CASE REPORT

Lung Adenocarcinoma with Unusual Genetic Mutations: Case Report

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ABSTRACT

Introduction: **Lung adenocarcinoma is the most common malignant tumor of the lung. According to the statistics, it is the cancer with the highest mortality rate. In its diagnostic process, genetic testing is routinely performed to detect common mutations: *EGFR*, *ALK*, *KRAS*, *BRAF* or *ROS1*. However, these mutations are not always present, and expanding the screening to the other alterations may be found useful. Expanding tumor's genetic detection profile offers targeted treatment options. Finding atypical mutations can be proven crucial in further diagnosis and the treatment process. More accurate genetic testing of patients makes it possible to select an appropriate treatment that acts on a drug-specific biomarker. More accurate genetic testing of patients enables/ creates possibility to select an appropriate treatment according to the specific tumor's cells characteristics as a high TMB score for pembrolizumab.**

Case Description: **A 68-year-old patient was admitted to the Department of Surgery for the removal of a nodule in the left lung. Histopathological examination revealed carcinoma nonmicrocellulare. Subsequently, the patient was hospitalized due to the complaints of a headache and right-sided hemiparesis. Imaging studies showed the presence of a frontal lobe brain tumor reaching 4-5 cm in diameter. A left frontal craniotomy was performed. Histopathological examination revealed metastatic papillary adenocarcinoma. The specimen was subjected to the genetic testing for mutations in the *EGFR* gene, *ALK* gene rearrangements, *ROS1* and PD-L1 protein expression. Immunohistochemical examination result depicted TC = 2% of cells showing positive reaction with anti-PD-L1 antibody. The gene mutations were found negative. The histopathological material was subjected to the next-generation sequencing, which revealed multiple mutations and TMB score of 71. The patient was qualified for a regimen of pemrolizumab and pemetrexed. The response to the treatment was good**

Conclusions: **Lung adenocarcinoma is a severe condition with high mortality rate. This cancer is characterized by multiple mutations. Awareness of the genetic profile and mutation status can be found very helpful in the treatment selection. The possibility of the usage of the new targeted medicaments in case of the atypical mutation occurence further highlights the importance of the wide genetic screening.**

KEY WORDS

lung adenocarcinoma, lung cancer, adenocarcinoma spectrum, immunotherapy, TNM

INTRODUCTION

Lung cancer is the leading cause of the cancer-related death worldwide, and lung adenocarcinoma is the most common subtype of the disease. Worldwide, treatment outcomes for lung cancer remain poor. Lung cancer is often asymptomatic in its early stages. Many patients are diagnosed with an advanced form of the disease with a poor prognosis for improvement. It is estimated that lung cancer will account for more than 21% of cancer-related deaths in 2023[1]. Depending on the stage, the 5-year survival rate is about 55% for localized lung cancer, in contrast to only 5% for the distant metastases[2].

The World Health Organization (WHO) Classification of Tumors published in 2015 presented a different approach and classifications of the lung adenocarcinoma compared to the previous editions. The various histological subtypes of the adenocarcinoma are now classified along a spectrum from the slow pre-invasive lesions to the aggressive forms of invasive adenocarcinoma with a poor prognosis[3]. Increasing emphasis is being placed on molecular and genetic analyses of adenocarcinomas due to the rapid development of new targeted therapies.

Genetic screening for *EGFR* or *ALK* mutations, occurring in 15% of patients[4] is now routinely used in patients with lung adenocarcinoma. Higher efficacy of the tyrosine kinase inhibitors treatment in comparison to usual chemotherapy accounts for common screening in said patients. The key mutations responsible for lung adenocarcinoma are *KRAS*, *EGFR* and *BRAF* mutations, which account for 29.1%, 14.2% and 7.2% of cases, respectively. Adenocarcinomas also often contain activating mutations in *ERBB2* and *PIK3CA* or translocations in *RET* and *ROS1*, as well as loss-of-function mutations and deletions in tumor suppressor genes such as *TP53*, *STK11*, *RB1*, *NF1*, *CDKN2A*, *SMARCA4* and *KEAP1*.Awareness of the additional gene mutations/ alterations in lung adenocarcinoma can be useful in the treatment selec-

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tion by favouring targeted therapy[5-7].

Tumor mutation burden (TMB) is an indicator associated with a better response to treatment with the immune checkpoint inhibitors (ICI) which is independent of the PD-L1 expression levels[8,9]. An analysis of 27 cancer types showed a positive association between TMB and ICI treatment benefit[10]. The detection of a variety of the gene mutations offers new wider treatment options. A *PALB2* mutation sensitizes the cell to mitomycin C[11] and cisplatin[12] and, in turn, amplification or activating mutation of *ERBB3* can confer sensitivity to *ERBB2*-targeted therapies, including antibodies such as trastuzumab, pertuzumab and trastuzumab emtansine[13].

Various studies show that *ATRX* alterations can confer sensitivity to WEE1 inhibition[14,15]. The same is true for tumors with *TP53* mutations[16,17]. Additionally, preclinical studies have linked NBN inactivation to sensitivity to PARP inhibitors[18,19]. And in turn, an anti-VEGFR inhibitor has shown efficacy in patients with VHL.[20]. All of these mutations can occur in a patient with lung adenocarcinoma and confer new therapeutic options.

CASE DESCRIPTION

A 68-year-old patient was admitted to the Department of Thoracic Surgery for surgical removal of a left lung nodule. VATS (Video Assisted Thoracoscopic Surgery) upper lobectomy was performed. A lung fragment measuring 20.5 x 10 x 5.5 cm with a pleural nodule measuring 1.9 cm in diameter and node No. 11 measuring 0.7 cm in diameter were retrieved. Intraoperative examination revealed carcinoma non-microcellulare without features of vascular invasion or infiltration of the perinephric spaces. Lymph nodes featured coal dust.

The patient was then admitted to the neurology department for complaints of a headache and right-sided hemiparesis. MRI (magnetic resonance imaging) of the head was performed, which showed the presence of a brain tumor with radiological features of the metastasis to the left frontal lobe, reaching 4-5 cm in diameter with a solid and cystic part, surrounded by a wide zone of edema. A left frontal craniotomy was performed. Histopathological examination resulted in diagnosis of the metastatic papillary adenocarcinoma.

The hispoathological material was subjected to the genetic testing for mutations in the *EGFR* gene, which was not detected. The material was forwarded for the determination of the *ALK* gene rearrangement, *ROS1* and PD-L1 protein expression. Immunohistochemistry resulted in TC = 2% of cells showing positive reaction with anti-PD-L1 antibody. Rearrangements of *ALK* and *ROS1* were found negative.

The material was subjected to the more thorough genetic screening. Next-generation FoundationOne CDx sequencing was performed. The results showed no changes in the typical genes: *ALK*, *BRAF*, *EGFR*, *ERBB2*, *KRAS*, *MET*, *RET* and *ROS1*. The TMB (tumor mutation burden) score was high, reaching 71 while no microsatelite instability was found. The mutations in the following genes were detected: *PALB2*, *ERBB3*, *STK11*, *ATRX*, *MCL1*, *NBN*, *NFKBIA*, *NOTCH3*, *RB1*, *TERT*, *TP53*, *VHL* and others.

During the next hospitalization, a follow-up CT (Computed Tomography) scan of the head, chest, abdomen and pelvis was performed in 2.5/5 mm layers in the overview scan and in 2.5 mm layers after intravenous shadowing agent administration. The examination was compared to the previous ones. Examination of the head showed slight postoperative changes with the suspicion of ischemia and edema in the postoperative locus. Structures of the Central Nervous System were found without obvious pathological changes and without features of the intracranial hemorrhage. Ventricular system was asymmetric and not displaced with typical width for age. Overall image of the pulmonary parenchyma depicted no obvious differences from the previous examination. No changes in the area of the surgical locus, including single small lymph nodes in the vicinity and the image of the mediastinal and hilar lymph nodes bilaterally were noted, including lack of the obvious features of pathological enlargement. Soft-tissue lesion of approximately 21 x 13 mm in the subcutaneous adipose tissue of the anterior chest wall was found on the right side. Other examinations, including abdominal cavity, pelvis and bones, did not find pathological changes.

For treatment, the patient was enrolled in the drug program: first-line treatment of patients with non-small cell lung cancer according to the regimen: pembrolizumab (200 mg) + Pemetrexed 500 mg/m2 + DPD 75 mg/m2 every 21 days, with efficacy evaluation every 3 months.

After 3 months, the patient completed treatment on the Pemetrexed 500 mg/m2 + DDP 75 mg/m2 regimen and was qualified to continue immunotherapy on the Pembrolizumab regimen. A follow-up CT was performed showing stabilization of the disease. During the most recent hospital stay, cycle 9 of the pembrolizumab was administered. The patient showed good tolerance to the treatment and was discharged home.

DISCUSSION

PD-1 is a trans-membrane receptor that binds to two ligands: the programmed cell death protein ligands PD-L1 and PD-L2. PD-1 is not present on the resting lymphoid cells, but is expressed on the activated CD4+ and CD8+ T cells, B NK cells, macrophages and dendritic cells. PD-L1 is expressed on the tumor cells of many different cancers. Binding to PD-1 on the T cells leads to their inhibition. PD-L-1 expression is the main mechanism by which cancer cells can evade immune attack[21]. Blockade of PD-1 prevents cell-cell interaction, leading to the restoration of T-cell-mediated anti-tumor immunity[22].

Pembrolizumab is a humanized IgG4 kappa anti-PD-1 monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2 ligands to enhance anti-tumor immunity[21]. Pembrolizumab or nivolumab show response rates of 40-45% for the first-line melanoma and 20% for the second-line non-small cell lung cancer. Therefore, more and more attention is being paid to identifying and developing predictive biomarkers for the efficacy of these inhibitors. In recent years, new data on tumor biomarkers have been obtained that may have implications for a better understanding of the response to these drugs[23]. A number of clinical trials have shown that cancer patients with TMB ≥ 10 Muts/Mb may show higher sensitivity to PD-1 or PD-L1 inhibitors[24,25]. Patients with a high TMB score additionally benefit more clinically from these therapies than patients with TMB < 10, what could be observed in the case of our patient.

Patients with a high TMB show significantly higher response rates and longer survival or disease remission times than patients with lower TMB. Moreover, the correlation between TMB and outcome was linear in patients treated with PD-1/PD-L1 blockade as a monotherapy[24]. The microsatellite stability of the tumor also appears to have an additional impact on the treatment outcomes. PD-1/PD-L1 blockade is also highly effective for tumors with high microsatellite instability with deficient repair of mismatched bases[25]. However, except for colorectal and endometrial cancer, few tumors have commonly detected high MSI[26]. Results from the KEYNOTE study showed that the strongest response to pembrolizumab was demonstrated in patients with high TMB with concomitant high GEP (gene expression profile) (37 to 57%) and 11 to 23% with low GEP. In comparison, the response to this drug in patients with low levels of these biomarkers was up to 9%[27]. Thus, the data shows that stable tumors having high TMB are more common than tumors with high instability and may benefit from the immunotherapy. Clinically validated biomarkers responding to the anti-PD-1 monoclonal antibody pembrolizumab include PD-L1 expression in specific tumors and high microsatellite instability regardless of tumor type; however, tumor mutation burden is a novel prognostic biomarker for pembrolizumab. In addition, a significant increase in survival was observed regardless of the size of the TMB in patients treated with pembrolizumab in combination with chemotherapy compared to the use of chemotherapy alone[28].

CONCLUSIONS

Lung adenocarcinoma is a severe condition with high mortality rate. This cancer is characterized by multiple mutations. Awareness of the genetic profile, biomarker and mutation status can be found very helpful in the treatment selection. The possibility of the usage of the new targeted medicaments in case of the atypical mutation occurence further highlights the importance of the wide genetic screening. The heavily personalized treatment choice based on the molecular characteristics of the tumor increases possibility of the high response rate to the therapy and greatly improves the chances of prolonged survival for the patient. Therefore, it is very important to carry out extended genetic and molecular screening and select a highly tumor-specific treatment.

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