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COVID-19 Convalescent Plasma, A Targeted Therapy For Immunocompromised Patients With Severe COVID-19. About Two Cases And Review Of The Literature.

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Abstract

Introduction

When immunocompromised patients are infected with COVID-19, the evolution towards a severe illness and even death is more likely than when dealing with immunocompetent patients. The best treatment regimen for these patients can be challenging to find, and the use of COVID-19 convalescent plasma can become necessary. We report two cases of immunocompromised patients treated with COVID-19 convalescent plasma, for which the outcome was satisfactory after treatment.

Case Report 1:

A 72-year-old patient with humoral immunodeficiency secondary to the treatment of lymphoma by anti-CD20 drugs. The patient tested positive for COVID-19 after a family reunion; he didn't have any symptoms at the time of testing. Three weeks later, he presented with a fever and respiratory symptoms. The chest CT scan showed ground-glass opacities. Further exploration of this condition led to the diagnosis of SARS-CoV-2 pulmonary infection. The patient received COVID-19 convalescent plasma, and his health improved rapidly afterward. He was declared cured forty-eight hours after having received the treatment.

Case Report 2:

A 52-year-old patient with humoral immunodeficiency secondary to the treatment of lymphoma by anti-CD20 drugs. He was tested for COVID-19 after having been in contact with a COVID-19-infected person; his test was positive. He didn't have any symptoms at the time of the testing. Two months later, he presented with dyspnea, coughing, and a fever. The chest CT-Scan found ground-glass opacities. After other analyses were done, the patient was diagnosed with SARS-CoV-2 pulmonary infection. He was treated with COVID-19 convalescent plasma and recovered to total health rapidly.

Conclusion

COVID-19 convalescent plasma can be a therapeutic option to treat patients suffering from humoral immunodeficiency diagnosed with a severe COVID-19 infection.

Keywords: COVID-19, convalescent plasma, humoral immunodeficiency

Introduction

COVID-19, an infectious disease caused by the SARS-CoV-2 virus, was described for the first time at the end of December 2019 **[1,2]**. Since the beginning of 2020, COVID-19 has spread worldwide, leading to a global pandemic **[3]**. COVID-19 is an airborne and contact-transmitted disease **[4]**. Most patients infected with COVID-19 present with simple to mild cases. However, around 15% of COVID-19 cases can lead to severe disease, and 5% of COVID-19 patients present with acute symptoms such as acute respiratory failure, septic shock, or multiple organ failure **[5-8]**. Old age, chronic organ failure, history of immunodeficiency, and history of solid or haematologic cancers are risk factors associated with severe COVID-19 cases. The risk of dying from a COVID-19 infection for cancer patients is high (29%) **[10]**. Choosing a treatment regimen at the pandemic's beginning was challenging since no specific therapy was available **[11]**. During those times, COVID-19 convalescent plasma (CCP) was identified as a potential treatment **[12]**. Several recent studies have found this treatment beneficial to patients **[13-15]**, even though other studies found contradictory results **[16-17]**. However, some studies found immunocompromised patients to be the ones to receive the most benefits from the use of CCP, especially if they still needed to develop humoral immunity to the SARS-CoV-2 virus **[18-19]**. In this context, we report two cases of pulmonary infection by the SARS-CoV-2 virus in immunocompromised patients with an excellent response to COVID-19 convalescent plasma. This article

aims to show how this therapy can be an exciting option in managing immunocompromised patients with severe COVID-19.

Case report 1

A 72-year-old patient with a history of diabetes Mellitus, follicular lymphoma in complete remission treated by OBINUTUZIMAB, and an asymptomatic case of SARS-CoV-2 infection three weeks before admission. A COVID-19 PCR test was done after the patient participated in a family reunion, and this test came back positive. The patient was vaccinated against COVID-19, with three vaccine shots administered. He was initially admitted to the Emergency Department for a coma secondary to hypoglycemia caused by the intake of hypoglycemic sulfonamides. His neurological state improved significantly after sugar administration; he was hospitalized afterward so that his diabetic treatment regimen could be altered.

During his hospital stay, a fever of 38.5°C was fortuitously discovered. There were no clinical signs consistent with an active infection. The patient presented with mild asthenia (World Health Organization score 2); there was no cardiac murmur, stiff neck, or adventitious sounds. This fever was explored with the following exams: the haemogram found a lymphopenia (lymphocytes count: 0.13G/l); the C-Reactive Protein (CRP) was at 120mg/l; a urine culture came back positive with *E.Coli* culture; the chest x-ray was expected; the blood cultures were negative, and the COVID-19 PCR test was once again positive (just like the prior testing done three weeks before admission). We concluded that the patient suffered from a urinary tract infection as well as from an asymptomatic SARS-CoV-2 infection. The patient was first treated with ciprofloxacin. After 5 days of antibiotics, the patient still had a fever, and he developed a dry cough with low oxygen levels. We further investigated this fever with a whole-body CT scan: ground glass opacities were found in the lungs (middle lobe and left superior lobe). Our hypothesis at this time was that of SARS-CoV-2 pneumonia. A bronchoscopy with bronchoalveolar lavage was performed to rule out another diagnosis: bacteriological culture, virological testings, mycobacterium culture, and parasitology testings all came back negative, as well as pneumococcal and legionella urinary antigens tests. The COVID-19 blood serology was also negative, even though the patient was administered 3 doses of vaccine shots. With all these findings, our diagnosis was that of a persistent fever due to SARS-CoV-2 pneumonia affecting a patient with a history of deep immunodeficiency secondary to an OBINUTUZIMAB treatment. After discussing the case and the convalescent plasma treatment in a national Multidisciplinary Team Meeting, the patient was administered two doses of convalescent plasma for two days. The patient improved rapidly forty-eight hours after this treatment, and the fever and inflammation markers receded.

Case report 2

52-year-old patient unvaccinated against COVID-19 and treated by RITUXIMAB for a mantle cell lymphoma. He tested positive for COVID-19 on a PCR test; the test was performed because he had been in contact with someone infected with COVID-19. At the time of the testing, the patient was asymptomatic. Two months after the test, during a hematology follow-up consultation, the patient presented with symptoms (fever, coughing, dyspnea with low oxygen levels) that had been ongoing for the past couple of days. The patient was admitted right after the consultation to investigate this fever. During the physical exam, crackling sounds could be heard in both lungs. The chest CT scan showed ground-glass opacities, more noticeably in the lower lobes. The other tests the patient underwent found lymphopenia (0.47G/l) on the haemogram; CRP at 30 mg/l; multiplex PCR (nasal swab; influenza, RSV, COVID-19) was negative; pneumococcal and legionella urinary antigens; aspergillosis, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae* serologies were negative. The blood cultures were negative as well. The patient underwent a bronchoscopy, during which a bronchoalveolar lavage was performed. The culture of the bronchoalveolar lavage was negative, and testing for aspergillosis and *Pneumocystis Jiroveci* came back negative; PCR testing for HSV and VZV was negative; mycobacterium culture was negative. The multiplex PCR performed on the bronchoalveolar lavage was only positive for SARS-CoV-2. The COVID-19 blood serology was negative. We concluded that this immunocompromised patient was suffering from an ongoing SARS-CoV-2 pneumonia. The case was discussed in a national Multidisciplinary Team Meeting, and a treatment by COVID-19 convalescent plasma was decided. The patient was treated with two doses a day of convalescent plasma for two days. The fever receded, as well as the coughing and the dyspnea; the patient's global health improved forty-eight hours after the treatment was administered.

Discussion

The convalescent plasma taken from people who had recovered from a peculiar medical condition has been used to treat several infectious diseases ever since 1890 **[20]**. For instance, during the Spanish flu pandemic in 1918, convalescent plasma was used to treat pneumonia patients **[21]**. More recently, convalescent plasma was used successfully in treatment regimens against MERS **[22]**, Ebola **[23]**, H5N1 **[24]**, H1N1 **[25]**, and SARS **[26]** infections. This therapeutic option is used all over the world. No industrial process is involved in the production of the convalescent plasma. The convalescent plasma is obtained by secured pathogen-reduced apheresis using amotosalen. This therapy is legally included in France as a decision of the General Director of the National Medical Drug Security Agency (ANSM) **[27]**. Since the beginning of the COVID-19 pandemic, the use of convalescent COVID-19 plasma (CCP) has been very regulated: CCP has either been administered during clinical trials or a Therapeutic Use Protocol (PUT) when a patient couldn't be included in a trial **[27]**. Our patients were administered the CCP during a PUT. Since the beginning of the pandemic, several clinical trials and data on the use of CCP in France have improved the scientific knowledge on the use

of this treatment. In the literature, CCP was nonsignificant in improving hospitalized patients and lowering the mortality rate **[16-17]**. However, some studies have shown a positive impact on the outcome of severely immunocompromised patients **[12,18-19]**. Based on those results, ANSM decided that the PUT for the use of COVID-19 convalescent plasma would be limited to hospitalized patients with severe humoral immunodeficiency, whether this immunodeficiency was secondary to a peculiar illness (especially B lymphoid homotopies) and secondary to an immunosuppressive treatment such as monoclonal anti-CD20 antibodies. For those patients, convalescent plasma can be used if all other treatments that can be used in this condition have been inefficient or are contraindicated or unavailable **[28]**. Our patients fulfilled those ANSM criteria since they both had a history of B lymphoid hemopathy treated with anti-CD20 antibodies and since they both had a humoral immunodeficiency. Moreover, they didn't respond to the symptomatic treatment and were not eligible for the use of anti-SARS-CoV-2 antibodies because of the time between their first positive test and their hospital admission. Indeed, the use of monoclonal anti-SARS-CoV-2 antibodies is limited to patients who can get the treatment as soon as they have a positive PCR test and within the first five days after the beginning of the symptoms **[29]**. The humoral immunodeficiency of previously described patients makes them unable to produce enough antibodies to clear out the virus. The lymphopenia and the SARS-CoV-2 serologies in our patients' blood tests are sizeable consequences of this immunodeficiency. It is even more interesting that the COVID-19 serologies were negative even if one patient had had a full vaccinal procedure and the other was admitted a month after his first positive PCR test. The humoral immunodeficiency leads to a long COVID; if no treatment is administered, the infection's outcome can be a severe illness case with a high mortality risk. Since our patients fulfilled the PUT's criteria, we discussed their cases during an infectiology Multidisciplinary Team Meeting, and the use of COVID-19 convalescent plasma was validated. According to the protocol, the advised dosage is one or two PCC units of 200 to 240 mL each, given by an intravenous transfusion, and one or two more PCC units twenty-four hours after the first administration for two to four units per patient **[27]**. Our patients received two CCP units for two days in a row, meaning that each received four PCC units. Those transfusions must respect the ABO plasma transfusion compatibility rules with the same blood type or, if it is not possible, with a compatible blood type **[27]**. PCC must preferentially come from donors who have been infected with the most common virus variant, and the donors must fulfil the following criteria: they must be fully vaccinated, and they must have been cured of COVID-19 for at least 14 days; they must be in good general health and eligible to donate plasmapheresis according to the current guidelines regarding blood donors **[27]**. Those selection criteria contribute to having efficient antibodies against the most common viral variant, and it also contributes to having a high antibody concentration by plasma unit. The use of those criteria maximizes the probability of recovery. PCC seems to be a good alternative to monoclonal anti-SARS-CoV-2 antibodies. They make for a concentrated solution of efficient antibodies since those antibodies contribute to the recovery of the donors. This is also a good way to avoid inefficiency because of emerging variants, as can be the case with monoclonal antibodies since they are precise. What's more, the use of PCC is less costly than the use of monoclonal antibodies. There has been a decrease in COVID-19 cases in the general population, and there has been limited access to PCC since the vaccination campaign: PCC is less available in laboratories. After the transfusions, none of our patients suffered from side effects. The outcomes were good, with a full recovery within forty-eight hours of the transfusions for each of them.

Conclusion

COVID-19 is an infectious disease known since the end of 2019. It is an airborne disease. Most patients infected will only suffer from a simple to mild COVID-19 case. However, some patients might come down with a severe infection leading to acute respiratory failure. Some risk factors for a severe illness have been identified, such as chronic organ failure, solid cancers, hematological cancers, and humoral immunodeficiency. In patients with a history of humoral immunodeficiency, CCP can be used after discussing the case in a Multidisciplinary Team Meeting if all other treatments for said condition have been inefficient or are either contraindicated or unavailable. This treatment regimen is quickly efficient in improving our patients' condition.

List of abbreviations:

ANSM: National Medical Drug Security Agency

CCP: COVID-19 convalescent plasma

PUT: Therapeutic Use Protocol

PCR: Polymerase Chain Reaction

Déclarations

Ethics approval and consent to participate: As our patients were part of a thematic use protocol, they had given positive consent to participate in the study.

Consent for publication: patients agreed to the publication of their data.

Availability of data and materials: the data was available for writing the manuscript.

Competing interests: the authors declare that they have no conflict of interest in this article.

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