

Multifocal Angiosarcoma of the Scalp: Review of the Literature and Report of Two Cases

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Abstract

Cutaneous angiosarcoma of the head and neck is a rare disease with a very difficult treatment. We report two cases of patients with cutaneous angiosarcoma of the scalp and a review of the literature. Both patients were female and their average age was 70.3 years. In the two cases, the clinical presentation of the angiosarcoma was a multifocal tumor of the scalp with bleeding and ulceration. One of the patients had regional lymph node metastasis and the other had lung metastasis. Both lesions received surgical treatment with wide excision and were reconstructed immediately; negative margins were reported in the definitive section. One patient underwent a posterolateral neck dissection. Cutaneous angiosarcoma of the scalp is an aggressive tumor that has a high metastatic potential; its treatment consists of a wide surgical resection with negative margins and radiation therapy; despite this, its prognosis is generally poor.

Keywords: Cutaneous angiosarcoma; Head and neck; Scalp

Introduction

Soft tissue sarcomas are rare and aggressive tumors, which in the head and neck area account for 1%. Angiosarcomas represent less than 1% of all sarcomas; being most frequent in head and neck region, and especially in the scalp [1-3]. Mainly, treatment of this tumor is usually wide excision with reconstruction, whenever possible, followed by radiation therapy. In cases of extensive or unresectable tumors, chemotherapy and radiation therapy could be used.

We present two cases of angiosarcomas of the scalp that developed as multifocal lesions. Both were treated with wide excision with reconstruction.

Clinical Case N°1

A 70-year-old female patient who presented a scalp ulcerated and ill-defined tumor for 6 months, with rapid growth and bleeding; later on, another similar tumor appeared next to this first tumor. On her first examination, a 7×4.5 cm lesion was seen over the left temporoparietal region of the scalp. It was brownish in color, with irregular margins and a large amount of crust; next to this lesion, there was another similar lesion of 2 cm in its major size (Figure 1). The rest of the scalp was normal. There was a 2 cm palpable lymph node in the posterior region of the neck. The incisional biopsy reported a mesenchymal vascular tumor that suggested cutaneous angiosarcoma, with vasoformative neoplasm involving the dermis (Figure 2a and 2b). Immunohistochemically, CD31 was strongly positive (membranous and cytoplasmic) in the both spindle and endothelial cells (Figure 3a), and factor VIII-related antigen positivity (membranous) was diffuse (Figure 3b). Cytokeratin (AE1/AE3) and CD34 were negative in tumor cells. These findings were related to a high-grade angiosarcoma with an important mitotic rate. The fine-needle aspiration cytology of the suspicious lymph node was reported negative for malignancy. CT was done without compromise of the bone under the lesion. A surgery was performed with a wide excision of both lesions with 2cm of margins, with resection of the outlet table of the skull at a depth margin (Figure 4). The suspicious lymph node was resected; its aspect was of a metastatic node, the frozen section confirmed the presence of metastatic cells. A left posterolateral neck dissection was performed

(Figure 5). The reconstruction was made with local rotation flap of the scalp. The definitive biopsy reported a high grade cutaneous angiosarcoma of classic pattern with epithelioid areas and 16 mitoses per 50 high-power field. The major lesion sized 8cm and its invasion in depth involved the pericranium. All margins were reported negatives (Figure 6). Of the 21-lymph node resected in the neck dissection, four of them were metastatic with extra-capsular invasion. Patient died 10 days after the surgery due to cardio-pulmonary complications.

Clinical Case N°2

A 67-year-old female patient who presented multiple ulcerative lesions in the scalp for 9 months, with rapid growth and bleeding. On the physical exam, there were multiple lesions in the left



Figure 1: Multifocal lesion in the left temporo-parietal region.

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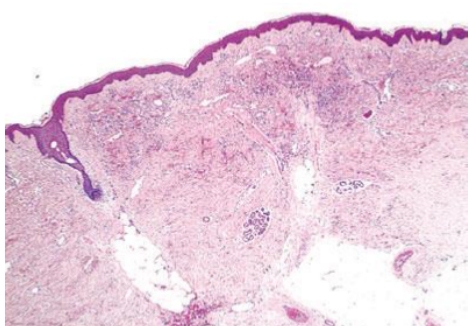


Figure 2a: H&E 4x showing presence of mesenchymal neoplastic cells from papillary to reticular dermis.

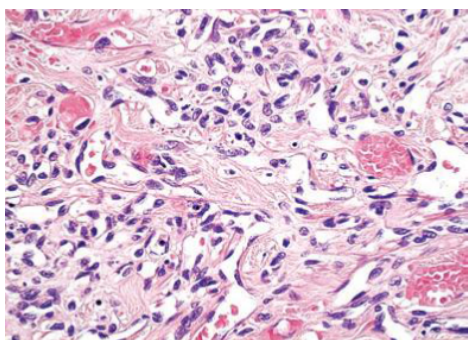


Figure 2b: H&E 40x Spindle endothelial cells surrounding vessel and neoformed channels.

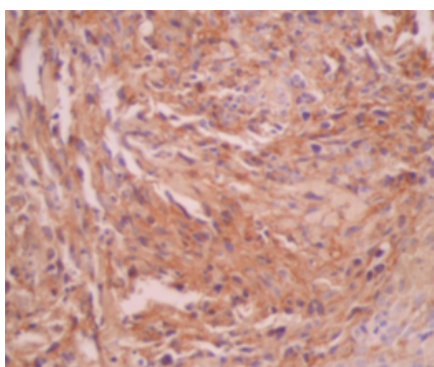


Figure 3a: Immunohistochemistry CD31 10x showing strongly immunolabeling membrane and cytoplasmic in neoplastic cells.

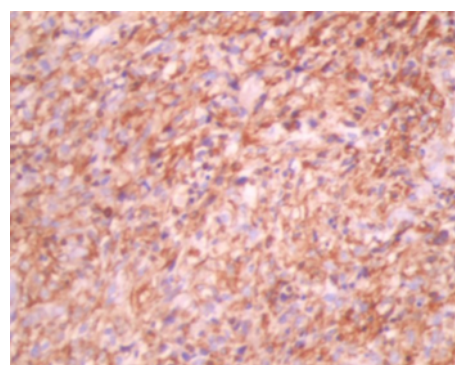


Figure 3b: Immunohistochemistry Factor VIII-related antigen 10x showing strongly immunolabeling membrane in neoplastic cells.



Figure 4: Surgical defect after perform a wide resection of the tumor.

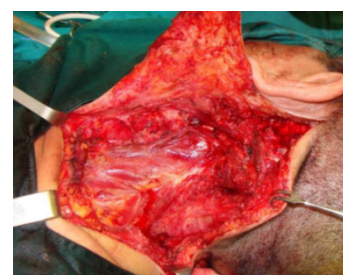


Figure 5: Left posterolateral neck dissection.

temporoparietal region, which involved the helix of the left ear (Figure 7a and 7b). The major lesion was 10 cm in size. The biopsy reported a poorly differentiated spindle cell tumor with neoplastic opened vascular channels, anastomosing, and lined by plump atypical endothelial cells with focal tuft formations (Figure 8a and 8b); the immunohistochemistry reported positive for antibodies CD31 and factor VIII-related antigen and negative for cytokeratin AE1-AE3 and EMA, suggesting cutaneous angiosarcoma. CT of skull reported a tumor involving scalp and left ear without osseous infiltration (Figure 9). Thoracic CT showed a suspicious nodule located in left lung in its basal lobe. Due the continuous bleeding of the tumor, it was necessary

to perform a surgery. A wide excision of the tumor including the entire left ear was done (Figure 10). The large surgical defect was reconstructed with a free-flap of greater omentum, however this flap was lost due to vein thrombosis. The definitive biopsy observed a high grade tumor with extensive areas of necrosis and involving the pericranium; all the margins were negatives for malignancy. She received post-operative radiotherapy and she currently has two years of disease-free survival.

Discussion

Head and neck sarcomas are infrequent, being angiosarcomas 10% of them [4]. Angiosarcoma is a malignant tumor of vascular endothelial cells that can arise in any location of the body. In contrast to the deep location of most soft tissue sarcomas, angiosarcomas have a predilection for the skin and superficial soft tissue. Therefore, it is not uncommon to find them in the face and scalp [5]. It was first described



Figure 6: Surgical specimen showing the resection of the whole tumor.



Figure 7a: Multifocal lesion in the left temporo-parietal region involving the ear.



Figure 7b: Multifocal lesion in the left temporo-parietal region involving the ear.

by Livingston and Klemperer in 1926, when they reported a tumor of scalp in a 38-year old white male who later died from an uncontrolled hemorrhage [6].

Patients who most often developed angiosarcoma are caucasians, with very few cases reported in other races. They occur commonly in elderly male patients over 60 years old with an overall male-to-female ratio of 3:1 [3,5].

There are conditions that may be associated with cutaneous angiosarcomas: chronic lymphedema after treatment of breast carcinomas (Stewart-Treves Syndrome) [6,7], previous radiation therapy and immunosuppression in renal transplant patients. However, most common cutaneous angiosarcomas are those unrelated to lymphedema (de novo tumors) [3,5,8]. Other proposed risk factors include exposure to vinyl chloride, insecticides, thorium dioxide and hormones such as anabolic steroids and synthetic estrogen

[9]. On the other hand, pathogenesis of angiosarcoma is still unclear. Mendenhall et al. [10], support the hypothesis that the upregulation of the glycopeptide VEGF-D, a vascular endothelial growth factor, as a responsible for the endothelial cell proliferation. Shuborg et al. [11] demonstrated that angiosarcomas show frequent rearrangement of 5pter-p11, 8p12-qter, 20pter-q12, losses of 7pter-p15 and 22q13-qter and -Y.

Clinical behavior of angiosarcoma of the scalp in early stages is apparently slow, having characteristics of a bruise or a capillary hemangioma; however, angiosarcoma, in its course, become an aggressive tumor with rapid and invasive growth. This tumor arises in

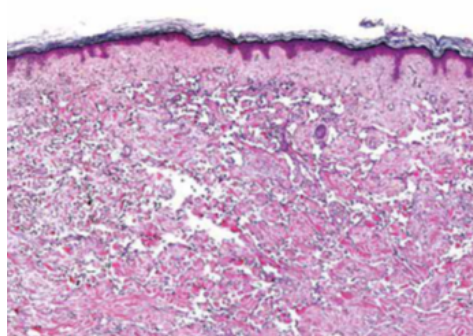


Figure 8a: H&E 4x Proliferation of newly formed vessels, forming channels. Endothelial lined by spindle cell.

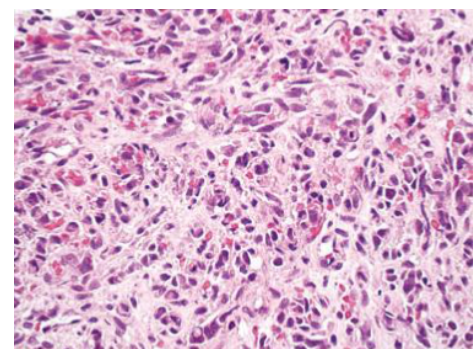


Figure 8b: H&E 25x Spindle endothelial cells surrounding vessel and neoformed channels.

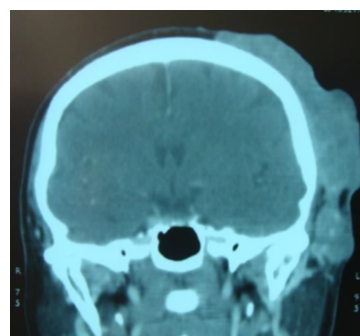


Figure 9: CT of skull showing a tumor involving scalp without osseous infiltration.



Figure 10: Surgical specimen showing the resection of the whole tumor and the left ear.

the dermis, may extend into subcutaneous tissue, and can reach great dimensions in its size [1,5].

Due to their rare occurrence and common resemblance to benign conditions in early stages, these lesions are often diagnosed late, causing increase in size and diminish overall-survival [3,5].

Clinical presentation of angiosarcomas is variable. The tumor may be single or multifocal; bluish or violaceous; nodules, plaques or flat areas; and they can usually bleed or ulcerate [5].

Angiosarcoma has the tendency for metastasis by lymphatic and hematogenous routes. It has been described that angiosarcomas have the highest rate of lymph node metastases among all soft tissue sarcomas of the head and neck. Distant metastasis may occur in up to 50%, being the lung the most common site followed by the liver [3,6].

Microscopically, numerous, irregular and anastomosing vascular channels typically characterize a cutaneous angiosarcoma [8]. These features may change according to histologic grade. Low-grade angiosarcomas are well-differentiated lesions that retain some of the functional and morphologic features of normal vascular endothelium. Poorly differentiated tumors have sheets of pleomorphic cells, areas of hemorrhage, disordered architecture and large cells with hyperchromatic and pleomorphic nuclei; cells often display prominent mitotic activity. When tumors have high pleomorphism, they may mimic other tumors such as melanomas and carcinomas [5], in these cases immunohistochemistry helps to make differential diagnosis. Immunohistochemistry studies commonly demonstrate positivity for CD31 and factor VIII-related antigen [8].

Regarding treatment, due to the rarity of this type of tumor, it is infrequent in the medical literature to find reports with large group of patients, therefore prospective studies about its treatment do not exist. Despite this, it is recommended that treatment of cutaneous angiosarcoma be multimodal, including surgery and radiation therapy.

Surgical treatment is often difficult due the pattern of diffuse growth of this tumor, which makes it problematic to achieve clear margins during the resection. Frozen section of margins during surgery do not warrant negative margins. In the work of Pawlik et al. [5], nine patients had negative margins by frozen section, in six of them positive microscopic margins in definitive sections were reported.

During wide surgical excision, most of the times, the defect created is greater than expected due to the difficulty to obtain negative margins. This situation creates a serious problem to the reconstructive surgeons team. Various reconstructive options are available such as split-thickness skin grafts, local flaps and free flaps [1,3].

Radiation therapy is generally indicated in patients after surgical treatment. It has described to yield improved survival rates with routine use of postoperative low-dose, very wide-field radiation. Use of high-dose brachytherapy with a surface mold technique to avoid marginal recurrence common with conventional technique, in extensive angiosarcoma of the scalp, has also been reported [3].

Chemotherapy has been suggested only for unresectable tumors, but has not proven to be beneficial [12]. Current regimens involve anthracyclines and taxans. Anthracyclines have been most commonly used, either as a single agent or as a component of combination therapy [1]. Complete remission of angiosarcoma has been reported with the use of liposomal doxorubicin alone [13]. The association doxorubicin-ifosfamide produces a modest response rate [14]. At Memorial Sloan-Kettering Cancer Center, in a small report of nine patients with angiosarcoma of the scalp and face treated with paclitaxel weekly or every 3 weeks, 8 patients had a response [15]. Also have been reported responses with paclitaxel associated with radiotherapy [16]. Liposomal doxorubicin and paclitaxel have also demonstrated response in angiosarcoma [17]. In one case of disseminated or multifocal lesions, perfusion of the scalp using liposomal doxorubicin injected through a controlled perfusion of the external carotid artery and intralesional injection of pegylated interferon alpha has been described to yield good results [18].

The use of angiostatic chemotherapy has been reported in a small series, but with promising results [19]. Bevacizumab, a recombinant humanized antibody against vascular endothelial growth factor (VEGF) which has been shown to be a primary regulator of angiogenesis and linked to tumor growth and metastases, has been used with successful results. De Yao et al. [9] described a 88-year old patient with an extensive angiosarcoma of the scalp who was not a candidate for surgery because of his poor performance. Bevacizumab plus radiation therapy was given with good response, but he had local relapse 7 months after finishing the whole treatment. Agulnik et al. [20] in an open-label, multicenter, phase II study, concluded that Bevacizumab is an effective and well-tolerated treatment for metastatic or locally advanced angiosarcoma and epithelioid hemangioendotheliomas.

One of the limitation for treatment in patients with angiosarcomas is age. Often we found angiosarcomas in elderly patients, who may have more comorbidities than younger patients; that results in difficulties to choose the best treatment.

The overall prognosis of angiosarcomas is poor even compared to other head and neck sarcomas with the 5-year survival ranging from 4 to 20% for angiosarcomas while the rate for fibrosarcomas is 60 to 70% and for dermatofibrosarcomas it is around 100% [21]. Pwalik et al. [5] reported a 5-year survival rate of approximately 10%, with an overall median actuarial survival of 28.4 months.

Local recurrence and metastasis are very frequent, regardless of the treatment modality employed [12]. Some prognostic factors are related to these types of relapses. One of the most important prognostic factor is histologic grade. Köhler et al. [21] reported in their work that the only prognostic factor significantly affecting survival was histological grade ($P=0.003$) being the high-grade sarcomas survival of 15% while the low-grade sarcomas survival was 77.5%. In this work, grade also had a significant impact on distant relapse ($P=0.010$) but not on local relapse ($P=0.082$).

Another factor associated with poor prognosis is the presence of multifocal disease. This factor is associated with a shorter interval between initial presentation and recurrence. In the report of Pawlik

et al. [5], multifocality was strongly associated with poor disease-free survival ($P=0.02$) Some authors report that multiple lesions on presentation are due to the delay in the diagnosis of the tumor, resulting in an eventual worse prognosis [3].

Size has been associated with poor prognosis, the larger the lesion, the more difficult it is to achieve negative margins. Most of the published works, have reported difficulties to achieve negative margins due to size, multifocality and the diffuse growth of the tumor. Farhood et al. [22], reported positive margins in more of 50% of patients during wide surgical excision. Despite surgical margins status is considered an important predictor factor for local relapse and overall survival, some authors have reported that negative margins have not been statistically associated with improved survival [5]. The use of postoperative radiation therapy has reported that decrease local relapse rates. Due to the poor results obtained with surgery alone, radiation therapy is considered a necessary adjuvant treatment. Although some authors report that radiation therapy provides no benefit, others have suggested that surgery combined with radiation therapy improves the prognosis. In the study of Pawlik et al. [5] patients who received radiation therapy had a median survival almost 4 times longer than patients who did not receive radiation therapy (36.1 months vs. 9.2 months respectively; $P=0.033$).

In conclusion, angiosarcoma is an aggressive mesenchymal tumor that may appear in any part of the body, but has predilection for head and neck, mainly in the scalp. At early stages, its apparently benevolent behavior mimicking benign lesions, make an important delay in its diagnosis; but over time, angiosarcoma becomes rapidly aggressive, growing and reaching larger sizes, sometimes making the tumor unresectable. The diagnosis is made through biopsy and immunohistochemistry with CD31 and factor VIII-related antigen stains. Surgery remains the cornerstone of treatment, followed by radiation therapy. Despite the treatment received by the angiosarcoma, it has great local relapse rates and poor overall-survival.

Author's Contribution

All the authors participated in the treatment of the patients, collection of cases details, literature search and drafted the manuscript. The authors have read and approved the final manuscript.

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