



The First Evidence of a Disturbed Immune Response toward *Candida Albicans* in Patients with Sars-Cov-2 and Co-Morbidity. A Novel Case Report

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Abstract

The novel coronavirus disease (COVID-19) caused by the acute and atypical respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly spread around the globe since its discovery in Wuhan, China, in December 2019 and has been declared a global pandemic by the World Health Organization (WHO) on the 11th of March. As of 1st July 2021, globally infections are crossing 182 million and there are over 3.950.000 fatalities [1]. The immune deregulation triggered by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been hypothesized as a causal pathway for the increasingly reported oral manifestations associated with coronavirus diseases (COVID-19), especially the ones of fungal origin [2]. In COVID-19 patients with Acute Respiratory Distress Syndrome, COVID-19 associated pulmonary aspergillosis and Sars-Cov-2 associated candidiasis have been described to complicate the clinical course [3,4]. Although the exact pathogenesis of these confections remains unclear, there are several immunological mechanisms that can facilitate the development of fungal diseases. We report a case of patient of Long-Term positivity Sars-Cov-2 and Severe *Candida Albicans* with Parkinson's disease And Lewy's Corp Demency.

Keywords: Sars-Cov-2; Disturbed immune response; *Candida albicans*

Introduction

Our Italian patient 79-year-old, female, developed fever up to 38.7 degrees C, asthenia, myalgia, dyspnea, cough, seizure, headache, visual disturbances, desaturation, catatonic state, worsening of the neurological picture (dysphagia, marked rigidity, left upper limb clonias) on 9 April 2021. In the Hospital of Alghero, Sardinia, Italy she was admitted immediately after computed tomography scan (CT scan) imaging of her chest showed multiple and bilateral ground-glass opacities located in both subpleural and apico-basal spaces (especially on the left) and extensive left spontaneous pneumothorax with subtotal lung collapse. Nasopharyngeal swab specimens were collected to

detect severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) nucleic acid. The swab specimens were tested by real-time reverse transcriptase–polymerase chain reaction; a positive result was received 6 hours later on 10 April 2021. Concomitant diseases: Parkinson's disease, dementia with Lewy bodies, arterial hypertension, renal failure, pressure ulcer II stage at the heels, condition of allurement. Patient with central venous catheter in right femoral vein, bladder catheter, parenteral nutrition. April 11, 2021, in the Hospital our patient started to feel throbbing pain related to her tongue and oropharynx. On examining intra-oral images we have found white membranous patches spread over the tongue dorsum, mouth floor, soft palate, oropharynx region, and to a lesser extent the buccal mucosa. The tongue coating was

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friable and not bleeding; however, the patient reported bitter taste while eating probably due to bleeding. To manage her oral candidal infection, the patient was given a topical antifungal, nystatin (Micostatin), four times/day and a local antibacterial mouthwash, chlorhexidine 0.2%, twice daily. Alongside the oral symptoms, the patient was reported to have got vaginal candidal infection meanwhile. Our patient was diagnosed with COVID-19 and several fungal diseases. She received 100 mg Remdesivir (Veklury) tablets orally, 3 times daily, Tocilizumab was given I.V.400 mg single dose for “cytokine storm”, O₂ Therapy; Proton Pump Inhibitors (pantoprazole 40 mg , 2 times daily), antibiotics (Piperacillin tazobactam 4.5 g , 3 times daily), antifungal (fluconazole 200 mg), thromboembolic prophylaxis (Enoxaparin 4000UI), rehydration therapy, total parenteral nutrition (Olimel 1500 cc/24H), , steroid (dexamethasone 6 mg for 10 days), Caspofungin 70 mg loading dose then 50 mg / day for 14 days, Clonidine TTS2 1 bottle / week, Clozapine 25 mg ½ cp bid, and correction of electrolyte imbalance. Hematochemical examinations: neutrophilic leukocytosis, increase of: c-reactive protein, procalcitonin, fibrinogen, ferritin, urea, LDH, cholinesterase, hypokalaemia, hypocalcaemia Peripheral vein and CVC blood cultures positive for caspofungin-sensitive *Candida albicans*; central venous catheter culture positive for *Candida albicans* (CVC removal),β-D-glucan positive. On April 20, 2021

our patient show important sense of encumbrance at the glottic level associated with cough, pharyngodynia, odynophagia, dysphagia for liquids and solids and dysphonia. On April 29, 2021 Molecular swab for SARS-CoV-2 always positive (Long-Term Covid-19) Emogasanalysis: FiO₂ 21% (aa) pH 7.43, pO₂ 92.8 mmHg, pCO₂ 40.8 mmHg, SO₂ 97.4% P/F 433. Fibrolaryngoscopic examination: slight edema of the epiglottis, glottic plane in the normal mobility and morphology, good respiratory space. Diffuse pharyngolaryngeal hyperemia, hypertrophy of the posterior commissure compatible as laryngeal mycosis. On May 12, 2021, our patient was computed tomography (CT) imaging of her chest a complete resolution of bilateral areas of altered density a ground glass after treatment. After 8 day the swab specimens were tested by real-time reverse transcriptase–polymerase chain reaction is negative and asthenia, myalgia, dyspnea, cough, seizure, headache, visual disturbances disorientated have been missing and her oral mycosis had resolved completely within 15 days of Caspofungin. On May 30, 2021, nasopharyngeal swab specimens was negative and after the maintenance of intensive medical treatment in hospital computed tomography (CT) imaging of her chest a complete resolution. Currently, our young patient continues with complex therapy Parkinson’s disease, dementia with Lewy bodies (Figure 1).

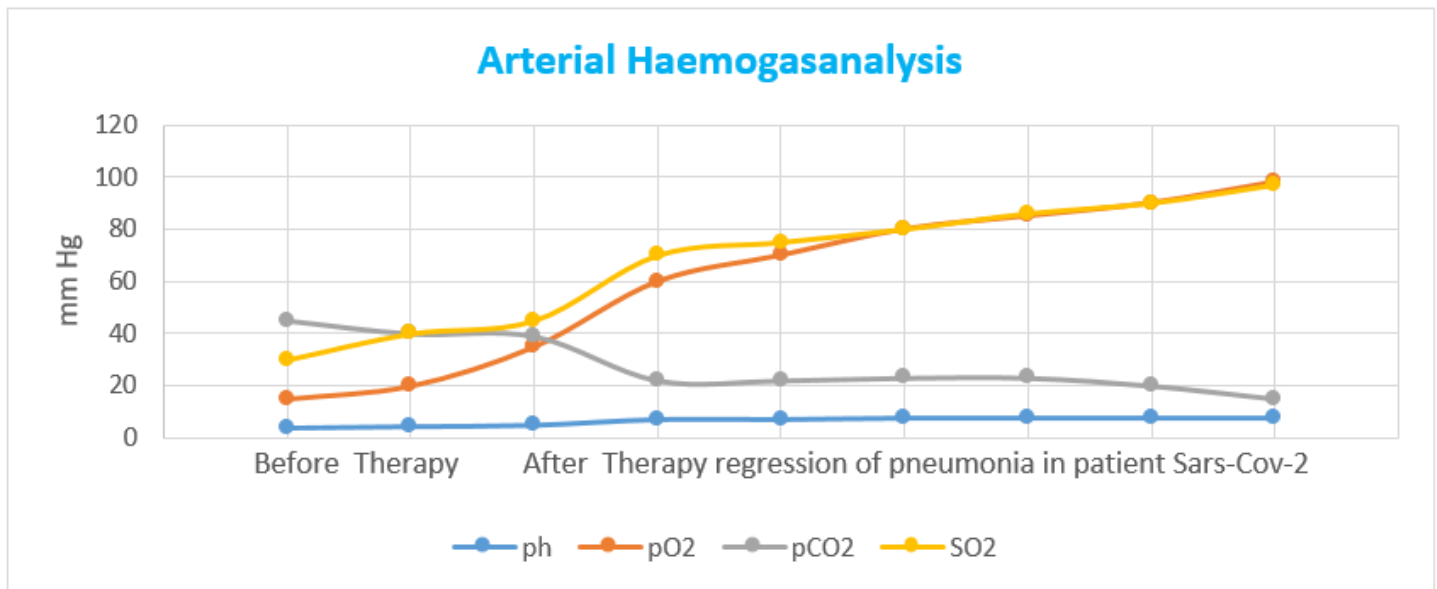


Figure 1: Arterial haemogasanalysis.

Discussion

People with severe COVID-19, such as those in an intensive care unit (ICU), are particularly vulnerable to bacterial and fungal infections. The most common fungal infections in patients with

COVID-19 include aspergillosis or invasive candidiasis [5]. These fungal co-infections are reported with increasing frequency and can be associated with severe illness and death [6]. Awareness of the possibility of fungal co-infection is essential to reduce delays in diagnosis and treatment in order to help

Symptoms of some fungal diseases can be similar to those of Sars-Cov-2, including fever, cough, and shortness of breath. Laboratory testing is necessary to determine if a person has a fungal infection or COVID-19. Some patients can have COVID-19 and a fungal infection at the same time prevent severe illness and death from these infections. With incomplete understanding of the pathogenesis and without any causative therapy available, secondary infections may be detrimental to the prognosis. SARS-CoV-2 infection leads to the release of danger-associated molecular patterns (increased HLA-DR+CD38+ and PD-1+ CD4+ and CD8+ T cells, and elevated CD8+CD244+ lymphocytes, monocyte activation markers and elevated cytokines IL-6, IL-8, TNF, IL-10, and sIL2R α). This consecutive activation of innate pattern recognition pathways may cause hyper inflammation during the antiviral immune response, leading to lung tissue damage and causing disruption of mucous membranes, thus contributing to an environment that allows for fungal infections [7]. While most microbiological detection of *Candida* spp. as commensals does not have pathological relevance, transition into invasive candidiasis during critical illness has a reported lethality rate of up to 70% and is considered a relevant complication in COVID-19 patients [8,9]. Persistent viral antigen exposure during chronic viral infections such as HIV was found to induce a terminal differentiation into effector type over memory type CD8+ T cells, which ultimately experience immune exhaustion before pathogen eradication [10]. The pathomechanism of SARS-CoV-2 infection differs from chronic HIV or HCV infection, however, given the reduced proportion of central memory CD8+ T cells, it may be speculated that prolonged SARS-CoV-2 exposure leads to excessive T cell activation, where terminal differentiation into effector cells predominates memory cell development. This can be followed by cell exhaustion, resulting in lymphopenia and thus, may be relevant for the outcome of COVID-19 [11]. We need prospective studies of treatment options and additional patient characteristics to further understand the variables associated with COVID-19-associated death in patients with fungal diseases.

Conclusion

Monitoring evidence suggests that immune compromised patients have a higher risk of developing severe symptoms upon SARS-CoV-2 infection and *Candida Albicans* compared with the general population. Despite these limitations, our results provide first evidence of a disturbed immune response toward *C. albicans*,

which may hint at an increased susceptibility toward infection with *C. albicans* in critically ill COVID-19 patients. We consider the immune response characterization of critical COVID-19 cases as relevant for the field, and the blunted cytokine response to stimulation with *C. albicans* noteworthy to both immunologists and clinicians.

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