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Case Report

Persistently positive PCR SARS-CoV-2 at low cycle threshold in an immunosuppressed patient

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ABSTRACT

We describe the very prolonged course of the disease in an immunosuppressed patient with persistently positive PCR against SARS-CoV-2 with low cycle threshold for at least 114 days.

Introduction

During the COVID19 pandemic, we have learned that certain conditions can lead not only to a poor prognosis, but also to a prolonged course of the disease. Immunosupressed patients, especially those with hematological malignancies and/or certain immunosuppressive treatments such as anti-CD20 monoclonal antibodies have been described at particularly high risk.[1,2]

We report a patient diagnosed with non-Hodgkin's lymphoma who had completed her treatment with rituximab 4 months earlier with no signs of relapse, who was diagnosed with COVID-19 infection and persisted with PCR against SARS-CoV-2 with low cycle threshold (ct) in nasopharyngeal swabs for at least 114 days.

Case description

Herein, we report a 70-year-old woman who had been diagnosed with follicular non-Hodgkin's lymphoma three years earlier, having followed a 6-cycle course of R-CHOP followed by a bimonthly course of rituximab as maintenance that ended four months earlier with no signs of disease (last axial computerized tomography performed five days before symptoms onset). She received the first dose of the SARS-CoV-2 vaccine (mRNA-1273) six days before symptoms onset.

On day 1 of symptoms, she presented with general malaise, low-grade fever and arthralgias. On day 3, an antigen test was performed with a positive result.

On day 19, she attended the emergency department with a 3-day history of fever and worsening general malaise. She was breathing 97% room air, her chest radiograph showed peripheral opacities in the right middle and lower lobes and subtle opacities in the left lung. Her analyses showed normal D-dymer, a C-Reactive Protein (CPR) of 46.5 mg/dL

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(cutoff 5 mg/dL), 400 lymphocytes/μL, and Lactate Dehydrogenase (LDH) 276 U/L (cutoff 120–246 U/L) as the most relevant findings. Urine antigens against *L. pneumophilae* and *S. pneumoniae* were negative. She was admitted to hospital and meropenem plus linezolid were started empirically. Due to persistence of fever at 48 hours and having negative procalcitonin levels and sterile blood cultures, antibiotics were discontinued, and dexamethasone was started with disappearance of fever and general improvement within a few hours, as well as laboratory improvement at discharge.

On day 34 (one day after discontinuation of steroid treatment) she was readmitted for dry cough and reappearance of fever. Her peripheral saturation was 93% in room air. Her blood test showed CPR 89.8 mg/dL, LDH 373 U/L, D-dymer 1350 ng/mL (cutoff <500 ng/mL), and 400 lymphocytes/μL. A chest CT showed bilateral pulmonary infiltrates, ground glass opacities and no signs of pulmonary thromboembolism. PCR against SARS-CoV-2 was positive (15.46 ct, B.1.617.2 variant). Dexamethasone was restarted due to the previous good response. During admission, the search for microorganisms and malignancy in peripheral blood samples and a bronchoscopy were unsuccessful and serology against SARS-CoV-2 reported the absence of antibodies. Clinically, the fever disappeared, the required oxygen flow was reduced, and the patient was discharged on a slow tapering course of dexamethasone, cotrimoxazole at a prophylactic dose, oxygen at 0.5 liters per minute and enoxaparin for the first days.

In the follow-up we highlight oral sores due to HSV type I treated with acyclovir, intermittent discontinuation of supplemental oxygen and development of chilblain-like lesions on the hands.

On day 81 she was readmitted for popliteal deep vein thrombosis and segmental pulmonary embolism. SARS-CoV-2 PCR was positive at 15.75 ct. An immunophenotypic study of the peripheral blood was consistent with previous rituximab treatment (absence of CD19+ B population and a slight inversion of the CD4/CD8 ratio). She also had a blood viral load for cytomegalovirus of 65,000 copies per milliliter, in the absence of retinitis, colitis or pneumonitis, so acyclovir was changed to valganciclovir with a drop in viral load in the following days. She also had a *P. aeruginosa* urinary tract infection, treated with piperacillin-tazobactam according to the antibiogram. Regarding the COVID infection itself, given the persistence of low ct, the therapeutic approach was reconsidered, and steroids were discontinued on day 99 of symptoms.

On day 106 she presented again urinary tract infection symptoms, and a more resistant strain of *P. aeruginosa* was isolated in urine culture, treated with ceftazidime-avibactam and amikacin. Her PCR for SARS-CoV-2 was persistently positive (20.42 ct). After initial improvement, fever reappeared, and her respiratory status worsened. A body CT scan showed greater involvement of the lung parenchyma and bilateral pleural effusion. As a consequence, she was admitted to ICU on day 114, with SARS-COV-2 PCR positive for less than 20 cycles (quantification not reported). Convalescent plasma, linezolid, voriconazole, cotrimoxazole, ganciclovir and high-flow nasal cannula oxygen therapy were prescribed. Bronchoscopy was performed without respiratory secretions or endobronchial lesions and with negative cultures and *P. jirovecii* test.

The evolution was not adequate, presenting multiorgan failure and progressive respiratory worsening that required a change to mechanical ventilation and prone sessions with increasing difficulty for effective ventilation, respiratory acidosis and decreasing PaFi. The patient finally died on the 136th day of symptoms.

Discussion

To our knowledge, relatively few cases of immunosuppressed patients with oncohematological malignancies and prolonged disease courses have been described.[3]

In our experience, despite the good initial response to steroid treatment, which was attributed to its anti-inflammatory effect, it did not show a beneficial effect on the course of the disease. Given her persistent low ct, which was expected to correlate with viral persistence and activity,[4] her impaired immunity by immunophenotypic study highlighting the immunosuppressive effect of previous rituximab, and considerations suggesting that steroids could prolong the viremic phase, we discontinued them and considered alternative approaches.

Studies and reports have been published with different treatments, including several monoclonal antibodies,[5] immunoglobulins, remdesivir and convalescent plasma,[6] but few of them focused in immunosuppressed patients with prolonged disease courses [7,8] with diverse results. Although these treatments were considered, they were not prescribed on first attempt, mainly due to non-availability, difficulty in prescribing them as they were not included in the protocols and expected procoagulability. During the course, given the deterioration of the situation and the lack of effective measures, the patient could be included in an external clinical trial and convalescent plasma was administrated, without improvement.

The advent of vaccines has been a major breakthrough in the management of SARS-CoV-2 disease, with reduced severity and improved prognosis. Undoubtedly, this is especially important in immunosuppressed patients with poorer prognosis and response to conventional treatments.

Not only are prolonged disease courses associated with poor patient outcomes, but it has also been observed that these patients may have mutations in the virus sequences during the course of the disease,[9-12] which could eventually facilitate the emergence of new SARS-CoV-2 variants with the consequent public health problems derived from them.[13] In addition, observations have recently emerged about the possibility of promoting escape variants with convalescent plasma treatment[14,15] and other treatments.[11]

In conclusion, special considerations must be taken when in the treatment of immunosuppressed patients due to their greater susceptibility to more severe and prolonged disease courses, and we must continue to investigate effective treatments not only for the benefit of the patient, but also to decrease the possibility that new variants emerge with global implications.

Ethical approval statement

This manuscript represents a descriptive case, and not an experimental study. Treatment was guided by local protocols

and informed consent was obtained from the patient prior to publication of this case report.

Conflicts of interest

The authors declare no conflicts of interest.

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