

Invasion of *Aureobasidium Pullulans* in kidney and eyes of immunosuppressed patients

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ABSTRACT

There were series of proven cases revealing opportunistic fungal infections in the cornea, cutaneous, subcutaneous and renal transplant patients. Renal involvements of opportunistic mold in immunocompromised especially in renal transplant recipients have remained a significant problem and a major cause of death worldwide. However, extensive literature reviews revealed no case of invasion in urolithiasis and rarely reported in endophthalmitis. Here, we report the case series of two rare cases related to a dematiaceous fungus, *Aureobasidium pullulans*. Both had an atypical presentation. Possible modes of entry and dissemination were discussed. Invasive surgical procedures, frequent uses of antibiotics and steroid could possibly predispose to its invasion in immunocompromised patients. This organism was identified through molecular techniques since culture yielded no growth. There was a good outcome following surgical intervention in both cases.

Key words: *Aureobasidium pullulans*, Endophthalmitis, Immunocompromised, Opportunistic, Urolithiasis.

With an increase in life-expectancy of the human being, opportunistic fungal infections are increasingly common [1]. Fungal infection is an emerging disease and contributes to morbidity and mortality among immunosuppressed individuals [2]. *Aureobasidium pullulans* is a dematiaceous fungus known for causing cutaneous, subcutaneous and corneal infections. Loss of cell-mediated immunity predisposes individuals to fungal infection. Many reported fungal cases were found among diabetes, cancer, HIV and renal transplant patients [3]. It can be transmitted via direct inoculation through penetrative injury or via inhalation of dust [4,5].

Although known for its global significance, it is often reported from subtropical and tropical climates nations [5,6]. Herein, we report the case series of *Aureobasidium pullulans* fungal infection with atypical presentations among two immunosuppressed patients.

CASE SERIES

Case 1: A 29-years-old aboriginal lady with no known medical illness presented with bilateral lower limb weakness with hypokalemia for one month. General examination and vital signs were unremarkable; however, power on bilateral lower limbs was 3/5. An ultrasound of kidney-ureter-bladder showed mild right renal hydronephrosis and severe left renal hydronephrosis secondary to multiple renal calculi concomitant with a bilateral renal parenchymal disease, graded 1-2. A Chest X-Ray upon admission was normal.

She attempted bilateral ureteric stenting but failed for the left side. A Computed tomography (CT)-urography was performed to rectify failure of the surgical procedure. The imaging revealed mild right renal hydronephrosis secondary to multiple right renal calculi conforming staghorn calculi with an inferiorly migrated ureteric stent, severe left renal hydronephrosis secondary to left upper ureteric calculi and chronic left renal disease. Subsequently, she underwent first right percutaneous nephrolithotripsy (PCNL) and left ureteroscopic surgery (URS) with stenting. In the right kidney, 90% clearance was achieved with minimal pus noticed during the renal stone evacuation. However, incomplete clearance achieved for left upper ureteric stone. Intraoperative urine culture and sensitivity yielded no growth. Blood urea 8.1mmol/L and serum creatinine 200 umol/L Diethylenetriamine penta acetic acid (DTPA) renal scan revealed non-functioning left kidney (13ml/min, 13%) and moderately impaired right kidney function, (28ml/min, 69%).

A second right renal PCNL and left renal URS performed on her after 3 months from the first PCNL. Left ureteric renal stones were extracted via antegrade approach and re-stented while the right kidney remained not accessible. A reassessment CT-Urography after 2 months from the second surgery revealed multiple right renal calculi with mild hydronephrosis and resolved left renal hydronephrosis with chronic renal parenchymal disease. Consequently, left ureteric renal stent removed 2 months after the assessment.

Right retrograde intra-renal surgery (RIRS) was planned for the patient, approximately a year later. Throughout her follow-ups

to the clinic, despite stable renal profile, the patient complained of intermittent right loin pain. A complete clearance achieved over the upper and mid pole right kidney calyx, however lower pole was not accessible. Intra-operatively, a blackish tubular foreign body (Fig. 1) observed in the calyx of the kidney. It was sent for histopathology examination (HPE), culture and sensitivity, parasite and ova test. All these were found to be negative and HPE revealed blood clot. Culture yielded no growth in Sabouraud Dextrose Agar (SDA), after 4 weeks. Later, the sample (foreign body) was sent to Mycology laboratory, Institute for Medical Research (IMR) for molecular identification. Sample was also cultured in Brain Heart Infusion (BHI) and yielded no growth also. *Aureobasidium pullulans* DNA was detected through fungal Polymerase Chain Reaction (PCR). The patient remained asymptomatic with an improved renal profile since RIRS.

Case 2: A 72-years-old Malay lady with underlying end-stage renal failure (ESRF) which was newly diagnosed in 2018, diabetes mellitus (DM) since 20 years, hypertension since 15 years and latent syphilis (completed treatment) had a history of left eye cataract surgery (phacoemulsification and intraocular lens implantation) in 2016. Then, she developed postoperative left eye inflammation for which she was treated with antibiotics and steroid eye drops for 3 weeks. In 2018, she presented to the eye clinic at Kedah with the left eye redness and worsening left eye vision one week after right internal jugular catheter (IJC) insertion for dialysis. A Brightness scan (B-scan) revealed flat retina and vitreous opacity. A diagnosis of left eye endophthalmitis was made. Blood and urine culture in hospital yielded no growth. Vitrectomy, anterior chamber washout and left eye vitreous biopsy planned for her. Before surgery, she was started on oral antibiotics, topical steroid and antibiotics. Intravitreal tap with Vancomycin, Fortum and Dexamethasone had also been given. Postoperatively retina was flat and clear vitreous cavity from B-scan. Vitreous bodily fluid from biopsy cultured on SDA, almost 4 weeks and was repeated in IMR with BHI which yielded no growth. Hence fungal PCR was carried out. *Aureobasidium pullulans* DNA was detected. Her left eye redness resolved after surgery and a month post-surgery, the patient is clinically well with no active complaints.

DISCUSSION

Aureobasidium pullulans is more known to cause spleen infection [7], jaw infection [8], peritonitis [9], pneumonitis [10] and several

cases have been reported on its pathogenicity in causing corneal infection such as keratitis [11,12] and sclerokeratitis [13]. *A.pullulans* is a dematiaceous fungus which is widely distributed as a saprophyte in the environment, and it can be isolated from soil, wastewater, plants, wood, rock, household dust as well as on human hair, skin, and nails [14,15]. The patient who is an aborigine thus raises a high index of clinical suspicion of acquiring *A.pullulans* as it is widely distributed in rural areas [6].

The fungus is considered a contaminant when isolated from biological samples from immunocompetent patients, however, its pathogenic ability in humans is becoming recognized as an important, emerging causal agent of phaeohyphomycoses, especially among immunocompromised and diabetic patients [16]. This was evident in both cases. In the first case, the patient had chronic kidney disease at presentation and another had diabetes and ESRF.

Aureobasidium pullulans in most cases begin to infect lungs via inhalation of spores and spreads to tissues by haematogenous spread [17]. In our first case, there was insufficient evidence to suggest lung infection as the patient had no signs and symptoms of lung infection. The only possible mode of entry was through direct traumatic inoculation during multiple invasive renal surgeries [4]. Another reason could be from the contamination of medical devices used in major surgical procedures. When sterilization is inadequate, some of these organisms capable to produce yeast like synamorphs and cause medical devices contamination [4]. Besides stenting and attempts of stone clearance, the foreign body found in renal calyx which was later identified as *A.pullulans*, if not removed early may cause further deterioration of the patient's condition.

Though rare, disseminated systemic infections by *A.pullulans* can occur in immunocompromised patients and through invasive devices such as central venous catheters [2,11,14,17,18,19]. There is a close association of both in the acquisition of endophthalmitis [20]. It can be related in our second case that patient was not only immunocompromised (ESRF and diabetes mellitus), but had left eye redness and worsening eye vision following right IJC insertion. However, it is difficult to determine whether the source is from the catheter as neither culture available nor information on documented fever after insertion, erythema or swelling at catheter indwelling site.

In another study of ninety-one consecutive cases proven oculomycosis in relation to clinical features and epidemiological

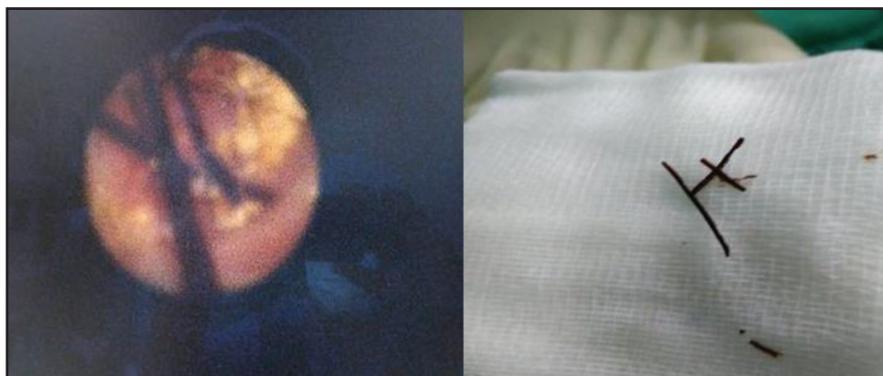


Figure 1: During surgery, a blackish tubular foreign body from the right kidney (left) was removed and sent for further identification (right).

parameters, Renuka Srinivasan *et al.* reported mycotic endophthalmitis was seen in 64% cases following cataract surgery [21]. Similarly, the patient in our case had a history of left eye cataract surgery before diagnosed as endophthalmitis which may be caused via direct inoculation from intraocular surgery.

Frequent use of antibiotics and corticosteroid eye drops might be responsible for fungal growth in the eye and *A. pullulans* should be considered a cause for keratomycosis [11]. Prolonged use of steroids and antibiotics eye drops prior to this might have also enhanced the growth of *A. pullulans* in our second case. Surgical intervention in the form of vitrectomy and anterior chamber washout as in this case, along with topical and direct intravitreal therapy has produced a good outcome in this patient in concordant with previous reports of endophthalmitis management [22].

Molecular identification used for in both cases is conventional fungal polymerase chain reaction (PCR). PCR method was performed using DNA extracted from the blackish tubular foreign body from case 1 and the left eye vitreous biopsy from case 2. For both cases, *Candida glabrata* DNA was used as the positive control and *Leptospira interrogans* serovar Copenhageni as the negative control. The pairs of primers used were Internal Transcribed Spacer (ITS) 3 and ITS 4. ITS region in rRNA gene was amplified and sequenced. Sequencing results are *Aureobasidium pullulans* for both cases. Molecular techniques are necessary for detecting *A. pullulans* especially in negative culture specimens where it has proven vital. In their series of cohort studies, Sowmya *et al* demonstrated a 100% identification rate by PCR in infectious endophthalmitis be it fungal or bacterial whereas culture and standard sampling only detected 37.5% of isolates[23,24].

CONCLUSION

The emergence of molecular diagnostics tests has helped clinicians to identify the etiology in a shorter span and more precisely. This is useful especially in situations when cultures yielded no growth. Traumatic inoculations by multiple surgeries and contaminated medical instruments used during procedures suggest the mode of invasion of *Aureobasidium pullulans* in immunocompromised condition. While most cases of *Aureobasidium pullulans* infection require antifungal therapy; its use is limited by the case to case basis. Improved patient's general condition following eradication of localized infection through surgery may not require antifungal treatment as seen in these two cases.

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