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Case Report

A rare presentation of disseminated invasive aspergillosis

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ABSTRACT

Here's presenting a case of disseminated invasive aspergillosis in a young female patient with pulmonary and CNS complications and the difficulty one faces while diagnosing such a case due to variable presentation of symptoms with no prior history of any underlying immunodeficiency. It also focuses on how diagnosing such a case can be further delayed due to clinical and radiological miss-match. Thus, it is important to have a high index of suspicion in such patients as prolonged antibiotics and systemic steroids worsens the course of illness.

Keywords: Aspergillosis, Immunodeficiency, Steroids

INTRODUCTION

Aspergillus species have emerged as an important cause of life-threatening infections in immunocompromised patients. This expanding population is composed of patients with prolonged neutropenia, advanced HIV infection, and inherited immunodeficiency and patients who have undergone allogeneic hematopoietic stem cell transplantation (HSCT) and/or lung transplantation.[1]

Invasive diseases caused by *Aspergillus* species include infections of the lower respiratory tract, sinuses, and skin as portals of entry. The CNS, cardiovascular system, and other tissues may be infected as a result of hematogenous dissemination or direct extension of the contagious foci of infection.[2] *Aspergillus fumigatus* is the most common species recovered from cases of invasive fatal aspergillosis. The next most commonly recovered species are *Aspergillus flavus*, *Aspergillus niger*, and *Aspergillus terreus*.[3,4] The most common portal of entry is the respiratory system. The major predisposing factors for development or progression to invasive aspergillosis are: deficiency of agglutinating surface surfactant proteins and C3, C5 complement factors, inhibition of anticonidial macrophageal activity, thrombocytopenia and neutropenia, low count of CD4+T lymphocytes or failure to produce IL (interleukin)- 12, INF (interferon) or TNF (tumour necrosis factor), prolonged antibiotic or steroids therapy.[5-9] In the presence of severe granulocytopenia and in patients with cerebral abscesses mortality is as high as 100%.[10]

CASE REPORT

An 18 years old female, student, presented with complaints of a) High grade fever associated with headache and generalized body ache for 10 days and b) Dry cough for 5 days and c) Breathlessness for 3 days. Patient gave a history of Chicken pox 15 days back for which she was treated in an outside hospital and was still recovering from the same. There was no history of chest pain, abdominal pain, gastrointestinal complains, seizures, burning micturition, joint pain to start with. She had no history of any known co-morbidities or h/o Koch's or Koch's contact. Her personal and family history was insignificant; there was no history of any travel in the recent past. She had a normal regular menstrual history.

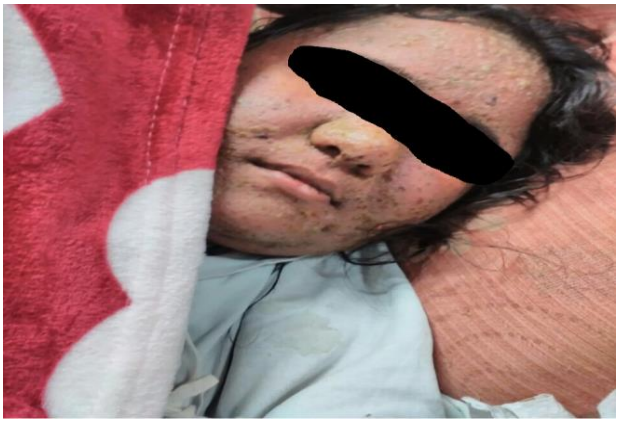

Figure 1: Condition of the patient during presentation.

On examination

The patient was toxic on appearance, febrile to touch. Her Pulse: 120b/minute; BP: 106/60 mmHg and RR: 20breaths/minute with 97% oxygen saturation. She was conscious, alert and attentive with no neck stiffness and Kernig's was negative with normal tone and power in all four limbs. There was Pallor present. However, no icterus/Cyanosis/Clubbing/Lymphadenopathy noted. Her Heart sounds were normal with no murmurs and had a soft abdomen with no organomegaly. On respiratory examination pts breath sounds were diminished in intensity in bilateral lung fields and fine crepitation and rhonchi were heard all over the lung fields.

Chest X-ray revealed diffuse nodular opacities all over bilateral lung fields. A provisional diagnosis of Post varicella pneumonitis was made and patient was treated. IV fluids, Paracetamol/500mg/12hourly, IV ranitidine 50mg/8hours, IV Inj. Amoxicillin plus clavulanic acid 1.2/8hourly, T. Valacyclovir 500mg BD and Nebulization.

Investigations

- CBC: HB: 8.6 WBC: 11.5 PLT: 718
- ESR-70 and CRP-203
- Liver function test: Total bilirubin: 0.8, SGOT/SGPT: 50/47 and ALP: 47
- Urine reports: Normal
- USG Abdomen: Normal
- CULTURES (BLOOD/URINE): No growth.

Fever profile: malarial antigen test, dengue antibodies, typhoid, Mantoux test and HIV were all negative. Sputum could not be induced after repeated attempts. Despite treatment patient continued to have daily spikes of High grade fever. Varicella titres were send (VZV IgG AND IgM) which turned out to be raised. Thus, Valacyclovir was continued and antibiotic coverage was stepped up to Inj. Moxifloxacin 400 IV OD and T. Fluconazole 100 OD. Patient was also transfused 2-pint PCV in view of severe anaemia.

An HRCT was done which revealed multiple randomly distributed nodules scattered in Bilateral lung parenchyma with few nodules showing central cavitation suggestive of active infective etiology likely koch's with milliary spread.

Figure 2: HRCT film which was suggestive of pulmonary Koch's with milliary spread.

A Bronchoalveolar lavage was taken which showed 12 Wbc's with 70% lymphocytes and 30 % neutrophils. No AFB was seen. Gene expert and MGIT was also negative. Cytology was also negative for malignant cells. BAL culture was positive for Enterococcus species. An initial 7 days trial of culture sensitive antibiotics Inj. Meropenem 500mg/8hourly and Inj Linezolid were given but when the patient did not respond AKT was initiated. After initiation of AKT patient responded initially for the first 5 days where the fever subsided and clinical betterment was observed.

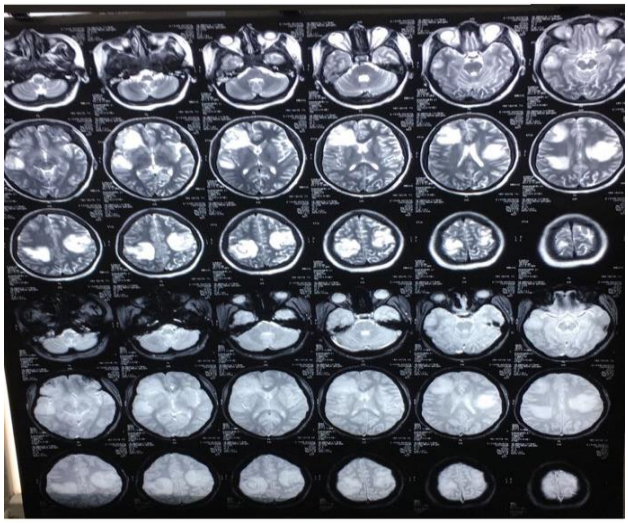

Figure 3: MRI brain film which was suggestive of metastasis.

One day she had a sudden onset of left sided focal seizures followed by weakness of the left upper limb. An MRI brain and CSF study was done immediately. MRI revealed multiple variable sized well defined lesions seen scattered in bilateral cerebral hemisphere largest measuring 2.4*2.8 cm in the right frontal cortex which appeared hypointense with central restriction on diffusion weighted images with surrounding perilesional edema. Features were most likely suggestive of metastasis than infective etiology.

CSF study on the other hand showed Total count of 10 cells with 100 % lymphocytes and sugars of 55 and proteins of 38.2 No AFB seen. No growth on culture; MGIT/Gene expert and cytology were all negative. All her investigations were reviewed again. A CT abdomen plus pelvis was done to look for a primary focus. Oncologist was consulted and tumour markers such as Beta HCG/ Alpha feto protein and LDH were send which were all normal. An MRI spectroscopy was done post discussion with the radiologists which showed a lipid Lactate peak with no obvious choline peak which was more in favour of Infective than that of Malignancy.

Meanwhile an ECG AND 2D echo was done in view of persistent tachycardia. ECG was suggestive of sinus tachycardia whereas the 2^{d} echo revealed a mass on the lateral aspect of the left ventricle attached on the outside measuring 7/3 cm which required a cardiac MRI for further evaluation.

Now with no further delay a PET Scan and a cardiac MRI was done. PET scan was suggestive of findings which were more likely to be infective however required histopathological correlation for final diagnosis. Cardiac MRI revealed subtle enhancement of the pericardium in the mid lateral wall of the LV with no involvement of epicardium or myocardium seen. The findings were suggestive of infective/ inflammatory etiology. A CT guided biopsy was suggested of one of the lung nodules in order to rule out metastasis.

At last a CT guided lung biopsy was taken which revealed fungal Hyphae which was consistent of Mycotic infection of probable Aspergillus etiology. Patient was started On IV Inj. Voriconazole 6mg/kg BD, Inj. Amphotericin B 3mg/kg q day, IV Inj. Clindamycin 600mg BD and IV Inj. Meropenem 1g BD.

Despite of treatment being initiated patient developed severe breathlessness and had to shifted to the intensive care unit. XRAY revealed left sided pleural effusion. USG of the chest stated that patient had left sided effusion with septae within and consolidation of the underlying lung parenchyma. On pleurocentesis it was haemorrhagic fluid. As there were too many underlying septae and patients' breathlessness progressed ICD Insertion was done. Furthermore, she developed hepatotoxicity and Inj. Amphotericin B was also reduced to half its dose. After 2 weeks of treatment patient developed skin lesions all over her body which were diagnosed as Disseminated reactivation of Varicella.

Immunological markers like IgG levels and complement C3, C4 were all normal. Finally, a flow cytometric analysis of Peripheral blood smear was done which revealed an extremely low absolute lymphocyte count with 0 CD19 B lymphocytes and 1 Natural Killer cell. CD3 T lymphocytes, CD3 CD4 Th lymphocytes and CD3/CD8 Tc lymphocyte values were also significantly reduced.

A CT brain and HRCT chest were repeated after three weeks of treatment with Voriconazole which was suggestive of increase in size and number of lesions with increase in the perilesional edema. HRCT revealed scattered nodules with bilateral pleural effusion with development of pericardial effusion. After about 1 month of diagnosis and correct treatment patient did not respond well and her clinical condition deitiorated further until she finally succumbed to death.

DISCUSSION

In the past aspergillus was considered as a weak pathogen and cases of disease in immunocompetent host were regarded as scientific curiosity. More, recently with increase in the number of immunosuppressed patients, aspergillus became the most common pathogenic mould worldwide. The average incidence of invasive aspergillosis at autopsy is 0.19%.[9] It is estimated to be 5 to 25% in patients with acute leukaemia and 0.5 to 5% after cytotoxic treatment of blood disease.[11,12] It is increasingly being reported in AIDS patients (1-12%) and also a common complication of chronic granulomatous disease (25-40%).[8]

Invasive aspergillosis still remains a big clinical challenge and diagnosis relies largely on histopathological evidence of mycelial growth in tissue. Unfortunately, the time gap between the decision to take a biopsy and the commencement of appropriate treatment often tends to get too long in order to obtain favourable results in such patients.[13,14] The management of cerebral fungal abscesses remains controversial. Antifungal therapy alone reportedly has a poor outcome for patients with CNS aspergillosis, with a high mortality rate of >90%; this is likely due to the poor penetration of the CNS by the antifungal drugs.[15] Other research has indicated that surgical resection of focal CNS aspergillosis lesions reduces the mortality rate from 64% to 39%.[15] Overall, voriconazole seems to be the drug of choice for the treatment of aspergillosis.[15] Unfortunately, no facilities are available to monitor the patient's exact voriconazole drug levels.

In this case particularly, the symptoms in the beginning were obscure. Complaints of fever with dry cough and a history of Chicken pox a few days back drew us to think about a post viral sequalae. Clinical and radiological

mismatch in coming to an accurate diagnosis made it furthermore challenging. As Tuberculosis is the most widespread and common infection in the Indian subcontinent, and the initiation of AKT at the beginning brought clinical wellbeing in the patient for a few days probed us to stick to our initial diagnosis of tuberculosis with milliary spread for a long time. Once neurological symptoms like seizures and weakness developed and the possibility of malignancy was introduced things started to get difficult.

Further differential diagnosis was considered. Biopsy initially wasn't possible due to lack of facilities and an expert hand. All possible tests were hence done in order to rule out malignancy. The continued use of antibiotics and subsequent use of steroids only worsened the disease course until a final diagnosis was made. Finally, an expert opinion was taken in order to achieve a lung biopsy which led to the final diagnosis. However, the time taken in initiation of the actual treatment, complications of the therapy and hospital acquired infections and the financial constraints of the patients' relatives makes it all the more difficult to obtain a healthy outcome. Thus, a high index of suspicion, vigorous search for fungi by cultures and empirical treatment for highly suspicious cases remain the mainstay of management of these cases.

CONCLUSION

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