Complete response induced by concurrent chemoradiotherapy in a patient with NUT carcinoma: a case report

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Case Report

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Abstract

Background

NUT carcinoma (NC) is a rare and extremely aggressive carcinoma that occurs in young individuals. Although NC has a dismal prognosis, recommended therapies have not been established.

Case presentation

An 18-year-old man presented with sudden vision loss in his left eye. Magnetic resonance imaging revealed a rapidly growing tumor, which had directly invaded the left optic nerve and epidural space, originating from the left posterior ethmoid sinus. A pathological examination of the tumor revealed a dense proliferation of polygonal-to-round tumor cells with enlarged round nuclei and conspicuous nucleoli, and positive staining for NUT protein in the nuclei of tumor cells. The patient was diagnosed with locally advanced NC. We initiated concurrent chemoradiotherapy (CCRT), consisting of chemotherapy with vincristine, doxorubicin, and cyclophosphamide (VDC), alternating with ifosphamide and etoposide (IE) according to a regimen for Ewing sarcoma, plus radiation therapy (70 Gy/35 Fr). The patient completed CCRT and achieved a complete response.

Conclusions

CCRT, comprising a VDC–IE regimen, can be a useful treatment option for adolescent and young adult patients with NC, even when the cancer is at a locally advanced unresectable stage.

Background

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. NC 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* with 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 interventions. Herein, we describe the successful treatment of an adolescent and young adult (AYA) patient with unresectable NC using concurrent chemoradiotherapy (CCRT).

Case Presentation

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 increased fluorodeoxyglucose uptake but evidence of metastasis was not found (Fig. 1B). The tumor rapidly grew during examinations including in images. Endoscopic-assisted surgery was performed to diagnose the tumor; we found that the tumor had filled the area behind the basal lamella of the middle turbinate, and directly invaded the left optic nerve and epidural space (Fig. 2). A pathological examination of the tumor revealed a dense proliferation of polygonal-to-round tumor cells with enlarged round nuclei and conspicuous nucleoli (Fig. 3A). Immunohistochemical analyses identified positive staining for NUT protein in the nuclei of tumor cells (Fig. 3B). The malignant cells retained nuclear staining for INI-1, and were positive for CK-AE1/AE3 (focal), CK5/6 (mild), p40 (focal), and vimentin. We performed FISH analysis of *NUTM1-BRD4* to detect the rearrangement. However, *NUTM1-BRD4* rearrangement was not detected. In contrast, FISH analysis of *NUTM1* showed a *NUTM1* split signal in 90% of the tumor (Fig. 4). The patient was diagnosed with 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 1200 mg/sqm on day 1), alternating with IE (ifosfamide 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) repeating every 14 days, according to a regimen for Ewing sarcoma [3], plus radiation therapy (70 Gy/35 Fr). To avoid the cardiotoxicity of doxorubicin, we administered the VDC regimen for up to five cycles, subsequently replacing this with a VAC–(consisting of vincristine, actinomycin D [at a dose of 1.25 mg/sqm on day 1]) IE regimen, which was continued for four cycles. Conventional radiation therapy was applied to the tumor simultaneously from 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 have been observed. After completion of the CCRT, we conducted MRI, and PET–CT (Fig. 5), and biopsied the tumor area. Images and pathological examination revealed no evidence of residual tumor, and we therefore diagnosed the patient as having achieved a complete response (CR). At the time of writing, the patient had maintained a CR for 8 months after the cessation of treatment. The patient has now been alive for 18 months from the initial diagnosis, although his left vision has not recovered.

Discussion And Conclusions

A recent retrospective study demonstrated that median overall survival (OS) was 6.5 months in patients with NC, with around a 70% chance of death within a year, highlighting the need to develop effective treatment strategies for this disease [3]. 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 are recommended because the treatment is associated with good clinical outcomes [5]. Of note, upfront complete resection prolonged OS significantly. However, in our case, we conducted CCRT consisting of a VDC–IE regimen since the patient was ineligible for a complete resection as the tumor had directly invaded the epidural space; the patient also wanted to retain his physical appearance. We selected CCRT comprised of a VDC–IE regime as a first-line treatment because several reports have demonstrated that such a regimen was effective for Ewing sarcoma; combined with radiotherapy and surgery this regimen was also effective for patients with NC (Table). To maximize the dose intensity, we treated the patient every two weeks [11]. According to a previous report and our case, regimens for Ewing sarcoma are also adequate and useful for not only children but also AYA generations as patients with NC [9]. Unfortunately, other chemotherapeutic regimens have not been successful clinically [5, 12]. Therefore, to date, regimens for Ewing sarcoma are the best strategies for patients with advanced-stage NC or in a CCRT or adjuvant chemotherapy setting.

Interestingly, most patients with sustained CR received upfront or planned surgery (Table 1), implying surgery was effective in the treatment of patients with NC. In our case, a surgical resection of the tumor was not performed, and, as such, we need to be attentive to any local recurrence.

Recently, several bromodomain and extra-terminal (BET) protein inhibitors have induced clinical responses in patients with NC [13, 14]. Consequently, BET inhibitors will continue to be used for patients with NC, and to improve the prognosis in the near future.

Our findings suggest 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.

Declarations

Ethics Approval and Consent to Participate

Not applicable

Consent for Publication

Written informed consent was obtained from the patient for publication.

Availability of data and materials

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

JM and KT: analyzed data, and wrote and edited the manuscript. SS: performed the pathological analysis, including FISH. TT and KS: were radiologists who provided radiation therapy. KY: performed the nasopharyngeal endoscopy and tumor biopsy. KM, SA, KM, JK: was involved in the patient's care. YA: advised on the pathophysiology of NC. All authors have read and approved the final manuscript.

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Tables

Table Efficacies of regimens for Ewing sarcoma in patients with NUT carcinoma.

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Case	Age (y) /Sex	Primary	Metastasis	NUT fusion type	1 st line therapy	2 nd line Therapy	Efficacy	OS
1 ⁶	10/M	ilium	-	BRD4	VAI-PAI-VAI x4 RT(60 Gy/40 Fr)	-	CR	13 y (alive)
2 ⁷	9/M	sublingual gland	cervical L/N	NA	Surgery VAI-PAI-VAI x4 RT (54 Gy/32 Fr)	-	CR	6 y (alive)
3 ⁷	9/M	parotid gland	cervical L/N	NA	Surgery VAI-PAI-VAI x4 RT (59.4 Gy/33 Fr)	-	CR	15 M (alive)
4 ⁸	49/M	nasal sinuses	ilium	NA	VDCx6	CDDP RT (75 Gy/35 Fr) Surgery	PD	9 M
5 ⁹	15/F	nasal sinuses	-	BRD3	VAI-PAI-VAI x4 RT(68.4 Gy/38 Fr) Surgery	-	CR	34 M (alive)
6 ¹⁰	12/F	nasal sinuses	vertebral body, right sacrum, femur, tibia	NA	VDC-IE x14 RT(55.8 Gy) Surgery	-	CR	40 M (alive)
Our case	18/M	ethmoid sinus	-	NA	VDC-IE x17 RT(70 Gy/35 Fr)	-	CR	18 M (alive)

Cases 1–3, and 5 were treated with a vincristine, doxorubicin, ifosfamide (VAI)–cisplatin, doxorubicin, ifosfamide (PAI) regimen. Cases 4, 6, and our case were treated with a vincristine, doxorubicin, and cyclophosphamide (VDC) or VDC–ifosfamide and etoposide (IE) regimen.

CR, complete response; PD, progressive disease; CDDP, cisplatin; L/N, lymph node; NA, not applicable; OS, overall survival; RT, radiotherapy

Figures

Figure 1

Magnetic resonance imaging (MRI) (A) and positron emission tomography (PET)–computed tomography (CT) scan (B). MRI revealed a left posterior ethmoid sinus mass (arrows), and PET-CT demonstrated the mass with increased FDG uptake.

Figure 2

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

Figure 3

Microscopic findings of the resected tumor. (A) Hematoxylin and eosin (H&E) staining. Scale bars, 50 μ m. (B) NUT staining.

Figure 4

NUTM1 FISH of the tumor. Fluorescence in situ hybridization analysis (FISH) of NUTM1 showing a NUTM1 split signal in the tumor. Arrows indicate split signals, and an arrowhead indicates a fused signal.

Figure 5

MRI (A) and PET-CT (B) after treatment. MRI, magnetic resonance imaging; PET, positron emission tomography, CT, computed tomography. MRI and PET-CT showed no abnormalities with signs of relapse.

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