

Coronavirus Pandemic

Fatal invasive candidiasis in COVID-19 patient with severe bleeding and extensively drug-resistant *Klebsiella enterobacter*

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Abstract

Introduction: Multi-organ dysfunction caused by thromboembolic complications may complicate the course of SARS-CoV-2 infection. Most patients require anticoagulant therapy which predisposes them to the development of hemorrhagic syndrome. In critically ill COVID-19 patients secondary infections due to opportunistic pathogens are associated with a high mortality rate.

Case report: Herein, we present a COVID-19 patient with severe hemorrhage at unusual sites complicated with invasive candidiasis and an extensively drug-resistant (XDR) strain of *Klebsiella enterobacter*.

Conclusions: Clinicians should be aware of the possibility for invasive fungal infections in severely ill patients with SARS-CoV-2 infection due to pre-existing conditions, risk factors, and COVID-19 associated pathological mechanisms. Management of invasive candidiasis is challenging because of the high prevalence of comorbidities, risk of toxicities, and drug interactions.

Key words: COVID-19; candida; hemorrhage; operation; resistance.

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Introduction

Bacterial and viral co-infections at the time of the SARS-CoV-2 diagnosis seem to be rare. On the contrary, secondary infections arise in hospitalized patients with coronavirus disease-19 (COVID-19), especially in the critically ill [1]. The pathogens most frequently involved in secondary infections are bacterial, while fungal pathogens are less commonly found. The most prevalent yeast species belong to the *Candida* genus, including *Candida albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis* and *C. krusei*, inhabiting numerous mucosal surfaces such as the skin, respiratory, digestive, and urinary mucosa. *Candida* belongs to the most frequently encountered pathogen in the intensive care unit (ICU), with an increasing trend for candidemia in the past few years. It affects between 6% and 10% of Intensive Care Unit (ICU) patients with a high mortality rate approaching 70% [2]. The

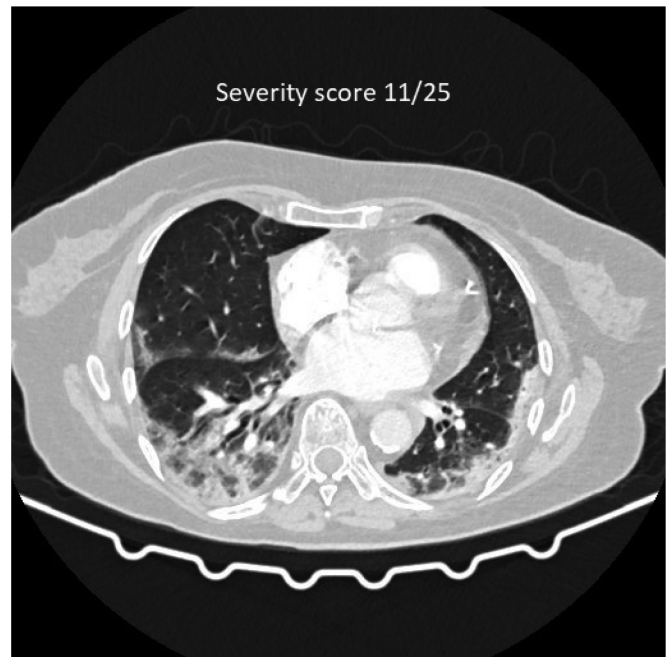
incidence of invasive candidiasis (IC) among COVID-19 patients in ICU is 5-fold greater as compared to non-COVID patients [3]. Common risk factors predisposing ICU patients to IC include diabetes mellitus, renal failure requiring hemodialysis, parenteral nutrition, abdominal surgery, triple lumen catheters, use of broad-spectrum antibiotics and corticosteroids, and prolonged stay (> 7 days) in ICU [4].

Case report

A 75 year old woman presented in the COVID hospital at Batajnica, Belgrade with a 4-day history of fever up to 39 °C, productive cough, and fatigue. She received the first dose of Sinopharm vaccine (China National Pharmaceutical Group, China) twelve days before hospital admission. Medical history included previous arterial hypertension. A pharyngeal swab was taken and real-time Polymerase Chain Reaction (RT-

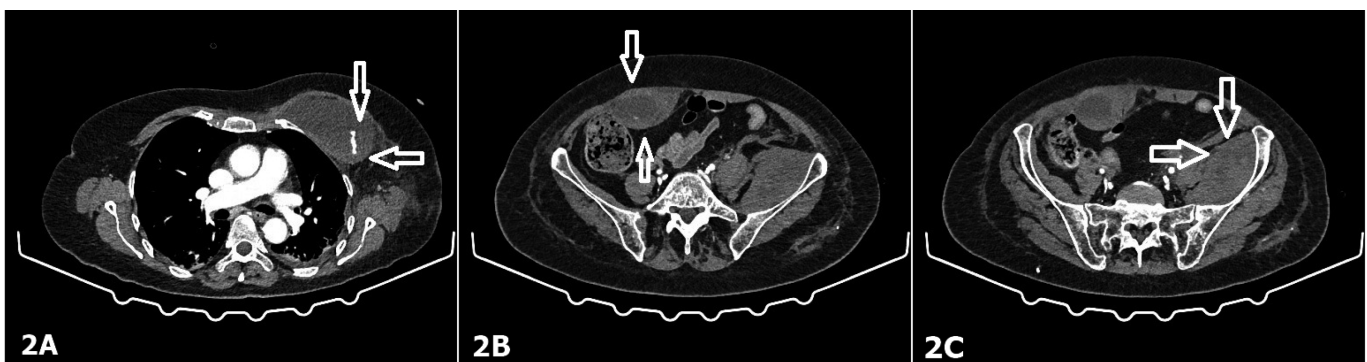
PCR) was positive for SARS-CoV-2. On admission, her temperature was 38.7 °C, blood pressure 130/80 mmHg, heart rate 100 beats/min, respiratory rate 20 breaths/min, and oxygen saturation (SpO₂) 95% in ambient air. Laboratory results revealed elevated acute phase reactants: C-reactive protein (CRP) 56 mg/dL, white blood cell (WBC) count $2.9 \times 10^9/L$, with lymphopenia 4%, hemoglobin level 128 g/L, platelet count $228 \times 10^9/L$, ferritin level 369 ug/L, D-dimer 1.36 mg/L (cut off 0.5 mg/L). Computed tomography (CT) of the chest revealed ground-glass opacities with a severity score of 11/25 (right upper lobe 2, right middle lobe 2, right lower lobe 2, left upper lobe 2, left lower lobe 3) (Figure 1). Treatment started with the second generation cephalosporins, prophylactic anticoagulant therapy with low molecular weight heparin (LMWH), intravenous vitamin C, and methylprednisolone (1 mg/kg). On day 10, the patient complained about severe and sudden pain in the left pectoral region. CT showed a heterogeneous mass, most likely hematoma in the left pectoralis minor muscle (48×36×45 mm) (Figure 2A), as well as a hematoma in the rectus abdominis muscle (42×68×73 mm) (Figure 2B), spreading to retroperitoneal and inguinal space (87×53×33 mm) (Figure 2C). Hemoglobin level decreased to 65 g/L and the patient was transferred to the intensive care unit (ICU) in the state of hemorrhagic hypovolemic shock. Upon admission to the ICU, she was intubated, transfused with packed red blood cells (PRBC) and fresh frozen plasma (FFP), and prepared for surgery. Laparotomy with hematomas evacuation, tamponade, and placement of two drains was performed. Broad-spectrum antibiotics were started including meropenem, metronidazole, and fluconazole. Three days later, the patient was re-operated when a revision of hemostasis was done with a re-tamponade of both spaces. Five days after the re-operation, the patient was extubated and both drains were removed. In the next few days, the patient's condition worsened due to fever

Figure 1. Bilateral pneumonia (CT severity score 11/25).



up to 40 °C. CRP increased to 289 mg/dL while procalcitonin was in the normal range. Chest CT scan revealed multiple disseminated excavated lesions concluded on septic mycosis (Figure 3). Fiberoptic bronchoscopy with aspiration was performed. The endoscopic finding showed thick white mucopurulent secretion with multiple necrotic deposits on the medial tracheal wall suggestive of fungal infection. Sputum samples were positive for *Klebsiella enterobacter* and *Candida albicans*. Laparotomy wound swab also confirmed the presence of *K. enterobacter*. Blood cultures taken twice were positive for *C. albicans* as well as mycotic culture from broncho-aspiration. Echinocandin (caspofungin) was added. The susceptibility testing confirmed an extensively resistant *K. enterobacter* strain, susceptible only to ceftazidim/avibactam, was unavailable in our country due to reimbursement policy. Laboratory analyses

Figure 2. A) Hematoma in m. pectoralis major l. sin; B) Hematoma in m. rectus abdominis l. dex; C) Hematoma in left inguinal space.



showed elevated CRP 175 mg/dL, hemoglobin level 94 g/L, and thrombocytopenia $88 \times 10^9/L$. The repeated chest CT scan on 4th day showed the enlargement of excavated lesions with ground-glass opacities (Figure 4). The patient died due to multi-organ failure after 42 days of hospitalization.

Discussion

We present a rare case of IC in a patient with SARS-CoV-2 infection with numerous risk factors such as older age, prolonged hospitalization, use of broad-spectrum antibiotics and corticosteroids, and the presence of a central venous catheter. An additional risk factor usually associated with IC was repeated abdominal surgery, but not frequent in other SARS-CoV-2 infected patients [5]. In COVID-19 patients with a severe form of the disease, one well-known risk is the use of tocilizumab, an IL6 receptor monoclonal antibody which was not given to our patient. A recently published paper reported three cases of IC after tocilizumab treatment, in a cohort of 43 patients with COVID-19 [6]. A novel study that compared candidiasis in COVID-19 versus non-COVID-19 patients showed that the mortality rate is high in both groups (non-COVID 61%, vs. 75% in the COVID group) [3]. About 5% of COVID-19 patients are critically ill and require ICU admission. It is also well known that ICU patients, especially those mechanically ventilated, are at a greater risk to develop bacterial or fungal infections [7]. Severe COVID-19 is associated

with immune dysregulation, affecting both Th2 and Th1 responses with cytokine release syndrome and lung damage which contribute to microbial proliferation [8]. SARS-CoV-2 infection by itself increases the risk of invasive fungal infection such as IC and invasive pulmonary aspergillosis [9]. Few cohort studies reported that IC in the form of candidemia occurs in 0.3% to 10% of SARS-CoV-2 infected patients [10].

Although respiratory symptoms are the landmark of SARS-CoV-2 infection, coagulopathy is the predominant cause of multiple organ dysfunctions. The vast majority of patients require some anticoagulant therapy. In a recently published study of 184 ICU patients with COVID-19, 31% of patients had a thrombotic complication, but no one had a hemorrhagic episode [11]. The American Society of Hematology (ASH) recommends that all hospitalized adults with COVID-19 receive thromboprophylaxis with LMWH, unless the risk of bleeding is higher than thrombosis [12]. Bleeding is less commonly present in patients with COVID-19 than thrombosis and it may occur, especially in the setting of anticoagulant therapy. Our patient received prophylactic anticoagulation therapy which caused significant bleeding at unusual locations (pectoral, retroperitoneal and inguinal spaces) without other risk factors for bleeding such as disseminated intravascular coagulopathy (DIC), thrombocytopenia, or trauma. Significant bleeding at unusual sites may occur in COVID-19 patients upon anticoagulation therapy (therapeutic and prophylactic) and, therefore, a

Figure 3. Bilateral excavated lung lesions.

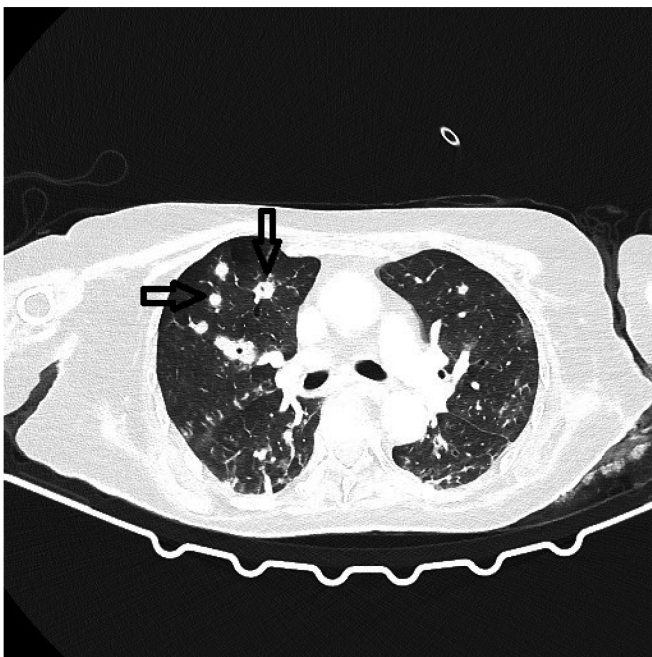


Figure 4. Progression of bilateral excavated lung lesions with ground glass opacities.



high degree of suspicion and careful monitoring is mandatory [13]

It is also well known that hospitalized patients with COVID-19, especially those who are critically ill are treated with broad-spectrum antibiotics. About 70% of COVID-19 patients have empirical antimicrobial therapy. The inappropriate use of broad-spectrum antibiotics may also predispose infections with *Clostridium difficile* in addition to *Candida* spp. [14]. The diagnosis of IC is challenging because blood cultures are positive in less than 50%. The use of some other markers of fungal infection is recommended such as β -D-glucan or non-culture-based methods such as the mannan test [15]. In the present case, the diagnosis of IC was established by both, blood and bronchoalveolar cultures. Both candidemia and deep-seated candidiasis were confirmed. Echinocandins are strongly recommended for the initial treatment of IC in critically-ill COVID-19 patients, and the de-escalation to fluconazole is advised after the susceptibility testing [16]. However, the presence of XDR *K. enterobacter* co-infection in our patient narrowed antimicrobial options and contributed to a lethal outcome.

Clinicians should be aware of the possibility for invasive fungal infections in severely ill patients with SARS-CoV-2 infection due to pre-existing conditions, risk factors, and COVID-19 associated pathological mechanisms. Management of IC is challenging because of the high prevalence of comorbidities, risk of toxicities, and drug interactions.

Authors' Contributions

TAV, ASR, and JV designed the manuscript and wrote the first draft; DV, SM and FP reviewed the literature; TAV, JM and ND did critical revision of the manuscript. All the authors contributed to manuscript conceiving, drafting, and approved the final version.

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