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Galactomannan Enzyme Immunoassay: Diagnosis & Monitoring Invasive Aspergillosis in Patients of Acute Leukemia & Stem Cell Transplant

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ABSTRACT

Introduction: Invasive fungal infections (IFI) are one of the major life threatening infections in patients of acute leukemias including those undergoing haematopoietic stem cell transplantation, of which candida and aspergillus are chief fungal pathogens. In most of the cases antifungal treatment is started empirically, due to lack of specific clinical radiological, and laboratory features, which has a mortality benefit but at the cost of overuse of antifungals in more than 50% of high risk patients, though incidence of IFI is only around 10%.
Aim & Objectives: Use of Galactomannan Enzyme Immunoassay for the diagnosis and monitoring of Invasive Aspergillosis in patients of Acute leukemia and Allogenic Hematopoietic Stem Cell Transplantation.
Materials & Methods: Serum Galactomannan levels of 100 patients who have received chemotherapy for acute leukemia or myelodysplastic syndrome or those who have undergone a myeloablative HSCT, were prospectively monitored for 16 weeks. These results were compared with probability of having invasive aspergillosis (IA) at any time during induction chemotherapy or allogenic stem cell transplantation as per EORTC/MSG criteria.
Results: Thirteen patients had proven IA whereas, 45 patients had probable or possible IA and 42 patients had no evidence of IA as per EORTC/MSG criteria. Mycological evidence of aspergillosis was obtained in 32 patients whereas CT chest & PNS at any time point showed evidence of aspergillosis in 34 out of 100 patients. Serum Galactomannan index at any time point was positive in 39 patients by taking cut-off of 0.5. S. Galactomannan was found to be positive earlier than CT positivity for IA (9 vs 14 days). Nineteen patients had persistent positive Galactomannan index. Sensitivity and specificity of S. Galactomannan for diagnosing IA was 75% & 83.3% respectively on day +1 of fever and 78.6% & 84.7% respectively on day +4 of fever. There was significant correlation between absolute neutrophil count and GM index.
Conclusion: Galactomannan index is an early predictor of invasive aspergillosis which was found to be positive earlier than CT positivity. Besides being a diagnostic marker of IA, serum GM can also be used to monitor response to therapy. However further studies are required to validate the hypothesis.
Keywords: Galactomannan Enzyme Immunoassay, Invasive Aspergillosis, Acute leukemia, Stem cell transplant.

INTRODUCTION

Invasive fungal infections (IFIs) are one of the life-threatening infections in patients of acute leukaemia including those who undergo haemopoietic stem cell transplant (HSCT). Candida and Aspergillus are the chief invasive fungal pathogens[1]. Classical clinical symptoms and signs may be missing in patients of acute leukemia patients and those undergoing HSCT, due to severe neutropenia and the inability to launch a complete immune response. Hence,

a high clinical suspicion with early start of therapy has been shown to be associated with better rates of successful control[2,3]. Empirical antifungal therapy, using the clinical symptom of persistent fever (beyond 5 days) despite high standard of care and broad spectrum antimicrobials during neutropenia, is well recognized to be associated with reduced mortality[4,5]. This widely practiced strategy has a number of shortcomings including the lack of specificity of fever as a reliable guide of who is in need of antifungal therapy, the overuse of antifungal therapy exposing many patients to needless, costly, and potentially toxic treatment, and the inadequate course of treatment given to those truly in need (since a diagnosis is not firm and stopping at the time of neutrophil recovery may not be long enough to ensure microbial eradication), resulting in as many as 40%–50% of the high-risk neutropenic population receiving empirical antifungal therapy, whereas the true incidence of IFI appears to be 10%–15%[6,7,8].

The radiological signs such as halo signs, macronodules, and cavitary lesions are enormously valuable and widely used as a high level of suspicion of Aspergillus, justifying the reason to initiate antifungal therapy. However, these radiologic findings are highly nonspecific as other mould pathogens (and occasionally bacteria, such as Nocardia) can give rise to similar radiographic features[9]. Aggressive invasive testing such as bronchoscopic lavage or biopsy, invasive biopsy may either be not always able to fetch positive results, or not possible in neutropenic patients. Thus, one may be justified to continue antifungal therapy based on presumption even in the absence of confirmation.

This uncertainty of presumption has been mitigated by new noninvasive diagnostic tools that offer the possibility to better target those in need of fungal therapy and to permit an earlier start of therapy, even before radiographic changes are apparent. The galactomannan and glucan assays are two such immunological tests that have both been has become a standard of care for the diagnosis of invasive disease in high risk patients[10,11]. In our country with limited resource setting, overtreatment, as well as the negative effect of delaying therapy until disease is proven, could be overcome by a preemptive approach. Progress could come from the incorporation of non–culture-based microbiological techniques, including screening for circulating *Aspergillus* galactomannan with an EIA and the early use of high-resolution thoracic CT scanning (HRCT). Both tools have a high diagnostic accuracy in neutropenic adults[12,13].

The aim of our prospective study was to assess the use of galactomannan enzyme immunoassay in diagnosis and monitoring of invasive aspergillosis in patients of acute leukemias and those undergoing hematopoietic stem cell transplantation.

MATERIALS & METHODS

Between October 2015 and March 2017, 100 patients who have received chemotherapy for acute leukemia or myelodysplastic syndrome or those who have undergone a myeloablative HSCT, were prospectively monitored for 16 weeks. The serum samples were tested for galactomannan (using enzyme immunoassay method) on the following occasions (i) Day of admission, (ii) Day when patient was first detected to have fever (defined as a sustained temperature of more than or equal to 100.4 F or one spike of fever of more than or equal to 101 F as per the definition of febrile neutropenia), (iii) Day +4 of fever (i.e on starting antifungals) and (iv) Twice weekly in second, third and fourth week.

The presence or absence of galactomannan antigen in the test sample was determined by calculation of an index for each patient specimen. The Index (I) is the OD (Optical Density) value of the specimen divided by the mean optical density of the wells containing 2 cut-off control samples provided with each kit. GM

index <0.5 and >0.5 was considered negative and positive respectively.

Microscopy and cultures from the appropriate specimens (blood, urine & sputum) were taken at baseline, twice in the first week and weekly thereafter for next three weeks. Radiological evidence of invasive aspergillosis was tested by computed tomography of chest or PNS or brain imaging by MRI (as clinically indicated) and lesions were defined for aspergillosis as per EORTC/MSG criteria. All patients received antifungal prophylaxis which was started from day of starting induction as per institution policy.

RESULTS

The baseline clinical and laboratory characteristics are mentioned in the table 1 & 2. The high preponderance of males in the study was noted as Army Hospital R&R is the apex institute of Indian army and caters to the whole armed forces, majority of which are male serving soldiers.

Out of 100 patients, 58 had evidence of invasive fungal disease (proven-13, probable-19, possible-26), 42 had no evidence of IA as per EORTC criteria (Table 3). Mycological evidence of aspergillosis was obtained in 32 patients with maximum positive results in sputum microscopy (11) followed by bronchoalveolar lavage for microscopy (8). CT chest & PNS at any time point showed evidence of aspergillosis in 34 out of 100 patients. The median day of CT evidence of fungal pneumonia from the time of inclusion into the study is 14 days (IQR 7-16).

A total of 813 serum samples were analyzed and GM levels were positive in 25.21%. The sensitivity and specificity of serum GM at day 1 of fever was 75% and 83.3 % respectively. Similarly, the sensitivity and specificity at day 4 of fever (at the time of initiating therapeutic antifungals) was 78.6% and 84.3% respectively (Table 4). Serum Galactomannan index at any time point was positive in 39 patients by taking cut-off of 0.5. Nineteen patients had persistent positive Galactomannan index. Out of 32 cases of IA (proven or probable), 15 patients had persistent GM positivity, of which 13(86.6%) succumbed to death. Twenty seven patients expired and the median day of expiry was 17 days.

There was no significant correlation between the type of lesions and the GM index tested at various time points as shown in table 5. There was significant correlation between absolute neutrophil count and GM index. High GM levels negatively correlates with the degree of neutropenia (r = -0.7526, p value 0.0194) as depicted in table 6 (Figure 1).

Table 1: Baseline clinical characteristics of all the patients (n=100).

Parameters	Units	Value
Age (median, IQR)	Years	39.18 (19.75 - 55.25)
Sex (M:F)	Percentage	74%/26%
Anemia (present/absent)	Percentage	97%
Duration of anemia (median, IQR)	Days	31 (25-38)
Bleeding (present/absent)	Percentage	31%
Duration of bleeding	Days	50 (30-77.5)
Lymphadenopathy (present/absent)	Percentage	22%
Hepatomegaly (present/absent)	Percentage	30/70
Splenomegaly (present/absent)	Percentage	33/67
ANC at presentation (median, IQR)	/mm^3	1309.87 (100 - 2900)
Type of leukemia ALL AML	Percentage	53% 47%
BM Blasts (median, IQR)	Percentage	73.00 (56.00 - 80.75)
Proven IA Probable IA Possible IA No IA	Percentage	13 19 26 42

Table 2: Clinical characteristics of all patients during follow-up (n=100).

Parameters	Units	Value
Sputum for microscopy/cytology positive for aspergillosis	Percentage	11
BAL for microscopy/cytology positive for aspergillosis	Percentage	8
Blood culture positive for aspergillosis	Percentage	0
Sputum Culture positive for aspergillosis	Percentage	3
Urine culture positive for aspergillosis	Percentage	0
BAL Culture positive for aspergillosis		4
Sinus aspirate microscopy positive for aspergillosis		6
1st CT (as per major clinical criteria-EORTC) n=100	Percentage	
Positive for fungal pneumonia		13 (13)
Negative for fungal pneumonia		87 (87)
2nd CT(as per major clinical criteria-EORTC) n=92	Percentage	
Positive for fungal pneumonia		23.9 (22)
Negative for fungal pneumonia		76.0 (70)
3rd CT(as per major clinical criteria-EORTC) n=86	Percentage	
Positive for fungal pneumonia		20.9 (18)
Negative for fungal pneumonia		79.0 (68)
4th CT(as per major clinical criteria-EORTC) n=73	Percentage	
Positive for fungal pneumonia		21.9 (16)
Negative for fungal pneumonia		78.0 (57)
CT evidence of fungal pneumonia at any time (as per major clinical criteria-EORTC)	Percentage	34
Day of CT evidence of fungal pneumonia (median, IQR)	Days	14 (7-14)
GM positive(≥0.5)	Percentage	
At day 0 (100)		12.00
At day 1 of fever (100)		33.00
At day +4 of fever (98)		33.67
At day 10 of fever (97)		35.05
At day 14 of fever (92)		35.86
At day 17 (89)		30.33
At day 21 (86)		19.70
A day 24 (76)		11.84
At day 28 (73)		9.58
Persistent GM index positive	Percentage	19
Galactomannan index (mean)	Index	0.4117 (0.12 - 1.99)
At day 0 (100)		0.5180 (0.12 - 1.88)
At day 1 of fever (100)		0.5509 (0.11 - 1.90)
At day +4 of fever (98)		0.7207 (0.12 - 2.44)
At day 10 of fever (97)		0.8033 (0.10 - 2.99)
At day 14 of fever (92)		0.6292 (0.12 - 2.76)
At day 17 (89)		0.5285 (0.10 - 2.90)
At day 21 (86)		0.4291 (0.17 - 2.99)
A day 24 (76)		0.3723 (0.12 - 0.99)
At day 28 (73)		-
ANC (mean)	/mm^3	
At day 0 (100)		1309.87 (100 - 2900)
At day 1 of fever (100)		486.81 (10 - 1300)
At day +4 of fever (99)		260.08 (10 - 1100)
At day 10 of fever (97)		151.29 (10 - 1200)
At day 14 of fever (93)		133.91 (10 - 1490)
At day 17 (89)		205.89 (10 - 1800)
At day 21 (86)		300.77 (10 - 1598)
A day 24 (75)		506.00 (10 - 1765)
At day 28 (73)		752.34 (90 - 2000)
Number of expiry	Percentage	27%
Day of expiry (median, IQR)	Days	17 (10 - 21)

TABLE 3 . EORTC/MSG study group criteria for diagnosis of Invasive Aspergillosis

Diagnosis	Criteria
Proven IA	Histopathological evidence of tissue invasion by filamentous fungi, Isolation of Aspergillus species from a normally sterile but clinically infected body site, And the presence of host factors.
Probable IA	One microbiological criteria, and One host criteria, and Clinical criteria (one major or two minor)
Possible IA	Host criteria, and Presence of one microbiological criteria, or Clinical criteria (one major or two minor)
Microbiological Criteria • Positive result of culture for aspergillus from sputum/bronchoalveolar lavage fluid samples, sinus aspirate. • Positive findings of cytologic/direct microscopic evaluation for aspergillus from sputum/ bronchoalveolar lavage fluid samples, sinus aspirate	

Host Criteria

- Recent history of neutropenia of <500 neutrophils/mm3 for >10 days, if temporally related to the onset of fungal disease
- Recipient of an allogeneic stem cell transplant
- Prolonged use of corticosteroids at a mean minimum dose of 0.3 mg/kg of body weight/day of prednisone equivalent for >3 weeks
- Treatment with other recognized T-cell immunosuppressants, specific monoclonal antibodies (such as alemtuzumab) , OR Inherited severe immunodeficiency

Clinical Criteria

- LRTI:

Major – Halo sign, Air crescent sign, Cavity within area of consolidation

Minor - Symptoms of LRTI (cough, chest pain, hemoptysis, or dyspnea), Physical finding of pleural rub, Any new infiltrate not fulfilling major criterion, Pleural effusion

- Sinonasal infection:

Major - Suggestive radiological evidence of invasive infection in sinuses (i.e., erosion of sinus walls or extension of infection to neighboring structures, and extensive skull base destruction)

Minor - Upper respiratory symptoms (e.g., nasal discharge and stuffiness), Nose ulceration or eschar of nasal mucosa or epistaxis, Periorbital swelling, Maxillary tenderness, Black necrotic lesions or perforation of hard palate.

Table 4. Diagnostic accuracy of serum galactomannan in invasive aspergillosis

GM	SENSITIVITY	SPECIFICITY	PPV	NPV	ACCURACY	AUROC
Day +1 of fever	75.0%	83.3%	63.6%	89.6%	81.0%	0.806 (p value < 0.001)
Day +4 of fever	78.6%	84.7%	66.7%	90.8%	81.0%	0.836 (p value < 0.001)

Table 5. CORRELATION OF GMI POSITYVITY WITH TYPE OF LESION ON CT

		Day 4		Day 14		Day 21		Day 28	
GM Index		-ve	+ve	-ve	+ve	-ve	+ve	-ve	+ve
Macronodules	1st CT	2	11	0	12	4	6	7	1
	2nd CT	1	2	0	3	1	2	3	0
	3rd CT	0	0	0	0	0	0	0	0
Halo sign	1st CT	2	5	2	4	5	1	4	0
	2nd CT	2	13	2	13	8	5	8	1
	3rd CT	1	4	1	4	1	4	3	1
Consolidation with cavity	1st CT	0	0	0	0	0	0	0	0
	2nd CT	0	0	0	0	0	0	0	0
	3rd CT	1	3	1	3	3	1	2	1
Air crescent sign	1st CT	0	0	0	0	0	0	0	0
	2nd CT	0	0	0	0	0	0	0	0
	3rd CT	1	1	1	1	1	1	1	1
Sinus involvement	1st CT	1	1	0	0	0	0	0	0
	2nd CT	0	3	0	3	1	2	1	0
	3rd CT	1	3	1	4	1	3	1	1
P value	1st CT	0.5010		0.1542		0.0907		0.7153	
	2nd CT	0.6619		0.7810		0.5194		0.4422	
	3rd CT	0.8774		0.8494		0.3430		0.9063	

CORRELATION OF ANC WITH GALACTOMANNAN INDEX

Table 6: GM index and ANC at day 0, 4, 10, 14, 17, 21, 24 and 28

	GM index (mean)	ANC (mean)	Pearson correlation coefficient r, R^2, p value
Day 0	0.4117 (0.12 - 1.99)	1309.87 (100 - 2900)	
Day 1	0.5180 (0.12 - 1.88)	486.81 (10 - 1300)	
Day 4	0.5509 (0.11 - 1.90)	260.08 (10 - 1100)	
Day 10	0.7207 (0.12 - 2.44)	151.29 (10 - 1200)	
Day 14	0.8033 (0.10 - 2.99)	133.91 (10 - 1490)	
Day 17	0.6292 (0.12 - 2.76)	205.89 (10 - 1800)	r = -0.7526
Day 21	0.5285 (0.10 - 2.90)	300.77 (10 - 1598)	R^2 = 0.5664
Day 24	0.4291 (0.17 - 2.99)	506.00 (10 - 1765)	P value = 0.0194
Day 28	0.3723 (0.12 - 0.99)	752.34 (90 - 2000)	

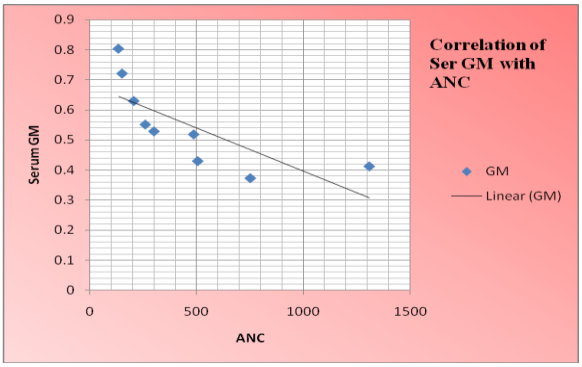

Figure 1

DISCUSSION

In our study, out of 100 patients of acute leukemia during induction therapy, 58 patients developed invasive fungal infection on the basis of EORTC/MSG criteria. A difficulty in analyzing our data was to accurately define IA. According to the EORTC–MSG, a positive GEI test result is a microbiological criterion to define

probable IA. Due to the outcome variables, it was problematic to use GEI test results for definition of IA in our study, hence results of GM EIA were not included among the diagnostic criteria.

Studies from US and Europe shows the incidence of IA 5-10 % in ALL, 12-20% in AML and 7-10% overall in all acute leukemia patients[14]. Indian study by Indranil Ghosh et al from BRAIRCH, AIIMS shows overall incidence of 28.7%[15]. One reason for such high incidence of IA in our patient could be delay in presentation.

GM assay sensitivity for IA has varied markedly among studies, from as low as 30% to as high as 100%[16, 17]. This variability in the assay may be related in part to the hosts and their exposure to antifungal agents. In the study, it was observed that sensitivity and specificity of serum galactomannan by ELISA at first day of fever was 75% and 83.3% respectively. The positive and negative predictive values were 63.6% and 89.6% respectively. Similarly, at day +4 of fever (on initiation of therapeutic antifungal therapy), the sensitivity, specificity, PPV and NPV of serum galactomannan by ELISA was 78.6%, 84.3%, 66.7% and 90.8% respectively. Importantly, the sensitivity was relatively low at onset of fever, but became higher when patients had persisting fever after therapy with broad-spectrum antibiotics or when they developed pneumonia. We found that the specificity was excellent in all those critical clinical situations. This is particularly interesting, given that we used a relatively low cut-off level for the GEI test (GM index - 0.5). Consequently, our results support the view that a lower cut-off level (e.g. A index = 0.5) is superior to the relatively high cut-off level (A index = 1.5), which was recommended in the past.

In our study the mean GM level was highest (0.8033) at day which correlates with peak neutropenia (median ANC was 133.91/mm^3), correlates with high disease burden. Galactomannan levels were high at day 1 of fever (in 33% patients) and were consistently rising till day 14 (in 66.66% patients) which is consistent with the peak neutropenia (p value 0.0194). Data by Park and Woods et al showed the rising levels of GM kinetics were consistent with high degree of neutropenia and deterioration patient condition[17,18].

Antigenemia declines during therapy[19]. Woods and colleagues reported that failure of antigenemia to decline during therapy was associated with a poor outcome, supporting earlier reports[19,20]. Survival was better in patients whose antigenemia cleared than in those with persistent antigenemia. The same was corroborated in our study. Also, it was noted that out of 32 cases of IA (proven and probable), 15 patients had persistently positive (till 04 weeks or death whichever was earlier) serum GM values. The persistent nature of positive GMI was associated with greater mortality, 13 out 15 succumbed to death (86.6%). These results support our previous findings that established GMI is a validated surrogate endpoint for aspergillosis outcome and that the test should be considered both as an enrolment criterion and an outcome measure in clinical practice.

On co-relating the patients of IA (both proven and probable) with CT findings, it was noted that 75% patients had positive GM values before the CT evidence of invasive aspergillosis which is in consistence with data from Sulahian et al that showed that 64.6% had positive GM values before the CT evidence of invasive aspergillosis. GM was noted to be positive around 9 days (mean) before CT positivity[13]. Overall, at the end of study, 60.7% of our patients with IA were found to have “halo sign”, the air crescent sign (14.2%) and cavity within consolidation (17.8%). Some patients had more than one finding and were hence, included in both groups. Macronodules exhibiting halo signs are identified in almost two-thirds of patients with confirmed diagnoses of IPA[21,22]. This suggests that, in high risk patients, the absence of a macronodule

argues against a diagnosis of IPA. Published reports have identified the halo sign as an early indicator of IPA, specifically in immunocompromised patients with hematological conditions, though time taken to develop CT findings suggestive of IA was found to be delayed as compared to Galactomannan positivity in our study.

CONCLUSION

Galactomannan index is an early predictor of invasive aspergillosis which was found to be positive earlier than CT positivity. Besides being a diagnostic marker of IA, serum GM can also be used to monitor response to therapy. Also persistence of high Galactomannan levels after initiation of antifungal therapy is associated with poor outcomes. However further studies are required to validate the hypothesis.

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