First results of Gold-induced activated serum injections (GOLDIC®) for Dupuytren disease

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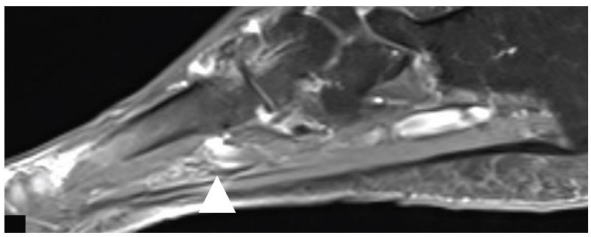
Introduction

Dupuytren disease (DD) is a highly prevalent hand affection in which contracted fingers compromise hand function. In a recent meta-analysis prevalence up to 30% in the Western countries was reported, increasing with age (24). Asymptomatic palmar fibrosis is more common than overt contractures, which require treatment (15). The standard treatment has been fasciotomy or fasciectomy ever since Baron Guillaume Dupuytren introduced cutting the strands in his the public sessions at the Hotel Dieu in Paris in 1831 (1). Since then, the pathology has been extensively studied, with historical milestones as the histology stages of Luck in 1959 (27) the identification of the myofibroblast by Gabbiani in 1972 (18). It is the collagen production of these myofibroblast that holds the finger contractures. This collagen is found more in the cords than in the nodules, which contain mostly myofibroblasts (46). Surgical intervention is still the current mainstay of treatment for DD, usually involving fasciotomy, fasciectomy or dermofasciectomy (45). A variety of non-operative techniques have been practiced but have failed to give long-lasting benefits. More recently, clinical investigation (phase II and III), including the use of clostridial collagenase injections, have shown encouraging results in some DD patients (49,50), but long-term follow-up results are required before this can be advocated as standard procedure in place of surgery.

Plantar fibromatosis, or Ledderhose disease, is another hyperproliferative disease located at the plantar aponeurosis. Georg Ledderhose described the disease in 1894 as a Dupuytren like disease of the foot. Nodules measuring 1 to 2 cm on the medial side of the foot arch are evidence for the disease. In a case report we reported about 53-year-old woman presented painful plantar nodules. Physical examination showed multiple fixed and solid nodules measuring 1 cm each on the plantar and medial side of her right feet. She had using orthopedic insoles for the last 4 years.
She was not taking any medication, and there was no family history of those nodules. She did not have Dupuytren disease, diabetes mellitus, alcohol addiction, penile fibromatosis, epilepsy, or frozen shoulder. MRI was performed right before and 2 weeks after GOLDIC treatment. After four local injections of the Goldic® serum directly into the nodules the tissue was soft and painless. In the control MRI aft er 2 weeks the fibrotic nodules transformed to a cystic structure. No sign for inflammation could be detected.

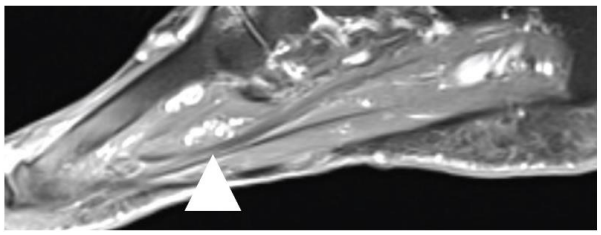
CASE: GOLDIC® treatment for a 52-year-old female with no significant medical history presented with an 4-year history of a plantar nodule of the right foot.

Before GOLDIC® treatment.



Patient suffered from load dependant pain during walking, each step was painful. In the MRI in the plantar aponeurosis showed nodular destruction of the plantar aponeurosis under the metatarsal bone 2 + 3 (white arrow).

The patient two (2) weeks **after** successful **GOLDIC®** treatment.



After four local injections of the Goldic® serum directly into the nodules the tissue was soft and painless. In the control MRI after 2 weeks the fibrotic nodules transformed to a cystic structure (white arrow). No sign for inflammation could be detected.

GOLDIC an innovative technique of producing a autologous conditioned serum rich in cytokines (Gold-IC) by utilizing specialized gold particles (42). Compared to other blood-based biological methods, only the GOLDIC® procedure has been demonstrated upregulation of plasma gelsolin (pGSN) and granulocyte colony stimulation factor (G-CSF), both of which play an important role in tissue regeneration (43).

Encouraged by these results of these initial study, we conducted this pilot study to evaluate the safety and clinical effectiveness of GOLDIC® in patients with Dupuytren contracture.

Material and methods

A 67-year-old man, affected by hypertension and prostatic hypertrophy, presented with a 4-month history of impairment of right-hand function, pain and difficulty grasping and opening a jar due to hand weakness and flexion deformities of digitus IV and V. He has not been evaluated neither treated before for this impairment. The pain started to get worse recently. On physical examination, on palpation, he presented thickening of the palmar skin, nodules and cords, and table top test positive. On the basis of clinical features and ultrasound images, we diagnosed DD (Fig. 1).

Fig.1: Clinical evaluation before treatment: thickening of palmar fascia and flexion deformities of digitus IV and V with a total flexion deformity of 30°.

We used a goniometer to measure the degree of finger's contraction and to determine the Tubiana grading system. Tubiana grading system assigns a score to the extension deficit of a digit by summing the total deficit angles of the metacarpophalangeal joint proximal interphalangeal and distal interphalangeal joints. The Tubiana stages are: N = palmar nodule without presence of contracture; 1 = total flexion deformity between 0° and 45°; 2 = between 45° and 90°; 3 = between 90° and 135°; 4 = >135° (11).

The daily limitation of DD in activities of daily living was analysed through the Disabilities of Arm Shoulder and Hand Questionnaire (DASH) and Michigan Hand Outcome Questionnaire (MHQ). Nowadays there are no Dupuytren-specific outcome questionnaires validated in the literature. DASH has 30 questions. Its domains are specific daily functions, symptoms (pain, strength, and sensation), impact on life of the patient and general disability and handicap. There are no questions investigating satisfaction. The minimal score is 30, the maximum is 150. The responses are summed to form a raw score that is then converted to a 0-to-100 scale with a lower score indicating higher degree of autonomy (11).

The MHQ was devised from the University of Michigan in 1998. It has 37 items and measures six domains: overall hand function, activities of daily living, work performance, pain, aesthetics, and patient satisfaction with hand function. Scores on MHQ range from 0 to 100, with a lower score indicating higher degree of disability (13).

For GOLDIC® therapy, 4 x 10 mL of blood was collected from thr patient using four GOLDIC® BTS syringes (Arthrogen GmbH, Gmund, Germany). The syringes were incubated at 37°C for 24 hours. Incubation must be less than 28 hours or the chances of red blood cell lysis is increased and is not desirable as it changes the characteristics of the serum injectate negatively. Addition of anti-clotting agent is not required as even if clot forms, it does not impact separating the cells and creation of the activated serum. After the incubation process, the blood was centrifuged at 4000 rpm (2250 g) for 10 minutes. Then supernatant conditioned serum was collected and filtered through a 0.22 µM syringe tip filter (Goldic SAS), and was then used for immediate injection or stored at -20°C . The patient underwent 4 injection every 3 to 4 days. No other treatment like physiotherapy or orthotic

device was utilized throughout the study period. The participant provided written consent to participate voluntarily in this clinical case report. Personal information was made anonymous. Our patient presented a total flexion deformity between 0° and 45° (30°), stage 1 by Tubiana. The DASH and MHQ results at first evaluation were 31.8 and 58, respectively.

The patient reported a temporary worsening of symptomatology for 24 h after the first 2 injections, but the overall hand function was improved (DASH score: 22.8). No adverse effects were reported.

After the third injection we observed a reduction of nodule and cord's dimension in the palmar fascia of left-hand. The total flexion deformity was reduced to 5° (stage 1 of Tubiana) (Fig. 2).

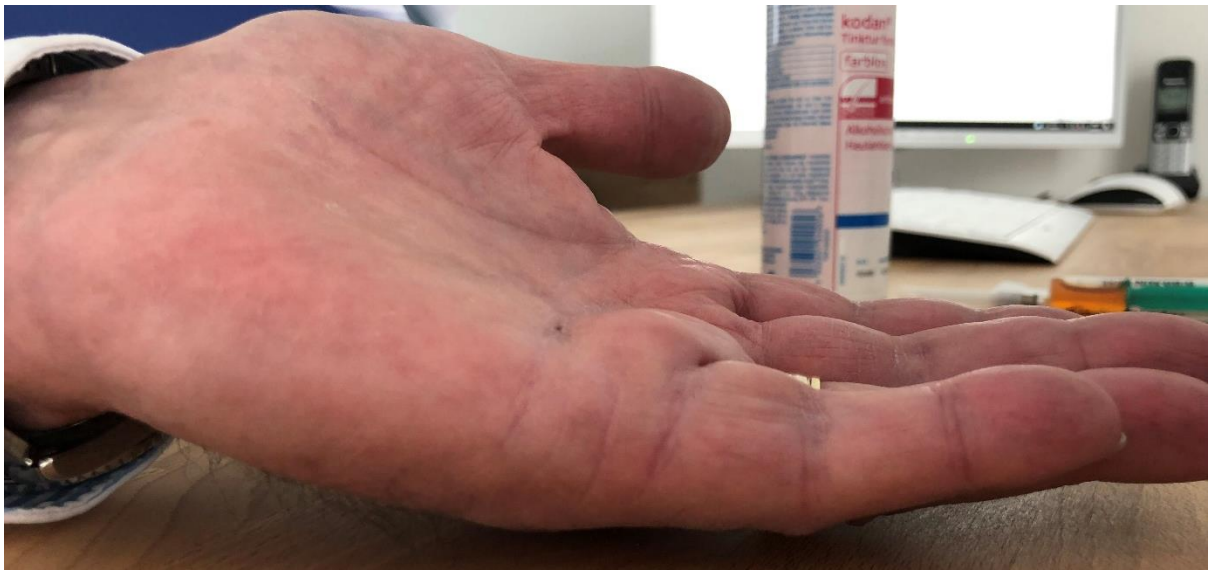


Fig.2: Clinical evaluation after 3 intra-lesional GOLDIC injections. The flexion deformity disapperared completely, the thickening of palmar fascia and local pain was reduced.

At the 3-month follow-up, the patient had maintained a similar hand function (score 10.3 in DASH and 76 in MHQ). Finally, we observed a reduction of flexion deformity of the affected fingers.

Discussion

Gold activated conditioned injection therapy is a safe non-invasive treatment option and it might be a tool for prevention of the progression and for treatment of DD. The treatment with Goldic is well tolerated and anesthesia is not necessary. Surgery treatment is not free from complications and these operations undertaken in early stages of DD is considered to be associated with a higher rate of recurrence (2)

Enzymatic fasciotomy with collagenase injections seems to be effective for reducing the contractures, but it requires an expert surgeon and it is not free from complications (skin rupture, tendon rupture, hematoma, pain, lymphangitis, and also severe allergic reactions or anaphylactic shock) (3) Collagenase injection and needle fasciotomy have 3-year recurrence rates of about 45% each (4).

Conclusion

GOLDIC treatment is a less-invasive and well-tolerated therapy with good initial results in the DD treatment. Further studies, including randomized controlled trials, are needed to evaluate the efficacy of GOLDIC in DD.

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