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## **Vasospasm after Collagenase Clostridium Histolyticum Infiltration in Dupuytren's Contracture**

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### **Authors' contributions**

*This work was carried out in collaboration between both authors. Author RS designed the study, took the images, and wrote the discussion. Author NF managed the literature searches, and wrote the case presentation. Both authors read and approved the final manuscript.*

**Case Study**

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### **ABSTRACT**

Treatment with collagenase clostridium histolyticum has been shown to be effective at the short- and mid-term against Dupuytren's contracture in which cords have formed. As with any new drug, pharmacovigilance studies will allow for reporting new complications with the treatment.

We present a clinical case of vasospasm after collagenase clostridium histolyticum infiltration in a patient with a 60° affection of the proximal interphalangeal joint forming an ulnar cord of fifth radius in the left hand. Evolution at one year presents the cord in the same contracture as before, and no vascular alteration.

In our opinion, most complications from infiltration with collagenase clostridium histolyticum take place when the treatment is performed and are due to extravasation of the infiltration into healthy tissue. In cases of greater extravasation, vessels may be affected causing transient vasospasms due to the local action of the enzyme, together with a secondary inflammatory reaction to the collagenase action.

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## **ABBREVIATIONS**

*CCH: collagenase clostridium histolyticum; PIP: proximal interphalangeal articulation; MCP: metacarpophalangeal articulation.*

## **1. INTRODUCTION**

Since its commercialization in the USA [1] and Europe [2], enzyme injection with collagenase clostridium histolyticum (CCH) has been shown to be an effective treatment for Dupuytren's contracture. Initial studies [3,4] allowed monitoring of the disease and showed that, in most cases, enzyme injection results in breaking the diseased cords of tissue that cause fingers to contract. Likewise, various studies and meta-analyses [5,6] show a positive cost-effectiveness benefit for this product. The long-term evolution of this treatment is still unknown and subject to phase IV pharmacological studies, given the possibilities of new complications and adverse reactions. Its safety profile over time with humans is also being studied.

One case of vascular affection in an ulnar cord of the fifth digit after infiltration with CCH has recently been published [7]. The collagenase profile is based on activity at the type I and III collagen levels [8], without affecting type IV collagen, which is the main constituent of nerves and blood vessels. We present a clinical case with transient vasospasm after CCH infiltration, with a 24-hour evolution and spontaneous resolution of the clinical presentation with no mid-term impact.

## **2. CASE PRESENTATION**

A sixty-five year old male suffering Dupuytren's contracture in the left hand forming an ulnar flange of the fifth digit with a contracture of the PIP of 60° and with no affection of the MCP. He has no personal history of alcoholism, diabetes mellitus, and epilepsy or family antecedents of epilepsy. He reports a moderate intake of alcohol daily.

Infiltration is performed according to the established protocol and the cord is manipulated 24 hours later [3,6] following the usual technique for soft extension of the finger with the wrist flexed to prevent the skin from breaking. The ulnar side of the hand presents swelling and edema both dorsal and volar with no signs of bruising or blood blisters (Fig. 1). However, a small cutaneous dehiscence is observed in the ulnar limits of the metacarpophalangeal fold along with an intense vasospasm at the distal finger with respect to the infiltration zone of the proximal interphalangeal (PIP) joint, affecting the whole finger (Figs. 2,3). It is impossible to assess the presence of alterations in sensitivity when performing manipulations with wrist blockage at the ulnar and median nerves. The patient was kept under observation in the outpatient surgical unit and was discharged after assessing the absence of progression of the clinical condition. He was requested to return for a visit 12 hours later to confirm the progressive disappearance of vasospasm during that time.

The patient was examined after 7 and 30 days, 6 months and one year observing the absence of vascular alterations in the finger and the absence of the Dupuytren's contracture cord breakage, maintenance of the flexion of the PIP with 50°, full extension of the MCP and palpation of the cord at the same site as at the start of the process (Fig. 4).



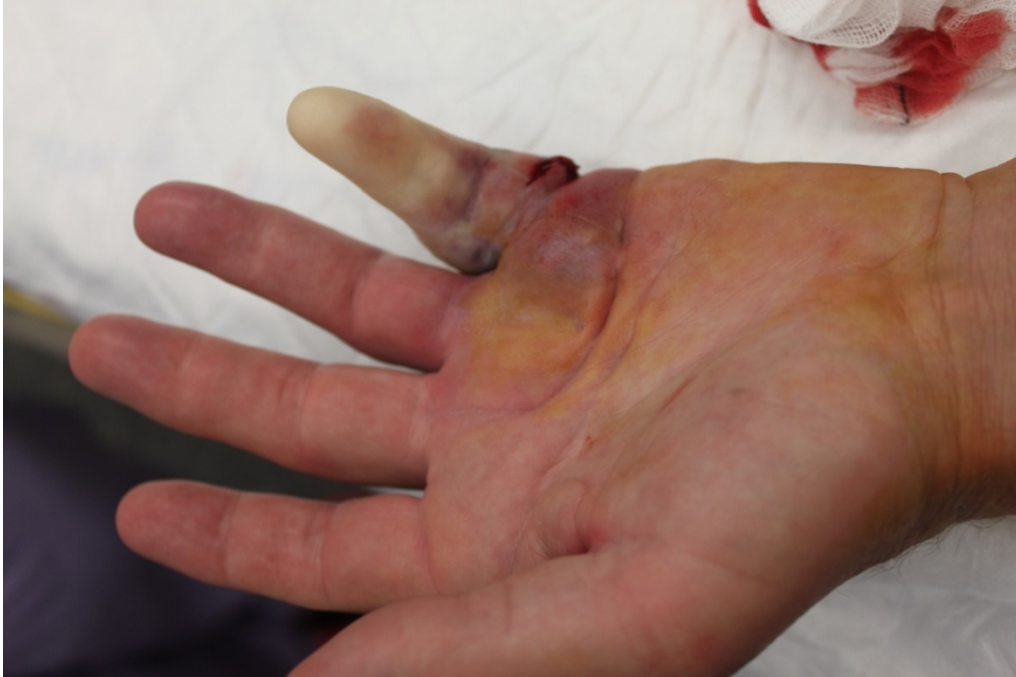
**Fig. 1. Initial state of the patient with 60° contracture of the PIP, with no MCF affection**

### **3. DISCUSSION**

*Collagenase clostridium histolyticum* is a treatment method that has been used for a long time for various pathologies, such as wound debridements or disc herniation [9] with varying results. Recent studies and meta-analyses [5,6] have demonstrated their short-term effectiveness for treating Dupuytren's contracture caused by cord formation. Collagenase is a metalloproteinase commonly present in the human body. It degrades collagen fibers allowing for connective tissue remodeling. In Dupuytren's contracture, collagenase is obtained from *clostridium histolyticum* as two isoenzymes acting on the collagen I and III types, at different sites of the collagen triple helix [8].

The way CCH affects healthy tissue varies, and may produce a digestion of healthy tissue. Kahl [10] observes a disruption in the basal lamina of the dermoepidermal junction as an effect of the enzyme with a later disruption of collagen fibers in pig skin after subcutaneous administration. In his study, Garvin [9] shows hemorrhaging and tissue digestion as a type of intravenous toxicity in rats, and digestion of the epidural venous plexus with epidural injection in dogs. Gelbard [11] assesses the affectation at the small vessel level, mainly in venules with no affectation in arterioles containing smooth muscle fibers. However, Li [12] indicates that in medium-sized vessels, type I collagen is the main constituent of the arterial walls. Bell [13] establishes a relation between the Pacinian corpuscles and the blood supply in the skin with a regulatory role of the Pacinian corpuscles; these ones have an encapsulated endings formed by condensed connective tissue in their external core and between the spaces of the corpuscles being possible the disregulation of the blood supply with the degradation of the collagen present in these structures as we have seen in our case.

Therefore, they could be affected by CCH injection. All of these studies explain the appearance of secondary effects that are present in 85% of patients in the form of edema, contusions, localized hemorrhages or blood blisters [3,4] after infiltration with Xiapex®.



**Figs. 2-3. Vasospasm**

Although the infiltration volume is small, and it is recommended that it be distributed in three different spots at the infiltration site, instilling the product creates a cavity in the Dupuytren's disease cord and the liquid seeps inside the cavity. This causes an increase in pressure that can be observed when the syringe plunger is pushed in to infiltrate the product, and when the needle is withdrawn. This increase in pressure causes some leakage of the product provoking dilution into healthy connective tissue and the appearance of secondary effects. Likewise, the amount of liquid that remains in the needle becomes disseminated into adjacent tissues that are not affected between the cord and the epidermis. In our opinion, the amounts of product are minimal, but enough to produce secondary effects that appear before the cord is manipulated and broken. These could not be explained if all the liquid remained inside the cord.

Spiers [7] published the case of periodical bluish discoloration of the finger in the form of pseudo-Raynaud's disease. He proposes various theories as to the cause, although the recurrence or, better yet, the continuance of the finger contracture over time, along with edema and skin rupture after 48 hours of evolution indicate a possible leakage of CCH outside the flange with direct affectation of the hand's healthy connective tissue. Our case is based on the same procedure. The skin rupture, edema and recurrence of Dupuytren's contracture indicate a failure in the infiltration technique and leakage or presence of Xiapex® outside the cord. In the same way, being subjected to abrupt manipulations with the wrist extended at a spot where there is already a local inflammatory reaction could cause skin and vessel breakages [10] that could be responsible for the vasospasm. There is no evidence that the extravasation of the collagenase is causing the secondary effects of treatment. Possibly studies using ultrasound or any imaging technique at the time of infiltration where it looks at the output or not the product outside of the cord of Dupuytren's disease will be able to clarify this aspect.



**Fig. 4. Evolution after one year, showing the proximal interphalangeal joint contracture remaining as it was before the infiltration**

#### **4. CONCLUSION**

CCH has proved to be an effective treatment for Dupuytren's contracture at the short- and mid-term. Although most patients present complications with this treatment, they are normally mild and due to the extravasation of minimum amounts of the product into healthy connective tissue, where the enzyme produces collagen digestion, as assessed in long-term studies. The vascular affectation may be due to this phenomenon, even though other causes, such as the abrupt manipulation when breaking the cord, could also be related to or even be responsible for the process.

#### **CONSENT**

All authors declare that written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images.

#### **ETHICAL APPROVAL**

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Helsinki Declaration.

#### **COMPETING INTERESTS**

Authors have declared that no competing interests exist.

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