VIA MEDICA

CASE REPORT

Piotr A. Chilczuk, Magdalena Knetki-Wróblewska

Department of Lung Cancer and Chest Tumours Maria Sklodowska-Curie National Institute of Oncology, Warsaw, Poland

Locally advanced thoracic NUT carcinoma — a case report and literature review

Address for correspondence:
Piotr A. Chilczuk, MD
Department of Lung Cancer and Chest Tumours Maria Skłodowska-Curie National Research Institute of Oncology
ul. W.K. Roentgena 5
02–781 Warsaw, Poland
e-mail: piotr.chilczuk@nio.gov.pl

Oncology in Clinical Practice
DOI: 10.5603/ocp.101460

ISSN 2450–1654
e-ISSN 2450–6478

ABSTRACT

NUT carcinoma is an extremely rare and aggressive cancer. It is characterised by the presence of a nuclear protein gene rearrangement (NUTM1) on chromosome 15q14. Nut carcinoma can occur at any age but mainly in third decade. Patients with NUT carcinoma have affects diffrent organs, mainly in the midline of the body. Average overall survival patients with nut carcinoma does not exceed one year. The very rapid course of the disease, non-specific symptoms and the lack of specific treatment guidelines constitute a therapeutic challenge for oncologists. New treatment standards are needed. In our case report, we proposed a treatment method that showed clinical benefit

Keywords: NUT, NUT carcinoma, gene rearrangement

Oncol Clin Pract

Introduction

NUT carcinoma (NC) is an aggressive subtype of squamous cell carcinoma with a low incidence. It is defined as a single gene fusion that involves the *NUTM1* gene. In most cases, the disease is diagnosed at a stage of significant progression, and the prognosis for this group of patients is poor, with median survival of approximately 6–9 months [1]. Treatment of NC in the generalised stage is based on multidrug chemotherapy regimens, while patients diagnosed with stage I–III disease are also treated with local therapy; however, no clear treatment guidelines have been developed. This article presents a case of a patient diagnosed with local-stage thoracic NC who was treated with radical intent.

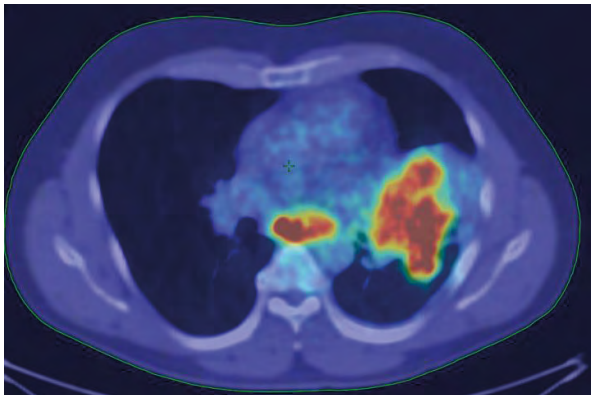

Figure 1. Baseline positron emission tomography–computed tomography (PET-CT)

Case report

The male 41-year-old patient, who never smoked and had no comorbidities, presented to his primary care physician in March 2023 with symptoms of an upper respiratory tract infection. A chest X-ray revealed an extensive left lung tumour. On positron emission tomography–computed tomography (PET-CT), the left lung tumour was found to be polycystic, 86 × 53 mm in size, with infiltration of the chest and mediastinal pleura- standardized uptake value [(SUV); SUV: 18.78] and metabolically active lymph nodes (right upper paratracheal and subcarinal — SUV: 24.16) (Fig. 1). The clinical stage (CS) was graded as IIIB, T4N2M0.

Received: 06.07.2024 Accepted: 30.09.2024 Early publication: 05.11.2024

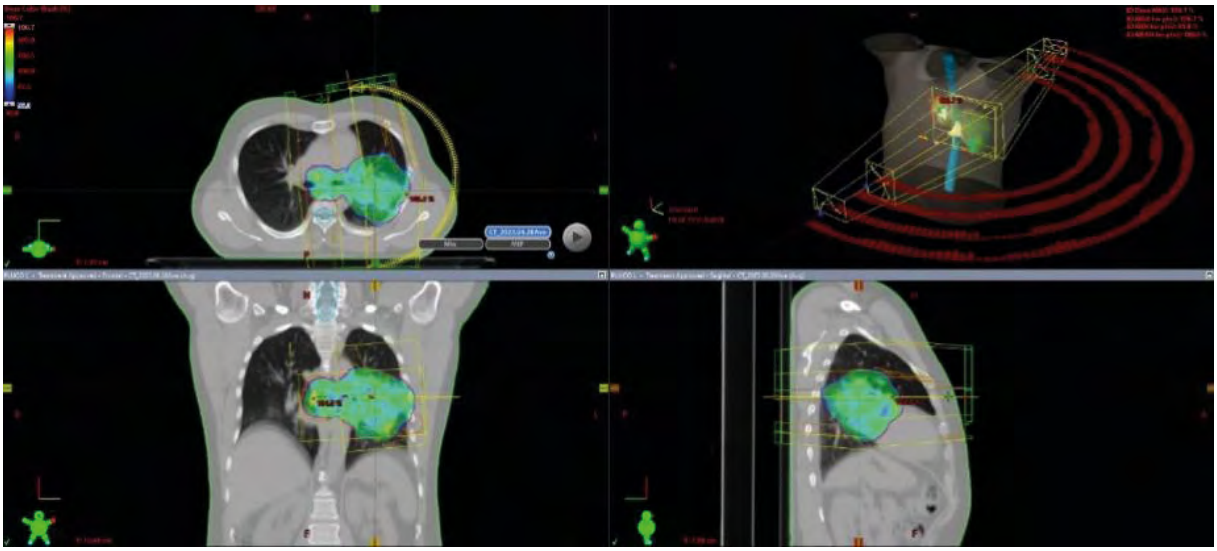

Figure 2. Treatment plan for the left lung and mediastinal tumour area

Based on the histopathological examination of bronchial specimens obtained during bronchoscopy (including immunohistochemical evaluation of NUT protein expression), NC was diagnosed. The patient, in good general condition with moderately severe respiratory symptoms, was qualified for treatment with radical concurrent chemoradiotherapy.

During radiation, two cycles of chemotherapy (cisplatin 75 mg/m^2, docetaxel 75 mg/m^2) were administered. A total dose of 30 Gy was administered to the left lung tumour area and the mediastinum at a fractional dose of 1.5 Gy twice daily with a minimum interval of 6 hours, with dose escalation to the tumour area and involved lymph nodes at a total dose of 45 Gy (Fig. 2). Total irradiation lasted 3 weeks (15 working days). It was performed using the 4D-image guided radiation therapy (4D-IGRT) respiratory gating technique, photons X6MV. Treatment was well tolerated, and radiotherapy was delivered at the planned dose and time. Post-radiation esophagitis of grade G2 was observed, which required additional analgesics. After completing the radiation therapy, chemotherapy was continued — a total of 4 treatment cycles were administered. A PET-CT scan performed 2 months after the end of treatment documented a partial regression (PR) of the thoracic tumour according to the Response Evaluation Criteria in Solid Tumours (RECIST 1.1), but at the same time, visualised a new metabolically active metastatic lesion in the left femur (Fig. 3).

Since the patient reported pain, hypofractionated radiotherapy was performed in the metastasis area of the femur, administered in 5 fractions to a total dose of 25 Gy using the volumetric modulated arc therapy (VMAT) technique, photons X6MV (Fig. 4). A few weeks after irradiation, a pathologic fracture occurred, requiring urgent orthopaedic nailing.

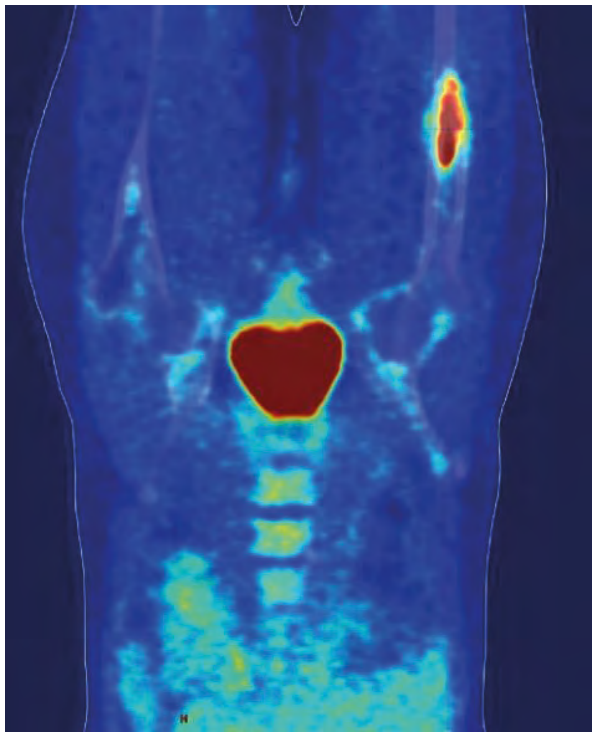

Figure 3. Positron emission tomography–computed tomography (PET-CT) study after completion of radio-chemiotherapy (RTH--CHTH) treatment. Visible metastasis to the left femur

In the following weeks, it was decided to replace the nail with an endoprosthesis. The procedure was complicated by a postoperative femoral abscess and significant progression of skeletal lesions (with persistent PR in the thoracic region). Due to the clinical deterioration, no further treatment was administered. The patient died 15 months after the onset of symptoms.

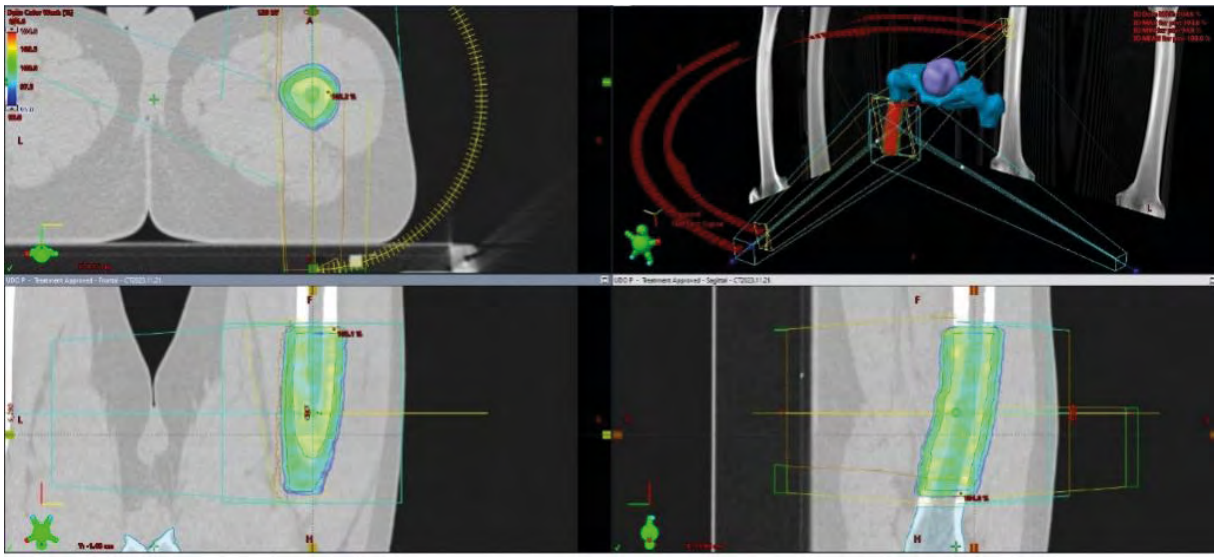

Figure 4. Treatment plan for the metastatic area in the left femur

Discussion

NUT carcinoma is an extremely rare subtype of squamous cell carcinoma. It is characterised by the presence of a nuclear protein gene rearrangement (*NUTM1*) on chromosome 15q14. This translocation results in fusion proteins that induce tumorigenesis that involve bromodomain and extra-terminal domain (BET) proteins. The resulting NUT-BRD fusion protein binds to the acetylated (Ac) portion of the chromatin with the BRD protein (bromodemin-containing protein belonging to the BET protein group). This allows the EP300 protein (histone acetyltransferase p300) to fuse, resulting in chromatin acetylation and the formation of active megadomains. As a result, genes that stimulate cell growth are overexpressed, which promotes tumour growth. NUT carcinoma usually involves organs in the midline of the body, most commonly the head, neck, and chest, but cases involving the kidney or pancreas have also been described [2]. It occurs more commonly in non-smoking men in the 3rd or 4th decade of life and presents clinically with chest pain, shortness of breath and cough [1–5]. Diagnosis of NC is based on immunohistochemical and molecular studies to confirm fusion.

Due to the low incidence of the tumour, the data in the literature on optimal therapeutic management are limited. Yuan's study [5] analysed 35 articles on NC, which described 55 patients with NC located in the chest. Their median age was 36 years. Cases were found in both young and old ages, showing that the disease can develop at any age. Cancer was found more often in men than in women (M:F — 1.9:1), especially in non-smokers. Patients presented uncharacteristic symptoms related mainly to lung involvement (cough, chest pain, shortness of breath). Imaging studies described extensive unilateral lung tissue involvement, mainly in the lower lung, usually with involvement of the hilar, mediastinal, or supraclavicular lymph nodes on the tumour side. Half of the cases had distant metastases to bone and other organs at the time of diagnosis. The median overall survival (OS) in the entire analysed population was only 4.4 months. The authors of the cited study pointed out that NC was sensitive to radiochemotherapy and that the best results had been achieved in patients treated concurrently. Patients who received combination treatment had better prognosis than those who received chemotherapy alone with median OS of 12 and 5.5 months, respectively. The benefit of adding immunotherapy to chemotherapy was questionable. The OS in this group ranged between 3 and 8 months. Six patients were treated with BET protein inhibitors and histone deacetylation inhibitors. The median OS in these patients was 7.45 months, confirming the lack of significant therapeutic gain with these types of drugs [5].

Hellquist et al. [6] describe 7 cases (4 of their patients and 3 taken from the literature) with diagnosis of NC cancer in head and neck localisation. All tumours were located in the supraglottic part of the larynx. Common features were young age and low-differentiated type of cancer, which is not typical for laryngeal cancers. The average survival time was less than 12 months. The 3 patients who received concurrent radiochemotherapy combined with surgery had the longest overall survival (7.8 and 11 months). By comparison, the patient who received chemotherapy alone had a survival of only 3 months. The localisation of NC at this site is extremely rare and often misdiagnosed. In young patients with diagnosis of low-differentiated laryngeal cancer with a component of squamous cells at a stage of significant local progression, the test for NC should be considered.

When this type of cancer is confirmed, a combination of therapeutic modalities (chemotherapy, radiation therapy, surgery) should be used, as it provides the best therapeutic results [6].

Giridhar et al. [7] analysed 64 publications with a total of 119 patients diagnosed with NC. The median age at the time of diagnosis was 23 years. The most common tumour sites were the lung (35.3%) and the head and neck (35%). More than a third of the patients had stage IV disease at diagnosis. The median survival for the entire group of patients was only 5 months. Surgery was performed on only 22 patients. Surgery alone was shown to not significantly prolong overall survival ($p = 0.232$). The 1-year survival rate (1-year OS) was 33.88% in patients who underwent surgery and 19.7% in those who did not. Radiotherapy was used as part of treatment in 49 patients, 17 of whom underwent radical surgery. Radiation was found to have a statistically significant effect on prolonging survival ($p = 0.001$). The greatest benefit was observed in patients who received doses > 50 Gy to the tumour. It should be noted that in the publication cited above, radical radiotherapy was administered most frequently to the head and neck (53%) and only 30% to the lungs. Radiation therapy up to a total dose of 50 Gy or more, administered in conventional fractionation (2 Gy/day each), can be used in patients with head, neck and lung cancers as a single treatment or in combination with chemotherapy [7]. Active cytostatic agents for this diagnosis include cisplatin, carboplatin, cyclophosphamide, etoposide, doxoribicin, vinorelbine, paclitaxel 5-fluorouracil, vinblastine, or actinomycin. Luo et al. [8] published an analysis of treatment outcomes in a group of 118 patients, including 62 patients with locally advanced disease (40% — thorax). Patients treated with ifosfamide had a higher objective response rate and a trend towards prolonged progression-free survival (PFS) compared to platinum-based chemotherapy [8]. Patients treated with immune checkpoint inhibitors and BET inhibitors have also been described although access to these therapies for NC patients is limited to clinical trials [9].

Conclusions

Concurrent chemoradiotherapy appears to be the standard of care in patients with locally advanced NC. However, the case presented here shows that the course of NC can be dynamic even in patients with initially limited disease. In this case, the predominant problem was progression of bone metastases, which significantly affected the patient's quality of life. Unfortunately, current therapeutic options do not provide satisfactory long-term treatment responses in NC patients. There is a need to qualify patients for treatment through clinical trials. It should be emphasised that in young patients with initial diagnosis of squamous cell carcinoma of the mediastinum or head and neck, NC should be included in the differential diagnosis.

Article Information and Declarations

Ethics statement

The patient's consent to the publication of the case report was obtained.

Author contributions

P.Ch., M.K.-W.: conceptualisation, preparation of manuscript.

Acknowledgments

None.

Funding

None.

Conflict of interest

Authors declare no conflict of interest related to this publication.

Supplementary material

None.

References

1. Lauer UM, Hinterleitner M, Horger M, et al. NUT Carcinoma-An Underdiagnosed Malignancy. Front Oncol. 2022; 12: 914031, doi: 10.3389/fonc.2022.914031, indexed in Pubmed: 35957893.
2. French CA. NUT Carcinoma: Clinicopathologic features, pathogenesis, and treatment. Pathol Int. 2018; 68(11): 583–595, doi: 10.1111/pin.12727, indexed in Pubmed: 30362654.
3. Alekseyenko AA, Walsh EM, Wang X, et al. The oncogenic BRD4--NUT chromatin regulator drives aberrant transcription within large topological domains. Genes Dev. 2015; 29(14): 1507–1523, doi: 10.1101/gad.267583.115, indexed in Pubmed: 26220994.
4. Chen J, Li M, Lu H. Nuclear protein in testis carcinoma of the lung. Transl Oncol. 2023; 30: 101640, doi: 10.1016/j.tranon.2023.101640, indexed in Pubmed: 36780749.
5. Yuan J, Xu Z, Guo Y. Diagnosis, Treatment and Prognosis of Primary Pulmonary NUT Carcinoma: A Literature Review. Curr Oncol. 2022; 29(10): 6807–6815, doi: 10.3390/curroncol29100536, indexed in Pubmed: 36290813.
6. Hellquist H, French CA, Bishop JA, et al. NUT midline carcinoma of the larynx: an international series and review of the literature. Histopathology. 2017; 70(6): 861–868, doi: 10.1111/his.13143, indexed in Pubmed: 27926786.
7. Giridhar P, Mallick S, Kashyap L, et al. Patterns of care and impact of prognostic factors in the outcome of NUT midline carcinoma: a systematic review and individual patient data analysis of 119 cases. Eur Arch Otorhinolaryngol. 2018; 275(3): 815–821, doi: 10.1007/s00405-018-4882-y, indexed in Pubmed: 29356890.
8. Luo J, Sanchez M, Lee E, et al. Initial Chemotherapy for Locally Advanced and Metastatic NUT Carcinoma. J Thorac Oncol. 2024; 19(5): 829–838, doi: 10.1016/j.jtho.2023.12.022, indexed in Pubmed: 38154515.
9. Kloker LD, Sidiras M, Flaadt T, et al. Clinical management of NUT carcinoma (NC) in Germany: Analysis of survival, therapy response, tumor markers and tumor genome sequencing in 35 adult patients. Lung Cancer. 2024; 189: 107496, doi: 10.1016/j.lungcan.2024.107496, indexed in Pubmed: 38301600.