CASE REPORT

Native valve endocarditis due to *Candida parapsilosis* in an adult patient

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Candida endocarditis is rare, but associated with a high mortality. The most common species implicated is *Candida albicans*. The epidemiology of invasive *Candida* infections is changing, with a predominance of non-albicans species causing invasive disease. We describe a case of *Candida parapsilosis* endocarditis in an HIV-positive patient with pre-existing mitral valve disease and renal failure on haemodialysis. The patient presented with fever and malaise. Clinical examination revealed pulmonary oedema and severe mitral regurgitation. Blood cultures were positive for *C. parapsilosis*. β-D-glucan assay levels were elevated. An echocardiogram showed large, friable vegetations on the mitral valve. *C. parapsilosis* was cultured from the haemodialysis tip and the vegetations. The patient responded well to mitral valve replacement and antifungal therapy. A high index of suspicion and aggressive diagnostic modalities and therapy are essential in patients with candidaemia, to decrease mortality due to this condition.

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Fungal endocarditis accounts for 2 - 4% of all endocarditis cases. Of these cases, 25% are attributed to *Candida albicans*, other *Candida* species account for 25%, and *Aspergillus* species and other fungi account for the remainder.[1-3] Predisposing factors for *Candida parapsilosis* endocarditis include prosthetic valves, intravenous (IV) drug use, parenteral nutrition, abdominal surgery, immunosuppression, treatment with broad-spectrum antibiotics and pre-existing valvular disease.[4] Mortality for *Candida* endocarditis is high (67%), with a lower mortality in younger patients with a history of IV drug use.[5] We present a case of native valve *C. parapsilosis* endocarditis, which to our knowledge, is the first reported case in South Africa.

Case presentation

A 46-year-old HIV-positive man with a history of hypertension and renal failure presented with fever and malaise. The patient was receiving antiretroviral therapy (ART) and haemodialysis. Clinical examination of the patient revealed fever, pulmonary oedema and severe mitral regurgitation. Blood cultures, β-D-glucan assays and a full blood count were undertaken. The patient remained febrile after 48 hours and antifungal therapy was commenced.

Laboratory findings

Upon admission, white blood cell and $CD4^+$ counts were 11.37 x 10^9 cells/l and 435 cells/μl, respectively. The HIV viral load on admission was undetectable, as it had been for the previous 6 months. Blood cultures were positive for *C. parapsilosis*, which was susceptible to all antifungals tested (amphotericin B, fluconazole, voriconazole and caspofungin). Fungal identification and susceptibility testing were performed using the Vitek 2 (Biomerieux, France) automated system. The patient was treated with IV fluconazole in view of the impaired renal function and susceptibility of the isolate to this agent. Blood cultures taken 48 hours after commencing fluconazole were positive. The haemodialysis catheter was removed and replaced. Culture of the catheter tip revealed *C. parapsilosis* with susceptibilities corresponding to the blood culture isolate. β-D-glucan assay results were elevated (>523 pg/ml) on the day of the initial blood culture. The patient was referred for cardiology assessment. The echocardiographic examination demonstrated large, friable mitral valve vegetations, in keeping with fungal infective endocarditis (Fig. 1).

The patient underwent mitral valve resection and tissue was submitted for microbiological and histological evaluation. The tissue culture isolate corresponded to the admission blood culture and catheter tip culture findings. Histological evaluation showed fibrotic, hyalinised heart valve, with stromal neovascularisation, suggesting a pre-existing chronic valvulitis (Fig. 2a). Friable surface vegetations composed of fibrin, degenerating neutrophils and numerous fungal yeast forms were noted (Fig. 2b). Blood cultures performed 2 weeks after surgery were negative. Repeat β-D-glucan assays remained elevated 4 weeks after therapy. The patient was re-evaluated,

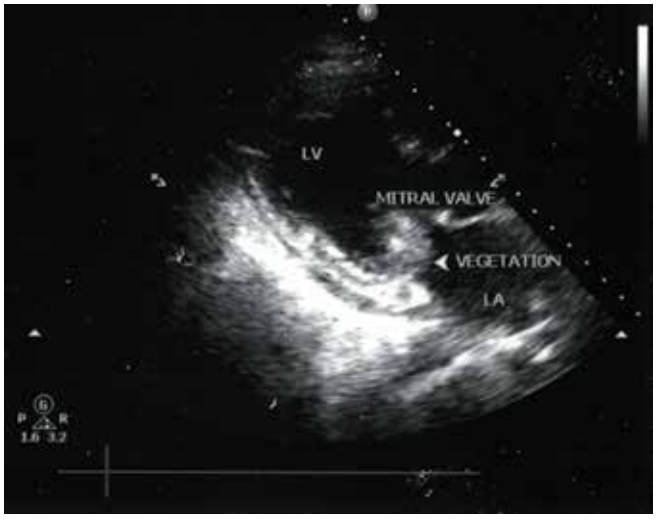

Fig. 1. Echocardiogram showing the size and position of the vegetation.

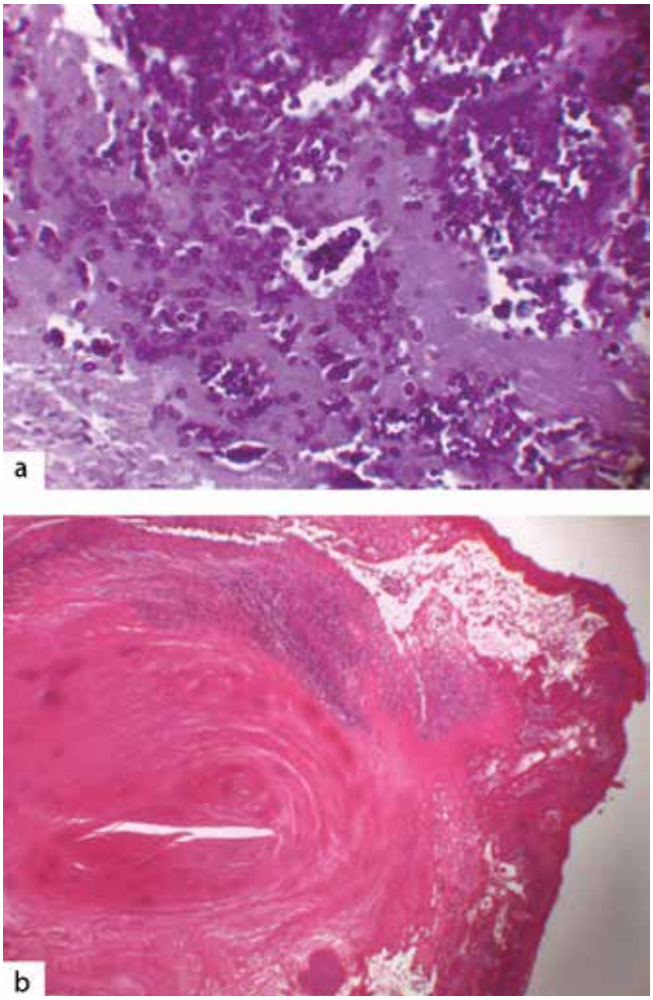

Fig. 2. Histological examination of the infected mitral valve with vegetations showing pre-existing fibrosis and infected vegetation.

but remained clinically stable. Treatment doses of fluconazole were discontinued after 6 weeks, and oral suppressive fluconazole therapy was continued. Two months following diagnosis, the patient remains clinically stable, and continues haemodialysis, fluconazole suppressive therapy and ART.

Discussion

This report presents an uncommon disease in a patient with several predisposing factors: renal failure, *in situ* IV catheter, admission broad-spectrum antimicrobial agents, pre-existing valvular heart disease and HIV infection. A catheter-related portal of entry has been reported in 80% of cases of *C. parapsilosis* endocarditis in one series of *Candida* endocarditis cases.[5] Other described risk factors include abdominal surgery, IV drug use and prosthetic heart valves.

Candidiasis is the most common opportunistic infection in HIV-positive patients with $CD4^+$ counts <200 cells/μl. The most prevalent presentation is mucocutaneous candidiasis, although invasive candidiasis has been reported.[6] Highly active antiretroviral therapy (HAART) has been shown to decrease the rate of candidiasis in this population.[7] Although this patient was HIV-positive, his disease state was controlled on ART at the time of diagnosis. Thus, the propensity for *C. parapsilosis* to adhere and form biofilms, together with the indwelling haemodialysis catheter, broad-spectrum antimicrobials on admission and chronic valvular disease, were more significant in the pathogenesis of endocarditis in this case.

The epidemiology of invasive *Candida* infection has changed. Improvements in medical therapy have resulted in increased survival of critically ill patients who are exposed to longer durations of broad-spectrum antimicrobial therapy. The incidence of non-albicans candidaemia has also increased, in some situations accounting for a higher percentage of isolates compared with *C. albicans* candidaemias.[8] This change is reflected in our local setting as well, where surveillance data from 2009 to 2012 from selected sites in SA were analysed. The data showed a predominance of non-albicans candidaemia in 4/6 sites, with *C. parapsilosis* being the most common non-albicans species (unpublished data, Dr N Govender, National Institute of Communicable Diseases, South Africa, 2012). This suggests a higher propensity for invasive disease, such as fungal endocarditis, to be caused by this species.

The clinical presentation of *Candida* endocarditis is non-specific. Fever and cardiac failure may be absent and embolic phenomena may be the presenting feature.[5] Most patients have a risk factor for invasive candidiasis. Documented predisposing factors in *C. parapsilosis* endocarditis present in this patient included *in situ* haemodialysis catheter, probable pre-existing chronic valve disease, admission broad-spectrum antibiotics, and immunosuppression mediated by HIV and renal failure. The aortic valve is most commonly affected.[4] Mitral valve involvement in this instance was likely due to pre-existing chronic valve disease.

Due to the non-specific clinical features, correct diagnosis requires a high index of suspicion in patients with known risk factors. Persistant candidaemia, as in this case, should prompt further clinical evaluation, as well as early transoesophageal echocardiography, as recommended by the European Society Clinical Microbiology and Infectious Diseases guidelines for non-neutropenic adult patients with candidaemia.[9]

The value of the β-D-glucan assay in diagnosis of invasive candidiasis has been reviewed.[5] The assay measures components of the fungal cell wall present in the bloodstream. This assay may be positive before the traditional culture results are available. It has a high sensitivity (77%) and specificity (83%).[10] The β-D-glucan assay levels were found to be significantly higher in patients infected with *C. parapsilosis, Candida tropicalis* and *Candida guilliermondii* endocarditis, than with *C. albicans* endocarditis.[5] There are no formal recommendations regarding the use

of this assay as a diagnostic tool; however, the β-D-glucan assay has a role in negating a diagnosis with a high negative predictive value and supporting a positive diagnosis where other clinical and laboratory features are in keeping with a fungal endocarditis.[3,9] Interestingly, the β-D-glucan assay remained elevated after commencement of treatment and following negative follow-up blood cultures. This has been described previously, where elevated levels during the early phase of the disease do not always return to baseline during the early stages of antifungal therapy.[5,10] This assay is also positive in patients with *Pneumocystis jiroveci* pneumonia. Thus, a positive assay must be interpreted with caution and correlated with the clinical picture in immunocompromised patients. This patient did not have any clinical features supporting a diagnosis of *P. jiroveci* infection. β-D-glucan assay levels may be elevated falsely in patients on haemodialysis where cellulose membranes have been utilised.[11,12] This patient's dialysis was performed using synthetic polysulfone membranes, which do not significantly elevate the assay.[12]

Treatment of fungal endocarditis includes medical or surgical interventions or a combination thereof. Although combined medical and surgical therapy has decreased the mortality of patients with *Candida* endocarditis, the mortality remains high.[1] Recommended first-line therapy includes early surgery plus liposomal amphotericin B or an echinocandin.[3,13] The source of *C. parapsilosis* in this patient was most likely the haemodialysis catheter. In patients with candidaemia, early removal of the catheter is recommended; however, this is not always possible. These situations require therapy with either amphotericin B or an echinocandin.[9] Individual case reports have shown successful medical treatment of *Candida* endocarditis using the echinocandins without surgical intervention;[14-16] however, there is insufficient experience with these agents to make a recommendation for medical management alone. The use of fluconazole in this patient was initially empirical and subsequently based on antimicrobial susceptibility results. Early aggressive surgical therapy combined with medical treatment resulted in a positive outcome. Long-term oral fluconazole therapy may be continued following IV therapy; however, the duration of suppressive therapy is not clearly defined, with some patients remaining on lifelong therapy.[3,16]

Conclusion

We describe a case of *C. parapsilosis* endocarditis in a patient with significant risk factors. The changing epidemiology of invasive fungal disease indicates that invasive disease due to this species may be more frequent. A high index of suspicion as well as aggressive diagnostic modalities and therapy are essential to decrease mortality due to this condition. The persistence of elevated β-D-glucan levels in the presence of negative blood cultures suggests that this test is not reliable as a marker for response to therapy. Although individual case reports suggest that the echinocandins offer promise as sole medical therapy, if surgery is not possible, then further evidence is required before this modality of therapy is pursued.

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