CASE REPORT

Rapidly enlarging malignant abdominal PEComa with hepatic metastasis: a promising initial response to sirolimus following surgical excision of primary tumor

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Abstract

Intra-abdominal perivascular epithelioid cell tumors (PEComas) are rare mesenchymal tumors. Although no effective therapies have been agreed upon, mTOR inhibitors are currently being investigated as a potential therapy for this extremely rare tumor. We present a case of a 64-year-old male found to have a large intra-abdominal PEComa with multiple metastatic lesions in the liver. Patient underwent surgical resection of the primary lesion in the abdomen and sigmoid colon followed by adjuvant therapy with the mTOR inhibitor, sirolimus. Initial response was noted with a decrease in size and number of lesions found in the patient’s liver. After 8 months of therapy, restaging imaging showed disease progression in the liver lesions. Patient subsequently failed treatments with pazopanib, investigational therapy TAK-228 (Sapanisertib) and nivolumab and ipilimumab. Overall the patient died after 22 months of disease. PEComas generally follow a benign course. This case is a much rarer entity given the malignant features/outcome.

INTRODUCTION

An intra-abdominal perivascular epithelioid cell tumor (PEComa) is a rare mesenchymal tumor that demonstrates both melanocytic and smooth muscle differentiation on histological/immuno-histochemical evaluation [1]. Metastatic disease is even more rare. mTOR inhibitors are increasingly being investigated as a potential therapy for this extremely rare tumor as no effective therapy has been established [2, 3].

CASE REPORT

A 64-year-old male presented to our hospital with increasing left lower quadrant pain and nausea with vomiting for several days. The patient had a known history of diverticulitis and previous colonoscopy demonstrating internal hemorrhoids and diverticula in the sigmoid, descending and ascending colon. Computed tomography (CT) abdomen showed a 12.6 × 10 × 9 cm lower pelvic mass abutting the sigmoid colon; an additional
lesion was seen in the right hepatic lobe, concerning for metastatic disease (Fig. 1).

Physical exam on admission revealed left lower quadrant fullness and mild tenderness to palpation. Differential diagnosis at the time included lymphoma, GI stromal tumor or adenocarcinoma. CT-guided biopsy confirmed poorly differentiated malignancy. Core biopsy demonstrated partial necrosis with epithelioid malignant tumor cells exhibiting scattered mitosis and marked nuclear atypia. Immunohistochemical staining showed tumor cells positive for MART1 (MelanA) and HMB45 though negative for S100. Complete dermatologic exam uncovered a basal cell carcinoma of the right ear, unrelated to the patient’s pelvis mass, otherwise no pigmented lesions.

Positron emission tomography (PET) scan revealed avid hypermetabolic uptake within the dominant bilobed mass in the liver lesions and left axillary adenopathy (Fig. 1). Pelvic magnetic resonance imaging performed 10 days after hospitalization showed rapidly enlarging pelvic mass; the patient was symptomatic at this time with urinary retention, overflow diarrhea and increasing pain.

The patient underwent sigmoid colon resection with colostomy, small bowel resection with primary anastomosis and pelvic mass resection 13 days after admission. The final dimensions of the abdominal tumor were $15.2 \times 11.6 \times 11.5$ cm. The operation was complicated by hemorrhagic malignant ascites and two intra-abdominal abscesses due to ruptured tumor. No radiofrequency ablation was performed on the hepatic lesions intraoperatively. Immunohistochemical staining on the resected tumor showed positive NSE, Vimentin, MART1 (MelanA) (Fig. 3) and PD-L1 stains. S100, CD45, CD30, Oct-4, MOC31, D2-40, Actin and PAS stains were negative. The pelvic washings...
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Figure 4: Positive HMB45 immunohistochemical stain (× 20).

strongly expressed MelanA and HMB45 (Fig. 4) but lacked SOX10, S100 protein and myogenic markers. Inhibin was obtained to rule out adrenal cortical carcinoma, which was negative. Given the overall histomorphology and immunophenotype, the tumor was most consistent with a malignant PEComa, which was supported by soft tissue consultations with Mayo Clinic and Emory University.

Repeat PET scan approximately 1-month post-op confirmed interval progression of hepatic metastatic disease with 20+ lesions identified in the liver (Fig. 5).

Treatment was started for PEComa with Sirolimus 4 mg daily. Dosage was increased to 6 mg daily, but due to side effects, dosage was decreased back to 4 mg. Restaging PET/CT at 2 months since onset of therapy showed marked improvement of multiple hypermetabolic masses in the liver with only two lesions identified by radiology (Fig. 6).

Patient continued to do well on Sirolimus for 8 months at which time restaging CT scan showed hepatic metastases increasing in both number and size, with no additional new sites of metastatic disease (Fig. 7).

At this time, molecular sequencing showed mutations in TSC2 and TP53. Patient was started on pazopanib 800 mg daily for 2 weeks before decreasing the dose to 600 mg daily. At the 9-week mark of pazopanib, CT scan showed disease progression in one liver lesion from 4.2 to 7.6 cm along with numerous other lesions increasing in size.

Patient was then trialed on TAK-228 (Sapanisertib), a non-rapamycin analog mTOR kinase inhibitor designed to target TSC-1 mutations. Disease progression was again seen, this time a month into the treatment. Finally, the patient was trialed on nivolumab and ipilimumab; however, therapy was stopped a month later due to side effects and continued disease progression. Overall, the patient died after 22 months of disease.

DISCUSSION

Malignant PEComas are still extremely rare mesenchymal tumors. Risk stratification criteria based on primary tumor size and high mitotic rate have been shown to predict recurrence following surgical resection [4]. Case reports, however, have been sparse regarding successful treatment for PEComas. Wagner et al. [3] noted that tumors within the PEComa family showed ‘high frequency of TSC1 or TSC2 mutations. These TSC1 and TSC2 genes are associated with mTOR regulation and as such provide an opportunity for therapy.’ They proposed the use of mTOR inhibitors as a potential therapy for patients with PEComas. In contrast, Scheppach et al. [5] presented a case of colon PEComa that was resistant to sirolimus but responsive to doxorubicin/ifosfamide.

In a small case study of three patients with advanced uterine PEComas, Starbuck et al. [6] had good response when mTOR
improvement of size and number of metastatic lesions while on Sirolimus following surgical excision of primary lesion. PEComas generally follow a benign course. This case is a much rarer entity given the malignant features/outcome. The patient’s disease remained stable for 8 months before increases in size and number of liver lesions were noted.

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CONSENT
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GUARANTOR
Dustin Uhlenhopp is nominated as a guarantor of this article.

REFERENCES
1. Okamoto K, Okada Y, Ohno K, Yagi T, Tsukamoto M, Akahane T, et al. A rare case of perivascular epithelioid cell tumor (PEComa) of the greater omentum. World J Surg Oncol 2018;16:113. doi: 10.1186/s12957-018-1407-5.
2. Wu JH, Zhou JL, Cui Y, Jing QP, Shang L, Zhang JZ. Malignant perivascular epithelioid cell tumor of the retroperitoneum. Int J Clin Exp Pathol 2013;6:2251–6.
3. Wagner AJ, Malinowska-Kolodziej I, Morgan JA, Qin W, Fletcher CD, Vena N, et al. Clinical activity of mTOR inhibition with sirolimus in malignant perivascular epithelioid cell tumors: targeting the pathogenic activation of mTORC1 in tumors. J Clin Oncol 2010;28:3835–40.
4. Bleeker JS, Quevedo JF, Folpe AL. “Malignant” perivascular epithelioid cell neoplasm: risk stratification and treatment strategies. Sarcoma 2012;2012:541626. doi: 10.1155/2012/541626.
5. Scheppach W, Reissmann N, Sprinz T, Schippers S, Schoettker B, Mueller JG. PEComa of the colon resistant to sirolimus but responsive to doxorubicin/ifosfamide. World J Gastroenterol 2013;19:1657–60. doi: 10.3748/wjg.v19.i10.1657.
6. Starbuck KD, Drake RD, Budd GT, Rose PG. Treatment of advanced malignant uterine perivascular epithelioid cell tumor with mTOR inhibitors: single-institution experience and review of the literature. Anticancer Res 2016;36:6161–4.