

Everolimus for the treatment of epithelioid hemangioma: a case report

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ABSTRACT

Epithelioid hemangioma is a rare benign vascular tumor manifested as slow-growing subcutaneous or dermal nodules. A previously therapeutic strategy involved surgical excision and sclerotherapy. However, no standard treatment has been established. Here, we reported an atypical case of epithelioid hemangioma that had a locally aggressive behavior and was successfully treated with everolimus, a rapamycin analog used for cancer therapy. A 1-year-old boy presented with an ulcerated lump in the left palmar region. The imaging test results, confirmed through histopathologic examination, suggested a diagnosis of epithelioid hemangioma. Targeted therapy with everolimus was administered orally because of a minimal response to initial transarterial sclerotherapy. The patient achieved a satisfactory response with a significantly reduced lesion size and improved hand function after a 2-year follow-up. This finding showed that patients with locally aggressive forms of epithelioid hemangioma may significantly benefit from everolimus as a potential targeted therapy.

KEYWORDS blood vessel tumor, everolimus, hemangioma

Epithelioid hemangioma is a benign vascular tumor of unknown etiology.¹ Lesions grow slowly, become tender and pulsatile, and tend to bleed easily.^{1,2} However, specific treatment guidelines for epithelioid hemangioma have not yet been developed. Current therapies include surgical resection, radiotherapy, endovascular embolization, and pharmacological management.^{3–5} Despite comprehensive treatments,

suboptimal responses still occur, particularly in cases involving the extremity and the appearance of lesions that may not be treated with surgery as the main option.⁶

The mammalian target of rapamycin (mTOR) inhibitor, particularly sirolimus, has been commonly used as a promising therapy for epithelioid hemangioma.⁵ It potentially blocks angiogenesis and

cell proliferation, so it is considered a candidate for targeting vascular origin lesions.⁷ However, studies have yet to describe another mTOR inhibitor, namely, everolimus, in epithelioid hemangioma.

Here, we reported a unique epithelioid hemangioma case with a locally aggressive behavior marked with an ulcerative presentation. After being previously unresponsive to chemotherapy and sclerotherapy, the lesion was successfully treated with everolimus, a novel targeted therapy for vascular malignancy. The patient achieved a partial response with a markedly reduced lesion size and showed evidence of ulcer healing after 6 months of treatment. His clinical function remarkably improved after 2 years of treatment.

CASE REPORT

A 1-year-old boy was admitted to the hospital with an ulcerated lump on his left hand. His parents noticed the lump growing progressively over the last 4 months. He was referred from a district hospital with a diagnosis of infantile hemangioma but was unsatisfactorily treated with a combination of propranolol, vincristine, and methylprednisolone for five cycles. No history of trauma or any familial disease was detected. His physical examination revealed a

bluish cystic appearance with a 9.5 cm × 9 cm × 7 cm in size, occupying the whole surface of the palmar region of the left hand. The dorsal view showed that the mass (Figure 1) appeared to compress the fingers. The upper part of the mass was ulcerating and becoming fully necrotic. The capillary refill test of the fingers revealed that distal perfusion appeared normal. Hematological and biochemical parameters were within normal values.

The clinical presentation suggested a vascular lesion. Doppler ultrasonography subsequently confirmed a mixed vascular lesion with an arteriovenous shunting component (Figure 2). Multislice computed tomography angiography with the contrast of the left hand revealed a large vascular mass surrounded by a soft necrotic tissue component (Figure 3). The lesion was subjected to two cycles of direct (transarterial) sclerotherapy with 10 U bleomycin on the basis of these findings, but no significant result was obtained. Therefore, an excision biopsy was performed on the lesion.

The pathology report revealed a diagnosis of epithelioid hemangioma (Figures 4, a and b). After the histopathology, immunohistochemical staining was also positive for CD34 (Figure 4c). Accordingly, systemic targeted therapy was administered as oral everolimus (Afinitor®) at 4.5 mg/m²/day (1.5 mg) once

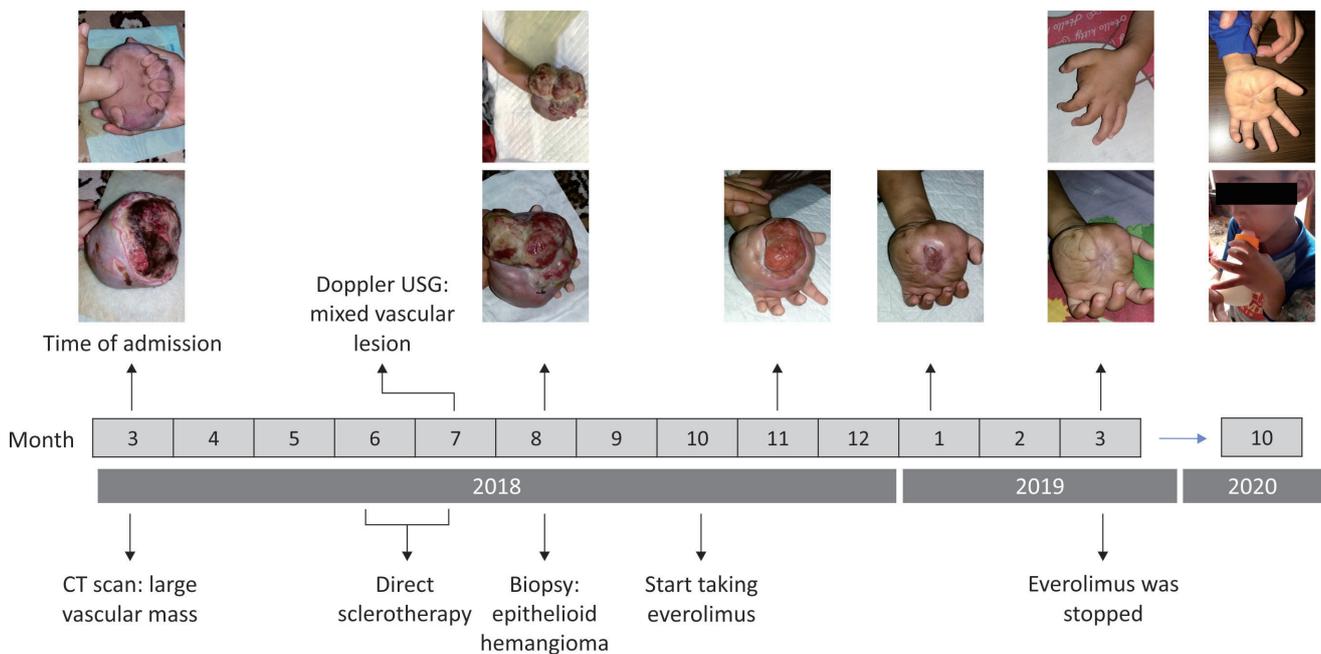


Figure 1. Time sequence of lesion appearance. Ulcerated mass with minor bleeding and a necrotic surface in March 2018. Treatment started in October 2018 and showed an improvement in the next 6 months (March 2019). After 2 years (October 2020), palmar region showed minimal soft tissue hypertrophy without any bluish bump or visible vascular lesion along with normal hand function

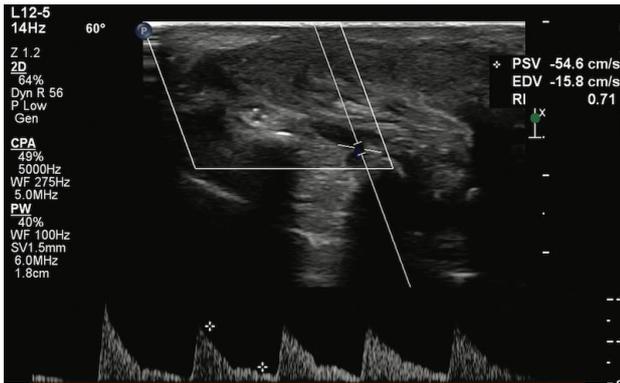


Figure 2. Doppler ultrasonography of the left hand. A prominent vascularity and a high-flow velocity of mixed venous–arterial components indicate a vascular lesion

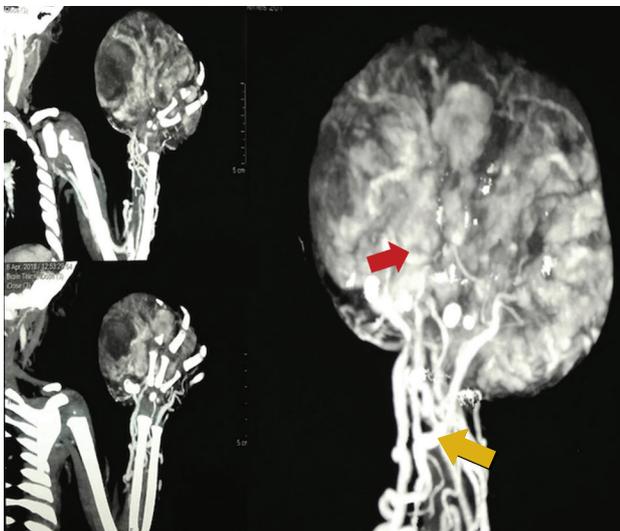


Figure 3. Multislice computed tomography (MSCT) scan angiography. A hypervascular tumor with multiple cavernous and necrotic contents (red arrow). The feeding artery and collateral vascular (yellow arrow) are prominent

daily. Wound treatment, along with everolimus, was routinely performed with alginate at the wound care unit and during home care to prevent ulcer bleeding.

In the 6-month follow-up, the lesion shrunk to the longest diameter of 5 cm (Figure 1). During the everolimus administration, no obvious adverse events or complications were observed. He had no chief complaints. Post-treatment evaluation based on clinical findings (Figure 1) and Doppler ultrasound indicated that the size of the lesion reduced by 75% after 6 months of treatment. Since then, no treatment was given to him. In the long-term follow-up (2 years after treatment), the lesion significantly achieved its clinical function. He could perform the pinch grip, indicating that he regained a near-normal function of his hand (Figure 1). His parents were fully informed and

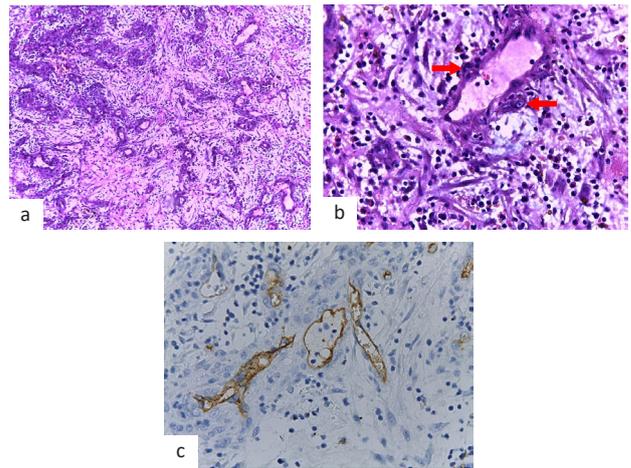


Figure 4. Histopathologic examination of the affected lesion. (a) Loose connective tissue stroma with proliferated blood vessels lined by epithelioid endothelial cells with numerous lymphocytes, plasma cells, and eosinophils (HE, 100× magnification); (b) blood vessels lined by epithelioid endothelial cells (red arrow; HE, 400× magnification); (c) endothelial cells were stained positive for CD34 immunohistochemical staining (400× magnification). HE=hematoxylin and eosin

agreed to report this case. Additionally, full anonymity on personal information was guaranteed.

DISCUSSION

According to the International Society for the Study of Vascular Anomalies classification system in 2018, epithelioid hemangioma is a benign vascular tumor.⁵ The round epithelioid endothelial cells and eosinophilic cytoplasm shown in the biopsy of the patient were consistent with the features of vascular tumors.^{1,2} The clinical, imaging, and histopathologic results and the positive endothelial marker (CD34) confirmed the diagnosis of epithelioid hemangioma.

The characteristic of epithelioid hemangioma in this case was unique. The predilection of epithelioid hemangioma is in the skin and subcutaneous tissues of the head, neck, bone, and spine. It frequently occurs in the second and third decades of life.⁸ However, in this case, epithelioid hemangioma developed in the palmar region of a male pediatric patient’s left hand. Furthermore, the bulky and ulcerated mass lesion manifested an atypical presentation of epithelioid hemangioma. Nevertheless, the low level of the proliferative index (Ki-67 of 0–1%) indicated the benign nature of this case, as Santini-Araujo et al⁹ argued that epithelioid hemangioma remains benign despite its locally aggressive behavior.

Specific guidelines for the treatment of pediatric patients with epithelioid hemangioma have not yet been established. In 2010, the only pediatric guideline for hemangioma and vascular malformations recommended steroid and propranolol or vincristine in high-risk hemangioma.⁸ Although these modalities were given to the patient at the previous hospital, an unfavorable outcome was observed. Sclerotherapy and intralesional bleomycin intervention in the hospital only resulted in a minimal response despite the high success rate in previous studies.^{10,11} Nevertheless, the aggressive presentations (ulceration and bulky mass) in this case prompted a more targeted approach as previous treatments might not be distributed to and targeted the entire lesion.

Generally, a surgical approach is recommended for hemangioma, especially under several conditions, including imminent airway obstruction, visible deformity, bleeding, or ulceration, and unresponsiveness to systemic treatments.⁸ In the patient, ulceration required an immediate surgical excision or even an amputation. However, after being resistant to other treatment modalities, the patient could preserve the affected extremity and improve his clinical outcome by switching to everolimus.

A newer class of drugs has been developed as hemangioma becomes resistant to the available treatment options. With an in-depth understanding of molecular pathophysiology, a molecule-targeted novel agent, namely, mTOR inhibitor, has been discovered; it binds to FKBP-12 and inhibits the mTOR activation complex.¹² The mTOR inhibitors, especially sirolimus, have been greatly introduced to malignant vascular tumors.⁷ In this case, the multidisciplinary team recommended giving an mTOR inhibitor after the previous treatment elicited a partial response. However, sirolimus is unavailable in Indonesia, so its analog, namely, everolimus, was used in this study.

The efficacy of everolimus against vascular tumors has been reported in some studies. Ozeki et al¹³ administered everolimus for 6 months and found that a metastatic pseudomyogenic hemangioendothelioma lesion, which was previously resistant to multiagent chemotherapies, completely disappeared. Uno et al¹⁴ showed that the size of kaposiform hemangioendothelioma decreased after 5 months of everolimus treatment. In the patient, the everolimus dose was 4.5 mg/m²/day, which was equivalent to 1.5 mg per day. This dosage was based on the Food and

Drug Administration recommendation for everolimus in subependymal giant cell astrocytoma.¹⁵

Everolimus was effective in the patient. In the 6-month and 2-year follow-up, the patient achieved a significant clinical improvement, which was evaluated following the response evaluation criteria in solid tumors criteria 1.1.¹⁶ In this study, everolimus was only administered for 1 year, which was longer than that in previous reports.^{13,14} This treatment time was considered necessary because of the lesion's severity at the initial presentation. However, in a similar case, patients may benefit from the early administration of everolimus, as targeting precisely and early may result in a better cosmetic outcome and a shorter treatment duration. Furthermore, as the first clinical case of everolimus treatment in Indonesia, our experience should be further validated with a large-scale study. With the emergence of everolimus as a novel therapy, a consensus specifically for epithelioid hemangioma and generally for vascular tumors should be established.

Everolimus had a high efficacy and did not elicit any side effects to the patient. However, side effects, including convulsion, stomatitis, nasopharyngitis, and diarrhea, must be observed in pediatric patients; among them, few patients suffer from an increase in blood cholesterol levels.¹⁷

In conclusion, ulceration in an epithelioid hemangioma lesion may suggest an atypical presentation of locally aggressive epithelioid hemangioma. Despite the broad treatment regimens for epithelioid hemangioma, this type still has unfavorable responses, thereby prompting the development of more targeted therapy. In this case, targeted therapy (everolimus) was highly efficacious in improving outcomes by decreasing the lesion size and restoring the clinical function of the affected organ.

Conflict of Interest

The authors affirm no conflict of interest in this study.

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