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BRAF mutation in five cases of sinonasal ameloblastic tumors and their clinical course: a case report

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Abstract

Background Sinonasal ameloblastic tumors exhibit unique clinical, pathological, and genetic traits distinct from mandibular bone cases, accounting for the majority of ameloblastic tumors. Recent findings emphasize a notable genetic disparity, showing high *BRAF* mutation rates in mandibular cases versus very low rates in maxillary cases.

Case presentation We analyzed five sinonasal ameloblastic tumor cases treated at Kyushu University Hospital. All patients were Japanese, four male and one female, and their age ranged from 43 to 73 years. Three were diagnosed with ameloblastoma, with one experiencing recurrence that progressed to a life-threatening condition owing to the lack of effective treatment. One patient was histologically diagnosed as ameloblastic carcinoma, and another patient, although histologically diagnosed as ameloblastoma, presented with lymph node metastasis, confirming it as a metastasizing ameloblastoma with clinical malignancy. Local radical resection was performed in all five patients; however, three of them had positive resection margins, and two received postoperative (chemotherapy) radiation therapy. Recurrence was confirmed in two patients, with one patient undergoing chemoradiation therapy and achieving local control. *BRAF* mutations were detected in only one patient.

Conclusion Owing to anatomical challenges in achieving negative resection margins and the low *BRAF* mutation frequency, sinonasal ameloblastic tumors exhibit poor prognosis with high recurrence, malignancy, and metastasis rates. When factors predicting recurrence post-radical resection in these tumors are identified, chemoradiation therapy is recommended as an adjuvant postoperative treatment. However, it should be noted that this presentation of adjuvant therapy is based on the experience of only five cases.

Keywords Sinonasal ameloblastic tumor, Ameloblastic carcinoma, Metastasizing ameloblastoma, Adjuvant chemoradiotherapy

Background

Ameloblastic tumors are rare epithelial odontogenic neoplasms that encompass entities such as ameloblastomas, metastasizing ameloblastomas, and ameloblastic carcinoma [1]. According to the 2017 World Health Organization classification, ameloblastoma and metastasizing ameloblastoma are categorized as benign tumors, whereas ameloblastic carcinoma is classified as a malignant tumor [1]. Ameloblastomas, which constitute a significant proportion of ameloblastic tumors, differ from

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typical benign tumors because of their locally invasive nature, frequent recurrence, and occasional metastasis (referred to as metastasizing ameloblastoma) [2]. The primary site of occurrence is the mandibular bone, with sinonasal ameloblastic tumors representing approximately 15% of all ameloblastic tumors [3]. Reports on sinonasal ameloblastic tumors are limited, with approximately 100 cases documented so far [4]. Given the rarity of sinonasal ameloblastic tumors, there is a lack of information on their clinical behavior and effective treatment options, posing a challenge to understanding the disease [3].

Another challenging aspect of sinonasal ameloblastic tumors is the variation in tumor characteristics between the mandibular bone and maxilla, even within the category of ameloblastic tumors [2]. This discrepancy is attributed to several factors, including the physical aspect that differs between the maxilla and spongy bone, making tumors more prone to infiltrate surrounding organs (such as the eyes and pterygoid muscles) than the mandibular bone [5]. Additionally, genetic differences play a role, with mandibular bone cases frequently exhibiting *BRAF* mutations, whereas maxillary cases show an extremely low frequency of such mutations [6]. As such, multiple factors are believed to contribute to these differences at both the physical and genetic levels. Notably, ameloblastoma may exhibit different driver gene mutations depending on the anatomical site of origin, namely the mandibular bone or maxilla, even though they are of the same tissue type.

The purpose of this report is to present information on the clinical course, treatment modalities, and *BRAF* mutations in five cases of sinonasal ameloblastic tumors. By accumulating more cases, this study aimed to contribute to the establishment of appropriate management strategies for sinonasal ameloblastic tumors.

Case presentation

This study was conducted in compliance with the principles of the Declaration of Helsinki and approved by the Institutional Ethics Review Board of Kyushu University (no. 2022–27). Written informed consent was obtained from all participants.

Case 1

A 43-year-old Japanese male presented with the chief complaint of an upper gingival mass, which prompted an investigation. Computed tomography (CT) revealed a tumor filling the right maxillary sinus, which was confirmed by biopsy to be an ameloblastoma (Fig. 1a, b). Subsequently, the patient underwent total maxillectomy, cervical lymph node dissection, and flap reconstruction. The final pathological diagnosis was ameloblastoma (*BRAF*-negative and 3% MIB-1 labeling index) with negative margins and no lymph node metastasis. The patient has had a 12-month disease-free survival period.

Case 2

A 58-year-old Japanese male presented with an upper gingival mass for further examination. CT revealed a tumor filling the left maxillary sinus (Fig. 2a, b), and a biopsy confirmed that there was an ameloblastoma. Subsequently, the patient underwent total maxillectomy with flap reconstruction. The final pathological diagnosis was ameloblastoma (*BRAF*-negative and MIB-1 labeling index not assessed) with positive margins. Postoperative

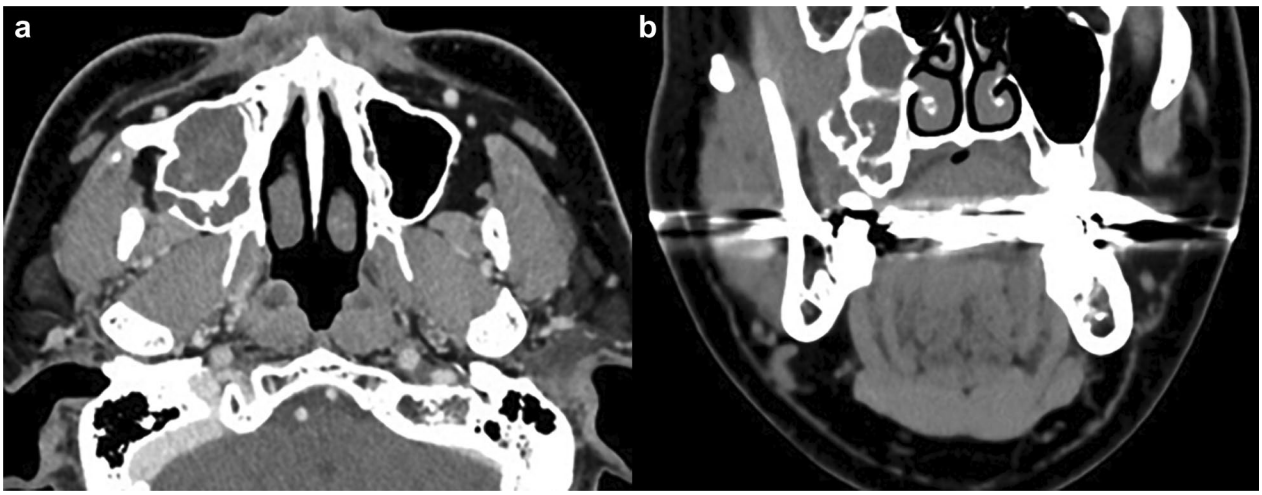

Fig. 1 Images of case 1. Tumor fills the right maxillary sinus. **a** Horizontal section of computed tomography. **b** Coronal section of computed tomography

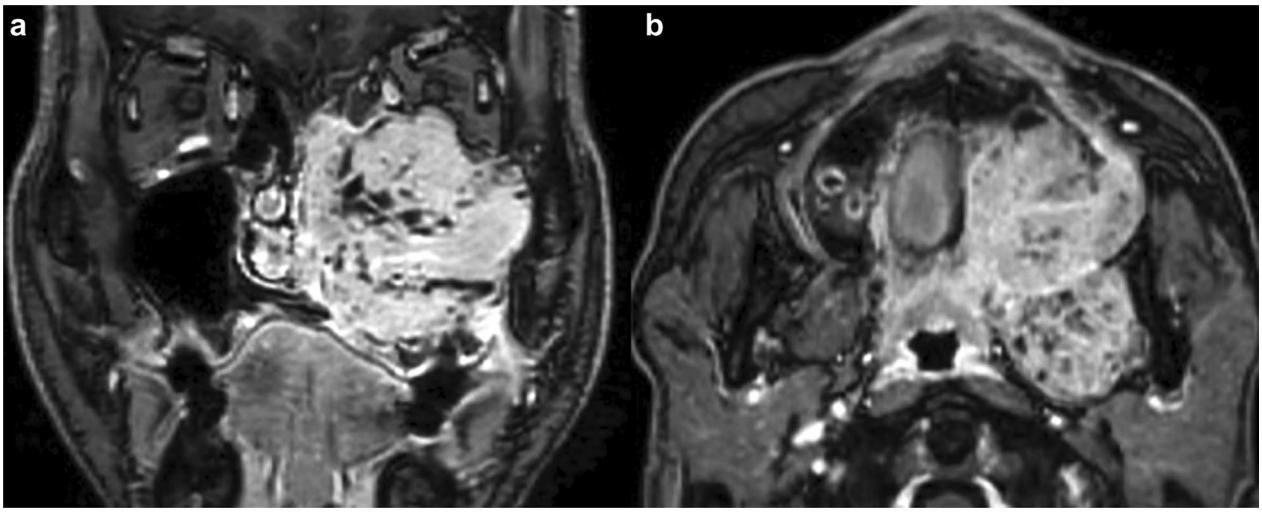

Fig. 2 Images of case 2. Tumor destroys the left maxillary sinus and extends into the orbit. **a** Horizontal section of magnetic resonance imaging. **b** Coronal section of magnetic resonance imaging

radiation therapy (60 Gy) was administered, but recurrence occurred 36 months after the initial treatment. Owing to a lack of suitable treatment options, the patient was transitioned to palliative care. With the slow progression of the disease, the patient has been alive for 60 months after the initial treatment.

Case 3

A 73-year-old Japanese male presented with an upper gingival mass for further examination. CT revealed a tumor filling the left maxillary sinus, and a biopsy confirmed an ameloblastoma (Fig. 3a, b). Subsequently, the patient underwent a partial maxillectomy. The final pathological diagnosis was ameloblastoma (*BRAF*-negative and MIB-1 labeling index 10%) with positive margins. However, 2 months later, the patient died for unknown reasons.

Case 4

A 48-year-old Japanese female who reported discomfort in the upper jaw underwent further examination. CT revealed a tumor filling the left maxillary sinus (Fig. 4a, b), and a biopsy confirmed the ameloblastic carcinoma. Subsequently, the patient underwent a partial maxillectomy. The final pathological diagnosis was ameloblastic carcinoma (*BRAF*-negative and MIB-1 labeling index

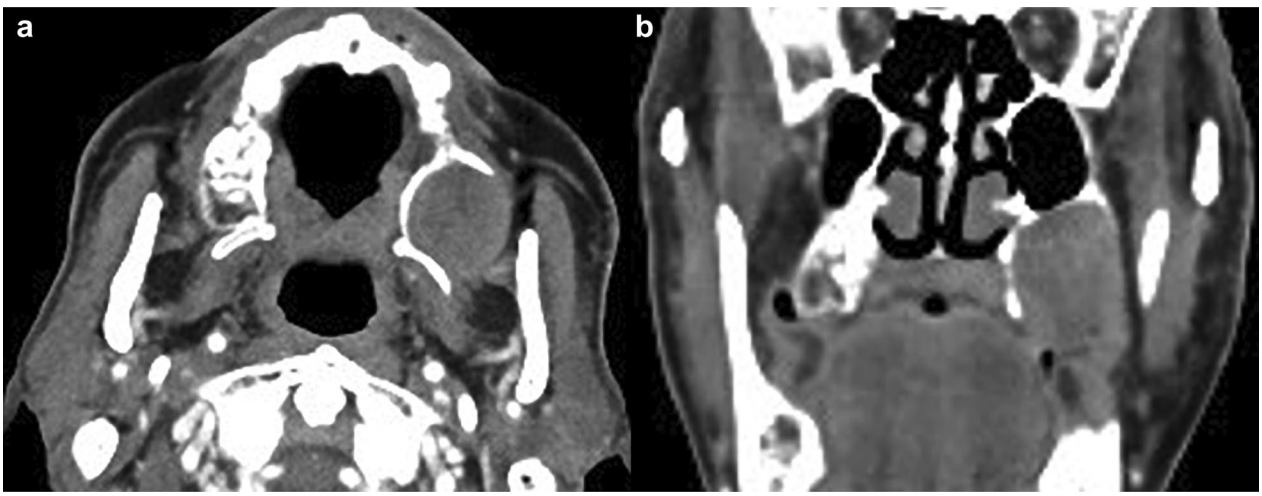

Fig. 3 Images of case 3. Tumor fills the left maxillary sinus. **a** Horizontal section of computed tomography, **b** coronal section of computed tomography

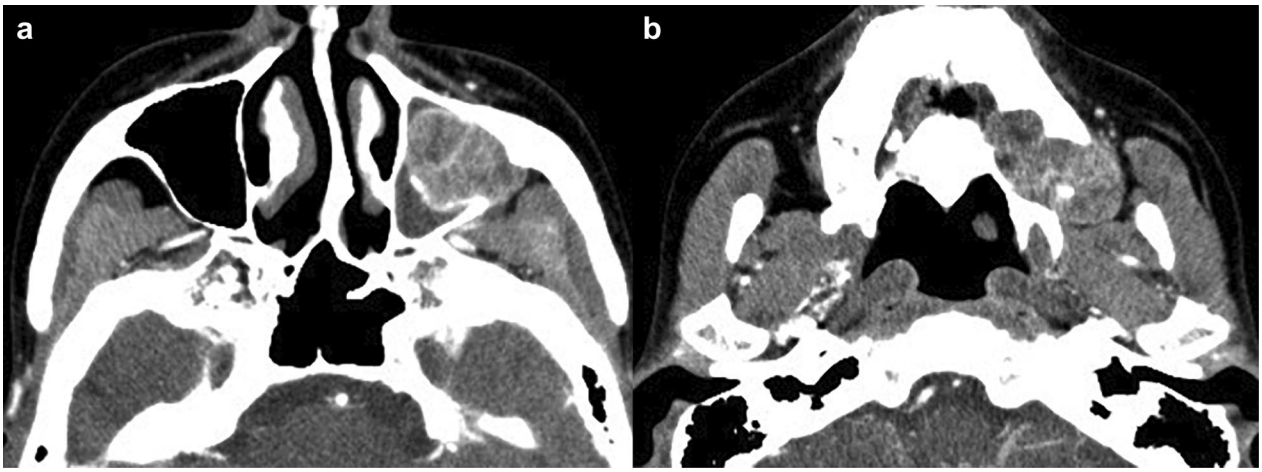

Fig. 4 Images of case 4. Tumor in the left maxillary sinus partially destroys the posterior wall. **a** Horizontal section of computed tomography. **b** Coronal section of computed tomography

22%) with positive margins. Following the first treatment, recurrence occurred 24 months later, requiring total maxillectomy and reconstruction with positive margins. A total of 18 months later (48 months after the initial treatment), a second recurrence prompted chemoradiotherapy with cisplatin. The patient has had a 48-month disease-free survival period.

Case 5

A 74-year-old Japanese male presented with swelling of the left cheek and underwent further examination. CT revealed a tumor filling the left maxillary sinus and extending into the orbit (Fig. 5a), and a biopsy confirmed the ameloblastoma. Considering the presence of swollen lymph nodes on the same side (Fig. 5b), the patient underwent total maxillectomy, cervical lymph node dissection, and flap reconstruction. Examination of the excised specimen revealed ameloblastoma in the primary lesion (*BRAF*-positive with MIB-1 labeling index 22%) with positive margins. Additionally, lymph node metastasis was observed, resulting in the final diagnosis of metastatic ameloblastoma. Postoperative cisplatin chemoradiotherapy was administered. Table 1 summarizes the five cases.

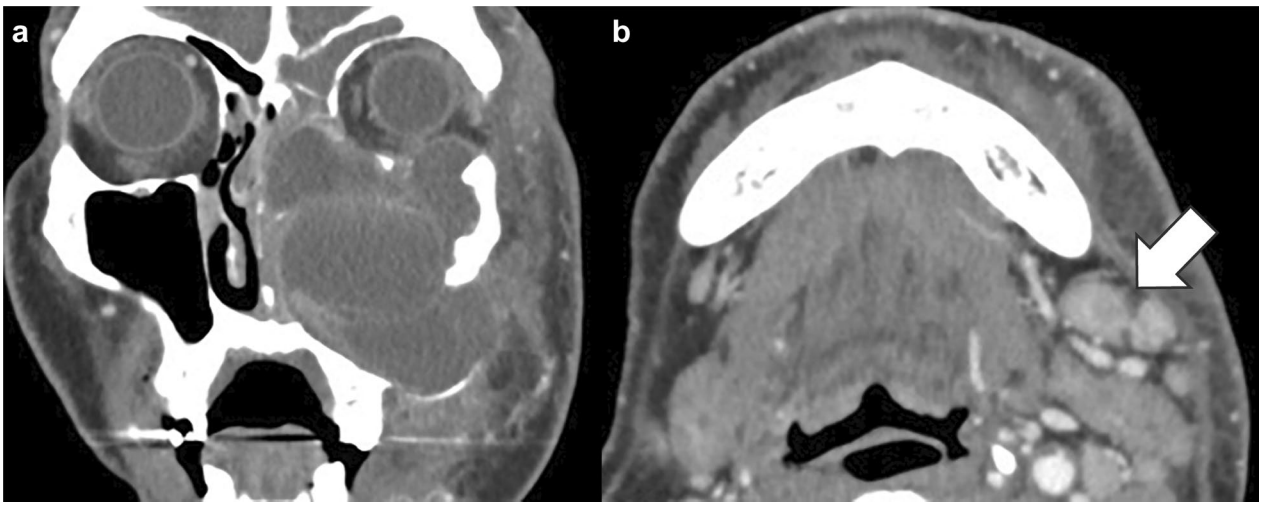

Fig. 5 Images of case 5. **a** Tumor destroys the left maxillary sinus and extends into the orbit and pterygoid muscle. **b** Cervical lymph node metastasis, indicated by white arrow

Table 1 Treatment and prognosis of the five cases

Age (years)	Case 1 43	Case 2 58	Case 3 73	Case 4 48	Case 5 74
Gender and ethnicity	Japanese male	Japanese male	Japanese male	Japanese female	Japanese male
Initial treatment	Total maxillectomy Lymph node resection Reconstruction	Total maxillectomy Reconstruction Postoperative RT	Partial maxillectomy	Partial maxillectomy	Total maxillectomy Neck dissection Reconstruction Postoperative CRT (CDDP)
Diagnosis	Ameloblastoma	Ameloblastoma	Ameloblastoma	Ameloblastic carcinoma	Metastasizing ameloblastoma
Margin status	Negative	Positive	Positive	Positive	Negative
LN metastasis	Negative	–	–	Negative	Positive
MIB-1/*BRAF V600E*	3%/negative	–/negative	10%/negative	22%/negative	5%/positive
Recurrence	None	36 months	None	24 months and 42 months	None
Treatment after recurrence	–	Best supportive care	–	First (24 months after) Total maxillectomy Reconstruction Second (42 months after) CRT (CDDP)	–
Dead or alive	Alive without disease	Alive with disease	Dead without disease	Alive without disease	Alive without disease
Survival period	12 months	60 months	2 months	96 months	1 month

CCDP, cisplatin, cis-diamminedichloroplatinum; LN, lymph node; RT, radiotherapy; CRT, chemoradiotherapy

Discussion and conclusion

Ameloblastic tumors are characterized by slow progression but exhibit locally invasive growth, with a recurrence rate of approximately 20% [7]. If maxillary tumors extend into the maxillary sinus (known as sinonasal ameloblastic tumors), their recurrence rate is approximately 50% [5]. Additionally, approximately 50 locations of ameloblastic carcinoma cases occur in the maxilla [7]. Sinonasal ameloblastic tumors are characterized by a strong tendency for recurrence and are associated with a high probability of malignancy.

The five cases of ameloblastic tumors reported here include one instance among the three cases of ameloblastoma in which recurrence occurred with no available treatment, leading to life-threatening progression despite being benign. Additionally, one case was histologically diagnosed as ameloblastic carcinoma and another case, histologically diagnosed as ameloblastoma, exhibited lymph node metastasis on pathological examination, confirming it as metastasizing ameloblastoma, clinically equivalent to malignancy. On the basis of these cases, it can be inferred that sinonasal ameloblastic tumors have a high recurrence rate, malignancy, and metastatic potential.

Conventionally, complete surgical removal is the mainstay treatment for ameloblastic tumors [2, 3]. However, in the case of sinonasal ameloblastic tumors, complete anatomical resection may be challenging and is thought to be associated with a strong tendency for recurrence. Of the five current patients, three had positive resection margins. Of the three patients with positive margins, one died of an unknown cause 2 months postoperatively, while two had local recurrence; notably, one of them recurred despite postoperative radiation therapy. In all three patients, the positive margins were near the base of the pterygoid process, which is the limit of resection, reaffirming that anatomic factors are one of the factors that determine prognosis. However, the high recurrence rate of sinonasal ameloblastic tumors is not solely attributed to anatomical factors but also attributed to histological factors. Ameloblastic carcinoma, for instance, is considered a disease with poor prognosis, with 5- and 10-year disease-free survival rates of 60.8% and 52.1%, respectively [4]. Metastasizing ameloblastomas, while histologically benign, pose a life-threatening condition, with recurrence rates ranging from 24.6% to 71.1% and mortality rates ranging from 18.4% to 25% [8]. Therefore, sinonasal ameloblastic tumors, which are highly likely to contain these aggressive variants, inherently exhibit a poor prognosis. Additionally, recent findings highlight genetic differences, with *BRAF* mutations being prevalent in 50–90% of ameloblastomas [2, 6, 9]. However, these mutations are predominantly observed in the mandibular bone; notably, *BRAF* mutations are less common in the maxilla, while *SMO* mutations are mainly observed [6, 9]. It has been suggested that this difference in driver gene mutations may result in distinct signaling between the upper and lower dentition during tooth development

[9], although this hypothesis has not yet been confirmed. A lack of *BRAF* mutations is associated with poor prognosis [6], which may contribute to the unfavorable prognosis of sinonasal ameloblastic tumors. In the current study, *BRAF* mutations were detected in only one patient.

Given the pronounced poor prognosis associated with sinonasal ameloblastic tumors, how should they be treated? On the basis of our experience, we propose postoperative adjuvant chemoradiotherapy. Ameloblastomas are radioresistant tumors, and radiotherapy (RT) for curative purposes in operable ameloblastomas is generally considered inappropriate, with limited data on its treatment outcomes [10, 11]. However, recent reports have suggested the potential benefits of postoperative RT in achieving local control in ameloblastomas [10]. Additionally, reports indicate that particle beam or proton therapy enables local control in cases deemed inoperable [11, 12]. The efficacy of cisplatin as chemoradiotherapy for inoperable patients has been reported [11]. In one case in our study, in which chemoradiotherapy was administered upon recurrence, local control was achieved for 4 years, indicating promising results. Conversely, local recurrence occurred in cases where postoperative RT was applied. It should be noted that, in the recent case, attempts were made to achieve local control with cisplatin-combined chemoradiotherapy.

Sinonasal ameloblastic tumors, even if histologically diagnosed as benign, can pose challenges in cases of recurrence, in which salvage surgery may not be feasible. Despite a benign histological diagnosis, there are a few instances in which the clinical course resembles that of malignancy. Although *BRAF* inhibitors have been expected to be effective for *BRAF*-positive solid tumors in recent years [13], the initial treatment to prevent recurrence is more important for sinonasal ameloblastic tumors, which are predominantly *BRAF*-negative, as the drug is unlikely to be effective when recurrence occurs. Considering our experience in conjunction with this, we propose the following conclusions regarding sinonasal ameloblastic tumors. In any one of the following cases: (1) cases with positive margins, (2) when the histological diagnosis is ameloblastic carcinoma, or (3) when there is lymph node metastasis, postoperative adjuvant therapy with cisplatin combined with radiotherapy may contribute to an improved prognosis. However, this presentation of adjuvant therapy is not based on comprehensive evidence or literature; instead, it is based on the experience of only five cases. Therefore, future additional cases should be reported.

In conclusion, sinonasal ameloblastic tumors that occur in the maxilla, unlike most ameloblastic tumors that arise in the mandibular bone, present with distinct clinical profiles and genetic abnormalities. Given the high recurrence rate, malignancy, and metastatic potential of sinonasal ameloblastic tumors, we propose the addition of chemoradiotherapy as a postoperative adjuvant treatment when factors indicating a higher likelihood of recurrence after radical resection are detected.

Abbreviations

CT Computed tomography
RT Radiotherapy

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Author contributions

Mioko Matsuo: writing—original draft and conceptualization; Ryosuke Kuga: data collection; Tomomi Manako: data collection; Kazuki Hashimoto: validation; Ryunosuke Kogo: validation; Masanobu Sato: data collection; and Takashi Nakagawa: supervision.

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Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

This study was conducted in compliance with the principles of the Declaration of Helsinki and approved by the Institutional Ethics Review Board of Kyushu University (no. 2022–27). Written informed consent was obtained from all participants.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare that they have no competing interests.

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