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【 CASE REPORT 】

Complete Response Induced by Concurrent Chemoradiotherapy in a Patient with NUT Carcinoma

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Abstract:
An 18-year-old man presented with sudden vision loss in his left eye. Magnetic resonance imaging revealed a tumor that had invaded the left optic nerve, originating from the left posterior ethmoid sinus. Immunohistochemical analyses identified positive staining for NUT protein in the nuclei of tumor cells. We diagnosed locally advanced NUT carcinoma (NC) and initiated concurrent chemoradiotherapy (CCRT), consisting of chemotherapy with vincristine, doxorubicin, and cyclophosphamide, alternating with ifosphamide and etoposide, plus radiation therapy. The patient achieved a complete response. CCRT can be a useful treatment option for adolescent and young-adult patients with locally advanced unresectable NC.

Key words: NUT carcinoma, concurrent chemoradiotherapy, VDC-IE regimen

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Introduction

NUT carcinoma (NC), which usually involves midline body parts, such as the head, neck, and thorax, is a rare and highly aggressive carcinoma that occurs in young individuals. NUT carcinoma consists mainly of sheets of undifferentiated cells with focal abrupt dyskeratosis and squamous differentiation. This tumor entity is defined by an acquired chromosomal rearrangement of the *NUT* gene at the 15q14 locus. The diagnosis requires identifying the chromosomal rearrangement of *NUT* using fluorescence *in situ* hybridization (FISH), reverse transcription polymerase chain reaction, or next-generation sequencing (1). Furthermore, a specific monoclonal antibody against NUT has been frequently used for the diagnosis of NC, showing a specificity of 100% and sensitivity of 87% (2). Although NC has a dismal prognosis, recommended therapies have not been established, especially in patients who are ineligible for surgical intervention.

We herein report the successful treatment of an adolescent and young-adult (AYA) patient with unresectable NC using concurrent chemoradiotherapy (CCRT).

Case Report

An 18-year-old man presented with sudden vision loss in his left eye. He was initially diagnosed with left retrobulbar neuritis and treated with steroid-pulse therapy for three days by an ophthalmologist. However, his left vision did not improve. Magnetic resonance imaging (MRI) revealed a tumor in the left posterior ethmoid sinus that had directly invaded the left optic nerve and epidural space (Fig. 1A). To manage the tumor, the patient was referred to the Department of Otolaryngology and Medical Oncology at our hospital.

Laboratory examinations showed a slightly elevated level of squamous cell carcinoma antigen [1.8 ng/mL (normal range: 0-1.5 ng/mL)]. Positron emission tomography (PET)-computed tomography (CT) demonstrated a left ethmoid sinus mass with an increased fluorodeoxyglucose uptake, but evidence of metastasis was not found (Fig. 1B).

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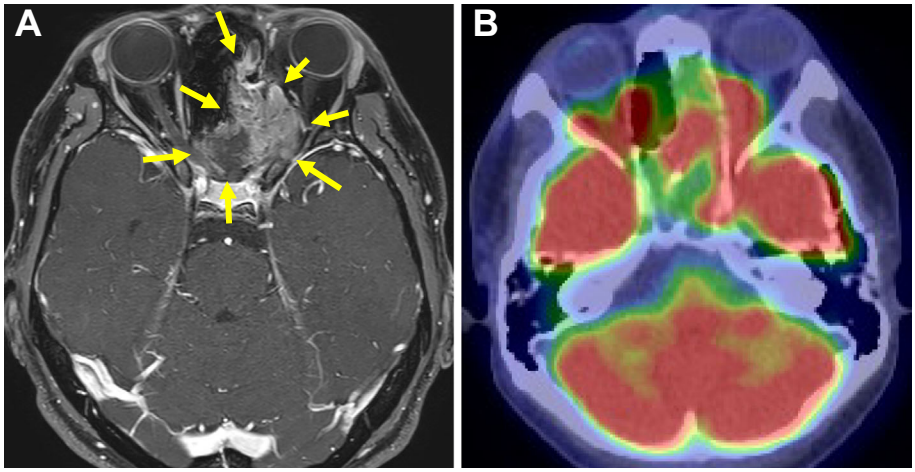

Figure 1. **Magnetic resonance imaging (MRI) revealed a left posterior ethmoid sinus mass (A, arrows), and positron emission tomography (PET)-computed tomography (CT) revealed a mass that showed an increased 18F-fluorodeoxyglucose (FDG) uptake (B).**

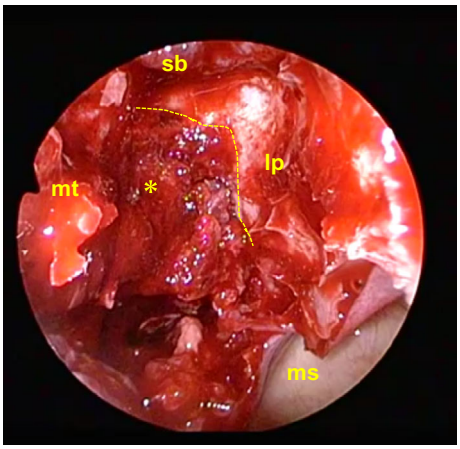

Figure 2. **Endoscopic findings of the middle nasal meatus in an operation. The tumor (asterisk) extended from the posterior ethmoid sinus into the skull base and the orbit (dotted line). lp: lamina papyracea, ms: maxillary sinus, mt: middle turbinate, sb: skull base**

The tumor grew rapidly according to images taken during examinations. Endoscopic-assisted surgery was performed. It was found that the tumor had filled the area behind the basal lamella of the middle turbinate and had directly invaded the left optic nerve and epidural space (Fig. 2). A pathological examination of the tumor revealed dense proliferation of polygonal-to-round tumor cells with enlarged round nuclei and conspicuous nucleoli (Fig. 3A). As shown in Table 1, we conducted comprehensive immunohistochemical analyses to diagnose this rare tumor. The malignant cells showed nuclear staining for INI-1 and stained positive for NUT in nuclei (Fig. 3B), CK5/6 (mild), p40 (focal), and vimentin but stained negative for CD3, CD4, CD8, CD20, CD56, S100, synaptophysin, and Epstein-Barr virus-encoded small ribonucleic acid *in situ* hybridization (EBER-ISH). A FISH analysis did not reveal a *NUTM1-BRD4* rearrangement, but an analysis of *NUTM1* showed a *NUTM1* split signal in 90% of the tumor (Fig. 4). Taken together, these results led to a final diagnosis of locally advanced unresectable NC.

We initiated CCRT, consisting of chemotherapy with VDC (vincristine at a dose of 1.5 mg/sqm on day 1, doxorubicin at a dose of 75 mg/sqm on days 1-2, and cyclophosphamide at a dose of 1,200 mg/sqm on day 1), alternating with IE (ifosphamide at a dose of 1.8 g/sqm on days 1-5 and etoposide at a dose of 100 mg/sqm on days 1-5), repeated every 14 days, according to a regimen for Ewing sarcoma (7), plus radiation therapy (70 Gy/35 Fr) (Fig. 5). To avoid cardiotoxicity of doxorubicin, we administered the VDC regimen for up to 5 cycles, subsequently replacing this with a VAC [consisting of vincristine, actinomycin D (at a dose of 1.25 mg/sqm on day 1), and cyclophosphamide]-IE regimen, which was continued for 4 cycles. Conventional radiation therapy was applied to the tumor simultaneously starting two weeks before the first VDC treatment. The patient was treated with 2.0 Gy once daily, with a total number of 20 fractions delivering a cumulative dose of 40 Gy to the tumor. Thereafter, intensity modulated radiotherapy was continued with 2.0 Gy once daily up to a cumulative dose of 30 Gy to control the tumor completely. Except for Grade 3 febrile neutropenia, no other serious adverse events were observed.

After completion of the CCRT, we conducted MRI and PET-CT (Fig. 6) and biopsied the tumor area. Images and a pathological examination revealed no evidence of residual tumor, so we determined the patient to have achieved a complete response (CR). The patient maintained a CR for seven months after the CCRT was completed.

However, follow-up MRI revealed a relapsed tumor in the left ethmoid sinus that had invaded directly into the skull base. We treated the relapsed tumor in the patient with proton beam radiotherapy (PBR) [70 Gy (relative biological effectiveness)/35 Fr]. Consequently, the patient again achieved a CR (Fig. 5). At the time of writing, the patient had been alive and well for 26 months after first presenting with vi-

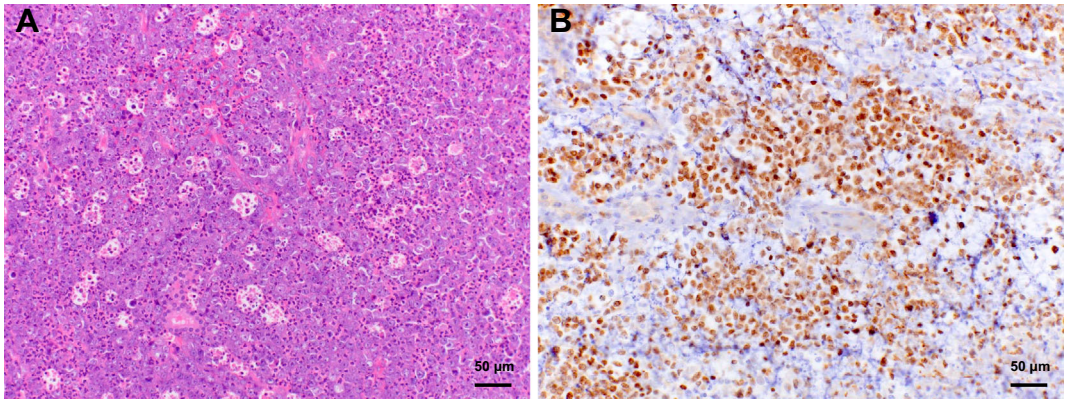

Figure 3. **Microscopic findings of the resected tumor. Hematoxylin and Eosin staining (A, ×200). NUT staining (B, ×200).**

Table 1. **Typical Immunohistochemical Staining Patterns of Various Small Round-cell Tumors in the Ethmoid Sinus.**

Ref.	Histology	CK5/6	p40	Cluster of differentiation*	S100	Synaptophysin	INI-1	EBER-ISH	NUT
3	NC	5/6+	+	-	-	-	+	-	+
3	SNUC	5/6-	-	-	-	-	+	-	-
3	Lymphoepithelial carcinoma	5/6+	+	-	-	-	+	+	-
4	Malignant lymphoma	5/6-	-	+	-	-	+	**	-
5	Olfactory neuroblastoma	5/6-	-	-	+	+	+	-	-
3	SMARCB1(INI-1)-deficient sinonasal carcinoma	5+	+	-		+(focal)	-	-	-
6	ESFT (PNET)	5/6-	-	-	+	+	+	-	-
Our case		5/6+(mild)	+(focal)	-	-	-	+	-	+

*CD3, 4, 8, 20, 56. **generally negative, except for NK/T cell lymphoma (100% positive), Hodgkin lymphoma (40% positive), or Burkitt lymphoma (10% positive). CK5/6: cytokeratin5/6, EBER-ISH: Epstein–Barr virus-encoded small RNA *in situ* hybridization, ESFT (PNET): Ewing sarcoma family of tumors (peripheral primitive neuroectodermal tumor), INI-1: integrase interactor 1, NC: NUT carcinoma, SMARCB1: SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1, SNUC: sinonasal undifferentiated carcinoma

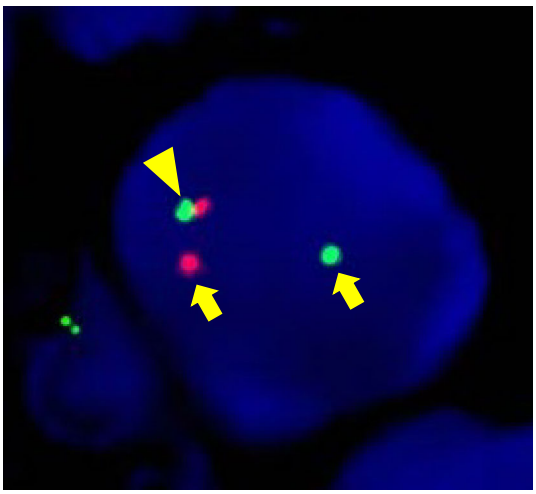

Figure 4. **Results of a fluorescence *in situ* hybridization (FISH) analysis of *NUTM1* showing a *NUTM1* split signal (arrows) and a fused signal (arrowhead) in the tumor.**

sion loss in the left eye.

Discussion

A recent retrospective study demonstrated that the median overall survival (OS) was 6.5 months in patients with NC, with around a 70% chance of death within a year (8), highlighting the need to develop effective treatment strategies for this disease. Currently, most patients with NC receive multimodal treatment composed of a combination of surgery, chemotherapy, and radiation. In patients with NC of the head and neck, aggressive surgery with or without post-operative chemo-radiotherapy or radiation is recommended, as the treatment is associated with good clinical outcomes (9). Of note, upfront complete resection prolonged the OS significantly. However, in our case, we conducted CCRT since the patient was ineligible for complete resection, as the tumor had directly invaded the epidural space; the patient also wanted to retain his physical appearance.

We selected CCRT consisting of a VDC-IE regime as the first-line treatment because several reports have demonstrated that such a regimen was effective for Ewing sarcoma; combined with radiotherapy and surgery, this regimen

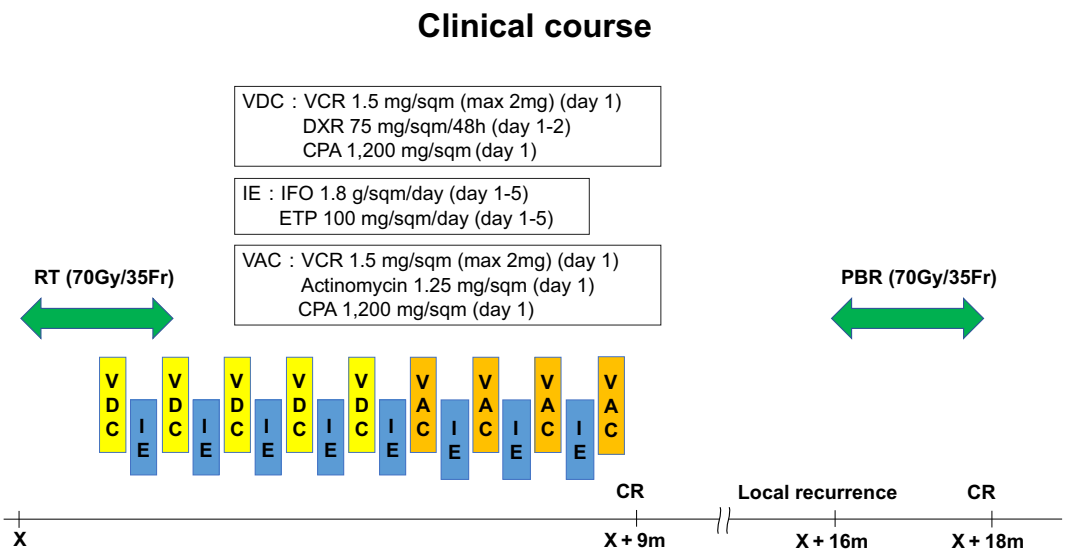

Figure 5. **Clinical course. CPA: cyclophosphamide, CR: complete response, DXR: doxorubicin, ETP: etoposide, IE: ifosphamide, and etoposide, IFO: ifosfamide, m: months, PBR: proton beam radiotherapy, RT: radiotherapy, VAC: vincristine, actinomycin D, and cyclophosphamide, VCR: vincristine, VDC: vincristine, doxorubicin, and cyclophosphamide, X: initiation of therapy**

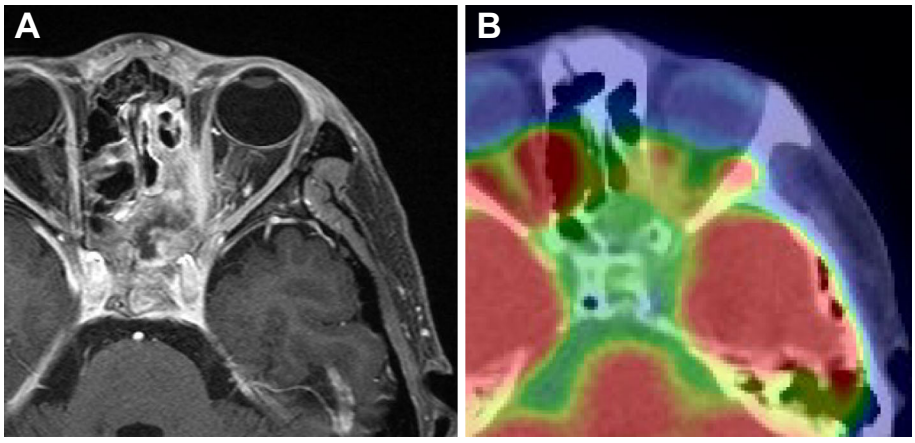

Figure 6. **Magnetic resonance imaging (MRI) (A) and positron emission tomography (PET)-computed tomography (CT) (B) after treatment. MRI and PET-CT did not reveal any abnormalities with signs of relapse.**

was also effective for patients with NC (Table 2). To maximize the dose intensity, we treated the patient every two weeks (15). According to a previous report and our case, regimens for Ewing sarcoma are adequate and useful for not only pediatric but also AYA patients with NC (13). Unfortunately, other chemotherapeutic regimens have not been successful clinically (9, 16). Therefore, at present, regimens for Ewing sarcoma are the best strategies for patients with advanced-stage NC or in a CCRT or adjuvant chemotherapy setting.

Recently, several bromodomain and extra-terminal (BET) protein inhibitors have induced clinical responses in patients with NC (17, 18). Consequently, BET inhibitors will continue to be used for patients with NC and to improve the prognosis in the near future.

After definitive CCRT, the patient presented with local recurrence within the irradiated field. Re-irradiation of the relapsed tumor ran the risk of inducing bilateral blindness because the optic chiasm and normal right optic nerve had already been irradiated. Consequently, we selected PBR as radical treatment for the relapsed tumor. The patient achieved a CR without any severe adverse events, such as blindness. To our knowledge, no reports have demonstrated the efficacy of PBR for NC. This case suggests that PBR may be an effective therapeutic option for NC originating in the head and neck region.

The factors of primary tumor site, lymph nodes/distant metastases, and the type of fusion gene present have been identified as prognostic factors for NC (8). Harboring an *NUTM1-BRD4* fusion gene was significantly associated with a poor OS (8, 19). In our case, an *NUTM1-BRD4* fusion gene was not detected with a FISH analysis, and we specu-

Table 2. Efficacies of Regimens for Ewing Sarcoma in Patients with NUT Carcinoma.

Case	Ref.	Age (y)/ Sex	Primary	Metastasis	NUT fusion type	1st line therapy	2nd line therapy	Efficacy	OS
1	10	10/M	Ilium	-	BRD4	VAI-PAI-VAI ×4 RT(60 Gy/40 Fr)	-	CR	13 y (alive)
2	11	9/M	Sublingual gland	Cervical L/N	NA	Surgery VAI-PAI-VAI ×4 RT (54 Gy/32 Fr)	-	CR	6 y (alive)
3	11	9/M	Parotid gland	Cervical L/N	NA	Surgery VAI-PAI-VAI ×4 RT (59.4 Gy/33 Fr)	-	CR	15 M (alive)
4	12	49/M	Nasal sinuses	Ilium	NA	VDCx6	CDDP RT (75 Gy/35 Fr) Surgery	PD	9 M
5	13	15/F	Nasal sinuses	-	BRD3	VAI-PAI-VAI ×4 RT(68.4 Gy/38 Fr) Surgery	-	CR	34 M (alive)
6	14	12/F	Nasal sinuses	Vertebral body, right sacrum, femur, tibia	NA	VDC-IE ×14 RT(55.8 Gy) Surgery	-	CR	40 M (alive)
Our case		18/M	Ethmoid sinus	-	NA	VDC-IE ×17 RT(70 Gy/35 Fr)	PBR [70 Gy (RBE)/35 Fr]	CR	26 M (alive)

Cases 1-3, and 5 were treated with a vincristine, doxorubicin, ifosfamide (VAI)-cisplatin, doxorubicin, ifosfamide (PAI) regimen. Cases 4 and 6 and our case were treated with a vincristine, doxorubicin, and cyclophosphamide (VDC) or VDC-ifosfamide and etoposide (IE) regimen. CDDP: cisplatin, CR: complete response, L/N: lymph node, NA: not applicable, OS: overall survival, PD: progressive disease, PBR: proton beam radiotherapy, RBE: relative biological effectiveness, RT: radiotherapy

late that this may be one of the reasons why the patient showed a such good clinical outcome.

Our findings suggest that CCRT, comprising a VDC-IE regimen, can be a useful treatment option for AYA patients with NC, even when the cancer is at a locally advanced unresectable stage.

The authors state that they have no Conflict of Interest (COI).

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