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CASE REPORT

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Acute generalized exanthematous pustulosis caused by gemcitabine after nivolumab in metastatic lung adenocarcinoma followed by a dramatic tumor response: A case report

Pierre Magdelaine[1] | **Adrien Costantini**[1,2] | **Lucie Fabre**[3] | **Etienne Giroux-Leprieur**[1,2]

[1]Department of Respiratory Diseases and Thoracic Oncology, APHP – Hopital Ambroise Pare, Boulogne-Billancourt, France

[2]University Paris-Saclay, UVSQ, EA 4340 BECCOH, Boulogne-Billancourt, France

[3]Department of pathology, APHP-Hopital Ambroise Pare, Boulogne-Billancourt, France

Correspondence
Etienne Giroux-Leprieur, Department of Pulmonary Diseases and Thoracic Oncology, APHP – Hopital Ambroise Paré, 9 avenue Charles de Gaulle, 92100 Boulogne-Billancourt, France.
Email: etienne.giroux-leprieur@aphp.fr

Abstract

Herein, we report a case of a 73-year-old female patient diagnosed with cT4N0M1a lung adenocarcinoma with *KRAS* G12C mutation, PDL1 < 1% and treated in fourth-line setting with gemcitabine after progression under nivolumab. After one infusion of gemcitabine, the patient presented with an acute worsening of general condition (performance status 4) with extensive skin lesions and fever, leading to hospitalization and diagnosis of acute generalized exanthematous pustulosis. Initial blood work revealed multiple organ failures with an important inflammatory syndrome. Patient state improved after intravenous hydration and local and systemic corticosteroids. The decision was made to stop systemic cancer treatment. Two months follow-up showed a remarkable response on all cancer localizations. Although immunotherapy is transforming cancer care, predicting response to immunotherapy remains challenging and resistant mechanisms remain mostly unknown. This case underlines that important immune-stimulation can lead to tumor response in a patient previously refractory to all antitumor treatments.

KEYWORDS

acute generalized exanthematous pustulosis, gemcitabine, lung adenocarcinoma, nivolumab

INTRODUCTION

Immunotherapy (IO) has transformed the treatment of advanced lung cancer. However, IO resistance mechanisms leading to treatment failure remain unclear and prognostic markers such as PD-L1 tumor proportion score (TPS) determined by immunohistochemistry (IHC) are not sufficient to predict tumor response. Acute immune events could be involved in immunotherapy efficacy by increasing therapeutic effects even for patients initially considered as nonresponders. Furthermore, some studies suggest that dermatological toxicity can be associated with the efficacy of IO although the related mechanism remains unclear.[1] Herein, we report a case of a patient with metastatic lung adenocarcinoma who had tumor progression with nivolumab in the third-line setting. After one infusion of fourth-line gemcitabine, she presented with acute generalized exanthematous pustulosis (AGEP) associated with worsening of general condition and a dramatic tumor response on follow-up CT-scan performed 2 months after hospital discharge.

CASE REPORT

A 73-year-old woman who presented with advanced (cT4N0M1a) non-small cell lung cancer (NSCLC) of adenocarcinoma histology with *KRAS* G12C mutation, PDL1 < 1% was admitted to the pulmonology ward with anorexia, nausea, dyspnea, fever and extensive skin lesions as well as impaired general condition with performance status (PS) at 4. She had previously received first-line chemotherapy with carboplatin and weekly paclitaxel (progression after 2 cycles), second-line pemetrexed (progression after 4 cycles) and third-line immunotherapy with nivolumab (progression after 6 infusions). Past medical history included hypothyroidism, infectious pneumonia and tobacco use. The last nivolumab

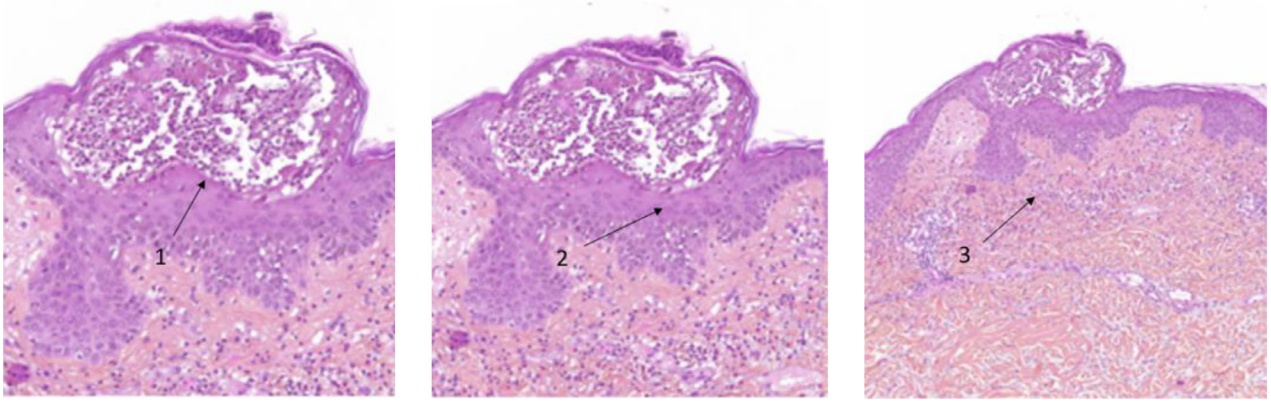

FIGURE 1 Skin biopsy of patient showing typical histological features of AGEP with subcorneal pustule (1), apoptotic keratinocyte (2) and eosinophil infiltration (3)

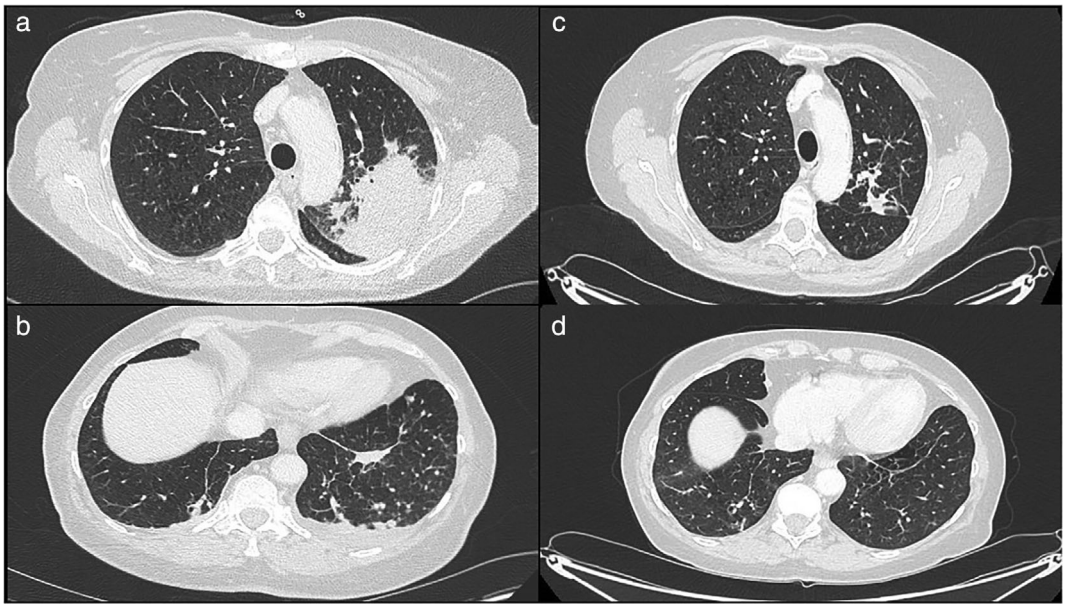

FIGURE 2 Chest computed tomography (CT) showing the dramatic response observed after one infusion of gemcitabine. (a, b) Baseline CT scan before gemcitabine. (c, d) CT scan after one injection of gemcitabine and AGEP, with a dramatic tumor response

infusion was performed three-weeks prior to admission, and the patient had received her first gemcitabine infusion a week prior to admission.

Initial clinical examination found oxygen saturation levels at 95% under 4 L/min of oxygen and erythematous maculopapular plaques of the trunk and limbs associated with micropustular lesions. Blood work revealed anemia (8.6 g/dl), lymphopenia with no other CBC defects, acute renal failure (creatinine 270 µmol/l, GFR = 14 ml/min/1.73 m^2), hepatic cytolysis (ASAT: 281 U/L, ALAT: 61 U/L) and C-reactive protein at 390 mg/l. Electrocardiogram was normal, and chest X-ray showed no new lesions. Dermatological consult concluded to AGEP caused by gemcitabine. The skin biopsy confirmed this diagnosis (Figure 1). The patient was treated with dermocorticosteroids, systemic corticosteroid therapy and intravenous hydration. Blood, sputum and urine cultures were negative. Respiratory multiplex polymerase chain reaction (PCR) as well as legionella and pneumococcus antigenuria were negative.

The patient's condition quickly improved, allowing weaning of oxygen and progressive normalization of the liver and kidney functions. The patient's erythematous lesions decreased and she was discharged 10 days later under 20 mg of oral prednisone per day.

A CT-scan was performed 2 months later. Compared to baseline CT-scan performed before the first infusion of gemcitabine (Figure 2a,b), a major tumor response with

70%–80% of target lesions reduction was observed (Figure 2c,d), and the patient's condition remained stable. Ten months after systemic treatment discontinuation, she was still alive without any tumor progression.

DISCUSSION

Cancer cells can evade the immune system through immunotolerance, by inhibiting CD8+ T cell proliferation as well as reducing interleukin production. A major immune checkpoint in lung cancer is the PD-L1/PD-1 interaction, targeted by anti-PD-1/PD-L1 antibodies. By inhibiting the PD-L1/PD-1 interaction, IO restores CD8+ T cells' anti-cancer activity, leading to improved tumor response and patient outcomes. However, predicting IO outcomes remains challenging. Immune related adverse events (irAEs) caused by excessive activation of the immune system by IO are associated with IO efficacy in advanced NSCLC,.[23] Hussaini et al.[4] reported that irAEs occurring in NSCLC patients treated with IO ($n = 1663$) were associated with better objective response rate (ORR: 41.49% vs. 18.01% without irAEs), longer PFS (median 8.97 vs. 3.06 months, respectively) and OS (median 19.07 vs. 7.45 months, respectively). A recent pooled analysis of prospective phase III clinical trials with atezolizumab in NSCLC confirmed this association.[2]

AGEP is a severe, rare, usually drug-related reaction (90%) with a potential genetic predisposition.[5] AGEP is a T cell related, sterile neutrophilic inflammatory response, involving the activation, proliferation, and migration of CD4 and CD8 T cell populations using specific proteins such as granzyme B and perforin. This causes the apoptosis of keratinocytes and increases proinflammatory chemokine production (IL-1, IL-6, IL-12, IL-17, IL-23).[4] In vitro tests showed that specific drug-reaction in AGEP patients is mediated by C-X-C motif chemokine ligand 8 (CXCL8)/IL-8, a potent neutrophil chemotactic chemokine.[4] Moreover, some patients with AGEP have IL36-Ra deficiency, leading to increased production of proinflammatory mediators (IL-1, IL-6, IL-12, TNFα, IL-8) and neutrophilic recruitment and activation.[4] Such mechanisms could have boosted the efficacy of IO in our case, promoting immune system reaction against the tumor. The prolonged half-life of nivolumab suggests that 3 weeks after the last infusion, the PD-1/PD-L1 axis would still be inhibited by the antibody in the tumor microenvironment.

Careful review of our patient's case did not find any new drug intake apart from gemcitabine in the weeks preceding the occurrence of AGEP. As for the timeline, the implication of gemcitabine seems more likely than nivolumab. Creadore et al.[6] found a median time from medication initiation to AGEP occurrence of 3 days (IQR, 1–9) in a large, retrospective, population of patients ($n = 340$). Furthermore, AGEP induced by gemcitabine has already been reported[7] with an interval of four days between gemcitabine infusion and onset of AGEP.

Moreover, AGEP caused by immunotherapy alone,[8] or in association with chemotherapy[9] in lung cancer has already been described with a short delay between immunotherapy initiation and first clinical signs of AGEP. Other reports suggest that AGEP induced by a combination of two different checkpoints inhibitors could appear later after the beginning of immunotherapy.[10]

We hypothesize that the resulting acute immune reaction induced a major antitumor response, possibly enhanced by the previous treatment line by nivolumab. It is indeed unlikely that a single infusion of gemcitabine in the fourth line setting would result in such a dramatic tumor response, and previous studies have shown that chemotherapy received after immunotherapy does not yield increased response rates.[11]

In conclusion, IO is a milestone in the treatment of advanced lung cancer. However, its efficacy remains difficult to predict, with unreliable markers and unknown resistant mechanisms. Our case suggests that acute immune reactions, such as AGEP, can greatly increase IO efficacy.

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Figure 1 was created with BioRender.com

CONFLICT OF INTEREST

EGL: BMS (advisory board, honoraria); PM, AC, JF: none.

ORCID

Etienne Giroux-Leprieur https://orcid.org/0000-0001-8441-1701

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