

Case Report

Severe Lichen Planus Pigmentosus Inversus in an Elderly Female Following Intra-Articular Injections of Homeopathic Substances

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Abstract

Lichen planus pigmentosus inversus (LIPPI) is a rare variant within the spectrum of lichenoid dermatoses, characterized by sharply demarcated hyperpigmented lesions predominantly affecting intertriginous areas. Its pathogenesis remains incompletely understood, but immune-mediated mechanisms triggered by exogenous factors have been proposed. We report the case of an 80-year-old Caucasian female who developed extensive, reticulated brownish-grey hyperpigmentation involving multiple flexural sites shortly after the fifth intra-articular injection of the homeopathic combination preparation Zeel comp. N for knee pain. Histopathological examination showed a markedly atrophic epidermis with compact orthokeratosis, focal hypergranulosis, basal vacuolar/interface change, pigment incontinence, and a band-like lymphocytic infiltrate; these findings were compatible with LIPPI. The temporal association with repeated intra-articular administration of botanical and sulfur-containing compounds suggests a possible trigger; however, causality remains speculative. Prick and patch testing with the injection solution were negative, no rechallenge was performed, and pharmacovigilance assessment by the Naranjo algorithm supported only a possible adverse drug reaction. Several constituents, including *Toxicodendron derivatives*, *Arnica montana* and *Solanum dulcamara*, are recognized sensitizers capable of inducing delayed-type immune responses. Importantly, allergic contact sensitization and lichenoid interface dermatitis are distinct processes; in the present case, sensitization or systemic immune stimulation is considered only as a potential upstream trigger of a lichenoid reaction pattern. Similar lichenoid eruptions, including LIPPI, have been reported after systemic immune stimulation such as COVID-19 vaccination or targeted therapies. Differential diagnoses, particularly ashy dermatosis, were considered less likely because of the inverse/flexural distribution and clinico-pathological evidence of lichenoid interface dermatitis with epidermal atrophy. Treatment with systemic corticosteroids, acitretin, and topical tacrolimus improved pruritus, whereas hyperpigmentation persisted. This case highlights a possible temporal association between intra-articular administration of biologically active compounds and LIPPI, while emphasizing the need for cautious interpretation, pharmacovigilance data, and further reports.

Keywords: interface dermatitis; hyperpigmentation; intertriginous; skin folds

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1. Introduction

First described by Pock et al. in 2001 [1], lichen planus pigmentosus inversus (LIPPI) is an uncommon form within the spectrum of lichenoid dermatoses. It differs markedly from both classic lichen planus (LP) and lichen planus actinicus (LPA) in terms of clinical appearance and histopathological features. In contrast to conventional LP, which typically presents as pruritic, erythematous papules predominantly affecting flexural sites and often involving mucous membranes, LIPPI shows a distinct pattern. The condition primarily affects intertriginous regions and is characterized by well-demarcated, oval, hyperpigmented plaques that are usually asymptomatic or only mildly pruritic. Notably, typical features such as papules or Wickham's striae are absent [1–3].

Although earlier case reports suggested a predominance among individuals with lighter skin types, recent findings indicate a broader demographic and phylogenetic distribution. In our systematic review of 105 patients, individuals of Caucasian origin constituted the largest subgroup, supporting previous observations that LIPPI is increasingly recognized worldwide and challenging the notion of a geographically or ethnically restricted entity. Clinical manifestations were heterogeneous. Lesions most frequently involved multiple intertriginous areas, but cases limited exclusively to the axillary or inguinal regions were also observed. The wide age range identified (5 to 84 years; median 58) underscored that LIPPI can occur across nearly all age groups, with a peak incidence in the sixth decade of life. The pathogenesis of LIPPI remains obscure. Increased friction, medications such as COVID-19 vaccines, and systemic immune phenomena, including contact sensitization in selected reports, have been discussed [4–22]. Here we describe a patient with LIPPI developing following intra-articular injections of homeopathic substances.

2. Case Presentation

An 80-year-old Caucasian female presented to our department with a 3-month history of severe pruritus and discoloration of intertriginous skin (Figure 1). She had a history of hypertension, hypothyroidism, iron deficiency anemia, and deep leg vein thrombosis complicated by pulmonary embolism 4 years earlier. She had also undergone right-sided total knee arthroplasty but continued to suffer from arthralgia.

One week before the rash developed, she had received her fifth intra-articular injection of the homeopathic combination preparation Zeel comp. N (2 mL = 2 g). The main components were as follows: *Rhus toxicodendron* dil. D4 (10 mg), *Arnica montana* dil. D4 (2 mg), *Solanum dulcamara* dil. D4 (1 mg), *Sanguinaria canadensis* dil. D4 (1 mg), and sulfur dil. D4 (3 mg). She had no other new medication, preceding infection, or recent vaccination. On clinical examination, there were sharply demarcated, reticulated brownish-grey discolorations on the neck, in the axillary regions, under the breasts, in the abdominal fold, and in the groins (Figure 1). Mucosal lesions were absent.

Histopathological examination revealed a markedly atrophic epidermis with compact orthokeratosis, focal hypergranulosis, basal vacuolar/interface change, pigment incontinence, and a band-like subepidermal inflammatory infiltrate composed of lymphocytes and pigment-laden macrophages (Figure 2). Only focal irregular rete-ridge changes were present; a classic sawtooth-like pattern was not prominent and was not considered a decisive diagnostic feature. Overall, the findings were compatible with LIPPI but not entirely specific. Periodic acid-Schiff (PAS), Giemsa, and iron stains did not demonstrate any specific histopathological findings. Direct immunofluorescence showed no specific deposits.



Figure 1. Clinical images show sharply demarcated, reticulated brownish-grey discoloration in the axillary region (a), under the breasts (b), abdominal fold (c), and groin (d).

A diagnosis of severe disseminated LIPPI was made based on the inverse/flexural distribution, clinical morphology, and compatible histopathology. Prick and patch tests using the injection solution of the homeopathic preparation were negative and therefore did not demonstrate IgE-mediated immediate hypersensitivity, irritant reactivity, or allergic contact sensitization to the tested material. Because of the extensive distribution, intense pruritus, and rapid clinical progression, an individualized short high-dose systemic anti-inflammatory regimen with prednisolone at an initial single dose of 150 mg/day was initiated, followed by rapid tapering (100 mg/day, 75 mg/day, etc.). This dose was used as rescue treatment for a severe disseminated eruption and should not be interpreted as standard LIPPI therapy. In addition, acitretin was started at a daily dose of 30 mg, and topical therapy was administered using tacrolimus 0.1% ointment. Under this treatment, there was a marked improvement of pruritus, whereas the hyperpigmentation showed only minimal fading.

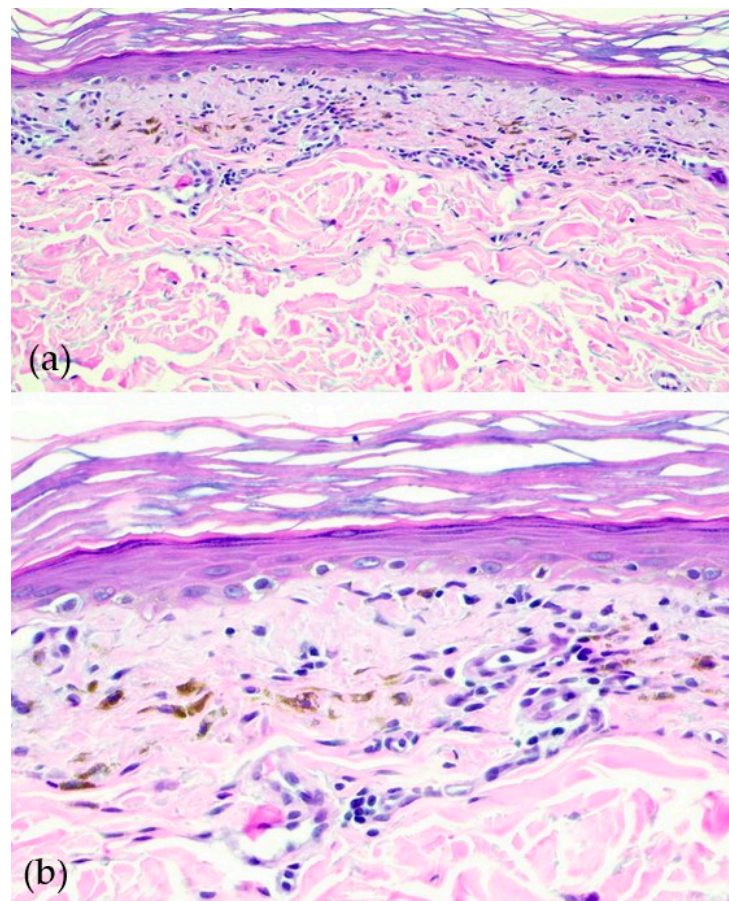


Figure 2. Histopathology showing orthokeratosis and a markedly atrophic epidermis. A band-like subepidermal inflammatory infiltrate composed of lymphocytes and pigment-laden macrophages is present ($\times 200$ (a), $\times 400$ (b)).

3. Discussion

In the present case, the close temporal relationship between the fifth intra-articular Zeel injection into the right knee and onset of disseminated LIPPI 1 week later raises the possibility of a trigger phenomenon. However, causality cannot be established from a single case, and the association remains speculative. To address this limitation, we applied the Naranjo adverse drug reaction probability scale, which yielded a score of 3, corresponding to a possible adverse drug reaction [23]. Points were mainly derived from the temporal sequence and partial improvement after withdrawal of further injections under anti-inflammatory treatment, whereas the absence of rechallenge, negative prick and patch tests, lack of an objective confirmatory causality marker, and the possibility of idiopathic LIPPI precluded a higher causality rating. Similar temporal associations have been described not only for LP, LPP, and LIPPI after COVID-19 vaccination, including Oxford-AstraZeneca and Pfizer-BioNTech vaccines, but also for drug-induced LIPPI under abemaciclib, supporting the concept that exogenous immune stimulation may unmask a lichenoid interface dermatitis in predisposed individuals [11–15,18,19]. Proposed mechanisms include a Th1-skewed cytokine response with increased IL-2, IFN-gamma and TNF-alpha, followed by activation of cytotoxic T cells directed against basal keratinocytes [7,15].

Mechanistically, a systemic allergic-contact reaction and a lichenoid interface dermatitis should be clearly separated. Allergic contact sensitization denotes a delayed-type immune response to a hapten or allergen, whereas LIPPI is a clinicopathological lichenoid interface dermatitis with basal keratinocyte injury and pigment incontinence. In classic LP, contact allergens and drugs can act as triggers, but cytotoxic CD8+ T-cell-mediated

injury at the dermoepidermal junction is the central effector process [7]. Thus, repeated intra-articular exposure to botanical and sulfur-containing compounds is considered only as a possible upstream immune stimulus that may have unmasked a lichenoid reaction pattern in a predisposed patient. Negative prick and patch tests weaken a sensitization hypothesis and argue against demonstrable immediate or epicutaneous contact allergy to the tested preparation. Nevertheless, they cannot fully exclude systemically induced immune mechanisms, because testing with a complex diluted intra-articular formulation may not reproduce metabolism, tissue distribution, cumulative exposure, or the inflammatory context of repeated injections. A comparison with symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) is limited: SDRIFE illustrates that systemic exposures may show a flexural predilection, but it is an acute non-lichenoid drug eruption and should not be regarded as a mechanistic equivalent or differential diagnosis of LIPPI.

The markedly atrophic epidermis in our biopsy is also worth emphasizing. Histopathological overlap exists between LIPPI and other acquired macular hyperpigmentations, particularly ashy dermatosis. Clinically, ashy dermatosis usually presents with grey-blue or ashy macules on the trunk and proximal extremities without a predominant inverse/flexural distribution, whereas LIPPI preferentially affects intertriginous sites as sharply demarcated brown-grey macules or plaques. Histologically, both entities may show basal vacuolar change and dermal melanophages; however, a more lichenoid band-like infiltrate, epidermal atrophy, compact orthokeratosis, and focal hypergranulosis are more supportive of LPP/LIPPI, whereas ashy dermatosis is often less specifically inflammatory [22]. In our case, the inverse distribution, marked epidermal atrophy, pigment incontinence, compact orthokeratosis, focal hypergranulosis, and band-like lymphocytic infiltrate supported LIPPI over ashy dermatosis. We agree that histology is supportive rather than pathognomonic, and the diagnosis rests on clinico-pathological correlation rather than a single feature such as sawtooth-like rete-ridge elongation.

From a pharmacological perspective, Zeel comp. N is used as a complementary anti-arthritic preparation [16]. Nevertheless, the injected mixture is not necessarily dermatologically inert. *Rhus toxicodendron* is a plausible candidate because Toxicodendron species are classic causes of delayed-type hypersensitivity and may even provoke systemic contact dermatitis after systemic exposure in sensitized individuals [4,5]. *Arnica montana*, a member of the Asteraceae/Compositae family, is another well-recognized sensitizer, and *Solanum dulcamara* has likewise been implicated in contact dermatitis in herbal preparations [8,9]. More generally, LP can be triggered by exogenous allergens, and oral lichenoid disease has long been linked to contact sensitization to metals, supporting the concept that allergen exposure may precipitate a lichenoid reaction pattern in selected patients [7]. In addition, *Sanguinaria canadensis* (bloodroot) has immunomodulatory and cytokine-enhancing effects in peripheral blood mononuclear cell models and is known for topical tissue toxicity, although a direct association with lichenoid eruptions has not been established [10]. Importantly, the D4 constituents are diluted but not absent and may still provide an antigenic or immunomodulatory stimulus in susceptible individuals [6,8,16]. In the present patient, however, the negative tests and absence of rechallenge prevent identification of a single constituent as the culprit; these data support biological plausibility only.

With regard to treatment, Chen et al. reported clinical improvement of LIPPI under combination therapy with acitretin and Chinese herbs, with noticeable lightening of hyperpigmentation after 3 months [17]. However, as a combined regimen was used, the individual contribution of the herbal component remains unclear. Moreover, a therapeutic effect of one botanical formulation does not preclude a trigger potential of other injected botanical extracts, as route of administration, composition, dose, and prior sensitization are likely to determine the net immunological effect. In our patient, the high initial cor-

ticosteroid dose reflected the exceptional extent of the eruption and intensity of pruritus and was followed by tapering; it was not intended as routine management for LIPPI. Because systemic corticosteroids, acitretin, and topical tacrolimus were combined, treatment response cannot be used to infer causality. Admittedly, this association remains hypothesis-generating. LIPPI may arise without an identifiable trigger, and patch and prick testing remained negative in our patient. No rechallenge was performed for ethical reasons. The chronology, absence of competing precipitating factors, flexural distribution, and biological plausibility of repeated allergen or immune exposure make the homeopathic injections a reasonable suspect, but not proof of causality [11–15,18–21,23]. A limitation of our report is that extended immunohistochemical profiling of the lichenoid infiltrate was not performed. Although markers such as CD4, CD8, Granzyme B, Perforin, cleaved Caspase-3, p53 and MBP may help to characterize cytotoxic T-cell activity, keratinocyte apoptosis or eosinophil activation, such findings are not specific for LIPPI and are currently not validated for confirming the diagnosis or establishing drug causality in individual cases. Future studies including larger case series may clarify whether reproducible immunophenotypic patterns exist in LIPPI, particularly in suspected drug-associated presentations.

4. Conclusions

In summary, this case documents severe disseminated LIPPI occurring 1 week after the fifth intra-articular Zeel injection. A causal relationship is unproven; the Naranjo score was compatible only with a possible adverse drug reaction, patch and prick testing was negative, and no rechallenge was performed. Thus, this report should be interpreted as a hypothesis-generating pharmacovigilance signal rather than evidence of a definite cause-effect relationship. Nevertheless, the chronology, lack of identified competing triggers, flexural distribution, and known sensitizing or immunomodulatory potential of several botanical constituents support consideration of repeated intra-articular homeopathic injections as a possible trigger. Clinicians should therefore ask about recent complementary intra-articular treatments and other immune stimuli when evaluating abrupt-onset flexural lichenoid hyperpigmentation. Further case reports, registry-based pharmacovigilance data, and mechanistic studies are needed to clarify whether Rhus-containing or other botanical preparations can precipitate LIPPI in predisposed individuals.

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Data Availability Statement: The data that support the findings of this study are included in the present work.

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