

79438_Auto_Edited.docx

Multimodality imaging and treatment of paranasal sinuses nuclear protein in testis carcinoma: A case report**Paranasal sinuses NUT carcinoma**

Wen-Peng Huang, Ge Gao, Yong-kang Qiu, Qi Yang, Le-Le Song, Zhao Chen, Jian-Bo Gao, Lei Kang

Abstract

BACKGROUND

Nuclear protein in testis (NUT) carcinoma is a rare aggressive malignant epithelial cell tumor, previously known as NUT midline carcinoma (NMC), characterized by an acquired rearrangement of the gene encoding NUT on chromosome 15q14. Due to the lack of characteristic pathological features, it is often underdiagnosed and misdiagnosed. The methods used to diagnosis include immunohistochemistry, karyotypes, FISH, RT-PCR, and next-generation sequencing. So far, there is no standard treatment plan for NMC and the prognosis is poor, related to its rapid progression, easy recurrence, and unsatisfactory treatment outcome.

CASE SUMMARY

A 58-year-old female came to our hospital with a complaint of eye swelling and pain for 8 days. The diagnosis of NMC was confirmed after postoperative pathology and genetic testing. The patient developed nausea and vomiting, headache, and loss of vision in both eyes to blindness after surgery. MRI and PET/CT performed after 1.5 mo postoperatively suggested tumor recurrence. The patient obtained remission after radiation therapy to some extent and after initial treatment with anti-angiogenic drugs and sonodynamic therapy (SDT), but cannot achieve long-term stability and eventually developed distant metastases, with an overall survival of only 17 mo.

CONCLUSION

For patients with rapidly progressing sinus tumors and poor response to initial treatment, the possibility of NMC should be considered and immunohistochemical staining with anti-NUT should be performed as soon as possible, combined with genetic testing if necessary. CT, MRI, and PET/CT imaging are essential for the staging, management, treatment response assessment and monitoring of NMC. This case is the first attempt to apply heat therapy and SDT in the treatment of NMC, unfortunately, the prognosis remained poor.

Key Words: Nuclear protein in testis; Recurrence; Magnetic resonance imaging; Treatment; X-ray computed tomography; Positron emission tomography; Case report

Huang WP, Gao G, Qiu YK, Yang Q, Song LL, Chen Z, Gao JB, Kang L. Multimodality imaging and treatment of paranasal sinuses NUT carcinoma: A case report. *World J Clin Cases* 2022; In press

Core Tip: This case demonstrates the aggressive and recurrence-prone biological behavior of NMC. The methods used to diagnosis include immunohistochemistry, karyotypes, FISH, RT-PCR, and next-generation sequencing. The patient achieved some degree of remission after radiation therapy and after initial treatment with anti-angiogenic drugs and sonodynamic therapy (SDT), but cannot achieve long-term stability and eventually developed distant metastases, with an overall survival of only 17 mo. This case is the first attempt to apply heat therapy and SDT in the treatment of NMC. ² CT, MRI, and PET/CT imaging are essential for the staging, management, treatment response assessment and monitoring of NMC.

INTRODUCTION

Nuclear protein in testis (NUT) carcinoma is a rare aggressive malignant epithelial cell tumor, previously known as NUT midline carcinoma (NMC), characterized by an acquired rearrangement of the gene encoding NUT on chromosome 15q14 [1]. NMC is most common in children and adolescents and is found in the mediastinum, head and neck and other midline anatomical structures, but can also involve the lungs, kidneys, bladder, ilium and other non-midline sites [2-3]. Due to the lack of characteristic histopathological features, it is often underdiagnosed and misdiagnosed.

Here, we report the treatment of a patient with paranasal sinuses NMC who developed tumor recurrence soon after surgical resection, achieved some degree of remission after radiation therapy and initial treatment with anti-angiogenic drugs and

sonodynamic therapy (SDT), but never achieved long-term stability and eventually developed distant metastases, with an overall survival of only 17 mo. Heat therapy uses the bio-thermal effect of non-ionizing radiation physical factor to heat up the tissue and kill the tumor tissue or promote the apoptosis of tumor cells [4]. SDT is a non-invasive method of anti-cancer treatment using chemical sonosensitizers and high-intensity focused ultrasound, the cancerous tissue is destroyed or denatured using a concentrated, high-intensity ultrasound beam [5]. This case is the first attempt to apply heat therapy and SDT in the treatment of NMC.

CASE PRESENTATION

Chief complaints

A 58-year-old female came to our hospital with a complaint of eye swelling and pain for 8 days.

History of present illness

Patient has not undergone any treatment and has no other symptoms.

History of past illness

No special circumstances.

Personal and family history

The patient had no family history of hereditary diseases.

Physical examination

No obvious abnormal physical examinations.

Laboratory examinations

Laboratory test results showed that the leukocyte count was $13.21 \times 10^9/L$ (normal range, $4-10 \times 10^9/L$); the neutrophil count $10.78 \times 10^9/L$ (normal range, $1.8-6.3 \times 10^9/L$); D-

dimer, 0.65 mg/L (normal range, 0–0.55 mg/L); C-reactive protein, 48.31 mg/L (normal range, 0–5 mg/L); no significant abnormalities in tumor markers.

Imaging examinations

The patient is placed in the supine position for computed tomography (CT) scans. The scanning range was from the inferior orbital wall with the tube voltage at 120 kV and the tube current using the automatic mA technique. CT revealed hypodense masses in the bilateral ethmoid and sphenoid sinuses, with irregular morphology and the plain CT attenuation value of the mass was approximately 44 HU, with a maximum cross-section of about 2.5 cm × 1.8 cm, and osteolytic destruction of surrounding bone (Figure 1). Magnetic resonance imaging (MRI) displayed a mixed-signal mass in the bilateral ethmoid and sphenoid sinuses, with a heterogeneous low signal on T1-weighted imaging (T1WI), a slightly high signal on T2-weighted imaging (T2WI), a slightly low signal on diffusion weighted image (DWI). After enhancement, the lesion showed obvious heterogeneous enhancement, with indistinct demarcation with the right internal rectus muscle and shallowing of the right pharyngeal fossa, measuring approximately 2.3 cm × 2.9 cm × 1.3 cm (AP×LR×SI) (Figure 2).

FINAL DIAGNOSIS

Ultimately, histopathology after surgery showed that diffuse distribution of undifferentiated round tumor cells, lamellar or focal arrangement, submucosal infiltrative growth, visible hemorrhage, necrosis, and invasion of bone. The nuclei were relatively uniform in size, but the karyotype was irregular, heterogeneity was obvious, nucleoli were obvious, nuclear fission images were easily seen, focal eosinophilic apoptotic vesicles were visible, cytoplasm was sparse, and localized squamous epithelial differentiation was visible. Immunohistochemical staining was positive for NUT, AR1/AE3, CK5/6, P63, P40, CK8/18, EGFR and negative for CD56, Syn, SOX-10, S-100, SALL-4, and MPO. NUT isolated probe fluorescence in situ hybridization (FISH): positive (+), red and green signal separation in the tumor nucleus, suggesting a break in

the gene. Combined with immunohistochemistry and FISH results, the diagnosis of NUT carcinoma was made (Figure 3-4).

TREATMENT

The patient underwent nasal endoscopic excision of a sinus mass under general anesthesia, and the mass was seen to be grayish-white and solid with osteolytic destruction of the adjacent bone.

OUTCOME AND FOLLOW-UP

The patient developed postoperative nausea and vomiting, headache, and loss of vision in both eyes to the point of blindness. PET/CT examination 1.5 mo after the surgery showed that the septal sinus, pterygoid sinus, right nasal cavity and anterior skull base soft tissue density shadows were radiolucent, maximum standardized uptake value (SUVmax) was about 64.1, localized convexity into the orbits bilaterally, bilateral compression of the internal rectus muscle and optic nerve, and localized bone destruction in the septal sinus and pterygoid sinus (Figure 5A-D). MRI showed tumor size of about 4.5 cm × 3.5 cm × 4.2 cm (AP×LR×SI) (Figure 5E-H). Intensity-modulated radiation therapy (69.96 Gy 2.12Gy/F/33F) with simultaneous cisplatin, temozolomide (75 mg/m²), and deep thermotherapy 3 times/week (42°C, 40 min) was performed after multidisciplinary consultation. The patient's tumor shrank significantly after 11 radiation treatments, with a size of about 2.5 cm × 2.9 cm × 2.6 cm (AP×LR×SI) (Figure 5I-L), but the radiation treatment was discontinued because of cerebrospinal fluid nasal leakage and grade III radiation oral mucosal reaction, so the dosage of temozolomide was increased (200 mg/m² for 5 d, 28 d for 1 cycle). 6 mo after surgery, the follow-up evaluation revealed that the disease continued to progress, the tumor size was about 5.0 cm × 3.6 cm × 4.0 cm (AP×LR×SI) (Figure 5M-P), and there was swelling in the left eye and headache, nausea and vomiting, after adding Apatinib (0.25 g/d) for 1 cycle, the lesion was significantly reduced, the size was about 3.3 cm × 3.2 cm × 3.5 cm. The disease progressed after 2 mo of continued treatment and was switched to docetaxel 100

mg d1 + raltitrexed 4 mg d1 + cisplatin 30 mg d1~3 in combination with anlotinib (12 mg/d) for 2 cycles, after which the disease was poorly controlled. It was replaced with gemcitabine 1.0 mg d1, d8 + oxaliplatin 150 mg d1, combined with anlotinib for 2 cycles, during which the swelling was reduced by SDT (ultrasound localization through the eye, SDT device 0.75 W, frequency 50%, 30 min, treatment started after 32 h of input of the acoustically sensitive drug hematoporphyrin, and continuous treatment for 3 d), and the disease was basically stable. After adding nitrozumab and continuing chemotherapy for 1 cycle, the patient developed low back pain and decreased sensation below the 10th thoracic vertebra, and MRI showed thoracic 1-sacral 1 intraspinal metastases. The patient abandoned treatment and was discharged from the hospital, and died 2 mo later. The patient had 15 mo from the onset of symptoms to the development of distant metastases and 17 mo to death.

DISCUSSION

About one case per 100,000 people is diagnosed with sinonasal malignancies each year, which make up 5% of all head and neck cancers [6]. NMC is a highly aggressive malignant epithelial cell tumor that accounts for approximately 2% of nasal tumors [7-8]. It has a unique molecular genetic alteration in which the NUTM1 (NMC family member 1) gene [t(15; 19)(q14; p13.1)] rearrangement with fusion partners bromodomain-containing 4 (BRD4) [t(15; 19)(q13.2; p13.1)], bromodomain-containing protein 3 (BRD3) (on chromosome 19), nuclear receptor binding SET domain protein 3 (NSD3), or other genes (NUT-variant carcinomas), the most common of these is the BRD4-NUT fusion gene [2]. The specific etiology, pathogenesis and risk factors of NMC are unknown [9]. Its occurrence may be related to MYC, P63, MED24 and Wnt, MAPK and PI3K signaling pathways [10-11]. The tissue origin of NMC is unknown, and the study have speculated that it may originate from cells of primitive neural sulcus origin [12].

Sinus NMC has a gender-neutral onset and can occur at any age, mostly in pediatric and young adult patients, often with aggressive growth, involving the orbit and dura mater, and patients usually present with non-specific symptoms associated with the

mass (e.g., nasal leakage, rhinorrhea, nasal congestion, protrusion, decreased vision, difficulty swallowing, or pain) [13-14]. Laboratory tests lack specificity while there is no specific tumor markers, and tumor marker test is normal in this case. Some patients may be accompanied by elevated levels of methemoglobin due to osteolytic destruction, who will probably develop hypercalcemia.

The morphology of NMC is difficult to differentiate from other poorly differentiated tumors such as squamous cell carcinoma, lymphoepithelioma-like carcinoma, malignant melanoma, olfactory neuroblastoma, and neuroendocrine carcinoma, with the possibility of misdiagnosis and challenging diagnosis, but it has unique NUT gene alterations. Histological features include small to moderate sized completely undifferentiated or hypodifferentiated tumor cells arranged in diffuse sheets with sparse cytoplasm, eosinophilic or biphasic, some with marked mesenchymal connective tissue hyperplasia, irregular nuclear contours, mostly naked nuclei with prominent nucleoli, and frequent nuclear schizophrasia [2,3,10,15]. Immunohistochemical analysis showed positive NUT staining of tumor cells with 100% specificity and 87% sensitivity [16]. Immunostaining for epithelial markers such as AE1/AE3, CK5/6, P63, P40 and EMA was often positive [17]. A variety of methods can be used to diagnose NMC, including immunohistochemistry, karyotypes, FISH, RT-PCR, and next-generation sequencing [18]. It is rare for NMC to be diagnosed routinely, resulting in a misdiagnosis or a late diagnosis. In this case, the microscopic tumor cells were round in morphology, diffusely or nest-like in distribution, showing hypodifferentiation or undifferentiation, and the immunohistochemical epithelial markers AE1/AE3, EGFR, CK8/18, CK5/6 and squamous epithelial markers p63 and P40 were positively expressed to varying degrees, and the NUT was diffusely positively expressed. The case characteristics were consistent with those reported previously.

² CT, MRI and PET/CT imaging are essential for the staging, management, treatment response assessment and monitoring of NMC [19]. NMC is most commonly associated with lymphatic metastases, followed by bone metastases [20]. CT shows a soft tissue density mass with osteolytic bone destruction, invasive, infiltrative growth, irregular

morphology, low density necrotic areas inside the mass, occasionally calcification [21], enhancement is mostly uneven and mild, commonly squamous cell carcinoma of the nasal cavity and sinuses and other malignant tumors such as rhabdomyosarcoma, calcification is very rare, perhaps as a clue to the diagnosis of the disease. The superior soft tissue resolution of MRI facilitates the assessment of detailed anatomical localization of soft tissue masses in the head and neck and skull base and shows the involvement of adjacent areas [22-23]. On MRI, NMC usually shows low signal on T1WI and high signal on T2WI. Non-enhancing necrotic areas within the tumor can also be identified, and enhancement is heterogeneous [24]. Since NMC is highly invasive and often accompanied by symptoms and signs caused by distant metastases, patients should be recommended to undergo PET/CT for comprehensive examination to evaluate whether there are other sites of invasion, which can help in tumor staging and early detection of metastases. PET/CT is able to assess the metabolic and anatomical characteristics of the tumor. PET/CT shows increased glucose uptake in the lesion and metastatic areas (standard uptake values can be as high as 18.6), and if the uptake values located in the center of the lesion are decreased, this indicates necrosis within the lesion [7,21,25-26]. In addition, PET/CT has good sensitivity for bone metastases that cannot be detected by bone imaging [10].

So far, there is no standard treatment option for NMC and the prognosis is poor, related to its rapid progression, easy recurrence and unsatisfactory treatment outcome [1,6]. If patients are diagnosed early, surgery remains the treatment of choice for NMC and will help improve the prognosis [18]. Due to the aggressive growth of the tumor, most patients already have metastases at the time of initial diagnosis and have poor surgical results or lost surgical opportunities [27]. Some studies have shown that systemic therapy should be intensified by postoperative, and patients who receive radiotherapy doses of 50 Gy or more have better survival [8]. Those who have symptoms should be reviewed promptly to detect micro metastases as early as possible, and the target area of radiotherapy should include all micro lesions as much as possible. According to a retrospective study of 48 patients diagnosed with head and neck NMCs,

the survival rate was significantly improved with aggressive surgical resection, whether or not postoperative chemoradiation or radiation was used, and the median overall survival was 9.7 mo, 2-year PFS rate of 26% [28]. It has also been suggested that about 40% of patients initially respond to chemotherapy and radiotherapy, but always relapse rapidly and do not respond to subsequent therapeutic interventions [9,18]. The patient in this case received multimodality treatment, including surgery, radiation therapy, chemotherapy, heat therapy and SDT. Unfortunately, the prognosis remained poor, with an overall survival of only 17 mo. The overall treatment outcome of NMC is unsatisfactory and molecularly targeted therapy is currently under investigation as a promising therapeutic approach, and two molecularly targeted drugs targeting the underlying causative mechanisms have emerged as being in clinical trials, with preliminary evidence of efficacy in some patients, they are bromodomain inhibitors (BETi) and histone deacetylase inhibitors (HDACi), both of which can induce differentiation and arrest cell growth in NMCs [3]. The BRD4-NUT oncoprotein binds and activates histone acetyltransferases, leading to chromatin acetylation and a feed-forward mechanism leading to tumorigenesis, and Beti can inhibit the function of the BRD4-NUT protein, allowing cell differentiation to proceed. HDACis can reverse BRD4-NUT function and restore normal cellular processes, and is expected to be a new therapeutic target for lung NUT cancer [3]. However, toxicity and side effects are still issues that need to be addressed [11]. One study found that OTX015/MK-8628, a novel oral BET inhibitor, reduced the amount of BET released into the blood, NMC-targeting drug that demonstrates rapid and impressive antitumour activity in preclinical studies, A significant difference was seen in survival between two patients (19 and 18 mo, respectively) compared with the median survival of 6.7 mo reported in the largest retrospective study of patients with NMC [29]. In this case, the patient relapsed soon after surgery and achieved some degree of remission after radiation therapy and initial treatment with anti-angiogenic drugs and SDT, but cannot achieve long-term stability and eventually developed distant metastases and died soon after.

CONCLUSION

In summary, we report the treatment of a patient with paranasal sinuses NMC who received multimodality treatment, including surgery, radiation therapy and chemotherapy, but never achieved long-term stability and eventually developed distant metastases. For patients with rapidly progressing sinus tumors and poor response to initial treatment, the possibility of NMC should be considered and immunohistochemical staining with anti-NUT should be performed as soon as possible, combined with genetic testing if necessary. ²CT, MRI and PET/CT imaging are essential for the staging, management, treatment response assessment and monitoring of NMC. This case is the first attempt to apply heat therapy and SDT in the treatment of NMC, unfortunately, the prognosis remained poor.

8%

SIMILARITY INDEX

PRIMARY SOURCES

- 1 www.hindawi.com 50 words — 2%
Internet
- 2 Mayur Virarkar, Mohammed Saleh, Nisha Subhashchandra Ramani, Ajaykumar C. Morani, Priya Bhosale. "Imaging spectrum of NUT carcinomas", Clinical Imaging, 2020 39 words — 1%
Crossref
- 3 Xiang Li, Hui Shi, Wei Zhang, Chong Bai, Miaoxia He, Na Ta, Haidong Huang, Yunye Ning, Chen Fang, Hao Qin, Yuchao Dong. "Immunotherapy and Targeting the Tumor Microenvironment: Current Place and New Insights in Primary Pulmonary NUT Carcinoma", Frontiers in Oncology, 2021 36 words — 1%
Crossref
- 4 www.wjgnet.com 31 words — 1%
Internet
- 5 f6publishing.blob.core.windows.net 25 words — 1%
Internet
- 6 Grosse Claudia, Grosse Alexandra. "Challenging Diagnosis in NUT Carcinoma", International Journal of Surgical Pathology, 2021 20 words — 1%
Crossref
- 7 "1 Brain (Intra-Axial Lesions)", Georg Thieme Verlag KG, 2017
Crossref

17 words — 1%

8 www.ncbi.nlm.nih.gov
Internet

16 words — 1%

9 www.iaslc.org
Internet

12 words — < 1%

EXCLUDE QUOTES ON
EXCLUDE BIBLIOGRAPHY ON

EXCLUDE SOURCES < 12 WORDS
EXCLUDE MATCHES < 12 WORDS