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 (PD(L)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 anticaner immunotherapy could trigger autoimmune diseases and especially lupus. 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 erythematous (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 erythematosus (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. 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. The DI-LE was variably reported after drug exposure such as hydralazine, procainamide, quinidine, oestrogen, tumour necrosis factor inhibitors, chlorpromazine, isoniazid, practolol, penicillamine and minocycline. 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. 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.

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

<table>
<thead>
<tr>
<th>Gender, age, cancer type</th>
<th>Previous cancer treatments</th>
<th>Drug</th>
<th>Time to occurrence of DI-LE (in weeks)</th>
<th>DI-LE form</th>
<th>Clinical and histological characteristics of a skin biopsy</th>
<th>Direct Immunofluorescence in skin biopsy</th>
<th>Autoimmune biomarker in serum</th>
<th>Serum complement values (normal range)</th>
<th>Other irAEs</th>
<th>Treatment for cutaneous lupus, and outcome</th>
<th>Best overall antimalarial response, and reintroduction of PD(L)1 (or reason for withdrawal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1, woman, 48 years old, triple-negative breast carcinoma</td>
<td>None</td>
<td>Pembrolizumab</td>
<td>6</td>
<td>SCLE</td>
<td>Clinical aspect and localisation: erythematous, macular</td>
<td>Negative for ANA: titre &lt;1/80; aDNA &lt;10; ENA negative</td>
<td>Low complement C4 and CH50 but normal C3 (C3=1.53; C4&lt;0.02; CH50&lt;10)</td>
<td>Normal (30 IU/L)</td>
<td>No</td>
<td>Topical steroids, resolution in 2 weeks</td>
<td>PR – No rechallenge of pembrolizumab</td>
</tr>
<tr>
<td>Patient 2, woman, 60 years old, diffuse large B-cell lymphoma</td>
<td>R-CHOP; R-GEMOX; R-lenalidomide</td>
<td>Pembrolizumab</td>
<td>14</td>
<td>SCLE</td>
<td>Clinical aspect and localisation: erythematous, papular</td>
<td>Positive for IgG: dislocated low-intensity band and epidermal dermal junction</td>
<td>Positive for SSA+/SSB+: titre for ANA&gt;1/1280; aDNA&lt;10; ENA&gt;28</td>
<td>Elevated: 238 IU/L when lupus appeared, then 181 IU/L15</td>
<td>Topical steroids, oral hydroxychloroquine, resolution in 4 weeks</td>
<td>CR – Permanently discontinued due to the adverse event and the CR</td>
<td>OI – Permanent discontinuation due to the adverse event and the OI</td>
</tr>
<tr>
<td>Patient 3, woman, 66 years old, carcinoma epidermoid</td>
<td>None</td>
<td>Pembrolizumab</td>
<td>22</td>
<td>SCLE</td>
<td>Clinical aspect and localisation: papular and macular</td>
<td>Lichenoid dermatosis with staged apoptotic bodies in the epidermis, Peripheral inflammatory mononuclear infiltrate in the upper dermis, Alcian blue staining: distinct oval mononuclear cell deposits in the dermis</td>
<td>Positive for IgG: discontinuous low-intensity band and epidermal dermal junction</td>
<td>Normal (58 IU/L)</td>
<td>Yes: vitiligo universalis</td>
<td>Topical steroids, oral hydroxychloroquine, resolution in 4 weeks</td>
<td>OI – Permanent discontinuation due to the adverse event and the OI</td>
</tr>
<tr>
<td>Patient 4, man, 63 years old, melanoma</td>
<td>None</td>
<td>Pembrolizumab</td>
<td>10</td>
<td>Chilblain lupus on the toes</td>
<td>Not performed</td>
<td>Not performed</td>
<td>Not performed</td>
<td>Normal (58 IU/L)</td>
<td>Yes: vitiligo universalis</td>
<td>Topical steroids, oral hydroxychloroquine, resolution in 4 weeks</td>
<td>OI – Permanent discontinuation due to the adverse event and the OI</td>
</tr>
</tbody>
</table>

**Notes:**
1. DI-LE: Drug-induced lupus erythematosus
2. SCLE: Subacute cutaneous lupus erythematosus
3. C3d: Complement component 3d
4. SSA: Sjögren’s syndrome-related antigen A
5. SSB: Sjögren’s syndrome-related antigen B
6. ANA: Antinuclear antibody
7. aDNA: Anti-DNA antibody
8. ENA: Extractable nuclear antigen
9. C3: Complement component 3
10. C4: Complement component 4
11. CH50: 50% complement hemolytic activity
12. CK: Creatine kinase

**Serum complement values:**
- 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.

**Other irAEs:**
- Vitiligo universalis
- Hepatitis grade 2
- Topical steroids, hydroxychloroquine

**Treatment for cutaneous lupus:**
- Topical steroids
- Oral hydroxychloroquine
- Resolution in 3 weeks

**Best overall antimalarial response:**
- PR – Permanent discontinuation due to the adverse event and the CR
- OI – Permanent discontinuation due to the adverse event and the OI
levels of autoimmune factors and cytokines may help better understand these immunological adverse events and autoimmune conditions in general.

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