CASE REPORT

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A RARE CASE OF LUNG NUCLEAR PROTEIN IN TESTIS CARCINOMA

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Abstract. *Nuclear protein in testis carcinoma is a very rare but extremely aggressive high-grade carcinoma characterized by the presence of a fusion NUT gene – an oncogene. It is also called midline carcinoma because it mainly affects structures along the midline – head, neck, and lungs. We report a case of a woman with lung nuclear protein in testis carcinoma, diagnosed by bronchoscopic fibro-punch biopsy. The histological examination showed massive infiltration of bronchial wall of predominantly spindle-shaped neoplastic cells with unclear cytoplasmic borders. In some areas groups of rounded cells with clearly visible nucleoli and high mitotic rate were present. Foci with necrosis were also found. Immunohistochemistry showed positive expression of cytokeratin, p63, CD56 and nuclear protein in testis antibodies and negative reaction for TTF1 and chromogranin A in neoplastic cells. The proliferative activity of tumor cells was very high (> 70%). Immunohistochemical study of the nuclear protein in testis expression is mandatory in cases with poorly differentiated lung tumors, with predominantly midline mass.*

Key words: *nuclear protein in testis, midline carcinoma, lung tumor, lung, NUT gene*

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INTRODUCTION

Nuclear protein in testis (NUT) carcinomas are extremely rare malignant neoplasms that can be found anywhere in the body, but they mainly affect midline structures – head, neck and lungs [1, 2]. The first reported cases of NUT carcinoma were among children and adolescents. Less than 100 cases have been reported [3]. Their etiology is still unclear. NUT carcinomas are often diagnosed at an advanced stage because the early manifestations are non-specific. Their microscopic characteristics include nests of monomorphic, small cells with irregular contours of the nuclei, with focal keratinization. They are often accompanied by necrosis. No in-situ lesions have been reported. They infiltrate adjacent structures. Expression of NUT is detected immunohistochemically. X-ray examination of the lungs visualizes their rapid progression – they form a significant consolidation – 2 to 8 weeks after the initial manifestation.

CASE PRESENTATION

A woman in her 20s was admitted to the hospital for the first time due to complaints of pain in the left chest area, cough with expectoration of dark blood, before that – clear blood, and a change in the voice. There was evidence of infiltrative pneumonic tuberculosis of the lungs and no other concomitant diseases. The

patient was a smoker – 10 cigarettes a day, and did not smoke for 3 months.

At the admission the patient was alert and fully oriented; the visible mucous membranes were pale pink; no evidence of peripheral lymphadenomegaly was present. Breathing was bilaterally vesicular, in the left area – bronchial, posterior and axillary, at the base and front – absent. No other deviations in the physical status were found. The patient had a negative PCR test for SARS-CoV-19. Laboratory tests and blood gas analysis were normal.

The endoscopy finding showed that the carina is enlarged (TBNA). The left bronchus was compressed and there was a stricture, with swollen mucosa. The right bronchus was without any change.

CT scan of the lungs, mediastinum and abdomen was performed. The left lung was narrowed. In the left hilus, a pathological formation, which completely obstructed the left main bronchus, was visualized. Atelectasis was present on the left and lung tissue was detected only in part of the left lower lung. In the pleura dorso-basal round lesions up to 1.5 cm in size were observed. A moderate pleural effusion on the left dorso-basal area was also observed. In the left adrenal gland a homogeneous pathological formation with a size of 1.5/1.5 cm was visualized. Multiple enlarged paratracheal and parabronchial lymph nodes were visualized in the left mediastinum. Enlarged lymph nodes were observed retroperitoneally, as well (Fig. 1).

A cytological examination was also performed: cytolytically altered cells, possibly neoplastic, were found. Histological examination (fibro-punch biopsies) described the presence of fragments of bronchial wall with massive infiltration among muscle fibers. Predominantly spindle-shaped neoplastic cells with unclear cytoplasmic borders were described. In some areas larger, rounded cells with clearly visible nucleoli were also detected. The presence of mitosis and foci of necrosis could also be observed. The immunohistochemical analysis showed positive expression of CKA1/A3, p63, NUT, focal expression of CD56 and negative expression of TTF1, Chromogranin A, CD34. The proliferative activity was high – Ki-67 – over 70%, which confirmed poorly differentiated carcinoma, defined by the presence of NUT gene rearrangement (Fig. 2, 3, 4, 5, 6, 7, 8, 9).

Driver mutations play a fundamental role in tumorogenesis, so analysis of these mutations can help to reveal the complex molecular pathogenesis of lung cancer. We did EFGR, ALK, PD-L1, ROS1 analysis. The expression was negative. The patient was referred to an oncology department for further therapeutic approach.

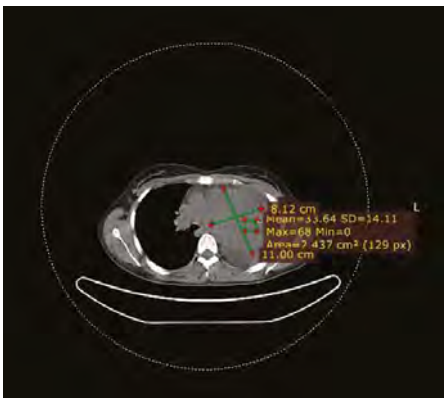

Fig. 1. CT scan revealed a large soft tissue formation with a heterodense structure in the matrix involving the left lung and left main bronchus at a distance below 20 mm from the carina.

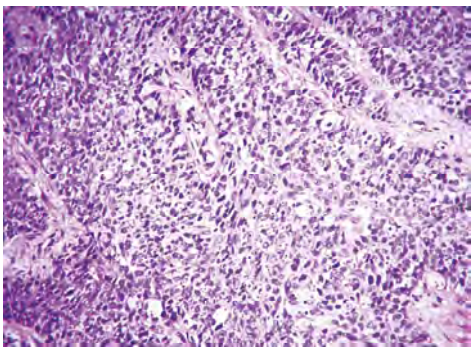

Fig. 2. Monomorphic, primitive-appearing tumor cells with pale to basophilic cytoplasm, irregular nuclei and distinct nucleoli infiltrating lung tissue.

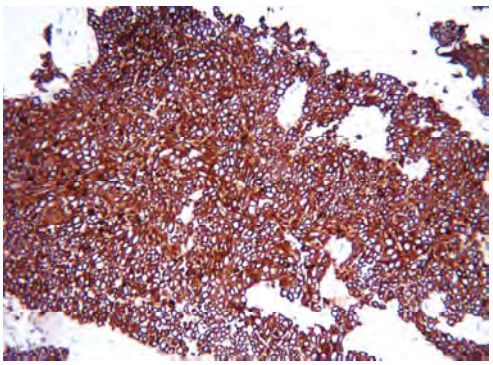

Fig. 3. A1/A3 (PANCK) – diffuse expression in neoplastic cells

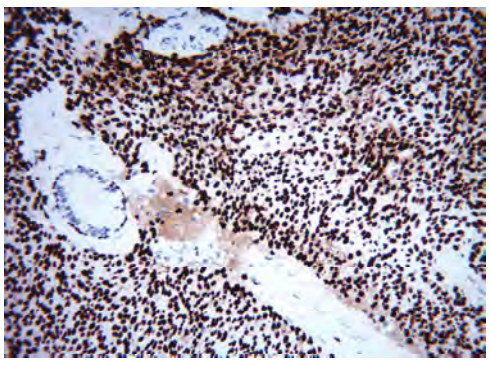

Fig. 4. P63 – diffuse expression in neoplastic cells

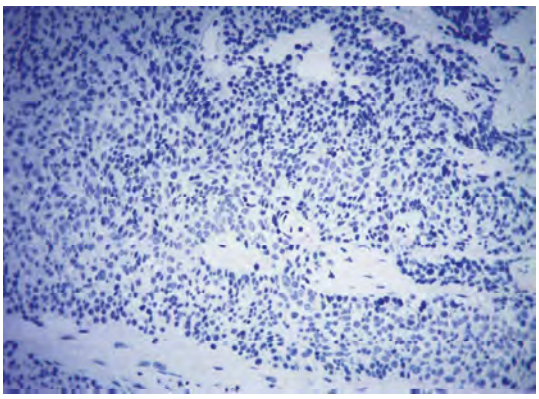

Fig. 5. TTF1 – negative expression

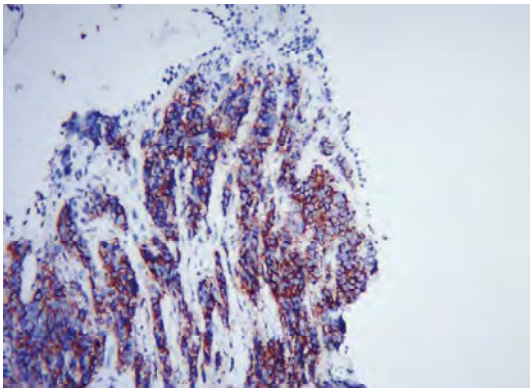

Fig. 6. CD56 – focal expression in neoplastic cells

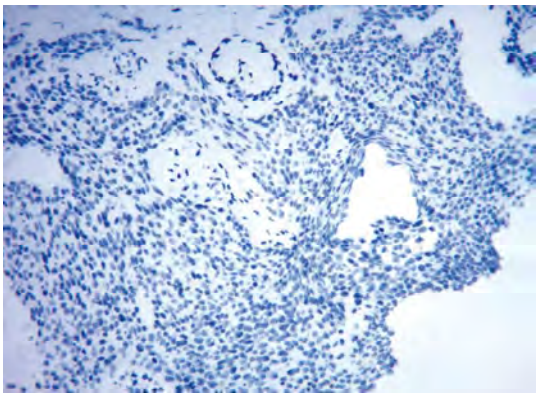

Fig. 7. Chromogranin A – negative expression

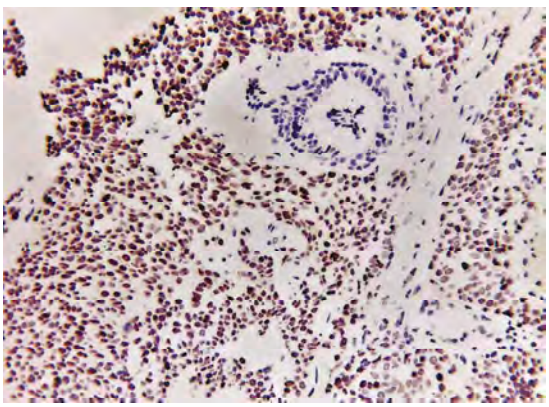

Fig. 8. NUT – moderate intensity expression in neoplastic cells

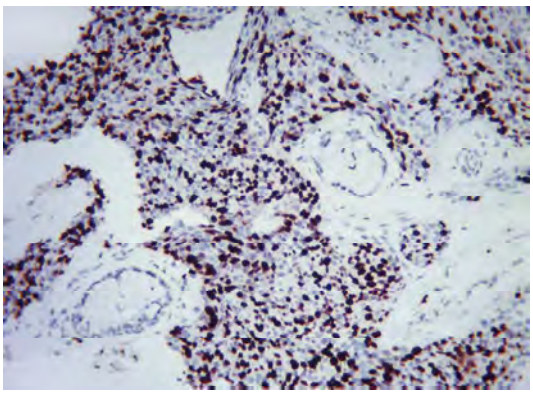

Fig. 9. Ki67 – high proliferative activity – over 70%

DISCUSSION AND CONCLUSIONS

NUT carcinomas are rare but extremely aggressive malignant neoplasms with a still unclear etiology. They are associated with chromosomal translocation between the NUTM1 gene in 15q14 and BRD4 (19p13.1) in approximately 70% and less commonly other genes such as BRD3 (9q34.2) and NSD3 [1, 2, 5, 6]. The resulting oncoprotein promotes proliferation of poorly differentiated cells [2]. The NUT translocation can be diagnosed using karyotyping, ICH, FISH or RT-PCR [1, 3, 7, 8, 13, 15]. The most common localizations are structures along the midline – head, neck, lungs, but can be found elsewhere [4, 6, 8, 12]. NUT carcinoma can arise in all ages, including younger patients [9]. Females and males are equally affected [6].

Histological and immunohistochemical analysis are of particular importance for the correct diagnosis. The microscopic finding includes clusters of monomorphic, poorly differentiated cells with irregular nucleoli, granular chromatin, and focal keratinization [3]. The expression of a NUT antibody that indicates NUTM1 gene rearrangement is positive. NUT protein expression in normal mature adult tissue is restricted only to the testis [11]. A large spectrum of cytokeratins is also positive, as well as p63, p40, which points to squamous cell origin. CD34 expression is also often positive [8, 10].

The differential diagnosis includes any neoplasm with low differentiation – squamous cell carcinoma, adeno-squamous carcinoma, small cell lung cancer, Ewing's sarcoma, sinonasal undifferentiated carcinoma germ cell tumor, acute leukemia. Immunohistochemical assay is key to the differentiation of these histological types [1, 6, 8, 15].

The clinical manifestation of NUT carcinomas is not specific. It depends on location of the tumor and usually produces mass-related symptoms [9, 16]. The

diagnosis is difficult. The treatment is complex – it includes surgical methods, radiotherapy and chemotherapy [9]. NUT carcinoma is usually refractory to conventional treatments and it is often unresectable because it is often diagnosed at an advanced stage with widely spread metastases [1, 9]. Trials investigating the treatment of NUT carcinoma with bromodomain inhibitors are ongoing [2, 6, 10]. The prognosis is extremely unfavorable – the mean survival is about 6-7 months [2, 3, 7, 11].

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