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Case study

Malignant transformation of polyostotic fibrous dysplasia with aberrant keratin expression☆,☆☆

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Summary Malignant transformation of fibrous dysplasia (FD) is exceedingly rare, occurring in less than 1% of all FD cases, and has been described in both monostotic and polyostotic forms of this entity. We report a case of a large proximal femur mass arising in a 45-year-old man. The biopsy revealed a high-grade pleomorphic malignancy that focally expressed multiple keratins. Based on the presence of keratin immunoreactivity, the morphologic differential diagnosis included metastatic sarcomatoid carcinoma. However, review of the clinical information revealed a history of polyostotic FD, and imaging findings were compatible with malignant transformation of FD. The resected neoplasm was biphasic and composed of areas of conventional FD admixed with a high-grade pleomorphic malignancy. Activating *GNAS* mutations were identified in both components. To the best of our knowledge, this is the first description of keratin expression in malignant transformation of FD.

1. Introduction

Fibrous dysplasia (FD) is a benign fibro-osseous lesion of bone. Rare cases undergo malignant transformation, and the first such case was reported in 1945 by Coley and Stewart [1-4]. Malignant transformation occurs in both monostotic and polyostotic forms of FD, occurring in less than 1% of all FD cases [2], and may be de novo or may follow exposure to radiation [2]. The malignant component is most commonly composed of high-grade osteosarcoma (osteoblastic, chondroblastic, and fibroblastic), chondrosarcoma, and undifferentiated pleomorphic sarcoma [2,3,5]. We report aberrant keratin expression in a case of malignant transformation of FD arising in the proximal femur of a 45-year-old man. Pathologists should be aware that the sarcomatous component of FD with malignant transformation may show anomalous keratin expression to avoid misclassification as metastatic sarcomatoid carcinoma.

2. Materials and methods

Immunohistochemistry was performed on 4-μm-thick formalin-fixed, paraffin-embedded tissue for the following antibodies: cytokeratin cocktails AE1/AE3 (clone AE1/AE3, 1:200; Dako, Santa Clara, CA) and OSCAR (clone OSCAR,

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1:100; BioLegend, San Diego, CA), desmin (clone DER11, 1:100; Leica Biosystems, Buffalo Grove, IL), S100 (polyclonal, 1:4000; Dako), CD31 (clone JC/70a, 1:350; Dako), FLI-1 (clone G146-254, 1:50; BD Biosciences, San Jose, CA), and INI-1 (clone 25, 1:800; BD Biosciences). *GNAS* mutations were detected by polymerase chain reaction using previously described methods [6].

3. Case report

A 45-year-old man with known polyostotic FD presented to clinic for possible hip replacement because of increasing pain, decreased range of motion, and shortening of his left lower extremity. Radiographs from 9 years before presentation document the extent of polyostotic FD involving the pelvis, left femur, and left tibia (Fig. 1A and B). Physical examination confirmed the limited range of motion. New radiographs of the pelvis and left proximal femur at the time of presentation again demonstrate the changes of polyostotic FD but reveal a new aggressive-appearing purely lytic destructive lesion with extensive cortical destruction anteriorly in the left proximal femoral intertrochanteric region (Fig. 1C and D). Computed tomography and magnetic resonance imaging (MRI) confirm the presence of an aggressive mass in the left proximal femur with cortical and medullary destruction and revealed a large enhancing nonmineralized soft tissue mass (Fig. 1E and F).

A core biopsy was performed, revealing a high-grade malignant neoplasm composed of pleomorphic spindle cells with nuclear hyperchromasia and occasional prominent nucleoli (Fig. 2A). Mitotic figures, including atypical mitoses, were frequently observed; however, osteoid or cartilaginous matrix production was not present. In an attempt to further characterize the tumor, a battery of immunohistochemical stains was performed. The tumor cells were focally strongly positive for keratin cocktails AE1/AE3 (Fig. 2B) and OSCAR (Fig. 2C) and negative for desmin, S100, CD31, and FLI-1. Nuclear staining for INI-1 was retained.

Given the presence of focally strong keratin expression, a diagnosis of metastatic sarcomatoid carcinoma was favored based on morphology alone. However, given the clinical history of well-documented polyostotic FD and careful correlation with current and previous radiographs showing a new malignant mass arising within a preexisting well-circumscribed FD lesion, previously containing central ground glass attenuation, within the left proximal femur, a diagnosis of FD with malignant transformation was made.

The patient was staged and fully evaluated with no evidence of metastatic disease or an occult carcinoma identified. He subsequently underwent 3 cycles of chemotherapy (ifosfamide and doxorubicin); however, on follow-up imaging, the neoplasm grew in size. Four months after the initial biopsy, the patient underwent an external hemipelvectomy. Gross examination revealed a 21 × 11.2 × 10.2-cm lobulated, soft, tan-pink homogenous mass involving the femoral neck and head and encasing the internal hardware placed during a valgus-producing osteotomy with blade-plate fixation that the patient underwent as a child. The tumor penetrated through the femoral cortex and extended into surrounding soft tissue (Fig. 3A). Microscopic examination revealed malignant cells arranged in loose fascicles and sheets with minimal treatment

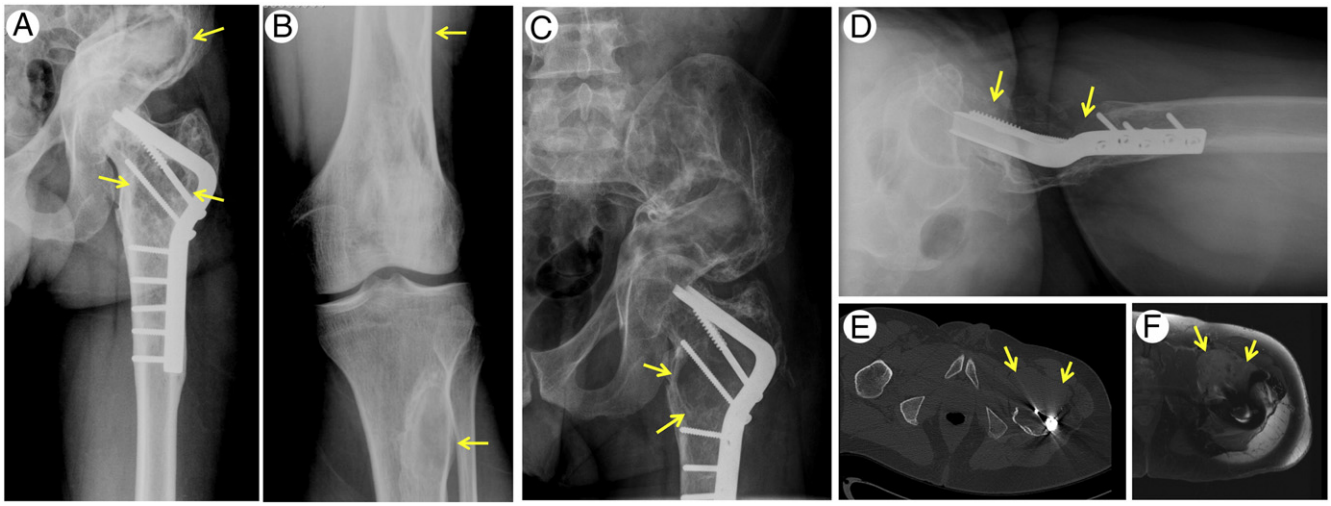

Fig. 1 Anteroposterior radiographs of the left hip (A) and left knee (B), taken 9 years before presentation, demonstrating the classic findings of polyostotic FD with bubbly mixed lytic and sclerotic, slightly expansile lesions with central ground glass attenuation in the left innominate bone, left proximal and distal femur, and within the left proximal tibia (arrows). In addition, noted are postoperative changes in the proximal left femur from prior femoral osteotomy with blade-plate and screw fixation. Anteroposterior (C) and lateral (D) radiographs of the left hip at presentation demonstrate changes of polyostotic FD in the left innominate bone and proximal femur with a new lytic destructive lesion in the left proximal femoral intertrochanteric region representing a change since the prior radiographs that is suspicious for malignant degeneration of FD (arrows). Axial computed tomography (E) and axial postcontrast fat-saturated T1-weighted MRI images (F) of the left proximal femur demonstrate an aggressive mass with cortical destruction anteriorly and a large enhancing soft tissue mass (arrows).