Lung ultrasonography in a patient with disseminated melanoma treated with nivolumab

Maria Binkiewicz-Orluk1, Marcin Konopka1, Edyta Kostarska-Srokosz1, Marek Kuch2, Wojciech Braksator1

1Department of Sports Cardiology and Noninvasive Cardiovascular Imaging, Medical University of Warsaw, Warsaw, Poland
2Department of Cardiology, Hypertension and Internal Diseases, Medical University of Warsaw, Poland, Mazovia Brodno Hospital, Warsaw, Poland

Introduction

Nivolumab is a monoclonal IgG4 antibody, that blocks programme-death receptor (PD-1) and works as an immune check-point inhibitor (ICP). It is valuable in various neoplasms treatment. In melanoma, it is used as monotherapy or in therapeutic regimens and has increased long-time survivals and quality of life [1]. The immune-related adverse events (irAEs) are a group of side effects after ICPs therapy and mostly concern mild complaints such as rash or diarrhoea, but there is a group of severe complications that sometimes require Intensive Care Unit treatment.

Case report

A 56-year-old woman, with disseminated skin melanoma with lymph-node metastasis and negative BRAF mutation, was admitted to the Cardiological Intensive Care Unit with strong, progressive dyspnoea. In her medical history, the patient developed myo-carditis due to nivolumab therapy two months earlier. She was treated in another cardiological centre with a systemic steroid therapy (infusions of methylprednisolone) with a good medical response to intervention.

On admission to our Intensive Care Unit during current hospitalization, she was in a serious condition, agitated, with severe dyspnoea and tachypnoea. Features of respiratory failure were developing (arterial blood gasometry: PaO2 44,6 mm Hg, SpO2 = 54%). On auscultation, there were massive crepitations over both lungs. Furthermore, skin changes typical for disseminated melanoma were found on the lower limbs (Fig. 1 A, B).

Following blood tests: a significant increase of inflammation markers was observed (with C-reactive protein at 263.2 mg/L, procalcitonin at 0.32 ng/mL,
In the preliminary diagnosis, first of all, cardiogenic reasons for observed dyspnoea were considered. Chest X-ray showed enlarged silhouette of the heart and diffuse parenchymal densities of both lungs (Fig. 2). During the next step, comprehensive ultrasonography was performed (echocardiography, lung ultrasonography, compression ultrasonography for deep vein thrombosis). Echocardiography revealed: the normal size and function of the heart chambers, the correct left and right ventricle contractility, without regional wall motion abnormalities, proper heart valves function and absence of pericardial fluid (Fig. 3). Compression ultrasonography did not reveal deep vein thrombosis. The bedside lung ultrasonography (LUS) showed the areas of inflammatory consolidations (Fig. 4 A, B, C).

Further on, computed tomography was performed. Pulmonary embolism was ruled out by computed tomography pulmonary angiogram. High resolution computed tomography for parenchyma evaluation revealed massive, both side, multiple diffuse ground-glass opacifications (Fig. 5).

In conclusion, the medical evaluation did not confirm cardiological reason for dyspnoea. The patient was transferred to the reference Pulmonary Unit, where the further diagnostic process ruled out other possible causes of interstitial pneumonia, so the final diagnosis was nivolumab induced pneumonia.

**Discussion**

There are plenty of potential reasons for dyspnoea in patients treated for neoplasm. The most possible are:

1. the progress of the proliferative process in the respiratory system;
2. pulmonary embolism (with frequency clearly increased in oncological patients);
3. infection;
4. presence of fluid within the pleural cavity due to: 
   a) neoplasm process or 
   b) heart failure.
Drug-induced pneumonia and/or myocarditis are uncommon, but still possible causes of dyspnoea. Cardiovascular IrAEs include myocarditis, pericarditis, arrhythmias, impaired ventricular function with heart failure and venous thromboembolism [2]. The clinical presentation is various, from mild (as fatigue, shortness of breath, mild chest pain) to moderate, or potentially life-threatening (acute heart failure, arrhythmia, cardiogenic shock or sudden death). They were divided into four groups of grading (G1–G4). The classical evaluation of patients with potential irAE includes ECG, blood tests (BNP, troponin, CK, and CK-MB concentration), chest X-ray. The decision about holding ICP is complicated and should be a balanced compromise between benefits and risk, but generally, it is recommended for all grades of complications after proper assessment [2].

Pulmonary irAEs mainly consider pneumonitis—which is defined as a focal or diffuse inflammation of the lung parenchyma [2]. In the literature, the overall incidence of pneumonitis due to all PD-1 inhibitors is estimated at 2.7%, and it is higher for therapy of non-small-cell lung carcinoma compared with melanoma (4.1% vs. 1.6%) and higher in the combination therapy group compared with the monotherapy group (6.6% vs. 1.6%) [3]. It also was divided into four groups of severity (G1–G4). The measurement of blood saturation, arterial blood gasometry, chest X-ray and computed tomography play an unquestionable role in the diagnostic process and grading patients who developed pneumonitis due to ICP therapy [2].

Regardless of the radiological examination, we would like to emphasize the usefulness of ultrasonography for differential diagnosis of acute dyspnoea. In particular, comprehensive ultrasonography (the combination of echocardiography, LUS and compressive ultrasonography) may be helpful in the group of patients treated of various neoplasms and developing severe dyspnoea.

In the presented case, the combination of different ultrasonographic modalities allowed for a fast preliminary assessment of a patient with life-threatening symptoms and made it possible to plan further diagnostic and therapeutic process.

In our situation, LUS revealing large consolidations suggesting pneumonia (lesions were later seen in computed tomography) proved particularly useful. LUS is a quick (2–3 min) investigation based on the imaging of lung parenchyma and pleural cavity. It is also an important component of different protocols (BLUE and FALLS) used in the assessment of seriously ill patients [4]. According to a number of authors, bedside LUS could be more sensitive and specific in severe/critical states than chest X-ray [5] so its usage in Intensive Care Units is still increasing [6]. We believe that LUS is worth further investigating in oncological practice.

In our opinion, the presented case raises two important topics: (1) Rare coincidence of myocarditis and
pneumonia due to nivolumab therapy; (2) usefulness of comprehensive ultrasonography including LUS in severely ill oncological patient.

Conflict of interest

The authors declare to have no conflict of interest.

References

1. Rogiers A, Boekhout A, Schwarze JK, et al. Long-term survival, quality of life, and psychosocial outcomes in advanced melanoma patients treated with immune checkpoint inhibitors. J Clin Oncol. 2019; 2019: 5269062, doi: 10.1155/2019/5269062, indexed in Pubmed: 31182961.

2. Brahmer JR, Lacchetti C, Schneider BJ, et al. National Comprehensive Cancer Network. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2018; 36(17): 1714-1768, doi: 10.1200/JCO.2017.77.6385, indexed in Pubmed: 29442540.

3. Nishino M, Giobbie-Hurder A, Hatabu H, et al. Incidence of programmed cell death 1 inhibitor-related pneumonitis in patients with advanced cancer: a systematic review and meta-analysis. JAMA Oncol. 2016; 2(12): 1607-1616, doi: 10.1001/jamaoncol.2016.2453, indexed in Pubmed: 27540850.

4. Lichtenstein DA. BLUE-protocol and FALLS-protocol: two applications of lung ultrasound in the critically ill. Chest. 2015; 147(6): 1659-1670, doi: 10.1378/chest.14-1313, indexed in Pubmed: 26033127.

5. Inglis AJ, Nalos M, Sue KH, et al. Bedside lung ultrasound, mobile radiography and physical examination: a comparative analysis of diagnostic tools in the critically ill. Crit Care Resusc. 2016; 18(2): 124, indexed in Pubmed: 27242110.

6. Mojoli F, Bouhemad B, Mongodi S, et al. Lung ultrasound for critically ill patients. Am J Respir Crit Care Med. 2019; 199(6): 701-714, doi: 10.1164/icip.201802-029OC, indexed in Pubmed: 30372119.