VIA MEDICA

CASE REPORT

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Immunochemotherapy in a 25-year-old male patient with small-cell lung cancer

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ABSTRACT

Lung cancer is the leading cause of cancer-related deaths, both in males and females. Small-cell lung cancer (SCLC) is a strongly tobacco-dependent type of lung cancer characterized by aggressiveness, rapid growth, and a high tendency to metastasize. SCLC is the most commonly diagnosed in an advanced — metastatic — stage in patients with many comorbidities and inadequate performance status. However, based on the most current recommendations, chemotherapy in combination with immunotherapy at the extensive stage (ES) of SCLC, significantly improves the therapeutic efficiency. Here, we present a case of a 25-year-old man, diagnosed with SCLC, with a medical history of 10 years of smoking e-cigarettes and marijuana as well as the use of amphetamine and alcohol. In the diagnosis process, considering the young age of the patient, the next-generation sequencing (NGS) was performed, but no molecular alterations in oncogenes were found. During the immunochemotherapy with atezolizumab, carboplatin, and etoposide, immune-related adverse events (irAEs), in the form of hepatotoxicity, were observed. After the toxicity subsided, the immunotherapy was continued with a very good effect and tolerance. The patient has remained in partial remission for 9 months. The presented case highlights the possibility of treatment continuation despite mild adverse events triggered by immunotherapy and the need for more research in the group of young patients diagnosed with SCLC.

Keywords: immunotherapy, immune-related adverse events, small-cell lung cancer, toxicity

Introduction

Small-cell lung cancer (SCLC) accounts for 10-15% of all lung cancer diagnoses worldwide [1]. It is characterized by a high proliferative rate and a strong tendency for early dissemination. Despite many years of research, the prognosis for SCLC is poor. It is recommended to classify the disease stage based on the TNM system (T — size of the primary tumor, N — regional lymph nodes that are involved, M — distant metastasis) [5]. However, SCLC is traditionally graded, based on the possibility of using radiotherapy, into a limited stage (LS) and an extensive stage (ES) [2]. Consequently, most patients (60–70%) have the ES of disease at the time of diagnosis — they are diagnosed when cancer extends outside the ipsilateral lung and regional lymph nodes, which cannot be covered by a single field of irradiation [3]. Treatment of LS SCLC consists of chemotherapy and radiotherapy, and this therapy can cure 20–25% of patients. Patients with ES SCLC have poor prognosis, but immunochemotherapy can improve quality of life and overall survival [4].

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Case report

In November 2022, a 25-year-old man was hospitalized in the Department of Pneumonology, Oncology and Allergology for a mediastinal tumor detected on his chest X-ray. The chest imaging examination was performed because of hemoptysis and suspected rib injury. During the diagnostics, the patient developed paraneoplastic hyponatremia. The patient's medical history included the use of stimulants of unknown origin (10 pack-years), marijuana, amphetamine, and alcohol abuse. In the family history, maternal thyroid cancer was disclosed. During hospitalization, chest computed tomography (CT) was performed, which revealed fluid in the right pleural cavity and a tumor of the lower lobe of the right lung with peripheral atelectasis. The tumor was connected with enlarged lymph nodes forming a pathological mass in the subcarinal cavity and in the right hilum, as well as enlarged lymph nodes of the left hilum and aortopulmonary window. The tumor was compressing the left atrium, tracheal carina, and lobar bronchi. It adhered to the aorta and esophagus, modeling the vessels in this area.

Bronchoscopy with endobronchial ultrasound transbronchial needle aspiration biopsy (EBUS-TBNA) was performed, and it revealed right-sided narrowing of the middle lobe bronchus and external compression of the right seventh segment bronchus. In-depth (due to an unusual case) pathomorphological examination of the tumor material was performed. Slides stained with hematoxylin and eosin showed a confluent infiltrate of small monotonous tumor cells. Immunohistochemical (IHC) staining was performed (Fig. 1). The expression of the following markers was found: CK AE1/AE3 (cytokeratin, weak, perinuclear), TTF1 (thyroid transcription factor 1, strong in 100% of tumor cells), chromogranin A (perinuclear) and synaptophysin (positive), FLI-1 (friend leukemia integration-1, positive), CD56 (positive), NSE (neuron-specific enolase, focal), Ki67 (strong in 90% of tumor cells), while p40, CD45, CD99, and nuclear protein of the testis (NUT) were not expressed. Low-grade neuroendocrine carcinoma (small-cell lung cancer) was diagnosed. The diagnosis of NUT midline carcinoma, primitive neuroectodermal tumor (PNET), and Ewing sarcoma was taken into account in the diagnosis.

Next-generation sequencing (NGS) is not a standard procedure in SCLC patients, but it was performed due to the very young age of the patient and unknown thyroid cancer in the family. We used the Ion Torrent S5 sequencer and the Oncomine Focus test (Thermo Fisher Scientific, US), which enable the examination of mutations, rearrangements, and copy number changes in 52 oncogenes. However, no oncogenic mutations were detected. Based on the tests carried out, the final diagnosis of small-cell carcinoma at the T4N2M1a stage was established.

By the decision of the multidisciplinary tumor board, the patient was qualified for immunochemotherapy with carboplatin, etoposide, and atezolizumab. After the fourth cycle of immunochemotherapy, hepatotoxicity manifested by an increase in bilirubin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels (Fig. 2) was observed as well as yellowing of the sclera. Grade 1 liver failure was diagnosed and, for this reason, the administration of subsequent cycles of immunotherapy was postponed. Systemic steroid therapy was not implemented.

After stabilization of the liver parameters, the treatment was continued with good tolerance. A follow-up CT examination showed partial response: a decrease in the size of the tumor of the lower lobe of the right lung, subcranial lymph nodes, right and left hilar lymph nodes, and a decrease in the amount of fluid in the right pleural cavity. Partial remission is maintained (Fig. 3). Currently (September 2023), the patient is in better general condition, with no report of any side effects or complications of the treatment.

Discussion

Fewer than 5% of SCLC patients achieve the 5-year survival rate. The majority of patients survive less than 1 year after diagnosis [6]. Small-cell lung cancer is characterized by an early relapse, and about one-third of relapsed patients have brain metastases. Slotman et al. showed that prophylactic cranial irradiation (PCI) may reduce the prevalence of brain secondary deposits and increase overall survival (OS) in SCLC patients [7]. Therapeutic options for SCLC patients are limited. Surgical treatment does not affect OS, and it is an option only for TNM stage I (T1-2N0M0) patients with no mediastinal or supraclavicular lymph node metastases. The first-line treatment for ES SCLC patients is a combination of cisplatin or carboplatin and etoposide. Nonetheless, median of OS for ES SCLC patients treated with standard chemotherapy is only approximately 10 months [8]. The newly recommended standard of treatment in ES SCLC patients consists of immunotherapy combined with chemotherapy. Results of two important phase III clinical trials (IMpower133 and CASPIAN) have shown a significant role of the combination of immune checkpoint inhibitors (ICIs) with first-line chemotherapy in the treatment of ES SCLC patients [9].

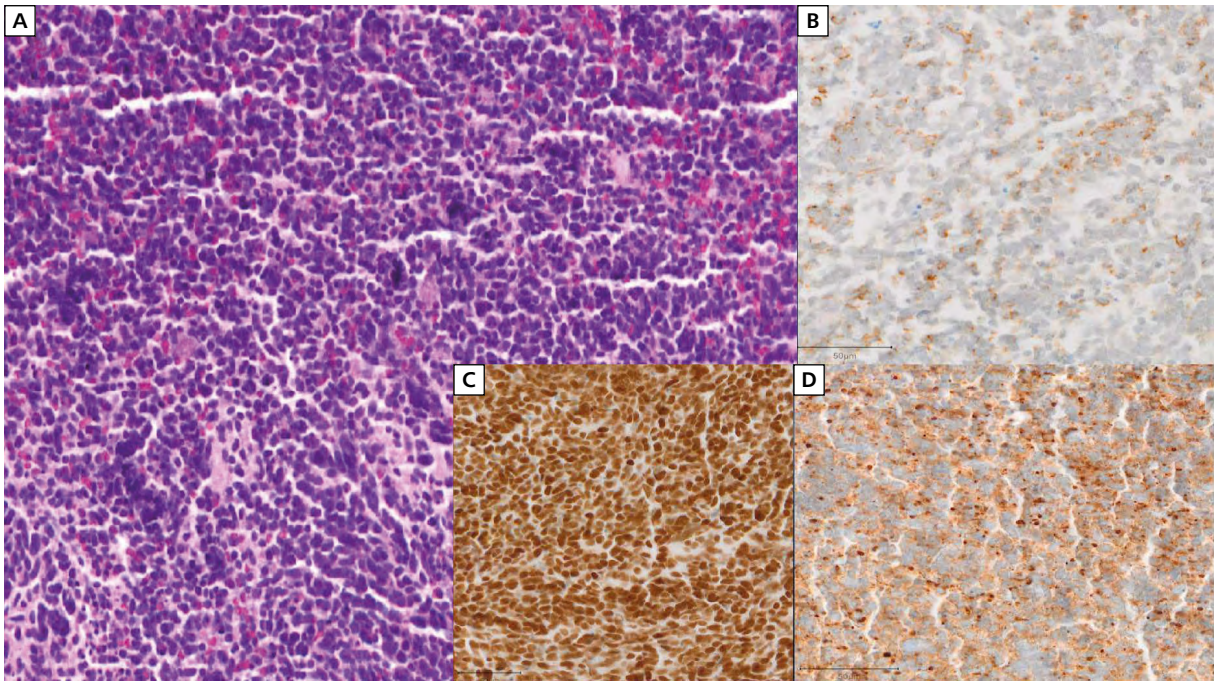

Figure 1. A. Diffuse tumor infiltration of small cells with scant cytoplasm. H + E stain. High magnification. Microphotograph; **B.** Weak, focal reaction with keratin in some neoplastic cells. Keratin AE1/AE3 stain. High magnification. Microphotograph; **C.** The tumor cells stain strongly for thyroid transcription factor-1 (TTF-1). TTF-1 immunohistochemical stain. High magnification. Microphotograph; **D.** Medium intense reaction with chromogranin A. Chromogranin A reaction. High magnification. Microphotograph

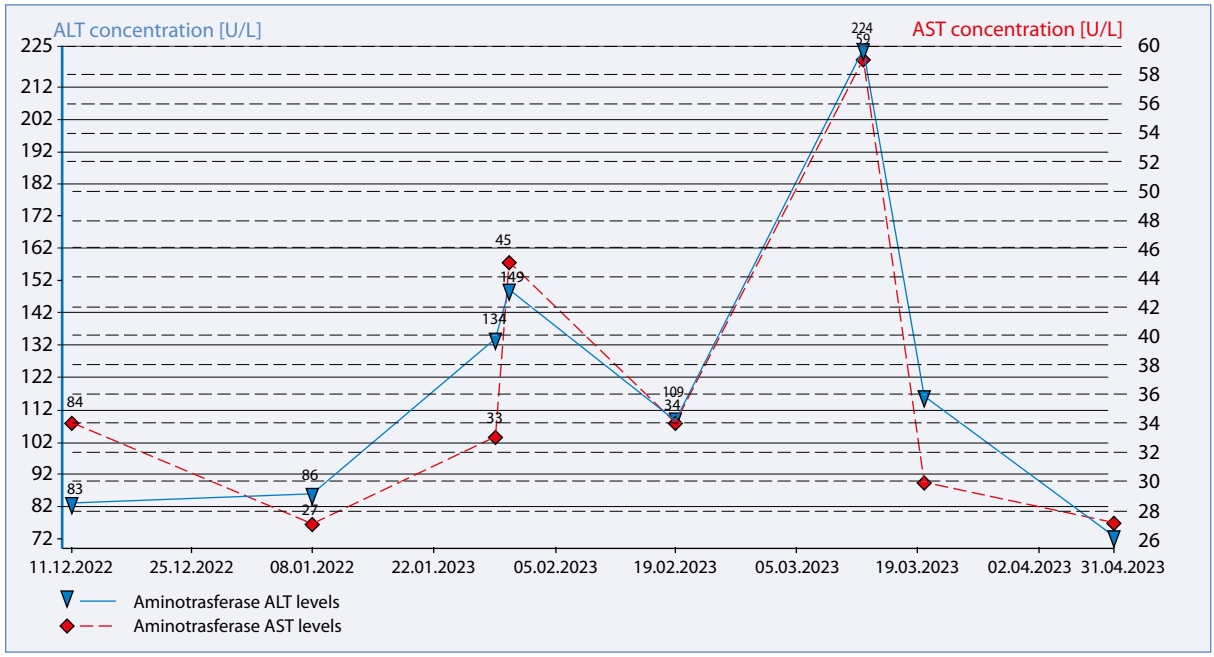

Figure 2. Graphic presentation of a treatment-related increase in the levels of aminotransferases; ALT — alanine aminotransferase; AST — aspartate aminotransferase

IMpower133

Atezolizumab is a humanized monoclonal antibody anti-programmed death ligand (anti-PD-L1) that inhibits the binding of PD-L1 to the PD-1 receptor on lymphocytes [10]. The IMpower133 study evaluated the safety and efficacy of using atezolizumab or placebo in addition to first-line chemotherapy treatment with

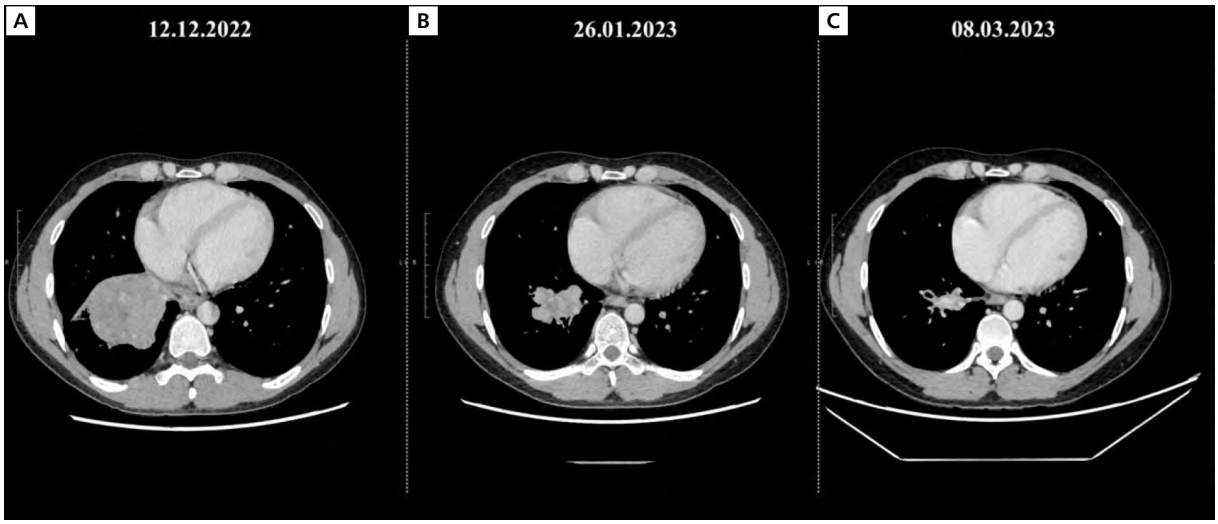

Figure 3A–C. Regression of the tumor shown in three consecutive computed tomography scans

carboplatin and etoposide (CP/ET) in ES SCLC patients [11]. This clinical trial recruited 403 patients who were randomly assigned into two groups (placebo plus CP/ET *vs.* atezolizumab plus CP/ET). Results showed that median OS in patients who received atezolizumab plus CP/ET was two months longer than in patients who received only CP/ET (12.3 months *vs.* 10.3 months, HR = 0.70; 95% CI 0.54–0.91; p = 0.0096). Median progression-free survival (PFS) of patients who received atezolizumab plus CP/ET was one month longer than un the case of patients who received only CP/ET (5.2 months *vs.* 4.3 months, HR = 0.77; 95% CI 0.62–0.96; p = 0.017). After 18 months of follow-up, 34.0% of patients were alive in the atezolizumab plus CP/ET group, and 21.0% of patients in the placebo plus CP/ETgroup [11, 12].

CASPIAN

Durvalumab is a humanized monoclonal anti-PD-L1 antibody [13]. The CASPIAN study examined the efficacy and safety of durvalumab added to first-line platinum (carboplatin or cisplatin) based chemotherapy with etoposide (P/ET) in ES SCLC patients. All 805 patients were randomly assigned to one of three groups: durvalumab plus P/ET, durvalumab plus tremelimumab (monoclonal antibody anti-CTLA-4, cytotoxic T lymphocyte antigen 4) plus P/ET and only P/ET [14]. The study reported the following results – median OS in the durvalumab plus P/ET group, in comparison to only P/ET, was extended by 2 months (12.9 months *vs.* 10.5 months, HR = 0.71; 95% CI 0.60–0.86; p = 0.0003). The two-year OS rate in the durvalumab plus P/ET group, compared to only P/ET group, was 22.9% *vs.* 13.9%, and the three-year OS rate in the durvalumab plus P/ET group, compared to the only P/ET group, was 17.6% *vs.* 5.8%. Furthermore, the rate of serious adverse events (SAEs) in the durvalumab plus P/ET group, compared to the only P/ET group, was 32.5% *vs.* 36.5% [12, 14].

Immunochemotherapy with atezolizumab or durvalumab in addition to first-line chemotherapy in ES SCLC patients resulted in a significant improvement in OS rates. Both studies have shown that atezolizumab and durvalumab had remarkable efficacy and favorable safety in ES SCLC patients [12].

Based on the decision of the Ministry of Health, atezolizumab immunotherapy combined with first-line chemotherapy (CP/ET) is reimbursed in Poland for patients with ES SCLC. In March 2023, durvalumab in combination with first-line chemotherapy (P/ET) was added to the program. Moreover, patients with ES SCLC and controlled central nervous system metastases can receive immunochemotherapy.

Toxicity of immunotherapy

The immunotherapy mechanism is to activate, expand, or redirect tumor-reactive T cells to increase cell anti-tumor immune responses. Immunotherapy apart from prolonging survival of patients with SCLC and many other cancers, may cause side effects. Among important complications are immune-related adverse events (irAEs) as a result of treatment-induced inflammation, which most commonly affects the skin, liver, digestive tract, and the endocrine system [15]. Hepatotoxicity induced by immunotherapy can range from a moderate increase of liver aminotransferases

Table 1. Management of immune-related hepatotoxicity according to the European Society for Medical Oncology (ESMO) recommendations and summary of product characteristics for durvalumab

Severity of symptoms	Assessment of investigations	Treatment modification and corticosteroid therapy
ALT or AST > ULN to 3 × ULN	• Monitor liver enzymes every 1–2 weeks	• Continue ICI therapy
ALT or AST 3–5 × ULN	• Check LFTs, INR, and albumin twice weekly • Test hepatitis B, C, and E (sometimes A) • Examine PCR, anti-ANA, SMA, LKM, SLA/LP, LCI, and iron levels • Review history of medications and alcohol • Consider imaging metastases and/or clot	• Withhold ICI therapy • Avoid hepatotoxic drugs • In the case of rising ALT and/or AST, start administration of corticosteroids 0.5–1 mg/kg/day • In the case of improvement, resume ICI therapy after tapering corticosteroids to < 10 mg/day • In the case of no improvement, discontinue ICI therapy and increase the dose of corticosteroids to 1–2 mg/kg/day
ALT or AST 5–20 × ULN	• Check LFTs, INR, and albumin daily • Imaging tests of the liver: US, CT, or MRI • Consider hepatologist consultation and/or liver biopsy	• Discontinue ICI therapy • If ALT and/or AST < 400U/l with normal INR, bilirubin, and albumin, start administration of cortcosteroids 1–2 mg/kg/day • If ALT and/or AST > 400 U/l with raised INR/bilirubin and low albumin, start administration of methylprednisolone 2 mg/kg i.v.
ALT or AST > 20 × ULN	As above	• Discontinue ICI therapy • Start administration of methylprednisolone 2 mg/kg i.v.
According to the summary of product characteristics for durvalumab		
• In the case of concomitance ALT or AST > 3 × ULN and total bilirubin > 2 × ULN — discontinue ICI therapy and start administration of prednisone 1–2 mg/kg/day or its counterpart and then reduce the dose • In the case of ALT or AST > 10 ULN or total bilirubin > 3 × ULN — discontinue ICI therapy and start administration of prednisone 1–2 mg/kg/day or its counterpart and then reduce the dose		

ALT — alanine aminotransferase; AST — aspartate aminotransferase; CT — computed tomography; ICI — immune checkpoint inhibitor; MRI — magnetic resonance imagining; **Proszę wyjaśnić wszystkie skróty: ULN, LFT, INR, PCR, anti-ANA, SMA, LKM, SLA/LP, LCI, US, i.v.**

and hyperbilirubinemia to, exceptionally, fulminant liver failure. Hepatotoxicity caused by ICIs may be clinically asymptomatic. However, symptoms such as fever, jaundice, fatigue, and maculopapular rash have been reported. During the diagnostic process, it is important to rule out other etiologies of hepatotoxicity. Management of hepatotoxicity usually includes cessation of immunotherapy and application of corticosteroids or other immunosuppressive agents. Most patients can restart the immunotherapy after recovery [16, 17]. Specific recommendations of the European Society for Medical Oncology (ESMO) for management of hepatotoxicity due to immunotherapy depend on symptom grade. Recommendations are also presented by ICI producers (Tab. 1) [18].

Small-cell lung cancer in young patients

Although lung cancer is most commonly diagnosed in older patients, there are patients with the diagnosis at a young age. Patients with non-small cell lung cancer (NSCLC) under the age of 30 are quite noften described in the literature. Such patients usually have single-driver alterations in oncogenes, e.g. in the *EGFR* (epidermal growth factor receptor), *ALK* (anaplastic lymphoma kinase), or *ROS1* (ROS1 protoncogene) genes. The literature presented a profile of younger NSCLC patients diagnosed with lung cancer. They are most frequently females with no smoking history and an advanced stage of disease. Young NSCLC patients have better OS only in early stages of the disease (I or II) when resection is

possible. However, the prognosis of patients with advanced NSCLC and with genetic alteration has also recently improved with the use of molecularly targeted therapies [19].

Small-cell lung cancer patients under the age of 30 are extremely rarely described (the cause of SCLC is most often long-term exposure to tobacco smoke). Otherwise, previous studies of SCLC suggested poor prognosis regardless of the patient's age. Lee et al. [20] found that young patients diagnosed with SCLC, despite being healthier than older patients and having no comorbidities, presented adverse survival outcomes, especially in those with extensive stages of cancer. Chemoimmunotherapy may change the prognosis in this group of patients, as evidenced by the effectiveness of this method of treatment in our patient.

There is a description of a similar case in the literature. A case of a 22-year-old patient with a final diagnosis of SCLC who had smoked one marijuana joint three times a week for three years but did not smoke cigarettes. Although rare, it should alert physicians that cannabis smoking may be a risk factor for lung cancer [21]. Further investigations in young patients diagnosed with SCLC are warranted to understand and determine age- and treatment-related factors to improve survival rates in this group.

E-cigarettes and the respiratory system

Electronic cigarettes (e-cigarettes) are non-combustible tobacco products that contain nicotine, and liquid propylene glycol and vegetable glycerin flavorings. The e-cigarette liquid is first heated, by using a battery-powered device and then inhaled as an aerosol [22]. E-cigarettes are considered an alternative to help patients struggling with smoking cessation [23]. Although e-cigarettes avoid the release of tarry substances, they still emit heavy metals, furans, volatile carbonyls, and reactive oxygen species. Moreover, e-liquids may contain much more toxic substances because the e-cigarette market is not well controlled by government organizations. E-cigarette users may have access to e-liquids of unknown origin or they may modify the composition of e-liquids themselves (e.g. by adding cannabinoids and solvents such as tocopherol — vitamin E).

Using e-cigarettes, called "vaping", significantly influences the pulmonary system, by downregulation of immune genes in the nasal epithelia, inhibiting ciliary beating, and enhancement of proinflammatory cytokine secretion in the bronchial epithelia. Additionally, e-cigarettes affect sputum by impaired macrophage function, increased levels of MUC5AC mucin and proteases, and bronchial endothelia by impaired vasoconstriction and increased bronchial wall stiffness. These processes may lead to mild chronic respiratory inflammation and injuries in the small airways. [24]. Respiratory tissue exposed via epithelium metaplasia, injuries and, indirectly, by chronic inflammation may be prospective areas for oncogenesis. Directly, e-cigarettes and vaping fluids contain nicotine derivatives and other organic compounds (polycyclic aromatic hydrocarbons, benzene, amines), which are defined as potential carcinogens [25]. Schall et al. [26] discovered that nicotine and e-cigarette components can promote the self-renewal of lung adenocarcinoma stem-like cells. The molecular and genetic pathways described the activation of transcription factors Oct4, Yap1, and E2F1 in response to signaling events from the α7 nAChR. Hence, the growth of lung adenocarcinoma is perhaps promoted by nicotine and e-cigarettes [26].

The relationship between the use of e-cigarettes and the development of lung cancer, including SCLC, at a young age has not yet been described. Our patient may be the first such case in the literature although the association of vaping and smoking marijuana with SCLC development in our patient is uncertain. However, the toxicity of e-liquids has already been well documented. Due to the widespread use of e-cigarettes, a new disease entity has been described. E-cigarette or vaping product use-associated lung injury (EVALI) is an acute lung injury associated with the use of electronic cigarettes, which may be severe and lead to death. The mortality rate is 2.4%. Most patients (up to 94%) diagnosed with the disease used e-liquids containing tetrahydrocannabinoids (THC) and high concentrations of tocopherol. The most common symptoms of EVALI are shortness of breath and cough. Approximately half of patients experience chest pain and sometimes they have hemoptysis. Common gastrointestinal symptoms are nausea, vomiting, diarrhea, and abdominal pain. Most patients experience fever, chills, and weakness. Infiltrative changes in the lungs and ground glass opacities in chest CT are characteristic. EVALI treatment involves high doses of glucocorticosteroids, antibiotic therapy, oxygen therapy, and in severe cases, respiratory therapy [27, 28].

Another concern is various e-cigarettes technologies with different nicotine exposure, flavorings, coil power, atomizer construction, and lack of general recommendations. Furthermore, electronic vaporization of nicotine causes the same addictive behaviors as nicotine in traditional cigarettes and promotes nicotine dependence [24]. In conclusion, e-cigarettes cannot be a tool helping patients with smoking cessation. Based on presented histological and molecular changes induced by vaping in multiple lung regions, there is concern about long-term consequences caused by e-cigarettes and their likely toxicity, which are currently being investigated.

Conclusions

Results from two important phase III clinical trials, IMpower133 and CASPIAN, have shown that immunotherapy combined with chemotherapy offers the hope of prolonging OS in patients with ES SCLC, compared with standard first-line chemotherapy. Although immunotherapy may cause many complications — an example is hepatotoxicity that was diagnosed in our patient. The diagnosis of SCLC, especially in young patients, requires extensive clinical review to select an appropriate treatment. There is a need for large population studies to define the molecular signature and clinical management of SCLC and improve treatment outcomes in young patients. More research is also necessary to inspect and prevent the consequences of immune checkpoint inhibitor treatment.

Article Information and Declarations

Ethics statement

Article have been conducted according to the principles stated in the Declaration of Helsinki.

Author contributions

A.Ł: methodology, investigation, writing — original draft; B.M.: writing — original draft; Ł.Ł.: writing — original draft; I.C.: conceptualization, writing, review and editing; I.P., R.L., M.G.: methodology; P.K.: conceptualization, review and editing.

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Conflict of interest

The authors declare no conflicts of interest.

Supplementary material

None.

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