



CANDIDA AURIS IS HERE

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PO 40 M was admitted at DMH with non H1N1 bilateral pneumonia requiring intubation, mechanical ventilation, various recruitment techniques for persistent hypoxia & finally ECMO. He developed acute kidney injury requiring hemodialysis, critical illness myoneuropathy, bilateral vocal cord palsy and a left shoulder dislocation. While gradually recovering from all these complications, he developed hemophagocytic lymphohistiocytosis (HLH). He was initially treated with steroids followed by etoposide. He gradually improved and was discharged after a prolonged ICU stay. The patient was later readmitted with headache. Lumbar puncture and CSF analysis was diagnostic of cryptococcal meningitis by both cryptococcal antigen test and later culture. A central line was inserted and treatment with amphotericin B deoxycholate & fluconazole was initiated. During treatment, he developed fever & paired blood culture revealed growth of yeast. Automated identification system identified the organism as *Cryptococcus laurentii*. However, the colonies tested negative by the cryptococcal antigen detection test. Hence, the isolate was sent to PGIMER Chandigarh, where it was identified as *Candida auris* by DNA sequencing. The isolate was susceptible to 5 fluorocytosine, caspofungin, micafungin, anidulafungin and voriconazole, but resistant to fluconazole and amphotericin B. The patient was treated with caspofungin, voriconazole & 5fluorocytosine. Despite this treatment, changing lines, & ruling out endocarditis with transesophageal echocardiography (TEE), candidemia could not be cleared. The patient had multiple relapses of HLH and could not be taken off immunosuppressive treatment. The patient's family decided to limit treatment and the patient finally succumbed to his illness.

This case highlights that despite all our efforts, the patient succumbed to *Candida auris*, a multi-drug resistant fungal pathogen which is emerging as a major threat. The story of *C. auris* is unique as it has unfolded within a relatively short period from 2009 through 2017 involving patients of multiple countries in five continents, which is unlike the behavior of any fungal disease. CDC (Centers for Disease Control & Prevention) of USA, Public Health of England, ECDC (European Centre for Disease Prevention and Control) of Europe and Indian Council of Medical Research have

Dear Friends,

It gives me great pleasure to present to you the 1st newsletter of this year. In this newsletter, we first discuss the fungus that is making headlines everywhere "*Candida auris*". Since treatment of this multidrug resistant fungus is challenging, control of this fungus in hospitals should be a top priority. Then we have two contrasting cases of cutaneous mold infections. The first that needed intense systemic therapy and the second which could be easily treated with local management. These two cases also share in common the phenomenon of adverse effects associated with use of current generation anti fungals.

Editor

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issued advisories, which is the first for any fungal disease.

The reasons for such alarm are: a) the fungus cannot be easily identified especially by conventional technique, b) the organism is easily transmitted by colonization and contamination of hospital environment, c) difficult to treat as the organism is multi-drug resistant, d) it causes severe infection. A multi-centre Indian ICU study involving 27 ICUs during 2011–2012 reported 5.3% of candidemia cases as due to *C. auris* in 18 ICUs across the country¹. Longer ICU stay, multiple interventions and prior fluconazole exposure were risk factors for infection². The source of the agent is possibly in the hospital environment, as the agent has never been isolated from the community. Whole genome sequencing of 47 isolates identified four clades (South Asia, South Africa, East Asia and South America) for this agent with little variation among the strains in each clade³.

The agent is not easily identified by conventional techniques as in our case. Our agent was identified as *Cryptococcus laurentii* by conventional technique. By API-20C, Vitek 2, BD Phoenix, Microscan, the agent is often misidentified as *Candida haemulonii*, *C. famata*, *C. lusitanae*, *C. parapsilosis*, *C. sake*, *Cryptococcus laurentii*, *Rhodotorulaglutinis*, *Saccharomyces cerevisiae* etc⁴. Only the improved database of MALDI-TOF and DNA sequencing can accurately identify the agent. These techniques are not available in most of the laboratories in India. Hence, laboratory personnel should suspect the agent when any *Candida* species is multi-drug resistant, grows at higher temperature (42°C), fails to grow in the presence of cycloheximide, and utilizes dextrose, dulcitol and mannitol². The isolate can be confirmed at Reference laboratory at PGIMER, Chandigarh (ICMR advisory).

Indian studies showed that 90% isolates are resistant to fluconazole, 50% isolates have elevated MICs to voriconazole, 15-30% isolates are resistant to amphotericin B and 2-8% isolates are even resistant to echinocandins. Resistance to two or more classes of antifungals are observed in 30-50% isolates, and 4% isolates are resistant to all classes of antifungal agents^{2, 4}. Though a few of the new antifungal agents are found to be effective *in-vitro*, the agents are still not available in Indian market. The recommended initial therapy for clinically relevant infections with *C. auris* in adults is an echinocandin at standard dosing. Patients should be monitored closely for resolution of infection given that resistance to echinocandins has been documented in 2-8% isolates and since resistance has emerged in serial isolates from a single patient after exposure to the drug. Switching to or adding liposomal amphotericin B (5 mg/kg daily) could be considered if the patient is clinically unresponsive to echinocandin treatment or has fungemia for >5 days. Posaconazole may be used in resistant cases, as it shows good *in vitro* susceptibility. Antifungal susceptibility testing should be performed for all isolates⁵.

A recently conducted study at PGI, Chandigarh, reported the spread of the organism rapidly and colonization of all patients in ICU within four days. The organism thrives on skin, contaminates the patient's room and spreads easily in the healthcare setting. To prevent and control *C. auris* infection CDC recommends contact precaution of patient in a single room and daily terminal cleaning of the patient room and equipment; this may not be feasible in most Indian hospitals due to over-capacity. However, interventions such as chlorhexidine body wash for colonized patients, appropriate use of common disinfectants and reinforcing hand washing are efficient methods in controlling the spread of the agent. Sometimes ridding of the agent from hospital environment may be a challenge, as the organism may persist for a long time on dry fabrics or environment⁶. Hence an early, aggressive approach to control the organism when it is newly emerging is more effective and efficient in controlling transmission than responding when the organism is more widespread. The presence of a single case in a healthcare facility should prompt an aggressive response and investigation because *C. auris* can cause healthcare-associated outbreaks.

It thus appears that *C. auris* is here to stay and a concerted effort to prevent and control infection is the need of the hour.

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A CURIOUS CASE OF A MOLD INFECTION

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KS, a 13 year old boy was diagnosed with B cell ALL with CNS involvement in November 2017. He was started on the UK-ALL 2003 protocol comprising of dexamethasone, vincristine, daunorubicin, pegylated L-asparaginase. As per the unit protocol he was also put on cotrimoxazole and fluconazole prophylaxis. During week-4 of induction chemotherapy, he presented to the outpatient department with some nasal stuffiness. Nasal evaluation showed no abnormality and he was prescribed symptomatic therapy. About one week later he presented with multiple painful skin lesions over the body. The lesions were ovoid in shape with blackish discoloration and ulceration of the central region with a surrounding rim of erythema and were extremely tender (Figure 1). He developed fever soon after admission to the hospital. CBC showed Hb 7.5 g%, TLC 310/mm³ with zero neutrophils and a platelet count of 62000/mm³. A clinical diagnosis of disseminated fusariosis was made, since this fungus has the greatest ability to produce multiple necrotic skin lesions owing to its ability to invade the blood stream by virtue of its yeast like properties. Aerobic and fungal blood cultures were sent and he was empirically started on piperacillin tazobactam, amikacin, liposomal amphotericin-B (3mg/kg/day) and oral voriconazole. A skin biopsy from the lesion was sent for bacterial culture, fungal culture and histopathology.

On KOH mount oval budding yeast cells and branching septate hyphae were seen. Tissue was cultured on Sabouraud's agar without antibiotics and incubated at 22°C as well on Sabouraud's agar with chloramphenicol

Figure 2: Lactophenol cotton blue (LPCB) mount showing the budding yeast and hyphae

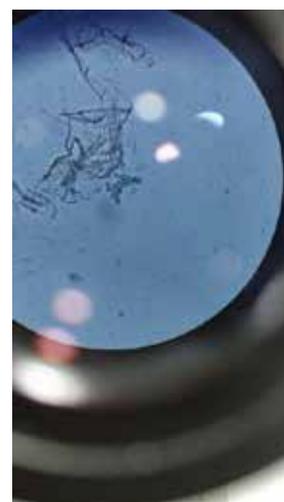


Figure 1: Lesions at presentation



and cycloheximide and incubated at 37°C. It was also cut into fine pieces and inoculated in liquid media for enrichment and was incubated at room temperature.

Since the morphology of the fungus was not typical of *Fusarium* or other molds and since the counts continued to drop with increase in size and number of lesions, the dose of liposomal amphotericin B was stepped up to 5 mg/kg/day and caspofungin was also added to the previous regime. Antibiotics were stopped. Dexamethasone was rapidly tapered and stopped. He was also given growth factors (inj. G-CSF at 10 mcg/kg/day subcutaneously q24 hourly) and despite of questionable efficacy, granulocyte infusions (1×10^{10} / recipient body weight (kg)) were also administered. A CT scan of the paranasal sinuses was normal and that of the chest revealed a small 8 mm nodule in the right lung. The TLC started rising by day 6 of hospitalization. On day 7 of hospitalisation, he started having restlessness, anxiety, disorientation to time and person along with hallucinations and urinary and bowel incontinence and then intermittent episodes of aphasia followed by aggressive behaviour. A MRI brain was done which was normal. A drug induced adverse reaction due to voriconazole was suspected and voriconazole was withheld. There was some improvement and voriconazole was substituted with posaconazole. The symptoms worsened again and posaconazole was stopped.

There was white cottony colony grown on day 5. A slide culture using corn meal agar was set up. LPCB mount was made from the slide culture which revealed septate branching fungal hyphae of non uniform width (Figure 2). The hyphae were not ribbon like and rhizoids were absent. A few circular spore like structures were seen in the cluster. The culture was sent identification of fungus by MALDI ToF at Metropolis, Mumbai, where it was identified as Fungi from Mucoraceae family. The culture has also been sent to PGI, Chandigarh for identification by sequencing. Results are awaited

With identification of the fungus as *Mucor*, liposomal amphotericin-B and caspofungin were continued. Even 2 weeks into treatment the lesions remained fairly active. Debridement was considered but deferred owing to the low platelet count. In the third week of treatment the patient developed fever with a generalised pruritic erythematous,

Figure 3: Healing skin lesions



macular-papular skin rash on his trunk. Drug hypersensitivity was suspected and caspofungin was stopped followed by amphotericin B. The rash resolved but reappeared within minutes with increased severity when challenged with another brand of liposomal amphotericin B. Posaconazole was then gingerly introduced which the child luckily tolerated. The skin lesions showed healing by the 4th week of therapy (Figure 3). Subsequently, the marrow examination revealed residual disease and the child was initiated on salvage chemotherapy. There was no resurgence of skin disease during the intense neutropenia that followed this highly intense chemotherapy. It is now 14 weeks since the onset of this highly debilitating invasive fungal disease and the child is awaiting a sibling matched stem cell transplant. In this case, the mold in all likelihood entered the body when the child complained of nasal stuffiness. On leading questioning, the parents revealed that there were multiple areas of seepage and damp walls at their residence.

This case conveys the following important messages

1. The extreme morbidity, interruption of chemotherapy, prolongation of length of stay and increased cost of therapy caused by invasive fungal infections in patients with acute leukemia.
2. The importance of tissue biopsies in establishing the diagnosis of IFI
3. The limitations of morphology and standard culture in identification of fungi and the importance of newer methods including MALDI ToF and sequencing in fungal diagnosis
4. The need to start combination antifungal therapy when rapid identification of fungi is not possible as well as the importance of reducing immunosuppression and rapidly increasing the neutrophil count.
5. The not so infrequent adverse effects of currently available anti fungal drugs
6. The importance of infection control in preventing invasive mold infections in severely immunocompromised hosts in both hospitals and homes

A TALE OF TWO MOLDS & A MYCOBACTERIUM

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A 58 year old male who is a known case of Diabetes mellitus and chronic kidney disease underwent living donor related kidney transplantation in 2015. He started dry cough in January 2017, was admitted elsewhere, CT showed bilateral cavitory consolidation (Figure 1) and bronchoscopy and BAL was done. MGIT culture grew Non-Tuberculous Mycobacteria which was identified as *Mycobacteria chelonae* by Line Probe assay (LPA). Though BAL galactomannan (GM) was 1.9, he was treated only for NTM with TMP-SMX, moxifloxacin and clarithromycin. In view of persistent cough, the patient got admitted to Hinduja hospital in Feb 2017. Repeat scan revealed resolution of some of the nodules and appearance of a few new ones while on treatment. Voriconazole was started in a view on the new nodules and the previous report of positive GM. Although the ATS IDSA criteria for NTM had not been met, it was decided to continue treatment as the patient was immunocompromised and there was resolution of some of the nodules with treatment. NTM treatment was modified to amikacin, azithromycin, linezolid to avoid

Figure 1: CT at initial presentation



Figure 2: Initial presentation



Figure 3: Ulcer following 2 months of natamycin therapy



interaction with voriconazole. In the 1st week of April the patient had a blunt injury to the posterior aspect of the right ankle by a metal rod. After a few days he developed a nodular swelling at the site which resolved spontaneously. In the last week of April 2017, voriconazole was stopped owing to development of hepatotoxicity and the fact that he had completed 3 months of treatment.

In mid May 2017 he developed an ulcer on the posterior aspect of right ankle joint at the same site as previous trauma (Figure 2). MRI right ankle was negative for osteomyelitis. Debridement of the ulcer was done and deep tissue was sent for culture and histopathology. Culture grew *Fusarium* species and histopathology revealed extensive necrotizing inflammation with necrotic debris. Systemic voriconazole could not be given because of previous toxicity. Debridement was done, local therapy with natamycin, a drug approved for fungal keratitis was used with an excellent response.

This case illustrates an unconventional approach towards treatment of a cutaneous fungal infection when systemic therapy was not possible. Natamycin is a drug that irreversibly binds to ergosterol, thus disrupting the fungal cell membrane leading to a loss of solutes from the cytoplasm and cell death. It is approved for the management of fungal especially *Fusarium* keratitis but may be tried for a local mold infection if debridement has been done and there is no deep seated focus (1).

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About FISF

The purpose of the Fungal Infections Study Forum is to conduct educational activities, undertake epidemiological and clinical studies and to promote research activities on invasive fungal infections. The results of such research would benefit the clinicians, mycologists and the general public. The trust was formed in view of emergence of Invasive fungal infections (IFIs) in India which is posing a serious challenge to the haematologists, critical care providers, ID specialists, pulmonologists, neurologists, medical mycologists and many other clinicians handling serious and immunocompromised patients. The trust is the independent working consisting of clinicians and mycologists and instituted on 3rd March 2012 at Mumbai, India. To know more about us visit www.fisftrust.org.