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# Photodermatitis following knee intra-articular hylan G-F 20 injection for osteoarthritis: two cases

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## Abstract

Hyaluronic acid (HA) intra-articular injections are increasingly used for the treatment of knee osteoarthritis. Described adverse reactions of HA intra-articular injections include injection site pain or swelling. A 71-year-old man and a 65-year-old woman independently presented with photodistributed lesions shortly after receiving a repeat HA injection (hylan G-F 20) intra-articularly. A punch biopsy was performed which was consistent with a photodrug or hypersensitivity reaction. Two cases are presented to describe a novel presentation of a photosensitivity reaction to HA.

*Keywords: drug eruption, hyaluronic acid, hylan G-F 20, osteoarthritis, phototoxicity, photosensitivity, photodermatitis*

## Introduction

Osteoarthritis (OA), the most common form of arthritis, affects millions of people around the world. There are more than 10 FDA-approved intra-articular hyaluronic acid (HA) products available for the treatment of knee osteoarthritis, a treatment known as visco-supplementation [1]. Hylan G-F 20 differs from other intra-articular HA products owing to its unique chemical structure and higher molecular weight. There are two intra-articular hylan G-F 20 products: one given as a series of three 2ml injections (Synvisc®) and one given as a single 6ml injection (Synvisc-One®).

Drug-induced photosensitivity, including phototoxicity or photoallergic adverse reactions, are common in the elderly population [2]. Drug-induced photosensitivity reactions are most frequently associated with several classes of oral medications, such as nonsteroidal anti-inflammatory, retinoids, antibiotics, anticancer, cardiovascular, and central nervous system drugs (eg, neuroleptics, antidepressants). To our knowledge, there have been no reported systemic photosensitive drug reactions to intra-articular HA products. Herein, we present two patients who developed an identical photo-distributed dermatitis after intra-articular knee injections of hylan G-F 20 for the treatment of knee OA.

## Case Synopsis

A one 71-year-old man with a history of OA and type two diabetes mellitus had multiple three-series 2ml hylan G-F 20 (Synvisc®) intra-articular right knee injections over the course of five years with no adverse reactions. He subsequently was switched to the new single 6ml hylan G-F 20 (Synvisc-One®) injection and immediately developed localized pain and swelling around his knee that resolved after several days. Five months later, the patient received a second injection and developed worsened pain, swelling, erythema, and warmth around his knee compared to his first 6ml hylan G-F 20 injection. The patient received a third injection six months later and developed a similar localized inflammatory reaction in his right knee but with associated chills



**Figure 1.** Cutaneous eruption in Patient One involving the right knee near the intra-articular HA injection site.

that evening. Eight days later, he developed erythematous, pruritic, scaly papules and plaques near his injection site (**Figure 1**) with subsequent involvement of his left leg and bilateral upper extremities. Several weeks later, he presented to the dermatology clinic with photo-distributed erythematous macules and papules with superficial scale and scattered excoriations on the bilateral cheeks and all four extremities; lesions were nearly confluent on the sun-exposed aspects of the arms with significantly less involvement on the medial aspect of the forearms as shown in **Figure 2**. The trunk, genitals, and buttocks were uninvolved.

A 4mm punch biopsy of the left forearm revealed solar elastosis with ortho- and parakeratosis, mild spongiosis, a mixed interstitial lymphohistiocytic infiltrate with neutrophils and eosinophils, superficial and deep perivascular dermatitis, and focal subcorneal neutrophilic pustules consistent

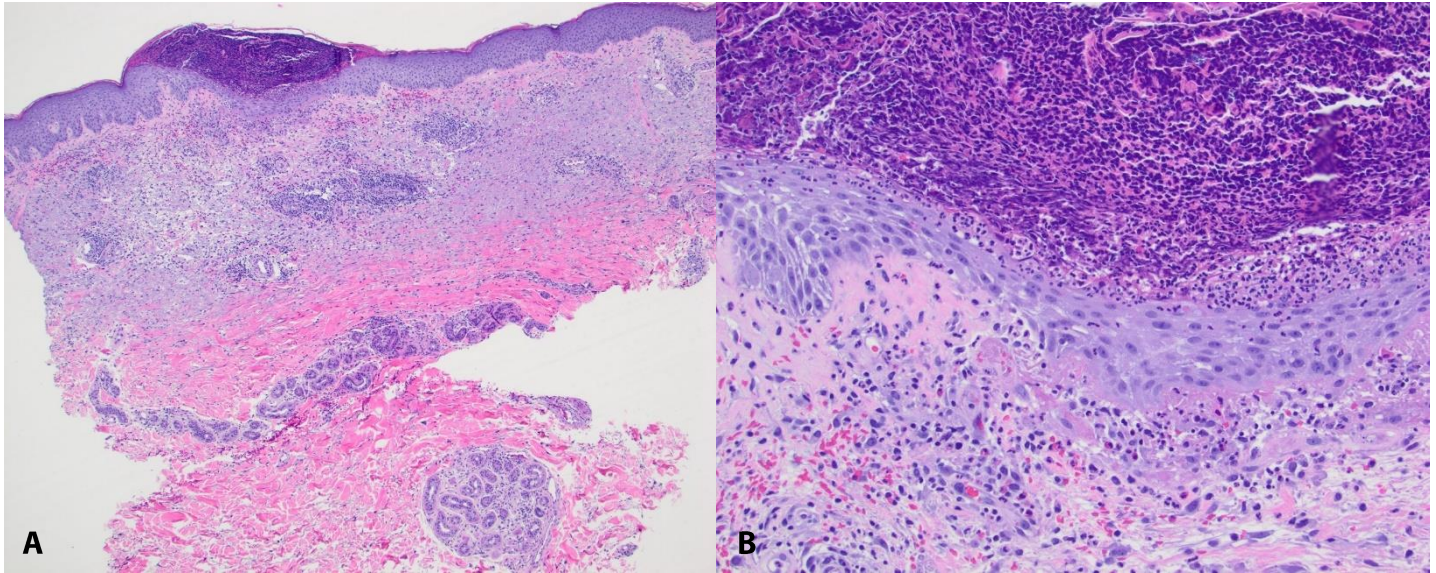
with a photodrug or hypersensitivity reaction (**Figure 3**). A primary infectious process was not observed in examined sections. The patient was prescribed triamcinolone ointment twice daily and oral prednisone (1mg/kg) for 10 days, which resulted in complete resolution of the rash within one week. The patient was taking amlodipine, aspirin, benazepril, famotidine, and hydroxyzine at the time of his presentation and has remained on these same oral medications without any similar skin eruptions for more than one year.

Patient two is a 65-year-old woman with a history of OA who presented to the dermatology clinic for evaluation of an acute cutaneous eruption following an intra-articular knee injection. She reported a history of multiple three-series 2ml hylan G-F 20 (Synvisc®) injections approximately 13 years prior without any adverse reactions. However, she developed a localized inflammatory reaction in her



**Figure 2.** Cutaneous eruption of the bilateral upper extremities in Patient One showing differences in between the lateral and medial aspects of the forearms.





**Figure 3. A)** Representative histology image demonstrating ortho- and parakeratosis, a mixed lymphocytic dermal infiltrate with eosinophils, perivascular and periadnexal dermatitis, and a prominent subcorneal pustule. H&E, 4x. **B)** Epidermal spongiosis with numerous lymphocytes, subcorneal neutrophils, and eosinophils with background solar elastosis and extravasated blood are present. H&E, 20x.

right knee following a single 6ml hylan G-F 20 (Synvisc-One®) injection, followed by the development of photo-distributed erythematous macules and papules with pustules and scale on the face and all four extremities. She was evaluated by her primary care physician prior to being referred to dermatology clinic. At the time of her dermatology presentation, she was using triamcinolone ointment twice daily and was completing a short taper of oral prednisone. She had subtle erythematous, blanching macules and papules with light scale on the sun-exposed areas of her bilateral upper extremities including the dorsal aspect of the hands. A punch biopsy was not performed since the patient was partially treated by her current use of topical triamcinolone and oral prednisone. The patient was taking metformin, levothyroxine, aspirin, atorvastatin, lisinopril, and meloxicam at the time of her presentation and has remained on these same oral medications without any similar skin eruptions for more than one year.

## Discussion

Drug-induced photosensitivity is a reported phenomenon for multiple oral and topical medications; subsequent exposure to ultraviolet

light triggers a photo-distributed skin reaction. The administered medication acts as a chromophore that can absorb photons entering the skin. The energy absorption creates free radicals including reactive oxygen species that create a variety of dermatologic reactions in photo-distributed skin [3]. The two main types of photosensitivity reactions are phototoxicity (an inflammatory reaction similar to sunburn in appearance) or a photoallergy (a type IV hypersensitivity reaction).

Hyaluronic acid has many uses across medical specialties, including cosmetic fillers and eye drops in addition to intra-articular treatment. Of the HA products injected into the intra-articular space, adverse reactions are rare and the most common reactions are injection site pain and swelling which occurs in 7% of patients [4]. Other reported adverse reactions for knee intra-articular hylan G-F 20 specifically are pseudogout, anaphylactoid reactions, and pseudosepsis (severe acute inflammatory reaction syndrome), [5]. Several dermatologic reactions to intra-articular HA have been reported in the literature. One previous study documented a systemic reaction of systemic inflammatory polyarthritis after an intra-articular hylan G-F 20 injection [6]. Chung et al. [7] reported a skin eruption with erythema, vesicles, and bullae on

the left arm and trunk five days after receiving an intra-articular injection on her left shoulder for the first time. Calvo et al. [8] reported a generalized targetoid rash after an intra-articular HA injection with a subsequent intradermal reaction that was diagnosed as erythema multiforme.

An interesting aspect of our case series is the systemic nature of the photosensitive reaction from a localized intra-articular injection. Both patients experienced adverse cutaneous reactions when transitioning from the three-series 2ml hylan G-F 20 (Synvisc®) to the single 6ml hylan G-F 20 (Synvisc-One®) injection. Their presentation was also characterized by a localized skin reaction near the injection site that spread to other UV-exposed areas of the body, like the face and upper extremities. Additionally, the first patient's initial injection site reaction following the single hylan 6ml G-F 20 seemed to worsen with repeat injections, which suggests a possible sensitization effect. This is consistent with the report from Leopold et al. [9] wherein patients who had received previous treatments with the three-series hylan G-F 20 had an increased likelihood of developing an acute local reaction (i.e., pain and swelling within 72 hours after the injection) compared to patients who were hylan G-F 20-naive.

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Limitations of this report include a small sample size and a lack of understanding of the exact mechanism for the photo-distributed skin eruption. Photopatch testing would have also been helpful to further determine the definitive source of the reaction (i.e., HA versus a preservative found in the injection product). However, we were unable to obtain definitive ingredient lists from the manufacturers of these two specific intra-articular HA products. Further studies on the potential photosensitive properties of hylan G-F 20 would be of benefit.

## Conclusion

We present two cases of an intra-articular HA injection leading to a localized inflammatory reaction and subsequent photo-distributed dermatitis. Dermatologists and specialists administering intra-articular HA injections should be aware of the potential local and systemic reactions that may occur in OA patients undergoing viscosupplementation.

## Potential conflicts of interest

The authors declare no conflicts of interest.