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# Toxic dermatitis secondary to treatment with collagenase *clostridium histolyticum* for Dupuytren´s disease

R. SANJUAN-CERVERO[1], J.E. POQUET-JORNET[2], F.J. CARRERA-HUESO[2]

[1]Department of Orthopedic Surgery and Traumatology, Hospital de Denia, Denia – Alicante, Spain
[2]Department of Pharmacy, Hospital de Denia, Denia – Alicante, Spain

**Abstract. – OBJECTIVE: Secondary effects and drug reactions relative to collagenase *Clostridium histolyticum* treatment for Dupuytren's contracture are frequent. In only a few cases these secondary effects are considered serious. The mechanism that produces these effects of production is not well understood.**

**CLINICAL REPORT: We present the case report of a woman with fifth finger interphalangeal joint treatment with generalized skin rash as a complication of collagenase *Clostridium histolyticum* treatment.**

**DISCUSSION: We discuss treatment, causes and mechanisms of this rare complication from this treatment and review the bibliography about mechanisms for the different types of immunological reactions that may occur after treatment with collagenase *Clostridium histolyticum* and the possibility of crossed reactions with Clostridiopeptidase A used to treat skin lacerations.**

Key Words
Dupuytren contracture, Collagenase *Clostridium histolyticum*, Toxic dermatitis, Rash, Secondary effect.

## Introduction

The use of Collagenase *Clostridium Histolyticum* (CCH) as a non-surgical treatment for Dupuytren's Contracture (DC) has greatly increased since its commercialization, as more and more hand surgeons choose this treatment option[1]. However, such use is not free from complications (around 90%), though most are self-limiting and mild[2]. CCH's effect on the organism is the same as that observed with any exogenous substance of bacterial origin, creating an immunological reaction that can be observed through the formation of anti AUX I and II antibodies[3] and the subsequent possibility of hypersensitivity reactions.

In his meta-analysis of 11 clinical trials, Peimer et al[2] studied the various adverse events caused by CCH use, and among them, the different types of immunological reactions that may occur after treatment with CCH. Lymphadenopathies (11.1%), axillary pain (6.7%) or lymph nodule pain (3.7%), normally self-limiting, have been described as frequent. In more severe cases, one anaphylactic reaction[4] and four instances of hypersensitivity in the form of localized rash or intense pruritus[5], were reported.

To date, no English or French literature publication exists that details the presence of generalized skin rash as a complication of CCH treatment. The present case should come to the attention of orthopedic surgeons who treat DC, dermatologists, and other physicians in general, because of the evolution of the clinical symptoms, the mechanism by which CCH activated the immune system, the type of hypersensitivity response that occurred, and the medical implications involved.

## Case report

A 69-year-old female with a bilateral affectation of both hands, a family history of DC and Ledderhose disease in both feet. She underwent surgery on her right hand with amputation of the 5th radius due to aggressive DC recurrence. Currently, she presents a residual cord at the ulnar border of the 4th finger with flexion of the proximal interphalangeal joint (PIP) at 23º. The left hand shows affectation in the form of a pretendinous cord at the 5th finger with PIP flexion at 63º with no alteration of the metacarpophalangeal joint (MCP), after previous fasciectomy


*Corresponding Author:* Rafael Sanjuan-Cervero, MD; e-mail: sanjuan.rafcer@gmail.com

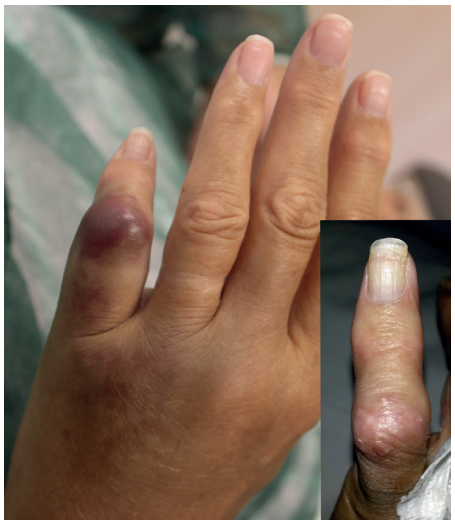

**Figure 1.** Hematoma at the dorsum of the articulation treated. Evolution at 6 months follow-up is shown at the right side. Different consistency of the skin and maintenance of the contracture of the articulation are shown.

intervention in the same finger. There were no medical antecedents for epilepsy, psoriasis, HIV or diabetes mellitus. She was receiving pharmacological treatment- amitriptyline, levothyroxine, fenofibrate, omeprazole, denosumab, pregabalin, calcium with vitamin D and leflunomide- for her various chronic pathologies. No previous drug allergies were reported.

Infiltration with collagenase *Clostridium histolyticum* (CCH) was performed at the PIP according to product specifications with 0.20 mL for a CCH total dose of 0.58 mg. Evolution until the moment of finger extension was uneventful. After removing the bandage, the patient presented local edema, ecchymosis, local pruritus and bruising. A 0.7 cm skin laceration during finger extension under truncal anesthesia of the median and ulnar nerves with Mepivacaine at 1% at the wrist was made. She presented a hematoma at the injected finger's PIP dorsum (Figure 1), which evolved into spontaneous bleeding. The wound at day was treated at days four and six with Clostridiopeptidase A (Iruxol©) and at day 10 she was discharged from the outpatient clinic with her skin healed and no systemic clinical symptoms.

The patient was examined one month after injection and presented exanthema which was treated with oral corticoids and antihistamines by a dermatologist. Residual lesions were scaly, and the patient reported pruritus and a greater intensity of the clinical symptoms in areas exposed to sunlight (Figure 2). Two weeks later, the patient returned to the outpatient's clinic with complete disappearance of the symptoms. A hemogram showed no significant changes (leukocytes 6.5 10e-3/mcL, neutrophils 4.05 10e-3/mcL (62.5%), monocytes 0.52 10e-3/mcL (8%), eosinophils 0.45 10e-3/mcL (6.9%), basophils 0.05 10e-3/mcL (0.8%), PCR 1.5 mg/L). The affected finger did not achieve complete extension, maintaining a contracture of 38º in the PIP and 0º in the MCF, 3 months after intervention.

Causality assessment was performed on our patient by means of the modified Karch-Lasagna algorithm[6], and the result was "probable". The outcomes were reported to the Spanish system of pharmacovigilance (*Servicio Español de Farmacovigilancia*), registry number 10-600961. The adverse event was not associated with any other medication previously taken by our patient.

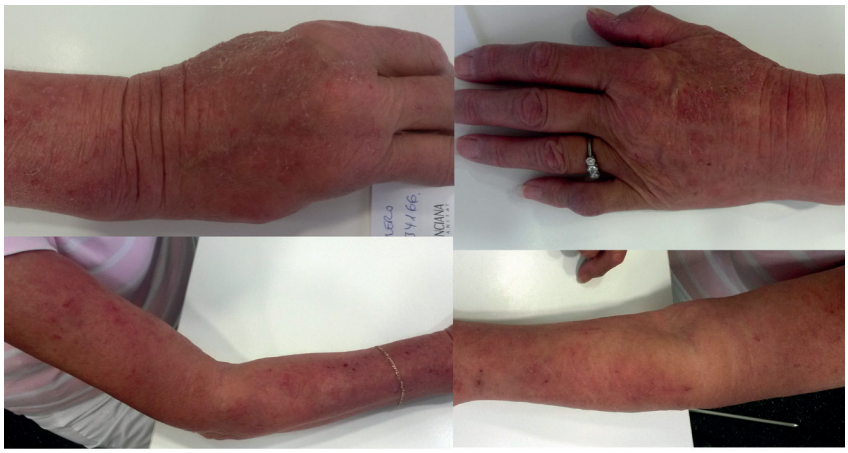

**Figure 2.** Image that shows the scaly exanthema in hands, at upper side of the image and arms, at the lower side of the picture. Images on the left side are from the left arm and right sided are from the right arm respectively.

## Discussion

Allergic reactions are the most frequent adverse reactions to drugs, also known as toxic dermatitis. Among these reactions, exanthema is the most frequent and least severe. Symptoms normally start 7-10 days after the drug is administered. The rash usually appears on the trunk and may progress symmetrically to the limbs. These reactions may include pruritus and/or generalized rash and/or photosensitivity. In the final stages of the process, exfoliative dermatitis may also be observed[7]. Regarding treatment, first and foremost is to stop administering the drug. In the case of CCH, administering the drug in a single dose avoids the increased risk associated with continual drug administration. The allergic reaction will progressively improve over one or two weeks, although a slight worsening could take place before the complete disappearance of symptoms. Symptoms should be treated with antihistamines and corticoids[7,8].

The exact mechanism of exanthema is unknown[7]. In those cases in which an allergic reaction occurs after the drug is first administered, as in a maculopapular rash, the mechanism is believed to involve T-lymphocytes[9,10] and a hypersensitivity reaction[11]. The two isoforms that comprise CCH (AUX-I and AUX-II) are protein macromolecules of bacterial origin acting as antigens. With CCH injection, skin Langerhans cells making up the immune system act as antigen-presenting cells, capture the collagenase, and transport it through the lymph system to the axillary lymph nodes, where anti-AUX I and II antibodies are produced. This process may cause local and systemic inflammatory responses that travel along the path of the lymph vessels. Systemic responses are responsible for the effects on the immune system caused by CCH (lymphangitis, adenitis, axillary pain…). An alternative mechanism could involve the high IgE titres found in some patients after the first dose of CCH, which could also explain other phenomena, such as anaphylaxis[12].

The recent commercialization of CCH allows for cases to be documented prior to treatment, and makes it easy to monitor the treated population. We must, however, bear in mind that another drug with collagenase in its composition, clostridiopeptidase A (Iruxol™), has long been used in the treatment of wounds with debriding action. This could lead to a cross-reaction with CCH and provoke allergic reactions. The evolution time followed by our patient could suggest this phenomenon. This cross-reaction could also be possible with other preparations of collagenase for the treatment of ulcers, despite its different origin *(Vibrio algynoliticum)*[13], given the similarity between the different types of collagenases biochemistry.

In our center, we do not have the necessary equipment to measure anti-AUX antibodies and so we have had to use exclusion diagnosis for our study. However, the few earlier references available to us[4,5], knowing precisely the time the drug was administered, and the opinions of two dermatologists coinciding in their diagnoses, come together to allow us to conclude that the cause of the patient's allergic reaction was CCH. The only concomitant treatment with CCH was mepivacaine, used as a local anesthetic before the finger extension. The previous and posterior administration of this medication to the patient without secondary effects has allowed us to rule it out as being responsible for the patient's clinical symptoms.

## Conclusions

Although CCH treatment presents a great variety of minor secondary effects, the possibility of severe complications in the treatment of DC cannot be discarded. The rash presented by our patient is, perhaps, the mildest form of toxic dermatitis, but any form of drug reaction may occur both in *de novo* treatments and in subsequent infiltrations. Treating the skin laceration with Clostridiopeptidase A and other collagenases should be avoided due to the possibility of cross-reactivity with CCH.

### Conflict of Interests

The Authors declare that they have no potential conflict of interests.

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