Transition of cutaneous into systemic lupus erythematosus following adenoviral vector-based SARS-CoV-2 vaccination

Dear Editor,

The recent approval of highly effective prophylactic vaccines against COVID-19 is a monumental step in the global fight against the ongoing SARS-CoV-2 pandemic. Two types of SARS-CoV-2 vaccines are currently used, messenger-RNA (mRNA) vaccines and recombinant adenoviral (AdV) vector vaccines.[1] Both of them encode the production of the SARS-CoV-2 spike protein, which is the primary target for neutralizing antibodies. We report a case of subacute cutaneous lupus erythematosus (SCLE) that transitioned into systemic lupus erythematosus (SLE) following AdV-vaccination with AZD1222.

A 62-year-old woman presented with a generalized morbilliform exanthema and new onset of fatigue and musculoskeletal pain (Fig. 1). Six months before the first visit to our department, the patient had experienced erythematosquamous papules and plaques symmetrically located in the sun-exposed areas (chest, upper back, lower arms, and dorsal hands). Laboratory investigations found a normal blood cell count and serum chemistry, but increased titres for antinuclear antibodies (1 : 320; normal <1 : 160) and positivity for anti-Ro/SSA(60) antibodies. All other extractable nuclear antigens were unremarkable. Further work up including chest X-ray, abdominal ultrasound, and heart echography was unremarkable. The patient felt otherwise healthy, and there were no trigger factors such as cigarette smoking, infections, drug intake or ultraviolet-light exposure. Based on these findings, a diagnosis of SCLE was made by her rheumatologist, and treatment with hydroxychloroquine (200 mg twice daily) was started, resulting in a significant improvement of skin lesions (leaving mild erythema at the upper back and dorsal hands).

On 15 March 2021, the patient received the first dose of the anti-COVID-19 AdV-vaccine AZD1222. There were no systemic or local side effects during the first days after vaccination. However, erythematous confluent macules spread out symmetrically over the entire body 10 days later, concomitantly with malaise, fatigue, and acute pain in multiple muscles and joints (Fig 1). The patient was, therefore, admitted to our hospital. A skin biopsy taken from the left lower leg revealed typical features of cutaneous lupus erythematosus (CLE; vacuolar interface dermatitis, dense dermal lymphocytic infiltrates, and strong mucin deposition) as well as a positive lupus band test (linear immunoglobulin class-G deposits at the dermoepidermal junction; Fig. 2). Laboratory investigations at this time revealed increased anti-double-stranded DNA antibody levels, leukocytopenia (3.2×10^9/L, normal 4.4–11.0×10^9/L) and C3/C4-hypocomplementemia (C3: 48 mg/dL, normal 90–170 mg/dL; C4: 3, normal 18–49 mg/dL). These findings indicate a transition of SCLE into SLE, fulfilling the current SLE classification

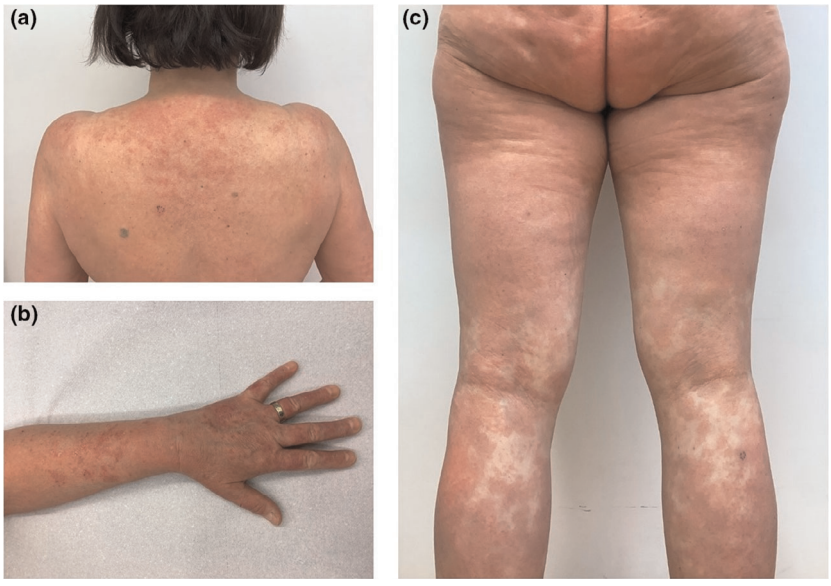

Figure 1 Clinical findings of the patient at the first presentation in our department. (a, b) Erythematous papules and plaques located at the upper back, lower arms and dorsal hands, characteristic for subacute cutaneous lupus erythematosus. (c) Concomitant widespread erythematous confluent macules on the buttocks and legs, characteristic for generalized acute cutaneous lupus erythematosus.

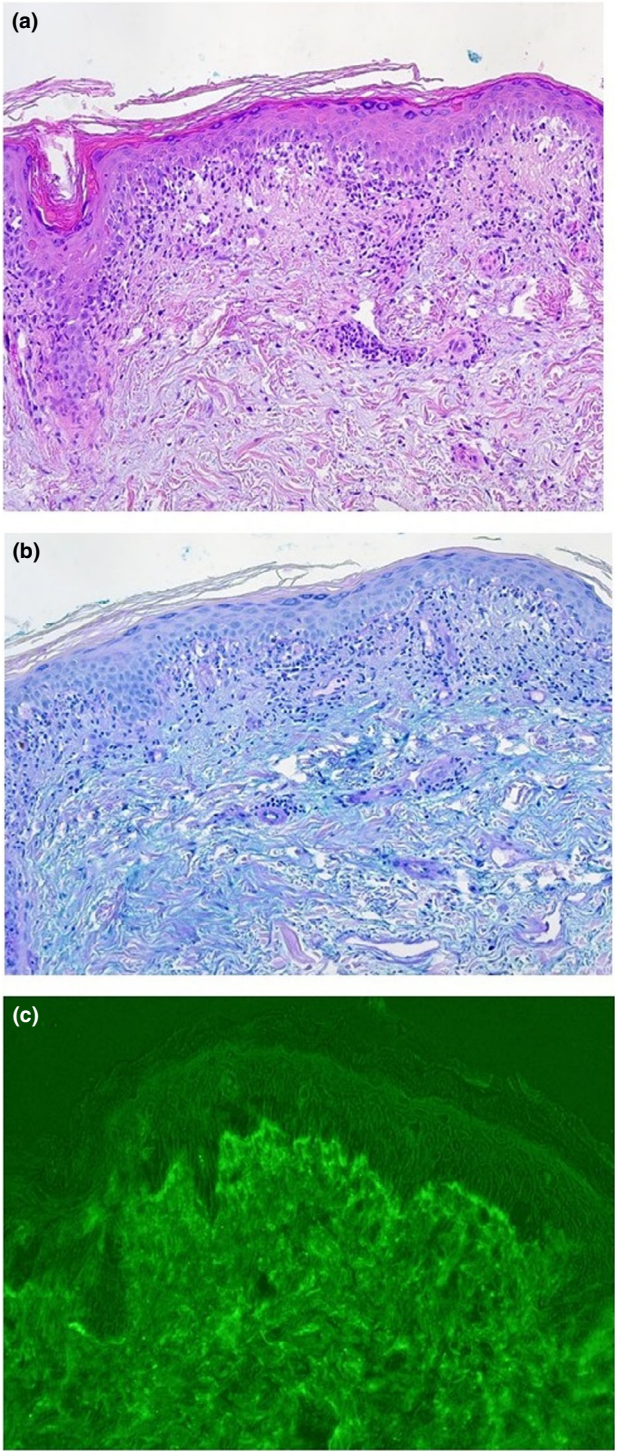

Figure 2 (a) Vacuolar interface dermatitis and dense dermal lymphocytic infiltrates, 4 mm punch biopsy taken from the left lower leg. (haematoxylin and eosin, original magnification ×100). (b) Strong dermal mucine deposition (alcian blue staining, original magnification x 100). (c) Linear immunoglobulin class-G deposits at the dermoepidermal junction (called positive lupus band) from non-UV-exposed skin (lower legs).

criteria.[2] Under tapered glucocorticosteroid therapy with prednisolone 250 mg/day, the skin lesions and systemic symptoms significantly improved within 7 days.

So far, there is limited knowledge about the safety and efficacy of the COVID-19 vaccines in patients with autoimmune rheumatic diseases, including cutaneous LE or SLE.[3] Nevertheless, a strong agreement exists that lupus patients should get vaccinated and might be prioritised before the general population.[3,4] Although rare, flares of SLE, new-onset SLE or lupus-like syndromes have been described following application of several vaccines, for example hepatitis-B, HPV or influenza.[5–7] Interestingly, besides the production of high spike-protein levels, both mRNA and AdV SARS-CoV-2-vaccines trigger innate sensors by intrinsic adjuvant activity, resulting in the production of type I interferon (IFN) and multiple pro-inflammatory cytokines.[1] Dysregulation of the type 1 IFN pathways plays a critical role in SLE. Moreover, type I IFN-related genes are highly upregulated in CLE and correlate with disease activity.[8,9] Facing the close temporal relationship and absence of other potential trigger factors we speculate that AdV-vaccination with AZD1222 might have caused the shift of SCLE into SLE in our patient. Interestingly, a case of Rowell's syndrome, a particular subtype of SCLE, was recently reported after application of the mRNA-vaccine BNT162b2, indicating that both types of SARS-CoV-2-vaccines might induce or aggravate lupus-like conditions.[10] Physicians treating patients with autoimmune rheumatic diseases should also consider SARS-CoV-2-vaccination as a potential cause of unexplained disease deterioration.

Acknowledgement

Anke Bartröver, Tanja Kleinecke, and Stefanie Fittkau provided excellent technical assistance. The patient in this manuscript has given written informed consent to the publication of case details.

Conflict of interest

None to declare.

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DOI: 10.1111/jdv.17514

Reduction in the number of early melanomas diagnosed during the COVID-19 pandemic: a single-centre cohort study

To the editor

Early detection of melanoma is an important intervention to reduce morbidity and mortality.[1,2] The COVID-19 pandemic has affected timely access to health care, potentially affecting patient outcomes. Marson *et al*.[3] showed that the incidence of melanoma decreased during the pandemic using the United States data. Lallas *et al*.[4] demonstrated an overall 30.1% decrease in cancers diagnosed during the pandemic in Greece. We sought to evaluate whether melanomas diagnosed during the pandemic at our medical centre differed in stage compared to the prepandemic time period.

This was an IRB-approved, retrospective study. We reviewed consecutive melanoma biopsy reports performed from January 2019 to March 2021 from Pontificia Universidad Catolica de Chile. We included adult (≥18 years) patients with histopathology-confirmed diagnosis of melanoma. We excluded patients that were not evaluated at our institution (e.g. tissue slides sent for consultation) and non-cutaneous melanomas. Patients' demographics and pathological characteristics were recorded. For study purposes and based on our local epidemiology, 'pre-COVID period (preCP)' ranged between January 2019 and March 2020. 'COVID period (CP)' ranged between April 2020 and March 2021. Means, medians and proportions were calculated. The chi-squared test was used for categorical variables. For continuous variables, student's *t*-test was used. All tests were two-sided and statistical significance was set at $P < 0.05$.

A total of 296 cases of melanoma were included in the study period (Table 1 and Fig. 1). The cases per month decreased from 12.7 in the preCP to 8.8 in the CP ($P = 0.013$); this reduction was primarily due to a decrease in early stage melanoma (i.e., in situ, stages I-II, and ≤2 mm melanomas). The number of in situ melanomas per month decreased from 5.1 to 2.3 ($P = 0.0009$). The number of ≤2 mm melanomas per month decreased from 4.8 to 3 ($P = 0.02$) and the number of stage I–II cases per month decreased from 6.2 to 3.8 ($P = 0.025$). There was a trend towards more advanced melanomas during the CP period. During the preCP, 26.3% of melanomas were >2 mm vs. 41.3% during CP ($P = 0.046$). During the preCP, 14.1% were diagnosed at an advanced stage (III & IV) vs. 27.8% during CP ($P = 0.008$; Table 1).

In this study, there was a 31.2% reduction in the melanoma cases diagnosed per month during CP with a decrease in the proportion and counts of localized and thin melanomas. The most probable explanation for this was lack of access to healthcare during the pandemic's lockdowns in association with patient reluctance to present for examination of both symptomatic lesions and screening examinations. Marson *et al*. showed a 43% decrease in melanoma diagnosis in the COVID period and estimated that 19 600 melanomas would be delayed in initial diagnosis/treatment in the United States. Lallas *et al*.[4] demonstrated a 36.4% reduction in melanoma diagnosis in Greece. This might be critical since melanoma is a highly curable disease in early stages and this window might be lost. Tejera-Vaquerizo *et al*.[5] estimated a 45% risk of upstaging after a 3-month delay in diagnosis using melanoma models; highlighting the potential future implications of our results. Limitations of our study include single institution and relatively low number of patients with short follow-up.

Despite the population-based skin cancer screening being not currently recommended,[6] hampering access to health care when needed might affect melanoma stage at diagnosis and

