A Rare Case Of Candida Tenosynovitis Successful Suppressed With Voriconazole After Fluconazole Failure. Case Report And Review Of Literature

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Citation

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Abstract

A 69-year-old patient presented with a Candida albicans bilateral tenosynovitis of the extensor digitorum muscles. Haematogenous spread was most likely as no trauma for direct inoculation was apparent, while he had been treated for Candida spondylodiscitis one year before. Although initial fungigram on the synovial fluid demonstrated susceptibility for fluconazole, therapy with fluconazole failed after in vivo resistance to fluconazole developed. Treatment with voriconazole was able to induce complete resolution of the tenosynovial inflammation without surgery. However, late recurrence occurred when voriconazole was stopped, possibly because of cross-resistance between fluconazole and voriconazole. Longterm oral therapy with voriconazole was able to supress the infection.

INTRODUCTION

To our knowledge, tenosynovitis caused by Candida infection has only been reported three times (Table I). The first reported case described a Candida tenosynovitis in a young boy with Buckley's immunodeficiency in 1985.(1) He was treated with two surgical debridements after amphotericin B and 5-fluorouracil failed. The second case reported a 50-year-old man suffering a Candida tenosynovitis of the wrist after multiple corticoid infiltrations for median nerve entrapment.(2) He was treated with two synovectomies and oral fluconazole. The third patient involved a 36-year-old HIV positive women with a Candida tenosynovitis of the wrist without any other apparent risk factors.(3) Incision and drainage of the infected hand was performed and she was treated with oral fluconazole. Initially, there was a clinical improvement but recurrence of the swelling and pain occurred 16 days after surgery. A second debridement was required and she was maintained on oral fluconazole for one month. She had no recurrence of the Candida tenosynovitis, however, she died three months after the initial diagnosis due to a Pneumocystis jirovici pneumonia. The authors present a fort case of Candida tenosynovitis.

Table 1

Overview of the literature describing Candida tenosynovitis

Authors	Year	Immune-compromised?	Treatment	Outcome
Yuan RT, Cohen MJ.(1)	1985	Buckley's immunodeficiency	Synovectomy after failure to amphotericin B and 5-fluorouracil therapy.	Successful treatment, no recurrence
Bienaith M, Geurdon JF.(2)	1990	No, Repeated steroid infiltrations	Two synovectomies and oral fluconazole.	Recurrence on day 16, Successful treatment.
Townsend DJ, Singer DI, Doyle JR.(3)	1994	Aids	Incision and drainage with oral fluconazole	Successful treatment, no recurrence.

CASE

A 69-year-old male presented with progressive pain and swelling of the tendons of the extensor digitorum muscles on both hands. This patient had a history of chronic obstructive pulmonary disease (COPD) with evolution to emphysema and bronchiectasis, peptic ulcera bulbi, diabetic mellitus with polyneuropathy and a Candida oesophagitis ten years before. There was a documented hypogammaglobulinemia with a total IgG of 428 mg/dl (normal range: 650-1600 mg/dl), due to chronic corticoid therapy, tapered to 4 mg daily for the last two months. One year before, the patient had a Candida spondylodiscitis of thoracic vertebra 11-12, due to a Candida sepsis, treated with fluconazole. His maintance medication consisted of digoxine 0.250 mg, molsidomine 16 mg, altizide 15mg, spironolacton 25mg,

amitriptyline 100mg, tramadol 50 mg. His diabetes was well controlled with a daily dose insulin of 40 IE. His inhalation therapy was a combination of salmeterol 50µg and fluticason 250µg and a combination of fenoterol 50µg and ipratropium 20µg as rescue therapy.

Clinical evaluation showed an afebrile cachectic man. The dorsum of both hands were red,warm and tender. The tendons of the extensor digitorum muscle were swollen in their sheaths, compatible with bilateral tenosynovitis. Both active and passive mobilisation were painful. No skin lesions were noticed. Culture of aspirated material grew Candida albicans, susceptible for fluconazole. Blood cultures remained sterile, nor was ocular candidiasis discovered. Fluconazole 200 mg twice a day was administered, following a loading dose of 800 mg. Both hands remained inflamed three months after fluconazole therapy initiation. Inflammatory parameters remained elevated during this period. Therapy was switched to voriconazole, initially intravenously for five days and then switched to oral maintenance of 300 mg twice daily. After nine months of voriconazole, inflammation had resided clinically and biochemically. A gallium 67 scan did not show residual inflammation and voriconazole was stopped. However, five months after cessation, the swelling and pain on the dorsum of both hands recurred. A culture of punctured synovial fluid grew Candida albicans. This time the fungigram showed a reduced sensibility to fluconazole with a with a minimum inhibitory concentration (MIC) of 32 mcg/ml. Voriconazole was restarted at a dose of 200 mg twice daily. No recurrences of tenosynovitis occurred during the following of twelve months with continuous voriconazole. The patient died one year after restart of the voriconazole due to bacterial sepsis.

DISCUSSION

As the previous reported cases our patient was also immunocompromised: he was on chronic steroids for his severe COPD with subsequent hypogammaglobulinemia and was diabetic. In all of the three cases previously reported, only one had an infiltration which could have caused an entrance for Candida tenosynovitis.(2) In the two others cases the mechanism of inoculation was not specified. In our case, no direct inoculation by trauma could be withheld. Haematogenous might have occurred, as he suffered from Candida spondylodiscitis one year earlier, although he was treated with fluconazole. Furthermore, there was aperiod interval of one year between these two Candida infections. The patient was treated with long term fluconazole 200 mg twice daily, considered first choice for invasive Candida albicans infections.(4) In contrast with the other previous reported cases, there was no clinical response, although the Candida albicans was initially reported as sensitive for fluconazole. Fluconazole is a very hydrophilic molecule and almost completely absorbed after oral administration. Furthermore it has an excellent penetration in the different body fluid and tissues.(5) Good penetration of fluconazole in the tenosynovial space achieving adequate fungostatic concentrations is reported in horses.(6) Based on the horse study, one may suggest insufficient tissue penetration to be less probable for therapy failure, although no data were found in humans.

In contrast with the previous reported cases, no synovectomy was done, given the severe COPD as a major risk factor for general anaesthesia, while the patient refused local anaesthesia. Fluconazole therapy may have failed because there was no source control by means of synovectomy. Another explanation for therapy failure may be the induction of fluconazole resistance. Indeed, new cultures at the time of relapse revealed reduced susceptibility for fluconazole. Resistance of Candida albicans to fluconazole is rare.(7-9) Approximately 2 % of Candida albicans seem to be resistant to fluconazole in an analysis from the ARTEMIS DISK global antifungal surveillance study(7). No trend to increasing numbers of fluconazole resistant Candida albicans species could be withhold over the last ten years. This resistance of Candida species to fluconazole is described mostly in immunosuppressed patients or patients who were treated with azoles before.(10, 11) From that point of view our patient was at risk for developing fluconazole resistance as he suffered in the past both Candida oesophagitis and spondylodiscitis which were treated with fluconazole and may have induced resistance to fluconazole. However, one may be irrelevant as both the Candida oesophagitis and the spondylodiscitis were over one year apart from the tenosynovitis and second, a sensitive strain of Candida albicans was documented in the first episode of Candida tenosynovitis.

After failure of fluconazole, voriconazole was started. This was a clinical decision rather than stated with microbiological data. Voriconazole is known to have a very high bioavailability of more than 90 % and is well distributed through the body with excellent penetration in the tenosynovial fluid. (12, 13) In addition, long term oral

therapy is possible with voriconazole. Complete resolution of the tenosynovial inflammation was achieved under therapy with voriconazole, although recurrence occurred when voriconazole was stopped. As voriconazole is also member of the azoles, it is prone to the same resistance mechanisms as those of fluconazole resistant Candida strains. Cross resistance between different azoles is known to occur especially in patients with prior azole exposure(14-16). In the ARTEMIS Disk global antifungal surveillance study 28.8% of the fluconazole resistant Candida albicans strains remained sensitive to voriconazole(8). In this case the tenosynovial inflammation recurred five months after ending the voriconazole, which may indicate that there might have occurred cross-resistance between fluconazole and voriconazole, leading to the development of a susceptible dose dependent strain. Susceptibility testing for voriconazole was not done, therefore decreased susceptibility could not be confirmed by microbiological data. The success in suppressing the symptoms again after restarting voriconazole, reduces the possibility that the strain reached complete resistance.

As this case presented a few years ago standard treatment guidelines for fungal infections evolved a lot. Current ECCMID guidelines recommend pharmacological treatment with echinocandin as first choice, but these were not available at the time of presentation or relapse(17).

To our knowledge this is the first reported case with successful suppression of Candida tenosynovitis without performing surgery to reduce the infected tissue. This may indicate that oral voriconazole penetrates adequately in the synovial fluid to reach fungostatic concentrations.

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