REVISTA DO INSTITUTO DE MEDICINA TROPICAL DE SÃO PAULO

JOURNAL OF THE SÃO PAULO INSTITUTE OF TROPICAL MEDICINE

CASE REPORT

http://doi.org/10.1590/S1678-9946202062102

Favorable outcome of COVID-19 in a young woman with severe Crohn's disease on regular use of adalimumab and prednisone: a case report

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ABSTRACT

COVID-19 is a viral disease caused by SARS-CoV-2 that compromises the host immune response in severe cases, promoting a hyperinflammation that results in acute lung injury and multiple organs failure. In this context, patients presenting with immune-related diseases, such as Crohn's disease, affected by COVID-19, may have an uncertain prognosis. We report on a case of a young female patient with a severe Crohn's disease that presented with COVID-19 pneumonia and a favorable outcome even maintaining the use of adalimumab, TNF - alpha inhibitor and prednisone. This case raises the hypothesis that aside from prednisone, TNF-α inhibitors such as adalimumab could be used to stop the progression to COVID-19 complications by blocking the TNF-alpha-driven inflammatory process that occurs in severe COVID-19.

KEYWORDS: COVID-19. Crohn's disease. TNF inhibitor. SARS-CoV-2.

INTRODUCTION

COVID-19 emerged as an important viral disease that spread quickly around the world, and the host immune response seems to be directly related to severe cases of the disease[1,2]. In these cases, a hyperinflammation is observed resulting in an acute pulmonary injury, designated as the acute respiratory distress syndrome (ARDS), along with multiple organs failure, culminating, in many cases in death[1]. Higher levels of inflammatory markers, such as C-reactive protein, ferritin, and D- dimer, increased production of inflammatory chemokines and cytokines such as tumor necrosis factor - alpha (TNF-α), interleukin - 6 (IL-6) and IL-7 are observed in severe COVID-19 patients[2]. Thus, patients with immune-related diseases may represent an important challenge, since the compromise of some immunity pathway can lead to an uncertain prognosis.

In this way, Crohn's disease (CD) is a chronic condition characterized by intestinal inflammation, being classified among the immune-mediated inflammatory diseases (IMIDs)[3,4]. Frequently, the treatment of IMIDs involves targeted interventions that neutralize disease-specific proinflammatory cytokines, such as the use of adalimumab, a TNF-α inhibitor[4].

We report here a case of a young female patient with severe Crohn disease affected by COVID-19 pneumonia, who had a favorable outcome even maintaining the use of the TNF-α inhibitor (adalimumab) and prednisone.

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Received: 22 October 2020

Accepted: 23 November 2020

CASE REPORT

A 36-year-old caucasian woman sought our emergency department on April 2, 2020 due to a dry cough for 16 days associated with a retrosternal pain. The patient denied dyspnea or hemoptoic sputum. She denied systemic or gastrointestinal symptoms. Her medical history is marked by a severe Crohn disease (CD) diagnosed 9 years before and treated with azathioprine 100 mg/day, adalimumab 40 mg every other week and prednisone 20 mg/day. The last two doses of adalimumab were administered on March 9 and 23, 2020. She had a close contact with a confirmed case of COVID-19 during a work trip on March 10, 2020. She underwent a RT-PCR for SARS-CoV-2 performed with oro- and nasopharyngeal swabs and the RT-PCR result was positive on April 2, 2020.

On admission, vital signs were an axillary temperature of 36.5 ºC, pulse rate 92 beats/min, respiratory rate 18 breathes/min and blood pressure 123/74 mmHg. The physical examination was unremarkable. The peripheral oxygen saturation was 99%. The electrocardiography was normal; chest CT scan showed small, peripheral and bilateral air space consolidations distributed sparsely in the apical segments of the lower lobes and ground-glass opacities in the left upper lobe (Figure 1A). Pleural and pericardial effusions were absent. The laboratory tests showed a mild anemia and thrombocytopenia, but a normal white cells count, accompanied by increased levels of C reactive protein (CRP) and erythrocyte sedimentation rate. The laboratory tests are detailed in Table 1.

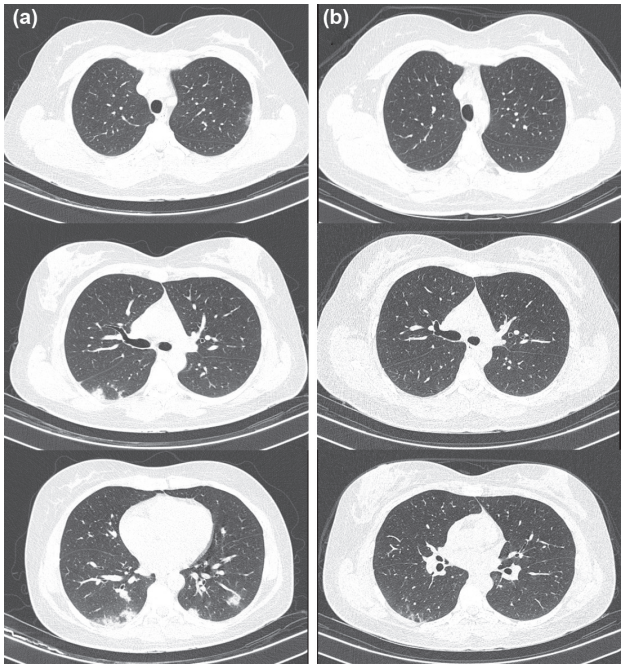

Figure 1 - The patient's chest CT showing multiple, bilateral and peripheral air space consolidations and ground-glass opacities in the lower and upper lobes (a); two months after the onset of the disease, residual ground-glass opacities were still present in the right lower lobe (b).

She presented a moderate COVID-19 pneumonia, and was admitted for clinical monitoring due to her immunosuppression. The patient only received supportive measures and there was no need of supplemental oxygen. Regarding the medical therapy of CD, azathioprine was withdrawn and adalimumab plus prednisone were maintained. The dose of adalimumab was administered on April 7, 2020 as scheduled. On the seventh day of hospitalization, she was discharged and given codeine for cough relief, which completely disappeared on April 13, 2020. On the same day, she repeated the SARS-CoV-2 RT-PCR on respiratory specimens and the result was negative. There was improvement of inflammatory markers as shown in Table 1. Two months later, a chest CT scan still showed residual ground-glass opacities in the lower lobes (Figure 1B). There was no CD exacerbation and the fecal calprotectin was normal (12 μg/g. Reference range: < 50 μg/g).

DISCUSSION

Patients treated with immunosuppressive drugs are at higher risk of developing more serious infections and atypical clinical presentations that may delay the diagnosis and/or lead to poorer outcomes. Immunosuppression has also been associated with severe illness and higher COVID-19 mortality[5]. However, this risk is probably not the same for all immune suppressive drugs. One of the exceptions could be the group of TNF inhibitors, such as adalimumab, which is a humanized monoclonal antibody that binds to TNF-α blocking the interaction with its soluble and membrane-bound receptors[6].

Our patient had a moderate COVID-19, as she presented lower respiratory tract symptoms and lung abnormalities on the chest CT, compatible with pneumonia by SARS-CoV-2, without hipoxemia[7]. She exhibited a favorable disease course even maintaining the adalimumab before and after the COVID-19 onset. The young age and female gender are possible explanations for this benign evolution, because both factors are related to better outcomes. The increasing age is associated with severe disease and higher mortality rates in COVID-19, especially in people aged 60 years or older[8-10]. Women produce less inflammatory cytokines during the course of COVID-19, which is associated with a shorter disease duration and higher survival rates[11]. On the other hand, complications of COVID-19 can also occur in otherwise healthy and young people.

The treatment of Crohn's disease with adalimumab might

Table 1 - Evolution of laboratory tests in the patient with Crohn's disease and COVID-19 pneumonia.

Laboratory Test	Temporal evolution				Reference range
	Apr 2, 2020 (Admission)	Apr 6, 2020	Apr 10, 2020	Apr 15, 2020	
Hemoglobin (g/L)	120	119	118	121	125 - 160
White-cell count (per mm^3)	5,330	5,600	7,200	7,100	4,500 – 10,000
Differential count (per mm^3)					
Total neutrophills	3,838	2,240	4,608	2,982	2,160 – 6,200
Total lymphocytes	1,226	3,136	2,160	3,408	800 – 3,500
Total monocytes	160	112	144	426	120 – 800
Platelet count (per mm^3)	137,000	180,000	290,000	219,000	150,000 – 450,000
Alanine aminotransferase (U/L)	35	27	56	22	10 - 39
Aspartate aminotransferase (U/L)	24	39	51	50	10 – 37
Gamma – glutamyl transferase (U/L)	27	ND	ND	ND	5 - 55
Lactate dehydrogenase (U/L)	169	156	456	148	100 – 250
Creatine kinase (U/L)	35	ND	ND	ND	21 – 215
Albumin (g/L)	34	ND	ND	ND	35 – 50
Globulin (g/L)	48	ND	ND	ND	20 – 40
Fecal calprotectin (µg/g)	12	ND	ND	ND	< 50
Blood Urea Nitrogen (mmol/L)	1.55	1.24	1.55	1.63	1.17 – 3.88
Creatinine (µmol/L)	53.9	61.9	55.7	54.8	53.4 – 123.7
Sodium (mEq/L)	138	135	137	135	135 – 145
Potassium (mEq/L)	3.8	3,7	4,8	3,9	3.5 – 5.1
Prothrombine time (sec)	11.7	12.1	11.7	12.5	≤ 14
Activated partial-thromboplastin time (sec)	26	26	26	26	≤ 26
Total bilirubin (µmol/L)	6.8	6.8	ND	8.5	Up to 20.5
Lactate (mmol/L)	2.0	1.9	1.5	2.5	0.5 – 2.2
Fibrinogen (g/L)	1.82	ND	1.82	2.16	1.5 – 4.5
D-dimer (mg/L)	< 100	299	284	296	Up to 400
High-sensitivity cardiac troponin I (pg/mL)	1	ND	ND	ND	Up to 26
Myoglobin (nmol/L)	0.85	ND	ND	ND	< 4
Creatine Kinase – isoenzyme MB mass (µg/L)	12	ND	ND	ND	Up to 25
BNP (pg/mL)	33	ND	ND	ND	< 100
Serum Ferritin (µg/L)	131	142	324	120	6 – 159
High-sensitivity C-reactive protein (mg/L)	42.1	9.4	62.6	4.5	< 5
Erythrocyte sedimentation rate (mm/h)	45	32	ND	ND	Up to 20
Blood gas analysis					
pH	7.42				7.35 – 7.45
PaO_2 (mmHg)	102.3				80 - 100
$PaCO_2$ (mmHg)	32.6	ND	ND	ND	35 – 45
HCO_3 (mEq/L)	20.8				22 – 26
SO2 (%)	97.4				95 - 100

ND = Not Done.

have contributed to stop the progression to severe disease by interfering with the TNF-alpha-driven inflammatory process that occurs in COVID-19. Severe COVID-19 pneumonia seems to be related to hyperinflammation driven by SARS-COV-2 infection, resembling a cytokine storm syndrome that is a consequence of the release of several pro-inflammatory chemokines and cytokines, including TNF-α, secreted mainly by macrophages and monocytes[12]. This uncontrolled exacerbated systemic inflammation response contributes to multiple organs failure and the development of the acute respiratory distress syndrome, acute kidney injuries, circulatory collapse, heart failure and central nervous system involvement[13].

Our patient presented with a progressive increase of serum ferritin, CRP and DHL levels throughout the hospitalization. After the peak of the last adalimumab dose, the serum levels of these laboratorial markers decreased. Proinflammatory cytokines, such as IL-1β, IL-6 and TNF-α,

promote the elevation of serum ferritin and CRP[14]. The increase of ferritin synthesis is part of the hypoferremic response that occurs early in inflammation[14]. Elevated serum LDH and CRP levels are associated with progression to respiratory deterioration and ARDS in patients with COVID-19[15,16].

The medical literature has already shown some adalimumab users that presented with uncomplicated forms of COVID-19[17-19]. Narcisi *et al.*[17] have described a case of a 57-year-old male patient with a 9- year history of psoriasis and psoriatic arthritis treated with adalimumab every 2 weeks for almost two years before the onset of COVID-19 symptoms and the development of lung pneumonia with no need of oxygen support. Papa *et al*.[18] have also described a 30-year-old male with ileal Crohn's disease, under treatment with mesalazine and adalimumab every other week for 5 years due to a steroid dependency. This patient developed a moderate COVID-19 pneumonia, evolved favorably and was completely asymptomatic on the fifth day of hospitalization.

Swaminath *et al*.[19] reported a case of a 60-year-old female nurse with a past medical history of autoimmune disease, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and ileocolonic inflammatory Crohn's disease in endoscopic remission. Both, the joint and bowel complaints, have been controlled for many years on weekly adalimumab and methotrexate. This patient presented with a severe COVID-19 pneumonia but required supplemental oxygen only for 2 days and was discharged after five days of hospitalization.

The previously reported cases involved people aged 50 years or older that could be related to a worse prognosis. However, none of them was using corticosteroids and we cannot rule out the potential role of corticosteroid in mitigating the lung damage caused by inflammation in the present case. In the RECOVERY trial, the use of glucocorticoids, specifically dexamethasone, resulted in a lower mortality among patients with COVID-19 under mechanical invasive ventilation or noninvasive supplemental oxygen therapy with respect to the usual care[20]. Nevertheless, no benefit was observed for patients with no oxygen therapy requirement[20]. In our case, besides the fact that the patient did not require supplemental oxygen therapy, she was already on a regular prednisone regimen at a dose of 20 mg once a day, a lower dose than the calculated anti-inflammatory dose of dexamethasone used in the trial.

The American Gastroenterology Association recommends that patients with Inflammatory Bowel Disease (IBD) who develop COVID-19 should discontinue the biological therapy during the viral infection and restart it after the complete resolution of symptoms[21]. However, based on what we observed in this case, it is plausible that the use of adalimumab has had a double protection role against COVID-19 severity and the recurrence of CD, not necessarily requiring the withdrawing of the TNF-α inhibitor. In spite of also reducing the production of inflammatory cytokines by macrophages suppression function, we decided to stop the azathioprine due to the concern of a potential interference on T- and B-lymphocytes function[22,23]. Thus, azathioprine could inhibit the cell-mediated immunity and the T-lymphocyte-dependent antibody synthesis against SARS-CoV-2.

The use of adalimumab may have influenced the oligosymptomatic presentation observed in our patient. This may have made the clinical suspicion of COVID-19 difficult and delayed the diagnosis. Fever and dyspnea, both absent in our patient, are common in COVID-19 pneumonia and upregulated TNF-α production is associated with flu-like symptoms, such as fever, malaise and lung injury[13,24-26]. The patient had no digestive symptoms, which, if present, could be attributed to the COVID-19 itself and/or to a CD flare triggered by the infection. However, the levels of fecal calprotectin were normal, ensuring that CD remained in remission[27].

Moreover, the patient had a longer duration of symptoms than that seen in mild COVID-19 that is around two weeks[28]. It remains unclear whether this longer duration of symptoms is acompanied by a prolonged transmission period. Despite this, she underwent a new SARS-COV-2 RT-PCR on respiratory specimens and the negative result opposes this possibility. Unfortunately, it was not possible to repeat the COVID-19 test on other days.

CONCLUSION

We reported on a case of a young woman with severe Crohn's disease that presented with COVID-19 pneumonia with a favorable outcome, without hypoxemia, despite maintaining the use of adalimumab and prednisone. This raises the hypothesis that it might not be mandatory to withdraw the TNF-α inhibitor adalimumab in patients with Crohn's Disease presenting with COVID-19, especially in severe cases of CD. This drug could have a double protection role: stopping the progression to COVID-19 complications by blocking the TNF-α -driven inflammatory process that occurs in severe COVID-19 and maintaining CD remission. On the other hand, it is possible that the use of adalimumab makes the olygosymptomatic clinical presentation last longer than usual, contributing to the diagnosis delay.

AUTHORS' CONTRIBUTIONS

HTV was one of the patient's physician and contributed writing and reviewing this manuscript; LRM contributed writing the manuscript, editing and proofreading the language; MMA was one of the patient's physician and contributed writing and reviewing the manuscript; JFRN contributed writing, editing, and reviewing the manuscript. All authors read and approved the final manuscript.

CONFLICT OF INTERESTS

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this manuscript.

ETHICAL APPROVAL

The patient has given permission and has signed the informed consent for the publication of this case report.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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