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Case report 679

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Radiological studies

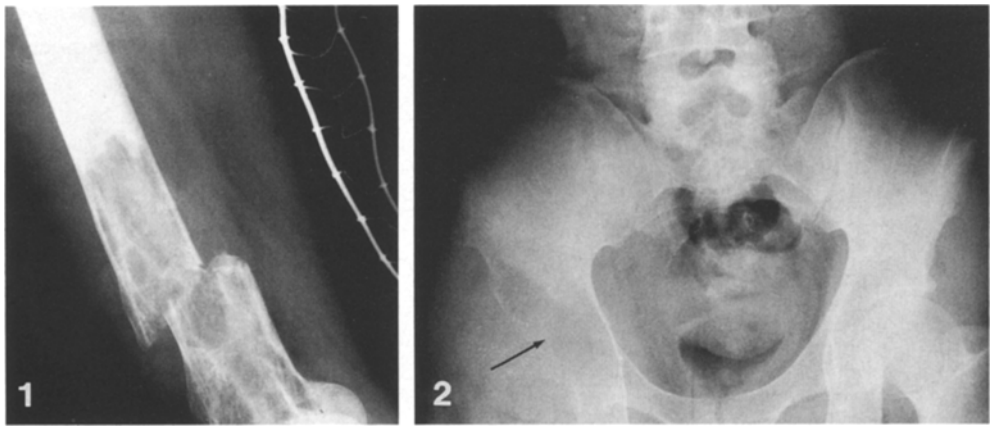

Fig. 1. Lateral view of the lower part of the right femur shows a large lytic lesion, associated with marked cortical attenuation and a pathological fracture line. A relatively sharp margin around the lesion is seen. No periosteal reaction is noted

Fig. 2. Radiograph of the pelvis reveals a large lytic lesion of the acetabulum (*arrow*) and an accompanying, bulky, soft-tissue mass

Clinical information

A 28-year-old Japanese man was referred to the Aoto Hospital of Jikei University because of a recurrent right femoral bone tumor.

He was well until 2 years previously when he sustained a pathological fracture of the right femur at the time of a fall. Radiographs of the femur revealed a wide area of irregular destruction extending from the distal end to the midshaft of the femur. Cortical thinning as well as a transverse fracture was noted, but no soft-tissue mass outside the bone or abnormal periosteal reaction was present (Fig. 1).

Following transient fixation of the right femur, the lesion was resected, and an endoprosthesis was inserted 2 months later. Postoperatively, he was in good condition for 1 year, then two subcutaneous nodules appeared in the lower part of the right thigh. These nodules were excised 3 months later. Subsequently, he had progressively increasing pain in the right thigh. Radiographic examination disclosed destructive changes suggestive of recurrent tumor at the resected end of the femur. Disarticulation of the right hip joint was performed. He then was referred to the Aoto Hospital of Jikei University because of intractable coxalgia.

On admission, radiological examination revealed irregular destruction of the upper part of the acetabular roof of the right iliac bone (Fig. 2). Right hemipelvectomy was performed 11 months later. Soon after the operation, pain developed over the left shoulder, and roentgenograms showed a destructive alteration in the outer portion of the left clavicle consistent with a metastatic lesion. The clavicular lesion was resected.

One month thereafter, the tumor recurred in the right inguinal area, which enlarged rapidly, forming a huge mass with hemorrhagic ulceration of the overlying skin.

Laboratory data at this time including complete blood count, alkaline phosphatase, hepatic and renal function were normal except for a slightly elevated lactate dehydrogenase (LDH) activity (206 mU/ml, normal range 55–135 mU/ml) and mild decrease in total protein content (5.3 g/dl).

The patient was given chemotherapy consisting of daily administration of Chromomycin A_3 and a single injection of cyclophosphamide and OK-432 with no appreciable effect.

Eight months after admission, pleural effusion and ascites appeared, probably due to metastatic neoplasm, and his condition deteriorated further, He died 1 month later. Autopsy was not permitted.

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Diagnosis: Central low-grade osteosarcoma with foci of dedifferentiation

Grossly, the medullary cavity was completely filled with the tumor tissue, which extended from the middle portion of the diaphysis of the femur down to the epiphyseal portion. The tumor was whitish-yellow in color, firm in consistency, and gritty in texture. The involved part of the femur showed a moderate degree of expansion. Thinning of the cortices was prominent, and the boundary between the metaphyseal bony cortex and the tumor was unclear (Fig. 3).

A transverse fracture through the lower end of the diaphysis was present without any hint of a healing process. Two nodular lesions with surrounding hemorrhage were noted in the femoral lesion above and below the fracture (Fig. 3). The tumor resembled fibrous dysplasia, except for the nodular lesions just described. The neoplasm extended into the area in close proximity to the resected margin. The articular cartilage itself showed no gross involvement by the tumor.

Histologically, most of the tumor tissue was composed of interlacing fascicles of spindle cells with a rich fibrous matrix admixed with pre-existing osseous trabeculae. In some areas, the woven trabeculae were surrounded by the spindle tumor cells in a manner similar to fibrous dysplasia (Fig. 4A). Not infrequently, spindle tumor cells were arranged in a storiform pattern. The cellularity in the tumor varied from place to place, and in some areas the neoplastic cells were densely packed, while in others they were distributed fairly sparsely. The tumor cells showed mild pleomorphism, and there were occasional atypical cells with plump, enlarged nuclei, increased chromatin, and small but clearly visible nucleoli

Pathological studies

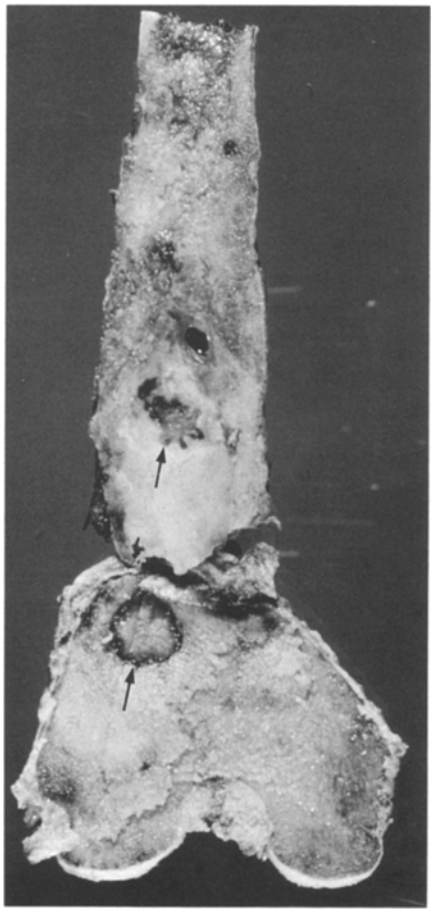

Fig. 3. Gross picture of the resected femoral tumor shows it to be mostly composed of fibro-osseous tissue. Two sharply demarcated nodules are present in the tumor (*arrows*)

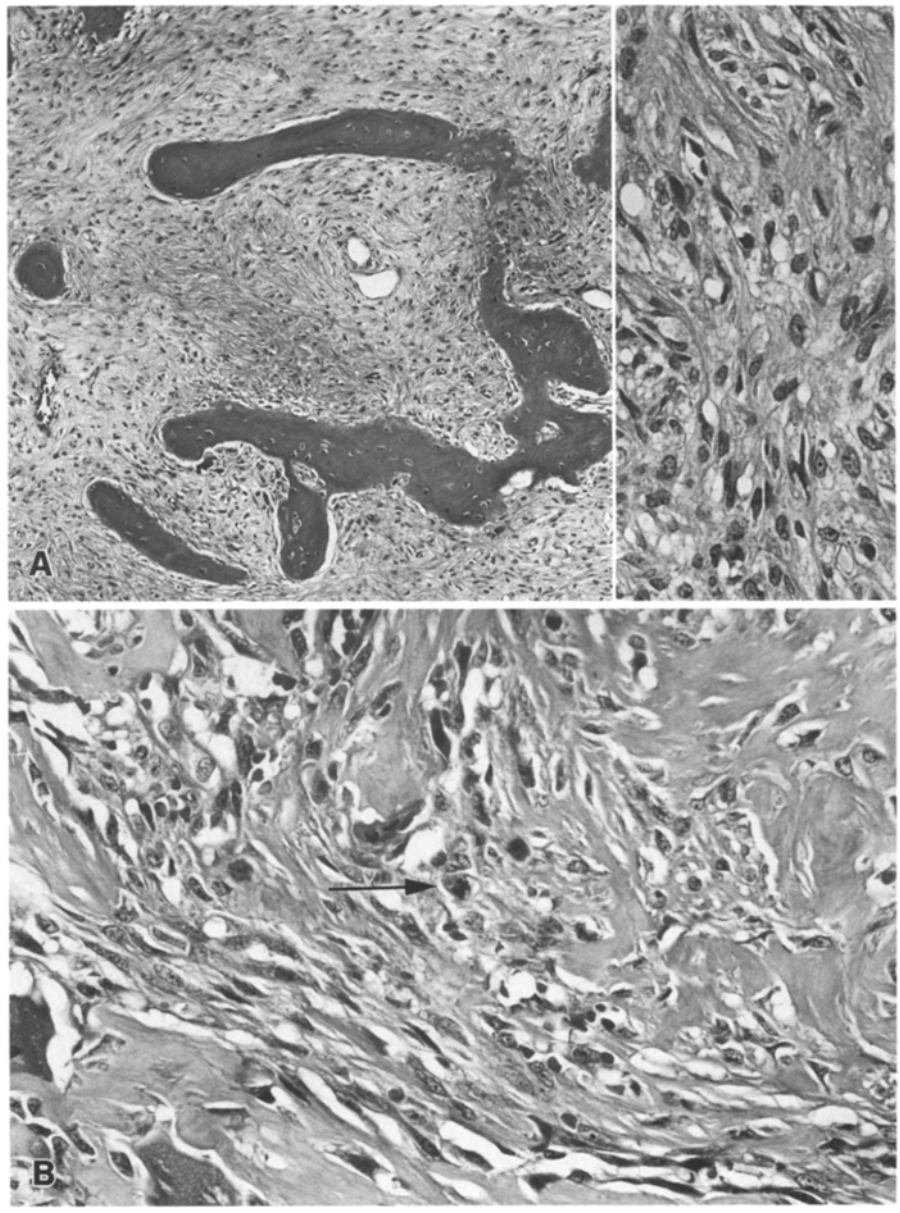

Fig. 4. A *Left*, the tumor is composed of spindle cell stroma and bony trabeculae, resembling fibrous dysplasia (HE × 40). *Right*, higher magnification demonstrates mild pleomorphism and cells with plump, enlarged nuclei (HE × 100). **B** A rare mitotic figure is noted (*arrow*). Osteoid formation is seen, containing neoplastic cells (× 100)

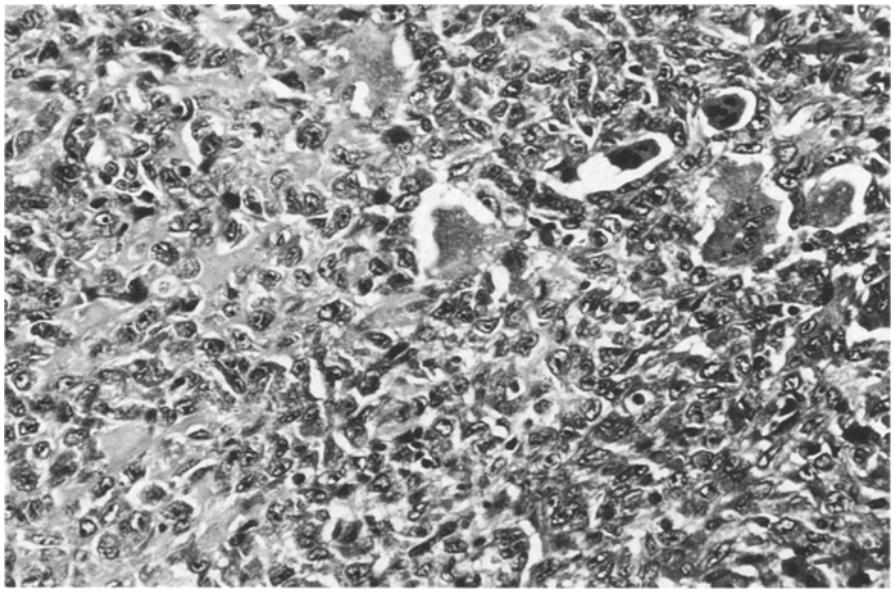

Fig. 5. Dedifferentiated foci disclose more anaplastic neoplastic cells than in well-differentiated portions and lacy osteoid production, as found in conventional osteosarcoma. Note the few osteoclast-type giant cells (× 100)

among tumor cells with slender nuclei or benign-looking, stellate cytoplasm. Mitotic figures were only rarely observed (Fig. 4B). There were a few irregular foci of osteoid tissue in which tumor cells were embedded and arranged haphazardly. Minute forci with chondroid differentiation containing cells suggesting malignancy were also observed. Osteoclast-like giant cells were also seen in small numbers. Necrosis was not present. In contrast, two nodular lesions grossly well-demarcated from the main fibro-osseous tumor showed a histological appearance totally different from the rest of the tumor. These foci consisted of more closely packed tumor cells with more pleomorphic, oval-to-short, spindle-shaped nuclei containing frequent prominent nucleoli. In both nodules, the neoplastic tissue was characterized by the existence of a distinct, lacy, osteoid formation among individual tumor cells, which could be observed in wide tracts, and showed a relatively homogenous staining pattern with embedded neoplastic cells (Fig. 5). The mitotic rate was raised, suggesting the more aggressive, malignant nature of these portions. Necrotic areas were also noted. Additionally, numerous osteoclast-type giant cells were present.

Histological findings in the metastatic lesions, including those from the right iliac bone, clavicle, and inguinal subcutaneous tissue, were essentially identical to each other and closely resembled those of the two nodules in the femoral lesion.

In these metastatic foci, however, there were more extensive necrotic areas, and mitoses were seen more frequently than in the two nodular lesions of the femur. Thus, the anaplasia had increased in these areas.

Discussion

The differential diagnosis must include fibrous dysplasia, which is composed of benign fibrous connective tissue stroma and trabeculae of woven bone arising directly out of the fibrous tissue stroma. In our case, the resected specimen showed localized areas which appeared to be similar to fibrous dysplasia, causing serious diagnostic difficulty. However, such histological features as the presence of densely cellular portions, nuclear pleomorphism, and scattered mitotic figures strongly suggested the possibility of a malignant neoplasm; the osteoid formation occasionally observed in our specimens most likely represents neoplastic osteoid. Considering the intimate contact between this substance and the neoplastic cells, such an appearance would be very unusual for fibrous dysplasia. Furthermore, minute chondroid areas were demonstrated in our case. These findings are totally compatible with and justify the diagnosis of osteosarcoma, especially of the central low-grade variant.

Central low-grade osteosarcoma (CLOS) is a rare primary bone tumor [2, 4], which accounted for just 16 of the 1373 cases of osteosarcoma in the Mayo Clinic, and only a few individual case reports have been described so far [1, 3, 6].

In Unni's series of 27 cases of CLOS [4], it was clinically characterized by a slightly older age distribution than conventional osteosarcoma and a good prognosis. The most common primary sites are the tibia and femur. Of the 27 patients with CLOS, only 4 developed metastatic tumor. According to Unni, radiologically speaking most CLOS lesions had indistinct margins, and occasionally surrounding sclerosis was seen. Trabeculation within the tumor was not uncommon. The tumor grew in an expanding fashion, with unequivocal cortical destruction. Charateristically, periosteal reaction was unusual. In our case, a trabeculated appearance and focal cortical thinning were noted on radiographs, with no significant periosteal reaction. The tumor at the proximal end of the femur had a distinct margin. Although rare, several of the cases in Unni's report also showed this appearance.

It has been stressed that the gross appearance of the tumor consisted of firm fibrous tissue, expanding the affected bone, Microscopically, the tumors were composed of interlacing bundles of spindle cells and osteoid formation. Their nuclei were fairly plump, enlarged, and uniform in shape, and, unlike a conventional osteosarcoma, bizarre nuclei were totally absent. Mitotic figures were rare and in some cases indiscernible. The cells were usually separated by collagen fibers, displaying heavy collagenization. Varying amounts of osteoid were observed in the neoplastic tissue, but most of the lesions showed fairly heavy bone trabeculae admixed with spindle cell stroma, as seen in parosteal osteosarcoma (POS). Most of the trabeculae seemed to arise di-

rectly from the spindle cells. Chondroid areas were observed infrequently, and, when present, this finding was considered to indicate malignancy. The spindle neoplastic cells showed a permeative growth pattern, surrounding preexisting trabeculae of bone, and in some instances invading and destroying the overlying cortex and extending into the soft tissues. These histological features, most of which were observed in our case, could lead to considerable diagnostic difficulty, especially with biopsy specimens, because of their striking similarity to benign fibro-osseous lesions, such as fibrous dysplasia. In making a diagnosis, Unni emphasized that in fibrous dysplasia stromal cells lacked atypia and were arranged parallel to the trabeculae whereas in CLOS the neoplastic cells were atypical and arranged in a herringbone pattern or in interlacing bundles. Xipell and Rush also stressed the importance of the prominence and irregularity of thick trabeculae as well as abnormal cellular arrangement in CLOS [6]. In addition, it has been pointed out that radiological findings such as cortical destruction and ill-defined permeative margins are extremely helpful in clarifying the nature of the lesion.

Patients with this tumor tend to have symptoms for a fairly long period of time, consistent with the slowly growing nature of CLOS, but recurrence is not uncommon. Unni described 11 cases of recurrence; in most the histological appearance was identical to the original lesions, but in some the recurrent tumors had become more biologically aggressive. In our case, foci of highly anaplastic areas were already present at the time of the first operation, and all recurrent lesions had the same microscopic characteristics as the anaplastic foci of the original neoplasm. This case is thus very unusual in that the dedifferentiated lesions were already present in the well-differentiated osteosarcoma prior to the first operation, although in POS, which generally shows quite similar histological features to those of CLOS, the presence of dedifferentiated foci at the first evaluation is occasionally reported [5]. We believe that this is the first case described of dedifferentiated CLOS at initial presentation. The other interesting finding in our case is that there were abundant giant cells in the dedifferentiated foci, most of which showed pleomorphic, atypical nuclei. These findings might lead to the erroneous conclusion that it was a malignant giant cell tumor. This possibility, however, is not justified because there was no other evidence of giant cell tumor.

Since simple excision of tumor resulted in a high rate of recurrence, Unni stressed that wide resection seemed to be the treatment of choice. The prognosis for an adequately treated patient with CLOS is far better than that associated with conventional osteosarcoma. Sundaram et al. also reported a patient with CLOS in whom the tumor in the distal end of the femur was initially treated by curettage, but when it recurred 13 years later, amputation of the leg was performed, and typical CLOS was demonstrated histologically. The postoperative course in this patient was excellent, with no evidence of metastasis or recurrence [3].

In POS, it is well-demonstrated that the existence of a dedifferentiated portion in the tumor is a definitely negative prognostic factor [5]. Likewise, as in our patient, this seems to be the case in CLOS; thus, careful pathological study of the surgical specimen is necessary to establish the correct diagnosis.

In *summary*, an infrequently encountered case of well-differentiated CLOS containing dedifferentiated tumor foci in a 28-year-old Japanese man is reported. The patient died from widespread metastases with a microscopic appearance identical to the anaplastic dedifferentiated lesions of the original tumor. This is, to our knowledge, the first report of a case of CLOS with dedifferentiation at the time of initial surgery. The literature concerning CLOS was reviewed and the diagnostic features of CLOS discussed.

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