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Giant cell tumor of femur transformation after radiation and denosumab: A rare case of lymph node metastasis

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Abstract

Background: Malignant transformation of Giant Cell Tumor (GCT) is not common. We report a case of GCT transformation after radiation and denosumab with iliac lymph node metastasis.

Case presentation: A 31-year-old man received surgery for his lesion in the left femur in 2010, without histological diagnosis. Eleven years later (2021), his tumor recurred. He received curettage and cement augmentation in another hospital. Unfortunately, he got second recurrence one year later (2021). He received biopsy and found no evidence of malignant transformation. Radiation (60 Gy/20 F) was prescribed for him with denosumab injection per month. However, he had knee pain which was more severe at night. He came to our department (2022) and ordered an MR scan for his left leg. MR imaging revealed soft tissue mass from distal femur. A Multidisciplinary Team (MDT) discussion was launched with the conclusion of suspected malignant transformation. Afterwards, the entire lesion was resected and reconstructed with a hinged prosthesis. The entire bone lesion was sent for histologic examination and malignant transformation was noticed. Two months later, a lump was palpated at his left iliac region and MR reveled multiple lymph nodes in the inguinal region. Ultrasound-guided needle biopsy confirmed lymph node metastasis. Chest and abdomen and pelvis CT did not find another metastasis.

Conclusions: Malignant transformation of recurrent GCT can occasionally occur after administration of radiation and denosumab. Malignant transformation should be suspected if the symptom did not alleviate after treatment. Transformed GCT can sometimes develop lymph node metastasis which is detected by physical examination and appropriate imaging studies.

Keywords: Femur; Giant cell tumor; Radiation; Denosumab; Metastasis; Lymph node.

Background

Malignant transformation of Giant Cell Tumor (GCT) of bone is uncommon [1,2]. It's still unclear the exact rate of malignant transformation after radiation and long-term administration of denosumab. According to the literature, lymph node metastasis of GCT is rare [3,4]. We report a case of recurrent GCT transformation after radiation and denosumab. Also, this patient developed lymph node metastasis, which is rare among literatures.

Case presentation

A 31-year-old Chinese man received surgery for his lesion in the left femur in 2010, without histological diagnosis. He had no family history of cancer. Eleven years later (2021), his tumor recurred. He received curettage and Polymethyl Methacrylate (PMMA) augmentation in another hospital. Unfortunately, he got second recurrence one year later (2021). He received biopsy and found no evidence of malignant transformation. Radiation (60 Gy/20 F) was prescribed for him with denosumab injection per month at local hospital. However, he had knee pain which was more severe at night. He was referred to our institution (2022) and ordered Magnetic Resonance (MR) imaging for his left leg. MR imaging revealed soft tissue mass from distal femur (Figure 1). A Multidisciplinary Team (MDT) discussion was launched with the conclusion of suspected malignant transformation. Afterwards, the bone lesion was resected and reconstructed with a hinged prosthesis. The entire bone lesion was sent for histologic examination and malignant transformation was noticed (Figure 2). Microscopic evaluation of the tumor revealed massive necrosis. The existing tumor cells were polygonal, spindle and eosinophilic, with plenty cytoplasm. The nuclei were enlarged and some vacuole nuclei were seen. Obvious nucleolus and mitosis were noticed. Pathological mitoses were also present. The tumor cells were H3.3G34 W (+) by Immunohistochemistry (IHC) staining. Ki-67 Proliferation Index was approximately 70%.

Two months later, a lump was palpated at his left iliac region and MR revealed multiple lymph nodes in the inguinal region (Figure 3). Ultrasound-guided needle biopsy confirmed lymph node metastasis (Figure 4). Chest and abdomen and pelvis CT did not find another metastasis.

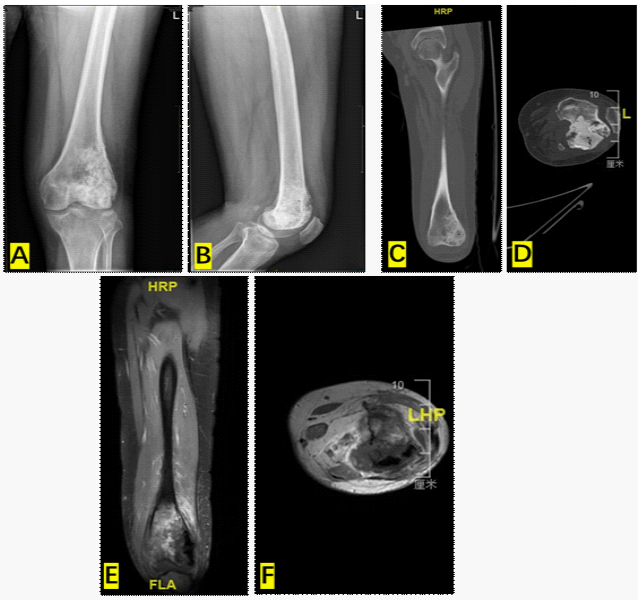

Figure 1: Imaging examinations after radiation and denosumab. **(A,B)** The femur AP and lateral X-ray shows mixed density of the femoral lesion. **(C,D)** The femur CT shows the lytic femoral lesion around the cement. E,F MRI shows mixed intensity with soft tissue extension.

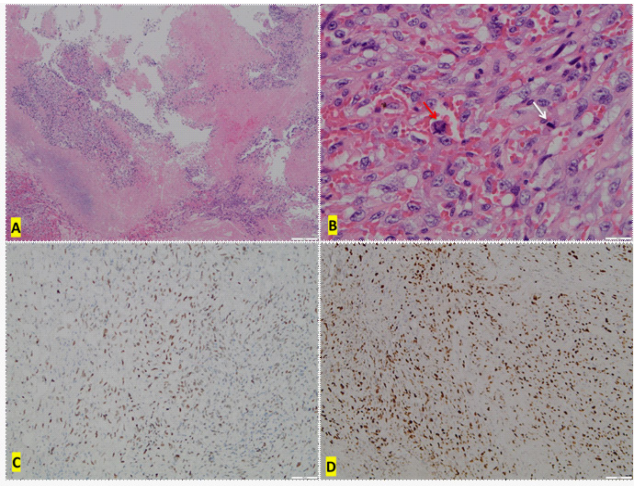

Figure 2: Pathological examination with the resected specimen. A. Massive necrosis was seen, with minor tumor cells existing; B. The tumor cells were polygonal, spindle and eosinophilic, with plenty cytoplasm. The nuclei were enlarged and some vacuole nucleus was seen. Obvious nucleolus and mitosis were noticed (white arrow). Pathological mitosis was also present (red arrow). C. Immunohistochemistry revealed H3.3G34 W (+) tumor cells. D. Ki-67 Proliferation Index was approximately 70%.

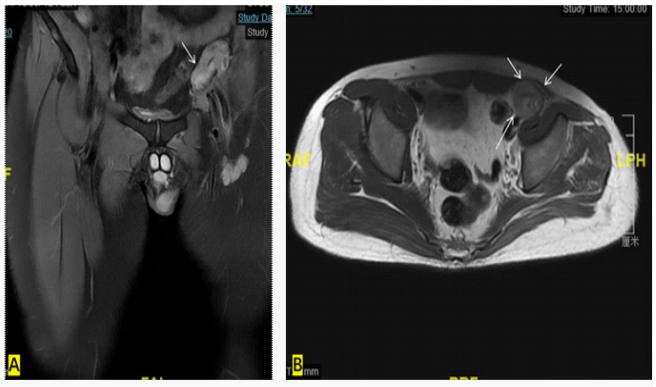

Figure 3: MR revealed multiple lymph node in the inguinal region (A,B).

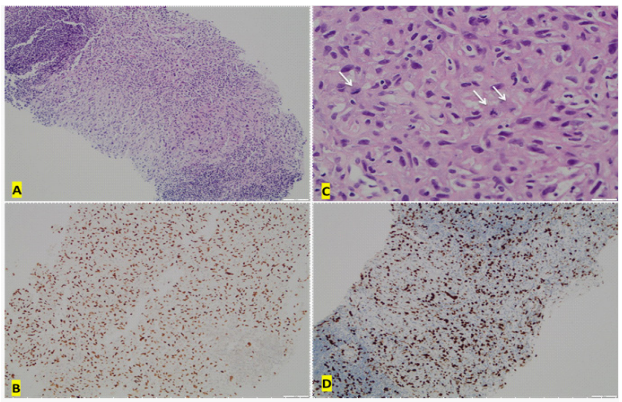

Figure 4: Ultrasound-guided needle biopsy confirmed lymph node metastasis. **(A)** Abundant tumor cells were seen in the biopsy specimen, **(B)** The tumor cells were polygonal, spindle and eosinophilic, with plenty cytoplasm and hyperchromatic nuclei. Mitosis were also noticed (white arrow). **(C)** H3.3G34W was positive in tumor cells by immunohistochemistry staining. **(D)** Ki-67 Proliferation Index reached approximately 70%.

Discussion

Giant Cell Tumor of Bone (GCTB) is a benign neoplasm with locally aggressive behavior. Surgery is the main treatment of choice for appendicular GCT. Local recurrence rate in the extremityis 15%-22% after curettage surgery with PMMA [5]. This case has second recurrences and biopsy is performed to evaluated the possibility of malignant transformation. No transformed cells were detected from the biopsy tissue.

Spontaneous malignant transformation of GCTB has been reported [1,6]. However, the exact incident of spontaneous malignant transformation is unknown. Radiation therapy is a potential risk factor for malignant transformation. Radiation Therapy (RT) is less effective for locally recurrent disease than the primary one [7,8]. In most circumstance, RT is considered only after failure of other treatment options.

Denosumab is approved for treatment of patients whose GCTB is unresectable or when surgery is likely to result in unacceptable morbidity. In a study [9], malignant transformation of benign GCTB was noticed in four patients (1%).

To date, it is not clear whether the rate of transformation is increased when RT is combined with denosumab. We presented here the case in which transformation arise post RT and denosumab. Patients must be aware that there is still the potential for RT and denosumab to induce malignant transformation, even with the advent of new RT technology. In clinical setting, if the patient experiences an unrelieved pain after RT or denosumab, malignant transformation should be suspected and further investigations are warranted. As presented in this case, the patient had intractable knee pain after RT and denosumab. When a transformed GCT is suspected, MDT discussion is recommended. Our MDT discussion pointed out a high possibility of malignant transformation. We performed surgical resection of the tumor and malignant transformation was finally confirmed. H3F3A mutations can help diagnose GCTB, but cannot entirely exclude transformed GTCB [10-12]. This case showed G34W mutation even after malignant transformation.

Lymph nodal involvement is very rare in GCT and is usually associated with pulmonary metastasis. The GCT of this patient here metastasized to external iliac lymph nodes without lung metastasis. We resected the external iliac lymph nodes and the final histopathology showed lymph nodal involvement. The prognosis of GCT with sole lymph node metastasis is unknown due to the very limited clinical cases.

Conclusion

In the present case, transformation of recurrent femur GCT developed after radiation and denosumab. Also, the disease spread to lymph node without lung involvement, which is very rare among literatures. Awareness of GCT transformation and lymph node metastasis is essential, and careful long-term follow-up is needed for a transformed GCT.

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