



MEDIASTINAL NUT-MIDLINE CARCINOMA IN 11- YEAR OLD BOY – A CASE REPORT

Radiology

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ABSTRACT

NUT-midline carcinoma is a rare and very aggressive tumor, with fast progression and poor prognosis. It should be suspected in poorly differentiated tumors, especially if located in midline structures of the head, neck, and thorax. It is characterized by gene translocation of nuclear protein in testis (NUT) gene from chromosome 15, most frequently to bromodomain containing protein 4 (BDR4) gene on chromosome 19. We present a case of mediastinal NUT-midline carcinoma in 11-year old boy. CT revealed a large mediastinal mass on the right side, with elevated serum alpha-fetoprotein (AFP), neuron-specific enolase (NSE), ferritin and lactate dehydrogenase (LDH). The patient was treated with chemotherapy, but the progression of disease was rapid, and he died within four months after the onset of disease.

KEYWORDS

NUT-midline carcinoma, alpha-fetoprotein, mediastinal tumors.

NUT midline carcinoma is a rare, poorly differentiated subtype of squamous cell carcinoma, characterized by rearrangement of NUT gene from chromosome 15, to the BRD4 or BRD3 genes on chromosomes 19 and 9, resulting in formation of fusion BRD4/BRD3 – NUT oncogenes, which are supposed to be responsible for blocking epithelial and squamous differentiation. (1,2,3,4)

NUT carcinoma can occur in any organ, but is most commonly located in midline structures of the thorax, head and neck. At the time of presentation it is often advanced disease, with distant metastases. (1,5,3) It can occur at any age, and it equally affects both sexes. (1) It is extremely aggressive tumor, with the average survival period about 6-7 months. (6)

Definitive diagnosis can be made by confirmation of fusion BRD4/BRD3 – NUT oncogene by fluorescent in situ hybridization (FISH), or by NUT immunohistochemistry with rabbit monoclonal antibody (C52B1). (5,7)

We present the case of mediastinal NUT-midline carcinoma in 11-year old boy, the first one that was recognized and confirmed in our hospital.

Case Presentation

An 11-year-old boy presented with dry, irritating cough, fatigue, loss of appetite, temporary headaches, and lip numbness, with no remarkable medical history. The initial chest x-ray revealed round consolidation in the right hilum, and widening of the mediastinum. (fig.1)

The boy received intravenous antibiotic therapy for suspected pneumonia, but there was no clinical improvement. He was referred to the pediatric hospital for further examination. On admission, the boy was afebrile, eupneic, with satisfactory nutritional status, and well hydrated. The color of the skin and mucosa were normal. Pulse rate was 120 per minute, oxygen saturation 98%. Auscultatory findings revealed decreased breath sounds in the central parts of the right lung. Blood tests revealed increased C-reactive protein (CRP) 297,5 mg/L (normal range 0,8-3 mg/L), lactate dehydrogenase (LDH) 2114 U/L (normal range 240-480 U/L), ferritin 1170 ng/ml (normal range 24-336ng/L), and tumor markers alpha-fetoprotein 1890 ng/ml (AFP - normal range <10,9ng/ml), and neuron-specific enolase 103,3 g/L (NSE - reference interval 0-12,5 ng/ml).

Investigation findings

A CT of the thorax revealed a bulky, heterogenous, mass in the right hilum >7cm, propagating to the lung lobes and posterior mediastinum, encasing vascular structures of the hilum, compressing and narrowing trachea, main bronchus and its branches, dislocating superior vena

cava ventrally. Central parts of the mass were hypodense due to large areas of necrosis. The mass was confluent with enlarged lymph nodes of the upper mediastinum. (figures 2.a and 2.b) Two metastatic supraclavicular lymph nodes were seen on the right side of the neck. Percutaneous biopsy of the mass was performed under the CT guidance, but pathology finding was inconclusive. A lymphoma was most suspected, but pathology examination ruled it out. Differential diagnosis included neuroectodermal tumor, mediastinal germ-cell tumor with poorly differentiated neuroepithelial component, and malignant small cell tumors of mediastinum.

FDG PET-CT was performed for tumor staging. The central lung and mediastinal sites of the tumor were intensively FDG avid, with SUV max measuring > 10,56. FDG avidity was confirmed in the two lymph nodes on the right side of the neck, in the numerous bone metastases in the spine, long bones of the upper and lower extremities, in the orbital part of both mandibula and maxilla, with SUV max 5,48. (fig.3)

One of the neck lymph nodes was extirpated for additional pathologic analysis. The slides with immunohistochemical staining and the paraffin blocks of the tumor were sent to an outside pathology clinic for consultation, where the diagnosis of NUT-midline carcinoma was eventually confirmed.

Follow-up and outcome

The patient received two cycles of systemic chemotherapy for poorly differentiated tumors, but the progression of disease and growth of the tumor were extremely rapid and unstoppable, despite the short episodes of clinical improvement after chemotherapy. Overgrowth of the tumor was followed-up with plain chest x-ray and CT. After the second cycle of chemotherapy, patients' condition progressively deteriorated, and he eventually died.

DISCUSSION

NUT midline carcinoma is a rare and very aggressive tumor, considered to be a subtype of squamous cell carcinoma. (6,8,7)

Risk factors for this malignancy are not known, nor its exact incidence. (8,5)

Although there have been more reports on this malignancy in the last decade, the awareness of this tumor is still rather low among radiologists, pathologists and oncologists, mainly due to its rarity. The malignancy was believed to affect primarily young patients, but it can occur in patients of all ages and both sexes. (5,8)

The characteristic location of NUT carcinoma is in midline structures

of the head, neck and mediastinum. The cases of NUT carcinoma in other organs of the body, including parotid gland, pancreas, orbit and iliac bone have also been reported. (1)

We report the case of mediastinal NUT midline carcinoma in 11-year old patient with extremely fast progression, and death within four months from the beginning of the disease. This is consistent with data from the literature, and the reported average survival period of 6-7 months. We initially suspected a lymphoma, but it was ruled out by immunostaining for leukocyte common antigen (LCA). According to the literature, the most frequent tumors in the anterior and middle mediastinum, in this age group, are lymphoma or leukemia, followed by germ cell tumors in the anterior mediastinum. In the posterior mediastinum, the most common malignant tumor in this age group is neuroblastoma, as well as tumors of neurogenic origin. (9)

In differential diagnosis, the pathology finding suggested a mediastinal germ-cell tumor (GCT), or a poorly differentiated neuroectodermal tumor. The patient had elevated tumor markers AFP and NSE; the first one can be elevated in nonseminomatous germ-cell tumors, but has also been reported in the cases of NUT carcinoma. (4, 7) NSE can be elevated in patients with neuroblastoma, small-cell lung tumors and neuroendocrine tumors. Our patient had also had elevated ferritin, which can be found in Hodgkin's lymphoma, while high levels of LDH suggested a rapid progression of a malignant disease (7).

The diagnosis of a NUT midline carcinoma was confirmed in an outside referral pathology center. The biopsy material featured a widely necrotic, undifferentiated tumor with small blue round nuclei, some clear cytoplasm, and focal squamoid nests. A NUT - immunohistochemistry of the tumor-containing cervical lymph node biopsy showed strong nuclear positivity, homogeneously detectable in the tumor infiltrates, diagnostic for a NUT-midline carcinoma. Molecular analysis detected presence of the BRD4-NUTM1 fusion transcript.

Clinically, NUT-midline mediastinal carcinoma has no specific features, except its aggressive nature and rapid progression. (4)

Radiologically, these tumors are usually large at presentation >5 cm, with necrotic areas in the central parts. It metastasizes most commonly in lymph nodes and bones, metastases are rarely seen in the abdominal organs, and no cases of brain metastases have been reported in the literature. (5,7) Multiphasic MSCT is a good tool for evaluation of the tumor and its relation to the neighboring structures. The bone metastases were seen on FDG PET CT, and it is a modality of choice for staging of the disease, and clinical response to treatment. (3,10)

An efficient treatment for NUT carcinomas has not been established yet. Patients are treated with heterogenous systemic chemotherapeutics, used in treatment of germ-cell tumors, non-small lung carcinoma and sarcomas, as was the case with our patient. (6) There has been some good response to dose-dense chemotherapy in patients with NUT Midline carcinoma as well. (11) According to the reported data, combination of radio- and chemotherapy have shown better results than the chemotherapy alone. In our patient, the planned radiotherapy was not conducted due to the patient's poor clinical condition.

Extent of surgical resection and radiotherapy are independent predictors of progression free and overall survival rates, but these tumors usually present at the advanced stage, and patients are rarely candidates for surgery. (6)

Novel, promising therapy options are emerging, with direct acting inhibitors for the BRD4 and BRD3 bromodomains (BETi), and histone deacetylase inhibitor (HDACi). (7) Small case series have demonstrated clinical response to BET inhibitors (BETi) in patients with NUT-BRD4 fusion oncogene. (12)

CONCLUSION

NUT carcinoma is very aggressive and fatal malignancy, still underrecognized by oncologists, pathologists and radiologists due to its rarity. Clinical and CT features of NUT-midline carcinoma are not specific, but it shows extremely fast progression, with predilection for the midline structures of the thorax, head and neck. Ongoing clinical trials with new drugs have demonstrated some promising results, thus prompt diagnosis of this disease is essential in finding better therapy

options for patients with NUT-midline carcinomas.

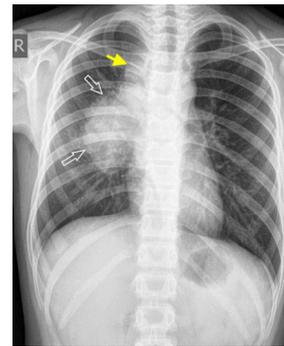


Figure 1. Chest x-ray showing round consolidation in the right hilum (open white arrows), and widening of the upper mediastinum (yellow arrow).

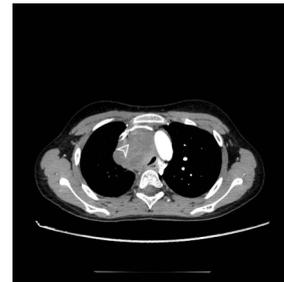


Figure 2.a Axial CT scan showing metastatic, confluent lymph nodes in the upper mediastinum (arrow head), compressing and dislocating trachea dorsally, and left brachiocephalic vein ventrally.

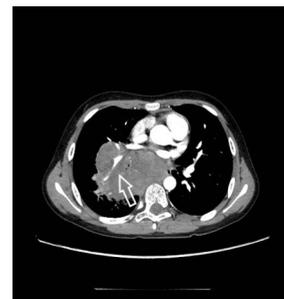


Figure 2.b Axial CT scan showing bulky, heterogenous, centrally necrotic tumor mass in the right hilum, propagating to the lung parenchyma, encasing branches of the pulmonary artery (white arrow), and narrowing main bronchus and its branches.



Figure 3. PET-CT scan showing avid metabolic activity of the mediastinal tumor mass, and metastases in the spine, right iliac bone, and long bones of the lower extremities.

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