Extracorporeal photopheresis and cyclophosphamide for cancer-associated systemic sclerosis worsening induced by immune checkpoint inhibitors: a case report

Sirs,

Cancer-associated systemic sclerosis (SSc), induced or not by immune checkpoint inhibitors (ICI), is an uncommon complication which therapeutic management, from ICI discontinuation to glucocorticoids and/or immunosuppressive agents, remains to be defined. Extracorporeal photopheresis (ECP) is an established therapy for the treatment of graft-versus-host disease but not in systemic sclerosis. Data regarding safety and efficacy of ECP for the treatment of immune-related adverse events are lacking. This case report suggests that ECP, in combination with immunosuppressive agents, could be an interesting approach for refractory cancer- and/or ICI-induced SSc without being detrimental for the control of the solid cancer.

Immune checkpoint inhibitors (ICIs) have a central role in the management of solid cancers, especially non-small cell lung carcinoma (NSCLC) (1). Resulting from an excessive activation of the immune system against the tumours, normal tissues may also be the target of the immune response and about half the patients develop serious immune-related adverse events (irAE), including musculoskeletal manifestations, colitis or myocarditis (2).

Systemic sclerosis (SSc) is mainly a primary autoimmune disease, but it can be more rarely associated with cancer or even complicate the use of ICIs. Based on the analysis of the WHO pharmacovigilance database, we previously reported that nivolumab and pembrolizumab showed a disproportionality in scleroderma reporting (3). However, the therapeutic management, from ICI discontinuation to glucocorticoids and/or immunosuppressive agents, remains to be defined.

Here, a 49-year-old woman was admitted for diffuse skin thickening. She had been diagnosed with metastatic NSCLC three months earlier. Although SSc was not initially diagnosed, Raynaud phenomenon, puffy fingers and gastroesophageal reflux disease were already noted at this time, supporting a cancer-associated SSc.

After 2 Pembrolizumab injections (2 mg/kg/3 weeks), treatment was withdrawn due to dramatic worsening and extension of skin thickening: within one month, patient's skin has changed from normal to diffuse sclerosis with a modified Rodnan skin score (mRSS) of 34. No SSc specific antibody was found and screening for visceral involvement revealed only mild infiltrative lung disease. Nailfold capillaroscopy showed mild to moderate microvascular abnormalities consistent with non-specific organic microangiopathy. Skin biopsy showed swollen collagen bundles in the dermis.

Prednisone was started at 10 mg/day without any improvement. Pulses of cyclophosphamide (0.7 g/m^2/month) were then initiated and rapidly combined with weekly extracorporeal photopheresis (ECP) owing to the extension of the cutaneous involvement (Fig. 1A).

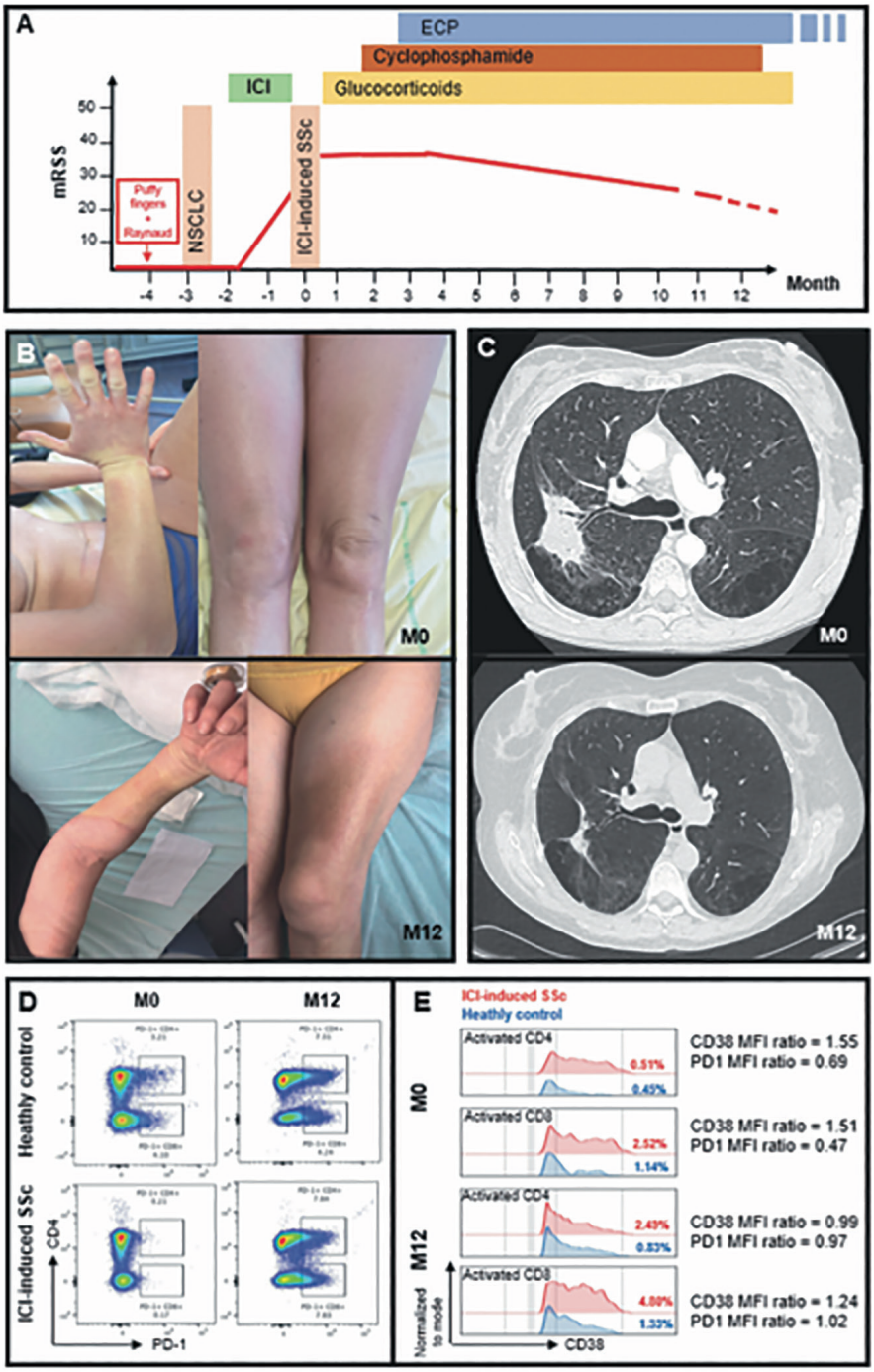

Fig. 1. Cyclophosphamide plus extracorporeal photopheresis (ECP) for paraneoplastic systemic sclerosis worsened by immune checkpoint inhibitors (ICIs).
A. Clinical evolution (according to modified Rodnan skin score) with different treatment over time.
B. Skin thickening evolution over time (M0 = SSc diagnosis; M12 = 12 months).
C. Evolution of tumour mass on CT scan over time.
D. FACS analysis on PBMCs over time compared to an age- and gender-matched healthy control. At M0, PD-1 expression is reduced and returned to normal level at M12.
E. CD38 histogram on the activated T cells (CD38+ HLA-DR+), with percentages of activated CD38+ HLA-DR+ CD4+ (or CD8+) T cells in the entire CD4+ T cells subset (or CD8+). Ratios of the mean fluorescence intensity (MFI, patient/control) illustrates the diminution of CD38 overexpression at M12, concomitant with a level of PD-1 expression back to normal (ratio close to 1).

Over the next 12 months, skin thickening has decreased (mRSS 19) (Fig. 1A), especially in areas not included in the mRSS (Fig. 1B), while the tumour mass has almost disappeared (Fig. 1C). Cyclophosphamide was stopped after 12 months, prednisone was progressively tapered, and ECP was spaced out every two weeks at last follow-up.

FACS (Fluorescence-activated cell sorting) analysis on PBMCs (peripheral blood mononuclear cell) at SSc flare-up revealed an increased expression of activation markers (CD38 and HLA-DR) on effector memory T cells compared to an age-gender-matched healthy control and the absence of PD-1 expression. FACS analysis during follow-up showed that PD-1 expression on T cells returned to normal level at 12 months (Fig. 1D). Otherwise, while the percentages of activated T cells (CD38+HLA-DR+) remained higher in the patient, CD38 mean expression decreases for CD8 T cells and normalises for CD4 T cells (Fig. 1E).

Although spontaneous improvement is possible in irAE after ICI discontinuation, and also in the natural history of SSc, the improvement of skin thickening and general health status, concomitant with a normalisation of the lymphocyte activation profile, suggests a specific effect of the combination therapy (cyclophosphamide and ECP). ECP is an established therapy for the treatment of graft-versus-host disease (4) but not in SSc (5). Data regarding safety and efficacy of ECP for the treatment of irAE are lacking (6). This case report suggests that ECP, in combination with immunosuppressive agents, could be an interesting approach for refractory cancer- and/or ICI-induced SSc without being detrimental for the control of the solid cancer.

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References

1. Herbst RS, Baas P, Kim DW *et al*.: Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* 2016; 387: 1540-50. https://doi.org/10.1016/s0140-6736(15)01281-7
2. McGonagle D, Bragazzi NL, Amital H, Watad A: Mechanistic classification of immune checkpoint inhibitor toxicity as a pointer to minimal treatment strategies to further improve survival. *Autoimmun Rev* 2020; 19: 102456. https://doi.org/10.1016/j.autrev.2019.102456
3. Terrier B, Humbert S, Preta L *et al*.: Risk of scleroderma according to the type of immune checkpoint inhibitors. *Autoimmun Rev* 2020; 19: 102596. https://doi.org/10.1016/j.autrev.2020.102596
4. Zeiser R, Blazar BR: Acute graft-versus-host disease – biologic process, prevention, and therapy. *N Engl J Med* 2017; 377: 2167-79. https://doi.org/10.1056/nejmra1609337
5. Kowal-Bielecka O, Fransen J, Avouac J *et al*.: Update of EULAR recommendations for the treatment of systemic sclerosis. *Ann Rheum Dis* 2017; 76: 1327-39. https://doi.org/10.1136/annrheumdis-2016-209909
6. Apostolova P, Unger S, von Bubnoff D, Meiss F, Becher B, Zeiser R: Extracorporeal Photopheresis for Colitis Induced by Checkpoint-Inhibitor Therapy. *N Engl J Med* 2020; 382: 294-6. https://doi.org/10.1056/nejmc1912274