Cutaneous adverse reactions in a lung cancer patient treated with pembrolizumab: A case report

CARMEN BOBEICA[1*], LAURA REBEGEA[2], GABRIEL MURARIU[3], MICHAELA DOBRE[1], AUREL NECHITA[2], ALIN LAURENTIU TATU[2,4*], ELENA NICULET[1,5], LUCRETIA ANGHEL[2], SILVIA FOTEA[2*] and MIHAELA CRAESCU[1,6]

[1]Department of Morphological and Functional Sciences, [2]Clinical Medical Department, Faculty of Medicine and Pharmacy, 'Dunarea de Jos' University, 800010 Galati; [3]Department of Chemistry, Physics and Environment, Faculty of Sciences and Environment, 'Dunarea de Jos' University, 800201 Galati; [4]Research Center in The Field of Medical and Pharmaceutical Sciences, ReFORM-UDJ, 'Dunarea de Jos' University, 800010 Galati; Departments of [5]Pathology and [6]Clinical Radiotherapy, 'Sfantul Apostol Andrei' Emergency Clinical Hospital, 800578 Galati, Romania

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Abstract. Lung cancer is the main cause of oncological death in the US and worldwide, constituting a significant public health problem. The incidence of lung cancer is on the increase. In the present study, the diagnostic process was carried out and treatment options were considered to determine the therapeutic response of a patient diagnosed with lung cancer. The case of an early stage lung cancer patient who benefited from surgical treatment was presented. The pathology report stated the complete diagnosis to be pleomorphic lung cancer with an adenocarcinoma component, pT2aN0M0, with focal positivity for thyroid transcription factor 1 (TTF1), without epidermal growth factor receptor (EGFR) mutations and ALK recombinations, having an initial clinical stage of IB and programmed death ligand-1 (PD-L1) positivity with a tumor proportion score of over 70%. The patient underwent radiotherapy treatment and was administered osteoclast inhibitors and immunotherapy, with no favorable therapeutic effect and with the presence of secondary cutaneous adverse effects to pembrolizumab. As a main cause of death, lung cancer registers a low general survival rate even in patients with targeted therapies or immunotherapy. By better identifying the patients at risk, one can establish a more efficient personalized treatment; the future objective of scientific studies is the follow-up of adverse effects of new therapies.

Correspondence to: Dr Elena Niculet, Department of Morphological and Functional Sciences, Faculty of Medicine and Pharmacy, 'Dunarea de Jos' University, 35 Alexandru Ioan Cuza Street, 800010 Galati, Romania
E-mail: helena_badiu@yahoo.com

Professor Gabriel Murariu, Department of Chemistry, Physics and Environment, Faculty of Sciences and Environment, 'Dunarea de Jos' University, 111 Domneasca Street, 800201 Galati, Romania
E-mail: gabriel_murariu@yahoo.com

[*]Contributed equally

Abbreviations: ALK, anaplastic lymphoma kinase; CT, computerized tomography; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor; FDA, Food and Drug Administration; LC, lung cancer; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein-1; PD-L1, programmed death ligand-1; RTE, radiotherapy; TD, total dose; TP53, tumor protein p53; TTF1, thyroid transcription factor 1; USA, United States of America

Key words: lung cancer, therapeutic strategy, pembrolizumab, cutaneous adverse effects, PD-L1

Introduction

Lung cancer (LC), the main cause of oncological death in the US and globally, is a significant public health problem. The incidence of LC is on the rise, much as in neuroendocrine tumor or gastric carcinoma cases (1,2). In general, LC is a highly aggressive form of cancer with a rapid rate of metastasis (3,4).

In recent decades, LC has become the most frequent form of cancer worldwide, with a possible IL-6 involvement through its pro-angiogenic properties, which helps in cancer development and/or progression. The number of new cases was estimated at 1,8 million in 2012 (3,5,6). As the leading cause of oncological death, with a poor prognosis, LC has one of the lowest 5-year survival rates at under 15% (7,8).

The aim of the current study was to present the case of a patient and the cutaneous side effects attributed to pembrolizumab therapy. The outcome of the current study revealed that pembrolizumab immune therapy use managed to prolong the patient's survival with about 4 months, having a good performance status of 2 (ECOG).

Case report

Subject. The aim of the current study was to present a case of a patient and the cutaneous side effects attributed to pembrolizumab therapy. A 63-year-old patient was admitted in March 2017 to the Military Hospital of Galați, Romania, suffering from right thoracic stabbing pain, dyspnea, dry cough and night sweats. The patient signed and provided written informed consent for the publication of data or any images, which is available in the patient's medical chart. Ethics approval and consent to participate were obtained from the 'Sfantul Apostol Andrei' Emergency Clinical Hospital's Ethics Committee, with the decision no. 11413 from 03.06.2021.

Computerized tomography scan. After a thoracic computerized tomography (CT) scan in September 2017, a tumor mass in the right superior pulmonary lobe with a background of diffuse moderate pulmonary emphysema was found.

In October 2017, the patient was subjected to a surgical procedure consisting of right superior lobectomy and mediastinal lymphadenectomy in the 'Marius Nasta' Institute of Pneumophysiology, in Bucharest, Romania. The pathology laboratory reported this tumor as a pleomorphic lung cancer with an adenocarcinoma component, pT2aN0M0, with focal positivity for thyroid transcription factor 1 (TTF1), without epidermal growth factor receptor (EGFR) mutations, nor anaplastic lymphoma kinase (ALK) recombinations, having an initial clinical stage of IB and programmed death ligand-1 (PD-L1) positivity with a tumor proportion score of over 70%.

A new thoracic CT scan was performed in March 2018 which revealed a right apex lung tumor with spine involvement and mediastinal paratracheal ipsilateral adenopathies (Fig. 1A and B).

A skeletal scintigraphy was carried out at the end of March 2018 which revealed multiple bone metastases localized in the head of the humerus, the T3 vertebra, right third rib and right iliac bone, for which the patient received a bone tissue protection treatment with zolendronic acid until September 2018 and also antalgic radiotherapy (RTE) with a total dose (TD) of 20 Gy/5 fr localized at the head of the humerus, right sacroiliac region and the thoracic spine, levels T1 to T4. No systemic anticancer treatment was administered from July 2018 until September 2019.

The CT scan of the thorax and abdomen, which was performed in September 2018, revealed a right apex tumor mass measuring 65/50/45 mm, which invaded the thoracic wall and destroyed the 2nd, 3rd and 4th posterior rib arcs. The tumor protruded from the dorsal medullary canal, as a local, continuous tumor evolvement. In November 2018, the magnetic resonance imaging (MRI) of the thoracic spine highlighted the right lung tumor mass which destroyed the thoracic vertebral bodies of T2 to T4, and which invaded the intervertebral pedicles on the right side and also the spinal canal. Consequently, the patient underwent a surgical procedure for spinal decompression and the pathology report revealed that the fibro-hyaline fragments of the vertebral discs had foci of poorly differentiated squamous cell carcinoma (G3).

Other factors and treatment. At the same time, the laboratory findings revealed high values for urea and creatinine; the decision for terminating treatment with zolendronic acid was taken, in favor of a systemic one, such as chemotherapy or immunotherapy. Due to the high, oscillating creatinine values, it was possible to administer chemotherapy based on carboplatin in association with pemetrexed, paclitaxel or gemcitabine.

The recent inclusion of pembrolizumab in the national cancer treatment program, the patient's ALK and EGFR statuses, his PD-L1 level of 70%, and that this drug is excluded from treatment only in cases with severe renal insufficiency, supported the initiation of first-line immunotherapy with pembrolizumab starting from September 2018. Two months after therapy with pembrolizumab was begun, a CT scan of the head, thorax and abdomen was carried out and it revealed an evolutionary stable disease. Immunotherapy was continued but some eczematous, psoriasiform and lichenoid secondary cutaneous side effects developed, which were localized on the left mandible and left superior limb and had a partial response to corticoid treatment with full resolution following pembrolizumab treatment termination (Figs. 2 and 3) (9-12).

The patient suffered from arterial hypertension for which he received metoprolol, daily. An important fact that is well known among physicians is that metoprolol should not be concomitantly administered with floctafenine, sultopride, bepridil, diltiazem or verapamil, nor should it be taken during or after a meal, as food has the property of increasing the bioavailability of metoprolol. The types of food that are ingested are important, not only in the case of metoprolol, but also for other medications such as statins (grapefruit, for example, has the ability to increase the drug's blood concentration). There are also other factors that can intervene in certain drug pharmacokinetics, as well as physiological factors such as decreased fatty tissue or gastric acidity, or decreased renal excretion. Diuretics (hydrochlorothiazide), and other anti-hypertensive drugs, can also have cutaneous adverse reactions including rashes or photosensitization. The cutaneous adverse reactions of some ß-blockers have been reported, such as psoriasis precipitation or exacerbation, but fortunately our patient did not suffer from this disease (13-19).

Due to the cutaneous adverse reaction development, dexamethasone was prescribed, as 8 mg injectable doses, 2 vials per day, for 5 days, which relieved the patient of the cutaneous lesions, initially attenuating them, followed by complete extinction. Thus, treatment with pembrolizumab could be reinstated and continued.

The patient developed a mediastinal compression syndrome (Fig. 4) for which mediastinal radiotherapy was administered with a TD of 30 Gy. Immunotherapy was continued in the subsequent months and was terminated by March 2019, after a thoracic CT scan was carried out which revealed progressive disease (Fig. 5A and B).

The patient received 4 doses of pembrolizumab, having a current unsatisfactory general health status with a prognosis index of 3 on the Eastern Cooperative Oncology Group performance status (ECOG). Consequently, immunotherapy was stopped.

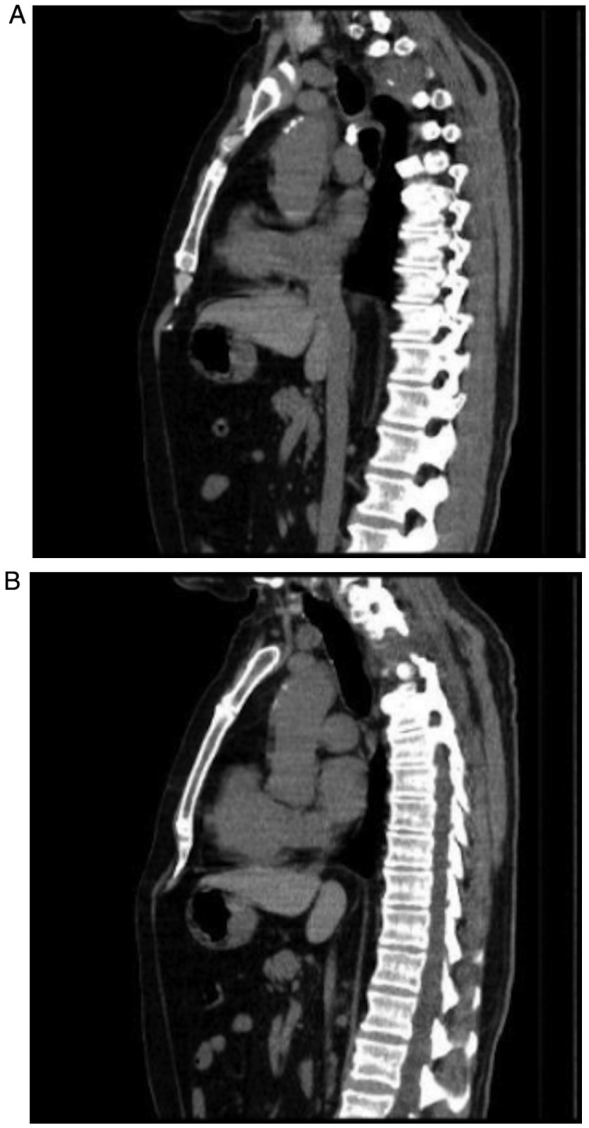

Figure 1. (A and B) Thoracic CT scan. Right lung apex tumor with spine involvement and mediastinal paratracheal ipsilateral adenopathies. CT, computerized tomography.

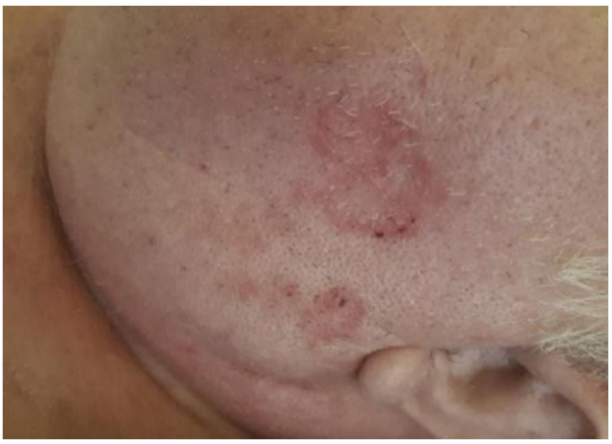

Figure 2. Secondary cutaneous adverse effects localized on the left mandible.

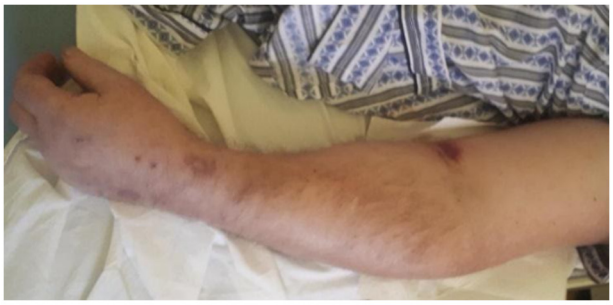

Figure 3. Secondary cutaneous adverse effects localized on the superior limb.

Discussion

Adenocarcinoma is the most frequent pathology subtype, registering an increased incidence rate among female patients in industrialized countries over the last decade, a tendency justified by some authors through a change in toxic habits, with a higher use of filtered cigarettes, leading to deeper inhalation with a more peripheral distribution (20,21). According to the new diagnostic and treatment guides, surgical intervention, radiotherapy, adjuvant chemotherapy, targeted therapy and immunotherapy are employed as therapeutic options in non-small cell lung cancer (NSCLC) with the possibility of being used as monotherapy or in combination, in accordance with the stage of disease. Although early diagnosis enables a complete surgical resection (the therapeutic option with the highest potential for cure), approximately 40% of patients relapse 5 years after the procedure (4,22,23).

As part of the NSCLC treatment, new compounds have been introduced, targeting immune control points, such as programmed cell death protein-1 (PD-1) or its ligand (PD-L1). Pembrolizumab is one such immunotherapeutic anti-PD-1 recommended for treating advanced-stage patients, without EGFR and ALK mutations, and with high PD-L1 (4,24). Tumor protein p53 (TP53) and EGFR mutations are strong parameters that can predict the response to anti-PD-1 treatment in NSCLC (25,26).

Pembrolizumab was approved by the Food and Drug Administration (FDA) in the USA for many advanced stage or metastatic cancers as this therapeutic agent acts by blocking the protein found on the surface of cancer cells, and the protein known as PD-L1, thus allowing immune cells to destroy the tumor. Recent findings suggest that treatment with pembrolizumab can help some NSCLC patients benefit from a higher survival rate with fewer adverse effects. The phase I clinical study known as KEYNOTE-001 proved that some advanced stage NSCLC patients who received pembrolizumab lived 3-4 times longer than expected. The most frequent cutaneous adverse effects identified were brief cutaneous eruptions which our patient developed since the second month of treatment with this medication (27-29).

The latest literature states that cases with mild cutaneous adverse reactions (such as lichenoid reactions, granulomatous skin reactions), as in our patient's case, can receive treatment with topical corticosteroids at low doses, moisturizing ointments or oral antihistamines (27,28,30,31).

Some patients who developed cutaneous adverse reactions such as vitiligo registered skin repigmentation, not as proof for skin lesion treatment response, but as proof for cancer

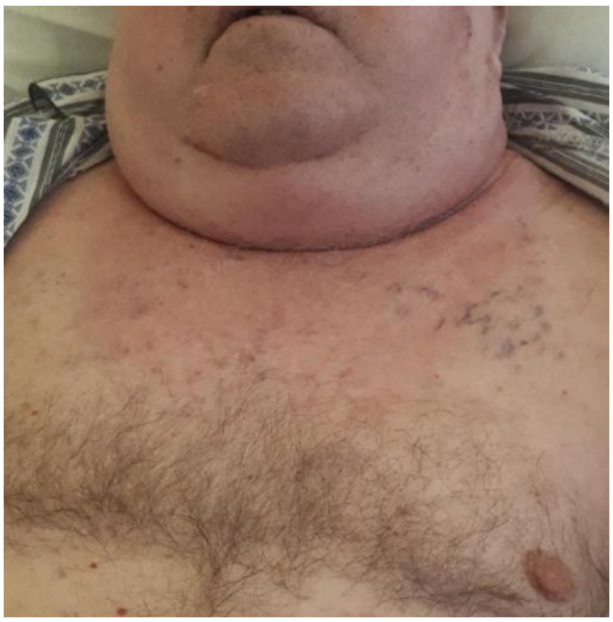

Figure 4. Mediastinal compression syndrome.

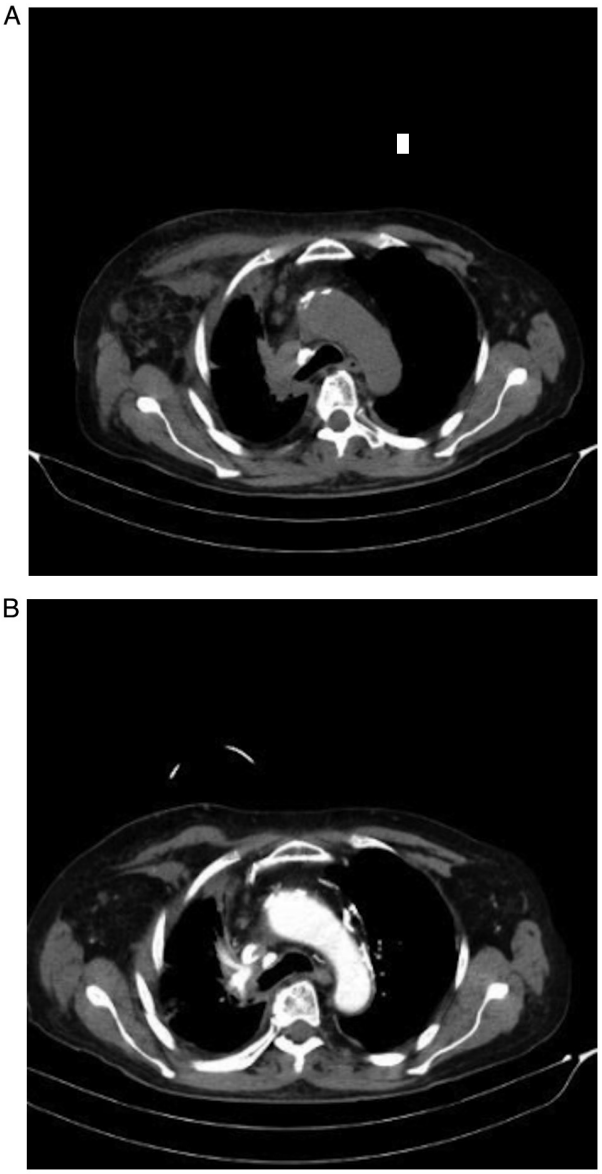

Figure 5. (A and B) CT of the thorax. Progressive disease is evident. CT, computerized tomography.

(melanoma) progression. The skin lesions were treated with classical vitiligo treatment, i.e., sun protection, phototherapy, calcineurin inhibitors, and topical corticosteroids. Psoriasis is a frequent adverse reaction to pembrolizumab and can develop as *de novo* lesions or as an exacerbation of the pre-existing lesions. Therapeutic management in these cases included topical steroids and/or vitamin D analogues, systemic retinoids, or even methotrexate. Cases of pityriasis rubra pilaris have also been reported after pembrolizumab therapy (some also as a paraneoplastic syndrome), these patients being successfully treated with acitretin and topical steroids (27-31).

More severe cutaneous adverse reactions (extensive bullous pemphigoid lesions) were treated with topical and systemic corticosteroids and treatment with pembrolizumab was withheld (as a temporary therapeutic management approach, or even as a permanent one; as in some patients with lupus erythematosus, toxic epidermal necrolysis, Stevens-Johnson syndrome or erythema multiforme). These adverse effects can evolve in various directions: they can resolve completely, can be ongoing, or they can become exacerbated. Some of the patients suffering from such therapeutic events, even after withholding pembrolizumab treatment, had a partial therapeutic response regarding their skin lesions (27,28,32).

An important issue to further research concerns the group of pembrolizumab drug interactions. For instance, one case report presented the case of a patient treated both with pembrolizumab and rivaroxaban, who developed an intra-cerebellar hemorrhage; as pembrolizumab seems to have an effect on the liver's CYP3/A4 system, it also seems to influence the metabolism of such new anticoagulant medication (33).

Notably, the cutaneous adverse effects treatment must not interfere with the therapeutic effects of pembrolizumab (anti-PD1) and patients need to adhere to treatment; such patients can opt for a dose decrease or can even stop treatment. Skin lesions being highly visible, the patients suffer from a low quality of life, with psychological distress and social refrain, similar to those with systemic sclerosis, for example. Topical steroids have been used as treatment for such adverse effects, having beneficial results, mostly due to their multiple biologic activities, which include anti-inflammatory, immune suppressive, or anti-proliferative activities. Complete pembrolizumab treatment withdrawal was found in rare cases in the literature, more often clinicians opting for continuation of treatment or only for a temporary withdrawal (for 1 or even 7 weeks) (27,28,33-36).

During clinical trials, patients who develop severe adverse reactions to immunotherapy (such as pembrolizumab) are not allowed to resume it, due to the high risk of reoccurrence. This is also an in-practice issue, as the choice to reinitiate immune therapy is challenging. One possible approach would involve a class switch, opting for an anti-CTLA-4, instead of an anti-PD(L)1 (pembrolizumab), these two having different mechanisms of action (the first one increases the diversity of the host's immune response, while the second reactivates

a suppressed host immune response). Another approach to patient treatment is the re-challenge itself, as many patients experience no recurrence of the side effects. Reintroducing the same anti-PD1 treatment can also result in some of the patients experiencing the same cutaneous adverse reactions, or some even new ones. Recurrence of the side effects may occur with decreased frequency (37-39).

In summary, even with targeted therapy or immunotherapy, lung cancer remains the main cause of death worldwide, having an increasing incidence in the last decade with a low general survival rate. It is mandatory to find a more favorable approach to identify patients at risk in order to establish more efficient personalized treatment and part of this is identifying the adverse effects of new therapies, as an objective for future studies.

Although immunotherapy is one of the newly reached frontiers in cancer therapy, clinicians need to have a watchful eye for (cutaneous) adverse reactions, their early diagnosis and management having a major impact on patient treatment concerning adherence, therapeutic result and overall survival. Treatment must be adapted to each patient, as they can react differently to pembrolizumab therapy, with various side effects.

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Availability of data and materials

The information generated and analyzed during the current study is available from the corresponding author on reasonable request.

Authors' contributions

CB, GM, ALT, SF, EN, MC, LA, LR, MD and AN were major contributors in writing the manuscript; they were involved in all the stages of the study, contributed to the conception and design of the work, as well as revising it; they helped analyze the data for the work, revised it for important intellectual content and approved the final version to be published. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work. All authors have had equal participation, contribution and equal rights to this article. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Ethics approval and consent to participate were obtained from the ‘Sfantul Apostol Andrei’ Emergency Clinical Hospital's Ethics Committee, with the decision no. 11413 from 03.06.2021.

Patient consent for publication

The patient provided written informed consent for the publication of any associated data and accompanying image.

Competing interests

The authors declare that they have no competing interests.

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