Pathological Characteristics of Giant Cell Tumor of Bone Treated with Denosumab

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We present a Giant Cell Tumor of Bone (GCTB) in a patient who presented with pathological fracture of the lower end of the femur. The patient was treated with Denosumab, an anti-RANKL inhibitor for four weeks followed by intralesional excision, screw reinforcement and bone cementation. Denosumab prevented the proliferation of stromal cells and osteoclastogenesis of the GCTB leading to its replacement by a fibrohistiocytic lesion (FHL) which has similar microscopic and immunohistochemical reactivity as that of fibrous histiocytoma. It increased the formation of reactive bone.

The patient was followed up for six months with no recurrence or activity. We describe and interpret the microscopic and immunohistochemical (IHC) post-Denosumab bone changes and the role of fracture repair and bone cementation in the organization of the FHL.

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Giant cell tumor of bone (GCTB) is a rare, benign, but focally aggressive tumor which commonly presents with pathological fracture[1,2]. The tumor is phenotypically composed of non-neoplastic multinucleated giant cells (formed by fusion of macrophages) and two lineages of mononuclear cells. Non-neoplastic is derived from the monocyte-macrophage system and the neoplastic produces receptor activator of nuclear factor k-ß-ligand (RANK/RANKL) complex, which in turn induces osteoclastogenesis[1-8]. Surgery combined with local adjuvant therapy is the standard management of GCTB[1,2,5-9]. However, during the last 10 years, Denosumab, a neoadjuvant monoclonal antibody to RANKL has been successfully used to inhibit the formation, activity, function, and survival of giant cells, thus decreasing bone destruction and increasing reactive bone formation[1,2,4-10]. It also led to the replacement of the tumor by a fibrohistiocytic lesion.

The aim of this presentation is to report a case of GCTB presenting with pathological fracture of the lower end of the femur, treated with Denosumab.

THE CASE

A thirty-three-year-old male electrician, not known to have any illness, presented with right knee pain after trivial trauma. He gave a history of 6 months dull ache in the same knee, relieved by analgesics. Examination revealed a swollen and tender knee with limited range of motion due to pain. X-ray, CT, and MRI showed a pathological fracture of the right distal femur with large lytic lesion consistent with GCTB, which was confirmed by open biopsy, see figure 1A. The patient was treated with Denosumab 120 mg weekly for four weeks and resection of the residual intralesional tumor. The tumor cavity was filled with polymethylmethacrylate cementation and four 7.3 mm screws reinforcement. Postoperatively, the patient was maintained on a monthly dose of Denosumab 120 mg for 6 months. A follow-up X-ray showed no recurrence in the first 6 months and a PET scan showed no residual tumor.

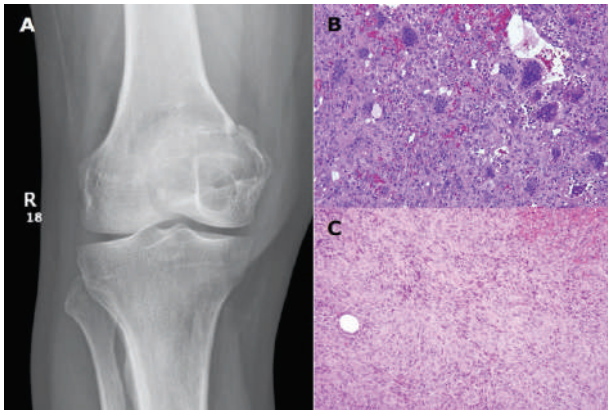

Figure 1: (A) X-ray with Fracture Line (B) HE Section with Hemorrhage x200 and (C) Areas Composed Entirely of Stromal Cells with Storiform Pattern x200

The bone biopsy obtained following the fracture composed of multiple irregular hard and soft pieces of tissue collectively measuring 34x25x7 mm and weighing 3 grams. All were processed

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for paraffin blocks. Microscopy revealed GCTB and areas of fibrohistiocytic stromal cells with prominent storiform changes and no multinucleated cells, see figures 1B-C. Blood clots and bone trabeculae with empty lacunae consistent with fracture were seen.

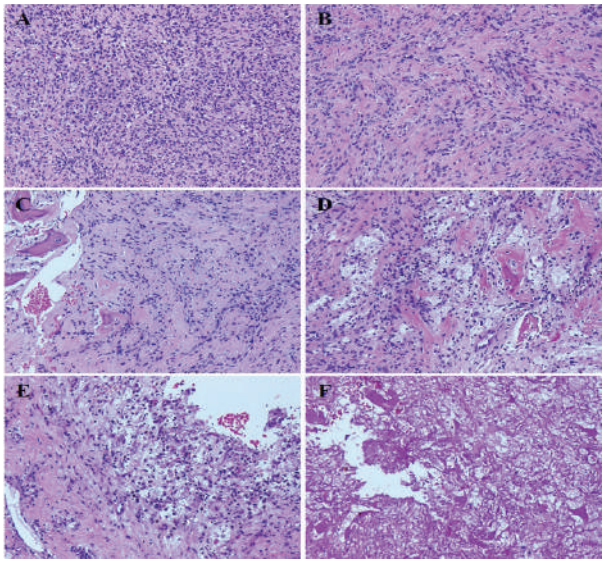

Figure 2: H&E X200. FHL Composed of (A) Central (B) Intermediate and (C) Peripheral Zones (D) Xanthogranulomatous Reaction Seen Throughout the Lesion (E) Granulation Tissue of Organized Fracture Repair (F) Coagulative Necrosis of GCTB Following 4 Weeks of Denosumab Therapy

The biopsy which was obtained four weeks after Denosumab treatment revealed small elongated hard irregular grayish-brown pieces of tissue measuring 39x20x6 mm and cut section showed white surface. The specimen was processed into paraffin blocks. Microscopically, three forms of tissue reactions were seen: (A) Ill-defined FHL composed of compact short fascicles of highly cellular ovoid to spindle cells with storiform pattern and little or no extracellular matrix and no nuclear atypia or mitosis; (B) Total coagulative necrosis of the GCTB composed of eosinophilic shadows of the stromal and giant cells with no viable tumor tissue; (C) Remnants of organized hematoma and callus with granulation tissue were made principally of macrophages with reduced vascularity and minimum neutrophils and lymphocytes with scattered hemosiderin-laden macrophages. Scattered hemosiderin granules and karyorrhexis debris were seen throughout the different zones of the FHL. In addition, nests and sheets of xanthogranulomatous tissue composed of large foam cells with abundant granular and vacuolated cytoplasm and bland nuclei were also seen. The tissue surrounding this lesion composed of bands of gradually increasing amount of fibrillary extracellular matrix. The bands immediately adjacent to the lesion were thin and wavy while those near the host bone were broader and trabecular with areas of osteoid matrix and prominent osteoblastic reaction merging into host tissue, see figures 2A-F. Osteoid formation and irregular trabeculae of reactive bone were seen. The diagnosis of the second biopsy was FHL associated with Denosumab therapy for the treatment of GCTB. The FHL was positive for Vimentin and smooth muscle actin (SMA) and negative for S100 and Desmin, see figures 3A-D.

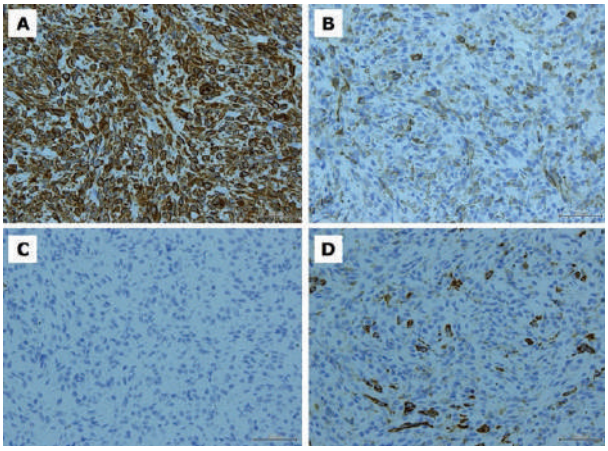

Figure 3: IHC Reaction of the FHL with Positive (A) Vimentin and (B) SMA and Negative (C) S100 and (D) Desmin

DISCUSSION

Our study findings are consistent with the belief that Denosumab therapy induces several histomorphological changes to the original classical appearance of GCTB[1,2,4-8,10]. The second resected specimen obtained four weeks after Denosumab therapy revealed the following: (a) no viable GCTB (b) disappearance of the characteristic multinucleated giant cells (c) appearance of FHL with characteristic storiform pattern surrounded by bands of gradually increasing amount of fibrillary extracellular matrix formation (d) new bone formation and osteosclerosis (e) presence of coagulative necrosis of tumor remnants (f) presence of organized hematoma and granulation tissue associated with fracture repair. It should be noted that Denosumab typically should not cause tumor tissue necrosis, since the mechanism of action is receptor inhibition rather than ischemic changes. Necrosis in these cases is most likely related to previous biopsy procedure, fracture and cementation[6-8].

The appearance of fibrohistiocytic or xanthogranulomatous changes is frequently seen in a variety of conditions other than those associated with Denosumab therapy. It is seen in ordinary GCTB without any preoperative therapy and may in some cases mimic the appearance of fibrous histiocytoma of bone[11-15]. In the present case, similar foci were seen in the first biopsy before the administration of Denosumab. The presence of similar secondary reactive proliferation of fibrohistiocytic tissue, fibrous tissue with a prominent storiform pattern, and xanthogranulomatous reaction are frequently seen in biopsy samples from therapy-naïve GCTB before the advent of Denosumab treatment[11-15]. However, with Denosumab neoadjuvant therapy, the proliferation of the stromal cells and giant cell formation are prevented leading to the enhancement of the fibrohistiocytic and xanthogranulomatous changes[1,2,4-10].

The second biopsy of the resected residual intralesional biopsy was a mixture of more than one tissue element of the above described 5 reactions. However, despite the anatomic disorientation of the specimen, we were able to reconstruct the "zonal distribution" of the FHL by applying the guidelines of Girolami et al[6]. We believe that the histological recognition of these zones is important to understand what happens to the GCTB after four weeks of Denosumab therapy. Therefore, at

the center of the intralesional biopsy, the main focus of the FHL was found and this possibly corresponded to the main bulk of the pretreatment GCTB. In this case, the lesion appeared as compact short fascicles of highly cellular ovoid to spindle cells with a storiform pattern, little or no extracellular matrix and no nuclear atypia or mitosis. Numerous hemosiderin granules and karyorrhexis debris were also noted. Near the host bone, the matrix became trabecular with osteoid and osteoblastic reaction merging into the host. In between these two zones, the matrix appeared broad and wavy. We interpret this gradual transition from (central) densely cellular fibrohistiocytic component to broad (intermediate) thick bands of (non-mineralized) matrix maturing into (peripheral) reactive bone formation as an indication that whatever is formed at the center is gradually displaced and organized towards the periphery to be remodeled and incorporated into the host bone[6]. Furthermore, we also interpret the presence of the spindle and ovoid cells seen throughout these three zones as a representation of remnants of subordinate type of GCTB being modified by the Denosumab therapy.

Except for fracture repair, all of the above-noted findings in the present report were previously observed in other studies[1,4,5,7,8,10]. In fact, most of these Denosumab studies were concerned with the reactivity of the FHL rather than the role of fracture repair, which together with bone cementation were important modifying factors in the overall reparative and remodeling process. In the present case, the fracture repair was demonstrated in the form of organized hematoma with granulation tissue, callus, and irregular trabeculae of reactive bone with osteoblastic reaction. These changes were seen in several fragments obtained from the second resected biopsy indicating that the fracture repair occurred at multiple sites and at different reparative phases. We would expect that the organization of the post-fracture granulation tissue (notably the role of phagocytes) is inhibited by the Denosumab and it would seem that the sclerotic outcome of the FHL must have overtaken the organization of the granulation tissue. We could not evaluate the effect of bone cementation, an adjuvant tumor cytotoxic agent which was applied along with screws reinforcement after the resection of the residual intralesional FHL. This is because no further biopsy sample was taken. We assume that cementation will enhance reactive new bone formation and osteosclerosis[4,10].

It is premature to speculate on the possible final outcome of the organization of the FHL, whether it will be replaced by osteosclerosis or that recurrence of the primary tumor may take place at some stage after the cessation of Denosumab therapy[5]. However, it is worth noting that in the present case, the X-ray and PET scan follow-up of the patient did not show any recurrence or activity of the tumor six months after the cessation of the Denosumab therapy.

The FHL observed following Denosumab therapy of GCTB is similar to fibrous histiocytoma occurring elsewhere in the body[4,6,10]. We question whether the immunohistochemistry (IHC) reactions of both of these conditions would be comparable. We found that the Vimentin +, SMA + S100 - and Desmin – pattern in the Denosumab-associated FHL is similar to that of fibrous histiocytoma. We believe that both conditions are benign and that the former is a reactive reparative reaction while the latter is categorized as neoplastic tissue.

CONCLUSION

The long-term efficacy of Denosumab regarding the possibility of tumor recurrence could not be judged from the results of a single case report. Larger long-term multicentric studies are required for better understanding of the outcome of this neoadjuvant therapy. Furthermore, studies on the long-term effects of bone cementation and fracture repair associated with these tumors are also required.

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