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Editorial

Angiosarcoma: Current Perspectives

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Editorial

Angiosarcoma is a rare soft-tissue sarcoma derived from endothelial cells. It accounts for approximately 1-2% of soft tissue sarcomas, and has an increased incidence in the elderly. This increase in the elderly is associated with a high degree of genetic complexity, similar to the genetic complexity seen in other tumors of the elderly. Other unusual characteristics of angiosarcoma compared to other sarcomas is that is has common mutations, but not a characteristic translocation that defines the malignancy. Many sarcomas, i.e. rhabdomyosarcomas, synovial sarcomas, Ewing's sarcoma and others have well characterized translocations that are used to define the malignancy. These translocation induced malignancies also characteristically occur in younger patients. Finally, angiosarcoma is often due to environmental mutagenic exposures, such as vinyl chloride and radiation therapy [1]. This well known association has led to another classification, that of primary angiosarcoma, that arises de novo, and secondary angiosarcoma, which arises from another lesion after environmental mutagenesis.

Angiosarcomas are unusual in humans, and especially in children. Syndromes associated with angiosarcoma include Aicardi's syndrome, an X linked condition associated with severe mental retardation and agenesis of the corpus callosum [2]. Angiosarcoma can affect any organ, but in humans, the skin and liver are the most common sites. However, angiosarcoma is relatively common in dogs, with a primary occurrence in the spleen. Predisposing conditions to cutaneous angiosarcoma include lymph edema, often after mastectomy, and radiation therapy. Post-irradiation therapy angiosarcoma has been historically called Stewart-Treves syndrome, and a precursor lesion has been observed, called atypical vascular proliferation [3-6].

Considerable confusion exists about the term angiosarcoma. There are other proliferative vascular lesions and malformations, including Kaposi's sarcoma, hemangioma, hemangioendothelioma, and others, but for the purpose of this review, angiosarcoma should be defined as a high grade malignancy with invasive and metastatic potential, which does not undergo spontaneous resolution like hemangiomas of infancy. Kaposi's sarcoma is histologically different and is associated with KSHV [7]. The literature of the 1920s to the 1960s is mostly descriptive, with case reports of angiosarcoma in virtually every organ. In the early 1960s, reports of angiosarcoma arising after long latency periods after Thorotrast injection started appearing in the literature [8]. Later, hepatic angiosarcoma was shown to be epidemiologically associated with vinyl chloride use [9].

Oncogenes and Tumor Suppressors in Angiosarcoma

Angiosarcoma is a genetically heterogenous neoplasm, so many oncogenes and tumor suppressors have been found to be mutated in angiosarcoma. Mutated Kras was the first oncogene to be discovered in angiosarcoma, and was identified in angiosarcomas arising from patients exposed to Thorotrast and vinyl chloride. A recent study has identified mutations in all three forms of Ras, Hras, Kras, and Nras. Myc amplifications have been observed primarily in radiation induced angiosarcoma, more so than in primary angiosarcoma. Most recently, a R707Q hotspot mutations in the *PLCG1* gene (3 and mutations in *PTPRB* have been demonstrated [10]. The study of Murali et al found that myc amplification appeared to be mutually exclusive to loss of p16ink4a [11]. In addition to myc amplifications in radiation induced angiosarcoma, Flt4 amplification was also noted in this group. Tumors with p53 mutation showed a UV signature and appeared to be mutually excluded from the radiation induced tumor group 11. In an epithelioid sample of angiosarcoma in younger patients, translocation of CIC genes was observed. These tumors have endothelial markers but lack vasoformative elements [12]. A rare cause of hereditary cardiac angiosarcomas is mutation of the protection of telomeres 1 (POT1) gene. This mutation leads to increased length and fragility of telomeres [11,13].

Mutations in PTPRB tend to be nonsense or frameshift mutations, causing inactivation of PTPRB [10]. PTPRB is also known as Vascular Endothelial Protein Tyrosine Phosphatase (VE-PTP) and negatively regulates the tie-2 receptor, so inactivation of PTPRB would be expected to increase the activity of tie-2. The PLCG1 gene encodes the enzyme phospholipase C gamma 1, which catalyzes the formation of inositol 1,4,5-trisphosphate and diacylglycerol from phosphatidylinositol 4,5-bisphosphate. This enzyme is activated by multiple angiogenic factors and is mutated in other cancers in addition to angiosarcoma. Blocking this enzyme is a logical druggable target for tumors with mutations in PLCG1. Of interest, treatment of a metastatic angiosarcoma with sunitinib resulted in the generation of metastatic tumors with novel R707Q mutations in PLGC1, implying that chronic blockade of VEGF signaling causes selection of VEGF independent signaling pathways [14].

Given the role of Ras oncogene mutation in angiosarcoma, we created a murine model of angiosarcoma through the sequential introduction of a temperature sensitive SV40 large T oncogene and oncogenic Hras [15]. The cells with the single oncogene are called MS1 cells and form small dormant tumors in mice. The ras containing tumors are aggressive and cause rapid growth and lung metastasis. This system has been extremely useful in the study of signaling events in angiosarcoma. We found that blockade of phosphoinositol-3 kinase (PI3K) by wortmannin led to decreased tumor growth in vivo, and this was the first in vivo demonstration of the role of PI3K inhibition

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on solid tumors *in vivo*. [15]. Blockade of MAPKK signaling by a dominant negative MAPKK or pharmacologic MAPK inhibitor led to morphologic reversion of ras transformed angiosarcoma cells. However, blockade of MAPKK led to a more aggressive in vivo phenotype, and this was the first demonstration of tumor promotion as a result of MAPK blockade [16]. This phenomenon has been observed clinically, in that patients treated with Braf inhibition with vemurafenib often develop squamous cell carcinomas of the skin. Overexpression of VEGF in MS1 immortalized endothelial cells results in malignant transformation to angiosarcoma [17]. This demonstrated that a VEGF-VEGFR2 loop plays a role in angiosarcoma, and led to trials of VEGF inhibitors in angiosarcoma [17]. The immune system plays a role in the pathogenesis of angiosarcoma, and both CD4 and CD8 T cells play a role in the control of angiosarcoma. We found that depletion of CD8 cells in mice that had knockouts in CD28, CD40, and CD40 ligand allowed SVR cells to grow in syngeneic C57BL6 mice. Thus, CD4 mediated rejection has a greater dependence of co stimulation than CD8 mediated rejection [18]. This may well be relevant given the relative immunosuppression of the elderly.

Treatment of Angiosarcoma

The rarity of this disease has precluded extensive highly powered studies, as seen in more common cancers like breast and lung. Surgery and radiation remain mainstays of treatment, but with significant disadvantages. Angiosarcomas are often not fully resectable because of extensive spread that is not clinically visible, and metastasis is common. In addition, primary angiosarcoma may appear in vital organs such as the heart. Angiosarcoma is moderately sensitive to radiation, but multifocal and metastatic disease limits the efficacy of therapy. The discovery of autocrine VEGF-VEGFR2 signaling in angiosarcoma led to the use of VEGF directed therapies in the treatment of angiosarcoma [17]. These include bevacizumab, in the presence or absence of adjuvant chemotherapy [19], and small molecule inhibitors such as sunitinib [14]. Inhibitors of PLCG1 are not currently available clinically, and the major compound used in laboratory studies is an aromatic steroid U 73122. Currently, I know of no companies targeting PLCG1 for development. The discovery of propranolol, a beta blocker, in the treatment of hemangiomas, has resulted in its use for angiosarcoma as well 19. Angiosarcomas, like hemangiomas, have been shown to express beta adrenergic receptors [20]. In a recent small series of seven patients, the combination of propranolol and metronomic chemotherapy (low dose vinblastine and methotrexate) led to increased progression free and overall survival compared with historical controls. The efficacy of this approach requires validation with more patients.

Currently, chemotherapy plays a major role in the treatment of angiosarcoma, given that it is usually a systemic disease at the time of presentation. The most common chemotherapeutic regimens are taxanes and doxorubicin, including liposomal doxorubicin [21]. The role of the VEGF inhibitor Avastin in angiosarcoma is not fully understood. A recent trial of the combination of Paclitaxel with or without Avastin did not show a major advantage of the combination versus Paclitaxel alone [22]. Finally, small molecule tyrosine kinase inhibitors have been employed against angiosarcoma with variable results. These include sorafenib, sunitinib, and most recently pazopanib, which inhibits multiple tyrosine kinases including VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-/, and c-kit [23-26,27].

There is evidence that angiosarcoma is an immune responsive tumor. A high level of intratumoral CD8 lymphocytes was associated with increased survival in a Japanese series of angiosarcoma [28]. The presence of tumor infiltrating lymphocytes in angiosarcoma was positively correlated with survival and inversely correlated with FasL expression [29]. Finally, expansion of tumor infiltrating lymphocytes has been used to treat a case of advanced angiosarcoma [30]. Angiosarcomas have been found to arise around chronic foreign bodies. These include Dacron grafts and chronic internal hematomas [31-33].

Angiosarcomas are tumors most commonly in the elderly, and resemble the mutagenic pattern of common epithelial tumors of the elderly rather than the translocations seen in traditional sarcomas. Most sarcomas occur in a younger population and likely have a lower mutational burden than angiosarcomas. Several mutagens and predisposing factors have been found to contribute to the development of angiosarcoma, including chemical carcinogenesis (vinyl chloride, Thorotrast), UV irradiation, X irradiation, chronic lymphedema, and chronic irritation from foreign bodies. The incidence of angiosarcoma is expected to rise as our patient population ages. There are a few common mutations in angiosarcoma, and these mutations may be druggable, notably PLC gamma. The high mutational burden seen in angiosarcomas indicates that these tumors, like other tumors with high mutational burden (ie melanoma), may be amenable to novel immunotherapeutic approaches. Our previous studies have indicated that both CD4 and CD8 lymphocytes control angiosarcoma growth. Future approaches to angiosarcoma therapy will likely be multidisciplinary, with potential neoadjuvant therapy to make tumors resectable. Diffuse disease may be treated with a combination of chemotherapy, radiation, and immunotherapy and the precise sequence will need to be guided by future preclinical and clinical studies.

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