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SARS-CoV-2 related ARDS and invasive fungal infections in intensive care patients

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ABSTRACT

SARS-CoV-2 infection can potentially necessitate intensive care management. An increasing number of case reports are found in the literature indicating patients admitted in an intensive care setting with COVID-19 pneumonitis being complicated with invasive fungal infections.

In a retrospective assessment of a three-month period at the national hospital of Malta, examining patients who were suffering from SARS-CoV-2 acute respiratory distress syndrome, 6 out of 63 patients (9.5%) were found to have confirmation or high probability of invasive fungal infection. The consensus definition for invasive fungal disease developed by the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium was utilised to aid in the identification of these patients.

In total, 15 patients received treatment with an anti-fungal agent in this three-month period, the decision being led by both clinical suspicion and the use of fungal markers obtained from the serum and bronchoalveolar lavage. Although several risk factors are attributed for the development of invasive fungal disease, the main factors identified in our cohort of patients is the SARS-CoV-2 ARDS in itself, along with the use of high dose corticosteroids. The average period of time between admission in intensive care and diagnosis of invasive fungal infection was noted to be 10.5 days.

This high incidence of invasive fungal disease in mechanically ventilated patients suffering from SARS-CoV-2 ARDS, relatively early in their course of disease, should guide the clinician to investigate further with fungal biomarkers and cultures in those patients who are clinically deteriorating despite optimal medical treatment, as well as possibly considering empirical anti-fungal treatment if suspicion remains high.

Introduction

SARS-CoV-2 related acute-respiratory distress syndrome (ARDS) has an associated mortality rate in intensive care of over 40% (Abate et al., 2020; Armstrong et al., 2020).

Several case reports (Hoegl, 2021; Nucci et al., 2021; Pemán et al., 2020) have described the occurrence of invasive fungal infections in intensive care patients with COVID-19 pneumonitis, including pulmonary aspergillosis, invasive Saccharomyces and Candida infections; as well an increasing number of reports of mucormycosis, especially in India (Singh et al., 2021). The pathogenesis leading to these infections remains unclear, with patients having no known particular risk factors other than SARS-CoV-2 related acute respiratory distress syndrome (ARDS).

Methodology

A retrospective assessment of patients who were admitted with the primary diagnosis of SARS-CoV-2 ARDS to the intensive care unit (ICU) at Mater Dei Hospital between the months of November 2020 to January 2021 was performed. All personal data was anonymised and deleted at the end of the study.

Online databases (iSOFT, PACS and Electronic Case Summaries) were utilised to gather all information required, including patient demographics and co-morbidities.

In the intensive care setting, diagnosis of IFI in intubated patients with SARS-CoV-2 related ARDS is often difficult as typical signs are lacking and radiology is very difficult to interpret. Therefore, diagnosis of an IFI often involves culture from either blood or bronchoalveolar lavage (BAL) and/or testing for fungal markers (Beta-D Glucan and...
Galactomannan assays) from the serum and BAL. Aspergillus PCR was not available.

Patients who were noted to deteriorate clinically whilst on intensive treatment and respiratory support, were tested for an IFI. Part of this patient group who were tested for an IFI were given empirical antifungal treatment, the decision led by both clinical features and serological fungal markers.

The updated consensus definition of an IFI by the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium (EORTC/MSG) (Donnelly et al., 2020) developed the following criteria to aid in the stratification for confirmed and probable diagnoses:

- **Confirmed IFI for Moulds (such as Aspergillus sp.)**
  - Microscopic analysis and/or culture of a sterile material (excluding BAL) obtained from a site which is normally considered sterile, plus clinical or radiological evidence of infection
  - Blood cultures which yield a mould in the compatible clinical context, however it is specifically noted that blood cultures recovering Aspergillus species is in most cases considered contamination and not reflecting the endovascular environment

- **Confirmed IFI for Yeasts (such as Candida sp.)**
  - Microscopic analysis and/or culture of a sterile material from a site which is normally considered sterile, plus clinical or radiological evidence of infection
  - Blood cultures cultivating yeast

- **Probable IFI for Moulds (such as Aspergillus sp.)**
  - Presence of immunocompromise and at least one of the following:
    - ‘Host Factors’ (e.g. neutropenia, haematological malignancies)
    - ‘Clinical Features’ (e.g. radiological signs of IFI such as segmental lobar consolidation)
    - ‘Mycological evidence’ (e.g. Aspergillus cultured from BAL or positive Galactomannan antigen from plasma/BAL)

- **Probable IFI for Yeasts (such as Candida sp.)**
  - Presence of immunocompromise and at least one of the following:
    - ‘Host Factors’ (e.g. neutropenia)
    - ‘Clinical Features’ (i.e. liver or splenic abscesses, and retinal/vitreal involvement)
    - ‘Mycological evidence’ (i.e. Positive Beta-D Glucan in two consecutive samples obtained from serum, whilst excluding other causes)

Our patients were stratified according to the above consensus definitions. Beta-D Glucan testing was carried out with Fungitell®, which assesses reactions in vitro via spectrophotometry, whilst for Galactomannan an ELISA test was used.

Patients in whom Aspergillus species was cultivated from BAL in the appropriate clinical context, were diagnosed with probable IFI since culture from BAL is considered insufficient to confirm the diagnosis. It is also noted that the latest update of the IFI definitions state that Beta-D Glucan alone is not suggestive of IFI for mould disease.

The consensus for diagnosis of an IFI (Donnelly et al., 2020) mentions the criteria for probable disease as the requirement of the presence of immunocompromise and three other factors (Host Factors, Clinical Features and Mycological evidence). All patients on ICU being treated for SARS-CoV-2 related ARDS were prescribed dexamethasone 6 mg daily for a minimum of 10 days. This steroid regimen in the context of severe COVID-19 ARDS was considered immunosuppressive and thus a sufficient risk factor for developing an IFI.

Assessment also included the length of ICU stay (LOS) prior to the detection of the fungal infection and whether an organism was cultivated.

**Results**

63 patients were admitted to intensive care over 3 months, between November 2020 and end of January 2021, with a diagnosis of ARDS secondary to SARS-CoV-2.

Due to significant deterioration on intensive treatment and support, 30 (47.6%) of these patients were further investigated for fungal infections with fungal cultures and markers from both the serum and bronchoalveolar lavage, as per EORTC/MSG recommendations. Out of the total 63 admitted patients, 15 (23.8%) required empirical treatment with an intravenous anti-fungal agent.

The mean duration of ICU stay for the patients who were investigated for an IFI was 31 days; whilst those who were treated for an IFI had a mean stay of 39.3 days. All patients investigated for IFI had treatment consisting of dexamethasone or another form of steroid during their inpatient stay.

Out of the patients who were treated for an IFI, 2 were considered confirmed, whilst 4 had probable IFI and 9 had low evidence for IFI, when applying the criteria described above. Table 1 below summarises this cohort. Therefore, out of all 63 patients in ICU in this 3 month period, a total of 6 patients (9.5%) had a confirmed or probable IFI.

The mean time period between admission to ICU and diagnosis of confirmed or probable IFI was 10.5 days.

With regards to co-morbidities, in the cohort of patients with a confirmed or probable IFI, half of these had diabetes mellitus, and none were on immunosuppressive treatment prior to admission. All of these patients were male and had an average age of 71.8 years.

Out of the 15 patients who were treated for an invasive fungal infection, 8 were given Caspofungin, 3 were treated with Voriconazole, 2 were given Voriconazole and Caspofungin, 1 was given Liposomal Amphotericin and 1 given Liposomal Amphotericin and Voriconazole. The choice of the anti-fungal was individualised, based on the suspected fungal infection, clinical features such as electrolyte disturbance or organ dysfunction and clinical response.

**Discussion**

An increasing number of case reports are being published in the literature on the incidence of invasive fungal infections in this particular patient population (Hoennigl, 2021; Nucci et al., 2021; Pemán et al., 2020), including multiple cases of mucormycosis. In a recent systematic review by Singh et al. (2021), over 101 cases of mucormycosis have been reported in patients with SARS-CoV-2 infection, particularly in patients who had diabetes mellitus (especially if uncontrolled) and received corticosteroid treatment. However, to date no studies have examined patient populations who are non-diabetic and developed mucormycosis in the context of SARS-CoV-2 infection and whether steroid treatment is an independent risk factor.

IFIs in patients being treated in intensive care have been classically linked to specific risk factors. Several risk factors are known to contribute to the risk of IFI (Meersseman et al., 2007); the highest risk being immunosuppression and haematological malignancy, whilst common intermediate risk factors being prolonged corticosteroid treatment, COPD, liver cirrhosis and HIV. The risk factors which are considered as lower risk (but still significant) include a prolonged stay in intensive care (21 days or beyond (Meersseman et al., 2007) and malnutrition.

As mentioned above, our patients were treated with Dexamethasone 6 mg daily for 10 days. However, this regimen falls below the duration threshold considered significant by the EORTC/MSG consensus group, which states that for the definition for probable IFI (Donnelly et al., 2020), a significant immunosuppressive therapeutic dose of steroids should be >0.3 mg/kg of prednisolone or equivalent for ≥3 weeks. Whilst keeping these criteria in mind, our assumption is that SARS-CoV-2 ARDS is in itself a risk factor for IFI.

In a systematic review by Chiurlo et al. (2021), it was noted that the...
increasing incidence of superinfections in patients with SARS-CoV-2 ARDS had no obvious pre-existing risk factors, therefore it was argued that the viral infection in itself could be postulated to be a significant contributing factor for these complications. In our patients, none had evidence of obstructive lung disease, whilst half of each group of confirmed and probable IFI had diabetes mellitus; none were on immunosuppressive treatment prior to ICU stay nor had HIV infection. None of the patients were administered tocilizumab, as the data from this patient cohort was prior to the recommendation of the latter.

It is also important to acknowledge the difficulty in the diagnosis of an IFI in this particular group of patients. The difficulties relate to strict isolation procedures complicating communication, physical examination and obtaining timely cross-sectional imaging. The latter being crucial in the assessment of IFI. Complicating all the above is the difficulty in determining whether a fungal organism being cultured is in fact reflecting colonisation or an active infection; the consensus definition for IFIs (Donnelly et al., 2020) is helpful in this regard. Patients were assessed and discussed individually with the respective intensivists prior to undergoing BAL sampling, to assess tolerability for the procedure. A deep endotracheal aspirate was obtained for analysis in those situations where the risk of worsening the respiratory failure was deemed to outweigh the potential benefit of BAL sampling.

From the data collected in our study, one can conclude that unexplained deterioration in patients with SARS-CoV-2 ARDS with no other obvious contributing factor, should be an indication for one to embark on investigating a possible complicating IFI; the consensus definition for IFIs (Donnelly et al., 2020) should serve as a guide for risk stratification. The role of prophylactic anti-fungal treatment in this particular patient population is not yet clear; further studies with larger patient numbers are required to determine the benefit of prophylactic treatment when compared to the risks of possible drug-related adverse effects and development of resistance, the latter being already a developing phenomenon especially in Candida infections (Jeffery-Smith et al., 2018).

Prior to the COVID-19 pandemic, several studies examined the incidence of an IFI in the intensive care setting. In a retrospective study performed by Meersseman et al. (Meersseman et al., 2004), assessing 1850 patients admitted in ICU over a three year period, without a history of malignancy, the incidence of IFI was estimated at 3.7%. These patients however had other co-morbidities, notably COPD, liver cirrhosis and autoimmune disease. In another more recent retrospective study in the United States by Baddley et al. (2013), looking at 2 million patients admitted in the intensive care unit, 412 were identifiable with IFI, accounting for 0.02% of the total cohort; 72% of the latter were mechanically ventilated and 76.5% were prescribed steroids, the mean LOS being 26.9 days. From an analysis of several studies of IFI in ICU by Meersseman et al. (2007), the incidence of IFI in was calculated to vary between 0.3% and 5.8%.

In our retrospective study conducted over three months, in patients with SARS-CoV-2 ARDS in intensive care, 9.5% (n = 6) of patients had confirmed or probable IFI (either Candida or Aspergillus). The time period between ICU admission and diagnosis averaged at 10.5 days. Comparing to other similar studies performed at various centres (Chiurlo et al., 2021), incidence rates of Candida IFIs ranged between 0.4% and 14%, with an average time period since admission of 7 days and a high mortality of >50%; the majority of these cases being recognised in an intensive care setting. Incidence rates of Aspergillus IFIs were reported to range between 1.7% and 34.4%, all patients being from intensive care.

**Conclusion**

In this 63 patient cohort, 15 patients (23.8%) were treated with an anti-fungal agent, 6 (9.5% of all patients) had confirmed or probable IFI (either Candida or Aspergillus). In conclusion, patients on ICU being managed for SARS-CoV-2 associated ARDS who are not improving or are deteriorating, should be screened for a possible IFI. Of note, limitations of this study include primarily the small number of patients, all recruited from a single centre, as well as this being a retrospective analysis.

**CRediT authorship contribution statement**

**Darren Borg:** Conceptualization, Investigation, Data curation, Writing – original draft, Visualization. **James Farrugia:** Methodology, Formal analysis, Resources. **Charles Mallia Azzopardi:** Writing – review & editing, Supervision, Project administration.

**Declaration of Competing Interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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