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Onychomycosis by *Fusarium oxysporum* probably acquired in utero

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ABSTRACT

Fusarium oxysporum has been described as a pathogen causing onychomycosis, its incidence has been increasing in immunocompetent and disseminated infection can occur in immunosuppressed individuals. We describe the first case of congenital onychomycosis in a child caused by *Fusarium oxysporum*. The infection being acquired in utero was proven by molecular methods with the identification of the fungus both in the nail and placenta, most probably as an ascending contamination/infection in a HIV-positive, immunosuppressed mother.

1. Introduction

Onychomycosis is any nail plate infection caused by dermatophytes, yeasts and non-dermatophyte molds (NDMs). The prevalence of onychomycosis is low in children when compared to adults due to reduced exposure to infected environments, less trauma due to smaller and thinner nail surface and faster linear nail growth [1]. Nevertheless, onychomycosis should be considered in differential diagnosis of nail plate disorders in children and even newborns [2,3].

Fusarium oxysporum is a NDM that has been described as a pathogen causing onychomycosis only in adults [4–6]. Predisposing factors include family history of onychomycosis, habit of walking barefoot, hyperhidrosis, close contact with soil, frequent emersion of hands in water, hot humid climate, systemic immunossupression and diabetes [4,7]. Onychomycosis by *Fusarium oxysporum* was found with high prevalence in immunocompetent patients in a study performed in Brazil [5].

We describe a case of onychomycosis by *Fusarium oxysporum* diagnosed in a 60-days-year-old child whose placenta, umbilical cord and amniotic membranes were also infected. As far as the authors are concerned, this is the first case of *Fusarium oxysporum* onychomycosis in a new born, acquired in utero.

2. Case

A 60-days-old Caucasian girl weighting 4850 g was admitted at a pediatric infectology division (day 60) with fever without source and nail dystrophy with leukonychia of all nails (that her mother described being present since birth). All screening tests for bacterial infection were negative. The child's mother was an 18-year-old vertically HIV infected asymptomatic primigravida with immunosuppression (TCD4 Lymphocytes at delivery of 101 cell/μl). The mother was being treated with high active antiretroviral therapy (HAART), which included zidovudine, lamivudine, tenofovir and lopinavir/ritonavir, but she stopped treatment 30 days before delivery. The baby was born (day 0) by cesarean section with intact membranes at 37 weeks of gestation, weighed 2655 g with Apgar scores of 8 at 1 min and 9 at 5 min, and screening for other congenital infections were negative (syphilis, hepatitis B and C, toxoplasmosis). She received AZT prophylaxis at birth and the first viral load (day+30) was undetectable.

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Because all tests resulted negative and the fever persisted, she was clinically diagnosed with onychomycosis by candida and probable candidemia, when oral fluconazole (6 mg/kg/d) was started. A clipping of the fingernail showed hyphae on microscopic analysis, but culture was not performed by the time she was evaluated. Blood cultures were negative for fungus and bacteria. Uroculture was negative for bacteria (day+64). Two days after admission the baby was afebrile and then discharged being addressed to Pediatric Dermatology division.

After 30 days of fluconazol (day+94) all nails have improved, but all the fingernails and the 1st and 2nd toenails bilaterally still presented yellow-white discoloration and thickening with involvement of the distal surfaces (Fig. 1).

A second nail clipping was performed for microscopic analysis and again fungal elements were seen (day+94). Ciclopirox nail laquer was added to oral fluconazole. As congenital fungal onychomycosis was under consideration microscopic evaluation of placenta, umbilical cord and amniotic membranes was made and revealed multiple fungal

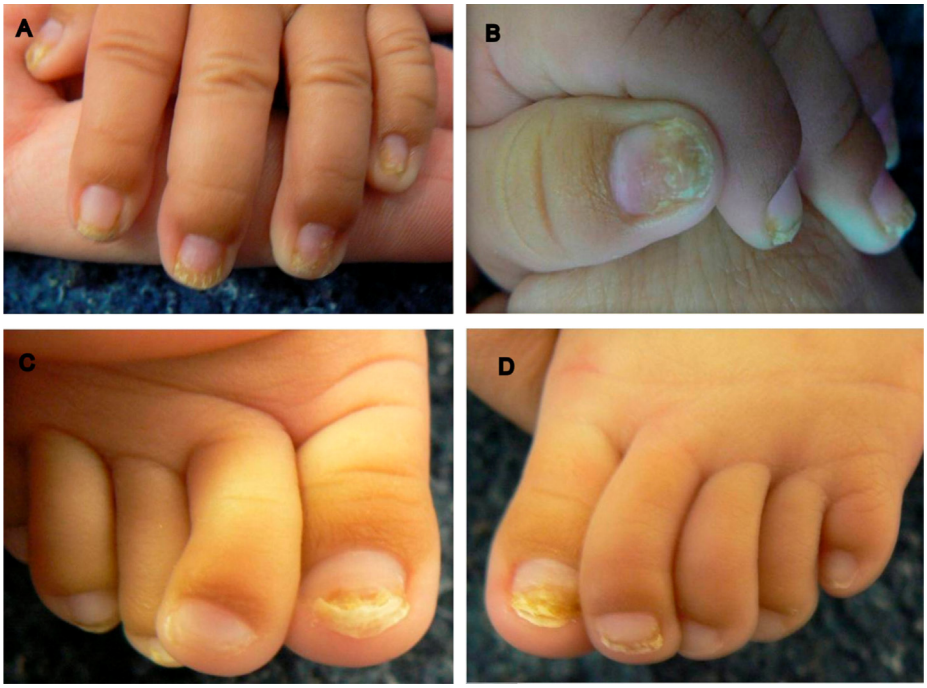

Fig. 1. A and B – Fingers nail with yellow-white discoloration roughness and thickening in distal surfaces. C and D – Toenails with yellowish discoloration, hyperkeratosis and roughness of the distal nail plates.

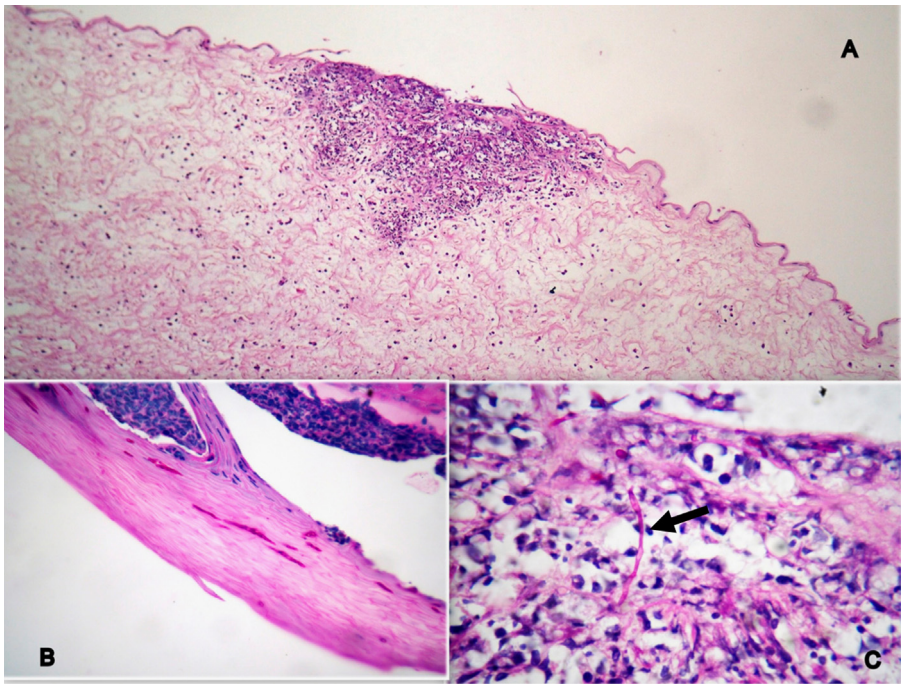

Fig. 2. A. Umbilical chord with foci of acute inflammatory infiltrate at the periphery. PAS with digestion, original magnification x100./ B. Nail Clipping microscopy analysis showed fungal hyphae on nail plate with neutrophil collections. PAS with digestion, original magnification x400. C. Detail of A, the arrow is showing fungal hyphae at the site of acute inflammation. PAS with digestion, original magnification x1000.

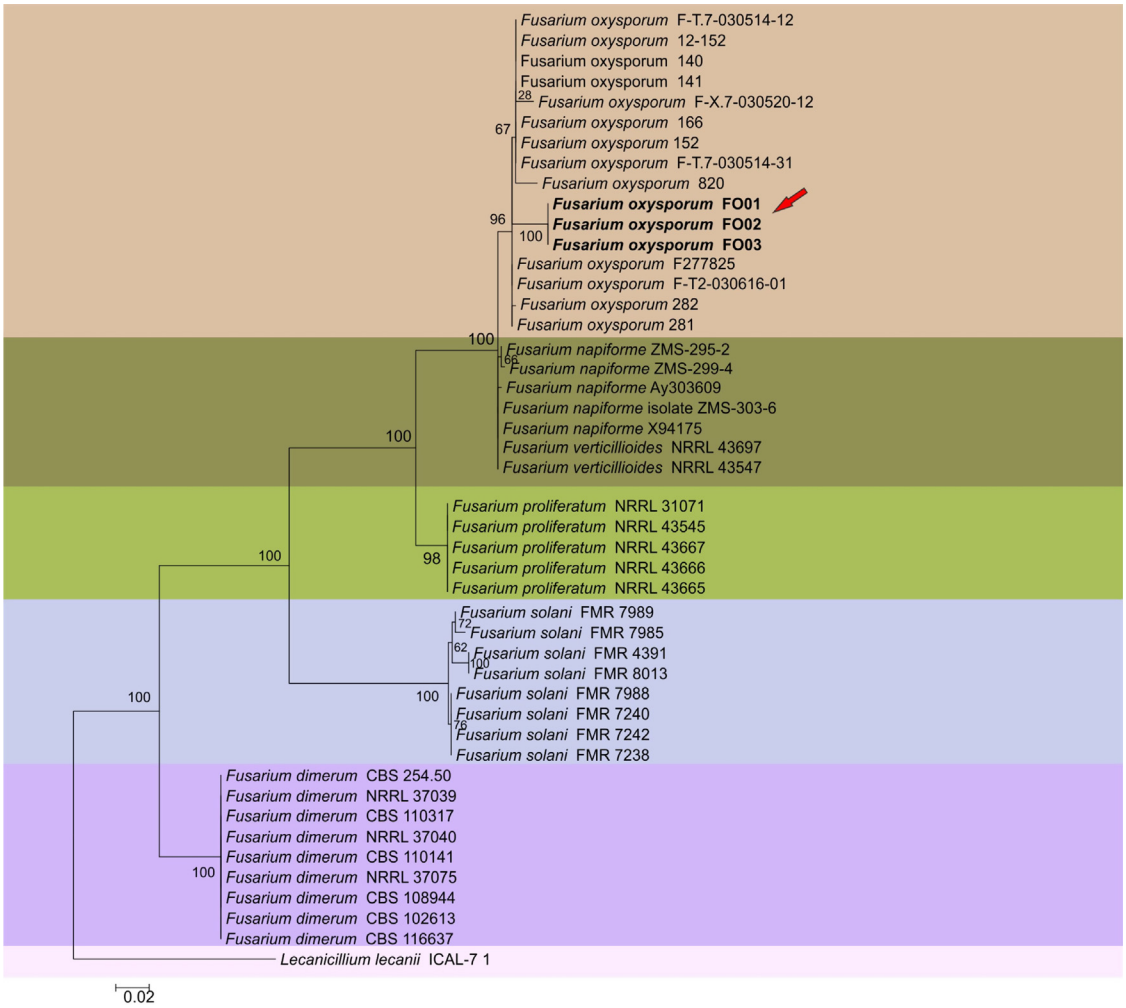

Fig. 3. Phylogenetic tree of *Fusarium* based on confidently aligned rDNA Internal Transcribed Spacer (ITS) sequences constructed with maximum likelihood, using the substitution model Jukes-Cantor, gama distribution, implemented in MEGA 5.10 [19]. Bootstrap support was calculated from 100 replicates. *Lecanicillium lecanii* was taken as outgroup. The arrow indicates the ITS sequencing of *Fusarium oxysporum* obtained from nail clippings (FO01), placenta (FO02) and umbilical cord (FO03).

elements in all structures (Fig. 2A–C). Again nail culture was not performed.

Judging from nested polymerase chain reaction using specie-specific oligonucleotides [8,9] and sequencing of ITS amplicons [10,11] generated from total DNA of nail clippings, placenta and umbilical cord, we confirmed *Fusarium oxysporum* from samples collected on day-0. A tree was built using the ITS sequences which were deposited in GenBank (FO01 KM001721, FO02 KM001722, FO03 KM001723) which were compared with reference strains of *Fusarium* genus (Fig. 3).

Total improvement of nails occurred after 60 days of fluconazole and 30 days of ciclopirox nail laquer 8% (day + 124).

3. Discussion

Nail infections caused by non-dermatophyte molds (NDMs) have been increasing [5,11]. The prevalence ranging between 1.45% and 45% [4,12] and this great variation may be secondary to increasing numbers of immunosuppressed individuals and geographic differences in mold distribution [4]. However, many immunocompetent patients have been described with infections caused by these agents [12]. NDMs are fungi that live in soil and plant debris and they are considered to be plant pathogens. They are not keratolytic and live on unkeratinized intercellular cement so they need previous keratin destruction by dermatophytes, trauma or any nail disease, but can also invade healthy nails [7].

The clinical manifestations vary with the host immunity, as well as with the form of contamination. Tosti and cols found that onychomycosis due to NDM resulted in proximal subungual nail alterations associated with painful periungual inflammation of the proximal nailfold [6]. Toenails are most affected (61.8%) [13]. Involvement of the nail is less severe in immunocompetent hosts and may lead to long evolution without complications, but disseminated infection has been described in immunosuppressed individuals [6,14].

The diagnosis of onychomycosis by NDM is not always straightforward. In the case described here the nail plate invasion by the fungus was confirmed by microscopic analysis of the nail clipping but molecular study was needed for the identification of *Fusarium oxysporum*.

The genus *Fusarium* is a *Hyalohyphomiceto* found in soil, air and water. The incidence of human infection by this mold has been increasing in recent years, both in imunossupressed [12] and immunocompetent patients [5].

All NDMs are not keratinolytic so they are usually regarded as a secondary invader of the nail plate. A predisposing factor such as immunosuppression or trauma may allocate the nail plate as a favorite location for invasion by the fungi. Ahmadi refers that in some adult patients the only factor that may have increased the

risk of infection by this type of fungus was working with water for a long period of time [15]. Moisture from the intrauterine environment and amniotic fluid contaminated by this agent may have been the determinant factors for nail infection by *Fusarium oxysporum* in our patient.

To the best of our knowledge this is the first case of onychomycosis by *Fusarium Oxysporum* in a newborn. In a previous study, infection by *Fusarium* represented 0.09% of the onychomycosis in a 15 years period in Tunísia. In another one, *Fusarium oxysporum* was identified in 20% (34 cases), and the youngest patient was 20-years-old [14].

NDMs are difficult to eradicate by using combining systemic treatments, and Fusarium onychomycosis was eradicated in only 40% of adult patients in a study performed in Italy [6]. The fact that the child was not infected with HIV may have contributed to good treatment response. In addition, the smaller and thinner nail surface and faster linear nail growth seen in children might have helped to eradicate the fungus. We wonder if the resolution would occur despite treatment, as it is known that azoles do not have activity against Fusarium species or if the ciclopirox could have accelerated the spontaneous clinical resolution.

We believe the same factors that determine the infection being restricted to the nail in congenital candidiasis can be extrapolated to congenital NDM infection. Because we were able to detect *Fusarium oxysporum* by molecular data, both in the placenta and the nail, and because signs of onychomycosis were present since birth, we assume the *Fusarium oxysporum*, just like in the case of Candida infection, was present in the mother's vagina and ascended to uterine cavity, invading amniotic membranes, contaminating amniotic fluid and finally invading placenta and umbilical cord, even the mother being asymptomatic. The mother was not treated for the fungal infection because of lack of symptoms during pregnancy and even at the time of the detection of the fungus in the placenta.

In the present case, *Candida* infection was first considered because onychomycosis by this agent was more probable in the clinical setting of the baby. Additionally, Candidiasis is frequent in HIV infected patients and her mother was HIV positive and immunosuppression was present at delivery. Congenital candidiasis usually presents as a skin rash but can also affect skin appendages [15]. In one case this infection was confined to nail plates and contamination was attributed to chorioamnionitis and transient amniotic fluid contamination [16]. A 6-week-old female with nail candidiasis was described and onychomadesis induced by the stress of a breech presentation during preterm labor and candidiasis limited to the bands of onychomadesis was attributed to weakened nail plate substrate that increased susceptibility to candida infection [17]. Sánchez-Schmidt et al. [18] reported 6 newborns with congenital candidiasis limited to nail plates. There were onycholysis, yellowish discoloration and roughness of the nail plates, hyperkeratosis and paronychia. Involvement of several fingernails was present in all patients and several toenails in 2 cases. Nail changes secondary to congenital candida infection were present at birth but also appeared between 2 and 6 weeks of life and there were no signs of immunosuppression in any of these cases. The authors stated that the direct contact of the fetus with the infected material may be the cause of congenital cutaneous candidiasis and the limited nail infection was attributed to flexion of fingers and fist that can result in entrapment of infected amniotic fluid around the nail bed.

In conclusion, we describe the first case to our knowledge of congenital onychomycosis in a child caused by *Fusarium oxysporum*. The infection being acquired in utero was proven by molecular methods with the identification of the fungus both in the nail and placenta, most probably as an ascending contamination/infection in a HIV-positive, immunosuppressed mother. We highly recommend considering NDM infection, including *Fusarium oxysporum*, as the differential diagnosis of suspected congenital fungal infection in HIV exposed or immunosuppressed newborns. Special attention should be given to the evaluation of the nails of HIV exposed newborns, for the purpose of early detection of potential life-threatening fungal infections.

Conflict of interest

There is no conflict of interest.

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