A Rare Aggressive Primary Hepatic Neoplasm: A Case Report of a Malignant Peripheral Nerve Sheath Tumor of the Liver and Literature Review

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Abstract

Primary malignant peripheral nerve sheath tumors (MPNST) of the liver are extremely rare. We report the case of a 77-year-old male with primary hepatic MPNST which demonstrated an aggressive clinical course with rapid growth after initial presentation and early recurrence with innumerable bilobar liver metastases, as well as abdominal soft tissue masses along the right paracolic gutter, within 3 months of treatment with complete radical surgical resection. The diagnosis of MPNST can often be challenging and relies not only on classic histomorphologic features, but also on immunohistochemical stains (such as S-100 positivity and complete loss of trimethylation of the lysine 27 residue of histone 3, H3K27me3). Surgery remains the mainstay of therapy for resectable tumors. Systemic doxorubicin-based therapy, such as doxorubicin plus olaratumab, is to be considered for unresectable or metastatic disease. Overall, primary hepatic MPNST have an aggressive clinical course with rapid growth, recurrence, metastasis and poor prognosis with little long-term follow-up data in the literature.

ABBREVIATIONS

MPNST: Malignant Peripheral Nerve Sheath Tumor; STS: Soft Tissue Sarcoma; NF1: Neurofibromatosis type 1; H3K27me3: Histone 3 Lysine 27 Trimethylation

INTRODUCTION

Malignant peripheral nerve sheath tumors (MPNST) are an uncommon type of soft tissue sarcoma (STS). Their reported incidence is 1 per 10^6 people per year in the general population, while they represent approximately 3-10% of STS in several large series [1,2]. MPNST are of ectomesenchymal origin, typically arising from Schwann cells or other peripheral nerve fibers and sheath cells. In the past they have been called by different names, such as malignant schwannoma, neurofibrosarcoma, neurogenic sarcoma, and malignant neurilemmoma. More than half of MPNST (50-60%) occur in the setting of neurofibromatosis type 1 (NF1) [1]. Among patients with NF1, approximately 10% develop MPNST. Typically, in NF1 patients the MPNST arise within preexisting plexiform neurofibromas and the age at diagnosis is younger. In a clinicopathologic study of 120 cases of MPNST by Ducatman et al., the mean age at diagnosis for NF1 patients was 28.7 years as opposed to 39.7 years in non-NF1 patients [2]. Another risk for development of MPNST is radiation exposure with approximately 10% of MPNST occurring in the setting of prior radiation.

Typical anatomic locations for MPNST are the trunk, extremities, and head and neck area, while primary visceral MPNST are extremely rare [2]. Only 12 cases of primary MPNST of the liver have been reported in the literature to date [3-14]. Here we describe a primary hepatic MPNST without NF1, treated by complete surgical resection, which had an aggressive clinical course with early recurrence with disease disseminated throughout the remaining liver. We also present a review of the pertinent literature.

PRESENTATION

Clinical presentation

A 77-year-old male, originally from Sri Lanka, presented to our cancer center with a progressively enlarging liver mass. This had originally been noted on a computed tomography (CT) scan of the abdomen and pelvis performed approximately 9 months prior to his presentation to us, which had been part of his evaluation...
for right-sided abdominal pain. At the time, a heterogeneously hypodense mass in segment 6 of the liver was noted, which was 4.5 cm in greatest dimension (Figure 1). Abdominal MRI (magnetic resonance imaging) once again demonstrated the partially exophytic right liver mass, which was heterogeneously hypointense on T2-weighted images and heterogeneously hypointense on T1-weighted images, both in the arterial and the venous phase (Figure 2). The patient’s past medical history was remarkable for hypertension and diabetes mellitus, but he had no pertinent personal or family history placing him at higher risk of liver tumors, and no history of neurofibromatosis type 1 or radiation exposure. His only past surgery was a laparoscopic cholecystectomy 5 years prior for benign disease.

An image-guided percutaneous biopsy of the mass performed at the outside facility was interpreted as undifferentiated malignant neoplasm of the liver. Given the fact that definitive diagnosis was not obtained based on the biopsy, the patient was not referred to a surgeon at the time. He underwent serial imaging, which revealed progressive increase in the size of the mass. Several additional percutaneous biopsies were performed in the following 6-8 months and were non-diagnostic. Eventually, a biopsy performed approximately 9 months after the initial CT was interpreted as high grade sarcoma.

At the time of his presentation to us, the patient had developed early satiety, anorexia and a 10-pound weight loss in addition to his persistent right-sided abdominal pain. He had no signs or symptoms of biliary obstruction. His exam was notable for a large firm palpable right abdominal mass. Serum alpha fetoprotein (AFP) was slightly elevated at 13.7 ng/ml, while carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) were within normal limits at 3.3 ng/ml and 2.1 U/ml, respectively. CT of the chest, abdomen and pelvis at this time revealed marked increase in size of the known right liver mass to 19.6 cm in greatest dimension, as well as signs of significant intra-tumoral necrosis (Figure 1). Close involvement and medial displacement of the ascending colon was noted, while there was questionable abutment of the duodenum, as well. There were no suspicious pulmonary lesions.

Surgical intervention

At initial diagnostic laparoscopy, there was no sign of metastatic disease or carcinomatosis. The liver surface appeared moderately nodular consistent with cirrhosis. After conversion to laparotomy, the tumor was identified and was indeed originating in the liver. It was fixed to the lateral abdominal wall, as well as to the ascending colon and distal ileum. We were able to carefully dissect the duodenum off the mass. The tumor was then resected en bloc with partial hepatectomy (segments 5 and 6), right colectomy and resection of the right abdominal wall. Intraoperative liver ultrasound was used to exclude multicentric disease, to define the extent of the known lesion, and to identify a clear resection plane. A large hepatic artery lymph node was identified, excised, and found to be negative for malignancy.

Pathologic findings

Gross evaluation revealed a 19.0 x 18.0 x 15.0 cm mass within the liver parenchyma. Sectioning of the mass demonstrated variegated red-tan hemorrhagic, grey-white firm, and some centrally softened areas. The mass involved the serosal surfaces of the colon, appendix and small bowel, but did not invade into the bowel wall. All resection margins were uninvolved. Microscopically, sections revealed a malignant neoplasm with a heterogeneous appearance (Figure 3). The dominant component consisted of relatively monotonous spindled to ovoid cell population set in a variably collagenous stroma.
These cells had moderate amounts of eosinophilic cytoplasm, inconspicuous nucleoli and scattered mitotic figures. Within this spindle cell background, there were scattered islands of more malignant-appearing epithelioid cells with increased nuclear pleomorphism, higher nuclear to cytoplasmic ratio, and a brisk mitotic rate (with 30/10HPF mitoses in certain areas). Multinucleated giant cells were present within these islands. Finally, there were foci of vasoformative architecture, with its vascular differentiation supported by positive immunostaining for cluster of differentiation (CD) 31. The spindle cell component was positive for CD34 (Figure 4).

This malignant neoplasm had a highly unusual appearance, making it difficult to classify. Thus, we requested expert pathology consultation outside of our institution. The potential differential diagnoses that were entertained included carcinosarcoma, dedifferentiated liposarcoma, follicular dendritic cell sarcoma, mesenchymal hamartoma, intrahepatic cholangiocarcinoma with mesenchymal differentiation, biphasic synovial sarcoma, or MPNST. Immunohistochemistry (IHC) was notable for focal positivity for S-100 protein in the epithelioid areas, while there was lack of significant human melanoma black-45 (HMB-45) staining (Figure 4). The latter helped rule out a spindle cell melanoma metastasis. Negative arginase staining helped rule out a primary hepatocellular neoplasm. The tumor was found to be negative for murine double minute protein 2 (MDM2) and cyclin-dependent kinase 4 (CDK4), arguing against liposarcoma. It was also negative for pan-cytokeratin (CK-OSCAR) and anti-cytokeratin CAM 5.2, which did not support a diagnosis of carcinosarcoma. Lack of staining for CD21 was inconsistent with a diagnosis of follicular dendritic cell sarcoma. Given that gastrointestinal stromal tumor (GIST) is the most common metastatic spindle-cell lesion of the liver, IHC staining for discovered on GIST 1 (DOG-1) was performed and was found to be negative. Lack of IHC staining for SALL4 helped rule out a germ cell tumor. Cytogenetic analysis by fluorescence in situ hybridization (FISH) with a probe specific for the SS18 locus on chromosome 18q11.2 revealed nonspecific gain of intact SS18 in 39% of nuclei, but did not detect evidence of t(X;18) translocation which would have suggested a synovial sarcoma. At this point, given the above information, we were still unsure of the diagnosis. Immunohistochemical staining demonstrated complete loss of histone H3 lysine 27 trimethylation (H3K27me3). This in conjunction with the patchy positivity for S-100 suggested high-grade MPNST. Glucose transporter 1 (GLUT1) was also diffusely positive, which could be an indication of a MPNST with perineural differentiation.

**Postoperative disease progression**

Despite negative resection margins and no evidence of residual disease after his operation, the patient had unexpected rapid progression of disease postoperatively. Within 3 months of his surgery he was found to have innumerable bilobar hepatic metastases, as well as several soft tissues nodules along the right paracolic gutter (Figure 5). He required paracentesis on several occasions for re-accumulating ascites. He was evaluated...
by medical oncology and a systemic regimen of doxorubicin and olaratumab was recommended.

**DISCUSSION**

As it occurred in our case, MPNST can be quite challenging to diagnose. The microscopic appearance may resemble other soft tissue tumors, and thus morphologic features alone may not allow a definitive diagnosis [15]. On classic hematoxylin and eosin staining, typically, there is a general fascicular growth pattern with alternating areas of hyper- and hypocellularity. It is not uncommon for MPNST to be high grade and thus it is no unusual to find a high mitotic rate (as in our case this was 30/10HPF in some areas).

Immunohistochemical stains classically demonstrate cytoplasmic vimentin positivity and focal nuclear S-100 positivity [12]. Markers of melanoma, such as HMB-45 and Melan A, as well as of epithelial differentiation, such as pan-cytokeratin, are negative. As it was noted in our case, classic markers for other types of sarcoma, such as DM2 and CDK4 for liposarcoma, CD21 for follicular dendritic cell sarcoma, and CD117 and DOG-1 for GIST, are typically negative. Cytogenetic testing usually does not reveal specific chromosomal translocations, although a complex karyotype may be present.

Several studies have identified loss of H3K27 trimethylation to be a specific marker for MPNST that can help distinguish it from histologic mimics [15,16]. H3K27 trimethylation has been shown to represent a key intermediary of the polycomb repressive complex 2 (PRC2) pathway of chromatin regulation and epigenetic modification. Schaefer et al., evaluated H3K27me3 expression via IHC staining on 100 MPNST (including NF1 associated, sporadic and radiation-associated tumors), as well as on 200 other spindle cell neoplasms representing potential histologic mimics (such as synovial sarcoma, leiomyosarcoma, dedifferentiated liposarcoma, malignant solitary fibrous tumor, GIST, radiation-associated unclassified sarcoma, spindle cell melanoma, etc.) [15]. Out of all MPNST, 51% stained negative for H3K27me3, with 70% of the NF1-associated, 49% of the sporadic, and 100% of the radiation-associated tumors showing loss of H3K27. Notably, when stratified by grade, loss of H3K27me3 was observed in 83% of the high-grade MPNST. Amongst the other 200 spindle cell tumors, most exhibited diffuse nuclear expression of H3K27me3. Only 20% (4/20) of the unclassified radiation-induced sarcomas showed complete loss of H3K27me3, while 10% (2/20) had heterogeneous staining. It is possible that at least some of these unclassified sarcomas could indeed be MPNST. Prieto-Granada et al., conducted a study on 68 MPNST samples and demonstrated that upon IHC staining with an anti-H3K27me3 monoclonal antibody 69% of the cases showed complete loss of H3K27me3 [16]. Notably, when only the sporadic cases were examined, the majority (95%, 17/18) exhibited H3K27me3 loss of expression. These findings suggest that loss of H3K27me3 can be used as a marker for MPNST and help differentiate it from other spindle cell tumors, as was the case with our patient’s tumor.

To our best knowledge only 12 cases of MPNST arising in the liver have been reported in the literature prior to our case (Table 1). Only two of the cases were in the setting of NF1. The median age at diagnosis, with our case included, was 63 years (range 21-83 years). The male to female ratio was 9:4. The median tumor size was 20cm. In 5 of the cases the definitive diagnosis had been made at autopsy. In 6 of the cases the primary treatment was surgical resection, while in 3 the treatment was conservative. In 2016 Jung et al., reported a case of a 33-year-old female who presented with a 20cm symptomatic liver mass, consistent with primary hepatic MPNST on pathology, who was treated with primary radical surgical resection, followed by adjuvant radiotherapy (60 Gy) and subsequent adjuvant chemotherapy (4 cycles of doxorubicin, ifosfamide and cisplatinum) [14]. She was followed for 36 months after her operation and did not have evidence of recurrence. Unfortunately, however, in most of the reported cases of primary hepatic MPNST, progression of disease is rapid and prognosis is fairly poor. In our case the patient rapidly developed (within 3 months of surgery) metastatic disease, which was not evident prior to or at the time of his surgical resection.

Similar to most high grade STS, most MPNST have an aggressive clinical course and relatively poor prognosis. MPNST have been reported to have a 5-year overall survival rate of 35-50% [15]. Unfortunately, we continue to lack effective systemic therapies not only for MPNST but for all STS in general. Surgical resection remains the mainstay of treatment for MPNST. Doxorubicin, alone or in combination, remains the standard of care systemic treatment for advanced unresectable and metastatic STS. Recently the results of a randomized phase 2 study of the use of doxorubicin plus olaratumab (a recombinant human antibody to platelet derived growth factor receptor-α, PDGFR-α, which prevents PDGFR-α signaling) versus doxorubicin alone demonstrated a significant improvement in median overall survival from 14.7 months in the doxorubicin alone arm to 26.5 months in the intervention arm [17]. Given these promising results, combination systemic therapy of doxorubicin and olaratumab will be the next step in treatment for our patient.

In conclusion, we present a rare case of a primary malignant peripheral nerve sheath tumor of the liver, which demonstrated an aggressive clinical course with rapid growth after initial presentation and early recurrence with innumerable bilobar liver metastases, as well as abdominal soft tissue masses along the right paracolic gutter, within 3 months of treatment with complete (R0) radical surgical resection. The diagnosis of MPNST can often be challenging and rely not only on classic histomorphologic features, but also on immunohistochemical stains (in our case patchy positivity for S-100 and complete loss of H3K27me3). Surgery remains the mainstay of therapy for resectable tumors. Systemic doxorubicin-based therapy, such as doxorubicin plus olaratumab, is to be considered for unresectable or metastatic disease. Overall, primary hepatic MPNST have an aggressive clinical course with rapid growth, recurrence, metastasis and poor prognosis with little long-term follow-up data in the literature.

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Table 1: Reported cases of primary hepatic malignant peripheral nerve sheath tumors.

<table>
<thead>
<tr>
<th>Source Author</th>
<th>Year</th>
<th>Age (y)</th>
<th>Sex</th>
<th>NF Status</th>
<th>Size (cm)</th>
<th>Clinical Presentation</th>
<th>Diagnosis</th>
<th>Treatment</th>
<th>Follow-up</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td>Young SJ [3]</td>
<td>1975</td>
<td>23</td>
<td>F</td>
<td>yes</td>
<td>20</td>
<td>RUQ pain, jaundice</td>
<td>autopsy</td>
<td>conservative</td>
<td>38 days</td>
<td>died of disease</td>
</tr>
<tr>
<td>Shmurun and Chibisov [4]</td>
<td>1977</td>
<td>68</td>
<td>M</td>
<td>no</td>
<td>20</td>
<td>NA</td>
<td>autopsy</td>
<td>NA</td>
<td>37 days</td>
<td>died of disease</td>
</tr>
<tr>
<td>Tudor and Moraes [5]</td>
<td>1984</td>
<td>74</td>
<td>M</td>
<td>no</td>
<td>21</td>
<td>epigastric mass</td>
<td>surgery</td>
<td>surgery</td>
<td>21 days</td>
<td>died at 21 days</td>
</tr>
<tr>
<td>Lederman, SM et al. [6]</td>
<td>1987</td>
<td>21</td>
<td>M</td>
<td>yes</td>
<td>30</td>
<td>severe RUQ pain</td>
<td>autopsy</td>
<td>hepatic artery embolization</td>
<td>NA</td>
<td>died of disease</td>
</tr>
<tr>
<td>Morikawa, Y et al. [7]</td>
<td>1995</td>
<td>63</td>
<td>M</td>
<td>no</td>
<td>21</td>
<td>severe abdominal pain</td>
<td>autopsy</td>
<td>conservative</td>
<td>4 mo</td>
<td>died of disease</td>
</tr>
<tr>
<td>Fiel, MI et al. [8]</td>
<td>1996</td>
<td>49</td>
<td>M</td>
<td>no</td>
<td>15</td>
<td>jaundice</td>
<td>biopsy</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Kóbori, L et al. [10]</td>
<td>2008</td>
<td>22</td>
<td>F</td>
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<td>26</td>
<td>RUQ pain, edema</td>
<td>biopsy</td>
<td>surgery</td>
<td>24 days</td>
<td>alive</td>
</tr>
<tr>
<td>Subramaniam K et al. [12]</td>
<td>2012</td>
<td>71</td>
<td>M</td>
<td>no</td>
<td>21</td>
<td>RUQ pain</td>
<td>surgery</td>
<td>surgery</td>
<td>NA</td>
<td>alive</td>
</tr>
<tr>
<td>Kakizaki, S et al. [13]</td>
<td>2016</td>
<td>73</td>
<td>F</td>
<td>no</td>
<td>18</td>
<td>epigastric mass</td>
<td>autopysie</td>
<td>conservative</td>
<td>16 mo</td>
<td>died of disease</td>
</tr>
<tr>
<td>Jung, HI et al. [14]</td>
<td>2016</td>
<td>33</td>
<td>F</td>
<td>no</td>
<td>20</td>
<td>right flank pain</td>
<td>surgery</td>
<td>adjuvant RT and CT</td>
<td>36 mo</td>
<td>alive, no recurrence</td>
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<td>Present case</td>
<td>2016</td>
<td>77</td>
<td>M</td>
<td>no</td>
<td>19.6</td>
<td>RUQ pain</td>
<td>surgery</td>
<td>surgery</td>
<td>3 mo postop</td>
<td>alive with metastatic disease</td>
</tr>
</tbody>
</table>

NF: Neurofibromatosis, NA: Not Applicable, RUQ: Right Upper Quadrant, RT: Radiation Therapy, CT: Chemotherapy

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REFERENCES


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