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Case report

Acute pneumothorax due to immunotherapy administration in non-small cell lung cancer

Chrysanthi Sardeli [a], Paul Zarogoulidis [a,b,*], Konstantinos Romanidis [c], Panagoula Oikonomou [c], Konstantinos Sapalidis [b], Haidong Huang [d], Chong Bai [d], Wolfgang Hohenforst-Schmidt [e], Kosmas Tsakiridis [f], Bojan Zaric [g], Branislav Perin [g], Aris Ioannidis [h], Sofia Baka [i], Konstantinos Drevelegas [j], Maria Kosmidou [k], Christoforos Kosmidis [b]

[a] Department of Pharmacology & Clinical Pharmacology, School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece
[b] 3rd Department of Surgery, "AHEPA" University Hospital, Aristotle University of Thessaloniki, Medical School, Thessaloniki, Greece
[c] Second Department of Surgery, University Hospital of Alexandroupolis, Medical School, Democritus University of Thrace, Alexandroupolis, Greece
[d] Department of Respiratory & Critical Care Medicine, Changhai Hospital, The Second Military Medical University, Shanghai, China
[e] Sana Clinic Group Franken, Department of Cardiology / Pulmonology / Intensive Care / Nephrology, "Hof" Clinics, University of Erlangen, Hof, Germany
[f] Thoracic Surgery Department, "Interbalkan" European Medical Center, Thessaloniki, Greece
[g] Institute for Pulmonary Diseases of Vojvodina, Faculty of Medicine, University of Novi Sad, Serbia
[h] Surgery Department, "Genesis" Private Hospital, Thessaloniki, Greece
[i] Oncology Department, "Intebalkan" European Medical Center, Thessaloniki, Greece
[j] Radiology Department, "Euromedica" Private Radiology Laboratory, Thessaloniki, Greece
[k] Internal Medicine, University Hospital of Ioannina, Ioannina, Greece

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ABSTRACT

Nowadays we have novel therapies for advanced stage non-small cell lung cancer. Immunotherapy has been introduced in the market for several years and until now its administration is mostly based on the programmed death-ligand 1. First line treatment with immunotherapy can be administered alone if programmed death-ligand 1 expression is $\geq$ 50%. All therapies for advanced stage disease have advantages and disadvantages, immunotherapy until now has presented mild adverse effects when compared to chemotherapy. However; it is known to induce inflammatory response to different tissues within the body. In our case acute pneumothorax was induced after immunotherapy administration.

1. Introduction

Lung cancer is the second cause of cancer death after prostate cancer for men and breast cancer for women [1]. It is still diagnosed at advanced stage since there are no early disease symptoms. Currently we are trying to identify high risk patients and develop and algorithm of diagnosis and pulmonary nodule follow up [2,3]. We have novel diagnostic equipment with radial-endobronchial ultrasound (R-EBUS), convex probe endobronchial ultrasound (CP-EBUS), electromagnetic navigation, Veran SPiNDrive system, transthoracic needle biopsy with under CONE BEAM CT, archimedes bronchoscopic *trans*-parenchymal nodule biopsy, bronchoscopic transparenchymal nodule access, thin-ebus [4–7]. The CP-EBUS is also used for non-small cell lung cancer staging (NSCLC) [8,9]. All these new diagnostic technologies have the advantage of making a biopsy with the most safe and efficient way with very low rate of adverse effects. There are several therapies for NSCLC from non-specific cytotoxic drugs to targeted agents such tyrosine kinase inhibitors (TKIs) and immunotherapy [10,11]. Non-specific cytotoxic agents are known to induce neutropenia, vomiting, loss of hair and fatigue [12]. All these adverse effects can be treated with different drugs however; in some cases patients had to stop their therapy due to the severe adverse effects. Targeted therapies with TKIs are based on the expression of the following genes epidermal growth factor (EGFR), anaplastic lymphoma kinase (ALK), ROS proto-oncogene 1 (ROS1), proto-oncogene B-Raf (BRAF) [13]. Targeted therapies have as adverse effects usually skin rash and pnumonitis which are known to be associated with the effectiveness of therapy [14]. These adverse effects are usually managed with dose reduction, antibiotics and corticosteroids.

* Corresponding author. 3rd Department of Surgery, "AHEPA" University Hospital, Aristotle University of Thessaloniki, Medical School, Thessaloniki, Greece.
E-mail address: pzarog@hotmail.com (P. Zarogoulidis).

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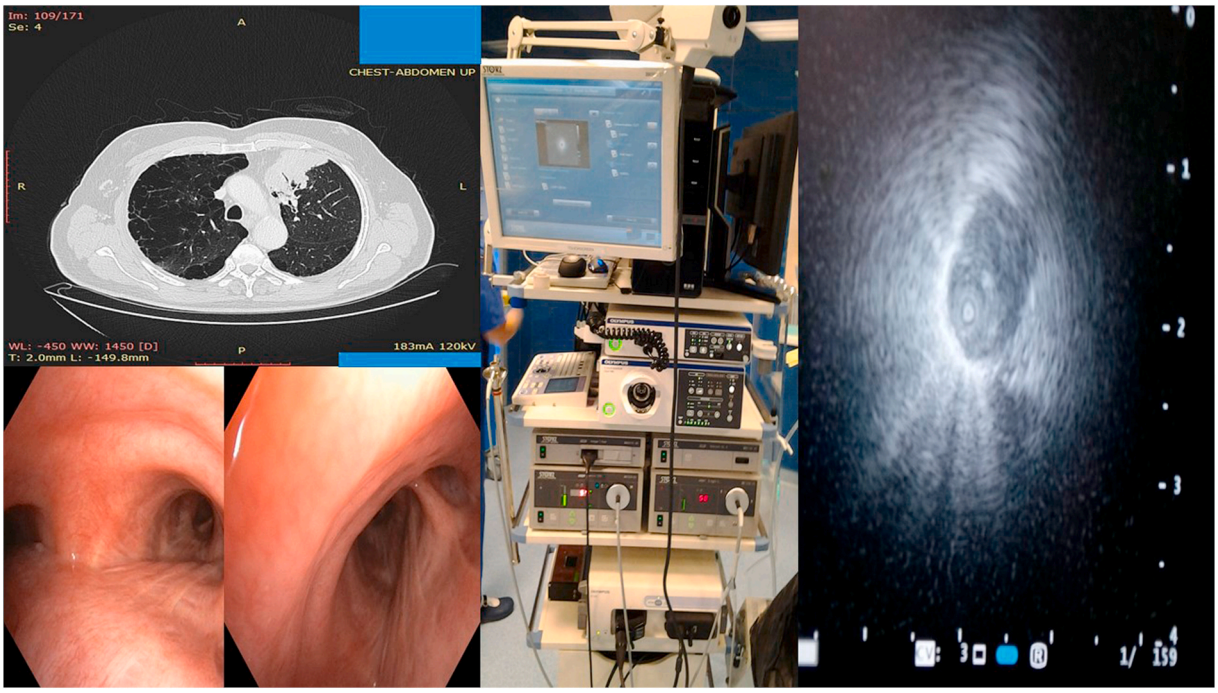

Fig. 1. Left CT of the thorax with the cancer lesion and endobronchial images, middle the radial-EBUS equipment, and right the ultrasound image from the cancer lesion with the radial-EBUS.

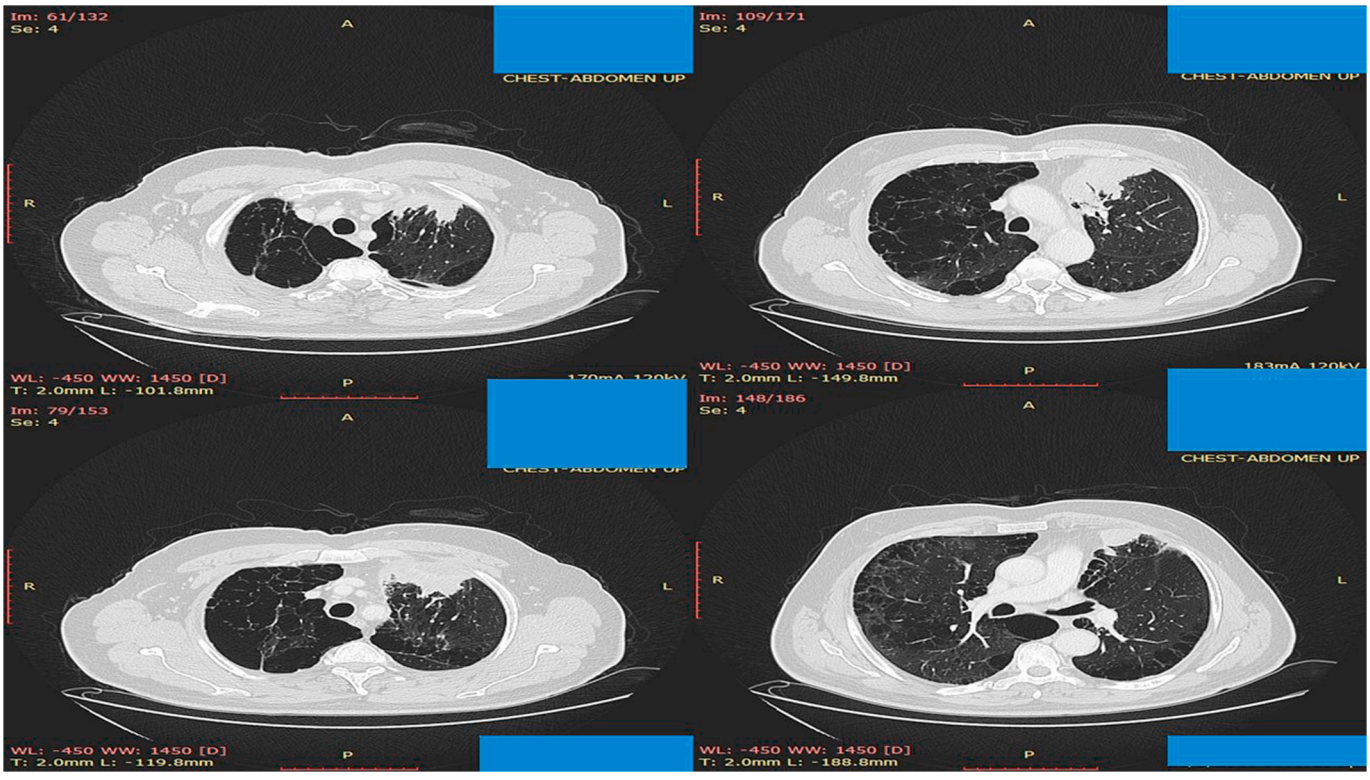

Fig. 2. CT of the thorax upon diagnosis.

Certainly there are cases where therapy has to stop due to serious adverse effects. In the case were programmed death-ligand 1 (PD-L1) gene expression is $\geq$ 50% then pembrolizumab can be admnistered as first line treatment [15]. In the case of lower expression of $\leq$50% PD-L1 then a combination of chemotherapy with immunotherapy can be administered [16]. Immunotherapy has adverse effects which will be presented in the discussion section.

1.1. Case report

A 65 year man was diagnosed with squamous cell carcinoma with radial-endobronchial ultrasound (R-EBUS) stage IV since he had bone

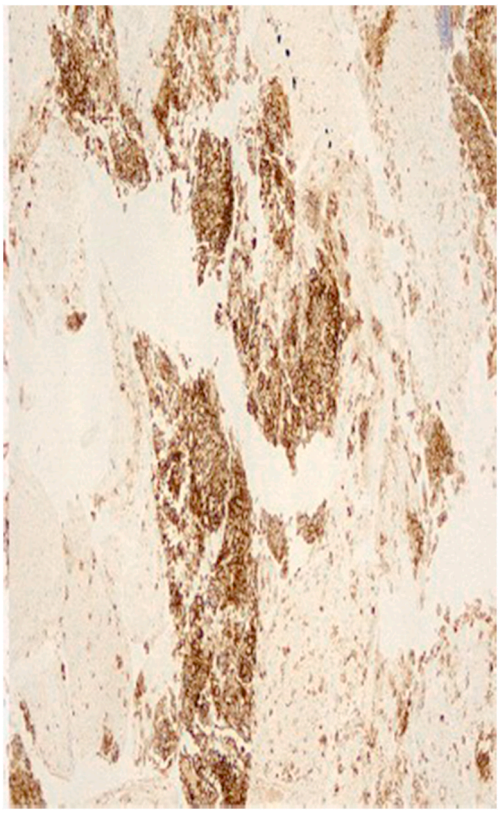

Fig. 3. DAKO technique ×40 magnification.

metastasis (Fig. 1.). The patient was diagnosed with chronic obstructive pulmonary disease (COPD) stage III and he had severe emphysema. (Fig. 2). The tissue sample was investigated for programmed death-ligand 1 (PD-L1) and it was found to have an expression of 100% (Fig. 3.). Pembrolizumab was initiated, however; after 3 h the patient presented severe dyspnoia and after electrocardiographic (ECG) and imaging inspection with CT of the thorax a massive pneumothorax was observed (Fig. 4.). A chest tube number 30F was inserted under fluoroscopy (Figs. 5–6.). The patient underwent pleurodesis with talc poudrage and continued its therapy. There were no other lesions on the right hemithorax. The patient was discharged after five days and today continues his immunotherapy treatment pending restaging. Pneumothorax has not re-occurred. Due to the high PD-L1 expression we provided only immunotherapy and not in addition with chemotherapy which we saved for the case of disease progression (see Fig. 4) (see Fig. 3).

1.2. Methods of programmed death-ligand 1 (PD-L1)

Immunohistochemistry was performed in 2-μm tissues on positive charged slides. Programmed death-ligand 1 (PD-L1) PD-L1, companion diagnostic system Dako, Denmark,EU. This protocol is a complete automate stable procedure, performed in AutostainerLink48 Dako platform. Each staining run includes external positive cell line control.

2. Discussion

Immunotherapy can be administered alone as first line treatment in NSCLC if PD-L1≥50% or in combination with chemotherapy if we have low PD-L1 expression [17–19]. In any case it is a very efficient treatment modality. However; immunotherapy in lung cancer has numerous side effects such as tumor necrosis syndrome, vitiligo, psoriasis, acute thyroiditis and hepatitis resuscitation [20–23]. Uveitis, pancreatitis, central nervous system disease, and peripheral neuropathies have also been reported [24]. IRAEs can be severe, even resulting in death in some cases. Immune checkpoint inhibitors (ICIs) are increasingly studied and used as therapy for a growing number of malignancies. ICIs work by blocking inhibitory pathways of T-cell activation, leading to an immune

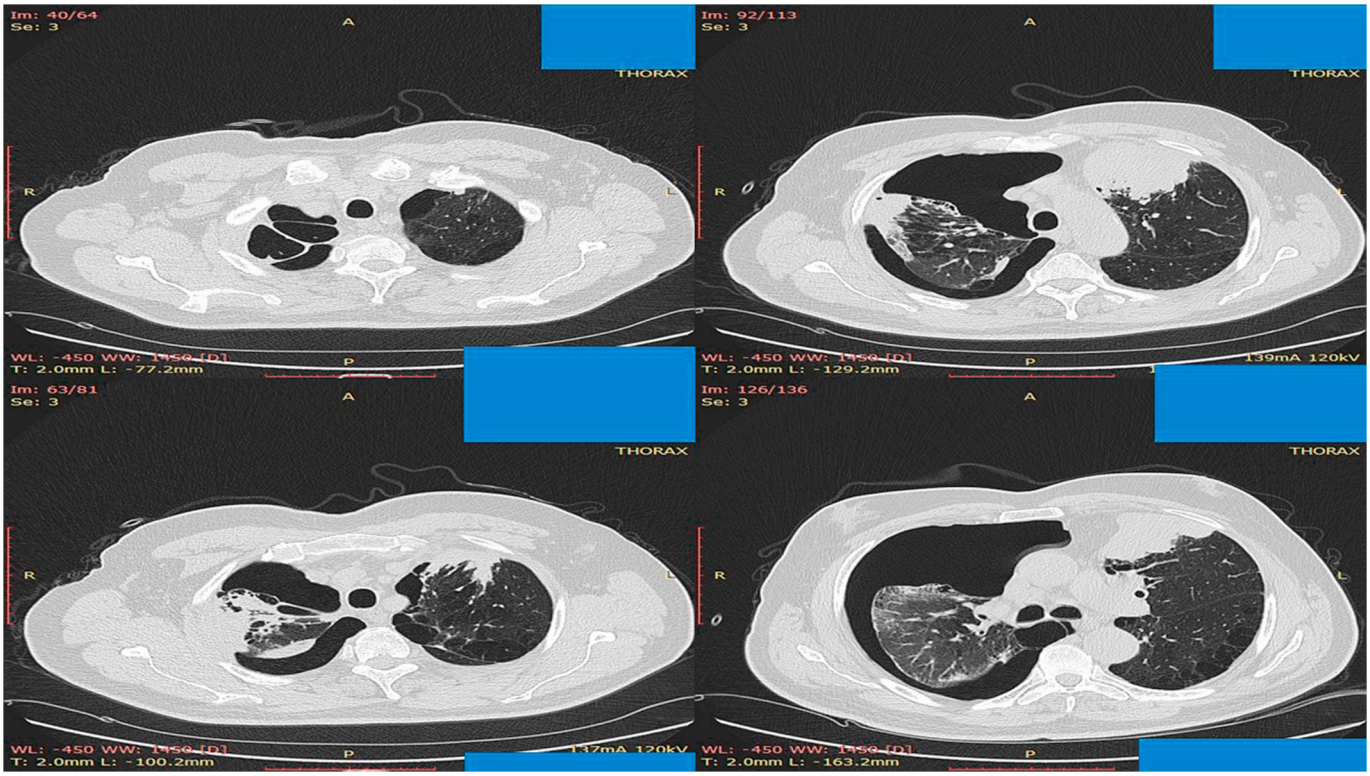

Fig. 4. CT of the thorax with pneumothorax.

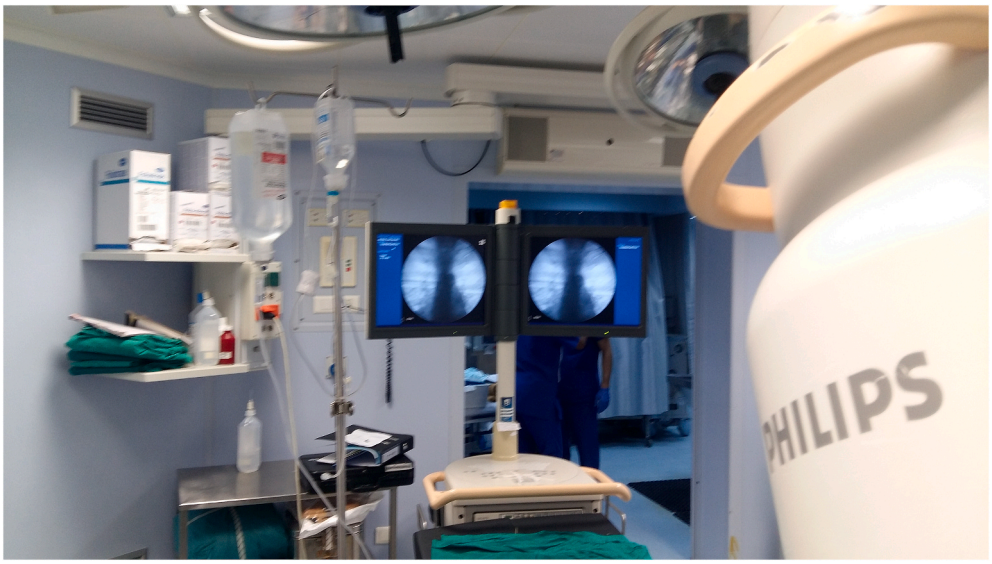

Fig. 5. Fluoroscopy during the chest tube insertion.

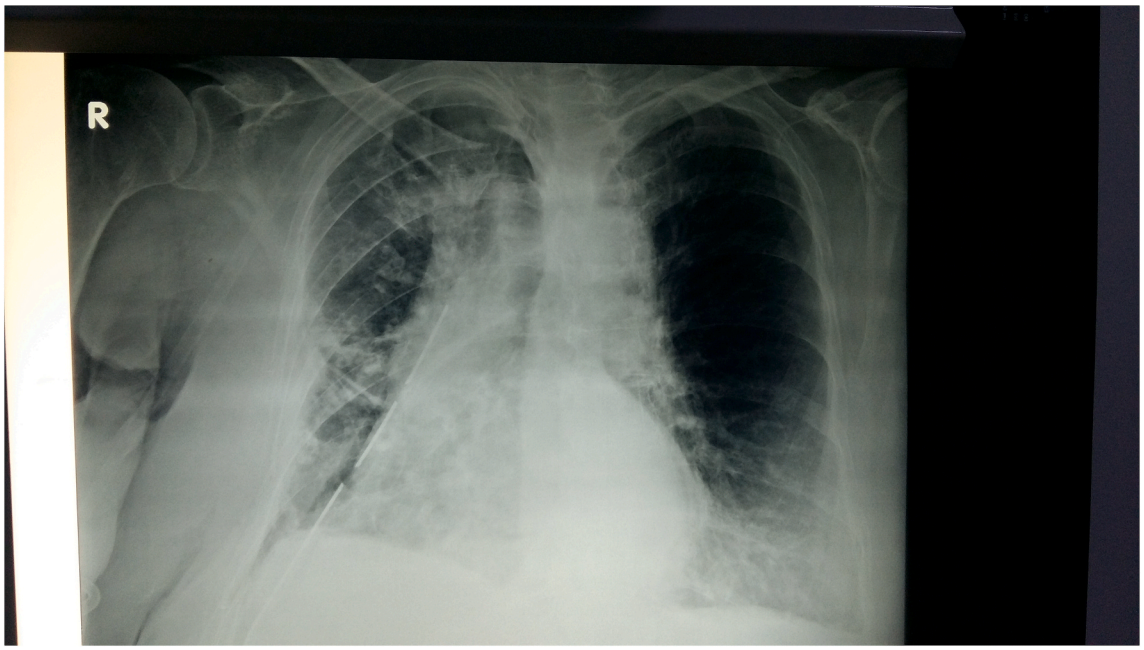

Fig. 6. Chest x-ray with the chest tube inserted, the right lung has expanded.

response directed against tumors. Such nonspecific immunologic activation can lead to immune-related adverse events (IRAEs). Some IRAEs, including inflammatory arthritis, sicca syndrome, myositis, and vasculitis. The time course for developing IRAE is variable and can occur after one dose or after several months of therapy [25]. A number of inhibitory pathways, known as immunologic checkpoints play critical roles in maintaining self-tolerance and preventing autoimmunity. ICIs non-specifically activate T-cells by blocking negative co-stimulatory ligands or receptors on T-cells, antigen presenting cells (APC), and/or tumor cells. The enhanced activation of T-cells can enhance tumor targeting and killing, but are not specific to only an anti-tumor response. Currently, ICIs with three targets, CTLA-4, PD-1 and PD-L1, are FDA approved. ICIs can cause adverse effects through immune-mediated tissue damage known as immune-related adverse events (IRAE). These events vary widely in severity and can affect nearly any organ system. Pneumothorax is an emergency situation where immediate care is necessary. Firstly we have to insert a chest tube in order to relieve the patient from the endothoracic air volume that has been accumulated [26]. This can be done in the emergency department. In our case our patient had emphysema, however, his medical status as the course of the pneumothorax development indicates that this situation occurred due to the administration of the immunotherapy and not from his underlying pulmonary disease [27,28]. It has been observed that immunotherapy affects the orogenic film in several systems [29]. In our patient we assume that the high expression of the PD-L1 expression was one of the main reasons to present pneumothorax. Although we did not have a mass on the right hemithorax, so that we can presume that the drug induced the local tumor lysis possibly due to small local cancer infiltrations to the pleura. However; this is also the reason to believe that the adverse effect was only due to the local interaction between the pleura and the cytokines produced (inflammatory cascade). We believe that during the drug administration the pleural was affected and

pneumothorax occurred. Multimodality treatment is again necessary for patients receiving this kind of therapy.

Declaration of competing interest

All authors declare no conflict of interest.

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