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# Bullous Lupus Under Nivolumab Treatment for Lung Cancer: A Case Report With Systematic Literature Review

ALICIA WOUTERS[1,2], VALÉRIE DURIEUX[2,3], ATHANASSIOS KOLIVRAS[4], ANNE-PASCALE MEERT[1,2] and JEAN-PAUL SCULIER[1,2]

*[1]Internal Medicine Department, Jules Bordet Institute, Free University of Brussels (ULB), Brussels, Belgium;*
*[2]Laboratory of Factual Medicine, Faculty of Medicine, Free University of Brussels (ULB), Brussels, Belgium;*
*[3]Health Sciences Library, Free University of Brussels (ULB), Brussels, Belgium;*
*[4]Inter-Hospital Department of Dermatology, CHU Saint-Pierre, CHU Brugmann and HUDERF, Free University of Brussels (ULB), Brussels, Belgium*

**Abstract.** *Background: Various immune-related adverse events (irAEs) have been reported associated with use of immune checkpoint inhibitors. We report a case of a patient with lung cancer treated with nivolumab who developed a bullous eruption and give a systematic review of the literature on irAEs in patients treated with immune checkpoint inhibitors for lung cancer. Case Report: A patients with lung adenocarcinoma developed a non-specific skin lesion at the time of his cancer diagnosis followed by flare episodes until the eighth cycle of nivolumab, when he developed a bullous lupus. As the first eruption had started a few months after his cancer diagnosis and was exacerbated during immunotherapy, a paraneoplastic origin is discussed. Since the patient also presented with flares under nivolumab, we reviewed reported irAEs. No bullous lupus was found but to date, 33 cases of paraneoplastic lupus and two of lupus erythematosus have been reported. Conclusion: To our knowledge, this is the first description of a bullous lupus exacerbated by nivolumab.*

Immune checkpoint inhibitors (ICIs) have proven their efficacy in immunotherapy of cancer, including lung cancer. These ICIs are monoclonal antibodies directed against membrane receptors of T-lymphocytes or their ligand expressed by antigen-presenting cells or tumor cells. The first target identified was the cytotoxic T-lymphocyte antigen-4 (CTLA-4), followed by programmed cell death 1 (PD1) and its ligands (PD-L1, PD-L2) (1). Antibodies directed against these targets block the immune escape of tumor cells, sometimes at the cost of deregulation of immune tolerance, therefore causing immune-related adverse events (irAEs) (1). Although irAEs can involve any tissue or organ (1), skin lesions are the most common (2). Nivolumab is a human monoclonal antibody to PD1 approved for melanoma, non-small cell lung cancer (NSCLC), renal carcinoma, Hodgkin's lymphoma, squamous cell carcinoma of the head and neck, and urothelial carcinoma (1). Regarding NSCLC, two randomized phase III trials showed a greater efficacy of nivolumab compared to docetaxel after non-response to a first-line of platinum-based doublet chemotherapy: CheckMate-017 (3) for squamous NSCLC followed by CheckMate-057 (4) for non-squamous NSCLC (3, 4). Results from the CA209-003 study of nivolumab after another therapeutic line in advanced NSCLC showed a 5-year overall survival rate of 16%, with a median overall survival of 9.9 months. These observations support the therapeutic breakthrough of nivolumab against advanced NSCLC (5).

We report a unique case of bullous lupus possibly paraneoplastic and exacerbated during nivolumab treatment. We conducted two systematic literature reviews in order to determine firstly if paraneoplastic bullous lupus has been described and secondly if bullous lupus occurring under ICI has been reported in lung cancer, with an additional description of the irAEs in lung cancer.

Approval of the Institutional Committee and Ethics Committee of the Jules Bordet Institute was obtained prior to this work being completed (Date of approval: 19/12/2017. Approval number: CE2774).

## Case Report

A 59-year-old patient with a 40 pack-year smoking history was diagnosed with stage IIIB lung adenocarcinoma. Initial chest

*Correspondence to:* Anne-Pascale Meert, Service de Médecine Interne, Institut Jules Bordet, Centre des Tumeurs de l'Université Libre de Bruxelles (ULB) et Laboratoire Facultaire de Médecine Factuelle (ULB), 1, rue Héger Bordet, 1000 Brussels, Belgium. E-mail: ap.meert@bordet.be

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computed tomography (CT) revealed a 43 mm long-axis diameter mass (Figure 1) with hypermetabolic hilar and mediastinal lymph nodes bilaterally on positron-emission tomography (PET) scan. The biopsy identified an adenocarcinoma without any molecular expression of anaplastic lymphoma kinase (ALK), epidermal growth factor receptor (EGFR) or c-ros oncogene 1 (ROS1). The patient had been exposed in his professional career to asbestos fibers, crystalline silica and metal oxides. His medical history included Raynaud's disease and atrial fibrillation. First-line chemotherapy of cisplatin and vinorelbine was initiated. After three cycles, the PET scan showed no response. A second-line treatment with nivolumab was then initiated. After the first dose, the patient presented to our Department with fever, arthralgia of the wrists and ankles, stiffness of the back, asthenia and appearance of an eczematous-like skin eruption with pruritus. Laboratory tests showed an inflammatory syndrome with a C-reactive protein (CRP) level of 29.0 mg/l, anti-nuclear antibodies (ANA) (titer 1:640) with a nucleolar pattern, anti-Sjögren's-syndrome-related antigen A (SSA/Ro) and anti-SSA/Ro52. Articular symptoms disappeared with non-steroidal anti-inflammatory drug, but the skin eruption persisted despite application of topical corticosteroids. After four cycles of nivolumab, the PET scan showed tumor regression, while the skin eruption continued to expand. After the sixth cycle, new similar skin eruptions appeared on both legs accompanied by vesicles on his upper limbs. The biopsy of the skin lesion on the right leg showed it to be a non-specific inflammatory lesion. After the eighth cycle, the patient presented to the hospital with asthenia, anorexia, digestive disorders and exacerbation of his skin lesions with a bullous eruption spreading on his upper and lower limbs and accompanied by oral and genital ulcers. Nivolumab was stopped and an oral treatment with methylprednisolone was begun. His medical condition improved, and the bullous lesions disappeared a few days later (Figure 2). Skin biopsy pleaded in favor of a bullous lupus (Figure 3). A complete immunology test showed ANA (titer 1:320) with a speckled pattern, anti-Ro/SSA, anti-RoSSA52 and perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA) (titer 1:20). The erythrocyte sedimentation rate was increased (18 mm/h) with CRP in the normal range. Screening for silica clotting time and dilute Russell viper venom time was negative. Serum complement level was normal, there was no hypergamma-globulinemia nor coagulation disorder. At follow-up, PET scan showed a new hypermetabolic mediastinal lymph node in the lower paratracheal 4R station for which the patient received stereotactic radiotherapy. It has been 2 years from initial diagnosis.

*Systematic review of literature*. We performed a literature research (ended in May 2018) using PubMed-Medline and Scopus databases. The PICO method was used to identify the concepts included in the research question. Only publications in English, French, Dutch, German, Spanish and Italian were retained.

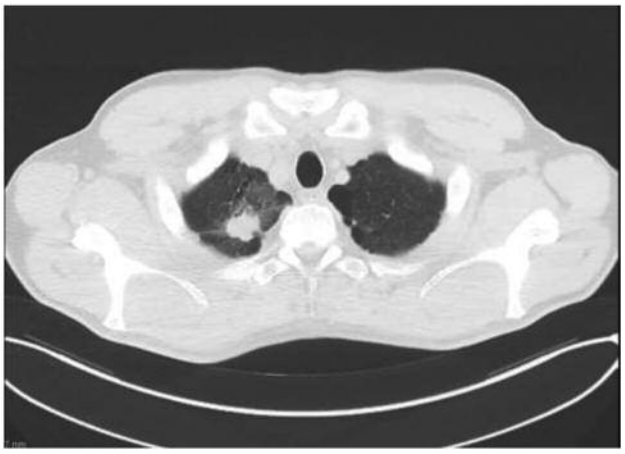

Figure 1. *Lung computed tomography at cancer diagnosis showing a mass 43 mm long-axis diameter in the apical segment of the right superior lobe of the lung.*

The first systematic review aimed to determine if paraneoplastic bullous lupus had already been described. We defined paraneoplastic syndrome based on criteria of Lortholary *et al*. (6). In total, 33 cases were described. Seven cases of systemic lupus erythematosus (SLE) are summarized in Table I.

The second review aimed to determine if bullous lupus occurring under ICIs had been reported in lung cancer, with an additional description of irAEs found. A total of 177 irAEs were found. Two cases of SLE were found and are detailed in Table I. A total of 26 cases of autoimmune disease exacerbation were found.

## Discussion

We report the case of a patient diagnosed with advanced adenocarcinoma of the lung who initially developed a localized eczematous-like skin lesion at the time of nivolumab beginning that was resistant to topic corticosteroid treatment. This lesion showed some episodes of flare until the eighth cycle of nivolumab with an exacerbation as a bullous eruption spreading on his upper and lower limbs with oral and genital ulcers. Combined clinical, histopathology and laboratory findings led to the diagnosis of a bullous lupus erythematosus. Bullous lesions disappeared after nivolumab cessation and oral treatment with methylprednisolone. In our patient's case, the hypothesis of a paraneoplastic origin is proposed. Many autoimmune paraneoplastic syndromes are well described in the literature (7) and some paraneoplastic dermatoses are

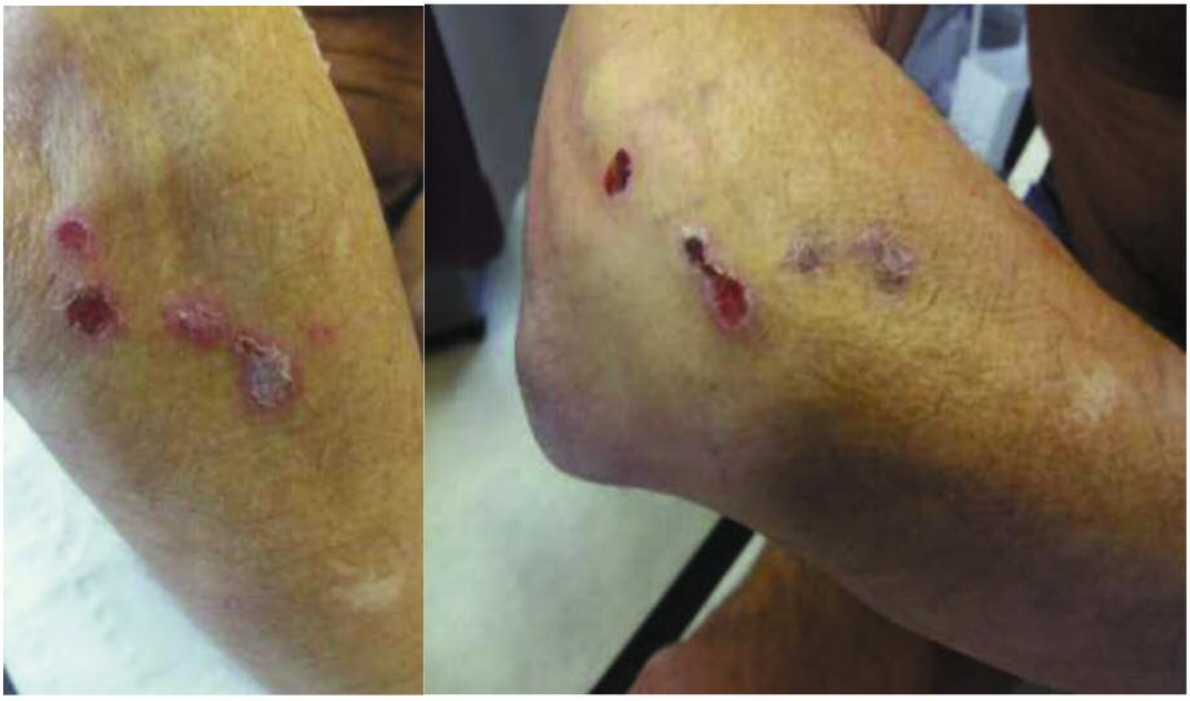

Figure 2. *Ruptured bullae on erythematous background accompanied by crusting on the upper limbs of the patient.*

well-known. However, with the arrival of ICIs in oncology, the distinction between autoimmune paraneoplastic syndrome and irAEs induced by immunotherapy has become challenging. Yet this distinction is important for appropriate therapeutic decision making.

No case of paraneoplastic bullous lupus was found in our first systematic review; other cases of paraneoplastic lupus have been described, mainly cutaneous forms but also seven cases of SLE (8-14). Nevertheless, the clinical course of our patient suggests a paraneoplastic origin as the skin eruption appeared 4 months after his cancer diagnosis followed by several flares under nivolumab. As Girard underlines, it is relevant to distinguish autoimmune diseases from paraneoplastic syndromes in thymic epithelial tumors before initiating a treatment by ICI because of a possible exacerbation of these (15). Bullous SLE is a rare presentation of SLE, therefore, literature data on this entity are scarce and consist mainly of case reports of case series (16). For SLE diagnosis, our patient fulfills three criteria of the American College of Rheumatology (17) and four of the Systemic Lupus International Collaborating Clinics (18). The hypothesis of bullous SLE is thus possible. The fact that we did not find any paraneoplastic bullous lupus in the literature can be explained by the rarity of this disease.

Patients with medical history of autoimmune disease are at risk of reactivation or exacerbation of their disease when taking ICIs (1). A systematic review on the use of ICIs in patients with pre-existing autoimmune disease reported that 75% either had an exacerbation of their disease, other irAE, or both (19). We had no autoimmune assessment of our patient before starting nivolumab because it is not a routine assessment in lung cancer. Since his systemic symptoms started after taking nivolumab, the hypothesis of a bullous lupus induced by nivolumab is also proposed. No bullous SLE arising under ICI was found in literature but one case of SLE appeared after 10 cycles of nivolumab (20) and one SLE exacerbation has also been described (21). A final hypothesis could be the emergence of an autoimmune disease independently of both cancer and immunotherapy. Sources from our systematic review mainly comprised case reports and case series. Thus, the presence of reporting bias must be emphasized. Nevertheless, we hope to promote reflection as to the possible paraneoplastic origin of irAEs.

## Conclusion

We report a unique case of bullous lupus possibly of paraneoplastic origin with exacerbation under nivolumab. In our systematic reviews, we did not find paraneoplastic bullous lupus nor bullous lupus induced or exacerbated under ICI treatment in lung cancer. However, seven cases of paraneoplastic SLE, one SLE induced by nivolumab and one SLE exacerbation under anti-PD1 immunotherapy were found. Thus, our case might be the first described and it is

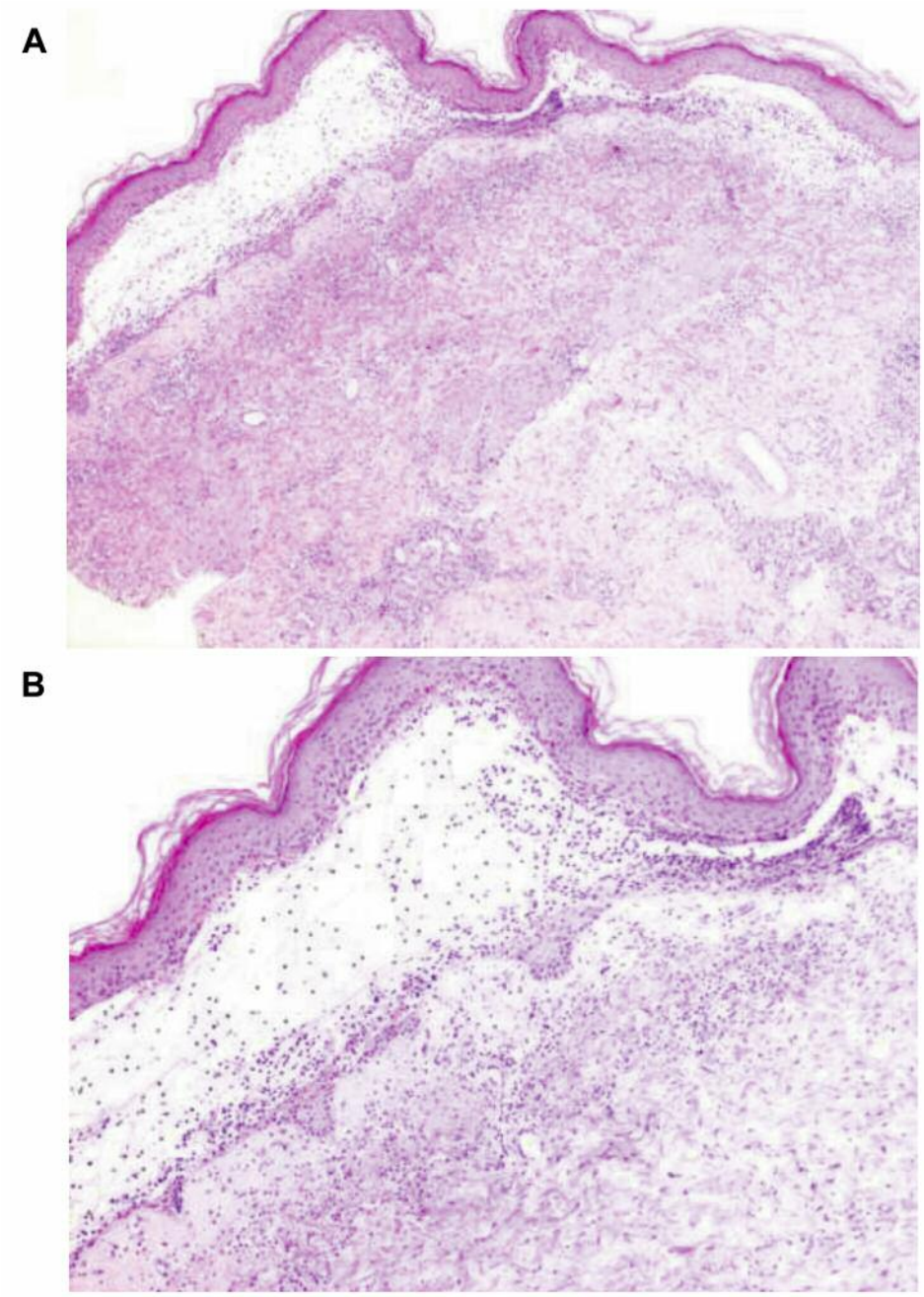


Figure 3. *Biopsy of a bullous cutaneous lesion on the right upper limb. Hematoxylin and eosin staining. Histopathological examination showed dermo-epidermal blistering, numerous apoptotic keratinocytes within the basal epidermal layer extending laterally from the bulla. Basal keratinocyte vacuolization was also seen. Papillary dermis was characterized by presence of neutrophil-rich infiltrate accompanied by abscess formation. Only few eosinophils were seen within the inflammatory infiltrate. There was not any evidence of vasculitis. Original magnification: A: 5×, B: 10×.*

through observation of similar cases in the future that our hypothesis might be reinforced.

## Conflicts of Interest

None.

## Authors' Contributions

Alicia Wouters, Valérie Durieux: Systematic review of the litterature; Alicia Wouters: wrote the text; Athanassios Kolivras: pathology contribution; Alicia Wouters, Valérie Durieux, Athanassios Kolivras, Anne-Pascale Meert, Jean-Paul Sculier: approved the final text.

Table I. *Cases of systemic lupus erythematosus found in both systematic reviews.*

Paraneoplastic SLE (first systematic review)

| Author (reference) | Age, years | Gender | Cancer | Treatment | Paraneoplastic syndrome | Clinical features | Evolution of paraneoplastic syndrome | Auto-antibodies |
|---|---|---|---|---|---|---|---|---|
| Mahler *et al*., 1998 (8) | 63 | M | Non-Hodgkin's lymphoma | Chemotherapy | SLE | Muco-cutaneous damage | Slight improvement during cancer remission | ANA, anti-Ro/SSA, anti-dsDNA, anti-Sm, anti-RNP |
| Loche *et al*., 2000 (9) | 68 | M | Non-small cell lung carcinoma | Surgery | SLE | Articular and cutaneous damage | Parallel to cancer | ANA, anti-phospholipid |
| Oliveri *et al*., 2005 (10) | 41 | F | MALT lymphoma | Radiotherapy + chemotherapy | SLE | Muco-cutaneous and articular damage | No data | ANA+, anti-Ro/SSA, anti-dsDNA |
| Sola *et al*., 2013 (11) | 45 | F | Thyroid papillary carcinoma | Surgery | SLE | Muco-cutaneous and articular damage | Parallel to cancer | ANA, anti-dsDNA |
| Thongpooswan *et al*., 2015 (12) | 58 | F | Thyroid papillary carcinoma | Surgery + radioactive iode | Mixed connectivity | Articular and cutaneous damage | Parallel to cancer | ANA, anti-RNP |
| Gonzalez-Amores *et al*., 2016 (13) | 70 | M | Cholangio-carcinoma | Surgery | SLE | No data | No data | No data |
| Mostmans *et al*., 2018 (14) | 63 | M | Small-cell lung carcinoma | Surgery + chemotherapy | SLE | Cutaneous damage | Parallel to cancer | ANA, anti-RNP, anti-Sm |
| Present case, 2018 | 59 | M | Bronchial adenocarcinoma | Chemotherapy + immunotherapy | Bullous SLE | Articular and cutaneous damage | Improvement after resuming immunotherapy | ANA, anti-Ro/SSA |

SLE during immunotherapy (second systematic review)

| Author (Reference) | Age | Gender | Histological type/stage | Type of ICI | Line of treatment | irAE | Timing of SLE onset | Auto-antibodies |
|---|---|---|---|---|---|---|---|---|
| De Chabot *et al*., 2017 (20) | 77 | F | Adenocarcinoma/ IV | Nivolumab | 3rd | SLE | After 10 cycles | ANA, anti-dsDNA, anti-SSA/Ro |
| Leonardi *et al*., 2018 (21) | No data | No data | Non-small cell lung carcinoma | No data | 3rd | Exacerbation of SLE | After 260 days | No data |
| Present case, 2018 | 59 | M | Adenocarcinoma /IIIb | 2nd | 2nd | Bullous SLE | After 8 cycles | ANA, anti-SSA/Ro |

ANA: Anti-nuclear antibodies; anti-dsDNA: anti-double stranded DNA; anti-RNP: anti-U1 ribonucleoprotein; anti-Ro/SSAs: anti-Sjögren's-syndrome-related antigen A; anti-Sm: anti-smith; F: female; ICI: immune checkpoint inhibitor; irAE: immune-related adverse event; M: male; SLE: systemic lupus erythematosus.

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