J Oral Med Oral Surg 2024;30:38
https://doi.org/10.1051/mbcb/2024041

https://www.jomos.org

JOMOS
Journal of Oral Medicine and Oral Surgery

Case Report

Maxillary osteonecrosis linked to Pembrolizumab therapy: a case report

Louise Gosselin-Rousselle[1,*], Zoé Gaudimier[2], Pierre-Olivier Pamelard[3], Paul Sader[1], Hervé Moizan[1]

[1] Service d'odontologie CHU de Rouen, Rouen, France
[2] Service d'odontologie CHU de Créteil, Créteil, France
[3] Service d'odontologie CH du Havre, Le Havre, France

(Received: 29 August 2024, accepted: 29 November 2024)

Keywords: Pembrolizumab / osteonecrosis / maxilla

Abstract – Introduction: Osteonecrosis of the jaw is a serious condition often associated with the use of bone-modifying agents or antiangiogenics. Recent evidence suggests that immune checkpoint inhibitors, including Pembrolizumab, might also contribute to osteonecrosis of the jaw. **Observation**: An 83-year-old male with metastatic non-small cell lung cancer treated exclusively with Pembrolizumab developed osteonecrosis of the maxilla. Management included sequestrectomy, curettage, placement of Platelet-rich-Fibrin (PRF) and antibiotics. Despite initial improvement, symptoms recurred. The patient eventually stabilized but passed away a few months later. **Discussion**: A literature review was conducted supporting the hypothesis that the mechanism may involve disrupted bone remodeling due to enhanced immune activity. This highlights the need for further research to clarify the potential association between Pembrolizumab and osteonecrosis, and to develop preventive and management strategies. **Conclusion**: While definitive causality between Pembrolizumab and osteonecrosis of the jaw cannot be established with the current evidence, this case adds to the growing body of literature suggesting that immune checkpoint inhibitors may be implicated in the pathogenesis of osteonecrosis of the jaw. As the use of immunotherapy expands in oncology, further research is essential to elucidate this association and provide guidelines.

Introduction

Osteonecrosis of the jaw (ONJ) is a severe bone disorder often linked to the use of medications like bone modifying agents or anti-angiogenics [1]. However, emerging evidence suggests that immune checkpoint inhibitors may also contribute to the development of ONJ. While immunotherapy has revolutionized cancer treatment, it has also been associated with a range of immune-related adverse events, reflecting its mechanism of action [2].

Pembrolizumab is a monoclonal antibody utilized in oncological immunotherapy. It is notably used for the treatment of multiple malignancies including metastatic non-small cell lung cancer (NSCLC), metastatic melanoma, recurrent or metastatic head and neck squamous cell carcinoma (HNSCC).

This article presents a case of osteonecrosis of the maxilla in a patient treated with pembrolizumab and who was naive to bone-modifying agents (biphosphonates, Denosumab), anti-angiogenics and radiotherapy. This case report aims to explore the potential link between pembrolizumab and ONJ while acknowledging the multifactorial nature of this adverse event. It contributes to the limited but growing body of literature on this association and highlights the need for increased awareness and monitoring of such adverse effects in clinical practices.

Observation

A 83-year-old male was referred to the Oral Medicine department of our hospital in May 2023 with a two-month history of acute pain and dental mobility to the right side of the maxilla. The patient had been under the care of the Respiratory Medicine service since 2018 for a metastatic NSCLC (adenocarcinoma), for which he had refused surgery. He was noted to have diffuse metastases to the sacrum, adrenal gland

* Correspondence: l.gosselinr@gmail.com

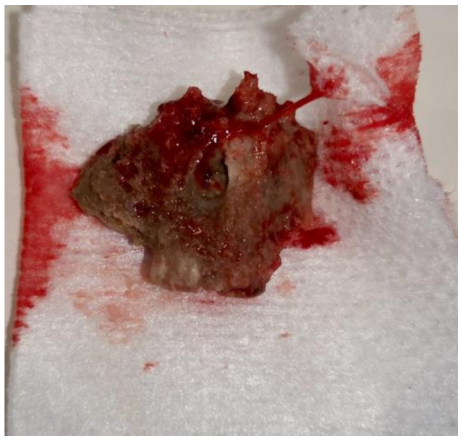

Fig. 1. Photograph of the bone sequestrum after removal.

and liver. Medical history was significant for type 2 diabetes and chronic renal failure. His current medication included pembrolizumab, metformine, tramadol, movicol. The patient also reported having quit smoking years ago. No history of cervicofacial radiotherapy, bone modifying agents (bisphosphonates or denosumab) or anti-angiogenics was retrieved.

Extra oral examination was found to be without particularity. However, intraoral examination revealed an exposed, avascular bone area on the vestibular right side of the maxilla. This yellow grayish area, greater than 5cm in width, extended from tooth number 16 to tooth number 12. The area was surrouned by swollen and inflamed gingiva. Additionally, the maxillary right first molar (tooth number 16) exhibited significant mobility. Palpation produced a purulent discharge, acute pain, and a vestibular bone sequestrum was well delineated and mobile.

CBCT imaging revealed right maxillary osteolysis surrounding teeth number 12 to 16, involving the maxillary sinus, which was consistent with osteonecrosis.

Given the situation, the entire bone sequestrum was removed (Fig. 1), and the sharp bone edges were smoothened. The non-restorable tooth number 16 was extracted and curettage was performed. Platelet-rich-fibrin (PRF) was placed into the alveolar bone following the department's protocol. The patient was started on Amoxicillin 1 g twice a day for 21 days in conjunction with Tramadol. He was also instructed to rinse with 0.12% chlorhexidine twice daily and to maintain proper oral hygiene.

Sequestrum's histopathology was consistent with osteonecrosis. The final diagnosis was stage 3 osteonecrosis (according to AAOMS).

At the three-weeks follow-up there was a significant improvement in symptoms and complete healing of the soft tissues was observed (Fig. 2).

Two months after the sequestrotomy, the patient returned for follow-up (Fig. 3). The right maxillary sinus was spontaneously painful, and upon palpation, a second mobile bone sequestrum, smaller than the first one, was detected and subsequently removed. The patient was prescribed amoxicillin 1g twice a day for 21 days.

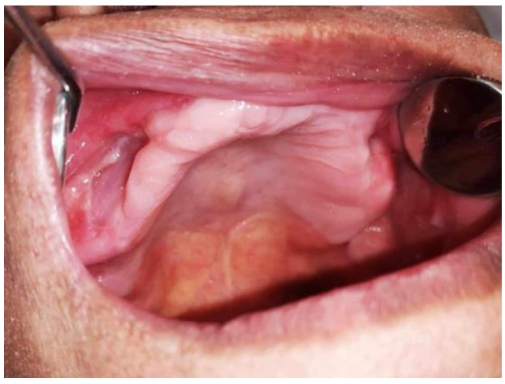

Fig. 2. Intra oral photograph of soft tissue healing at three weeks follow-up.

Two months later, in September 2023, the patient presented without symptoms. It was noted that the necrotic area had not progressed any further. The preliminary phases of the dental prosthetics were initiated, and the prosthetics were subsequently delivered to the patient. However, the patient unfortunately passed away a few months later.

Discussion

Pembrolizumab is known for causing immune-related adverse events, including cutaneous, endocrine or gastrointestinal reactions, but there is limited literature on its association with osteonecrosis of the jaw (ONJ).

Only few case reports have documented ONJ in patients treated with Pembrolizumab, often in combination with additional cancer therapies including chemotherapy (Tab. I). However, the current case is unique in its presentation, as the patient was naive to other commonly implicated therapies or anatomical risk factors. This suggests that Pembrolizumab alone, without adjunctive agents, could potentially lead to the development of ONJ, though the precise mechanisms remain unclear.

Pembrolizumab's mechanism of action, which involves the inhibition of the PD-1 pathway and subsequent activation of T-cell-mediated tumor responses, is thought to contribute to a spectrum of immune related adverse events. The adverse effects arise from the enhanced immune activity, which may inadvertently target normal tissues, including bone [7]. The pathophysiological link between immune checkpoint inhibition and ONJ is not entirely clear but may involve an imbalance in bone remodeling processes, where excessive immune activation leads to impaired healing and increased susceptibility to necrosis.

In the studies by Decaux *et al.* (2020) [4] and Myoken *et al.* (2020) [6], Pembrolizumab was administered in combination with other agents: Epacadostat and Denosumab. Importantly, neither Epacadostat nor Pembrolizumab alone is typically associated with ONJ. The combination of these agents, as described by Decaux *et al.* (2020), suggests a potential for enhanced risk when these drugs are used together, possibly

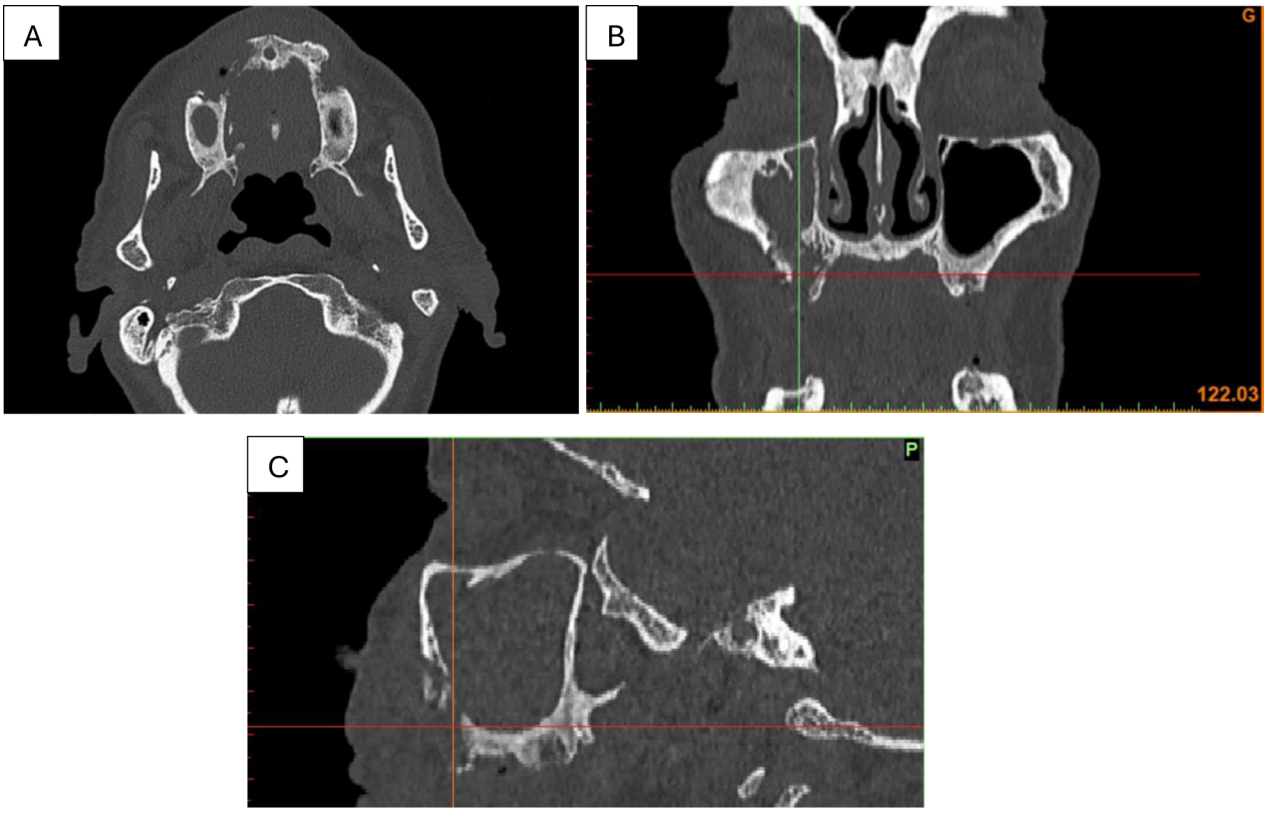

Fig. 3. CT scan at two months follow-up. A : Axial view. B : Coronal view. C : Sagittal view.

due to their combined effects on the immune system and bone health [4]. Similarly, Myoken *et al.* (2020), reported ONJ in a patient treated with Pembrolizumab and Denosumab. While Denosumab is known to be associated with osteonecrosis of the jaw, the addition of Pembrolizumab may have heightened the risk by further disrupting bone remodeling and immune regulation [6].

Penings *et al.* (2023) described a case of ONJ in a patient treated with a combination of Pembrolizumab and a chemotherapy regimen known as GVD (gemcitabine, vinorelbine and doxorubicin). While GVD is not typically associated with ONJ, the occurrence of osteonecrosis in this context suggests that Pembrolizumab may play a significant role in increasing susceptibility to osteonecrosis, possibly by intensifying the effects of chemotherapy on bone health [3].

Patel *et al.* (2023) and Penings *et al.* (2023) both reported ONJ cases, in patients treated with Pembrolizumab, located on mandibular torus. The mandibular torus is an area of the jaw with thin mucosal coverage and increased vulnerability to trauma making it particularly susceptible to osteonecrosis [8].

It is important to note that in the case reported by Patel *et al.* (2023), the patient, as in the current case, was also naive to other agents typically associated with ONJ [5]. However, the osteonecrosis in Patel's case was located on a mandibular torus, an anatomical site known to be a risk factor for ONJ [8].

Additionally, the patient's history of diabetes, a condition known to impair wound healing, likely contributed to the development and progression of osteonecrosis [1]. Diabetes can lead to micro vascular complications and reduced immune response, which negatively affects bone healing and increases susceptibility to necrosis. This comorbidity highlights the multi factorial nature of ONJ.

The patient's passing shortly after the follow-up illustrates the difficulty in gathering long-term data and feedback on treatment outcomes. This underscores the importance of early detection and intervention in managing complications like ONJ, particularly in patients with advanced cancer, where the prognosis may restrict the ability for extended follow-up. Regular dental assessments and timely management of oral symptoms are crucial to mitigate the risk of severe complications.

Conclusion

In conclusion, while the exact causality between Pembrolizumab and ONJ cannot be definitively established based on current data, this case contributes to the emerging narrative that immune checkpoint inhibitors may play a role in the pathogenesis of ONJ. As the use of immune checkpoint inhibitors continues to expand in oncology, further research, including larger cohort studies and mechanistic investigations, is warranted to clarify this association and to develop guidelines for prevention and management in affected patients.

Table I. Studies included in the literature review.

Case and year	Age/gender	Comorbidity	Malignancy (Cancer type)	Medication At Time of presentation	Previous medication	Initial symptoms and examination	Localisation	Treatment
Pennings *et al.* (2023) [3]	44 yo / F	None	Hodgkin lymphoma, Nodular sclerosis subtype, Metastatic	Pembrolizumab, GVD	Doxorubicin, Bleomycin, Vinblastine, Dacarbazine (2017 to 2021)	Pain, Dental mobility, Swelling	Mandible Right lingual area : Torus	Chlorexhidine rinse + oral hygiene, Bone smoothening, Sequestrotomy
Decaux *et al.* (2020) [4]	28 yo / F	None	Metastatic melanoma (stage IIIB)	Pembrolizumab, Epadocast	Interferon (2014 to 2015)	Pain, bleeding, Swelling, slight inflammation	Maxilla : posterior right side	Antibiotherapy, root canal treatment, chlorexhidine + hydrogen peroxide rinse, sequestrotomy + tooth extraction
Patel *et al.* (2023) [5]	73 yo / M	Asthma, Hypertension, Gastro-esophageal reflux, Smoker	Melanoma (stage 3)	Pembrolizumab, Losartan, Amlodipine, Omeprazole, Ventolin, Tadalafil		Pain, Bone exposure	Mandible right lingual area : Torus	Oral hygiene
Myoken *et al.* (2020) [6]	69 yo / F	Not available	Metastatic NSCLC (stage IVB)	Pembrolizumab + Denosumab		Pain, swelling, bleeding, purulent discharge	Mandible : posterior left side	Antibiotherapy, Local injection of minocylcine + hydrochloride, teeth extraction Sequestrotomy / surgical curettage, nasolabial flap reconstruction

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest

The authors declare that they have no conflicts of interest in relation to this article.

Data availability statement

This article has no associated data generated and/or analyzed.

Informed consent

Informed consent was obtained from the patient.

References

1. Ruggiero SL, Dodson TB, Aghaloo T, Carlson ER, Ward BB, Kademani D. American Association of oral and maxillofacial surgeons' position paper on medication-related osteonecrosis of the jaws-2022 Update. J Oral Maxillofac Surg 2022;80:920–943.
2. Martins F, Sofiya L, Sykiotis GP, Lamine F, Maillard M, Fraga M, Shabafrouz K, Ribi C, Cairoli A, Guex-Crosier Y, Kuntzer T, Michielin O, Peters S, Coukos G, Spertini F, Thompson JA, Obeid M. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. Nat Rev Clin Oncol 2019;16:563–580.
3. Pennings I, Moskowitz A, Shah G, Estilo C, Huryn JM, Yom SK. Osteonecrosis of the jan associated with pembrolizumab. Oral Surg Oral Med Oral Pathol Oral Radiol 2023;136:e11–e14
4. Decaux J, Magremanne M. Medication-related osteonecrosis of the jaw related to epacadostat and pembrolizumab. J Stomatol Oral Maxillofac Surg 2020;121:740–742.
5. Patel V, Carey B. Pembrolizumab related osteonecrosis of the jaw. Br J Oral Maxillofac Surg 2023;61:704–706.
6. Myoken Y, Fujita Y, Kawamoto K, Toratani S. Osteonecrosis of the jaw in a metastatic lung cancer patient with bone metastases undergoing pembrolizumab + denosumab combination therapy: case report and literature review. Oral Oncol 2020;111:104874.
7. Nicolatou-Galitis O, Kouri M, Papadopoulou E, Vardas E, Galiti D, Epstein JB, Elad S, Campisi G, Tsoukalas N, Bektas-Kayhan K, Tan W, Body JJ, Migliorati C, Lalla RV; MASCC Bone Study Group. Osteonecrosis of the jaw related to non-antiresorptive medications: a systematic review. Support Care Cancer 2019;27:383–394.
8. Schiødt M. Mandibular and palatal tori exposed by trauma are risk factors for medication-related osteonecrosis of the jaws: a report from the Copenhagen ONJ cohort. Oral Surg Oral Med Oral Pathol Oral Radiol. 2020;129

Cite this article as: Gosselin-Rousselle L, Gaudimier Z, Pamelard P-O, Sader P, Moizan H. 2024. Maxillary osteonecrosis linked to Pembrolizumab therapy: a case report. *J Oral Med Oral Surg*. 30, 38: https://doi.org/10.1051/mbcb/2024041.