

Case Report

Pterygoid Muscle Necrosis Caused by Radiation and Intra-Arterial Cisplatin Infusion Chemotherapy (RADPLAT): A Case Report

Kazuhiro Miyamoto Mitsuo Sato Satoru Koike Takayuki Kimura
Daisuke Abe Takahiro Wakasaki Mutsukazu Kitano Ryuji Yasumatsu

Department of Otolaryngology-Head and Neck Surgery, Faculty of Medicine, Kindai University, Osaka, Japan

Keywords

Maxillary sinus cancer · Radiotherapy · Intra-arterial infusion chemotherapy · Muscle necrosis · Adverse events

Abstract

Introduction: Radiation and intra-arterial cisplatin infusion chemotherapy (RADPLAT) for advanced maxillary sinus cancer has accumulated evidence as a treatment with fewer complications and better 5-year survival rates. In this study, we report a case in which pterygoid muscle necrosis occurred 6 months following RADPLAT treatment for maxillary sinus cancer. **Case Presentation:** The 45-year-old woman had a long history of taking immunosuppressants against rheumatoid arthritis (RA) prior to treatment. Although achieving complete response (CR) to RADPLAT, the patient developed trismus (1 fingerbreadth or less) 6 months following treatment. Abscess formation and recurrence were suspected from the imaging findings; however, the biopsy with endoscopy indicated necrotic tissue. Currently, 18 months have passed without cancer recurrence. Although trismus temporarily improved with rehabilitation, the width of the mouth opening is currently a few millimeters, so the patient can only take liquid food. **Conclusion:** Pterygoid muscle necrosis should be recognized as a new major complication.

© 2023 The Author(s).
Published by S. Karger AG, Basel

Correspondence to:
Ryuji Yasumatsu, ryuji.yasumatsu@med.kindai.ac.jp

Introduction

Since maxillary sinus cancer, a rare cancer of the head and neck, is often diagnosed once the disease has already advanced, optimal treatment methods taking functional preservation and cosmetic aspects into consideration are still being studied [1]. According to the National Comprehensive Cancer Network guidelines, treatment with a combination of surgery and radiation therapy (RT) has been proposed for advanced maxillary sinus cancer [2]. Regarding the surgery, a new reconstructive method such as palatal mucoperiosteal flap has provided better results in swallowing and speech function to date [3]. On the other hand, in recent years, radiation and intra-arterial cisplatin infusion therapy (RADPLAT) has been proposed as a new treatment option. RADPLAT was first reported in 1992 by Robbins et al. [4, 5] as a new treatment for advanced head and neck cancer. In Japan, it has also been applied to the treatment of advanced maxillary sinus cancer since the latter half of 1990, with excellent treatment results having been reported with few complications [6]. However, since the number of cases is insufficient to establish it as a treatment method, accumulating reports on safety is necessary. We herein report a case in which RADPLAT was performed on advanced maxillary sinus cancer, after which trismus due to pterygoid muscle necrosis occurred 6 months later, requiring hospitalization.

Case Presentation

A 45-year-old woman with a long history of taking immunosuppressant methotrexate (MTX) for RA visited a clinic with a chief complaint of nasal congestion and bleeding. She was then referred to our department for the purpose of further examination and treatment for a suspected tumor in her left maxillary sinus. There were no other symptoms including trismus, so oral intake was possible. A plain CT at the first visit showed a soft tissue shadow with total peripheral destruction of the left maxillary sinus bone. Although progression to the intra-orbital and subcranial fossa was also observed, no abnormal findings were found in the internal and external pterygoid muscles. Any other cranial nerve involvement was not observed. The tissue biopsy revealed squamous cell carcinoma, with various imaging tests, including PET-CT, leading to a diagnosis of left maxillary sinus cancer cT4aN0M0 (Fig. 1a). Considering her age, she underwent radiation and intra-arterial cisplatin (CDDP) infusion therapy (RADPLAT) from the viewpoint of functional preservation and cosmetic aspects. While irradiating a total RT of 70 Gy, a total of 5 doses of CDDP 120 mg/mm² were administered at a ratio of jaw artery:sacral artery:transfacial artery = 6:3:1. Complications during treatment included leukopenia G3, gastrointestinal symptoms such as nausea and loss of appetite G2, mucositis G3, and dermatitis G2. Two months after the end of treatment, while MRI confirmed CR, the STIR image showed a high signal intensity area in the left lateral pterygoid muscle group (Fig. 1b). During this period, conjunctivitis G2 also developed. The MRI taken 4 months following the end of treatment showed an increase in the high signal intensity area of the lateral pterygoid muscle (Fig. 1c), with the development of corneal perforation G4 as well. A skin ulceration with bone exposure emerged 5 months following the end of treatment (Fig. 1d). Six months following the end of treatment, she was admitted to the hospital due to trismus (1 fingerbreadth or less), significantly restricting oral intake. A contrast-enhanced CT examination confirmed a ring-shaped contrast effect within the left lateral pterygoid muscle, raising suspicions of abscess, tumor recurrence, and muscle necrosis (Fig. 2). Since the culture results of pus in the mouth showed only Penicillin G (PCG)-sensitive bacteria such as Methicillin-Susceptible Staphylococcus Aureus (MSSA), Sulbactam/Ampicillin (SBT/ABPC) 1.5 g/time/day × 4 times was initiated. This significantly

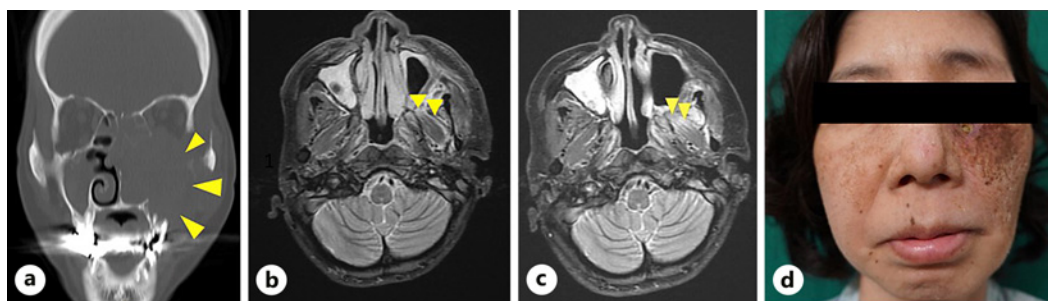


Fig. 1. **a** Plain CT prior to treatment. A peripheral bone fracture image was observed in the left maxillary sinus, as shown by yellow arrowheads. **b** MRI following 2 months of treatment. A high signal intensity area was observed in the left lateral pterygoid muscle, as indicated by yellow arrowheads. **c** MRI following 4 months of treatment. There was an increase in the high signal intensity area of the left lateral pterygoid muscle, as shown by yellow arrowheads. **d** A skin ulceration with bone exposure was observed on the left cheek around 5 months after treatment.

improved the inflammation according to the blood test findings; however, no improvement of the pterygoid muscle lesion was confirmed in the contrast-enhanced CT examination performed on the eighth day of hospitalization. Therefore, endoscopic drainage and biopsy were performed under general anesthesia. When the sphenoidal sinus fossa was opened by piercing through the medial wall of the left maxillary sinus (Fig. 3), a small amount of pus was observed. However, there was no abscess formation. Based on the intraoperative rapid pathological diagnosis and lesion appearance, muscle necrosis was primarily suspected; therefore, not all lesions were removed.

The permanent pathological result was muscle necrosis, with no recurrence observed. Although *Citrobacter freundii* (with PCG sensitivity) was detected in the pus, no signs of infection were observed after postoperative antibiotic administration. Following surgery, rehabilitation by conducting opening training by hand and opening training with the use of Heister improved the mouth opening from 5 mm to 11 mm at 2 months following surgery, enabling dietary intake. As of now, 18 months following treatment, the trismus persists, and the patient can only take liquid food. However, no recurrence of cancer was observed.

Discussion

We have reported a case in which RADPLAT was performed on a patient with maxillary sinus cancer cT4aN0M0 who had been on immunosuppressants for a long time, after which pterygoid muscle necrosis occurred 6 months later. To the best of our knowledge, this is the first report of such a serious complication. Therefore, we believe it is important to consider the cause. Robbins et al. [4] reported that the complication rate was significantly higher when performed in a facility with little treatment experience. RADPLAT has been used in our facility since 2010, with this case being the 19th case. Table 1 shows the details of complications of the facility to date. When defining early complications as 3 months or less following treatment with RADPLAT and late complications as 3 months or more following treatment with RADPLAT, the early complications included dermatitis, mucositis, leukopenia, lymphopenia, taste disorder, smell disorder, salivary gland disorder, conjunctivitis, nausea, fatigue, and cerebral infarction. In addition, late complications included eye disorders, salivary gland disorders, taste disorders, swallowing disorders, smell disorders, osteomyelitis, dermatitis, skin fistulas, pterygoid muscle necrosis, and lacrimal gland disorders. Characteristics of this case included a long history of treatment with MTX for RA, a low body weight with a body

Fig. 2. Contrast-enhanced CT following 6 months of treatment. A ring-shaped contrast effect was observed within the left lateral pterygoid muscle group, as shown by yellow arrowheads. There was no sign of bone destruction.

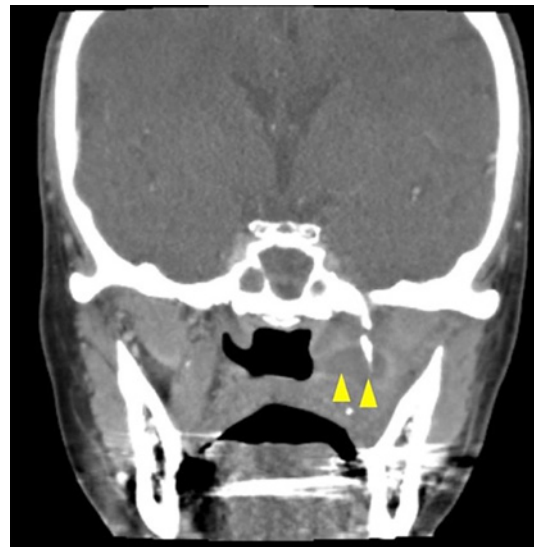
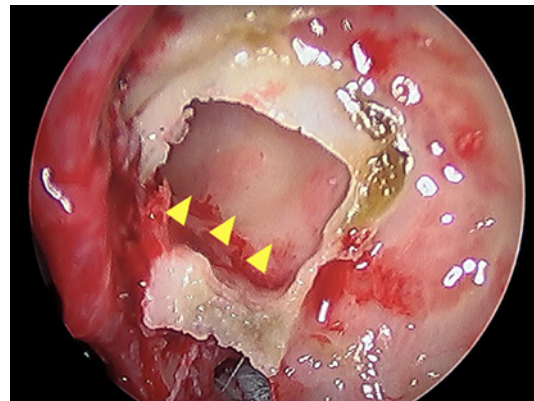


Fig. 3. Endoscopic view during surgery. The posterior wall of the left maxillary sinus was penetrated, and the sphenoidal sinus fossa was opened. A white fragile necrotic tissue was observed inside, as indicated by yellow arrowheads.



mass index (BMI) of 15.3, and the amount of CDDP being slightly high at $120 \text{ mg/mm}^2/\text{time} \times 5$ times. The combination of MTX and radiation therapy is said to potentially cause serious necrosis [7]. According to previous reports, a history of connective tissue diseases such as RA is suggested to be a risk factor for increasing radiation toxicity, which is believed to be involved in the necrosis of the pterygoid muscle in this case [8]. It has been reported that RA patients often have grade 5 complications, so complications should be carefully explained [8]. Furthermore, the higher the irradiation, the higher the complication rate tends to increase [9]; 70 Gy of irradiation may also be affected in our case. Additionally, extremely low BMI could increase the side effect of RT due to a small amount of fat around the pterygoid muscle, suggesting the pterygoid muscle and the lesion became closer than in normal cases.

Regarding the mechanism of this complication, the most likely process is that performing RADPLAT under the condition of sustained angiogenesis inhibition influenced by the antifolate effect of MTX resulted in pterygoid muscle necrosis [7]. It is inferred that an infection developed thereafter, causing strong trismus. Although we focused on posttreatment maxillary artery occlusion as a cause of triggering muscle necrosis based on a previous report [10], the maxillary artery was visualized in many cases, including this case, suggesting that occlusion of the artery was not a direct cause. In Robbins' report, while CDDP was performed

Table 1. List of complications

Early complications	
Dermatitis	12 cases (G1: 9 cases, G2: 3 cases): 63%
Mucositis	15 cases (G1: 2 cases, G2: 8 cases, G3: 5 cases): 79%
Leukopenia	10 cases (G2: 8 cases, G3: 2 cases): 53%
Lymphopenia	1 case (G3): 5.2%
Taste disorders	4 cases (G1: 3 cases, G2: 1 case): 21%
Smell disorders	1 case (G2): 5.2%
Salivary gland disorders	3 cases (G1): 16%
Conjunctivitis	2 cases (G1: 1 case, G2: 1 case): 11%
Nausea	8 cases: 42%
Fatigue	4 cases: 21%
Cerebral infarction	1 case: 5.2%
Late complications	
Eye disorders	5 cases: 26%
Salivary gland disorders	5 cases (G1): 26%
Taste disorders	3 cases (G1): 16%
Swallowing disorders	2 cases (G1): 11%
Smell disorders	1 case (G1): 5.2%
Osteomyelitis	1 case (G3): 5.2%
Dermatitis	1 case (G1): 5.2%
Skin fistula	1 case: 5.2%
Pterygoid muscle necrosis	1 case: 5.2%
Lacrimal gland disorders	1 case: 5.2%

with a protocol of 150 mg/mm²/time × 4 times, there were no cases in which muscle necrosis occurred, as in our case [11]. Therefore, we believe that the effect of the CDDP dose is not significant. However, 100 mg/mm²/time may be more suitable for Japanese people [12].

Another cause of pterygoid muscle necrosis is believed to be inflammation spreading to the pterygoid muscle because of radiation osteomyelitis caused by apical periodontitis. However, despite the 6th and 7th teeth of the left maxilla being mobile teeth, there were no signs of infection, and the teeth were removed by oral surgery for infection prevention. Therefore, this cause is considered not applicable in this case. Radiation osteomyelitis is also considered negative based on contrast-enhanced CT and MRI, so it is likely to be pterygoid muscle necrosis caused by RADPLAT.

Conclusion

When a patient has a history of taking immunosuppressants for connective tissue diseases such as RA and is underweight, we should be aware that performing RADPLAT can have serious complications such as pterygoid muscle necrosis, leading to trismus. Rehabilitation for it should be important, the effect of which could be limited. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see <https://doi.org/10.1159/000534939>).

Acknowledgments

We would like to thank Japan Medical Communication (<https://www.japan-mc.co.jp/>) for English language editing.

Statement of Ethics

This report was approved by the Institutional Ethics Review Board of Kindai University (29-191) and performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No financial support was obtained for this publication.

Author Contributions

Kazuhiro Miyamoto and Mitsuo Sato conceived of the presented idea. Satoru Koike, Takayuki Kimura, Daisuke Abe, Takahiro Wakasaki, Mutsukazu Kitano, and Ryuji Yasumatsu encouraged Kazuhiro Miyamoto and Mitsuo Sato to investigate and supervised the findings of this work. All the authors revised the manuscript, approved the manuscript to be published, and agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability Statement

All data supporting the findings of this case report was included in this article. Further inquiries can be directed to the corresponding author.

References

- 1 Ebara T, Ando K, Eishima J, Suzuki M, Kawakami T, Horikoshi H, et al. Radiation with concomitant super-selective intra-arterial cisplatin infusion for maxillary sinus squamous cell carcinoma. *Jpn J Radiol*. 2019;37(6):494–9.
- 2 Kano S, Hayashi R, Homma A, Matsuura K, Kato K, Kawabata K, et al. Effect of local extension sites on survival in locally advanced maxillary sinus cancer. *Head Neck*. 2014;36(11):1567–72.
- 3 Honda K, Nishimura K, Tsujimura T, Miura M. Palatal mucoperiosteal flap for oro-nasal fistula following maxillectomy for maxillary sinus cancer. *Auris Nasus Larynx*. 2023;50(2):266–71.
- 4 Robbins KT, Storniolo AM, Kerber C, Vicario D, Seagren S, Shea M, et al. Phase I study of highly selective supradose cisplatin infusions for advanced head and neck cancer. *J Clin Oncol*. 1994;12(10):2113–20.

- 5 Robbins KT, Kumar P, Wong FS, Hartsell WF, Flick P, Palmer R, et al. Targeted chemoradiation for advanced head and neck cancer: analysis of 213 patients. *Head Neck*. 2000;22(7):687–93.
- 6 Homma A, Oridate N, Suzuki F, Taki S, Asano T, Yoshida D, et al. Superselective high-dose cisplatin infusion with concomitant radiotherapy in patients with advanced cancer of the nasal cavity and paranasal sinuses: a single institution experience. *Cancer*. 2009;115(20):4705–14.
- 7 Bosacki C, Vallard A, Jmour O, Ben Mrad M, Lahmamssi C, Bousarsar A, et al. Radiotherapy and immune suppression: a short review. *Bull Cancer*. 2020;107(1):84–101.
- 8 Shaikh PM, Singh SA, Alite F, Vargo JA, Emami B, Wu MJ, et al. Radiation toxicity in patients with collagen vascular disease: a meta-analysis of case-control studies. *Int J Radiat Oncol Biol Phys*. 2021;111(5):1214–26.
- 9 Yoon SM, Chu FI, Ruan D, Steinberg ML, Raldow A, Lee P. Assessment of toxic effects associated with dose-fractionated radiotherapy among patients with cancer and comorbid collagen vascular disease. *JAMA Netw Open*. 2021;4(2):e2034074.
- 10 Manji F, Lam JC, Meatherall BL, Church D, Missaghi B. Severe facial necrosis in a type 1 diabetic patient secondary to mucormycosis masquerading as an internal maxillary artery occlusion: a case report. *BMC Infect Dis*. 2019;19(1):184.
- 11 Robbins KT, Vicario D, Seagren S, Weisman R, Pellitteri P, Kerber C, et al. A targeted supradose cisplatin chemoradiation protocol for advanced head and neck cancer. *Am J Surg*. 1994;168(5):419–22.
- 12 Homma A, Onimaru R, Matsuura K, Shinomiya H, Sakashita T, Shiga K, et al. Dose-finding and efficacy confirmation trial of the superselective intra-arterial infusion of cisplatin and concomitant radiotherapy for locally advanced maxillary sinus cancer (Japan Clinical Oncology Group 1212): dose-finding phase. *Head Neck*. 2018;40(3):475–84.