Drug-induced lupus erythematosus following immunotherapy with anti-programmed death-(ligand) 1

We read with interest the study of Kostine *et al* describing rheumatic immune-related adverse events (irAE), which occur in 6.6% of patients treated for cancer by anti-programmed death-(ligand) 1 (PDL1).[1] These new adverse effects pose significant challenges to patient care in terms of optimal management of these autoimmune damaging toxicities, while allowing effective antitumor therapy to continue.

The PD(L)1 pathway is involved in the maintenance of immune tolerance, and the blockage of this axis by anticancer immunotherapy could trigger autoimmune diseases and especially lupus.[2 3] We then searched in the pharmacovigilance register of our institution—the '*Registre des Effets Indésirables Sévères des Anticorps Monoclonaux Immunomodulateurs en Cancérologie* (REISAMIC)'—whether cases of drug-induced lupus erythematosus (DI-LE) were reported following anti-PD(L)1 immunotherapies.

Between October 2013 and July 2017, five cases of DI-LE were recorded in REISAMIC. Given the number of patients having received anti-PD(L)1 during the same period (n=1044), the estimated incidence of DI-LE was 0.48%. All patients gave their written informed consent for the use of their data in this report. The patients' characteristics are summarised in table 1. The patients had developed DI-LE at a median (range) age of 63 (48–80) years. None of the patients had a history of autoimmune disease before starting anti-PD(L)1. The most specific sign of DI-LE was subacute cutaneous lupus erythematous (SCLE) in four patients and chilblain lupus in the remaining patient. One patient having SCLE had also declared a systemic lupus erythematosus (SLE) according to the Systemic Lupus International Collaborating Clinics criteria.[4] The DI-LE was revealed by a frank maculopapular rash in the four patients with SCLE (figure 1). The median time of DI-LE occurrence was 10 (range: 4–22) weeks after the initiation of immunotherapy. Antinuclear antibodies in serum were found positive for two (40%) out of the five patients and were specifically positive for anti-Sjögren's syndrome-related antigen A (SSA). These two SSA-positive patients had SCLE but no eye or mouth dryness symptoms suggestive of Sjögren's disease. A skin biopsy was performed in all cases except the chilblain lupus. The skin biopsies revealed a lymphocytic infiltrate of the dermis, predominantly around adnexal sites. Alcian blue staining revealed mucin deposits in all patients. Direct immunofluorescence assays for IgG or C3 in skin biopsy were positive in two of the four patients tested (50%). The treatment of DI-LE was based on topical corticosteroids in all cases, with the antimalarial hydroxychloroquine added in the SLE case, and the outcome was favourable with a resolution in all cases.

This report is the first series of cases of lupus erythematosus induced by anti-PD(L)1 immunotherapy. A recent similar case report of pembrolizumab-related subacute cutaneous lupus erythematosus was provided.[5] The DI-LE has been variously reported after drug exposure such as hydralazine, procainamide, quinidine, oestrogen, tumour necrosis factor inhibitors, chlorpromazine, isoniazid, practolol, penicillamine and minocycline.[6] We believe that anti-PD(L)1 immunotherapies should also now be added to this list.

Based on our experience and the present case series, DI-LE induced by anti-PD(L)1 was characterised by an extensive, non-itchy and frankly macular or papular erythematous rash. The DI-LE diagnosis relies on the combination of the dermatological presentation associated with pathological features characterised by a lymphocytic dermal infiltration predominantly located at periadnexal sites, and mucin deposits.[7] The confrontation between the clinical appearance and the pathological aspects is often useful to differentiate between DI-LE and other non-specific cutaneous irAEs, or other specific autoimmune skin diseases that can be induced by anti-PD(L)1 such as psoriasis, toxic epidermal necrolysis, lichen planus, bullous dermatitis and dermatomyositis.[8]

These new cases of lupus induced by anti-PD(L)1 should incite rheumatologist and internists to dedicate further prospective study for irAE. Investigation of potential biomarkers of irAEs such as the genetic background, serum

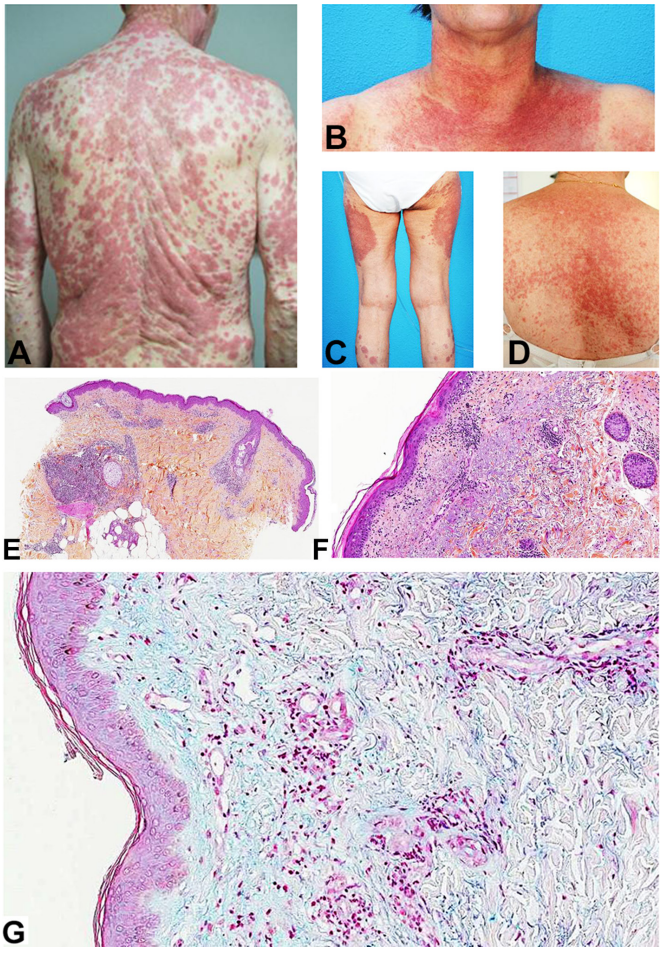

Figure 1 Photographs and histologic assessment of skin biopsies of cutaneous lupus erythematosus lesions induced by treatment with anti-PD(L)1. (A) Patient 4, erythematous papules and plaques with an annular, polycyclic configuration: generalised subacute lupus erythematous. (B) Patient 1, erythematous macules on the neck: subacute cutaneous lupus erythematosus. (C) Patient 2, symmetric papulosquamous erythematous rashes on the lower limbs. (D) Patient 3, erythematous macules and plaques on the back: subacute cutaneous lupus erythematosus. (E) Skin biopsy from patient 1, haematoxylin eosin saffron (HES) staining, ×2.5: peripheral and periadnexal monomorphic lymphocytic inflammatory infiltrate over the entire dermis. (F) Skin biopsy from patient 4, HES staining, ×5: lichenoid dermatosis with staged apoptotic bodies in the epidermis. Peripheral inflammatory mononuclear infiltrate in the upper dermis. (G) Skin biopsy from patient 3, Alcian blue staining, ×10: mucin deposits in the dermis.

Table 1 Characteristics of the patients having developed DI-LE following treatment with anti-PD(L)1 immunotherapy

Gender, age, cancer histology	Previous cancer treatments	Drug	Causal relationship	Time to occurrence of DI-LE* (in weeks)	DI-LE form†	Severity grade	Histopathological characteristics of a skin biopsy	Direct immunofluorescence in skin biopsy	Autoimmune biology in serum‡	Serum creatine kinase (normal value <145 IU/L)	Other irAEs	Treatment for cutaneous lupus, and outcome	Best overall antitumour response, and reintroduction of PD(L)1 (or reason for withdrawal)
Patient 1, woman, 48 years old, triple-negative breast carcinoma	Farmorubicine-endoxan-5-fluorouracil; eribulin, capecitabine; gemcitabine	Atezolizumab	Likely	6	SCLE Clinical aspect and location: erythematosus, neckline	1	Inflammatory monomorphic lymphocyte infiltrate in perivascular and periadnexal sites throughout the dermis. Alcian blue staining revealed mucin deposits in the dermis.	Positive for IgG, linear, moderate, epidermal dermal junction Negative for C3d	Negative Titre for ANA negative (<1/80), aDNA<10, ENA negative complement in normal range (C3=1.73; C4=0.26)	Normal (75 IU/L)	No	Topical steroids, resolution in 2 weeks	PR No interruption of atezolizumab
Patient 2, woman, 80 years old, diffuse large B-cell lymphoma	R-CHOP; R-GEMOX; R-lenalidomide	Nivolumab	Likely	14	SCLE Clinical aspect and location: papulosquamous erythematous in the lower limbs, symmetrical	2	Inflammatory perivascular lymphocytic infiltrate of the upper and middle dermis. Alcian blue staining revealed mucin deposits.	Negative	Negative Titre for ANA<1/80; aDNA<10; ENA negative Low complement C4 and CH50 but normal C3 (C3=1.53; C4<0.02; CH50<10)	Normal (28 IU/L)	Yes: hepatitis grade 2	Topical steroids, resolution in 3 weeks	PD Temporary withdrawal of immunotherapy due to lupus, and then definitive withdrawal of nivolumab due to disease progression
Patient 3, woman, 66 years old, carcinoma epidermoid	Radiotherapy; carboplatin-cetuximab-5-fluorouracil; paclitaxel-cetuximab; methotrexate-carboplatine	Nivolumab	Likely	4	SCLE Clinical aspect and location: erythematosus on the trunk, back and face	2	Perivascular lymphocytic infiltrate of the upper dermis with discrete vacuolisation of the epidermal basal layer. Alcian blue staining revealed mucin deposits in the dermis.	Negative	Positive with ANA+ and SSA+ Titre for ANA=1/640; aDNA<10; ENA=1.5 weakly positive; SSA=94 U/mL, complement in normal range (C3=1.42; C4=0.2; CH50 not done)	Normal (30 IU/L)	No	Topical steroids, resolution in 2 weeks	SD Temporary withdrawal of immunotherapy due to lupus
Patient 4, man, 63 years old, melanoma	None	Pembrolizumab	Certain	22	SCLE Clinical aspect and location: generalised, clearly erythematosus, papular and macular aspects on the trunk, back, abdomen and thorax Systemic lupus erythematosus (SLICC criteria[4] were SCLE+arthralgia+positive serum antibodies)	3	Lichenoid dermatosis with staged apoptotic bodies in the epidermis. Peripheral inflammatory mononuclear infiltrate in the upper dermis. Alcian blue staining did not reveal any mucin deposits in the dermis.	Positive for IgG: discontinuous low-intensity band and epidermal dermal junction. C3d positive: rough band	Positive with SSA+/SSB+ Titre for ANA>1/1280 (mottled aspect); aDNA<10; ENA>28 highly positive with SSA>241 U/mL and SSB=86 U/mL (n<7), complement in normal range (C3=1.07; C4=0.21; CH50>60)	Elevated: 238 IU/L when lupus appeared, then 181 IU/L 15 days later, then return to normal levels	Yes: vitiligo universalis, hepatitis grade 2	Topical steroids, oral hydroxychloroquine, resolution in 4 weeks	CR Permanently discontinued due to the adverse event and the CR
Patient 5, man, 48 years old, melanoma	Dacarbazine-fotemustine; ipilimumab	Pembrolizumab	Certain	10	Chilblain lupus on the toes	1	*Not performed*	*Not performed*	Negative Titre for ANA<1/80; aDNA<10; ENA not done; complement in normal range (C3=1.17; C4=0.2; CH50=49.3)	Normal (58 IU/L)	Yes: vitiligo universalis	Topical steroids, resolution in 2 weeks	PR No discontinuation of pembrolizumab
Total: Median (range) age 63 (48–80) years	–	–	–	Median (range): 10 (4–22) weeks	–	–	–	Positive in two of four cases tested (50%)	ANA positive in two of five cases (40%)	–	–	–	–

*Time between the first infusion of anti-PD(L)1 and the onset of symptoms of lupus erythematosus.
†Among Obermoser *et al*.[1]
‡Serum assays for autoimmune factors, with normal values indicated: ANA, serum titre, normal <1/80; aDNA, normal <10 IU/mL; ENA, ratio, normal <1.1 (ratio=sample absorption/standard absorption); SSA, normal <7 U/mL; SSB, normal <7 U/mL; C3, normal values=0.9–1.80 g/L; C4, normal values=0.10–0.40 g/L; CH50, normal value >31.6; creatine kinase (CK), normal values=0–145 IU/L.
aDNA, anti-DNA; ANA, antinuclear antibody; CH50, 50% complement haemolytic; CR, complete response; DI-LE, drug-induced lupus erythematosus; ENA, extractable nuclear antigen; irAE, immune-related adverse event; PD, progressive disease; PR, partial response; R-CHOP, rituximab-cyclophosphamide hydroxyadriamycine oncovin prednisone; R-GEMOX, rituximab-gemcitabine oxaliplatine; SCLE, subacute cutaneous lupus erythematosus; SD, stable disease; SLICC, Systemic Lupus International Collaborating Clinics[4]; SSA, Sjögren's syndrome-related antigen A; SSB, Sjögren's syndrome-related antigen B.

levels of autoimmune factors and cytokines may help better understand these immunological adverse events and autoimmune conditions in general.

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