Case Report

ANNALS OF MEDICINE & SURGERY

OPEN

Suspected NUT carcinoma progressing on pembrolizumab, carboplatin, and paclitaxel as first-line treatment: a case report

Ahmed Badran, MBBCh[a,d], Saad Salman Ali, MBBS[c], Tarek Ziad Arabi, MBBS[c,*], Abdulaziz Mohammed Alaklabi, MBBS[c], Hytham Mubarak Abdalla, MBBS[c], Shamayel Mohammed, MBBS[b], Belal Nedal Sabbah, MBBS[c], Mahmoud A. Elshenawy, MBBS[a,e], Jean Paul Atallah, MD[a]

Introduction and importance: NUT carcinoma of the thorax is an extremely rare neoplasm characterized by a translocation between the NUT M1 gene and members of the bromodomain genetic family. Due to the rarity of the neoplasm, standardized treatment guidelines have not yet been established. Several chemotherapeutic agents have been used with limited success, due to the rapid development of resistance to treatment. Pembrolizumab, an anti-programmed-death-1 antibody, has become increasingly used in non-small-cell lung carcinomas. Consequently, pembrolizumab may be beneficial in the treatment of NUT carcinoma.

Case presentation: In this article, we discuss the case of a 24-year-old man who was referred to our centre due to an incidental mass finding on an unrelated computed tomography scan. Morphological and immunohistochemical characteristics are highly suspicious of NUT carcinoma with bone metastasis. The patient was placed on carboplatin, paclitaxel, and pembrolizumab as first-line therapy. The patient later progressed and began receiving second-line treatment according to Ewing's protocol. 20 months later, the mass continued to grow, and the patient was started on docetaxel and gemcitabine, which was unsuccessful. After discussing with the patient, he decided to stop chemotherapy and begin palliative care.

Clinical discussion: NUT carcinoma is an aggressive tumour with poor prognosis. Treatment options are limited and pembrolizumab does not seem to influence the clinical outcome of the neoplasm.

Conclusion: Overall, pembrolizumab does not seem to improve the outcomes of NUT carcinoma patients. To the authors' knowledge, this is the second article reporting the effects of pembrolizumab on the progression of NUT carcinoma.

Keywords: case report, lung cancer, NUT carcinoma, PD1, pembrolizumab

Introduction

NUT carcinoma (NC), formerly known as NUT midline carcinoma, is a rare and extremely aggressive metastatic squamous cancer of unknown origin. NC commonly affects midline structures, such as the head, neck, and mediastinum, and younger patients are thought to be the main demographic of this tumour. The neoplasm is characterized by chromosomal translocation between the NUT M1 gene on chromosome 15q14 and members of the bromodomain genetic family (BET) , such as BRD3 on 9q34 or BRD4 on 19p13[1]. This translocation triggers overexpression of the MYC oncoprotein, exacerbating the rapid dissemination of NC[2]. Morphologically, NC displays sheets of poorly differentiated monomorphic cells with scant cytoplasm, like those found in squamous cell carcinoma[3]. The diagnosis can be confirmed by immunohistochemistry using anti-NUT antibodies, which demonstrate high sensitivity and specificity[2].

Although data are limited, the prognosis for NC patients remains extremely poor, with a median survival time of ~6-month and a 1-year survival rate of only 20%[1,2]. Due to the rarity of this malignancy, there is a lack of standardized treatment guidelines. Various chemotherapeutic agents, such as cisplatin and taxanes, have been used with limited success due to the rapid development of resistance to treatment[4]. Recently, pembrolizumab—an anti-programmed-death-1 (PD1)

HIGHLIGHTS

- NUT midline carcinoma is a rare, aggressive neoplasm characterized by NUT gene rearrangement.
- Pembrolizumab, an anti-PD1 antibody, may not prove effective in improving prognosis of NUT carcinoma patients.
- There is a need for Arab institutions to acquire diagnostic assays for NUT carcinoma, as new treatment modalities arise.

Departments of [a]Medical Oncology, [b]Pathology and Laboratory Medicine, King Faisal Specialist Hospital and Research Center, [c]College of Medicine, Alfaisal University, Riyadh, Saudi Arabia, [d]Department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Ain Shams University, Cairo and [e]Department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Menoufia University, Shebin El Kom, Egypt

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

**Corresponding author. Address: College of Medicine, Alfaisal University, Takhassusi Street Riyadh, 11533, Saudi Arabia Tel.: + 966 011 215 7777; fax: +966 011 215 7777. E-mail: tarabi@alfaisal.edu (T. Z. Arabi).*

Annals of Medicine & Surgery (2024) 86:1061–1065

Received 10 May 2023; Accepted 3 November 2023

Published online 2 December 2023

http://dx.doi.org/10.1097/MS9.0000000000001501

antibody—has replaced chemotherapy as the first-line treatment in non-small-cell lung carcinomas[5]. Therefore, pembrolizumab may prove beneficial in NC treatment. Gupta *et al.*[1] recently reported the case of a NC treated with pembrolizumab; however, the patient progressed and succumbed to his disease. To the authors' knowledge, this is the only other published report of pembrolizumab in the treatment on NC. Therefore, we present the case of a 24-year-old man with suspected lung NC who failed pembrolizumab as first-line treatment and two other lines of chemotherapy agents. This manuscript is reported in accordance with the CARE guidelines[6].

Case presentation

Our patient is a 24-year-old male referred to our centre after an incidental finding on a computed tomography (CT) scan indicated for blunt chest trauma [Fig. 1A]. The CT scan showed a large well-defined heterogenous mass with a central low attenuation component. The mass, measured at 6 × 6 × 9 cm in the transverse, anteroposterior, and craniocaudal dimensions, was partially occupying the left lower lobe, causing a mass effect and enhancing left lower lobe segmental atelectasis. The patient had no complaints of chest pain, shortness of breath, cough, or dysphagia. The patient has no significant medical history or family history. However, the patient reported weight loss of 20 kg in the last 3 months and pain in the lower right back for 2 months.

Whole body fluorodeoxyglucose (FDG) PET/CT scan demonstrated heterogeneous FDG metabolism within the suspected mass with an SUV maximum of 15 [Figure 1 B]. Additionally, there was increased uptake in several osseous locations, including the skull, T10 vertebrae, T11 vertebrae, posterior right iliac bone, and left lower femur. Therefore, a CT-guided biopsy was performed, and 6 small tissue biopsies were obtained and sent for examination.

Microscopic examination revealed sheets and clusters of undifferentiated round cells of small to intermediate size [Fig. 2], alternating with areas of neoplastic cells [Fig. 3] with squamous differentiation [Fig. 4]. Accordingly, the differential diagnosis for this case includes poorly differentiated squamous cell carcinoma, combined small cell-squamous cell carcinoma, and NC of the thorax. Immunohistochemistry showed that the tumour cells are positive for p63, p40, CK5/6 [Fig. 5], and negative for synaptophysin, chromogranin A, napsin A, thyroid transcription factor 1, and ALK(D5F3). The general features are highly suggestive of NC of the thorax with bone metastasis. However, the diagnosis could not be confirmed due to the unavailability of anti-NUT antibodies at our centre. There was no expression of PDL-1 using the PDL-1 DAKO 22C3 platform.

The patient was then started on a chemotherapy regimen consisting of carboplatin, paclitaxel, and pembrolizumab. After two cycles of chemotherapy, the patient was newly diagnosed with type 1 diabetes mellitus and suffered an episode of diabetic ketoacidosis. After three cycles of first-line therapy, the patient began to complain of increased lower back pain, initiating further investigation.

An FDG PET/CT scan showed progression of the T10 lesion, and a MRI scan was ordered to confirm the presence of spinal cord compression. The MRI scan revealed a T10 metastatic lesion with large perivertebral and epidural soft tissue components causing significant spinal canal stenosis. The spinal cord also showed myelomalacia changes, and soft tissue extension into the right neural foramina of T9/T10 and T10/T11, causing severe neural foramina narrowing [Fig. 6].

The patient underwent urgent laminectomy, decompression, and spinal fixation. Surgical biopsy showed poorly differentiated carcinoma with squamous differentiation, consistent with the previously suspected NC. The patient was started on "Ewing's protocol VDC/IE" as second-line treatment, alternating between phases of vincristine, doxorubicin, cyclophosphamide, and phases of ifosfamide and etoposide for eight cycles.

Twenty months after beginning second-line therapy, a follow-up CT scan revealed significant progression of the lower lobe mass with invasion of the left main bronchus bifurcation and development of left lung collapse with numerous right lung subcentimetre nodules and multiple right nodular pleural thickening reflecting progressive metastatic disease [Fig. 7]. Hence, the patient was started on a third chemotherapy regimen consisting of docetaxel and gemcitabine.

Unfortunately, after two cycles of docetaxel and gemcitabine, a follow-up CT scan demonstrated significant disease progression and increased bone metastasis [Fig. 8]. Therefore, the decision was made to cease chemotherapy and place the patient on a do-not-resuscitate order. The patient is currently following up with another centre and is receiving palliative care.

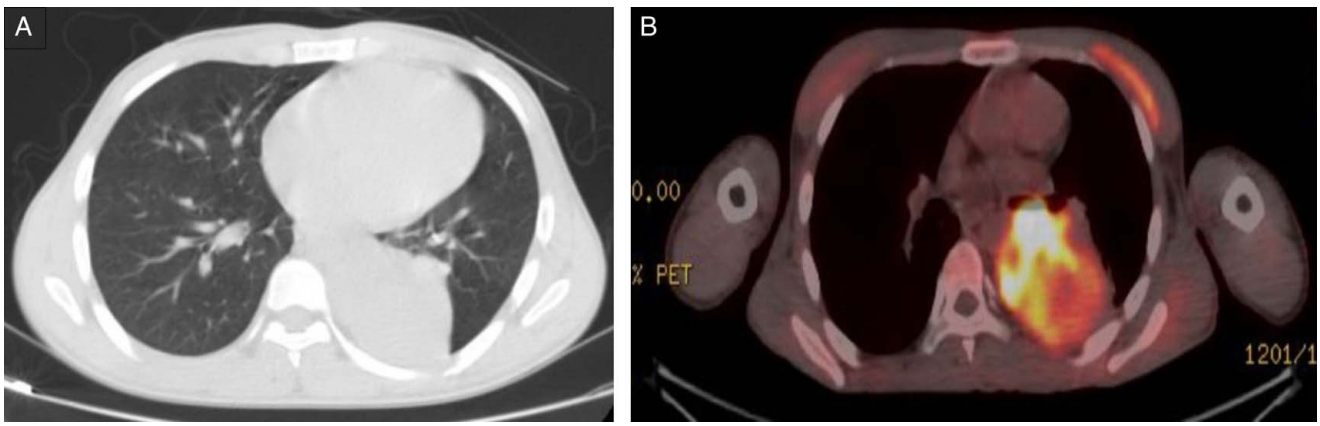

Figure 1. Staging work up for the primary thoracic tumour. (A) Axial computed tomography (CT) scan of the chest. (B) Axial PET/CT scan of the chest.

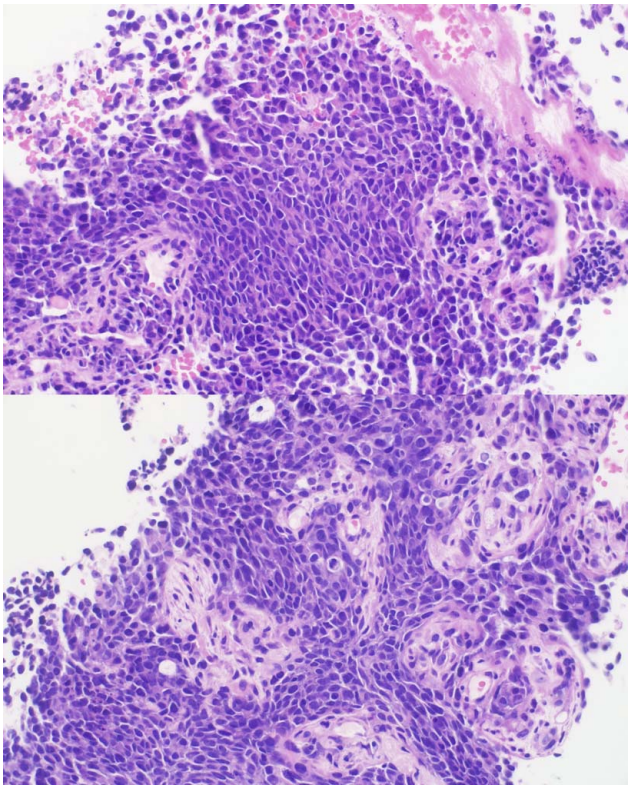

Figure 2. Diffuse sheets and nests of small round blue cells with high N/C ration and hyperchromatic nuclei.

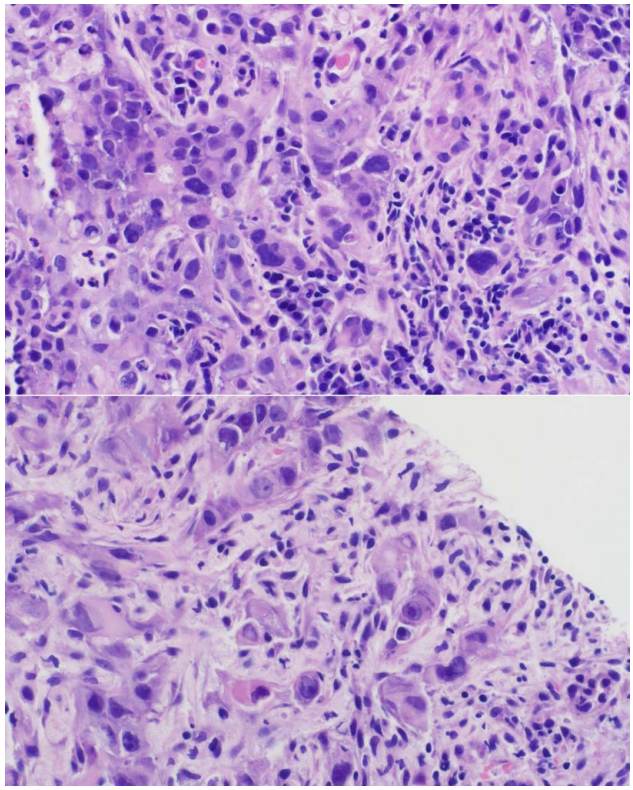

Figure 3. Nests of intermediate to large undifferentiated cells with irregular outlines, vesicular chromatin and prominent nucleoli.

Discussion and conclusion

NC is a very rare form of squamous cell tumour that can develop in several midline structures such as the thorax, head and neck, exhibiting various degrees of squamous differentiation and being distinguished by its aggressive clinical history[1]. They are poorly differentiated carcinomas that are genetically characterized by the rearrangement of the NUT M1 gene, located on chromosome 15q14, which is frequently fused with the BRD3 or BRD4 gene on chromosome 19p13.12. This leads to the most well-known reciprocal translocation t(15;19) seen in around 70–88% of cases, along with other variations such as BRD3-NUTM1 and NSD3-NUTM1, which result in epigenetic reprogramming and loss of cell differentiation[1,4].

Due to the rarity of NC, the prognosis of the neoplasm is not well known, although previous studies have demonstrated that certain translocations are associated with a significantly worse prognosis[7,8]. For example, the median overall survival for patients with primary thoracic masses due to NUTM1-BRD4 gene rearrangements was reported to be 4.4 months, compared to 36.5 months for patients with extra-thoracic, non-BRD-4 primary tumours[8]. Possessing other risk factors such as lymph node and organ involvement and a tumour size of greater than or equal to 6 cm can also lead to a worse overall outcome.

NC treatment guidelines have yet to be standardized, owing to the rarity of the neoplasm. However, multimodal regimens utilizing surgery, radiotherapy, and chemotherapy are highly recommended in both metastatic and non-metastatic patients[9]. If the tumour is resectable, initial treatment often involves surgical intervention after adjuvant radiotherapy or chemotherapy. Several lines of concurrent chemotherapeutic agents have been reportedly used including cyclophosphamide, etoposide, doxorubicin, actinomycin D, vinorelbine, vinblastine, cisplatin, docetaxel, 5-fluorouracil, S1, bleomycin, vincristine, ifosfamide, gemcitabine and an uncommon treatment choice, pembrolizumab[10]. In metastatic patients or those with unresectable tumours, combination chemotherapy is highly advised followed by local management of the tumour[9]. Recently, BET inhibitors have also emerged; however, studies assessing their effects are extremely limited. Piha-Paul *et al.*[11] conducted a phase 1 study of

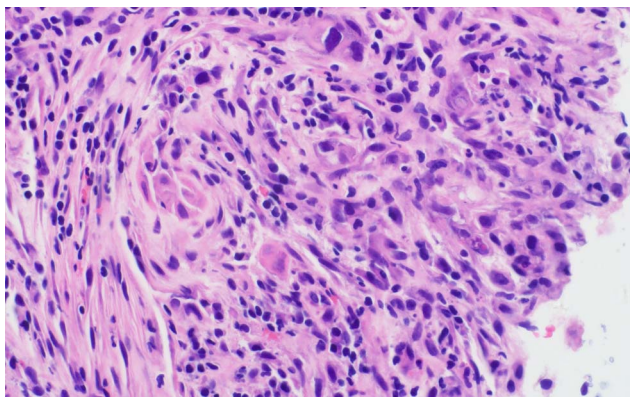

Figure 4. Focal areas exhibiting focal keratinization.

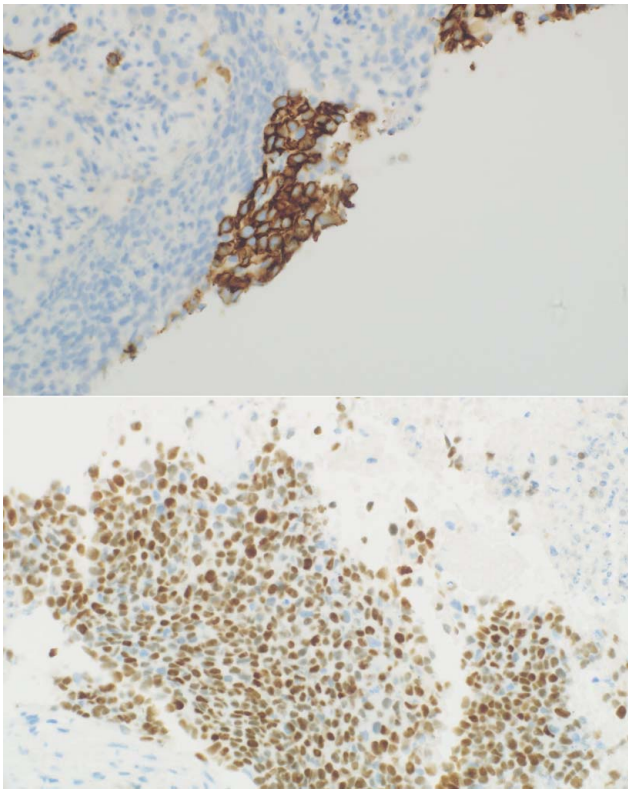

Figure 5. Tumour cells focally positive for CD34 (top panel) and diffusely positive for P63 (bottom panel).

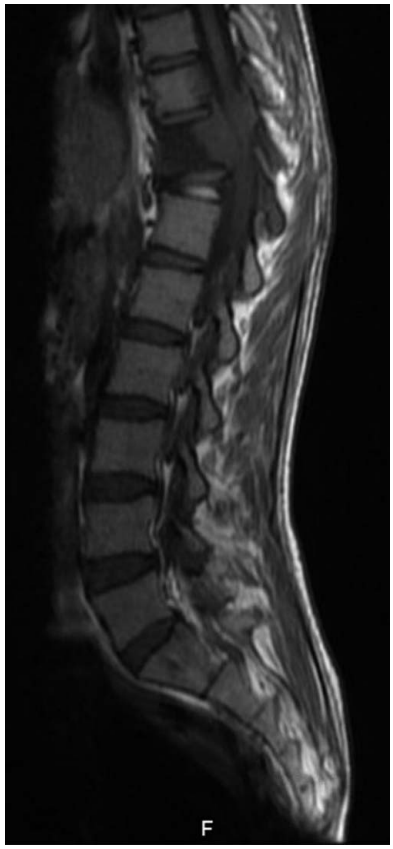

Figure 6. Sagittal MRI of the lower thoracic and lumbar vertebrae showing tumour infiltration of the spinal cord.

molibresib (BET inhibitor) in NC. Among NC patients, four patients showed a partial response and eight demonstrated stable disease. Furthermore, four patients had a progression-free survival of more than 6 months. Further studies are needed to confirm the effectiveness and safety of BET inhibitors.

Pembrolizumab is a selective humanized IgG4 monoclonal antibody which inhibits the PD1 receptors of lymphocytes. PD1 is an immune checkpoint, preventing immune cells from attacking the cells of their own host[12]. Cancer cells express PD1 as a mechanism of immune evasion, allowing the neoplasm to progress and metastasize elsewhere[13]. Although pembrolizumab has a good safety profile, several severe immune-related adverse effects may develop, such as pancreatitis, colitis, neuropathy, and myositis[14,15]. Therefore, it is crucial to closely monitor patients in order to recognize the wide spectrum of pembrolizumab-related adverse effects at an early stage. To our knowledge, there has only been report of pembrolizumab being utilized in the treatment of NC. Gupta *et al.*[1] reported the case of a 49-year-old NC patient treated with carboplatin and paclitaxel. The patient subsequently failed several lines of treatment and was placed on pembrolizumab as part of his regimen. The patient succumbed to his illness with an overall survival of 18 months[1]. Similar results can be seen in our patient who has failed three lines of treatment and is now receiving palliative care.

This study is limited by a couple of factors. It is important that all conclusions are taken with caution, since our patient may not accurately represent the majority of NUT carcinoma patients. Hence, we request that further studies are done on this rare neoplasm to identify the most effective management plans. Additionally, we wish to highlight the lack of NUT immunohistochemistry in the Middle East. To our knowledge, anti-NUT antibodies are not available in most large tertiary centres in Saudi Arabia. Often, hospitals do not wish to purchase a steady supply of anti-NUT antibodies due to its rarity. On the other hand, the correct diagnosis has several prognostic and therapeutic implications, especially with the recent emergence of BET inhibitors. Therefore, we urge health administrators in the Middle Eastern region to re-assess the cost-benefit analysis of NUT immunohistochemistry.

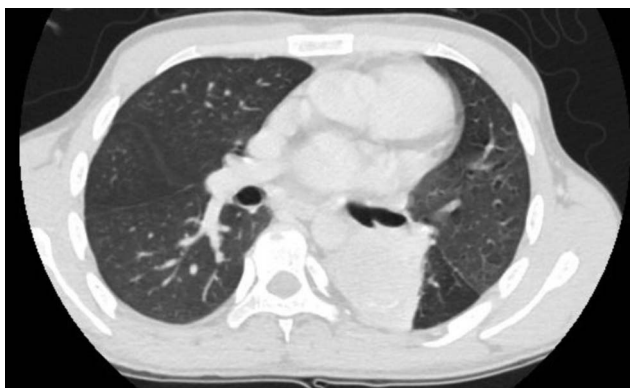

Figure 7. Axial computed tomoggraphy scan revealing progression of the intrathoracic tumour after second-line treatment.

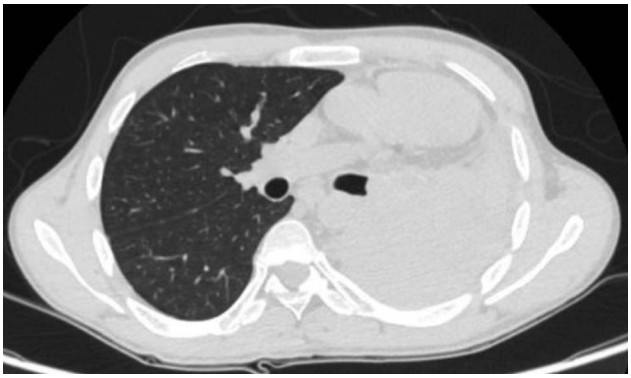

Figure 8. Axial computed tomoggraphy scan revealing progression of the intrathoracic tumour after third-line treatment.

In this article, we presented the case of a suspected NC patient who received carboplatin, paclitaxel, and pembrolizumab as first-line therapy. The patient subsequently progressed, and second- and third-line treatments failed to improve his condition. One major limitation of this present case is the lack of the anti-NUT confirmatory test, as the required antibodies are unattainable at our centre. However, other differential diagnoses have been excluded through microscopic examination and immunohistochemistry. To the authors' knowledge, this is the second article reporting the usage of pembrolizumab in NC treatment. Although larger long-term studies are needed to reach a conclusion, pembrolizumab does not seem to significantly improve the prognosis of NC patients. Future studies should also aim to develop standardized NC treatment guidelines.

Ethical approval

Written informed consent was obtained from the patient for the publication of this manuscript.

Consent to participate

Written informed consent was obtained from the patient for the publication of this manuscript.

Sources of funding

This study did not receive funding from any source.

Author contribution

All authors contributed to the research and/or preparation of the manuscript. All authors read and approved the final manuscript.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

Research registration unique identifying number (UIN)

NA.

Guarantor

Dr. Ahmed Badran.

Availability of data and material

Data are available upon reasonable request to the corresponding author.

Provenance and peer review

Not commissioned, externally peer-reviewed.

References

[1] Gupta R, Mumaw D, Antonios B, *et al*. NUT midline lung cancer: a rare case report with literature review. AME Case Rep 2022;6:2.
[2] Lantuejoul S, Pissaloux D, Ferretti GR, *et al*. NUT carcinoma of the lung. Semin Diagn Pathol 2021;38:72–82.
[3] Chatzopoulos K, Boland JM. Update on genetically defined lung neoplasms: NUT carcinoma and thoracic SMARCA4-deficient undifferentiated tumors. Virchows Arch 2021;478:21–30.
[4] Moreno V, Saluja K, Pina-Oviedo S. NUT carcinoma: clinicopathologic features, molecular genetics and epigenetics. Front Oncol 2022;12:860830.
[5] Udayakumar S, Parmar A, Leighl NB, *et al*. Pembrolizumab alone or with chemotherapy for metastatic non-small-cell lung cancer: a systematic review and network meta-analysis. Crit Rev Oncol Hematol 2022;173:103660.
[6] Gagnier JJ, Kienle G, Altman DG, *et al*. The CARE Guidelines: Consensus-based Clinical Case Reporting Guideline Development. Glob Adv Health Med 2013;2:38–43.
[7] Bauer DE, Mitchell CM, Strait KM, *et al*. Clinicopathologic features and long-term outcomes of NUT midline carcinoma. Clin Cancer Res 2012;18:5773–9.
[8] Chau NG, Ma C, Danga K, *et al*. An anatomical site and genetic-based prognostic model for patients with nuclear protein in testis (NUT) midline carcinoma: analysis of 124 patients. JNCI Cancer Spectrum 2019;4:pkz094. doi:10.1093/jncics/pkz094
[9] Lemelle L, Flaadt T, Fresneau B, *et al*. NUT carcinoma in children and adolescents: the expert european standard clinical practice harmonized recommendations. J Pediatr Hematol Oncol 2023;45:165–73.
[10] Wang S, Li J, Tong W, *et al*. Advances in the pathogenesis and treatment of nut carcinoma: a narrative review. Transl Cancer Res 2020;9:6505–15.
[11] Piha-Paul SA, Hann CL, French CA, *et al*. Phase 1 study of molibresib (GSK525762), a bromodomain and extra-terminal domain protein inhibitor, in nut carcinoma and other solid tumors. JNCI Cancer Spectr 2020;4:pkz093.
[12] Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev 2010;236:219–42.
[13] 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;275:815–21.
[14] Ofuji K, Hiramatsu K, Nosaka T, *et al*. Pembrolizumab-induced autoimmune side effects of colon and pancreas in a patient with lung cancer. Clin J Gastroenterol 2021;14:1692–9.
[15] Sun C, Chen H, Wang Y, *et al*. Safety and efficacy of PD-1 and PD-L1 inhibitors in relapsed and refractory Hodgkin's lymphoma: a systematic review and meta-analysis of 20 prospective studies. Hematology 2023;28:2181749.