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Case Report
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A Case Report of Primary Pulmonary NUT Carcinoma

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Abstract

NUT carcinoma feature as the rearrangement of the Nuclear Protein in Testis (NUT) gene on chromosome 15q14, and its clinical feature as rare, highly lethal, and fast development, easy misdiagnose, and no effective therapy, and have a depressed prognosis. We summary clinical features of a real lung nut carcinoma case in the department of thoracic oncology of a Chinese State Hospital, include radiation sensitive, chemotherapy and immunotherapy insensitive, and fast progressed. We explore the best strategy about the pulmonary nut carcinoma by analyzing our case and retrospective study a lot of others case report the clinical features and therapies.

Keywords: Pulmonary NUT carcinoma; Radiotherapy; chemotherapy

Background

NUT Carcinoma (NC) is a rare and highly aggressive malignant tumor with unknown histologic origin and without any clinical or histomorphological features to distinguish, except genetically defined by the presence of chromosomal rearrangements involving the NUT (also known as NUTM1, Nuclear Protein in Testis) gene [1-3]. In 1991, Kubonishi [4] first reported a case of thymic carcinoma characterized by t(15;19) translocation. But it was not until the discovery of the formation of a BRD4-NUT fusion oncogene in 2003, resulting from the t(15;19) translocation, NC was defined [1,5].

Although NC can occur in people of any age (0-81.7 years), the majority are adolescents or young adults (median age 16-22 years) and it affects males and females equally [6,7]. It is also known as NMC (NUT Middle Carcinoma) because it typically arises from midline upper airway locations, such as head and neck and thorax. However, some cases also occur in areas other than the above organs, including: Lungs [8], salivary glands [9], pancreas [10] and bladder [1].

NC is clinically distinct aggressive, often accompanied by extensive metastases at the time of diagnosis, and rapidly fatal [3]. Because NC often occurs in the mediastinum or lungs and is usually accompanied by distant and lymph node metastases, it is often mistaken for small cell lung cancer in clinical practice. However, NC progresses more rapidly and often affects young people. Despite such a poor prognosis for NC, there are not many effective treatments and not much research on this. Herein, we report a case of pulmonary NC that achieved long-term survival after a combination of chemotherapy, radiotherapy, and immunotherapy.

Case Presentation

A 56-year-old male presented to our hospital with "dizziness" and was found to have a 4.2 cm × 3.7 cm occupancy in the lower lobe of the left lung with obstructive atelectasis and enlarged mediastinal and supraclavicular lymph nodes on chest CT (Figures 1a1-1a3). No distant metastasis were founded in the head MRI, abdominal CT and SPECT bone scan. To further clarify the pathological type of the lung mass, a percutaneous puncture biopsy was performed. Immunohistochemical demonstrated strong and diffuse expression of PCK, P40 and CK5/6. There was focal expression of TTF-1 and Syn, whereas EBER1/2-ISH, CK7, Napsin A and CgA were negatived (Figure 2a, 2b). And no driver mutation was detected. The diagnosis of NC was confirmed following Fluorescence *in-situ* Hybridization (FISH) showed BRD4-NUT rearrangement. PD-L1 testing was not performed due to insufficient specimens. He was finally diagnosed as NUT carcinoma of the lower lobe of the left lung with hilar, mediastinal, and supraclavicular lymph node metastases, T3N3M0, stage IIIC (American Joint Committee on Cancer 8th Edition Cancer Staging Form). The patient refuses surgery. Cycle 1 nab-paclitaxel combined with carboplatin chemotherapy was then started. Chest CT was done to evaluate the efficacy before next cycle and suggested heterogeneous changes with a shrinking chest lesion and an increasing supraclavicular lymph node lesion (Figures 1b1-1b3). Supraclavicular

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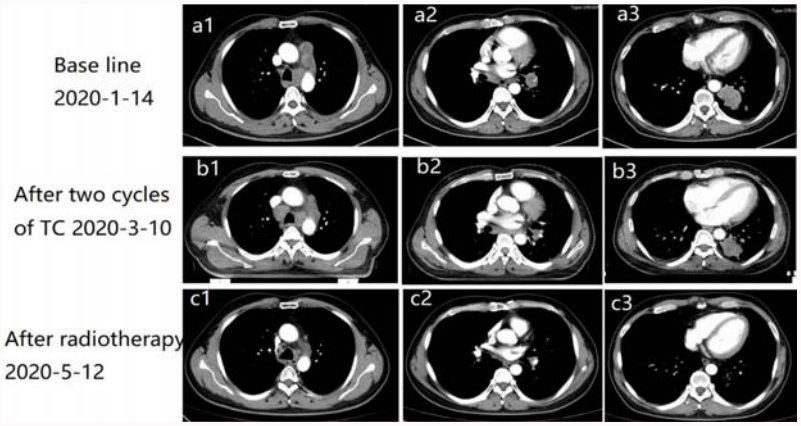


Figure 1: Serial abdominal CT scans show dynamic change from the base line to the radiation. a1 the base line of the metastatic mediastinal lymph nodes a2, a3 the base line of the primary tumor at the left lung. b1 after two cycles of chemotherapy with TC (Taxol and Carboplatin), the metastatic mediastinal lymph nodes shrink but a new metastatic lymph node occur. b2 b3 the primary tumor partly shrinks. c1 after radiotherapy, the all the metastatic lymph nodes obviously shrink. c2, c3 the primary tumor totally shrinks.

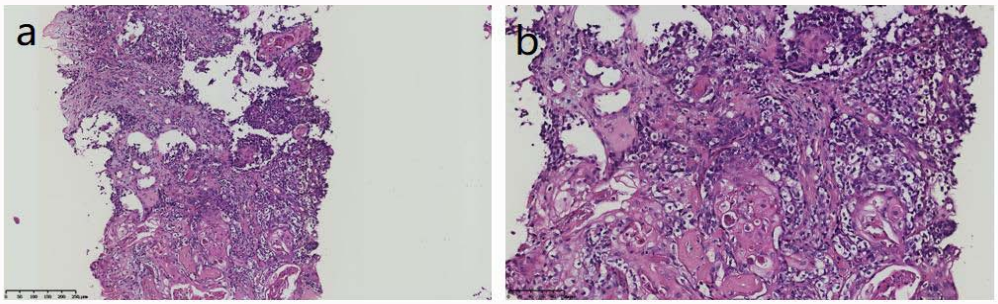
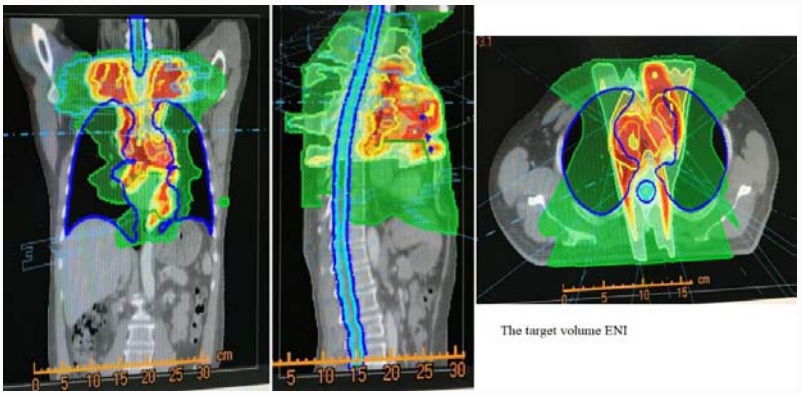


Figure 2: Histopathological examination shows poorly differentiated squamous cell mixture TTF1(+) and SYN(+) cells which small neuroendocrine cell carcinoma could not been excepted. A, (×200); B (×100).



Supplement Figure 1: The target volume of this case was preventability lymph node area radiation.

lymph node aspiration biopsy was performed at the same time as the second cycle of chemotherapy. Pathological findings showed poorly differentiated carcinoma in fibrofatty tissue, and FISH detected NUT gene translocation, indicating NC metastasis. Then chest and neck radiotherapy (56Gy/28f) were performed, and the target volume was preventability lymph node area radiation (Supplement Figure 1). Radiotherapy was suspended for 5 days for skin erosion of the neck caused by radiation during treatment. The 3rd and 4th cycles of chemotherapy were administered concurrently with radiotherapy. After the completion of radiotherapy, chest CT scan showed significant response of mediastinal and left lung tumors and the comprehensive efficacy evaluation was Partial Response (PR) (Figures 1c1-1c3). Four cycles of Durvalumab maintenance immunotherapy were then administered. However, a new lesion in the right middle lobe and enlarged left lower lobe lesion and right apical lesions were found by chest CT scan during the immunotherapy, which means disease progressed (Figures 3a1-3a3). Then, second-line treatment was given with chemotherapy of etoposide plus cisplatin combined with anti-vascular therapy of anlotinib. Two months later, chest intensive CT scans showed the mass at the lower lobe of the left lung and left hilus of the lung and the mediastinal obviously progressed, and the comprehensive efficacy evaluation was Progressive Disease

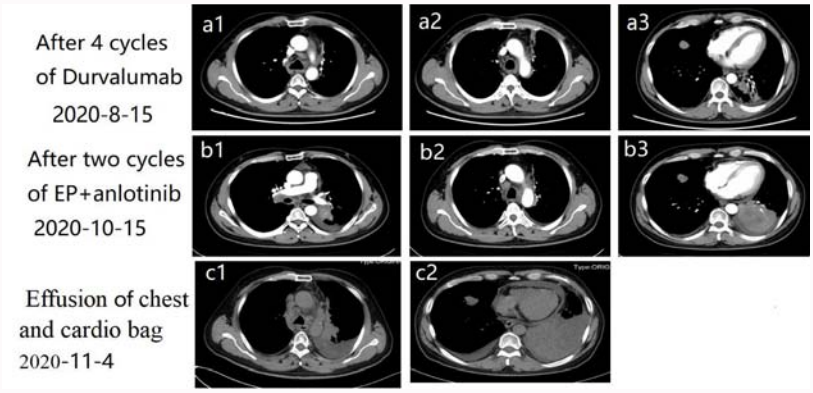


Figure 3: Serial abdominal CT scans show dynamic change of the follow-up treatment and the last period. a1, a2 after 4 cycles of immunotherapy with durvalumab, the mediastinal lymph nodes did not recur. a3 the primary tumor at the left lung recur and a new mass occur at the right low lung. b2 after two cycles of chemotherapy with EP (etoposide and cis-platinum) and anti-angiogenesis agent anlotinib, the mediastinal lymph nodes have no change compared before. b1, b3 the primary tumor progressed Fastly. c1, c2 at the last period, the pleural effusion and the pericardial effusion appeared.

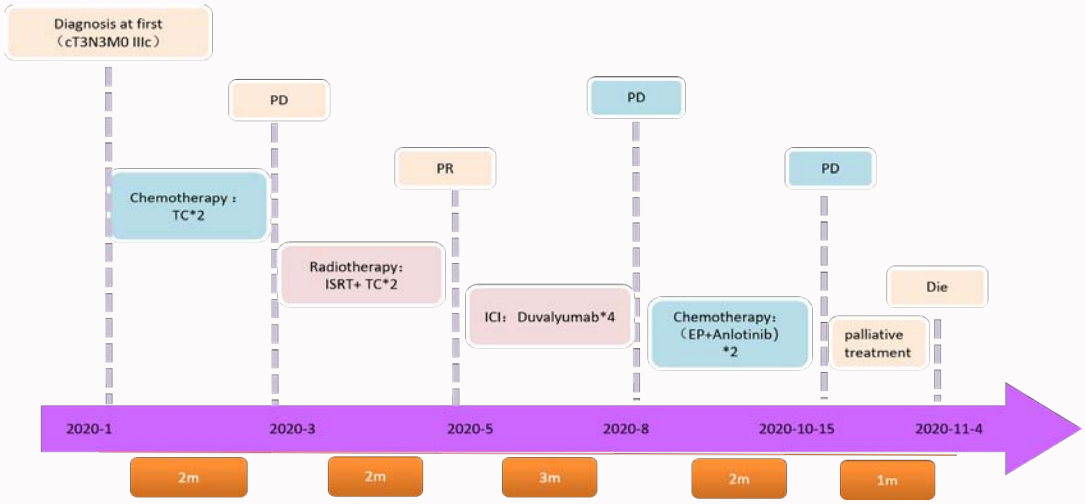


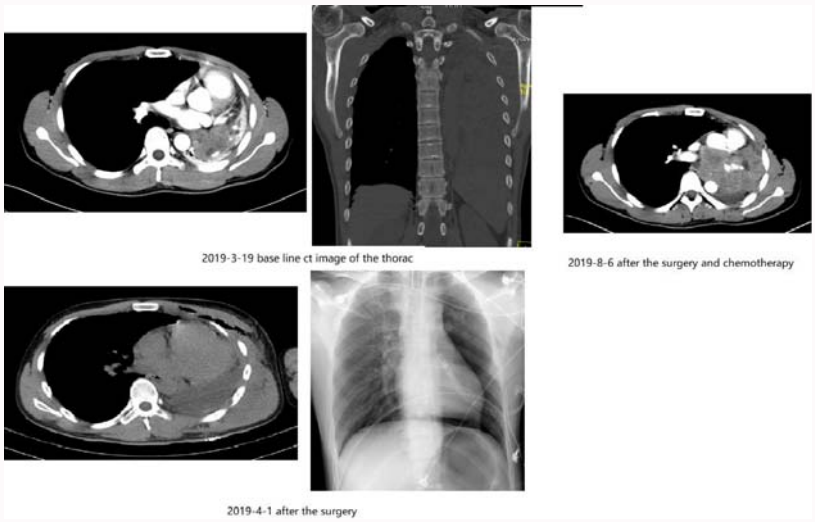
Figure 4: Overview of the whole treatment process.

(PD) (Figures 3b1-3b3). The patient cardiopulmonary function dramatically decreased because of the large effusion arise in the chest and a cardio bag (Figure 3c1, 3c2), and his general condition flow down, the ECOG 3 to 4. His overall survival time was 10 months.

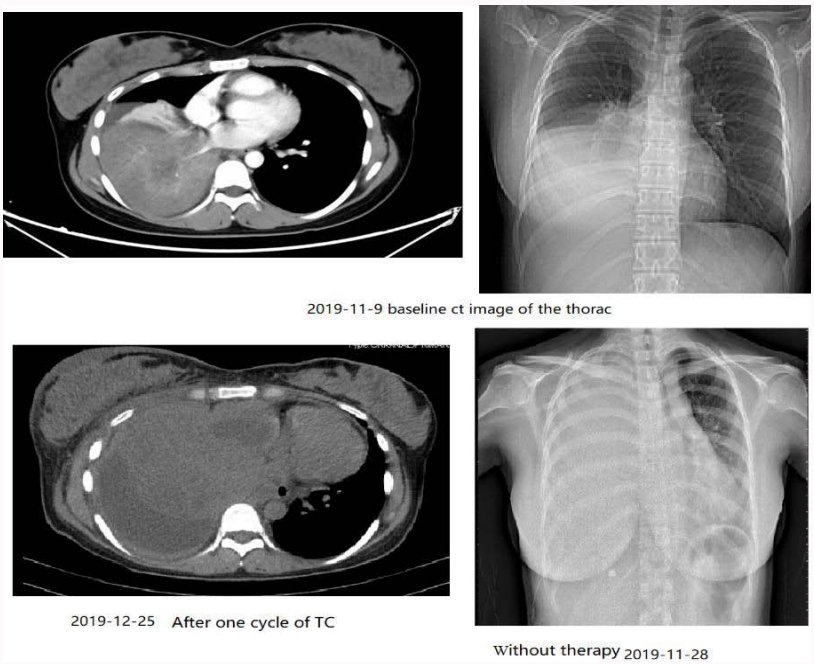
Discussion

NUT carcinoma is a rare, poor differentiated, high lethal cancer, which clinical feature as often occurred in the middle position of the body, and happened on from children to the old, no difference in gender, hard diagnosis, progressed fast, and no effective therapy, disaster ending [6,11-13]. Pulmonary nut carcinoma is a special kind with worse prognosis [14-18]. Recent years, a lot of reports were studied. Such as Xie et al. [1] have reported a retrospective study, they found the middle overall survival of 7 pulmonary nut carcinoma patient only were 4.1 moths [17]. Sholl et al. retrospective reported 8 pulmonary nut carcinoma patients, their middle overall survival time only 2.2 months [15]. In our case, the pulmonary nut carcinoma patient got 10 months survival through a series therapy, like chemotherapy, radiotherapy, immunotherapy (Figure 4). In our hospital, another two-lung NUT cancer patient were diagnosed in March and November 2019, they are 24 years old male, and 22 years old, female, whom were both found big mass in their chest, and were definitely as locally progressed stage T4N2M0 at the first diagnosis (Supplement Figure 2, 3). The male has through a unilateral lung resection, and chemotherapy with two cycles TP (Taxol and cis-platinum) were given after the surgery, and after progressing two cycles AIM (doxorubicin and ifosfamide) were given. Finally, he was dying after 6 months later from the first diagnosis. Another female patient only through two cycles chemotherapy with TC (Taxol and Carboplatin), and she only got 2 months survival.

The therapy of NUT carcinoma is a hard work, many reports showed us that no matter the traditional chemotherapy or radiotherapy and surgery, or the new method to antitumor, like anti-angiogenesis, immunotherapy both could not improve the prognosis of nut carcinoma [11,12,19]. The molecular mechanism of NUT carcinoma has not exactly explanation, and there have no any development of target therapy [20-23]. Though some new agent clinical trials for NUT carcinoma have been conducted, but the preliminary result is still unsatisfactory [20,21]. People know NUT carcinoma mostly from a lot of case reports and review of literature. Giridhar et al. analysis 119 NUT carcinoma cases from a lot of case reports, and pneumonia NUT carcinoma occupy 42 cases. They found that nut carcinoma first treated with radiotherapy to a dose exceed 50 Gy can significantly improve the overall survival of the patients [19]. In our cases, this



Supplement Figure 2: The CT scan images of the male from the base line to the last period.



Supplement Figure 3: The CT scan images of the female from the base line to the last period show the disaster nut lung cancer progressed so fast that there is no chance to treat.

one and the previously reported that radiation therapy can effectively release the tumor burden at any period [24]. In our previous report, radiotherapy at a dose of 20 Gy to 40 Gy can effectively release tumor burden, and after 40 Gy radiation, the tumor seemingly did not recur again in a long time [24]. In this case, the patient only received one time radiotherapy with a dose of 56 Gy, but still recured in situ after 3 months later of the radiation, it may relatively with the discontinuous radiation. Carefully comparing the images of CT scan, we found that recurs in the area where radiation target volume did not cover. Both radiation dose and the target volume and the radiation involved time could affect the prognosis of lung nut cancer patient.

Conclusion

As far as we can see from this case and we reported case before and those cases in other doctors' previous reports, the following few points need we consider carefully when we encounter lung NUT cancer. Firstly, it is very important to release the tumor burden at the first treatment, surgery, radiation, and chemotherapy should be considered, and the local treatment seems more important. Secondly, radiation should be considered during the whole disease process. Low dose (20-40 Gy), multi-course, multi-site, accurate target volume should be executed. And radiation should be getting involved timely at every time recur. As for chemotherapy, anti-angiogenic, and immune therapy, the effective are not sure in many cases. So, it acts according to the circumstances in the condition of guarantee radiation.

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