Successful treatment of chest NUT-carcinoma in a paediatric patient with a novel NUTM1 rearrangement: case report and review of literature

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Abstract

NUT carcinoma (NC) is an exceedingly rare and poorly differentiated carcinoma characterised by BDR4:NUTM1 gene translocation. It typically affects young adults, and due to its dismal clinical course, standardized therapeutic recommendations are lacking. In this study, we present a successful multimodal treatment approach for a 13-year-old boy diagnosed with primary chest NC harboring a novel NUTM1 rearrangement, achieving complete continuous remission 21 months after diagnosis.

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Short running title: Successful treatment in a paediatric thoracic NUT-Carcinoma

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Abstract

NUT carcinoma (NC) is an exceedingly rare and poorly differentiated carcinoma characterised by BDR4:NUTM1 gene translocation. It typically affects young adults, and due to its dismal clinical course, standardized therapeutic recommendations are lacking. In this study, we present a successful multimodal treatment approach for a 13-year-old boy diagnosed with primary chest NC harboring a novel NUTM1 rearrangement, achieving complete continuous remission 21 months after diagnosis.
Introduction

Nuclear protein of the testis (NUT) carcinoma (NC) is a recently described aggressive malignancy. In a recent survey, the estimated incidence of NC was stated around 0.41 per million children from 0 to 16 years of age, but the true incidence remains unknown due to histological overlap with other neoplasms. NC was originally named as “midline carcinoma” because of its propensity to arise in the midline structures but it can be found in various organs and the primary tumour is strictly laterализed in two third of patients. Both male and female are equally affected and it can occur at any age but it mainly affects young adults (median age 23 years). No aetiology or risk factors have been found and no correlation with environmental, viral or genetic factors is demonstrated. The most common histological description of NC is a poorly differentiated or undifferentiated carcinoma with focal squamous differentiation; high grade features are classically present. Similarly, the immunophenotypic profile of NC is nonspecific although immunolabeling using anti-NUT antibodies provides a highly accurate test to guide the diagnosis. Fish analysis identifying NUT translocation is a useful diagnostic tool, but may generate a false-negative result, alternatively NGS panels may be used. The chromosomal translocation t(15;19)(q14;p13.1) resulting in NUTM1 :: BRD4 fusion is detected in more than 75% of cases, other partner genes include BRD3 (9q34.2; ~15% of cases), ZNF532 (8p11.23; ~5%), ZNF592 or unidentified genes (~5%). NC exhibits an aggressive behaviour and usually presents either with regional lymph nodes involvement and/or metastatic dissemination. While surgery and radiotherapy (RT) are proven to be beneficial, the impact of chemotherapy (CT) on survival remains to be determined and the prognosis of NCs still remain dismal. In this report we present a case of a patient with a primary voluminous thoracic NC carrying a novel NSMCE2 - NUTM1 gene fusion in frame, who achieved complete remission with aggressive local treatment and systemic chemotherapy.

Case description

A 13 years old male was admitted with a hard, not painful bulging lesion of the anterior chest wall. The gadolinium-enhanced magnetic resonance imaging showed a 65x40x30 mm non-homogeneous, partially cystic, mildly enhancing with high T2 signal mass, located between the first and second left intercostal space with no apparent invasion of the pleural space (Fig.1). DWI sequences demonstrated restricted diffusion and low ADC values. Whole-body PET-CT scan depicted avid FDG uptake in the primary chest lesion (SUV max. 7.2) and in some homolateral axillary lymph nodes (SUV max. 3.7). The patient underwent a tru-cut biopsy, and histological examination revealed a solid tumour composed of epithelioid cells, with cosinophilic cytoplasm and medium-sized pleomorphic nuclei. A brisk inflammatory infiltrate was also seen. Small aggregates of foamy histiocytes were scattered within the neoplasm. Immunohistochemical analysis showed a focal and weak nuclear positivity for NUT in more than 50% of neoplastic cells. high Ki67 expression (40%), and focal expression for p63, CD34, CKAE1/AE3 and pancytokeratin MNF116. INI-1 and BRG1 nuclear expression was preserved. All other immunohistochemical markers, were negative. FISH resulted negative for BRD4-NUTM1 transcript. Archer FusionPlex-targeted RNA sequencing analysis performed on paraffin-embedded material detected a novel fusion between NSMCE2 gene exon 5 at chr8:126194468 (NM_173685.2) and NUTM1 gene exon 6 at chr15:34646647 (NM_175741.2) (Fig.2). A primary en-bloc anterior chest wall resection was carried-out, comprising the first and second ribs with intercostal muscles, major and minor pectoralis muscles, the skin and subcutaneous tissue over the mass along with left axillary lymphadenectomy. The chest wall was then reconstructed in the same surgical setting: the bone surface was replaced by a titanium plate, fixed with screws on the sternum and lateral portion of the residual second rib, and a synthetic (polypropylene) mesh was placed over the plate to guarantee a base for the soft tissue reconstruction. An antero-lateral thigh musculo-cutaneous flap was harvested and placed over the defect with vascular microanastomoses to the left mammary vessels. Histological examination confirmed margins free resection (R0) and absence of tumour in any of the lymph nodes removed. 5 weeks later, the patient received RT (61.2 Gy/35 Fr) on the tumour bed with volumetric modulated arc technique (VMAT). Chemotherapy was administrated according to the Scandinavian Sarcoma Group “SSG IX” protocol, and consisted of seven cycles of VAI (V - vincristine at a dose of 1.5 mg/sqm on day 1; A - doxorubicin at a dose of 30 mg/sqm on day 1 and 2; I - ifosfamide at a dose of 1000 mg/sqm/day for 5 days), alternated with four cycles of PAI (P - cisplatin at a dose of 90 mg/sqm on day 1; A - doxorubicin at a dose of 30 mg/sqm on day 1; I - ifosfamide at
a dose of 1000 mg/sqm/day for 5 days). Cycles were repeated every 21 days. The total dose of doxorubicin was capped at 450 mg/m², to avoid cardiotoxicity. No major or unexpected toxicities were recorded during the treatment plan. The patient is alive in CR at 21 months from diagnosis.

Discussion

According to a survey conducted in 2020 on 124 patients registered in the “NUT midline carcinoma Registry”, the median overall survival (OS) is of 6.5 months and no patient with thoracic primary NC had long-term survival. Adverse prognostic factors include age at diagnosis >18 years, primary thoracic location, presence of regional lymph node involvement (N >0), distant metastasis (M >0), low response to first-line treatments, lack of margin-free surgery and a primary tumor size >5 cm, as well as the BRD4-NUTM1 genotypic variant. Despite early resection significantly improves the progression-free survival, long-term survival remains dismal. In a retrospective analysis of 119 patients the 1 year overall survival for those who underwent surgery as primary treatment versus those who did not received surgery was 33.88% and 19.7% respectively, while the 5 year OS was <5% for both groups. Moreover, upfront R0 surgery appears to be curative only in patients with non-thoracic NC. Similarly, radiation doses between 50-70 Gy provide a significant improvement in 1 year OS (37.7% versus 13%) but 5 years OS remains unsatisfactory (11% versus 0%). Regarding adjuvant chemotherapy, our patient received an Ewing sarcoma-like regimen, but its contribution to the outcome remains uncertain. NC is usually refractory to conventional drugs or rapidly develops resistance to them. CT should be considered as a first-line treatment only for metastatic or unresectable tumours, long-term control with CT alone is described anecdotally and there is no consensus about the optimal schedule. Despite a high lymphocyte infiltration rate in the tumour sample suggesting the potential for add-on immunotherapy, the use of PD-1 inhibitors (nivolumab, pembrolizumab) or PD-L1 inhibitor (atezolizumab) is currently reserved for patients with relapsed or refractory tumors. Similarly, phase I/II trials with histone deacetylase (HDAC) or bromodomain (BRD) inhibitors have been conducted, but the efficacy of a single-agent approach remains limited and drug toxicity along with the acquisition of resistance are the main concerns. Our experience demonstrates that at least some patients with thoracic NC may achieve long-term survival. We remark the fundamental role of local treatment in localized disease, which includes demolitive surgery to reach a margin-free resection as well ad high-dose RT with VMAT, that has been proven to be highly efficient while providing increased organs at risk sparing and reduced toxicity. Moreover we first describe a novel NSMCE2-NUTM1 gene fusion; this fusion has never been reported in series of NUT-carcinoma previously. Knockdown of NSMCE2 induces chromosomal instability and increases the frequency of chromosomal breakage and loss. Although genotypic-prognostic correlation remains unclear, our observation seems to confirm that the typical BRD4-NUTM1 genotypic variant exerts a worse prognosis than others; hence determining NUTM1 fusion partners may be relevant in clinical, therapeutic and prognostic decision making.

Conflict of Interest statement

The authors declare they have no conflicts of interest.

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References


Legend listFigure 1 Figure 2