NUT midline carcinoma as a mediastinal tumor treated with cisplatin: A case report

Min Liu¹, Xia Wu², Qing Zhang*¹

¹ Department of Oncology, Beijing Hospital of Traditional Chinese Medicine, Capital Medical University, Beijing 100010, China.
² Beijing University of Chinese Medicine, Beijing 100029, China.

*Corresponding to: Qing Zhang, Department of Oncology, Beijing Hospital of Traditional Chinese Medicine, Capital Medical University, NO.23, Meishuguanhou Street, Dongcheng District, Beijing 100010, China.
E-mail: zhangqing@ccmu.edu.cn.

Author contributions
Min Liu collected the data and wrote the manuscript. Xia Wu collected the data. Qing Zhang collected the data and revised the manuscript.

Competing interests
The authors declare no conflicts of interest.

Acknowledgments
This study was funded by Enshi Prefecture Science and Technology Program Research and Development Project (No. 2019000040).

The authors would like to thank this patient and her family members.

Abbreviations
NUT: Nuclear protein of the testis; NMC: NUT midline carcinoma; DDP: Cisplatin; CT: computed tomography; IHC: Immunohistochemical; DIC: Diffuse Intravascular Coagulation.

Citation

Abstract
NUT (nuclear protein of the testis) midline carcinoma (NMC) is a rare malignant and poorly differentiated squamous cell tumor that typically presents in midline structures of the head, neck and mediastinum with high degree of invasion and mortality, which occurs at any age, especially in teenagers and young people. We report a case of NMC presented as a mediastinal tumor. A 14-year-old female patient who presented with progressive dyspnea, cough with expectoration, and right pleural effusion and mediastinal space-occupying. Cisplatin (DDP)-based chemotherapy was performed. The prognosis is bad with an overall survival of 3 months.

Keywords: NUT midline carcinoma, Mediastinal tumor, Cisplatin based chemotherapy
Introduction

NUT (nuclear protein in testis) midline carcinoma (NMC) is a rare and poorly differentiated squamous cell carcinoma, genetically defined by a characteristic reciprocal translocation t (15;19) (q14; p13). Though NMC is normally known to appear midline anatomic structures of the head, neck, and mediastinum, many cases have been diagnosed arising outside the midline, such as lung, pancreas, bladder, kidney and various soft tissue. Up to now, the absence of effective treatments lead to NUT carcinoma conferring an extremely poor prognosis with a median survival of less than 6 months [1]. The diagnosis is usually established immunohistochemically by using a monoclonal NUT specific antibody. Here we report a case of NUT carcinoma in a teenager that initially presented with progressive dyspnea, cough with expectoration and was found to have a rapidly growing pleural and pericardial effusions. At the same time, owing to the compression of mediastinal tumor, patient had a serious superior vena cava syndrome. Despite aggressive chemotherapy was performed, she quickly progressed and died from the disease just 2 months after diagnosis.

Case presentation

A 14-year-old female patient complained of chest tightness and cough with expectoration for 1 month and shortness of breath for 2 weeks. Enhanced chest computed tomography (CT) revealed mediastinal mass with multiple necrosis foci, right pleural effusion, collapse of the right lung with consolidation and atelectasis. The clinical picture was dominated by shortness of breath due to severe superior vena cava syndrome with pleural-pericardial effusion. We performed puncture biopsy of mediastinal mass guided by CT (Figure 1). Pathological report: (mediastinal mass) a few irregular nest-like malignant tumor cells with invasive growth can be seen in fibrous connective tissue. The tumor has a high nucleolus-cytoplasmic ratio, with nucleoli and mitotic images, and is associated with coagulation necrosis and squamous epithelial differentiation. A battery of immunohistochemical (IHC) markers were applied. Immunohistochemistry was positive for P63, CD34 (focal +), CK7 (focal +), CK19, CEA, P40, Ki-67 (index 50%), Muc-1 (focal +), and negative for CD30, Oct-4, PAX8, TdT, SALL4, S-100, CgA, CD20, CD5, CD117, Muc-2. On permanent histology, sheets with focal squamous differentiation were diagnosed, which led to the possibility of NUT midline carcinoma. IHC staining with NUT protein revealed diffusely positive, then the diagnosis of NMC was confirmed. Due to the compression of mediastinal tumor, patient had a serious superior vena cava syndrome. The patient was started on Cisplatin (DDP)-based chemotherapy (DDP regimen for 75 mg/m²). Unfortunately, however, at the initial chemotherapy treatment, the CT demonstrated bilateral lungs, bilateral adrenal gland, thoracic-peritoneal and multiple lymph node metastasis, which believed to represent an unusually rapidly progressive neoplastic process. In addition, she demonstrated signs of being critically ill with multiorgan failure. She died from the disease almost 2 months after diagnosis. Since a definitive diagnosis had been established for our patient and accordance with her family’s wishes, no autopsy was performed.

Discussion

NUT carcinoma is an extremely rare and highly aggressive tumor defined by chromosomal rearrangement of the gene NUT. The tumor was first reported in 1991 by Kubonishi et al. in a patient in retrospect mistakenly described as thymic carcinoma [2]. The mediastinum is the most common location of occurrence followed by diverse midline structures of the head and neck, and cases being seldom reported in the pancreas and the gynecological tract [3, 4]. Although recognition

Figure 1. Puncture biopsy of mediastinal mass guided by CT.

Mediastinal mass with multiple necrosis foci, right pleural effusion, collapse of the right lung with consolidation and atelectasis.
of NUT carcinoma as a distinct clinicopathological entity was found by French [5], and morphologically, an abrupt transition of immature cells juxtaposed to well-differentiated, mature appearing squamous nests is regarded as the only distinct feature, NUT carcinoma continues to be an under-diagnosed entity due to its nonspecific clinicopathological, cytopathologic, and immunophenotypic profile [3, 6]. Actually, the term “midline” was removed from the entity’s name in the current World Health Organization Classification of Head and Neck Tumors. In spite of our case presents the patient is a young people, NMC can occur in patients of all ages, including older adults, as exemplified in the presented case [7].

NMC is usually diagnosed by the coding sequence of the NUT gene on chromosome 15 and the coding sequence of the BRD4 gene on chromosome 19 with FISH or RT-PCR. Another the findings in the mediatinum tissue block material can support the diagnosis of NMC, including immunohistochemical staining for NUT which can serve as an initial screening tool. Immunohistochemistry (IHC) markers can help preclude malignancy in some situations. The role of IHC in establishing the diagnosis of NMC cannot be ignored. NMC is epithelial in origin and shows positivity for epithelial markers as seen in our case. Immunoreactivity to p63 and p40 is also predicted, as NMC is a poorly differentiated squamous cell carcinoma. Some undifferentiated nature of the tumor cells shows staining with CD34. It is reported CD34 positivity in 7/11 cases of NMC.

Also, the NUT gene can be identified by staining with anti-NUT antibodies in immunohistochemistry. In general, immunohistochemical staining is useful in differential diagnosis of NMC. The NUT monoclonal antibody is mentioned (specificity of 100%, sensitivity of 87%, and positive predictive value of almost 100%) [8], also can facilitate the quick and cost-effective diagnosis of NMC. We combined the imaging data, the NMC is diagnosed.

Due to the small number of cases with NMC, there is no standard therapy regimen being established. Patients are often diagnosed as other symptom associated disease in addition to NMC. Therefore, patients usually undergo individualized therapeutic regiments aiming at symptoms. NMC patients tend to be performed surgical therapy if he/she has a limited mass, while patients with multifocal disease usually undergo chemotherapy. The previous study also reported treating NMC patients with intensive chemotherapy regiments typically combining with radiation therapy [9, 10].

In our case, the young patient underwent rapid disease progression and the development of metastasis, so we chose a broad-spectrum antitumor drug, Cisplatin (DDP), and we made a chemotherapy regimen for 75 mg/m² (DDP: 40 mg day 1-2). But after only once DDP chemotherapy, the patient performed a CT reexamination showing bilateral lung, bilateral adrenal gland, thoracic-peritoneum and multiple lymph node metastasis. This indicated the progression of tumor, and the patient subsequently developed systemic infection, finally died of Diffuse Intraocular Coagulation (DIC).

It took less than three months from the discovery of the disease to the death of the patient. The previous study had been reported the nature of this disease is that it often relatively fixed in one site until the primary tumor is treated, no matter the surgical treatment or chemotherapy; then the patient typically relapses with aggressive metastatic disease. Another possibility is that treatment of the primary tumor unintentionally allows for or promotes seeding of other sites with cancer cells. Finally, it is likely that the primary tumor generates out some type of growth control over the metastases and after being removed, this restriction is released [11]. Then the NMC as the average overall survival for patients is just 6-7 months with the progression of primary tumor and the NMC patient died of recurrent infection.

**Conclusions**

NMC is a rare and rapidly advanced cancer. In progressively developed, poorly differentiated carcinomas, especially in teenagers or younger patients, the clinical diagnosis for NMC should not be ignored and forgotten. Once the diagnosis is confirmed, the positive therapy and systemic therapy are needed. As for the disease its own rapid development and widespread metastases, the basic test result, close follow-up, and adjusting treatment plan timely are the key point in prognosis.

**References**