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Case Report

NUT MIDLINE CARCINOMA: A CASE REPORT

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ABSTRACT

NUT midline carcinoma (NMC) is a rare, highly lethal malignant epithelial tumor caused by rearrangements in the *nuclear protein testis* (NUT) gene in chromosome 15, and few studies have described the condition. This report describes NMC in an 8-year-old girl presenting an asymptomatic lesion on the tongue dorsum. Cervical lymph nodes were significantly increased, and the patient presented dysphagia, dyspnea, severe fatigue, and marked weight loss. Immunohistochemical examination afforded to diagnose the lesion as poorly differentiated, high-grade carcinoma with cytokeratin expression and positive staining for protein p63 and NUT. Despite treatment, the patient died eight months after diagnosis. The standard treatment for NMC is not significantly effective. Therefore, early diagnosis may be useful to better characterize progression of NMC, allowing health professionals to start more timely interventions based on new therapeutic protocols.

INTRODUCTION

Midline carcinoma of the NUT type (nuclear protein in testis) (NMC) is an aggressive subtype of squamous cell carcinoma. NMC usually stores BRD4/3-NUT fusion oncoproteinsthat block cell differentiation and sustain tumor growth (French *et al*., 2014). NMC is identified exclusively based on the detection of chromosomal rearrangement of the NUT protein gene located at chromosome 15q14 with members of the BRD gene family. In approximately 80% of cases translocation occurs between the BRD4 gene in chromosome 19 and the NUT gene in chromosome 15, which induces the formation of a BRD4-NUT gene (French *et al*., 2008; Haack *et al*., 2009; French, 2013). This case report describes the diagnosis of NMC in a child, confirmed by a specific immunohistochemical protocol, with death as outcome eight months later.

Case Report

A previously healthy 8-year-old African-American girl that lived and studied in rural district of the city of Piripiri, inner state of Piauí (PI), Brazil, was admitted to Hospital São Marcos, city of Teresina (PI) in May 2012. Asymptomatic bilateral lymphadenomegaly that evolved rapidly in the previous quarter was detected. Anorexia, dysphagia, and weight loss had emerged in the two weeks preceding the visit. The right and left cervical lymph nodes measured approximately 4 and 6 cm, respectively, upon initial clinical examination. Firmly located in deep planes and with no phlogistic or suppurative signs, both lymph nodes were hard but painless upon palpation. Intraoral examination revealed papulose lesions and oropharynx hyperemia, in addition to a red patch on the left side of the tongue dorsum. Also, recent tooth extractions were noticeable, and the condition of dental elements showed that eruption chronology was compatible with the patient's age. The patient's medical record did not list any serious condition, and family history did not include any relevant pathology. Imaging-based exams and laboratory tests were carried out. Biopsy indicated poorly differentiated malignant neoplasm infiltrating muscle tissue requiring complementary immunohistochemical investigation. In this sense, the neoplasm was cytokeratin-positive**,** confirming an epithelial origin (Figure 1A). Moreover, the NUT protein was positive (Figure 1B) indicating a Midline carcinoma of the NUT type. Treatment included surgery, chemotherapy, and radiotherapy. Lymph node drainage was performed, and

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histopathological analyses of the organs revealed the presence of metastatic carcinoma. All six lymph nodes at levels 3, 4, and 6 (left) and one at level 2 (right) were affected. Immunohistochemical investigation indicated metastatic NMC. The tongue dorsum was defined as the primary lesion site (CID C02.0), and the neoplasm was categorized as T2N1M0 (grade III) based on the TNM mouth cancer classification criteria developed by the American Joint Committee for Cancer Staging (UICC/AJC). After surgery, a combination treatment with radiotherapy (six 49.5-Gy/day sessions) and chemotherapy (two 1-h sessions of vincristine 1.2 mg e.v, doxorubicin 50 mg e.v., cyclophosphamide 1.24 g e.v.). The treatment was discontinued when the patient died in January 2013, eight months after diagnosis of NMC.

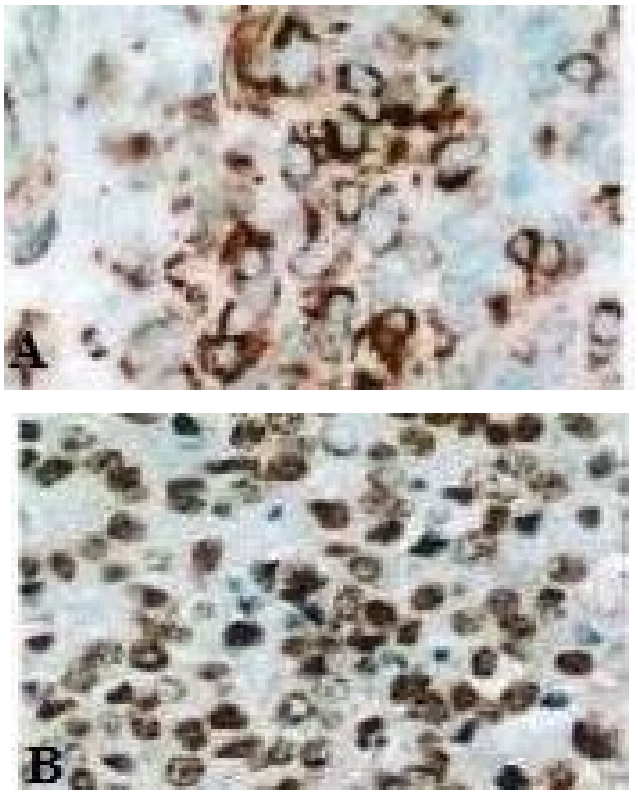

Figure 1. Immunohistochemical staining of cytokeratin (A) and NUT protein (B) in biopsy of tongue

DISCUSSION

NMC is a rare, aggressive subtype of squamous cell carcinoma genetically characterizedbya chromosomal translocation involving the NUT gene of chromosome 15q14 (French *et al*., 2004; French, 2013). NMC is a rare epithelial cancer that may have established a genetic bypass as a means to express this phenotype, as revealed in cytogenetic investigations of the disease (Alekseyenko *et al*., 2015). The NUT protein fusions into protein BRD4 [t, (15; 19)] in approximately two thirds of cases. In the others, the NUT protein fusions into BRD3 [t (9; 15)] or some other unknown partner (NUT-variant) (Suzuki *et al*., 2014; French, 2013). Few fusion oncogenes have been identified in epithelial tumors, though BRD4-NUT is the first oncogene fusion mechanism to be identified in a highly lethal form of this carcinoma (French, 2008). NMC spreads evenly along the midline, more commonly on the mediastinum (Evans *et al*., 2009; French, 2008) and on the head and neck (as in the present case), though it may also emerge in the bladder, ilium, pancreas, parotid gland, and lungs (Bhaijee *et al*., 2011; Ball *et al*., 2013; Hsieh *et al*., 2016). These advanced grade tumors have cervical, bone, lymphatic, or pulmonary metastases (French, 2010). NMC is rarely dry, and in many cases it is not a primary tumor, but a metastatic transfer (Stelow, 2011), as observed in the present case report. NMC has not been linked with smoking habit or environmental toxins (Mills *et al*., 2014) or even the HIV and Epstein Barr viruses (Stelow, 2011). It has been speculated that NMC originates in primitive neural crest cells (French, 2008). The neoplasm expresses p63 and cytokeratin immunoreactivity consistent with its squamous differentiation and epithelial origin (Stelow, 2011; Mills *et al*., 2014; Park *et al*., 2014). In the present case, this finding was confirmed by immunohistochemistry. NMC affects people of either gender (Stelow, 2011; Hack *et al*., 2009; French *et al*., 2014) in the 0 – 78 demographic, though it seems to be more prevalent in children and young adults (Evans *et al*., 2009), which was also verified in the case reported. The NMC analyzed was refractory to the treatment prescribed. Several studies have discussed the refractory character of NMC toconventional chemotherapy and radiotherapy, when patients evolve to a fatal outcome within a mean survival of 6.7 months (Bishop and Westra, 2012; French *et al*., 2014) and overall survival of 19% in 2 years (Ball *et al*., 2013). As observed in this case, NMC does not respond to conventional treatments, and new therapeutic options have become the object of research in recent years, pointing to the essential nature of early, accurate diagnosis (Schwartz *et al*., 2011; Mills *et al*., 2014). As in anunderrecognized and underdiagnosed entity, NMC incidence is not clear, and diagnosis is reached only using molecular or immunohistochemical assays (French, 2008; French, 2014). This highlights the need for more attention from health professionals in suspected cases of aggressive tumors in the upper aerodigestive tract or the mediastinum that present themselves as histologically undifferentiated carcinomas (Hsieh *et al*., 2016). PCR and FISH tests are fundamental to accurate diagnosis, though the cost and the labor-intensive character of these protocols are a drawback in many scenarios (Mills *et al*., 2014; Park *et al*., 2014; Suzuki *et al*., 2010). This difficulty was observed in the present case, interfering in the treatment prescribed. A more accessible diagnostic assay is at its trial phase. It affords an accurate, fast diagnosis, paving the way towards the development of new treatments (Bishop and Westra, 2012; Ball *et al*., 2013; Hsieh *et al*., 2016).

Conclusion

NMC is an undifferentiated, very aggressive tumor. The findings described in the present case report are consistent with previous results. The fast progression and high mortality of NMC highlights the need for efficient, more accessible diagnosis approaches as part of more appropriate treatment approaches, affording better perspectives and quality of life to patients.

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Ethical Approval

The present study was approved by the Ethics Committee for Research with Humans, Universidade Luterana do Brasil, authorization number 31205114.5.00005349.

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