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Case Report

Primary pulmonary NUT midline carcinoma and its diagnostic challenges: A case report

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ABSTRACT

NUT midline carcinoma (NMC) is a rare and aggressive cancer genetically characterized by a chromosomal rearrangement of the NUT gene. Primary pulmonary NMC is even more rare. NMC typically presents with histological features of a poorly differentiated squamous cell carcinoma. We report a case of a 23-year-old female patient with NMC in the lung and pleura presented to a midsize, midwestern Canadian hospital. This article emphasizes the diagnostic challenges posed by NMC and highlights an encounter with this aggressive cancer, which had not previously been diagnosed in our health region.

1. Introduction

NUT midline carcinoma (NMC) is a rare, aggressive, and poorly differentiated cancer. NMC commonly presents in the head, neck, and mediastinum.[1,2] NMCs presenting as primary lung and pleural tumors are extremely rare, with only a few published cases.[3,4] Thus, existing research describing the pathologic, radiologic, and clinical features of primary pulmonary NMC is lacking.[3]

Prognosis of NMC is extremely poor with a mean survival of less than one year.[2,5] NMCs are uncommon, but the true incidence remains unknown as it is morphologically indistinguishable from other poorly differentiated carcinomas.[6] This rare tumor affects people of all ages and develops in males and females without predilection.[6,7] NMC typically arises within midline structures; however, uncommonly, NMCs have been described in non-midline structures.[2,8] We present a case of NMC in the lung and pleura of a 23-year-old female patient. This article describes the pathological and clinical features of primary pulmonary NMC and the diagnostic difficulties encountered with this tumor.

Due to the rarity of the disease, clinical features of NMC have not yet been systematically characterized.[9] Patients commonly present with mass-related symptoms due to the primary tumor.[10] Histologically, the features of NMC are not distinctive. NMC shows various degrees of squamous differentiation with the poorly differentiated component typically predominating.[9] NMC is currently diagnosed using immunohistochemical staining with NUT monoclonal antibody, which is reliable, highly specific (100%), and highly sensitive (87%).[5] Diagnosis of NMC can also be made through detection of NUT gene translocation by fluorescence in situ hybridization (FISH) or reverse transcriptase-polymerase chain reaction (RT-PCR).[11] FISH and RT-PCR tests required for an NMC diagnosis are not universally available, likely contributing to its underdiagnosis. Given its underdiagnosis and frequent misdiagnosis, the true incidence of NMC is unknown.[5,11]

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2. Case Presentation

The Saskatoon Health Region comprises of four major hospitals with an approximate total bed strength of 2,200 and a catchment population of over 330,000 people. In late 2020, the Royal University Hospital in Saskatoon, SK, was presented with a case of a 23-year-old female patient with clinical and radiological features of a malignant tumor in the right lung and pleura. The patient had a history of smoking and reported various chronic complaints, including fatigue, weight loss, headaches, and shortness of breath. A tuberculosis test was performed and was negative.

Radiological examination showed a 6.5 cm mass in the right lobe of the lung extending to the right hilum, multiple other pulmonary nodules, and a moderate right pleural effusion. Additionally, there were multiple bony lesions primarily located in the thoracic vertebrae and a lytic lesion located in her left lateral tenth rib. The patient also presented with a large occipital mass invading into the left parietal bone and extending into the superior sagittal sinus. No midline shift was identified, and the patient had no major neurological issues. The patient was found to be hypercalcemic and had a suppressed parathormone level, which was improved with fluids and bisphosphonates.

The patient underwent a diagnostic pleural biopsy, which was sent for hematopathological review. A lymphoma was excluded and the case was then redirected to the anatomical pathology department. Histological examination of the biopsy showed skeletal muscle infiltrated by a malignant tumor with two histological patterns: sheets of poorly differentiated dark blue epithelial cells interspersed with areas of abrupt transition to well differentiated squamous pearls. The squamous pearls were pale stained and were in stark contrast against the basophilic background of poorly differentiated epithelial cells (Figure 1).

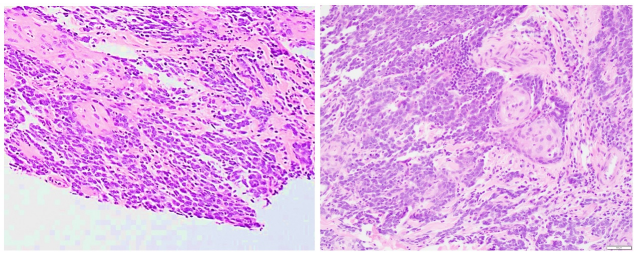

Fig. 1: Hematoxylin and eosin stain showing sheets of basophilic poorly differentiated epithelial cells with an abrupt transition into a well differentiated squamous component. The images are shown at 20x (left) and 40x (right) magnification.

These histologic features were consistent with a poorly differentiated squamous cell carcinoma. Immunohistochemical stains showed the tumor cells to be strongly positive for pankeratin and p40 (Figures 2 and 3).

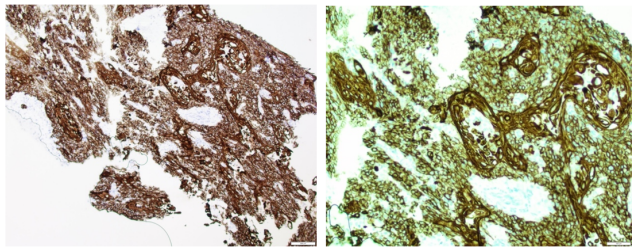

Fig. 2: Pankeratin stain showing strong dark brown cytoplasmic positivity in all components of the tumor cells. The images are shown at 10x (left) and 20x (right) magnification.

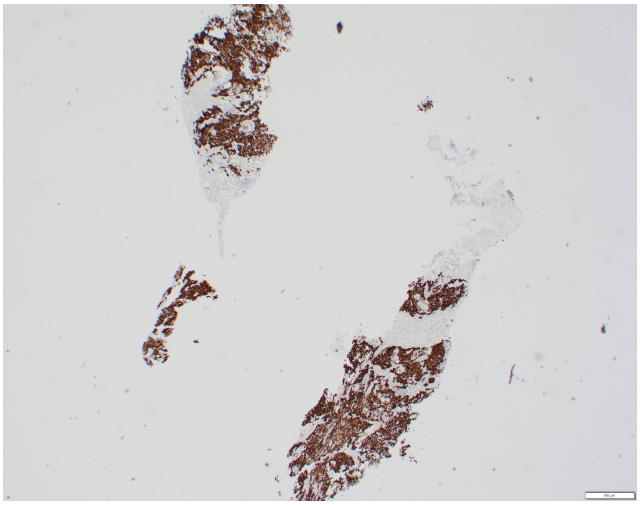

Fig. 3: p40 stain showing strong brown nuclear positivity in all tumor cells. The image is shown at 2x magnification.

Postulating that there might be a primary tumor in the cervix, a p16 immunostain was performed which showed equivocal staining, namely, positive staining only in the squamous pearls and negative staining in the poorly differentiated component (Figure 4).

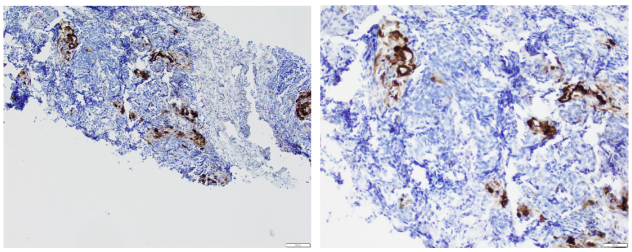

Fig. 4: p16 immunostain showing definitive positivity in the squamous pearls and no staining in the rest of the tumor. The images are shown at 10x (left) and 20x (right) magnification.

Additional immunostains, including CD56, chromogranin, TTF, S100, CD45, CD3, and CD20, were negative. An NTRK immunostain was also performed and was negative (Figure 5).

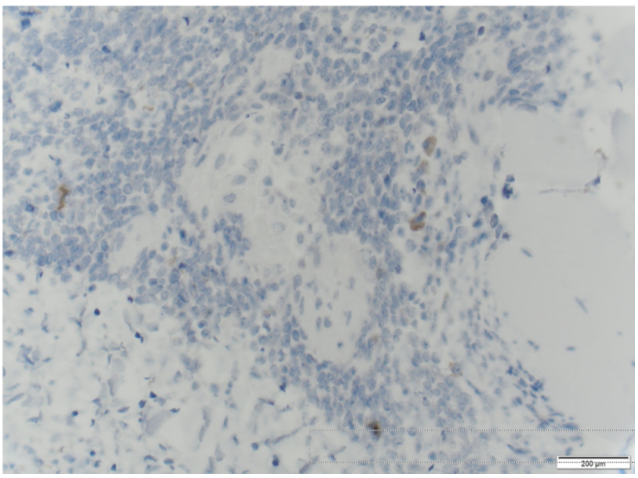

Fig. 5: NTRK immunostain showing a lack of brown positive staining in the poorly differentiated component and the squamous pearls. The image is shown at 20x magnification.

The histological features of this malignant tumor were unusual. However, based on the presence of a poorly differentiated epithelial cell component and squamous pearls, the tumor was diagnosed as a poorly differentiated squamous cell carcinoma. Subsequent internal review and discussion raised the possibility of NMC and, following a search to find a laboratory that could perform a NUT immunostain, the case was sent to the Mayo Clinic in Rochester, Minnesota, for consultation and performance of NUT immunohistochemistry.

The NUT immunohistochemical stain (Figure 6) confirmed a diagnosis of a poorly differentiated squamous cell carcinoma with NUT expression, which is consistent with NMC.

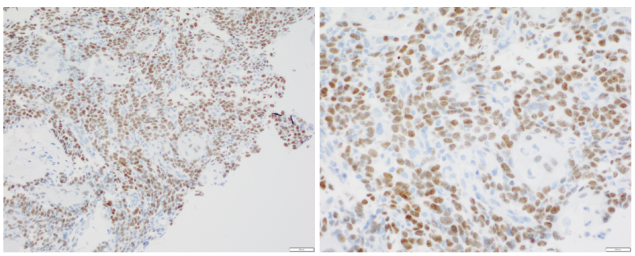

Fig. 6: NUT immunohistochemical stain showing brown nuclear positivity in the poorly differentiated component. The squamous pearls are negative for this stain. The images are shown at 20x (left) and 40x (right) magnification.

The patient was treated with palliative radiation to the spine and subsequently received her first cycle of chemotherapy. Her pain was treated with a combination of opioids and other analgesics. She was later discharged two months after presentation, at which time the patient was fully ambulatory despite extensive disease burden. The patient reported feeling relatively well and was eager to go home. A close outpatient follow-up care was advised. Three months after presentation, a follow-up appointment revealed stable calvarium metastases, a slight reduction in lymph node burden, and a slight decrease in right pleural effusion. However, bony metastases were identified in the axial and appendicular skeleton.

Due to disease progression, it was decided that further chemotherapy was no longer beneficial. The patient was later transferred to a palliative care center and was managed symptomatically. The patient's condition deteriorated and she, unfortunately, died five months after presentation.

3. Discussion

NMC is a rare and deadly cancer.[12] The first report of NUT carcinoma goes back to 1991.[13,14] Currently, immunohistochemical staining for NUT is a quick and cost-effective method for diagnosis.[5] NMC is characterized by NUT gene rearrangement on chromosome 15q14.[1,6] Approximately 70% of NMC cases present with a coding sequence of NUT fused with BRD4 on chromosome 15q14, forming the BRD4-NUT fusion gene.[15,16] In the remaining cases, NUT fuses with BRD3 or other unknown partner genes, referred to as NUT-variant fusion genes.[2]

Currently, there are no effective or standard treatment strategies for primary pulmonary NMC. Chemotherapy is a commonly used treatment but it is not always effective. Surgical resection and radiotherapy may be successful treatments for prolonging patient survival.[17] Yet, advanced disease progression can hinder clinical management and lead to a grave prognosis.

We report a case of a 23-year-old female patient presented to our midwestern Canadian hospital with primary pulmonary NMC. Based on the authors' knowledge, NMC has not been previously diagnosed in the Saskatoon Health Region. This case demonstrates the diagnostic challenges NMC can pose in centers unfamiliar with NMC or without access to NUT immunohistochemistry testing.

As per our experience, the primary difficulties of diagnosing this rare cancer resulted from the young age of the patient, the peculiar histology of poorly differentiated squamous cell carcinoma with two different cell patterns, and the presentation in the lung. Before a diagnosis of NMC was made, it was theorized that an inherited genetic abnormality in the patient caused the unusual histology of this tumor and the presentation at a young age. The differential diagnosis of a primary cancer in the gynecological tract was also considered but ruled out by the p16 immunostain and lack of evidence of a primary gynecologic tumor. The diagnosis of NMC did not emerge until after further collegial review of this perplexing tumor and external consultation.

Case reports and descriptions of primary pulmonary NMC are scarce.[14] However, the present case has many

common clinical and histological features with previously reported cases of primary pulmonary NMC. A retrospective review reported seven cases of primary pulmonary NMC between 2015 and 2018.[17] Similar to the reported cases in that cohort, our patient also presented with a primary tumor in the lung. The gender and age of our patient are consistent with the demographics of that series, which showed an age range of 23-74 years and consisted of both males and females. Four patients in that cohort had a history of smoking, similar to our patient, and the most common symptoms were cough, dyspnoea, chest pain, fever, and hemoptysis. Our patient did not particularly suffer from cough but did present with dyspnoea, fatigue, weight loss, and headache. The median survival time of NMC from diagnosis is approximately 6 to 7 months.[9] However, the median survival within this retrospective review of patients with lung masses was 2.75 months, suggesting that, despite receiving multiple treatments, primary pulmonary NMC may be more aggressive than NMC located at other sites.[17] Unfortunately, our patient survived only five months following initial presentation.

4. Conclusion

In summary, we present a case of primary pulmonary NMC in a young female patient and emphasize the diagnostic difficulties associated with this rare disease. This report also highlights the importance of spreading awareness of this aggressive cancer and its peculiar histological presentation among both pathologists and clinicians to allow for more accurate and timely diagnosis.

5. Source of Funding

None.

6. Conflict of Interest

None.

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