Psoriasis: Targets and Therapy

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CASE REPORT

Secukinumab Causing Medication-Related Osteonecrosis of the Jaw, in a Patient Diagnosed with Psoriasis and Rheumatoid Arthritis

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Abstract: The use of antiangiogenic and antiresorptive medications, particularly in patients with cancer or osteoporosis, can lead to osteonecrosis of the jaw following tooth extraction, trauma or arising spontaneously- A condition known as medication-related osteonecrosis of the jaw (MRONJ). In this article, we present a unique case of MRONJ in a patient with no history of antiresorptive or antiangiogenic drug use, who was instead taking the anti-interleukin 17-A (Secukinumab) medication for severe psoriasis. This association has not been previously reported in the literature.

Keywords: plaque psoriasis, anti-interleukin 17-A, immunomodulator, interleukins inhibitors, MRONJ

Introduction

Psoriasis is an autoimmune disease, characterized by chronic inflammation and atypical keratinocyte proliferation, resulting in formation of red patches with silver-colored scales on the skin.[1,2] It can also affect the joints and is most commonly seen as plaque psoriasis.[3] Both males and females are affected, with genetic factors playing a predominant role (60 to 90% hereditary), exacerbated by comorbidities such as high stress levels, obesity, and histories of medications for hypertension or cardiovascular disease, lithium use, and smoking.[4] Commonly affected areas include nails, face, scalp, soles, palms, elbows, and knees, highlighting the systemic nature and variable clinical manifestations of the disease,[2,4,5] affecting patients' quality of life with negative influence on patient's psychological state and social life.[6] Whilst there is not a cure for psoriasis at the time, there are a number of treatment options that can help maintain control over the disease's symptoms, which are selected based on the severity of the symptoms.[3]

Psoriasis can be treated, among other therapeutic modalities, with three types of systemic medications: biologics, small molecules, and non-biologic drugs. Biologics are proteins (such as antibodies), that specifically target immune system components like cytokines and interleukins. Small molecules are organic compounds, such as apremilast, which affect immune cells. Non-biologic medications, including retinoids, methotrexate, and ciclosporin have been used for years to treat psoriasis.[3]

Medication-related osteonecrosis of the jaw is a serious condition that may develop in patients with a history of antiresorptive (AR) or antiangiogenic (AA) medication, predominantly for the treatment of cancer or osteoporosis. This condition may occur with or without concurrent immunosuppressant medications. It presents in the absence of radiation therapy to the head and neck area or obvious metastatic disease to the jaws.[7] Clinically, MRONJ manifests as unhealed, exposed necrotic bone or persistent fistula that probes to bone in the maxillofacial region for more than eight weeks.[7] Symptoms include pain, halitosis, tooth loss, sensory impairment in the trigeminal nerve's innervation area, pathological fractures of the lower jaw, oroantral and oronasal communication or fistula, sinus and orofacial space infections.

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Preventing MRONJ is crucial, requiring both dentists and physicians to be aware of the predisposing factors and appropriate preventive measures. Therefore, it is essential for healthcare providers to stay informed about the latest medications that may cause MRONJ and to implement strategies minimizing this risk.[8,9]

There is a potential link between MRONJ and systemic therapies like immunosuppressants and biologics used for psoriasis or rheumatoid arthritis. A number of these medications have the potential to induce disturbances in bone homeostasis caused by the impairment of cells from the monocyte-macrophage lineage, leading to reduced bone remodeling and the inhibition of local bone defense mechanisms against infection. This is currently as considered one of the main pathogenetic mechanisms in the MRONJ development.[10] This connection highlights the need to investigate the broader implications of such treatments on oral health, particularly for patients with autoimmune conditions. Understanding these risks is vital for developing effective prevention strategies and ensuring optimal patient care.

Case Presentation

In July 2023, a 65-year-old female patient was referred to the Department of Stomatology in the Faculty Hospital in Pilsen due to an unhealed lesion with the formation of a fistula in the past 3 months after the extraction of tooth 46 in March 2023. This procedure was performed without any preventive measures, including antibiotic prophylaxis, primary wound closure, and/or using mouthwashes before and after surgery, etc. Since the tooth extraction, the patient has suffered from pain and an unpleasant feeling at the extraction site with pus discharged.

The patient's medical history includes severe psoriasis vulgaris including significant nails involvement of the upper and lower extremities and psoriatic arthritis of the distal interphalangeal joints. Additional conditions involved seropositive rheumatoid arthritis of 4th stage (immunoglobulins M (IgM) – and immunoglobulins A (IgA) - rheumatoid factors positivity, cyclic citrullinated peptide (aCCP) positivity) with the radiocarpal, carpometacarpal, metacarpophalangeal and proximal interphalangeal joints involvement, hypertension, subclinical hypothyroidism, and dyslipidemia. The patient has undergone several surgeries in the past, including a hysterectomy for a benign diagnosis, laparoscopic cholecystectomy for lithiasis, appendectomy, and total endoprosthesis of the right shoulder, left knee, and right hip because of osteoarthritis. Her pharmacological history includes Levothyroxine 25 mcg, Leflunomide 20 mg, Amlodipine 5 mg, Ramipril 2.5 mg, Rosuvastatin 20 mg, calcium 500 mg and vitamin D3 1000 IU. All medicaments are received once daily, and Ibuprofen 600 mg as needed. Rheumatoid arthritis was treated with methotrexate, which had to be discontinued in 2011 due to liver function alterations and lower intestinal dyspepsia. Since November 2020, the patient has been treated for psoriasis with anti-interleukin 17-A medication, secukinumab, currently at 300 mg once a month, which has led to significant improvement in both joint and skin conditions. Additionally, the patient received topical therapy with betamethasone dipropionate and salicylic acid for psoriasis. The patient had no allergies, and her history regarding substance abuse was negative.

The patient was diagnosed with MRONJ stage II (characterized by symptoms of infection) (Figure 1A), according to the staging system developed by American Association of Oral and Maxillofacial Surgeons (AAOMS).[7] The patient's chief complaint was occasional pain at the site of extracted tooth 46. Clinically, a fistula with pus discharge in the oral vestibule of same area was noted. Teeth 44 and 45 were firm without looseness, painless on percussion. No swelling in the alveoli was present. The innervation of both, the inferior alveolar and the mental nerve, was undamaged and intact. Radiographic findings revealed significant osteolytic bone destruction and localized sequestration in the areas of teeth 45 and 46 of size 20×15×10 mm (Figure 1B–D). Teeth 45 and 44 were endodontically treated with definitive root fillings, with the apex of tooth 45 extending into the osteolytic defect. The tooth 44 has a small periapical lesion not associated with this defect. To address the current situation and prevent further complications, the patient underwent sequestrectomy and debridement of necrotic bone, as well as extraction of teeth 44 and 45 under local anesthesia. This procedure included a mucoperiosteal flap elevating in the range of teeth 44–47 (Figure 1E), smoothening of sharp bony edges and carefully dissecting and preserving of mental nerve (Figure 1G). The specimen of necrotic bone (Figure 1F) was sent for the histopathological examination (Figure 2A and B), and after local antisepsis the wound was closed primarily, with absorbable sutures (Figure 1H). Perioperative antibiotics were prescribed, specifically phenoxymethylpenicillin 1.5 MIU every eight hours orally for ten days. The patient was also advised to improve oral hygiene and chlorhexidine-containing mouthwash rinses.

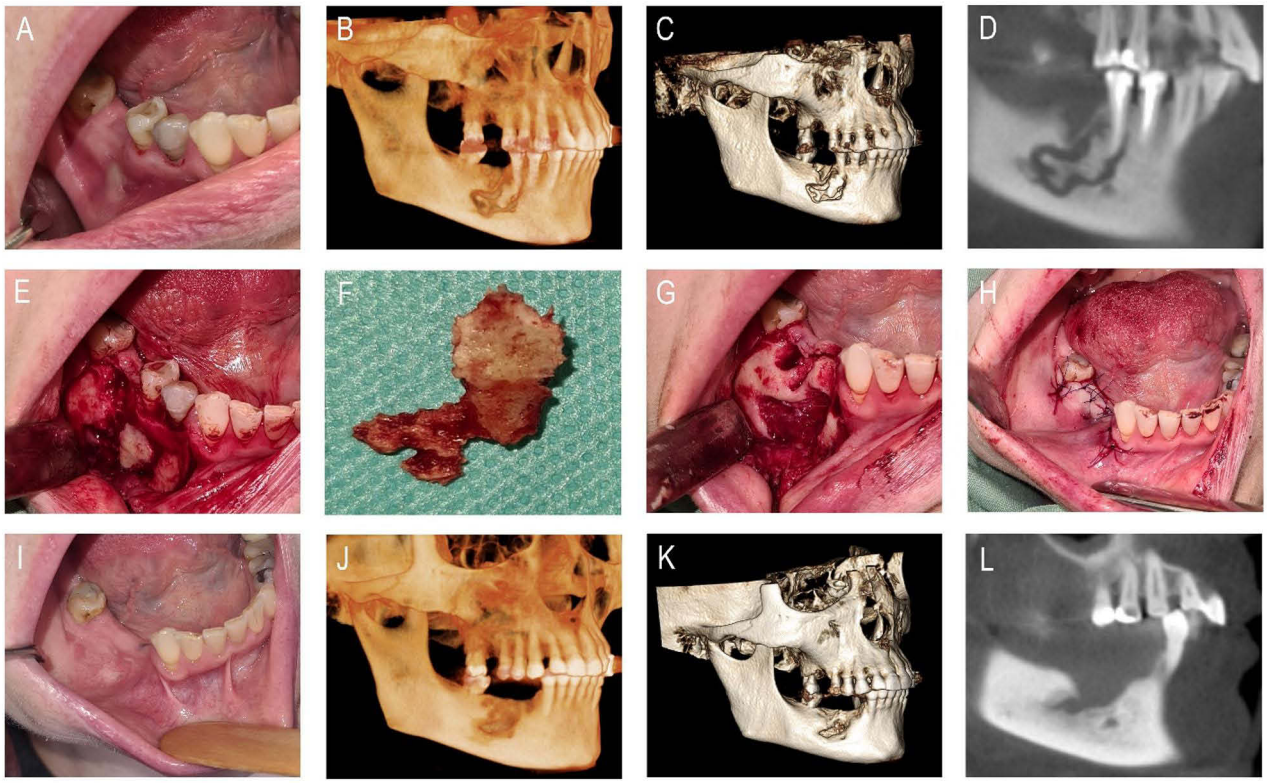

Figure 1 Clinical and radiographic images of the patient. (**A**) clinical findings at the time of diagnosis - fistula with purulent exudation in the vestibule of the lower jaw in area of missing tooth 46. (**B**) CBCT 3D reconstruction - osteolysis and sequestration of the mandibular bone in area of teeth 45, 46. (**C**) CBCT 3D reconstruction - osteolysis and sequestration of the mandibular bone in area of teeth 45, 46. (**D**) CBCT sagittal section - osteolysis and sequestration of mandibular bone in area of teeth 45, 46, teeth 44 and 45 are endodontically treated. (**E**) sequestrectomy and osteonecrectomy of the mandible under local anesthesia with atraumatic preservation of the mental nerve and extraction of teeth 44 and 45 - elevation of the mucoperiosteal flap with marked bone sequestration. (**F**) sequestrectomy and osteonecrectomy of the mandible under local anesthesia with atraumatic preservation of the mental nerve and extraction of teeth 44 and 45 - bone sequestration removed. (**G**) sequestrectomy and osteonecrectomy of the mandible under local anesthesia with atraumatic preservation of the mental nerve and extraction of teeth 44 and 45 - state after smoothening sharp bone edges and wound debridement, before primary wound closure. (**H**) sequestrectomy and osteonecrectomy of the mandible under local anesthesia with atraumatic preservation of the mental nerve and extraction of teeth 44 and 45 - primary wound closure with monofilament absorbable suture. (**I**) condition 7 months after the procedure, healed soft tissue, without signs of MRONJ. (**J**) CBCT 3D reconstruction - mandibular defect with signs of bone healing. (**K**) CBCT 3D reconstruction - mandibular defect with signs of bone healing. (**L**) CBCT sagittal section - mandibular defect with signs of bone healing.

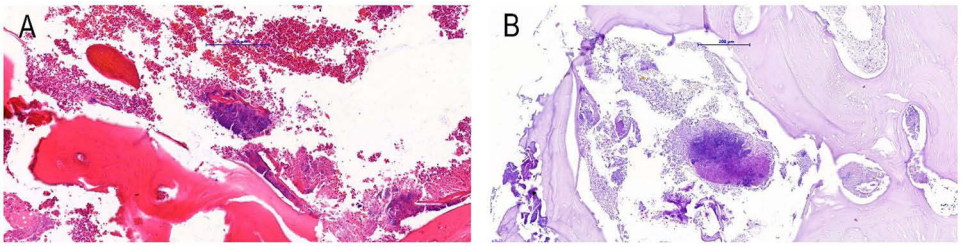

Figure 2 Histopathological images of osteonecrosis of the jaw. (**A**) Bone fragments, fibrinous-purulent exudate and the presence of actinomycotic drusen, stained with Hematoxylin and eosin, and magnified by 10–100x. (**B**) Bone fragments, fibrinous-purulent exudate and the presence of actinomycotic drusen, with Periodic Acid-Schiff staining, and magnified by 10–84x.

The patient has been followed up regularly, with oral examinations showing signs of lesion healing. No signs of exudation or dehiscence have been detected. Similarly, imaging studies have revealed evidence of bone healing 7 months after surgery (Figure 1I–L).

Discussion

Medication-related osteonecrosis of the jaw (MRONJ) is a well-documented, serious pathological condition that, although rare, can be life-threatening or pose a risk of causing permanent consequences due to its complications. It can also lead to a decreased quality of life in affected patients and negatively impact the treatment of their underlying disease.[10] MRONJ is primarily associated with the use of antiresorptive medications (especially aminobisphosphonates and denosumab).[7] However, recent scientific literature increasingly describes the occurrence of MRONJ in patients receiving antiangiogenic agents, such as vascular endothelial growth factor inhibitors, or protein kinase inhibitors, including tyrosine kinase inhibitors or mammalian target of rapamycin inhibitors, despite not being on antiresorptive medications.[8,11,12]

Many recent studies, primarily only in the form of case reports or case series, explore the association between MRONJ development and targeted non-specific immunosuppressive or immunomodulatory therapies, such as anti-interleukin agents (anti IL-6 or anti IL-23), TNF-α inhibitors, B-Raf inhibitors, methotrexate, or monoclonal antibodies used in immunotherapy (eg, Ipilimumab, Nivolumab, Rituximab).[12–19] However, evidence linking these treatments to the development of MRONJ is limited, necessitating cautious interpretation of these findings.[11]

Non-antiresorptive medication-related osteonecrosis of the jaw affecting non-oncologic patients is extremely rare. Currently, this phenomenon is primarily described in patients treated for Crohn's disease or rheumatoid arthritis (RA).[13,14,16–19] Based on current knowledge, patients with psoriasis, who are treated with systemic therapy, are also potentially at risk of developing MRONJ, especially those taking TNF-α inhibitors, methotrexate, or potential interleukin inhibitors. The first case of a patient with psoriatic arthritis and plaque psoriasis treated with guselkumab (anti-IL-23) who developed a lesion in the upper jaw that could resemble MRONJ following tooth extraction has only recently been published.[15] To date, no other cases of this adverse effect of the treatment of psoriasis patients have been published in the world literature.

Rheumatoid arthritis and Crohn's disease are inflammatory conditions frequently treated with TNF-α inhibitors, which serve as immunomodulators. These medications are essential for managing such conditions, offering targeted therapy compared to traditional, non-specific immunosuppressive agents. However, they are associated with significant adverse effects, including an increased risk of lymphoma and susceptibility to infections.[16] Despite their benefits, there is insufficient evidence to definitively determine the relative risk of MRONJ from TNF-α inhibitor treatment, necessitating higher-quality studies to assess these risks more accurately.[16] Pathophysiological research suggests a potential link between TNF-α inhibitors and MRONJ. TNF-α, a proinflammatory cytokine, not only plays a role in bone destruction and osteoclastogenesis, but its inhibition could reduce bone turnover, potentially contributing to MRONJ. Furthermore, anti-TNF-α therapy may increase susceptibility to infections due to immune dysfunction.[18]

In addition to TNF-α inhibitors, interleukin inhibitors may also be associated with MRONJ development. To date, only isolated cases of MRONJ associated with tocilizumab, an IL-6 receptor inhibitor, in patients with rheumatoid arthritis or coronavirus disease 2019 (COVID-19) have been published, indicating that anti-IL-6 therapy may exacerbate osteomyelitis or lead to MRONJ.[13,14] IL-17, produced primarily by Th17 cells, is a pro-inflammatory cytokine that plays a significant role in immune-mediated inflammatory responses. Similar to other interleukins, where inhibition is currently being considered in the MRONJ development (IL-6 and IL-23), IL-17 is classified as an osteoclastogenic cytokine, promoting osteoclastogenesis by increasing the production of receptor activator of nuclear factor-kappa B ligand (RANKL), which in turn stimulates osteoclast differentiation and bone resorption.[20,21] While excessive or even insufficient osteoclast activity can lead to bone damage, controlled osteoclast function is essential for maintaining normal bone remodeling and repair, particularly after injuries such as tooth extraction. In addition, IL-17 is a key factor in recruiting and activating neutrophils, bolstering the body's ability to combat infections and is a critical factor in preventing complications such as MRONJ, where local bacterial infection in the jawbones appears to be a significant risk factor. IL-17 is also implicated in promoting angiogenesis, an important process for ensuring adequate vascular supply to support soft tissue and bone repair.[20,21] In conclusion, IL-17 may play a protective role against MRONJ by facilitating bone remodeling, strengthening immune defense mechanisms, promoting angiogenesis, and maintaining immune homeostasis. However, suppression or inhibition of IL-17 could potentially disrupt these processes, leading to impaired healing, increased risk of infection, and thereby higher susceptibility to MRONJ. Secukinumab is a recombinant fully human IgG1 kappa monoclonal antibody produced in Chinese hamster ovary cells that inhibits the interaction of IL-17A with its receptor, expressed on various cell types, including keratinocytes.

Methotrexate, a first-line treatment for RA and a chemotherapeutic agent for various cancers and also psoriasis, is known for its serious side effects including myelosuppression, liver damage, and synovitis. Previous reports have also linked methotrexate to MRONJ, highlighting its potential risk in patients undergoing long-term treatment.[17,19]

In the case report we present, the patient had rheumatoid arthritis, but interleukin inhibitors, especially anti-IL-17-A treatment were indicated for psoriasis. From the patient's pharmacological history, which does not include antiresorptive medications, this drug is the most suspected, being associated with MRONJ development, with a possible additional effect from the immunosuppressive agent leflunomide. We assume methotrexate, which was indicated for the treatment of rheumatoid arthritis, had no influence on the development of the jaw lesion, as it had been discontinued for nine years at the time of MRONJ onset.

To our knowledge, this is the first case of MRONJ possibly associated with anti-IL-17-A treatment and the second case of MRONJ in a psoriasis patient where the lesion probably arose solely due to the treatment of psoriasis and not any other reasons.

This case and existing literature underscore the need for increased awareness and research regarding MRONJ, particularly in patients treated with new biologic agents and immunomodulatory drugs. Continuous evaluation of these treatments is crucial to better understand their risks and manage complications effectively, especially as new medicaments are introduced. Healthcare professionals must remain vigilant and monitor patients closely for MRONJ symptoms to mitigate potential risks associated with these therapies.[13,14]

Currently, there is no evidence-based approach to secondary prevention of MRONJ in patients taking potentially high-risk non-antiresorptive medications in the case of invasive procedures in the oral cavity. It is unknown whether periprocedural antibiotic prophylaxis and jaw bone smoothing with primary wound closure are effective in preventing MRONJ, similar to patients on antiresorptive therapy.[7,10,12] However, primary prevention of MRONJ before initiating this pharmacotherapy, which involves oral health assessment and addressing infectious foci, could be recommended, as it generally enhances the oral health status of these patients and also reduces the risk of other complications.

Conclusion

In conclusion, this case report highlights a potential risk of MRONJ in a patient receiving secukinumab, despite the absence of antiresorptive or antiangiogenic medication history. While no prior reports have associated MRONJ with secukinumab, this case report emphasizes the need for further research and larger studies to clarify this potential link. Although it is rare, proactive dental assessments and preventive measures should be considered before starting systemic pharmacological treatments for psoriasis patients.

Abbreviations

MRONJ, medication related osteonecrosis of the jaw; AA, antiresorptive; AR, antiresorptive; IL-6, interleukin 6; IL-17A, interleukin 17-A; IL-23, interleukin-23; IgM, immunoglobulins M; IgA, immunoglobulins A; aCCP, cyclic citrullinated peptide; TNF-α, Tumor necrosis factor alpha; COVID-19, coronavirus disease 2019.

Ethical Approval

The procedure was conducted according to ethical standards, with the patient's consent, and by the Helsinki Declaration. Approved by Ethical Committee University Hospital Pilsen and Faculty of Medicine in Pilsen, Charles University with reference number 236/24.

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Consent for Publication

Written informed consent for publication of patient's details was obtained from the patient, provided by Taylor and Francis group.

Disclosure

The authors report no conflicts of interest in this work, and there is no financial interest to declare.

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