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Maxillary Sinus NUT Carcinoma: A Case Report

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Abstract. *Background/Aim: Nuclear protein in testis (NUT) carcinoma is extremely rare, occurs in the midline of the body, progresses rapidly and is refractory to treatment; most patients die within a year. Here, we describe a case of maxillary sinus NUT carcinoma presenting with epistaxis and nasal obstruction that was treated as a standard head and neck carcinoma. Case Report: The patient was a 41-year-old male with a left buccal swelling; the diagnosis was made of primary NUT carcinoma of the left maxillary sinus and bone metastasis in the cervical spine. After induction chemotherapy with docetaxel plus cisplatin and 5-fluorouracil, the tumor decreased in size, and the patient was further treated with cisplatin and radiation therapy. One month after that, the tumor remained small, however, lung metastasis was observed. Therefore, nivolumab was administered. Cetuximab and paclitaxel were administered after the lung metastasis worsened, but the patient developed progressive disease and died 11 months after diagnosis. Conclusion: Effective treatments for NUT carcinoma have not yet been established. However, early testing to establish the diagnosis may provide useful insights to guide clinical decisions to improve patient outcomes.*

Nuclear protein in testis (NUT) carcinoma is extremely rare. As of 2016, approximately 50 cases involving the head and neck region had been reported globally. NUT carcinoma is characterized by the presence of the bromodomain containing 4 (*BRD4*)–NUT midline carcinoma family member 1 (*NUTM1*) fusion gene, and typically involves the midline of the body. The nasopharynx is the most reported site of occurrence in the head and neck region. In this report, we describe a rare case of NUT carcinoma of the maxillary sinus that was discovered after epistaxis and nasal obstruction and was treated as head and neck carcinoma.

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Case Report

The patient was a 41-year-old male. His chief complaints were nasal obstruction and left-sided buccal swelling. He had no relevant medical history; however, he had smoked 10 cigarettes a day between the ages of 20-30 years and drank alcoholic beverages only occasionally. He had been treated for chronic sinusitis by a local doctor 3 months earlier, however, his symptoms did not improve. He was referred to his doctor a day before he visited our facility.

Sinus computed tomography (CT) revealed a soft shadow filling the left maxillary sinus, bone destruction, and invasion beyond the hard palate and nasal septum. The patient was referred to our Department the day after visiting his doctor on suspicion of maxillary sinus cancer. Initial examination revealed swelling and ocular deviation of the left cheek (Figure 1A), a mass in the left nasal cavity (Figure 1B) on nasal fibroscopy, and a ridge on the left side of the hard palate in the oral cavity; no mucosal irregularity was observed (Figure 1C). He was examined by an ophthalmologist, who found no visual impairment or diplopia. Blood tests on the same day of the visit showed no elevated inflammatory response. Although lactate dehydrogenase was slightly elevated at 340 U/l, carcinoembryonic antigen, squamous cell carcinoma-related antigen, and alpha-fetoprotein were within the normal ranges. The concentration of soluble interleukin-2 receptor was within the normal range at 33 U/ml. Sinus CT revealed a mass centered in the left maxillary sinus, with involvement of the ethmoidal and frontal sinuses; however, no skull base involvement or obvious findings suggestive of cervical lymph node metastasis were observed (Figure 2).

A forceps biopsy of the nose was performed under outpatient local anesthesia. However, the results showed only inflammatory changes. As malignancy was strongly suspected based on these findings, another biopsy (Caldwell–Luc method) of the left nasal cavity and left maxillary sinus was performed under general anesthesia 13 days later. The intraoperative rapid pathological diagnosis was suspected carcinoma. The definitive pathological diagnosis was reported 11 days after surgery; hematoxylin and eosin staining showed abrupt differentiated squamous cells mixed with poorly differentiated tumor cells with a high nuclear-cytoplasmic ratio (abrupt keratinization) (Figure 3A), which suggested NUT carcinoma. Specific immunohistochemistry using NUT monoclonal antibody (C52B1, 1:200, Cell Signaling Technology, Danvers, MA, USA) was positive (Figure 3B), which led to the diagnosis of NUT carcinoma of the left maxillary sinus.

During the period between the initial visit and the definitive diagnosis, the tumor size increased markedly, and ocular deviation was apparent (Figure 4A). Upper gastrointestinal endoscopy revealed no overlapping cancer in the gastrointestinal tract. Positron-emission tomography-CT showed abnormal fluorodeoxyglucose (FDG) uptake in the cervical spine and bone metastasis was suspected (Figure 4B). PET-CT also showed abnormal FDG uptake in the left maxillary sinus (Figure 4C). The disease was expected to progress rapidly, as no established treatment for NUT cancer involving the head and neck has been reported. Therefore, induction chemotherapy was planned for local control, and chemoradiotherapy was planned to be additionally administered depending on progress.

TPF treatment (60 mg/m^2 docetaxel plus 60 mg/m^2 cisplatin and 600 mg/m^2 5-fluorouracil every 3 weeks) was initiated 10 days after diagnosis. No severe adverse events leading to treatment discontinuation were observed, and contrast-enhanced CT on day 11 after the initial evaluation showed a partial response despite a residual local tumor. Therefore, TPF was continued for three courses. Evaluation CT after three courses of treatment showed that the tumor continued to shrink (Figure 5).

When treatment started, we also ordered FoundationOne CDx Cancer Genome Profile (Foundation Medicine, Cambridge, MA, USA), using DNA isolated from formalin-fixed, paraffin-embedded tumor tissue. The test comprehensively detects and analyzes mutations in 324 cancer-related genes and is used as an aid in diagnosis and treatment decisions for patients with solid tumors, including companion diagnostic indications. The results of this were obtained approximately 2 months after treatment was started. The actionable gene was MutS homolog 2 (*MSH2*) p.T754A. However, there was no druggable gene abnormality, and no treatment was recommended. Based on these results, the patient was administered concomitant chemoradiotherapy with 80 mg/m^2 of cisplatin every 3 weeks and radiation therapy for curative

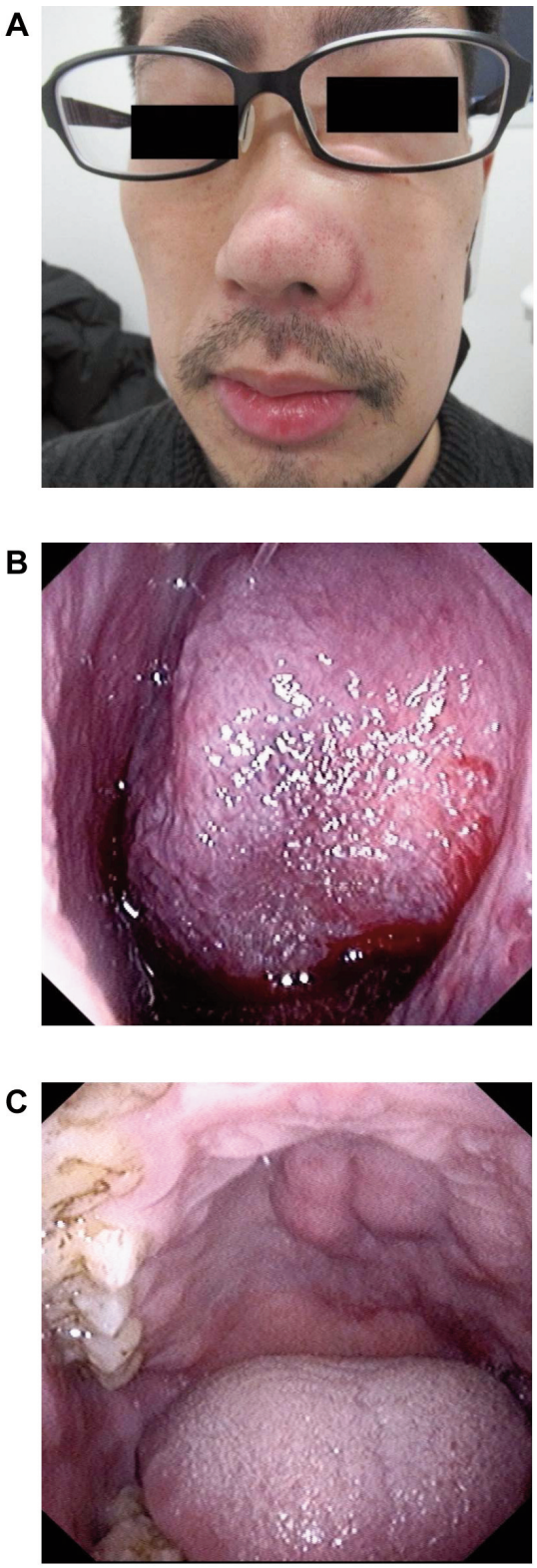

Figure 1. *A: Physical findings at initial visit; swelling of the left cheek and ocular deviation are visible. B: Endoscopic examination of the left nasal cavity revealed a filling mass. C: Intraoral findings showing a protuberant lesion on the left side of the hard palate.*

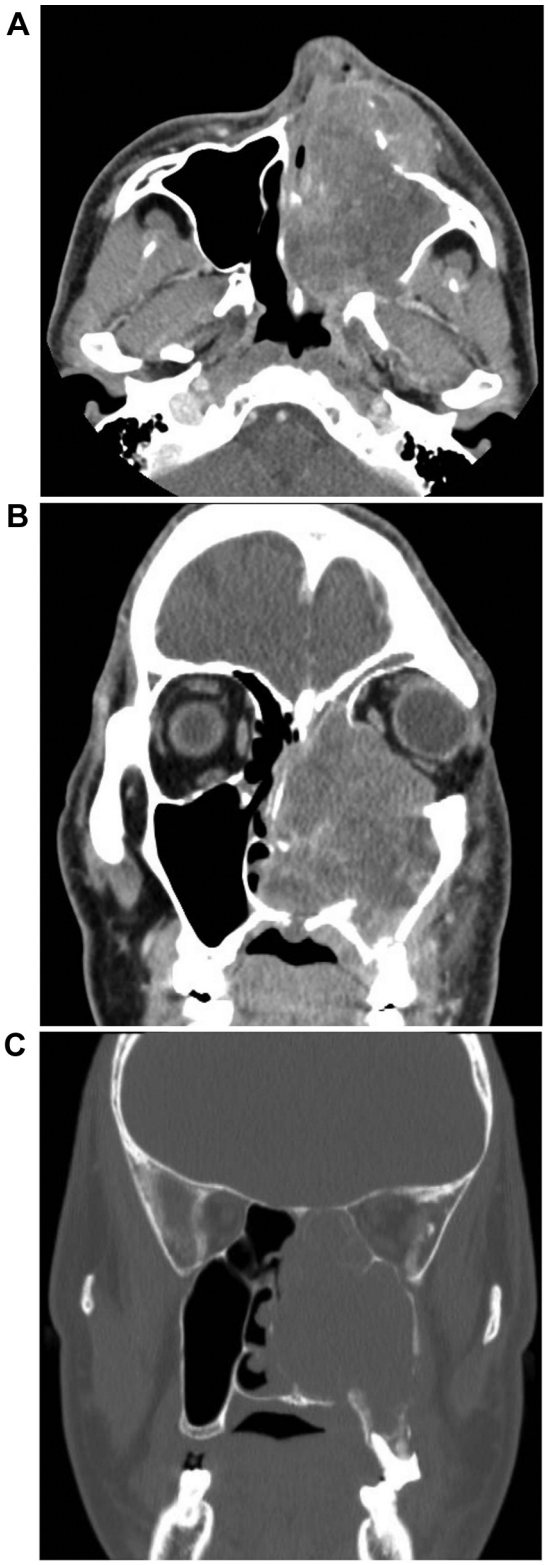

Figure 2. *Sinus computed tomography at initial examination revealed a mass centered in the left maxillary sinus, with involvement of the ethmoidal and frontal sinuses. A: Axial plane. B: Coronal plane showing the soft-tissue condition. C: Coronal plane showing the bone condition.*

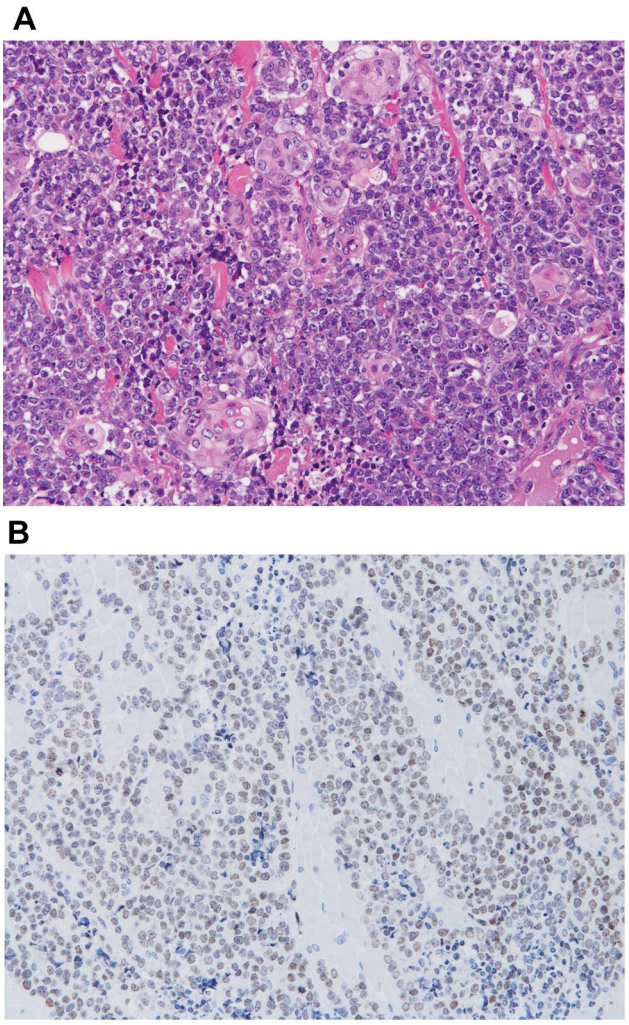

Figure 3. *Pathological diagnosis. A: Hematoxylin and eosin staining showing abrupt squamous differentiated cells mixed with poorly differentiated tumor cells with a high nuclear-cytoplasmic ratio (abrupt keratinization). B: Positive staining with nuclear protein in testis monoclonal antibody using immunohistochemistry.*

treatment as the tumor had shrunk significantly with the current treatment. Three courses of cisplatin plus local radiotherapy at 60 Gy/30 Fr for 11 weeks were administered after diagnosis. Initial CT after concomitant chemoradiotherapy showed that the mass in the left maxillary sinus was shrinking, however, there was a 20-mm nodule shadow in the right lung at S1 and a nodule shadow in the right pulmonary apex. These findings suggested multiple lung metastases (Figure 6). The sclerotic image of the suspected bone metastasis in the root of the C4 right vertebral arch showed no significant changes. Positron-emission tomography-CT was repeated to diagnose the metastases and showed no FDG uptake in the left maxillary sinus region and the cervical bone lesion but abnormal FDG

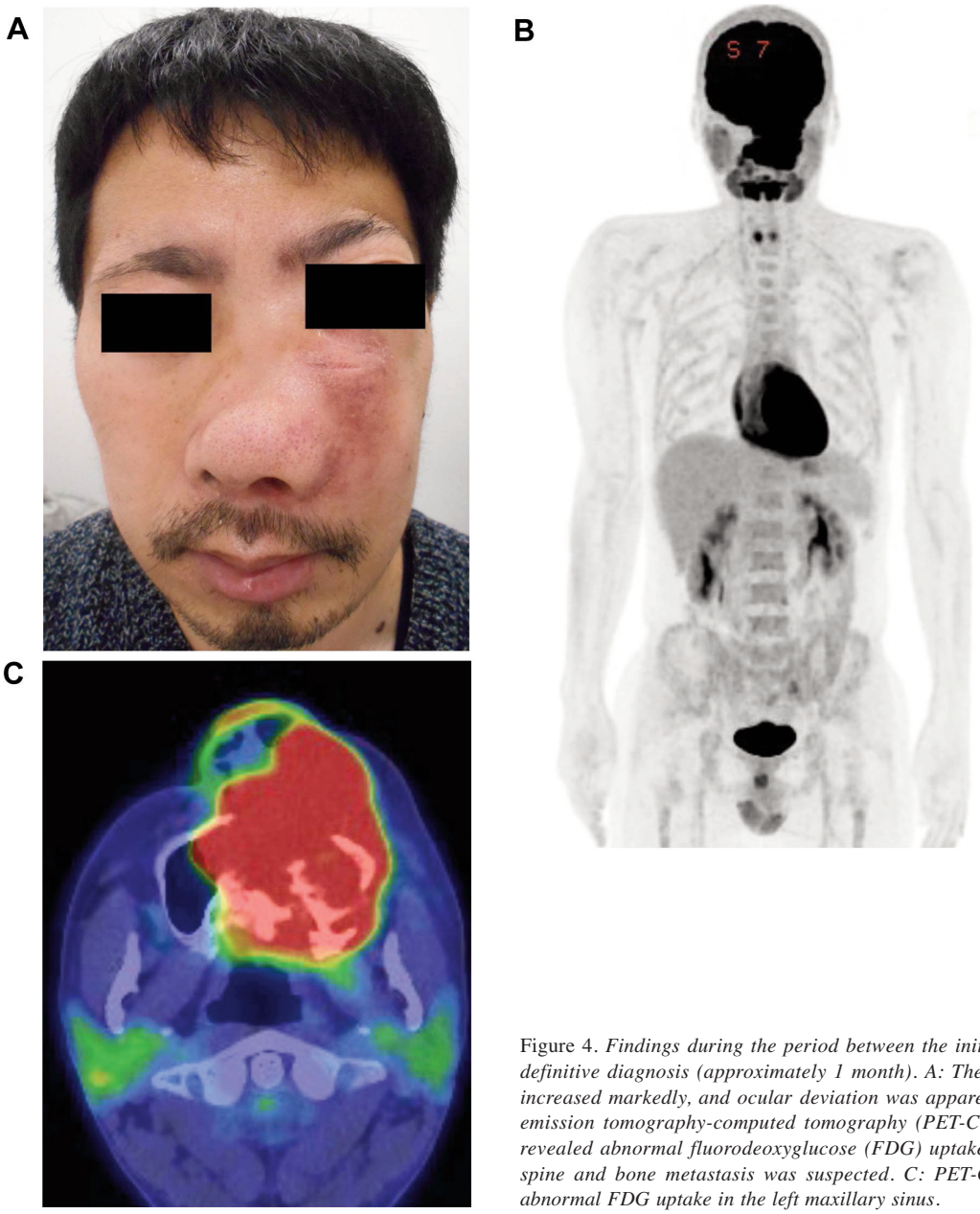

Figure 4. *Findings during the period between the initial visit and the definitive diagnosis (approximately 1 month). A: The tumor size had increased markedly, and ocular deviation was apparent. B: Positron-emission tomography-computed tomography (PET-CT) (axial plane) revealed abnormal fluorodeoxyglucose (FDG) uptake in the cervical spine and bone metastasis was suspected. C: PET-CT also showed abnormal FDG uptake in the left maxillary sinus.*

uptake in the lung lesion (Figure 7). The patient was diagnosed with multiple lung metastases 1 month after receiving cisplatin, which were determined to be platinum-refractory. Nivolumab was administered (240 mg every 2 weeks) over three courses, from 27 weeks after the diagnosis. However, the initial CT evaluation at the end of three courses showed that the multiple lung metastases had increased markedly in size, and the patient was switched to cetuximab plus paclitaxel (weekly). However, the lung lesions evolved to marked progressive disease after two courses, and tracheal compression and recurrent nerve palsy were detected. The treatment was discontinued (Figure 8). Symptoms of superior vena cava syndrome were observed, and the patient died 11 months after diagnosis.

Ethical approval. Written informed consent was obtained from the patient for the use of personal information, privacy protection, and publishing.

Discussion

NUT carcinoma was initially described as a malignant tumor of the mediastinum and thymus (1). However, it has recently

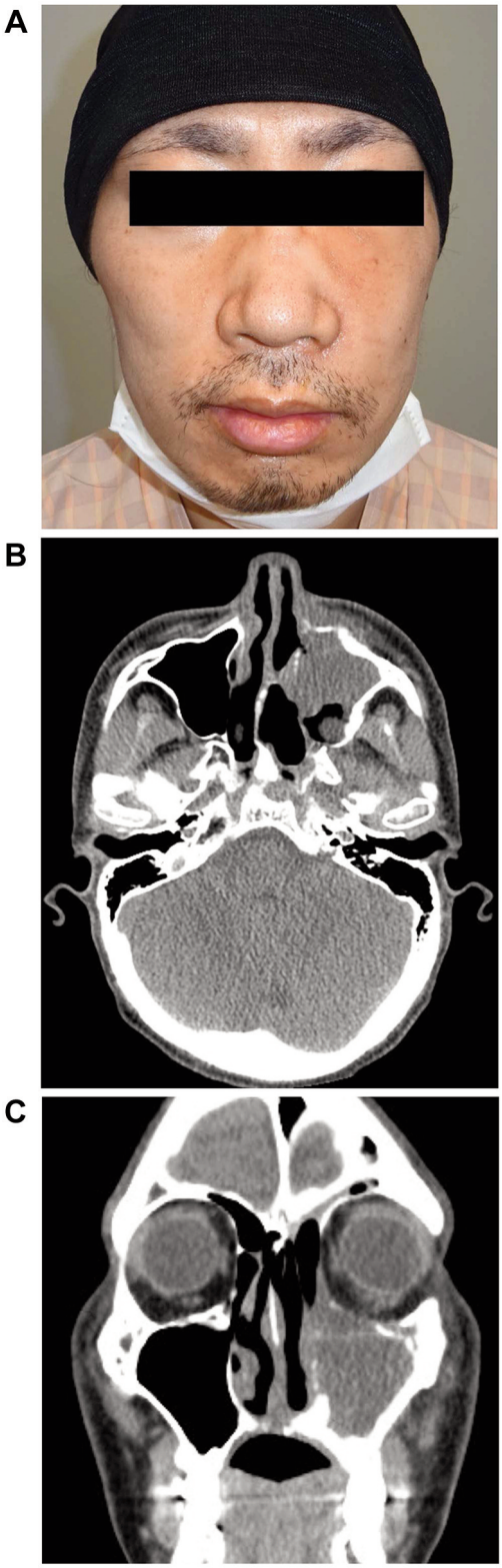

Figure 5. *Evaluation after three courses of docetaxel, cisplatin, and 5-fluorouracil. A: The left ocular deviation had improved. B and C: Sinus computed tomography showed shrinkage of the tumor in the left maxillary sinus (axial and coronal planes, respectively).*

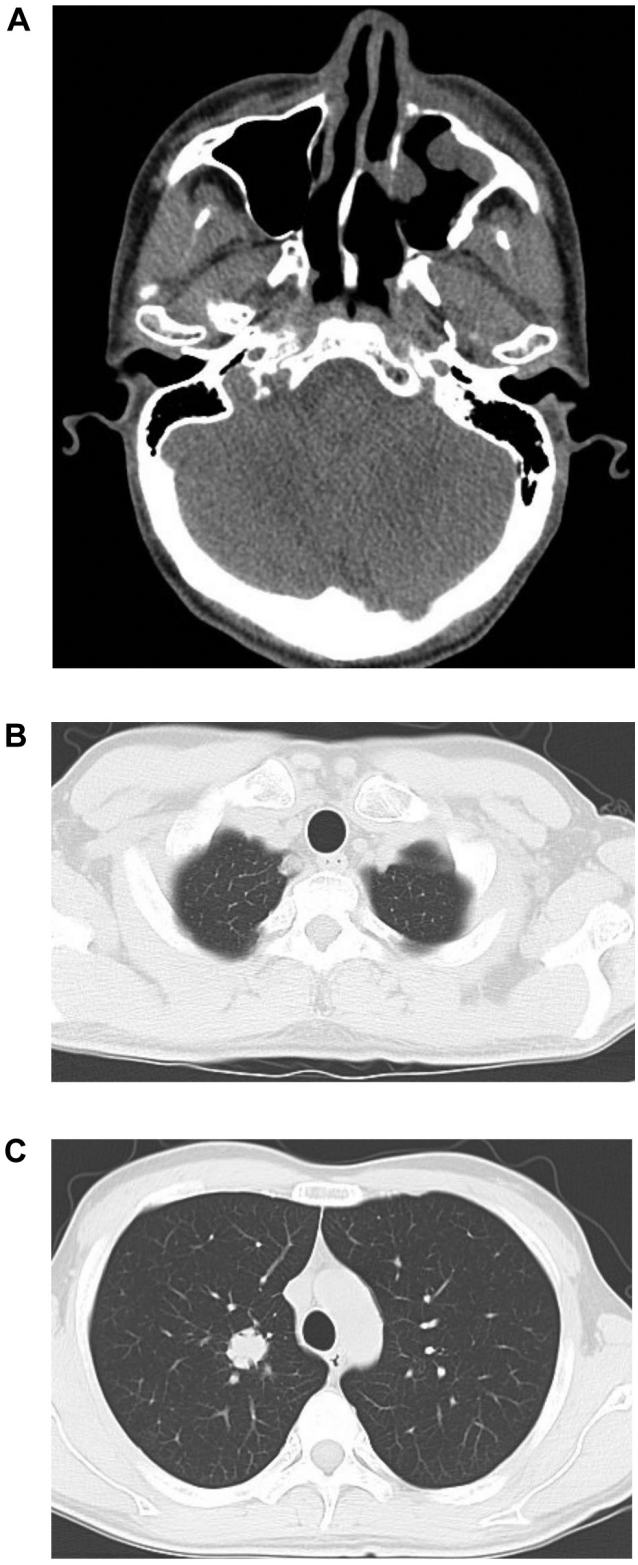

Figure 6. *Initial computed tomography after concomitant chemoradiotherapy (axial plane). A: The mass in the left maxillary sinus had shrunk. B: A 20-mm nodule shadow is apparent in the right lung (S1). C: A nodule shadow is apparent in the right pulmonary apex.*

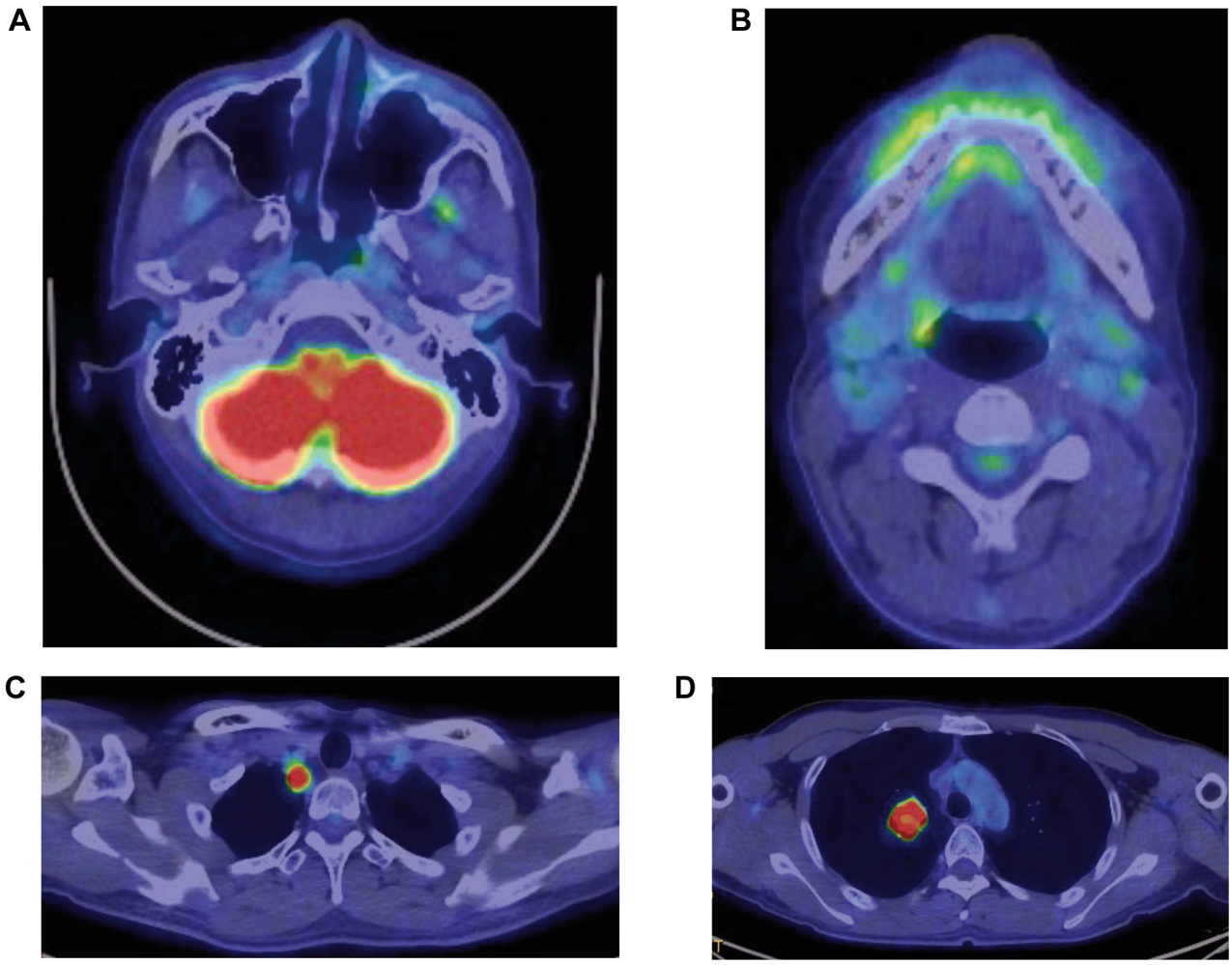

Figure 7. *Positron-emission tomography-computed tomography (axial plane) findings after concomitant chemoradiotherapy. There was no fluorodeoxyglucose uptake in the left maxillary sinus region (A) nor at the cervical bone lesion (B) but there was abnormal accumulation in the lung (C and D).*

been detected in other parts of the body, including the stomach, kidney (2), eye (3), and pancreas (4). Its incidence in the head and neck region is approximately one-third to a half of all NUT carcinomas, and the nasopharynx accounts for more than half of all cases in the head and neck region (5-7). Other sites, including the parotid gland (8), submandibular gland (9), larynx (10), hypopharynx (11) and palatine tonsils (12), have also been reported. The present case involved the maxillary sinus. NUT carcinomas often develop at a young age in the head and neck (13), and thus help in differential diagnosis from other head neck cancer such as squamous cell carcinoma. However, this case was reported to have developed in the fourth decade of life, which is a rather advanced age for disease onset.

NUT carcinoma diagnosis is difficult using only hematoxylin and eosin staining, which is usually performed in pathology, due to the lack of disease-specific histology and the diversity of the disease. Thus, it is often diagnosed as poorly differentiated or undifferentiated carcinoma, or sometimes as squamous cell carcinoma with differentiation into squamous cells (7, 14). In a previous report, close examination of poorly differentiated and undifferentiated carcinomas of the head and neck revealed NUT carcinoma in 4/362 (1.1%) cases (15). A review of specimens diagnosed as sinonasal carcinoma and poorly differentiated carcinoma in the upper digestive tract and mediastinum showed that approximately 2% (1/51) of both types were NUT carcinomas (14, 16). Diagnosis by conventional pathological examination alone is difficult. Moreover, it is not practical to perform the chromosomal tests necessary for a definitive diagnosis for all cancer cases, and the time required to obtain the results is lengthy. In recent years, immunohistochemical diagnosis

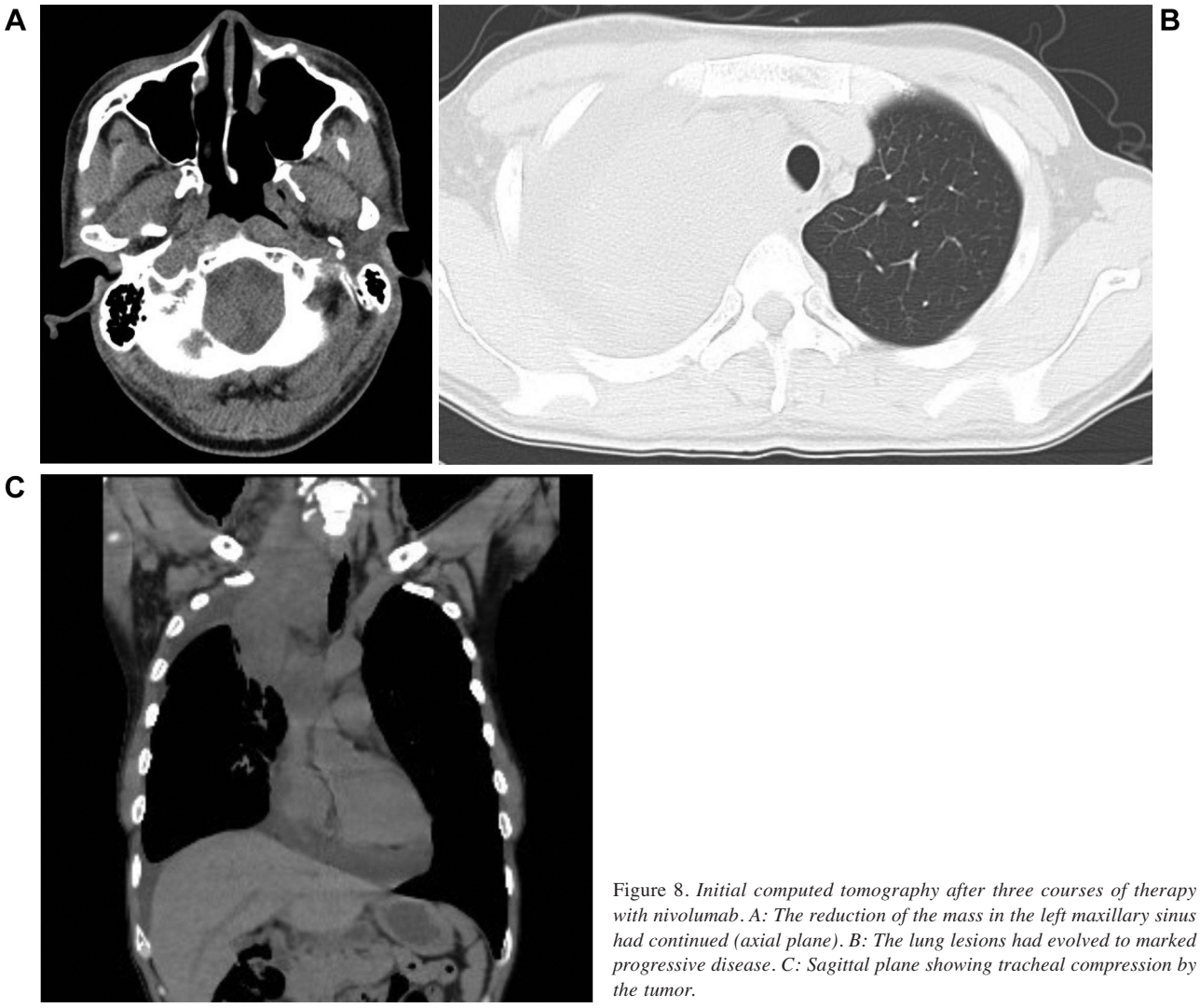

Figure 8. *Initial computed tomography after three courses of therapy with nivolumab. A: The reduction of the mass in the left maxillary sinus had continued (axial plane). B: The lung lesions had evolved to marked progressive disease. C: Sagittal plane showing tracheal compression by the tumor.*

using a monoclonal antibody against NUT carcinoma has become a useful alternative to chromosomal testing. This NUT antibody can be used to diagnose the disease with considerable accuracy: sensitivity, 87%; specificity, 100%; negative predictive value, 99%; and positive predictive value, 100% (17). In our case, this NUT antibody was also used, and the diagnosis was made within approximately 2 weeks of obtaining the pathology specimen. As mentioned above, NUT carcinoma is diagnosed in a small percentage of poorly differentiated or undifferentiated carcinomas of the head and neck. Therefore, it is important to perform testing with NUT antibody for undifferentiated and poorly differentiated cancers of the head and neck region, as well as cancers that occur at a young age and in the nasopharynx, to prevent missing NUT carcinoma and to allow early therapeutic intervention. Furthermore, viruses that have been closely associated with the development of head and neck cancer include Epstein–Barr virus in the nasopharynx and human papillomavirus in the oropharynx. However, there is no evidence of an association of NUT carcinoma with these infections; a recent report of a p16-positive case stated no association with human papillomavirus (18).

Regarding treatment, it has been reported that primary gross total resection is significantly associated with prolonged survival (19). However, because NUT carcinoma grows rapidly, it is possible to experience patients whose tumors are too large to be completely resected or who have metastatic disease from the early stages and for whom surgery is not indicated. There are a few reports of patients who have benefited from chemotherapy and radiation therapy without surgery. Furthermore, NUT carcinoma may be positive for CD99, which is a marker for Ewing's sarcoma, often leading

to this as a diagnosis, and there have even been reports of treatment with sarcoma regimens and their efficacy (20, 21). Additionally, there have been reports of tumor shrinkage after ifosfamide-etoposide therapy for patients who were unresponsive to radiotherapy with cisplatin (22), and one report of a patient who achieved complete response after gemcitabine and docetaxel therapy (23). Thus, no specific anticancer drugs have been established as being effective. The patient in our case had metastatic disease at an early stage, and complete surgical removal was not possible. In accordance with the treatment guidelines for head and neck cancer, induction chemotherapy with TPF was administered as the initial treatment, and tumor shrinkage was achieved. As far as we are aware, there have been no reports on the use and effect of TPF for NUT carcinoma. However, we hope that TPF will be useful in the treatment of NUT carcinoma in the future. The primary tumor remained small in our case, but new metastases developed during treatment, therefore, it is difficult to conclude whether TPF was effective. In addition, the smaller primary tumor size was maintained even with cisplatin and radiation therapy post TPF treatment, suggesting that the cisplatin included in TPF may have been effective. In our case, the patient was then treated with nivolumab. When the lung metastasis worsened, cetuximab and paclitaxel were administered, however, the patient died from marked progressive disease. It was not possible to confirm the efficacy of nivolumab, cetuximab and paclitaxel for NUT carcinoma because of the small number of courses administered. A recent treatment of interest is an inhibitor that blocks the bromodomain and extra terminal domain family, including the *BRD4–NUTM1* fusion gene, which has been reported to be involved in NUT carcinoma. This may be a promising option and there are reports of temporary but positive results with its use (24-29).

Moreover, gene-panel testing, which is covered by insurance in Japan, may also be used to predict the response to treatment and, in some cases, to select investigational drugs. The test requires a sufficient sample volume and may require time to obtain results. Even if a potentially successful treatment is identified, some treatments remain unapproved, and their safety has not yet been established. It is desirable to perform the test to expand treatment options, but NUT carcinoma progresses rapidly, and gene-panel testing is time-consuming. Therefore, it is preferable to conduct the test when the diagnosis is made. In our case, we subjected the patient to the gene-panel test as soon as the diagnosis was made, and the results were available within approximately 2 months. Although the early testing facilitated early acquisition of results, unfortunately, none of the treatment regimens were effective.

Here, we reported the development, progression, and treatment of a case of NUT carcinoma, which is rare and has a poor prognosis. We hope that this report will assist doctors who may encounter this disease when making treatment decisions.

Conclusion

We encountered a rare case of NUT carcinoma arising in the maxillary sinus. The patient had a temporary local response to standard head and neck cancer treatment but developed new metastases that were refractory to treatment. While effective treatments have not yet been established, early testing may provide insights and expand treatment options to improve patient outcomes. The progression of this case and the details of the treatment may guide clinical decisions for future cases, and aid in determining an effective treatment.

Conflicts of Interest

There are no conflicts of interest to declare.

Authors' Contributions

Sayaka Arai drafted the article. Ryota Tomioka revised the article. Yuri Ueda and Akira Shimizu treated the patient. Isaku Okamoto devised the method. Kiyoaki Tsukahara supervised the preparation of the article.

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