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Letter

Lymphangitis occurring after intralesional *Candida* antigen injection for verruca vulgaris

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Abstract

Verruca vulgaris is a common dermatological disease with many treatment options including destructive modalities and more recently, immunotherapy. Intralesional injections of *Candida* antigen have been described as a safe and effective treatment with the most common adverse reactions including local reactions (burning, blistering, peeling), local erythema, and pain at the injection site. We describe the first reported case of lymphangitis after intralesional *Candida* antigen injection for verruca vulgaris in a healthy 18-year-old woman. The lymphangitis rapidly resolved with ibuprofen and cold compresses. Physicians should be aware of this potential adverse reaction when using this treatment modality and should be familiar with appropriate treatment of subsequent lymphangitis.

Introduction

Verruca vulgaris is one of the most common dermatologic disorders, but does not have a definitive cure. Various treatments have been described, including salicylic acid preparations, liquid nitrogen cryotherapy, cantharidin, laser therapy, electrodessication, topical 5-fluorouracil, and intralesional bleomycin, among others. More recently, intralesional injections of *Candida* antigen have been described as a safe and effective treatment [1, 2, 3]. It is thought to work by upregulating the cell-mediated immune response, augmenting the overall clearance of the HPV virus [4]. The most common reported side effects of intralesional *Candida* antigen injection include pruritus, pain immediately and up to 24 hours following injections, local reactions (burning, blistering, peeling), local erythema, and edema [1, 2, 5]. To date, there have been no case reports of lymphangitis occurring after intralesional *Candida* antigen injection. Herein, we report a case of lymphangitis resulting from *Candida* antigen immunotherapy.

Case synopsis

A healthy 18-year-old woman presented to the dermatology clinic for treatment of verruca vulgaris located on the left and right hand. She initially responded well to a liquid nitrogen therapy in combination with intralesional *Candida* antigen injections at two separate visits (1,000 Protein Nitrogen Units [PNU], HollisterStier, Spokane, WA). This therapy was continued, but the *Candida* antigen injection was changed to a new formulation (1:10 weight to volume ratio in a 1:100 dilution, HollisterStier, Spokane, WA). The patient tolerated this new formulation well for the first injection. The patient then had a second intralesional injection with the same formulation approximately one month later with 0.2 cc of *Candida* antigen divided amongst six sites including three warts in the left hand and three warts in the right hand. Approximately 12 hours later, the patient developed streaking and erythema extending from the palm down the forearm of the right hand (Figure 1). At 24 hours after the *Candida* antigen

intralesional injection, the patient developed a more pronounced appearance of the streaky erythema in addition to pain, soreness, and tenderness of the affected area (Figure 2). The patient was instructed to take ibuprofen 600 mg three times a day as needed and place cold compresses to the affected area for 15 minutes every 2 hours. At 36 hours, the patient had improved clinically with resolution of the streaky erythema (Figure 3). The remaining erythema was most attributable to post-procedure erythema from liquid nitrogen cryotherapy. At 48 hours, the patient was started on cephalexin 500 mg twice a day and continued to improve clinically. Given the aforementioned physical exam findings soon after *Candida* antigen injection, the diagnosis of lymphangitis

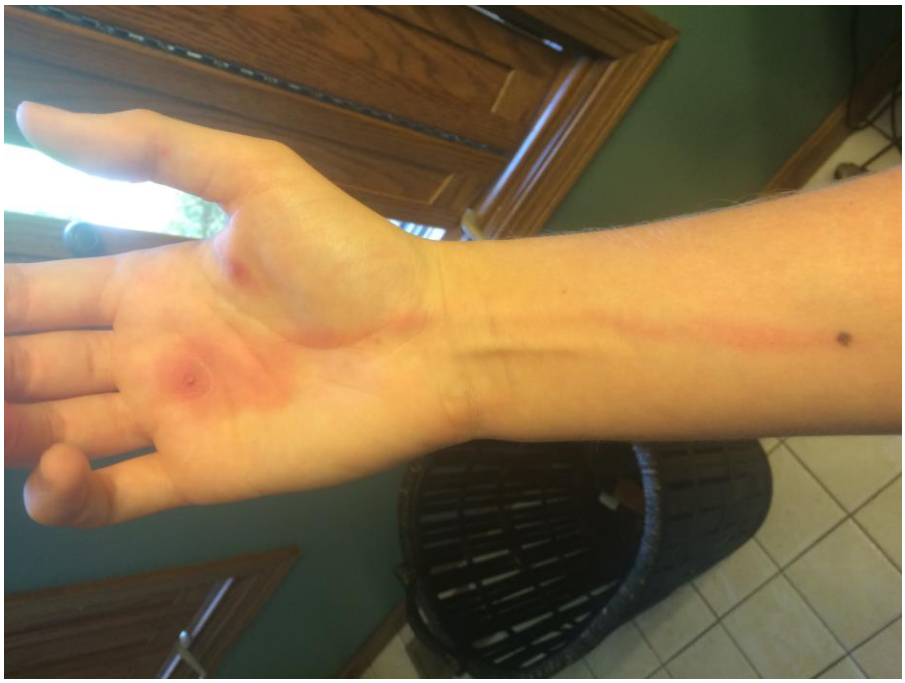

Figure 1. 12 hours after intralesional injection of *Candida* antigen into three warts on the right hand. Note the streaky erythema extending from the palm down the forearm.

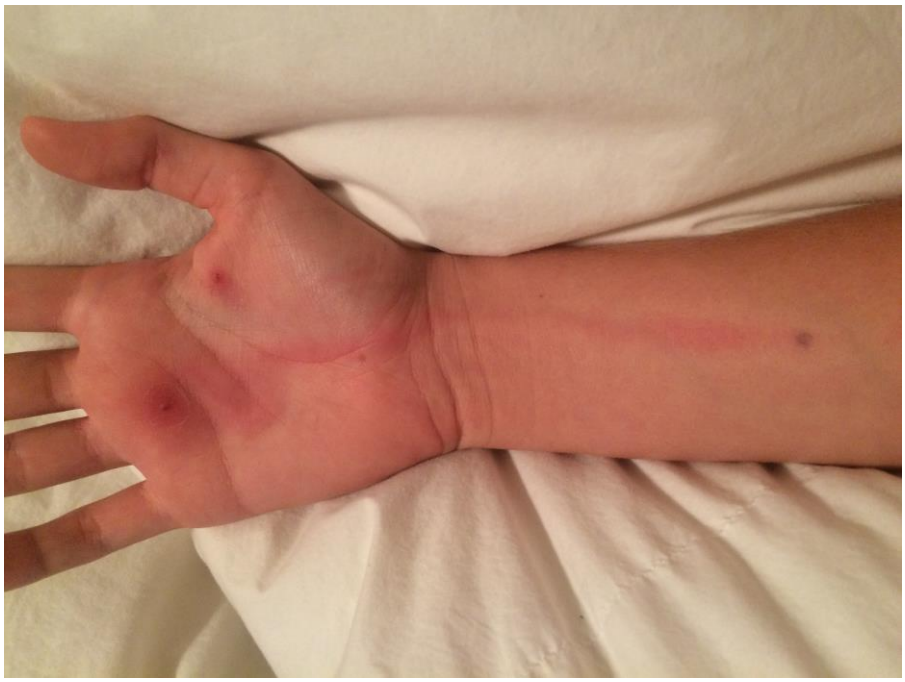

Figure 2. 24 hours after intralesional injection of *Candida* antigen into three warts on the right hand. The streaky erythema extending from the palm down the forearm is now more pronounced.

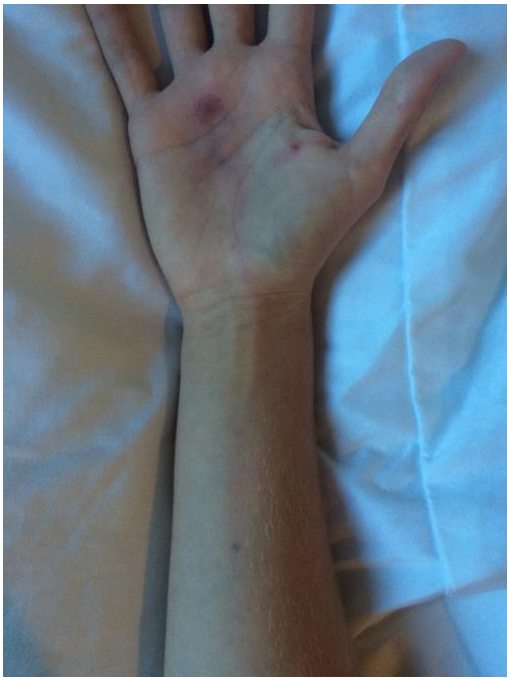

Figure 3. 36 hours after intralesional injection of *Candida* antigen into three warts on the right hand. The streaky erythema has resolved and the remaining erythema is most attributable to post-procedure erythema from liquid nitrogen cryotherapy.

Discussion

Studies on *Candida* antigen immunotherapy for verruca vulgaris have generally described local, self-limited, and minor side effects, with excellent tolerability. The most common side effects of intralesional *Candida* antigen injection include pruritus, pain immediately and up to 24 hours following injections, local reactions (burning, blistering, peeling), local erythema, and edema [1, 2, 5] (Table 1). Nevertheless, there have been reports of *Candida* antigen injection causing edema and vascular compromise with compartment syndrome-type reactions in the distal fingertips as well as vitiligo in a pediatric patient [6, 7].

Table 1. The most commonly reported side effects of intralesional *Candida* antigen injection.

Common Side Effects	Rare Side Effects	Case Reports
Pruritus	Rash	Vitiligo
Pain immediately and up to 24 hours after injection	Numbness	Compartment syndrome-type reactions
Local reactions (burning, blistering, peeling)	Oozing	
Local erythema and edema	Scarring	
	Transient constitutional symptoms (fever, aches)	

Lymphangitis is inflammation of the lymphatic system secondary to infectious or non-infectious causes. Lymphangitis typically occurs following a cutaneous inoculation of microorganisms such as fungi, bacteria, viruses, or parasites. The site of inoculation is usually a distal location and the microorganism then subsequently invades the lymphatic vessels. Symptoms of lymphangitis typically include erythematous tender streaks that travel proximally towards the lymph nodes. The most common causes of lymphangitis include *Streptococcus pyogenes* and *Staphylococcus aureus* in patients with normal immunity and gram negative bacterial infections in those who are immunocompromised [8]. Lymphangitis may be seen in a variety of other clinical infectious settings including *Pasteurella multocida* after animal bites [9], *Erysipelothrix* infections after contact with fish and animals [9], cutaneous anthrax [10], herpes simplex virus in the setting of limb or genital infection [11], rickettsiosis secondary to *R. sibirica mongolotimonae* [12], and African tick bite fever due to *R. africae* [13]. Lymphangitis may also occur in noninfectious settings. There have also been several case reports of lymphangitis after injection of purified protein derivative (PPD) tuberculin for tuberculin skin tests [14] and a case report involving noninfectious superficial lymphangitis after an arthropod bite [15]. There has been one case report of lymphangitis occurring after intralesional injection of bleomycin to multiple plantar warts [16].

The *Candida* antigen that is injected is made from cells of *Candida albicans*. These cells are propagated in a chemically defined medium, subsequently lyophilized, and finally extracted and diluted [17]. The components of the *Candida* antigen are thus unlikely to contain living *Candida albicans*. Exposure of this antigen likely stimulates an inflammatory response associated with lymphocytes and macrophages in a delayed-type hypersensitivity reaction in a previously exposed individual.

Given the acute onset after intralesional Candida antigen injection, it is likely that this patient experienced acute lymphangitis. Acute lymphangitis typically occurs after trauma or abrasion to the skin at a distal site with or without lymphadenitis with accompanying systemic symptoms such as fever. Lymphangitis in this patient was likely secondary to vigorous response of the patient's immune response to the Candida antigen. We hypothesize that the antigen likely traveled through the lymphatic system causing an immune response and subsequent lymphangitis. Interestingly, the patient experienced lymphangitis after the 4th injection of Candida antigen. One explanation for this finding is that the first formulation (the first two injections) was weaker in potency or strength in comparison with the new Candida antigen formulation (the second two injections).

Our case is the first report of lymphangitis following *Candida* antigen injection. Our patient rapidly improved with ibuprofen and cold compresses. At the time of antibiotic initiation, the majority of the lymphangitis had resolved, but treatment was started as a precaution owing to the low risk of infection. Physicians should be made aware of this possible complication when *Candida* antigen is used to treat verruca vulgaris.

Conclusion

Verruca vulgaris is one of the most common dermatologic disorders that can be difficult to treat. Intralesional injections of *Candida* antigen have been described as a safe and effective treatment. We report a previously unknown complication of intralesional *Candida* antigen injection in a patient who developed lymphangitis 12 hours after exposure. The lymphangitis resolved with ibuprofen and cold compresses. Physicians should be aware of this potential complication and the appropriate treatment when using intralesional *Candida* antigen injection for verruca vulgaris.

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