Overview and different perspectives on possible treatments related to NUT carcinoma: a systematic review

Visão geral e perspectivas diferentes sobre possíveis tratamentos relacionados ao carcinoma NUT: uma revisão sistemática.

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ABSTRACT

NUT carcinoma (midline testicular carcinoma nuclear protein) is a relatively new, rare, aggressive and underdiagnosed entity. Its sites of involvement are medial structures of the head and neck and mediastinum, but other sites may be affected, and even in so-called common structures, the clinical course may impress. The objective of this systematic review was to describe the pathophysiological characteristics of NUT carcinoma and to analyze the types of treatments employed and their efficacy. Throughout the text, treatment - chemotherapy-related forms have been discussed that have led to the complete remission of tumors in some cases, such as the treatment regimen: alternating cycles of vincristine / doxorubicin / ifosfamide and cisplatin / doxorubicin / ifosfamide combined with focal radiotherapy (Scandinavian protocol for inoperable Ewings sarcoma). Other possible future therapies are discussed, in addition to the role of alpha- fetoprotein as a prognostic factor.

Keywords: Carcinoma; Drug Therapy; Medical Oncology.

RESUMO

O carcinoma NUT (proteína nuclear no carcinoma testicular de linha média) é uma entidade relativamente nova, rara, agressiva e subdiagnosticada. Seus locais de envolvimento são estruturas mediais da cabeça e pescoço e mediastino, mas outros locais podem ser afetados e, mesmo em estruturas comuns, o curso clínico pode impressionar. O objetivo desta revisão sistemática foi descrever as características fisiopatológicas do carcinoma NUT e analisar os tipos de tratamentos empregados e sua eficácia. Ao longo do texto, foram discutidas formas relacionadas ao tratamento quimioterápico que levaram à remissão completa de tumores em alguns casos, como o regime de tratamento: ciclos alternados de vincristina / doxorrubicina / ifosfamida e cisplatina / doxorrubicina / ifosfamida combinados com radioterapia focal (Protocolo escandinavo para sarcoma de Ewings inoperável). Outras possíveis terapias futuras são discutidas, além do papel da alfa-fetoproteína como fator prognóstico.

Descritores: Carcinoma; Quimioterapia; Oncologia.

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INTRODUCTION

NUT carcinoma (midline testicular carcinoma nuclear protein) is a relatively new entity that, because of its poor recognition, becomes underdiagnosed. The aggressive nature is marked, with presence of lymph node involvement and / or metastatic invasion. The preferred metastatic NUT carcinoma sites are distal lymph nodes, bone marrow and pleura[1,2]. Expression of the NUT protein is usually exclusive to the testes and its expression outside the testis is diagnostic of NMC (NUT midline carcinoma)[3,4].

It has been postulated that these tumors arise from remnants of epithelial progenitor cells that are observed early in life in the first two to three decades. This hypothesis was further supported by the frequent immunoexpression of CD34, a marker of the stem cell phenotype in cells of this tumor. The incidence of NMC remains unknown due to its rarity, lack of pathognomonic morphological features and the need for molecular diagnostic methods, such as fluorescence in situ hybridization (FISH) or reverse transcriptase (PCR), which unfortunately are not available in most laboratories in the world. The recent development of an immunohistochemical staining for NUT, which proved to be sensitive and specific for the diagnosis of CMN, led to an increase in the number of diagnosed cases and in patients of any age presenting "undifferentiated carcinoma", antibody immunostaining NUT must be extensivelyperformed to allow definitive diagnosis in histology and immunohistochemistry, which can then be characterized by FISH or RT-PCR[1].

Although their sites of involvement are generally defined as in medial structures of the head and neck and in the mediastinum, other sites may be affected, such as the larynx, and even in so-called common structures, the clinical course may impress. Data on mediastinal NUT midline carcinoma with extensive cardiac invasion have been reported in two cases and in one case it was possible to demonstrate extensive coronary involvement that causes a fatal myocardial infarction[5]. Another study reports the second case that appears in the lacrimal fossa[6].

Because it is one of the most common sites of involvement, it is reported here the clinic that can be found in head and neck NUT tumors: proptosis, decreased vision, nasal obstruction and epistaxis. However, a brief clinical history with rapidly progressive tumor mass is present in all cases.

Because incidence rates and published data are lacking, there is no standardized treatment for NUT midline carcinoma.

The objective of this systematic review was therefore to describe the pathophysiological characteristics of NUT carcinoma and, mainly, to analyze the types of treatments used and their efficacy, in order to improve the knowledge about the subject, to decrease the rate of underdiagnosis and to guide the possible treatments, in view of experiences held by other professionals and demonstrated in other articles.

METHODS

The systematic review of the literature is a form of synthesis of the information available at any given time on a specific topic. It is a scientific investigation that brings together relevant studies on a formulated question, using the database of the literature that deals with a question as a source and methods of identification, selection and systematic analysis, with the purpose of performing a critical and comprehensive review of the literature. Therefore, the systematic review seeks to overcome possible bias in all stages, following a rigorous method of searching and selecting the research.

In this context, this work began with the elaboration of the clinical question, that is, the main objective, and of a revision project. Next, a careful analysis was carried out in the literature with the objective of identifying the largest possible number of studies related to the subject. Once selected, criteria for methodological quality evaluation were applied according to the design of the original study, with emphasis on the academic relevance of the selected material.

Thus, an electronic literature search was performed in the Medline database, using the keyword "NUT carcinoma", which contained articles from 01/01/2001 to 12/31/2018. We identified 755 articles and submitted to the inclusion criteria: articles published in the period; Languages English, Portuguese and Spanish; case report or case series, cohort, control case, literature review, double-blind randomized controlled trials and meta-analyzes. From this, 70 valid articles for the proposal were selected and submitted to the exclusion criteria: article with duplicate databases or incomplete access, inadequate methodologies to the proposed objective, non-corresponding or tangential abstract to the central theme of the research and article not reviewed by expert. At the end, there were 15 articles relevant to the theme, which were read in full, so that each contributed to the construction of the present study.

RESULTS AND DISCUSSION

NUT midline carcinoma is a relatively recent entity, recognized and considered one of the most aggressive solid human malignancies. It is a genetically defined neoplasm[6,7]. Tumors tend to distribute along the midline axis with a predilection for head and neck, mediastinum, and lung. In addition, there are rare reports of involvement of the primary bladder, breast, endometrium, kidney and orbit[8]. There is a propensity for early metastases in the lymph nodes and lungs, and the tumors are almost inevitably fatal. Based on the frequent expression of keratin, it has been concluded that the NUT midline carcinoma represents a carcinoma. The presence of squamous keratinization led to the classification of the midline NUT carcinoma as a subtype of squamous cell carcinoma.

The incidence of NUT-associated tumors is unknown and occurs mainly in adolescents and young adults, and is most commonly found in the second and third decades of life[8], and it is assumed that cases in soft tissues and viscera have not been recognized until now[9]. More than 80% of patients die in the first year of diagnosis of NUT carcinoma; locoregional and distant metastases are common and, in addition to complete surgical resection, there is currently limited therapeutic benefit of chemoradiotherapy. The prognosis remains extremely poor, with a median survival of 6.7 months and an overall survival of 19% in the first two years after diagnosis[9].

Pathophysiology involves a rearrangement of the NUT gene on chromosome 15q14 with members of the BRD gene family (BRD4 and BRD3) resulting in a BRD- NUT fusion product, which decreases histone acetylation and therefore suppresses squamous cell differentiation. Pathological examination may reveal positivity for cytokeratins (CKs) and p63, a squamous basal cell marker, leading to an incorrect diagnosis of squamous cell carcinoma[9].

The recent availability of a commercially available NUT antibody for immunohistochemistry facilitated the diagnosis of NMC, providing an economical and robust method to distinguish it from other low differentiated carcinomas[6]. Positive immunoreactivity for anti-CK antibodies AE1 / AE3, as well as EMA (a marker for the epithelial nature of neoplastic cells), p63 and p40 (basal cell carcinoma markers) are the usual immunohistochemical findings and should raise suspected carcinoma NUT in young individuals with a tumor in the midline[9].

Nuclear positivity of more than 50% for the anti-NUT antibody with fluorescence in situ hybridization (FISH) analysis allows the diagnosis of NUT carcinoma with 100% specificity. The characterization of both BRD4-NUT and BRD3-NUT fusion genes, and more rarely NSD3-NUT, is not mandatory for diagnosis but is recommended for itspossible association with unique prognostic features. NUT carcinomas without the BRD4 fusion gene rearrangements are more differentiated and therefore possibly less aggressive[9].

It was predicted that a set of 18, 33 and 34 miRNAs (micro RNAs) targeted the transcript of the BRD4-NUT fusion gene, BRD4 mRNA and NUT, respectively. The comparative analysis of these miRNAs and functional enrichment of the pathway revealed that a set of 48 miRNA can be deregulated to target critical genes other than parental genes (BRD4 and NUT), causing cancer. The amplification at the level of expression of these miRNAs can be used for the diagnosis and prognosis of CMN[1].

Currently, there is no consensus on the optimal treatment strategy. In the absence of optimal treatment, platinum-based regimens and lymphoma types were used[10]. In addition to its rarity, the NUT midline carcinoma may initially and transiently respond to several cytotoxic agents used to treat undifferentiated carcinomas, making it less likely to give rise to the correct diagnostic suspicion. Regardless of the treatment chosen, the activity was at most transient and short duration[2].

Initial non-surgical treatment is employed in most patients, and the majority of patients undergoing definitive radiation were head and neck. Chemotherapy was also used as part of the treatment[11]. However, the low chemoSensitivity of NUT carcinoma is proven, with a very transient response rate to chemotherapy of approximately 36%, rapidly followed by tumor progression, independently of the pharmacological schemes used[12].

Other combinations of second or subsequent conventional chemotherapy were not effective. Responses to chemotherapy with anthracyclines and alkylating agents (ifosfamide) have also been reported in the literature, but with limited efficacy. In a review of the literature based on 31 cases of NUT intrathoracic carcinoma in adults, it was concluded that the best treatment option was a combination of cisplatin, gemcitabine and docetaxel. However, only transient responses were obtained[12].

As the currently available chemotherapy regimens are ineffective, new therapies have been developed for this cancer, supported by preclinical studies reporting a positive response to HDAC14 inhibitors (histone deacetylase inhibitors), such as vorinostat, and BRD inhibitors (inhibitors of bromodomain), which induce the squamous differentiation of NUT carcinoma cells and block their growth, however, the use of the NUT has been limited due to serious side effects[12].

Several phase I / II clinical trials have been completed or are underway using BRD inhibitors (TEN-010 protein inhibitors [NCT01987362], GSK525762 [NCT01587703], MK-8628 [NCT02698176], INCB057643 [NCT02711137], BAY1238097 [NCT02369029]) CUDC-907 [NCT02307240]) which could effectively have a place in the treatment of this disease, possibly as first-line treatment alone or in combination with other therapeutic agents, in view of the poor prognosis of this tumor. Therefore, NUT carcinoma is essential to propose the inclusion of these patients in targeted therapeutic studies as soon as possible[12].

In terms of local treatment, patients undergoing complete surgery and / or initial radiotherapy had significantly higher disease-free survival and progression-free survival. Local treatments appear to be potentially useful for controlling disease, especially when localized[13].

In the literature, a patient with NUT carcinoma has been reported to be cured and with long-term follow-up: a 10-year-old male, treated in 1991, with a 10-cm tumor involving iliac bone with soft tissue extension. Cytogenetic analysis revealed a translocation (15; 19) (q13; p13) and FISH reported a specific translocation of BRD4- NUT. This patient was treated with conventional chemotherapy with alternating cycles of vincristine / doxorubicin / ifosfamide and cisplatin / doxorubicin / ifosfamide combined with focal radiotherapy according to the Scandinavian protocol of inoperable Ewing's sarcoma. The patient remained in complete remission 13 years after treatment[13].

In one study, two cases, the first of a nine-year-old boy with enlarged cervical lymph nodes, and a sublingual gland identified as the site of the primary tumor, and the second of a nine-year-old boy with swelling of the left cheek and magnetic resonance imaging revealing a 1.3 × 3 cm mass gently rising over the masseter muscle, contiguous with the parotid gland, entered complete remission after initiation of treatment using chemotherapy according to the protocol of the Scandinavian Sarcoma Group (SSG) IX for inoperable Ewing's Sarcoma. This protocol provides for 4 cycles of chemotherapy, each including two courses of VAI (vincristine, adriamycin and ifosfamide) alternating with a course of PAI (cisplatin, adriamycin and ifosfamide). To avoid late toxicity of cumulative high doses of drugs, 3 cycles were given. Radiotherapy was applied to all involved regions simultaneously[13].

Another study provides a framework for deconvolution and prediction of genotype-chemootype relationships in a large-scale kinase inhibitor screen and identifies CDK9 as a drugable target in NMC. One of the most notable specific vulnerabilities of genotypes on our screen was the excellent activity of LDC67, a known inhibitor of CDK9 in NMC cells. The chemical genomics approach revealed a role for CDK9 as a non-oncogenic factor for tumorigenesis in BRD4-NUT-dependent cells mediated by transcriptional regulation and Myc protein levels in NMC. It is indicated that the inhibition of BRD4 leads to the dissolution of hyperacetylated nuclear foci, release of p53 with induction of p21, cell cycle arrest and differentiation. CDK9 may be an attractive drug target in NMC patients. Inhibition of CDK9 specifically modulates transcriptional elongation and effectively impairs viability by inducing apoptosis and DNA damage response of NUT midline carcinoma cells[14]. In the past, clinical studies investigating spectrum CDK inhibitors such as dinaciclib or flavopiridol have reported high rates of dose-limiting side effects and toxicities, but more selective compounds such as ribocyclib (CDK4 and CDK6) have demonstrated the feasibility of inhibiting CDK even as treatment of first line cancer. For this reason, several CDK9 inhibitors with better selectivity profiles have been developed and promising for future development in clinical applications. Such findings may therefore be relevant to the future development of these drugs and to the stratification of patients receiving these types of selective CDK9 inhibitors[14].

Another point is the observed elevation of alpha-fetoprotein in NUT medial carcinoma, which may be related to the suggested hypothesis that these cells arise from cells derived from the primitive neural crest. In fact, both the gene expression profile similar to the adult ciliary ganglion and the absence of the in-situ component are consistent with that cell of origin. Alpha-fetoprotein levels during treatment were not reported in the majority of available cases. Considering these findings, it is suggested not to exclude and, instead, to take into account the diagnosis of NUT medial carcinoma when facing a patient with a rapidly growing nodule in the midline structures and elevation of alpha-fetoprotein. Of course, assessment of alpha- fetoprotein levels in other cases of medullary NUT carcinoma may help to better define the role of this serum marker in this challenging disease. It is suggested to measure alpha-fetoprotein levels during tumor treatment to monitor the course of the disease[2].

Several publications advocate a multimodal strategy that adapts to the aggressive behavior of NUT carcinoma. In line with this, an aggressive combined approach with radiotherapy and surgery, whenever possible, as part of the initial multimodal treatment should be used[15].

Due to the rarity, the data that are available are limited, especially in relation to the care standards and prognostic factors of that tumor, that is uniformly weak. Cases report metastasis via the hematogenic route, in addition to almost all patients succumbing to the disease, despite aggressive management strategies, thus emphasizing the lethal behavior of this neoplasm.

AUTHOR'S CONTRIBUTION

Antonia Nayra Gomes Lopes: Collection and assembly of data, Conception and design, Data analysis and interpretation, Final approval of manuscript, Manuscript writing, Provision of study materials or patient.

Martinho Hermeson de Matos Furtado: Collection and assembly of data, Data analysis and interpretation, Final approval of manuscript, Manuscript writing, Provision of study materials or patient.

Karen Giselly Paulo Silva: Collection and assembly of data, Data analysis and interpretation, Final approval of manuscript, Provision of study materials or patient.

Lindvaldo de Oliveira Sousa: Collection and assembly of data, Conception and design, Data analysis and interpretation, Final approval of manuscript.

Andrezza Vasconcelos do Vale Aguiar: Collection and assembly of data, Final approval of manuscript, Manuscript writing.

Giovanni Ciarline Silveira: Conception and design, Final approval of manuscript.

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