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REVIEW

Ustekinumab-associated morphoea: systematic review of the literature and a real-world case

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Abstract

Ustekinumab, an IL-12/IL-23 inhibitor with an established safety profile, has recently been associated with paradoxical cutaneous immune reactions. Amongst these, morphoea developing during therapy represents a rare but mechanistically relevant phenomenon that highlights cytokine imbalance in skin homeostasis. We performed a systematic review of published cases of morphoea occurring in patients treated with ustekinumab to better define their clinical and therapeutic patterns, and coupled it to the description of a new case of morphoea in a patient receiving ustekinumab for Behçet disease. A search of PubMed, Web of Science and SciELO through October 2025 identified six eligible reports. Patients (median age 55.5 years) received ustekinumab for psoriasis, psoriatic arthritis or inflammatory bowel disease. Morphoea developed after 6–64 months of treatment and presented exclusively as plaque-type lesions with one showing overlap with lichen sclerosus. Discontinuation of ustekinumab led to improvement or remission in most patients, whilst continued therapy was associated with progression in one case. The temporal pattern, morphology and response to withdrawal support a drug-related effect, potentially reflecting a shift from a T helper 1 (T_H1)/T_H17 pathway towards profibrotic T_H2 and TGFβ pathways. Interpretation is limited by the very small number of published cases, heterogeneity of clinical descriptions, and lack of standardized diagnostic or therapeutic criteria, restricting firm causal inference. Despite these limitations, awareness of this paradoxical reaction is important for timely recognition and management. Further mechanistic investigation and pharmacovigilance are needed.

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Introduction

Ustekinumab is a fully human monoclonal antibody targeting the p40 subunit shared by IL-12 and IL-23, thereby inhibiting the T helper 1 (T_H1) and T_H17 cytokine pathways central to several chronic immune-mediated disorders.[1] Through this dual blockade, it exerts potent immunomodulatory effects and is approved for the treatment of psoriasis, psoriatic arthritis and inflammatory bowel disease (IBD). Although its safety profile is generally favourable, the expanding use of cytokine-targeted biologics has revealed paradoxical cutaneous immune reactions that highlight the intricate balance of cytokine networks in skin homeostasis.[2] Amongst these, the development of morphoea during biologic therapy represents a rare but increasingly recognized phenomenon.[3]

Morphoea, or localized scleroderma, is an autoimmune fibrosing disorder characterized by excessive dermal and subcutaneous collagen deposition triggered by endothelial injury and sustained by profibrotic cytokines such as IL-4, IL-6 and transforming growth factor-β (TGFβ).[4] Traditionally viewed as a T_H2-polarized condition, morphoea contrasts sharply with the T_H1/T_H17-dominant immune milieu of many diseases treated with ustekinumab. This paradox suggests that inhibition of T_H1/T_H17 signalling may, in predisposed individuals, promote a shift towards T_H2-driven and TGFβ-driven fibrogenesis.[5,6]

Although most reported cases have involved psoriasis, similar events in IBD and other inflammatory disorders indicate that ustekinumab-associated morphoea is a drug-related rather than disease-specific phenomenon.[5,7,8] Here, we describe a new case of morphoea developing during ustekinumab therapy for Behçet disease and review all published reports, integrating clinical, histopathological and therapeutic findings to explore potential immunopathogenic mechanisms underlying this paradoxical fibrotic reaction.

Methods

A systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[9] The search strategy was applied to PubMed, Web of Science and SciELO using the keywords "morphea" and "ustekinumab" (Supplementary Table 1; available at: https://www.drugsincontext.com/wp-content/uploads/2026/01/dic.2025-11-1-Suppl.pdf). The final search was completed on 20 October 2025 with no language or date restrictions. All records were imported into reference management software, and duplicates were removed. Two reviewers independently screened titles and abstracts, and subsequently full texts, for eligibility. Reports describing new-onset morphoea during ustekinumab therapy, regardless of the underlying disease, were included. The reference lists of all included articles were manually screened to identify additional eligible reports. Data were extracted independently by two reviewers using a standardized form; disagreements were resolved by consensus or third-party review. Extracted variables included study type, demographics, indication, regimen, latency, clinical and histopathological findings, management, and outcomes. Given the descriptive and heterogeneous nature of the data, a qualitative synthesis was performed. Results were summarized narratively and tabulated, emphasizing clinical features and treatment outcomes. Risk of bias and reporting quality were assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Reports.[10] The review protocol was not registered.

For the accompanying index case, institutional review board approval was not required, and all clinical information was fully de-identified to prevent any possibility of patient identification; therefore, signed informed consent was not necessary.

Results

Systematic review

Amongst 12 records identified, six fulfilled the inclusion criteria (Figure 1),[5,6,8,11–13] encompassing six patients (median age, 55.5 years), of whom three were women (Table 1). Ustekinumab was prescribed for plaque psoriasis or psoriatic arthritis in four patients, ulcerative colitis in one, and Crohn's disease in another. The latency from treatment initiation to morphoea onset ranged from 6 to 64 months (median, 12 months).

All cases exhibited plaque-type morphoea confirmed by characteristic histopathological findings with one case additionally demonstrating overlapping features of lichen sclerosus. Most patients developed multiple lesions, whilst a single plaque was reported in one case. Treatments included high-potency topical corticosteroids (n=2), phototherapy (n=1), methotrexate (n=1) and cyclosporine after methotrexate failure (n=1). Ustekinumab was discontinued in four cases: two achieved complete remission, one showed recurrence after initial resolution and one lacked outcome data. Continued ustekinumab therapy was associated with progressive lesion enlargement in one patient over 36 months despite topical corticosteroids. Follow-up duration ranged from 2 to 36 months (median, 13.5 months), with variable length across reports, precluding consistent assessment of long-term disease stability or recurrence.

The assessment of risk of bias and reporting quality for all included studies is presented in Supplementary Table 2. Four studies were rated as low risk and two as moderate according to the JBI checklist.

Case report

A 62-year-old woman with a 22-year history of Behçet disease complicated by fistulizing and stenosing intestinal involvement was referred to dermatology for evaluation of new-onset hyperpigmented lesions on the back. Her history included multiple abdominal surgeries and prior systemic therapies, including azathioprine, infliximab and adalimumab, the latter discontinued in July 2024 due to secondary loss of response. She was subsequently transitioned to ustekinumab 90 mg every 4 weeks following the induction phase, in the context of severe intestinal disease with secondary loss of response to prior anti-TNF therapies.

Three months after switching to ustekinumab, she developed two atrophic, hyperpigmented plaques with ill-defined borders and centrifugal growth on the bilateral lumbar region, associated with local discomfort (Figure 2). Incisional biopsy demonstrated thickened dermal collagen bundles and loss of adnexal structures, consistent with circumscribed plaque morphoea.

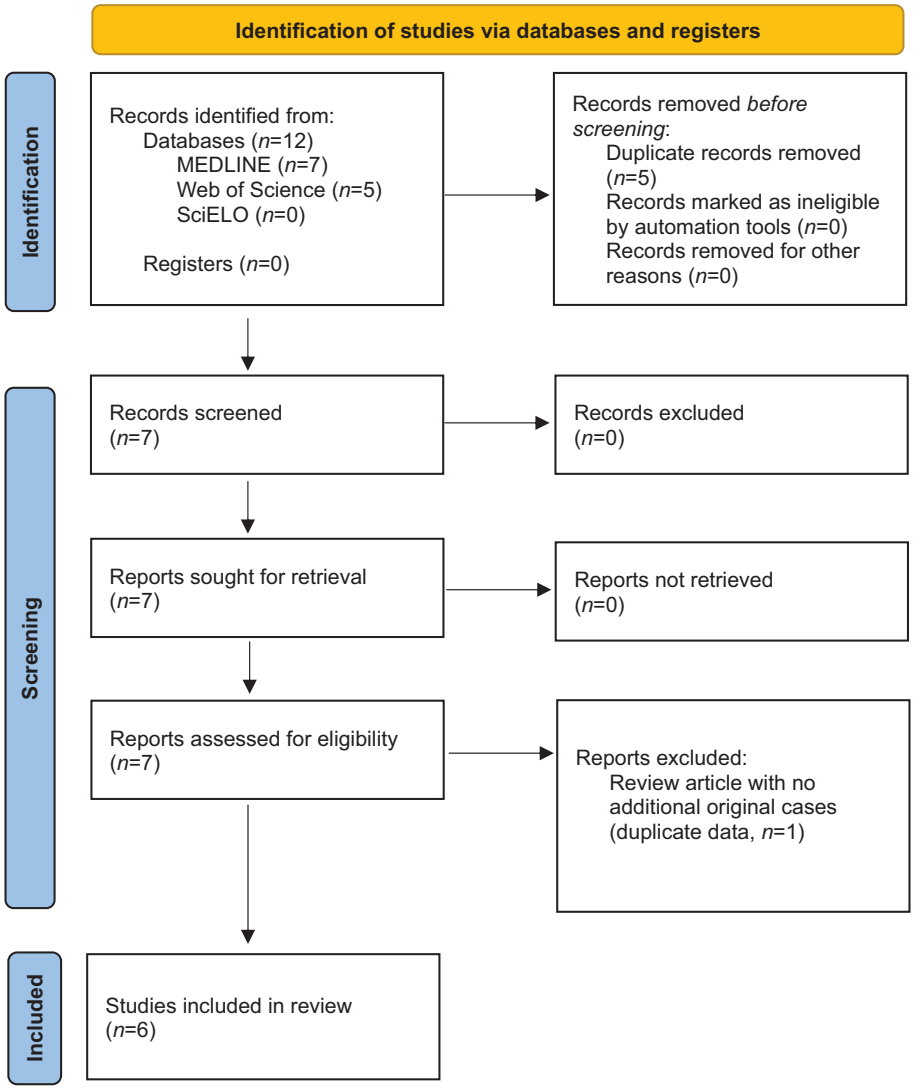
Given the sustained disease control, ustekinumab was maintained and topical clobetasol propionate was initiated. After 3 months, the plaques stabilized with residual

Table 1. Demographic and clinical characteristics of six cases of new-onset morphoea during ustekinumab treatment: literature review.

Case	Ref.	Age/sex	Comorbidities	Previous systemic treatments	UST dose and frequency	Indication for UST	Latency (months)	Morphoea type	Number and location of lesions	Histological confirmation	Treatment for morphoea	Post-diagnosis follow-up (months)	UST discontinued	Morphoea outcome
1	6	64/M	Obesity; urolithiasis; recurrent cellulitis, bilateral inguinal hernia repairs; colonic adenoma	MTX, adalimumab, etanercept, secukinumab and ixekizumab	90 mg every 8 weeks	Plaque psoriasis and PsA	64 (interrupted treatment for 6 months)	Plaque type (with lichen sclerosus)	Multiple, left calf, lower back	Yes	NA	NA	NA	NA
2	11	65/F	NA	Cyclosporine and etanercept	NA	Plaque psoriasis	36	Plaque	Multiple, bilateral lumbar regions	Yes	Topical calcipotriol + clobetasol propionate ointment	NA	Yes	NA
3	12	63/F	NA	Acitretin and phototherapy	NA	Pustular and plaque psoriasis	6	Plaque	Multiple, left and right legs	Yes	Phototherapy, dose and frequency NA	15	Yes	Resolved after UST discontinuation
4	13	44/M	NA	NA	NA	Plaque psoriasis and PsA	11	Plaque and deep	Multiple, forearms, face, back and right shoulder	Yes	–	2	Yes	Resolved after UST discontinuation, but with new lesions years later
5	5	48/F	Presumed psoriasis	Antibiotics, tofacitinib and mesalamine	NA	Ulcerative colitis	12	Plaque	Multiple, back, trunk, bilateral upper and lower aspect of extremities	Yes	MTX, non-modified cyclosporine, 200 mg daily	12	Yes	Progressed under MTX and UST; resolved after treatment with cyclosporine and UST discontinuation
6	8	18/M	–	Adalimumab	NA	Crohn's disease	12	Plaque	Single, left axilla	Yes	Topical steroid ointments	36	No	Lesion expansion

Deep morphoea refers to inflammation and sclerosis that affects primarily the deep dermis and subcutaneous fat and may involve underlying structures (e.g. the fascia). F, female; M, male; MTX, methotrexate; NA, not available; PsA, psoriatic arthritis; UST, ustekinumab.

Figure 1. PRISMA 2020 flow diagram illustrating the identification, screening and inclusion of studies in the systematic review.



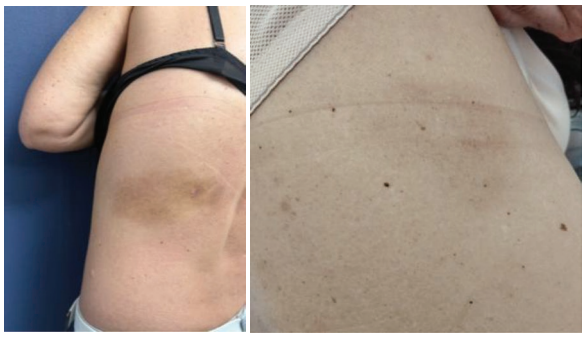
post-inflammatory hyperpigmentation, and after 6 months of follow-up, no increase in lesion number was observed.

Discussion

Ustekinumab, a fully human monoclonal antibody targeting the p40 subunit shared by IL-12 and IL-23, modulates T_H1 and T_H17 pathways central to the pathogenesis of psoriasis, psoriatic arthritis and inflammatory bowel disease.[1] Although its safety profile is generally favourable, a growing number of paradoxical or immune-mediated cutaneous reactions have been documented, including alopecia areata, linear IgA bullous dermatosis, and eczematous or lymphomatoid eruptions.[2] The occurrence of morphoea under ustekinumab therapy remains exceptional yet mechanistically significant, reflecting the complexity of cytokine cross-regulation within the skin.

Morphoea pathogenesis involves an imbalance between collagen synthesis and degradation, typically triggered by vascular injury. Endothelial activation induces the expression of adhesion molecules and facilitates the recruitment of profibrotic cytokines such as IL-4, IL-6 and transforming growth factor-β (TGFβ) into the affected dermis.[4] This cytokine milieu drives fibroblast activation, increased collagen deposition and reduced extracellular matrix turnover, culminating in localized dermal fibrosis. Although fibrotic remodelling is classically T_H2-dominant, emerging evidence implicates T_H17-related cytokines (IL-17, IL-23, IL-21), suggesting convergence of both pathways on common profibrotic circuits.[14–16]

Figure 2. Two atrophic, hyperpigmented plaques with ill-defined borders and centrifugal growth on the bilateral lumbar region, appearing 3 months after initiation of ustekinumab.



Ustekinumab's suppression of T_H1 and T_H17 activity underlies its therapeutic benefit but may simultaneously disrupt cytokine balance, promoting fibrosis in predisposed individuals. Inhibition of T_H1/T_H17 signalling can diminish restraint on T_H2 responses, creating relative T_H2 predominance and subsequent fibroblast activation.[5,6] The resulting overproduction and deposition of collagen, together with inhibition of matrix degradation, reproduce the histopathological features of morphoea. This mechanistic disequilibrium offers a biologically coherent explanation for localized scleroderma under ustekinumab therapy. The recurrence of a similar phenotype across different diseases, including psoriasis, IBD and Behçet disease further supports a drug-related rather than disease-specific process.

Notably, though the immunological effects of ustekinumab are systemic, the fibrotic manifestations observed across reported cases have remained confined to the skin. The absence of systemic involvement suggests a preferential effect on cutaneous rather than systemic fibrotic pathways, potentially mediated by localized fibroblast–immune interactions within the skin microenvironment, particularly at sites of prior inflammation or vascular injury. The wide latency range (6–64 months) may reflect heterogeneity in baseline susceptibility, cumulative exposure effects and, importantly, variable timing of clinical recognition. In some patients, morphoea can begin subtly and remain clinically unapparent for prolonged periods, raising the possibility that lesions were preclinical or minimally symptomatic before detection. Alternatively, delayed onset may be compatible with gradual immune network remodelling under sustained p40 blockade rather than an immediate paradoxical shift.

Findings from other fibrosing disorders provide further insight. Elevated levels of IL-17A and IL-23 and increased T_H17 cell numbers have been documented in fibrosing dermatoses, whereas IL-17 inhibition has paradoxically reduced fibrosis in some models.[15–18] These results highlight the context-dependent and bidirectional roles of the T_H17 pathway: in certain settings, T_H17 signalling sustains fibrosis, whilst in others, its suppression may unmask T_H2-mediated fibrogenesis.[19,20] Such reciprocal dynamics mirror the well-recognized paradox of psoriasis induction during tumour necrosis factor (TNF) inhibition, in which blockade of one cytokine axis triggers compensatory activation of another.[21]

Clinically, ustekinumab-associated morphoea generally follows a benign, reversible course when recognized early. Most patients achieve partial or complete improvement, often after drug withdrawal. Management should be individualized according to lesion extent and the need for continued systemic therapy. For localized, non-progressive plaques, continuation of ustekinumab with close dermatological monitoring may be reasonable, as in our case. Conversely, rapidly expanding or generalized lesions warrant discontinuation of the biologic and initiation of established antifibrotic treatments such as phototherapy or systemic immunosuppressants.

Although causality cannot be established from isolated case reports, several observations support a plausible association between ustekinumab exposure and the development of morphoea. Temporality is consistently observed, with lesion onset occurring after treatment initiation in all reported cases, and consistency is suggested by a recurrent clinicopathological pattern — predominantly plaque-type disease with histological confirmation — across diverse underlying indications. Partial reversibility following drug discontinuation further supports a drug-related effect, whereas continued exposure was associated with progression in at least one case. At the same time, coincidental coexistence, confounding by indication, concomitant therapies and alternative mechanisms, including Wolf's isotopic response, cannot be fully excluded.

Beyond clinical relevance, this phenomenon underscores the intricate redundancy of cutaneous cytokine networks. The IL-12/IL-23–T_H17 axis interacts closely with T_H1 and T_H2 pathways; inhibition of a central node may shift immune homeostasis towards a profibrotic state, particularly in individuals with latent endothelial dysfunction or genetic susceptibility. Whether this effect extends to selective IL-23 p19 inhibitors remains uncertain. To the best of our knowledge, morphoea has not been reported in association with selective IL-23 p19 inhibitors, raising the possibility that dual IL-12/IL-23 (p40) blockade confers a distinct immunological risk profile. Preservation

of IL-12 signalling under selective IL-23 inhibition may maintain T_H1 counter-regulatory pathways and mitigate fibrotic skewing, though this hypothesis remains speculative. Until more robust pharmacovigilance data are available, clinicians should remain vigilant for new indurated or atrophic plaques in patients receiving IL-12/IL-23-targeted therapies.

Current evidence is limited to isolated case reports, with heterogeneity in diagnostic criteria, concomitant treatments and follow-up duration, and without formal causality assessment. These limitations introduce potential confounding and publication bias. Nonetheless, the recurrence of a consistent clinicopathological pattern — plaque-type morphoea arising after variable latency and often resolving upon drug withdrawal — supports a plausible pharmacological mechanism. Prospective studies incorporating immunophenotyping, cytokine profiling and endothelial biomarkers are warranted to clarify susceptibility factors and elucidate the immunological pathways underlying this paradoxical fibrosing reaction.

Conclusions

Morphoea arising during ustekinumab therapy is a rare, yet reproducible adverse event reported across diverse immune-mediated diseases, including psoriasis, inflammatory bowel disease and Behçet disease. It most often presents as plaque-type lesions after months to years of treatment and generally stabilizes or resolves following drug withdrawal, although localized cases may improve with topical treatment or phototherapy whilst therapy is continued. A pharmacologically driven shift from T_H1/T_H17 to T_H2/TGFβ signalling likely underlies this paradoxical fibrotic reaction. Early recognition, individualized management and systematic reporting are essential to identify predisposing factors and determine whether selective IL-23 inhibitors pose a comparable risk.

Supplementary Material available at: https://www.drugsincontext.com/wp-content/uploads/2026/01/dic.2025-11-1-Suppl.pdf

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