Primary Dedifferentiated Parosteal Osteosarcoma in a 21-Year-Old Man

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Surface osteosarcomas are a group of tumors that account for approximately 4% to 10% of reported osteosarcomas.[1,2] There are 4 types of surface osteosarcomas: parosteal, periosteal, dedifferentiated parosteal, and high-grade surface.[2,3] Conventional parosteal osteosarcoma (c-POS) is the most commonly occurring variant; it accounts for approximately 75% of diagnosed surface osteosarcomas.[2,4] It is characterized as a low-grade (Broders grade 1-2), slow-growing malignant tumor arising from the juxtacortical tissues with low potential for metastasis and a good prognosis after surgical resection.[3,5-7]

Dedifferentiated POS (dd-POS) is a variant in which a low-grade c-POS is associated with a high-grade sarcoma either at time of presentation (primary dd-POS) or time of recurrence (secondary dd-POS). Such tumors are associated with a higher rate of systemic metastasis and a worse prognosis when compared with c-POS cases.[3,5,6,8,9]

We describe the case of a patient who presented with a distal femur lesion that was thought to be a low-grade c-POS, but was subsequently found to be primary dd-POS. This case illustrates the difficulties in correctly diagnosing such tumors. The patient provided written informed consent for print and electronic publication of this case report.

Case Report

In January 2006, a 21-year-old man was referred to our institution with a large, painful mass on the left distal femur that had been progressively enlarging and becoming more painful over the preceding 2 years. At presentation, he said the pain was sharp, intermittent, 8/10 in intensity, and not associated with night pain. He also reported of knee movement being limited by the mass. On examination, a nontender, nonmobile bony mass roughly 10 cm in diameter was found on the left distal femur. Knee extension was limited to approximately 100° in the left knee. Plain radiographs showed a blastic lesion of the left distal femur, destructive changes within the femoral canal, and an enlarged periosteal reaction that was consistent with classic osteosarcoma (Figure 1A), though POS was considered a less likely differential consideration. Magnetic resonance imaging (MRI) showed a large soft-tissue mass around the distal femur near the femoral vessels with cortical destruction in the posterior aspect of the femur (Figure 1B). Whole-body bone scan showed isolated, increased activity in the left distal femur. Biopsy results showed the lesion to be a POS (Figure 2), and the patient was scheduled for surgery.

Two weeks later, the patient underwent radical, en bloc resection of the 29-cm distal area of the left femur. Surgical margins were not ideal because of the adherence of the femoral vessels and the sciatic nerve to the tumor, but they were as wide as possible. After the attending pathologist determined that the intraoperative frozen-section margins were negative, an oncologic left total knee arthroplasty was performed using the Global Modular Replacement System (GMRS; Stryker Orthopaedics, Mahwah, New Jersey). On postoperative day 3, however, the pathologist notified us that the permanent section showed the proximal marrow margins were positive for tumor involvement and that the tumor had undergone dedifferentiation from low-grade to high-grade osteosarcoma (Figure 3).

After discussion regarding options, the patient decided on a limb-salvage attempt and began a 3-month course of adjuvant chemotherapy. He was treated with a high-risk osteosarcoma chemotherapy regimen. After the initial

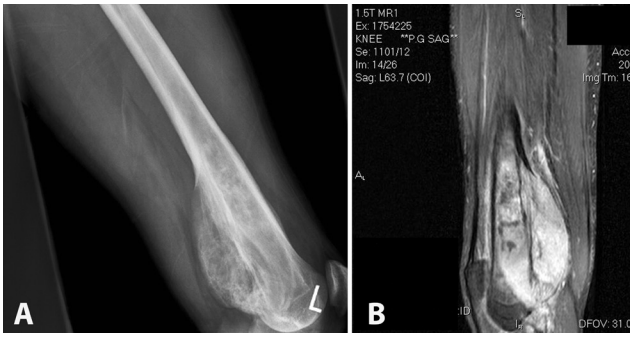

Figure 1. (A) Preoperative radiograph shows destructive lesion in distal femur with large soft-tissue component. (B) Preoperative magnetic resonance imaging shows large soft-tissue mass arising from distal femur and extending nearly to femoral vessels with significant posterior cortical destruction.

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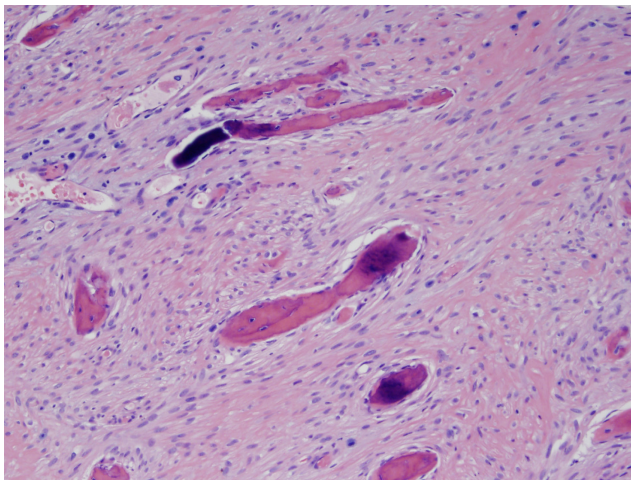

Figure 2. Biopsy specimen shows low-grade spindle-cell pattern with bone spicules—consistent with parosteal osteosarcoma (hematoxylin and eosin stain, original magnification ×100).

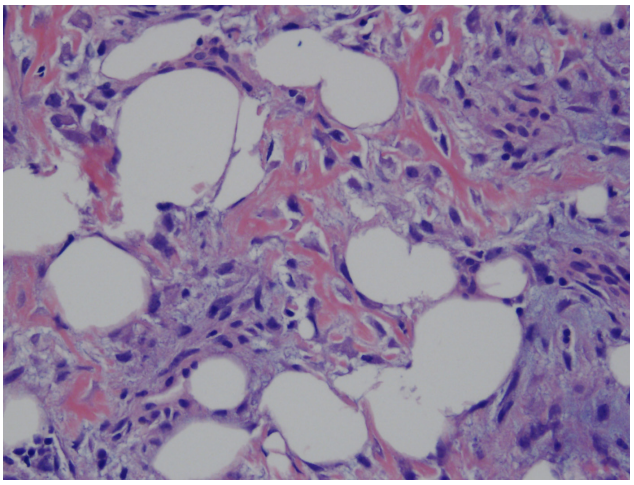

Figure 3. Postresection specimen shows high-grade pleomorphic spindle-cell lesion with lacelike osteoid—consistent with classic osteogenic sarcoma (hematoxylin and eosin stain, original magnification ×200). When this finding is combined with low-grade histology in majority of specimen, dedifferentiated parosteal osteosarcoma can be diagnosed.

courses of adjuvant chemotherapy were complete, staging studies showed no evidence of distant disease or new tumor progression. The patient then underwent radical resection of the left proximal femur, including the proximal portion of the prosthesis that was placed at his index operation. The prosthesis was then converted to a total femur replacement with hemiarthroplasty using the GMRS (Figure 4). Permanent sections showed that the proximal femur had residual high-grade osteosarcoma, as identified from endosteal scrapings, and that 20% to 30% of the residual tumor was viable. Although the chemotherapeutic response was less than optimal, the patient then underwent the remainder of the high-risk adjuvant chemotherapy. At 48-month follow-up, he had no known local or distant disease.

Discussion

Dedifferentiated POS is an extremely rare form of osteosarcoma (approximately only 89 cases of dd-POS have been reported in the literature[5]). Surface osteosarcomas represent only 4% to 10% of all osteosarcomas, and c-POS accounts for roughly 75% of these tumors.[1,2,4] The incidence of dedifferentiation in POS has ranged from 16% to 20% at the Mayo Clinic[6,9] and from 24% at the Rizzoli Institute[3] to 43% at the MD Anderson Cancer Center.[7]

In their original study, Wold and colleagues[9] found secondary dd-POS to be more prevalent (10/11 cases) than primary dd-POS. However, more recent studies have proved primary dd-POS more common (11/12 cases at MD Anderson Cancer Center,[7] 19/29 cases at Rizzoli Institute[5]). These tumors occur most typically between the third and fifth decades of life.[3,5,10,11] Most recently, Bertoni and colleagues[5] reported a higher mean age for patients with dd-POS (36 years) than for patients with c-POS (28 years). Although some studies have found that dd-POS affects women more often than men,[3,5,12] others have found equal rates of tumor incidence for the sexes.[7,10] Most parosteal osteosarcomas, both c-POS and dd-POS, arise from the metaphyseal region of long bones.[3,5,7,13] The most common site of involvement is the distal femur; other frequent sites include the proximal humerus and the proximal tibia.[2,3,5-7,13,14] Our patient presented for workup of his lesion at the start of his third decade, and his case is an example of primary dedifferentiation. Furthermore, his tumor was located in the most common POS location, the distal femur.

Clinically, POS most often presents as a slow-growing mass with or without pain.[3,5,7,14] Sheth[7] found that mean duration of symptoms at presentation was 15 months for c-POS and 7 months for dd-POS. Bertoni and colleagues[5] found that all dd-POS cases in their study were stage IIB at presentation. Macroscopically, POS appears as a hard, lobulated, calcified mass that attaches to the bony cortex by a broad tumor base that typically wraps around the long bone.[5,13] Often POS is closely related to neurovascular bundles, which can make wide surgical margins very difficult to obtain during tumor treatment.[5] Our patient had the typical onset of symptoms before presentation, and his tumor was noted to be adhering to the femoral vessels and the sciatic nerve, which made the surgical margins less than ideal in the resection. On gross inspection, the cut surface of c-POS typically displays a "homogenous, solid ivory-type bone appearance."[5] In contrast, the cut surface of dd-POS is "nonhomogenous" and demonstrates "solid gritty areas intermixed with a tan soft sarcoma component that occasionally showed destruction of the cortex and medullary canal extension."[5] During surgery, our patient's lesion seemed not to have a grossly appearing high-grade tumor; microscopically, the tumor proved otherwise.

Histologically, c-POS is a low-grade (Broders grade

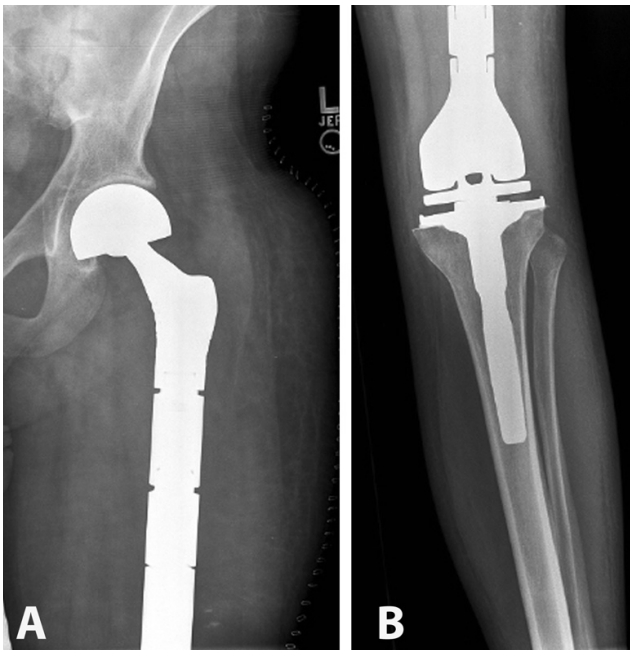

Figure 4. Postoperative AP radiographs of the hip (A) and knee (B) show total femur replacement with hemiarthroplasty.

1-2) tumor that consists of well-formed osseous trabeculae surrounded by spindle cells with minimal nuclear atypia and little to no pleomorphism.[3,5,7,8,13-15] In cases of dd-POS, this low-grade tumor component is associated with a high-grade tumor component that histologically shows a high mitotic rate and prominent anaplasia, either at initial presentation in primary dd-POS, or during recurrence of an earlier c-POS tumor in secondary dd-POS.[3,5,6,11,16] Most commonly, this high-grade component has the appearance of high-grade osteogenic osteosarcoma, fibrosarcoma, or malignant fibrous histiocytoma.[11] However, cases of dedifferentiation into giant cell–rich osteosarcoma, chondroblastic osteosarcoma, liposarcoma, and rhabdomyosarcoma also have been reported.[5,11,12] In the past, there was some controversy as to whether medullary canal involvement of the tumor correlated with presence of high-grade lesions.[7] Studies have shown no significant differences between c-POS and dd-POS in incidence of medullary canal involvement and concluded that this involvement cannot be used as an indicator of tumor aggressiveness or in prognosis.[5,7] In the present case, our patient had a primary dd-POS tumor with a high-grade component consisting of osteogenic osteosarcoma, and this tumor involved the medullary canal.

Radiologically, c-POS is an eccentric, lobulated, densely mineralized lesion that appears "pasted on" the cortex of the bone by means of a broad base.[8,13] Typically, this lesion is attached to the cortex in sessile fashion and a cleavage plane may separate the remaining tumor from the underlying bone.[14] The question has been raised as to whether areas of radiolucency within the POS tumor signify areas of dedifferentiation.[8,9,11,17] Sheth and colleagues[7] found that, whereas all patients with dedifferentiated tumors had radiolucent areas that corresponded with high-grade tumor, 77% of patients with c-POS also had areas of radiolucency. Bertoni and colleagues[5] more recently found that only 62% of dd-POS cases in their study had evidence of radiolucency. Both Sheth and colleagues and Bertoni and colleagues concluded that, though these radiolucencies are not specific for dd-POS, they should raise suspicion of dedifferentiation and are areas from which biopsies should be taken. In addition, absence of such lucencies does not rule out the diagnosis of dd-POS.[5,7] In our patient's case, radiographs showed a blastic lesion and did not show evidence of radiolucencies.

Although there can be local recurrences, and incomplete surgical removal can lead to a high recurrence rate, c-POS is a low-grade sarcoma with low potential for systemic metastasis and a good prognosis after tumor resection.[3] Long-term survival with the tumor can be as high as 90%, with a local recurrence rate of approximately 35% and a distant metastatic rate of approximately 5%.[3,6,7] Unfortunately, dd-POS is associated with a worse prognosis, and patients are subject to a higher rate of systemic metastasis.[3,5-7] Most commonly, the tumor metastasizes to the lungs.[5,7,8,10,11,15,16] Wold and colleagues[9] stated that the prognosis of dd-POS was similar to that of conventional intramedullary osteosarcoma, and Bertoni and colleagues[5] stated that the prognosis is better than that of high-grade surface osteosarcoma. Okada and colleagues[6] and Sheth and colleagues[7] found an almost 50% mortality rate for the tumor. However, Bertoni and colleagues[5] more recently found a dd-POS mortality rate of approximately 28% and concluded that there was no difference in prognosis between primary and secondary forms of the tumor.

Management of POS is primarily surgical and usually includes limb salvage. Surgical resection without adjuvant chemotherapy is warranted for c-POS, though surveillance is important because of the risk for local recurrence.[3,5,7] For dd-POS, management involves adjuvant chemotherapy followed by wide resection.[3,5,7,16] However, results from studies by Sheth and colleagues[7] and Bertoni and colleagues[5] have not been encouraging with respect to the effectiveness of adjuvant chemotherapy in improving mortality.[5,7] When we determined that our patient's tumor was a case of dd-POS, we administered a 3-month course of adjuvant chemotherapy. Unfortunately, pathology from the second surgery showed that the tumor's response to treatment was less than optimal.

This scenario may also arise with other bone and soft-tissue sarcomas, such as dedifferentiated liposarcoma. When MRI shows what appears to be a low-grade fatty neoplasm with a discrete area of heterogeneity, one must beware that dedifferentiation may have occurred. Metabolic imaging, such as 2-(fluorine-18) fluoro-2-deoxy-D-glucose (^{18}FDG) positron emission tomogra-

phy (PET), may be helpful in assessing the potential for a higher grade lesion within a mass that appears to be low-grade overall. PET may also be helpful in identifying the best place to perform a biopsy on a tumor, as it will likely demonstrate distinct areas of higher metabolic activity that should not be present in a low-grade lesion.

In conclusion, dd-POS is an extremely rare type of osteosarcoma in which a low-grade tumor with an excellent prognosis is found to be associated with a high-grade tumor, and therefore, the lesion has a much poorer prognosis and increased risk for metastasis. In this article, we report a case of dd-POS of the left distal femur. This is a unique case because this type of tumor is so rare. Furthermore, this case is unusual because of the way it unfolded. Originally, this was believed to be a case of c-POS, and resection was performed with limb salvage using total knee arthroplasty. After the procedure was completed, further histologic assessment showed that the lesion had a high-grade component at the intramedullary extent of the surgical margins. Wide margins are needed to treat all osteosarcomas. The index procedure would have achieved adequate margins except for the discordance between frozen-section and permanent-section analysis. After we examined this case in retrospect and thoroughly reviewed the literature, it became apparent that a challenge in dealing with this tumor is being able to correctly characterize the lesion. Unfortunately, presurgical biopsy in this case was performed outside an area of dedifferentiation. In the future, metabolic imaging studies such as PET may help in assessing prebiopsy evaluation of the tumor.

Authors' Disclosure Statement

The authors report no actual or potential conflict of interest in relation to this article.

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This paper will be judged for the Resident Writer's Award.