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Case Report

Rapidly Progressive Malignant Rhabdoid Tumor of the Omentum in an Adult. A Case Report and Review of the Literature

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Abstract:

Introduction: Malignant Rhabdoid Tumors (MRT) are exceedingly rare neoplasms that characteristically occur in infants and children and sparsely develop in adults. Primary MRTs of the omentum are particularly rare.

Presentation of Case: A previously healthy 24-year-old male who presented with progressive abdominal distention and nausea. Further investigations revealed ascites with multifocal omental-based tumors. Biopsy with immunohistochemistry demonstrated dually positive cells for cytokeratin and vimentin and loss of Integrase Interactor 1 (INI1), and Next generation sequencing showed a copy number loss of SMARCB1 which established the diagnosis of malignant rhabdoid tumor. The patient's clinical course was characterized by rapid local and metastatic progression with subsequent clinical deterioration, and he expired within three weeks of his initial presentation.

Conclusion: Herein we describe the clinical course, difficulty with diagnosis, and paucity of treatment options for a rare and very aggressive malignant tumor. The ideal treatment regimen for MRTs has yet to be elucidated and additional studies are required to discern therapies that offer benefit.

Keywords: SMARCB1/INI; malignant rhabdoid tumor; omentum; oncology

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Introduction

Malignant Rhabdoid Tumors (MRT) are extremely rare tumors thought to predominantly occur in infants and young children, with very few cases occurring worldwide in adults. These were first described in the literature in 1978 by Beckwith and Palmer, and much of the current data is based on pediatric populations [1]. The majority of these tumors are of renal origin but extrarenal sites, including soft tissues, have also been documented [2]. These tumors are associated with early metastases and high mortality rates with less than 30% of patients surviving to 1 year [3]. Diagnosis of patients with intra-abdominal MRT may be delayed in this rapidly progressive disease course, as initial symptoms are non-specific and include abdominal discomfort and distention [4].

This malignancy is coined “rhabdoid” due to the close resemblance of the cells to rhabdomyoblasts, although they do not exhibit myogenic elements [1]. The cells distinctly feature a genetic inactivation of the SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1 (SMARCB1) gene, also known as the integrase interactor 1 (INI1), which is a component of the SWI/SNF chromatin remodeling complex on the long arm of chromosome 22 and acts as a tumor suppressor gene [3]. Due to the clinical rarity of MRT worldwide, and only one other reported case of MRT of the omentum in an adult after extensive literature review, little has been explicated of the specific behavior of this tumor or the optimal treatment modality and as such, prognosis remains quite poor for the affected patients [4]. The case presented herein highlights the aggressive behavior of MRTs as well as the importance of rapid characterization of potential therapeutic modalities for prolongation of survival as these strategies have yet to be elucidated.

Case Presentation

A previously healthy 24-year-old United States Marine Corps Active Duty Caucasian male initially presented with the chief complaint of generalized abdominal pain and progressive abdominal distention for 5-6 days that was associated with intractable nausea, vomiting, and poor oral intake. His surgical history was significant for an appendectomy with benign pathology. The remainder of the history was unremarkable and evaluation revealed minimal abdominal distention and mild tenderness in all quadrants.

Laboratory studies to include hematology, chemistry, and tumor markers carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP) and carbohydrate antigen 19-9 (CA 19-9) were within normal limits. Paracentesis revealed 5.5 liters of serosanguinous ascites and negative cytology. Computed tomography (CT) scan with contrast demonstrated moderate ascites and omental-based tumors with peritoneal lesions.Subsequent ultrasound-guided biopsy of the omental mass was completed and initial pathology assessment demonstrated carcinoma of uncertain primary. The tissue underwent thorough immunohistochemical staining evaluation and next generation sequencing as described below.Positron emission tomography–computed tomography (PET/CT) scan 6 days later showed multifocal hypermetabolic activity within the omentum and peritoneal lining consistent with known disease, as shown in Figure 1, along with new hepatic, pleural, and pericardial metastases. Esophagogastroduodenoscopy and colonoscopy were negative for malignancy.

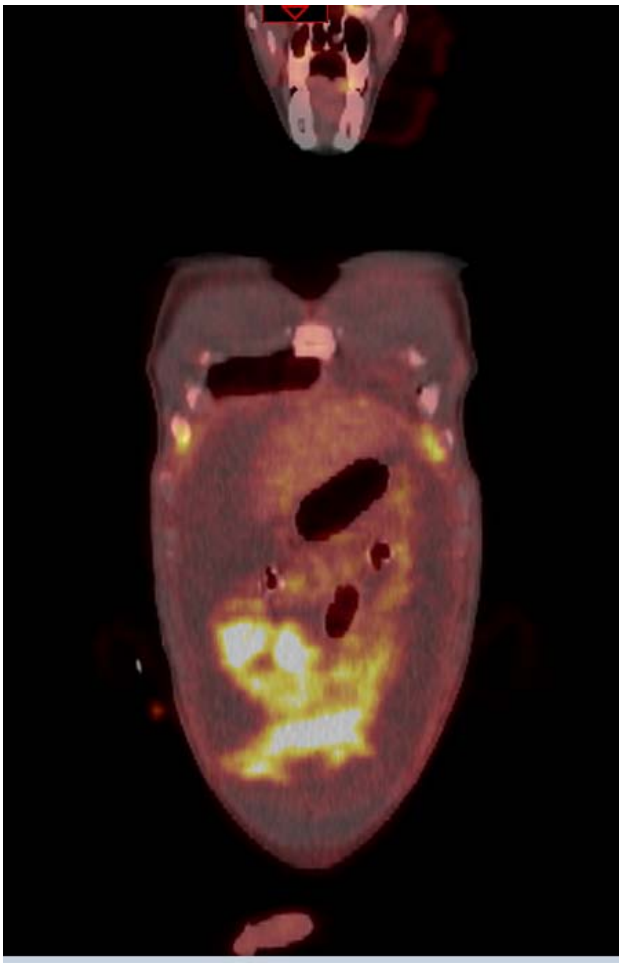
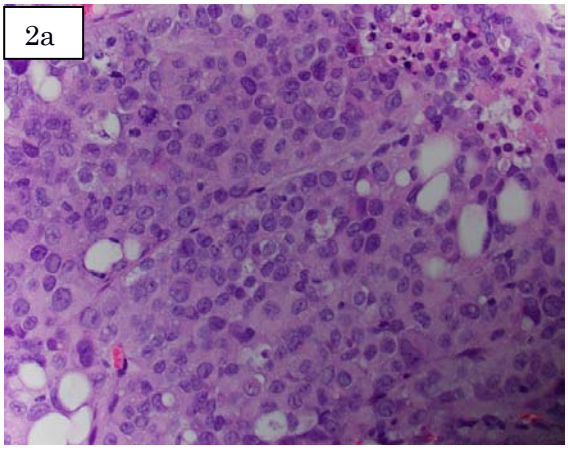
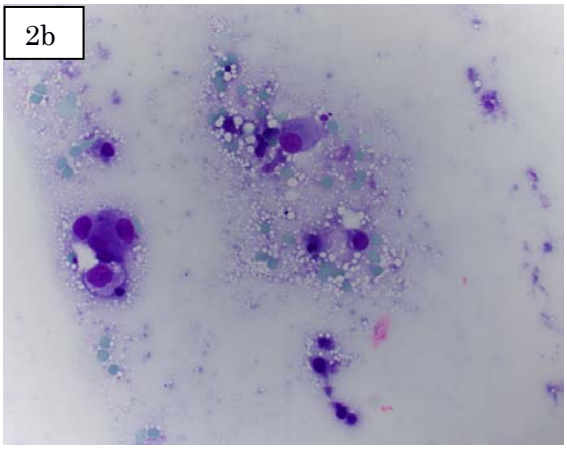
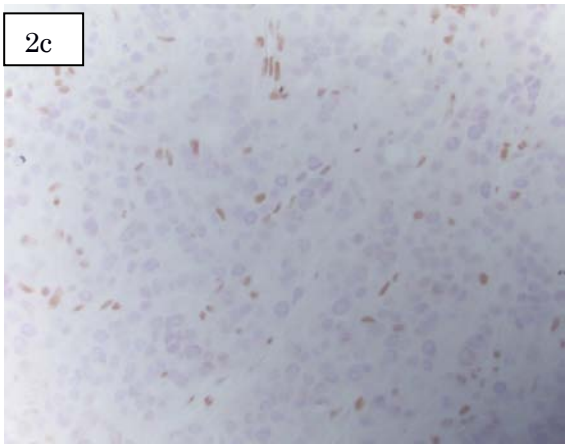


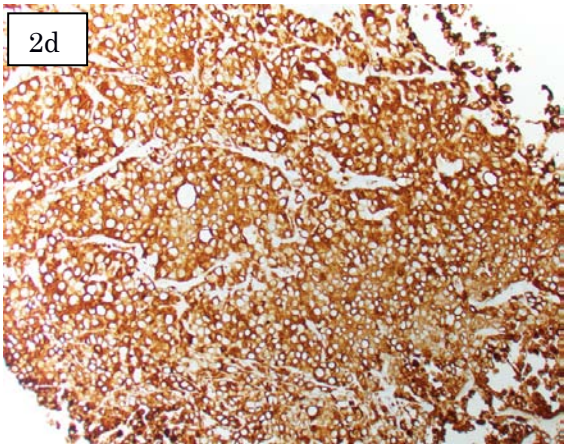
Figure 1 Positron emission tomography–computed tomography showing diffuse hypermetabolic activity within the omentum and peritoneal lining with large volume ascites.

In the first 10 days of the patient's hospital course, he developed progressive abdominal discomfort despite nasogastric tube decompression, symptomatic management, and serial large volume paracenteses every 2-3 days. Nutritional goals were achieved with parenteral nutrition. Given the potential for management with cytoreductive surgery and hyperthermicintraperitoneal chemotherapy (HIPEC), the patient was transferred to a regional hospital with expertise in peritoneal surface malignancies. Repeat CT scan demonstrated progression of intraperitonealand extraperitoneal tumor burden. Within the span of 8 days, a pericardial deposit had grown from 0.9 cm to 1.4 cm and a cardiophrenic lymph node had grown from 0.9 cm to 1.2 cm. Retrospective review of the CT on initial presentation 14 days prior demonstrated no evidence of extraperitoneal metastases. After multidisciplinary review of the available pathology, PDL1 expression of 15%, in the setting of rapid and distant disease progression,the treating team, patient and family agreed on initiation of palliative immunotherapy. The patient received 1 dose of nivolumab, 240mg, six days after transfer, however, he demonstrated rapid clinical deterioration with tense ascites,marked cachexia, and anasarca with weight documented as 222 lbs, compared to 185 lbs from the time of presentation. Nine days after the transfer, the patient was transitioned to comfort care, and he expired 20 days after his initial presentation. Final pathology was still pending at that time.









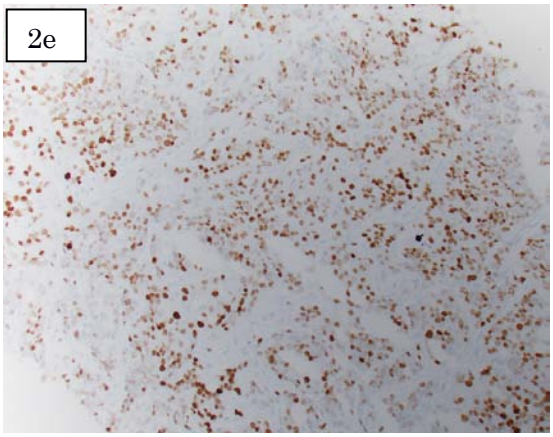


Figure 2a. Sheets of large epithelioid cells with abundant eosinophilic cytoplasm with eccentric nuclei with macronucleoli. Mitoses are easily identified. There is a background of necrosis. (H&E, 400x). **Figure 2b**. Smear preparation showing large cells with rhabdoid morphology (Diff-QuikStain, 400X). **Figure 2c**. There is loss of nuclear INI-1 in the tumor cells, but it is intact in the intervening capillary network. (400X). **Figure 2d**. Pankeratin shows strong and diffuse cytoplasmic staining. (200X). **Figure 2e**. SALL4 shows patchy nuclear positivity in the tumor cells (200x).

Pathology findings and diagnosis

Tissue cores of the intra-abdominal mass, of presumed omental origin, revealed diffuse sheets and clusters of large atypical cells with subtle rhabdoid features in a background of extensive geographic necrosis and apoptotic debris displayed in Fig. 2a. The neoplastic cells have moderate to abundant pink cytoplasm with eccentric nuclei but without obvious striations. The nuclear contours are predominantly round, though some are irregular, with open chromatin and large prominent nucleoli as illustrated in Fig. 2b. Mitotic figures are readily identified. Immunohistochemical (IHC) studies show that the tumor is strongly positive for pancytokeratin, as seen in Fig. 2d, vimentin, patchy positive for CDX2, GATA3, SALL4 (as observed in Fig. 2e), EMA, carbonic anhydrase IX and focally positive for MOC31, calretinin and CD30. The tumor cells are negative for desmin, myogenin, D2-40, CD45, HMB45, MART1, HSA, arginase, inhibin, villin, CD99, CD56, synaptophysin, AFP, OCT4, PLAP, SOX-10, PAX-8, NKX3.1 and several specific cytokeratins. Immunostaining for WT-1 lacks nuclear staining and shows only non-specific cytoplasmic positivity. CD117 shows nonspecific staining. PAS-D stain shows occasional scattered diastase-resistant globules, but not intracytoplasmic mucin. Importantly, there is loss of nuclear INI1 staining in the malignant cells as shown in Fig 2c. Molecular testing (OmniSeq^{R} Advanced via Integrated Oncology) revealed a copy number loss of *SMARCB1*. Given the rhabdoid morphology, high grade sarcoma features, immunohistochemical profile, loss of INI1 by immunostain and loss of *SMARCB1* by molecular testing, these pathologic findings are most consistent with a malignant rhabdoid tumor.

Discussion

Malignant Rhabdoid Tumors are exceedingly rare and characteristically occur in infants and childrenwith the median age of diagnosis reported to be 6 months to 1.5 years, and sparsely occur in adults without any gender predilection [3,6]. The literature suggests an incidence of 0.04 per million in ages 10-14 years that decreases with age [3]. Due to the clinical rarity, little is known about the exact behavior or cell of origin of this tumor. However, MRTs may arise from the soft tissue, liver, gastrointestinal tract, genitourinary tract, mediastinum, orbit, and central nervous system [3,5,7].It is thought that children often manifest renally localized MRTs while extrarenal MRTs have a broader age of presentation [5] Of the reports documented, MRTs behave aggressively and are highly lethal with early widespread dissemination [3,8]. Survival times are dismal with estimations ranging from 5 days to 5 months[7]. Omental MRTs, as seen in our patient, are particularly rare with few cases reported in the medical literature [7,9]. The patient described in this report illustrates the accelerated progression of MRTs with a striking doubling time estimated in days and with death occurring within three weeks after presenting in a normal state of health. Although a comprehensive evaluation occurred conjointly between two regional referral centers, a definitive diagnosis could not be established prior to the patient's death. Further, the optimal treatment for MRTs remains unknown and further studies are required to discern therapies that offer benefit.

Recognizing and diagnosing MRTs early is imperative albeit challenging given the rare and rapidly progressive nature of the malignancy.Index of suspicion for MRTs should be high when a tumor with rhabdoid features on biopsy demonstrates an accelerated growth rate with an unclear origin. To diagnose MRTs from other tumors associated with cytologic rhabdoid-like features, an absence of SMARCB1, formerly known as INI1, must be demonstrated histologically [10,11]. The loss of SMARCB1 is due to an inactivating mutation or deletion of this tumor suppressor gene on chromosome 22. The loss of expression results in the lack of a protein product which can be

demonstrated on immunohistochemistry [6]. The loss of expression of the SMARCB1 gene can be seen in other malignancies thus the diagnosis should be made with other associated histologic elements [3,6]. For example, SMARCB1 dysfunction and/or the existence of rhabdoid cells have been implicated in epithelioid sarcomas, leiomyosarcomas, synovial sarcoma, extraskeletal myxoid chondrosarcomas, and malignant mesothelioma [6,9,12]. Uniquely, MRTs do not exhibit composite features of other primary malignancies (i.e. colorectal carcinoma) and only display pure rhabdoid morphology irrespective of the location of origin [12]. Furthermore, distinguishing features of MRTs relative to other malignancies include cytomorphology characterized by extensive pleomorphism, vesicular and eccentrically positioned nuclei, eosinophilic cytoplasm, and large nucleoli in polygonal cells that are arranged in discohesivesheets [3,6,9,12]. Similar to the cited literature, our patient displayed abundant pleomorphism and co-expression of immunoreactivity in both mesenchymal markers (vimentin) and epithelial markers (cytokeratin) [13]. Although our patient exhibited patchy focal positivity for EMA, IHC was negative for desmin and did not demonstrate cytomorphology indicative of epithelioid sarcoma or other malignancies [3,12]. While these rhabdoid features and the homozygous SMARCB1 aberrations confer a poor prognosis [9], the underlying mechanism behind the rapid progression of MRTs remains poorly understood.

The pathogenesis for MRT development hinges on the dysfunction of the SMARCB1 gene and most commonly results from large deletions, frameshift mutations, or premature stop codon mutations [3]. These mutations occur as both de novo homozygous mutations as well as inherited single mutations of the SMARCB1 gene with the latter occurring predominantly in children [3,6]. SMARCB1 produces the functional protein BAF47 which operates as a subunit of the ATP-dependent complex SWI/SNF and regulates cell growth and controls gene transcription activation and suppression through chromatin remodeling [3,6,12]. Specifically, the SWI/SNF complex inhibits the polycomb complex 2 methylation complex through the Enhancer of Zeste Homolog 2 (EZH2) and directly inhibits histone deacetylase (HDAC) [3,6,12]. This process is critical in embryologic development [12], and dysregulation of this process through SMARCB1 mutations is thought to result in aberrant chromatin remodeling in stem cells which ultimately leads to a population of the undifferentiated cells hypothesized to be the cells of origin in MRTs. Given the otherwise stable genome, these epigenetic changes likely do not generate significant immune response and may be associated with early MRT cell dissemination, immune evasion, and poor prognosis. While further studies are required to delineate the exact mechanism between SMARCB1 mutation and the aggressive nature of MRTs, evolving preclinical investigations are underway to develop targeted therapy towards the affected downstream histone complexes [3,6]. Preclinical studies have begun evaluating EZH2 and HDAC inhibitors and preliminary findings suggestthat EZH2 inhibition may sensitize MRTs to radiation therapy [6].

Due to the exceptional infrequency and early lethality of MRTs, recommended treatment guidelines or therapeutic modalities showingimprovement in survival or morbidity havenot been described in the clinical literature [3,10]. Currently, a multimodality approach with chemotherapy, surgery, and radiation is employed in eligible patients with local disease, to attempt to control the disease and prolong survival [10]. In patients with disseminated disease, the survival benefitsof systemic therapy remain unclear. Cytotoxic chemotherapy regimens including combination of platinum agents, vincristine, dactinomycin, and/or methotrexate have had limited response rates in case reports [3,5,10,14,15]. The role of chemotherapy, immunotherapy, and other treatment modalities in MRT of the soft tissue and omentum is currently unknown, but based on available case reports cytoreduction may be considered in patients with localized disease[2], and radiotherapy is considered in

attempt to control residual disease [4,11].

Conclusion

This case report is intended to describe the behavior of a multifocal malignant rhabdoid tumor of the omentum in an adult as there are only few cases reported worldwide and to suggest early consideration for screening with SMARCB1/INI1 staining in malignancies with a rapid and progressive clinical course.It is critical to differentiate and diagnose MRTs from similar aggressive pathologies with comprehensive IHC as the diagnosis of MRTs carries a far worse prognosis than other malignancies associated with rhabdoid cytology and has implications for therapy. Ultimately, the goal to enhance treatment in the future is geared towards earlier diagnosis and implementation of targeted therapeutic modalities allowing for the possibility of prolonging survival. In the setting of limited therapeutic benefit of current chemotherapy regimens, new targeted molecular modalities against the epigenetic products downstream of a mutated SMARCB1, HDAC and EZH2 inhibitors, may show more promise in achieving prolonged survival benefits in those with MRT and other cancers arising from SMARCB1 dysregulation and deficiency [3,6]. More data and molecular studies are needed to elucidate further novel targets and their potential benefits in patients with MRTs.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient's next of kin has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patient's next of kin understand that the names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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