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SURGERY

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NEW DRUGS WITH POTENTIAL CAUSES OF DIONJ

- ACTEMRA (Tocilizumab)
- PROLIA (Denosumab)
- CABOMETYX (Cabozantinib)

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ACTEMRA (Tocilizumab)

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- HPI: 48 year-old male referred for evaluation of painful exposed bone in the left posterior mandible, which was initially noticed 2 years ago after extraction of tooth #19. The extraction site was not healing well for 2 years. The patient related a known history of rheumatoid arthritis for which he has been treated with low dose of prednisone (5-8 mg daily) and Enbrel (etanercept) in the past, which were discontinued five years ago in favor of Tocilizumab (TCZ) and low dose Methotrexate, once a week. He has received TCZ for the past 5 years.

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- PMH: As per HPI
- PSH: Total knee replacement, dental extractions and aortic valve repair.
- SH: Denies any use of bisphosphonates, RANK L inhibitors or any other cancer drugs. Denied any tobacco, drug or alcohol abuse.
- Med: Tocilizumab 4mg/kg Q 4 weeks and methotrexate.
- All: NKDA

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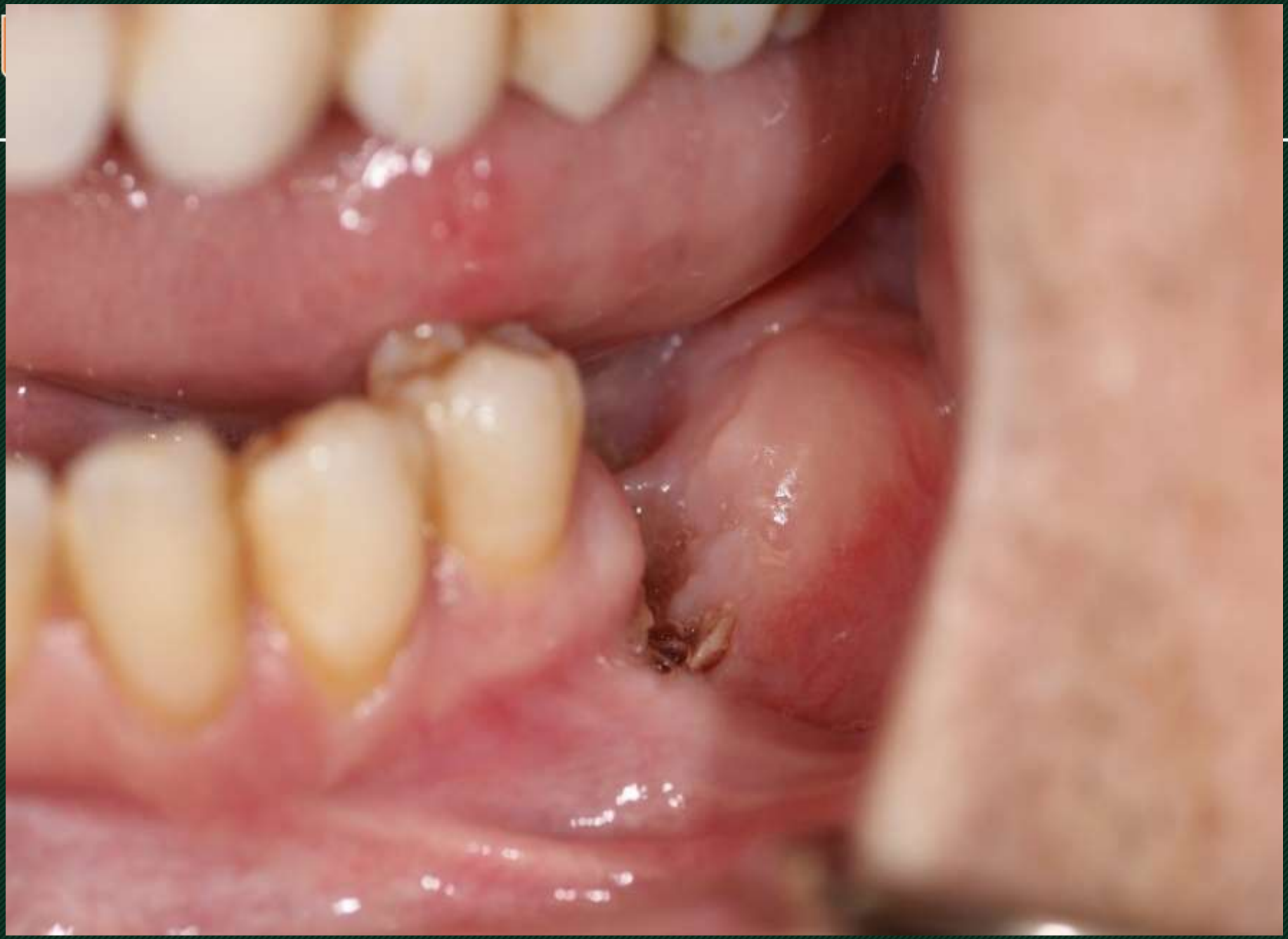
- A clinical examination revealed a painful non healing exposed bone (around 15 mm) at extraction site #19 with mild edema and erythema around the exposed bone. There was no drainage or signs of infection and no other intraoral lesions that were present. The patient had a loss of sensation on the lower left lip and chin.



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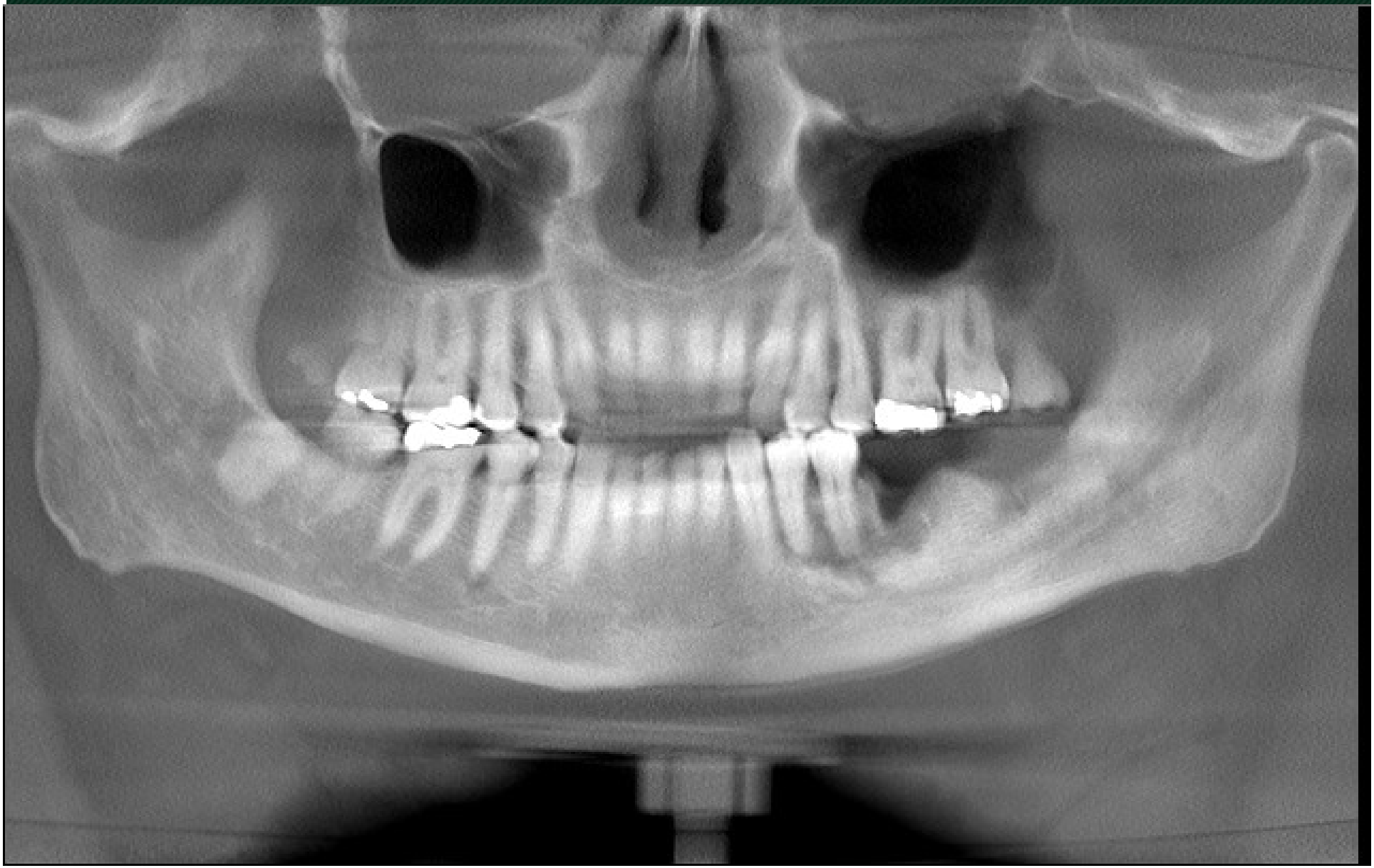

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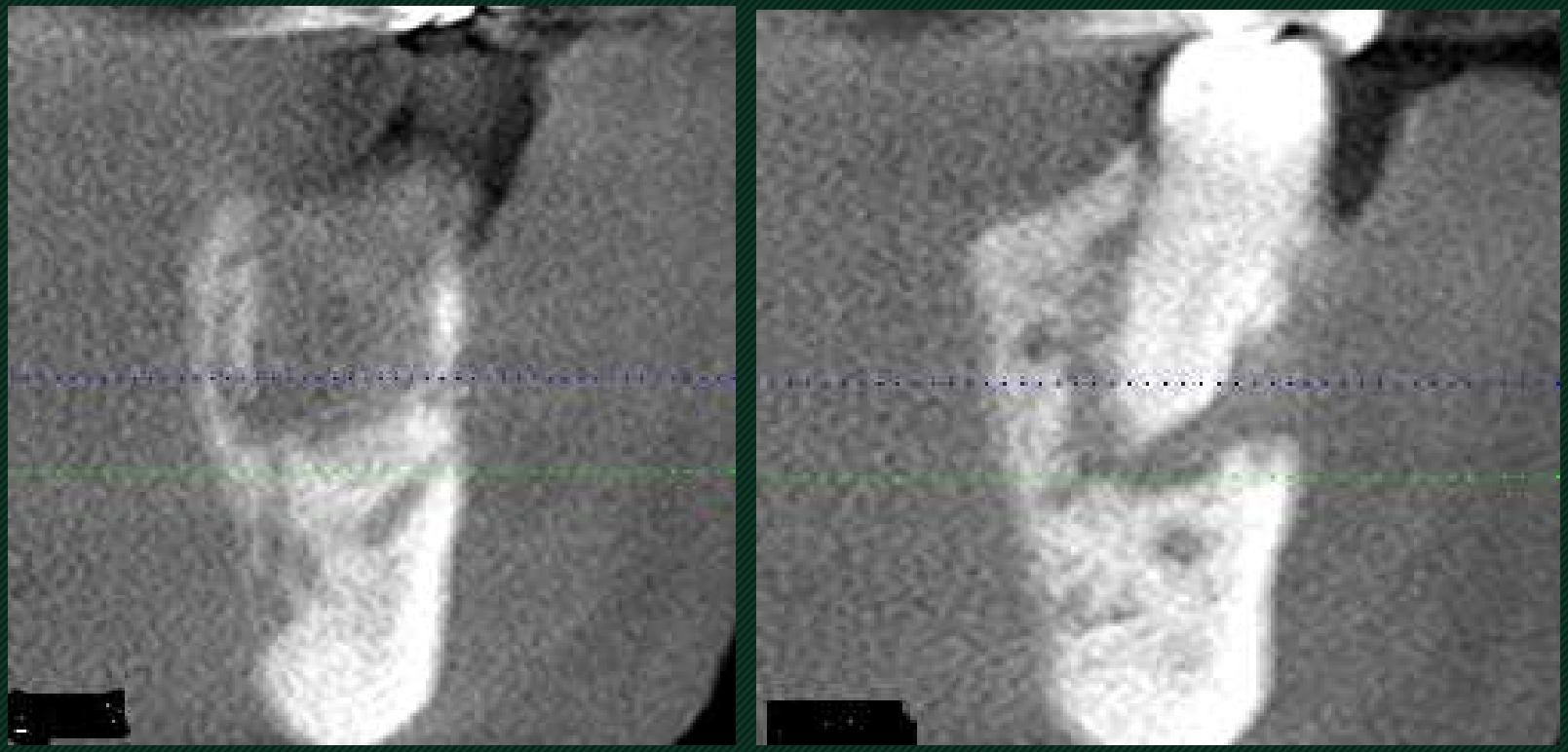

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- Dx: Stage III Drug Induced Osteonecrosis of the Jaw.
- Plan: A treatment plan was discussed with the patient that included resection of the left hemimandible, a fibula free graft, extraction of teeth #’s 20 and 21 as well as nerve grafting to rebuild his sensation of the left chin and lip region.

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- Tocilizumab (TCZ) is a recombinant humanized anti-IL-6 receptor monoclonal antibody.
- IL-6 is a proinflammatory cytokine produced by endothelial cells, B and T cell lymphocytes, monocytes and fibroblasts in areas affected by inflammation.
- Inhibition of IL-6 receptors by TCZ leads to a reduction in cytokine and acute phase reactant production.

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- Randomized clinical trials show the benefit of TCZ in active RA at the FDA approved dose of 4-8 mg/kg every four weeks with or without combination MTX/DMARDS.
- TCZ monotherapy was proven superior to MTX monotherapy in those who had not had prior treatment failure and was significantly more effective than DMARDS in those who had prior treatment failure.
- TCZ was also effective in those patients who previously had failed treatment with a TNF-alpha inhibitor.

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- TCZ interferes with osteoclast development and function, as well as reducing VEGF production and inflammatory reactions.
- By inhibiting osteoclast function, TCZ induces prolonged inhibition of bone resorption with over-suppression of bone remodeling (ie, low bone turnover).
- This was seen as a hypermineralization of the mandibular marrow space, an observation also noted in cases of osteonecrosis of the jaw caused by bisphosphonates and Denosumab.

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- This combination of significantly adversely affecting bone turnover and its antiangiogenic effects likely explains the mechanism behind the osteonecrosis of the jaw seen in our patient.
- These chain of events is initiated in patients who have had dental extractions as occurred in our case which is also the most common initiator of osteonecrosis of the jaw cases caused by bisphosphonates and Denosumab.
- ACTEMRA half life is 11 days, so it lends itself to drug holiday.

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PROLIA (Denosumab)

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MW

- HPI: This is a 73-year-old female, who underwent a bone graft to the left posterior mandible for ridge augmentation in January 2018. However, the bone graft was debrided one month later due to persistent localized infection. She continues to report pain and bad taste. She has received 3 injections of Denosumab 60 mg subcutaneously Q 6 months for the treatment of osteopenia from March 2016 to November 2017.

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MW

- PMH: Osteoporosis, GERD, Hyperlipidemia.
- PSH: Cardiac surgery, cervical fusion.
- SH: Denied any tobacco, drug or alcohol abuse.
- Med: Nexium, Crestor, Vitamin D.
- All: Penicillin (rash).

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- A clinical examination identifies a subtle amount of exposed bone in the left posterior mandible and tenderness particularly in the lingual aspect extending from the mental foramen to the midline. There is an edentulous area there with a root canal treated teeth #17 and #21. The remainder of the clinical examination identifies a heavily restored dentition with no other areas of exposed bone.

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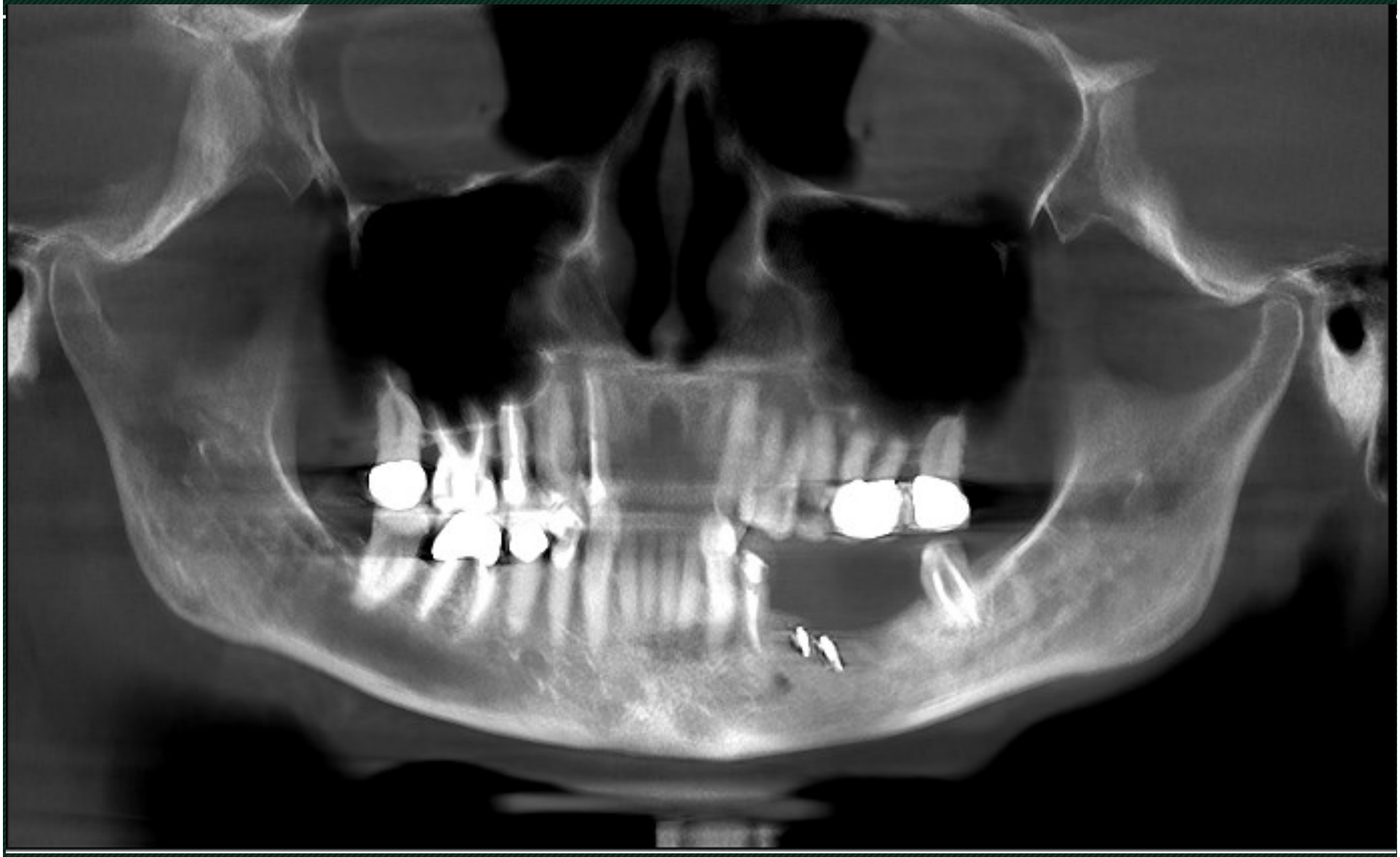

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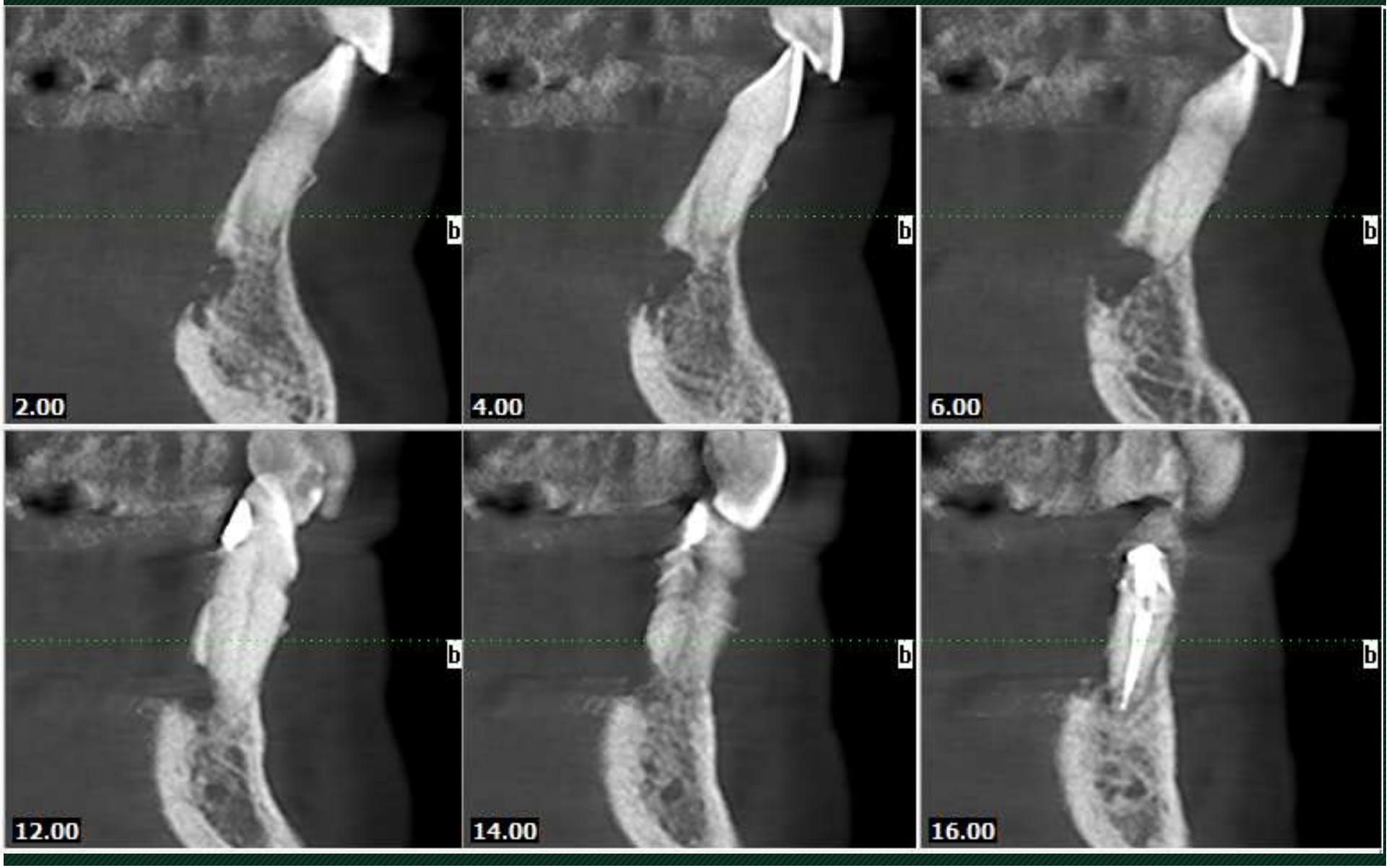

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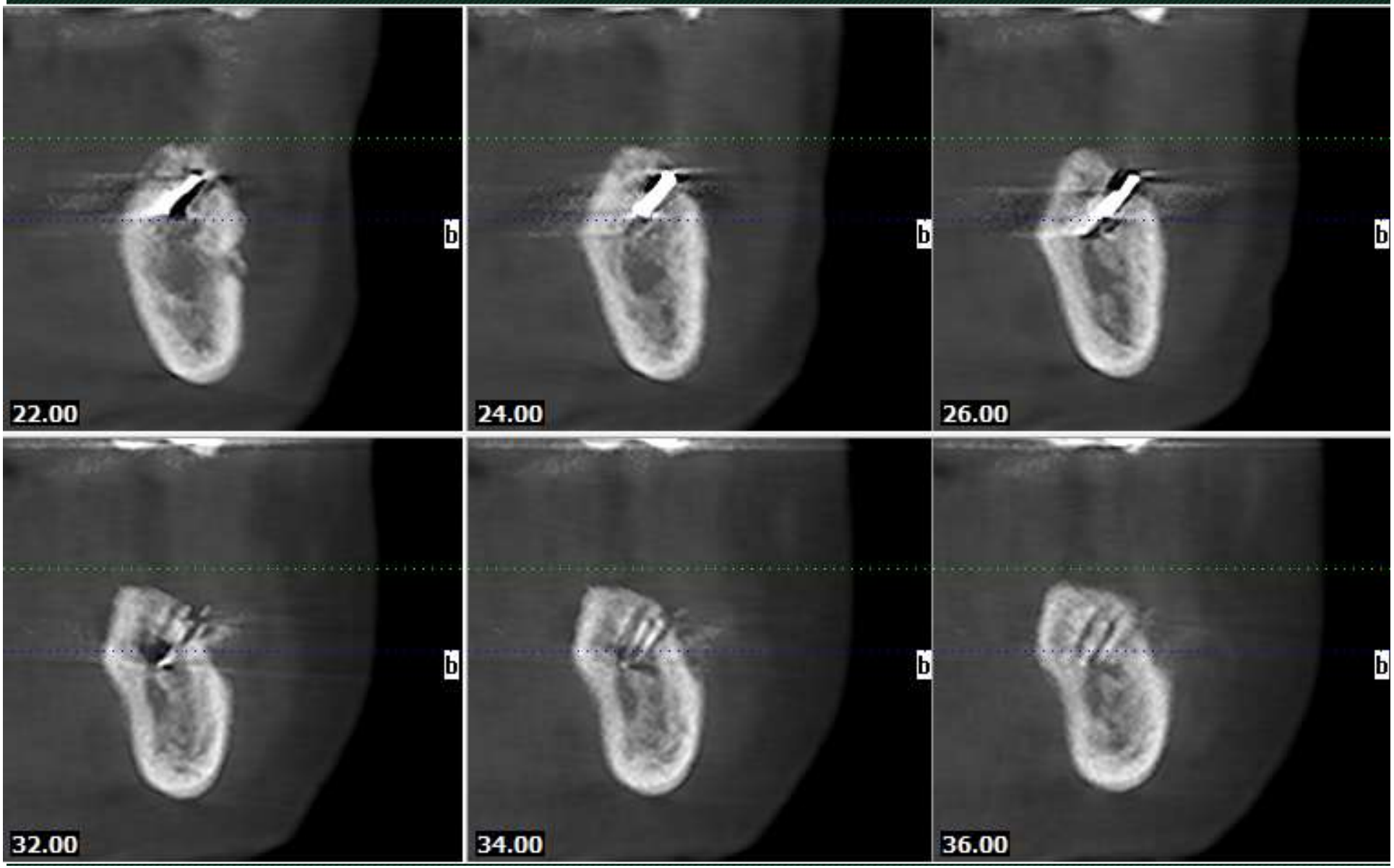

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MW

- Dx: Drug Induced Osteonecrosis of the Jaw with secondary infection.
- Plan: Doxycyclin 100 mg Q daily while on drug holiday from Denosumb, re-evaluate in 3 months, if pain and halitosis persist, then surgical intervention with removal of 2 screws of left mandible and debridement under GA.

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Mechanism of Action of Denosumab

- It is a RANK-L inhibitor and Osteoclast inhibitor at resorption sites, in blood and tissue spaces and in bone marrow.

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Key Differences

- Bisphosphonates: most affect osteoclasts resorbing bone and some affect precursors in bone marrow.
- Denosumab affects mature osteoclasts and their precursors everywhere.

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Key Difference-half life in bone

- Bisphosphonates: 11+ years
- Denosumab: 26 days

- Denosumab cases will occur sooner and be more extensive but are more straightforward to treat because of the low half life, because they lend themselves to drug holidays.

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Key Difference

Bisphosphonate → by a RANK-L inhibitor

- Rapid onset of DIONJ
- More extensive
- More severe

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Manzaneque A, Chaquaceda C, Mensa M.

Use and Safety of Denosumab in Cancer Patients.

Int J Clin Pharm

June 2017

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Use & Safety of Denosumab in Cancer Patients

- Method: Retrospective study of patients who started Denosumab between January 2013 and June 2015.
- The study population comprised 104 patients, of whom 86 (82.7%) were receiving concomitant outpatient cancer treatment and 39 (38%) had previously received Zoledronate.
- Most common adverse effects included hypocalcaemia which was recorded in 38.5% of patients and osteonecrosis of the jaw in 12.5%.
- Conclusion: higher incidence of all-grade osteonecrosis of the jaw than reported in the literature.

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CABOMETYX (Cabozantinib)

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- HPI: 62 year-old male with a history of Renal Clear Cell Carcinoma and being treated with Cabometyx (Cabozantinib) since February 2017. He presented for evaluation of exposed bone and severe pain in the bilateral mandible which began few months before his presentation.

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JR

- PMH: RCCC, HTN, CAD.
- PSH: resection of left kidney in September 2017.
- SH: Denied any tobacco, drug or alcohol abuse.
- Med: Plavix, ASA, Cabometyx 60 mg daily, Lipitor, amlodipine and lisinopril.
- FH-brother with RCCC as well.
- All: NKDA

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JR

- A clinical examination revealed exposed bone in the right and left posterior mandible with purulent discharge and bad odor. Exposed bone at areas of teeth #17 through 20, as well as #29 and 30. No cutaneous changes noted.

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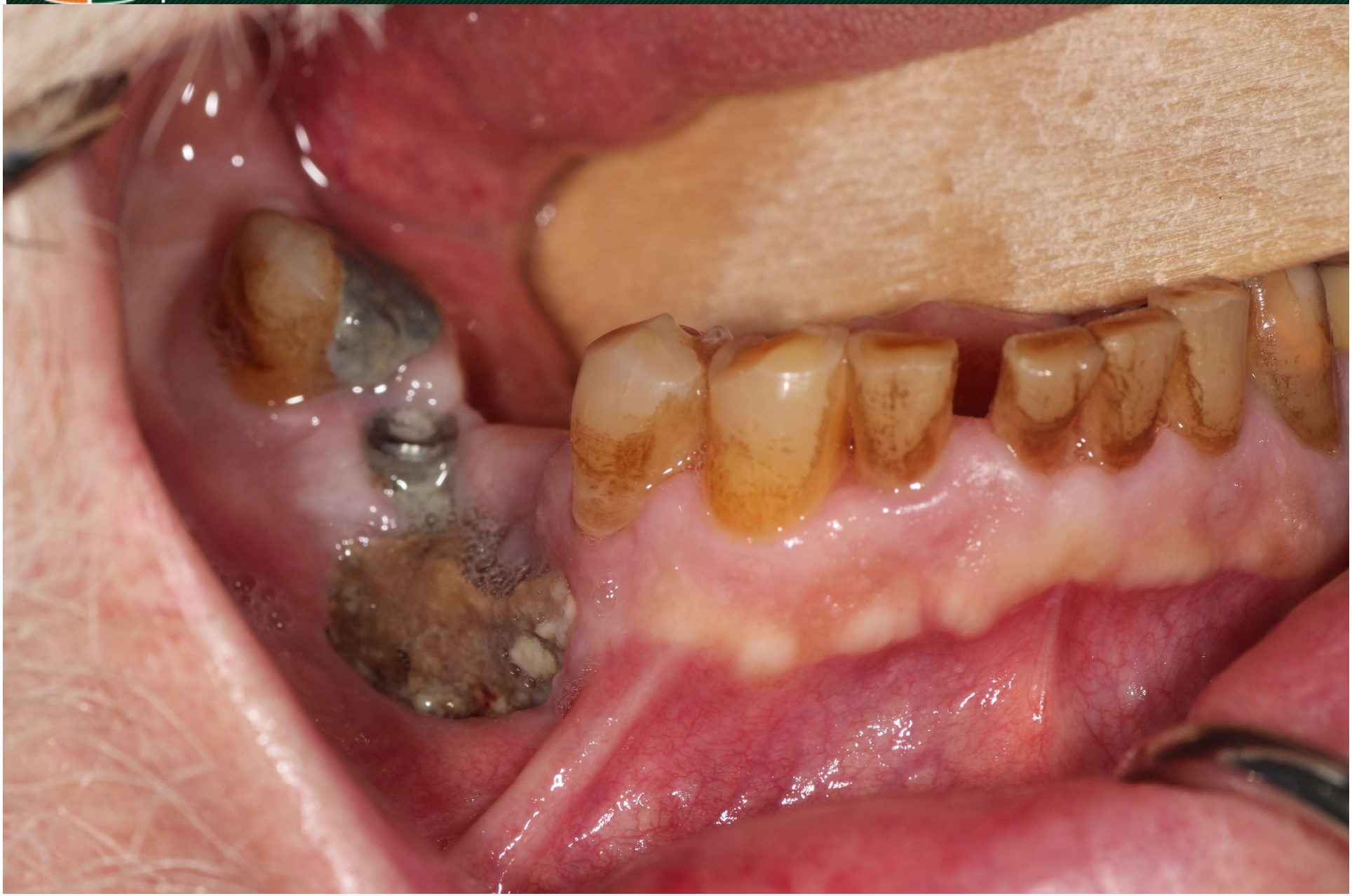

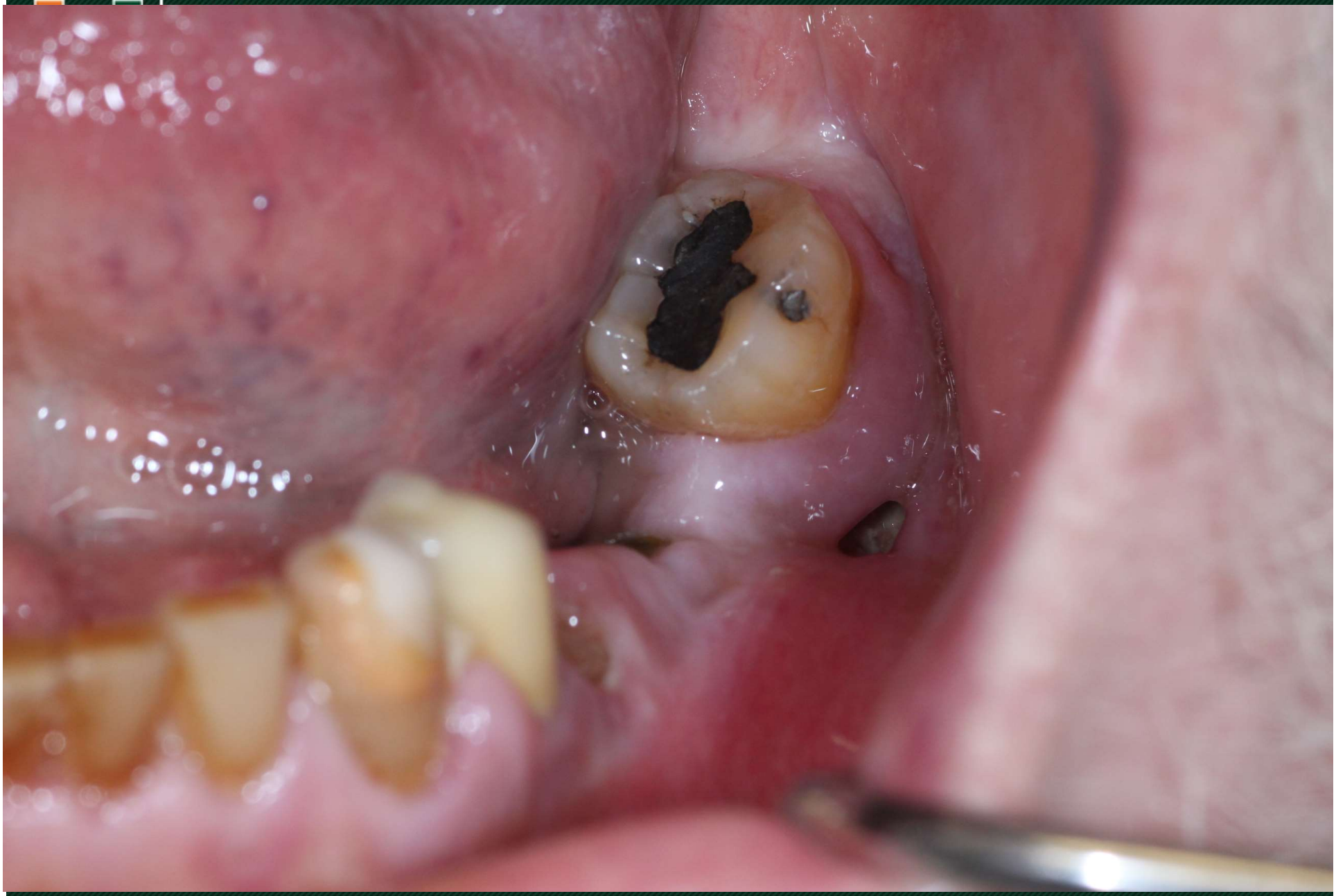

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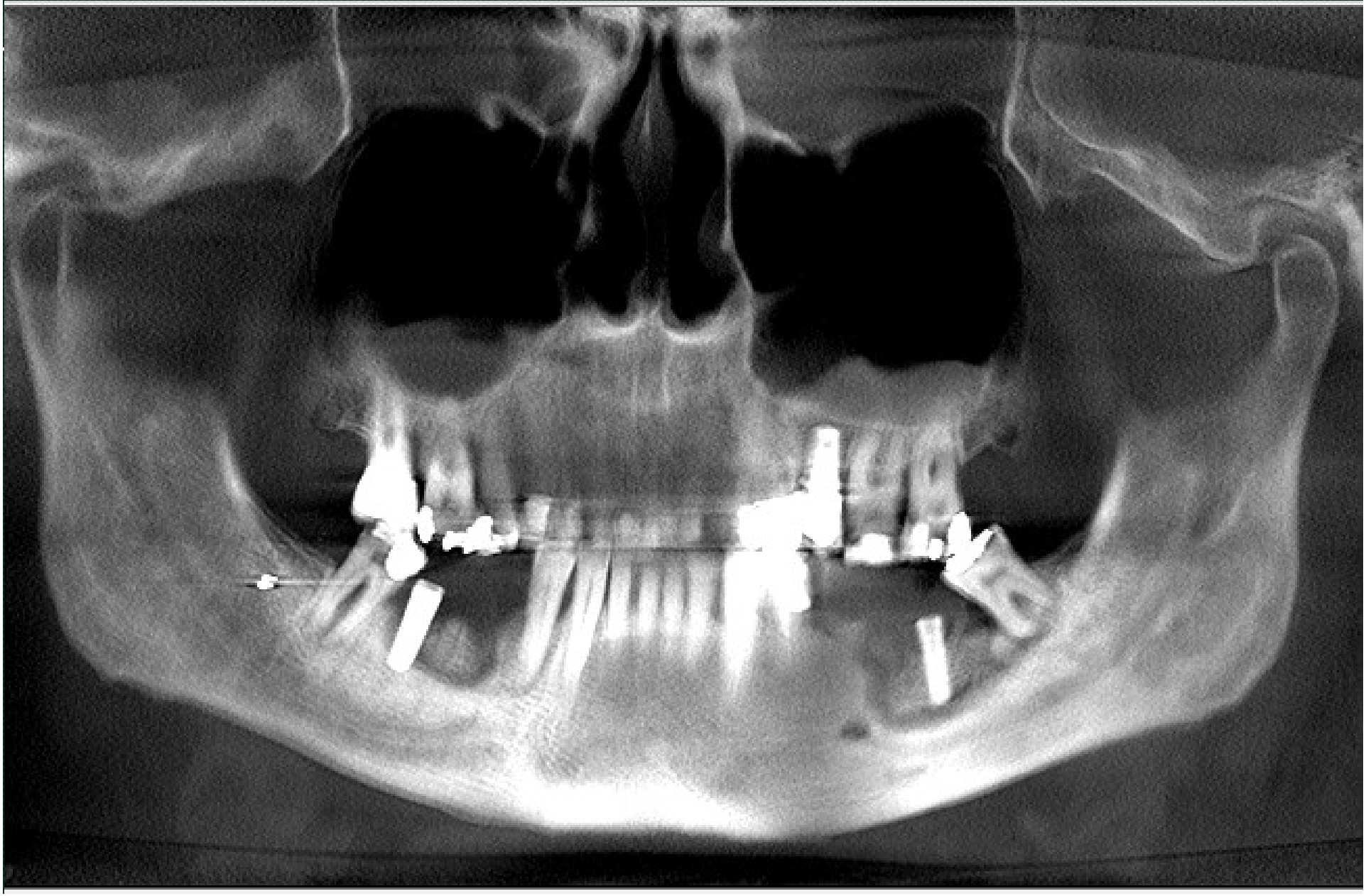

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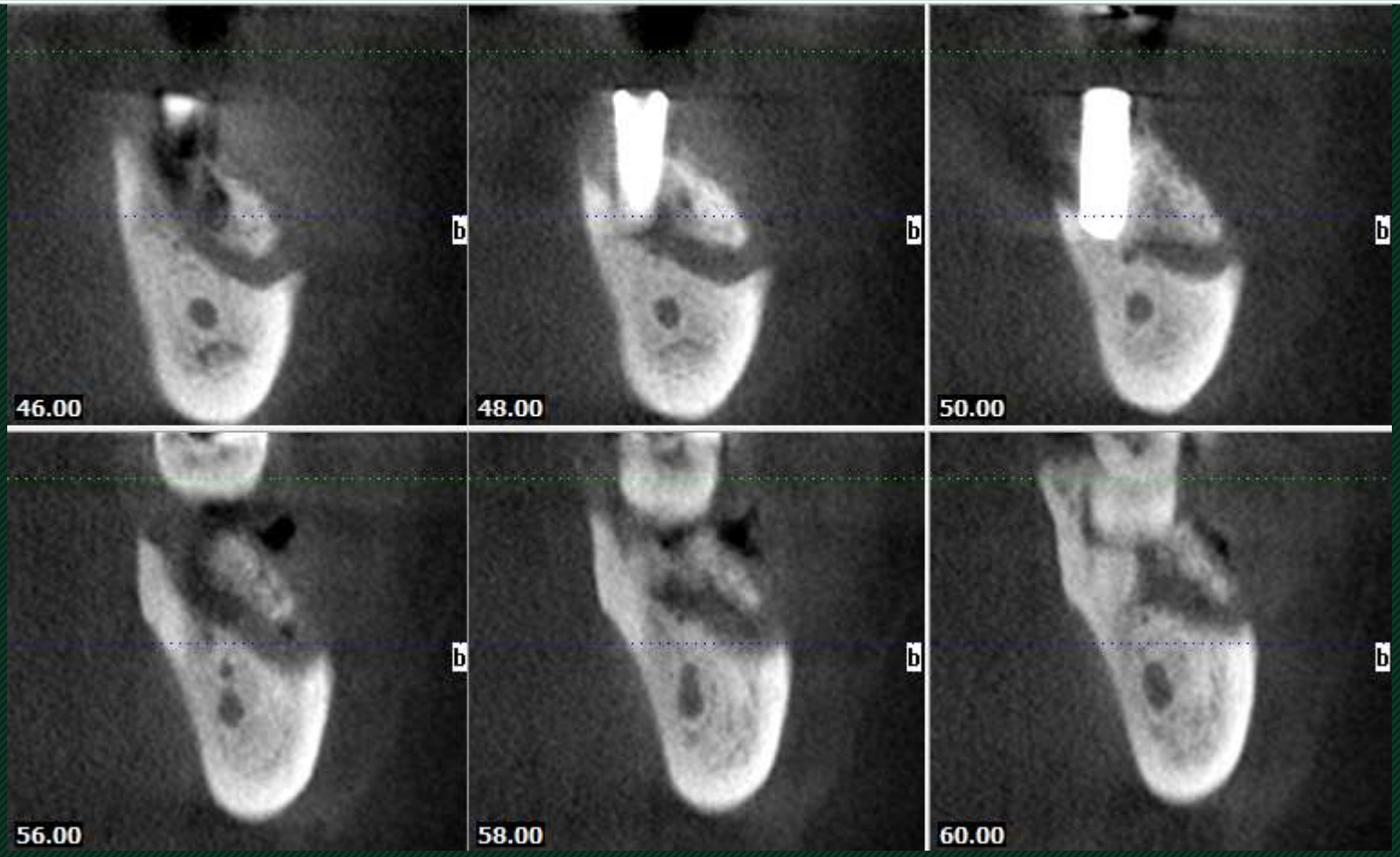

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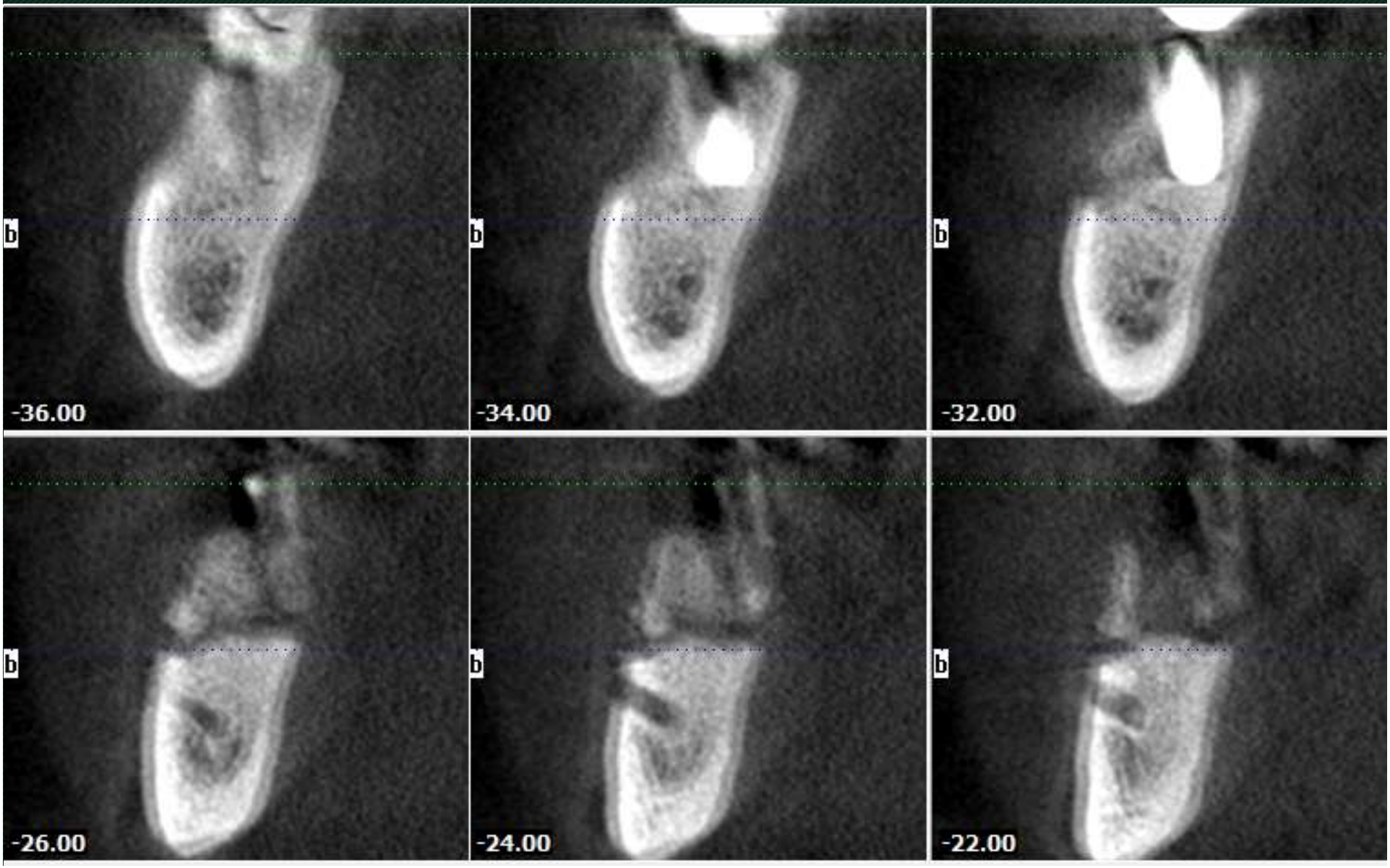

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JR

- Dx: Stage III Drug Induced Osteonecrosis of the Jaw.
- Plan: Drug holiday from Cabometyx for at least 4 weeks (half life of drug is 55 hours) and then debridement surgery to eradicate his exposed bone, pain, and halitosis.

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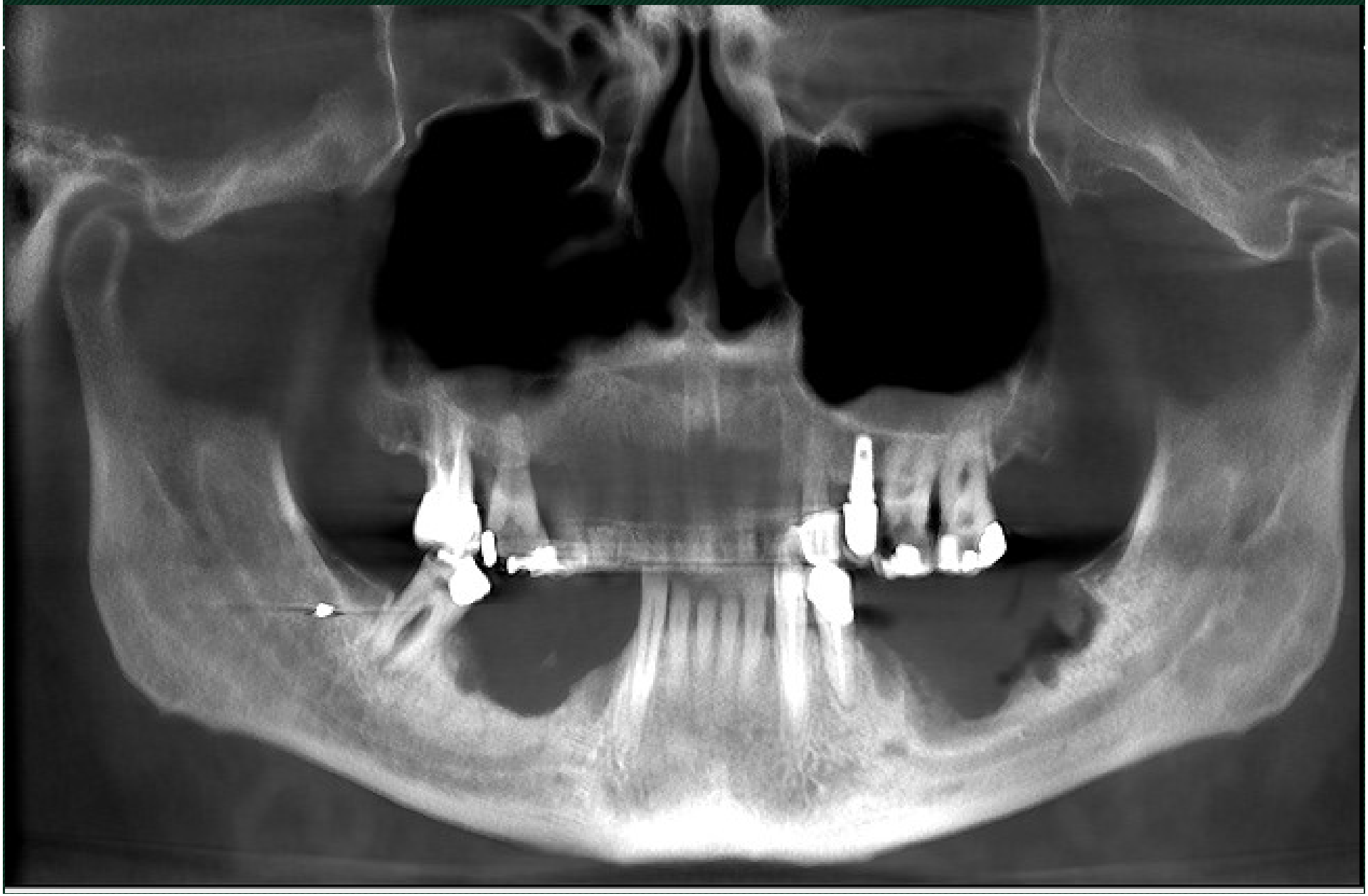

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Mechanism of Action of cabometyx

- It is a Tyrosine Kinase Inhibitor to treat advanced renal cell carcinoma.
- The pathogenicity of RCCC is almost the same as VHL disease, as RCC patients show loss of heterozygosity at the VHL locus on chromosome 3p25, and 65% of VHL patients end up with bilateral RCCC.

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Mechanism of Action of cabometyx

- Agents of treatment target the VEGF pathways such as Cabometyx. These antiangiogenic activities are the potential cause of DIONJ seen in RCCC patients.
- Half life for Cabometyx is 55 hours, so it also lends itself to drug holiday.
- Treatment is a short drug holiday followed by surgical intervention for symptomatic patients.

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Summary

- Include these medications in your history questions as well as other osteoporosis or cancer treating drugs.