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Lung ultrasonography in a patient with disseminated melanoma treated with nivolumab

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ABSTRACT

A number of complications after oncological therapy increase with the number of patients who receive the treatment. The diagnostic process might be complicated and requires the use of multimodality imaging to rule out other causes. The immune-related adverse events (irAE) due to nivolumab — as myocarditis and pneumonitis are uncommon but potentially life-threatening. We present a case of a patient who developed both of them in a short-time interval.

Key words: lung ultrasonography, melanoma, nivolumab, side effects, pneumonitis, pulmonary toxicity

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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 ICPis 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 myocarditis 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. After improvement of the clinical status, lack of abnormalities in ECG (12-lead ECG, ECG monitoring) and echocardiogram, according to the proper guidelines [2] it was decided to continue ICP therapy.

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,

white blood cells at $10.8 \times 10^3/\mu\text{l}$), elevated D-dimer (1915 ng/mL) and high NT-proBNP concentration (1680 pg/mL); troponins were not elevated. Blood and urine cultures were negative — information obtained during further hospitalization.

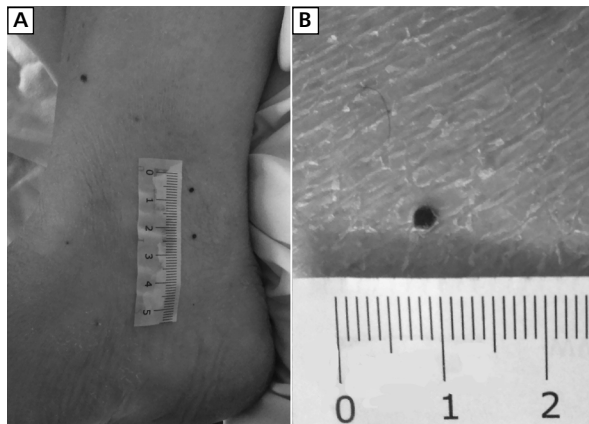


Figure 1A, B. Melanoma skin changes on the lower limb of patient



Figure 2. The chest X-ray: Enlarged silhouette of the heart. Diffuse parenchymal densities of both lungs

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.

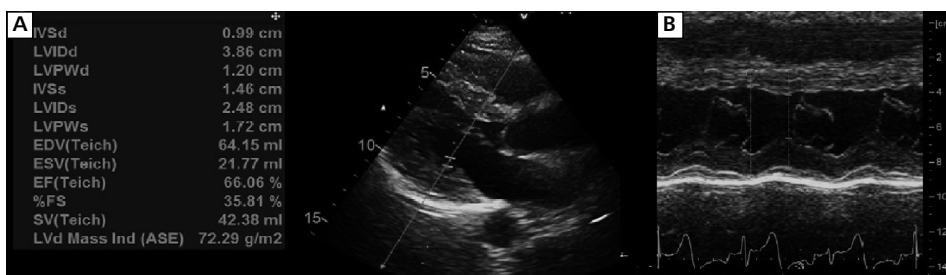


Figure 3. Transthoracic echocardiography, parasternal long axis: A. 2D imaging; B. M-mode presentation: the normal size and contractility of the heart chambers, the absence of pericardial effusion. The first assessment of ejection fraction (EF) calculated by Teicholz method is 66%. The value comparable to further exams

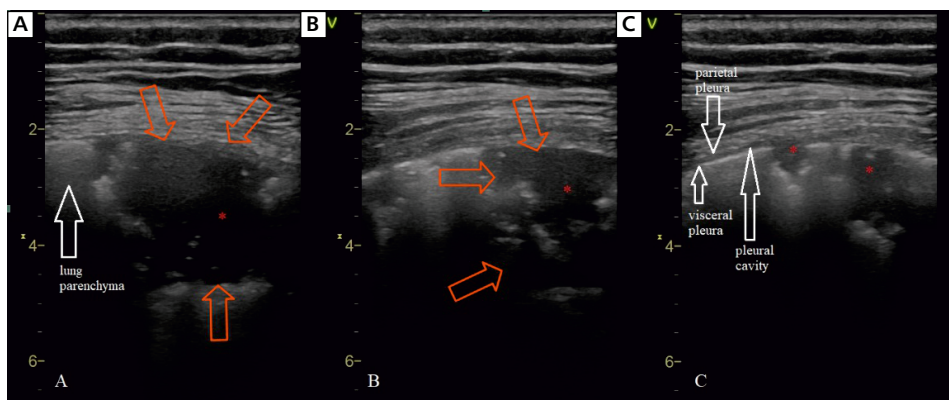


Figure 4. Lung ultrasonography. A, B. Large inflammatory consolidation (red arrows); C. Pleural thickening with pleural line irregularity. Visible two subpleural minor consolidations. Absence of fluid in the pleural cavity

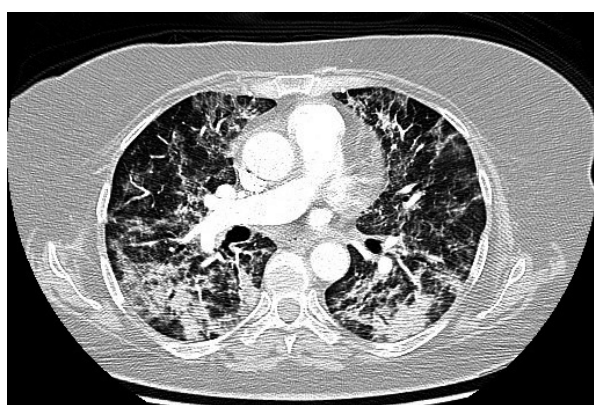


Figure 5. High resolution computed tomography of the chest: massive, both side, multiple diffuse ground-glass opacifications

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.

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