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Epithelioid hemangioma of bone: A unique case with multifocal metachronous bone lesions

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ABSTRACT

Epithelioid hemangioma of bone is a rare vascular neoplasm with a ubiquitous distribution. To date, up to 25% epithelioid hemangioma of bone presents synchronous bone lesions. We report a unique case of epithelioid hemangioma with multifocal metachronous bone lesions without any fatal outcome observed after a long period. Importantly, a strong nuclear expression of FOSB antibody was detected by immunohistochemical analysis. In this case, the pathologic and radiologic findings are also described. We suggest that epithelioid hemangioma can present multifocal metachronous bone lesions without producing a fatal outcome.

1. Introduction

Epithelioid hemangioma (EH) is a vascular neoplasm with a ubiquitous distribution, including bone and soft tissue.[1] EH exhibits distinctive well-formed vascular channels composed of cells that have an endothelial phenotype and epithelioid morphology.[1–3] World Health Organization (WHO) defines EH as a locally aggressive bone neoplasm with no connotation of it being a benign or intermediate tumor,[4] indicating a controversial definition of EH.

The clinical behavior of EH is complicated because of its multifocal presentation and rare lymph node involvement.[1,5–8] EH could be aggressive locally with a recurrence in 11% of cases.[9] These manifestations of the tumor lead to diagnostic difficulties since EH lacks characteristic radiological features.[5]

Recently, a novel and recurrent FOS gene rearrangement was present in nearly one third of EH across a variety of locations.[2,10,11] Another recurrent ZFP36-FOSB fusion has been reported in a small subset of epithelioid hemangioma with atypical morphological features that do not reveal FOS gene rearrangement.[1] Before the discovery of gene rearrangements specific to this rare entity, EH was often misdiagnosed as epithelioid hemangioendothelioma (EHE)[12] or angiosarcoma.[13]

We present the first case of EH with multifocal metachronous bone lesions without any fatal outcome observed after a long period. Another important feature of our work in this study is that we carried out FOS gene rearrangement to confirm the diagnosis of this case. The findings of radiographs and pathologic studies are also described.

The independent ethics committee of Istituto Ortopedico Rizzoli approved the study, which was registered with ClinicalTrials.gov (identifier NCT03169595).

1.1. Case report

A 20-year-old Caucasian female with no history of major illness was admitted with complaints of pain in the proximal humerus of

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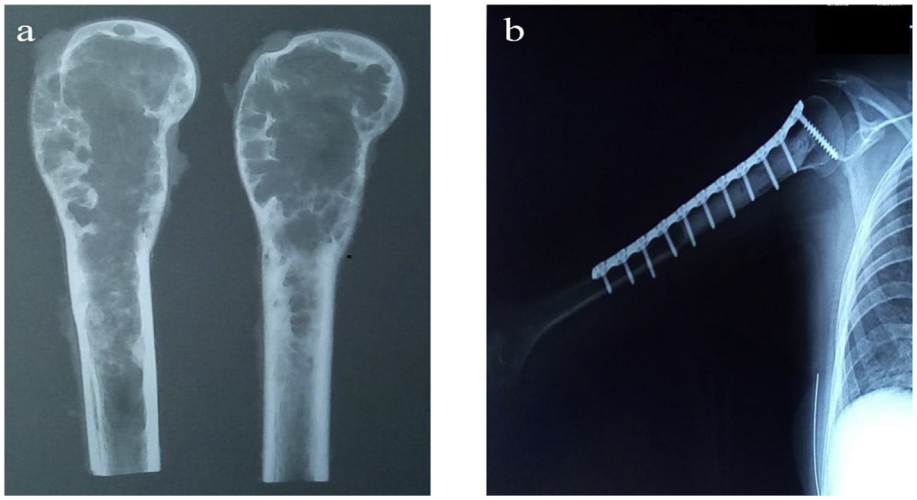

Fig. 1. **A** Tumor specimen radiograph showing an expansile lytic lesion of the proximal humerus extending into the metaphyseal region. **B** postoperative radiograph shows massive bone allograft replacement and plating.

the right arm in 2001. Radiographs revealed an expansile and osteolytic lesion of her right proximal humerus with focal cortical thinning and destruction (Fig. 1). An incisional biopsy was performed and the diagnosis was EHE, a low-grade malignant vascular tumor. Consequently, the patient received a massive bone allograft and plating construct after a resection of the right proximal humerus was performed. In the follow-up, no evidence of local recurrence and distant metastases were found in the next 13 years. In 2014, the patient exhibited pain in her right elbow. Radiographs revealed a lytic and expansile intramedullary lesion of the proximal radius (Fig. 2a). A bone scan displayed an increased uptake not only in the proximal radius but also in the left frontal skull (Fig. 2b). On 1.5-T magnetic resonance imaging (Signa Infinity, General Electric, Fairfield, CT, USA) a round lesion was observed in the frontal skull with a high signal on axial T1-weighted images and coronal T2-weighted images (Fig. 2c and d). Since we assumed both lesions were from the same origin, it would be detrimental to obtain tissue from the lesion in the frontal skull. For this reason, the patient only underwent a trocar biopsy of the lesion in the right proximal radius. From this biopsy, the diagnosis of EHE was confirmed for the second time. The patient was then treated with a curettage of the lesion in the proximal radius, filling the bone cavity with cement

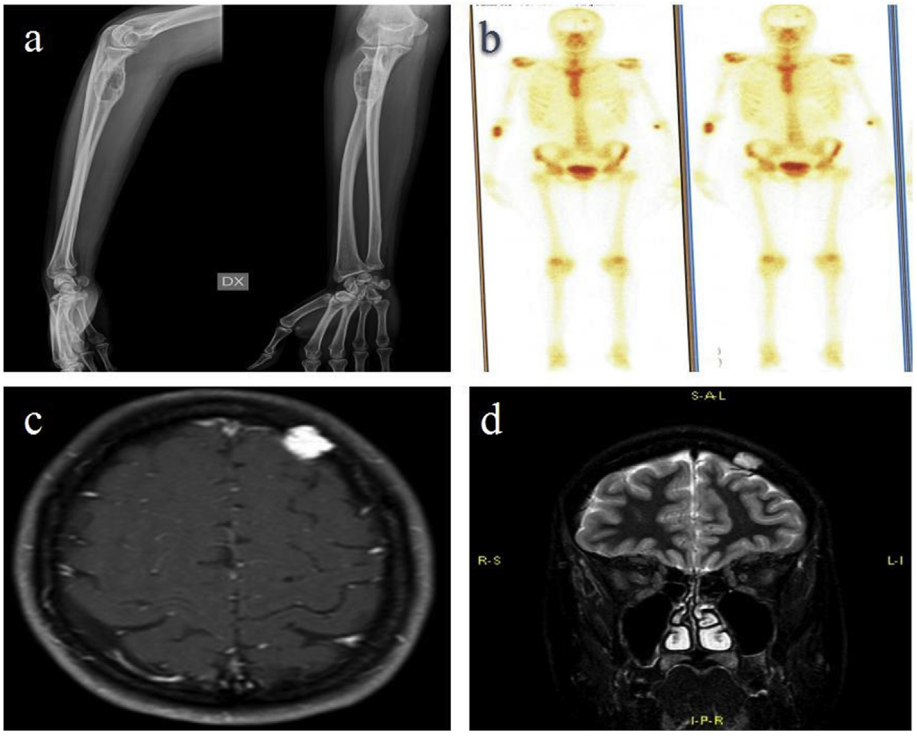

Fig. 2. **A** Radiographs show a lytic and expansile intramedullary lesion of the proximal radius. **B** Bone scan shows an increased uptake in the proximal radius and the left frontal skull. **C** Axial T1-weighted post contrast enhanced MR image showing a lobulated extra-axial enhancing lesion from left frontal skull with hyperintensity. **D** Coronal T2-weighted image shows a small hyperintense extra-axial lesion of the left frontal region.

(Fig. 3), and resection of the lesion in the skull. At the follow-up in January 2018, 17 years after the initial diagnosis, radiographs showed another osteolytic lesion in the right distal humerus, distal to the initial lesion (Fig. 4). The patient underwent a trocar biopsy guided by computed tomography, followed by a curettage of the lesion and the filling of the bone cavity with cement. Considering the progress of genetics in the diagnosis of vascular tumors in recent years, the histological diagnosis of the latter sample was based not only on the morphological features but also the molecular analysis. The neoplastic cells were immunoreactive for specific endothelial markers (ERG and CD31) and negative for cytokeratin AE1/AE3, (which exclude the diagnosis of pseudomyogenic hemangioendothelioma) and for CAMTA1 and TFE3, (which exclude the diagnosis of EHE). Thus, PCR analysis was undertaken for the specific genetic translocation of EHE, involving chromosomes 1 and 3 t (1; 3) (p36.3:q25), and it was negative in all our samples. After excluding the diagnosis of EHE, molecular analysis was conducted to discover the new FOS rearrangement specific of EH on the above-mentioned specimens. FOS gene rearrangement was not detected by FISH analysis. However, immunohistochemical analysis showed that the neoplastic endothelial cells were strongly positive for FOSB antibody (Fig. 5b). The immunohistochemical analysis was performed on the previous pathological tissues and the diagnosis of EH was confirmed in all specimens. Histologically, the neoplasm is characterized by a prominent proliferation of small, capillary-sized vessels, sometimes lacking a well-defined lumen associated with areas of solid growth and increased cellularity (Fig. 5a and c). The vessels are lined by epithelioid endothelial cells with an enlarged nucleus, with focal nuclear atypia and nuclear pleomorphism. Occasional eosinophils and lymphocytes were present in all samples. At the last follow-up, the patient was still alive without evidence of any EH-related fatal disease.

2. Discussion

EH of bone usually occurs in the long tubular bones[9] and it could involve more than one bone in up to 25% of cases.[5] So far, multifocal EHs reported in the literature present synchronous bone lesions at the presentation of the disease.[5,14,15] To our best knowledge, EH with multifocal metachronous bone lesions has not been described before. Hence, we reported the first case of EH with multifocal metachronous bone lesions. According to this case, multiple metachronous bone lesions of EH seem to behave like their contiguous counterparts: localized pain to the involved bone and a mixed osteolytic and sclerotic feature on radiographs.[8] Our case report shows the possible existence of multifocal metachronous EH without producing a fatal outcome.

The diagnosis of EH remains challenging, particularly in osseous locations, because of its atypical histologic features being confused at the spectrum with other epithelioid vascular neoplasms such as EHE or epithelioid angiosarcoma.[1,2] In the presented case, this patient was misdiagnosed as EHE at the beginning. Morphologically, it is difficult to distinguish between EH and EHE due to a considerable overlap at the pathological level, where epithelioid cells show well-defined cell borders and abundant, densely eosinophilic cytoplasm, while a mild degree of cytologic atypia can be seen both in EH and EHE.[5] However, several recent studies have confirmed that the involvement of FOS gene in fusion events could be a highly specific driving event in EH.[2,10,11] After investigating the incidence of FOS rearrangements in a large cohort of EH, Huang et al. found FOS rearrangements were present in a third of EH across different anatomical locations with more prevalence in intra-osseous lesions in comparison with lesions in other locations.[1] Members of the FOS family dimerize with Jun proteins to form the AP-1 transcription factor complex, which plays a pivotal role in cell growth, differentiation and survival.[11,16] Interestingly, FOS is the AP-1 transcription factor and FOSB represents its paralogue; thus, the presence of FOS and FOSB is mutually exclusive.[17] Furthermore, a new translocation was identified as recurrent ZFP36-FOSB fusion in a subset of EH with atypical histological features, confirmed to FOSB immunohistochemical expression as we found in our case.[1] On the other hand, previous studies demonstrated the distinctive gene fusion of WWTR1-CAMTA1 and YAP1-TFE3 in EHE, which cannot be identified in other epithelioid vascular tumors, providing a strong and objective molecular tool to assist its diagnosis and classification.[18,19] The importance of distinguishing these two entities is paramount,

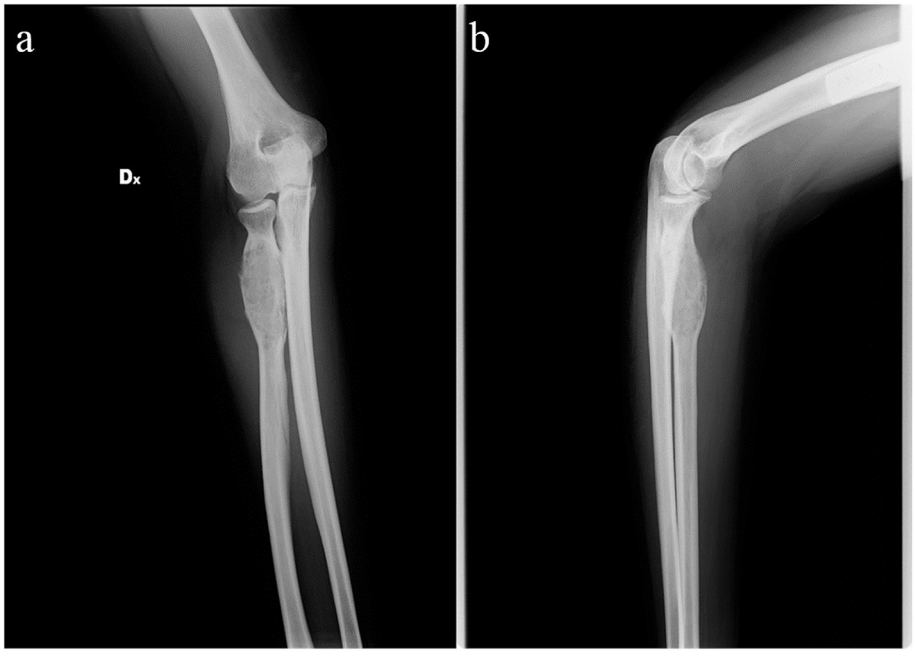

Fig. 3. Postoperative radiographs of the right proximal radius after curettage of the lesion and filling the bone cavity with cement.

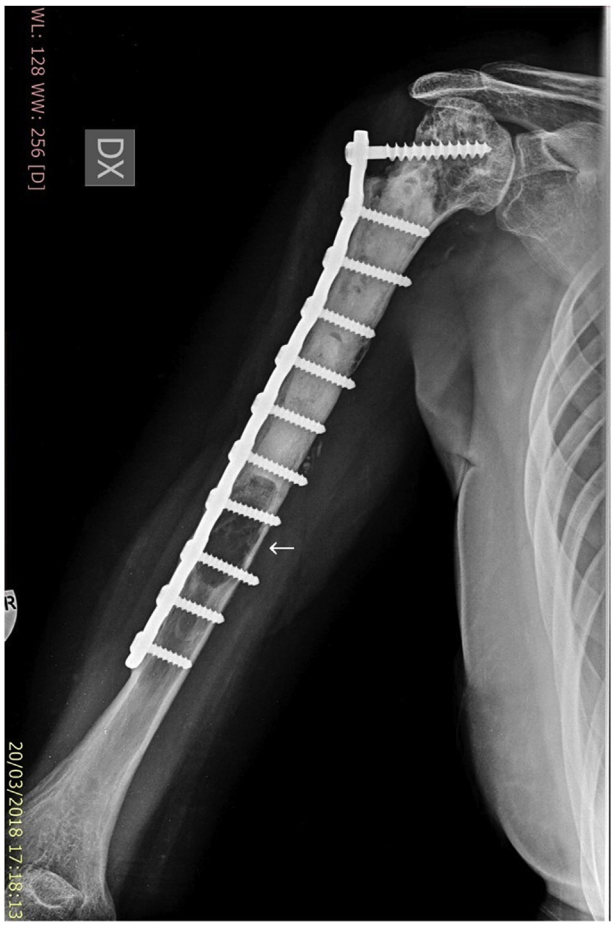

Fig. 4. 17 years after the initial diagnosis, radiograph shows new lytic lesion of the humeral diaphysis (*arrow*) distal to the initial lesion.

as EHE exhibits a much more aggressive clinical course with a fatal outcome and a higher incidence of distant metastases.[20,21]

Given the controversial clinical behavior of EH, no specific treatments have been reported in literature. In a series of 13 patients with so-called hemangioendothelioma reported by Evans et al.,[12] 3 patients were treated with chemotherapy and another 3 underwent amputation. Remarkably, none of the patients in their series died. However, in a "Letter to the Editor" in the International Journal of Surgical Pathology, Rosenberg argued that Evans et al.'s illustrations of the tumors showed characteristics of EH.[6,22] So far in literature, treatment could vary from biopsy to segmental resection.[22] From a study analyzing 50 cases of EH with a long follow-up, most patients could be effectively treated with intralesional curettage or marginal excision[9]: 35 patients were treated with curettage and 13 patients had a local resection while 3 patients were treated with surgery and radiation therapy. Throughout the follow-up, no patients died of EH and none of them had a reported adverse outcome. Furthermore, EH frequently behaves indolent instead of a fatal clinical progression.[5,9] Based on the above, it is indicated that aggressive treatments like radiation treatment and systemic treatment are not mandatory for EH and could be considered for more aggressive vascular tumors such as EHE or epithelioid angiosarcoma. Twice, our patient underwent a resection of lesions involving frontal skull and proximal humerus as well as a curettage of proximal radius and distal humerus. During the 17-year follow-up, the patient had an excellent prognosis without any evidence of local recurrence. Hence, our treatment strategy for this patient seems to be in favor of this less aggressive surgery, as curettage is usually associated with less surgical complications and better functional results.[9]

So far, no study has reported patients dying of this disease, suggesting EH appears to have a favorable prognosis and could be considered as a benign tumor.[9,18,23] Approximately 18–25% of osseous EHs demonstrate multifocal presentation and this multifocality seems to have a monoclonal origin.[3] Van Ijzendoorn et al. provided evidence that multifocal EH resulted from a metastasis of the same neoplastic clone rather than a simultaneous neoplastic formation of multiple EH cell clones, indicating the monoclonal origin of multifocal EH.[3] A similar result could also be found in multifocal EHE of the liver,[25] suggesting that the separately located bone lesions of EHE within one patient are derived from one single clone. Therefore, it seems that multifocal vascular tumors are more likely to be a metastatic disease rather than a manifestation of

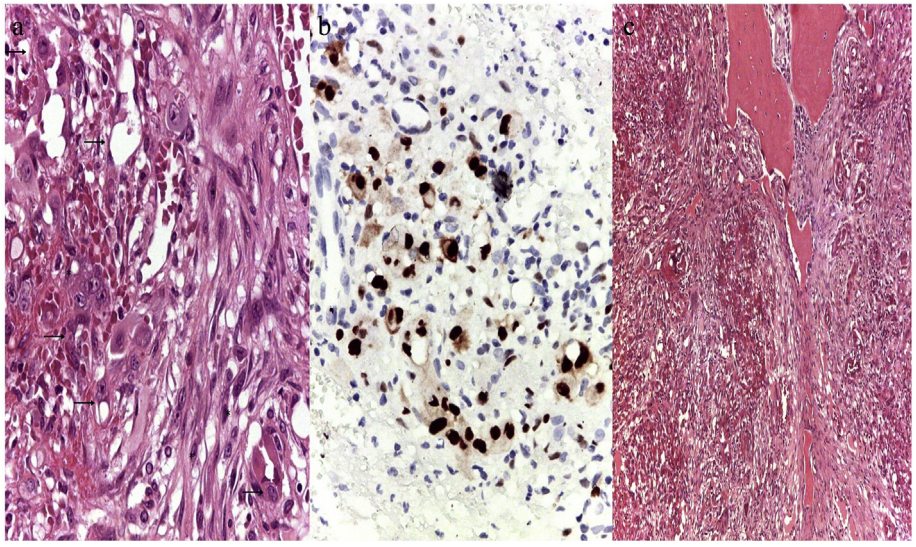

Fig. 5. **A** Large epithelioid cells line well-formed vascular spaces (*arrows*) associated with isolated prevalent epithelioid or slightly spindled cells (*asterisks*) adjacent to a well-formed neoplastic vessel are evident (haematoxylin and eosin; 400× magnification). **B** These neoplastic endothelial cells show a strong nuclear expression for FOSB antibody (400× magnification). **C** haematoxylin and eosin staining at a low power field (100× magnification).

multicentricity.[3,22,25] In the literature, 4 cases of osseous EH with lymph nodes involvement have been reported.[6,7,9] Among them, 2 patients underwent treatment with excision of the involved lymph nodes and all patients had an excellent prognosis without any related fatal outcome. Thus, we can speculate that EH could be a benign vascular tumor with metastatic potential. The possible existence of benign metastases is further supported by the behavior of giant cell tumor, another type of benign bone tumor that can metastasize without producing a fatal outcome.[26]

In summary, we report the first case of EH with multifocal metachronous bone lesions diagnosed by FOSB immunohistochemical expression. We highlight that EH could be a rare benign vascular tumor with a metastatic potential from monoclonal origin without producing any related fatal outcome. Immunohistochemical and molecular analysis are mandatory to obtain a correct diagnosis by FOS gene rearrangement. Curettage seems to be the treatment of choice and should be considered as the main surgical strategy. Future studies are warranted to have a better understanding of the prognosis of this rare entity.

Compliance with ethical standards.

Conflicts of interest

No external funding was received for this case report, and the authors have no conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcot.2019.03.009.

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