

Case Report

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Cellular response guards against severe COVID-19 in an immunocompromised dialysis patient with undetectable humoral response to vaccination: A case report

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Abstract

Corona Virus Disease-19 (COVID -19) is still a menacing pandemic, especially in vulnerable patients with co- morbidities as old age, Diabetes Mellitus, immunosuppression and kidney failure on dialysis. Vaccination against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2) seems to offer protection in these patients by boosting both humoral and cellular immunity. The advent of specific assays in order to detect the natural and acquired immunity to SARS-CoV2 has opened new horizons both in diagnosing COVID-19, in cases of negative SARS-CoV-2 Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) testing, and in optimization of vaccination plans. For example, these assays would help decoding the relative contribution and importance of humoral vs cellular community in cases of vaccination and concomitant B depletion by common immunosuppressive drugs, as Rituximab (RTX). We present here a case of an old diabetic female patient on peritoneal dialysis because of ANCA vasculitis on RTX that presented with fever, two weeks after vaccination with Pfizer-BioN Tech against SARS-CoV2. Humoral assays unmasked a diagnosis of COVID-19, despite negative nasopharyngeal RT-PCR and revealed null humoral response to vaccination. Despite that, the patient experienced a very mild COVID-19, with documented strong cellular immunity, probably boosted from vaccination. Such cases strengthen the importance of studying both humoral and cellular immunity in COVID-19 in order to optimize treatment and vaccination strategies, especially in vulnerable and immunosuppressed patients.

Introduction

Comorbidities including old age, diabetes mellitus, End-Stage Kidney Disease (ESKD) on dialysis and immunosuppressive therapy are known to be associated with adverse outcomes of Corona Virus Disease-19 (COVID -19) [1,2]. Vaccination against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2) in vulnerable patients seems to offer protection by boosting both humoral and cellular host immunity, although in dialysis patients response to vaccination appears problematic and thus

a personalized approach should be applied [3]. Adaptive immunity, both cellular and humoral form the armamentarium against SARS-CoV2, although their contributive role and association with severe Coronavirus Disease 2019 (COVID-19), is still under investigation [4], as well as their protection against a second SARS-CoV-2 infection [5]. Moreover, assessment of T cell immunity together with humoral immunity may be helpful for differential diagnosis of COVID-19 in case of negative SARS-CoV-2 Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) testing [4].

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We present in here a case of an immunocompromised dialysis patient recently vaccinated for SARS-Cov2 presenting with fever and negative RT-PCT testing, where humoral testing revealed COVID-19 disease and mostly cellular, as opposed to humoral, immunity appeared to be lifesaving against severe COVID-19.

Clinical history

A 80-year female on peritoneal dialysis from August 2020 due to renal-limited MPO-ANCA vasculitis, was admitted to our hospital on March 25th, 2021, complaining for fever 38.4°C starting 4 days prior to presentation. Apart from fever once daily, she did not have any other signs/symptoms that could pinpoint to a cause. Peritoneal dialysis fluids were reported clear with no signs of peritonitis. Her past medical history was significant for diabetes mellitus type 2 for 30 years, coronary artery disease, arterial hypertension and moderate to severe aortic stenosis.

She had received 1st dose of the COVID-19 vaccine (Pfizer-BioNTech) two weeks prior to admission and a single dose of rituximab (500 mg) for remission maintenance for vasculitis at the beginning of January, 2021. As induction treatment for ANCA-vasculitis she had received, 3 iv pulses of methylprednisolone, followed by prednisolone tapering per os and oral cyclophosphamide for a total of 3 months (1.5 mg/kg body weight). Her outpatient medications included prednisone 5 mg, olmesartan, betaxolone, ezetimibe, simvastatin, acetylsalicylic acid and insulin basal bolus regimen (insulin glargine and aspart respectively).

Physical examination was unrevealing while laboratory testing showed a high C- reactive protein level CRP 68 mg/l (reference <6), mild leukocytosis 10260/ μ l with lymphopenia (neutrophils 9130/ μ l lymphocytes 718/ μ l), stable renal function [serum creatinine 3.8 mg/dl, urea 187 mg/dl, Estimated Glomerular Filtration Rate (eGFR) 11ml/min/1.73m²] and anemia close to her baseline values, Hb 11.6 g/dl on erythropoietin treatment. Peritoneal dialysis fluid revealed 70 cell/ μ l with 80% lymphocytes and 20% neutrophils and negative culture. Nasopharyngeal testing using PCR for SARS CoV-2 was negative for three consecutive times 2 days apart each. Computed Tomography (CT) of the chest and abdomen revealed no attributable cause of fever and blood cultures were also negative. Vasculitis was clinically and serologically quiescent.

Immunological testing for COVID-19 and vaccination

After 12 days of mild fever the serum of the patient was tested for humoral and cellular responses against SARS-CoV-2 as follows. Considering the day of fever onset, i.e the 1st day of presumed COVID-19 (21st March) the days of testing were April 6th, April 9th, May 7th, May 27th and June 24th and respectively the days 16, 19, 47, 67 and 95 of disease (Figure 1): Humoral Response: Enzyme Linked Immunoassay (ELISA) (Vircell Microbiologists, Granada, Spain) IgM+IgA and IgG antibodies (Ab) against recombinant spike glycoprotein (S) and nucleocapsid protein (N) antigens of SARS-CoV-2 was used in order to detect COVID-19 disease. Chemiluminescent Microparticle Immunoassay (CMIA) (Abbott's) IgG antibodies against Spike Protein (SP) was used in order to detect humoral response to SARS-CoV2 vaccination. Antibodies IgM+IgA (ELISA) against S+N antigens

were positive on April 6th (day 16) and remained positive until the last testing date, May 27th (day 67). Antibodies IgG (ELISA) against S+N antigens were initially negative (April 6th and 9th, (days 16-19) but turned positive on May 7th (day 47) and remained so until May 27th (day 67). In contrast, all samples tested for the presence of Ig antibodies using CMIA against SP remained negative from day 16 till day 95.

Cellular response: SARS-CoV-2-specific T-cell responses were quantified by IFN- γ enzyme-linked immunosorbent spot assay (CTL, Immuno Spot) of PBMC after stimulation with Spike protein-derived overlapping peptide pools (Jpt Peptides). Results were expressed as the number of spot forming cells per million PBMC, as described [6]. The median values from healthy, immunocompetent non-vaccinated (n=20) and fully vaccinated (two doses of Pfizer vaccine) individuals were used, respectively, as negative and positive response reference values. On June 24th 2021 (day 95) T cell response against the spike protein was readily detectable and well above the median response of the immunocompetent vaccinated cohort.

Flow cytometry was used to further characterize her lymphopenia. As expected, due to previous treatment with rituximab, CD19/CD20 positive B lymphocytes were near zero, while CD4 positive T lymphocytes were also diminished (<200 cells/ μ L. Cytotoxic and NK cells were within normal range.

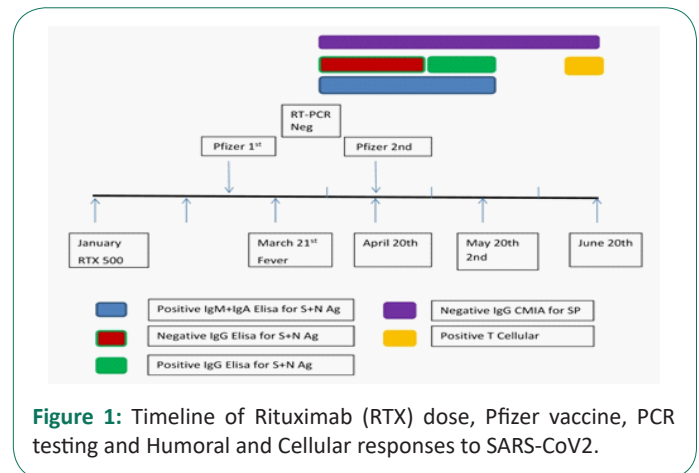


Figure 1: Timeline of Rituximab (RTX) dose, Pfizer vaccine, PCR testing and Humoral and Cellular responses to SARS-CoV2.

Clinical management

As the results of the assays of the humoral response were positive test for IgM+ IgA Ab to N+S antigens while there was a gradual appearance of IgG Ab to the same antigens and testing for IgG Ab to SP protein remained negative, diagnosis of COVID-19 was unmasked. Prednisolone was increased to 10 mg qid for a week and then tapered to previous dose of 5 mg/day. Chest CT was negative for pulmonary infiltrates and the patient had no other symptoms or signs of COVID -19. She was discharged two weeks later afebrile, in good condition. A second dose of the COVID-19 vaccine (Pfizer-BioNTech) was administered one month later, since humoral response was null.

Discussion

False negative PCR- tests have been described in the general population [7] and in dialysis patients [8] with COVID-19. Identification of humoral responses to SARS-CoV2 aids diagnosis,

since specific timeline of appearance of IgM, IgA and IgG Ab has been described [9]. We present in here an immunosuppressed patient on peritoneal dialysis, who showed a positive humoral response to SARS-CoV-2 antigens nucleocapsid and surface, at first IgM +IgA and then IgG on top, pointing to a diagnosis of recent COVID-19 disease. However, Ab response to spike protein was null from the beginning of symptoms until 3 months later, despite the second boost of vaccination.

The key immunologic feature in our patient is that she had Received Rituximab (RTX) 500 mg² months prior to her vaccination. Given the lasting B cell depletion by rituximab, recent guidelines for SARS-CoV2 vaccination in immunologic diseases, suggest at least 6 months waiting period after the last dose, in order to gain B cell repletion [10,11]. Prednisolone dose should ideally be below 20 mg qid [10], as was the case in our patient. But as shown by flow cytometry B cells were near zero, while T cells detected. In prospective studies of humoral and cellular response to SARS-CoV2 vaccination with an mRNA vaccine in RTX treated patients, it was shown that patients with no detectable B cell population do not develop specific antibodies. Nevertheless they were able to mount a T cell mediated response [12,13]. In patients with COVID-19, T cell response was reported to be correlated with the severity of the disease and the levels of reactive antibodies [14]. Accordingly, we believe that T cell response, probably driven by vaccination was functioning and protective against severe disease. Uremia per se hampers humoral response to vaccination, posing a challenge to effective protection against SARS-CoV2 [15].

Conclusion

In conclusion, immunocompromised patients may test negative by RT-PCR for COVID-19 infection. In suspected cases humoral testing may contribute to the final diagnosis. RTX treatment should be distanced from vaccine dosing in order to mount a detectable humoral response. Nevertheless a T cell response is detectable and could be lifesaving as in our patient. Vaccination against SARS-CoV-2 seems indispensable in immunocompromised patients in order to protect from the severe disease.

Declarations

Disclosure: Nothing to disclose.

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