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Case Report

Epithelioid angiosarcoma of the bone with eosinophilia: report of a case and review of literatures

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Abstract: We presented a case of 46-year-old man who developed right foot pain and activity limitation 7 months prior to initial evaluation at our hospital. Radiographic evaluation demonstrated osteolytic lesion in the bones of toes and biopsy revealed the diagnosis of angiolymphoid hyperplasia with eosinophilia. Surprisingly, malignant angiosarcoma was diagnosed in resected specimen. Histologically, the whole lesion was composed with inflammatory infiltration and hyperplasia of vascular endothelial cells. Numerous eosinophils infiltrated in the stroma with the local formation of eosinophilic abscess. In superficial area of the foci, some endothelial cells were epithelioid like gravestones. However, irregularly anastomotic vessels, which were lined with nests or sheets of atypia endothelial cells, were the predominant lesions in deep area, and these cells showed eosinophilic or basophilia cytoplasm containing lumina, round or oval vesicular nuclei, large and red nucleoli. Immunohistochemistry study presented intensely positive expression of CD31 and vimentin, negative expression of CD68, CD1a, S-100, CK pan, SMA, CD34, EMA and FVIIIRA which suggested that the diagnosis of bone epithelioid angiosarcoma with eosinophilia. To our knowledge, it is an extremely rare case.

Keywords: Bone, epithelioid angiosarcoma, eosinophil

Introduction

Angiosarcoma is a malignant mesenchymal neoplasm in which the tumor cells exhibit endothelial differentiation. It frequently develops in skin, viscera and soft tissues. It is characterized by spindle cells with variable atypia, which are often lined inside the anastomosing vessels.

Epithelioid angiosarcoma is a rare variant of angiosarcoma, in which the malignant endothelial cells show a predominantly epithelioid appearance. It most often arises in the deep soft tissues of the extremities, but a variety of primary sites such as the thyroid gland, skin, and adrenal glands are encountered Hart and Mandavilli Epithelioid angiosarcoma: a brief diagnostic review and differential diagnosis [1], Fletcher et al. Epithelioid angiosarcoma of deep soft tissue: a distinctive tumor readily mistaken for an epithelial neoplasm [2]. However, bone is a very rare primary site for this malignancy Hasegawa et al. Epithelioid angiosarcoma of bone [3], Kudva et al. Primary epithelioid angiosarcoma of bone: a case report with immunohistochemical study [4], Deshpande et al. Epithelioid angiosarcoma of the bone: a series of 10 cases [5]. Herein, we report a case with epithelioid angiosarcoma of the bone characterized by eosinophilic hyperplasia, which the initial diagnosis on biopsy was angiolymphoid hyperplasia with eosinophilia.

Case presentation

A 46-year-old man developed pain with activity limitation in the right foot seven months prior to initial evaluation in our hospital. He came to the hospital with the aids of crutches.

Clinical history

The physical examination of the right foot was remarkable. The colour of acrotarsium skin was dark. The active movements of the first and second metatarsophalangeal joints were limited while the passive activities were poor and

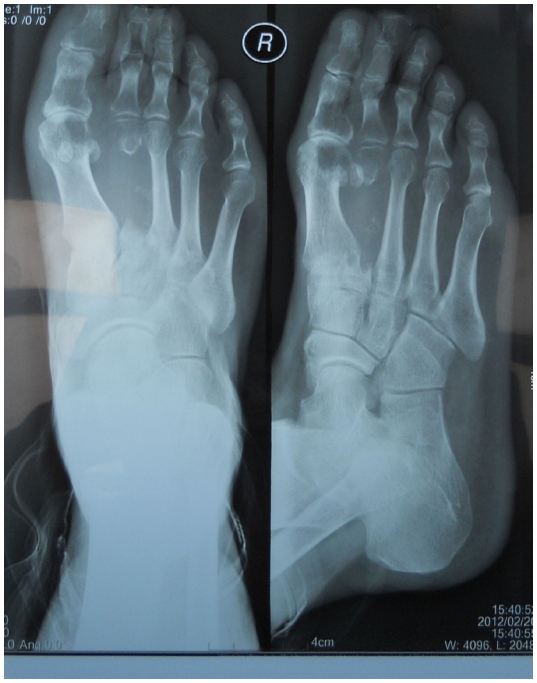

Figure 1. Plain X-radiographs. Osteoclastic lesion of multi bones in the right foot suggested the aggressive clinical course of this tumor.

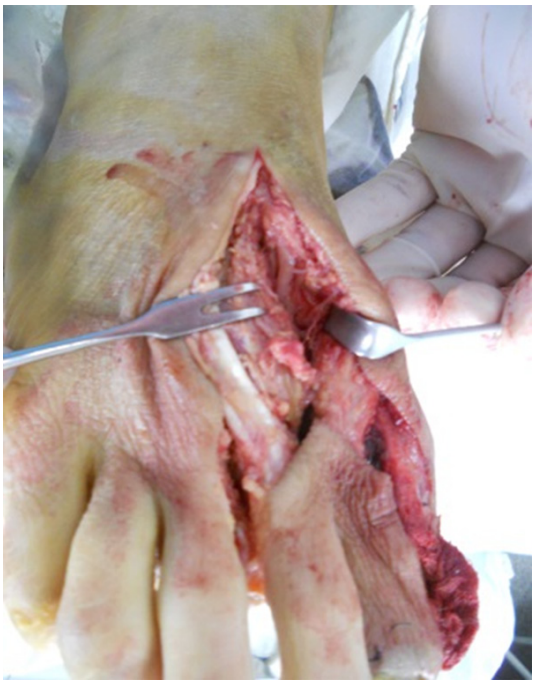

Figure 2. Resection of the foci. Anatomical structure of the foci and boundary of the lesion were unclear. Neoplasma showed a fish-like appearance.

with obvious pain. Laboratory findings showed that eosinophils (EO) count was 2.21 × 10^9/L (reference range 0.05-0.5 × 10^9/L) and EO percentage was 30.41% (reference range 0.5-5.0 × 10^9/L), although white blood cell count (WBC) was 7.26 × 10^9/L (reference range 4.0-10.0 × 10^9/L). Evaluation of Plain X-radiographs demonstrated osteoclastic lesion of multi bones in the right foot, which suggested the aggressive course of this tumor (**Figure 1**). The patient underwent puncture biopsy, and the specimen taken from the lesion was diagnosed to be angiolymphoid hyperplasia with eosinophilia (ALHE). Then the patient underwent resection and bone grafting (**Figure 2**). Surprisingly, malignant angiosarcoma was found in resected specimen. The patient refused further amputation surgery with adjuvant therapies, and died one year later for pulmonary metastasis.

Figure 3. Gross features of the lesion. Sample resected from the lesion was broken, with a total of 2.0 × 2.0 × 2.0 cm size, irregular shape, and dark red color.

Materials and methods

The resected specimens were embedded in paraffin after decalcified and fixed with 10% neutral buffered formalin. Tissue blocks were cut into 4 μm thick slides, deparaffinized in xylene, rehydrated with graded alcohols. Hematoxylin & eosin (HE) staining and reticulin staining were performed as formal. Heat-induced epitope retrieval was performed using a steamer. Immunostaining was performed with primary antibodies including CD31 (1:100, DAKO, Denmark), CD34 (1:100, DAKO, Denmark), CD68 (1:50, DAKO, Denmark), CD1a

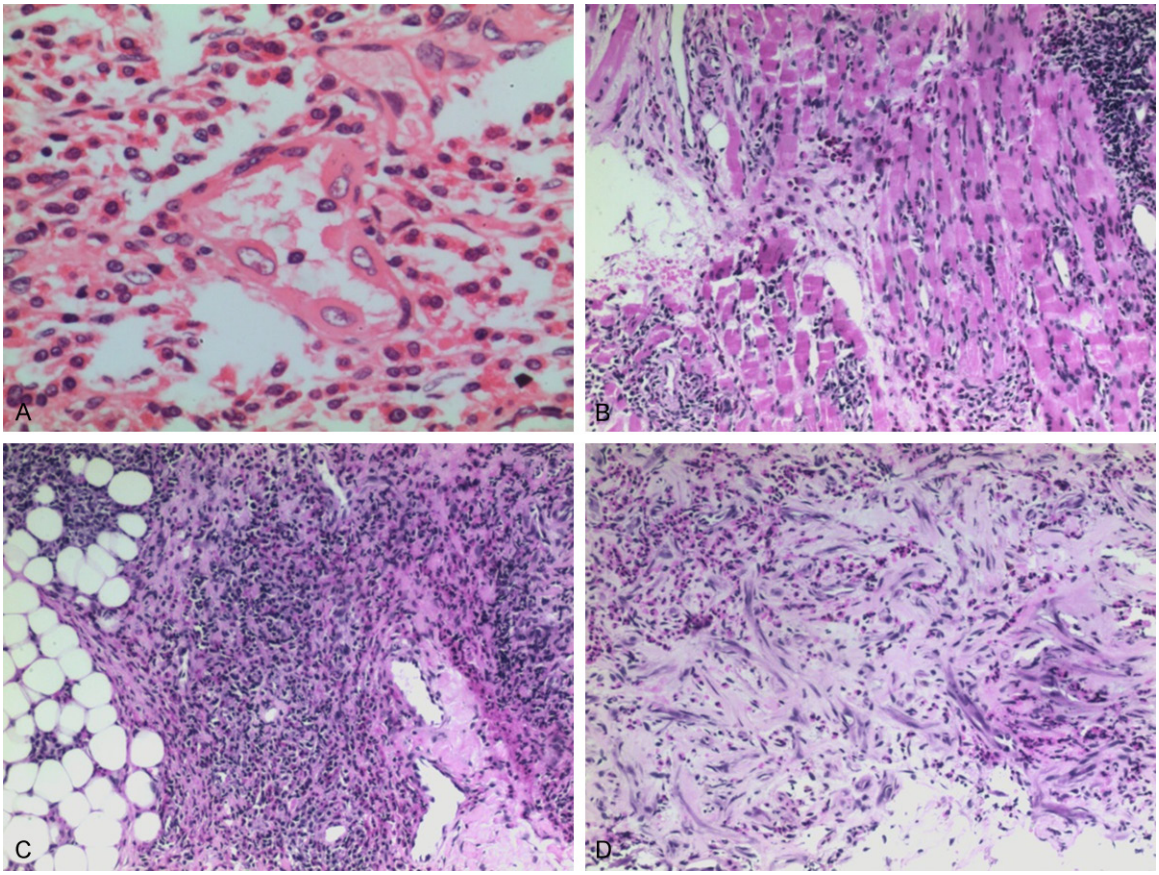

Figure 4. Histological features in superficial area of the foci. A. Inflammatory infiltrate dominated by eosinophils with the formation of small eosinophilic abscess. Vascular proliferated and lined with gravestone-like pleomorphic endothelial cells. HE × 400. B. Inflammation infiltrated inside striated muscles, HE × 100. C. Inflammation infiltrated subcutaneous fatty tissue, HE × 100. D. Inflammation infiltrated fibrous connective tissues, HE × 100.

(1:100, DAKO, Denmark), S-100 (1:100, Santa Cruz, USA), pancytokeratin (CKpan, AE1/AE3, 1:50, DAKO, Denmark), epithelial membrane antigen (EMA, 1:50, DAKO, Denmark), smooth muscle actin (SMA, 1:200, DAKO, Denmark), vimentin (1:100, DAKO, Denmark), Factor VIII-related antigen (FVIIIRA, 1:100, DAKO, Denmark), and Ki67 (1:100, Santa Cruz, USA). Sections were stained with a streptavidin-peroxidase system, and diaminobenzidine tetrahydro-chloride substrate (Maixin, China) was used as the chromogen. Sections were then slightly counterstained with hematoxylin, dehydrated, cleared and mounted. Appropriate positive and negative controls were included for each antibody.

All images subjected to HE staining, reticulin staining, and IHC were viewed under a light microscope (Nikon ECLIPSE 80i, Japan). The study was approved by the ethics committee of San Ai Tang Hospital and conducted in accordance with the ethical guidelines of the Declaration of Helsinki.

Results

Gross and microscopic features

Grossly, soft and osseous tissues resected from the lesion were broken, with a total of 2.0 × 2.0 × 2.0 cm size, irregular shape, dark red color and fish appearance (**Figure 3**).

Histologically, HE staining showed marked hyperplasia of thin-walled vessels and notable inflammatory infiltration in dermis, subcutaneous fat layer, striated muscle, and tranecula bone tissues. The vessel lumen was uneven in size and lined with pleomorphic endothelial cells, with numerous eosinophils, and a small amount of lymphocytes, plasma cells and marcrophages infiltrated in stroma. In superficial

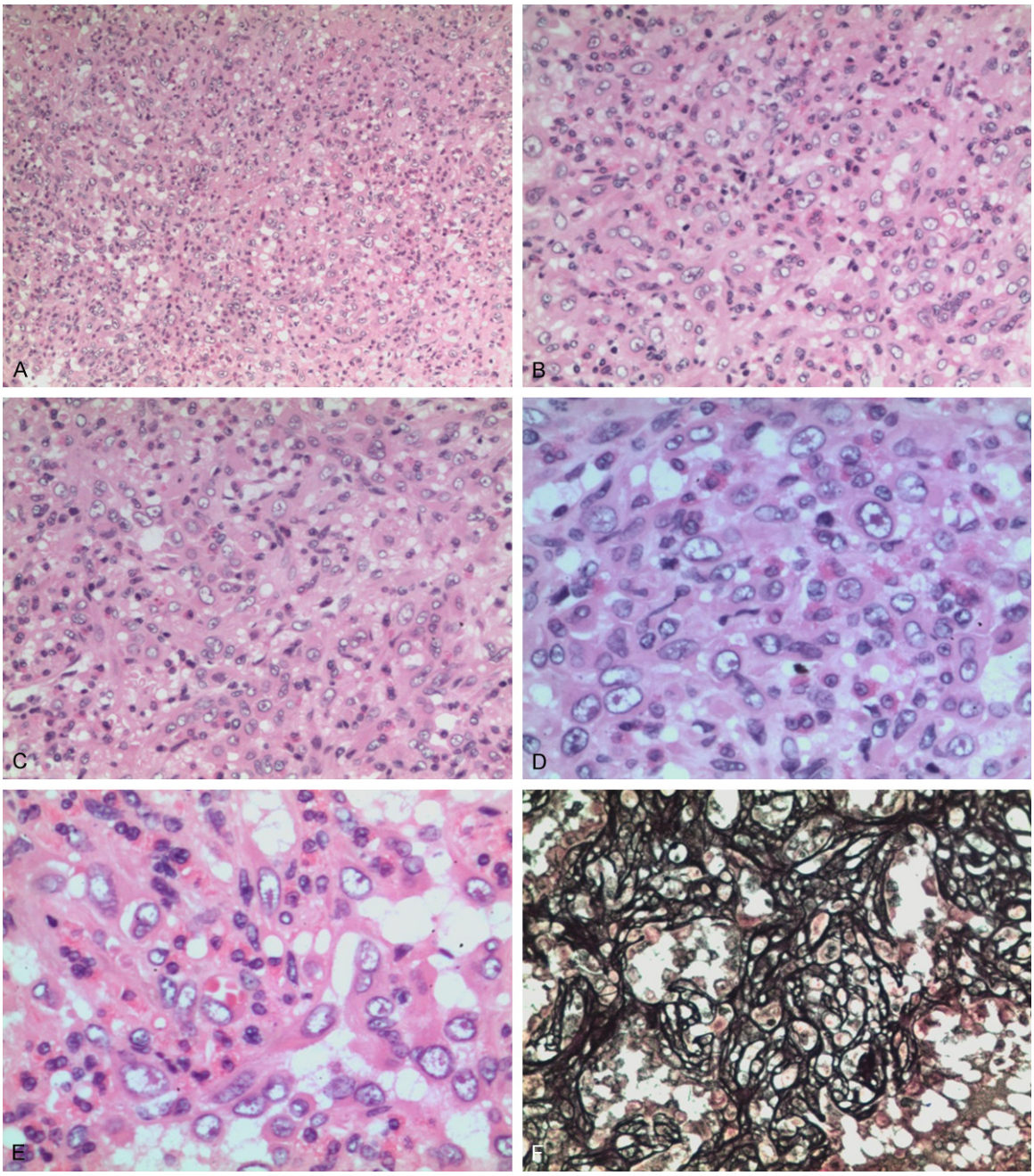

Figure 5. Histological features in deep area of the foci. A. Anastomosing vessel formation suggested the endothelial origin of this tumor. HE × 100. B. Malignant endothelioid cells arranged in nests or sheets. HE × 200. C. Malignant endothelioid cells organized into primitive tube. HE × 200. D. Large round to polygonal malignant epithelioid cells with copious basophilic or eosinophilic cytoplasm, centrally or slightly eccentrically placed vesicular nuclei and prominent nucleoli. A few mitotic figures could be seen. HE × 400. E. Nests of epithelioid cells organized into gaping sinusoid-like spaces with papillary projections. Intracytoplasmic lumina contained erythrocytes. Numerous eosinophils infiltrated in stroma. HE × 400. F. Irregularly anastomotic vessels suggested the redimentary vasoformation. Reticulin staining × 200.

area of the foci, vasoformative architecture was obvious and some endothelial cells were epithelioid like gravestones (**Figure 4**). However, irregularly anastomotic vessels, which were lined with monolayer or multilayers of atypia endothelial cells, were the predominant lesions in deep area. These malignant endothelial cells were large, round, oval or polygonal, focally

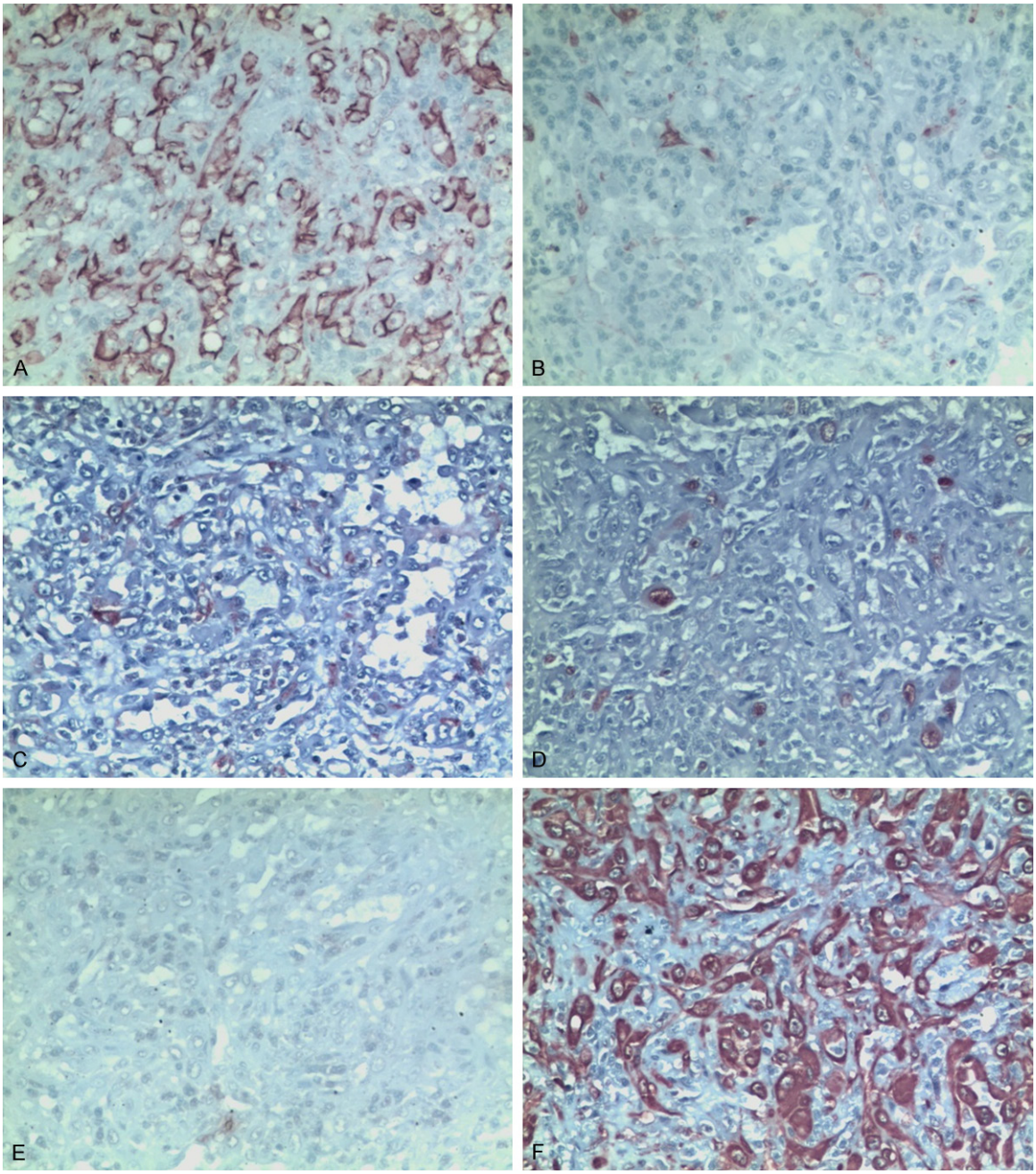

Figure 6. Immunohistochemical staining. A. CD31 demonstrated intense membranous and cytoplasmic staining, × 200. B. Most of tumor cells were negative for CD34, × 200. C. Most of tumor cells were negative for FVIIIRA, × 200. D. Less than 5% of tumor cells were positive for Ki67, × 200. E. Tumor cells were negative for SMA, × 200. F. Vimentin showed intense cytoplasmic staining, × 200.

arranged in sheets or nests or into gaping sinusoid-like spaces, with eosinophilic or basophilia cytoplasm containing lumina, round or oval vesicular nuclei, large and red nucleoli. Mitotic figures including abnormal mitoses could be encountered. Focal necrosis was present. Reticulin staining clearly showed irregularly anastomotic vessels (**Figure 5**). Osseous tissue was widely destroyed and only a few bone chips were left, with atrophy of striated muscles.

Immunohistochemistry

Immunohistochemical staining showed atypia epithelial cells were diffusely positive for CD31 and vimentin, negative for CD68, CD1a, S-100,

Ck pan, SMA, CD34, EMA and FVIIIRA while Less than 5% of tumor cells were positive for Ki67 (**Figure 6**).

Discussion

Angiosarcomas account for a small proportion of all vascular tumors, and they constitute less than 1% of all sarcomas Weiss SW Enzinger and Weiss's Soft Tissue Tumors [6]. The histological appearances of angiosarcoma vary and involve diverse patterns of growth, including papillary, spindled, and epithelioid morphological features.

So far, etiology of epithelioid angiosarcoma (EA) remains unknown. Endothelial malignancies are derived from mesenchymal cells, which undergo blood vessel and/or lymphaticendothelial differentiation.

EA most often arises in the deep soft tissues (usually intramuscular) of the extremities, but a variety of primary sites, including the thyroid gland, skin, adrenal glands, and bone are encountered Hart and Mandavilli Epithelioid angiosarcoma: a brief diagnostic review and differential diagnosis [1]. The disease affects more men than women over a wide age range from 19 to 77 years, predominantly affecting patients in their sixties and seventies Wu et al. Epithelioid angiosarcoma: a clinicopathological study of 16 Chinese cases [7].

A variety of clinical presentations may be encountered, ranging from painful, enlarging soft tissue masses to long bone fractures to arteriovenous shunting and subsequent high-output cardiac failure Hart and Mandavilli Epithelioid angiosarcoma: a brief diagnostic review and differential diagnosis [1]. Radiologically, EA has no specific features but exhibits non-specific imaging signs of malignancy Wenger and Wold Malignant vascular lesions of bone: radiologic and pathologic features [8]. Radiologic examinations may be required to determine the extension of the lesions.

Grossly, EA tends to form hemorrhagic, spongy masses. The lesions typically have indistinct borders and commonly extend beyond the obvious gross confines of these borders Hart and Mandavilli Epithelioid angiosarcoma: a brief diagnostic review and differential diagnosis [1]. Histologically, the tumors are often characterized by sheets or nests of large round to polygonal cells with copious basophilic or eosinophilic cytoplasm and centrally or slightly eccentrically placed vesicular nuclei. Nucleoli are usually present and mitotic activity is generally brisk. Additional aspects are geographic-type tumor necrosis, mixed inflammatory infiltrates, and fibrosclerotic changes of the ground substance. In some cases, the observations suggesting a vascular neoplasm included architectural (patent spaces containing red cells with papillary projections or angiomatioid spaces) and/or cytological findings (cytoplasmic vacuolation, in tracellular red blood cells) Wu et al. Epithelioid angiosarcoma: a clinicopathological study of 16 Chinese cases [7]. The rudimentary vasoformative architecture can clearly be demonstrated by reticular staining. Generally, sheeted areas contain a scant amount of stroma, but in less cellular regions it is often abundant, with a desmoplastic to fibromyxoid appearance. In EA of the bone, foci containing prominent infiltrate of neutrophil rather than eosinophil (not associated with necrosis) have been described Hart and Mandavilli Epithelioid angiosarcoma: a brief diagnostic review and differential diagnosis [1]. However, in our case, many eosinophils infiltrated in stroma of the lesion, with the formation of small eosinophilic abscess and increase of peripheral blood eosinophils. Therefore, the case may be a distinct entity which is different from EA reported before. Significance of eosinophilia in this case are unknown.

Immunohistochemistry is very helpful in the diagnosis of EA. CD31, CD34, Ulexeuropaeus agglutinin-1, FVIIIRA and Fli-1 were common markers of endothelial origin used frequently in reported cases of EA. CD31 and Fli-1 are more sensitive than CD34 and FVIIIRA, and CD31 is the best marker of endothelial differentiation in routinely fixed tissues. As a highly nonspecific marker, vimentin is invariably positive Wu et al. Epithelioid angiosarcoma: a clinicopathological study of 16 Chinese cases [7].

Histologic features reminiscent of EA may also appear in HE stained sections of melanoma, anaplastic lymphoma, metastatic cancer, ALHE, haemangioendothelioma (EHE). Negative staining for S-100 and HMB-45 are contributed to exclude melanoma. Lymphocytic antigens such as CD45, CD30, CD3 and CD45RO are positive in anaplastic large cell lymphoma. EA

may be distinguished from metastatic cancer for its vascular differentiation on HE evaluation and expression of endothelial markers. Although cytokeratin is present in about one-third of soft-tissue angiosarcomas, especially the epithelioid subtype, noncutaneous angiosarcomas will not express epithelial membrane antigen (EMA). ALHE most often occurs in younger patients and is characterized by vascular proliferation within an inflammatory infiltrate made up of lymphocytes, macrophages, and eosinophils Zaraa et al. Angiolymphoid hyperplasia with eosinophilia: a study of 7 cases [9]. It shows well-circumscribed lesions in which the soft-tissue component is usually less marked. Well-formed vessels are characteristic and severe nuclear atypia is absent, signifying the benign nature of the condition. In our case, the diagnosis of ALHE was made at first when puncture biopsy was performed because samples from superficial area of the foci showed the features of ALHE. But resection samples demonstrated sheets or nests of sarcomatous component in deep area. Nuclear atypia is present in EHE, but to a lesser extent than in EA Stavridis SEpithelioid angiosarcoma of the adrenal gland. Report of a case and review of the literature [10]. Plump endothelial cells without significant pleomorphism invade a hyalinized to myxoid stroma. Nuclei are vesicular and have less conspicuous nucleoli Zaraa et al. Angiolymphoid hyperplasia with eosinophilia: a study of 7 cases [9].

Surgery, radiotherapy, and chemotherapy, singly to in combination, are therapeutic options for EA. Although wide excision is recommended, adjuvant therapies are needed, and further studies were certainly required to establish the role of adjuvant radiation or chemotherapy in the treatment of angiosarcoma Xu et al. Epithelioid angiosarcoma of esophagus [11].

The prognosis of EA is determined by the tumor site, size, stage, cellularity, pleomorphism, and mitotic activity. Other poor prognostic indicators include bleeding, pain and lesions greater than 5 cm in size Sundaram et al. Primary multicentric cutaneous epithelioid angiosarcoma [12]. The prognosis of EA is poor because of its rapid growth and metastasis to lung, bone, soft tissue, lymph nodes and brain Kacker et al. Multifocal angiosarcoma of the scalp: a case report and review of the literature [13], Glickstein et al. Cutaneous angiosarcoma of the head and neck: a case presentation and review of the literature [14].

Conclusion

We presented here a 46-year-old male with epithelioid angiosarcoma of the bone characterized by eosinophilia in China. The histology and immunochemistry supported the diagnosis very well. To our knowledge, the case is very rare that few cases of occurrence have been reported.

Acknowledgements

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Disclosure of conflict of interest

None.

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