VIA MEDICA

CASE REPORT

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Pulmonary pleomorphic carcinoma treated with immune checkpoint inhibitors — a case series

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ABSTRACT

Pulmonary pleomorphic carcinoma (PPC) is a rare subtype of primary lung cancer, accounting for less than 2% of annual diagnoses. It is characterized by a low response rate to systemic treatment, an unusual molecular profile, an average high tumor mutation burden score, and poor prognosis. This article presents four cases of patients with PPC treated with immune checkpoint inhibitors.

Two patients were women diagnosed with spindle cell carcinoma, while the other two were men diagnosed with pleomorphic carcinoma. The mean age was 68.75 years, and the clinical stage varied between II and IV. Two patients received immunotherapy as a second-line treatment, while the other two received it as a first-line therapy. Most patients had a history of smoking, with half of the patients smoking during the treatment. Only one patient experienced disease progression during treatment, while three achieved partial response, and two patients maintained response for over 40 treatment cycles. The toxicity of the treatment in patients reached up to grade 3 according to the Common Terminology Criteria for Adverse Events, and involving multiple sites.

Given the highly specific molecular landscape and the promising results observed in the majority of patients, immunotherapy appears to be a favorable viable treatment option for the management of this rare neoplasm.

Keywords: non-small cell lung carcinoma, pulmonary pleomorphic carcinoma, immunotherapy, immune checkpoint inhibitors, nivolumab, pembrolizumab

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Introduction

Checkpoint inhibitor immunotherapy (ICI) belongs to one of the most promising therapeutic regimens of recent years. The heightened significance of this treatment is visible in pulmonary pleomorphic carcinoma (PPC). This unusual subtype of non-small cell lung carcinoma (NSCLC) is characterized by rare occurrence, low response rates towards systemic treatment, and poor prognosis. In addition to a highly specific molecular landscape with low expression of potentially "druggable" targetable alterations, this rare neoplasm usually has a high tumor mutation burden (TMB) score. Therefore, immunotherapy seems to be a favorable treatment of choice in its management. We present a series of four clinical cases of PPC patients treated with ICI.

Case reports

Case 1

A 60-year-old female, with a 40-pack-year smoking history, was admitted to the Department of Clinical Oncology and Chemotherapy with a presumptive diagnosis of lung cancer. This was based on the observation

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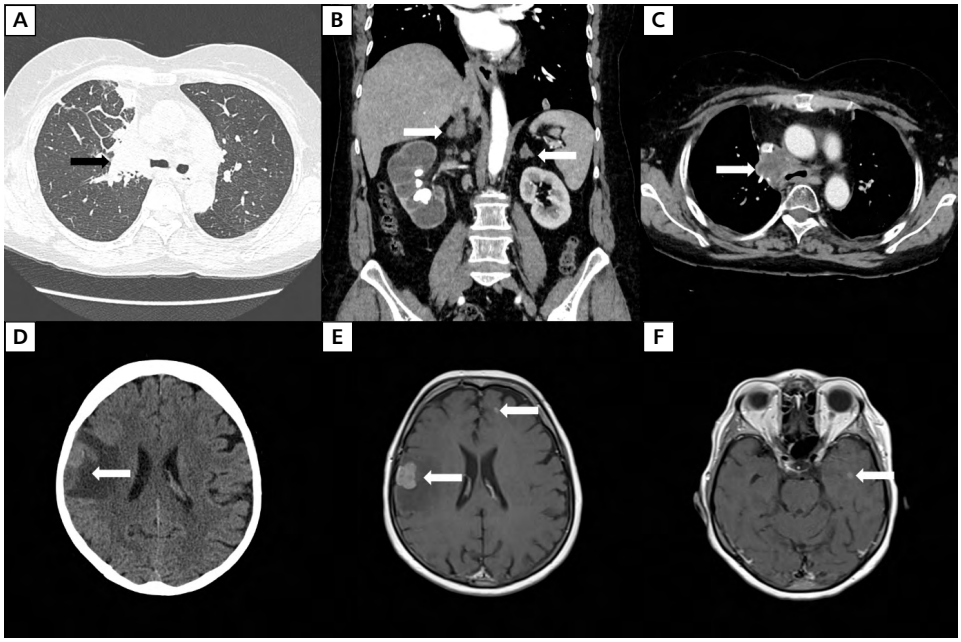

Figure 1. A. Computed tomography (CT) scan of the chest visualizing a tumor in the right lung; **B.** CT scan of the abdomen demonstrating the presence of metastatic lesions within the right and left adrenal glands; **C.** CT scan of the chest depicting compression of the mediastinal mass on the superior vena cava; **D.** CT scan of the brain showing the presence of a metastatic lesion in the temporal-frontal region of the brain; **E, F.** Magnetic resonance imaging (MRI) scans of the brain showing the presence of multiple metastatic lesions in the brain

of radiographic abnormalities on a chest X-ray, which were identified as a tumor of the right lung on the computed tomography (CT) scan (Figure 1A). The primary treatment included right upper lobectomy accompanied by lymphadenectomy and partial resection of the eighth rib achieving a complete resection (R0). Examination of the specimen revealed pleomorphic carcinoma of the lung. Approximately one half the tumor was spindle cell carcinoma, and the remainder was adenocarcinoma and large cell carcinoma. The histopathological evaluation showed distinct staining patterns for the tissues. The spindle cell component exhibited positive staining for vimentin and CK AE1/AE3, negative staining for p40, and no staining for CK7 and TTF1. In contrast, the large cell component demonstrated positive staining for CK AE1/AE3, CK7, TTF1, and negative staining for vimentin. Additionally, local positive staining for mucicarmine was observed. Necrosis was identified in 35% of the examined tissues. The tumor was diagnosed as pT2aN1Mx (stage IIB) pleomorphic carcinoma of the lung, exhibiting a predominantly spindle-cell pattern with partially mixed components of adenocarcinoma and large-cell carcinoma.

Two months after tumor resection, a control CT scan found multiple pathological mediastinal lymph nodes and an irregular tissue area near the resection line, suggesting a possible recurrence of the neoplastic process. According to the decision of the oncological team, the patient was qualified for four cycles of chemotherapy consisting of gemcitabine and cisplatin followed by radical radiotherapy. A partial response was observed on the control CT after administering the 2nd cycle of chemotherapy. Molecular profiling demonstrated an absence of mutations in the *EGFR* gene and rearrangements in the *ROS1* and *ALK* genes and the programmed cell death ligand 1 (PD-L1) expression of 50%. Radiotherapy of the right lung cavity, mediastinum, and supraclavicular regions was performed in 5 daily fractions of 4 Gy up to a total dose of 20 Gy using the VMAT technique. A follow-up CT scan revealed disease progression, with evidence of dissemination in the lungs, mediastinal infiltration, and distant metastases (Fig. 1B). Due to the progression and metastatic spread, palliative immunotherapy treatment was implemented. Only five cycles were possible, as the patient experienced anaphylaxis following the last administration.

A control CT scan showed further disease progression including brain metastases, and the patient developed symptoms of superior vena cava syndrome (Fig. 1C, D). The patient was hospitalized at the Department of Neurology due to slowed speech and upper limb weakness. A magnetic resonance imaging (MRI) scan confirmed the brain metastases found on CT (Fig. 1E, F). Immunotherapy was discontinued due to the progression of the primary disease.

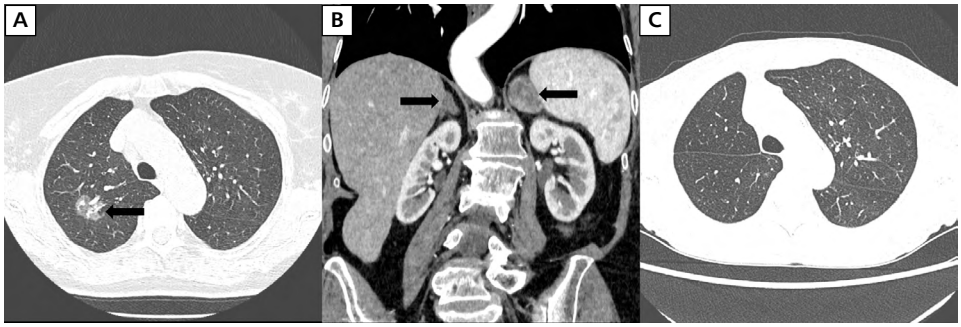

Figure 2. A. Computed tomography (CT) scan of the chest visualizing a tumor in the right lung; **B.** CT scan of the abdomen demonstrating the presence of metastatic lesions within the right and left adrenal glands; **C.** CT scan of the chest showing stabilization of the disease

Case 2

A 75-year-old female patient, never a smoker, was admitted to the Department of Clinical Oncology and Chemotherapy for suspected lung cancer. The suspicion was initially identified through the analysis of a CT scan, which was conducted as part of the patient's evaluation for back pain and suspected degenerative changes in the spine (Fig. 2A). As part of the oncologic management plan, the patient was referred for right upper lobectomy with lymphadenectomy. Subsequently, the patient contracted the SARS-CoV-2 virus, necessitating hospitalization, which resulted in a delay in the initiation of adjuvant treatment. The histopathological diagnosis of the material obtained during surgery was T3NxMx (stage IIB) spindle cell carcinoma. The patient was classified as clinical stage III. Molecular testing of the specimen revealed a high expression of PD-L1 in tumor cells (TC = 60%), while genetic testing indicated the absence of mutations in the *EGFR* gene and rearrangements in the *ROS1* and *ALK* genes. A subsequent CT scan showed the presence of metastatic disease in the adrenal glands (Fig. 2B). Due to the metastatic spread, the patient started a systemic treatment with pembrolizumab every three weeks. A follow-up CT scan conducted three months later demonstrated a notable reduction in the size of the metastases, indicating a partial response to the administered treatment. A follow-up scan showed stabilization of the disease (Fig. 2C). After the 12th cycle of immunotherapy, we observed acquired vitiligo of the skin in the hip region, but it resolved after the 14th cycle of immunotherapy. With the disappearance of the vitiligo, new symptoms emerged, including tingling, pain, and mild loss of motor function in the fingers and forearms. These symptoms were consistent with ICI-induced arthritis. Despite treatment, the symptoms persisted. The patient received 51 cycles of ICI with pembrolizumab and remains stable with ongoing therapy.

Case 3

A 70-year-old male patient, with a 20-pack-year smoking history, was urgently admitted to the Clinical Oncology and Chemotherapy Department. The patient had been diagnosed with stage II pleomorphic carcinoma of the left lung, following a left upper lobectomy performed two years before that moment (Fig. 3A, B). He was referred to our Department due to the disease's exacerbation and to be qualified for chemotherapy. The patient had already been treated with two cycles of chemotherapy based on the vinorelbine and carboplatin regimen and four cycles of chemotherapy based on the paclitaxel regimen. Additionally, the patient had undergone nephrectomy due to a clear cell carcinoma of the left kidney. The patient had already been diagnosed with an abdominal aortic aneurysm, had a bifurcated stent graft implanted, and had undergone a cholecystectomy. Other priorly diagnosed chronic diseases were hypertension and type 2 diabetes mellitus.

After a check-up chest X-ray, the image showcased reduced volume of the left lung and visible surgical clips' shadows in the hilar projection of the lower left lung. Due to the patient's deterioration, he was qualified for a clinical trial drug program based on the nivolumab regimen, whose efficacy was assessed quarterly. The follow-up ultrasonographic examination revealed focal lesions in the periaortic region and the left lobe of the liver, and the patient was referred for further diagnosis. The follow-up CT scan of the chest and abdominal cavity showed signs of disease stabilization. It was recommended to continue the current treatment. During the nivolumab therapy, the patient experienced descending levels of thrombocytes during the 12th cycle. Moreover, the patient developed grade II renal toxicity during the 8th cycle. Therefore, the withdrawal of the drug was necessary until the patient's laboratory parameters normalized. When the patient's condition was stable, the treatment was resumed. Early treatment

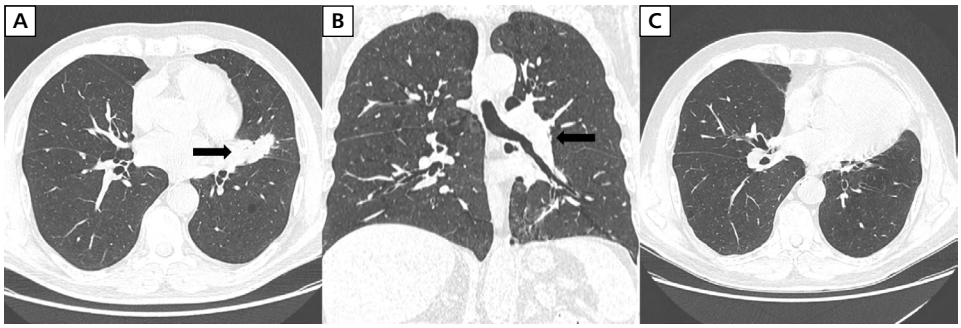

Figure 3. A, B. Computed tomography (CT) scans of the chest visualizing a tumor in the left lung; **C.** CT scan of the chest showing stabilization of the disease

tolerance was considered adequate. During the 32nd cycle, the patient required hospitalization due to the severity of symptoms related to cancer and the worsening of his general condition. The follow-up examinations demonstrated stabilization of tumor progression, and the patient was qualified for continuation of the current therapy (Fig. 3C).

Case 4

A 70-year-old male patient, with a 50-pack-year smoking history, was admitted to the Clinical Oncology and Chemotherapy Department for further diagnosis of a lesion located in the middle lobe of the right lung. The CT scan revealed an irregular tumor-nodular mass in the right hilar region protruding into the mediastinum involving the superior vena cava, compressing the arc of the azygos vein, and involving the bronchi. Lymph nodes adjacent to the main tissue mass showcased features of disintegration. Additionally, the image showed singular enlarged right hilar lymph nodes (Fig. 4A–C). Moreover, vertebral bodies of Th12 and L3 vertebrae had suspicious lesions, which may have been the result of the cancer's metastasis (Fig. 4D, E). Given the inability to provide a definitive diagnosis, the patient was referred for an endoscopic examination, which also facilitated the acquisition of histopathological material for further diagnostic purposes.

Histopathological examination of the collected bronchial aspirate revealed a squamous tumor type (5%) and low-differentiated non-epithelial tumor (30%) cells. Immunohistochemical staining was positive for p40 and negative for TTF1. The patient was diagnosed with stage IV pleomorphic lung carcinoma and was treated with immunochemotherapy based on the pembrolizumab and chemotherapy regimen. Following the third immunochemotherapy cycle, grade 3 neutropenia without neutropenic fever, grade 2 thrombocytopenia, and peripheral neuropathy were observed. Subsequently, the patient was qualified for continuation of the specialized treatment in the clinical trial drug program involving pembrolizumab, carboplatin, and paclitaxel, with efficacy assessment every quarter. A follow-up CT scan revealed signs of stabilization of the underlying disease (Fig. 4F).

Discussion

Pulmonary pleomorphic carcinoma is a rare subtype of primary lung cancer, with an occurrence rate of between 0.1% and 0.4% of the total number of NSCLC cases diagnosed annually. Pulmonary pleomorphic carcinoma is a poorly differentiated NSCLC — squamous cell carcinoma, adenocarcinoma, or undifferentiated NSCLC that contains at least 10% of sarcomatoid components — spindle or giant cells, or a carcinoma with only sarcomatoid components [1]. Pleomorphic carcinomas are known to exhibit more aggressive clinical outcomes compared to NSCLC. Due to its low gene-related enzyme expression and heightened epithelial-mesenchymal transition expression, this particular subgroup remains mostly chemo- and radio-resistant. Studies have consistently shown that pleomorphic carcinomas are less responsive to those treatments, which complicates the management and worsens prognosis [2–4]. An unusual molecular array of PPC with a low rate of positive expression for commonly tested genes in NSCLC creates clinical management challenges. However, recent research has identified a possible association between pleomorphic carcinomas and *MET* exon 14 skipping mutations [5]. This finding suggests that, despite the rarity of actionable mutations, there may be potential for targeted therapy in selected cases.

Immunotherapy, particularly treatments targeting the PD-L1 pathway, represents another therapeutic avenue. The success of immunotherapy is influenced by several factors, including the expression level of PD-L1 on tumor cells and the overall TMB. TMB is a measure of the number of mutations within a tumor,

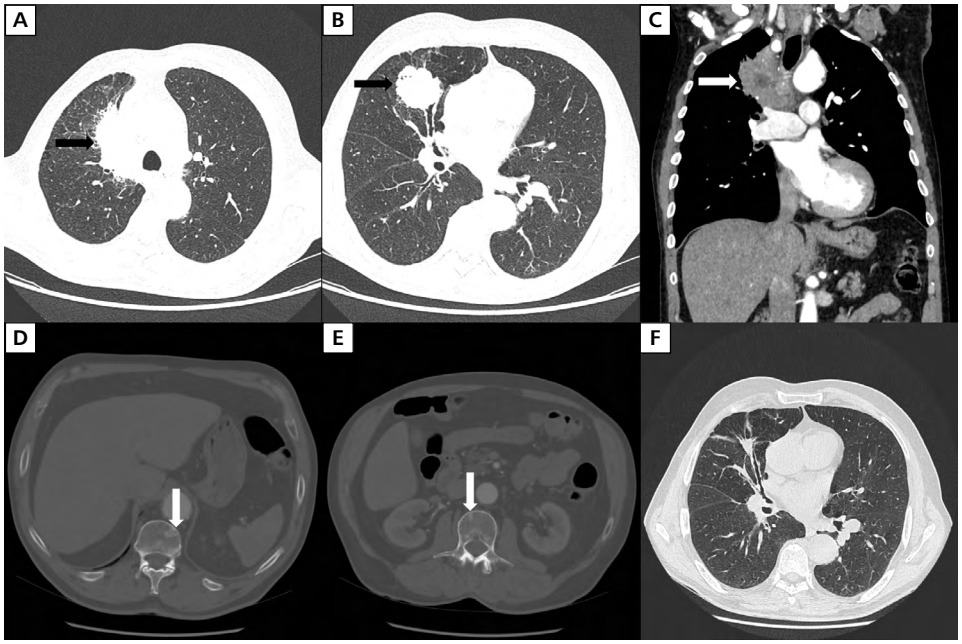

Figure 4. A, B. Computed tomography (CT) scans of the chest visualizing a tumor in the right lung; **C.** CT scan of the chest depicting an irregular mass in the right hilar region protruding into the mediastinum; **D, E.** CT scans of the chest and abdomen demonstrating lesions in the bodies of Th12 and L3 vertebrae; **F.** CT scan of the chest showing stabilization of the disease

which correlates with the presence of neoantigens that can be recognized by the immune system. The higher the TMB, the more likely it is that the immune system can identify and attack the cancer cells when supported by immunotherapy [6, 7].

Pleomorphic differentiation is linked with higher PD-L1 status compared to other NSCLC subtypes [8, 9, 10]. Considering this along with a high average TMB rate, major difficulties within other therapeutic options and a high response rate checkpoint inhibitor immunotherapy resurfaces as the most promising treatment of choice. Simultaneously high PD-L1 is marked as an indicator of poor prognosis and pleural invasion in the course of PPC [9, 11, 12]. However, in the light of strong association between strong PD-L1 expression with longer progression-free survival and better overall survival in the course of immunotherapy, it might be considered a positive predictive factor [13].

The high correlation between high TMB and positive PD-L1 status described in the Domblides study further cements the role of ICI as the most prospective promising PPC treatment. The authors reported that a group of 37 patients with PPC achieved an objective response rate equal to 40.5%, and over half of the cohort (64.8%) obtained disease control, regardless of PD-L1 status. Median OS was 12.7 months, which can be considered a therapeutic success taking into account the higher mortality rate of PPC patients [14, 15]. According to a study by Babacan et al. [16], ICI remains one of the favorable treatments in PPC, as any PD-L1 level higher than 1% elicited a positive response in over half (54%) of cases reported. Another comprehensive study of 49 cases treated with ICI performed by Lee et al. [13] found partial response in 24 patients and the objective response rate was 49.0% and occurred only in the high-PD-L1 group. Several cases of successful management of pleomorphic lung carcinoma with low PD-L1 expression with ICI regime were reported [17– 19]. The vast majority of PPC cases that responded to ICI had positive PD-L1 status, with the best results in the high-expression group [13, 14, 17–27].

Article Information and Declarations

Ethics statement

Ethic statement not required due to no intervention.

Author contributions

A.R.: conceptualization, writing — original draft preparation, writing — review and editing, supervision, visualization; K.J.: conceptualization, writing — original draft preparation, writing — review and editing, visualization; J.O: conceptualization, writing — original draft preparation, writing — review and editing, supervision; M.J.: conceptualization, writing — original draft preparation, writing — review and editing, visualization; E.K.: conceptualization, writing — original draft preparation, writing — review and editing, visualization; A.P.: conceptualization, writing — original draft preparation,

writing — review and editing, visualization; K.S.: conceptualization, writing — original draft preparation, writing — review and editing, supervision, visualization. All authors have read and accepted the published version of the manuscript.

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Conflict of interest

The authors declare no conflict of interest.

Supplementary

None.

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