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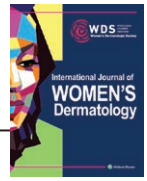

Association of lichen sclerosus and morphea with immune checkpoint therapy: a systematic review

Keywords: adverse events, immune checkpoint, lichen sclerosus, morphea, systematic review

Dear Editors,

The use of immune checkpoint inhibitors (ICIs) has been associated with various cutaneous immune-related adverse events (irAEs), including eczematous, psoriasiform, lichenoid, and bullous dermatoses.[1,2] Here, we evaluated reports of lichen sclerosus (LS) and morphea associated with ICIs.

A literature search was conducted October 7, 2022 of PubMed, Cochrane, Embase, CINAHL, and Web of Science. Search terms: "lichen sclerosus," "scleroderma, localized," "morphea," "immune checkpoint inhibitor," "immunotherapy," "ipilimumab," "nivolumab," "pembrolizumab," "atezolizumab," avelumab," "durvalumab," "cemiplimab," "dostarlimab," and "relatlimab," yielding 318 studies. Titles, abstracts, and full-text manuscripts were screened for relevance. Twenty-three studies were included (Fig. 1).

Twelve studies reported LS (case reports/series = 10 retrospective study = 2). Ten reported morphea (case reports/series = 9 and retrospective study = 1). One case reported new onset LS with relapse of morphea on the breasts after ICI initiation. In total, there were 29 patients with LS and morphea (LS = 17, morphea = 11, and LS/morphea = 1) (Table 1). There were no reports of linear morphea. Of studies reporting sex and age, there were 5 males and 8 females with LS age 39–78 years, and 2 males and 8 females with morphea age 31–74. Ethnicity was not reported in most studies. Of studies that specified LS location, there were 9 genital and 4 extragenital cases. ICIs implicated in both LS and morphea were nivolumab (n = 14), pembrolizumab (n = 9), ipilimumab (n = 5), and one instance of atezolizumab-associated LS.

Time to presentation ranged from 3 weeks following ICI initiation to 2 years after discontinuation. Histological assessment was performed in 18 (75%) cases. Other irAEs included hypothyroidism, vitiligo, eosinophilic fasciitis, colitis, and autoimmune hepatitis. LS was treated with topical steroids (12/17) and tacrolimus (2/17), while morphea was most frequently treated with a combination of topical (4/11) and/or systemic steroids (5/11). Other successful therapies included narrowband ultraviolet b phototherapy (NB-UVB) in LS, and calcipotriol, physiotherapy, infliximab, hydroxychloroquine, and methotrexate for morphea. All reported improvement in cutaneous manifestations with treatment.

Due to limited reports and study design, we cannot determine incidence of LS or morphea on ICIs. It is possible that LS/morphea development after ICIs is coincidental. However, given that other autoimmune skin conditions are increased in patients on ICIs, it is possible that LS and morphea may also be associate. Anti-PD1/PDL1 or CTLA-4-induced T-cell activation may trigger an autoimmune response against keratinocytes and/or fibroblasts, potentially inducing LS or morphea.

Most ICI-treated patients who developed LS or morphea were female, which is consistent with both conditions being more common in women. Overall, patients who developed LS/morphea after ICIs were younger than the classically reported age demographic. Most LS cases presented on genitalia. Since the true incidence of LS in the population is unknown and likely underdiagnosed, we suspect that patients on immunotherapy, may also have underreported genital LS. While topical and/or systemic steroids have primarily been utilized in treating these conditions with success, future studies should focus on assessing treatment outcomes.[3] Increased understanding of LS and morphea association with use of ICIs, including time of onset, distribution, and treatment response, is necessary to establish individualized treatment modalities for patients on immunotherapy who develop these conditions.

Conflicts of interest

None.

What is known about this subject with respect to women and their families?

- Immune checkpoint inhibitors (ICIs) have become one of the most widely prescribed anticancer treatments in the past decade and are associated with a number of cutaneous immune-related adverse events (irAEs).
- Lichen sclerosus (LS) and morphea are more commonly seen in women, and LS in particular is underdiagnosed and has not been examined in the ICI population.

What is new in this article with respect to women and their families?

- There have been reports of LS and morphea associated with ICIs.
- Presentation ranged from weeks after ICI initiation to years after cessation.
- Most cases of LS were on the genitalia.
- Given that a genital examination may not be included in a full body skin examination and patients may not feel comfortable disclosing symptoms or findings in this area, clinicians screening patients for irAEs should consider including genital examinations or asking about genital symptoms.

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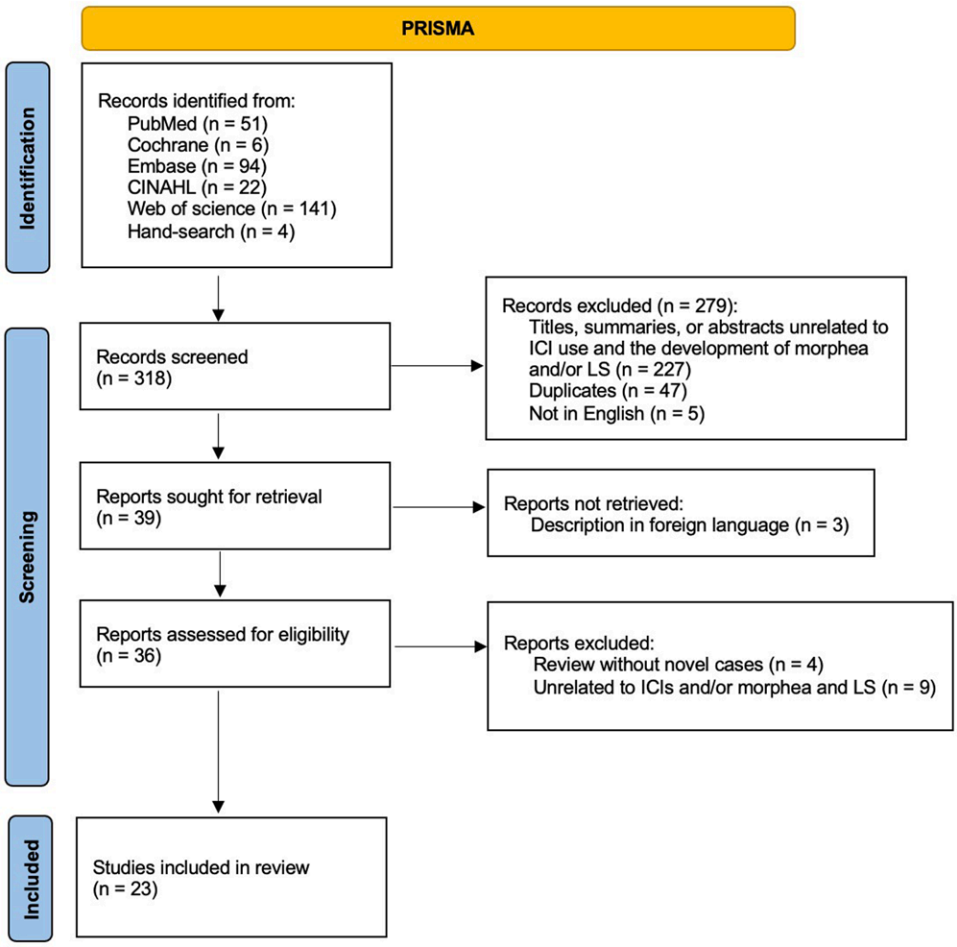

Fig. 1. PRISM flow diagram of the systematic review for lichen sclerosus and morphea development with immune checkpoint inhibitors.

Table 1

Case summaries for LS and/or morphea associated with ICI therapy

irAE	ICI	W to irAE	Age (y); Sex (M, F)	Treatment	Additional irAEs	Location	Malignancy	Diagnostic method	Cancer outcome	PubMed ID
LS	Nivolumab 3 mg/kg q2wa (n = 6)	8–92	48–78; 1 M, 5 F	Clobetasol, prednisone, and/or narrow band UVB	EF (n = 1); melanoma-associated leukoderma vitiliginous reaction (n = 1)	Genital (n = 3); Extragenital (n = 3)	Metastatic melanoma (n = 5); Lung (n = 1)	Clinical (n = 1); biopsy (n = 5)	No progression (n = 1); median progression-free and overall survival were 17 m and 33.5 m, respectively (n = 1)	**31498907,** 33342187, 31205068, 30430637, 34705086
	Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg q3w × 12w, then Nivolumab q2wa (n = 2)	16; 72–88	63, 39; 1 M, 1 F	Mometasone; clobetasol + tacrolimus ointment	EF; not reported	Genital; extragenital	Bladder; metastatic melanoma	Clinical; biopsy	Progression of tumor and death of patient; not reported	29797309, 33117707
	Ipilimumab, unspecified (n = 1)	12	48; 1 M	Clobetasol	Preexisting vitiligo	Genital	Metastatic melanoma	Clinical	Median progression-free and overall survival were 17 and 33.5 m, respectively	34705086
	Pembrolizumab, unspecified (n = 5)	0–104	57–-76; 2 M, 1 F	Topical steroids ± anti-HA, or topical calcineurin inhibitor + cyclosporine	Preexisting psoriasis	Genital (n = 3)	Endometrial (n = 1); lung (n = 2); kidney (n = 1)	Clinical (n = 2); biopsy (n = 1)	Median progression-free and overall survival were 17 and 33.5 m, respectively (n = 2)	34705086
	Atezolizumab, unspecified (n = 1)	52	76; 1 F	DC ICI, clobetasol + hydroxyzine	Not reported	Genital	Non-small cell lung cancer	Biopsy	Not reported	
Morphea	Nivolumab 3 mg/kg q2w or 480 mg q4wa (n = 4)	3–66	37–72; 1 M, 3 F	DC ICI, topical steroids or alternating topical mometasone + calcipotriol	Hypothyroidism and vitiligo (n = 1); EF (n = 1)	Neck, trunk, axillae, inguinal folds	Metastatic melanoma (n = 4)	Clinical (n = 1); biopsy (n = 3)	Stable (n = 1); CR (n = 1)	33355973, 34013609, 34911674, 35325471
	Ipilimumab 3 mg/kg q3wa (n = 1)	12–16	74; 1 F	Prednisone 25 mg taper	Not reported	Abdomen	Metastatic vaginal melanoma	Biopsy	Not reported	34013609
	Ipilimumab, then Pembrolizumab, then Ipilimumab 3 mg/kg + Nivolumab 1 mg/kg × 4 cyclesa (n = 1)	40	61; 1 F	ICI DC 8m prior to morphea, dexamethasone 100 mg × 4 + clobetasol + physiotherapy	Severe colitis (after first 3 cycles of ipilimumab), thyrotoxic crisis	Forearms, breasts, abdomen, legs	Metastatic melanoma	Biopsy	Progressive brain metastases and death 22 m after the development of morphea	33879687
	Pembrolizumab 3 mg/kg q3w or 200 mg q3wa (n = 4)b	15–69	31–74; 1 M, 3 F	DC ICI, prednisone ± hydroxychloroquine, MTX, or infliximab 5 mg/kg q8w	Vitiligo (n = 2); Hypothyroidism (n=1);Autoimmune hepatitis (n = 1)	Neck, trunk, axillae, arms, legs	Metastatic melanoma (n = 4)	Biopsy (n = 4)	CR (n = 3); Lung nodules with prednisone use, which decreased after cessation of prednisone (n = 1)	31202088, 33323722, 29931792
LS + Morphea	Nivolumab 3 mg/kg q2w	8	65, 1 F	DC ICI	Relapse of morphea	Breasts	Lung adenocarcinoma	Biopsy	Not reported	27663405

EF, eosinophilic fasciitis; CR, complete response; DC, discontinued; HA, histamines; ICI, immune checkpoint inhibitor; irAEs, immune-related adverse events; m, months; MTX, methotrexate; LS, lichen sclerosus; w, weeks; y, years.

Studies that did not report a specific ICI were left out. Number of cases may not add up because some studies did not report certain information.

[a] Based on the studies that specified dosage.

[b] One patient was on Ipilimumab 1 y prior to morphea onset and developed hypothyroidism, vitiligo, and colitis while on Ipilimumab. Another patient was also on IDO, an indoleamine 2,3-dioxygenase inhibitor.

[c] Patient on infliximab previously failed steroids, colchicine, and cyclophosphamide.