Case Report

**Perivascular Epithelioid Cell Tumors (PEComas) Refractory to mTOR Inhibitors**

San-Chi Chen, Chian-Wen Yang, Chueh-Chuan Yen, Cheng-Huai Tseng, Ta-Chung Chao*

*Division of Hematology and Oncology, Department of Internal Medicine, Taipei Veterans General Hospital, Taipei, Taiwan*

**Abstract.**

Perivascular epithelioid cell tumors (PEComas) are mesenchymal tumors with a particular perivascular epithelioid cell differentiation. These tumors are extremely rare and represent a form of malignancy with certain characterizations. The TSC1/2 gene mutation can develop in both tuberous sclerosis complex (TSC)-related PEComa and sporadic cases. The mTORC1 pathway activation is also found in these tumors. Currently, mTOR inhibitors have been used for the treatment of PEComas, and some reports have shown durable responses with the use of such mTOR inhibitors. We present a 71-year-old woman who had recurrent PEComa which was refractory to temsirolimus and everolimus.

**Keywords**: perivascular epithelioid cell tumors (PEComas), mTOR inhibitors, temsirolimus, everolimus

**INTRODUCTION**

Perivascular epithelioid cell tumors (PEComas) are rare tumors classified by the World Health Organization as “mesenchymal tumors composed of histologically and immunohistochemically distinctive perivascular epithelioid cells” [1]. The PEComa family
includes angiomyolipoma (AML), LAM (lymphangioleiomyomatosis) and PEComas which have not been otherwise specified (PEComas-NOS). AML presented as an asymptomatic renal lesion with vascular, muscle and adipocytic differentiation. LAM is caused by a proliferation disorder of the smooth muscle throughout the lung in premenopausal women. Both of the diseases are commonly seen in tubular sclerosis complex [2].

The PEComa-NOS can develop at any age, and is female predominant. In one review, 40% of PEComa-NOS cases were of gynecologic origin; other originating sites included the colon, pancreas, retroperitoneum, heart, adrenal gland, breast, eye, biliary tract, bone, urinary bladder, skull base, liver, skin and soft tissue [3]. Most PEComa-NOSs are benign, but some presented with malignant behavior involving invasion, local recurrence or distant metastasis. There are no optimal treatments for malignant PEComa besides tumor resection. Though the subset of PEComa-NOS is less associated with TSC, the disease activates the mTOR pathway as well. We presented a case of pelvic PEComa and shared the experience of treatment with mTOR inhibitors.

CASE REPORT

A 71-year-old woman presented with moderate abdominal pain 1 month in duration. She further reported a sensation of fullness, poor appetite and constipation. A subsequent physical examination revealed a distended abdomen with a palpable mass in the lower abdominal area. There were no stigmata of tuberous sclerosis complex on the skin. Additionally, the patient’s medical history included left temporal arachnoid cyst status post shunt insertion, major depression and left ovarian cyst status post operation. The ab-

*Corresponding author: Ta-Chung Chao M.D.
*通訊作者：趙大中醫師
Tel: +886-2-28757529
Fax: +886-2-28757762
E-mail: tcchao@vghtpe.gov.tw

Figure 1. (A) A 13 cm mass in the pelvic cavity was identified with peritoneal seeding. (B) CT image obtained after resection of pelvic tumors

Figure 2. Gross feature: well demarcated with capsule formation, tan to black with foci of necrosis
Figure 3. (A) Microscopic examination showed sheets of epithelioid cells with abundant clear to eosinophilic cytoplasm, vested with a prominent capillary vasculature. (B) The tumor cells were immuno-reactive for HMB-45. (C) The tumor cells were non-reactive for Melan A. (D) The tumor cells were non-reactive for S-100.

Abdominal CT revealed a 13 cm mass in the pelvic cavity with peritoneal seeding (Figure 1A). The tumor was heterogeneous with central necrosis. The CBC showed a WBC of 3800/cumm, Hb 10.3 g/dl, and platelets at 198,000/cumm. Her biochemistry revealed LDH 645 U/L and normal liver and renal function. The patient’s serum tumor marker showed CA125 was 282.0 U/ml (<35 U/ml) and CEA 1.59 ng/ml (<6 ng/ml). Soon thereafter, the patient underwent resection of the pelvic mass, retroperitoneal mass, part of the peritonea, total hysterectomy and bilateral salpingo-oophorectomy (Figure 1B).

In gross, the patient’s tumor had invaded the retroperitoneal cavity, the left pelvic wall, sigmoid colon and bladder wall (Figure 2). Microscopic examination showed a tumor composed of sheets of epithelioid cells with abundant clear to eosinophilic cytoplasm, vested with a prominent capillary vasculature (Figure 3A). Marked nuclear pleomorphism, tumor necrosis and mitotic activity (2/10 high power field) were present. Within the tumor, some hyalinized small vessels and large thick-walled vessels were identified. Intra-cytoplasmic brown to black melanin pigment was identified with Fontana-Masson stain. The tumor cells were immuno-reactive for HMB-45 (Figure 3B), while non-reactive for Melan A (Figure 3C), S-100...
protein (Figure 3D), muscle specific actin (HHF-35), desmin, CD10, and RCC. The pathology report confirmed the diagnosis of perivascular epithelioid cell tumor (PEComa).

After the surgery, the patient did not receive adjuvant therapy. She remained disease-free for 4 months until a follow-up CT scan showed pelvic recurrence (Figure 4A). Temsiolimus was initially given 25 mg i.v. weekly, and thereafter a tumor evaluation carried out 2 months later revealed her disease had stabilized (Figure 4B). However, the CA125 level increased rapidly from 282 U/ml to 659 U/ml. After discussing these changed circumstances with the patient, her treatment was changed to oral everolimus 5 mg twice daily. However, interstitial pneumonitis occurred after 6 weeks use of everolimus (Figure 4C). The everolimus regimen was suspended, and then resumed at a lower dose with 5 mg daily three weeks later. Thereafter, a new tumor evaluation carried out 16 weeks later revealed disease progression with new lung lesions. Due to poor performance status, we withheld further curative or sustaining medication and provided supportive care. One month later, the patient died of disease progression.

**DISCUSSION**

The natural course of PEComa can be variable, ranging from benign to aggressive behavior including metastasis. Folpe et al. proposed criteria for the classification of PEComas in 2005 using these features: 1) tumor size >5 cm, 2) infiltrative growth pattern, 3) high nuclear grade, 4) necrosis and 5) mitotic activity >1/50 HPF [4]. These authors describe PEComa as “benign” if none of the criteria are met, “uncertain malignant potential” if the tumor is larger than 5 cm or has high nuclear grade, and “malignant” if the tumor fulfills more than 2 worrisome features. Our case satisfied the criteria for “malignant”, which was compatible with the disease’s clinical course. However, the role and efficacy of using this classification for guiding treatment options in the future remains uncertain.

Tumors in the PEComa family usually develop sporadically. Among this group of diseases, LAM and AML are often seen in patients with tuberous sclerosis.
complex (TSC). TSC is caused by the mutation of TSC1 or TSC2 tumor suppression genes. Studies have found the frequent loss of heterozygosity of the TSC2 gene on 16p12 in both TSC-related PEComa and sporadic cases[5]. Thus, the TSC1/TSC2 protein complex lost its ability to inhibit the activation of mTORC1 through the Rheb GTPase [2]. The upregulation of mTORC1 pathway resulted in cell survival, proliferation and protein synthesis.

Kenereson et al. [6] described an activated mTORC1 pathway with increased levels of phospho-p70S6K detected by immunohistochemical assay in all 15 PEComas. They also found that with the reduction of AKT phosphorylation, there was a noted loss of TSC1/2 function in 14 of 15 PEComas. Pan et al. [7] also reported similar results with elevated phospho-p70S6K, and the absence of AKT phosphorylation in 12 PEComas. No strong evidence was shown which supported whether the effect of mTOR inhibitor correlates with the status of mTORC1 activation. Only one study showed that detection of phospho-p70S6K can potentially predict mTOR inhibitor response.

Bissler et al. [8] reported using sirolimus to treat 25 patients with AML or LAM. In their study, the typical tumor regressed during sirolimus treatment for 1 year but rebounded after sirolimus use was halted. In addition, there are several case reports presented where mTOR inhibitors were used to treat PEComas. Wagner et al. presented 3 PEComas that responded to sirolimus treatment, though only one patient experienced a response duration greater than 1 year [9]. Dickson et al. reported using mTOR inhibitors with a 5/11 (45%) complete response, 1/11 (9%) partial response and 5/11 (45%) progression disease [10]. The treatment was tolerable and the longest response duration was up to 2 years. In that study, no significantly different effects between the use of sirolimus, temsirolimus and everolimus were observed. However, our patient who was subsequently treated with temsirolimus and everolimus derived only marginal benefit from them. The mechanism of drug resistance to mTOR inhibitors remains unknown. In addition, there is still no established factor that predicts mTOR inhibitors response.

The mTOR inhibitors have shown promising response in about half of the malignant PEComas, and have become an important treatment option for this rare disease. Further studies are needed to define the optimal treatment strategy.

REFERENCES
8. Bissler JJ, McCormack FX, Young LR, et al. Si-
