International Journal of Current Research and Academic Review

ISSN: 2347-3215 Volume 3 Number 1 (January-2015) pp. 35-45

www.ijcrar.com

Analysis of Morphological and Immunohistochemical Patterns of Angiosarcomas of Bone and Soft Tissues

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KEYWORDS

Angiosarcomas, CD 31, and immuno-histochemical

A B S T R A C T

Angiosarcomas in bone and soft tissues are rare tumors and are characterized by an aggressive course and they form a diagnostic challenge, in view of varied histomorphology. The present study is a comprehensive analysis of clinicopathological features, including immunohistochemical (IHC) profile of a series of angiosarcomas of bones and soft tissues. Ninety six cases of musculoskeletal and soft tissue angiosarcomas were analysed. On review clinical, histopathological and immunohistochemical features of 96 angiosarcoma cases, diagnosed during a period from January 2002 to December 2010, at a tertiary hospital, India, were analyzed with outcome. Statistical analysis was carried out using SPSS (version 14). Disease free survival (DFS) was calculated by Kaplan-Meir analysis at the end of 1 year. IHC analysis included vascular markers like CD31, CD34, and Factor VIII-related antigen and cytokeratin. Sixty-eight cases were identified in men and 28 in women (M: F = 2.42:1), with age ranging from 11-81 years (mean = 48.7 years). More cases were identified in > 40 years age (75 cases, 78.12%) group. The commonest presentation was an enlarging, painful soft tissue mass in 66 cases (71.8%); anemia in 12 cases (12.5%) and coagulopathy in 4 cases (4.16%). Fifty three cases (55.2%) occurred in the soft tissues, most commonly in the scalp (15 cases, 26%); while 43 cases (%) in the bones, (44.7%), commonest in the humerus (11 cases, 23.9%). Multifocality was seen in 5 cases (5.2%). Grossly, tumor showed 'reddish-brown' cut surface with tumor size varying from 2–14 cm. Average tumor (T) size was 7.9 cm, with 84% cases having T size between 5–10 cm. Ninety three cases were of high grade (96, 96.8%) and three cases were of low grade and of the 40 cases in which follow up was available 30 cases were up G2/T1 with metastases (75%) and 10 cases (25%) were of G2/T2 with metastases. 100 % cases underwent surgery, including wide excisions and amputations (R0) in 40 cases of bone angiosarcomas, and marginal excisions (R1) in 3 cases. 71 (73.95%) cases underwent adjuvant treatment. Out of the 40 cases in which follow up were available (100%) showed recurrences and showed metastasis. Median survival was 12.03 months for males and 11.4 months for females and 13.06 months for angiosarcomas of bones and 11.4 months for soft tissue angiosarcomas. 40 cases in which follow up was available with T size > 5 cm, and with high grade (P = 0.18) and stage (P = 0.00) showed recurrences, metastasis, and death. Microscopically, commonest histologic pattern was vasoformative (78 cases 81.25%), followed by retiform, solid and papillary patterns, with predominantly, spindly cells in 86 cases (89.58%) and epithelioid in 10 cases (10.41%). On IHC, CD31 was positive in 77/96 cases (80.21%); CD34 in 29/45 cases (55.93%) and Factor VIII-related antigen in 12/ 46 cases (26.08%) and cytokeratin positivity in 6/12 cases (50%). Angiosarcomas have varied histomorphology. Its objective identification necessitates the incorporation of clinicopathological features and IHC with CD31 and CD34. A diverse morphology with vasoformative, as the commonest "pattern" and spindly forms as the commonest cell type was noted. CD31 was found to be the most useful IHC marker for an angiosarcoma.

Introduction

Angiosarcoma of bone is a rare malignant tumor. It represents less than 1 percent of primary malignant neoplasms in the bone (Mirra, 1989; Huvos, 1991; Fechner and Mills, 1993) and 2 % of the soft tissue sarcomas. The average age group affected is 35-40 years and sex ratio is 1.7: 1.Similarly to hemangioma and hemangio-endothelioma, its benign and borderline malignant counterparts that originate in the intraosseous blood vessels, angiosarcoma of the bone may be solitary (unifocal) or multicentric (multifocal). Multi-centricity is observed in 20 to 50 percent of cases and consists of multiple lesions in a single bone, in the same extremity, or throughout the skeleton. When involves adjacent bones it is multifocal, contiguous and noncontiguous when bones more than one joint away is involved. The characteristic pattern of bony involvement is clustering of lesions in a single limb or in a single anatomic region such as the shoulder or hip (Mirra, 1989; Huvos, 1991; Fechner and Mills, 1993; Wold *et al.,* 1982). 33% of these tumors occur in the axial skeleton, 33% in long tubular bones, and the rest in the small bones of the hands and feet. An occasional case of angiosarcoma has been reported to develop in bone infarcts (Abdelwahab *et al.*, 1992) and in Paget's disease (Dorfman *et al.,* 1971). Clinically, patients with angiosarcoma of the bone initially seek medical help with dull local pain and swelling followed by an aggressive course with rapidly developing metastases. Sometimes, swelling and increased size of the affected limb due to affectation of a superficial bone or to soft tissue extension characterize the presentation. Pathologic fractures occur in 10% of patients.

A comprehensive overview of bone and soft tissue angiosarcoma has not been obtained, and the similarities and differences among angiosarcomas in different sites have not been thoroughly studied. This study aims to analyse the standard histopathological features and to correlate with immuno-histochemical (IHC) features of a series of bone and soft tissue angiosarcomas.

Materials and Methods

This is a retrospective analysis of the cases diagnosed as angiosarcoma over a period of 10 years (2000–2010). Hundred and seven cases of angiosarcomas of bone and soft tissues were retrieved from the database. On review 96 cases were included and analyzed and 11 cases were deleted because of inadequate histopathological material. The demographic data, clinical details, and the treatment modalities were studied. The period of follow-up ranged from 1 month to 10 years and the data was analyzed with reference to the outcome (using Kaplan Meier survival analysis). Cases were accepted for the study only when there was adequate histologic material and clinical information. Of the total 96 cases, follow-up details were available in 40 cases (41.6%) and outcome details were obtained in 40 cases (41.6%). Clinical charts of the patients and the hospital data information system (DIS) were accessed for various clinicopathological parameters, including chief complaints. The documentation of treatment details, tumor recurrence, multifocality, and metastasis was made. The diagnostic material included "in-house" operative specimens as well as specimens from peripheral hospitals in the form of paraffin blocks and slides and/or specimens. The specimens included excision biopsies; wide excisions; and amputations. Details regarding tumor location, gross examination, and tumor (T) size in the largest dimension, circumscription and gross marginal status were noted. Surgical excisions were

categorized as Rx, R0, R1, and R2. While Rx was considered as an excision lacking marginal status, R0 was a resection with free gross and microscopic margins, R1 was grossly free, but microscopically positive margin, and R2 excision comprised, both, grossly and microscopically positive margins. The staging for bone and soft tissue sarcomas, the 2 most commonly used staging systems are those developed by the AJCC and by Enneking. These systems for soft tissue sarcomas rely on an ability to determine accurately both the local and distant extent of disease.

- Ia - Low grade, intracompartmental G1/T1/M0
- Ib - Low grade, extracompartmental G1/T2/M0
- IIa - High grade, intracompartmental G2/T1/M0
- IIb - High grade, extracompartmental G2/T2/M0
- IIIa - Low or high grade, intracompartmental G1-G2/T1/M1 with metastases
- IIIb - Low or high grade, extracompartmental G1-2/T2/M1 with metastases

Ninety three angiosarcomas were high grade G2. Based on tumor size and metastases, 30 angiosarcomas were of stage G2/T1 with metastases and 10 angiosarcomas were of G2/T2 with metastases. Conventional hematoxylin and eosin (H and E)-stained sections were available in each case.

The microscopic slides were examined, and the following features were specifically evaluated: depth of involvement (*i.e.,* skin, subcutis, muscle); histologic pattern (especially the proportion of vasoformative and solid areas); pleomorphism, graded as none. slight, moderate, or marked mitotic figures per 10 high-power fields and inflammatory infiltrate, graded as none, slight, moderate, or marked, with type(s) of inflammatory cells and presence or absence of lymphoid germinal centers noted. The patients' charts were reviewed separately from the histologic evaluation, and the following data were obtained: age (at diagnosis): sex: race: predisposing factors (*i.e.,* previous surgical procedures, previous radiotherapy, lymphedema, and vascular stasis): location; symptoms; clinical appearance; and therapy. IHC analysis included vascular markers like CD31, CD34, and Factor VIII-related antigen. Formalin-fixed paraffin-embedded sections were immunostained with endothelial cell markers (CD31 and CD34) using the streptavidin-biotin-peroxidase method. In brief, 5 micron thick sections were incubated with 3% hydrogen peroxide to quench endogenous peroxidase activity. The sections were then incubated for 1 hour at room temperature with mouse monoclonal antibodies to detect TM (TM 1009, 7.8 _g/ml), EPCR (1489,0.2 mg/ml),9 CD31 (DAKO, Carpinteria, CA), and CD34 (DAKO) expression, respectively.

Microwave heat-induced antigen retrieval in citrate buffer, pH 6.0, was required for optimal staining with the anti-CD31 and anti-CD34 antibodies. Primary antibody incubation was followed sequentially by biotinylated horse anti-mouse antibody (Vector Laboratories, Burlingame, CA) for 20 minutes, then streptavidin-peroxidase complex (DAKO) for 30 minutes. For negative controls, a monoclonal mouse IgG1 was used at equivalent concentration. Diaminobenzidine was used as chromogen

and hematoxylin was used for nuclear counter stain.

Statistical analysis

Chi-square and Fisher's exact tests were used for descriptive analyses. Overall survival (OS) was calculated from the date of diagnosis to the date of death or last news; progression-free survival (PFS) was calculated from the date of diagnosis to the date of first local or metastatic progression, or death, or else to the date of last news, using the method of Kaplan–Meier. The data were analyzed using SPSS software.

Results and Discussion

Out of the total ninety six cases, sixty eight cases were identified in men and twenty eight in women (M: F = 2.42:1), with age ranging from 11-81 years (mean = 48.7 years). The median age for males was 49 years and for females 55.5 years. The commonest presentation was an enlarging, painful soft tissue mass in 66 cases (71.8%); anemia in 12 cases (12.5%) and coagulopathy in 4 cases (4.16%). Fifty three cases (55.2%) occurred in the soft tissues, most commonly in the scalp (15 cases, 26%); while 43 cases (%) in the bones, (44.7%), commonest in the humerus (11 cases, 23.9%). Multifocality was seen in 5 cases (5.2%). Based upon differences in presentation, location and depth of tumor, the cases fell into six groups. Forty three angiosarcoma cases occurred in the bones (44.7%), commonest was in humerus (11 cases n=96, 23.9%). Nineteen cases of angiosarcoma occurred in the scalp and skin (21.8%), and two cases in the nose, in organs heart 7 cases, brain 2 cases, lungs 3 cases and liver 6 cases. Another group in which neoplasm was deeply situated one case in the mediastinum and five because the location was unusual, although not deep, two in the axillary subcutis, two in the gluteal region and one in inguinal region. One case each in the colon and mesentery. The last and sixth group was one case each in larynx and tongue. Grossly, maximum cases showed 'reddish-brown' cut surface with tumor size varying from 2–14 cm.

Tumor location and size

Tumor location is shown according to clinical group in Table No 1**.** Bone angiosarcomas were 43, out of which 12 measured between 5–10 cm in diameter and 19 were less than 5 cm in diameter and in two cases the gross tumor size was >10 cm. Nineteen angiosarcomas were located on the scalp and skin which measured less than 5 cm in diameter and two cases measured 6.5 cm in diameter.

In parenchymal organs like heart 7 cases, brain 2 cases, lungs 3 cases, liver 6 cases out of which 9 measured less than *5* cm in greatest extent, and nine cases were larger measuring between 5-10 cm. Mediastinum and soft tissue of axilla, gluteal region, back and inguinal region 3 cases measured 5 cms and 3 cases between 5–10 cm in diameter. Two cases in the Larynx and tongue measured <5 cm in diameter, two cases in the colon and mesentery measured between 5–10 cm.

Predisposing factors

The patients were involved in a wide variety of occupations, both indoors and outdoors, and had a range of skin complexion types from fair to black. One patient in this group was a man who had received external radiation for squamous cell carcinoma of the left pyriform sinus and then developed angiosarcoma in the skin and subcutaneous tissue over the larynx eight years later. The post mastectomy and lymphoedema

associated cases were excluded from the study.

Clinical findings

The most common presenting complaint throughout this series was a painful rapidly growing mass. Only five patients cited pain or tenderness as a specific reason for initial concern, and three of these were in the miscellaneous group (mediastinum, inguinal region, and axilla). One patient with extensive facial involvement reported pain early in the course of the disease. The duration of symptoms before biopsy ranged from one to five weeks and differed little among the clinical groups and fourteen of 25 patients on whom peripheral blood count available had eosinophilia of 5 to 15%.

Microscopic findings

The pattern of tumor growth showed remarkable variation within individual cases. Microscopically, commonest histologic pattern was vasoformative (78 cases, 81.25%), 4 with retiform pattern (4.16%), 4 cases with nonsolid growth pattern (4.16%), 10 cases showed areas of solid growth (10.41%). The solid areas consisted of sheets of epithelioid cells. Four cases (4.16%) of nonsolid growth were found: an infiltrating pattern in which individual tumor cells extended between preexisting collagen bundles or fat cells; a papillary vasoformative pattern demonstrating irregularly shaped spaces and papillary projections.**;** a nonpapillary vasoformative pattern consisting of discrete round or elongated spaces lined by neoplastic cells and a sieve like pattern showing a network of vascular channels not separated by stroma. These patterns typically blended imperceptibly into one another, although occasionally the solid nests were well defined and had pushing borders. 86 cases had predominantly spindle cells and epithelioid cells in 10 cases. Most cases showed no or only slight nuclear pleomorphism, but a few of the tumors contained cells with enlarged, irregularly shaped nuclei and were judged to have moderate or marked pleomorphism. Two cases of angiosarcoma demonstrated cords and channels formed by plump to flattened cells within a prominent, loose, fibrous stroma. The mediastinal tumor was somewhat similar, but had plumper cells, smaller lumina, and less abundant stroma. Mitotic activity varied tremendously within individual cases, but was most marked in the solid areas. Mitotic figure counts (per 10 high-power fields) ranged from 3 to 4 in predominantly vasoformative neoplasms to as many as 150 in one predominantly solid scalp tumor; the distribution of high and low rates was relatively even throughout the different clinical groups. Eighty six cases were classified as high grade angiosarcoma and 10 cases as epithelioid angiosarcomas. Only 24 angiosarcoma cases showed a slight tumor associated lymphocytic infiltrate, two cases demonstrated a moderate infiltrate.

Immunohistochemical profile

Table No 2 shows IHC profile of angiosarcomas. CD31 was positive in the cytoplasm of the malignant cells in 77/96 (73.92%), CD34 showed cytoplasmic positivity in 33/59 (55.93%), Factor VIII showed cytoplasmic positivity in 12/46 (11.52%), pancytokeratin positivity was seen in 6/10 (40%) cases.

Rates of local recurrence, uncontrolled recurrence and metastasis

Uncontrolled recurrence refers to the presence of locally recurrent tumor at the time of death. As the data demonstrate, not only was local recurrence a frequent finding,

but it also was difficult to treat the recurrence successfully. Cases in which local tumor was known to remain after initial therapy were considered to have a time to recurrence of zero, and those in which metastases were present at the time of therapy were designated as having a time to metastasis of zero.

In bone angiosarcomas out of the 43 cases in which follow up was available 18 had recurrence and metastases, in scalp and face skin and nose 8 recurred with metastases out of 21 cases, and in soft tissues and organs 14 out of 29 underwent recurrence and metastases.

Overall survival and survival by clinical group

Median survival for patients with bone angiosarcomas was 13.06 months and with soft tissue angiosarcomas 11.4 months. The differences among the survival time in different groups were not statistically significant (P = 0.06 and 0.1, respectively). None of the patients had long-term disease free survival.The PFS of the series was 10 months. In univariate analysis, PFS and OS were significantly worse in metastatic patients as compared with patients with local disease.

Survival and tumor behavior by tumor size

Tumor size was shown to be an important prognostic indicator. Some of the larger tumors (>5 cm) were not amenable to surgical therapy, and, thus, local control was never achieved even transiently. However, the location of the tumor demonstrated some prognostic significance in that group, with distal tumors allowing somewhat better survival than proximal tumors (P = 0.12).

Survival and tumor behaviour by microscopic findings

No correlation could be found between survival and two time-honored markers of malignant behavior, rate of mitotic activity and percentage of solid or "undifferentiated" neoplasm. The histologic variable most strongly associated with the length of patient survival proved to be the degree of lymphocytic inflammation admixed with and surrounding the tumor. Recurrence (mean 13 months, range 4–16 months for moderate to marked inflammation; versus mean 4.0 months, range 1–6 months for no or slight inflammation), and to metastasis (mean 12 months, range 2–14 months for moderate to marked inflammation: versus mean 7.5 months. Range 1–18 months for no or slight inflammation), but also to a somewhat lower absolute rate of metastasis 54 cases in which follow up was available and in which microscopically there was no inflammatory response 38 had recurrence, metastases and death (70.3%) and 16 cases in which there was moderate inflammation 12 had recurrence, metastases and death (22.2%). Out of the 40 cases in which there was no pleomorphism 20 (50%) had recurrence, metastases and death and which there was moderate pleomorphism 7 out of 10 cases (70%) showed recurrence, metastases and death.

Pleomorphism, showed lesser prognostic significance. Those cases graded as “none” or “slight” had somewhat better survival than those graded as “moderate” or ”marked”, but the difference was not statistically significant (P = 0.08). The rate of metastasis was somewhat lower in cases with less pleomorphism, but the mean intervals to recurrence and metastasis were comparable in both categories.

Survival and tumor behavior by type of initial therapy

Most patients in all groups were initially treated surgically, although a few received chemotherapy also as the first treatment. Median survival of patients who were treated surgically and with chemotherapy was 12.03 months and patients who received only surgical treatment median survival was 11.2 months. The surgical resections and amputations were all R0 with all margins negative. Various combinations of excision, amputation, and chemotherapy failed to prevent early recurrence or metastasis in the cases in which follow-up data was available.

Location of metastases by clinical group

A propensity for metastasis to regional lymph nodes was noted particularly in the scalp-face group, and all groups showed evidence of widespread (hematogenous) metastases.

Angiosarcomas are relatively rare neoplasm. On histology, they are suspected frequently since many lesions have a very angiogenic component. The tumors which were confirmed as angiosarcomas in our study on the basis of morphology and immuno-histochemistry were analysed and compared with other studies. Radiologically, the lesions are purely osteolytic with minimal periosteal reaction. The overlying cortex is partially or totally eroded, with an occasional zone of sclerosis surrounding the tumor. In advanced cases, cortical permeation is associated with soft tissue masses (Mirra, 1989; Huvos, 1991; Fechner and Mills, 1993; Wold *et al.,* 1982). These radiographic appearances in the case of solitary angiosarcoma are completely nonspecific and solitary plasmacytoma, medullary fibrosarcoma, or osteolytic metastasis from an unknown primary tumor is commonly considered. In multicentric angiosarcoma with small ‘‘punched out’’ areas, the characteristic clustering of lesions in a single limb or a single anatomic region increases the diagnostic accuracy considerably. Grossly the tumor is spongy, red haemorrhagic. The solid areas are more soft and fleshy. Morphologically, angiosarcoma of bone is a neoplasm characterized by the formation of irregular anastomosing vascular channels lined by one or several layers of atypical endothelial cells having an anaplastic, immature appearance (Huvos, 1991; Fechner and Mills, 1993). There is loss of polarity in angiogenesis. The tumor cells may be arranged in small nests grouped around a lumen or may show single or cord like arrangement of univacuolated cells and slit like vascular channels. Solid areas consisting of sheets of polygonal cells with abundant amphophilic cytoplasm and vesicular nuclei may be seen. Spindled tumor cells are also identified. The three types of endothelial cell patterns are hobnail, syncitial or papillary cell tufts or shedding of individual or clusters of cells into the lumen. Some parts of the tumor may show hemangioma like areas and some like organizing thrombus. Multinucleated giant cells may be seen in the tumor. Mitosis varies from 3-4 in predominantly vasoformative neoplasm to as high as 150 as seen in some scalp angiosarcomas.

Epithelioid angiosarcoma (EA) is a rare variant of angiosarcoma that is characterized by large cells with an epithelioid morphology. In small series EA has been reported to occur in diverse sites, such as skin, thyroid gland, adrenal gland, deep soft tissues, and rarely in bone (Huvos, 1991; Dorfman *et al.,* 1971; Unni *et al.,* 1971) Histologically, EA can mimic poorly differentiated carcinoma because of the epithelioid appearance of the neoplastic

cells, and immunohistochemically they frequently express epithelial markers in addition to endothelial antigens. Furthermore, epithelioid angiosarcoma (EA) usually affects older individuals, a population in which metastatic carcinoma is more common.

Angiosarcoma of soft tissue (extremities, retroperitoneum, and abdominal wall) is very rare and it is presumed to be a high grade sarcoma and little data is available in support of this contention. Patients with these angiosarcomas usually present with a moderately paced growing mass in the extremities. The rapid progression of the disease is sometimes the clue to the correct diagnosis. Retroperitoneal angiosarcomas usually present as asymptomatic masses and generally grow to large sizes because the abdomen can accommodate tumors. Patients may present with neurologic symptoms from compression of lumbar or pelvic nerves. Approximately 33% of patients have evidence of recent hemorrhage or coagulopathy, including anemia, persistent hematoma, hemothorax, hemorrhagic ascites, and gastrointestinal bleeding. Frequently, the adjacent nodes are enlarged because the incidence rate of node metastasis is as high as 45% compared to other soft tissue sarcomas. Immunohistochemical study is an important adjunctive procedure in the diagnosis of angiosarcomas particularly for poorly differentiated forms. Tumor cells stain for the usual vascular and endothelial markers including CD31, CD34, CD144 (VE-cadherin), and at least focally for factor VIII–related antigen. The new marker FLI-1, a nuclear transcription factor, appears to be expressed in almost 100% of different vascular tumors, including angiosarcoma. 11 Nearly all cells stain strongly for vimentin, which accentuates the endothelial cells and vessel lumen formation. BNH9 is detected in 72%, and cytokeratins in 35% of tumors. Epithelial membrane antigen, S100 protein, human herpesvirus 8, and HMB-45 are consistently negative. Fifty-five percent of the tumors have intracytoplasmic aggregates of laminin. Immunostains for smooth muscle actin demonstrate a prominent pericytic component in several tumors (24%). Ki-67 immunostains with MIB1 indicate high proliferative activity (10%) in 72% of cases. p53 immunoreactivity (20% nuclear staining) is observed in 20% of cases. Ultrastructural studies performed on poorly differentiated areas show groups of cells, which are frequently epithelioid, surrounded by basal lamina and closely associated with pericytes, along with intercellular and intracellular lumina with or without red blood cells. Whorls of abundant intermediate filaments, occasional tonofilament like structures, and pinocytotic vesicles are also noted. Soft tissue angiosarcoma must be differentiated from Kaposi's sarcoma, epithelioid hemangio endothelioma, hemangiopericytoma, and spindle cell hemangioendothelioma whose prognosis is different. In Kaposi sarcoma, there is usually a more prominent spindle cell proliferation around preexisting blood vessels containing red cells. The spindle cells are typically factor VIII negative. Angiosarcoma may occasionally duplicate the picture of epithelioid hemangio-endothelioma. Histologically, this lesion is composed of epithelioid endothelial cells arranged in a typical strand or cordlike pattern set in a distinctive myxohyaline stroma. On immunohistochemistry, in addition to vascular antigens (CD31, CD34, FLI-1), it may also express epithelial membrane antigen, which is negative in angiosarcoma (Meis-Kindblom and Kindblom, 1998). Spindle cell hemangioendothelioma may also be confused with angiosarcoma. The presence of cavernous vessels, which are not seen in

angiosarcoma, is the most reliable feature for distinguishing the 2 tumors (Virtanen *et al.,* 2007). Composite hemangioendothelioma is a complex low-grade lesion mimicking angiosarcoma. Hemangiopericytoma can be recognized by its uniform cellularity and vascular pattern with typical ‘‘antler’’ or ‘‘staghorn’’ configuration. Angiosarcomas have the close mimicry it provides with other sarcomas such as rhabdomyosarcomas, epithelioid osteosarcomas, malignant peripheral nerve sheath tumors, synovial sarcomas, and melanomas.

The incidence of angiosarcomas of bone in the present study is 36% of all the primary bone tumors which is well within the range described by Mirra (1989) but marginally higher than that described by Unni *et al.* (1971). The incidence of soft tissue angiosarcomas is 2.2% which is also within the range of 2% as described by Meis Kindblom (Meis-Kindblom and Kindblom, 1998). The average age of presentation of angiosarcomas in our study was 48.7 yrs with range of 11–81yrs which corroborates well with the observation of Volpe and Mazabraud (1982) (median 32 yrs). Rosenberg *et al.* (1994 n=10) in their study of angiosarcomas found median age 62 years, Meis Kindblom and Maddox Evans *et al.* (1981) found median age of 58 yrs in their study. Sixty-eight cases were identified in men and 28 in women (M: F = 2.42:1) in our study, in contrast to 1.6:1 observed at Foundation Curie and 1.2:1 observed at Mayo clinic (Vikram Deshpande *et al.,* 2003). Rosenberg *et al.* (1994) in their study of 10 angiosarcomas found 8 cases in males and 2 cases in females. Kindblom and Kindblom (1998 n=80) and Maddox Evans *et al.* (1981 n=51) found 50 cases in males and 30 cases in females cases in their study.

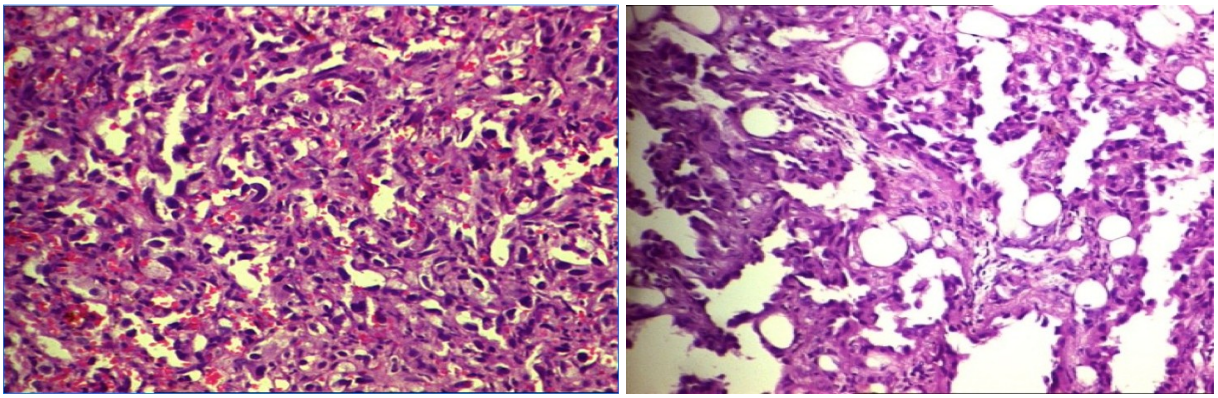
Maximum bone tumors occurred in the long tubular bones while literature documents long bone involvement in one third of all the angiosarcomas. The lower extremity was more commonly involved than the upper extremity in the present study. Multifocality was seen in 5% of angiosarcomas which is comparably less than that observed in Mayo clinic study. Rosenberg *et al.* (1994) in their study of 10 angiosarcomas found tibia involved in 8 cases out of 10. Kindblom and Kindblom (1998 n=80) and Maddox Evans *et al.* (1981 n=51) found commonly the involvement of limb girdles. In our study of bone and soft tissue angiosarcomas 78 cases had vasoformative pattern in 78 cases with spindle cell type in 84 cases. Rosenberg *et al.* (1994) in their study of 10 angiosarcomas found epithelioid cells in all 10 cases. Carter *et al.* (2005 n=16) angiosarcomas in their study of 16 cases found vascular pattern with spindle cell type in all 16 cases, Kindblom and Kindblom (1998 n=80) found admixture of patterns and cell types and Maddox Evans *et al.* (1981 n=51) found rete pattern with spindle cells.

In our study of bone and soft tissue angiosarcomas CD 31 was positive in 77 out of 96 cases, CD 34 positive in 33 out of 59, pancytokeratin was positive in 10 cases of epithelioid angiosarcomas and SMA positive in 1 case. Rosenberg *et al.* (1994) in their study of 10 angiosarcomas found CD 31positive in 9 out of 10, Cytokeratin positive in 7 out of 10. Kindblom and Kindblom (1998 n=80) in their study of 80 soft tissue angiosarcomas found CD 31 positive in 8 out of 24 cases and CD34 positive in 29 out of 39 cases and F VIII positive in 26 out of 29 cases and Maddox Evans *et al.* (1981 n=51) found CD 31 positive in 41 out of 51 cases and CD34 positive in 29 out of 51 cases and F VIII positive in 26 out of 29 cases.

Angiosarcomas are high-grade lesions with a capacity to invade into peripheral tissue and to metastasize (Mark *et al.*, 1996). Tumor size is a key prognostic variable for soft tissue sarcomas, and a tumor diameter of 5 cm is generally used as a cutoff for risk-grouping purposes. Poorly differentiated neoplasms and mitotic count are also found to be independent prognostic factors. Espat *et al.* (2000) demonstrated that the factor predictive of tumor-related mortality was presentation status. Treatment consists of local complete excision. Nevertheless, treatment modalities are variable, depending on resectability and disease extent. In treatment planning of pediatric angiosarcomas, the role of chemotherapy is still unknown. In the review of the Italian and German Soft Tissue Sarcoma Cooperative Group, objective response to chemotherapy was observed in only 1 of 12 patients, and the overall behavior of this tumor is found to be identical to angiosarcoma in adults. Drugs that target angiogenesis should be of particular interest in malignant vascular tumors. Because the origin of angiosarcoma is the endothelial cell, it is conceivable that the antiangiogenic activity of paclitaxel is a mechanism that contributes to its efficacy in angiosarcoma. Indeed, this drug could have a double action, targeting tumoral vascularization and tumor cells directly. In adult patients, the report from Fata et al from the Memorial Sloan-Kettering Cancer Center seems particularly relevant, in which paclitaxel was shown to be effective as a single agent against angiosarcoma (Skubitz and Haddad, 2005). The treatment of recurrent tumor in the remaining patients was varied and tailored to individual patients. So comparisons among therapies for recurrence were not feasible. Reports of successful treatment of local recurrence by simple excision are found in the literature. Although our findings do not suggest any meaningful way to "grade" angiosarcomas according to growth patterns, mitotic activity, or cytologic features, one histologic parameter did emerge which appeared to have a significant relationship to the interval of survival, namely, the amount of lymphocytic inflammation admixed with and surrounding the tumor. The presence of a moderate to marked amount of lymphocytic inflammation was associated with a significantly better survival interval, longer intervals to local recurrence and metastasis, and. perhaps a decreased rate of metastasis (Mark *et al.*, 1996; Meis-Kindblom and Kindblom, 1998).

Fig.1(a) Histomorpological spectrum of angiosarcomas of bone and soft tissues showing vasoformative; **(b)** rete pattern of angiosarcoma

a **b**



Conclusion

Pathologists should be aware of the differential diagnosis and rare variants.It is important to differentiate these tumors from each other as they differ in prognosis and treatment. Multicentric epithelioid angiosarcoma of the bone is a pitfall in pathological diagnoses, especially if a strong radiological impression of metastatic carcinoma is provided.

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