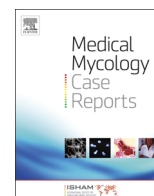




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Thermomyces lanuginosus infective endocarditis: Case report and a review of endocarditis due to uncommon moulds [☆]

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ABSTRACT

We describe a case of *Thermomyces lanuginosus* endocarditis, the first reported in a living patient, and review the literature to delineate the clinical characteristics, investigations and management of endocarditis due to such rare but emerging mould pathogens.

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1. Introduction

Fungal endocarditis, which accounts for less than 10% of all cases of infective endocarditis, is most often due to *Candida* and *Aspergillus* species [1]. *Thermomyces lanuginosus*, on the other hand, is an example of a diverse group of previously rare or emerging mould pathogens with protean clinical manifestations, including cardiac valve infection. The first report of *T. lanuginosus* endocarditis was made postmortem over 20 years ago in a patient who had prior valvular surgery for *Staphylococcus aureus* infective endocarditis [2]. There have been no published reports of *T. lanuginosus* endocarditis in a living patient. In this report, we highlight the clinical course and management of a patient with *T. lanuginosus* endocarditis whose illness spanned more than 9 years. We also review the literature for endocarditis caused by this, and other uncommon but emerging non-*Aspergillus* moulds.

2. Case

A 31-year-old lady, 10 weeks postpartum, developed fever, chills and lethargy after a caesarean section in July 2003 (Day 0).

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The temperature was 39.3 °C and there was a vasculitic lesion on the right great toe. Cardiovascular examination revealed new ejection systolic and diastolic murmurs. Blood cultures grew *Enterococcus faecalis* and a transoesophageal echocardiogram (TOE) showed a 12 mm vegetation on the aortic valve with aortic regurgitation. A porcine aortic valve prosthesis was inserted. Microscopic examination of the native valve revealed gram positive cocci but no microorganisms were cultured. She received 6 weeks of intravenous ampicillin and gentamicin with clinical response.

Twelve months later (Day 365), she represented with fever and embolic lesions to the left great toe and sole of foot. Multiple blood cultures were negative. A transthoracic echocardiogram (TTE) demonstrated 13 mm × 5 mm vegetation at the left coronary cusp. She underwent radical debridement and replacement of the bioprosthetic aortic valve with another (bioprosthetic valve) and had the ascending aorta reconstructed with autologous pericardium.

Culture of intraoperative specimens inoculated onto blood and chocolate agars grew a white fluffy fungus within 4 days of incubation at 35 °C in air. Unusually, the fungus was thermophilic, growing better at 42 °C than at 30 °C or 35 °C. The fungus was identified as *T. lanuginosus* by conventional morphology [3] (Figs. 1–3) and the species identity was confirmed by DNA sequence analysis of the internal transcribed spacer (ITS) 1 and 2 regions of the fungal ribosomal RNA gene using published primers and standard sequencing methodologies [4]. The isolate's sequence was compared to those in the GenBank database using the BLASTn search tool. The PCR product showed 100% identity to

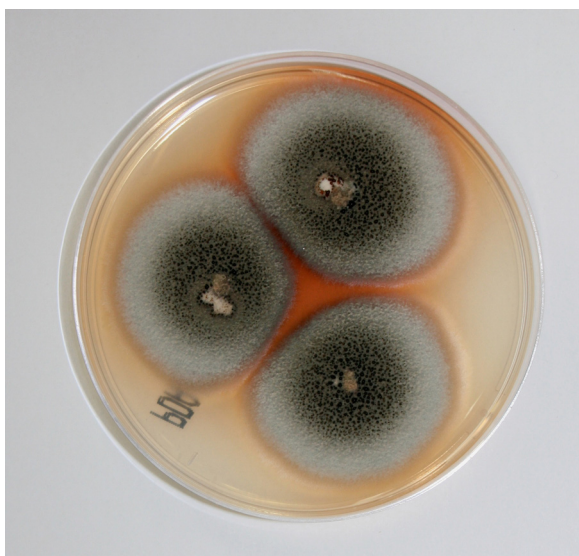


Fig. 1. *Thermomyces lanuginosus* colonies growing on Potato Dextrose Agar (PDA) at 5 days at 42 °C demonstrating greenish grey colonies with a pink vinaceous pigment diffusing into the agar.

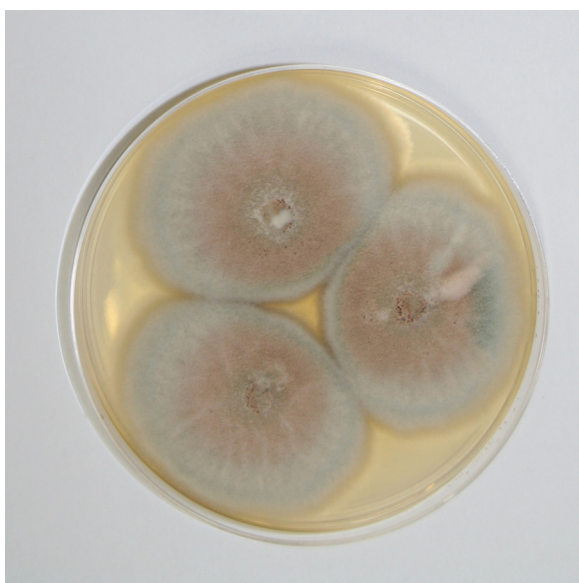


Fig. 2. *Thermomyces lanuginosus* colonies on Sabouraud agar at 5 days at 42 °C.

GenBank sequence JN106393 and >99% identity to GenBank sequence AF096278. Antifungal susceptibility testing was performed using Etest strips (AB Biodisk, Solna, Sweden) after incubating plates in air for 4 days at 42 °C. The longer incubation time was necessary to allow sufficient growth of the fungus and 42 °C rather than 35 °C was selected as the better temperature for growth. The following MICs (in mg/L) were observed: amphotericin >32, itraconazole 0.032 and voriconazole 0.006. She was treated with intravenous liposomal amphotericin (LAMB: 6 mg/kg daily) for 2–3 weeks followed by oral voriconazole (4 mg/kg daily after a loading dose of 6 mg/kg daily).

However, she developed severe back pain six weeks later (Day 407) with discitis and osteomyelitis at the T10–11 and L2–4 vertebral levels evident on magnetic resonance imaging (MRI). An abdominal computed tomography (CT) scan showed a left common femoral artery mycotic aneurysm, later repaired with a venous patch. CT guided core biopsy of the spine were unrevealing. A TOE showed no vegetations. She had empiric ceftriaxone

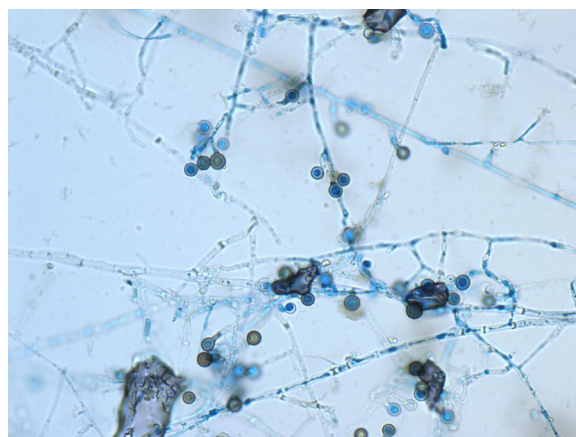


Fig. 3. Microscope slide (×400 magnification) from a subculture (PDA) stained with lactophenol cotton blue showing short, unbranched conidiophores bearing solitary thick-walled, dark brown conidia.

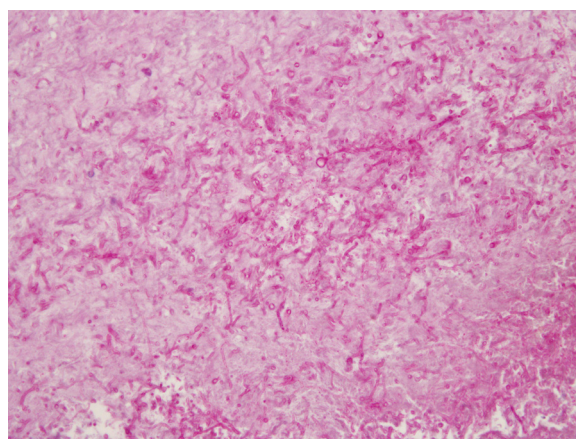


Fig. 4. PAS stain of valvular tissue (x400 magnification) demonstrating abundant fungal hyphae and conidia.

and vancomycin for 6 weeks. Voriconazole 4 mg/kg twice daily was continued and was ceased after a total of 18 months of therapy in July 2005 (day 954). Her history was complicated by two further episodes of endocarditis. In December 2007 (day 1784), she was treated with a course of intravenous penicillin (6 weeks) and gentamicin (2 weeks) for *Streptococcus acidominimus* endocarditis. She subsequently had ceftriaxone and vancomycin for an additional episode of presumed culture negative endocarditis associated with vasculitic lesions to the foot in June 2009 (Day 2229).

In October 2010 (Day 2714), she re-presented with acute onset of bilateral cold and pulseless lower limbs. A CT angiogram demonstrated bilateral common iliac artery occlusive thrombi. TOE revealed the prosthetic aortic valve to be dehisced from the aortic root, with dilatation of the root and presence of large thrombi. She had an urgent aorto-iliac thromboembolectomy, followed by a mechanical aortic valve replacement as well as insertion of a permanent pacemaker for complete heart block. Histopathological examination of tissue from the valve (Fig. 4) and embolus demonstrated numerous branching fungal hyphae, and *T. lanuginosus* was grown on culture.

Antifungal susceptibility testing using the Sensititre YeastOne (TREK, Thermo Scientific, USA) colorimetric broth microdilution method and incubated at 42 °C for 4 days revealed the following MIC results (in mg/L): amphotericin 4, posaconazole 0.25 and voriconazole 0.06. She was commenced on voriconazole 4 mg/kg twice daily following a loading dose of 6 mg/kg twice daily and

was discharged with view to lifelong voriconazole therapy. Plasma voriconazole levels ranged between 0.8 to 1.7 mg/L.

In April 2011 (Day 2894), she developed a worse cardiac failure. A TOE demonstrated aortic regurgitation and vegetations. She underwent her fourth cardiac surgery with replacement of the aortic valve and root with a homograft. Operative tissue again cultured *T. lanuginosus* with similar antifungal susceptibility results to those in 2010. Whilst awaiting susceptibility results, she was started on posaconazole given the apparent failure of voriconazole therapy. However, once susceptibilities were available she was re-started on voriconazole and terbinafine 250 mg daily. With higher doses of voriconazole to maintain adequate voriconazole levels, she developed hepatitis and severe photosensitivity complicated by multiple actinic keratoses requiring excision and fluorouracil (5-FU). She was changed to itraconazole 200 mg twice daily in December 2012 (Day 3499) with levels maintained above 1000 ng/L. Upon cessation of voriconazole, her liver function tests normalised and photosensitivity markedly improved. At 25 months of follow up (Day 3709) since her last surgery there was no evidence of recurrence. We plan to continue itraconazole indefinitely.

3. Discussion

The case of *T. lanuginosus* reported here is notable for its rarity, and for its long course of illness over more than 9 years in an otherwise immunocompetent patient. Previously only one case of endocarditis has been reported to be caused by *T. lanuginosus*. In contrast to this report, our patient (i) had the diagnosis made during life (ii) had complications with discitis and osteomyelitis (iii) had massive emboli to bilateral common iliac arteries (iv) had concurrent bacterial endocarditis (v) relapsed many years after initial diagnosis and treatment (vi) and thus far has survived on azole therapy and recurrent surgeries. In addition, this case also highlights many features of endocarditis due to moulds other than *Aspergillus* species.

Our patient had a prosthetic heart valve inserted following bacterial endocarditis, and the *T. lanuginosus* endocarditis was most likely the result of contamination with the fungus at the time of her initial surgery. In cases of prosthetic valve endocarditis, the time delay between initial surgery to the diagnosis of endocarditis can range from a few days or weeks [5], up to 14 years [6]. As in our patient, the valve often becomes infected at the time of surgery in cases of early infections [5]. In others, intravenous drug use [7], infected intravenous lines [8], intracavernous penile injections [6] and contaminated traumatic injuries are implicated [9].

Risk factors for mould endocarditis include valvular heart disease [10], prior cardiac surgery, including valvular surgery [2,5,6,11,12], coronary artery bypass grafting [13], pacemaker or defibrillator insertion [14,15] and surgery of the aorta [16], immunosuppression including pregnancy and prematurity [8,12,14,17], intravenous drug abuse [7] and having intravenous lines [8]. A key finding in our patient was the presence of major embolism at presentation which was recurrent. Major peripheral embolism is a common finding in non-*Aspergillus* mould endocarditis, given the propensity for fungi to result in large vegetations [1]. Embolism can occur to the arteries of the lower limbs including the aorta and the vertebral discs, as in our patient, and to other areas such as the brain, lungs, mesenteric vessels, spleen, kidney and liver [5–7,12,16]. Symptoms at presentation may include fever, chills, cardiac failure, neurological symptoms including weakness, confusion and visual impairment, respiratory symptoms, skin lesions, chest pain, leg pain, back pain and constitutional symptoms such as anorexia, malaise and weight loss [5–7,10–16]. Our patient presented twice with systemic embolisation and the third time with cardiac failure yet remaining afebrile with normal white cell count during all three presentations.

Diagnosis of mould endocarditis is challenging. Often there is a delay as blood cultures can be negative, as in our patient. The diagnosis may be made from tissue histopathology [5,10–12,14,17], tissue microscopy and culture [6,7,10,11,13–17] and nucleic acid amplification tests [7]. Unusual or atypical fungal isolates can be misidentified or mistaken for environmental contaminants [17]. In many cases, the diagnosis is made after a postmortem [2,5]. Concurrent bacterial endocarditis can occur, as in our patient when she presented with persistent *S. acidominimus* bacteremia [10]. Culture negative embolic events in a patient with a history of mould endocarditis or an episode of bacterial endocarditis on a background of prior mould endocarditis should raise suspicion for relapse of fungal endocarditis.

Fungal endocarditis is fatal without treatment. Successful treatment requires both medical and aggressive surgical management. Amphotericin has been available for clinical use since the 1960s, itraconazole since 1992, voriconazole since 2002 and posaconazole since 2006. Of the rare mould endocarditis cases published in the literature, the majority were published prior to year 2000. Hence, data on the use of the newer second generation azoles in rare mould endocarditis is limited. We report the first case of prolonged survival to 9 years with aggressive surgery and voriconazole therapy for *T. lanuginosus* endocarditis. Voriconazole has excellent *in vitro* activity against less common filamentous fungi [18]. In our patient relapse occurred whilst she had subtherapeutic voriconazole levels. However, maintaining appropriate therapeutic levels can be challenging due to large inter and intrapersonal variations in voriconazole levels due to factors including non-linear saturable pharmacokinetics and genetic polymorphisms of CYP2C19 [19]. The role of terbinafine in these rare mould endocarditis cases is unclear. There are *in vitro* data and case reports to support the use of terbinafine in the treatment of filamentous fungi [20]. Antifungal synergy testing and combination therapy with voriconazole and terbinafine may have a role in such difficult cases. There is one published case report of *Curvularia lunata* aortic valve endocarditis managed successfully with 60 days of ketocozazole, followed by 7 years of terbinafine 125 mg twice daily with the patient being alive at 18 month follow up postcessation of therapy [11]. After the most recent relapse, we added terbinafine to our patient's management.

Despite appropriate treatment, the mortality rate from uncommon mould endocarditis remains high. Relapses may occur, often late as in our patient, and short term follow up will miss these. Our patient had her first diagnosed relapse 6 years after the initial diagnosis. Given the high morbidity and mortality, and the potential for relapse, patients with uncommon non-*Aspergillus* mould endocarditis may require, lifelong suppressive antifungal therapy, with maintenance of appropriate therapeutic drug levels.

Conflict of interest statement

None.

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