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Journal of Cancer Research and Practice

journal homepage: www.ejcrp.org

Case Report

Total Metabolic Regression after Everolimus in an Adult Patient with Pseudomyogenic Hemangioendothelioma

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Abstract

Pseudomyogenic hemangioendothelioma (PHE) is a rare vascular tumor harboring the pathognomonic *SERPINE1-FOSB* fusion. Most patients are treated primarily with surgical resection, but some patients require systemic therapy due to multiple metastases at initial presentation or multifocal recurrence after definitive resection. The most optimal treatment strategy for the disease has yet to be clearly defined; however, mammalian target of rapamycin inhibitors show promise-given–reported anecdotal responses from case reports of pediatric patients. We present an adult patient with multifocal PHE who was successfully treated with everolimus with a significant clinical response.

Keywords: Everolimus, mammalian target of rapamycin, pseudomyogenic hemangioendothelioma

Introduction

Pseudomyogenic hemangioendothelioma (PHE) is an extremely rare locally aggressive vascular tumor predominantly affecting young male adults.[1] Most patients present with multifocal disease involving multiple tissue layers in the lower extremities, but other primary sites have also been reported. Histologically, the tumor is characterized by a myogenic appearance with endothelial differentiation in immunohistochemical staining.[1,2] A specific recurrent balanced translocation of chromosome 7 and 19 resulting in a *SERPINE1-FOSB* fusion is the molecular hallmark of PHE.[2] This translocation leads to the overexpression of FOSB and upregulation of downstream phosphoinositide 3-kinase (PI3K)-Akt and mitogen-activated protein kinase (MAPK) signaling pathways.

PHE is clinically indolent, and many patients are treated primarily with surgical excision of the tumor.[1] Unfortunately, local or distant recurrence frequently develops, and many patients require systemic treatment for better disease control. Systemic treatment with various chemotherapy combinations has been reported, but the efficacy was only modest, and the toxicities were poorly tolerated.[3-5]

Mammalian target of rapamycin (mTOR) has been shown to have extensive dynamic interplay with the PI3K-Akt

Submitted: 19-Jul-2021 **Revised:** 13-Aug-2021
Accepted: 17-Aug-2021 **Published:** 01-Jun-2022

Access this article online

Quick Response Code:

Website: www.ejcrp.org

DOI: 10.4103/2311-3006.346409

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How to cite this article: Huang DD, Liao YH, Lee JC, Chen TW. Total metabolic regression after everolimus in an adult patient with pseudomyogenic hemangioendothelioma. J Cancer Res Pract 2022;9:65-8.

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pathway, and mTOR inhibitors such as sirolimus, temsirolimus, and everolimus have been used to treat vascular tumors or anomalies with some success.[6,7] Although evidence regarding the effect of mTOR inhibition in PHE is limited, a few case reports have indicated promising efficacy. Three case reports of pediatric PHE showed that everolimus and sirolimus were effective as the first-line or later-line treatment.[8-10] In adults, only one case report has demonstrated at most a mild clinical response to everolimus as the second-line salvage.[5] Whether everolimus can provide significant clinical benefits in adult patients as a front-line treatment has not been previously reported. Herein, we present an adult PHE patient with total regression of the tumor after everolimus treatment.

Case Report

The patient was a previously healthy 40-year-old man, who presented to a dermatology clinic with multiple asymptomatic skin lesions on the scalp and buttocks [Figure 1]. An excisional biopsy of the scalp lesion revealed proliferation of spindle cells with mild nuclear atypia, eosinophilic cytoplasm, and occasional mitoses, infiltrating the dermis through the superficial subcutis between hair follicles [Figure 2]. Immunohistochemically, the tumor cells were positive for CD31, ERG, AE1/AE3 (multifocally), and FOSB (diffusely and strongly), while HHV-8 was negative [Figure 2]. A diagnosis of PHE was made. Staging positron emission tomography-computed tomography (PET-CT) disclosed multiple hypermetabolic lesions at the skull, spine, left upper limb, pelvic bone, and right femur [Figure 3]. Contrast-enhanced CT of the brain showed a 15-mm enhancing nodule at the right frontal lobe and a 5-mm enhancing nodule at the left frontal lobe. The median frontoparietal scalp was uneven with enhancing nodules. The disease was therefore deemed to be unresectable due to multiple metastatic lesions, and systemic therapy was indicated.

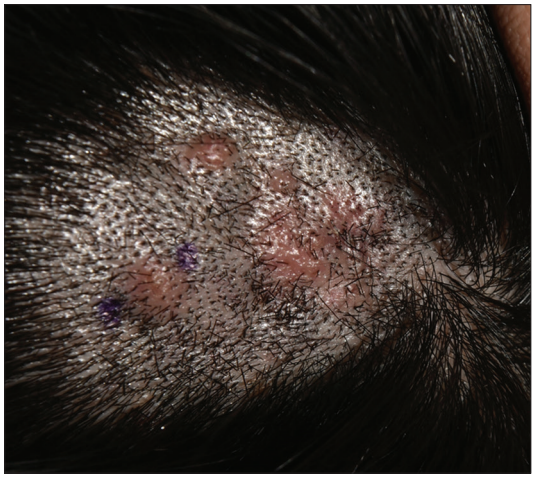

Figure 1: Scalp lesions. Several erythematous firm nodules and plaques of various sizes on the scalp

The patient was treated with everolimus 5 mg daily and received Cyberknife (6 MV) to the right frontal nodule and the left posteromedial frontal nodule. Follow-up PET-CT 18 months after treatment showed total metabolic regression of the skeletal metastases [Figure 3]. There were no significant adverse effects related to everolimus, except for mild insomnia. Since the patient was very concerned about the potential side effects of long-term everolimus exposure, the dose was not further increased. Subsequent magnetic resonance imaging (MRI) of the brain at 19 months showed radiation necrosis at the right frontal lobe, for which bevacizumab was administered. His PHE remained well controlled on everolimus at 21 months.

Discussion

PHE was first proposed by Hornick and Fletcher in 2011 as a distinct tumor entity sharing features of epithelioid

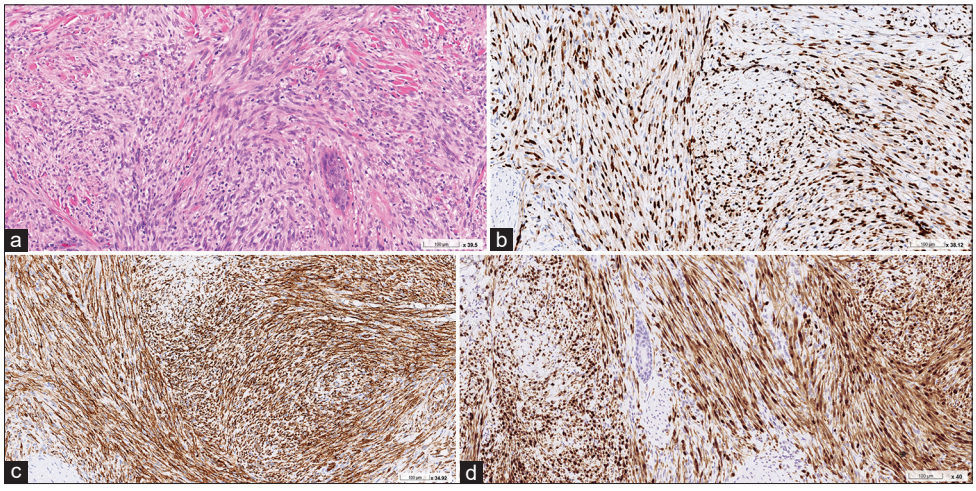

Figure 2: Pathologic examination of the tumor. (a) Hematoxylin and eosin stain showing proliferation of spindle cells with nuclear atypia. (b) Immunohistochemical stain showing positive ERG expression. (c) Immunohistochemical stain showing positive CD 31 expression. (d) Immunohistochemical stain showing FOSB overexpression

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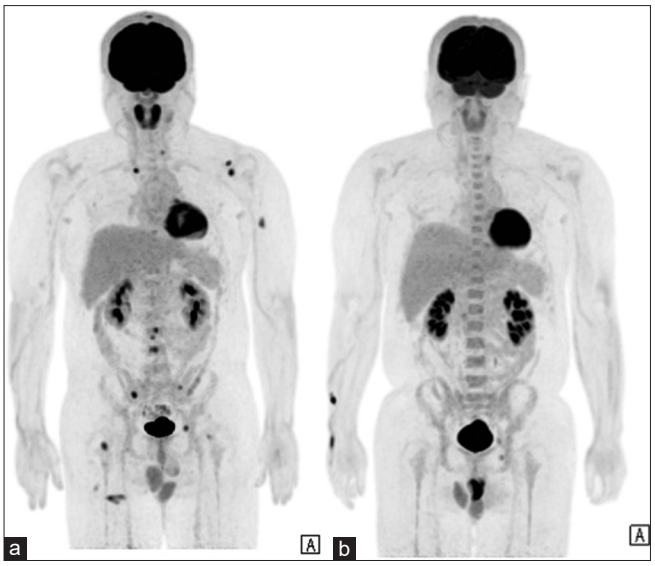

Figure 3: Whole-body positron emission tomography-computed tomography. (a) Positron emission tomography-computed tomography at diagnosis showed multiple hypermetabolic lesions at skull, spine, left scapula, left humerus, pelvic bone, and right femur (maximal standard update value = 9.5). (b) Positron emission tomography-computed tomography at 18 months showed total resolution of previous bone lesions

sarcoma but immunophenotypically with endothelial differentiation.[1] The pathognomonic *SERPINE1-FOSB* fusion was first reported by Walther *et al*. in 2014, enabling fluorescent *in situ* hybridization or RT-PCR to aid in the usually very difficult differential diagnosis process.[2] The molecular consequences of the *SERPINE1-FOSB* fusion remained elusive until 2020 when the molecular mechanism of PHE was investigated using a human-induced pluripotent stem cell (hiPSC) model.[10] In this model, hiPSCs engineered to express the *SERPINE1-FOSB* fusion were shown to successfully recapitulate the phenotypic and functional features of PHE, making it a useful model to study the tumorigenic mechanisms of PHE. The *SERPINE1-FOSB* fusion was shown to cause an increase in the expression of FOSB, which resulted in VEGF-independent endothelial cell proliferation.[11] Transcriptome analysis showed that several signal transduction pathways, especially the PI3K-Akt and MAPK pathways, were upregulated in hiPSCs carrying *SERPINE1-FOSB*.[11] Interestingly, another model using normal endothelial cells to express the fusion product of *SERPINE1-FOSB* demonstrated that the truncated FOSB protein functioned as an active transcription factor to regulate its own expression, which also resulted in overexpression of FLT1 and PDGFRA.[12] These upregulated pathways are considered central to the tumorigenesis process, and disruption of tumor growth could reasonably be anticipated with the use of appropriate inhibitors.

mTOR is a well-known downstream molecule of the PI3K-Akt pathway, and mTOR inhibitors have been widely used in the field of immunosuppression and cancer treatment.[6] Several case reports have demonstrated variable clinical responses to mTOR inhibition in PHE. Ozeki *et al*. reported a 15-year-old PHE patient who presented with multifocal painful tumors involving the left lower limb and spine.[8] The primary tumor shrunk within 4 weeks of everolimus treatment, along with a significant improvement in the pain. Follow-up PET-CT at 10 months showed complete metabolic remission. Gabor *et al*. demonstrated that sirolimus was effective in a 9-year-old PHE patient who had rapid and extensive recurrence involving the pubic bone and left lower limb after initial primary surgical resection.[9] He received first-line systemic therapy with a chemotherapy combination consisting of ifosfamide, vincristine, actinomycin-D, carboplatin, epirubicin, and etoposide, but progressive disease was confirmed on the first radiographic follow-up. Second-line sirolimus was then administered as salvage treatment. While follow-up MRI 7 months later showed stable disease, the patient had regained the ability to walk. Another successful case of sirolimus treatment was reported by Danforth *et al*. in a 6-year-old boy with multifocal PHE on the leg.[10] Amputation was initially suggested but was later successfully avoided after treatment with sirolimus and zoledronic acid. A complete metabolic response on PET-CT was seen at 13 months, and the patient had a normal functional life. To the best of our knowledge, only one adult PHE patient treated with mTOR inhibitor has been reported in the literature. This case was a 22-year-old man with PHE of the right distal femur and metastases in the left ilium who was treated with everolimus after failing two lines of systemic chemotherapy.[5] Mild shrinkage of the tumor was observed at 2 months by MRI, and he remained stable during subsequent follow-up. The above cases suggest that mTOR inhibitors are reasonable treatment options for patients with PHE who require systemic treatment.

In addition to mTOR, other potential treatment targets have also been investigated. Targeted therapy with the VEGFR1–4/PDGFRA inhibitor telatinib showed an impressive complete response in one PHE patient.[12] Unfortunately, the drug is currently not available in most countries. Many drugs targeting the PI3K-Akt pathway have been successfully developed. PI3K or AKT inhibitors could theoretically block the signal transduction pathways crucial for the tumorigenesis of PHE; however, whether they can bring meaningful clinical benefits in PHE patients in a real-world setting remains to be explored.

In conclusion, first-line everolimus is a reasonable treatment option with tolerable toxicity for adult PHE patients. Standard systemic therapy for PHE has yet to be defined due to the extremely low incidence and lack of well-designed clinical trials. Our case report adds to the growing body of evidence that mTOR inhibition may be efficacious in both pediatric and adult patients with PHE.

Ethical approval and declaration of patient consent

This study was approved by the Institutional Review Board at National Taiwan University Hospital (approval number: 202105092W), and the patient consent was waived.

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Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References
1. Hornick JL, Fletcher CD. Pseudomyogenic hemangioendothelioma: A distinctive, often multicentric tumor with indolent behavior. Am J Surg Pathol 2011;35:190-201.
2. Walther C, Tayebwa J, Lilljebjörn H, Magnusson L, Nilsson J, von Steyern FV, *et al*. A novel SERPINE1-FOSB fusion gene results in transcriptional up-regulation of FOSB in pseudomyogenic haemangioendothelioma. J Pathol 2014;232:534-40.
3. Stuart LN, Gardner JM, Lauer SR, Monson DK, Parker DC, Edgar MA. Epithelioid sarcoma-like (pseudomyogenic) hemangioendothelioma, clinically mimicking dermatofibroma, diagnosed by skin biopsy in a 30-year-old man. J Cutan Pathol 2013;40:909-13.
4. Sheng W, Pan Y, Wang J. Pseudomyogenic hemangioendothelioma: Report of an additional case with aggressive clinical course. Am J Dermatopathol 2013;35:597-600.
5. Joseph J, Wang WL, Patnana M, Ramesh N, Benjamin R, Patel S, *et al.* Cytotoxic and targeted therapy for treatment of pseudomyogenic hemangioendothelioma. Clin Sarcoma Res 2015;5:22.
6. Blay JY. Updating progress in sarcoma therapy with mTOR inhibitors. Ann Oncol 2011;22:280-7.
7. Saxton RA, Sabatini DM. mTOR signaling in growth, metabolism, and disease. Cell. 2017;168:960-76.
8. Ozeki M, Nozawa A, Kanda K, Hori T, Nagano A, Shimada A, *et al.* Everolimus for treatment of pseudomyogenic hemangioendothelioma. J Pediatr Hematol Oncol 2017;39:e328-31.
9. Gabor KM, Sapi Z, Tiszlavicz LG, Fige A, Bereczki C, Bartyik K. Sirolimus therapy in the treatment of pseudomyogenic hemangioendothelioma. Pediatr Blood Cancer 2018;65:10.1002/pbc.26781.
10. Danforth OM, Tamulonis K, Vavra K, Oh C, Brickman A, Ebersole J, *et al.* Effective Use of sirolimus and zoledronic acid for multiosteotic pseudomyogenic hemangioendothelioma of the bone in a child: Case report and review of literature. J Pediatr Hematol Oncol 2019;41:382-7.
11. van IJzendoorn DG, Salvatori DC, Cao X, van den Hil F, Briaire-de Bruijn IH, de Jong D, *et al.* Vascular tumor recapitulated in endothelial cells from hiPSCs engineered to express the SERPINE1-FOSB translocation. Cell Rep Med 2020;1:100153.
12. van IJzendoorn DG, Sleijfer S, Gelderblom H, Eskens FA, van Leenders GJ, Szuhai K, *et al.* Telatinib is an effective targeted therapy for pseudomyogenic hemangioendothelioma. Clin Cancer Res 2018;24:2678-87.