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Parosteal osteoliposarcoma: A new bone tumor (from imaging to immunophenotype)☆

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ABSTRACT

Introduction: Parosteal osteosarcomas and well-differentiated liposarcomas (WDLPS) of soft tissue share several features: they are slowly progressive, locally aggressive tumors, tend to recur locally, and rarely or never metastasizes if not dedifferentiated. Their treatment is wide surgical resection.

Microscopically, both are well differentiated tumors, very like their normal tissue counterpart. They share simple karyotypes with supernumerary ring chromosomes or giant marker chromosomes containing amplified 12q sequences including *MDM2* and *CDK4* genes, with subsequent overexpression of MDM2 and CDK4 proteins.

We present the case of a parosteal osteoliposarcoma made of closely intermingled components of a low-grade osteosarcoma and a WDLPS.

Case: In a 34 year-old woman with a slowly growing mass of the arm, imaging revealed a large well-defined heterogeneous parosteal mass of the upper humerus, with two main components: bone at the base and fat at the periphery. Microscopically, these two components were consistent respectively with low grade osteosarcoma and WDLPS. Cells of the two components were labeled with anti-CDK4 antibody. No labeling with anti-MDM2 antibody and no signal detected with *MDM2* FISH analysis were likely due overdecalcification. No frozen tumor tissue was available for FISH analysis nor array-CGH.

Discussion: Differential diagnoses of this new entity would be a well-differentiated liposarcoma with a low-grade osteosarcomatous component that originates from the soft tissues, ruled out on imaging, and an ossifying parosteal lipoma, ruled out on immunohistochemistry.

Conclusion: This is the first description of a low-grade parosteal sarcoma with two components that morphologically and immunophenotypically demonstrate characteristics of a parosteal osteosarcoma and of a well-differentiated liposarcoma.

1. Introduction

Parosteal osteosarcoma is a rare primary bone tumor, representing about 4% of all osteosarcomas [1]. Most occur in the third and fourth decades, approximately 10 years after the conventional osteosarcomas tend to be seen. Its location is usually metaphyseal with the distal femur affected in about 70% of cases; the majority of other cases occur in the proximal tibia and proximal humerus.

It is a slowly progressive, locally aggressive tumor, tends to recur locally, and rarely metastasizes [2]. This tumor has the distinction of being able to dedifferentiate, de novo or in a recurrence or metastasis; in the two largest series of parosteal osteosarcoma, dedifferentiation was found in 16% and 24% of the cases respectively [2,3]. In the setting of dedifferentiation, the incidence of metastases rises (31%) [4]. Given the low initial incidence of metastasis for these low grade tumors, the mainstay of treatment for parosteal osteosarcoma without dedifferentiation is wide surgical resection only.

Diagnosis is often easy on imaging, even with standard radiographs: a large lobulated mineralized mass on the surface of the metaphysis of a long bone. The mineralized matrix seen is bone of varying density, denser centrally. Axial computed tomography (CT) images allow for better analysis of the relationship of the mass to the cortex and observe the encircling of the diaphysis by the tumor. A thin radiolucent partial cleavage plane between the tumor

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and the underlying cortex corresponds to the periosteum. Despite being visible on radiographs and CT in more than half cases [2], it is best demonstrated on magnetic resonance imaging (MRI). MRI can also identify any cartilaginous component, most often seen in the form of a pseudo-cap that mimics the cartilaginous cap of osteochondroma [5].

From a microscopic point of view, parosteal osteosarcomas differ significantly from conventional high grade osteosarcomas; they appear as a fibro-osseous lesion with trabeculae of nearly mature bone, separated by fibrous stroma. Cell density is usually low to moderate. Stromal spindle cells show few atypias: enlarged hyperchromatic nuclei and minimal pleomorphism. Mitoses are absent or scarce. The bone component is prominent in the dense, sclerotic areas demonstrated on imaging. In contrast, the fibrous component can be very developed, mimicking a desmoplastic tumor or fibromatosis [6]. In the osteochondroma-like form, the pseudo-cap consists of well-differentiated cartilage. No other component has been described to date, in particular fat.

Cytogenetic studies and/or molecular biology studies performed for parosteal osteosarcoma and/or low-grade central osteosarcoma showed simple karyotypes with supernumerary ring chromosomes or giant marker chromosomes containing amplified 12q sequences [7] including *MDM2* and *CDK4* genes [6,8]. Overexpression of the protein product of these genes in relation to their amplification can be demonstrated by immunohistochemistry performed with anti-MDM2 and anti-CDK4 antibodies, thus helpful to differentiate these low grade osteosarcomas from benign fibro-osseous lesions [6,9].

Several features of low-grade osteosarcoma are similar to those of well-differentiated liposarcomas. As with parosteal osteosarcoma, well-differentiated liposarcoma is a slowly progressive, locally aggressive tumor that may recur locally and may dedifferentiate either de novo or in a recurrence. While in the absence of dedifferentiation there is no metastatic risk, metastases are observed with dedifferentiated liposarcomas [10].

Unlike parosteal osteosarcoma, which is a very rare tumor, well-differentiated and dedifferentiated liposarcomas of the soft tissues are relatively common, occurring in adults and most frequently in the retroperitoneum and thigh [11].

Morphologically, well-differentiated liposarcomas, as the name indicates, are well-differentiated adipose tumors, resembling normal adipose tissue. This tumor consists of sheets of mature adipocytes intermingled with varying numbers of immature fat cells called lipoblasts. The diagnosis rests in the presence of large fusiform cells with large, hyperchromatic nuclei (atypical stromal cells) preferentially seen in the fibrous septae between adipocytic sheets. A morphologic variant of well-differentiated liposarcoma, composed of components of low-grade osteosarcoma (similar to parosteal osteosarcoma or central low grade osteosarcoma) has been recently described [12]. This variant has long been underdiagnosed because the bone component was commonly mistaken for bone metaplasia. The bone component is not metaplastic but of tumor nature, as it over-express MDM2 and CDK4 proteins. The significance of this is uncertain: dedifferentiation of a well-differentiated liposarcoma in the setting of a low-grade osteosarcoma or well-differentiated liposarcoma with divergent differentiation into bone.

In bone, well-differentiated liposarcoma and dedifferentiated liposarcoma are uncommon. To our knowledge, only one case of well-differentiated liposarcoma in parosteal location has been reported: a thigh mass in a 68 year-old man [13]. The absence of any periosteal reaction in the images published, however, suggests that this may be a simple well-differentiated liposarcoma of the deep soft tissues of the thigh, surrounding the femur, and not a tumor originating from the bone surface.

We present the first description of a low grade parosteal sarcoma comprised of closely intermingled components of a low-grade osteosarcoma and a well-differentiated liposarcoma, which we have chosen to name parosteal osteoliposarcoma. This tumor is not a malignant mesenchymoma of the bone, sometimes referred as primary osteoliposarcoma of the bone [14].

2. Patient

A 34 year-old Chinese woman was admitted to the hospital, with a complaint of a painless mass in her right arm that has grown slowly over the past year. On examination, a large firm ovoid mass was appreciated at the anteromedial aspect of her right proximal arm. The mass was painless to palpation; she had full active range of motion of her shoulder.

Radiographs revealed a large mass on the medial aspect of the right proximal humerus (Fig. 1A). It was largely radiolucent with thin portions of mineralization at the periphery and a broad, densely mineralized base with extension of the mineralization into the main portion of the mass. CT scan images (Fig. 1B and C) demonstrated a well-defined heterogeneous mass with two main densities, fat and bone. The well-mineralized component was contiguous with the cortical bone along the base of the lesion, with focal cortical destruction but without apparent medullary cavity involvement. T1 weighted MRI images (Fig. 1D) revealed a fatty peripheral component. It was not possible to exclude marrow involvement based on these images. Bone scan demonstrated only increased uptake at this location.

A core needle biopsy was performed. On microscopic examination, the sample consisted of fibrous tissue, bone, and cartilage, without obvious atypia. Wide resection of the proximal humerus was performed with subsequent megaprosthesis reconstruction.

Gross examination revealed an ovoid mass with a smooth, pseudoencapsulated surface attached to the cortex of the humeral shaft by a wide base. On cut section (Fig. 1E), this base consisted of very dense bone. Bony branches extended throughout the rest of the mass, which was comprised mostly of yellow fatty tissue with whitish fibrous septae. The cortex was focally destroyed by the tumor, but the medullary canal was uninvolved.

On microscopic examination of the resection specimen, the bone component consisted of nearly mature trabeculae, often long and parallel to each other (Fig. 2A). The trabeculae were separated by a fibrous tissue containing some atypical spindle cells, with enlarged hyperchromatic nuclei. The most peripheral bone component, in close contact with the adipose tissue, was often associated with small foci of hypercellular well differentiated cartilage. All these features were consistent with low grade osteosarcoma. This component was closely intermingled with a component that had aspects of a well-differentiated lipoma-like liposarcoma, consisting of sheets of mature adipocytes and fibrous septa containing atypical stromal cells (Fig. 2B).

Ancillary studies (immunohistochemistry and FISH analysis) were performed on a representative paraffin block in order to precisely determine the exact nature of the tumor. Osteocytes in newly formed trabeculae (Fig. 2C), chondrocytes (Fig. 2D), spindle cells in the fibrous tissue between the bone trabeculae, atypical stromal cells of the fibrous septae and rare adipocytes of the component of well-differentiated liposarcoma (Fig. 2E) were labeled with anti-CDK4 antibody (clone AHZO 202, 1:100 dilution, Invitrogen). No labeling was observed with anti-MDM2 antibody (clone IF2, dilution 1:200, Zymed), not even a few non-neoplastic osteoclasts, raising suspicion that the technique lacked sensitivity on this decalcified tissue. In addition, FISH analysis of the *MDM2* gene (SPEC ZytoLight MDM2/CEN12 Dual Color Probe, ZytoVision) was not evaluable, as no signal was detected. The negative status of the MDM2 immunohistochemistry analysis and the inability to assess