerve sheath tumor with loss of H3K27me3 expression. Thorac Cancer. 2017;8(6):720-3.
12. Pernick N. S100. 2013.
13. Pernick N. SOX10. 2014.
14. Stuart LN. INI1. 2013.
15. Chen Y, Zynger. MelanA/MART1. 2019.
16. Han Y, Zhang P, Chen T, Yum S, Pasha T, Furth E. Connexin 43 Expression Increases in the Epithelium and Stroma along the Colonic Neoplastic Progression Pathway: Implications for Its Oncogenic Role. Gastroenterol Res Pract. 2011;2011:561719.
17. Mjønes P, Sagatun L, Nordrum IS, Waldum HL. Neuron-Specific Enolase as an Immunohistochemical Marker is Better Than Its Reputation. J Histochem Cytochem. 2017;65(12):687-703.
18. Pernick, N. CD45. 2013.
19. Jo VY, Fletcher CD. Epithelioid Malignant Peripheral Nerve Sheath Tumor: clinicopathologic analysis of 63 cases. Am J Surg Pathol. 2015;39(5):673-82.
20. Pernick N. Desmin. 2012.
21. Kim A, Stewart DR, Reilly KM, Viskochil D, Miettinen MM, Widemann BC. Malignant Peripheral Nerve Sheath Tumors State of the Science: Leveraging Clinical and Biological Insights into Effective Therapies. Sarcoma. 2017;2017:7429697.
22. Reilly KM, Kim A, Blakely J, Ferner RE, Gutmann DH, Legius E, et al. Neurofibromatosis Type 1-Associated MPNST State of the Science: Outlining a Research Agenda for the Future. J Nat Cancer Inst. 2017;109(8).
23. Shankar V. Epithelioid MPNST. 2012.