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CASE REPORT

Extraskeletal Osteosarcoma of Subcutaneous Soft Tissue with Lymph Node and Skin Metastasis: A Case Report with Fluorescence in Situ Hybridization Analysis

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Introduction

Osteosarcomas represent the 35% of all malignant bone neoplasms and affect mainly children and young adults [1]. Their principal histopathologic feature is the production of osteoid or bony matrix by the tumor cells [2]. Extraskeletal osteosarcoma (EOS) arises from mesenchymal cells of soft tissues and accounts for approximately 2–4% of all osteosarcomas [3]. Unlike its skeletal counterpart, EOS occurs primarily in adulthood (5th to 7th decades of life). The thigh, buttock, upper extremity and retroperitoneum are the most common anatomic locations [3–5]. EOS has a very poor prognosis, and 75% of the patients die within 5 years of the initial diagnosis. In 60% of the cases they develop metastases, mainly to the lungs and bones [4].

Although osteosarcoma is one of the few sarcomas that develop regional lymph node metastases, metastasis of a soft tissue EOS to the skin and subcutaneous soft tissue are extremely uncommon. In this report, we describe a case of a primary subcutaneous EOS with skin and subcutaneous metastasis.

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Case Report

The patient we describe is a 54-year-old African American male with a medical history of sickle-cell anemia, presented to his primary care clinic with a soft tissue mass located at his left lower extremity (Fig. 1a). Underlying bone was not involved clinically or radiologically. The patient underwent surgical ablation of the mass. Paraffin embedded tissue blocks and hematoxylin and eosin slides of the excised mass were sent to the Department of Pathology of the University of Pittsburgh Medical Center for consultation. Histologic assessment disclosed a circumscribed neoplasm, the peripheral portions of which displayed actual bone formation with focal calcification and areas with true "filigree" osteoid that was surrounded by spindle cells and multinucleated osteoclast—like giant cells. Abnormal mitotic figures were rarely detected (Fig. 1b). A diagnosis of extraskeletal osteosarcoma was made. Extensive clinical and radiological workup did not demonstrate metastatic disease. The patient received chemotherapy consisting of 4 cycles of ifosfamide, Mensa and Decarbazine (DTIC).

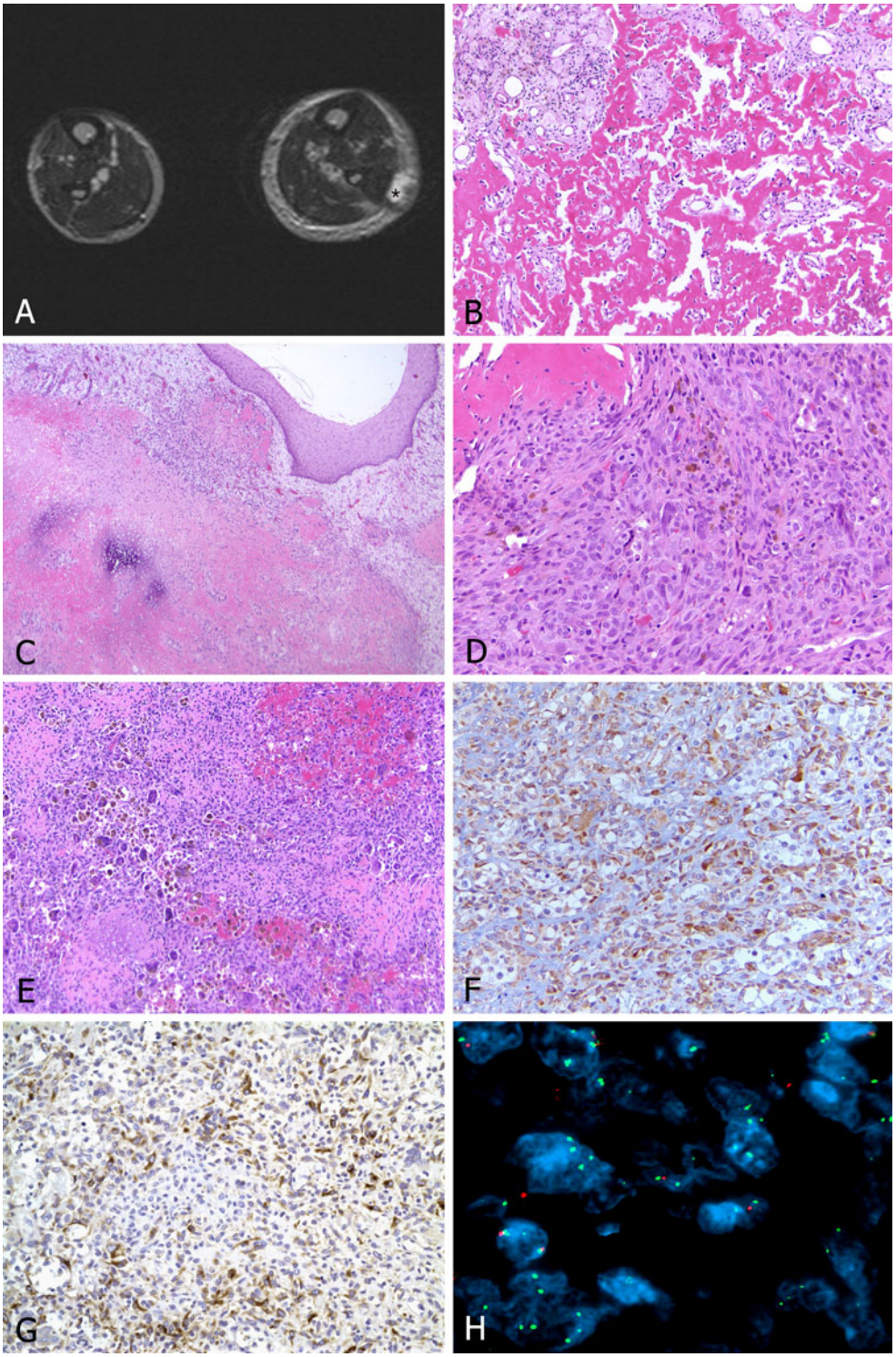

Fig. 1 **a**: MRI image showing the extraskeletal location of the mass (*asterisk*). **b**: True filigree osteoid surrounded by malignant osteoblasts is the diagnostic feature of the primary extraskeletal osteosarcoma (hematoxylin-eosin, original magnification X10). **c**: Histologic section showing cutaneous and subcutaneous localization of the metastatic extraskeletal osteosarcoma (hematoxylin-eosin, original magnification X10). **d**: Increased mitotic activity is observed at the site of skin metastasis (hematoxylin-eosin, original magnification X20). **e**: Giant cells are easily identified within the metastatic neoplasm (hematoxylin-eosin, original magnification X20). **f**: Strong diffuse nuclear and cytoplasmic immunostaining for the osteoblast-specific marker osteonectin (osteonectin, original magnification X20). **g**: The metastatic tumor reveals intense principally cytoplasmic immunoreactivity for osteocalcin (osteocalcin, original magnification X20). **h**: Dual color I-FISH detected remarkable deletion of the locus 17p13.1 of the *p53* gene (*red color*) as well as hyperploidy, identified with the application of specific centromeric probe for chromosome 9 (*green color*)

Overall, the patient tolerated the chemotherapy relatively well. Ten months after the initial diagnosis he presented with a gradually enlarging, tender left tibial mass and an enlarged multinodular mass of the left groin involving adjacent skin. Excision of the mass and the lymph node was performed. Macroscopic examination of the surgical specimens revealed a subcutaneous, well-demarked tumor, measured 8.0×3.5×2.0 cm. On sectioning, the lesion was variegated, solid to cystic, gray to brown, with a gritty calcified surface and was extended to the overlying skin. Focal skin ulceration was also observed. The histopathologic findings of the tumor and the lymph node were essentially similar to that seen in the primary neoplasm (Fig. 1c). However, the tumor appeared to be more cellular and

pleomorphic. The mitotic activity was remarkably increased (12 mitotic figures per 10 high power fields) and extensive necrosis was observed (Fig. 1d). Large ectatic vascular spaces with osteoclast-like giant cells were present (Fig. 1e). Small satellite nodules of tumor occurred around the main mass. Sickled red blood cells were detected within almost all vascular spaces. The malignant cells displayed strong nuclear and cytoplasmic immunoreactivity for osteonectin and osteocalcin (Fig. 1f,g), while they were negative for desmin, pancytokeratin, S-100 protein and cell cycle regulator, p53. Dual color interphase fluorescence in situ hybridization (I-FISH) analysis using probes for LSI p16 (9p21)/CEP 9 (9p11-q11), LSI p53/CEP 17 and LSI Rb-1/LSI 13q34 (Vysis, Inc. Downers Grove, IL) revealed genomic imbalances involving the chromosomes 9, 17 and 13. Chromosome 9 (*p16* locus), chromosome 17 (*p53* locus) and chromosome 13 (*Rb-1* locus) deletion was detected in 74%, 52% and 40% respectively in the targeted malignant cells. In addition, FISH analysis with the centromere probe of chromosome 9 detected hyperdiploidy in 30% of the examined cells (Fig. 1h). After 2 months the patient developed innumerable, bilateral pulmonary metastatic foci visible on chest CT. Imaging studies of the abdomen and the pelvis did not show evidence of tumor.

Discussion

EOS is a highly malignant neoplasm that arises from the mesenchymal cells of soft tissues. Although the vast majority of these tumors arises *de novo*, in 10% of cases they have been associated with antecedent trauma and local radiation [6]. Osteosarcoma has also been described as a component of malignant peripheral nerve sheath tumors (MPNSTs) in patients with type 1 neurofibromatosis [7]. EOS, like its skeletal counterpart is characterized by the synthesis of bone or osteoid by the tumor cells. The tumor may also contain cells that resemble fibroblasts, smooth muscle or cartilage cells [8]. This reflects on their variegated immunohistochemical profile. EOS has been noted to exhibit positivity for smooth muscle actin (SMA), desmin, S-100 protein and epithelial membrane antigen (EMA) in 68%, 25%, 52% and 20% of the cases, respectively [8]. The bone-specific marker osteocalcin is detected in the transformed osteoblasts in 82% of the patients [8] and is an indicator of malignant bone formation [9]. The presence of these "protean" histopathologic characteristics makes the diagnosis of EOS sometimes difficult. Other benign lesions, notably myositis ossificans, should be included in the differential diagnosis and other sarcomas that occasionally form dystrophic/metaplastic bone should always be excluded. In our case, the tumor was composed of malignant spindle cells, as well as multinucleated osteoclast-like giant cells. There was no evidence of pattern zonation that is typically present in myositis ossificans. Actual bone formation, areas with true "filigree" osteoid formed by cytologically malignant spindle tumor cells and radiological features were "key" to the diagnosis.

EOS is very aggressive tumor. It recurs locally in 75% of the cases and develops distant metastases in 60% of the patients, primarily to lungs [4]. Cutaneous metastasis from sarcoma is rare [10]. Metastasis of EOS to the skin is extremely rare, and only one case of breast osteosarcoma that gave metastasis to cutaneous tissue has been reported in the literature [11]. In our case, skin metastasis was discovered before the radiologic detection of the pulmonary nodules. Groin lymph node was invaded by the tumor, suggesting that the neoplasm spread largely through the lymphatic channels. Sarcomas in general metastasize hematogenously to viscera, notably to lungs, in contrast to epithelial malignancies that disseminate via lymphatics to regional lymph nodes. Incidence of lymph node metastasis from sarcomas is low, although some subtypes such as angiosarcomas and rhabdomyosarcomas may do so [12].

The progression of a specific neoplasm towards a more "aggressive" phenotype at the site of metastasis can be observed in several neoplasms. The precise mechanisms that promote this phenomenon have not been identified yet. However, the role of the metastatic site microenvironment should be taken under consideration. Malignant cells interact with both the cellular and extracellular components of the host microenvironment via the production and secretion of stimulatory growth factors and cytokines, namely VEGF, TGF-beta, MMP, EGF, MAPK [13–15]. It is very possible that this "cross-talk" alters the biological behavior of EOS and promotes phenotypic diversification. Furthermore, in the present report we attempted to make a molecular characterization of an EOS at its metastatic site. Immunohistochemical staining for the cell cycle regulatory protein p53 did not display positive immunoreactivity. This finding is in concert with a previous study of Jensen and colleagues, which showed that p53 is immunopositive only in 24% of EOS [4]. It is well established that genomic instability is frequent in primary osteosarcomas, and is associated with unfavorable outcome [5, 16]. Evaluation of gene loss or chromosome aneusomy by FISH on paraffin sections is often difficult due to artifacts related to truncation and overlapping cells. In our patient, detailed FISH analysis revealed significant losses of chromosomes 9 (*p16* locus), 13 (*Rb* locus) and 17 (*p53* locus). However, the significance of the copy number gains in the centromere probe for chromosome 9 is unknown and may indicate involvement of genes other than *p16*, *Rb* and *p53* in tumor progression of EOS.

Soft tissue and cutaneous metastases from mesenchymal neoplasms are rare. Some myxoid liposarcomas have been known to develop distant soft tissue metastases [17, 18].

The possibility of multifocality has been raised in such cases. In our patient, the temporal sequence of events indicates true metastasis. The reasons of the infrequency of cutaneous and subcutaneous metastases remain obscure. Molecular and genetic analyses in large series of cases have to be carried out in order to provide new insights into the biological events that are implicated in the pathogenesis of metastases to unusual sites.

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