

An Update on Cutaneous Angiosarcoma Diagnosis and Treatment

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PRACTICE POINTS

- Dermatologists should be aware of challenges in diagnosing cutaneous angiosarcoma (CAS) due to its clinical similarity to benign entities such as ecchymosis and hemangioma.
- Surgery with negative margins is the first-line treatment of CAS with the best prognosis.
- Mohs micrographic surgery is useful for well-defined lesions measuring less than 5 cm on the head and neck; however, further studies are needed to determine its use in other areas.
- Paraffin-embedded sections may be more reliable than frozen sections in determining margin clearance.

Cutaneous angiosarcoma (CAS) is a rare aggressive malignancy that most commonly manifests in White men older than 60 years and often appears as an enlarging ecchymosis on the head, neck, or scalp. Surgery with negative margins is the first-line treatment. The role of Mohs micrographic surgery (MMS) is uncertain but can be used in smaller, well-circumscribed lesions on the head and neck. The greatest impact that dermatologists can have in the management of CAS is through a thorough total-body skin examination and heightened awareness resulting in a shortened time to diagnosis. Until quality evidence allows for the creation of consensus guidelines, multidisciplinary care at a cancer center that specializes in rare difficult-to-treat tumors is essential in optimizing patient outcomes

Angiosarcomas are aggressive endothelial cell tumors of vascular origin that account for 1% to 2% of all soft tissue sarcomas in the United States.^{1,2} They can affect any organ in the body but most commonly

affect the skin and soft tissue. Cutaneous angiosarcoma (CAS) is a rare type of skin cancer that can present in 2 forms: primary and secondary. The primary form lacks a known underlying cause, but secondary CAS commonly is linked to prior radiation therapy of the breast as well as lymphedema of the breast and arm. Secondary CAS may require different treatment than primary CAS, as radiation therapy poses risks to patients with radiation-induced CAS.³ The prognosis of CAS is poor due to delayed diagnosis. Current treatment modalities have a high rate of local recurrence and/or distant metastasis, but recent advances in surgery and other therapies such as radiation and immunotherapy provide hope for more successful disease control.

Dermatologists may be responsible for the initial diagnosis and management of CAS. They must be familiar with its presentation, as this condition can be difficult to diagnose and mimics other diseases. Additionally, dermatologists must understand the role of varying treatment modalities including Mohs micrographic surgery (MMS) in the management of CAS. This review will provide an overview of the epidemiology, presentation, and pathologic features of CAS and will discuss both emerging and existing treatments.

Epidemiology

Cutaneous angiosarcoma may present in various locations in the body, predominantly on the head and neck.^{4,5} Approximately 85% of cases arise in patients older than 60 years, and most of these patients are White men.^{1,4,5} The risk factors for the development of CAS include prior radiation exposure; chronic lymphedema (ie, Stewart-Treves syndrome); and familial syndromes including

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neurofibromatosis 1, *BRCA1* or *BRCA2* mutations, Maffucci syndrome, and Klippel-Trenaunay syndrome. Exogenous exposure to toxins such as vinyl chloride, thorium dioxide, or anabolic steroids also is associated with angiosarcoma, primarily in the form of visceral disease such as hepatic angiosarcoma.⁶

The average tumor size is approximately 4 to 5 cm; however, some tumors may grow larger than 10 cm.^{7,8} Metastasis through hematogenous or lymphatic spread is fairly common, occurring in approximately 16% to 35% of patients. The lungs and liver are the most common sites of metastasis.^{9,10} The age-adjusted incidence rate of CAS is decreasing for patients younger than 50 years, from 1.30 in 1995 to 2004 to 1.10 in 2005 to 2014, but increasing for individuals older than 70 years, from 2.53 in 1995 to 2004 to 2.87 in 2005 to 2014.⁴ The incidence of angiosarcoma also has grown in the female population, likely due to the increasing use of radiotherapy for the treatment of breast cancer.¹¹

The high rates of CAS on the head and neck may be explained by the increased vascularity and UV exposure in these locations.¹² In a Surveillance, Epidemiology, and End Results population-based study (N=811), 43% of patients with CAS had a history of other malignancies such as breast, prostate, genitourinary, gastrointestinal tract, and respiratory tract cancers.⁴ Cutaneous angiosarcoma can develop secondary to the primary cancer treatment, as seen in patients who develop CAS following radiation therapy.¹¹

The underlying mechanism of CAS is believed to involve dysregulation of angiogenesis due to the vascular origin of these tumors. Studies have identified overexpression of vascular endothelial growth factor (VEGF), *TP53* mutations, and RAS pathway mutations as potential contributing factors to the pathogenesis of angiosarcoma.⁶ Molecular differences between primary and secondary angiosarcomas are not well documented; however, radiation-associated CAS has been found to have higher expression of *LYN* and *PRKCE*, while non-radiation-induced lesions express *FLL1* and *AKT3*.² Chromosomal abnormalities have been identified in a small set of primary CAS patients, but the specific role of these abnormalities in the pathogenesis of CAS remains unclear.⁷

Prognosis

Cutaneous angiosarcoma has a poor prognosis, with 3-year disease-specific survival rates as low as 40% and 5-year rates as low as 17%.^{4,5,13,14} Survival rates increased from 1985 to 2014, likely due to earlier diagnoses and more effective treatments.⁴ Several factors are associated with worse prognosis, including metastatic disease, increasing age, scalp and neck tumor location, tumor size greater than 5 cm, necrosis, multiple skin lesions, and nodular and epithelioid morphology.^{4,5,10,13-16} Factors including sex, race, and presence of another malignancy do not affect survival.^{4,5} Prognosis in CAS may be evaluated by TNM

tumor staging. The *American Joint Committee on Cancer Staging Manual* (8th edition) for soft tissue sarcoma (STS) commonly is used; however, CAS is not included in this staging system because it does not share the same behavior and natural history as other types of STS. This staging system provides separate guidelines for STS of the head and neck and STS of the extremities and trunk because of the smaller size but paradoxically higher risk for head and neck tumors.¹⁷ Given that there is no agreed-upon staging system for CAS, prognosis and communication among providers may be complicated.

Clinical Presentation

Early CAS typically presents as single or multifocal ill-defined, enlarging, violaceous or dusky red macules or patches (Figure 1). Lesions often rapidly develop into raised nodules and plaques that may bleed and ulcerate. Other common symptoms include pain, edema, neuropathy, anemia, and weight loss; however, it is not uncommon for lesions to be asymptomatic.^{8,18-20} Nodular lesions are more common on the scalp, and patches are more common on the face and neck.¹⁶ Tumors typically extend into the dermis, and aggressive cancers may invade the subcutaneous tissue and fascia.²

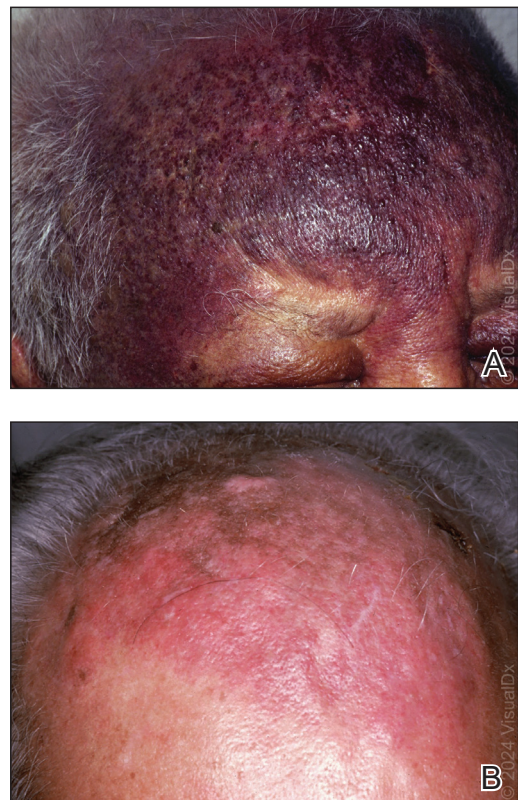


FIGURE 1. A, An extensive, deeply violaceous plaque with cobblestone appearance in areas on the forehead and a similar plaque on the left upper eyelid. B, An extensive reddish-brownish cutaneous angiosarcoma plaque on the scalp and forehead. Reprinted with permission from VisualDx (<http://www.visualdx.com>).

Cutaneous angiosarcoma may mimic ecchymosis, hemangioma, lymphangioma, edema, cellulitis, or scarring alopecia. Its nonspecific features make it difficult to recognize without dermoscopy or ultrasonography, which often results in delayed diagnosis and treatment. The median delay typically is 5 to 7 months and up to 1 year for some patients.^{7,16} Cutaneous angiosarcoma of the scalp tends to have a longer diagnostic delay than other areas of the body, which may be attributable to challenges in tumor identification and visualization by patients.¹⁶

Dermoscopy and ultrasonography can aid in the diagnosis of CAS. Dermoscopy may demonstrate a range of colors with yellow, brown, or red areas in a violaceous background. Other reported features include white veils and lines, purple ovals, pink-purple “steamlike” areas, and atypical vessels (Figure 2).²¹⁻²³ Dermoscopic findings may appear similar to other vascular tumors, such as hemangioma and Kaposi sarcoma, or nonvascular tumors, including amelanotic melanoma, Merkel cell carcinoma, and primary cutaneous B-cell lymphoma. Ultrasonography may show ill-defined, hypoechoic areas with anechoic reticular channels and a hypoechoic subepidermal layer.²¹ Other radiologic modalities, such as computed tomography, magnetic resonance imaging, or positron emission tomography, are nonspecific and are more useful in eval-

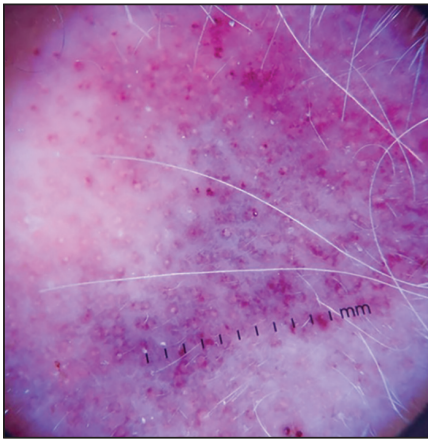


FIGURE 2. Dermoscopy of cutaneous angiosarcoma demonstrating white lines and circles in a violaceous background.²³ Republished under the Creative Commons Attribution (CC BY-NC 3.0). <https://creativecommons.org/licenses/by-nc/3.0/>

uating the extent of tumor spread in visceral angiosarcoma. Magnetic resonance imaging in CAS may indicate malignancy with the presence of high T2 and T1 signal intensity and high-flow serpentine vessels.²⁴

Histopathology

Histologically, angiosarcoma is characterized by anastomosing irregular vascular channels lined by a single layer of endothelial cells displaying slight to moderate

atypia.²⁵ These vascular channels dissect between collagen bundles and adipocytes. Monocyte infiltration may be observed.⁶ The neoplastic endothelial cells may present as spindle-shaped, round, polygonal, or epithelioid with eosinophilic cytoplasm. Histologic features differ based on the type of clinical lesion (Figure 3). In a study of CAS in Asian populations, nodular tumors showed solid sheets of pleomorphic spindle cells, many mitotic figures, and widely hemorrhagic spaces, whereas nonnodular tumors showed irregular vascular spaces dissecting collagen.¹⁶ Poorly differentiated tumors may present with hyperchromatic nuclei and prominent nucleoli, papillary

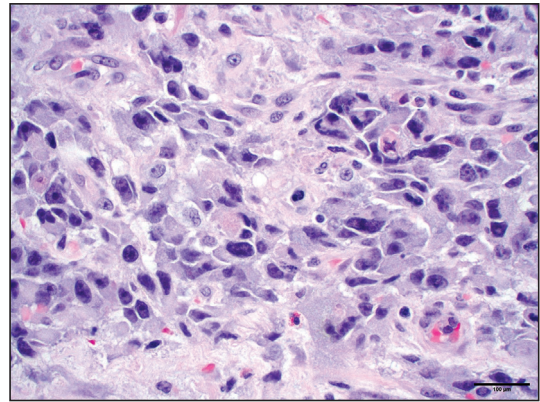


FIGURE 3. Histopathology of epithelioid angiosarcoma demonstrating irregular vascular channels with moderately atypical epithelioid cells (H&E, original magnification $\times 400$). Photograph courtesy of Kim Hookim, MD (Camden, New Jersey).

endothelial formations, mitoses, and possible hemorrhage or necrosis.^{2,6,8} Histologic specimens also may reveal calcified bodies and hemosiderin particles.¹⁹ Angiosarcomas typically are invasive without a clear capsule or border.⁶

Secondary CAS in the setting of lymphedema and radiation therapy has *MYC* amplification and is positive for *MYC* via immunohistochemistry, which is uncommon in primary angiosarcoma.²⁶ Immunohistochemical staining of tumor specimens is helpful to confirm the diagnosis of CAS. These markers include CD31, CD34, CD117, cytokeratin, vimentin, epithelial membrane antigen, factor VIII–related antigen, *Ulex europaeus* agglutinin-1, von Willebrand factor, and VEGF.^{6,19,27,28} Notably, advanced angiosarcomas with progressive dedifferentiation often lose these markers.

Treatment

Surgery—The majority of patients treated for CAS undergo surgical resection, as surgery has been shown to have the best prognosis for patients.^{5,9,10,13,15} Achieving R0 resection (microscopically negative margins) is the most important factor in determining the success of treatment, with incomplete surgical resection resulting in higher rates of systemic and local spread.²⁹ Abraham et al⁸ found

that the median disease-specific survival of patients with microscopically negative margins was 83.7 months; patients with microscopically positive and grossly positive margins had median disease-specific survival of 63.4 and 18.1 months, respectively. In a case series of patients undergoing resection with negative surgical margins, 4 patients demonstrated no evidence of local recurrence or systemic disease at an average of 4.3 years after therapy, and the other 4 patients each had 1 local recurrence but were disease free an average of 4.8 years after removal of the recurrent lesion. In a series of 27 patients with positive surgical margins, there was local recurrence within 2 years for most patients.¹²

Large tumors invading nearby structures may not be amenable to surgical resection because of extensive local growth, propensity for skip lesions, and localization near vital organs of the head and neck.^{5,7} The extended delay in diagnosis often seen in CAS allows for advanced local progression, resulting in large areas of resection. In a case series (N=8), the average surgical defect measured 14.3×11.8 cm, necessitating reconstruction with either a tissue flap or split-thickness skin graft in every case because primary closure was not possible. More than 80% of patients in this study still had positive margins after surgery, necessitating the use of additional chemotherapy or radiation to eradicate remaining disease.⁷ In several studies, multimodality therapy was associated with improved overall survival.^{7,14,30}

Mohs Micrographic Surgery—Mohs micrographic surgery is the standard of care for many aggressive cutaneous malignancies on the head, but its utility for the treatment of CAS is uncertain. Only a few studies have compared the efficacy of MMS vs wide local excision (WLE). There have been reports of recurrence-free follow-up at 12, 16, 18, 20, and 72 months after MMS.³¹⁻³⁶ The latter case showed a patient who underwent MMS with a 72-month relapse-free survival, whereas other patients who underwent WLE only survived 5 to 7 months without recurrence.³⁶ In another study, there was a local recurrence rate of 42.9% after a median follow-up of 4 years in 7 patients with CAS treated with complete circumferential peripheral and deep margin assessment, which is less than the reported recurrence rates of 72% to 84% after standard excisional procedures.^{28,37}

Houpe et al³⁸ conducted a systematic review of the use of WLE vs MMS; the median overall survival was longest for WLE in conjunction with chemotherapy, radiotherapy, and immunotherapy at 39.3 months, followed by MMS alone at 37 months. Mohs micrographic surgery in conjunction with chemotherapy and radiotherapy was used in 1 patient, with a median overall survival of 82 months. Wide local excision alone resulted in a median overall survival of 19.8 months. Although these data are promising and suggest that the combination of surgery with adjuvant therapy may be more beneficial than surgery alone, it is important to note that there were only 9 cases treated with MMS compared with 825 cases treated with WLE.³⁸

Several studies have documented that paraffin-embedded sections may be more useful than frozen sections in the determination of margin positivity from a surgical specimen, as frozen sections showed a poor negative predictive value of 33.3%.^{7,35} Mohs micrographic surgery has been proposed for tumors measuring less than 5 cm; however, the most recent appropriate use criteria for MMS of the American Academy of Dermatology, American College of Mohs Surgery, American Society for Dermatologic Surgery Association, and American Society for Mohs Surgery deemed the use of MMS for angiosarcoma uncertain.^{32,33,37} Further research is necessary to elucidate the role of MMS in the management of CAS.

Radiotherapy—Radiotherapy is a common adjuvant to surgical resection but has been used palliatively in patients with tumors that are unresectable. Improved local control and disease-free survival have been observed with the combination of radiation and surgery. A dose response to radiotherapy has been demonstrated,^{18,30} with 1 study showing that patients who received more than 5000 cGy of radiotherapy achieved better local control than patients who received 4500 cGy or less.¹⁸ Pawlik et al⁷ showed a decreased chance of death with the addition of adjunctive radiotherapy, and patients who underwent post-operative radiotherapy demonstrated a median survival almost 4-times longer than patients who did not receive radiation. Morrison et al³⁹ reported that radiation therapy administered to patients with no clinically evident disease after surgical resection resulted in improved local control and overall survival vs patients who were irradiated with clinically evident disease.

Complications of radiotherapy for angiosarcoma have been reported, including xerostomia, nonfunctionally significant fibrosis, chronic ulceration/cellulitis of the scalp, necrosis requiring debridement, severe ocular complications, and fibrosis of the eyelids requiring surgical intervention.¹⁴ Radiation therapy also poses unique risks to patients with radiation-induced angiosarcoma of the breast, as many of these patients have already received the maximum recommended dose of radiation in the affected areas and additional radiation could exacerbate their CAS.

Chemotherapy—Chemotherapy occasionally is used as an adjunct to surgical resection with positive margins or as palliative care when surgical resection is not possible. Unfortunately, STSs have a response rate of less than 40% to standard chemotherapy.⁴⁰ Studies in which the use of chemotherapy is evaluated for CAS have mixed results. Mark et al¹⁸ reported no significant overall survival benefit when comparing CAS treated with surgery plus radiotherapy with or without chemotherapy. Torres et al⁴¹ evaluated radiation-induced angiosarcoma of the breast and found a reduced risk for local recurrence in patients receiving chemotherapy in addition to surgery, indicating that chemotherapy may be useful in this subset of patients when radiation is not recommended.

Cytotoxic chemotherapy agents such as paclitaxel, doxorubicin, or doxorubicin in combination with mesna and ifosfamide (MAI) are common.³⁹ Median progression-free survival is 5.4 months, 4 to 5.6 months, and 3.9 months for MAI, paclitaxel, and doxorubicin, respectively.^{8,9,42-46} Improved prognosis with MAI may indicate that combination chemotherapy regimens are more effective than single-agent regimens. Cutaneous angiosarcomas may respond better to paclitaxel than doxorubicin, and angiosarcomas of the scalp and face have shown a better response to paclitaxel.^{47,48}

Other Therapies—Although there have not been large-scale studies performed on alternative treatments, there are several case reports on the use of immune modulators, biologics, β -blockers, and various other therapies in the treatment of CAS. The following studies include small sample sizes of patients with metastatic or locally aggressive disease not amenable to surgical resection, which may affect reported outcomes and survival times.⁴⁹⁻⁵⁷ In addition, several studies include patients with visceral angiosarcoma, which may not be generalizable to the CAS population. Even so, these treatment alternatives should not be overlooked because there are few agents that are truly efficacious in the treatment of CAS.

Results on the use of VEGF and tyrosine kinase inhibitors have been disappointing. There have been reports of median progression-free survival of only 3.8 months with sorafenib treatment, 3 months with pazopanib, and 6 months with bevacizumab.⁴⁹⁻⁵¹ However, one study of patients who were treated with bevacizumab combined with radiation and surgery resulted in a complete response in 2 patients, with no evidence of residual disease at the last follow-up of 8.5 months and 2.1 years.⁵²

Studies on the utility of β -blockers in the treatment of CAS have shown mixed results. Pasquier et al⁵³ evaluated the use of adjunctive therapy with propranolol and vinblastine-based chemotherapy, with a promising median progression-free survival of 11 months compared with an average of 3 to 6 months with conventional chemotherapy regimens. However, in vitro studies reported by Pasquier et al⁵³ indicated that the addition of propranolol to doxorubicin or paclitaxel did not result in increased efficacy. Chow et al⁵⁴ demonstrated that propranolol monotherapy resulted in a reduction of the proliferative index of scalp angiosarcoma by 34% after only 1 week of treatment. This was followed by combination therapy of propranolol, paclitaxel, and radiation, which resulted in substantial tumor regression and no evidence of metastasis after 8 months of therapy.⁵⁴

Immune checkpoint inhibitors have been a recent subject of interest in the treatment of angiosarcoma. Two case reports showed improvement in CAS of the face and primary pleural angiosarcoma with a course of pembrolizumab.^{55,56} In another case series, investigators used immune checkpoint inhibitors in 7 patients with cutaneous, breast, or radiation-associated angiosarcoma and found partial response in several patients

treated with pembrolizumab and ipilimumab-nivolumab and complete response in 1 patient treated with anti-cytotoxic T-lymphocyte-associated protein 4 antibodies. The authors of this study hypothesized that treatment response was associated with the mutational profile of tumors, including mutational signatures of UV radiation with a large number of C-to-T substitutions similar to melanomas.⁵⁷

Conclusion

Cutaneous angiosarcoma is a rare and aggressive tumor with a poor prognosis due to delayed detection. A thorough skin examination and heightened awareness of CAS by dermatologists may result in early biopsy and shortened time to a definitive diagnosis. Until quality evidence allows for the creation of consensus guidelines, care at a cancer center that specializes in rare and difficult-to-treat tumors and employs a multidisciplinary approach is essential to optimizing patient outcomes. Current knowledge supports surgery with negative margins as the mainstay of treatment, with adjuvant radiation, chemotherapy, and targeted therapies as possible additions for extensive disease. The role of MMS is uncertain, and because of the lack of continuity in CAS, it may not be an optimal treatment.

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