Oral Propranolol Used as Adjunct Therapy in Cutaneous Angiosarcoma

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PRACTICE **POINTS**

- In one classic presentation, cutaneous angiosarcoma characteristically appears as a bruiselike patch on the head and neck of an elderly gentleman.
- Although cutaneous angiosarcoma typically portends a poor prognosis at the time of diagnosis, adjunctive oral propranolol may be a promising and relatively benign therapy, posited to afford benefit in a manner similar to its efficacy in the treatment of infantile hemangiomas.

To the Editor:

Angiosarcoma is a malignancy of the vascular endothelium that most commonly presents on the skin.[1] Patients diagnosed with cutaneous angiosarcoma, which is a rare and aggressive malignancy, have a 5-year survival rate of approximately 30%.[2,3] Angiosarcoma can be seen in the setting of chronic lymphedema; radiation therapy; and sporadically in elderly patients, where it is commonly seen on the head and neck. Presentation on the head and neck has been associated with worse outcomes, with a projected overall 10-year survival rate of 13.8%; the survival rate is lower if the tumor is surgically unresectable or larger in size. Metastasis can occur via both lymphatic and hematogenous routes, with pulmonary and hepatic metastases most frequently observed.[1] Prognostications of poor outcomes for patients with head and neck cutaneous angiosarcoma via a 5-year survival rate were identified in a meta-analysis and included the following: patient age older than 70 years, larger tumors, tumor location of scalp vs face, nonsurgical treatments, and lack of clear margins on histology.[2]

Treatment of angiosarcoma historically has encompassed both surgical resection and adjuvant radiation therapy with suboptimal success. Evidence supporting various treatment regimens remains sparse due to the low incidence of the neoplasm. Although surgical resection is the only documented curative treatment, cutaneous angiosarcomas frequently are found to have positive surgical margins and require adjuvant radiation. Use of high-dose radiation (>50 Gy) with application over a wide treatment area such as total scalp irradiation is recommended.[4] Although radiation has been found to diminish local recurrence rates, it has not substantially affected rates of distant disease recurrence.[1] Cytotoxic chemotherapy has clinical utility in minimizing progression, but standard regimens afford a progression-free survival of only months.[3] Adjuvant treatment with paclitaxel has been shown to have improved efficacy in scalp angiosarcoma vs other visceral sites, showing a nonprogression rate of 42% at 4 months after treatment.[5] More recently, targeted chemotherapeutics, including the vascular endothelial growth factor inhibitor bevacizumab and tyrosine kinase inhibitor sorafenib, have shown some survival benefit, but it is unclear if these agents are superior to traditional cytotoxic agents.[4,6-10] A phase 2 study of paclitaxel administered weekly with or without bevacizumab showed similar progression-free survival and overall survival, albeit at the expense of added toxicity experienced by participants in the combined group.[10]

The addition of the nonselective β-adrenergic blocker propranolol to the treatment armamentarium, which

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was pursued due to its utility in the treatment of benign infantile hemangioma and demonstrated ability to limit the expression of adrenergic receptors in angiosarcoma, has gained clinical attention for possible augmentation of cutaneous angiosarcoma therapy.[11-14] Propranolol has been shown to reduce metastasis in other neoplasms—both vascular and nonvascular—and may play a role as an adjuvant treatment to current therapies in angiosarcoma.[15-20] We report a patient with cutaneous angiosarcoma (T2 classification) with disease-free survival of nearly 6 years without evidence of recurrence in the setting of continuous propranolol use supplementary to chemotherapy and radiation.

A 78-year-old man with a history of multiple basal cell carcinomas, hypertension, and remote smoking history presented to the dermatology clinic with an enlarging red-brown plaque on the scalp of 2 months' duration. The lesion had grown rapidly to involve the forehead, right temple, preauricular region, and parietal scalp. At presentation, the tumor measured more than 20 cm in diameter at its greatest point (Figure 1). Physical examination revealed a 6-mm purple nodule within the lesion on the patient's right parietal scalp. No clinical lymphadenopathy was appreciated at the time of diagnosis. Punch biopsies of the right parietal scalp nodule and right temple patch showed findings consistent with angiosarcoma with diffuse cytoplasmic staining of CD31 in atypical endothelial cells and no staining for human herpesvirus 8 (Figure 2). Concurrent computed tomography of the head showed thickening of the right epidermis, dermis, and deeper scalp tissues, but there was no evidence of skull involvement. Computed tomography of the thorax, abdomen, and pelvis showed no evidence of metastatic disease. After a diagnostic workup, the patient was diagnosed with T2bN0M0 angiosarcoma.

The lesion was determined to be nonresectable due to the extent of the patient's cutaneous disease. The patient was started on a regimen of paclitaxel, scalp radiation, and oral propranolol. Propranolol 40 mg twice daily was initiated at the time of diagnosis with a plan to continue indefinitely. Starting 1 month after staging, the patient completed 10 weekly cycles of paclitaxel, and he was treated with 60 Gy of scalp radiation in 30 fractions, starting with the second cycle of paclitaxel. He tolerated both

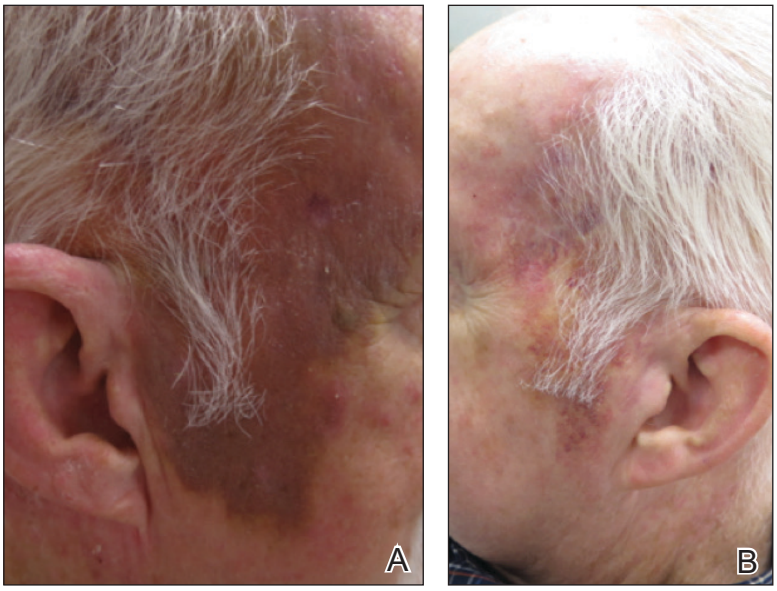

FIGURE 1. Cutaneous angiosarcoma at the time of diagnosis. A, An ecchymotic patch showed extensive involvement of right scalp, forehead, and temple. B, Extension of the ecchymotic patch on the left side of the face.

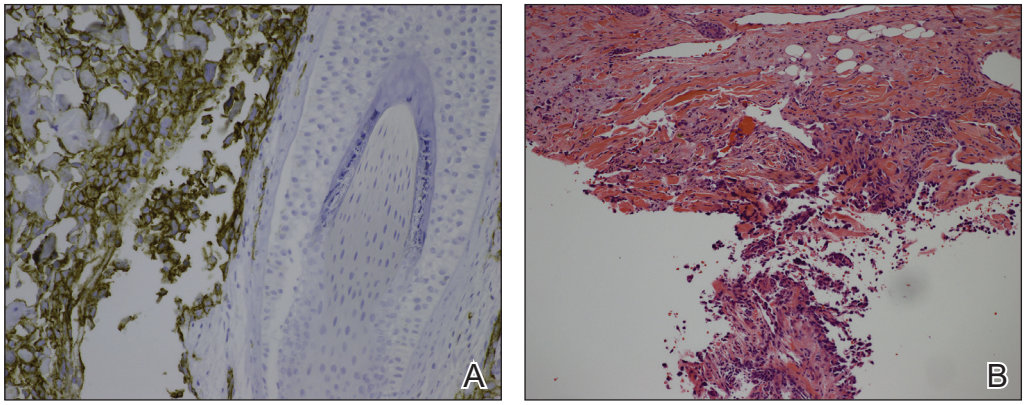

FIGURE 2. A, A punch biopsy of the right parietal scalp showed cytologically atypical endothelial cells forming slitlike vascular spaces in the dermis (H&E, original magnification ×100). B, Cytoplasmic CD31 staining of endothelial lining of slit-like atypical vascular spaces (original magnification ×400).

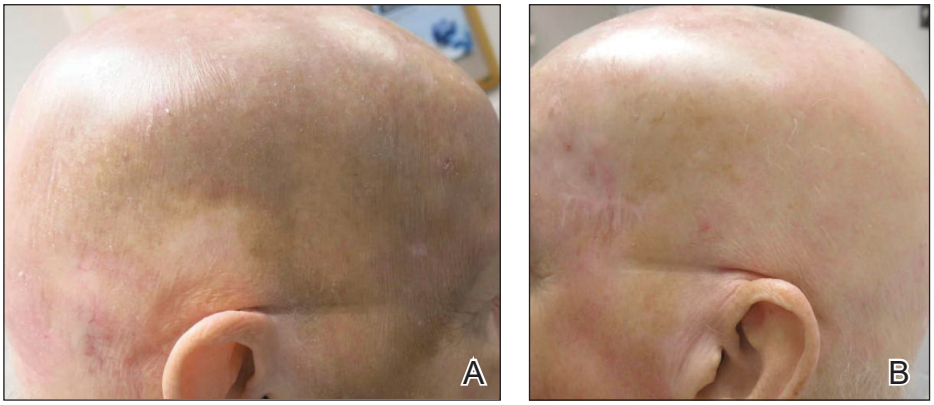

FIGURE 3. A and B, No clinical evidence of disease 8 months after initial diagnosis following treatment with radiation therapy and adjunctive propranolol 40 mg twice daily. Only postinflammatory pigment change remained on examination.

well with no reported adverse events. Repeat computed tomography performed 1 month after completion of chemotherapy and radiation showed no evidence of a mass or fluid collection in subcutaneous scalp tissues and no evidence of metastatic disease. This correlated with an observed clinical regression at 1 month and complete clinical response at 5 months with residual hemosiderin and radiation changes. The area of prior disease involvement subsequently evolved from violet to dusky gray in appearance to an eventual complete resolution 26 months after diagnosis, accompanied by atrophic radiation-induced sequelae (Figure 3).

The patient's postchemotherapy course was complicated by hospitalization for a suspected malignant pleural effusion. Analysis revealed growing ground-glass opacities and nodules in the right lower lung lobe. A thoracentesis with cytology studies was negative for malignancy. Continued monitoring over 19 months demonstrated eventual resolution of those findings. He experienced notable complication from local radiation therapy to the scalp with chronic cutaneous ulceration refractory to wound care and surgical intervention. The patient did not exhibit additional signs or symptoms concerning for recurrence or metastasis and was followed by dermatology and oncology until he died nearly 5 years after initial diagnosis due to complications from acute hypoxic respiratory failure secondary to COVID-19. The last imaging obtained showed no convincing evidence of metastasis, though spinal imaging within a month of his death showed lesions favored to represent benign angiomatous growths. His survival after diagnosis ultimately reached 57 months without confirmed disease recurrence and cause of death unrelated to malignancy history, which is a markedly long documented survival for this extent of disease.

Cutaneous angiosarcoma is an aggressive yet rare malignancy without effective treatments for prolonging survival or eradicating disease. Cutaneous angiosarcoma of the head and neck has a reported 10-year survival rate of 13.8%.[1] Although angiosarcoma in any location holds a bleak prognosis, cutaneous angiosarcoma of the scalp with a T2 classification has a 2-year survival rate of 0%. Moreover, even if remission is achieved, disease is highly recurrent, typically within months with the current standard of care.[3,21,22]

Emerging evidence for the possible role of β-adrenergic receptor blockade in the treatment of malignant vascular neoplasms is promising. Microarrays from a host of vascular growths have demonstrated expression of β-adrenergic receptors in 77% of sampled angiosarcoma specimens in addition to strong expression in infantile hemangiomas, hemangiomas, hemangioendotheliomas, and vascular malformations.[19] Research findings have further verified the validity of this approach with the demonstration of b_1-, b_2-, and b_3- adrenergic receptor expression by angiosarcoma cell lines. Propranolol subsequently was shown to effectively target proliferation of these cells and induce apoptosis in a dose-dependent manner and moreover be synergistic in effect with other chemotherapies.[15] Several genes have exhibited differential expression between control tumor cells and propranolol-treated cells. Specifically, target genes including *AXL* (a receptor tyrosine kinase associated with cell adhesion, proliferation, and apoptosis and found to upregulated in melanoma and leukemia) and *ERBB* receptor feedback inhibitor 1 (receptor tyrosine kinase, with *ERBB* family members commonly overexpressed or mutated in the setting malignancy) have been posited as possible explanatory factors in the observed angiosarcoma response to propranolol.[23]

Several cases describing propranolol use as an adjunctive therapy for angiosarcoma suggest a beneficial role in clinical medicine. One case report described propranolol monotherapy for lesion to our patient, with a resultant reduction in Ki-67 as a measure of proliferative index within 1 week of initiating propranolol therapy.[13] Propranolol also has been shown to halt or slow progression of metastatic disease in visceral and metastatic angiosarcomas.[12-14] In combination with oral etoposide and cyclophosphamide, maintenance propranolol therapy in 7 cases of advanced cutaneous angiosarcoma resulted in 1 complete response and 3 very good partial responses, with a median progression-free survival of 11 months.[11] Larger-scale studies have not been published, but the

growing number of case reports and case series warrants further investigation of the utility of propranolol as an adjunct to current therapies in advanced angiosarcoma.

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