Prevalence of inverse psoriasis subtype with immune checkpoint inhibitors

Abdulhadi Jr1,2,3,4,5,6,7,8, Bonnie Leung3,8, Jordan T. Said1,2,3, Yevgeniy Semenov1,8,10 and Nicole R. LeBoeuf1,2,3,*

1Dermatology Department, Harvard Medical School, Boston, MA, USA, 2Department of Dermatology, Brigham and Women’s Hospital, Boston, MA, USA, 3Center for Cutaneous Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, 4Division of Dermatology, King Abdulaziz Medical City, Jeddah, Saudi Arabia, 5College of Medicine, King Saud Bin Abdulaziz University for Health Sciences, Jeddah, Saudi Arabia, 6King Abdullah International Medical Research Center, Jeddah, Saudi Arabia, 7Division of Dermatology, Department of Medicine, Ministry of the National Guard-Health Affairs, Jeddah, Saudi Arabia and 8Department of Dermatology, Massachusetts General Hospital, Boston, MA, USA

*Correspondence: Nicole R. LeBoeuf, Department of Dermatology, Harvard Medical School, Boston, MA, USA. nleboeuf@bwh.harvard.edu.

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

Received: March 25, 2022; Accepted: September 20, 2022
© The Author(s) 2022. Published by Oxford University Press on behalf of the British Society for Immunology. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (https://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com
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, infrabdominal 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 undercaptured 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-B 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 1334 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       | 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 tacrolimus + betamethasone                                               |
| 65  | F      | Lung               | Nivolumab + ipilimumab | PD1+CTLA4       | Inguinal, inframammary, gluteal cleft                                    | Chronic flared | 4                                                          | 6                                                                | Chronic plaque psoriasis           | Topical calcipotriene                                                           |
| 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 desonide                                                                   |
| 77  | M      | Cutaneous SCC      | Nivolumab            | PD1             | Inguinal                                                                      | New         | 4                                                          | 5                                                                | Psoriasiform eruption               | Topical desonide                                                                   |
| 73  | F      | Esophageal         | Pembrolizumab        | PD1             | Axilla                                                                       | Chronic     | NA                                                         | 12                                                                | Psoriasiform eruption               | Topical desonide                                                                   |
| 67  | M      | Tongue SCC         | Pembrolizumab        | PD1             | Inguinal, gluteal cleft                                                    | Chronic flared | 6                                                          | 3                                                                | Chronic plaque psoriasis           | Topical desonide                                                                   |
| 81  | M      | Lung               | Pembrolizumab        | PD1             | Inguinal, gluteal cleft                                                    | New         | 3                                                          | 6                                                                | Psoriasiform eruption               | Topical desonide                                                                   |

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.
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 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).](image)

![Figure 2. Candida intertrigo (a) demonstrating satellite lesions vs. inverse psoriasis (b) that lacks satellite lesions.](image)
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 ENCA DO 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, Cutrono 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, preserving antimicrobials for superinfection. Initiating appropriate therapy can reduce impact on quality of life and prevent unnecessary cancer treatment interruption.

Funding
N.R.L. is supported by NIH/NCI grant U54-CA225088.

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.”

References
1. Omland SH, Gniadecki R. Psoriasis inversa: a separate identity or a variant of psoriasis vulgaris?. Clin Dermatol 2015; 33(4):456–61. https://doi.org/10.1016/j.clindermatol.2015.04.007
2. Wang G, Li C, Gao T et al. Clinical analysis of 48 cases of inverse psoriasis: a hospital-based study. Eur J Dermatol 2005; 15(3):176–8.
3. Van de Kerkhof PCM, Murphy GM, Austedal J et al. Psoriasis of the face and flexures. J Dermatolog Treat 2007; 18(6):351–60. https://doi.org/10.1080/09546630701341949
4. Kato Y, Otsuka A, Miyachi Y et al. Exacerbation of psoriasis vulgaris during nivolumab for oral mucosal melanoma. J Eur Acad Dermatol Venereol 2016; 30(10):e89–91. https://doi.org/10.1111/jdv.13336
5. Matsumura N, Ohtsuka M, Kikuchi N et al. Exacerbation of psoriasis during nivolumab therapy for metastatic melanoma. Acta Derm Venereol 2016; 96(2):259–60. https://doi.org/10.2340/00015555-2212
6. Phillips GS, Wu J, Hellmann MD et al. Treatment outcomes of immune-related cutaneous adverse events. J Clin Oncol 2019; 37(30):2746–58. https://doi.org/10.1200/JCO.18.02141
7. Ohtsuka M, Miura T, Mori T et al. Occurrence of psoriasiform eruption during nivolumab therapy for primary oral mucosal melanoma. JAMA Dermatol 2015; 151(7):797–9. https://doi.org/10.1001/jamadermatol.2015.0249
8. Bonigen J, Raynaud-Donzel C, Hureaux J et al. Anti-PD1-induced psoriasis: a study of 21 patients. J Eur Acad Dermatol Venereol 2017; 31(5):e254–7. https://doi.org/10.1111/jdv.14011
9. Said JT, Elman SA, Perez-Chada LM et al. Treatment of Immune Checkpoint Inhibitors-Mediated Psoriasis: A Systematic Review. J Am Acad Dermatol, 2022; 87(2):399–400. https://doi.org/10.1016/j.jaad.2022.02.030
10. Totonchy MB, Ezaldein HH, Ko CJ et al. Inverse psoriasiform eruption during pembrolizumab therapy for metastatic melanoma. JAMA Dermatol 2016; 152(5):590–2. https://doi.org/10.1001/jamadermatol.2015.5210
11. Janniger CK, Schwartz RA, Szepietowski JC et al. Intertrigo and common secondary skin infections. Am Fam Physician 2005 Sep; 72(5):833–8.
12. Flytnström I, Bergrant IM, Bråed J et al. Microorganisms in intertriginous psoriasis: no evidence of candida. Acta Derm Venereol 2003; 83(2):121–3. https://doi.org/10.1080/00015550310007463
13. Wilmer EN, Hatch RL. Resistant “candidal intertrigo”: could inverse psoriasis be the true culprit?. J Am Board Fam Med 2013; 26(2):211–4. https://doi.org/10.3122/jabfm.2013.02.120210
14. Cohen JM, Halimi K, Joyce CJ et al. Shedding light on the “hidden psoriasis”: a pilot study of inverse psoriasis burden of disease (IPBOD) questionnaire. J Drugs Dermatol. 2016;15(8):1011–6.
15. Balak D, Hajdarbegovic E. Drug-induced psoriasis: clinical perspectives. Psoriasis: Targets and Therapy. 2017; 7:87–94. https://doi.org/10.2147/PTT.S126727
16. Nikolou V, Sibaud V, Fattore D et al. Immune checkpoint-mediated psoriasis: a multicenter European study of 115 patients from the European Network for Cutaneous Adverse Event to Oncologic Drugs (ENCADO) group. J Am Acad Dermatol 2021; 84(5):1310–20. https://doi.org/10.1016/j.jaad.2020.08.137
17. Cutrono P, Ingrasciotta Y, Isgró V et al. Psoriasis and psoriasiform reactions secondary to immune checkpoint inhibitors. Dermatol Ther 2021; 34(2):e14830. https://doi.org/10.1111/dht.14830