**NUT midline carcinoma: Two case reports and review of the literature**

Nadia Abazid¹, Johannes Friemann², Heiko Alfke³, Reinhard Büttner¹, Nicolaus Friedrichs¹*

¹ Institute of Pathology, University of Cologne Medical School, Cologne, Germany ² Institute of Pathology, Klinikum Lüdenscheid, Lüdenscheid, Germany ³ Klinik für Diagnostische und Interventionelle Radiologie, Klinikum Lüdenscheid, Lüdenscheid, Germany

**Abstract**

NUT midline carcinoma is a rare epithelial cancer characterized by a simple karyotype with a single abnormality: the translocation t(15;19)(q14;p13.1). In this way it resembles fusion gene-driven leukemias, sarcomas, and a small subset of other carcinomas. These tumors occur throughout life and in most cases are accompanied by distant metastases at the time of diagnosis. There is so far no effective treatment for NUT midline carcinoma; therefore, the international, Web-based NMC Registry (www.nmcregistry.org) was recently established for this cancer. The registry provides access to treatment guidelines based on the experiences of oncologists, and gives patients the opportunity to participate in clinical trials. He were present two case reports, and a review of the definition, clinicopathologic features, genetics, pathogenesis, diagnostic criteria and therapeutic treatment of this aggressive tumor.

**Citation:** Abazid N, Friemann J, Alfke H, Büttner R, Friedrichs N (2016) NUT midline carcinoma: Two case reports and review of the literature. Adv Rare Dis 3:1. doi:10.12715/ard.2014.3.1

**Received:** November 30, 2015; **Accepted:** March 22, 2016; **Published:** July 14, 2016

**Copyright:** © 2016 Abazid et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

* Email: nicolaus.friedrichs@uk-koeln.de

**Introduction**

*Definition and clinicopathologic features of NUT midline carcinoma*

NUT midline carcinoma (NMC) is a very rare, aggressive, genetically defined human cancer (1). It is considered to be a subtype of squamous cell carcinoma that is defined by chromosomal rearrangement of the nuclear protein in testis gene (NUT; also known as NUTM1). This is most commonly fused to the gene for bromodomain-containing protein 3 (BRD3) or 4 (BRD4); members of the bromodomain and extra terminal (BET) family of chromatin readers. In most cases, the NUT gene on chromosome 15 is fused to the BRD4 gene on chromosome 19 (2), resulting in a reciprocal translocation t(15;19) (q14;p13.1) (3).

Most epithelial malignant tumors are characterized by multiple sequential mutations that lead to a multistep carcinogenesis pathway. In contrast, some mesenchymal and hematopoietic cancers are driven by translocation-associated, oncogenic fusion proteins leading to blockage of differentiation (4). Epithelial cancers that are accompanied by chromosomal translocations are uncommon, but they are important to diagnose: ALK-fusion or ROS1-fusion-driven lung adenocarcinomas are examples. Epithelial malignancies that have recently been associated with chromosomal translocations and gene fusions include renal cell carcinomas (5), papillary thyroid carcinomas (6), mucoepidermoid carcinomas of the parotid gland (7), and nearly 50% of prostatic adenocarcinomas (8). NUT midline carcinoma is one further example of an epithelial cancer driven by a fusion oncogene (4).

The first two cases of NMC were described in 1991 (9, 10). These two cases involved the thorax and the mediastinum and were considered to be thymic in origin. They both harbored the translocation t(15;19). Since then, fewer than 100 cases of NMC have been reported (3).
NMC ranges from carcinoma with prominent squamous differentiation to entirely undifferentiated carcinoma composed of sheets of undifferentiated cells (11). It is considered to be an “orphan disease” because it is not only rare, it also has no clear organ or tissue of origin (2). It can occur anywhere along the trunk or the head, but characteristically locates to the midline, with typical sites being the upper aerodigestive tract (UADT; in 50% of cases) and the mediastinum (41%) (12). Nevertheless, cases have been described arising in the bladder (13), pancreas (14), salivary glands (15, 16), orbit (17), lung (18), iliac bone (19), and the gynecologic organs (20), challenging the concept that this is a strictly midline neoplasm. A recent study (21), which identified 38 published cases of primary intrathoracic NMC, showed that only 14 of these cases were localized in the mediastinum, while 19 cases were suggestive of pulmonary origin, another 2 cases were derived from the thymus, and 3 cases were reported to be intrathoracic. These observations suggest that NMC may arise from early epithelial stem cells that increase in number during the first decades of life. The fact that NMC shows CD34 reactivity – a marker known to be associated with hematopoietic stem cells, some epithelial cell precursors, vascular endothelium, and soft tissue tumors – might also support this hypothesis (13). Another hypothesis, which is yet to be confirmed, is that NMC arises from primitive neural crest-derived cells (22, 23).

It is important to recognize NMCs from both a prognostic and a therapeutic perspective (24). However, NMC is a newly described disease; it is often under-diagnosed because few pathologists know about it. Sometimes, NMC may be misclassified as Ewing’s sarcoma, sinonasal undifferentiated carcinoma (SNUC), or as squamous cell carcinoma arising most often in the aerodigestive tract (1, 2). The sinonasal tract is considered a favorable site for the occurrence of NMC, but until 2012 there were just 10 documented cases of sinonasal NMCs (24). Nevertheless, an early study using fluorescence in situ hybridization (FISH) found that 20% of pathology specimens of undifferentiated carcinomas of the upper aerodigestive tract (UCUAT) not associated with Epstein–Barr virus (EBV) infection had NUT rearrangements, consistent with the diagnosis of NUT carcinoma (25). Thus, the true incidence of NMC is currently unknown.

It was originally thought that NUT fusion-positive midline carcinomas affected only younger patients (children and young adults under the age of 30), based on the increased likelihood that tumors from younger patients are analyzed for cytogenetic abnormalities. A 2012 study (26), which assessed the largest cohort of NMC patients studied to that date (n: 63), showed that NMCs can occur at any age from birth to the eighth decade (range 0.1–78 years) (3, 26), with a median age of 16 years and affecting males and females equally (3, 26). Another study that was not restricted to children and young adults showed that the average age of patients with NMC was 47 years (25). However, in a 2014 study that assessed clinicopathologic variables from 40 patients with NMC of the head and neck (HN; the largest cohort of HN NMC studied to that date) the median age of occurrence was 21.9 years (range 0.1–81.7 years) with a male: female ratio of 45:55% (27).

The average survival time of NMC is 6.7 months (range 0.7 months to 19+ years) (3, 26), despite aggressive chemotherapy and radiation treatment. Thus, NUT midline carcinoma is considered to be more aggressive than typical squamous cell carcinomas or small cell lung carcinoma (which has a median survival time of 14–20 months).

**Genetics and pathogenesis**

The development of NMC requires a single alteration in the *NUT* gene; the translocation t(15;19). This explains why NMC occurs more frequently in children and neonates (14). The fact that, unlike squamous cell carcinoma, NMC never arises from in situ lesions also supports the idea of a stem cell-like origin (2).

In approximately 70% of cases, *NUT* (15q14) is fused to *BRD4* (19p13.1), resulting in a *BRD4-NUT* fusion gene (3). In the remaining 30% of cases, *NUT*-variant tumors arise from fusion of the *NUT* gene to another partner gene such as *BRD3*, *NSD3* (8p 11.23), or other uncharacterized genes (1, 28).

Some studies suggest that patients with *NUT*-variant NMCs may have a longer survival time than patients...
with BRD4-NUT carcinomas. One study from 2004 (13) showed that the average survival for NUT-variant carcinomas was 96 weeks, which was longer than for BRD4-NUT carcinomas (28 weeks). Moreover, clearly squamous differentiation was detectable in the NUT-variant cases (13). However, more recent studies have shown that squamous differentiation is commonly seen in NMCs, does not necessarily predict the NUT partner gene (22), and that the type of translocation is not prognostic of the median overall survival for patients with NMC (26).

NUT encodes an unstructured polypeptide (NUT) expressed only in brain and post-meiotic spermatids. Its function remains equivocal (1, 29). It has been suggested that the normal function of NUT is to increase histone acetylation by binding to and activating p300 histone acetyltransferase (28).

Furthermore, BRD4 binds acetylated histones, which are associated with actively transcribed DNA. It marks regions for the re-initiation of transcription following mitosis and so functions as a preserver of cellular memory (1).

The mechanisms by which BRD4-NUT causes NMC progression remain uncertain (30). BRD4, and possibly NUT, are involved in chromatin modification, suggesting that the fusion protein BRD4-NUT may somehow regulate chromatin so as to suppress the expression of genes required for epithelial maturation and squamous differentiation (1, 28). Thus, BRD4-NUT may block cellular differentiation and promote proliferation of carcinoma cells, making it a potential therapeutic target (1).

A study from 2014 (4) has described a NUT-variant NMC with a novel gene fusion between the gene for methyltransferase (NSD3), and NUT. The fusion oncogene NSD3-NUT was found to be both necessary and sufficient for the blockage of differentiation and maintenance of proliferation in NMC cells. Furthermore, NSD3 is necessary for the blockage of differentiation in BRD4-NUT NMCs so is another potential therapeutic target (4).

NMCs with a translocation involving three chromosomes are also rare, though an example is an invasive hypopharyngeal NMC in a 23-year-old male (28). Pathologic evaluation showed a three-way translocation resulting in the novel karyotype 46XY, t(9;15;19; q34;q13;p13.1) (28).

As previously mentioned, BRD4-NUT acts by suppressing the differentiation of NMC precursor cells. This action depends on both the expression of MYC and the repression of histone acetylation (2). One study (30) showed that the set of genes whose expression is maintained by BRD4-NUT is highly enriched for MYC-upregulated genes. However, further molecular studies are needed to determine whether the regulation of MYC by BRD4-NUT is direct or indirect (2).

In another study from 2014 (31), it was discovered that NMC cells express a high level of SOX2, a stem cell marker, and they have the ability to transform into stem cell-like spheres and proliferate. The abnormal activation of SOX2 in NMC cells requires the BRD4-NUT fusion oncogene. This study has identified SOX2 as a novel target of BRD4-NUT that drives stem cell-like proliferation and cellular transformation, and supports the highly aggressive phenotype of NMC (31).

**Diagnosis**

NMC usually spreads by local invasion, and by lymphatic and hematogenous metastasis (3). Most patients present at an advanced stage of NMC with pleural invasion, lymph node metastases, and distant metastases, usually in the bones (3). Tumors are not typically surgically resectable, and, as a result, the gross pathological features of NMC are not well described (11, 22). Patients usually present with mass-related symptoms from the primary tumor, or the metastases, such as pleuritic chest pain, a non-productive cough and shortness of breath (3), as well as non-specific symptoms such as fever and weight loss (11, 29).

The histologic features are also not diagnostic of NMC. The most common morphology is that of sheets of poorly differentiated cells, occasionally arranged in nests within a desmoplastic stroma (11, 22). Tumor cells show scant basophilic or pale eosinophilic cytoplasm, irregular nuclei with slightly coarse chromatin, and small nucleoli (3). They are usually round, small-to-medium sized and monomorphic (3, 32). The monoclonal appearance of
NMC cells is a distinctive characteristic that helps by distinguishing NMC from other poorly differentiated carcinomas, which consist mostly of highly pleomorphic large cells (32). Focal squamous differentiation is frequently seen (22, 33). Another characteristic finding, which is rarely seen in carcinomas other than NMC, is the abrupt appearance of squamous differentiation, which lacks stratification and gradual differentiation (3, 22). Other histologic features commonly seen in NMC are coagulative necrosis, cystic formation, mitotic figures, and apoptotic bodies (11). Chondroid differentiation has also been described in one case of NMC arising in the parotid gland (16).

The immunoprofile of NMC resembles that of some other epithelial tumors. Immunohistochemical antibodies against cytokeratin (CK) were found to be positive in NMC (13, 22). Most tumors are immunoreactive with antibodies to pan-cytokeratin (3), CK7, and sometimes focally to CK20 (11, 13). P63/p40 immunoreactivity is mostly present, which exists with squamous differentiation (3, 11), and CD34 immunoreactivity has also been reported in a study of NMC in children and young adults (13). NMC sometimes stains for synaptophysin, chromogranin and TTF1 (3), but shows no immunoreactivity with other markers expressed in muscles (smooth muscle actin, desmin, myoglobin), or melanocytic tumors (HMB45, S100 protein) (33). NMCs also do not react with antibodies to leukocyte common antigen (LCA), neuron-specific enolase, placental alkaline phosphatase, alpha-fetoprotein, CD99, or CD57 (22).

As a result, diagnosis of NMC based only on clinical and morphological features, and conventional immunohistochemistry, is difficult. It is frequently under-diagnosed. Other reasons for under-diagnosis include the absence of an easily accessible diagnostic test, other than molecular genetic analysis (24, 32). Furthermore, many physicians do not include NMC in their differential diagnosis of poorly differentiated carcinomas in adult patients (32).

Differential diagnosis for NMC includes any poorly differentiated monomorphic neoplasm including poorly differentiated squamous cell carcinoma, sinonasal undifferentiated carcinoma, small cell carcinoma (3), small round blue cell tumors such as Ewing’s or primitive neuroectodermal tumor (PNET) (34), rhabdomyosarcoma, neuroblastoma (35), melanoma, acute leukemia (3), endocrine tumors, pancreatoblastoma (14), salivary gland carcinoma (16), and thymic carcinoma (36).

Analysis by immunohistochemistry, in situ hybridization, and the polymerase chain reaction (PCR) has shown that NMCs do not harbor EBV or human papillomavirus (HPV) infections (22, 28). Therefore, the association of one of these viruses with a poorly differentiated carcinoma virtually excludes NMC from the differential diagnosis (11).

To ensure NMC is not missed, it should be considered in the differential diagnosis for any poorly differentiated non-cutaneous carcinoma showing no glandular differentiation (2), and in any poorly differentiated squamous cell carcinoma in a non-smoking patient (22): a history of smoking makes the diagnosis of NMC highly unlikely (32). Traditionally, a definitive diagnosis of NMC has been made using FISH or reverse transcription PCR (RT-PCR) to demonstrate the NUT translocation (1, 33). RT-PCR detects only BRD3-NUT or BRD4-NUT tumors, while dual-color, break-apart FISH can detect all NMCs including NUT-variants. Therefore, FISH is much preferred for the practical diagnosis of NMC (1, 22). However, FISH and RT-PCR are not available in many diagnostic laboratories, so a specific and reliable diagnostic test is needed (37).

Based on the fact that NUT is only normally expressed in the testis and brain, and that it has never been identified in non-germ cell tumors other than NMC, a sensitive and specific monoclonal antibody to the NUT fusion protein (clone C52) was developed in 2009 (37). In this study, a panel of 1000 carcinomas including 30 FISH-positive cases of NMC, were immunohistochemically stained with the anti-NUT antibody. Nuclear reactivity was found to be 100% specific and 87% sensitive for the diagnosis of NMC, and the negative and positive predictive values were 99% and 100%, respectively (37). Nuclear staining with C52 in NMC appears to be diffuse (≥ 50% of nuclei) and speckled, unlike in germ cell tumors (such as germinoma and embryonal carcinoma) (3), which display focal (< 5%) and smooth nuclear staining (37). This antibody is used
currently as a first-line test for the routine diagnosis of NMC.

Although diagnosis of NMC was made easier by the development of C52, a remaining challenge is to determine the appropriate time to perform the immunohistochemical test. Guidelines recommend to test for NUT expression in all non-cutaneous, poorly differentiated carcinomas of the head, neck, and chest in a never-smoking patient, with no tumoral glandular differentiation, and without the tumoral presence of carcinoma-related viruses such as EBV and HPV (2, 25). Diagnosis is made if more than 50% nuclear staining is demonstrated with anti-NUT antibody in analyzed carcinoma cells (37). If NUT staining is negative yet it is highly suspected that the tumor is indeed an NMC, FISH should be used to investigate the presence of NUT rearrangements (37).

The simplicity of this test, and the availability of C52 in many laboratories, means we would expect an increase in the diagnosis of NMC worldwide. As a result, the frequency of NMC could be more accurately measured within the next few years (1).

Case Reports

Ethical approval to use patient tissue was granted by the University of Cologne Ethics Committee (approval No. 13091). Patients treated in the Center for Integrated Oncology in Cologne consent and donate their materials for scientific purposes. The consent form has been approved by the Ethics Committee of the Medical Faculty ("BioMaSoTa - 091-2013").

Case report 1

A 17-year-old non-smoking female presented with a 1-year history of an undifferentiated squamous cell carcinoma of the right lung. The tumor was exophytic, located < 2 cm from the main carina, and was accompanied by cervical lymphadenopathy. It tested positive for CK5/6 and Bcl-2, and negative for HPV. Since the tumor was considered non-resectable, the patient was considered for neoadjuvant chemotherapy with four cycles of cisplatin (50 mg/m²) and vinorelbin (30 mg/m²), as well as radiotherapy (40 Gy) beginning with the third cycle, followed by restaging and reassessment of resectability. The first therapeutic cycle was interrupted by the progression of right basal thoracic pain and shortness of breath, diagnosed as vertebral invasion. On physical examination at admission, the patient was found to be in poor general condition, with loss of appetite without weight loss, and exertional dyspnea. Auscultation revealed attenuated right basal breath sounds, and percussion revealed right basal dullness. Thoracic vertebrae in the area of T7 were painful to percussion. Laboratory findings showed elevated infectious markers and leukopenia. Later, during her hospital stay, the patient suffered from multiple episodes of fever and chills, and was successfully treated with antibiotics.

Ultrasonography of the chest and abdomen showed a pleural effusion with right atelectasis. Histological examination of pleural aspirate showed mainly macrophages and reactive mesothelial cells with some lymphocytes and neutrophils, and no indication of malignancy. A computed tomography (CT) scan of the chest revealed a restricted mass caused by the tumor located in the right lung. Nevertheless, alveolar compression was noted in the right middle lobe, representing a pneumonic infiltration. CT showed marked osteolysis of the spinal column on the right lateral dorsal side, and in the right peduncle of T7, with invasion of the tumor to the right intervertebral foramen causing thoracic pain.

Initial histopathology of a bronchial biopsy revealed an advance-stage undifferentiated squamous cell carcinoma. TNM classification was cT4, cN2, Mx. Paraffin blocks were sent to our institute for immunohistochemical and molecular pathological confirmation. FISH revealed no gene amplification of FGFR1 in tumor cells, nor any evidence of the translocation of ALK, ROS1, or RET genes. Immunohistochemical analysis revealed weak, incomplete perinuclear staining for CK5/6, and no LCA or CD20 immunoreactivity. Tumor cells had speckled nuclear staining for NUT1, therefore the diagnosis of NUT midline carcinoma was made. The patient passed away shortly after the diagnosis.
Case report 2

A 22-year-old male smoker presented with left thoracic pain of several months duration, and progressive dysphagia over the past few weeks. At the time of admission, the patient suffered from pronounced dysphagia located in the neck and upper pharynx. On physical examination the patient was found to be in poor general condition, and auscultation revealed attenuated breath sounds on both sides. Esophageal manometry revealed high pressure in the area of the aortic arch. A chest CT scan revealed a heterogeneous central mass, located in the left hilum measuring 10.2 x 8.9 x 7.5 cm (Fig. 1A). The tumor extended along the ipsilateral bronchovascular tree (Fig. 1B) and reached the contralateral right hilum. It caused partial compression on the left pulmonary artery, the wall of the descending aorta (Fig. 1A), and the left lower bronchus. Other suspected nodules (Fig. 1B) measuring 4 mm across were identified in the left first, second and third segments; 7 mm across in the left sixth segment; and 5 mm across in the right eighth segment. Multiple subcarinal lymph nodes were also identified. CT also revealed minor pleural effusion and possible invasion into the esophagus. A CT scan of the abdomen showed hepatomegaly and splenomegaly, and a suspected hypodense lesion measuring 20 mm across in the eighth segment of the liver. Multiple enlarged retroperitoneal and mesenteric lymph nodes were also identified. Bone scan revealed no skeletal metastasis.

**Figure 1.** Contrast-enhanced computed tomography of Case 2

The reconstructed soft tissue window (Panel A) shows a mass lesion in the midline with encasement of the descending aorta and the left pulmonary hilar structures. Tumor density is relatively low, indicating poor vascularity. Panel B shows extensive peribronchovascular tumor spread towards the caudal end of the lung window ( Lexer) as well as some intrapulmonary nodules (*). Enlarged lymph nodes in the upper abdomen were also depicted (not shown).
Clinical differential diagnoses included lymphoma and lung carcinoma (TNM: cT4 cN3 cM1a). Biopsies of the gastroesophageal junction showed only reactive acanthosis, and chronic inflammation caused by reflux disease. Bronchial endoscopy revealed an indirect sign of a tumor in the left main bronchus, as well as an external compression of the right main bronchus. Histologic analysis of tissue samples revealed infiltration of small monomorphic tumor cells with irregular nuclei and coarse chromatin (Fig. 2A). Again, histologic differential diagnoses included lymphoma and neuroendocrine tumors. Immunohistochemical staining (Fig. 2B–G) revealed tumor cells that were strongly positive for CK7, positive for CK5/6 and P63, and variably positive for chromogranin. They showed also a dot-like immunostain pattern for epithelial membrane antigen (EMA), and some isolated tumor cells were positive for CD15. Tumor cells showed no immunoreactivity with TTF1, CD56, or LCA, which excluded lymphoma and small cell carcinoma of the lung from differential diagnosis. They were also negative for 1A4-actin, vimentin, desmin, non-specific esterase (NSE), and WT1. Immunohistochemistry for Ki67 revealed a mitotic rate of 20–30%. NUT1 immunohistochemistry revealed strong, diffuse, speckled, nuclear staining, and the patient was diagnosed with a NUT midline carcinoma.

Therapy and clinical trials

No effective treatment for NMC has so far been established. Most cases are inoperable, and receive a combination of radiotherapy and multidrug chemotherapy. Many patients show an initial response to chemotherapy regimens used to treat germ cell tumors, head and neck squamous cell carcinoma, small cell carcinoma of the lung, and sarcoma, but overall outcomes for these patients remain very poor (26). Bauer and colleagues summarized the long-term follow-up of 54 NMC patients in the largest cohort studied to date (26). Analysis of these patients suggested that gross total resection and initial treatment with radiotherapy are independent predictors of prolonged survival (both progression-free survival [PFS] and overall survival [OS]).

They showed also that clinical responses to therapy were not significantly correlated with sex, tumor location, translocation type, tumor histology, or lymph node involvement. However, complete response was positively associated with the absence of metastases (3, 26).

Although NMC does not usually respond to standard therapeutic protocols, there is one known long-term
survivor, who was treated with a chemotherapeutic regimen designed to treat Ewing’s sarcoma. This 10-year-old patient presented with a BRD4-NUT-positive NUT midline carcinoma of the iliac bone, which was originally diagnosed as Ewing’s sarcoma lacking features of carcinoma. He received combined modality therapy according to the Scandinavian Sarcoma Group (SSG) IX protocol for inoperable Ewing’s sarcoma, and remained in complete continuous remission for about 13 years (19). The second longest known survivor is a 16-year-old boy, who was treated with complete surgical resection of mediastinal NMC followed by adjuvant cisplatin and docetaxel with radiation therapy; he showed no evidence of recurrence 34 months after diagnosis (38). Another two mediastinal NMC cases described in the literature showed encouraging initial responses to docetaxel (39), and to carboplatin with paclitaxel (40), suggesting that the use of these chemotherapeutic regimens with surgical resection and radiotherapy might be considered in treating locally advanced NMC of the mediastinum.

The reduced effectiveness of conventional chemotherapy means there is an urgent need for the development of targeted therapeutics. The existence of a consistent chromosomal translocation t(15;19), and the BRD-NUT fusion proteins, may provide targets for biological therapeutic agents. BRD-NUT fusion proteins contribute to the pathogenesis of NMC by blocking differentiation, which depends on the repression of histone acetylation, and the deregulation of MYC transcription. Consequently, knocking down BRD4-NUT or BRD3-NUT by small interfering RNA (siRNA) has been shown to induce rapid squamous differentiation accompanied by arrest of proliferation (41). These findings highlight that targeting these proteins might offer a “differentiation therapy” (32, 41).

The globally decreased histone acetylation induced by the expression of BRD4-NUT can be reversed with histone deacetylase inhibitors (HDACi) – a promising means of targeted therapy – engaging a program of squamous differentiation and arrested proliferation both in vitro and in vivo (32, 41). These results closely mimic the effect of the siRNA-mediated knockdown of BRD4-NUT expression (41). There are currently two HDACi reagents approved by the US Food and Drug Administration (FDA): vorinostat and romidepsin. Based on the results of studies performed with patient-derived primary tumor cells, a 10-year-old child with mediastinal NMC invading the left atrium and pulmonary vein was treated with vorinostat. An objective response was obtained after 5 weeks of vorinostat therapy as a single agent, as assessed by positron emission tomography (PET). Unfortunately, the patient suffered from marked thrombocytopenia and intolerable severe nausea and emesis, which led to vorinostat withdrawal followed by recurrence of the tumor. The patient died 11 months after initial diagnosis (32, 41). Differentiation therapy with HDACi is being now tested in patients with NMC. One Phase 2 clinical trial investigating a dual PI3 kinase/HDAC inhibitor drug, CUDC-907, has been shown to have potent activity against cultured NMC cells (ClinicalTrials.gov identifiers: NCT02307240).

Another type of targeted differentiation therapy currently under investigation is the use of small molecule BET inhibitors (BETi). These inhibitors bind competitively to the acetyl-histone binding pocket of BET-family protein bromodomains, leading to the dissociation of BRD4–NUT from the MYC promoter (2, 42). This causes dissolution of BRD4-NUT nuclear speckles and loss of MYC transcription, resulting in rapid squamous cell differentiation and growth arrest of NMC cells, both in vitro and in mice (32, 42). However, the toxicity of BET inhibitors is as yet unknown; they also inhibit the acetyl-histone binding of native BRD4 and BRD3 proteins, which reserve cellular memory (41). There are two recruiting Phase I clinical trials investigating the use of BETis for treating NMC, and other cancers expressing normal BRD4 (ClinicalTrials.gov identifiers: NCT01587703 and NCT01987362).

The most specific targeted therapy for NMC would be directed against NUT, because it is not widely expressed outside the testes or ovaries (23). This requires the development of NUT-directed inhibitors. It is also important to determine the effects of combined HDACi and BETi therapy. As in many other cancers, combination therapies may be essential for the treatment of NMC (32).

However, further questions must be answered to fully understand the pathogenesis and potential genomic vulnerability of NMC. It is hoped that these clinical
trials will help to answer these questions, as well as providing general guidelines on how to treat this tumor.

References

Advances in Rare Diseases


