Case report

Therapeutic approach for severe COVID-19 and immunocompromised patients. A case series

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ABSTRACT

Background: COVID-19 is a potentially critical infectious disease. Inflammatory response and disease severity may vary according to immune system status. The aim of this case series is to investigate different presentation of COVID-19 in immunocompromised patients.

Methods: this is a single centre case series about 17 immunocompromised patients admitted to our respiratory department during the recent COVID-19 pandemic. White blood cell count, C reactive protein, interleukin 6, lymphocytic subpopulation count (CD4+, CD8+, CD20+) and immunoglobulin count (IgG, IgM, IgA) were measured at hospitalization.

Results: the most common causes of immunosuppression observed in our severe COVID-19 population are hematological malignancies, immunosuppressant drugs for transplant, primary immunodeficiency and inflammatory bowel disease. Onset symptoms were fever (88%), cough (53%), dyspnoea (24%), asthenia (35%), anosmia and/or ageusia (17%), expectoration (12%). Compared to benign conditions, patients with malignancies show a lower lymphocytic count (490 vs 1100 cells/uL) and higher interleukin 6 (33 vs 13 pg/mL).

Conclusions: immunocompromised patients are at risk of adverse outcome from COVID-19. Hematological malignancies and anti-CD20 therapies induce a high risk. Primary immunodeficiency and classical immunosuppressant such as calcineurin inhibitors and antimetabolites share an intermediate risk.

1. Background

Coronavirus disease 2019 (COVID-19) is an emergent infectious disease caused by a novel coronavirus named SARS-CoV2. Clinical manifestations can widely range between mild respiratory symptoms and severe acute respiratory distress syndrome (ARDS). In early 2021 more than 80 million cases have been confirmed worldwide, with 1.7 million of deaths [1]. Certain medical conditions are at risk of severe COVID-19. Older age, chronic cardiovascular and pulmonary diseases, diabetes mellitus are commonly observed in critical cases. Tumors and antitumoral therapy potentially compromise the immune system thus influencing the disease severity and prognosis. It has been reported that hematological malignancies have higher mortality for COVID-19 than general population [2]. A decrease in the innate antiviral response and chronic lymphopenia are common in neoplastic patients. Nevertheless an immune dysregulation can be observed in many other conditions such as primary and acquired immunodeficiency and immune diseases. Since the underlying mechanisms and potential therapies are controversial, the aim of this case series is to investigate different presentation of COVID-19 in immunocompromised patients.

2. Methods

This is a single centre case series involving immunocompromised patients admitted to our respiratory department during the recent COVID-19 pandemic. We admitted patients affected by respiratory failure and severe illness. SARS-CoV-2 infection was confirmed by reverse transcriptase polymerase chain reaction (PCR) on nasopharyngeal swab. Data collection at admission included clinical history, previous therapy, onset time and symptoms. At hospitalization all patients underwent blood gas analysis to determine PaO2/FiO2 (PF), and high resolution chest tomography (HRCT) with assessment of total severity.
score (TSS) from 1 to 20 sec. Chung. We also evaluated white blood cell molecular weight heparin; ICU: intensive care unit admission; PTE: pulmonary thromboembolism. Administered therapies and outcomes. IVIG: intravenous immunoglobulin; HXC: hydroxychloroquine; AZI: azithromycin. SCS: systemic corticosteroid. LMWH: low Table 2

Baseline characteristics. CVID: common variable immunodeficiency; HIV: human immunodeficiency virus; HBV: hepatitis B virus; DM: diabetes mellitus; DCM: dilated cardiomyopathy; AF: atrial fibrillation; hypertension: chronic systemic hypertension; PTE: pulmonary thromboembolism; COPD: chronic obstructive pulmonary disease; CAD: coronary artery disease.

Table 2

Administered therapies and outcomes. IVIG: intravenous immunoglobulin; HXC: hydroxychloroquine; AZI: azithromycin. SCS: systemic corticosteroid. LMWH: low molecular weight heparin; ICU: intensive care unit admission; PTE: pulmonary thromboembolism.

3. Results

Data from 17 patients were collected. Age range was 29–83 years, 14 were males and 3 females. All patients were considered immunocompromised hosts due to a previous diagnosis. The most commonly represented causes were hematological malignancies such as non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia and myelodysplastic syndrome (9 patients). Immunosuppressant drugs were also represented (1) immunodeficiency was observed. Furthermore, we included chronic inflammatory bowel disease (2). The estimated prog

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dyspnoea (24%), asthenia (35%), anosmia and/or ageusia (17%), expectoration (12%).

At hospitalization, patients with malignancies (group M) showed a median PF of 103 (86.5–206) and a median TSS of 15 (8.5–16.5), while patients affected by benign diseases (group B) had a median PF of 86.5 (81–220) and a TSS of 10.5 (6–14.5). Median lymphocytes were 490 cells/µL (275–2846) in group M and 1100 cells/µL (620–1340) in group B. Median CRP and IL6 were respectively 8.1 mg/dL (2.8–20) and 33 pg/mL (18.6–103) in group M, while 6.6 mg/dL (3.95–12) and 13.6 pg/mL (6.4–50.65) in group B.

Administered therapies, outcomes and complications are reported in Table 2.

3.1. Therapeutic approach and case description

Reduction of at least 2 classes of immunoglobulin was very common in our cohort. 5 out of 9 patients in group M. It was less common in Group B, affecting 2 patients with primary immunodeficiency and 1 patient previously treated with Rituximab. A reduction of B lymphocytes was very common affecting 6 patients in group M, and 7 patients in group B. Subsequently, intravenous immunoglobulin (IVIG) was administered at the dose of 5 mL/kg for 3 consecutive days, or 5 days in case of Ig reduction at baseline.

A 41-years old female affected by common variable immunodeficiency, bronchiectasis and recurrent respiratory infections received IVIG for 5 days, low dose systemic corticosteroid (SCS) and prophylactic low molecular weight heparin (LMWH). Oxygen support with high flow nasal cannula (HFNC) was also required for a severe ARDS. The patient showed a complete remission of symptoms and seroconversion at day 26 of disease. She was then discharged without oxygen supply and with a negative PCR for SARS-CoV2. HRCT showed a complete resolution of pneumonia (Fig. 1).

Among hematological malignancies, 6 patients out of 9 received IVIG but only 3 subjects obtained seroconversion despite normalization of Ig
classes after treatment. 4 cases of malignancies were previously treated with anti-CD20 drugs such as Rituximab and Obinutuzumab. None of them obtained seroconversion over a follow up of 6 months.

This is the case of a 67-years old man affected by non-Hodgkin lymphoma and humoral deficiency who experienced fever, dyspnoea and asthenia. At hospital admission a moderate ARDS and extensive interstitial pneumonia were observed. CRP was 9.1 mg/dL and IL6 was 70.7 pg/mL. The subject underwent continuous positive airway pressure (CPAP) via Helmet (PEEP: 10 cmH2O and FiO2 70%) and a combination of IVIG and Remdesivir for 5 days. Since persistence of symptoms and respiratory failure, convalescent plasma was administered for 2 days. Nevertheless clinical conditions rapidly deteriorated and the patient was intubated, then died at day 45 of disease (Fig. 2).

On the other side SARS-CoV2 infection can also determine a slow progression and an initially indolent clinical manifestation in certain subjects, especially those with a significant impairment of B lymphocytes induced by Rituximab. A 51-years old woman affected by non-Hodgkin lymphoma had quite subtle symptoms at onset of disease, with relatively mild radiologic extension of disease (TSS 8/20). CRP was 1.9 mg/dL and IL6 was 13.2 pg/mL. The subject firstly received Tocilizumab, hydroxychloroquine, azithromycin and low dose SCS. Secondly, she was treated with IVIG for only 2 days because of an allergic adverse event. Finally she also received a 10 days course of intravenous Remdesivir. After every of the 3 drug regimens a clinical and radiological improvement was observed, but no antibody response followed and SARS-CoV2 was persistently detected by PCR. A COVID-19 relapse occurred with even more severely compromised conditions (Fig. 3) and finally the patient died after 230 days of viral persistence.

4. Discussion

IVIG is made up of human immunoglobulins, mostly IgM and IgG. It is not routinely recommended for COVID-19 treatment and many countries are currently experimenting IVIG efficacy by randomized controlled trials. The mechanism of action of the drug remains unclear. Based on previous evidences, IVIG inhibit neutrophils and monocytes degranulation while activating phagocytes to internalize viruses [3]. In addition it has been suggested that IVIG can counterbalance the cytokine storm that typically characterizes severe COVID-19 [4]. Single cases of successful IVIG for severe COVID-19 have been reported in immunocompetent patients [5].

Based on our experience, the early reduction of B lymphocytes observed during SARS-CoV2 infection may lead to a less efficient humoral immunity. It is a threatening condition, therefore indicators such
as Ig classes and B lymphocytes should be routinely measured at hospitalization for SARS-CoV2 infection. Since IVIG has immunomodulatory effects, we suggest its use in case of multiple Ig classes reduction or B lymphocytes decrease.

The overall prognosis for immunocompromised patients is worse than other subjects. Particularly, hematological malignancies and anti-CD20 drugs induce a lower survival rate and a higher risk of complications. On the other hand, patients receiving classical immunosuppressant drugs and patients affected by primary immunodeficiency share a better prognosis. In our case series 5 patients underwent endotracheal intubation and died. Intensive care showed no improvement of prognosis neither in malignant nor in benign conditions. This observation leads in favour of a conservative care for immunocompromised patients especially in the elder population.

Declaration of competing interest

All authors declare they have no conflict of interest.

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