Fungal Infections Study Forum

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"FUNGAL" PNEUMONIA IN AN IMMUNOCOMPROMISED HOST

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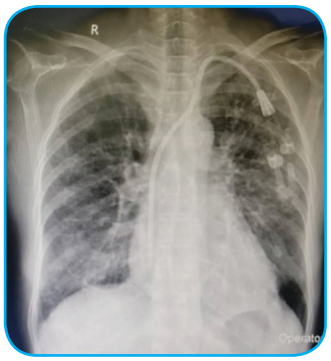
A 55-year-old lady, post kidney transplant on long term steroids for chronic allograft nephropathy, presented to our hospital with dry cough and intermittent low grade fever for 2 months. She denied history of chest pain, palpitations or orthopnoea.

She underwent live-related donor kidney transplant 4 years prior to her current presentation. Her initial immunosuppression regimen consisted of tacrolimus, mycophenolate mofetil and steroids. One year prior to presentation, she had developed chronic allograft nephropathy for which she had received 3 doses of rituximab and high dose steroids. Six months prior to presentation while on high dose steroids, she had pulmonary tuberculosis and CMV disease which was treated with 1st line anti-tuberculous drugs and valganciclovir. A month prior to presentation, her immunosuppressants were withheld and she was commenced on thrice weekly hemodialysis via left permacath. At the time of presentation she was not on cotrimoxazole or valganciclovir prophylaxis.

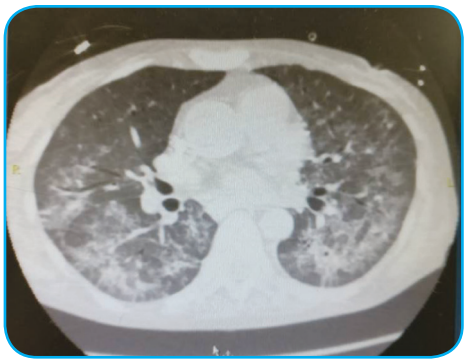
On examination, the patient was drowsy with a temp of 99^{0}F, PR of 110/minute, respiratory rate of 20 breaths per minute and a oxygen saturation of 93%. Her chest was clear. Her white cell count on presentation was 3400/µL. Her chest radiography (Figure 1) showed bilateral interstitial infiltrates. Other routine laboratory test results were normal.

Figure 1: Chest Radiograph showing interstitial pattern



After obtaining blood cultures from left subclavian permacath and peripheral venipuncture, patient was empirically started on meropenem and teicoplanin. The next day, patient developed high grade fever (T max: 102°F), became acutely tachypnoeic and desaturated. Her chest radiograph showed bilateral dense opacities with no evidence of pleural effusion. Her ABG showed PaO2 of 64 mm of Hg. She was intubated. Her antibiotic cover was broadened to include polymyxin B and azithromycin. Her respiratory virus multiplex PCR from the nasopharynx revealed presence of coronavirus. CMV Viral load was negative. Her LDH was 608U/L (reference range: 130-240U/L). LDH/PaO2 ratio was 9.5. Her CT scan (Figure 2) showed diffuse interstitial pattern, ground glass opacities and patchy bilateral consolidation.

Figure 2:CT scan showing ground glassing and bilateral patchy consolidation



The various differentials considered included the following:

1. Bacterial sepsis secondary to catheter related blood stream infection with ARDS
2. *Pneumocystis jiroveci* pneumonia
3. Cytomegalovirus pneumonitis
4. Coronavirus pneumonia
5. Fluid overload

With regards to the differentials considered, sepsis could be possible in view of presence of permacath with the characteristic history of fever occurring a few minutes into dialysis. However, low counts, negative

Dear Friends,

This newsletter is a medley of cases. These cases have been chosen from those presented at a FISF meeting on fungal infections at Jupiter Hospital, Pune on 25th February, 2018. We discuss some very common fungi (Candida and Aspergillus) and then some of the rare ones. Let us not forget Pneumocystis which is also a fungus. Hope you can identify with some of the clinical situations discussed in this issue. We would welcome contributions from our readers for publication in this newsletter. The word count should not exceed 1000 words with less than 5 references; colourful images are welcome.

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cultures and deterioration whilst on meropenem and teicoplanin made the diagnosis unlikely. CMV pneumonitis was considered in view of background immunosuppression, lack of valganciclovir prophylaxis, chest imaging and prior history of CMV syndrome. However the fact that the patient was off immunosuppression since 1 month and the negative CMV viral load made the diagnosis less likely. Coronavirus pneumonia may present with a similar clinical picture in an immunocompromised host. However, it would be more acute in presentation. Fluid overload was unlikely in this patient since the event had occurred after dialysis. Secondly, there was no pleural effusion on imaging.

Presence of fever and non-productive cough for 2 months, hypoxemia on examination, classical radiological imaging, with high serum LDH and LDH/Pao2 ratio makes PCP the most likely diagnosis in this patient. A bronchoalveloar lavage was peformed which revealed presence of cysts of Pneumocystis jiroveci on direct fluorescence microscopy .Patient was commenced on IV cotrimoxazole and high dose steroids as per standard guidelines. Caspofungin was also added. Unfortunately, a few days into therapy, the patient succumbed due to a gastro-intestinal bleed.

Pneumocystis pneumonia (PCP) is an opportunistic fungal infection most commonly seen in patients with HIV. Important predisposing factors for PCP include conditions which cause defects in cell mediated immunity. These include HIV, solid organ transplant, chronic steroids, cancer, chemotherapy and severe malnutrition. Recently rituximab has emerged as an important risk factor for PCP. PCP presents with sub acute onset of non-productive cough, fever and breathlessness which gradually worsens over weeks to months. These patients are tachypnoeic and may be profoundly hypoxemic. Chest radiography typically reveals presence of diffuse interstitial infiltrates in the perihilar region. CXR's may be normal but CT scan typically reveals presence of diffuse ground glass opacities5. HRCT findings may range from ground glass opacities (most common) to presence of consolidation, cysts, nodules and sometimes spontaneous pneumothorax. Pleural effusions are uncommon and warrant search for an alternative diagnosis.

Bronchoalveloar (BAL) samples demonstrating presence of PCP either on microscopy, culture or PCR is the current gold standard for diagnosing PCP. However, there are a few serum markers which may help tweak a physician's mind towards the diagnosis of PCP before BAL is performed. Serum LDH is one such marker which is elevated in PCP. It is a marker of lung injury and may be used for monitoring of treatment. Interestingly, LDH/Pa02 ratio of more that 4.5 was found to have an excellent specificity (~90%) and positive predictive value (95%) in the diagnosis of PCP. Very high levels of serum Beta-D Glucan are also seen in PCP.

Cotrimoxazole in a dose of 15-20 mg/kg/day of TMP for 14-21 days is the drug of choice for management of PCP. Recently caspofungin has been found to have a role in the management of PCP.Though steroids are indicated for severe PCP in HIV; the role of steroids in non HIV PCP is still not well defined.

It is important to consider the need for cotrimoxazole prophylaxis in at risk patients particularly those on long term corticosteroids. Though there is no clear consensus, patients with an underlying immune defect and receiving more than 20 mg per day of prednisone for longer than 4 weeks may be considered for PCP prophylaxis.

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CANDIDA IN THE URINE: NOT ALWAYS A COLONIZER

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A 42 year old diabetic male with recent HBA1C 6.8 had a stricture urethra, for which he was on self catheterization, which he stopped 1 month ago. At this time his urine culture was positive for *Candida glabrata*. He presented with complaints of frequency and urgency of urination with low grade fevers since 2 days. He was started on piperacillin-tazobactam after sending urine culture. His serum creatinine was 1.5 mg/dl, he had 8-10 pus cells in urine, and WBC count was 7000. He complained of significant dysuria and incomplete evacuation of bladder. On uroflowmetry, there was bladder outlet obstruction. He underwent cystoscopy with bladder neck incision. After the procedure, he started developing high grade fevers. His case was referred to infectious diseases (ID) after the urine culture report showed non albicans candida and intravenous fluconazole was started.

On evaluation by the ID team, we found that he was febrile ($10^0$2F) with normal vitals, he had tenderness in suprapubic region but no renal angle tenderness. There was no hematuria. He was catheterized and had significant crusting in his urobag. His lab parameters were reviewed. Post-procedure his WBC had risen to 12500 and urine showed plenty pus cells. The impression was that of cystitis. Vitek identification of the candida was requested and intravenous fluconazole was continued. Vitek identified the isolate as *Candida parapsilosis* with susceptibility to voriconazole, echinocandins, amphotericin B and flucytosine but resistance to fluconazole (MIC 32)

There were several issues in this case. He had symptomatic candidal cystitis caused by *Candida parapsilosis*. He had no stent in situ, otherwise biofilm activity of the agents was an important issue. Fluconazole

which has excellent urinary levels was resistant. Voriconazole and echinocandins were sensitive but both have poor urinary levels. Flucytosine (5-FC) was an option, as it has reasonable urinary levels, but its use is less well characterized as a single agent for symptomatic cystitis and resistance emerges with monotherapy. So no one drug fitted the bill.

We did some lateral thinking and used some pharmacokinetic and pharmacodynamic properties to choose the drug. At a dose of 400 mg per day, fluconazole is likely to have 360 mg in urine (90% excretion). We assumed that he may have 300 mg of fluconazole in bladder. His urine output was 1500 ml per day, leading to a concentration of 200 µg per ml in urine. *Candida parapsilosis* was having minimum inhibitory concentration (MIC) of 32 for fluconazole. It could be possible to overcome it at such a high urinary concentration. Hence we decided to continue fluconazole. The patient's fever resolved in 3 days while on fluconazole. He was discharged and fluconazole was stopped after 14 days.

This case illustrates the fact that the choice of antifungal drug depends not only on the susceptibility but also the site of infection and that due attention to pharmacokinetics and pharmacodynamics is very important

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DISSEMINATED INVASIVE MOLD INFECTION IN A SEVERELY NEUTROPENIC HOST

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A 47year old gentleman was diagnosed with MDS-CMML type 1 in 2015 for which he, received 8 cycles of azacytidine. In December 2017, he was diagnosed with acute myeloid leukemia with 60% blasts in peripheral smear and functional neutropenia. He was started on induction chemotherapy, achieved complete remission and planned for allogenic SCT. He was then admitted with complaints of fever and dry cough. At admission, he was profoundly neutropenic with total WBC counts of 120. Blood cultures were sent and imipenem empirically started. Bone marrow showed 35% blasts, hence salvage chemotherapy planned. Since his low-grade fever persisted, CT chest and sputum studies were advised. CT chest showed bilaterally scattered nodules with surrounding halo. Serum Galactomannan was sent, sputum KOH stain (Calcofluor not available) was inconclusive. Blood culture was sterile, serum procalcitonin was negative. He was started on chemotherapy- FLAG regimen: fludarabine + high dose cytarabine + G-CSF.

Serum Galactomannan was elevated (3.04), sputum grew *Aspergillus fumigatus*. ID opinion was sought. The case met the EORTC criteria for probable invasive pulmonary aspergillosis and hence therapy with voriconazole was advised. Meanwhile, the patient developed 2 episodes of seizures and was shifted to the ICU. MRI brain showed multiple large abscesses having multilayered appearance, central hemorrhage with marked cerebral edema. The neurologist opined that the cerebral lesions were suggestive of TB and hence empiric ATT was started.

ID consultation at this juncture involved in-depth discussion regarding the etiology of the cerebral lesion. Taking into consideration that the patient was a neutropenic host, had radiological findings of multilayered cerebral lesions with intracavitatory projections, edema and hemorrhage and with a previous mold infection of the lung, a mold infection seemed to be the best fit. This mold could be aspergillus or mucor or demetiaceous fungus; with aspergillus most likely. Whilst biopsy of the cerebral lesion and evaluation of CSF are indicated, it was not feasible in this patient due to thrombocytopenia. CSF galactomannan levels may be elevated in cerebral aspergillosis. The treatment recommended was Voriconazole and LAmB, with discontinuation of ATT. Liposomal AmB was added to cover for possible Mucor, and for combination therapy for aspergillosis as the patient was at a highest risk for adverse outcome. Also, since he had received rifampin, voriconazole would take a longer time to achieve therapeutic levels; in which case L AmB would bridge therapy. Voriconazole TDM was advised after a week to document adequate therapeutic levels, followed by withdrawal of L AmB (under assumption of cerebral aspergillosis)

This case has several messages to convey. The first error was proceeding with intense chemotherapy in a patient who had radiologic evidence for an invasive fungal infection in the lung. The second error was starting empirical TB treatment in a patient with a preexisting invasive fungal infection who now presents with CNS lesions with radiologic features highly suggestive of fungal disease. Administration of rifampin with voriconazole is contraindicated, since rifampin upregulates voriconazole metabolism and leads to nearly undetectable levels. The third message is that one has to be alert to the possibility of more than one fungal infection in a severely immunocompromised host and try to obtain a diagnosis from each affected site (which was not possible in the index case). Nowithstanding these roadblocks, the patient made a recovery.

Fig 1: CT chest showing lung lesions

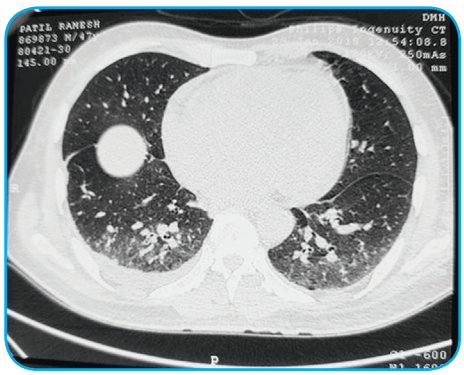
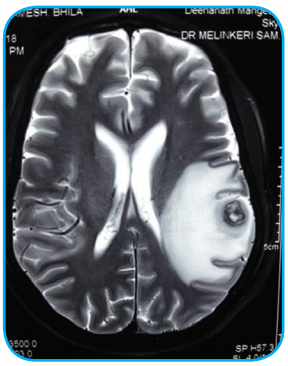


Fig 2: MRI brain showing cerebral lesion



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AN UNUSUAL CASE OF FUNGAL OSTEOMYELITIS

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An eleven year old boy, resident of Beed district, Maharashtra, sustained an injury to the left knee joint and left leg after falling into a gutter three months back. He underwent suturing of the lacerated wound over left knee on the same day at Beed, received short course of oral antibiotics.The wound did not heal over next 3 weeks. Patient underwent debridement four times in 2.5 months at Beed and Aurangabad and received multiple courses of antibiotics. MRI of joint showed osteomyelitis and joint effusion (Figure 1). Pus swab grew pan-susceptible *E. coli* for which he was treated with ceftriaxone for 3 weeks followed by oral ciprofloxacin for the next 4 weeks. Recovery was incomplete. The wound had still not healed.

Meanwhile, the fungal culture revealed *Pseudallescheria boydii* (Figure 2), for which he was treated with oral voriconazole 200mg twice daily for 2 days then half tablet twice daily for 1 week. Voriconazole levels were 1.8 mg/l (Therapeutic range 2-6), hence dose was increased to 200mg 1-0-1/2. Levels after 2 weeks were 1.4, dose further increased to 200mg 1-0-1. After 4 weeks, clinical improvement was seen, wound healed, but levels continued to be sub-therapeutic. The voriconazole dose was increased to 200 mg thrice daily and terbinafine 250mg half tablet daily was added. Six months into treatment, the patient was walking without a limp and gained 4 kg of weight. Repeat MRI of the knee joint showed marked improvement. Voriconazole level is currently in the therapeutic range. It is planned to continue therapy for a year.

Pseudallescheria boydii a saprophytic filamentous fungus found in soil and fresh water, especially stagnant and polluted water, is the causative agent of mycetoma and pseudallescheriasis (scedosporiasis). Immunocompetant hosts usually have subacute to chronic course and localized skin, soft tissue, eye disease and osteo articular infection following local inoculation. The disease can be disseminated in the immunocompromised (prolonged neutropenia, steroids, or allogenic stem cell recipients) where entry is usually by inhalation. Treatment of local disease includes surgical debridement. There is no effective anti fungal therapy for disseminated diseae. However there is some data to suggest a combination of amphotericin B with voriconazole may be effective. Fortunately, our patient showed a satisfactory response to voriconazole. Terbinafine was added to the regime, since there is some data about using terbinafine in patients with the closely related *S. prolificans*. Mortality is high in patients with CNS and disseminated disease.

This case illustrates the need to evaluate for fungal infection in patients with non healing wounds after trauma and exposure to soil and dirty water. It also illustrates the need for higher doses of voriconazole in children due to increased renal clearance and the need for therapeutic drug monitoring of voriconazole.

Figure 1

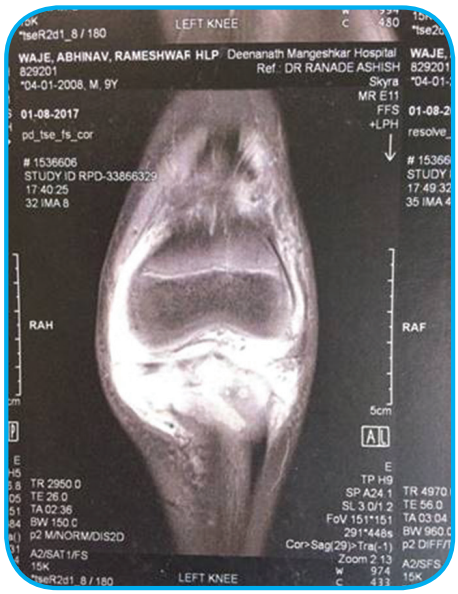
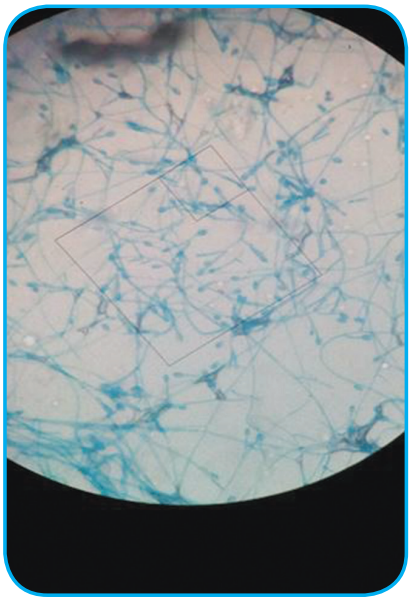


Figure 2



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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.