Clinical accuracy and utility of plasma microbial cell free DNA NGS in the diagnosis of invasive aspergillosis in patients with hematologic malignancy and COVID-19

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Background

Invasive aspergillosis (IA) is a great threat to the severely immunocompromised patients, but diagnosis of IA is often difficult due to need for invasive and low sensitivity of diagnostic tests. Next-generation sequencing (NGS) of plasma cell free DNA (cfDNA) can be a novel non-invasive diagnostic modality. We evaluated the clinical accuracy and utility of microbial cfDNA NGS for diagnosis of IA in patients with hematologic malignancy (HM) and coronavirus disease-19 (COVID-19).

Objectives

To evaluate the diagnostic performance and detection rate of invasive aspergillosis in patients with suspected fungal infection according to the European Organization for Research and Treatment of Cancer and Mycoses Study Group(EORTC/MSG) or modified Aspergillosis in intensive care unit(AspICU) diagnostic criteria.

Methods

A single-center prospective cohort study was conducted in a tertiary hospital in South Korea. We enrolled adult patients with HM and COVID-19, who suspected of IA. IA cases were diagnosed according to EORTC/MSG definitions in patients with HM, and modified AspICU criteria in patients with COVID-19.

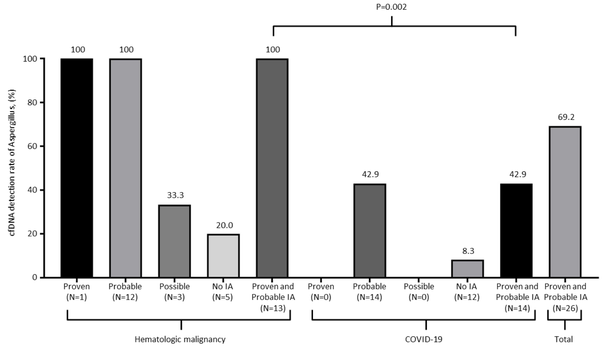
Results

Between March 2021 and January 2022, a total of 33 participants (22 [64.7%] male, median age 66.0 [50.5, 72.0]) were enrolled;19 participants with HM and 15 with COVID-19 were analyzed (Table1).

Table 1. Baseline characteristics of participants suspected of invaisve aspergillosis performing microbial cell free DNA NGS

	All (N=33)	Hematologic malignancy (N=19)	COVID-19 (N=15)
Gender , male	22 (64.7)	12 (63.2)	10 (66.7)
Age, years	66.0 (50.5, 72.0)	64.0 (38.0, 68.0)	70.0 (64.0, 77.0)
BMI, kg/m^2	22.6 (20.1, 26.3)	20.6 (19.0, 25.3)	23.8 (21.5, 28.0)
Hematologic malignancy			
Leukemia	11 (32.4)	11 (57.9)	0 (0.0)
Lymphoma	1 (2.9)	1 (5.3)	0 (0.0)
MDS	5 (14.7)	4 (21.1)	1 (6.7)
MM	1 (2.9)	1 (5.3)	0 (0.0)
HSCT	9 (26.5)	9 (47.4)	0 (0.0)
GVHD	2 (5.9)	2 (10.5)	0 (0.0)
COVID-19	15 (47.1)	1 (5.3)	15 (100.0)
Underlying disease			
Hypertension	14 (41.2)	4 (21.1)	10 (66.7)
Diabetes mellitus	13 (38.2)	3 (15.8)	10 (66.7)
Chronic kidney disease	9 (26.5)	3 (15.8)	6 (40.0)
Cardiovascular disease	13 (38.2)	4 (21.1)	9 (60.0)
Cerebrovascular accident	5 (14.7)	2 (10.5)	3 (20.0)
Autoimmune disease	4 (11.8)	4 (21.1)	0 (0.0)
Solid cancer	3 (8.8)	1 (5.3)	2 (13.3)
Recent chemotherapy	13 (38.2)	13 (68.4)	0 (0.0)
Neutropenia	12 (35.3)	12 (63.2)	0 (0.0)
Antifungal agent exposure			
At the time of examination	22 (64.7)	16 (84.2)	6 (40.0)
More than 2 weeks	7 (20.6)	6 (31.6)	1 (6.7)
Final IA status			
Proven	1 (2.9)	1 (5.3)	0 (0.0)
Probable	25 (73.5)	12 (63.2)	13 (86.7)
Possible or putative	3 (8.8)	3 (15.8)	0 (0.0)
No IA	5 (14.7)	3 (15.8)	2 (13.3)
Suspected IA site, lung	28 (82.4)	15 (78.9)	13 (86.7)
Suspected IA site, sinusitis	1 (2.9)	1 (5.3)	0 (0)

Figure 1. cfDNA detection rate in participants with suspected fungal infection according to the EORTC/MSG or modified AspICU diagnostic criteria



In participants with HM, aspergillus cfDNA was detected in 100% of both proven (1/1) and probable (12/12) IA cases, and 33.3% of both possible (1/3) and no IA (1/3) cases. In participants with COVID-19, 46.2% of probable IA (6/13) showed positive aspergillus cfDNA. Detection rate of aspergillus cfDNA was significantly higher in proven/probable IA cases in participants with HM compared to participants with COVID-19. (100% vs 46.2%, p=0.005) (Figure 1).

As shown in Table 2, among proven/probable IA cases, participants with positive aspergillus cfDNA showed significantly higher rate of having uncontrolled hematologic disease, receiving stem cell transplantation and recent chemotherapy.

Table 2. Factors associated with increasing detection rate of aspergillus cfDNA NGS results in participants with proven/probable IA

	All (N=26)	positive Aspergillus cfDNA (N=18)	negative Aspergillus cfDNA (N=8)	P-value
Gender , male	16	11 (61.1)	5 (62.5)	0.999
Age above 65	13	9 (50.0)	4 (50.0)	0.999
Hematologic malignancy	13	13 (72.2)	0 (0.0)	**0.002**
Leukemia	6	6 (33.3)	0 (0.0)	0.132
COVID-19	14	6 (33.3)	8 (100.0)	**0.002**
Final IA status				
Proven	2	2 (11.1)	0 (0.0)	0.999
Probable	24	16 (88.9)	8 (100.0)	0.999
Aspergillus galactomannan	25	17 (94.4)	8 (100.0)	0.999
Beta-D-glutan	21	13 (72.2)	8 (100.0)	0.281
Antifungal agent exposure	15	12 (66.7)	3 (37.5)	0.218
More than 7-day	7	5 (27.8)	2 (25.0)	0.999
More than 14-day	5	4 (22.2)	1 (12.5)	0.999
Neutropenia	6	6 (33.3)	0 (0.0)	0.132
Underlying disease				
Hypertension	12	6 (33.3)	6 (75.0)	0.09
Diabetes mellitus	12	5 (27.8)	7 (87.5)	0.009
Chronic kidney disease	9	6 (33.3)	3 (37.5)	0.999
Cardiovascular disease	10	6 (33.3)	4 (50.0)	0.664
Cerebrovascular accident	4	1 (5.6)	3 (37.5)	0.072
Autoimmune disease	3	3 (16.7)	0 (0.0)	0.529
HSCT	8	8 (44.4)	0 (0.0)	**0.031**
GVHD	2	2 (11.1)	0 (0.0)	0.999
Recent chemotherapy	8	8 (44.4)	0 (0.0)	**0.031**

Conclusion

Detection of aspergillus cfDNA showed high concordance with conventional diagnostic methods in proven/probable IA and could be a helpful to diagnosis IA in immunocompromised patients.