

## Case Report/Case Series

# Growth Attenuation of Cutaneous Angiosarcoma With Propranolol-Mediated $\beta$ -Blockade

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**IMPORTANCE** Patients with stage T2 multilesion angiosarcomas of the scalp and face that are larger than 10 cm demonstrate a 2-year survival rate of 0%. To our knowledge, major therapeutic advances against this disease have not been reported for decades. Preclinical data indicate that blocking  $\beta$ -adrenergic signaling with propranolol hydrochloride disrupts angiosarcoma cell survival and xenograft angiosarcoma progression.

**OBSERVATIONS** A patient presented with a  $\beta$ -adrenergic-positive multifocal stage T2 cutaneous angiosarcoma ( $\geq 20$  cm) involving 80% of the scalp, left forehead, and left cheek, with no evidence of metastasis. The patient was immediately administered propranolol hydrochloride, 40 mg twice a day, as his workup progressed and treatment options were elucidated. Evaluation of the proliferative index of the tumor before and after only 1 week of propranolol monotherapy revealed a reduction in the proliferative index of the tumor by approximately 34%. A combination of propranolol hydrochloride, 40 mg 3 times a day, paclitaxel, 2 mg/m<sup>2</sup> infused weekly, and radiotherapy during the subsequent 8 months resulted in extensive tumor regression with no detectable metastases.

**CONCLUSIONS AND RELEVANCE** Our data suggest that  $\beta$ -blockade alone substantially reduced angiosarcoma proliferation and, in combination with standard therapy, is effective for reducing the size of the tumor and preventing metastases. If successful,  $\beta$ -blockade could be the first major advancement in the treatment of angiosarcoma in decades.

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Current treatment for angiosarcomas of the scalp, face, and neck typically involves surgery, radiotherapy, and neoadjuvant and/or adjuvant chemotherapy with doxorubicin hydrochloride or taxanes; yet, even following aggressive therapy, patient survival is abysmal.<sup>1-4</sup> Use of  $\beta$ -blockers, such as propranolol hydrochloride, has shown remarkable efficacy against benign vascular tumors,<sup>5</sup> and the use of  $\beta$ -blockers has been reported in a retrospective analysis to increase patient survival and reduce tumor metastasis and/or recurrence in several major cancer types.<sup>6</sup> We report that monotherapy with the  $\beta$ -blocker propranolol is capable of reducing the proliferative index of a cutaneous angiosarcoma. In addition, the combination of propranolol, paclitaxel, and radiotherapy led to substantial regression of a cutaneous facial angiosarcoma.

Institutional review board approval for working with tissue samples donated by the patient was granted by Texas Tech University Health Sciences Center. Patient and family consent was verbal and documented.

## Report of a Case

In May 2014, a man in his 60s presented to his dermatologist for an enlarging purpuric patch on his left lateral superior fore-

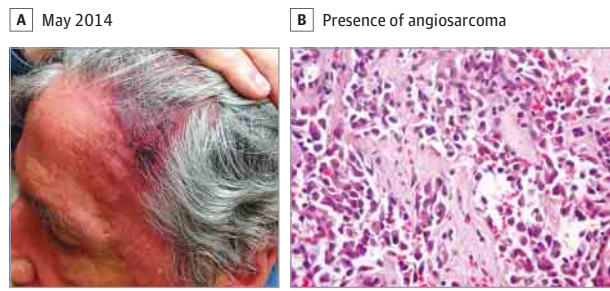
head and left anterior scalp. The lesion was reported to have been present for 2 weeks. Clinical examination revealed a non-palpable purpuric patch consistent with a contusion (Figure 1A). A punch biopsy was performed and a 4-mm sample taken from the left anterior scalp. Histopathologic evaluation of the biopsy specimen revealed that the dermis was permeated by irregular, slitlike spaces containing erythrocytes and lined by plump oval cells, many of which had pale eosinophilic cytoplasm and hyperchromatic nuclei. These cells stained positively with CD31 and were negative for CK5, confirming their endothelial lineage (Figure 1B). The patient was diagnosed as having angiosarcoma and referred to our clinic for evaluation in late June 2014. Further discussion revealed that the lesion first developed in March 2014 and was fairly stable until the beginning of June 2014, when there was rapid growth and extension of the lesion followed by central ulceration and bleeding. Clinical examination revealed a 30 × 25-cm centrally eroded purpuric plaque with multifocal peripheral reddish-purple patches, papules, and macules involving the left anterior scalp with extension posteriorly on the left parietal scalp to the superior aspect of the left occipital scalp, anteriorly on the left forehead and left lateral cheek, and medially to the right frontal and right parietal scalp. There was no evidence of lymphadenopathy in the preauricular, cervical, occipital, and submandibular or supraclavicular areas. In June 2014, a chest

and abdominal computed tomographic (CT) scan with contrast was performed and revealed no evidence of nodal, pulmonary, or liver metastases of the angiosarcoma. The patient's neoplasm was staged T2NOMO and his case was presented at the otolaryngology department tumor board at the University of California, San Francisco. The board recommended chemotherapy with paclitaxel as a first-line treat-

ment. Surgery and/or radiotherapy were not recommended owing to the extensive surface area involved by the angiosarcoma and the significant morbidity associated with either surgery or radiotherapy.

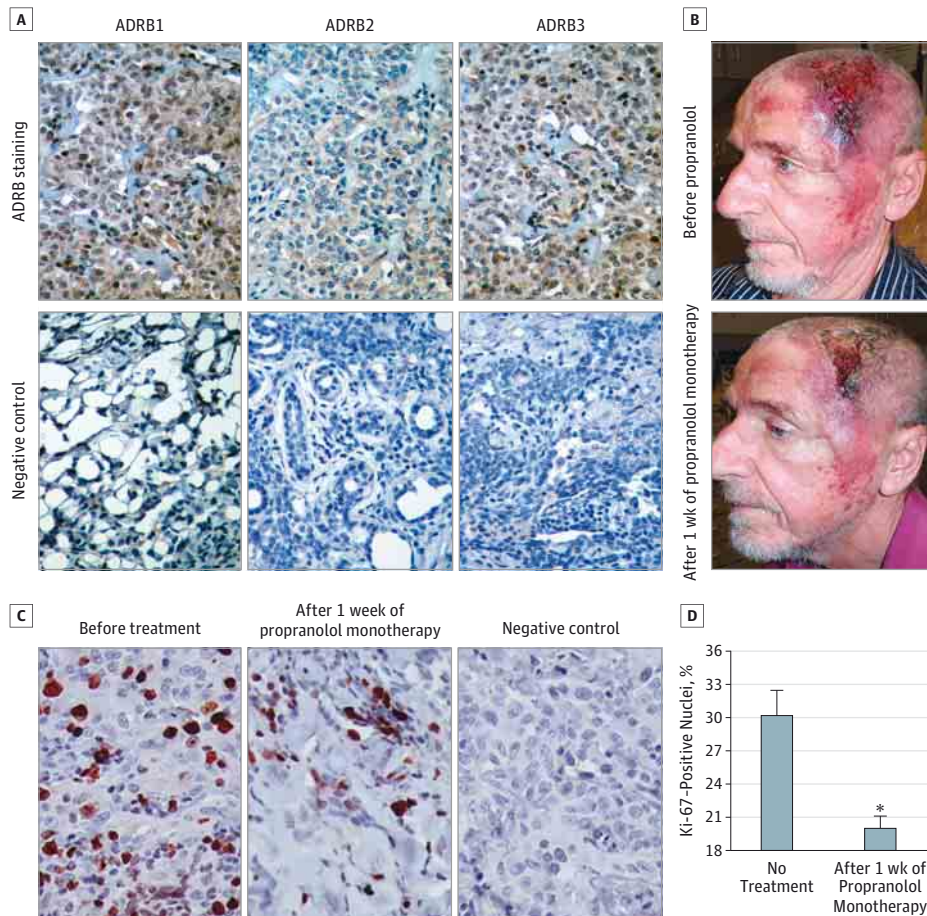
As paclitaxel treatment would not begin until early July 2014, we sought to mitigate the rapidly expanding growth of the tumor during the interim. Immunohistochemical analysis of the diagnostic punch biopsy taken in June 2014 revealed strong immunopositivity for the 3  $\beta$ -adrenergic receptors ADRB1, ADRB2, and ADRB3 (Figure 2A). Based on the extensive literature indicating that infantile hemangiomas respond rapidly to propranolol<sup>5</sup> and a preclinical study that demonstrated the efficacy of  $\beta$ -blockade against angiosarcomas,<sup>7</sup> propranolol hydrochloride was immediately started at 40 mg twice a day based on clinically tolerated doses that were shown to be effective against infantile hemangiomas. After 1 week of the propranolol treatment regimen, the tumor appeared to have ceased its rapid expansion since there was no evidence of clinical enlargement or extension of the angiosarcoma. The central ulceration had improved, with almost complete resolution of bleeding, and there was fading of the intense dark purple color at the periphery of the tumor. Figure 2B shows the side-by-side comparison of the angiosarcoma before the propranolol treatment and after only 1 week of propranolol mono-

**Figure 1. Rapid Growth and Extension of the Angiosarcoma Before Treatment**



A, Photograph of the patient's rapidly enlarging tumor in May 2014.  
B, Hematoxylin-eosin staining confirming the presence of angiosarcoma (original magnification  $\times 400$ ).

**Figure 2.  $\beta$ -Blockade Reduces the Proliferative Index of the Angiosarcoma**



A, Tumor sections were stained for the  $\beta$ -adrenergic receptors ADRB1, ADRB2, and ADRB3. Brown alkaline phosphatase precipitate indicates positive ADRB receptor expression in this angiosarcoma. Negative control staining is depicted in the bottom panels (original magnification  $\times 400$ ).  
B, Photographs were taken of the patient immediately before propranolol hydrochloride treatment and after 1 week of propranolol monotherapy.  
C, Ki-67 was detected via immunohistochemistry in the angiosarcoma before treatment and 7 days after propranolol monotherapy. Brown alkaline phosphatase precipitate indicates positive expression for the Ki-67 proliferative marker (original magnification  $\times 400$ ).  
D, Histogram indicating the mean (SEM) Ki-67 staining in each tumor sample. Ki-67-based proliferative index was quantified via manual counting by an individual (C.N.A.) who was blinded to the tumor data on the same specimen and to the corresponding Ki-67 staining in the sample pair. A fixed number of 800 tumor cells in both the initial and subsequent biopsies were counted from representative areas of the tumor. The asterisk indicates statistical significance as determined by an unpaired t test ( $P < .05$ ).

therapy. A biopsy adjacent to the original biopsy site on the left frontal scalp was performed after 1 week of treatment to determine, in a controlled manner, whether propranolol monotherapy could affect the proliferative index of this patient's angiosarcoma. A second biopsy of the midline scalp at the periphery of the angiosarcoma was also performed to document the pathologic staging as T2. Immunohistochemical detection of Ki-67, a proliferative marker that stains the nucleus of dividing cells, was performed on each biopsy specimen, revealing that propranolol monotherapy led to a reduction in the proliferative index of the angiosarcoma tumor by 34% relative to the baseline (Figure 2C and D). To our knowledge, these are the first clinical data reported in the literature suggesting that propranolol monotherapy is capable of reducing angiosarcoma tumor cell proliferation in a patient. As there were no adverse effects noted from the administration of propranolol hydrochloride at 40 mg twice a day, the dosage was increased to 40 mg 3 times a day (1.5 mg/kg).

Ten weekly infusions of paclitaxel, 2 mg/m<sup>2</sup>, were administered from early July through September 2014 with propranolol hydrochloride, 40 mg 3 times a day. Paclitaxel monotherapy has shown positive activity against angiosarcomas of the scalp or face, with positive responses reported in 75% to 89% of patients and a median time to progression of 5 months.<sup>8</sup> During the period when the patient was taking paclitaxel plus propranolol, there were no clinical signs of enlargement or extension of the angiosarcoma. There was, however, an increase in the size of the ulceration at the central purpuric portion of the tumor. Another biopsy was performed in August 2014 adjacent to the original biopsy area near the center of the tumor on the left frontal scalp. Interestingly, immunohistochemical analysis of the biopsy revealed that the proliferative index of the tumor after approximately 1 month of combined paclitaxel and propranolol therapy was not less than that seen after propranolol monotherapy, suggesting that propranolol was a major therapeutic contributor to the reduction in angiosarcoma tumor cell proliferation in this patient.

In mid-September 2014, after completion of 10 weeks of paclitaxel and propranolol therapy, coadministration of propranolol, paclitaxel, and radiotherapy was proposed to eradicate the tumor owing to the lack of clinical progression of the angiosarcoma, no evidence of lung metastasis on lung CT scans from August and September 2014, and mild to moderate clinical improvement of the angiosarcoma. Seven weekly paclitaxel infusions of 2 mg/m<sup>2</sup> were administered from October through December 2014, plus a total dose of 60 Gy (6000 rads) of radiotherapy to the entire scalp and left side of the face and neck, with a 2-week hiatus for both treatments in late November owing to radiation dermatitis. During this entire period, the patient continued taking propranolol hydrochloride, 40 mg 3 times a day, with no adverse effects. During this same period, there were no clinical signs of enlargement or extension of the angiosarcoma, with a slight increase in the size of the ulceration at the central portion of the tumor (Figure 3). As the radiation dermatitis resolved, there was clear evidence of regression of the tumor and slow, progressive healing of the central erosion. A lung CT scan with contrast in early February 2015 and a whole-body positron emission tomographic and CT

Figure 3. Clear Regression of the Angiosarcoma and Slow, Progressive Healing of the Central Ulceration With No Detectable Metastases



Progressive images of the patient during and following combination therapy with propranolol hydrochloride, paclitaxel, and radiotherapy.

scan later that month revealed no evidence of metastases and no evidence of metabolically active tumor on the scalp or face. Following completion of the paclitaxel and radiation treatment regimen, the patient continued to receive propranolol hydrochloride, 40 mg 3 times a day.

## Discussion

Cutaneous angiosarcoma of the head and neck area is a rare and thus understudied soft-tissue sarcoma composed of malignant vascular endothelial cells. Multiple randomized studies fail to show a survival benefit from chemotherapy or radiotherapy in patients with advanced metastatic angiosarcomas.<sup>9</sup> A review of the literature revealed that the most important favorable indicators for survival of patients with angiosarcomas of the scalp and face are T1 pathologic staging, absence of multifocal lesions,<sup>10</sup> and Ki-67 values less than 10%.<sup>11</sup> Conversely, patients with pathologic stage T2 angiosarcomas of the scalp and face (>5 cm) exhibit a 2-year survival rate of 0% to 18% at 24 months and 0% at 5 years.<sup>4,10,12-14</sup> Several additional studies reporting data on large numbers of patients with angiosarcoma revealed a 13% overall survival rate for patients with T2 angiosarcomas for all sites of involvement, including the head and neck.<sup>1-3</sup>

A landmark study published in 2008 demonstrated the efficacy of the  $\beta$ -blocker propranolol against infantile hemangiomas and revolutionized the management of these very common pediatric tumors.<sup>5</sup> Since that time, others have demonstrated that  $\beta$ -blockade induces apoptosis in malignant vascular tumor cells, such as hemangioendotheliomas and angiosarcomas, and inhibits angiosarcoma progression in a xenograft tumor model.<sup>7</sup> Furthermore, clinical relevance of the use of  $\beta$ -blockers in cancer therapy has been demonstrated through retrospective analysis, showing a 17% reduction in cancer-related mortality across all major cancer types and 57% reduction in breast cancer metastatic development.<sup>6</sup>

We were presented with a patient exhibiting a rapidly expanding uniformly fatal tumor with no realistic options for a favorable outcome based on current standard treatments. This patient was positive for the 3  $\beta$ -adrenergic receptors ADRB1, ADRB2, and ADRB3, and given the dramatic response and efficacy of the nonselective  $\beta$ -blocker propranolol in the treatment of infantile hemangiomas as well as the preclinical efficacy of  $\beta$ -blockade against malignant vascular tumors, we immediately prescribed propranolol to the patient while chemotherapy treatment was being coordinated. This treatment plan allowed us to control for the effects of propranolol alone, before any treatment with chemotherapy or radiotherapy. Our immunohistochemical data clearly demonstrate in a controlled fashion that propranolol hydrochloride monotherapy at 1 to 1.5 mg/kg was capable of reducing the proliferative index of this patient's angiosarcoma tumor by up to 34% after only 1 week of treatment. Moreover, within 1 week of propranolol monotherapy, the rapid expansion of the tumor was attenuated, suggesting that early mitigation with propranolol may have prevented further enlargement of the tumor. During our study, Banavali et al<sup>15</sup> reported that the combination of propranolol hydrochloride, 40 mg twice a day, and 2 cycles of metronomic chemotherapy during a 6-month period re-

sulted in complete response of a relapsing metastatic angiosarcoma on a patient's upper extremity. While the study by Banavali et al sheds positive light on the use of  $\beta$ -blockers for this type of cancer, their experimental setup could not distinguish the contribution of propranolol from the contribution of metronomic chemotherapy toward the tumor relapse. It must be acknowledged that angiosarcomas are very often rapidly fatal tumors. Although propranolol therapy demonstrated significant diminution of the angiosarcoma tumor cell proliferation and clinical extension initially, no assumptions can be made pertaining to overall patient survival from these studies. In addition, more studies with expanded patient populations are necessary to fully evaluate the adjuvant nature of propranolol in the setting of other treatment regimens.

## Conclusions

Our findings reveal that propranolol monotherapy is capable of reducing the proliferative index of a rapidly enlarging stage T2 angiosarcoma of the scalp and face. If this finding extends to a broader patient population, administration of propranolol may be a major advancement in the treatment of angiosarcomas.

### ARTICLE INFORMATION

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Histology Core Facility, performed immunohistochemical analysis for this study but were not directly compensated for these services. Also, we thank the patient for granting permission to publish this information.

**Correction:** This article was corrected on November 12, 2015, to fix errors in the text.

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