Think Fungus! – Clinical profile, Risk factors and Diagnostic Utility of Galactomannan in diagnosis of Invasive Aspergillosis in Non-Neutropenic patients – A Prospective Study from India

Dr Akshatha R[1], Dr.Deepak Kumar[1],, Dr.Gopal Krishna Bohra[1], Dr Neetha TR[1],Dr Yash Khatod[1],Dr.Durga Shankar Meena[1], Dr.Naresh Kumar Midha[1], Dr.Vidhi Jain[2,], Dr.Kuldeep Singh[3], Nishant Kumar Chauhan[4], Dr Ankur Sharma[5]

1. General Medicine,2. Microbiology, 3.Pediatrics, 4. Pulmonary Medicine, 5. Anaesthesia

AIIMS, JODHPUR

Poster no. 361

Introduction

- Invasive aspergillosis (IA) is a serious opportunistic infection with high mortality rates of 30-60%(1,2)
- Early diagnosis of IA and treatment initiation is the single most important factor in reducing morbidity and mortality from IPA but diagnosis can be difficult to establish
- In patients with traditional risk factors for IA, such as those with hematological malignancies and prolonged neutropenia, the use of mold-active prophylaxis has been associated with a decrease in prevalence of IA
- Conversely, there has been a trend of increasing cases in Non-neutropenic host with the emergence of newer risk factors like DM, cirrhosis, COVID-19, HIV etc. The diagnosis of IA is challenging due to non-specific symptoms, lack of clinical suspicion leading to delay in diagnosis.
- Given this increase and the importance of early treatment to improve survival, there is an unmet need for better tests for early diagnosis IPA in non-neutropenic patients
- Serum galactomannan (GM) testing is the gold-standard test that is used in consensus definitions for diagnosing IPA in neutropenic patients with angioinvasive disease, but sensitivities decrease to 30% and less in nonneutropenic patients

Aims & Objectives:

- To evaluate the clinical features & risk factors of IA in non-neutropenic patients
- To look at the clinical utility of galactomannan in diagnosis of IA

Materials & Method:

- Study was commenced after the approval from the Institute Ethics Committee
- We screened 243 patients with suspected IA of which Fifty patients (Proven/Probable/Possible) were enrolled from April 2021 to May 2022 in tertiary care centre, AIIMS Jodhpur
- Patients with a hematological disease or granulocytic deficiency were excluded
- IA was divided into proven, probable and possible cases according to the EORTC/MSGERC criteria
- Proven: Histopathology or culture positive for Aspergillus
- Probable: There were dependable evidence of host factors, clinical manifestations, imaging findings on chest CT scan, and microbiological evidence [serum galactomannan (GM) or BALF GM or CSF GM]
- Possible: Preseence of Host factors with imaging findings
- We performed analysis of the general conditions, clinical manifestations, laboratory tests, and imaging features
- The data were statistically analyzed using SPSS 25.0, and graphs were generated using Microsoft Excel

Results

- A total of 50 patients which included – proven IA , probable IA, and possible IA patients. The mean age was 47.8±18.5 years
- Of all IA cases 68%(n=34) were IPA, 20% (n=10) were CNS aspergillosis & 10% (n=5) showed disseminated form of IA

Results

Table 1:Demographic data and underlying diseases of the study population

	Proven (N=16)	Probable (N=17)	Possible (N=17)
Baseline factors			
Male	64.2	80	57.1
Female	42.8	13.3	42.9
Age	48.2 (15-83)	48.21(14-71)	48.5 (14-86)
Underlying Pulmonary Disease in percent			
	N=14	N=15	N=14
Bronchiectasis	35.7	33.3	21.4
Pulmonary TB	35.7	6.6	50
COPD	0	20	14.2
Asthma	14.2	20	0
Extrapulmonary Disease in percent			
	N=14	N=15	N=14
Liver cirrhosis	0	6.6	0
Autoimmune disease	7.1	6.6	0
HIV/AIDS	7.1	20	0
DM	21.4	26.6	21.4
ICU	21.4	40	35.7
Respiratory symptoms in percent			
	N=14	N=15	N=14
Cough	85.7	46.6	14.2
Expectoration	64.3	26.6	50
Fever	71.4	60	85.7
Hemoptysis	35.7	6.6	14.2
Dyspnea	71.4	53.3	64.2
Immunosuppressants	7.1	6.6	0
Long term steroids (>2 weeks)	21.4	20	7.1
Short term steroids (<2 weeks)	28.5	0	0
CNS symptoms			
	N=3	N=3	N=4
Altered sensorium	66.6	66.6	75
Headache	100	100	100
Seizures	0	0	100

- The common symptoms included cough (71.3%), expectoration (44.7%), fever (71.4%) & dyspnoea (59.1%) in IPA, while in CNS aspergillosis, presented with fever (73.3%), altered sensorium (53%)
- The predominant risk factor included previous TB (28.5%), DM (24.4%),Previous steroid use (18.3%), COVID -19 (16.3%),& fungal sinusitis(16.3%)
- The radiological manifestations in IPA included the typical cavity (40.4%, n=17), while a large proportion of patients were having centrilobular nodules with tree in bud appearance (56.5%, n=23)
- The CNS aspergillosis was associated with ring enhancing lesion (41.6%, n=5) with leptomeningeal enhancement (50%, n=6), while cerebral abscess was seen in two patients
- The positivity of galactomannan in various fluids included were Serum in 24.4%, BALF in 91.3% & CNS in 87.5%
- Average galactomannan in serum was 1.42 (0.31-6.1), BAL was 3.7(0.86-12.7), CSF was 2.24(0.12-6.01)
- Patients with high serum GM (OD>1) was associated with more severe symptoms & outcomes
- Culture positivity was 18.3%, with predominant species being *Aspergillus fumigatus*
- Direct smear demonstrating thin hyaline septate hyphae were seen only in 28.5% of the cases
- Antifungal treatment was initiated in 75.5% of the patients, with Voriconazole being the predominant one used
- The overall mortality in our study was 20.4% (n=10). Complete response in 3 months follow-up period was seen in 69.3% (n=34) patients

	Proven	Probable	Possible
Laboratory findings in percent			
	N=14	N=15	N=14
CBC	9.91	15.4	9.53
ESR	69.3	77.85	57
CRP	93.82	86	96
Neutrophils	75.32	78.4	68.8
Mycological findings in percent			
BAL galactomannan (>1)	100	100	100
CSF galactomannan	80	100	83.3
Serum galactomannnan (>1)	25	44.4	25
Culture	60	0	0
Biopsy	93.3	0	0
CT Thorax findings in percent			
	N=12	N=9	N=10
Consolidation	33.3	44.4	40
Cavity	50	33.3	60
Ground-glass opacity	33.3	33.3	10
Centrilobular Nodule	50	66.6	60
Air crescent sign	0	0	0
Halo signs	0	0	0
Aspergilloma	8.3	11.1	10
Single lesion	33.3	22.2	40
Multiple lesion	41.6	44.4	50
Diffuse lesion	75	33.3	0
CT/MRI Brain findings in percent			
	N=3	N=3	N=4
Ring enhancing lesion	66.6	66.6	33.3
Nodules	0	0	33.3
Vasculitis	0	0	33.3
Sinusitis	100	33.3	33.3
Abscess	100	100	0
Overall Mortality	28.5	26.6	21.4

Table 2: Laboratory parameters and Radiological findings in the study population

Conclusions

- The clinical symptoms & radiological manifestations of IA in non-neutropenic are diverse & non-specific, which could lead to delayed diagnosis & mortality if not treated
- As the clinical manifestations are mild, culture & direct microscopy lack sensitivity, diagnostic markers like Galactomannan can be used for early & rapid diagnosis of IA in patients with newer emerging risk factor
- Further, the typical manifestation of IA may not be appreciated in all non-neutropenic patients

References:

1. Bassetti M, Azoulay E, Kullberg BJ, Ruhnke M, Shoham S, Vazquez J, Giacobbe DR, Calandra T. EORTC/MSGERC Definitions of Invasive Fungal Diseases: Summary of Activities of the Intensive Care Unit Working Group. Clin Infect Dis. 2021 Mar 12;72(Suppl 2):S121-S127. doi: 10.1093/cid/ciaa1751. PMID: 33709127.
2. J Peter Donnelly, Sharon C Chen, Carol A Kauffman, William J Steinbach, John W Baddley, Paul E Verweij, et a l, Revision and Update of the Consensus Definitions of Invasive Fungal Disease From the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium, *Clinical Infectious Diseases*, Volume 71, Issue 6, 15 September 2020, Pages 1367–1376