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Research Article

Prevalence of inverse psoriasis subtype with immune checkpoint inhibitors

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Summary

Background:

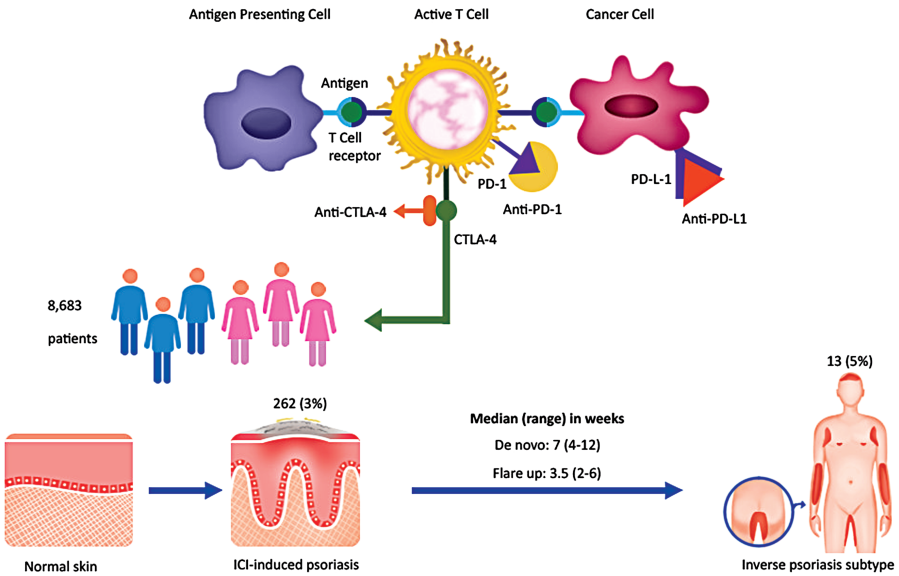
Cutaneous immune-related adverse events (irAEs) are the most common irAEs caused by immune-checkpoint inhibitors (ICI). Psoriasiform eruptions, both *de novo* and flares, may occur. Evidence is lacking on inverse psoriasis subtype.

Methods: A retrospective study was conducted at Dana-Farber Cancer Institute/Mass General Brigham through February 2020 using databases. Confirmed inverse psoriasis cases pre-/post-ICI initiation either independently or in conjunction with other psoriasis subtypes were included. Known psoriasis cases without flare post-ICI were excluded.

Results: A total of 262 (3%) individuals with any ICI-mediated psoriasiform cutaneous irAE were identified out of the 8683 DFCI ICI-treated patients. Of these, 13 (5% of psoriasis patients) had inverse psoriasis (mean age 68.7 years; 7/13 male sex). Median (range) time from ICI initiation to inverse psoriasis development or flare was 7 (4–12) and 3.5 (2–6) weeks, respectively. Pruritus occurred in 12/13 (92.30%) cases. 11 (85%) had inguinal involvement; other sites included gluteal cleft (6; 46%), inframammary (3; 23%), perianal (2; 15%), axilla (2; 15%), umbilicus (2; 15%), and infra-abdominal folds (1; 8%). Most (9/13) individuals had more than one site involved. The Common Terminology Criteria for Adverse Events severity was 1 in 10 (76.92%) individuals and 2 in 3 (15.38%) individuals. Six (46.15%) patients were treated initially by oncology with topical (nystatin, econazole, or clotrimazole) or systemic antifungals (fluconazole) for median (range) of 3.5 (1–7) months without improvement, for presumed candida intertrigo.

Conclusion: Patients on ICI may develop inverse psoriasis, which may be initially confused for fungal intertrigo. Delayed diagnosis can prolong symptoms, while patients are treated ineffectively with topical/systemic antifungals for presumed candida infection. Oncologist and dermatologist awareness is important to improve diagnosis of ICI-mediated inverse psoriasis, its management and affected patients' quality of life.

Graphical Abstract



Keywords: inverse psoriasis, intertriginous psoriasis, flexural psoriasis, immune checkpoint inhibitors, immune-related adverse events, skin toxicity

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Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; CTLA-4, Cytotoxic T-lymphocyte-associated protein-4; DFCI, Dana-Farber Cancer Institute; ICI, Immune-checkpoint inhibitors; irAE, Immune-related adverse events; MGB, Mass General-Brigham; PD1, Programmed cell death-1; PDL1, Programmed cell death ligand-1; SCC, Squamous cell carcinoma.

Introduction

Inverse psoriasis, also known as intertriginous or flexural psoriasis, is a disease phenotype that can present simultaneously with chronic plaque psoriasis (psoriasis vulgaris) or as a separate clinical entity. It may involve any of the body folds, including axilla, inframammary, umbilical, infra-abdominal inguinal folds, or perianal gluteal clefts [1]. The prevalence of inverse psoriasis varies between 3% and 7% among patients with any diagnosis of psoriasis, outside the immune-checkpoint inhibitors (ICI)-treated setting [2]. Estimating the prevalence of inverse psoriasis in studies is difficult due to likely under-reporting, given that it mimics other intertriginous differential diagnoses (i.e. candida intertrigo). Psoriasis as a specific phenotype of cutaneous immune-related adverse event (irAE) is not classified in Common Terminology Criteria for Adverse Events (CTCAE) guidelines through version 5.0, and thus is likely also under-captured in the ICI treatment setting; its variants have not been specifically described [3].

With the recent widely increased use of ICIs among oncology patients and with more data emerging on cutaneous irAEs, evidence remains lacking on ICI-mediated psoriasis, including the quality-of-life-threatening inverse phenotype and the most appropriate therapy regimen in cancer patients. This study aimed to analyze the prevalence of *de novo* and exacerbated inverse psoriasis among ICI-treated individuals and provide guidance on differentiating it from its mimickers, particularly from infectious intertrigo.

Methods

All patients treated with ICIs at the Dana-Farber Cancer Institute through February 28, 2020 were identified through the oncology research database and the Mass General-Brigham (MGB) and Dana-Farber Cancer Institute (DFCI) registries were then identically queried by searching the patient databases using ICD.10 and the following key terms: 'psoriasis', 'palmoplantar pustulosis', 'psoriasiform', 'psoriatic', 'pustulosis palmaris', 'pustulosis plantaris', 'guttate', 'sebopsoriasis', 'inverse plaques', 'inverse patches' and 'programmed cell death-1', 'programmed cell death ligand-1', 'immune checkpoint inhibitor', and 'cytotoxic T-lymphocyte-associated protein-4'. In-depth medical record review was performed by study staff to identify patients with disease onset or flare after ICI and with inverse subtype. Of these confirmed individuals, those with inverse psoriasis, occurring alone or in combination with other psoriasis phenotypes, were included in this study.

Results

A total of 8863 ICI-treated DFCI patients were identified through February 2020; among these patients, an initial 1354 individuals were returned by the search strategy for preliminary psoriasis either before or after the initiation of ICI. After retrospective review, a total of 262 (3%) individuals had confirmed clinical psoriasis of any subtype. Among these, 13 (5%) patients had clinically confirmed inverse psoriasis associated with ICI.

The characteristics of this cohort are summarized in **Table 1**. The median age was 72 years; 7/13 (54%) were male. Roughly one-third of the individuals (4; 31%) had only the inverse psoriasis phenotype while the remaining 9 (69%) had inverse psoriasis with an unspecified non-inverse psoriasiform eruption [4], chronic plaque psoriasis (psoriasis vulgaris) [2], or scalp psoriasis [1]; of these, the latter two subtypes preceded the onset of inverse psoriasis. *De novo* ICI-induced psoriasis occurred in 9 (69%) patients. The median (range) time from ICI initiation to inverse psoriasis development vs. flare of pre-existing disease was 7 (4–12) and 3.5 (2–6) weeks, respectively. Pruritus at the site of psoriatic lesions was reported in 12/13 (92.30%) patients. The most frequent site was inguinal in 11 (84.61%) followed by gluteal cleft in 6 (46.15%), inframammary in 3 (23%), and two individuals (15.38%) each with involvement of the perianal, axilla, and umbilicus; lastly, 1 (7.69%) individual had disease in the infra-abdominal fold (**Fig. 1**). The severity grade based on the CTCAE was 1 in 10 (76.92%) patients and 2 in 3 (15.38%) patients.

Almost half of the patients 6 (46.15%) were treated initially by oncology with antifungal topical [5] or systemic antifungals [1] without improvement for presumed candida intertrigo for median (range) 3.5 months (1–7 months). Antifungal treatment included topical nystatin, topical econazole nitrate 1%, topical clotrimazole 1%, or oral fluconazole. One of the 13 cases was diagnosed by oncology as inverse psoriasis and started on topical steroid; this patient had a known history of chronic plaque psoriasis. The median time (range) from inverse psoriasis onset until dermatology evaluation was 6 weeks (3–30 weeks); the diagnosis was made or considered in all 12 cases at initial dermatology consultation visit for the intertriginous rash. Of these, 5 underwent confirmatory biopsy.

Best response to psoriasis directed treatment was as follows: seven complete remissions, four partial responses with infusion-related flares, one initially worsened on topicals and improved upon transition to the systemic agent (apremilast) achieving a complete remission and treatment was held in one patient for one cycle.

Discussion

Psoriasiform eruptions—either *de novo* or flares of pre-existing disease—have been reported with the use of ICIs and dAEs have been correlated with tumor response [4–8]. In a systematic review of 242 cases of ICI-mediated psoriasis (including five cases with the inverse phenotype), the mean numbers of ICI cycles prior to ICI-induced *de novo* or flare of pre-existing psoriasis were 9.9 cycles and 6.4 cycles, respectively [9]. As ICIs are administered every 3–4 weeks, this study found notably reduced median times to onset of ICI-mediated inverse psoriasis: 7 weeks for *de novo* vs. 3.5 weeks for exacerbation of pre-existing disease.

Inverse psoriasis is often confused with other causes of intertrigo and its diagnosis is particularly challenging when

Table 1. Patients' demographics and characteristics

Age	Gender	Primary malignancy	ICI	ICI class	Body location	Onset New chronic/ chronic flared	Time from ICI initiation to psoriasis onset/ flare (weeks)	Time from psoriasis onset to dermatology evaluation (weeks)	Associated other psoriasis subtypes	Psoriasis treatment
77	F	Breast	Pembrolizumab	PD1	Inguinal, perianal, inframammary, axilla, infra-abdominal folds	New	6	30	None	Topical betamethasone + calcipotriene
65	F	Lung	Atezolizumab	PDL1	Inguinal, inframammary	Chronic flared	4	14	None	Topical betamethasone
72	M	Thyroid	Nivolumab + ipilimumab	PD1+CTLA4	Inguinal, perianal	New	4	6	None	Topical mometasone ointment
78	F	Lung	Nivolumab	PD1	Gluteal cleft, umbilicus	New	2	8	None	Topical mometasone ointment
69	M	Urothelial	Pembrolizumab	PD1	Inguinal	New	4	4	Psoriasiform eruption	Topical triamcinolone + oral acitretin
37	M	Melanoma	Ipilimumab	CTLA4	Inguinal	New	3	5	Psoriasiform eruption	Topical calcipotriene
65	F	Lung	Nivolumab + ipilimumab	PD1+CTLA4	Inguinal, Inframammary, gluteal cleft	Chronic flared	4	6	Chronic plaque psoriasis	Topical tacrolimus+ betamethasone
81	M	Urothelial	Atezolizumab	PDL1	Inguinal, gluteal cleft	New	5	4	Psoriasiform eruption	Topical desonide
51	F	Melanoma	Nivolumab + ipilimumab	PD1+CTLA4	Inguinal, umbilicus, gluteal cleft	New	3	3	Psoriasiform eruption	Topical betamethasone + oral apremilast
77	M	Cutaneous SCC	Nivolumab	PD1	Inguinal	New	4	5	Psoriasiform eruption	Topical triamcinolone
73	F	Esophageal	Pembrolizumab	PD1	Axilla	Chronic	NA	12	Scalp	Topical desonide
67	M	Tongue SCC	Pembrolizumab	PD1	Inguinal, gluteal cleft	Chronic flared	6	3	Chronic plaque psoriasis	Topical triamcinolone+ oral methotrexate
81	M	Lung	Pembrolizumab	PD1	Inguinal, gluteal cleft	New	3	6	Psoriasiform eruption	Topical triamcinolone

CTLA-4, Cytotoxic T-lymphocyte-associated protein-4; ICI, Immune-checkpoint inhibitor; PD1, Programmed cell death-1; PDL1, Programmed cell death ligand-1; SCC, Squamous cell carcinoma.

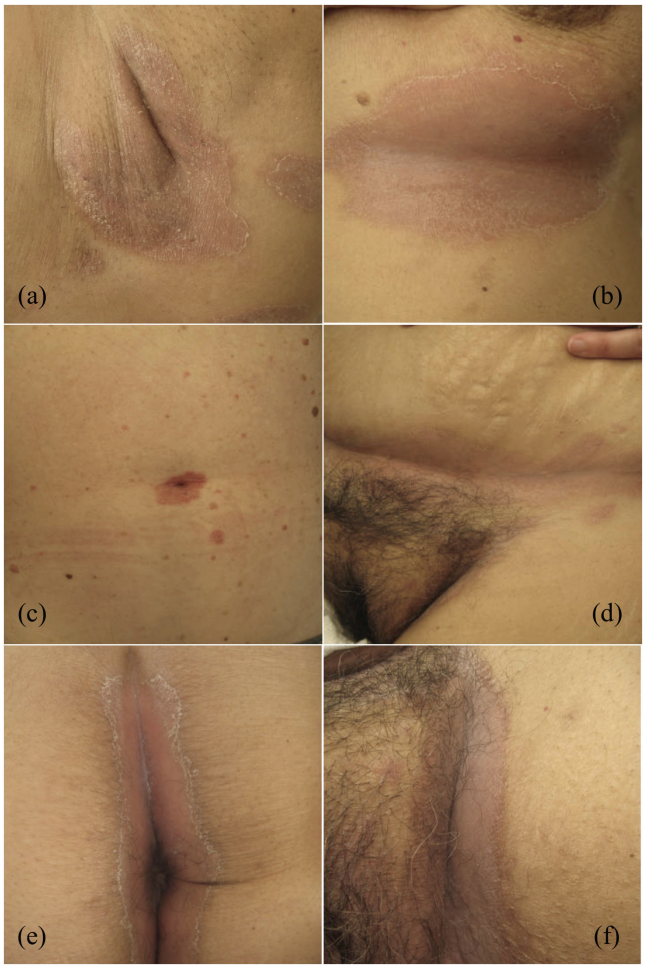

Figure 1. Inverse psoriasis. Well demarcated erythematous plaques involving axilla (a), inframammary (b), umbilicus (c), infra-abdominal folds (d), gluteal cleft and perianal (e), and inguinal (f).

it is the only subtype of psoriasis presenting in the patient. In the literature, case reports reveal that new psoriasiform inverse eruptions that developed after the second cycle of pembrolizumab were initially confused with fungal infection, bacterial cellulitis, or even early-stage necrotizing fasciitis [10]. In our study, almost half of the patients (46%) were treated by oncology with a trial of topical antifungal without improvement before being seen by dermatology; recognition of ICI-mediated inverse psoriasis by oncology could lead to earlier therapeutic intervention, particularly when access to dermatology is limited.

In contrast to inverse psoriasis, fungal intertrigo may be candidal or caused by dermatophytosis. Candida intertrigo typically presents with red macerated patches with satellite papules or pustules. Dermatophytosis (tinea cruris) presents with leading edge of scale and often concomitant involvement of the feet. Inverse psoriasis presents with well demarcated red plaques that may lack the classic thick scaly surface commonly seen in other variants and moist environment of the folds (**Fig. 2**) [11]. It is important to note that superinfection with bacteria or yeast is also possible with inverse psoriasis given the moist nature of the body folds, making the diagnosis challenging [12, 13].

Management is critical, as studies that focus specifically on the impact of inverse psoriasis subtype on patients' quality of life show an average DLQI (dermatology quality of life index) score of 8.5, correlating to moderate effect on patient's quality of life with the majority of patients (93.8%) reporting its largest effect on body self-image [14]. There are no published evidence-based guidelines on the management of ICI-induced psoriasis. However, it is generally considered reasonable to proceed with the classic therapies for managing sporadic inverse psoriasis, taking the patient's malignancy factors, comorbidities, and quality of life into consideration. Topical steroids are the most frequently used treatment for ICI-induced psoriasis, and may be used as a monotherapy in up to half of cases [15].

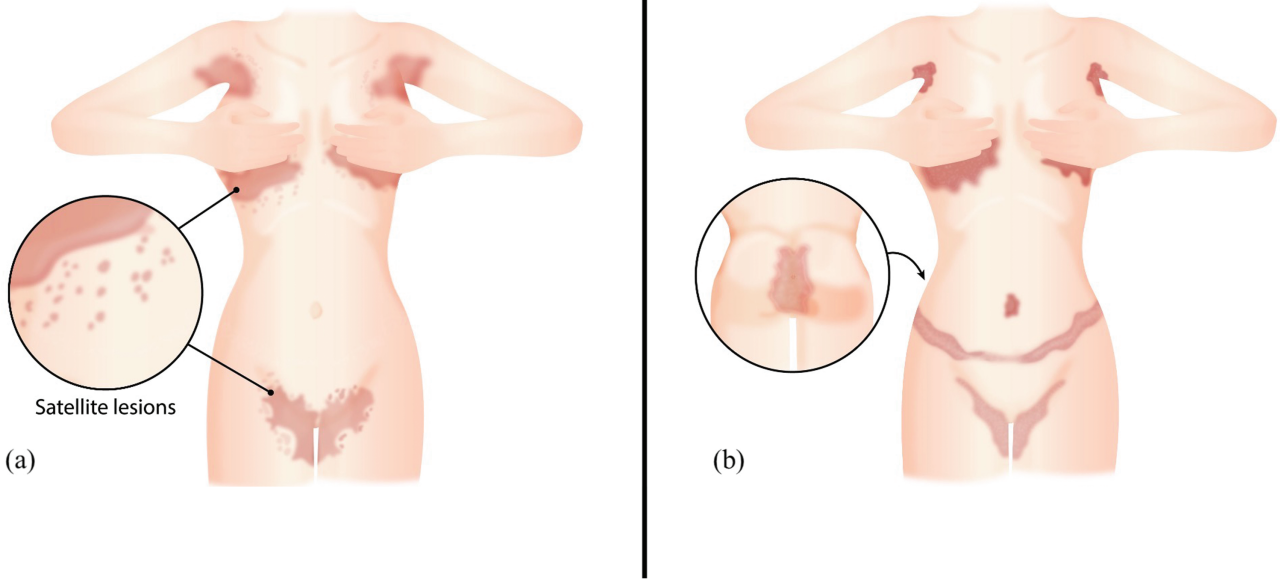

Figure 2. Candida intertrigo (a) demonstrating satellite lesions vs. inverse psoriasis (b) that lacks satellite lesions.

In the intertriginous areas, topical steroids and vitamin D analogs may be sufficient. Topical retinoids are often too irritating for this location. Phototherapy, including the use of excimer laser for localized areas, systemic retinoids, methotrexate, apremilast, and biologic therapies may be considered in the appropriate patients, with attention to exclude therapies associated with increased malignancy risk [16]. In the ENCADO study, the authors reported that 60% of patients were treated solely with topical agents, mainly topical steroids, followed by calcipotriol plus betamethasone and, to a lesser extent, with topical retinoids [16]. Likewise, Cutroneo *et al*. found that 46% of patients were treated with topical agents, mainly steroids or a combination of steroids with vitamin D analogs [17].

The limitations include retrospective nature of analyses and inclusion of cases by keywords. Cases of pre-existing inverse psoriasis would not be captured if not examined and/or documented in the chart and thus, discussion of details of flares is limited.

Conclusion

Inverse psoriasis can present as a phenotype of ICI-induced psoriasiform eruptions, or as a separate entity commonly confused with infectious etiologies such as candida intertrigo or tinea cruris. Careful physical examination and consideration of this diagnosis is imperative to guide management with topical steroids, vitamin D analogues or additional therapies, reserving antimicrobials for superinfection. Initiating appropriate therapy can reduce impact on quality of life and prevent unnecessary cancer treatment interruption.

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Conflict of interest

Dr LeBoeuf is a consultant and has received honoraria from Bayer, Seattle Genetics, Sanofi, Silverback, and Synox Therapeutics, outside the submitted work. Authors Abdulhadi Jfri, Bonnie Leung, Jordan Said, Yevgeniy Semenov have no conflict of interest to declare.

Ethics approval

This study was approved by the Mass General Brigham Institutional Review Board, which waived the informed consent requirement because only deidentified data were used.

Patient consent statement

The patients in this manuscript have given informed consent to publication of their deidentified case details. The authors acknowledge that care has been taken to not include patient-identifying information or images in this manuscript, and that data reporting was consistent with the IRB-approved protocol for deidentified reporting of patient data.

Conflict of interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. N.R.L. is a consultant and has received honoraria from Bayer, Seattle Genetics, Sanofi, Silverback and Synox Therapeutics outside the submitted work.

Data availability

"The data that support the findings of this study are available from the corresponding author, N.R.L., upon reasonable request."

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