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LETTER TO THE EDITOR

Infarct associated sarcoma: A possible pathogenesis based on histological observation of repair tissue origin in two cases

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To the Editor,

Although the absolute majority of bone sarcomas are primary in origin, transformed sarcomas occasionally arise from benign bone tumors or even non-neoplastic bone diseases [1,2]. Indeed, it has been proven that sarcomas develop from chronic infarct of the long bone, the incidence of which has been reported to be 1% of all bone sarcomas [3,4]. To date about 60 cases of infarct associated sarcomas (IAS) have been filed in the world literature.

The pathogenesis of IAS is not established although the reparative tissue adjacent to an infarct has been assumed as source of sarcomatous transformation [1,5–8]. To our knowledge no actual histological evidence to support the assumption has been published. Recently, we observed a definite transition zone to exist in the space between ancient infarct and transformed sarcoma in our two cases. The transition zone consisted of granulation tissues that included interlacing spindle cell fascicle, capillary proliferation with foamy macrophage and chronic inflammatory cells and also cellular atypism of varying degrees. Furthermore, in the distal (sarcoma-side) transition zone atypical spindle cells were observed to imperceptibly merge into high-grade spindle cell sarcoma. We describe our histological observation of a transition zone between infarct and sarcoma, which might be an origin of sarcomatous transformation in bone infarct.

A 58-year-old Korean male was referred to us because of severe, painful swelling of his left knee. Earlier, the pain was negligible lasting for four years but became aggravated during the recent six month period. He was bedridden due to intervening schizophrenic disorder and diabetes mellitus for years. No history of alcohol or steroid abuse, dysbaric working conditions, hemoglobinopathies, pancreatitis, Gaucher's disease, or hereditary bone dysplasia was elicited. Pertinent laboratory data was within normal limits except mild anemia. Conventional radiography showed classic signs of multiple, ancient, bone infarcts involving both the right and left distal femora and proximal tibiae (Figure 1A). The infarct in the left proximal tibia was attended by bizarre expansive bone destruction with cortical rupture. Magnetic resonance (MR) imaging demonstrated bizarre signal intensity changes that matched well with radiographic findings of infarcts and malignant transformation (Figure 1B). Scan microscopy showed a bone infarct (I) and sarcoma (OS) with a typical transitional zone (TZ) in-between (Figure 2A). Low-power microscopy revealed TZ to commence at the distal part of disintegrated infarct in where interlacing spindle cells were definitely bland on high power view (Figure 2B). The islands of infarct in the transformed part presented trabecular and marrow necrosis with irregular calcifications while the infarcts proper were completely free of malignant change. Medium-power view showed TZ to contain interlacing spindle-cell fascicles and capillary proliferation with foamy macrophage, chronic inflammatory cells as well as atypical cells of varied populations. Atypical cells were sparse in number, if any, at the center of TZ (Figure 2C) and gradually increased in number and grade of cellular atypism as the sarcoma region was approached (Figure 2D). In the distal TZ atypical spindle cells imperceptibly

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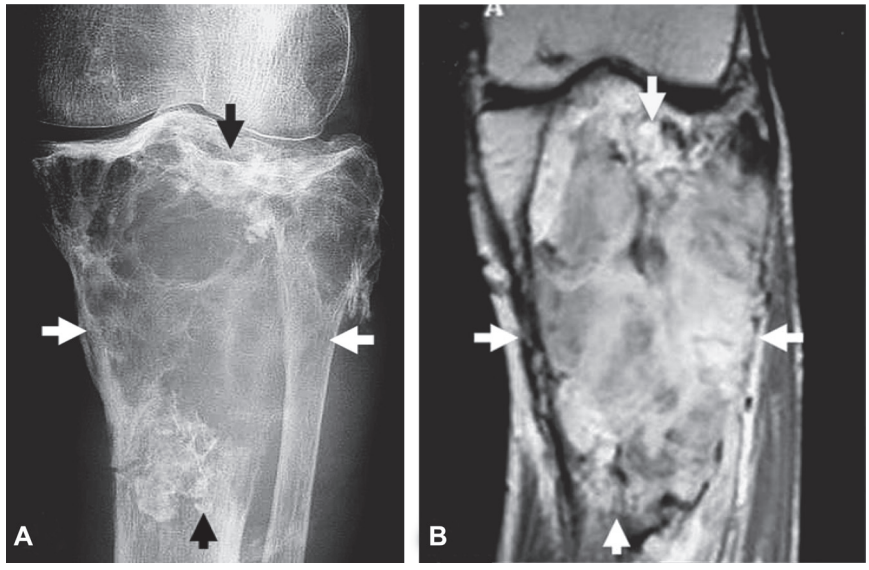

Figure 1. Case 1.

merged into high-grade spindle cell sarcoma (Figure 2E), and lastly high-power view confirmed sarcoma to consist of pleomorphic spindle cells now with occasional atypical mitoses (Figure 2F). In addition there were multiple osteoid foci scattered in other microscopic fields indicating the tumor to be conventional type osteosarcoma (OS in Figure 2A). A below-knee amputation was performed. Permanent section diagnosis was osteosarcoma arisen from bone infarct. Adjuvant chemotherapy was not instituted because of poor performance of patient. He died of metastases 11 months after the initial diagnosis.

The second patient was a 63-year-old Korean male, who was admitted because of pain in the left knee of four month duration. In recent weeks the pain became worsened with expansive swelling of the knee. He had had gastric cancer cured by gastrectomy 10 years ago and colon cancer treated by hemicolectomy two years ago. Familial history and environmental factors were non-contributory in this case either. Pertinent laboratory data were within normal limits except mild anemia. Conventional radiograph showed multiple bone infarcts in both the right and left distal femora and proximal tibiae as in Case 1. The infarcts in the metadiaphysis of the left proximal tibia were blurring in appearance due to osteolysis with the invasion of the medial cortex and MR imaging confirmed cortical rupture and tumefaction denoting malignant transformation. Histological examination confirmed the presence of TZ of repair tissue in this case, too. Medium-power microscopic study of the central TZ showed relatively bland spindle cells arranged in ill-defined long fascicles (Figure 3A) and the distal TZ showed fascicles of spindle cells and moderate to marked atypism towards transformed sarcoma (Figure 3B) and lastly high-power view confirmed the presence of anaplastic spindle cells with abnormal mitosis representing fibrosarcoma (Figure 3C). Patient refused treatment and was lost for follow-up two years after the initial diagnosis.

Sarcoma may develop from bone infarct as cancer arises from draining sinus of chronic osteomyelitis, large burn scars and around a metallic implant [4]. Theoretically, the possibility of intraosseous sarcoma association with a bone infarct was mentioned as early as in 1953 by Johnson [8]. Years later, Furey et al. [9] reported the first two cases of fibrosarcoma arisen from bone infarcts. Torres and Kyriakos [10] published an extensive review of 39 cases of IAS compiled from the literature with the addition of their own case. Thereafter a few cases have sporadically been added. Interestingly most of these sarcomas have been malignant fibrous histiocytoma (MFH), relatively rare primary sarcoma of bone. On the contrary, osteosarcoma, the most common primary bone sarcoma, has rarely reported in association with a bone infarct.

Although the reparative tissues of infarcts have long been suspected as potential resource of sarcomatous transformation no histological evidence has been published. As early as 1953 Johnson [8] stated that there was a propensity for excessive reparative cell proliferation to progress to neoplasia and Dorfman [1] in 1973 proposed that the excessive proliferative activity of reparative tissue would incite malignant transformation. Mirra [4] hypothesized that transformed sarcomas might originate from one of repair-tissue cell components including histiocytes, osteoblasts or fibroblasts, and vessels.

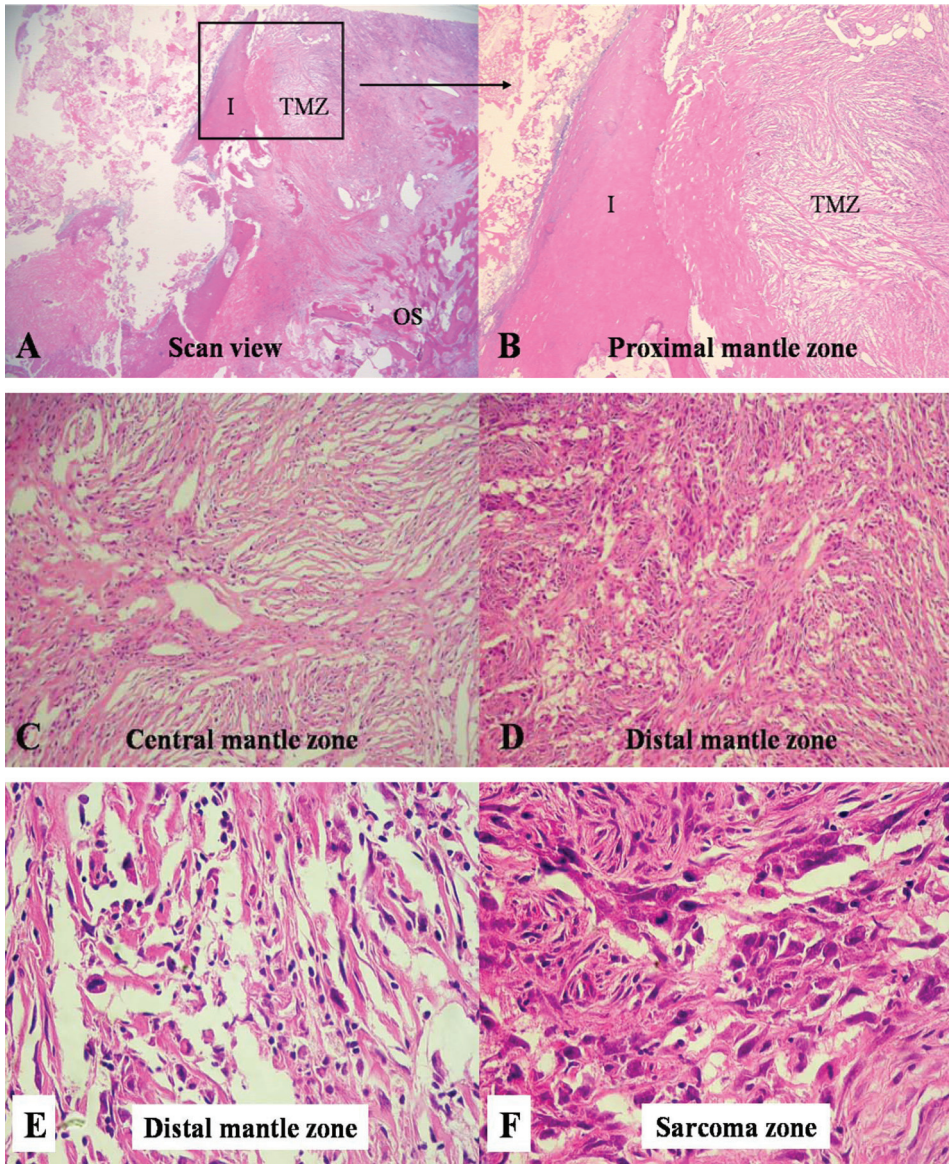

Figure 2. Case 1.

He further postulated that the sarcomas produced by malignant transformation of those cells would be in the form of osteosarcoma, fibrosarcoma, MFH, or angiosarcoma. Indeed, MFH, osteosarcoma, fibrosarcoma, and angiosarcoma have been reported in association with bone infarct but chondrosarcoma, neurogenic sarcoma, or rhabdomyosarcoma has not. In contrast, however, Torres and Kyriakos [10] did not agree with the proposal that sarcoma might arise as a result of some "excessive" or "high degree" of chronic proliferative activity of reparative tissue adjacent to the infarct. Desai et al. [3] contended that they were unable to see increased cellularity or atypia in reparative tissues in infarct and stressed that the presence of areas of low-grade sarcoma with minimal atypia around the infarcts should not be interpreted as reparative changes. They also failed to observe increased cellular changes or cellular atypia in the adjacent stroma surrounding the necrotic bone in asymptomatic and uncomplicated long-bone infarcts and suggested at the present time the pathogenesis of IAS was unknown. Bahk et al. [11] published a case of osteochondritis dissecans, in the periphery of which a transition zone containing bland, atypical repair tissue imperceptibly emerged into frank osteosarcoma. We observed the presence of a same transition zone bridging the periphery of bone infarct and contiguous transformed sarcoma in our cases. Histologically, transition zone consisted of granulation tissues including loose, bland, low-to-high cellular fibrous tissue with capillary proliferation, chronic inflammatory cells, and cellular atypism of varying degrees. The proximal portion (the infarct side) of transition zone consisted of bland cells without

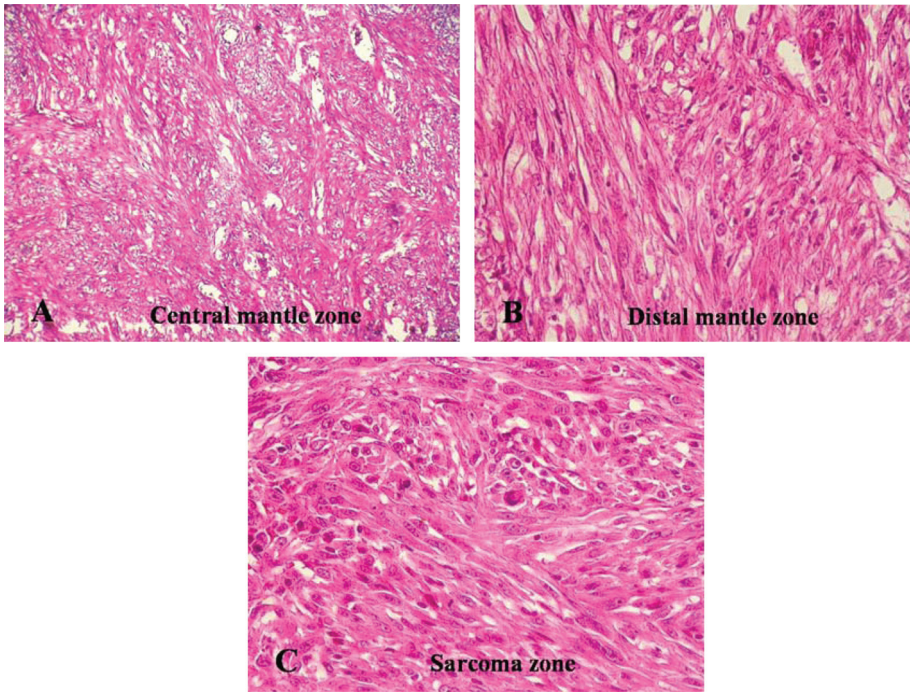

Figure 3. Case 2.

atypism but the central portion demonstrated mild atypism that gradually increased in grade as sarcoma was approached. The distal portion (the sarcoma side) of transition zone showed atypical spindle cells that imperceptibly merged into a frank, high-grade spindle cell sarcoma.

It is concluded based on our histological observation that the continuous spectral transition of pathological changes from granuloma to sarcoma observed in TZ formed between inert bone infarct and sarcoma would support the assumption that IAS arises from reparative tissues at the periphery of ancient infarcts.

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