VIA MEDICA

CASE REPORT

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Dual-organ toxicity during treatment with nivolumab and ipilimumab in combination with chemotherapy in the first-line treatment of non-small cell lung cancer

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ABSTRACT

Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of non-small cell lung cancer (NSCLC). The combination of nivolumab and ipilimumab with two cycles of chemotherapy improves treatment efficacy; however, this combination therapy is also associated with a high incidence of adverse events. We report a rare and significant case of dual-organ failure following treatment with nivolumab and ipilimumab in a 65-year-old male patient with stage IV lung adenocarcinoma. During treatment with chemotherapy combined with nivolumab and ipilimumab, the patient developed severe diarrhea and was later found to have autoimmune colitis, leading to a suspension of immunotherapy and initiation of steroid treatment. After a brief recovery and partial tumor regression, the patient experienced grade 3 pneumonitis upon resuming nivolumab monotherapy, necessitating intensive treatment and discontinuation of immunotherapy. Following cessation of treatment, the patient's condition remained stable with no disease progression observed over three months. ICIs can induce non-specific immune activation, resulting in widespread inflammatory effects. Early recognition and prompt treatment with high-dose steroids are essential to prevent rapid deterioration in patients experiencing immune-related adverse events (irAEs). Given the widespread use of ICIs in cancer therapy and ongoing clinical trials, there is a need for increased education on irAE and updated management algorithms for NSCLC patients.

Keywords: NSCLC, immunotherapy, multi-organ toxicity, pneumonitis, colitis

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Introduction

Lung cancer is the second most diagnosed malignancy worldwide and the leading cause of cancer deaths [1]. The most common type of this cancer is non-small cell lung cancer (NSCLC), which accounts for about 85% of cases and is histologically divided into adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and other rare types [2]. Because the disease is so prevalent and the mortality rate among patients is high, new therapeutic options for lung cancer are still being sought. Immunotherapy has become one of the main treatment options for NSCLC in recent years. This innovative method harnesses the immune system's ability to fight cancer cells, opening new treatment options for NSCLC patients, especially in advanced stages.

Recently combined therapy has found use in the treatment of NSCLC, which includes nivolumab

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and ipilimumab. Nivolumab is an anti-programmed death receptor type 1 (PD-1) monoclonal antibody that blocks the interaction of PD-1 with its ligand (PD-L1), leading to the activation of the immune system against cancer cells. In contrast, ipilimumab is an anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibody, which acts on a different immune regulatory pathway to improve T-cell activity against tumors [3]. Combining these two antibodies with two cycles of platinum-based chemotherapy is currently one of treatment options for patients with locally advanced, unresectable (stage IIIB), or advanced (stage IV) NSCLC, which has been reimbursed for patients in Poland since January 2023. The first-line treatment regimen using the immunochemotherapy program may include patients with documented PD-L1 expression on < 50% of tumor cells and the absence of mutations in the *EGFR* gene as well as rearrangements in the *ALK* and *ROS1* genes. However, the European Medicine Agency registration of this treatment method covers patients regardless of PD-L1 expression and without mutations in the *EGFR* gene or *ALK* gene rearrangement [4].

Immunotherapy and chemotherapy act synergistically, but a significant difference in their action is the toxicity profile. Chemotherapy is characterized by high toxicity, and adverse effects result from its nonspecific impact on every cell in the body. In contrast, the advantage of immunotherapy is the rare occurrence of adverse events, mainly resulting from excessive stimulation of the immune system [5].

Case presentation

A 65-year-old male patient diagnosed with stage IV right lung tumor was admitted to the pulmonary department for treatment qualification. In September 2023, based on material obtained during bronchofiberoscopy with endobronchial ultrasound-guided transbronchial needle aspiration biopsy of the lung and lymph node biopsy (EBUS-TBNA), a histopathological diagnosis of adenocarcinoma was obtained. A positron emission tomography–computed tomography (PET-CT) scan from early October revealed metastatic changes in both lungs with bilateral involvement of mediastinal lymph nodes. Molecular testing excluded the presence of mutations in the *EGFR* gene and rearrangement of the *ALK* and *ROS1* genes, while the expression of PD-L1 was observed on 5% of tumor cells. The patient's medical history included arterial hypertension. In November 2023, he was qualified for systemic immunochemotherapy with the nivolumab and ipilimumab regimen with two cycles of carboplatin and pemetrexed. In December, after two cycles of therapy following the guidelines, chemotherapy treatment was discontinued, and immunotherapy was continued.

In January 2024, the patient reported diarrhea with intermittent blood streaks lasting for about a month, with a severity of up to 10 bowel movements per day. Infectious were excluded on the basis of negative cultures for *Shigella* and *Salmonella* bacteria; carriage of alarm pathogens was ruled out as well. In addition, calprotectin levels were determined in a fecal sample and were > 800.00 μg/g. Gastroscopy showed features of chronic gastritis and esophageal candidiasis, and *Helicobacter pylori* infection was excluded based on the material collected. During a colonoscopy, a segment of the large intestine from the rectum to the hepatic flexure was visualized, showing reddened and swollen mucosa, a visible? vascular pattern, exudate of fibrin, spontaneous bleeding, and small clots, as well as ulcers. This image suggested autoimmune changes in the intestines. It was decided to suspend oncological treatment due to suspicion of toxic colitis grade 3, a likely complication of immunotherapy. Treatment with sulfasalazine and steroid therapy was initiated. After about a month, the dose of prednisone was reduced to 10 mg per day without recurrence of symptoms.

At the end of January, a follow-up computed tomography (CT) scan was performed, which showed partial regression of the tumor lesions. On February 23, the patient presented to the department to resume oncological treatment. The patient's overall condition was good, with an Eastern Cooperative Oncology Group (ECOG) performance status of 1. The patient was qualified for treatment with nivolumab as monotherapy and received the treatment with good drug tolerance. Treatment was continued until the third dose was administered. Then, the patient reported shortness of breath, cough, and general weakness. Crepitations over the lungs were present in the physical examination. Chest CT revealed ground glass opacities throughout the lungs (Fig. 1). Pneumonitis grade 3 in the course of immunotherapy was diagnosed. Intensive treatment including methylprednisolone in a dose of 1 mg/kg intravenously resulted in rapid symptom reduction and recovery. There was no presence of colitis at this time. However, since another toxicity of high grade occurred, nivolumab was also discontinued. Despite the end of treatment, there was no progression of the disease present after 3 months of observation. (Fig. 2).

Discussion and summary

Immunochemotherapy with nivolumab and ipilimumab is an effective therapeutic option for patients with advanced NSCLC, but toxic colitis may be one of the potential adverse events that limit its use. The CheckMate 9LA study evaluated the efficacy and safety of this therapy. The published results confirmed

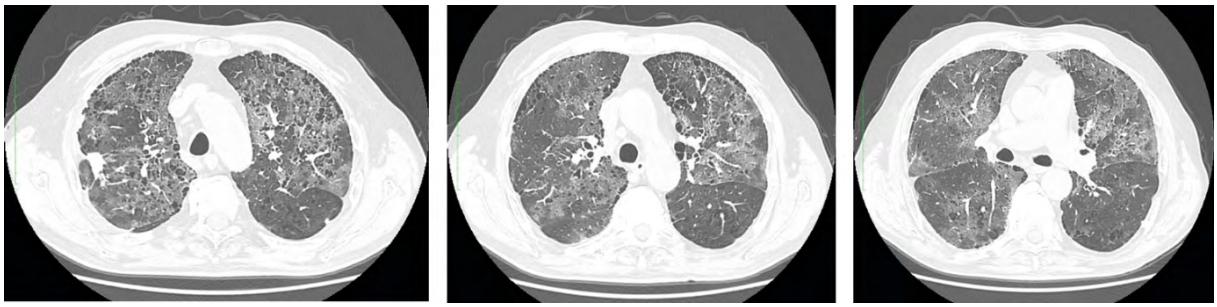

Figure 1. Ground glass opacities in both lungs

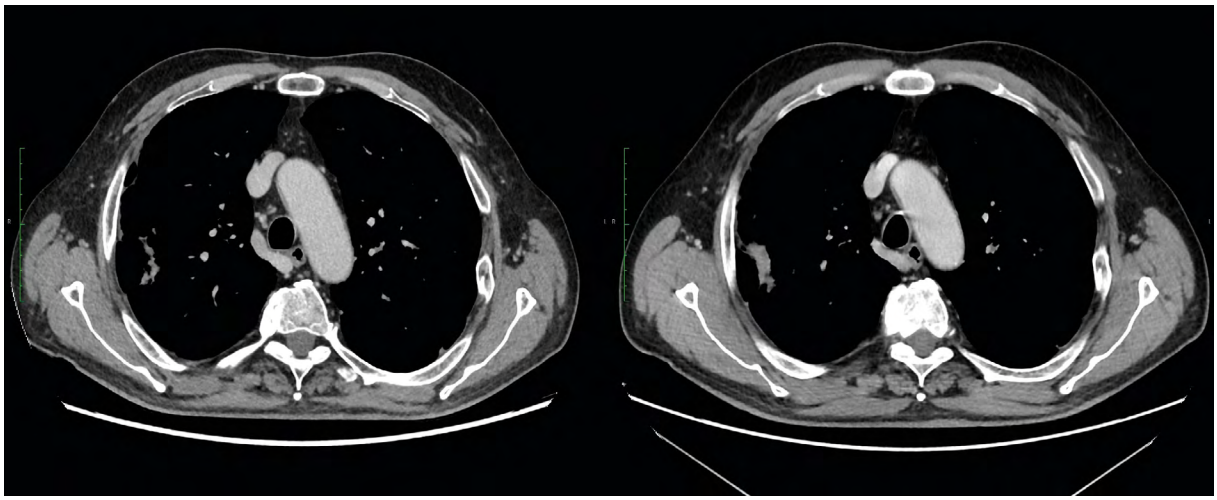

Figure 2. Computed tomography scans showing no progression despite stopping immunotherapy — Jan/Apr 2024

the superiority of ipilimumab and nivolumab-based therapy with chemotherapy limited to two cycles compared to standard chemotherapy. In both groups of patients with PD-L1 expression on < 1% and > 1% of tumor cells, the analysis showed that patients receiving combination therapy had significantly longer overall survival and progression-free survival compared to the group receiving chemotherapy alone. The majority of adverse events observed in patients receiving immunochemotherapy were characterized by mild or moderate severity. However, adverse events of grade 3 or 4 occurred in 47% of the combination therapy group and 38% of the control group [6].

The most commonly reported treatment-related adverse events (those that may have a potential immunological cause) of grade 3 or 4 in the experimental group were gastrointestinal disorders (6%), skin reactions (4%), and liver disorders (4%) [6]. On the other hand, Nielsen et al. [7] demonstrated that the use of PD-1/PD-L1 antibodies was associated with diarrhea in 10% of patients and colitis in 2% of patients, while the anti-CTLA-4 antibodies induced these symptoms in 33% and 7% of patients, respectively. After combining ipilimumab with nivolumab, the percentage of patients experiencing diarrhea ranged from 21% to 37%, and colitis ranged from 4% to 8%, depending on the treatment regimen [7].

These data suggest that the occurrence of gastrointestinal complications due to immunotherapy in NSCLC patients may be a significant issue. The onset of diarrhea in oncology patients should first prompt consideration of infectious causes. For patients undergoing immunotherapy with diarrhea and no identifiable infectious factor, attention should be focused on a possible autoimmune etiology. To confirm this cause, a colonoscopy and histopathological examination should be performed. In most patients, gastrointestinal inflammation after immunotherapy primarily localizes in the rectum and/or the left half of the colon. In the case of bowel damage caused by nivolumab, the colonoscopy appearance of the intestines is similar to the changes observed in ulcerative colitis [8]. However, in the case of ipilimumab, these changes are different from those typically seen in nonspecific bowel inflammations and occur with greater severity [9]. In addition, an important aspect of the differential diagnosis for the symptoms of the above patient is fecal

Table 1. Differential diagnosis of colitis according to clinical guidelines [10]

Disease unit	Diagnostic test performed on a patient	Results
Bacterial enteritis	Fecal culture for *Salmonella* and *Shigella*	Negative culture
Infection with alert pathogens	Rectal swab for carriage of alert pathogens	Rectal swab negative
Celiac disease	Gastroduodenoscopy with biopsies	No characteristic changes for celiac disease
Microscopic enteritis	Colonoscopy with biopsies	No characteristic changes for microscopic enteritis
Crohn's disease (CD)	Colonoscopy with biopsies,	No changes characteristic for CD
Ulcerative colitis (UC)	Colonoscopy with biopsies,	In colonoscopy image, changes characteristic for UC (intestinal mucosa swollen, congested, inflamed, with erosions present, without a visible vascular pattern) and in microscopic study features of UC
Inflammatory bowel disease, gastrointestinal infections, gastrointestinal cancers, colonic diverticular disease	Fecal calprotectin (significant result > 250 μg/g)	Fecal calprotectin > 800.00 μg/g

calprotectin, determined in the feces. Its concentration correlates with the intensity of inflammation in the gastrointestinal tract, so a positive result confirms the organic cause of symptoms, and its concentration further indicates the severity of the disease (Tab. 1) [10]. New possibilities in identifying patients at risk of severe immunotherapy-induced colitis and adjusting treatment strategies for them include monitoring the level of IL-17. Tarhini and colleagues [11] demonstrated that the level of IL-17 at the beginning of treatment was significantly associated with the subsequent occurrence of severe diarrhea and colitis in ipilimumab therapy.

Depending on the severity of diarrhea or colitis, occurring as adverse effects of immunotherapy, the severity grade for a given complication is determined from 1 to 5 (where 1 represents mild, and 5 represents death). In mild cases (grade 1), it is not necessary to discontinue checkpoint inhibitors, and treatment should involve antidiarrheal medications and hydration. However, if diarrhea worsens (grade 2, 3, or 4), immunotherapy should be discontinued, and corticosteroids should be added to the treatment regimen in a dose and form depending on the severity grade (Tab. 2) [12].

Multi-organ immune-related adverse events (irAEs) are common. Xie et al. [13] described it in 65.2% of patients with myocarditis. There was a case report of an uncommon, multi-organ failure in a patient following a single dose of nivolumab plus ipilimumab [14]. However, reports of the co-occurrence of colitis and pneumonitis in patients receiving immunotherapy are rare. In our patient, pneumonitis occurred after the termination of ipilimumab therapy and was related to nivolumab therapy. Wang H et al. summarized the results of several meta-analyses on the incidence of pneumonitis in cancer patients receiving immunotherapy. A meta-analysis of 125 clinical trials included 18 715 cancer patients treated with single anti-PD-1 or anti-PD-L1 antibodies. The incidence of pneumonitis was about 3%-5% of patients. In another meta-analysis including 12 876 patients from 23 randomized trials, the incidence of pneumonitis associated with anti-PD-1 antibodies was 5.17%, with an incidence of grade 3-5 toxicity of 4.14%. Anti-CTLA-4 treatment alone did not seem to increase the incidence of pneumonitis, but the incidence of pneumonitis increased when anti-CTLA-4 antibody was combined with anti-PD-1 or anti-PD-L1 antibodies. The incidence of pneumonitis is related to tumor type, and it is higher in NSCLC and renal cell cancer than in melanoma. The symptoms of pneumonitis include dyspnea, weakness, cough, and fever. Exclusion of infectious pneumonia is necessary in patients with fever. Moreover, sputum and elevated white blood cell count can indicate infection. On CT scans of patients with immune-related pneumonitis, ground-glass opacity, consolidation, nodules, and reticular shadow are observed. Bronchoscopy is used to confirm the diagnosis and exclude infectious pneumonia. Close monitoring of the course of pneumonitis without treatment is recommended only in patients with grade 1 toxicity, while corticosteroids should be considered if clinical progression is observed. A high dose of corticosteroids and discontinuation of immunotherapy is recommended in patients with pneumonitis in grades 2–3. Corticosteroid therapy should last from 6 to 8 weeks and, in some patients, even up to 12 weeks [15]. Recommendations for treating pneumonitis are presented in Table 3.

Table 2. Management of toxic colitis during immunotherapy [19]

Severity	Clinical symptoms	Management
Grade 1	Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline no fever or weight loss	Continue or temporarily hold immunotherapy Monitor for dehydration Dietary changes Expedited patient contact Gastroenterology consultation if prolonged
Grade 2	Diarrhea or colitis 5–7 stools/day over baseline, mild weight loss or fever	Temporarily hold immunotherapy Corticosteroids (1 mg/kg/day prednisone) Supportive care Gastroenterology consultation Consider gastrointestinal endoscopy
Grade 3	Diarrhea or colitis > 7 stools/day, fever, significant weight loss, or evidence of colonic perforation	Temporarily hold immunotherapy High-dose corticosteroids (1–2 mg/kg/day prednisone) Hospitalization if needed Corticosteroids *iv.* or infliximab if symptoms persist Consider gastrointestinal endoscopy
Grade 4	Severe symptoms with evidence of colonic perforation or life-threatening complications	Permanently discontinue immunotherapy Hospitalize High-dose methylprednisolone (1–2 mg/kg/day) Infliximab (if refractory) Consider gastrointestinal endoscopy

iv. — intravenous

Table 3. Management of toxic pneumonitis during immunotherapy [19]

Severity	Clinical symptoms	Management
Grade 1	Asymptomatic (radiographic changes only)	Hold immunotherapy if progression Close monitoring (symptoms and imaging)
Grade 2	Mild symptoms (cough, slight shortness of breath)	Hold immunotherapy until resolution to G1 Initiate corticosteroids (prednisone 1–2 mg/kg/day, taper over 4–6 weeks) Consider antibiotics Consider bronchoscopy with BAL Regular monitoring of symptoms and imaging If no improvement after 48–72 hours, treat as G3
Grade 3	Moderate symptoms (significant shortness of breath, limiting daily activities)	Permanently discontinue immunotherapy Hospitalization Empirical antibiotics
Grade 4	Severe symptoms (life-threatening, requiring mechanical ventilation)	Consider bronchoscopy with BAL High-dose corticosteroids (methylprednisolone 1–2 mg/kg/day) Regular monitoring of pulmonary function and imaging Consider additional immunosuppressive agents if no improvement after 48 hours (e.g., infliximab, mycophenolate mofetil)

BAL — bronchoalveolar lavage

In an analysis of the CheckMate 9LA trial, it was noted that patients who had terminated treatment due to TRAE (treatment-related adverse events) had longer survival compared to the overall patients included in the study [16].

Conclusions

In conclusion, attention should be paid to the complications of immunotherapy in the form of toxic colitis and pneumonitis, which may pose a particular threat

to patients treated with nivolumab and ipilimumab. A swift response is crucial in such cases, as it often entails suspending immunological treatment and necessitates additional interventions. These actions aim not only to improve the patient's clinical condition but also to enable the continuation of anticancer therapy in the future. Significant knowledge gaps exist among residents and faculty physicians across multiple specialties regarding the recognition and treatment of irAEs due to immune checkpoint inhibitors (ICIs) [17].

There is still a lack of certain data and guidelines regarding the resumption of immunotherapy after controlling colitis or pneumonitis. However, it seems that the decision to reintroduce checkpoint inhibitors into treatment should be based on the severity of the immunotherapy-related complications and their resolution after appropriate intervention (including high-dose steroids). On the other hand, multi-organ irAEs were associated with improved overall survival compared with no irAEs or single-organ irAEs [18].

Article Information and Declarations

Ethics statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient.

Author contributions

A.D.-K., K.K.: conception and design, provision of study materials or patients, data analysis and interpretation, manuscript writing, final approval of manuscript; E.S.-W.: provision of study materials or patients, manuscript writing, final approval of manuscript; J.M.: administrative support, manuscript writing, final approval of manuscript; I.C.: conception and design, administrative support, provision of study materials or patients, data analysis and interpretation, manuscript writing, final approval of manuscript; P.K.: conception and design, administrative support, data analysis and interpretation, manuscript writing, final approval of manuscript.

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Conflict of interest

A.D.-K., K.K., E.S.-W., J.M.: declare no conflict of interest.

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Supplementary material

None.

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