

Nuclear Protein in Testis Midline Carcinoma Simulating Germ Cell Tumor of the Mediastinum

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Abstract

Nuclear protein in testis (NUT) midline carcinoma (NMC) is a very rare and aggressive human cancer characterized by overexpression of the nuclear protein in testis (NUT) most commonly due to a chromosomal translocation that fuses the NUT gene on chromosome 15 with the BRD4 gene on chromosome 19. It has been described mainly in younger individuals in the mediastinum and head and neck regions and known to be highly aggressive with poor outcomes. We report the case of 23 years old male, diagnosed with locally advanced mediastinal malignancy metastatic to the lung with elevated serum alpha-fetoprotein (AFP) suggestive of germ cell tumor. However, pathology with immunohistochemistry excluded the diagnosis of germ cell tumor and confirmed the diagnosis of poorly differentiated carcinoma. Despite aggressive treatment, evolution was marked by rapid clinical deterioration leading to death within 1 month of initial diagnosis. We report this case to underline the rarity of this disease, clinico-radiological and pathologic features, especially misleading presentation with germ cell tumors, treatment management and prognosis.

Keywords

NUT Midline Carcinoma, Mediastinal Mass, Alpha-Fetoprotein, Germ Cell Tumor

1. Introduction

NUT midline carcinoma (NMC) is a very rare, genetically defined, poorly diffe-

renciated carcinoma characterized by the rearrangements of the gene NUT.

The most common locations are midline structures such as the mediastinum or the head and neck area [1]. The diagnosis is difficult because of the rarity of these tumors and their indistinguishable morphology from other poorly differentiated carcinomas, which has led to an increased need in development of accurate and timely diagnosis of NMC by using NUT split-apart probes for FISH-mapping [2], but unfortunately this test is not widely available [1] [2].

These tumors are known to be aggressive and highly lethal, with poor response to conventional chemotherapy and an average survival of less than one year [1]. Further researches on molecular alterations and new trials are needed to overcome differentiation arrest in these tumors and improve outcomes of patients.

The aim of this work is to describe the clinico-radiological, pathologic and prognostic features of this rare disease especially the misleading presentation mimicking mediastinal germ cell tumors.

2. Case Presentation

We report the case of 23 years old patient, with unremarkable medical history, especially no smoking, treated in the Department of Medical Oncology at Hassan II University Hospital. He presented 2 months before his admission cough and chest pain associated with dyspnea. Chest X-ray showed an enlarged mediastinum with left para-hilar mass.

Thoraco-abdomino-pelvic CT scan showed voluminous left para-hilar mediastino-pulmonary mass with irregular contours measuring $90 \times 88 \times 76.5$ mm, invading pulmonary artery, the left bronchus and lobar division branches in addition to pulmonary veins and intimate contact with the descending aorta (Figures 1(a)-(d)). It was associated with lymphadenopathies in the left side of the hilum and para-tracheal and latero-aortic regions measuring 25×18.5 mm for the largest. These findings were suggestive of a differential diagnosis including mediastinal germ cell tumor (GCT), thymic tumor, lymphoma, and lung cancer. Laboratory exams found an elevated serum lactate dehydrogenase LDH at 2500 IU/L and elevated AFP at 350 ng/mL. Serum levels of β -human chorionic gonadotropin (β -hCG), was normal. Endobronchial ultrasound-guided transbronchial needle aspiration biopsy was performed and revealed at histological examination a poorly differentiated carcinoma. Tumor cells expressed intensively and focally cytokeratin AE1/AE3 (Figure 2), with intense and diffuse expression of p63 (Figure 3) and negative TTF1 and Cytokeratin 7 (CK7) (Figure 4) evoking a squamous origin. Synaptophysin and chromogranin were negative eliminating a neuro-endocrine origin (Figure 5 and Figure 6). Tumor cells were negative for Placental alkaline phosphatase (PLAP) as well as for CD30 eliminating a germinal origin.

CD3 and CD20 were negative excluding diagnosis of lymphoma, as well as CD5 which eliminated the thymic origin.

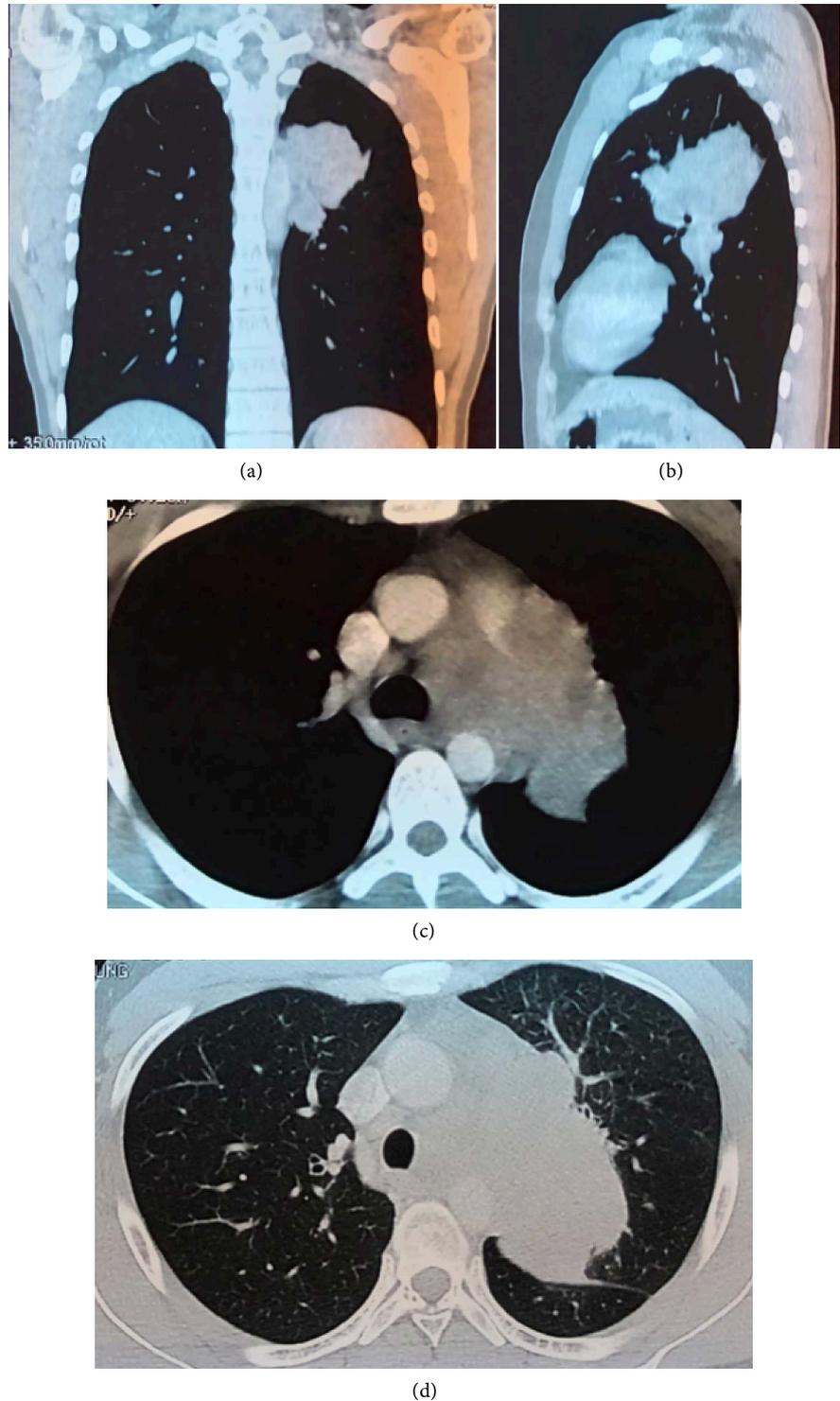


Figure 1. (a)-(d) Chest CT scan showing left para-hilar mediastino-pulmonary mass with irregular contours invading pulmonary artery, the left bronchus and lobar division branches in addition to pulmonary veins and intimate contact with the descending aorta associated with regional lymph nodes.

Taking into consideration the age of the patient, the undifferentiated character of the carcinoma, the mediastinal localization and the exceptional character of

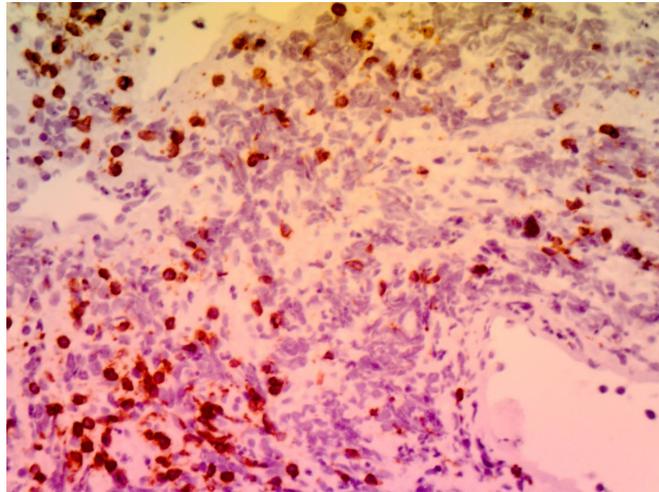


Figure 2. Immunohistochemistry showing intensive positive expression of cytokeratin AE1/AE3.

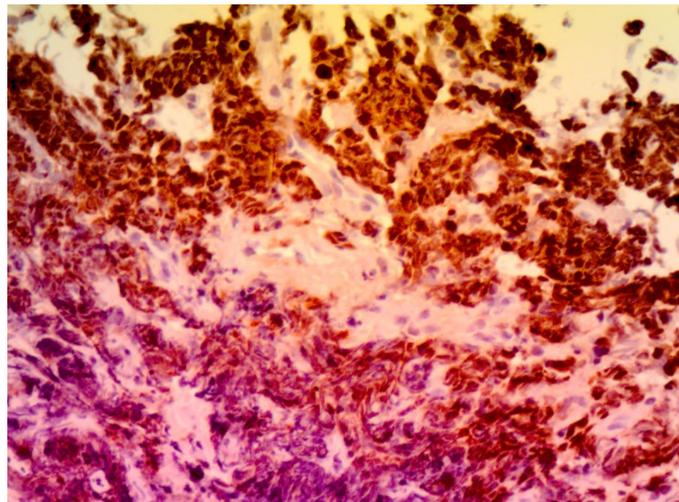


Figure 3. Immunohistochemistry showing intense and diffuse expression of p63.

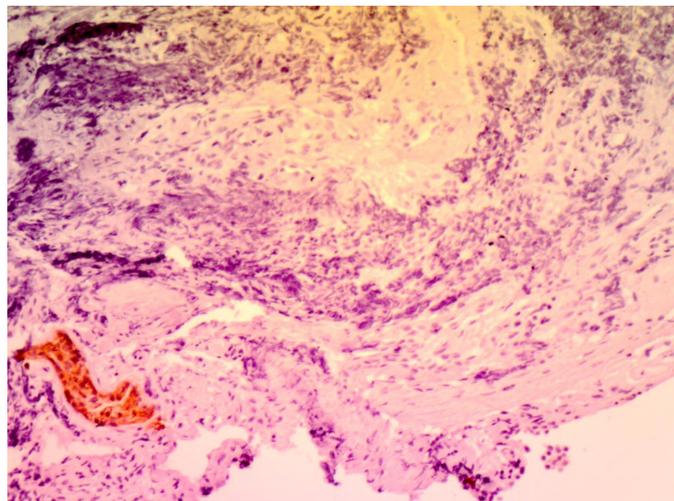


Figure 4. Immunohistochemistry revealing negative staining for CK7.

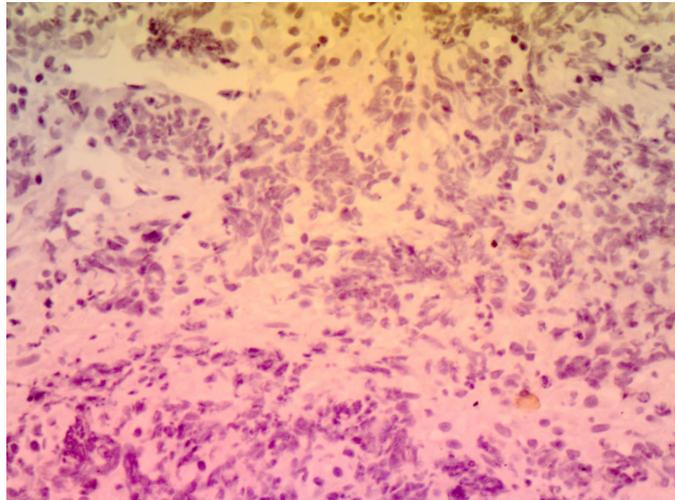


Figure 5. Immunohistochemistry revealing negative staining for Synaptophysin.

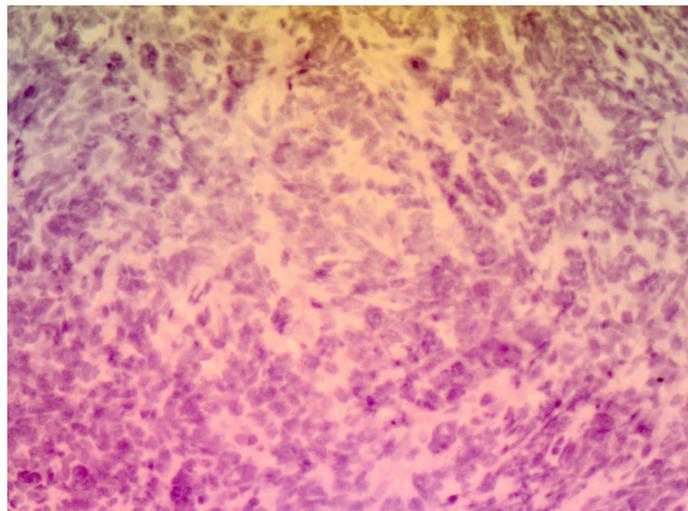


Figure 6. Immunohistochemistry with negative staining for Chromogranin.

squamous cell carcinoma at this age, the histological aspect and IHC were more suggestive of NUT midline carcinoma, and the Fish-mapping was requested to confirm the diagnosis.

Cisplatin based chemotherapy was decided while waiting for the NUT testing. The patient received first cycle of Cisplatin 20 mg/m² on days 1 - 5 and Etoposide 100 mg/m² on days 1 - 5; with few days of clinical improvement, then the evolution was marked by rapid deterioration of patient's conditions and elevation of serum levels of LDH increased to 3325 IU/L, and AFP to 2000 ng/mL suggesting a rapid progression of the disease leading to the death of patient one month after the initial diagnosis of NMC.

3. Discussion

Nuclear protein in testis (NUT) midline carcinoma is an extremely rare subtype of poorly-differentiated carcinoma and is considered one of the most lethal can-

cers [1]. The first two cases of NMC were described in 1991 [3] [4]. They interested the mediastinum and were considered thymic origin. It is considered to be an “orphan disease” because it is not only rare, it also has unclear tissue of origin [2]. The current frequency of NMC is not known and it is often under-recognized and under-diagnosed. This tumor might affect all ages and organs, but most frequently NUT midline carcinoma arises along the trunk or the head and neck regions in midline structures such as the mediastinum. But this concept of strict midline development has been challenged after reporting cases arising in the upper aerodigestive tract [5], bladder [2], pancreas [6], salivary glands [7] [8], orbit [9], lung [10], iliac bone [11], and the gynecologic organs [12].

These tumors were considered to affect mainly younger patients reflecting the higher likelihood that these tumors are analyzed for cytogenetic alterations.

A large study of Bauer *et al* including 63 patients with NMC showed that NMCs affected equally males and females and may occur at any age (range 0.1 - 78 years), with a median age of 16 years [13]. Another study of Stelow *et al.* showed an median age of 47 years among patients with NMC [14].

NMC usually spreads by local invasion, in addition to hematogenous and lymphatic metastasis [15]. Therefore, patients are usually diagnosed at an advanced stage of the disease with locally advanced unresectable tumor with lymph node metastases and distant metastases in the lung and bones [15] [16]. This high tumor burden is responsible of symptoms such as dyspnea, chest pain, cough and potential rapid performance status deterioration [15] [16] [17].

NMC may be mis-diagnosed as any other poorly differentiated monomorphic malignancy such as poorly differentiated squamous cell carcinoma, sinonasal undifferentiated carcinoma, small cell carcinoma or Ewing sarcoma [3]. At immunohistochemistry, NMCs were found to express antibodies against cytokeratin (CK) [2] [18] and usually react with antibodies to pancytokeratin [3], CK7, and sometimes focally to CK20 [2] [16]. They also express mostly P63/p40 which exists with squamous differentiation [15] [16]. In a study conducted in children and young adults, NMCs were found to have CD34 immunoreactivity [2]. Neuroendocrine markers including TTF1, synaptophysin and chromogranin may sometimes be positive [15]. However, NMCs show no immunoreactivity with melanocytic tumors (HMB45, S100 protein) and markers expressed in muscles (smooth muscle actin, desmin, myoglobin) [19]. No immunoreactivity was found with AFP, neuron-specific enolase (NSE), placental alkaline phosphatase (PLAP), CD57, CD99 [18].

Confirmation of NMC diagnosis should be done by FISH to demonstrate the NUT translocation [1] [19], which can detect all NMCs including NUT-variants. [1] [18]. Pathognomonic chromosomal rearrangement between the NUT gene with either bromodomain-containing protein 4 (BRD4) or, less frequently, with BRD3 (on chromosome 9), leading to the fusion genes BRD4-NUT or BRD3-NUT, respectively [13] [20] [21].

Therefore, Immuno-histochemistry for NUT is recommended in all poorly differentiated carcinomas with lack of glandular differentiation developing in the mediastinum or everytime the clinical presentation is not completely consistent with frequent and common tumors such as midline or uncommon localization, no smoking habit, young age and rapid resistance to chemotherapy [13].

Regarding the elevation of serum AFP level, it has been associated with chronic liver diseases and certain cancers such as hepatic primary tumors and metastases, bilio-pancreatic, gastric and lung cancer, and non-seminoma germ-cell tumors. Furthermore, the mediastinal localization and young age, in addition to elevation of AFP is more suggestive of a non-seminoma germ-cell tumor (NSGCT) [20] [21]. This elevation of serum level of AFP in NMCs might be explained by the hypothesis that these cells arise from primitive neural crest-derived cells [22].

But, despite the elevation of serum tumor markers for GCT, NMC must be evoked, and the definitive diagnosis can be confirmed only by using the monoclonal antibody (clone C52B1) for the NUT protein, which has high sensitivity (87%) and specificity (100%) in non-GCTs even without positive testing of the fusion oncogene with FISH [22].

In our case, the presentation mimicked the one of an extra-gonadal NSGCT given the young age of patient, the midline location and the elevated serum AFP level. But to avoid misleading diagnostic interpretation in such cases, patient information should be shared between clinicians and pathologists in addition to considering NUT midline carcinoma in the differential diagnosis for poorly differentiated carcinoma arising in midline structures. Measuring serum AFP levels may be an option in monitoring the disease.

Regarding treatment, there is no specific effective treatment for NMCs, and conventional chemotherapy is still the mainstay of treatment for advanced disease despite the poor results in term of response and the poor survival outcomes which does not exceed one year [13]. Even dose-dense chemotherapy regimen was tested but not found to have better results [23]. Therefore, novel targeted therapeutic approaches are highly needed. New drugs such as BET inhibitor (BETi) and histone deacetylase inhibitor (HDACi) are now under investigation and inclusion of patients with NMC in clinical trials should be encouraged [24] [25].

4. Conclusion

NUT midline carcinoma is a rare aggressive genetically defined cancer known to be highly lethal, with poor response to conventional chemotherapy and an average survival of less than one year. Clinical features similar to those of mediastinal non-seminomatous germ cell tumors as serum levels of AFP can be elevated. Therefore, immunohistochemistry for NUT should be considered in all poorly differentiated carcinomas arising in midline structures and further researches on molecular alterations and new therapeutic approaches are needed to improve the outcome of patients with NMC.

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