VIA MEDICA

CASE REPORT

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Combined immunotherapy in lung cancer — a case report highlighting immune response dynamics and clinical success

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ABSTRACT

Immunotherapy with the use of immune checkpoint inhibitors (ICIs) is one of the key therapeutic options in cancer, especially in advanced non-small cell lung cancer (NSCLC). The combination of chemotherapy and immunotherapy — nivolumab (anti-programmed death-1, anti-0PD-1) and ipilimumab (anti-cytotoxic T-lymphocyte-associated protein 4, anti-CTLA-4) — has been found beneficial in clinical trials addressing advanced NSCLC. Here, we present a case of a female patient with PD-1 ligand (PD-L1)-negative, advanced squamous-cell carcinoma with a long response to chemoimmunotherapy. The patient had several episodes of adverse events and exacerbation of autoimmune disease. An analysis of immunological background was performed, and it revealed changes in the percentages of certain immune cell subpopulations in the patient's blood during immunotherapy.

Keywords: chemoimmunotherapy, nivolumab, ipilimumab, NSCLC, lymphocytes subpopulations

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Introduction

Immune checkpoint inhibitors (ICIs) have become irreplaceable in the treatment of lung cancer patients, particularly in non-small cell lung cancer (NSCLC), accounting for approximately 85% of all primary lung neoplasms. These therapies act by targeting immune checkpoints, such as programmed death 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), which are critical regulators of immune activation and tolerance [1]. By inhibiting these checkpoints, ICIs unleash the body's immune system to recognize and attack cancer cells more effectively. Over the past decade, clinical trials and real-world evidence data have demonstrated that ICIs, either as monotherapy or in combination with other agents, such as chemotherapy, can significantly improve the survival rates and life quality of lung cancer patients [1]. However, not all patients respond equally, and there is a growing need to understand better the factors that influence response to ICIs to optimize their use and maximize clinical benefits [2].

Evaluation of the immune response in lung cancer patients treated with ICIs could be valuable for understanding the mechanisms underlying treatment efficacy and optimizing therapeutic strategies. The variability in patient responses highlights the need to investigate immune dynamics more closely. By analyzing the immune response, including biomarkers of response, immune cell profiles, and intracellular cytokine levels, we can better understand which patients are likely to benefit from combined immunotherapy, manage potential toxicities, and develop personalized treatment approaches to improve clinical outcomes. The immune system analysis could be a valuable complement to standard imaging techniques, such as computed tomography (CT). Furthermore, immune-related adverse events (irAEs), which can also reflect the immune system's activation

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against tumors, might be predicted and monitored through immune profiling [3–5]. Therefore, integrating immune system analysis with conventional imaging can offer a more comprehensive picture of treatment efficacy, enabling clinicians to make more informed decisions about continuing, adjusting, or combining therapies for optimal patient outcomes.

Here, we present a case report of a patient with advanced NSCLC undergoing therapy with nivolumab, ipilimumab, and chemotherapy, in whom the activity of the immune system was assessed during subsequent clinical monitoring of the treatment effectiveness.

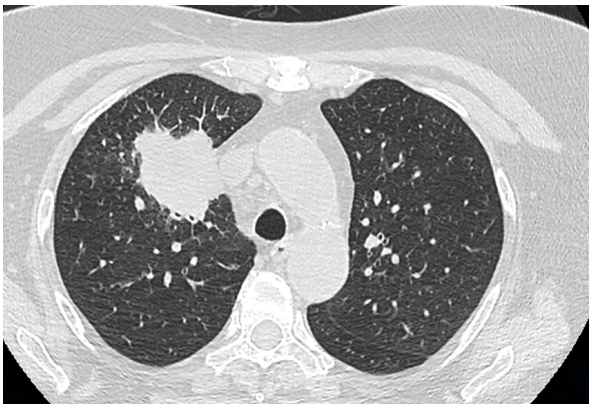

Figure 1. Baseline chest computed tomography (CT) scan

Case report

Clinical characteristics, immunotherapy efficacy, and toxicity

A 58-year-old woman was admitted to the Department of Pneumonology, Oncology, and Allergology of the University Clinical Hospital No. 4 in Lublin (Poland). She was referred by her family doctor with suspected lung cancer for diagnostics and treatment qualification. Due to persistent cough, dyspnea on exertion, and a 6-kg weight loss, a chest X-ray was performed, revealing a round shadow in the right lung. The history included smoking (30 pack-years), rheumatoid arthritis (RA) currently not requiring treatment (previously treated with methotrexate), hypertension, and type 2 diabetes. Family history was not significant.

A computed tomography (CT) scan was performed, and a heterogeneous tissue mass measuring 45 × 55 mm located in the third right segment was found, most likely with an adjacent area of atelectasis (Fig. 1). Enlarged right paratracheal lymph nodes (13 × 12 mm) at the level of the tracheal bifurcation (17 × 13 mm), subcarinal (21 × 13 mm), and right hilar (23 × 20 mm) were found. Fluid was present in the right pleural cavity. The clinical stage was established as T3N2M1a (IVA). During hospitalization, a bronchoscopic examination with a transbronchial needle aspiration (TBNA) biopsy of the mediastinal lymph nodes under ultrasound guidance was performed. The histopathological examination revealed squamous cell carcinoma and no PD-L1 expression was detected on tumor cells [tumor predictive score (TPS) < 1%].

The patient was qualified for treatment under the Polish Drug Program. The patient met all the criteria for inclusion, both laboratory tests and electrocardiogram were normal without deviations that could exclude her from therapy. The patient did not report any allergies or drug intolerances. She was qualified for treatment with the use of nivolumab and ipilimumab combined with two cycles of chemotherapy (carboplatin and paclitaxel) in the standard dose and for

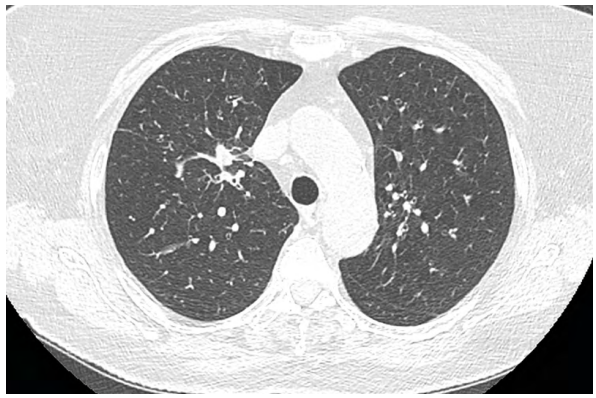

Figure 2. First control computed tomography (CT) scan

prophylactic granulocyte growth factor therapy. During the treatment, symptoms of chemotherapy toxicity were observed in the form of grade 2 granulocytopenia and grade 1 anemia, as well as grade 2 nausea and vomiting and grade 2 alopecia.

A control CT scan after 3 months showed a partial response according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria (tumor largest diameter — 21 mm) (Fig. 2). The response was maintained in subsequent imaging studies. Currently, after 17 months, an almost complete response was observed (Fig. 3).

During treatment, the patient experienced RA exacerbations twice (after 2 months and after 10 months from the start of the treatment), which manifested as joint pain. At the first exacerbation, the patient required corticosteroid therapy (methylprednisolone) followed by prednisone and leflunomide therapy. At the second exacerbation, the dose of prednisone was increased from 5 mg/day to 10 mg/day. These episodes did not result in the discontinuation of immunotherapy.

After 14 months from the start of treatment, the patient had an increase in the concentration of aspartic and alanine transaminases in the blood serum without

an increase in bilirubin concentration. After the exclusion of other causes, including viral hepatitis type B and C, grade 2 immune hepatitis was diagnosed. Immunotherapy was stopped, and hepatoprotective drugs were used, as well as corticosteroid therapy at a dose of prednisolone 10 mg/day. Sixteen months after the start of treatment, the patient reported to the Clinical Emergency Department due to 4 days of severe gastrointestinal symptoms (3–4 loose stools per day, abdominal pain). A preliminary diagnosis of immunological grade 2 enteritis was made, immunotherapy was stopped, and the patient was hospitalized in our Department. A colonoscopy revealed swollen large intestine mucosa with widespread petechiae and ulcerations. Samples were taken from the mucosa of the large intestine (microscopic image corresponded to focal active colitis). *Clostridium difficile* infection and others were excluded. Due to the diagnosis of an immunological complication, corticosteroid therapy was used at an initial dose of prednisolone 50 mg/day, reduced by 10 mg every 7 days. After 4 weeks of such treatment, the symptoms subsided, and it was decided to continue the treatment with nivolumab in monotherapy, without ipilimumab. The timeline of the treatment is shown in Figure 4.

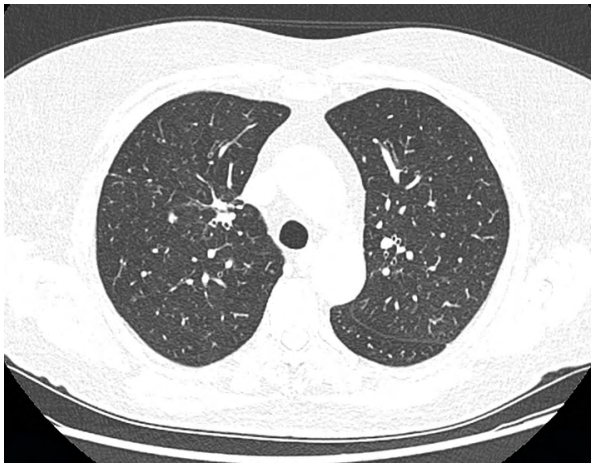

Figure 3. Second control computed tomography (CT) scan

Immunological analysis

Blood samples were obtained before (BT) and during the treatment: I–V (in 3-month intervals). Standard tests such as blood count were also commissioned. Peripheral blood mononuclear cells (PBMCs) were isolated, and flow cytometry analysis was performed with FACS Calibur flow cytometer (Beckton Dickinson, US). Table 1 shows markers assessed by flow cytometry and cell subsets identified by those markers. Further analyses were carried out using FlowJo™ v10.10 (FlowJo, LLC). The data revealed that certain subsets of cells' percentages and expression of molecules on their surface changed during the treatment. The neutrophil-to-lymphocyte ratio (NLR) was calculated by dividing the number of neutrophils by the number of lymphocytes in standard peripheral blood count analysis. The platelet-to-lymphocyte ratio (PLR) was calculated by dividing the number of platelets by the number of lymphocytes obtained from the same blood sample.

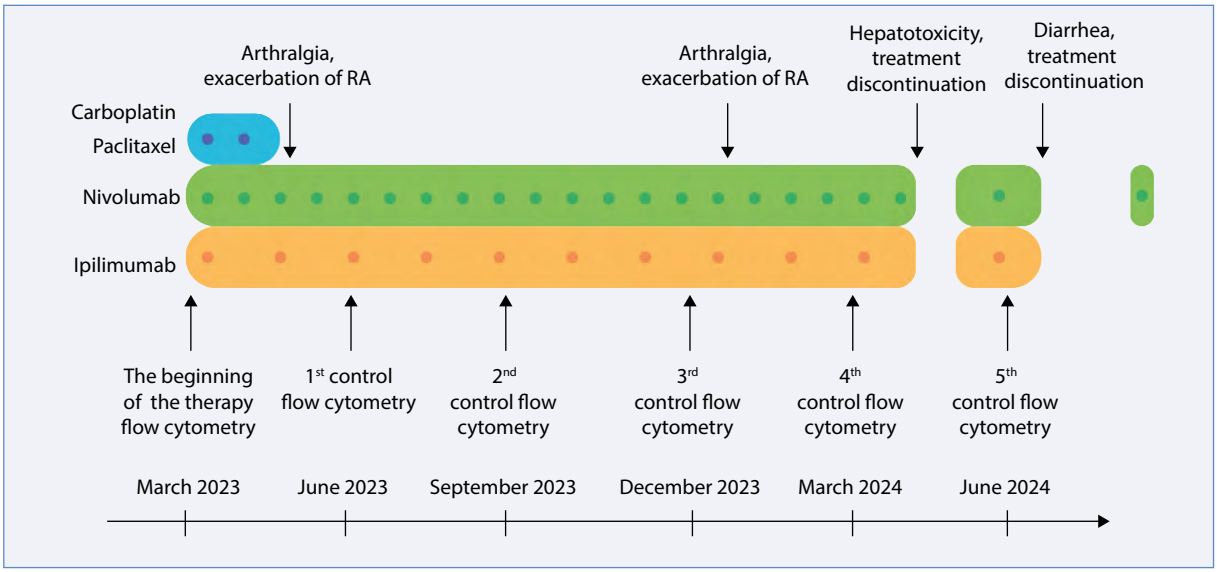

Figure 4. Treatment timeline of the described patient; RA — rheumatoid arthritis

The number and percentage of lymphocytes decreased, and it was accompanied by an increased NLR (Fig. 5A) and PLR (Fig. 5B), although the NLR changes were clearer. A decrease in the percentages of PD-1-positive cytotoxic T lymphocytes (Fig. 6A) and PD-L1-positive monocytes was observed (Fig. 6B). However, during the third imaging follow-up of the treatment effectiveness, an increase in the percentage of these cells was found. The percentage of CD27-positive B lymphocytes and memory lymphocytes with eomesodermin (EOMES) expression escalated (Fig. 6C, D, respectively). The percentages of T lymphocytes $CD4^+$ and $CD8^+$ with PD-1 expression were elevated at the baseline and decreased during the chemoimmunotherapy (Fig. 6E). Concerning the expression of assessed molecules [referred to as the mean fluorescence

Table 1. A cytometric panel for evaluation of peripheral blood mononuclear cell (PBMC) subpopulations

Cluster of differentiation and other markers used for defining distinct cell subpopulations	Short characteristics of identified PBMC subpopulations
CD45/CD14	Lymphocytes and monocytes
CD3/CD19	T lymphocytes and B lymphocytes
CD3/CD16+CD56	NK cells
CD4/CD25/CTLA-4	T regulatory (Treg) cells with negative immune checkpoint CTLA-4 expression
CD4/CTLA-4/FoxP3	Activated Treg cells with negative immune checkpoint CTLA-4 expression
CD4/CXCR3/GATA3	Th2 cells with chemotactic abilities
CD4/PD-1/EOMES	Th cells with memory potential and with negative immune checkpoint PD-1 expression
CD4/CD44/EOMES	Effector memory Th cells
CD4/CD8/T-bet	Th1 cells or Tc cells with T-bet expression
CD4/CD8/Bcl-2	Th cells or Tc cells resistant to apoptosis
CD4/CD8/IFN-γ	Th cells or Tc cells with the ability to produce IFN-γ
CD8/CD62L/TIM-3	Tc cells with negative immune checkpoint TIM-3 expression
CD8/CD62L/LAG-3	Tc cells with negative immune checkpoint LAG-3 expression
CD8/CD62L/PD-1	Tc cells with negative immune checkpoint PD-1 expression
CD14/CD16/CCR2	Monocytes with chemotactic abilities
CD14/CD16/CX3CR1	Monocytes with chemotactic abilities
CD14/CD16/PD-L1	Monocytes with PD-L1 expression
CD14/CD202b	Monocytes with an angiopoiesis signaling ability

Bcl-2 — B-cell lymphoma-2; CCR2 — C-C chemokine receptor type 2; CD — cluster of differentiation; CTLA-4 — cytotoxic T lymphocyte antigen 4; CX3CR1 — chemokine c-x3-c receptor type 1; EOMES — eomesodermin; FoxP3 — forkhead box P3; GATA3 — GATA binding protein 3; IFN-γ — interferon-gamma; NK — natural killer; PD-1 — programmed death 1; PD-L1 — programmed death ligand 1; T-bet — T-box transcription factor; Tc — T cytotoxic; Th — T helper; TIM-3 — T-cell immunoglobulin mucin-3; Treg — T regulatory cell

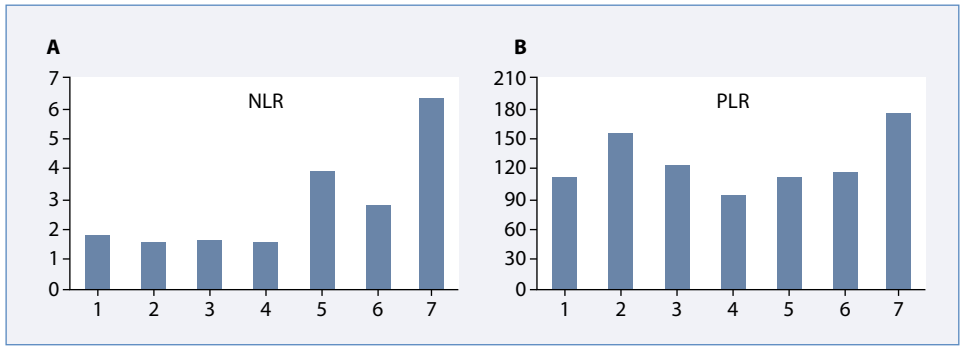

Figure 5. A. Neutrophil-to-lymphocyte ratio (NLR) values at the time of consecutive controls (blood count); **B.** Platelet-to-lymphocyte ratio (PLR) values at the time of consecutive controls (blood count)

Figure 6. Flow cytometric analysis; **A.** The percentage of Tc cells with programmed death 1 (PD-1) expression before and during the treatment; **B.** The percentage of different populations of monocytes with programmed death-ligand 1 (PD-L1) expression before and during the treatment; **C.** The percentage of B lymphocytes with CD27 expression before and during the treatment; **D.** The percentage of T CD4$^+$ cells with eomesodermin (EOMES) expression before and during the treatment; **E.** The percentage of T CD4$^+$ and CD8$^+$ cells with PD-1 expression before and during the treatment; **F.** C-C chemokine receptor type 2 (CCR2) expression [mean fluorescence intensity (MFI)] on different monocyte populations before and during the treatment; **G.** Interferon (IFN)-γ expression on CD4$^+$ and CD8$^+$ lymphocytes before and during the treatment; BT — before treatment

intensity (MFI)], C-C chemokine receptor type 2 (CCR2) expression on monocytes increased (Fig. 6F). Interferon-gamma (IFN-γ) expression in both T helper (Th) and T cytotoxic (Tc) cells was constantly decreasing during therapy with an incidental increase during the fourth imaging follow-up (Fig. 6G).

Discussion and conclusions

The combination of double immunotherapy and chemotherapy has been shown to be beneficial for patients with NSCLC. The open-label, multicenter, randomized phase III CheckMate 9LA study compared

the efficacy of dual immunotherapy combined with two cycles of chemotherapy versus chemotherapy alone. The benefit of combined immunotherapy was documented in relation to the study endpoints in the entire analyzed population. The results of this study led to the registration of nivolumab and ipilimumab regimen combined with two cycles of chemotherapy in patients with advanced NSCLC. The safety profile of combined immunotherapy was consistent with the known safety profiles of immunotherapy and chemotherapy used in the first-line treatment of NSCLC patients.

Adverse events leading to discontinuation of one of the therapy's components occurred in both study groups. In patients receiving dual immunotherapy combined with two cycles of chemotherapy, fatal adverse events occurred in 2% of patients, and serious adverse events occurred in approximately 30% of patients. Comparing the safety and toxicity profile in both groups of patients (receiving combined immunotherapy and chemotherapy alone), it can be seen that adverse events — such as anemia, neutropenia, alopecia, thrombocytopenia, or peripheral neuropathy — related to chemotherapy and occurred much more frequently in patients receiving chemotherapy alone. In the group of patients receiving combination therapy, adverse events related to immunotherapy were mostly in grades 1 and 2 and less frequently in grades 3 and 4. They mainly included adverse events related to the skin, endocrine, gastrointestinal, and hepatic disorders [6].

An abstract presented in 2024 at the American Society of Clinical Oncology (ASCO) meeting showed the results of a 5-year follow-up from the phase III CheckMate 9LA study. It included updated data on the safety profile and efficacy of therapy in patients whose treatment had been discontinued due to adverse events. It turned out that, in terms of overall survival (OS), in patients who had to discontinue treatment due to toxicity, the results were initially comparable, and with the duration of the study significantly better than the results of patients who completed the planned therapy and did not experience adverse events [7].

The predictive value of peripheral blood biomarkers is more and more often described in the literature in the context of cancer immunotherapy and irAEs. Minimally invasive material collection and the ability to perform multiple examinations make them advantageous, compared to e.g. immunohistochemistry. Data presented by Kimura et al. [8] in the group of NSCLC patients treated with ICIs had shown that the proportions of circulating natural killer (NK) cells and PD-1$^+$/ T cell immunoglobulin mucin domain-3 (TIM-3$^+$) within CD4$^+$ cells population were significantly elevated in NSCLC patients who experienced progression disease (PD) compared to those with stable disease (SD) or partial response (PR) according to the RECIST 1.1 [8]. The overexpression of PD-1 and TIM-3 on T cells can occur in response to chronic exposure to tumor antigens, leading to a state known as 'T cell exhaustion.' Exhausted T cells exhibit reduced proliferative capacity, decreased cytokine production, and impaired cytotoxic activity, diminishing their ability to mount an effective anti-tumor response. Moreover, TIM-3 often co-expresses with PD-1 on the most dysfunctional T cells, marking no response to the treatment [9]. The patient described in our case report had a high baseline proportion of CD4$^+$/PD-1$^+$ and CD8$^+$/PD-1$^+$ cells that decreased during therapy.

A marked decrease in the percentage of cytotoxic T lymphocytes with PD-1 expression indicates activation of the immune system. Similarly, we observed an increase in CCR2 molecule expression on monocytes during therapy. C-C chemokine receptor type 2 plays a critical role in the recruitment and migration of monocytes from the bone marrow into the bloodstream and then into inflamed or damaged tissues, including tumor sites [10]. To be more precise, this could suggest the stimulation of the nonspecific arm of the immune system activity. Stimulation of the immune system is also related to the differentiation of memory T lymphocytes, which are to be a future source of fast-acting specific responding cells. Then, the CCR2 expression on monocytes somehow correlates temporally with the onset of hepatotoxicity and diarrhea.

Changes in IFN-γ expression in T cells followed a similar pattern but with a decrease in the 5th imaging follow-up of ICI efficacy. In our patient, we observed an increase in the percentage of memory T cells with high EOMES expression. EOMES is a key transcription factor in the differentiation and maturation of CD8-positive T cells into effector and memory cytotoxic T lymphocytes. EOMES helps promote the expression of cytotoxic molecules, such as perforin and granzyme B, which are essential for the killing of infected or malignant cells [11].

Krizova et al. [12], in the cohort of 224 NSCLC patients who received immunotherapy alone or with chemotherapy, showed a correlation between high baseline T regulatory cells (Treg) proportion, high baseline mean platelet volume (MPV), high hemoglobin, and low monocyte level, with longer progression-free survival (PFS) and overall survival. However, based on receiver-operating characteristic (ROC) analysis, the authors concluded that those parameters and the NLR are not useful as predictive biomarkers of PFS prolongation in patients treated with ICIs, and they can only indicate a trend in response to the treatment and should be investigated carefully in the future [12].

In the presented case, the percentage of suppressive T regulatory cells defined as CD4$^+$/FoxP3$^+$/CTLA-4$^+$ (7.48% of CD4$^+$ cells) and the percentage of monocytes

(6.9%) was relatively high before the treatment, which could indicate the benefit from immunotherapy. However, when compared with the results of Krizova et al. [12], the hemoglobin concentration in our patient was low at the therapy's beginning (11.7 g/dl).

A study by Zhen et al. [13] proposed dynamic changes in lymphocyte subsets after four treatment cycles as the distinction between responsive and non-responsive patients receiving combined immunotherapy. A significant decrease in the counts of all main lymphocyte subsets (CD4+ and CD8+ T cells, B cells, and NK cells) was observed in patients from the non-responsive group, whereas in responsive patients, such changes were not observed [13]. In our patient, we did not observe a significant reduction of the main cell subset during therapy.

The coexistence of autoimmune disease (rheumatoid arthritis) and the occurrence of immunotherapy complications (hepatotoxicity, colitis) may be associated with higher treatment efficacy [3]. Also, an increase in the proportion of B lymphocytes expressing CD27 (a costimulatory molecule) has been associated with immune complications in melanoma patients undergoing combination checkpoint blockade [14]. However, some of the dynamics of changes in the immune system in this patient were different from most patients responding to immunotherapy. The increased NLR rate in the patient responding to treatment is unexpected and perhaps related to increased lymphocyte recruitment to the tumor. Usually, an increase in the NLR ratio is associated with disease progression [15]. Nevertheless, the NRL increase was observed not at the beginning of the treatment but after 8 months of therapy.

It appears that immunotherapy is more effective in patients with high PD-1 levels and with activated immune systems. Although there are concerns about the potential exacerbation of autoimmune symptoms, recent studies and the present case report have shown that with careful monitoring and individualized treatment plans, many patients can safely benefit from treatment with immune checkpoint inhibitors. The potential to extend survival and improve the quality of life in these patients highlights the importance of considering immunotherapy as a viable option, particularly when the benefits outweigh the risks.

In conclusion, the utility of PBMC subpopulation analysis and different markers expression on PBMCs needs to be further evaluated in prospective studies to fully exploit their potential. Nevertheless, such an examination provides interesting insights into the immune response mechanisms during immunotherapy. It should also be mentioned that immunotherapy presents a promising treatment option for lung cancer patients with coexisting autoimmune diseases despite the complexity of managing both conditions simultaneously.

Article Information and Declarations

Ethics statement

The patient gave her written consent to participate in the research based on the consent of the local Bioethics Committee at the Medical University of Lublin (No. KE-0254/160/2021).

Author contributions

T.J.: article concept, writing, clinical data collection, literature data collection; N.K.: carrying out exeriments, writing, clinical data collection, literature data collection; K.W.-K.: experimentation, writing, literature data collection, supervising the article; P.K.: writing, revising the article; J.M.: revising the article.
All authors have read and agreed to the published version of the manuscript.

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None.

Conflict of interest

The authors declare no conflict of interest related to the submitted manuscript.

Supplementary material

None.

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