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EDİTÖRE MEKTUP
LETTER TO THE EDITOR

Is COVID-19 a risk factor for invasive pulmonary aspergillosis in critically ill patients?

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To the Editor,

Recently, several studies have emphasized the impact of invasive pulmonary aspergillosis (IPA) in COVID-19 (1). Regardless of the presence of underlying pathologies or interventions specified as host factors defined in EORTC/MSG Consensus report, the use of immunosuppressive and immunomodulatory therapies for COVID-19 and the presence of risk factors such as chronic obstructive pulmonary disease in these patients may facilitate development of IPA (2). On the other hand, as influenza was reported as an independent risk factor for developing IPA, a similar situation may occur in COVID-19 patients (3). Although diagnosis of IPA is further challenged by reluctance to take lower respiratory tract samples because of increased risk of viral transmission, and radiologically non-specific

findings in the non-neutropenic patient, it has been shown in a prospective study that with an IPA algorithm developed for COVID-19, the frequency of IPA reached approximately 28% (4). With an increased mortality and prolonged hospitalization, as reported in the study of White et al., IPA maintains its importance, especially in severely ill patients followed in the intensive care (5).

Our hospital is a referral center with an extensive experience in invasive fungal infections in hemato-oncological patients and our medical intensive care unit has served exclusively to critically ill COVID-19 patients since March 2020. This study was approved by the ethical committee of our hospital. We compared the frequency of invasive fungal infections in patients admitted to the medical intensive care unit in the last six-month period (April 1 2020-September 30 2020; COVID-19 period) with those in the same months in

2019 (pre-COVID-19 period). Galactomannan (GM) index of serum and lower respiratory tract samples, blood cultures, thoracic computed tomography reports were reviewed from hospital charts and laboratory reports. A total of 220 patients were hospitalized in COVID-19 period compared to 205 admissions in pre-COVID-19 period. The prevalence of candidemia was similar - 14/220 patients (6.3%) in 2020 vs 14/205 (6.8%) in 2019. Lower respiratory tract fungal culture was sent from 27 vs 27 patients ($p=0.7$), tracheal aspirate/bronchial lavage-GM from 17 vs 11 patients ($p=0.17$), serum GM from 28 vs 11 patients ($p=0.002$) in 2019 and 2020, respectively. There was one case of IPA in pre-COVID-19 period compared to 4 cases in the last 6 months. Although this suggests a trend of increase in IPA, it did not reach a statistically significant level ($p=0.2$) because of few cases (Table 1).

Table 1. Clinical features of patients with COVID-19 associated invasive pulmonary aspergillosis

Patients	1	2	3	4
Age	55	80	51	54
Gender	Male	Female	Male	Male
Comorbidities	Renal transplantation	Hypertension Good-Pasture Syndrome	Diabetes, Hypertension Renal transplantation Ischemic heart disease	Bronchiectasis
Corticosteroids/ immunosuppressive therapy	Methyl-prednisolone (Pulse Methyl-prednisolone, prednisolone, mycophenolate mofetil prior to COVID-19)	Methyl-prednisolone (Pulse Methyl- prednisolone, cyclophosphamide prior to COVID-19)	Methyl-prednisolone (prednisolone, tacrolimus, mycophenolate mofetil prior to COVID-19)	Dexamethasone Methyl- prednisolone
PCR test result for diagnosis of COVID-19	(+)	(+)	(+)	(+)
Specific therapies for COVID-19	Favipiravir, hydroxychloroquine Hemoabsorption therapy, intravenous immunoglobuline	Favipiravir, hydroxychloroquine, Azithromycin, intravenous immunoglobuline	Favipiravir, intravenous immunoglobuline	Favipiravir, Tocilizumab, inhaled nitric oxide
Timing of IPA (*/†), days	20/25	4/4	5/8	16/29
Mycology results	ETA-GM-EIA: 1.28 ETA-Fungal Culture: negative	ETA-GM-EIA: 15 Serum GM-EIA (x2): 0.79, 2.4	Serum GM-EIA (x2): 9.2, 12 ETA-Fungal Culture: negative	Serum GM-EIA: 3.2 ETA-Fungal Culture: negative
Radiology	Non specific ground-glass opacities	Non specific ground-glass opacities	Nodules, cavitation	Cavitation
Antifungal agent	voriconazole	voriconazole, posaconazole	voriconazole	voriconazole
Secondary infections	CMV pneumonitis <i>Pseudomonas aeruginosa</i> / <i>Klebsiella pneumonia</i> (ETA)	<i>Acinetobacter baumannii</i> (blood culture)	<i>Pseudomonas aeruginosa</i> (blood culture)	<i>Acinetobacter baumannii</i> , <i>Enterococcus faecalis</i> (ETA)
ICU mortality	Yes	Yes	Yes	No

IPA: Invasive pulmonary aspergillosis, ETA: Endotracheal aspirate, GM-EIA: Galactomannan enzyme immunoassay.

* Time from intensive care admission to IPA diagnosis, † time from COVID-19 to IPA diagnosis.

Although less serum GM tests were performed, the number of patients with IPA was higher in the COVID-19 period. Further data is needed to confirm this trend in prospective studies.

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