Case Report

Hilar/endobronchial NUT midline carcinoma: A case report

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A B S T R A C T

Nuclear protein of the testis (NUT) midline carcinoma (NMC) is a rare aggressive tumor described in the midline in the chest and head and neck. Initially reported in younger individuals, it has subsequently been shown to have a wider age distribution. The defining feature of these tumors is its association with BRD-NUT rearrangements. Occasionally NMC has been observed in a non-midline location. This case report describes an unusual rapidly progressing non-midline hilar/endobronchial location of an NMC in a 34-year-old man. The clinical and histologic features were that of an undifferentiated neoplasm concerning for a small cell carcinoma or a lymphoma. A broad panel of immunohistochemical markers for carcinoma, lymphoma and melanoma were negative which led us to suspect a diagnosis of NMC. A positive immunostaining with p63 and NUT protein antigen confirmed the diagnosis. The p63 positivity and cytokeratin negativity suggest a primitive/precursor squamous cell derivation.

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1. Introduction

NUT (nuclear protein in testis) midline carcinoma (NMC) is a recently described aggressive poorly differentiated subtype of squamous cell carcinoma [1–9]. It is one of the few solid tumors with a defining translocation in absence of complex cytogenetic changes commonly associated with squamous cell carcinoma. The defining feature of this tumor is the rearrangement of the NUT gene on chromosome 15. The partner gene in most instances is the BRD4 gene on chromosome 19 resulting in a t(15;19) translocation. In some cases, the partner gene is BRD3 while in other cases it remains unresolved [1]. The diagnosis in most cases is elusive because of its rarity and its ability to mimic common neoplasms such as small cell carcinoma and lymphoma. Its early recognition and consideration by a pathologist are imperative since these are aggressive lesions with a fatal outcome in most instances. This case report describes a very unusual NMC in hilar/endobronchial location with a rapid fatal clinical course that we recently encountered in our consult service.

2. Materials and methods

A 34-year-old man in prior good health presented with sudden onset of exertional dyspnea and interscapular pain of 1-month duration not relieved by acetaminophen. He developed nonproductive cough without high fever and chills 1 week before hospitalization. A chest X-ray at the urgent care center 2 days before admission revealed right lower lobe pneumonia for which he was treated with broad-spectrum antibiotics. The patient had been in good health all his life and denied any childhood or adult illnesses. There was no family history of chronic pulmonary or cardiac illness and no history of cancer. He did not use tobacco products, rarely drank alcohol and denied use of recreational drugs and risk factors for HIV. He did not have any pets and had not traveled outside of Texas in the recent past. A computed tomography scan of chest (Fig. 1A and B) with administration of contrast documented a large 9 cm mass involving the right main-stem bronchus with post-obstructive pneumonia in right lower lobe and right pleural effusion. This mass encased the right pulmonary artery and vein as well as the esophagus circumferentially and caused compression of superior vena cava. There was bulky mediastinal lymphadenopathy. During bronchoscopy it was noted that the right main-stem bronchus was closed past the level of right upper lobe bronchus. He had an endobronchial lesion in this area with splaying of the carina consistent with lymphadenopathy. Transbronchial lung biopsy and bronchoalveolar fluid were obtained and sent to pathology.

The clinical differential diagnosis considered was primary lung cancer, lymphoma and sarcoma. Following this, staging work up was initiated that demonstrated a probable 2.1 cm left adrenal mass, malignant retroperitoneal lymphadenopathy and probable metastatic lesion at lumbar 5 vertebra. Additionally, a magnetic resonance imaging of his brain after administration of gadolinium revealed metastatic lesions involving the right posterior frontal and anterior parietal region. The lesion involved the bony cranium and scalp with minimal compression.

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of the underlying cerebral cortex. Despite aggressive supportive treatment, the patient continued to develop progressively worsening hypoxemia, tachypnea and respiratory insufficiency. No specific therapy directed at his presumed malignancy could be initiated due to diagnostic uncertainty. A repeat computed tomography scan of the chest just 4 days later demonstrated complete consolidation and/or collapse of right upper and lower lobes and large right pleural effusion. These findings were significantly worse compared to the initial computed tomography done on the day of admission. His overall prognosis was felt to be grim by the treating physicians and his family opted against chemotherapy. He was terminally extubated on hospital day 10 and expired shortly thereafter.

3. Pathology

The cytology material was referred for consultation to our hospital. The smears were cellular with non-cohesive sheets of small round cells. There was nuclear overlapping and cells had distinct cell borders with a high nuclear:cytoplasmic ratio. Focal rosetting was seen. The nuclei were characterized by dispersed chromatin with conspicuous small 1–2 nucleoli. H&E stained sections of the cell-block (Fig. 2A) showed similar findings of small round blue cells underlying the respiratory mucosa. The cells were in sheets with round to oval small hyperchromatic nuclei with conspicuous nucleoli, lacked molding, and had scant amphiphilic cytoplasm. The morphological differential diagnosis was that of undifferentiated small round blue cell tumor which included lymphoma, melanoma and undifferentiated carcinoma. The non-cohesive pattern of cells with lack of molding and occasional nucleoli was features against a small cell carcinoma. The cells were negative for markers for lymphoma and granulocytic sarcoma including CD45RB (leukocyte common antigen), CD20, CD3, CD25, CD30, kappa, lambda, MUM-1, CD43, terminal deoxynucleotidyl transferase (TDT), CD68, myeloperoxidase and lysozyme. Markers for small cell carcinoma (CD56, synaptophysin and chromogranin) and melanoma (S-100) were also negative. Additionally, all epithelial markers CAM 5.2, cytokeratins 5/6, 7 and 20 were negative. The tumor was highly proliferative on a Ki-67 immunostain.

The cells were strongly immunoreactive for p63 (Fig. 2B). Based on the p63 positivity and the rapid clinical course the possibility of NUT midline carcinoma (NMC) was considered. The case was sent for NUT-antigen (Fig. 2C) immunostain (Propath, Dallas) which was positive in majority of the tumor nuclei in a speckled pattern, confirming the diagnosis.

4. Discussion

This case report illustrates a highly unusual hilar/endobronchial presentation of an NMC. Usually described in midline in the chest, head and
neck, there have been only 3 prior reports of a pulmonary hilar presentation [2,3; Table 1]. All 4 patients, including the current patient were young with the age range of 7–36 years. Two were Japanese and 2 were white. Two patients presented with a mass in the left lower lobe while one with a right hilar mass. Our patient had an endobronchial component in addition to hilar involvement with complete collapse of the right lung. Histopathologically two patients had overt epithelial features with one having bland abrupt keratinization. The other 2 had discohesive cells mimicking a lymphoma. NMCs have been thought to be poorly differentiated primitive subtypes of squamous cell carcinoma based on the p63 positivity and ultrastructural findings [2]. NMCs have been shown to have incomplete intercellular junctions and sparse organelles. After chemotherapy, features of differentiation like basal lamina and more developed intercellular junctions and intracellular organelles were demonstrated.

NMC is a diagnostic challenge to pathologists because it can mimic both a small cell malignancy as well as a large cell malignancy. It may also mimic a lymphoma as well as a carcinoma. In our case the cytology was most helpful in eliminating a small cell carcinoma and lymphoma.

Our case was also a challenge to the clinicians because both age and bulky lymphadenopathy supported a diagnosis of lymphoma, whereas as the presence of metastases to the adrenal gland, brain and bone supported a lung carcinoma. The presence of p63 in the absence of a positive high and low molecular weight cytokeratin was helpful in eliminating a garden-variety squamous cell carcinoma.

These carcinomas are associated with a dismal prognosis with a median survival of 6.7 months and a greater than 80% likelihood of death within the first year of diagnosis [6]. Various therapeutic modalities have been tried, but the most promising relate to the bromodomain containing NUT fusion proteins that result in aberrant histone acetylation and blocking the differentiation. Consequently direct acting inhibitors of BRD3 and BRD4 bromodomains like JQ1 are potential targets for therapy. These have been shown to promote differentiation in tumor cells in research studies [6]. Two phase 1 trials with BET (bromodomain and extra terminal) inhibitors for NMC are currently open [10].

NUT midline carcinomas have clearly been overlooked in the past. To address this issue, Evans et al. examined NUT protein expression retrospectively in 114 cases of poorly differentiated carcinomas or unclassified mediastinal malignancies using a clinically validated NUT-specific monoclonal antibody [11]. Four of 114 (3.5%) cases showed nuclear NUT expression that was confirmed by fluorescence in situ hybridization in 3 of these cases. These cases were initially diagnosed as undifferentiated epithelioid or round cell malignant neoplasm and one case with focal squamous differentiation was reported as poorly differentiated squamous carcinoma of probable thymic origin. NMC should be considered in the differential diagnosis of any poorly differentiated epithelioid mediastinal tumor, regardless of age.

### 5. Conclusion

This case report presents a rare hilar/endobronchial occurrence of NMC in a young adult with a rapid and fatal clinical outcome. A high index of suspicion and awareness of NMC when facing undifferentiated epithelioid or round cell malignant neoplasm and one case with focal squamous differentiation was reported as poorly differentiated squamous carcinoma of probable thymic origin. NMC should be considered in the differential diagnosis of any poorly differentiated epithelioid mediastinal tumor, regardless of age.

### References


