

Angiosarcoma Scalp: An Under-Reported and Under-Discussed yet Aggressive Entity

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Abstract

Angiosarcoma is a rare malignant soft tissue sarcoma and carries a very poor prognosis because of its multifocal and aggressive behaviour. Angiosarcoma most commonly occurs in head and neck region but can involve any organ of the body. This often occurs in elderly males with a male preponderance. It may mimic benign vascular region clinically but as the lesion grows with time it may ulcerate a wedge biopsy provides the diagnosis. Surgical excision is so far described as a best treatment modality and radiation treatment and chemotherapy are used as an adjunct to surgical excision. An excision with positive resection margins on histopathological examination cannot be complemented with the adjuvant radiation therapy and re- wide excision needs to be considered as there are always chances for the disease recurrence. Chemotherapeutic agents claim to improve response rates and overall survival in a metastatic angiosarcoma. Molecular researches have shown the presence of biological molecules in the lesion and hence targeted chemotherapeutic agents may prove to be useful in some cases though no randomised trials are there in literature till date to prove the use of targeted agents in angiosarcoma scalp. Recent animal studies have been shown to have longer progression free survival with the use of combination β - adrenergic blocker and metronomic chemotherapy.

Keywords: Angiosarcoma; Chemotherapy; Malignant; Targeted Agents; Biological Molecules

Introduction

Angiosarcomas are a rare malignant soft tissue sarcoma and arise from both vascular and lymphatic endothelium. These lesions comprise of 1-2% of all sarcomas and 5.4% of cutaneous soft tissue sarcoms [1]. More than two-thirds of angiosarcomas are cutaneous and majority of these are reported in head and neck region with special predilection to face and scalp though any viscera of the body can get affected [2-4]. Angiosarcoma of scalp is a multifocal disease and may

involve skin extensively and wide local excision to achieve negative margins free may become technically difficult and challenging quite often. These are highly aggressive sarcomas and hence their prognosis is dismal too, despite offering aggressive and multimodality treatment. A 5-year survival of 10-54% in non-disseminated cases is reported [5,6]. Surgery is the most effective treatment for localised and resectable head and neck angiosarcomas with the radiation therapy reserved for high grade and recurrent cases. Chemotherapy is usually indicated for metastatic cases where Epirubicin and Dacarbazine based regimen

are utilised, though there is no standardised chemotherapy regimen has been proposed so far and no prospective randomized studies have been conducted to provide treatment guidelines for angiosarcoma of face and scalp [1]. In this review we aim to briefly review the literature on angiosarcoma scalp where all the multimodality treatment options will be discussed briefly to improve loco-regional control and survival as well.

Epidemiology

Angiosarcomas as such is more common in older age group though it has also been reported in younger age group as well but incidence further increases beyond 50 years with a predilection towards male sex and it's a very fatal disease. Angiosarcoma accounts for less than 2% of all cases of soft-tissue sarcoma and less than 1% of cases of head and neck cancer [3]. Angiosarcoma accounts for approximately 5% of cutaneous soft tissue sarcomas [7]. Due to the rarity of the disease angiosarcomas are often diagnosed very late. The incidence of angiosarcoma has increased over past three decades which could be attributed to environmental changes, increased use of radiotherapy and public awareness.

Etiopathogenesis

Majority of the times etiology is not known and it's idiopathic where these lesions usually arise spontaneously but few reports support their malignant transformation from benign vascular lesions. However, some factors are proposed to play a causal role such as prior radiation exposure, chronic lymphedema (Stewart-Treves syndrome), and exposure to chemicals such as polyvinyl chloride, thorium dioxide, arsenic, and radium [8]. Radiotherapy is an independent risk factor although radiation induced angiosarcoma best described in case of breast cancer therapy where sarcoma develops 5-10 years following completion of adjuvant radiation therapy [9].

Clinical Presentation

Angiosarcoma scalp can mimic a bruise initially or a raised popular lesion and is a multifocal and when it can be mistaken for a simple benign lesion delaying the diagnosis. With time size of the tumor increases and it may ulcerate and bleed as well and present as a fungating, ulcerated, foul discharging lesion on scalp [10]. Angiosarcoma may also metastasize hematogenously and lung being the most commonly involved viscera where it can lead to pleural disease, pleural effusion or pneumothorax apart from multiple parenchymal pulmonary metastases. Other sites to be involved in later stages are liver, bone and distant lymph nodes [11].

Classification

Angiosarcoma can occur in any region of the body and is sub-divided into various groups depending upon the endothelial component of origin such as; lymphoma associated angiosarcoma, cutaneous angiosarcomas, radiation-induced angiosarcomas, soft-tissue angiosarcomas etc [10].

Pathologic Characteristics: microscopically these lesions are pleomorphic and arise from malignant endothelial cells and are usually well-differentiated but poorly - differentiated type is also reported and refers to an aggressive tumor biology which carries very poor prognosis. Poorly-differentiated tumors have areas of necrosis and haemorrhage which makes diagnosis very critical. Mitotic bodies are common and appear as small clusters of erythrocytes within the cytoplasm of abnormal endothelial cells. In many poorly differentiated cases, continuous sheets are formed by malignant endothelial cells with areas of haemorrhage and necrosis within and make discrimination from malignant melanoma difficult [12]. Immunohistochemical markers may be helpful in differentiating these angiosarcoma from malignant melanoma where CD 34, CD 31, von Willebrand factor (VwF) and Vascular endothelial growth factors (VEGF) and U europaeus agglutinin-1 favors the diagnosis of the former one and most useful among these are CD 31 and U europaeus agglutinin- 1 [1].

Prognostic Factors

Primary soft-tissue sarcomas are associated with a 5-year survival of 50-60%, but angiosarcomas have 5-year survival of only upto 35% [13]. Researchers suggest that poorly differentiated and high grade tumors are associated with poor prognosis. Other factors of poor outcome are old age, metastatic and recurrent disease, angiosarcoma of liver, head and retroperitoneum [5].

Diagnosis

Definite diagnosis is mandatory before offering any treatment. Biopsy with histological confirmation is necessary and contrast enhanced CT scan is required to evaluate lung and to rule out metastatic disease. Integrated PET- CT scan may be useful to detect metastasis [14].

Multimodality Treatment Approaches

Angiosarcoma is a highly aggressive malignant tumor with a high rate of loco-regional recurrence and tends to metastasize at an earlier stage. There are no randomised trials published in literature to recommend guidelines for

managing angiosarcoma scalp and hence no evidence based approach can be drawn for specific angiosarcoma subtypes. So far, surgical resection with tumor free margin is the preferred and the best described method of choice for angiosarcoma scalp. Adjuvant radiation therapy is employed as a adjunct to reduce the loco-regional recurrences and to improve local control. Taxane based chemotherapeutic agents taxanes have been shown to improve survival and used in combination with surgery followed by radiotherapy; however the role of chemotherapy is still not well defined and accepted [15].

Surgical Excision

Goal is to achieve complete (R0) resection. Positive margins are common because of invasiveness and multifocal nature of angiosarcoma scalp. Choi et al suggested that wide local excision with intraoperative frozen examination of lateral and deep margins with neck dissections in selected subset of patients is the minimum acceptable surgical treatment. In their study neck was addressed in cases where clinical assessment or imaging revealed cervical lymph node involvement. Large scalp lesions may be reconstructed using free flap and split thickness skin grafting. Free myocutaneous flaps are described for this purpose and most common of these is Latissimus Dorsi myocutaneous flap where thoracodorsal pedicle is anastomosed with superficial temporal artery and vein or occipital vessels depending upon the location of raw area [16]. Revision surgery in locally recurrent disease to achieve a pathological complete resection may improve survival [17].

Radiation Therapy

As angiosarcoma scalp has high risk of local recurrences and therefore adjuvant radiation therapy, with large doses (>50 Gy) involving wide treatment fields in radiation portal is recommended [18]. Whole scalp irradiation is rarely indicated however it may be employed in certain situations where scalp skin is extensively involved such as in scalp angiosarcoma [19]. Sparing critical structures such as optic nerve and underlying neural tissue may be challenging while delivering an adequate target dose with a uniform dose distribution to extensive superficial scalp [19]. Photon beam techniques have been investigated in order to spare brain and neural tissue [20]. Wojcicka et al. in 2009 compared qualities of a LINAC-based photon IMRT and lateral electron-photon technique and reported superior dose homogeneity and sparing of critical structures including the optic nerve and the brain for the IMRT-based approach. 3D-conformal radiotherapy produced hot spots in the brain but it spared optic structures

whereas brachytherapy imparted highest doses to the brain and optic nerve system; however, it was the most conformal treatment plan earlier [21]. Nonrandomized controlled trials have been done to certify the efficacy of radiation but retrospective studies suggest that it not only improves loco-regional control but also improves overall survival in selected cases [19].

Chemotherapeutic Considerations

Angiosarcomas are notorious for loco-regional and systemic metastases and the majority of recurrences i.e; 75% occur within 24 months of the primary treatment. In a Japanese series of 55 cases of angiosarcoma, multimodality treatment i.e; surgery and chemotherapy with or without radiation therapy was shown to be of better prognosis [22]. Authors have reported encouraging results of 15 cases of periorbital angiosarcoma where neoadjuvant chemotherapy was administered [23]. However, there is no convincing evidence to suggest the role of systemic chemotherapy in neoadjuvant setting of angiosarcoma scalp.

Metastatic Angiosarcomas

These are usually treated with systemic chemotherapy which in majority of the cases is either Taxane based or Anthracycline based such as; Docetaxel or Dacarbazine are used on weekly doses. Liposomal doxorubicin and paclitaxel have also been reported to be useful in angiosarcoma [24]. A large meta-analysis suggested the effect of anthracycline-based chemotherapy on overall response rate and median overall survival which were 26% and 51 weeks respectively [25]. In a larger retrospective study of 32 patients of angiosarcoma scalp, progression free survival of 7.6 months was reported following the use of Paclitaxel [26]. In another study, researcher has shown survival of 38 months following multiple lines of chemotherapy for metastatic Angiosarcomas [27].

Targeted Agents

Broad spectrum tyrosine kinase inhibitors against VEGF have been assessed in phase II trials, where 37 cases of angiosarcoma were treated with Sorafenib [28]. Partial responses were seen in four patients and complete response in one case and median progression free survival of 3.8 months was observed. In another study of Sorafenib, median progression free survival of 4.7 months and overall survival of 13.5 months was attained [29]. Bevacizumab as a single agent have also been tried in 29 patients, where 3 patients had partial responses and 13 had stable disease [30].

Novel Advances in Treatment

Oncologically acceptable wide local excision is the standard of care for local disease. There is no randomized trial available and as a result; no evidence-based recommendation can be made for specific angiosarcoma subtypes. However the efficacy of anti-angiogenic agents, such as sorafenib and bevacizumab have been tested in small case series, but promising results have not been shown [28,30]. Recently published preclinical and clinical evidence support the use of β -adrenergic receptor blockers [31]. Use of Propranolol in combination with metronomic therapy and radiation therapy in metastatic angiosarcoma scalp has reported tumor regression with overall survival benefit [32,33].

Conclusion

Angiosarcomas is though, very rare malignant tumor but yet adjuvant and optimal treatment policies has not been standardised and nor the follow up protocol are proposed so far in literature unlike other malignancies. However, a multimodality approach of wide excision and radiotherapy is broadly accepted as the upfront standard treatment where chemotherapeutic agents may be added for metastatic cases. Antiangiogenic agents such as Thalidomide and Endostatin may play some role in survival improvement of metastatic angiosarcomas but their role still needs to be defined and large- scale trial are required to demonstrate their efficacy in the metastatic.

Contributors

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Conflicts of Interest

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