Human Pathology (2014) **45**, 1541–1545

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Human PATHOLOGY

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Case study

Squamous cell carcinoma arising in dedifferentiated chondrosarcoma proved by *isocitrate dehydrogenase* mutation analysis☆

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Received 4 October 2013; revised 26 November 2013; accepted 10 February 2014

Keywords:
Chondrosarcoma;
Dedifferentiation;
IDH;
Squamous cell carcinoma

Summary Dedifferentiated chondrosarcoma is a primary bone tumor characterized by the presence of both low-grade cartilaginous and high-grade malignant noncartilaginous components. The high-grade noncartilaginous component is typically a pleomorphic fibroblastic spindle cell sarcoma. Dedifferentiation into a malignant epithelial component is extremely rare. In this report, we present a 74-year-old woman who developed a metastatic squamous cell carcinoma in the right inguinal area 1 year after wide resection of her right proximal femur for a dedifferentiated chondrosarcoma. The dedifferentiated component was composed of poorly differentiated epithelioid cells with foci of squamous cell carcinoma. Mutational analysis was performed, and the *isocitrate dehydrogenase 1* R132C mutation was detected in the low-grade chondrosarcoma, dedifferentiated chondrosarcoma as well as the metastatic squamous cell carcinoma. And this mutation was not detected in patient's normal tissue. Our study supports the theory that both the chondrosarcoma cells and dedifferentiated epithelioid tumor cells arose from the same clonal origin.

1. Introduction

Dedifferentiated chondrosarcoma is a distinct variant of chondrosarcoma and accounts for 10% of all chondrosarcomas. It is the most aggressive type of chondrosarcoma and has a poor prognosis [1]. By definition, it is composed of a low-grade cartilaginous neoplasm with an abrupt transition to a high-grade noncartilaginous component, which is almost always mesenchymal in differentiation [2]. The dedifferentiated component usually demonstrates the features of a high-grade pleomorphic fibroblastic sarcoma or osteosarcoma and infrequently rhabdomyosarcoma, leiomyosarcoma, or angiosarcoma. Steps in the molecular pathogenesis of dedifferentiated chondrosarcoma have recently been elucidated, and an important driver is believed to be a mutation of the metabolic enzyme isocitrate dehydrogenase (*IDH*) genes (*IDH1* and *IDH2*),

☆ Disclosures: The authors declare no conflict of interest.

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http://dx.doi.org/10.1016/j.humpath.2014.02.016
0046-8177/

which has been identified in 56% of dedifferentiated chondrosarcomas [3].

Dedifferentiation of chondrosarcoma into an epithelial component is extraordinarily rare. To date, only 2 cases of primary chondrosarcoma with a distinct squamous cell carcinoma component have been described in the literature [4,5]. Herein, we describe the clinicopathological features of an unusual case in which a dedifferentiated chondrosarcoma with a component of squamous cell carcinoma subsequently metastasized as squamous cell carcinoma. To further determine the relationship between the squamous cell carcinoma and the dedifferentiated chondrosarcoma, mutational analysis was performed on the *IDH1* and *IDH2* genes from different components of the tumor and the metastasis.

2. Case report

2.1. Clinical features

A 73-year-old Hispanic woman presented with a several-week history of progressive pain in her right femur and inability to walk. A radiograph of the right hip showed a radiolucent lesion with stippled calcifications that produced deep endosteal scalloping in the medial proximal femur. The margins of the tumor were poorly defined, and there was no evidence of a fracture. Magnetic resonance imaging revealed a 20-cm long intramedullary tumor that had low signal intensity on T1-weighted images and high signal intensity on T2-weighted images, which extended from just below the lesser trochanter into the diaphysis (Fig. 1A). The patient underwent complete resection of the right proximal femur with negative margins. The diagnosis of dedifferentiated chondrosarcoma was rendered. The patient did not receive any adjuvant treatment and remained disease-free until 1 year later when she developed pain in the right inguinal area that radiated to the right thigh. A computer-aided tomographic scan revealed a right inguinal mass and right pelvic lymphadenopathy. An incisional biopsy revealed metastatic squamous cell carcinoma in the inguinal lymph nodes. The patient then received 3 cycles of chemotherapy including carboplatin and docetaxel, and her course was complicated by chest pain, diarrhea and renal failure. Positron emission tomographic scan did not demonstrate any noticeable regression of the tumor. Subsequently, the patient had a right femoral and external iliac lymphadenectomy that revealed metastatic squamous cell carcinoma in 2 of 8 superficial femoral lymph nodes and 1 of 2 external iliac lymph nodes. The patient was under rehabilitation and recovery from surgery during the last follow-up 4 months after resection of her metastatic squamous cell carcinoma.

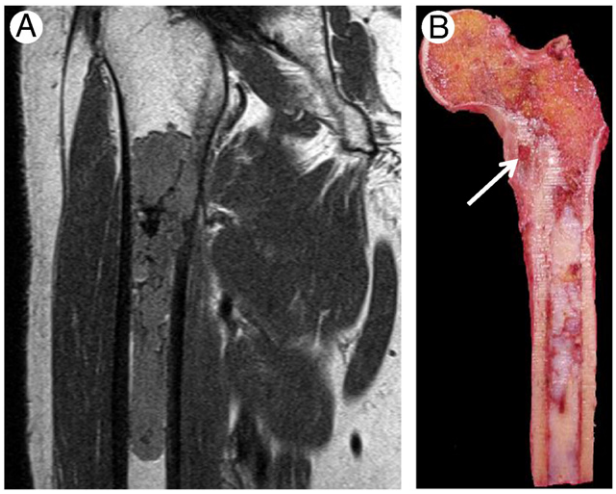

Fig. 1 A, T1-weighted magnetic resonance imaging image shows a 20-cm long intramedullary tumor that extends from just below the lesser trochanter to the middiaphysis. B, Resected proximal femur shows the cartilaginous neoplasm in the medullary cavity with one distinct eccentric red nodule, which represents the dedifferentiated component (arrow).

2.2. Pathologic features

Coronal section of the proximal femur revealed an intramedullary 20-cm long, white-to-bluish gray, glistening lobulated cartilaginous tumor. In the proximal medial portion of the tumor, eroding into but not through the outer surface of the cortex was a 0.8-cm ill-defined distinct hemorrhagic tan component (Fig. 1B, arrow). There was no soft tissue extension.

Microscopically, the cartilaginous component consisted of lobules of neoplastic hyaline cartilage that replaced the marrow and grew with an infiltrative pattern encasing preexisting bony trabeculae (Fig. 2A). The cartilage showed moderate hypercellularity, and the chondrocytes demonstrated mild cytologic atypia manifested by nuclear enlargement and hyperchromasia. The distinct tan nodule consisted of sheets of polyhedral cells with well-defined cell borders, moderate amounts of eosinophilic cytoplasm and large vesicular nuclei with prominent nucleoli, and scattered osteoclast type giant cells (Fig. 2B). In one focus, the tumor cells demonstrated the morphologic features of squamous differentiation and grew in small nests, contained intensely eosinophilic keratinized cytoplasm, and were surrounded by desmoplastic stroma (Fig. 2C). Immunohistochemistry showed that the nonkeratinized epithelioid cells focally expressed pancytokeratin (Fig. 2D), whereas the keratinized cells were intensely positive (Fig. 2E). The open biopsy from the inguinal mass and enlarged lymph nodes that developed 1 year later revealed metastatic keratinizing squamous cell carcinoma that was identical in appearance to that present in the dedifferentiated component of the chondrosarcoma (Fig. 2F).

2.3. *IDH* mutation analysis

DNA samples were extracted from formalin-fixed, paraffin-embedded, and decalcified (specimens from bone)