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Original article

Nails and skin co-infection by *Fusarium verticillioides* and *Proteus vulgaris* secondary to arterial occlusion of lower extremity

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ABSTRACT

Background: Post-traumatic *Fusarium* infection is rare. Arterial occlusive disease, a common vascular disorder in the elderly, often leads to ischemic necrosis of the lower extremities, which in turn increases the likelihood of secondary infections. Those secondary infections can be caused by bacteria, virus, or fungi.
Case report: We present the case of a 64-year-old male patient with a co-infection by *Fusarium verticillioides* and *Proteus vulgaris* on nails and foot skin, secondary to senile arterial occlusion on the lower extremities. The skin and nails recovered well after following stent implantation and a combination treatment of itraconazole and a macrolide antibiotic. A retrospective analysis of the literature identified 17 patients with *Fusarium* infection, all of whom were immunocompetent.
Conclusions: Trauma may be a predisposing cause of *Fusarium* infection. Combination of oral itraconazole and terbinafine, or amphotericin B and surgical means, are all effective treatments.

Coinfección en uñas y piel por *Fusarium verticillioides* y *Proteus vulgaris* secundaria a oclusión arterial de extremidad inferior

Palabras clave:
Oclusión vascular
Fusarium verticillioides
Proteus vulgaris
Traumatismo

RESUMEN

Antecedentes: Las infecciones postraumáticas por *Fusarium* son raras. La enfermedad oclusiva arterial, un trastorno vascular frecuente en los ancianos, suele provocar necrosis isquémica de las extremidades inferiores, lo que a su vez aumenta la probabilidad de infecciones secundarias. Dichas infecciones pueden estar causadas por bacterias, virus u hongos.
Caso clínico: Presentamos el caso de un paciente varón de 64 años con una infección por *Fusarium verticillioides* y *Proteus vulgaris* en las uñas y piel de los pies, secundaria a una oclusión arterial no traumática en las extremidades inferiores. Tanto la piel como las uñas se recuperaron bien tras la implantación de una endoprótesis vascular, y el tratamiento combinado de itraconazol y un antibiótico macrólido. Un análisis retrospectivo de la literatura arrojó los casos de 17 pacientes con infección por *Fusarium*, todos ellos inmunocompetentes.
Conclusiones: Los traumatismos pueden ser una causa predisponente de infección por *Fusarium*. La combinación de itraconazol oral y terbinafina, o anfotericina B y medios quirúrgicos, son tratamientos eficaces.

Members of the genus *Fusarium* are widely distributed in plants and soil, and are among the most challenging pathogenic fungi in domesticated crops. Some *Fusarium* species can be causative agents of disseminated infections in humans with severe or even moder-

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ate immunocompromised conditions, leading to a mortality rate up to 75%. While *Fusarium* infection may occur in immunocompetent humans, the clinical manifestations are usually localized and less invasive.[2,14,22,25] Today, the most common species isolated from clinical samples are *Fusarium solani* species complex (FSSC), followed by *Fusarium oxysporum* species complex (FOSC) and the *Fusarium fujikuroi* species complex (FFSC). *Fusarium verticillioides* is the most commonly isolated species in the FFSC group, and one of the most common plant pathogens.

Proteus vulgaris is a gram-negative bacterium widely distributed in the environment and in the intestinal tracts of humans and animals. Infections caused by *P. vulgaris* can affect urinary tract, (burn) wounds, bloodstream and respiratory tract.[18] The pathogenic mechanism is largely attributed to the adherence of pili or fimbriae to the host epithelium. Furthermore, *P. vulgaris* produces cytotoxic hemolysins that lyse red blood cells, and the consequent iron release supports bacterial growth.[18]

Senile lower limb vascular occlusion is a common vascular disorder in the elderly, characterized by lower limb ischemic pain, decreased skin temperature, or even gangrene in advanced stages. Secondary microbial infection under these conditions is very common.[28] We report a case of complicated nail and foot skin infection due to *F. verticillioides* (a member of FFSC) and *P. vulgaris*, both of which were secondary to senile arterial occlusion in lower limb. The patient presented with soft tissue ulcers on the foot and onychomycosis. A rapid recovery was achieved after the administration of arterial occlusion treatment combined with antifungal agents and antibiotics.

Clinical data

Clinical information

The patient was a 64-year-old man with a history of smoking for over 30 years, but the patient had stopped smoking approximately one year before. At that time (12 months before seeking medical advice), the patient had started feeling chills and pain in his left foot. He did not seek medical attention, but attempted to self-manage with topical warming measures. Two months later, the patient began to suffer an increasingly severe pain on the foot, which quickly developed a severe claudication. Four months later the patient was diagnosed with vasculitis in a local hospital, and a shot of an unknown drug was intradermally administered in the left foot. The symptoms were not significantly relieved after one month, and an ulcer appeared at the local injection site. Two months before coming to our hospital, all toenails on the patient's left foot began to thicken and acquired a brownish black color. The patient denied suffering from any underlying disease, including diabetes, hypertension or other cardiovascular disease, as well as having any family history disease that could explain those symptoms.

At day 0, the toenails showed a uniform brown to black color, with conspicuous thickening and massive debris underneath (Fig. 1A). A skin ulcer between the third and fourth toes was observed (Fig. 1B). The ulcerative wound at the injection site on the dorsum of the foot is shown in Fig. 1A. When examining the lesion it was noticed that the skin temperature of the affected foot was lower than that in the right foot, which suggested a local circulatory occlusion. The patient's bilateral iliac artery showed occlusion, and the left lower limb presented multiple arterial stenoses and occlusions under vascular CT examination (Fig. 1E and F).

The patient underwent comprehensive blood tests at day 0 as well, including complete blood count, electrolyte analysis, liver function, kidney function, blood glucose, glycosylated hemoglobin, and a standard lipid panel. The results of all tests were within normal ranges.

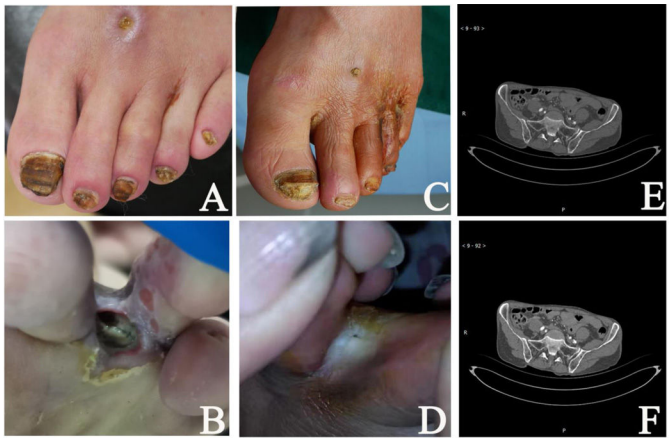

Fig. 1. The nail lesions, dorsalis pedis ulcers (A) and interphalangeal erosion (B) before treatment. (C) The postoperative follow-up showed that the toenails had improved, and the ulcer on the dorsum of the foot had partially healed. (D) The deep ulcer between the toes also partially healed. (E and F) Atherosclerotic occlusion of the left internal iliac artery.

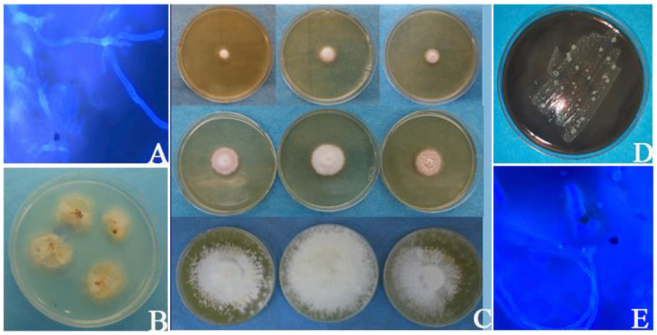

Fig. 2. (A) Ulcer secretions stained with calcofluor white and observed under microscopy. (B) Culture of the samples in PDA medium at 27 °C for 5 days. (C) From left to right and from top to bottom, plates with the colony were incubated at 20 °C, 27 °C and 37 °C for 48 h, 5 days and 10 days, respectively. (D) Bacterial culture of the samples on blood agar medium at 27 °C for 3 days. (E) Ulcer secretions stained with calcofluor white at postoperative follow-up.

Fungus isolation and identification

At day 0, a large number of long hyphae were observed under fluorescent microscopy with calcofluor white staining after KOH-digestion in both nail clippings and ulcer secretions of the foot (Fig. 2A). Toenails debris and ulcer secretion were also individually inoculated on blood agar and potato dextrose agar (PDA) supplemented with chloramphenicol. Both sets of plates were incubated at 27 °C.

The colonies grew rapidly on PDA plate. On day 5, white cottony colonies reached 5 cm in diameter at 27 °C (Fig. 2B). In order to test the temperature effect on the growth rate, the isolated fungal strain was cultured again on PDA at 20 °C, 27 °C and 37 °C, and we saw that the optimal temperature for this fungus was 27 °C (Fig. 2C). Under the microscope, conidiogenous cells strictly monophialidic were observed. Clusters of small, oval or short rod-shaped conidia (microconidial cells) surrounded by macroconidia were also observed (Fig. 3). Conidiogenous structures developed after 5 days at 27 °C; they were delicate, slender and falcate, but rather straight with 3–5 septa (Fig. 3A–F).

To identify the fungal species, we amplified and sequenced the *TEF1* gene in the isolated fungal strain for molecular identification. BLAST analysis showed 99.85% similarity to the *TEF1* sequence of *F. verticillioides* strain mrez44, deposited in the NCBI GenBank. A phylogenetic tree was then built using MEGA v6 with maximum

Table 1
Antifungal MICs of *Fusarium verticillioides* strain (CCJNMM-1399).

Strain	MCF (μg/ml)	TBF (μg/ml)	AMB (μg/ml)	VRC (μg/ml)	ITC (μg/ml)
CCJNMM-1399	>8	0.5	0.5	2	4
ATCC 22019	0.125	0.015	0.5	<0.03	<0.03

The minimum inhibitory concentration (MIC) corresponded to the lowest drug concentration that caused 100% of inhibition of visible fungal growth at 48 h. The test was performed in duplicate. The American Type Culture Collection (ATCC) strain *Candida parapsilosis* (ATCC 22019) was included as quality control.
Abbreviations: MCF: micafungin; TBF: terbinafine; AMB: amphotericin B; VRC: voriconazole; ITC: itraconazole; CCJNMM: Culture Center of Jining Medical Microbiology.

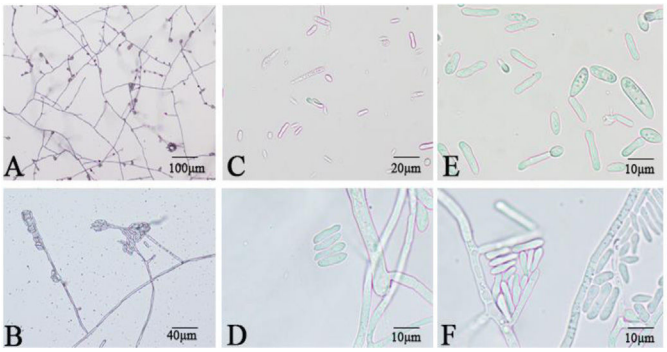

Fig. 3. (A) In slide culture, many slender hyphae and multiple right-angled branches were seen under the microscope. (B) The conidiogenous cell is a single bottle peduncle, and the small conidial conidiogenous cell is on the aerial hyphae, slender and columnar. (C) Small conidia, oval or short rod-shaped, most of them having no septum, but some of them having one septum. Macroconidia are linear, slender, straight or slightly curved, mostly 3- to 4-septate, and a few 1- to 2-septate or 5-septate. (D–F) Growth morphology and arrangement of conidia.

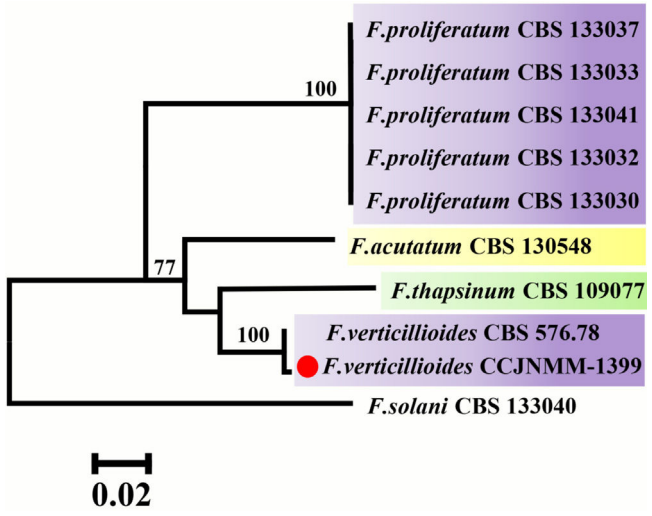

Fig. 4. Maximum likelihood (ML) phylogenetic tree created from the *TEF1* sequences of 10 FFSC including our isolate CCJNMM-3 and 9 representative strains. Sequences with bootstrap above 70% are shown. The tree was rooted with *Fusarium solani* CBS 133040 (FSSC).

likelihood (ML) analysis with nonparametric bootstrapping using 1000 replicates. In this phylogenetic tree, the *TEF1* gene sequences from molecular siblings of *F. verticillioides*, *Fusarium proliferatum*, *Fusarium acutatum*, *Fusarium thapsicum*, and the epitype strain *F. verticillioides* CBS 576.78, all rooted from *F. solani* CBS 133040 – were compared to our cultured and isolated strain. The isolate from our patient showed 99.5% similarity to CBS 576.78, with a 100% support rate (Fig. 4).

Bacterial identification

On the blood agar culture plate at 27 °C, no fungal colony was recovered the third day. Instead, a thin film composed of bacterial colonies with corrugated edges were observed, which were presumptively identified as *Proteus* spp. (Fig. 2D). Matrix-assisted laser desorption ionization time of flight mass spectrometry (MALDI-TOF MS) was then used for the species identification. When compared to reference strains in the MALDI-TOF database, our bacterial strain was identified as *P. vulgaris*.

Based on the clinical symptoms of the patient and the identification of the microorganisms isolated, the patient was diagnosed with post-traumatic *F. verticillioides* and *P. vulgaris* co-infection secondary to arterial occlusion.

Treatment

At day 0 the patient began an empirical treatment of oral itraconazole 200 mg, and clarithromycin 500 mg, twice per day to control the infection. He was also treated topically once a day with a wound cleaning procedure and iodophor in the ulcered area. At day 15 the ulcer on the dorsal surface of the foot started to heal; however, a new deep ulcer appeared between the third and fourth toe, accompanied by odorous secretions. At day 20 the patient had an arterial stent implanted in the left lower limb. The skin temperature of the left foot quickly rose to normal values after that surgery.

At day 10 the isolated fungal strain was submitted to an antifungal susceptibility testing. The results showed that voriconazole and amphotericin B were effective against that strain, itraconazole had an intermediate activity, and the strain was resistant to terbinafine and micafungin, as shown in Table 1. The patient, thus, continued the treatment with itraconazole 200 mg twice a day, but this treatment was combined with topical tinidazole (cream formulation) for treating the fungal infection, and roxithromycin, to treat the bacterial infection, based on our clinical experience with such infections.

At day 27, one week after the surgery, the foot pain was relieved, the ulcer had stopped its progress, the color of the toenails was noticeably lighter, there was less subungual debris (Fig. 1C), and the mycelium in the skin lesion site was significantly reduced, as observed in a biopsy specimen looked at under fluorescent microscopy (Fig. 2E).

At day 65, the nails and foot lesions had significantly improved, and the ulcer had significantly healed (Fig. 1D). The timeline of disease progression is shown in Fig. 5, and the patient is currently being followed up.

Literature review

Fusarium species are rather a common cause of invasive infection in severely immunocompromised patients, but are rare in immunocompetent individuals. A comprehensive literature search for similar cases was carried out with the keywords "*Fusarium* / Skin infection / Ulcer" in medical databases including CNKI, WANFANG DATA, CQVIP, PubMed, and Embase. We searched articles published between January 2000 and January 2020. The cases included immunocompetent patients in whom the infection showed up with ulcers, and the identification of *Fusarium* was achieved by means of culture and/or molecular test. Those cases lacking both a culture

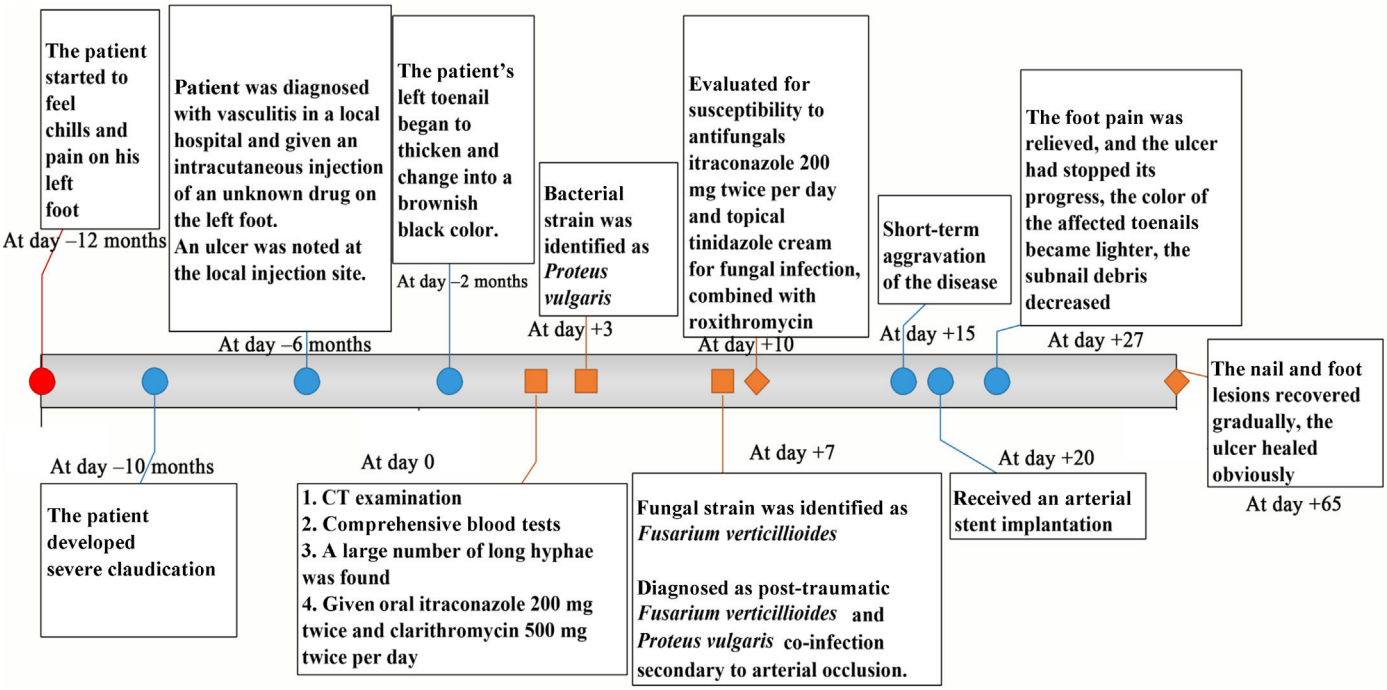

Fig. 5. Patient's disease evolution over time.

Table 2
Cases of *Fusarium* infections in people with normal immunity and skin ulcers: summary of cases reported in the literature.

Case no.	Age (years)	Sex	Body site	Country or region	Cause	Species	Treatment	Identification technique
1[43]	59	M	Leg	China	Trauma	*F. verticillioides*	ITC FCZ	EF-1α
2[8]	24	M	Leg	Spain	Trauma	*F. solani*	KCZ	SEM
3[46]	50	F	Foot and leg	China	Trauma	*F. solani*	AMB Surgery	Culture
4[47]	54	M	Perineum	China	–	*F. solani*	–	Culture
5[36]	73	F	Leg	–	Trauma	*Fusarium* sp.	ITC KCZ	SEM
6[17]	68	M	Leg	China	–	*F. verticillioides*	ITC	Culture
7[24]	15	F	Face and hand	China	–	*F. verticillioides*	TBF	SEM
8[34]	55	M	Leg	China	–	*F. solani*	ITC	SEM
9[40]	68	M	Feet	Qatar	Gangrene	*F. oxysporum*	Surgery	ITS
10[9]	72	F	Foot	China	Trauma	*F. sublutinans*	TBF	Culture
11[45]	56	M	Leg	China	Gangrene	*F. solani*	Surgery	Culture
12[44]	59	M	Arm	China	Trauma	*F. verticillioides*	Herbal	Culture
13[20]	9	M	Perineum and leg	China	Trauma	*F. oxysporum*	TBF Surgery	Culture
14[33]	64	M	Leg	China	Trauma	*F. solani*	Surgery	Culture
15[35]	29	F	Hand	Italy	–	*F. oxysporum*	Surgery	SEM
16[21]	54	M	Foot	China	Trauma	*F. solani*	TBF Surgery	ITS
17[39]	35	M	Leg	China	–	*F. verticillioides*	FCZ VOC	SEM

Abbreviations: EF-1α: elongation factor-1α; SEM: scanning electron microscope; ITS: internally transcribed spacer; ITC: itraconazole; FCZ: fluconazole; KCZ: ketoconazole; AMB: amphotericin B; TBF: terbinafine; VOC: voriconazole; M: male; F: female

and molecular identification that were diagnosed by pathological biopsy or clinical experience only were excluded. The search showed a total of 17 cases.

Among the 17 patients, the male-to-female ratio was 12:5. The age of the patients ranged 9–73 years old, with a median age of 55 (interquartile range, 57–69 years). Patients over 50 years old accounted for 70.6% ($n = 12$) of the sample. Fifteen patients (90%) had skin lesions located in the extremities, and nine (53%) had a history of trauma. *F. verticillioides* and *F. solani* were the most common pathogens among these patients ($n = 12$, 70.6%). Surgery, antifungal drugs or a combination of both treatments led to good results in these immunocompetent patients (Table 2). Our case closely resembles the cases above in its broad outlines, except for being a co-infection with a bacterium, and in having a vascular occlusion as a possible suppressor of local immune response (none of the cases reported any vascular occlusion).

Discussion

The *Fusarium* genus, consisting of plant pathogens mainly, is found all over the world, especially in the tropics and subtropics.[11,19,38] Occasionally, however, it can be found as an opportunistic pathogen in humans. In patients with long-term neutropenia and immunodeficiency, such as patients with hemato-

logical malignant tumors, *Fusarium* strains may cause systemic or disseminated infections.[26] The frequency of such deep and disseminated *Fusarium* infections has increased in recent years due to the growing number of immunocompromised patients.[4] Some studies have shown that *Fusarium*, when superficial and deep infections occur together, is the second most common fungal opportunist after *Aspergillus*.[29,30,41] The infection in most of the patients with normal immunity shows up with onychomycosis, corneal infection, or soft tissue infection.[3,12,16,25,31] Several major *Fusarium* complexes have been connected to human infection, including the FSSC complex that is commonly found in soil.[48] Members of FSSC, together with FOSC, are responsible for about 80% of soft tissue infections in humans and animals worldwide, and can cause onychomycosis as well.[14] On the other hand, FFSC members – including *F. verticillioides,* described in this case report – are generally associated with plant diseases and are well known for their mycotoxin production. However, they are much fewer common causes of traumatic or disseminated infection.[10]

In our clinical case, the isolated pathogen, *F. verticillioides*, grew slower at 37 °C when compared to the growth at 27 °C, which is consistent with the natural habitat in tropical and subtropical zones. The artery occlusion in the lower extremity of our patient, probably due to a long history of heavy smoking, restricted blood circulation and thereby decreased the temperature on the lower extremity. We speculate that the decreased skin temperature provided a more suitable environment for the fungal growth. Also, the local immune function might have been impaired due to the lower limb blood circulation disorder, which failed to stop the secondary infection by both fungus and bacterium as we describe (in this case, an infection by *P. vulgaris*). Unlike the strong temperature preference of the fungus, *P. vulgaris* has a wider range of temperature and can propagate rapidly in the range 20–40 °C.

The rapid growth rate, the morphology of conidia, and the observations through the mycological examination immediately led to a diagnosis of *Fusarium* infection. However, because members of the different *Fusarium* complexes are morphologically similar, molecular testing is often required for an accurate species identification, as identification at the species or even strain level is important for subsequent antifungal drug selection and treatment,[15,31] particularly in *Fusarium* due to its high intrinsic antifungal resistance. Traditional ITS sequencing is sufficient to differentiate between species complexes, but it is not for identifying any species within a complex. Numerous molecular phylogenetic approaches have been employed to facilitate accurate species identification within the genus *Fusarium* over the past 20 years. Among these methods, polymorphism in gene sequences, such as the *TEF1* gene, have shown a high capability for differentiating among closely related species.[27] In addition, the *RPB2* gene also shows a high resolving power and allows a correct setting of clinically relevant clades. Although both *TEF1* and *RPB2* markers are suitable for species identification, some studies suggest that *RPB2* yields more reliable results in *Fusarium* than the *TEF1*, while others report that *TEF1* shows statistically supported intraspecific variability that is not observed with *RPB2*.[37,49] In addition, MALDI-TOF has also been used for the identification of clinical isolates of *Fusarium* at the species level.[43]

Proteus species can cause wound infection, food poisoning, septicemia, and other infections. The genus comprises dynamic, phenylalanine deaminase- and urease-positive, hydrogen sulfide-producing bacteria, which are widely distributed in soil, water and fecal matter. Among them, *Proteus mirabilis* and *P. vulgaris* are the main infectious species. A Chinese study showed that the isolation rate of *P. vulgaris* in infected wounds was about 48%.[23] Multicenter antibiotic sensitivity tests revealed that *P. vulgaris* is sensitive to β-lactam antibiotics, followed by macrolides, but more than half of the strains were resistant to sulfonamides.[7,24] In our case, the skin infection responded well to macrolides.

The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the European Confederation of Medical Mycology (ECMM) recommend amphotericin B and voriconazole as the first treatment of fusariosis.[42] In immunocompromised patients, *Fusarium* is resistant to most antifungal agents, which is particularly problematic[5]; however, terbinafine, voriconazole and itraconazole are usually quite effective to treat skin infections in immunocompetent patients, like happened in the cases reviewed in this report. Drug sensitivity tests from several laboratories showed that *F. verticillioides* had highly consistent sensitivities to antifungals. Amphotericin B, terbinafine and voriconazole show a high antifungal activity against this species, with MICs ranging from 2 to 4 μg/ml, 0.125 to 1 μg ml and 2 to 4 μg/ml, respectively. According to the aforementioned organizations, itraconazole is not recommended as a first-line treatment, and its antimicrobial effect is indeed poor in *in vitro* testing.[1,6,13,32] In the present case, however, the strain showed an intermediate susceptibility to itraconazole in an *in vitro* fungal susceptibility test, and the patient responded well to the oral treatment with this antifungal agent, perhaps due to the patient's immunocompetence. Based on the foregoing evidence, it is not difficult to conclude that *in vitro* antifungal susceptibility testing does not have an absolutely reliable role in the treatment of *F. verticillioides* infection.

Conclusion

Co-infection secondary to senile arterial occlusion of lower extremities is not rare. The possibility of bacterial and fungal co-infection should be considered in patients who do not respond well to antibiotics alone. Early and accurate etiological diagnosis and drug sensitivity testing may reduce the likelihood of disseminated infections. However, the improvement to pre-vascular conditions by surgery and active local treatments to stimulate blood circulation are likely to prove decisive for effective control of the infection.

Conflicts of interest

The authors have no conflicts of interest in relation to this study.

Acknowledgements

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