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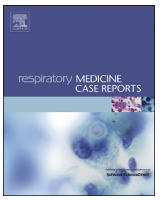

Case Report

Cryobiopsy for pneumonitis diagnosis in NSCLC immunotherapy

Paul Zarogoulidis [a, b, *], Christoforos Kosmidis [b], Eleni-Isidora Perdikouri [c], Wolfgang Hohemforst-Schmidt [d], Chrisanthi Sardeli [e]

[a] Pulmonary Department, General Clinic Euromedica, Thessaloniki, Greece
[b] 3rd Surgery Department, AHEPA University Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece
[c] Oncology Department, General Hospital of Volos, Greece
[d] Sana Clinic Group Franken, Department of Cardiology / Pulmonology / Intensive Care / Nephrology, ''Hof'' Clinics, University of Erlangen, Hof, Germany
[e] Department of Pharmacology & Clinical Pharmacology, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece

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ABSTRACT

Nowadays immunotherapy is considered the tip of the arrow as treatment for non-small cell lung cancer for inoperable patients. Programmed death-ligand 1 is considered a valuable marker for the success of immunotherapy. The higher the score ≥50% the more successful the treatment will be. However; previous studies have presented favorable data even for those patients where the programmed death-ligand 1 was ≤50% or even 0%, therefore it can be administered as first line treatment in these patients with the addition of chemotherapy or radiotherapy. Other treatment modalities are tested as surrogates like gene therapy with immunotherapy to improve the results in patients with programmed death-ligand 1 was ≤50% or even 0%. The main issue for these patients is an adverse effect pneumonitis, in case we will present the valuable method of lung parenchyma sampling with cryobiopsy for early diagnosis of immunotherapy induced pneumonitis.

1. Introduction

Non-small cell lung cancer is still diagnosed at advanced stage and systemic treatment administration is required. We have nowadays novel tools for the diagnosis and staging of lung cancer like radial-ebus, electromagnetic navigation and convex probe-ebus [1–28]. However; we still need a successful lung cancer screening program for early lung cancer diagnosis [9]. Since most patients are diagnosed at advanced stage we have several different therapies for non-small cell lung cancer like (NSCLC) like chemotherapy, tyrosine kinase inhibitors, radiotherapy, immunotherapy or combination of those treatment modalities [10–15]. Immunotherapy is considered nowadays the tip of the arrow for non-small cell lung cancer and it can be administered alone when the programmed death-ligand 1 (PD-L1) is ≥ 50% or in combination with chemotherapy when the PD-L1 expression is ≤ 50%. This type of therapy is considered to have mild adverse effects like fatigue, cough, nausea, itching, skin rash, loss of appetite, constipation, joint pain, diarrhea and it care trigger thyroiditis, hepatitis and induce pneumonitis [16–18]. These adverse effects can be addressed with different measures based on their severity. In very severe cases the patient has to stop the treatment and switch to another treatment modality. Regarding colitis [19],thyroiditis and hepatitis monoclonal antibodies have been administered in severe cases like infliximab, while for pneumonitis cortisone in different dosages [20,21]. Usually NSCLC patients are having positron emission computed tomography (PET-CT)

* Corresponding author. 3rd Department of Surgery, "AHEPA" University Hospital, Aristotle University of Thessaloniki, Medical School, Lida Maria Faethon B, number 0, Thessaloniki, 57001, Greece.
E-mail address: pzarog@hotmail.com (P. Zarogoulidis).

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for initial staging and restaging. In the case where pneumonitis is suspected special care should be given to these patients. Disease relapse is a different situation from pneumonitis imaging techniques do not provide the diagnosis, therefore the diagnosis should be made through tissue samples. Tissue samples from the lung parenchyma can be provided with cryobiopsy (endoscopy), videoassisted thoracic surgery (VATS) and needle biopsy under computed tomography guidance [22,23].

2. Case presentation

A 65 year old male was diagnosed with lung adenocarcinoma with programmed death-ligand 1 (PD-L1) expression ≥75%, pembrolisumab 200mg every 3 weeks was initiated. After 2 months persistent cough was reported by the patient and a computed tomography was performed and diffuse parenchymal infiltrates were observed more intense in the right lower lobe. A positron emission tomography was performed and the infiltrates were observed highly active. Because the diagnosis was adenocarcinoma which is known to present as infiltrates in the lung parenchyma and because the infiltrates were only in the right lower lobe and highly active on pet-ct initially disease progression was hypothesized. However; since pneumonitis is an adverse effect observed with immunotherapy, biopsy was proposed to the patient. Since there are no evidence based clinical trials regarding the methodology of diagnosis other than imaging techniques we proposed to the patient biopsy under computed tomography with an 18G needle. However; although the sample was satisfying producing more than 16 slices, unfortunately diagnosis from pneumonitis could not be obtained (Figs. 1–3). Therefore based on publications for diagnosis of diffuse parenchymal disease with endoscopic crybiopsy, we proposed to the patient this methodology [23–26]. Indeed with the tissue sample obtained from the cryobiopsy we were able to identify non-other specific interstitial lung disease (NSIP) which is usually observed in these cases and mild cortisone treatment was administered with 4mg every day for the next 30days (Figs. 4–6). We used a Fuji radial-endobronchial ultrasound system with a C-arm as fluoroscopy system and an Olympus bronchoscope with a 2.8mm working channel. The patient was under sedation and we used also two cryo probes ERBEII a 1.7mm and the new one 1.1mm in order to obtain as many samples as possible. We did not perform cytometry in bronchoalveolar

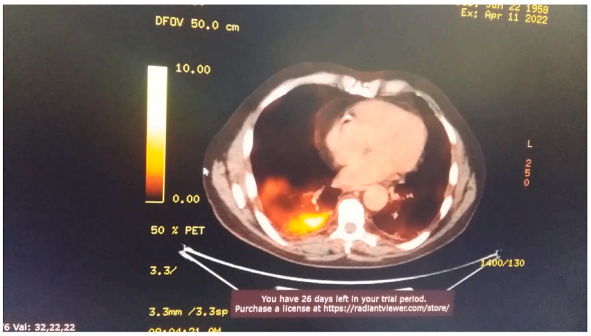

Fig. 1. Positron emission tomography with an area of high 16SUV uptake.

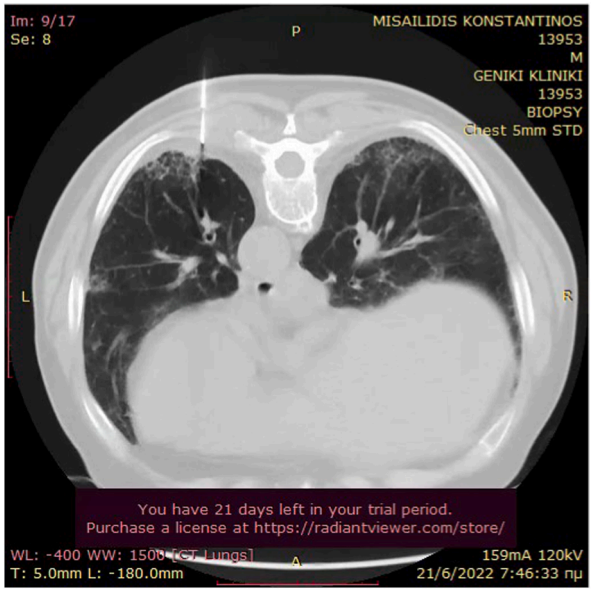

Fig. 2. Biopsy with 18G needle under CT guidance of the region with positive 16SUV uptake.

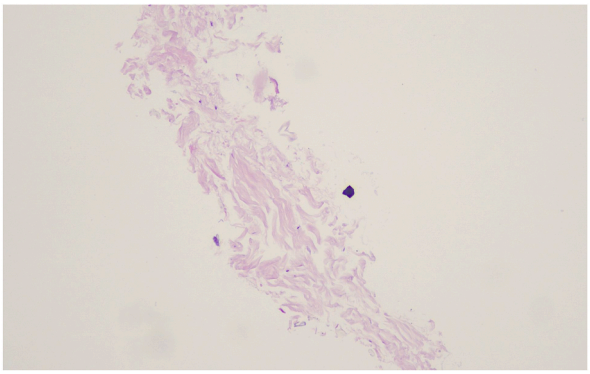

Fig. 3. Hematoxylin and eosin stain X100 with tissue fragments not revealing any pneumonitis.

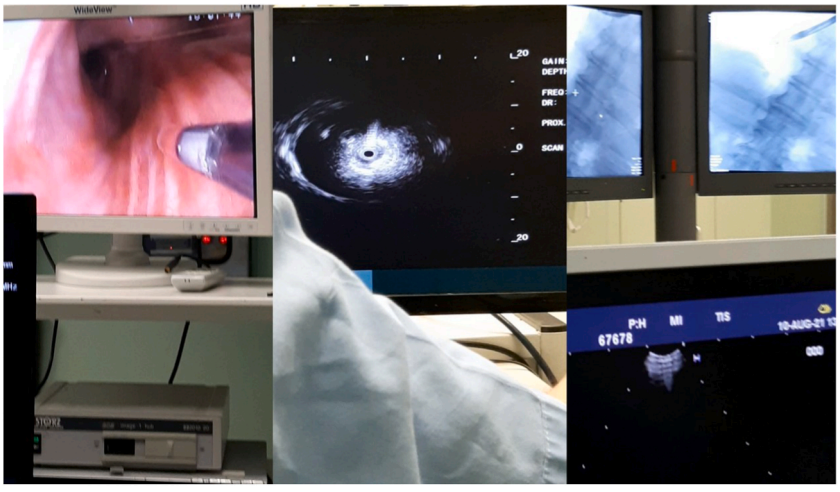

Fig. 4. Radial-EBUS and C-Arm.

Fig. 5. Cryo-Probe ERBEII and the rest of the equipment.

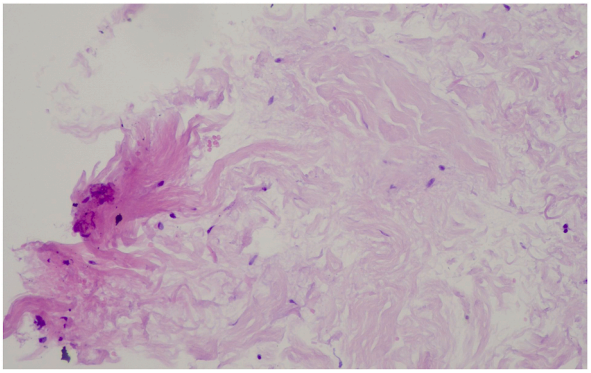

Fig. 6. Cryo-Biopsy sample. Multiple sections revealed fragments of reactive fibrous connective. Inflammatory round cell aggregates were also observed. Hematoxylin and eosin stain X 200.

lavage (BAL) sample since tissue sample is considered to have a higher diagnostic value than that of the BAL cytometry [27]. A new ct scan revealed regression of these infiltrates and the patient continues its treatment.

3. Discussion

All treatment modalities have their advantages and disadvantages. Certainly chemotherapy has the most severe adverse effects versus tyrosine kinase inhibitors and immunotherapy. There are different criteria for re-staging of non-small cell lung cancer based on the different treatment that the patient is receiving. Regarding immunotherapy due to the pseudo-progression new criteria had to be created the immune recist criteria [28]. In the case of hepatitis, colitis and thyroiditis the diagnosis can be made due to the laboratory findings and clinical findings, however; regarding pneumonitis there is still an issue. Chronic obstructive pulmonary disease which is diagnosed in most lung cancer patients induces damage to the lung parenchyma as emphysema, and diffuse infiltrates. Therefore we observe and correlate the initial lung parenchymal damage with the new images in re-staging to be able to evaluate properly the progression of lung cancer. Positron emission tomography findings might be misleading because inflammation can provide pseudo progression evaluation as in the case of adenocarcinoma. Therefore we need pulmonary function tests for the evaluation of these patients and cryobiopsy can certainly provide the best tissue sample for the diagnosis of pneumonitis. The treating physician will then act quickly by adding steroids to the patient. Thin cryo probes have been introduced in the market for the past two years making it easy for any bronchocopist to obtain tissue samples even in the most peripheral parts of the lung. Also, the small size of the cryo probe 1.1mm makes it easy to manipulate its guidance with the radial-EBUS to the periphery of the lung. Based on previous publications cryobiopsy is easy and safe to perform, with minor adverse effects such as minor bleeding [22,26]. However; special care should be made for those patients with severe emphysema.

Statement of ethics

Subjects have given their written informed consent to publish their case (including publication of images). *This case report was approved by the ethical committee of the General Clinic Private Hospital, Thessaloniki, Greece, ID number 15/2022.* Written informed consent was obtained from the participant for publication of the details of its medical case and any accompanying images.

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Author contributions

Paul Zarogoulidis wrote the manuscript and performed the procedure, Christoforos Kosmidis wrote the manuscript and performed the procedure, Eleni-Isidora Perdikouri wrote the manuscript, Wolfgang Hohenforst-Schmidt wrote the manuscript and assisted in the procedure, Chrysanthi Sardeli wrote the manuscript and interpreted the pharmacological data, collected data and was involved in the conception of the procedure.

Data availability statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Declaration of competing interest

The authors declare no conflict of interest.

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