Midline Carcinoma with NUT Rearrangement in a 23-year-old male: A Case Report

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ABSTRACT

Objectives:

1. Report the clinicopathologic features of a rare, midline carcinoma
2. Review the literature on NUT Midline Carcinoma and associated treatment protocols

Case Presentation:

A 23-year-old Chinese male presented with a 10-day history of enlarging nontender cervical lymphadenopathy, dysphagia, and dysarthria. Clinical exam demonstrated right tongue atrophy and a 6cm ipsilateral level III neck mass. CT of the neck with contrast revealed an infiltrating hypopharyngeal lesion and bilateral necrotic cervical lymphadenopathy. At microlaryngoscopy, the patient was noted to have a friable postcricoid mucosal lesion that on multiple biopsies revealed only necrosis. Cytogenetic analysis of a lymph node biopsy demonstrated chromosomal rearrangements consistent with a translocation between chromosomes 15 and 19, i.e. t(15;19), resulting in the fusion oncogene BRD4-NUT consistent with diagnosis of NUT Midline Carcinoma (NMC). NMC is a newly recognized entity identified by the presence of chromosomal rearrangements involving the Nuclear protein in testis (NUT) gene on chromosome 15q14. The clinical course is rapid and fatal and to date there is not a well-established treatment protocol. NMC is likely under-diagnosed and should be considered within the differential diagnoses in all poorly differentiated and undifferentiated midline carcinomas, particularly in young adult, non-smokers. Accurate and prompt diagnosis of this rapidly progressing carcinoma is crucial to improving prognosis and identifying effective treatment regimens.

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INTRODUCTION

Nuclear protein in testis (NUT) midline carcinoma (NMC) is a newly recognized, poorly-differentiated and rapidly progressive carcinoma most commonly involving mid-line structures. The majority of the cases involve the upper aerodigestive tract and mediastinum, but cases have been reported of the lung,[1, 2] bladder,[1] bone, [3] orbit[1] and submandibular gland.[4]

Although rare, the exact frequency of NMC has not been defined.[5] The average age at diagnosis is 25, but the described age range is 3 to 78 years with an increasing number of patients being in the third or fourth decade of life at the time of diagnosis .[1] Males and females are relatively equally affected.[4] To our knowledge frequency by race or ethnicity has not been described. The average survival is 9.5 months, despite aggressive treatment with chemoradiation. Presently, there is no well-defined, viable treatment protocol.

CASE PRESENTATION

A 23-year-old Chinese male presented with a 10-day history of enlarging nontender cervical lymphadenopathy, dysphagia and dysarthria. Clinical exam demonstrated right tongue atrophy, decreased right shoulder range of motion and a 6cm ipsilateral level III neck mass. On fiberoptic exam he had a large hypopharyngeal post-cricoid submucosal mass. CT of the neck with contrast revealed an infiltrating hypopharyngeal lesion and bilateral necrotic cervical lymphadenopathy (Figures 1-3). At microlaryngoscopy, (Figures 4-6) the patient was noted to have a friable postcricoid mucosal lesion that on multiple biopsies revealed only necrosis. PET-CT performed on 1/28/12 demonstrated multiple bilateral enlarged soft tissue attenuation masses in the neck with FDG avidity, the largest of which was in levels II and III of the right neck and measured 8.5 x 5.2 x 6.5 cm. This was markedly larger compared to prior CT performed on 1/10/12. Additionally there were multiple focal groundglass densities in the lungs without appreciable FDG uptake. A subsequent incisional lymph node biopsy was interpreted as poorly differentiated carcinoma, EBV negative. Cytogenetic analysis of this specimen demonstrated chromosomal rearrangements consistent with a translocation between chromosomes 15 and 19, i.e. t(15;19), resulting in the fusion oncogene BRD4-NUT consistent with a diagnosis of NMC.

He was started on a course of chemoradiation with docetaxel. After approximately 1 month of treatment, he required emergent tracheotomy. Shortly thereafter he was admitted for progressive bilateral pleural effusions requiring bilateral pleurex catheters. At this point docetaxel was held given elevated transaminases and he was initiated on Romidepsin histone deacetylase (HDAC) inhibitor via compassionate use. His disease continued to progress and he expired within three months of initial presentation.

DISCUSSION

NMC is a relatively newly described disease which may frequently go unrecognized by unfamiliar pathologists in favor of diagnoses such as squamous cell carcinoma, Ewing Sarcoma, Sinonasal undifferentiated carcinoma,[6] and small-cell neuroendocrine carcinoma.[7] NMC demonstrates the cytologic features of a poorly or undifferentiated malignancy[7] and is named for and defined by DNA mutation of the NUT gene in which NUT is fused to another gene. The majority of these cancers harbor the BRD4-NUT fusion oncogene resulting from a *t*(15;19) translocation. The remaining cases harbor NUT-variant fusions and interestingly seem to confer a longer median survival, although the prognosis is still dismal.[6] Viral associations with Epstein Barr Virus (EBV) and Human Papilloma Virus (HPV) have not been identified. Since BRD4-NUT positive and NUT-variants lack distinguishing histological or immunohistochemical features, molecular diagnosis of poorly differentiated, aggressive midline lesions is crucial for accurate diagnosis and treatment.[4] Ultimately the diagnosis of NMC relies on identifying the NUT translocation.[7] Diagnosing this translocation can be accomplished by a variety of methods including karyotyping, fluorescent in situ hybridization (FISH) and reverse transcription polymerase chain reaction (RT-PCR).[7]

CONCLUSIONS

To date, all but one described case of NMC have been identified as rapidly progressive and fatal. The case of this 23 year old Chinese male confirms this clinical progression. This disease entity should be considered as a differential in all young and middle-aged, non-smoking patients with aggressive, poorly differentiated and undifferentiated pathology of midline structures. Viable treatment options have yet to be identified therefore it is crucial to make expedient diagnosis and report cases and response to various treatment regimens in an attempt to improve patient prognosis. Studying propensity for disease based on race and ethnicity and uncovering possible viral associations may also enhance our understanding of disease epidemiology and viable treatment options.

Figure 1

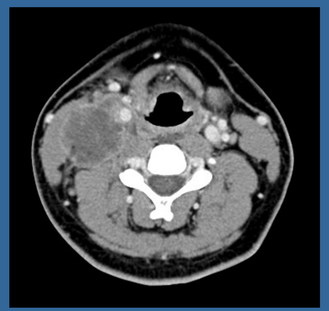


Figure 2

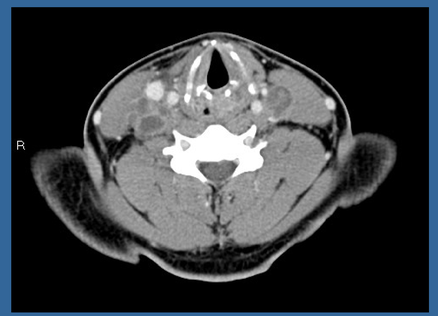


Figure 3

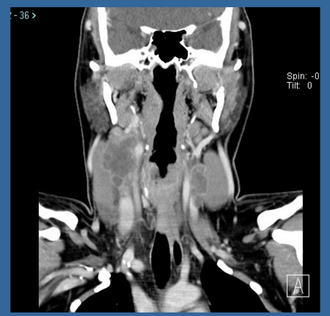


Figure 4

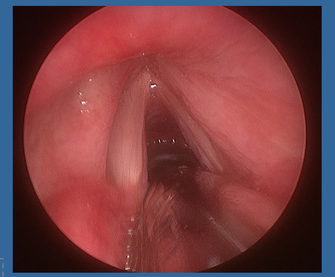


Figure 5

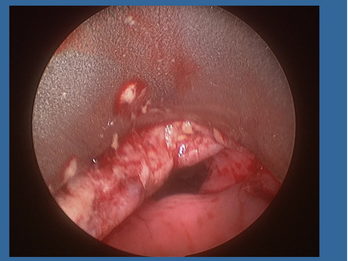
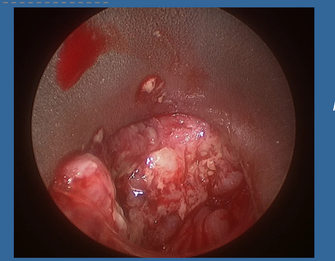


Figure 6



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