Reshrinkage of Giant-Cell Tumor of the Bone in the Thoracic Vertebrae after Resumption of Denosumab Treatment: A Case Report

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A 76-year-old woman with lower back pain was histologically diagnosed with giant-cell tumor of the bone (GCTB) following computed tomography (CT)-guided needle biopsy of a T11 spinal tumor. The patient received 120-mg of denosumab per month, and the tumor shrank significantly after one year of treatment (Fig. 1).

After two years, denosumab was suspended for seven months because of the deterioration of the patient's dementia. However, one year after resuming treatment, the patient self-suspended her medical examination because of the coronavirus disease 2019 pandemic. Two years after the second discontinuation, the patient presented with severe bilateral lower extremity edema. Her lower extremity manual muscle testing score was ≥4, and no obvious paresthesia was noted. Thoracic CT revealed a massive tumor in the right retroperitoneum, with a maximum diameter of approximately 16 cm. The inferior vena cava was compressed and displaced superiorly (Fig. 2). GCTB recurrence was suspected, prompting re-referral. Blood biochemical examination revealed a markedly high tartrate-resistant acid phosphatase 5b level (≥1500 mU/dL) without any other abnormalities.

Proliferation of osteoclast-like multinucleated giant cells without high-grade cell atypia or pleomorphism in the short spindle-shaped cells was histologically observed after the second CT-guided needle biopsy (Fig. 3). This finding was consistent with GCTB.

Because the tumor was too large for removal, proton beam therapy and denosumab injection were considered as treatment options; however, proton beam therapy was contraindicated because the patient could not rest due to dementia. Thus, the patient received denosumab treatment again. Significant edema improvement was observed after six months, and the patient could walk using a walker. Remarkable tumor shrinkage was observed on CT (Fig. 4).

En bloc resection is the primary treatment for GCTB; however, it causes functional disability[1)]. Denosumab is a monoclonal antibody that inhibits the receptor activator of nuclear factor-kB (RANKL) and prevents bone destruction[2)]. Currently, denosumab administration is considered for GCTB in which resection may cause significant functional impairment or for unresectable GCTB in the spine and pelvis[3)].

In this case of thoracic GCTB, tumor shrinkage was observed after primary denosumab treatment. However, rapid tumor regrowth was observed, which significantly compressed the inferior vena cava, when treatment was discontinued. Considering past reports, total en bloc spondylectomy (TES) should have been considered when the tumor had once shrunk. However, because the tumor had shrunk and was controlled, the previous doctor decided to continue denosumab because TES was a highly invasive treatment. For unresectable GCTB, the reported median denosumab treatment duration is 54 months (range, 9-115 months)[1)]. Although the optimal administration period remains unclear, long-term administration is necessary. However, 40% of the patients who discontinued denosumab experienced tumor progression after a median of 8 months (range, 7-15 months), which suggests the importance of treatment con-

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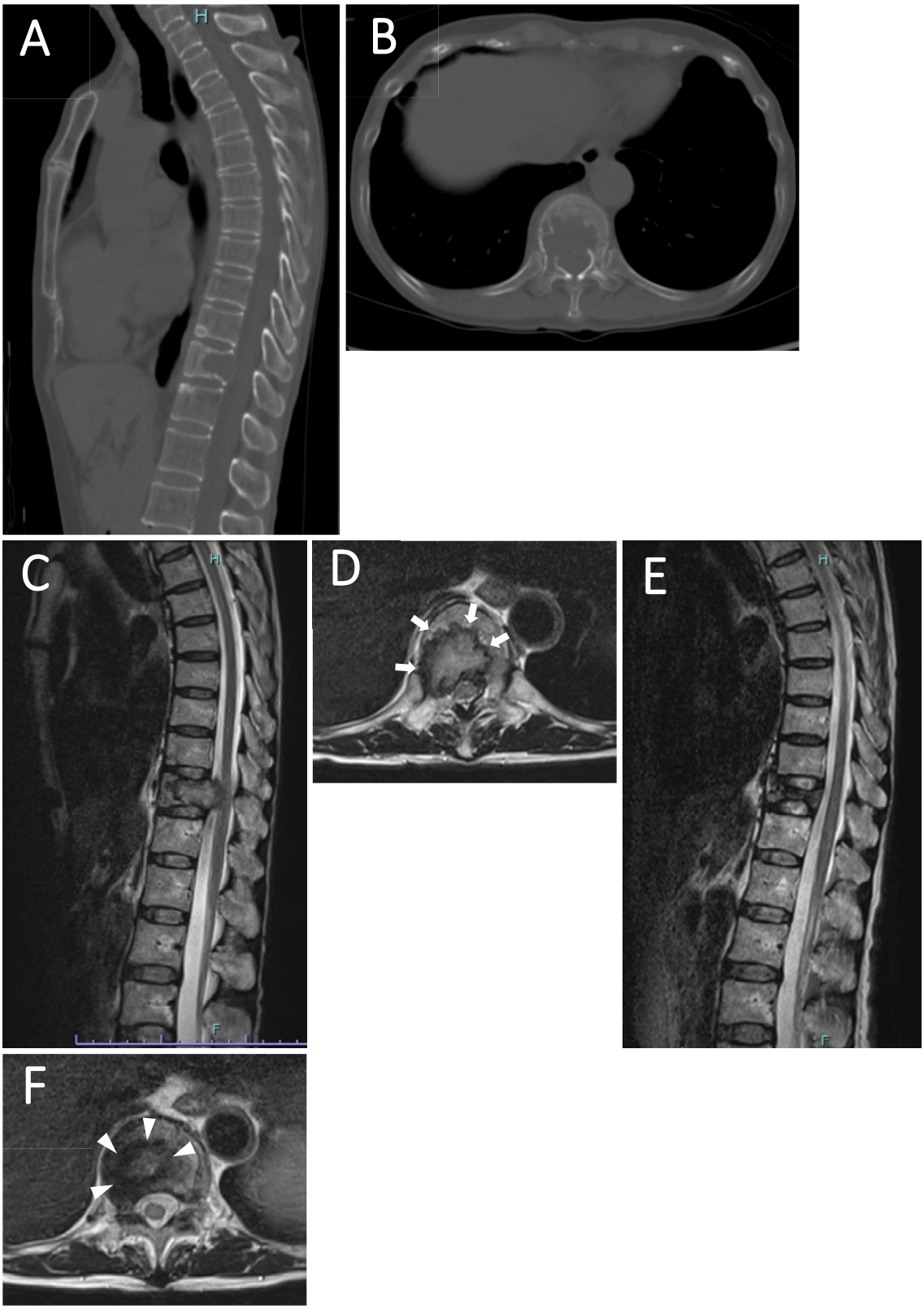

Figure 1. Before treatment—CT images showed geographical bone destruction and expansion of the T11 vertebral body (A, B), and MRI images showed tumorous lesions (white arrow) partially invading the right pedicle (C, D).
After treatment—MRI images after 1 year of denosumab treatment showed tumor shrinkage (white arrow head) (E, F).
A, C, E: sagittal sections.
B, D, F: axial sections.
CT, computed tomography
MRI, magnetic resonance imaging

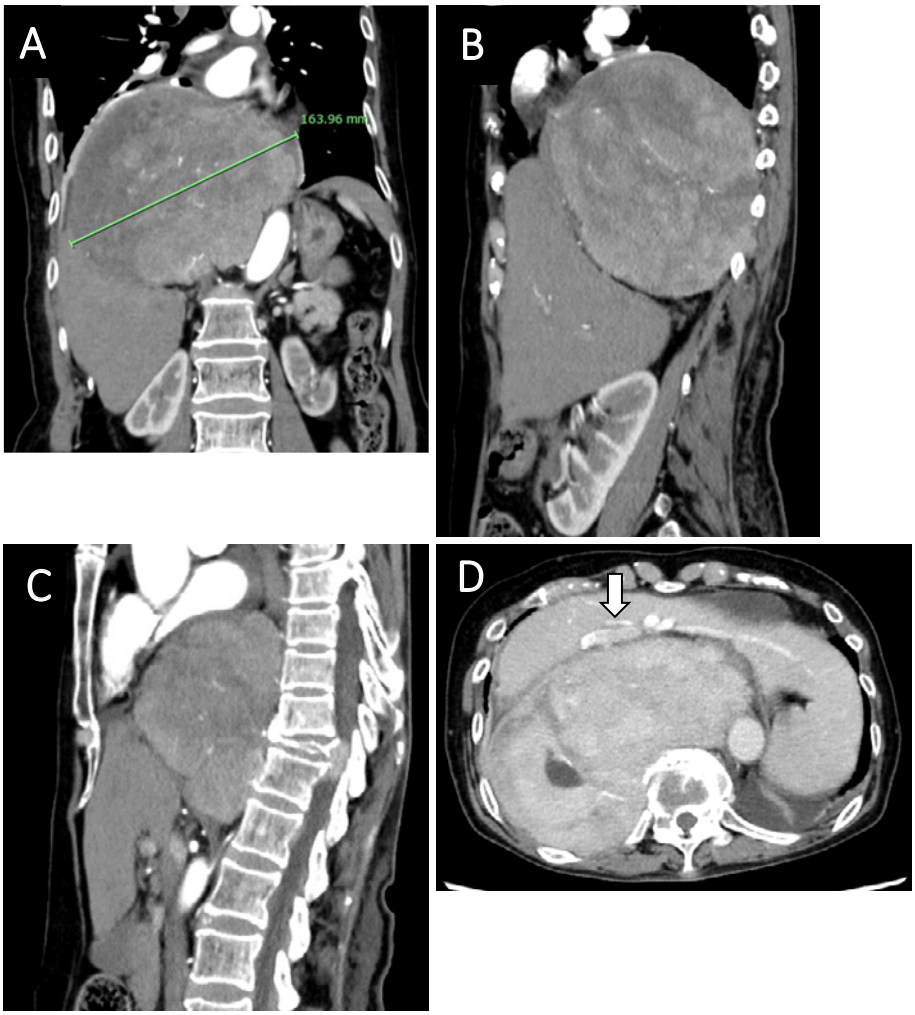

Figure 2. CT images after denosumab discontinuation revealed a larger tumor with a maximum diameter of 16 cm in the right retroperitoneum (A, B). The vertebral body of T11 exhibited extreme thinning (C), and the inferior vena cava (white arrow) was significantly compressed and displaced superiorly (D).
A: coronal section.
B, C: sagittal section.
D: axial section.
CT, computed tomography

tinuation[1]. Complications associated with denosumab use include osteonecrosis of the jaw, with an incidence of approximately 1%-6%[1,2]. Once the complication arises, it may be difficult to treat. However, if denosumab is discontinued, there is a possibility of tumor regrowth, as in this case; thus, denosumab administration should be continued while paying attention to the occurrence of osteonecrosis of the jaw.

Mak et al. revealed that when giant-cell tumor tissue was no longer exposed to denosumab in vitro, stromal cells continued to proliferate, albeit to a lesser extent[4]. In tumor cell lines isolated using real-time polymerase chain reaction from denosumab-treated patients, RANKL gene expression is suppressed compared with that in cell lines from untreated patients[4]. This suggests that discontinuation of denosumab treatment leads to tumor cell proliferation because of the downregulation of RANKL.

In a previous study, resumption of denosumab after discontinuation did not prevent tumor growth, and the authors suggested that surgical resection should be considered after denosumab initiation[5]. Contrary to previous reports, we encountered the first case of tumor reshrinkage after resumption of denosumab. However, the underlying mechanism remains unclear. Therefore, more cases are needed to clarify the optimal duration of denosumab administration and the effects of resumption after discontinuation. For recurrent cases in which surgical treatment is challenging, readministration of denosumab may be worth considering.

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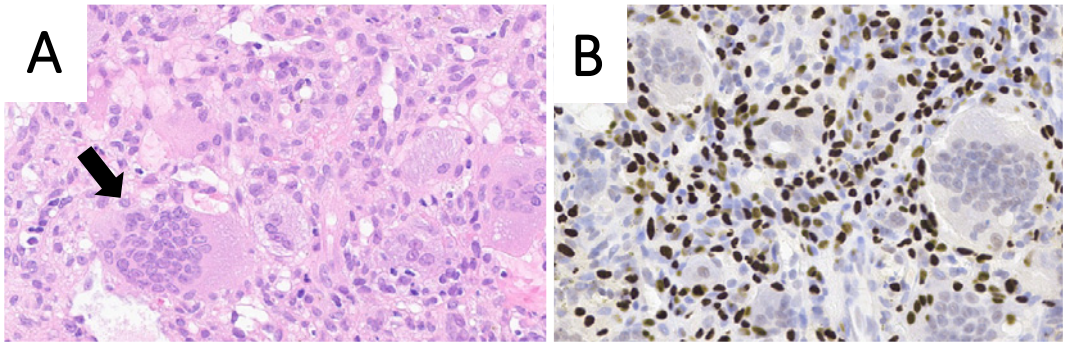

Figure 3. Proliferation of osteoclast-like multinucleated giant cells (black arrow) and short spindle-shaped cells with mildly dilated and branched capillaries was observed. No high-grade cell atypia or pleomorphism was observed in the short spindle-shaped cells, and no atypical mitotic figures were observed (A). Immunohistologically, spindle-shaped cells were positive for H.3G34W and negative for H3.3G34V and STAT6 (B).

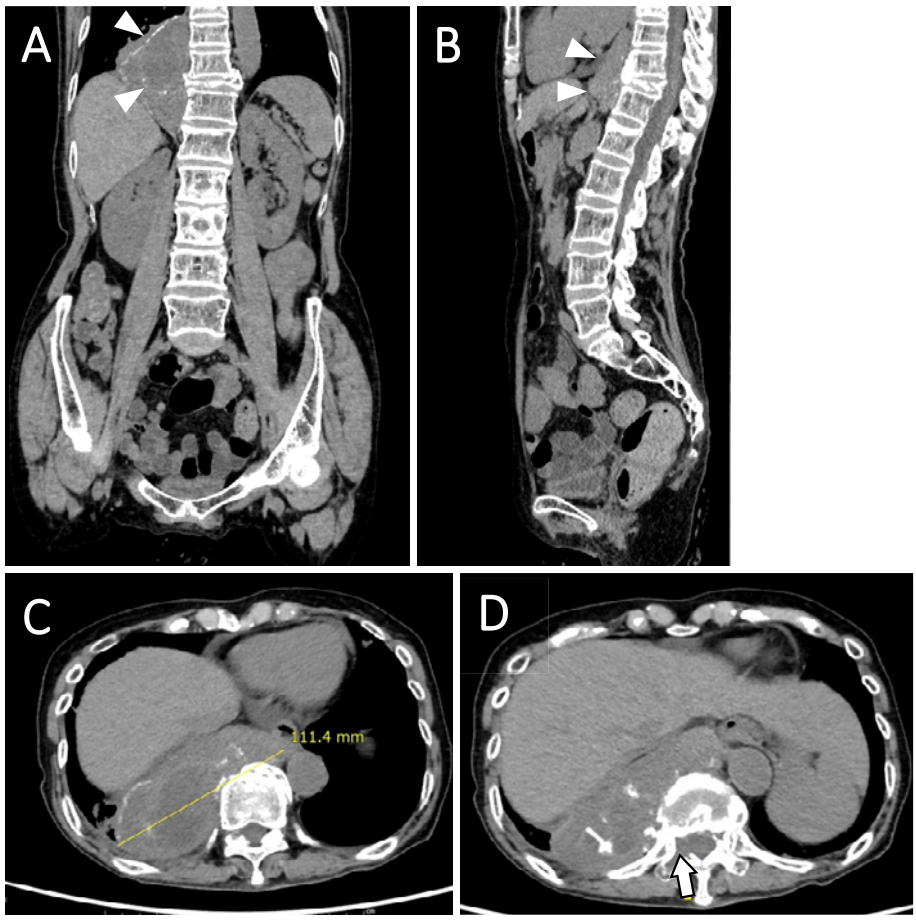

Figure 4. CT images 6 months after restarting denosumab showed considerable tumor shrinkage (white arrow head; A, B). The tumor has shrunk to 11 cm (C). The bulge in the spinal canal has also shrunk (white arrow; D). The tumor appears to have hardened and is responding to treatment.
A: coronal section.
B: sagittal section.
C, D: axial sections.
CT, computed tomography

gawa, Yu Yamato, Go Yoshida, Tomohiro Banno, Hideyuki Arima, Shin Oe, Yuh Watanabe, Koichiro Ide, Tomohiro Yamada, Kenta Kurosu, Yukihiro Matsuyama designed the study; Keika Nishi wrote the manuscript.

Ethical Approval: Ethical approval was waived by the ethics committee because of the retrospective study design.

Informed Consent: Informed consent for publication was obtained from the patient.

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