Case Report

Definitive radiotherapy for cutaneous epithelioid hemangioendothelioma: a case report and literature review

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Abstract: Epithelioid hemangioendothelioma (EHE) is a rare tumor of the vascular endothelium and the most common involved sites are liver, lung and bone. Approximately one-third are also known to occur in other sites, such as the skin or large vessels. Although a number of treatment modalities have been tried, treatment responses after definitive radiotherapy (RT) have not been well described. Here, we report the case of multiple cutaneous EHE on both feet in an 81-year-old woman successfully treated by definitive RT. She underwent definitive RT of 60 Gy using a volumetric modulated arc therapy and all involved lesions were completely resolved with a small residual discoloration. At 20 months of follow-up after completion of RT, no progressive or recurrent lesions on either foot were observed.

Keywords: Epithelioid hemangioendothelioma; radiotherapy; angiosarcoma

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Introduction

Epithelioid hemangioendothelioma (EHE) is a rare tumor of the vascular endothelium first described in 1975 by Dail and Liebow (1). The most common original sites of development are liver, lung and bone (2). Approximately one-third of reported cases are also known to occur in other sites, such as the skin or large vessels. Although there is no established standard treatment, surgical resection, including an adequate surgical margin with appropriate adjuvant therapy depending on the risk factors, seems to be suitable treatment method for resectable EHE. On the other hand, there is no consensus on the treatment of unresectable EHE. Here, we report the case of multiple cutaneous EHE on both feet in an 81-year-old woman treated by definitive radiotherapy (RT).

Case presentation

Past history and clinical presentation of patient

An 81-year-old female patient presented with a 2-month history of multiple painful purple-colored patches and papules on both soles and toes (*Figure 1*). She had no preexisting medical illness or medication history except for hypertension.

Diagnosis

Biopsy was performed from the cutaneous papules and nodules. On haematoxylin and eosin staining, round cells with prominent cytoplasmic vacuolization and erythrocytes within the cytoplasmic vacuoles were observed (*Figure 2*) (3). In the immunohistochemical analysis, CD31

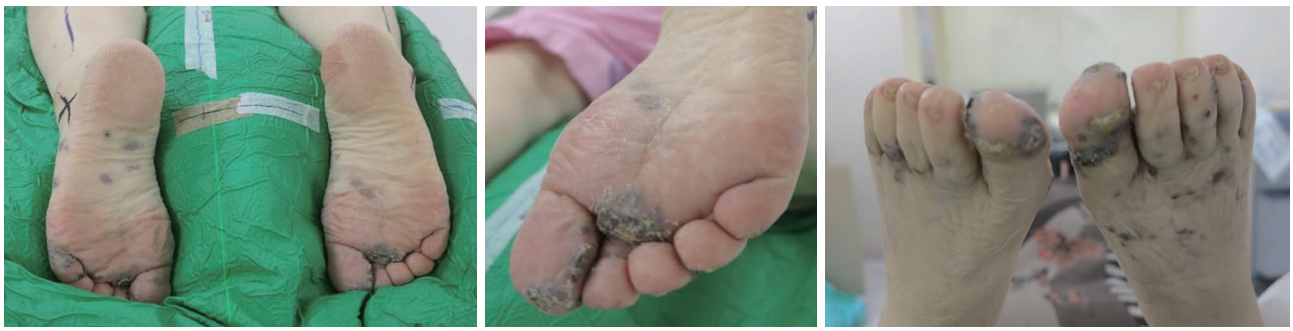

Figure 1 Multiple purple-colored patches and papules on the soles and dorsum of both feet.

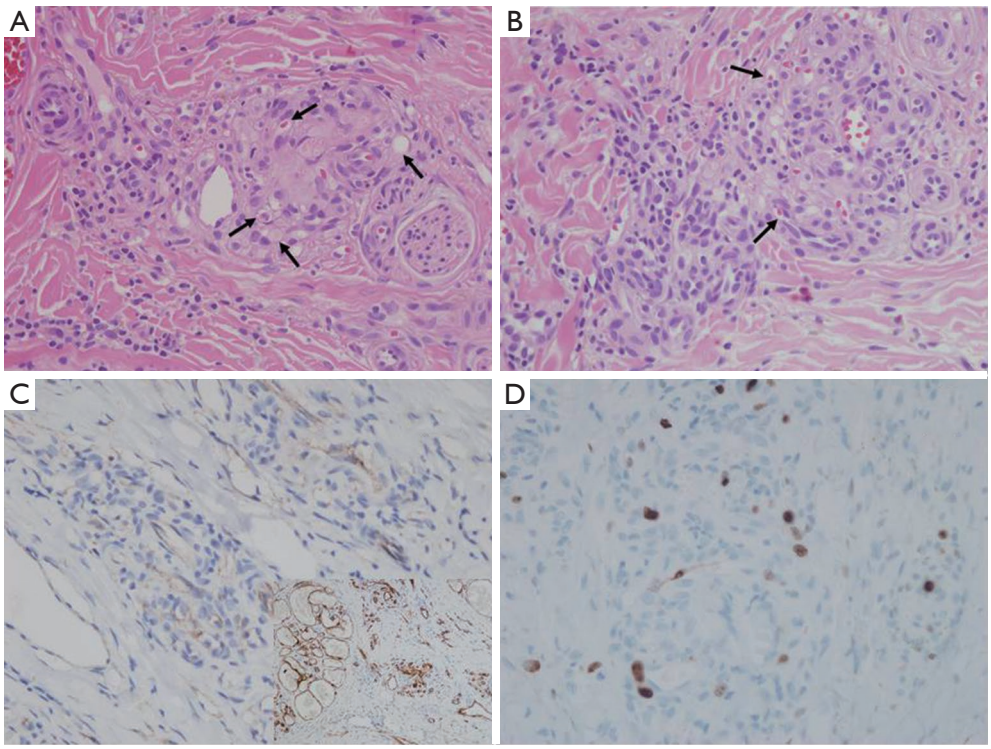

Figure 2 The incisional biopsy specimens from cutaneous papules showed epithelioid tumor cells (hematoxylin-eosin, ×400). The tumor cells were round to oval and demonstrated cytoplasmic vacuoles occasionally (arrows) (A). The presence of erythrocytes within the cytoplasmic vacuoles was also observed (arrows) (B). Immunohistochemical staining showed that the tumor cells were weakly positive for CD31 (×200) and CD34 (inset, ×200) (C). The Ki-67 index was 5–7% (×200) (D).

was weakly positive and CD34 was positive. The Ki-67 index was 5–7%. An experienced pathologist examined the biopsy specimens, and the histological diagnosis of EHE was histopathologically confirmed. The patient visited other institution for additional diagnostic consultation, and the diagnosis of EHE was reconfirmed. Systemic staging work-up procedures were conducted, including chest, abdomen and pelvis computed tomography (CT) scans. Imaging indicated no evidence of distant metastasis.

Treatment and clinical outcome

A non-steroid anti-inflammatory drug was prescribed for conservative purposes. Initial symptoms, such as pain and

swelling, were improved. However, disease progression was notably observed after 2 months. The size of previously known lesions was enlarged and new lesions were found on the soles and dorsum of both feet.

In the multidisciplinary discussion, we decided to treat the patient with curative RT to control tumors rather than surgical resection because multiple lesions were widely and superficially spread. She underwent CT simulation using an immobilization vac-lock bag to improve the reproducibility of daily treatment. A volumetric modulated arc therapy (VMAT) (4) planning using 6 megavoltage energy was designed with a 0.5 cm bolus to entirely cover involved lesions (*Figure 3*).

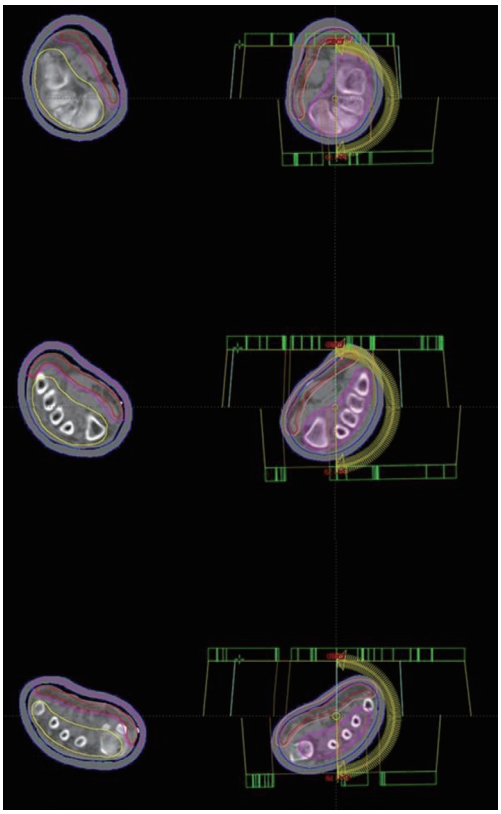

Figure 3 Radiotherapy planning using volumetric modulated arc therapy using a 0.5 cm bolus.

A total dose of 40 Gy over 20 daily fractions at 2 Gy per fraction was delivered. EHE lesions were widely spread on both soles and an area of the right foot dorsum; thus, the RT field included nearly whole soles and involved part of the foot dorsum to eradicate all lesions. There was a break of 2 months after delivering 40 Gy due to dermatitis and edema. RT was continued for residual disease thereafter with an additional 20 Gy. Four months after the completion of RT, lesions on both soles were completely resolved and there were a few remaining lesions on the foot dorsum (*Figure 4*). There was grade 1 foot edema, swelling and skin erythema. At the 7-month follow-up, the lesions were almost completely resolved. Foot edema was much improved but remained in a mild state. The patient's last visit was 20 months after the completion of RT. There was no evidence of disease recurrence.

Discussion

EHE is a rare vascular tumor, classified as a locally aggressive tumor with metastatic potential by World Health Organization (WHO) 2002 (5).

EHE was initially thought to be an aggressive form of bronchioalveolar cell carcinoma and was thus called intravascular bronchioalveolar tumor (1). However, in 1982,

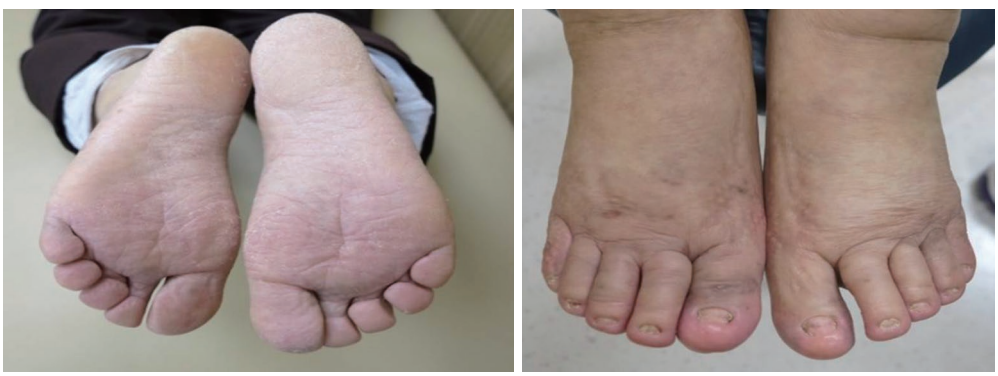

Figure 4 After radiotherapy of 60 Gy, epithelioid hemangioendothelioma lesions of both feet were completely resolved, except for a few lesions of the dorsum.

Weiss and Enzinger named it EHE, a vascular tumor of bone and soft tissue that presented features between those of hemangioma and angiosarcoma (6). Although its incidence is not clear, the majority of EHE develops in middle-aged adults (7). However, cases in children and elderly people also have been reported (8,9). No gender preference has been reported (5).

As the name suggests, EHE originates from vascular endothelial or pre-endothelial cells. Although approximately two-thirds of reported cases were observed in the liver, lung or bone, it can arise from any organ that has vascular tissue. It may be difficult to determine whether the tumor is multicentric or if it is a primary lesion with metastases in other tissues, as EHE can originate in either organ and metastasize to the other sites or it may have more than one primary site. The disease location in most reports was solitary. However, multifocal disease locations were also reported (10). There are no definitely determined predisposing factors in the development of EHEs, but possible associations with trauma and hormonal factors have been postulated (11). A new hypothesis of the pathogenesis refers to a causal relationship between the development of EHE and chronic Bartonella infection (2). Skin manifestations caused by Bartonella species are well described in the study by Chian *et al.* (12).

So far, complete surgical resection with adequate margins has been the treatment of choice in EHE. Deyrup *et al.* reported a retrospective survival analysis of patients with EHE of soft tissue who received surgical resection with or without adjuvant therapy (7). According to this analysis of 49 cases, the 5-year disease-specific survival in patients with EHE of soft tissue was 81%. In univariate analysis, patients with tumors larger than 3 cm or more than 3 mitoses per 50 high power field showed poor prognosis. They reported a 59% 5-year survival rate of the patients who had disease with any of these features, and patients who had disease without these features showed a 100% 5-year disease-specific survival rate. Other factors, such as age, sex, tumor site, cytologic atypia or adjuvant therapy, were not shown to be prognostic.

The usefulness of RT for several cutaneous malignancies was well reported (13-15). In EHE, RT is usually used for postoperative adjuvant therapy; thus, the results of definitive RT have been rarely reported. Wedmid *et al.* (16) performed induction chemotherapy followed by RT to multiple penile skin lesions. The lesions were completely resolved after treatment and no recurrence developed by 18 months.

Several case reports have described the treatment outcomes of palliative RT for EHE without surgical resection. Suga *et al.* (17) reported treatment results following palliative RT on multiple liver lesions. They delivered 60 Gy in 10 fractions of RT and achieved a complete metabolic response in positron emission tomography CT (PET-CT) after 7 months of follow-up. Saste *et al.* (18) performed conventional RT and radiosurgery on bone EHE lesions and achieved metabolic complete response at 2 years of follow-up. Sardaro *et al.* (2) treated a spine lesion compressing the spinal cord with 30 Gy in 10 fractions of RT and achieved complete symptom resolution. On the other hand, there were also discouraging reports on the use of RT. Van Kasteren *et al.* (9) treated spinal cord compressing lesions with 40 Gy of RT and chemotherapy, but the disease continued to grow and the patient developed a quadriparesis. Despite the use of doxorubicin chemotherapy, the tumor was disseminated and progressive, and the patient eventually died of respiratory insufficiency. Bahrami *et al.* (19) also reported disease progression after palliative RT on a thoracic lesion. The patient had a large hilar mass involving the large vessels and bronchus, resulting in atelectasis, pericardial and pleural effusion. In both cases, the patients had metastatic lesions in multiple organs such as the lung, liver or bones, resulting in poor general condition and organ failure.

Ma *et al.* (20) reported the results of neoadjuvant RT followed by surgical resection. The patient had a huge EHE lesion in the right iliac bone; thus, complete resection was impossible. They performed neoadjuvant RT using intensity-modulated radiation therapy and observed partial regression of the tumor. Complete surgical resection was attempted after RT, and no evidence of disease was observed after 1 year of follow-up. The results of RT in previous studies are summarized in *Table 1*.

Although RT could not provide satisfactory results in cases of aggressive progression, it achieved complete resolution in cases of small but inoperable lesions, such as our case or that of Wedmid *et al.* (16). Furthermore, as a neoadjuvant therapy, RT could help local control after complete surgical resection with an adequate margin (20).

In conclusion, this report described a case of EHE developing on both feet of an 81-year-old woman. Surgical resection was rejected due to the multiplicity of the lesions and the advantageousness of RT in terms of organ preservation; thus, 60 Gy of definitive RT was administered. All of the lesions were nearly completely resolved after our treatment, while the patient suffered foot edema and skin dermatitis for several periods. Our study suggests that

Table 1 Summary of epithelioid hemangioendothelioma cases treated by radiotherapy

Author	Gender	Age (years)	Location	Dose (Gy)	Fraction	Modality	Purpose	Co-treatment	Response to RT	F/U
Wedmid *et al.* (16)	M	48	Penis	63	35	–	Consolidation	CTx-RT	CR	18 months
Ma *et al*. (20)	F	50	Right iliac bone	50	25	IMRT	Preoperative	Op (RM–)	PR	1 year
Suga *et al.* (17)	M	59	Liver	60	10	–	Palliative	–	mCR	7 months
Sardaro *et al.* (2)	F	46	Spine	30	15	–	Palliative	–	SD	1 year
van Kasteren *et al.* (9)	M	30	Spine	40	20	–	Palliative	CTx	PD	3 months
Bahrami *et al.* (19)	M	37	Lung	N/A	N/A	–	Palliative	CTx	PD	11 months

M, male; F, female; CTx, chemotherapy; RT, radiotherapy; CR, complete response; F/U, follow-up; IMRT, intensity modulated radiation therapy; Op, operation; RM, resection margin; PR, partial response; mCR, metabolic complete response; SD, stable disease; PD, progressive disease; N/A, not available

primary RT can be a good treatment option for patients who have multiple and inoperable cutaneous EHE that is not amenable to complete resection.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2017.08.40). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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