Multifocal Epithelioid Hemangioendothelioma

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Abstract

A case of a rare epithelioid hemangioendothelioma (EHE) with multifocal location in a 32 year-old male is reported. The patient presented to our hospital with a knee pain. After thorough investigations and establishing the diagnosis, surgical treatment was done. This tumor involves bones of the axial skeleton and long tubular bones. EHE is usually multifocal in more than 50% of the cases. The management of a bone and liver location was exposed in this case report.

Keywords: Hemangioendothelioma; Epithelioid; Multifocal

Introduction

Epithelioid hemangioendothelioma (EHE) is an intermediate malignant vascular tumor, which occur in bone, skin, soft tissue, and visceral organs like the lung and liver [1,2]. EHE of bone is identified as a separate entity by the current World Health Organisation (WHO) classification 2013 of vascular tumors based on its unique histology and clinical outcome [3]. EHE of bone is an uncommon and rare tumor that represents less than 1% of primary bone tumors. It involves bones of the axial skeleton and long tubular bones [2]. EHE is usually multifocal in more than 50% of cases [4,5].

Case Report

We report the case of a 32-year-old hypertensive man who presented, six months previously, with left knee pain resistant to analgesic therapy, weight loss and lameness. He had no history of trauma. Physical local examination of the knee showed no effusion. There was no palpable inguinal or popliteal lymphadenopathy; neither warmth nor erythema was detected. Moreover, there was no ligamentous instability or joint line tenderness. The range of motion of the left knee was not limited. The rest of his musculoskeletal examination showed wasting and weakness of the left quadriceps femoris. Besides, the general physical examination was unremarkable. The laboratory workup showed no remarkable or specific findings.

The knee X-ray displayed a mixed lytic and sclerotic large lesion in the proximal metaphysis of the tibia extending to epiphysis. No periosteal reaction was noticed (Figure 1). The magnetic resonance imaging (MRI) revealed intra-articular and distal femoral epiphysis extension (Figure 2). Preoperative assessment of the tumor extension detected multiple synchronous locations involving the liver (Figure 3).

Figure 1: AP and lateral radiographs of the knee reveal a well-delineated osteolytic lesion of the posterior aspect of the proximal tibia without periosteal reaction.

Figure 2: (a) Coronal non-enhanced T1-weighted MR image shows multiple hypointense lesions. (b) On sagittal gadolinium-enhanced fat-suppressed T1-weighted MR image, the lesions demonstrate marked homogeneous enhancement. Note also the bone marrow and soft tissue edema (arrows).
Figure 3: Enhanced CT scans shows multifocal tumors appeared as low density lesions with rim enhancement and capsular retraction (arrow).

The proximal tibial lesion was biopsied. Histologically, the tumor was characterised by the presence of epithelioid and spindle cells with round or elongate nuclei, prominent nucleoli and abundant eosinophilic cytoplasm.

Partial intracytoplasmic lumen formation containing erythrocytes was observed. Immunohistochemically, the tumor cells showed positive and intense reactivity for both vascular endothelial immunohistochemical markers CD31 and CD34 (Figure 4). The diagnosis of HEH was confirmed, based on pathological and immunohistochemical results.

Figure 4: (a) Epithelioid endothelial cells have densely eosinophilic cytoplasm and contain round clear vacuoles. (b) Intermediate-power image showing tumor cells infiltrating cancellous bone. (c) Microscopic evidence of vascular differentiation: Intracytoplasmic lumen containing an intact erythrocyte (head of the arrow). (d) The tumor cells of epithelioid hemangioendothelioma are positive for CD34 by Immunohistochemical staining. Segmental resection-arthrodesis of the knee with fixation by medullary nailing according to the surgical technique of Juvara was performed (Figure 5), associated with adjuvant chemotherapy.

Figure 5: Segmental resection-arthrodesis of the knee with fixation by medullary nailing according to the surgical technique of Juvara was performed. Post-operatively, the resected segment was sent to pathology. Macroscopically, the metaphyseal epiphyseal tibial tumor was 5.5 cm in size and eccentric. In addition, cortical disruption and extent to the posterior soft tissue was noticed. As for the femoral tumor, it was 3 cm and involved the two femoral condyles. Both lesions were rubbery, thin and poorly demarcated. The neoplastic tissue infiltrated the joint cavity through the cruciate ligaments. Synovial fluid filling the knee joint was clear (Figure 6).

Figure 6: The metaphyseal-epiphyseal tibial tumor. Cortical disruption and extent to the posterior soft tissue was noticed with an infiltration of the joint cavity through the cruciate ligaments.

Discussion

EHE was described for the first time by Weiss and Enzinger in 1982 as a soft tissue neoplasm [6]. EHE of the bone is a rare vascular tumor that occurs at any age especially in adults, in the second and third decades of life, rarely in the childhood [1], and affects the sexes equally but in some studies there is a slight male predominance [2,7]. It generally involves the metaphysis, diaphysis, and very rarely the epiphysis of the long bones [2]. The most frequently affected long bones are the tibia (23% of cases), femur (18%), and humerus (13%) [8]. It's a multicentric tumor involving multiple bones or multiples tissues, as observed in our case, which involved the tibia and the femur [5,9]. The most common symptoms of EHE are local pain and swelling. Pathological fracture may occur [2,7]. Radiographic findings are non-specific. Radiography and CT reveal osteolytic or expansive lesions, in the cortical or medullary bone. Cortical disruption, joint invasion can
be present and a soft tissue extension is present in 40% of cases [7,10]. Periosteal reaction is rare in the absence of pathologic fracture. There is no specific pattern of signal intensity at MR imaging. Most frequently EH has low to intermediate signal intensity on T1-weighted images and high signal intensity on T2-weighted images, with homogeneous enhancement after the injection of gadolinium-based contrast material. The radiological differential diagnosis for EHE of the bone includes osteomyelitis, skeletal angiomatosis, langerhans cell histiocytosis (LCH), angiosarcoma, infection, myeloma, metastasis, and lymphoma [2,10]. Grossly, EHE is an ovoid, rubbery, soft or solid, ill-defined nodular mass, with red hemorrhagic appearance, and ranges from 2 to 10 cm in size [7,10]. Histologically, the tumor consists of solid nests and anastomosing cords of round, polygonal or spindle-shaped cells with eosinophilic cytoplasm and which have an epithelioid appearance. The nuclei are round, eccentric and show a moderate pleomorphism. The most characteristic feature is the presence of intracytoplasmic vacuolization containing erythrocytes. There is a little or no mitotic activity. The cells are present in a myxochondroid or myxohyaline matrix. Well-formed vascular channels, which are observed in epithelioid hemangioma, are absent [4,7]. One third of EHE are called high-grade or malignant EHE which show atypical histologic features that include nuclear atypia, mitotic activity (>1/10HPF), necrosis and sheet-like growth [2,4]. The main differential diagnosis in this form is epithelioid angiosarcoma which grows in solid sheets, and irregularly anastomosing vascular channels, with presence of necrosis and desmoplastic reaction [2]. The other histological differential diagnoses include metastatic carcinoma and epithelioid hemangioendothelioma [2,7]. Immunohistochemical study is necessary to establish the definitive diagnosis. EHE of bone express endothelial markers such as CD31, CD34 and friend leukemia integration 1 transcription factor (Fli 1) [4,7]. They are more sensitive than Von Willebrand factor (factor VIII). Otherwise, cytokeratin expression is noted in 38% of cases and tumoral cells can focally express epithelial membrane antigen [4,11]. Cytogenetic study shows a translocation involving chromosomes 1 and 3 t (1; 3) (p36; q23-25) resulting in a WWTRI-CAMTA1 fusion or chromosomes 1 and X t(1; X) (q13; p11) [12]. A new fusion was recently found, consists in the YAP1-TFE3 fusion [13].

The treatment depends on the size, location and number of the tumors [5]. The treatment of choice of EHE of the bone consists in complete surgical excision to reduce local recurrence [2,7]. However, in a series of 7 patients with osseous EHE, treatment consist in wide excision in 2 cases, a limited surgery (curettage) in 4 cases and a below-knee amputation in one case [14]. Chemotherapy and/or radiotherapy are administered if the tumor involves multiples sites or in the case of incomplete resection [7]. However, a 70-year-old man with unincentric EHE of the bone was successfully treated by intravenous pamidronate (bisphosphonate), and the tumor was in complete remission after 6 years [15]. EHE of bone is a locally destructive tumor with intermediate behavior and a variable clinical course. Some studies reported that multifocal disease has better prognosis than solitary disease [16,17] but in other series, the overall survival in the case is 89% in unincentric tumor and 50% in multifocal disease [4]. The local recurrence rate of EHE of bone is about 13%, 30% develop regional or distant metastasis, and the mortality rate is 20% [7,18]. The prognosis is poor when visceral involvement is present and it's usually associated with multifocal tumors [4,6]. For this reason, assessment of extension includes CT of the chest and abdomen, bone scintigraphy, and a skeletal survey [10].

Conclusion

Primary vascular tumors of the bone are very rare. EHE is an uncommon tumor of the bone. It's the only intermediate-grade vascular tumor of the bone characterized by endothelial cells with epithelioid appearance. The clinical course is variable and depends on multifocality and/or visceral involvement. Radiologic findings are nonspecific. The definitive diagnosis is made by histological examination with immune-histochemical study. Wide surgical resection is the ideal treatment and radiation therapy is reserved for inoperable cases or metastatic disease. The role of chemotherapy is not yet clear. The detection of new molecular alterations and the identification of the fusion genes will possibly offer new opportunities to study this entity, especially concerning the classification of vascular tumors of the bone and the therapeutic approaches.

References
