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CASE REPORTS

Multiple Vertebral Osteonecroses (Kümmell's Disease) After 10 Years on Denosumab: Is Osteocyte Apoptosis to Blame?

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Abstract We report here a case of multiple vertebral osteonecroses with intrasomatic gaseous dissection (Kümmell's disease) occurring 1 year after the end of a 10-year course of denosumab treatment for osteoporosis without fractures. Histomorphometry and bone remodeling markers revealed major bone resorption and the persistence of an inhibition of bone formation. The presence of multiple empty lacunae in the bone provided evidence for high levels of osteocyte apoptosis. Osteocytes direct bone resorption (via the RANK/RANK-L/osteoprotegerin system) and formation (Wnt system, with SOST and DKK1) pathways. The vertebral osteonecrosis in our case may, therefore, have resulted from osteocyte apoptosis, decompensated by the sudden reactivation of bone remodeling after the cessation of denosumab treatment.

Keywords Osteoporosis · Vertebral osteonecrosis · Denosumab · Osteocyte apoptosis

Case Report

After an initial measurement of bone mineral density (BMD) by Dual-energy X Absorptiometry (DXA) in 1989, a female patient born in 1935 stopped rapidly all initiated treatments (Fluoride, Etidronate, Alendronate, and Risedronate), due to digestive disorders. A new DXA performed in September 2004 revealed a *T*-score of − 2.5 in the lumbar region and − 2.4 at the total hip. The patient was thus included in the FREEDOM (AMGEN 162) cohort, in a 3-year phase III trial evaluating the use of an anti-RANK-L monoclonal antibody, denosumab (60 mg subcutaneously every 6 months). The initial X-ray showed no vertebral fractures. The patient was then included in an extension study, in which she received treatment for a further 7 years (last injection in April 2014). At the end of the protocol, she did not report any adverse effect or fracture. When blinding was lifted in October 2014, she was found to have been treated with denosumab during the first 3 years. X-rays in November 2014 revealed an absence of vertebral fracture, and no intervertebral disk vacuum or osteoarthritis of the spine. The final DXA showed a linear increase in bone mass of + 24.0% (*T*-score of − 0.8) for the lumbar region and of + 13.4% (*T*-score of − 1.6) for the hip.

Nevertheless, in April 2015, the patient was admitted to hospital for acute non-traumatic low back pain related to a grade 3 wedge fracture of T8 (Fig. 1). A second, grade 3 wedge fracture of the T10 vertebra occurred in August 2015. These fractures had the typical appearance of intrasomatic gaseous dissection on standard X-rays, leading to a diagnosis of vertebral necrosis. A CT scan of the spine in October 2015 confirmed the presence of intrasomatic gaseous necrosis (Fig. 2). MRI confirmed the recent nature of the fracture (Fig. 3a), with the detection of a specific "fluid sign" (Fig. 3b). New X-rays demonstrated the occurrence of a third vertebral fracture in 6 months, at T12. The biological evaluation was unremarkable: calcemia, phosphatemia, PTH, 25-OH vitamin D, creatininemia, and protein electrophoresis were normal. Serum CTX was 0.988 ng/ml (normal < 0.53), and bone alkaline phosphatase was 3.7 ng/ml (normal < 22). In February 2016, BMD had decreased in both the lumbar spine (− 10.4%, *T*-score − 1.7) and the hip (− 12.8%, T-score − 2,4). An

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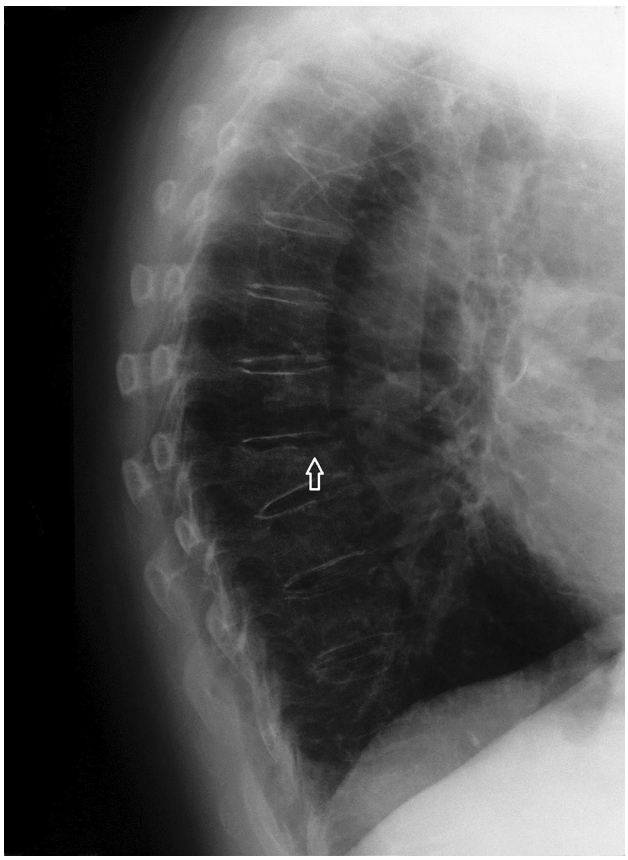

Fig. 1 Standard X-ray: grade 3 wedge fracture of T8, with secondary dorsal kyphosis and osteonecrosis of the superior facet of the vertebra, as demonstrated by intrasomatic gaseous dissection (arrow)

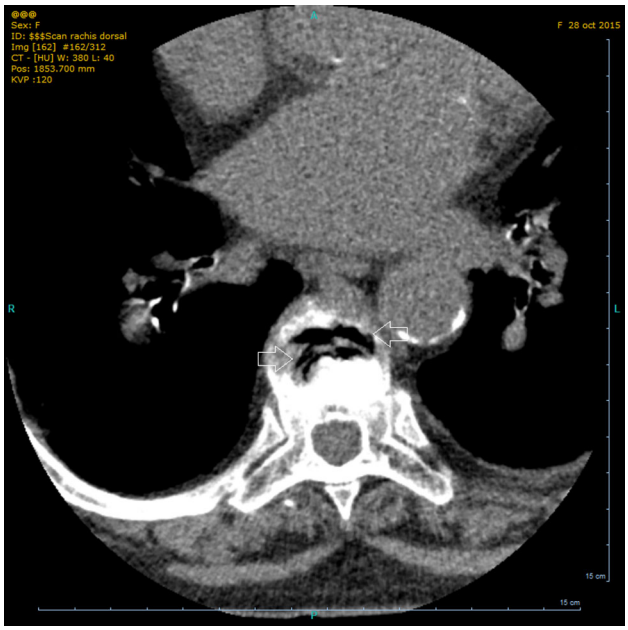

Fig. 2 CT scan: superior facet of T8: the presence of an air-filled, oblong, subcortical zone is confirmed on this CT scan

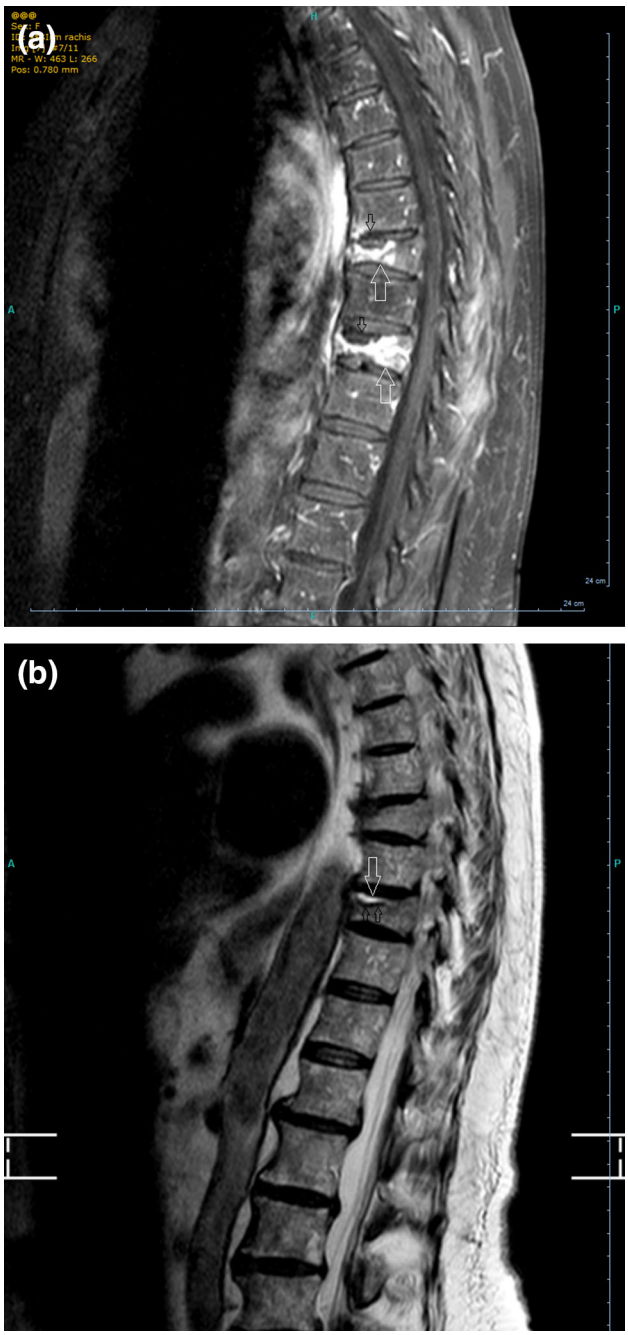

Fig. 3 **a** MRI, T1 Fat Sat sequence with gadolinium injection: bone hypersignal demonstrating the recent nature of the fractures of the T8 and T10 vertebrae (large white arrows), with gadolinium contrast. The underlying necrotic zones (small black arrows) did not take up gadolinium. **b** MRI, T1: characteristic fluid sign. Intrasomatic image with a hyposignal on T1 (arrows) and a hypersignal on T2 similar to that for the cerebrospinal fluid (arrows)

iliac bone biopsy, with histomorphometry and double-labeling with tetracycline, was performed in December 2015, 20 months after the end of denosumab. Cortical thickness was normal for age (0.715 mm, normal: 0.651 ± 0.291), and osteon texture was normal, but porosity was high

(8.38%; normal: 5.0 ± 0.4%). The volume of the trabecular bone was above the upper limit of the normal range for age (15.6%; normal: 12.5 ± 2.1%), with spans of irregular bone thickness and large empty medullary spaces devoid of osteocytes (Fig. 4a). Osteoblast apposition activity was low (0.32 µm; normal: 0.41 ± 0.08 µm). The eroded surface was abnormally large (5.8%; normal: 3.6 ± 1.1%) (Fig. 4b) and the area of active resorption was normal (1.48%; normal: 2.4 ± 1%). No mineralization defect or abnormal medullary infiltration was observed. Teriparatide treatment was initiated in February 2016, to stimulate osteoblast activity. Seven months later, there were no new fracture, and lumbar spine BMD had an increase of + 4.8%.

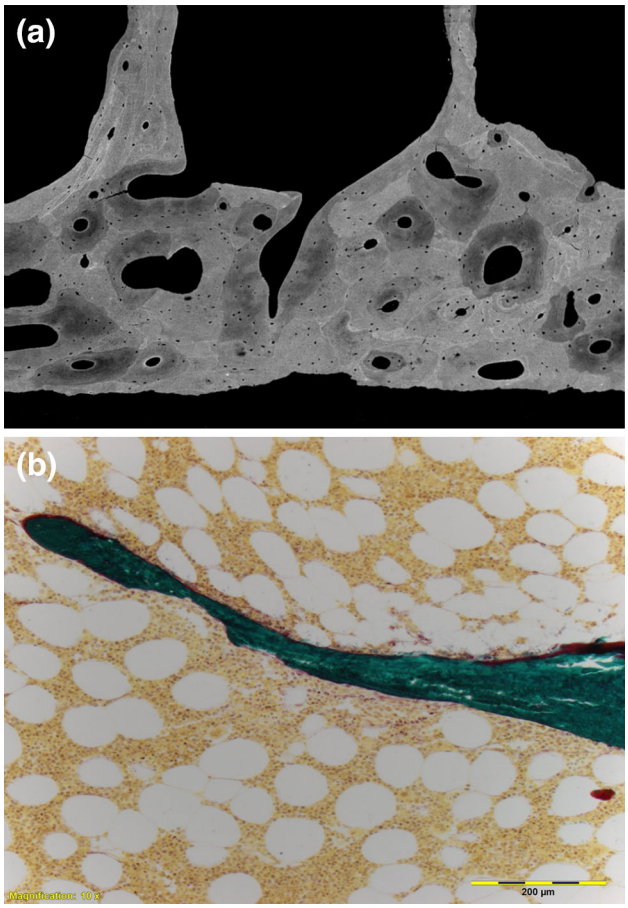

Fig. 4 **a** Large lacunae and high level of porosity (micro-CT Skyscan 1172). Magnification ×10. **b** Undecalcified iliac bone biopsy with tetracycline double-staining and inclusion in Methacrylate and Goldner trichrome stain. Bone lacuna with high level of resorption of the bone trabeculae with TRAcP + osteoclast. No mineralization defect. Low osteoblastic activity. Magnification ×10

Discussion

Mandibular osteonecrosis has been reported as a possible consequence of treatment, for both bisphosphonates and denosumab [1]. We report here the first case of multiple vertebral osteonecroses in a patient treated continuously with denosumab for 10 years. This patient presented no fracture before or during the period of denosumab treatment, but suffered a series of three spontaneous vertebral fractures, accompanied or caused by osteonecrosis, 1 year after the last denosumab injection.

These multiple fracture episodes may have been triggered by a combination of two bone processes. Osteoclast activity may have increased following the cessation of denosumab treatment, as attested by the increase in serum CTX concentration and the high levels of osteoclast activity observed on histomorphometry. Conversely, there was a decrease in bone formation, as demonstrated by the low serum concentrations of bone alkaline phosphatases and the decrease in osteoblastic parameters on histomorphometry. Bone formation remains poor almost 2 years after the cessation of denosumab treatment. This association of high levels of bone resorption with low levels of bone formation has led to rapid bone loss, with DXA revealing an important decrease in lumbar BMD, over a period of less than 2 years, to values close to (T-score for the spine − 1.7 vs − 2.5) or identical (hips: T-score of − 2.4 vs − 2.4) to those recorded before the introduction of denosumab 10 years earlier, despite the linear gain in BMD of 24% for the lumbar region and 13.4% for the hip achieved on this treatment. Popp et al. described a similar rebound effect, with a series of fractures, following the cessation of denosumab treatment [2] with 5 other cases reported in 2016 [3–5]. A 60% increase in serum CTX concentration relative to initial values is observed after the cessation of denosumab [6]. This increase begins shortly after treatment cessation but persists for a long period (almost 2 years). In parallel, the BMD of the hips and lumbar region deteriorate and return to the values recorded before treatment, within a period of about one year [6]. The importance of this rebound effect after discontinuing denosumab, with major bone resorption, is probably the cause of these vertebral fractures. We will have to identify such patients in the future, perhaps with an evaluation of the bone markers after denosumab discontinuation.

However, trabecular bone volume was subnormal in our patient, and X-ray, CT scans, and MRI clearly demonstrated the presence of three sites of vertebral osteonecrosis, as shown by the intrasomatic gaseous dissection observed (Kümmell's disease [7]) and a specific fluid sign on MRI [1, 8, 9]. Our patient had no risk factor for necrosis. Vertebral osteonecroses are comparable to

mandibular osteonecroses. The incidence of mandibular necrosis had been reported in the FREEDOM study [10]. The vertebral (and extravertebral) osteonecroses triggered by high doses of corticosteroids are directly due to the apoptosis of osteocytes and osteoblasts [11]. If this phenomenon becomes irreversible, with a loss of mechanoreception, particularly in the subchondral bone, necrotic bone collapse may occur. Thus, the vertebral fractures induced by high-dose corticosteroid treatment may be related to osteoporosis or osteonecrosis [12]. The rebound of bone resorption may have contributed, through signals generated by osteoclast precursors or the bone matrix, to an induction or acceleration of the apoptosis of the remaining osteocytes. The reason for the lack of osteoblastic activity in our patient may be this high level of apoptosis in the osteocytes, or even in the stem cells from which osteoblasts originate, with deleterious effects on the Wnt pathway regulated by osteocytes [13]. Excessive osteocyte apoptosis can be doubly pathogenic, because it both inhibits osteoblast function (through sclerostin release), and triggers focal osteoclast resorption to cleanse the body of these dead cells [14, 15].

In experimental studies in mouse models, bisphosphonates, denosumab, osteoprotegerin, and RANK-Fc have all been shown to cause mandibular osteonecrosis [16]. It may be associated with the presence of empty lacunae lacking osteocytes and an inhibition of periosteum formation [16]. Thus, osteocyte apoptosis due to a persistent blockade of bone turnover after 10 years of denosumab treatment would appear to be a plausible etiology in this case. Osteocytes are, by far, the most abundant cells in bone tissues. They are enclosed in a network of channels and lacunae, from which they remotely direct the behavior of osteoblasts and osteoclasts [17]. Osteocytes are the principal source of RANK-L, which activates the RANK/RANK-L/osteoprotegerin osteoclast differentiation pathway. Osteocytes also secrete SOST/DKK1, which triggers activation of the Wnt-β/catenin pathway responsible for regulating bone formation [18]. Osteocytes generally survive for as long as the mineralized tissue surrounding them, but their numbers decrease with aging (75-year-olds have 40% fewer osteocytes than 20-year-olds). Osteocyte density is correlated with the mechanical resistance of the bone, and its hydration, vascularization, and mineral content. A possible role for osteocyte deficiency in the rebound effect (rapid loss of bone mass) observed after the cessation of denosumab treatment has been suggested [13].

The therapeutic management of these fractures is not straightforward. Some more data are needed to know if Zolédronate could stop the bone loss after the denosumab rebound, with a partially deceived result in a preliminary report, especially at the hip [19]. Teriparatide seems to be the least bad solution for stimulating the remaining osteocytes, as it is able to activate osteoblast differentiation, even if its use after denosumab appears to lower its efficacy [20]. However, this effect appears to be temporary, delaying the increase in BMD by 6 months for the lumbar vertebrae and 1 year for the hip, as biological markers of bone formation respond more rapidly [6]. Furthermore, the observations reported to date suggest that Teriparatide has a beneficial effect on the course of mandibular osteonecrosis [21]. We therefore decided to prescribe this drug for our patient. Nevertheless, rebound effect can occur after discontinuing Teriparatide, and we will have to use bisphosphonate to prevent the bone loss.

In conclusion, massive osteocyte apoptosis may favor the development of vertebral bone necrosis, due to a lack of sustained osteocyte stimulation followed by an excessively strong signal following the rebound of bone resorption after the cessation of denosumab treatment. The best way to stop denosumab in individuals treated for a number of years is open to discussion, particularly if any other cases of vertebral osteonecrosis come to light. Further studies of the effect of treatments for osteoporosis on osteocytes are required to identify factors predictive of apoptosis.

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Compliance with ethical standards

Conflict of interest Yves Maugars, Géraldine Bart, Pascale Guillot, Marguerite Chemel-Mary, Joëlle Glémarec, Mélanie Gahier-Penhoat, Benoit Le Goff, and Christelle Darrieutort-Laffite declare no conflict of interest.

Human and Animal Rights and Informed Consent All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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