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Clinical and Molecular Biology of Angiosarcoma

N.J. Andersen[1], R.E. Froman[1], B.E. Kitchell[2] and N.S. Duesbery[1]
[1]*Laboratory of Cancer and Developmental Cell Biology, Van Andel Research Institute Grand Rapids,*
[2]*College of Veterinary Medicine, Michigan State University East Lansing, Michigan, USA*

1. Introduction

'*Skepticism is a healthy response to diagnosis of any tumor as angiosarcoma.*' (Lane, 1952)
Angiosarcoma (AS) is an aggressive malignancy of vascular tissue or vessel forming cells (Requena & Sangueza 1998). AS is rare in humans, making up 1-2 % of soft-tissue sarcomas (Young et al. 2010) and having an estimated incidence of 0.2/100,000 persons per year. Although AS can present anywhere in the body, in humans they typically arise in the skin or superficial soft tissues. It is most frequently noted on the face and scalp of elderly men where their persistent growth causes ulceration and infection, as well as on breasts, and extremities (Brennan et al. 2001; Fayette et al. 2007; Glazebrook et al. 2008). Less frequently AS arises in liver, heart, and spleen (Young et al. 2010). The literature is replete with retrospective analyses and case studies on AS but the rarity of patients diagnosed with this disease makes it difficult to perform more than a superficial investigation on the biology and clinical behavior of AS. However, the occurrence of AS is not restricted to humans and there are several alternative animal models with the potential to inform human studies. We have written this review to collect, compare, and contrast diverse reports on the biology and treatment of AS in humans and alternative animal models. Our objective is to establish a comparative framework to focus further discussion and scientific enquiry.

2. Types of AS

While there is general agreement angiosarcomas arise from endothelial cells, its causes are uncertain. There appears to be no single cause of AS in humans; rather, a variety of factors have been reported to contribute to risk of disease. Broadly speaking the causes of this disease may be classified as environmental, familial, and iatrogenic.

2.1 Environmental AS

Chronic exposure to any of several environmental risk factors has been linked with AS. Each of these directly or indirectly induce genetic mutations and alter gene expression. Vinyl chloride was first identified as an AS inducing compound when it was noticed that industrial plastic and synthetic rubber manufacturers as well as beauty salon personnel had

an elevated incidence of AS. Exposure to vinyl chloride was the only common element identified in both populations (Creech & Johnson 1974; Infante et al. 2009; Sahmel et al. 2009). Vinyl chloride was used for the production of industrial resins and as a hairspray propellant. Interestingly, vinyl chloride increases the rate of hepatic AS because vinyl chloride is a carcinogen that is predominantly directed towards hepatic endothelial cells. The metabolism of vinyl chloride produces reactive metabolites that form pro-mutagenic DNA adducts (reviewed by Bolt (2005)).

Chronic exposure to arsenic in pesticides or in a traditional medicinal tonic (Fowler's solution) has also been linked to hepatic AS (Centeno et al. 2002; Falk et al. 1993). The precise mechanism(s) of arsenic carcinogenesis is uncertain, although it appears to act in an epigenetic fashion rather than as a classical mutagen, causing pleiotropic cellular effects that promote tumorigenesis (reviewed by Flora (2011)).

No link between AS and UV exposure has been documented. However, there are published case reports of xeroderma pigmentosum patients developing cutaneous AS. Xeroderma pigmentosum is a rare autosomal recessive disease causing defects in nucleotide excision repair; the patients are sensitive to UV radiation and are at higher risk for developing skin cancers (de Boer & Hoeijmakers 2000; Kraemer et al. 1987). Whereas cutaneous AS normally develops in older patients with a mean onset of 63 years (Aust et al. 1997), cutaneous AS in xeroderma pigmentosum patients appears to have an earlier onset, ranging from 13 to 40 years with a mean of 19.2 years (Arlett et al. 2006; Arora et al. 2008; Ludolph-Hauser et al. 2000; Marcon et al. 2004; van Geel & den Bakker 2009). Further work is needed to establish whether there is a role for UV as a causative agent of cutaneous AS.

2.2 Iatrogenic AS

There are several examples of AS being induced as a consequence of prior medical treatment. Exposure to Thorotrast® (colloidal thorium-232 dioxide) has been linked to hepatic AS. Thorotrast® was used in the United States from the 1930's through the 1960's as a radiographic contrast compound to visualize blood vessels. Upon injection, Thorotrast is absorbed by bones, liver, spleen, and lymph nodes where it has a high bioavailability and releases alpha particles for imaging. While useful as an imaging agent, Thorotrast® was found to have unanticipated toxicities. Because it has a long biological half-life, patients were exposed to high levels of ionizing radiation for extended (lifelong) periods (Autenrieth & Lange 1979; Kiyosawa et al. 1989). Thorotrast® exposure has also been associated with increased risk of other cancers including hepatic ductal carcinoma and leukemia (Johnson et al. 1977; Looney 1960).

Radiotherapy is an infrequent but well-recognized risk factor for AS (Botros et al. 2009; Fury et al. 2005; Miura et al. 2003). A study of 274,572 breast cancer patients in the SEER Cancer Incidence Public-Use Database (Yap et al. 2002) found that incidence of a subsequent sarcoma while low, was modestly elevated in patients receiving breast irradiation compared to patients not receiving such therapy (87/82,296 [0.0011%] versus 176/192,276 [0.0009%] respectively). Further, whereas AS accounted for approximately 6% of subsequent sarcomas in unirradiated patients, it represented almost 60% of cases within a previously irradiated field (Yap et al. 2002). It seems radiation therapy not only increases the incidence of secondary malignancies but also changes the spectrum of tumors associated with treatment. These results were consistent with a prior study using the same SEER database that showed increased incidence of AS in irradiated breast cancer patients versus unirradiated patients (Huang & Mackillop 2001).

However, a recent retrospective study of Finnish cancer patients showed different results (Virtanen et al. 2007). Surveying more than 300,000 cancer patient records accrued over a 50-year period, Virtanen et al. (2007) failed to identify a statistically significant association of AS with prior radiation treatment. These results agree with an earlier Swedish study of 122,991 women with breast cancer that showed no statistically significant correlation between radiation therapy and angiosarcoma, although they did observe a correlation with lymphedema (Karlsson et al. 1998). The Finnish research team did note a five-fold increase in AS among women with breast or gynecologic cancers when compared with the rest of the population. However, while the SEER-based studies focused on the incidence of subsequent sarcoma within the irradiated field of women with breast cancer, the Finnish study examined incidence irrespective of radiation field within a mixed population of men and women treated for several tumor diagnoses. Thus, the latter studies may have failed to demonstrate a statistically significant association between AS and radiotherapy because they were underpowered.

Chronic lymphedema is another risk factor for AS. The most well known form is Stewart-Treves syndrome, in which lymphedema presents in the adjacent arm after radical mastectomy (Stewart & Treves 1948). Although rare, AS is also associated with other chronic lymphedema disorders such as Milroy disease and elephantiasis (Hallel-Halevy et al. 1999; Offori et al. 1993). It is not immediately apparent why failure of lymph node drainage should promote AS. One possibility is that edema restricts perfusion and induces an ischemic response involving endothelial proliferation. If this were the case one might expect to see increased incidence of AS in association with peripheral arterial disease. However, such an association has not been reported. Alternatively, edema-mediated changes may create a permissive microenvironment allowing phenotypic expression of an otherwise masked trait that promotes endothelial proliferation.

2.3 Familial AS

Although patients with Von Hippel-Lindau disease show increased incidence of cranial hemangioblastoma (Kaelin 2007), no highly penetrant, causal mutation for AS in humans has been reported. This should not be interpreted as an indication that hereditary factors do not influence the risk of developing AS, but that the incidence of AS is so low that identifying such genetic factors may be exceedingly difficult. However, indirect evidence supports a role for hereditary factors in the onset or progression of AS. The incidence of all vascular tumors appears to be increased in offspring whose parents were diagnosed with kidney cancer, nervous system hemangioma, or hemangioblastoma, and AS of the trunk and extremities has been associated with maternal breast cancer (Ji & Hemminki 2007). Moreover, there is strong evidence for breed and strain-specific predisposition of AS in mice and dogs (see below).

3. Clinical features

3.1 Presentation

The presentation of AS is tied to the site of occurrence. In cutaneous AS, tumor may begin as a bruise-like bluish coloration or a red nodular rash (Lane 1952; Morgan et al. 2004). It can also present as purplish multicentric lesions as seen in Stewart-Treves syndrome (Stewart & Treves 1948). Unfortunately due to the innocuous appearance of the initial dermal lesion, a large percentage of patients initially disregard the lesion and as a consequence have

systemic disease at the time of ultimate diagnosis (Morgan et al. 2004). For visceral and cardiac disease, AS most often presents as organ failure. Cardiac AS patients commonly have atrial fibrillation, malaise, and resting tachycardia (Ge et al. 2011; Matzke et al.). Splenic AS presents with splenomegaly (enlarged spleen) or abdominal pain and fatigue from splenic rupture (Falk et al. 1993); these patients may also have cytopenia, leukocytosis, and thrombocytosis. Hepatic AS patients initially present with jaundice and may also experience abdominal pain and fatigue (Mahony et al. 1982; Valenzuela et al. 2009).

3.2 Diagnostic pathology

There are two subtypes of angiosarcoma defined by pathology. Angiosarcoma is classically defined by a growth of spindle-shaped endothelial cells (Figure 1). In 1982, Weiss and Enzinger described a new subtype, epithelioid AS, with large rounded or polygonal cells that have an epithelial-like morphology (Weiss & Enzinger 1982). In reality, most tumors have a mixture of both spindle and round endothelial cells (Morgan et al. 2004). Angiosarcoma tumors classically consist of sheets of endothelial cells with multiple irregular anastomosing channels. These channels can be perfused and blood-filled or void and can be lined with a single or multiple layers of atypical endothelial cells (Koch et al. 2008; Ohsawa et al. 1995; Yang et al. 2010). Areas of hemorrhage and necrosis are also common in AS (Armah et al. 2007; Ge et al. 2011; Gong et al. 2011; Neuhauser et al. 2000; Ohsawa et al. 1995; Yang et al. 2010). Low grade lesions display irregular vascular channels lined with atypical endothelial cells in single or multiple layers (Koch et al. 2008). High-grade lesions are comprised of sheets of undifferentiated, pleomorphic cells which can make them difficult to distinguish from carcinomas (Koch et al. 2008). High grade lesions also have large areas of hemorrhage. There is no clinical or survival advantage between low- and high-grade lesions. Definitive diagnosis is made by biopsy and immunohistochemistry with antibodies against the endothelial marker CD31 and Factor VIII-related antigen. Staining with antibodies against von Willebrand's factor II and CD34 may also be used to confirm a diagnosis of AS (Ohsawa et al. 1995).

3.3 Differential diagnosis

Cutaneous AS can initially be misdiagnosed as bruising, multiple different skin infections, and even insect bites. It is the duration and spreading of the lesion that prompts concern. Cutaneous AS is similar in appearance to another endothelial derived malignancy, Kaposi sarcoma. Kaposi sarcoma is a virus-induced cancer (Chang et al. 1994; Kemeny et al. 1996). Both Kaposi sarcoma and AS can be multicentric skin lesions with spindle cell pathology (Morgan et al. 2004; Nickoloff & Griffiths 1989). To further complicate the diagnosis, a percentage of Kaposi cells are CD31 positive and up to half of AS cells are positive for the endothelial lymph factor podoplanin by immunohistochemistry. However, only Kaposi sarcoma are positive for the presence of Kaposi's sarcoma causative virus (Human Herpes Virus 8) by immunohistochemistry using antibodies against Latency nuclear antigen-1 (LANA-1) or by amplifying viral DNA by PCR (reviewed in (Mesri et al. 2010; Schmid & Zietz 2005)). Cutaneous AS may also be confused with irregular growths of superficial vasculature or benign hemangiomas, mostly seen in infants (Lawley et al. 2005). These vascular malformations are commonly referred to as port wine stains or angel kisses. These may be distinguished from visceral AS by immunohistochemistry with antibodies against the Wilms tumor 1 transcription factor (Ge et al. 2011; Lawley et al. 2005).

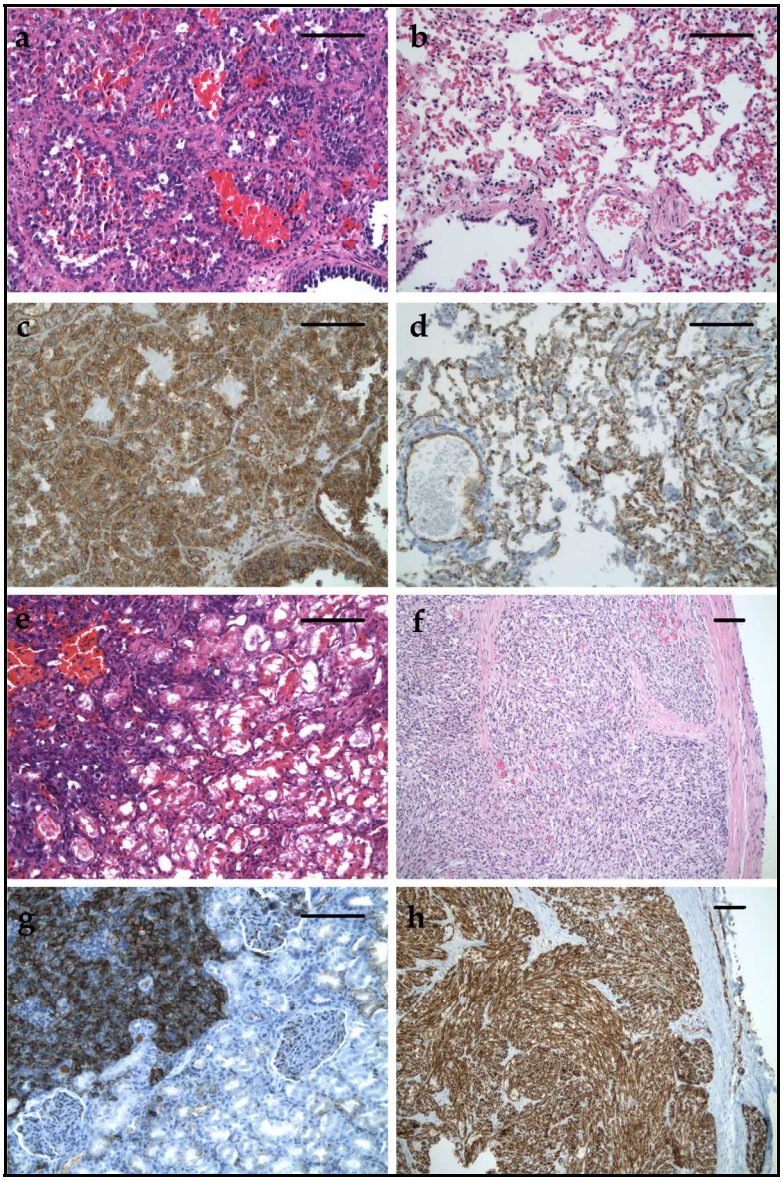

Fig. 1. **Histology of human and canine angiosarcoma.** Stained with Hematoxylin and Eosin (a,b,e,f) or immunostained with antibodies against CD31 (c,d,g,h) both human (a, c) and canine (b, d) splenic angiosarcoma as well as canine kidney angiosarcoma (e, g) show extensive networks of endothelial (CD31 positive) cells with multiple irregular anastomosing channels filled with blood. In contrast this canine cutaneous angiosarcoma (f, h) shows a highly vascular tumor with spindle-shaped CD31-positive endothelial cells. Bars = 100 micrometers.

The main discernible clinical sign of splenic AS is splenomegaly (Neuhauser et al. 2000; Thompson et al. 2005). Any known cause of spleen enlargement is a differential diagnosis for splenic AS. This includes but is not limited to lymphoma or infection (reviewed in (Pozo et al. 2009; Suzuki et al. 2010)). In addition, visceral disease often presents with vague flu-like symptoms such as malaise and abdominal pain (Falk et al. 1993).
Since the epithelioid AS subtype is defined by endothelial cells that have a large, round cell morphology similar to that of epithelial cells, AS may be confused with a carcinoma (Lin et al. 2010; Weiss & Enzinger 1982). However, epitheloid AS cells stain positive for CD31 and Factor VIII on immunohistochemistry (Fletcher et al. 1991; Lin et al. 2010).

3.4 Prognosis and treatment

Over the years AS treatment has changed very little. The usual treatment for primary AS is surgery followed by high-dose radiotherapy either alone or with doxorubicin-based chemotherapy. Even with such interventions survival rates are poor. In addition, there is no current standard of care based on disease subtype or location.
Surgery is the mainstay for the treatment of primary AS. Surgical intervention is limited to local control and is not recommended for widely disseminated disease. Current guidelines call for total surgical resection of the tumor with wide negative margins to reduce re-occurrence (Lahat et al. 2009; Mendenhall et al. 2006). However, the multicentric nature of cutaneous AS and its proximity to vital organs in visceral disease makes achieving complete tumor resection difficult. In a review of head and neck soft tissue sarcomas, positive margins were found in 50% of patients (Farhood et al. 1990).
Survival rates after surgery alone are poor (Holden et al. 1987). While the addition of postoperative radiotherapy improves survival, there are drawbacks to radiation. Effective radiation treatment requires wide radiation fields and often doses of more than 50 Gy to achieve tumor control (Mark et al. 1996; Pawlik et al. 2003). Furthermore, radiotherapy is not recommended for radiation-induced AS (Mark et al. 1996).
Doxorubicin is considered the most efficacious chemotherapy agent for local and metastatic AS but provides minimal tumor control or survival benefit. The response rate to doxorubicin has been reported to be 16 - 36%. In addition, doxorubicin causes long-term damage to the heart at cumulative total doses over 400 mg/m^2 of body surface area (Chlebowski 1979). To reduce cardiotoxicity, doxorubicin can be encased in liposomes, reducing the amount of free doxorubicin (Cattel et al. 2003). Liposomal doxorubicin treatment of soft tissue sarcomas has equivalent activity but fewer adverse effects relative to free doxorubicin, and thus it is included in the current National Comprehensive Cancer Network guidelines for the treatment of soft tissue sarcomas (Judson et al. 2001). However, the lipid envelope increases doxorubicin absorption and retention by the skin. Side effects of liposomal doxorubicin may include dermal rash or sores on the palms and soles of the feet called palmar-plantar erythodysesthesia (Judson et al. 2001; Lorusso et al. 2007). The latter can be severe enough to require a dosage decrease, treatment interruption, or termination of treatment (Lorusso et al. 2007).
Other adjuvant treatments are reported to have had minimal success. The use of taxanes such as paclitaxel to treat AS has increased. In a small study of 9 patients, 8 responded to paclitaxel (Fata et al. 1999). A 32-patient retrospective paclitaxel study documented a 62% response rate with one complete response. A 30-patient prospective study demonstrated a 19% response rate after 6 months with 3 complete responses with surgery and a median

overall survival of 7.6 months (Penel et al. 2008). Paclitaxel did show a subtype specificity; the response rate in head and neck AS was 75%, while for other primary tumor locations the response rate was 58%. The median time to progression of head and neck disease was 9.5 months compared with 7 months for AS of other primary sites (Schlemmer et al. 2008). In another study, scalp AS had a progression-free survival of 6.8 months, but only 2.8 months of progression free survival was documented for AS arising below the clavicle (Fury et al. 2005). In comparison to spontaneous tumors that have a median survival expectation of nearly 9 months, radiation induced AS are more resistant to paclitaxel treatment and have a median overall survival of less than 6 months (Penel et al. 2008). Paclitaxel has also been used as a neoadjuvant therapy to decrease primary tumor size prior to surgery for splenic AS (Vakkalanka & Milhem 2010).

4. Etiology

4.1 Cellular origins

The origin of AS tumor cells is still unknown. Angiosarcoma tumors are generally thought to arise from endothelial cells. The majority of cells stain positively for the endothelial cell markers: CD31, CD34, and Factor VIII-antigen. However, up to 70% of CD31 positive AS cells are also positive for the lymph endothelial marker podoplanin (Breiteneder-Geleff et al. 1999). This suggests contributions of both lymph and vascular endothelium in AS. Alternatively, the tumor microenvironment may differentiate a population of undifferentiated endothelial cells to lymph or vascular-like endothelium.

Cancer stem cells or cancer progenitor cells have been documented in a variety of tumors, but the presence of angiosarcoma cancer stem cells is not known. Interestingly, Wnt1 was recently found to be expressed and activated in AS cells. Furthermore, Wnt1 increases endothelial progenitor cell (EPC) proliferation and EPC-dependent angiogenesis (Gherghe et al. 2011). These data suggest a possible role of EPCs in AS tumorigenesis and tumor angiogenesis through a Wnt1 mechanism. As of yet, no study has clearly determined the role of EPCs in tumorigenesis, and the importance of tumor stem cells in AS tumorigenesis is still unknown.

4.2 Molecular biology

Angiosarcoma has no clearly defined causative mutation or chromosomal changes, but genomic abnormalities including chromosomal deletions, amplifications, and rearrangements, have been identified in a variety of these tumors. In general, the karyotypes of AS are complicated and display both clonal and non-clonal chromosomal changes. The breadth and variety of aberrations suggest they may represent chromosomal alterations from unbridled cell proliferation. The importance of these mutations or gene amplifications for tumorigenesis and tumor development is not known. The most common aberrations involve the loss of heterozygosity of chromosome 22 (Gil-Benso et al. 1994; Kindblom et al. 1991; Quezado et al. 1998; Schuborg et al. 1998; Wong et al. 2001; Zu et al. 2001). The genes of both platelet-derived endothelial cell growth factor (PD-ECGF) and the tumor suppressor NF2 mapped to chromosome 22 (Kindblom et al. 1991) but the significance of this observation has not been explored. Losses of the short arm of chromosomes 4 and 7 are also common in AS (Wong et al. 2001). MYC amplification has been found in radiation-induced AS tumors that have an 8q24 gain (Guo et al. 2011).

The loss of tumor suppressor function likely plays an important role in AS development. The tumor suppressor p53 is mutated in a subset of AS tumors. In cardiac AS, mutant p53 is overexpressed and localizes to the nucleus (Hollstein et al. 1994; Soini et al. 1995; Zu et al. 2001). Mutations in p53 codons 141 and 136 were identified in a small cohort of hepatic AS (Soini et al. 1995) and mutations in p53 codons 249 and 255 have been associated with vinyl chloride exposure (Hollstein et al. 1994). Other studies indicate the INK4a-ARF locus is frequently inactivated in liver AS independent of p53 mutations (Weihrauch et al. 2002). Mutations in the PTEN tumor suppressor have also been identified in hepatic AS; an exon 7 mutation codes for a premature stop codon resulting in a nonfunctional protein (Tate et al. 2007).

Activating mutations in key signaling molecules promote AS tumorigenesis. K-Ras2 mutations have been associated with AS (Marion 2005; Przygodzki et al. 1997) and have been detected in hepatic AS after exposure to vinyl chloride (Weihrauch et al. 2002). Ten percent of AS tumors showed activating KDR (VEGFR2) mutations (Antonescu et al. 2009). Also, 25% of a 20 patient study of radiation-induced AS showed a co-amplification of FLT4 (VEGFR3) and MYC (Guo et al. 2011).

Interestingly, vascular endothelial specific cadherin (VE-cadherin) is absent or decreased in AS (Martin-Padura et al. 1995; Tanioka et al. 2001; Zanetta et al. 2005). Loss of VE-cadherin may promote AS growth in several ways. Like other cadherins, VE-cadherin interacts with and retains β-catenin at adherens junctions. Through this mechanism, cadherins indirectly control the free (cytoplasmic) pool of β-catenin. Free β-catenin can be transported to the nucleus to regulate transcription. Thus, loss of VE-cadherin may represent a pathway to induce cancer gene dysregulation. Retention of β-catenin at adherens junctions by VE-cadherin has been inversely correlated with vascular tumor growth and hemorrhage (Zanetta et al. 2005). During angiogenesis, endothelial cells detach and invade surrounding tissue, where they replicate and branch into a vascular network. The loss of VE-cadherin may facilitate angiogenesis. In addition, change in the cadherin profile of cells, or cadherin switching, has been implicated in tumor cell invasion and metastasis (reviewed in Maeda et al. (2005)). Whether cadherin misregulation in AS cells explains the invasive and metastatic nature of AS is not known.

5. Insight from other sources

The rarity of angiosarcoma has restricted the scope of basic and clinical research on this disease. In this section we will discuss experimental models for generating further insight into the biology and treatment of AS, including the study of more common (but related) human tumors, genetically engineered or chemically induced mouse models, and the emerging relevance of studies of naturally occurring AS in companion dogs.

5.1 Related tumors in humans

5.1.1 Kaposi sarcoma

The similarity between Kaposi sarcoma (KS) and AS may provide a foundation for understanding pathways vital for AS tumorigenesis and development. Like AS, KS is an endothelial cell-derived tumor, but Kaposi is derived from lymphatic endothelial cells. Kaposi sarcoma is a vascular tumor characterized histologically by a high degree of angiogenesis and the presence of proliferating spindle cells (Brash & Bale 2001). The spindle cells act in a paracrine fashion, releasing pro-inflammatory and angiogenic factors,

including VEGF, which are necessary to promote KS lesions. Kaposi sarcoma is caused by human herpes virus 8 (HHV8 or KSHV; (Ablashi et al. 2002; Chang et al. 1994)). The expression of a single viral gene encoding a constitutively active G-protein coupled receptor (vGPCR) in endothelial cells is sufficient to induce angioproliferative tumors in mice that closely resemble human KS (Montaner et al. 2003). Among other functions, Kaposi sarcoma vGPCR has been demonstrated to activate the mitogen- and stress-activated protein kinases MAPK1/2 and p38 MAPK in a variety of cell lines (Arvanitakis et al. 1997; Bais et al. 1998; Burger et al. 1999; Cannon et al. 2003; Cannon & Cesarman 2004; Sodhi et al. 2000). Significantly, KS vGPCR-induced expression of VEGF depends upon increased activity of both MAPK1/2 and p38 MAPK (Bais et al. 1998; Sodhi et al. 2000). Since these are direct downstream targets of mitogen activated protein kinase kinases (MKKs) (Lewis et al. 1998), MKKs present an attractive potential therapeutic target for treatment of AS. In support of this we have observed that when mouse endothelial cell tumor xenografts expressing vGPCR are treated with a proteolytic inhibitor of MKK tumor growth is blocked and vascularization is decreased (Depeille et al. 2007). MEK inhibitors tested in clinical trials for a variety of tumors, most notably melanoma, have not shown marked efficacy (Lee & Duesbery 2010). However, these drugs target only MEK1 and 2, leaving other MKK signaling pathways intact.

The similarity between Kaposi sarcoma and AS raises interesting questions regarding the etiology and molecular biology of AS. Are there spindle cell equivalents in AS that release cytokines and drive tumor growth? Could AS also have a viral origin? Indeed, several other human cutaneous cancers have viral origins (e.g. Merkel cell carcinoma and polyomavirus, squamous cell carcinoma and HPV) and viruses can cause AS in mouse models (see below). Moreover, similar to iatrogenic KS, cases of AS have been reported to develop in kidney transplant patients taking immune suppressants (e.g. Farag et al. (2005) and references therein). Evidence for a viral origin of AS has been sought through detection of HHV8 viral expression sequences. However, an initial report showing evidence of an HHV8 sequence in a subset of AS (McDonagh et al. 1996) was contradicted by subsequent studies (Lasota & Miettinen 1999). Though it appears HHV8 does not play a role in the origin of AS, we can not yet rule out a viral contribution to AS tumorigenesis.

5.1.2 Hemangioma

Hemangiomas are benign growths arising from vascular endothelial cells. In hemangiomas, endothelial cells form a tortuous network of blood vessels. These lesions are common in newborns as strawberry patches or port wine stains. The causative mechanism of growth is unknown, but serum levels of VEGFA and HIF-1alpha are elevated in children with hemangiomas (Kleinman et al. 2007) suggesting hypoxic signals may be driving AS growth. Hemangiomas have been successfully treated with the beta-blocking agent propranolol (Leaute-Labreze et al. 2008; Sans et al. 2009). While the mechanism of action is not known, Sans et al. (2009) speculate that propranolol inhibits beta-adrenergic receptors expressed in endothelial cells, and in this manner down-regulates MAPK signaling and VEGF release.

5.2 Similar tumors in other species

The incidence of AS has been documented in a variety of species. For discussion purposes we have separated these into 1) genetically engineered or chemically induced AS models and 2) spontaneous or naturally occurring AS.

5.2.1 Induced angiosarcoma

Mice develop AS in response to a viral infection, toxicologic treatment, or genetic manipulation. Study of the common properties or convergent signaling of these diverse agents may reveal a unified mechanism for AS induction.

Viral Infection – Injection of Moloney mouse sarcoma virus (Stoica et al. 1990; Yuen et al. 1991), Harvey Sarcoma virus (Chesterman et al. 1966; Harvey 1964), or Kirsten Sarcoma virus (Pitts et al. 1983) into mice or rats induces the formation of angiomatous lesions resembling angiosarcoma or Kaposi's sarcoma. These viruses encode mutant, oncogenic forms of cellular oncogenes encoding c-Mos, H-Ras, and K-Ras, respectively. Each of these genes stimulates cellular proliferation and oncogenic transformation by activation of the mitogen-activated protein kinase (MAPK) signaling pathway.

Toxicologic treatment – Rodent bioassays have been used to identify several carcinogenic compounds capable of inducing angiosarcoma (reviewed by Cohen et al. (2009)). Some of these compounds react with DNA, acting in a manner similar to vinyl chloride or Thorotrast. Others, such as 2-butoxyethanol, are non-genotoxic and act indirectly through production of reactive oxygen species and cytokines to stimulate endothelial cell proliferation (Corthals et al. 2006; Kamendulis et al. 2010; Klaunig & Kamendulis 2005).

Genetic manipulations – Mice engineered to express knock-in mutations (D1226N or Y1228C) in the activation loop of Met develop a high incidence of angiosarcoma with moderately pleiomorphic endothelial cells, cavernous blood vessels, and palisading epithelioid-like cells (Graveel et al. 2004). Met is a tyrosine kinase receptor for the hepatocyte growth factor/scatter factor and is a potent activator of the MAPK signaling pathway, regulating among other things the epithelial-to-mesenchymal transition and metastatic behavior (Birchmeier et al. 2003). There are several Met antagonists in clinical trials for a variety of tumors (Eder et al. 2009).

As noted above, the loss of tumor suppressor function likely plays an important role in AS development. Not surprisingly then, loss of tumor suppressor function in mice induces AS formation. Heterozygous deletion of p53 causes a broad-based cancer predisposition in which 57% of mice develop a variety of sarcomas including AS (Jacks et al. 1994). The incidence of AS in p53-null mice is dramatically increased from 15% to 53% when mice are crossed to Wrn^{hel} mice harboring homozygous deletions in the helicase domain of the *Wrn* gene (Lebel et al. 2001). Similarly, p53-null mice crossed with mice lacking alleles of Ink4d and/or Ink4c show as high as 75-85% incidence of angiosarcoma (Zindy et al. 2003). The Wrn protein interacts with p53 to promote genomic stability. The Ink4 proteins bind and inactivate cyclin dependent kinases, preventing cell cycle progression and maintaining cells in a quiescent state.

These data show that genomic manipulation resulting in deregulation of cell cycle control and genomic instability in mice readily promotes endothelial cells to switch to a malignant phenotype. Why then do mice develop AS at such high rates in response to a viral infection, toxicologic treatment, or genetic manipulation? The answer may be linked to unidentified hereditary factors since studies of spontaneous tumorigenesis in mice indicate mice are predisposed to develop AS (see below).

5.2.2 Spontaneous tumors

Mice have a substantially higher incidence of spontaneous AS than do humans, but the incidence varies by strain. In a two-year study of approximately 2000 $B6C3F_1$ mice, Haseman

et al. (1998) noted that 2.5-2.7% spontaneously developed AS. Although AS arose at many sites, the predominant locations were liver (male/female; 0.7/1.1%), spleen (0.7/1.0%), and uterus (0.4%). Similarly, a second study of $B6C3F_1$ mice (Chandra & Frith 1992) noted 4.5/1.0% (male/female) of mice spontaneously developed AS. In contrast CD-1 and Icr:Ha mice have spontaneous rates of AS around 0.7% and 0.4%, respectively (Chandra & Frith 1992; Eaton et al. 1980). The increased incidence in $B6C3F_1$ mice indicates that certain strains are genetically predisposed to develop AS.

Naturally occurring (spontaneous) AS are not restricted to humans and mice. They have been detected in a variety of animals including rhesus macaques (Mejia et al. 2009; Myers et al. 2001), horses (Schultheiss 2004), cows (Sutton & McLennan 1982), ferrets (Schultheiss 2004), dogs (Hargis et al. 1992), cats (Miller et al. 1992), rats (Schultheiss 2004), and snakes (Tuttle 2006). Any of these animals could potentially serve as a surrogate model system for human disease in an experimental context but dogs seem best suited for this purpose. While sharing many features in common with humans as patients, dogs have a much higher incidence of AS and a more rapid time course of disease progression. The canine model also offers some unique, advantageous features distinguishing it from other animal models and opening novel experimental opportunities. First, because of selective breeding, genetic variation within canine breeds is very low. Second, since each breed is derived from a small group of founders, most tracing back approximately 150 years, many of the genes associated with polygenic traits are fixed, so only a few variable genes determine phenotype. This means that it will be much easier to identify genetic disease determinants in dogs than in humans. Finally, companion dogs share the same environmental exposures as humans and thus may more accurately reflect the human condition. The ability to identify, recruit, and study cancers within a breed of dog offers new avenues of hope for research into clinical oncology and the underlying causes of AS (Gordon et al. 2009; Paoloni & Khanna 2008).

6. Canine AS

In contrast to AS in humans, AS is relatively common in dogs, with an overall incidence of 24/100,000 (Dobson et al. 2002). There is substantial variability in the incidence of canine angiosarcoma (cAS, more commonly referred to as hemangiosarcoma) among breeds, with large breed dogs such as Golden retrievers and German shepherds having a much higher incidence. A health survey of Golden retrievers attributed 62% of all deaths to cancer, with cAS representing 16% of reported cancers (Glickman et al. 1999). Why this tumor is more common in dogs than in humans is uncertain. It is possible that disease-causing genes were over-represented in the founding populations for these dogs. Alternatively, genes promoting susceptibility to cAS may have been co-selected along with artificially selected traits in the directed evolution of these breeds. Regardless, the genetic uniformity within breeds offers a unique and unbiased opportunity to identify genes that cause AS.

6.1 Presentation and diagnosis

cAS may present in virtually any tissue of the body, including bone, kidney, skeletal muscle, liver, lung, aorta, urinary bladder, intestine, oral mucosa, tongue, prostate, vulva/vagina, perineum and the cornea, nictitans or conjunctival tissue of the eye (Bergman 2010; Bulakowski et al. 2008; Hargis et al. 1992; Schultheiss 2004; Withrow & MacEwen 1996). Metastasis can involve any portion of the body, including the central nervous system. While most dogs present with splenic or liver lesions, some breeds show elevated incidence of

cutaneous (Whippets, Italian greyhounds) or cardiac (Saluki) cAS (Hargis et al. 1992; Prymak et al. 1988; Schultheiss 2004). This demonstrates that not only do genetic factors influence susceptibility to cAS, but also they determine the location at which the disease will present. From a research perspective, it opens new avenues for discovery of the basic mechanisms of the origin and progression of cancer that could be translated to further our understanding of the etiology, pathophysiology, and treatment of AS in human patients.

Canine AS is the most common malignancy of the spleen in dogs (Spangler & Culbertson 1992). Middle-aged, large (> 20kg) dogs are most prone to splenic cAS. Golden retrievers, German shepherds, and Labrador retrievers are overrepresented, as are other large breeds such as Clumber spaniels. A health survey conducted by the Golden Retriever Club of America/Golden Retriever Foundation reported that 16% of Golden retrievers with cancer die from cAS at an average age of 10 years (Glickman et al. 1999). Mixed breeds are also commonly affected. Dogs with visceral cAS typically present acutely, with profound lethargy, anemia, or sudden collapse. There may be intermittent, nonspecific clinical signs such as inappetance, weight loss and occasional episodes of weakness. Hemoperitoneum most often leads to diagnosis, often on an emergency basis.

Splenic tumor size varies, but the lesions are frequently very large and multinodular, with one to many saccular, blood filled lesions. The tissue is extremely friable, which often leads to spontaneous rupture. It is the acute loss of blood which causes the presenting signs. Dogs may recover from intra-abdominal hemorrhage through resorption of the blood (autotransfusion) and erythrocyte regeneration. However, there will frequently be further hemorrhaging. Anecdotally, more dogs are lost to euthanasia than to spontaneous hemorrhage, as the owners do not wish their dogs to suffer further such episodes.

In contrast to humans, in whom left atrial AS is more frequent (Casha et al. 2002), cardiac cAS most commonly occurs in the right atrium and dogs of the Saluki breed are particularly prone to development of such tumors. Right atrial cAS is also seen in Golden retrievers and German shepherd dogs. Cardiac cAS can be devastating from the outset, with many dogs presenting for cardiac tamponade and signs of right heart failure. The pressure of blood from a ruptured cAS in the right atrium (RA) fills the pericardial sac and leads to extreme respiratory distress, anxiety, and collapse. Alternatively, dogs may simply die acutely from cardiac arrest, and the disease is discovered upon necropsy of what seemed to be an otherwise healthy dog. Many cases are likely never conclusively diagnosed, as necropsy is infrequent in veterinary medicine.

Cardiac cAS are typically red to dark red or purple in color, and ranging from millimeters to centimeters in length. Such tumors are prone to spontaneous hemorrhage, which may lead to pericardial effusion and cardiac tamponade. While no definitive studies have delineated time course for these tumors, anecdotal reports suggest progression may be very rapid. Cardiac cAS can occur with or without splenic involvement and is more likely to present as a solitary lesion in some breeds such as the Saluki. It has not been determined if right atrial involvement is a primary tumor site or reflects a site of metastasis when concurrent visceral disease is present.

As in human AS, cutaneous cAS most often presents as solitary or multiple small dermal masses, which can extend into the subcutis or even into underlying musculature. They are frequently seen on non-haired skin on the ventral abdomen of light-colored dogs (Italian greyhounds, whippets, Dalmatians, pit bulls), especially when those dogs have excess exposure to solar radiation (southern latitudes, tendency towards sunbathing). Cutaneous

cAS may also occur on haired skin of darker colored dogs. Solar elastoses has been associated with cutaneous cAS in a large retrospective study involving many dogs from California practices (Hargis et al. 1992). A more recent retrospective study conducted at the University of Colorado did not confirm this finding (Schultheiss 2004), but the patient population for this study may have been comprised of more dogs from northern latitudes. The geographic location of the patients themselves was not annotated in either of these studies.

The small, solitary or multiple dermal lesions of cutaneous cAS are often less than 1 cm in diameter, but may exceed 3 cm (Hargis et al. 1992). Mitotic figures are usually seen in malignant cAS. Conclusive diagnosis is always via histopathology, regardless of tumor location. Several markers can be used (e.g. CD31, factor VIII, Claudin-5, and cardiac troponin) to aid in confirmation of diagnosis (Chun et al. 2010; Jakab et al. 2009; Shaw et al. 2004; Withrow & MacEwen 1996).

6.2 Differential diagnosis

As in human AS, the differential diagnosis of canine AS varies with the location of the disease. Visceral tumors must be distinguished from other neoplasms such as hemangiomas, other sarcomas, lymphoma, leiomyomas, and hematomas (Jakab et al. 2009). Signs of acute anemia, extreme lethargy, or collapse, requires exclusion of immune mediated hemolytic anemia (IMHA), trauma, coagulopathy, toxin exposure and allergic reaction. One retrospective study reported that among anemic dogs presenting with a splenic mass and abdominal bleeding requiring transfusion, 70% had splenic cAS (Hammond & Pesillo-Crosby 2008). Conclusive diagnosis of cAS requires histopathology of the excised tissue.

Cardiac cAS must also be differentiated from other tumors and from idiopathic pericarditis (IP), both of which can cause pericardial effusion. In one retrospective study conducted in the UK, dogs with cardiac masses detected by ultrasound (echo-positive) had significantly shorter survival times than echo-negative dogs (Johnson 2004). Patients with a discernible cardiac mass, ascites, or collapse had a much less favorable prognosis than patients with IP. Another retrospective study reported that dogs with right atrial cAS treated surgically by pericardectomy and chemotherapy had a mean survival time of 164 days, compared to 46 days for dogs treated by pericardectomy alone (Weisse et al. 2005). However, this report also noted that dogs receiving chemotherapy were significantly younger and had significantly lower white blood cell counts than the dogs that did not receive chemotherapy, so case collection bias was a concern.

Cutaneous cAS must be differentiated from other cutaneous tumors, nevi, and cysts. Histopathology is the only conclusive method of diagnosis. Because dogs may suffer from hemangiomas as well as hemangiosarcomas, and because depth of invasion can be a prognostic indicator, it is recommended that all tumors be submitted for histopathologic examination and confirmation of clear surgical margins.

6.3 Prognosis and treatment

The behavior of cAS is also linked to the site of origin, with visceral lesions being more aggressive than cutaneous lesions (Schultheiss 2004). For visceral disease, the high rate of early metastasis and the lack of early clinical signs or hematologic changes lead to late diagnosis and extremely poor prognosis. The average life span upon diagnosis of splenic cAS is less than three months for dogs treated with splenectomy alone (Spangler &

Culbertson 1992). Dogs treated with adjunctive chemotherapy (usually doxorubicin-based protocols) average less than six months survival (Kim et al. 2007; Sorenmo et al. 2004). Owners frequently elect to euthanize the dog at the time of diagnosis or shortly thereafter.

Cardiac cAS is equally grim, with many dogs dying of acute cardiac arrest prior to any overt clinical signs. This sudden death syndrome is seen particularly among Saluki. Dogs may appear clinically normal and sometimes die in their sleep. Others may develop exercise intolerance, weakness, lethargy, and inappetance prior to developing ascites secondary to cardiac tamponade. One retrospective study of 23 cases of right atrial cAS treated surgically, with or without chemotherapy, reported a mean survival time of 175 days or 42 days, respectively (Weisse et al. 2005). Another retrospective study from the UK which evaluated dogs with pericardial effusion reported a mean survival time of 26 days for dogs with echocardiograms revealing a cardiac mass versus 1068 days for those with effusion but no detectable mass. However, in this study, no dogs with detectable masses had treatment beyond pericardiocentesis, and many were euthanized at diagnosis (Johnson 2004).

In stark contrast is the positive prognosis for cutaneous cAS. A majority of dogs with strictly cutaneous cAS survive many years with local recurrent disease (Schultheiss 2004). Schultheiss reported that complete surgical resection of cutaneous cAS was the most important prognostic factor for survival (Schultheiss 2004). A retrospective study of 25 dogs reported that those with cutaneous cAS confined to the dermis had a mean survival time of 780 days, compared with 172 and 307 days for dogs with a primary tumor involving the hypodermis or underlying muscle, respectively (Ward et al. 1994). Confinement to the dermis also was correlated with better outcome, most likely due to complete surgical resection (Schultheiss 2004).

The response of cAS tumors to treatment varies greatly depending on the site of the tumor. Dogs with splenic tumors survive a few months beyond splenectomy but live longer than those that do not have surgery. Survival time is measured in months regardless of treatment, but owners frequently elect splenectomy for palliative care, extension of quality time, and reduction of the worry regarding continued intra-abdominal hemorrhage. The addition of doxorubicin-based chemotherapy protocols may add a few more months of survival. Single agent doxorubicin, administered intravenously every three weeks for up to five cycles is commonly used if chemotherapy is elected. Alternate protocols include doxorubicin plus cyclophosphamide, or doxorubicin, vincristine and cyclosphosphamide. No protocol is superior. Doxorubicin can induce dose-dependent cardiotoxicities in dogs; the total cumulative dose should not exceed 180-240 mg/m^2. A study evaluating the potential use of epirubicin in splenectomized cAS patients reported no cardiac toxicity *(Kim et al. 2007)*. However, gastrointestinal side effects occurred in a majority of the patients, and neutropenia was also common. The expense of this treatment may also preclude this drug from becoming more commonly used, although it may provide an option for dogs with preexisting cardiac disease *(Kim et al. 2007)*.

Cutaneous cAS is generally treated with complete surgical excision. There are minimal long-term consequences apart from the necessity of multiple surgeries often being required. This is not generally due to recurrence of excised tumors; rather, patients tend to develop tumors spontaneously in multiple sites. It is unclear whether these represent new primary tumors or metastatic disease (Hargis et al. 1992; Ward et al. 1994). Multiple surgeries can create a financial hardship for the owner, and may be the cause for dogs to be relinquished to rescue organizations or euthanized.

6.4 Cell and molecular biology

Molecular insight into cAS is limited and focuses primarily on visceral disease, but what is known is consistent with the biology of human AS. Tumor-derived cell lines and cell isolates express endothelial and hematopoietic stem cell markers, suggesting they may arise from pluripotent bone marrow-derived stem cells and/or cells committed to the endothelial lineage (Fosmire et al. 2004; Lamerato-Kozicki et al. 2006; Tamburini BA 2010; Thamm et al. 2006). Cells form branching vascular structures when grown on Matrigel (Thamm et al. 2006), secrete pro-angiogenic factors including VEGF and bFGF , and express elevated levels of Ang-1 and Ang-2 mRNA (Kato et al. 2006). Upon injection into immune-compromised mice, such cells readily form AS-like tumors expressing endothelial markers including CD31, vWF, VEGF-A, bFGF, flt-1, flk-1, FGFR-1, HoxA9, HoxB3, HoxB7, HoxD3, Pbx1, and Meis1 (Kodama et al. 2009). Although mutations in p53 have not been detected, cAS stain positively for nuclear p53 (Yonemaru et al. 2007). As in the human disease, cAS lesions have been found to harbor point mutations or deletions in the C-terminal domain of PTEN (Dickerson et al. 2005).

7. Conclusions

The rarity of angiosarcoma has had a profound impact on its clinical management and research. Most clinicians are unfamiliar with this disease and thus do not have experience to guide management decisions. Much of the literature regarding these rare tumors is comprised of anecdotal case reports or retrospective analyses which are difficult to assimilate and interpret. Thus, we must be especially wary not to assume all AS are equivalent. The varied morphology and presentation of these lesions indicates we may be dealing with not one, but several diseases with unique physiologic or clinical properties and pharmacologic responsiveness. For instance, it has been reported that tumor behavior might depend on the site of origin, with superficial tumors associating with a longer progression-free survival after initial treatment (Fury et al. 2005; Schlemmer et al. 2008). However, it is unclear whether this is caused by intrinsic biologic differences or differences in clinical presentation and prior treatment. Unfortunately, when AS is examined prospectively in clinical trials it is usually included as a limited number of cases within a larger study of various soft-tissue sarcomas. Further progress in our understanding of the biology and treatment of AS depends on the willingness of the medical research and clinical oncology communities to share resources through multi-center collaborations. In the absence of such efforts, alternative strategies are needed to generate meaningful insight into this disease.

Significant insight into the biology of AS has been generated through translational studies of related human tumors and mouse models. Collectively, studies of Kaposi sarcoma and hemangiomas, plus studies conducted in mouse models provide strong support for the hypothesis that MAPK signaling is a key event in the induction of endothelial cell proliferation and AS in mice and humans. This pathway has been invoked to explain the origins of many other tumor types. MAPK signaling pathways are frequently activated in endothelial cells during developmental and pathologic angiogenesis (reviewed in (Depeille et al. 2007)). Further, MAPK signaling is physiologically activated in response to shear stress (Azuma et al. 2000) and in pre-atherosclerotic plaques (Muslin 2008). A key question that needs to be addressed may therefore be not how these events trigger AS, but why they do not trigger AS more frequently. An examination of the role of MAPK phosphatases in endothelial cells and in AS tumorigenesis may be instructive.

However, important questions remain to be asked and answered. What are the key biochemical pathways involved in this disease? Does misregulation of MAPK signaling by phosphatases allow constitutive signaling to promote tumorigenesis? Do genetic mutations contribute to or establish a microenvironment that predisposes scalp, spleen, liver, or heart to develop AS? Why is angiosarcoma infrequent in humans, while it is more prevalent in dogs? Can we identify molecular targets for drug therapies? Can we devise a fundable and meaningful clinical trial to test novel therapies for such a rare disease? Will the use of spontaneous animal tumor models prove useful in informing human clinical trials?

The canine model is of growing interest in this regard since it closely resembles human disease. Studies of spontaneous cAS offer a clear experimental advantage through genome-wide association studies of single nucleotide polymorphisms that provide an unbiased approach to identify the genes contributing to the onset and progression of disease in a compressed time frame. This, combined with the availability of tumor material and the presence of multi-institution consortia such as the Canine Comparative Oncology and Genomics Consortium, the LUPA consortium, the Canine Hereditary Cancer Consortium, and the Canine Oncology Trials Consortium, may facilitate rapid identification and translation of novel therapies through clinical trials that may benefit dogs and humans alike.

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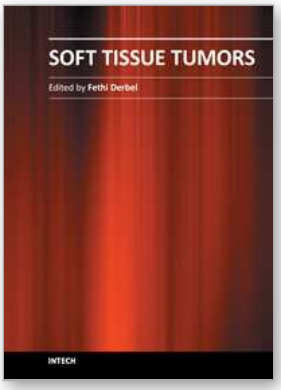

Soft Tissue Tumors

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Soft tissue tumors include a heterogeneous group of diagnostic entities, most of them benign in nature and behavior. Malignant entities, soft tissue sarcomas, are rare tumors that account for1% of all malignancies. These are predominantly tumors of adults, but 15% arise in children and adolescents. The wide biological diversity of soft tissue tumors, combined with their high incidence and potential morbidity and mortality represent challenges to contemporary researches, both at the level of basic and clinical science. Determining whether a soft tissue mass is benign or malignant is vital for appropriate management. This book is the result of collaboration between several authors, experts in their fields; they succeeded in translating the complexity of soft tissue tumors and the diversity in the diagnosis and management of these tumors.

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Phone: +86-21-62489820
Fax: +86-21-62489821