findings point to the need for studies on sex and age differences in pediatric melanoma.

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De novo cutaneous connective tissue disease temporally associated with immune checkpoint inhibitor therapy: A retrospective analysis

To the Editor: With the success of immune checkpoint inhibitors (ICI) in cancer therapy, there is urgency to better characterize dermatologic immune-related adverse events (irAEs). De novo cutaneous connective tissue disease (CTD) has been associated with immunotherapy including reports of 2 cases of scleroderma, 7 cases of dermatomyositis, 6 cases of subacute cutaneous lupus erythematosus (SCLE), and 11 cases of eosinophilic fasciitis (EF).[1,2] In this study, we evaluated the frequency of immunotherapy-associated de novo cutaneous CTD among our institutions and reported clinical features and management.

In this retrospective cohort study, we queried electronic pharmacy and medical records to find the total number of adult patients treated with pembrolizumab, nivolumab, durvalumab, atezolizumab, tremilimumab, and/or ipilimumab at Dana-Farber Cancer Institute/Mass General Brigham between December 2013 and July 2019. Using institutional billing codes, diagnosis codes, and key word searches throughout notes and reports, we extensively reviewed medical records to identify patients with de novo cutaneous CTD (systemic sclerosis, dermatomyositis, cutaneous lupus [acute, subacute, chronic], systemic lupus erythematosus [SLE], EF, and morphea) up to 1 year after last ICI dose (Supplementary data available on Mendeley at https://doi.org/10.17632/8chdj89vhj.1). We excluded exacerbation(s) of pre-existing disease. In addition to diagnosis by the patient's dermatologist, 3 board-certified dermatologists reviewed cases and unanimously agreed with diagnoses.

A total of 4,487 patients received immunotherapy across our institutions. Among this cohort, 11 patients had immunotherapy-associated cutaneous CTD, for a frequency of 0.025%. Six (54.5%) were men. Median age was 59 years (53-69). Median time to onset was 8 months (0.5-26). There were 8 cases of SCLE (72.7%), 1 case of SLE (9.1%), 1 case of EF (9.1%), and 1 case of dermatomyositis (9.1%), with clinical and diagnostic features described in Table I. Among 9 patients tested, all had positive antinuclear antibodies (range, 1:80-1:5120). Among 7 patients with SCLE tested, 6 (85.7%) had positive anti-Ro(SSA) and 5 (71.4%) had positive anti-La(SSB) antibodies. Patients were treated with skin-directed (100%) and/or systemic therapies (36.3%). ICI was discontinued in 1 patient for dermatomyositis and held in 1 patient for SCLE.

Major findings include the rarity and striking lack of heterogeneity of immunotherapy-associated cutaneous CTD. We did not observe systemic sclerosis, morphea, or other types of cutaneous lupus beyond SCLE; we found only 1 case of SLE. There is 1 report of ipilimumab-associated lupus nephritis in the literature.[3] A possible mechanism for the disproportionate number of SCLE cases may be from immunologic recognition of previously immunologically tolerated drug antigens (all on longstanding, previously tolerated drugs reported to cause drug-induced SCLE), increased ultraviolet radiation

Table I. Patient characteristics, diagnostic features (clinical, laboratory, and histologic), and management details of 11 patients with de novo cutaneous CTD associated with immunotherapy

Age/sex/race*	Cancer type†	ICI/onset, mos	Concomitant drugs reported to cause SCLE	Clinical features	Autoantibody testing/ laboratory findings	Histopathology/DIF/ radiologic studies‡	Treatment(s)	Response	Impact on ICI
Eight cases of immunotherapy-associated SCLE									
(1) 54/F/W§	Lung, small cell	Nivolumab/20	Ciprofloxacin¶ Nitrofurantoin¶ Omeprazole#	Photo distributed annular macules and papules on trunk, upper extremities (Fig 1)	ANA: 1:5120, speckled**, Anti-Ro(SSA): >8.0, Anti-La(SSB): >8.0	HE: Focal interface dermatitis with focal lichenoid dermal lymphocytic infiltrate. Mild dermal mucin deposition noted. DIF: N/P	Topical CS Antihistamine Photoprotection HCQ	CR	Not interrupted by SCLE
(2) 54/F/W	Ovarian	Dostarlimab/4	Omeprazole#	Photo distributed annular macules and papules on upper extremities, trunk	ANA: 1:80, Anti-Ro(SSA): <0.2, Anti-La (SSB): <0.2	HE: Interface dermatitis with epidermal spongiosis and superficial dermal perivascular lymphocyte infiltrate and rare eosinophils. Follicular plugging and subtle dermal mucin deposition present. DIF: 1+ granular C3, IgM, and IgG along the DEJ	Topical CS Antihistamine Photoprotection	PR	Held and re-started at full dose 1 mo later for SCLE
(3) 57/F/W	Breast	Atezolizumab/11.5	Omeprazole# Ranitidine#	Photo distributed annular macules and papules on upper extremities, face, trunk	ANA: 1:320, speckled, Anti-Ro(SSA): >8.0, Anti-La(SSB): 0.4	HE: Interface dermatitis with, focal lichenoid infiltrate, and superficial to mid-dermal perivascular lymphocytic infiltrate. Increased dermal mucin deposition and follicular plugging were observed. DIF: negative	Topical CS Antihistamine Photoprotection	PR	Discontinued 2 mo prior to SCLE

Continued

Table I. Cont'd

Age/sex/race*	Cancer type†	ICI/onset, mos	Concomitant drugs reported to cause SCLE	Clinical features	Autoantibody testing/ laboratory findings	Histopathology/DIF/ radiologic studies‡	Treatment(s)	Response	Impact on ICI
(4) 65/M/W	Lung, small cell	Pembrolizumab/3	Omeprazole#	Photo distributed annular macules and papules on trunk and upper extremities	ANA: 1:320, speckled, Anti-Ro(SSA): >8.0, Anti-La(SSB): <0.2	HE: Prominent interface dermatitis with focal vesicle formation and lichenoid infiltrate. Prominent dyskeratotic keratinocytes with epidermal necrosis and florid acute-on-chronic inflammation represent extensive cytotoxic effect. Features of follicular plugging and superficial to mid-dermal perivascular and peri-adnexal lymphocytic infiltrate suggestive of background SCLE. DIF: negative	Topical CS Antihistamine Photoprotection HCQ	PR	Not interrupted by SCLE
(5) 60/M/W	Melanoma	Nivolumab/0.5	Omeprazole#	Photo distributed annular macules and papules on upper extremities, anterior trunk	ANA: 1:320, speckled, Anti-Ro(SSA): >8.0, Anti-La(SSB): 0.4	HE: Prominent interface dermatitis with lichenoid infiltrate and clefting. Prominent superficial to deep dermal perivascular and peri-adnexal lymphocytic infiltrate and increased dermal mucin deposition. DIF: negative	Topical CS Antihistamine Photoprotection	PR	Not interrupted by SCLE

(6) 55/M/W	Esophageal	Pembrolizumab/20	Metoprolol[#] Omeprazole[#]	Annular macules and papules on posterior trunk	N/P	HE: Lichenoid interface dermatitis with eosinophils DIF: N/P	Topical CS	NR	Not interrupted by SCLE
(7) 69/M/W	Lung, squamous cell	Atezolizumab/4	Metoprolol[#] Olanzapine[¶]	Photo distributed annular macules and papules on upper extremities, trunk	ANA[††]: 1:160, speckled, SS-A(Ro): 91.91, SS-B(La): 1.11	HE: Subacute spongiotic and focal interface dermatitis DIF: N/P	Topical CS HCQ	PR	Discontinued 3 mo prior to SCLE
(8) 61/F/W	NSCLC	Pembrolizumab/8	Omeprazole[#]	Photo distributed annular scaly macules and papules on trunk, upper extremities	ANA: 1:1280, speckled, Anti-Ro(SSA): 143.9, Anti-La(SSB): 26.1, Smith antibodies: 4.12, Anti-dsDNA: 1:10	HE: Interface dermatitis with follicular involvement, thickening of the epidermal basement membrane, dermal mucin deposition and superficial perivascular lymphocytic infiltrate with pigment incontinence. DIF: N/P	Topical CS Photoprotection	PR	Discontinued 5 mo prior to SCLE
One case of immunotherapy-associated SLE									
(9) 69/M/W[‡‡]	Melanoma	Ipilimumab, nivolumab/0.75	—	Photo distributed erythematous macules and papules on face, neck, trunk, groin, oral ulcers, myalgias, photo-sensitivity	ANA: 1:160, diffuse pattern, anti-dsDNA: 2, SS-A(Ro): 1, SS-B(La): 0, Sm Ab: 2, RNP Ab: 0, Platelets: 91	HE: Interface dermatitis and interface folliculitis, vacuolar type with perivascular chronic inflammation. DIF: N/P	Topical CS Photoprotection	NR	Not interrupted by SLE

Continued

Table I. Cont'd

Age/sex/race*	Cancer type†	ICI/onset, mos	Concomitant drugs reported to cause SCLE	Clinical features	Autoantibody testing/ laboratory findings	Histopathology/DIF/ radiologic studies‡	Treatment(s)	Response	Impact on ICI
One case of immunotherapy-associated EF									
(10) 59/M/W§§	NEC	Nivolumab/26	—	Woody indurated plaques and restricted motion of upper and left lower extremity	Eosinophils: 0.12 K/uL, SPEP: negative	HE: *Skin*: Diffuse dermal and subcutaneous sclerosis *Fascia*: Prominent fascial sclerosis DIF: N/P MRI (forearm): Mild intrafascial and intrafasicular enhancement	Topical CS N-UV, physical therapy	PR	Not interrupted by EF
One case of immunotherapy-associated dermatomyositis									
(11) 53/F/W¶¶	Melanoma	Ipilimumab/15	—	Photosensitivity, abnormal nail fold capillaries, symmetric proximal muscle weakness, Gottron papules, heliotrope eruption, periungual erythema	ANA: 1:650, speckled, Anti-Ro(SSA): 2.0, Anti-La(SSB): 1.0, CRP: 28.6, ESR: 48, Aldolase: 10.4, CPK: 1854, Jo-1: negative, myositis panel: N/P	HE: N/P Muscle biopsy: Skeletal muscle with type II fiber atrophy; no evidence of inflammatory MRI: Mild short TI inversion recovery hyperintensity of the bilateral vastus lateralis and rectus femoris muscles	Topical CS Topical tacrolimus Systemic CS HCQ	PR	Discontinued for dermatomyositis

ANA, Antinuclear antibodies; *CR*, complete response; *CRP*, C-reactive protein; *DEJ*, dermoepidermal junction; *DIF*, direct immunofluorescence; *DI-SCLE*, drug-induced subacute lupus erythematosus; *ESR*, erythrocyte sedimentation rate; *HCQ*, hydroxychloroquine; *HE*, hematoxylin and eosin; *ICI*, immune checkpoint inhibitor; *irAE*, immune-related adverse event; *IV*, stage 4 cancer; *MRI*, magnetic resonance imaging; *NEC*, neuroendocrine carcinoma; *NSCLC*, non−small-cell lung carcinoma; *N-UV*, natural ultraviolet light; *NR*, not reported; *NP*, not performed; *PR*, partial response; *RT*, radiation therapy; *systemic CS*, systemic corticosteroids; *topical CS*, topical corticosteroids.

*Age at initial ICI therapy. All patients identified as non-Hispanic or Latino ethnicity.

†All patients had stage IV malignancies.

‡Histology slides for patients 1-6 are presented in Mendeley supplemental Fig 2.

§Patients 1-5 were recently accepted for publication as a case series, currently in press.[1]

¶Concomitant drugs that were started <3 months before SCLE onset; however, ciprofloxacin and nitrofurantoin (case 1) and olanzapine (case 7) were immediately discontinued because of SCLE with persistence of SCLE more than a month later. Hence, ICI was felt to be the offending agent.

#Concomitant drugs that were longstanding and were started >12 months prior to SCLE onset.

**Reference ranges were as follows for the following autoimmune serologies: ANA, <1:140; Anti-Ro(SSA), <0.2, Anti-Ro(SSB), <0.2, eosinophils, 0.00-0.52 K/uL.

††Of 10 patients with autoimmune serologies, only patient 7 was previously tested for ANA for unrelated reason and was found to have negative ANA previously (1:40).

‡‡Patient 9 fulfilled the 1997 ACR criteria (positive ANA, photosensitivity, oral ulcers, malar rash, and thrombocytopenia) and the 2012 SLICC criteria (acute cutaneous lupus, oral ulcer, thrombocytopenia, positive ANA) for the diagnosis of SLE.

§§Patient 10's case was previously published as a case report.[2]

¶¶Patient 11's case was previously published as a case report (DOI: 10.1001/jamadermatol.2014.2233).

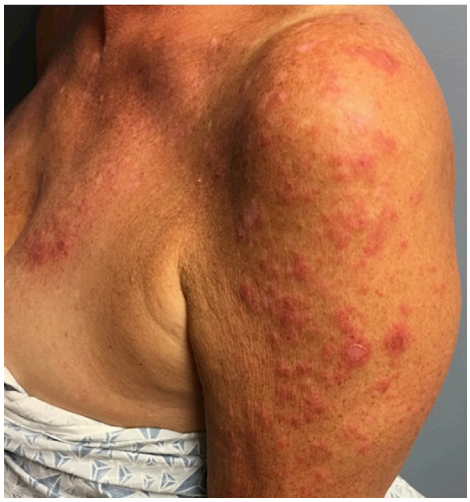

Fig 1. Immunotherapy-associated subacute cutaneous lupus erythematosus. Clinical presentation of patient in case 1. Annular, photo-distributed macules and papules on upper extremities and trunk.

exposure (all presented in summer months), and/or direct stimulation of B-cell–mediated humoral immunity causing autoantibody development against cutaneous antigenic targets.[1] Our incidence rate for immunotherapy-associated SCLE is approximately 0.04%, which is greater than expected than rates reported in the general population (estimated incidence rate of 0.009% for drug-induced lupus).[4] SLE may be more challenging to diagnose, as it presents with broad clinical and laboratory findings; other systemic rheumatologic irAEs may present earlier or later requiring a persistent index of suspicion. Immunotherapy-associated EF and dermatomyositis have been previously reported.[1,2] Furthermore, these idiopathic disorders tend to occur more in women than men with rates ranging from 2:1 to 9:1[5]; interestingly, we observed similar rates of immunotherapy-associated cutaneous CTD among women (5 of 1938, 0.26%) and men (6 of 2549, 0.24%) among our cohort. As we would have expected higher rates of cutaneous CTD among women compared with men, this relationship may warrant further investigation.[5] Some patients may have escaped detection because of billing variations or systemic steroid use before disease classification. Clinicians must have a high index of suspicion to appropriately diagnose these disorders to prevent immunotherapy interruption.

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A randomized, vehicle-controlled clinical trial of a synthetic TRPM8 agonist (Cryosim-1) gel for itch

To the Editor: Cooling of the skin and topical menthol are known traditional remedies with antipruritic actions. The effects of physical cooling and of cooling mimetic agents (menthol) on itch are attributed to the activation of an ion channel called transient receptor potential melastatin 8 (TRPM8).[1] Peripheral afferents expressing TRPM8 presumably inhibit, at the spinal level, the nociceptive afferents that are conducing pain and also itch information.[2]