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Cryosurgery for the treatment of cutaneous sporotrichosis: Experience with 199 cases.

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Sporotrichosis is a worldwide distributed subcutaneous mycosis caused by the dimorphic fungi belonging to the genus *Sporothrix*.¹ Since 1998, Rio de Janeiro (RJ), Brazil, became a hyperendemic region for cat-transmitted zoonotic sporotrichosis associated with the most virulent species, *S. brasiliensis*.^{1,2} Itraconazole is the first choice of treatment for cutaneous sporotrichosis, terbinafine and potassium iodide are alternative options. The median time until the cure is around 12 weeks, but it can be longer for some patients and adverse effects may lead to discontinuation of treatment.²⁻⁵ Cryosurgery is an effective method largely used in dermatology. The main mechanisms consist of direct freezing effect on skin constituents, with necrosis and immunological responses, this last not seen in other local therapies.⁶⁻⁸ There are few sporotrichosis cases reported, treated with cryosurgery.

Between 2006 and 2016, 3,677 patients with sporotrichosis were treated at Evandro Chagas National Institute of Infectious Diseases / Oswaldo Cruz Foundation and 199 (5.4%) of them underwent cryosurgery sessions. Cryosurgery was indicated due to incomplete response of oral therapy (improvement but not cure) and to failure of antifungals (no improvement despite of high doses) (91.0%); chronic verrucous or extensive ulcerated and vegetative lesions (6.0%) and suspension of antifungal due to adverse reactions (3.0%) (Fig. 1). The sessions were carried out monthly up to clinical cure (reepithelization, absence of crusts and infiltration), using a liquid nitrogen spray gun (Fig. 1). In each session, lesions were treated with double freeze-thaw cycles, intermittent spray technique, with freeze time depending upon the lesion size. Sporotrichosis was diagnosed based on the isolation of *Sporothrix* spp. and all patients were treating or treated with itraconazole (100 - 400 mg) (67.3%), terbinafine (250 to 500 mg) (14.1%), or both, together or in distinct periods (18.6%).

There was a predominance of women (67.3%) engaged with domestic activities (41.7%), with history of close contact with cats (82.4%), presenting the lymphocutaneous (58.6%), fixed (26.2%) and disseminated cutaneous forms (15.2%), a profile previously described.^{2,5} However, the population was older (the mean age was 55.7), with more comorbidities (60.3%) such as high blood pressure ($n=88$); diabetes mellitus ($n=35$); dyslipidemia ($n=16$); gastrointestinal diseases ($n=16$); cardiovascular disease ($n=11$); neuropsychiatric diseases ($n=10$) and others ($n=11$).

The median time of the beginning of oral antifungal until cryosurgery onset was 151 days (range: 0 to 2,632 days), with a late onset (>90 days) in 71.9% of the cases, and early onset in 28.1% (≤ 90 days). The number of cryosurgery sessions varied from 1 to 20 (median=3). Clinical cure was achieved by 91% of the patients, 8% were lost to follow-up, and 2 patients died due to other causes. The median total treatment time was 325 days (range: 28 to 2,901 days). In the exploratory analysis, the group of patients subjected to a larger number of sessions (> 4 , $n=67$) was older ($p=0.034$, t-test) had more comorbidities in general ($p=0.047$); diabetes mellitus ($p=0.028$); cardiovascular disease ($p=0.001$); and late onset of cryosurgery sessions ($p=0.030$), when compared to the group subjected to up to four sessions of cryosurgery ($n=132$). The Kaplan-Meier analysis demonstrated two risk factors for the clinical cure (Log-rank and Peto p -values <0.05): cardiovascular disease and late onset of cryosurgery. A multiple Cox survival model was performed (adjusted by age, sex and diabetes) with two stratified Cox models fitted at 180 days (due to lack of proportionality, $p=0.0281$). Patients with no cardiovascular disease tended to provide 8.5 times faster healing (HR=9.45, 95% CI=1.27 – 69.83) and the late onset of cryosurgery had the opposite effect, with larger course to cure (HR=0.48, 95% CI=0.29 – 0.78). The effects were important only in patients with up to 180 days to cure.

This is the first cohort study describing the cryosurgery as an effective and safe method in a large number of patients with sporotrichosis who presented difficulty in their therapeutic management. Cryosurgery emerges as an interesting alternative in a scenario of few therapeutic options for sporotrichosis. It should be indicated as soon as a slow treatment response is identified, especially in patients with comorbidities such as cardiovascular disease. In cases of verrucous or vegetative lesions that chronicity can be predictable, cryosurgery could be indicated even earlier, as it possibly improves antifungal penetration into the skin due to epidermal necrosis and also facilitating fungal exposure to the host immune system.⁸ In cases that adverse effects lead to interruption of the antifungals, cryosurgery was a subsequent treatment capable of leading to cure. Further controlled and randomized trials are necessary to confirm the efficacy of cryosurgery to treat and/or abbreviate sporotrichosis treatment time, especially for slow-responder patients.

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Figure Legend

Figure 1. Patient with a 10 cm verrucous lesion of cutaneous sporotrichosis, fixed form, in the right forearm, with incomplete response with oral antifungals (a). Crust removal before cryosurgery (b). Cryosurgery application with cryo gun (c). Two months after clinical cure (d).

