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Benign COVID-19 in an immunocompromised cancer patient – the case of a married couple

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Summary

Respiratory failure in COVID-19 is a common feature in fatal cases and has been considered as a failure of the immune system to control the virus. Here we report the case of COVID-19 affecting an immunocompromised women and her presumably immunocompetent spouse. A married couple (age 60 years) was simultaneously admitted to the emergency department on 10 March 2020 because of dyspnoea and fever, consistent with COVID-19. The wife (patient 1) was partially immunocompromised as a consequence of a recently started chemotherapy with fulvestrant and abemaciclid for recurring breast cancer, her husband (patient 2) had been healthy except for a history of controlled arterial hypertension. Both patients were treated with darunavir/cobicistat and hydroxychloroquine. The clinical course of the immunocompromised partner was benign, without need of intensive care. She was able to leave the hospital on day 6 after admission. In contrast, her husband needed intensive care and his recovery was slow, although eventually successful too. These findings suggest that the course of COVID-19 is not necessarily ominous in the presence of a compromised immune response and tend to reinforce the emerging therapeutic concepts of a controlled mitigation of the immune cascade following SARS CoV-2 infection.

Keywords: *COVID-19, chemotherapy, immunosuppression, outcome, case report*

Introduction

The relationship between immunological response to coronaviruses and the severity of the disease has been a conundrum since the first severe acute respiratory syndrome (SARS) corona virus outbreak in 2002−2003 [1]. In the discussion of their paper on T cell responses to whole SARS corona virus in humans, Ka-Fai Li et al. [2] wrote: "It has been unclear whether the adaptive immune response contributes to recovery or disease. The development of severe disease as the viremia declines suggests the latter as do some studies with other coronaviruses…" [3, 4].

In a recent study, Gralinsky et al. [6] demonstrated that complement activation is related to more severe respiratory consequences in SARS coronavirus infections, another hint of the importance of understanding the cascade of events that enhance damage to the host in infections with novel corona viruses.

A report by Mehta in *The Lancet* [7] showed that acute respiratory distress syndrome (ARDS) is the main cause of death with COVID-19 and that ARDS is the common immunopathological event for SARS-CoV-2, SARS-CoV and MERS-CoV infections. One of the main mechanisms for ARDS is the cytokine storm [8], the deadly uncontrolled systemic inflammatory response resulting from the release of large amounts of pro-inflammatory cytokines − interferon (IFN)-α, IFN-γ, interleukin (IL)-1β, IL-6, IL-12, IL-18, IL-33, tumour necrosis factor-α, transforming growth factor-β, etc. − and chemokines − CC-chemokine ligand (CCL)2, CCL3, CCL5, CXC ligand (CXCL)8, CXCL9, CXCL10, etc.).

During the emerging COVID-19 pandemic, various novel pharmacological interventions have been used, in part on an empirical basis [9, 10], but increasingly based on clinical trials [11] too.

Lu et al. [12], in an early overview of possible options for COVID-19 treatment, mentioned lopinavir/ritonavir, nucleoside analogues, neuraminidase inhibitors, remdesivir [13], peptide EK1 [14]), arbidol [15], RNA synthesis inhibitors (such as tenofovir disoproxil fumarate, lamivudine), anti-inflammatory drugs (such as hormones and other molecules), along with Chinese traditional medicines, such as ShuFengJieDu [16] and Lianhuaqingwen [17].

One substance group that has emerged as an interesting candidate is chloroquine [18] and hydroxychloroquine. Dan Zhou [19] recommended examining the multiple sites of action of both substances for the prevention of both infection with and progression of COVID-19. Hydroxychloroquine was used in the treatment of the patients presented here, along with darunavir and cobicistat [20].

Another substance, the non-halogenated inhalable corticosteroid ciclesonide, could qualify as a candidate – with a double target. According to a report by Matsuyama [21], in addition to its known anti-inflammatory properties it seems to be able to block coronavirus RNA replication.

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Informed consent

The patients gave informed consent to the diagnostic and therapeutic strategies chosen and to the use of their biological data in anonymous form for this report.

Case descriptions

Patient 1

A 60-year-old female Caucasian, living in northern Italy with her husband (patient 2) and a son, 28: occupation employee, height 1.68 m, weight 79 kg, body mass index 29 kg/m^2.

Presentation

Fever up to 38.5°C, cough, dyspnoea.

She was brought by ambulance to the emergency room on the request of her family physician. She was accompanied by her husband (patient 2) and their son, 28 years of age. (The son tested positive for COVID-19 on 10 March 2020, was asymptomatic at that time and sent home into quarantine. Reportedly he eventually became symptomatic later and was not fully recovered on 24 March 2020.)

Past medical history

Nonsmoker, history of angiodysplasia of the descending colon, bicuspid aortic valve with slight insufficiency, varicosis of lower extremities.

Seven years previously she was diagnosed with breast cancer. On 3 December 2013 she underwent a quadrantectomy of the left breast, followed on 19 December 2013 by an axillary lymph node dissection for a ductal infiltrative carcinoma G3, probably(?) luminal B-HER2 negative: pT2 pN1a (2/11) Mx, stage IIB. She received adjuvant chemotherapy with adriamycin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 21 days for four cycles, plus a single dose of docitaxel, which was stopped because of a serious allergic reaction, as well as radiotherapy. Hormone therapy with anastrozole was planned for 5 years (and was eventually suspended after the diagnosis of lymph node recurrence described below).

Recent medical history

In October 2019, 6 years after initial diagnosis, she developed lymphoedema of the left upper extremity plus a supraclavicular adenopathy. A whole-body computed tomography (CT) scan plus an echographic assessment of the lymph nodes was ordered.

On 29 November 2019, The CT scan revealed several intrapulmonary and mediastinal lymph nodes >6 mm in diameter and moderate bilateral pleural effusions, plus the presence of multiple submandibular and cervical lymph nodes of >1.5 cm diameter. There was no intrahepatic irregularity, but a suspect lesion was seen in the head of the pancreas. No cerebral lesions were detected. A bronchoscopy did not produce evidence of neoplastic cells. Biliary-pancreatic endoscopy confirmed the presence of an IPMN (intraductal papillary mucinous neoplasm of the pancreas). Echocardiography confirmed of the number and dimensions of the cervical lymph nodes and the absence of axillary nodes. A positron emission tomography (PET) scan revealed several skeletal focal lesions.

On 23 January 2020 a left supraclavicular lymphadenectomy was performed. At this point, the patient was diagnosed with lymphatic and osseous metastases, CD ER (Cd estrogen receptor) 98%, PGR (progesterone receptor) 55%, MIB1 (proliferation marker) 12%, c-erbB2 (human epidermal growth factor receptor 2) score 1+.

On 17 February 2020 treatment with fulvestrant 500 fl intramuscularly was initiated and repeated once on 3 March 2020. Abemaciclib orally 150 mg twice daily was started on 19 February 2020.

On 20 February 2020, a check-up CT confirmed that the pulmonary lesions previously detected were not progressing and showed regression of the pleural effusions.

On 3 March 2020, chemotherapy was suspended after the appearance of fever. On 10 March 2020 she was admitted to the emergency room.

Oncological summary

December 2013: Diagnosis of left sided breast cancer, surgery, irradiation, adjuvant chemotherapy.

December 2019: Lymphoedema, detection of cervical and axillary lymph node metastases, involvement of lung and mediastinum, suspicion of osseous metastases.

17 February 2020: Start of chemotherapy with fulvestrant and abemaciclib.

3 March 2020: Suspension of chemotherapy after appearance of fever.

Diagnostic workup

On admission to the ER, the patient was tested positive for COVID-19.

The diagnostic workup, consisting of measurement of arterial gases, haematogram, a chest x-ray, and blood, urine and stool cultures, revealed the following:

Normocapnic hypoxaemia: pH 7.44, pO_2 47 mm Hg (6.3 kPa), pCO_2 40 mm Hg (5.3 kPa).

Moderate anaemia (haemoglobin 107 g/l) and marked leucocytopenia (white blood cell count 1300/l, neutrophils 600/l, lymphocytes 600/l) with platelets <90 × 10^9/l and CRP 1.3 mg/l.

An anteroposterior chest x-ray with the patient in bed and in the supine position, showed “asymmetric” and bilateral diffuse “patchy” parenchymal opacities [22], more marked in the left hemithorax where they were present from the apex to the base (fig. 1). The opacities were predominantly supleural and with a mantellar distribution. They were accompanied by a veil of moderate bilateral pleural effusions, once again more prominent in the left hemithorax.

The results of bacteriological checks including blood, stool and urine cultures were eventually negative.

Initial clinical diagnosis

Community acquired SARS CoV-2 pneumonia in an immunocompromised woman.

Therapeutic intervention and course

Patient 1 was transferred to the pneumology department and treated with triple antibiotic therapy [23] (levofloxacin, piperacillin plus tazobactam) combined with the antiviral combination of darunavir/cobicistat [20] To this

combination, hydroxychloroquine [24] was added. Leucopenia was corrected by filgrastim.

Within 24 hours after admission, her clinical status was stable, the white blood cell count restored to 4900/l, with neutrophils 4050/l, lymphocytes 710/l and platelets 96 × 10^9/l. Within 5 days after admission, patient 1 was afebrile.

On 16 March 2020, analysis of arterial gases showed a pH of 7.41, a pO_2 of 73 mm Hg (9.73 kPa) and a pCO_2 of 38.9 mm Hg (5.1 kPa). The second anteroposterior chest x-ray (fig. 2), taken with the patient sitting in bed, showed a reduction of the density and extent of the parenchymal opacities seen on admission at the right base and the left hemithorax in the previous image. Patient 1 left the hospital the same day.

On 24 March 2020, she tested negative for COVID-19 and was reported to be at home, afebrile, in good general status.

Patient 2

60-year-old man, Caucasian, living in Italy, husband of patient 1.

Past medical history

Arterial hypertension, controlled with losartan and hydrochlorothiazide.

Recent medical history

Nausea, vomiting, diarrhoea for 7 days prior to admission, eventually fever and dyspnoea.

Diagnostic workup

On admission to the ER, the patient was conscious, febrile, dyspnoeic. At pulmonary auscultation no rales were found.

A swab for COVID-19 was positive. The haematogram showed normal haemoglobin and white blood cell count, with thrombocytopenia. Initial arterial pO_2 was 69 mm Hg (kPa 9.2 kPa).

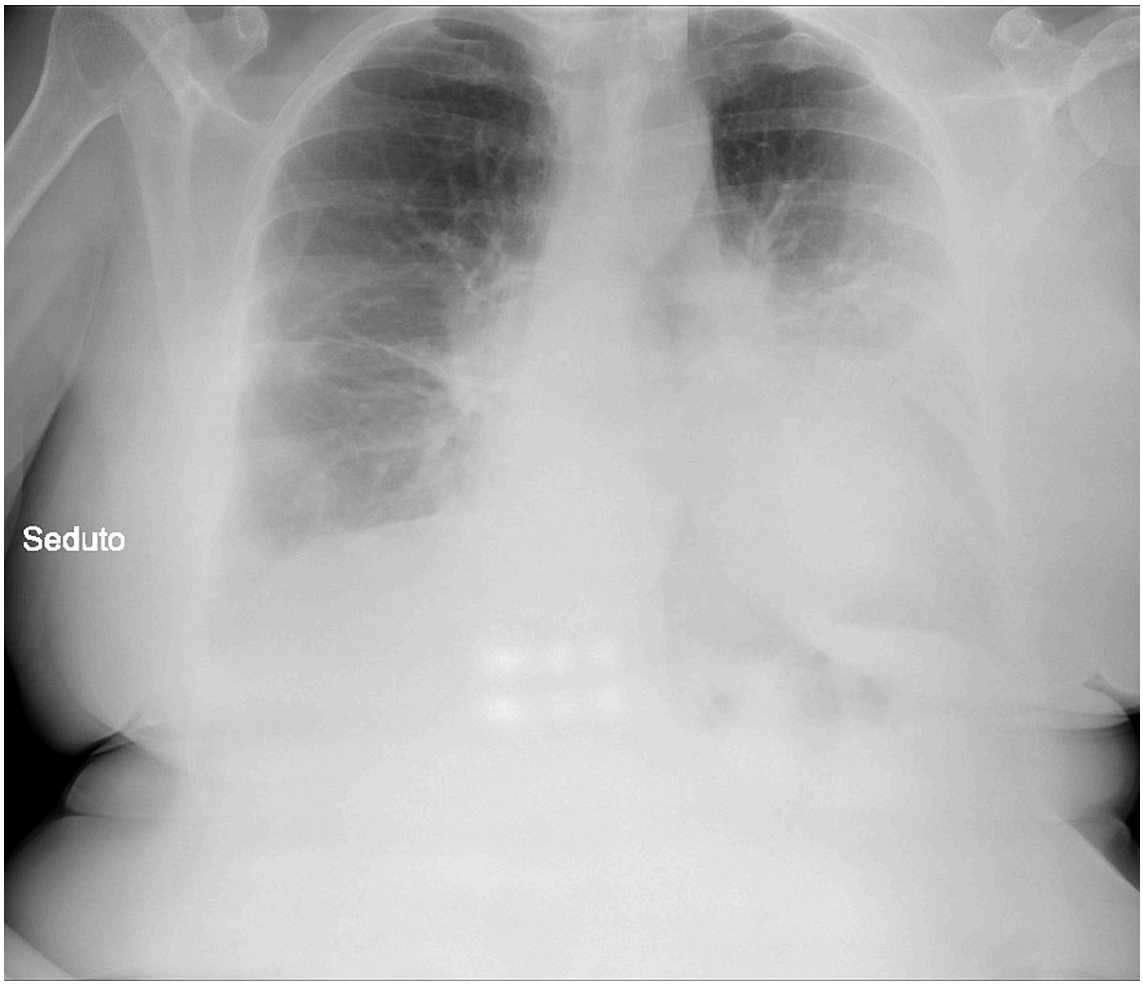
A chest x-ray in anteroposterior projection, with the patient in a sitting position, showed moderate bilateral parenchymal opacities, mostly subpleural and with a mantellar distribution, accompanied by discrete basal pleural effusions (fig. 3).

Therapeutic procedures and evolution

Antiviral therapy with darunavir/cobicistat and hydrochloroquine 200 mg 2 twice daily. and antibiotic treatment with ceftriaxone were started.

Despite these measures, fever up to 40.5 °C developed, with a respiratory rate of 35/min and worsening hypoxaemia with an arterial pO_2 of 60 mm Hg (7.9 kPa) despite oxygen 2 l/min. The patient remained lucid (Modified Ear-

Figure 1: Chest x-ray of patient 1 on admission, 10 March 2020. Courtesy Ospedale di Sassuolo. In addition to the morphological abnormalities due to the past medical history of the patient and the more recent alterations described in the CT scans performed on 20 February 2020, this image shows opacities strongly suspicious of SARS Cov-2 pneumonia (see description by the radiologist in the text).



ly Warning Score 6) but suffering. In consequence, he was transferred to the intensive care unit of the hospital, intubated and ventilated. Azithromycin was added to the antibiotic treatment with ceftriaxone.

Despite a complicated course, which had necessitated intensive care, patient 2 survived, was weaned from artificial ventilation on 21 March 2020 and stayed in standard hospital care for CoVID-19 patients until 2 April when he was able to return to his home. A swab for SARS CoV-2 was negative at discharge.

Initial clinical diagnosis

Respiratory insufficiency secondary to community acquired SARS CoV-2 pneumonia in a previously healthy man.

Discussion

The cases described here are an example for the diversity of clinical courses in COVID-19 and for the role of the immunocompetence of the host at the time of infection.

We observed:

– the rapid recovery of the initially immunocompromised patient 1 from COVID-19, on combined antiviral and antibiotic treatment, combined with hydroxychloroquine, within 6 days (table 1);

– the prolonged and more severe course of CoVID-19 in patient 2, her husband, despite an inconspicuous medical history and relatively low risk profile (except for hypertension) and the same antiviral treatment combined with hydroxychloroquine.

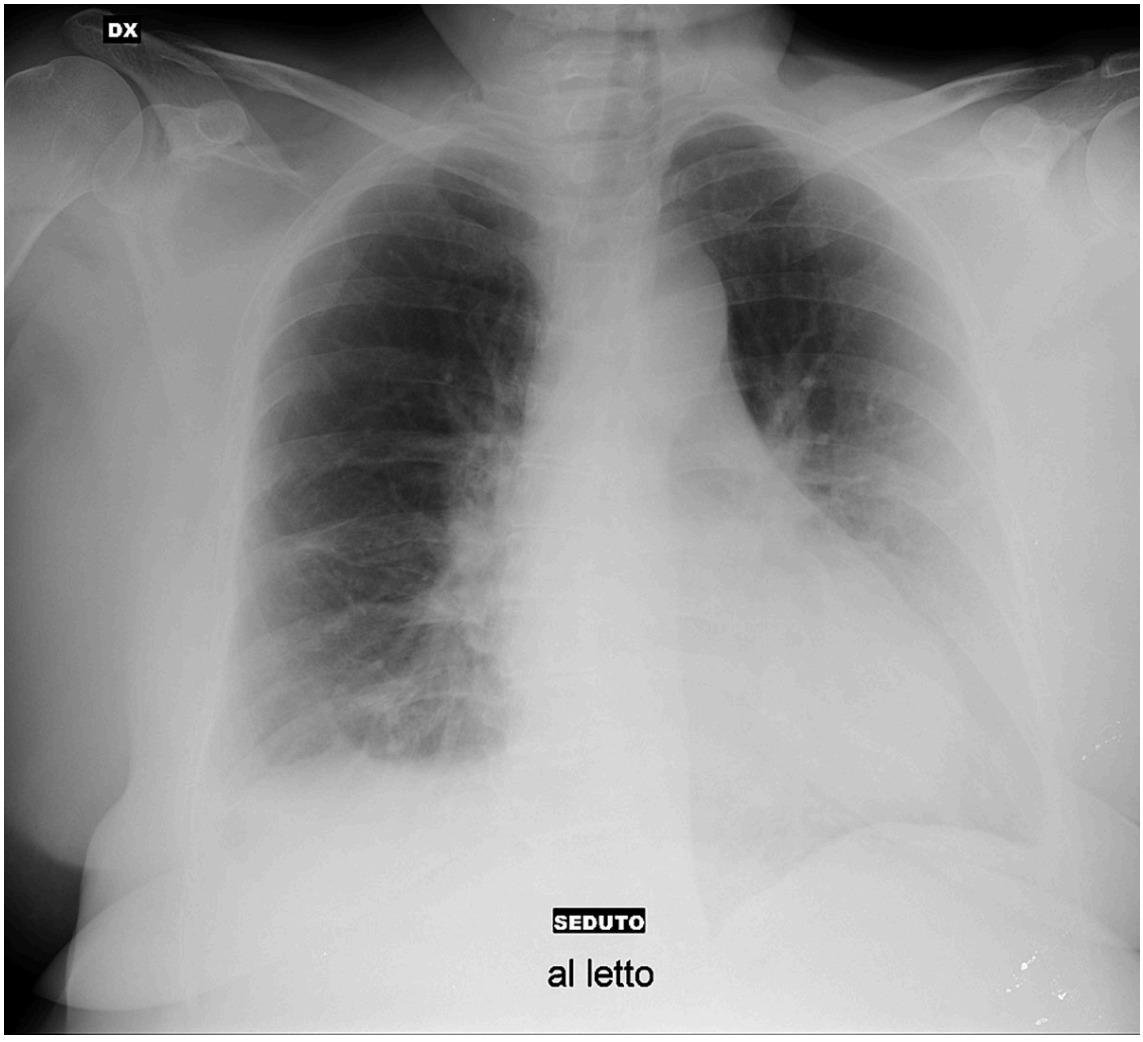
The recent history of patient 1, with metastatic breast cancer and recent exposure to antineoplastic chemotherapy that had produced leucopenia at admission to the hospital were indicative of a state of immunosuppression, whereas there was no hint of a significant immunosuppression of patient 2. However, the clinical course was strikingly different, as described above.

We conclude that the low degree of immunocompetence in patient 1 did not induce serious complications and that it could even have offered an advantage in the prevention of cytokine storm. However, we can only hypothesise on the mechanisms actively involved in the benign course of patient 1.

Several explanations should be discussed:

– general alterations of the immune response in cancer, independent of the treatment [25];

Figure 2: chest x-ray of patient 1 on day 6 after admission, 16 March 2020. Courtesy Ospedale di Sassuolo. It shows a marked reduction of the opacities noted in figure.1 (see detailed radiological description in the text).



– modulation and/or mitigation of the immune response to COVID-19 by the antineoplastic agents used in patient 1, namely the anti-oestrogen fulvestrant [26] and abemaciclid [27];
– rapid recovery of immunocompetence by use of the recombinant granulocyte colony-stimulating factor fligrastim as described by Johannesen et al. [27] and Xiao et al [28];
– a combination of two or all of the above-mentioned mechanisms.

Regarding the complications and the slow recovery of patient 2, in sharp contrast to patient 1, a role of his pre-COVID-19 medication in determining his response to SARS CoV-2 cannot be excluded a priori. Both losartan and hydrochlorothiazide have been shown to act on inflammatory pathways [29, [30].

Our motivation for publishing our observations is threefold:

– to invite a reconsideration of immunosuppression as a universally valid risk factor for severe complications of COVID-19 (a similar case of recovery from COVID-19

Figure 3: Chest x-ray of patient 2 on admission, 10 March 2020. Courtesy Ospedale di Sassuolo. Subpleural opacities dominate (see detailed description in the text).

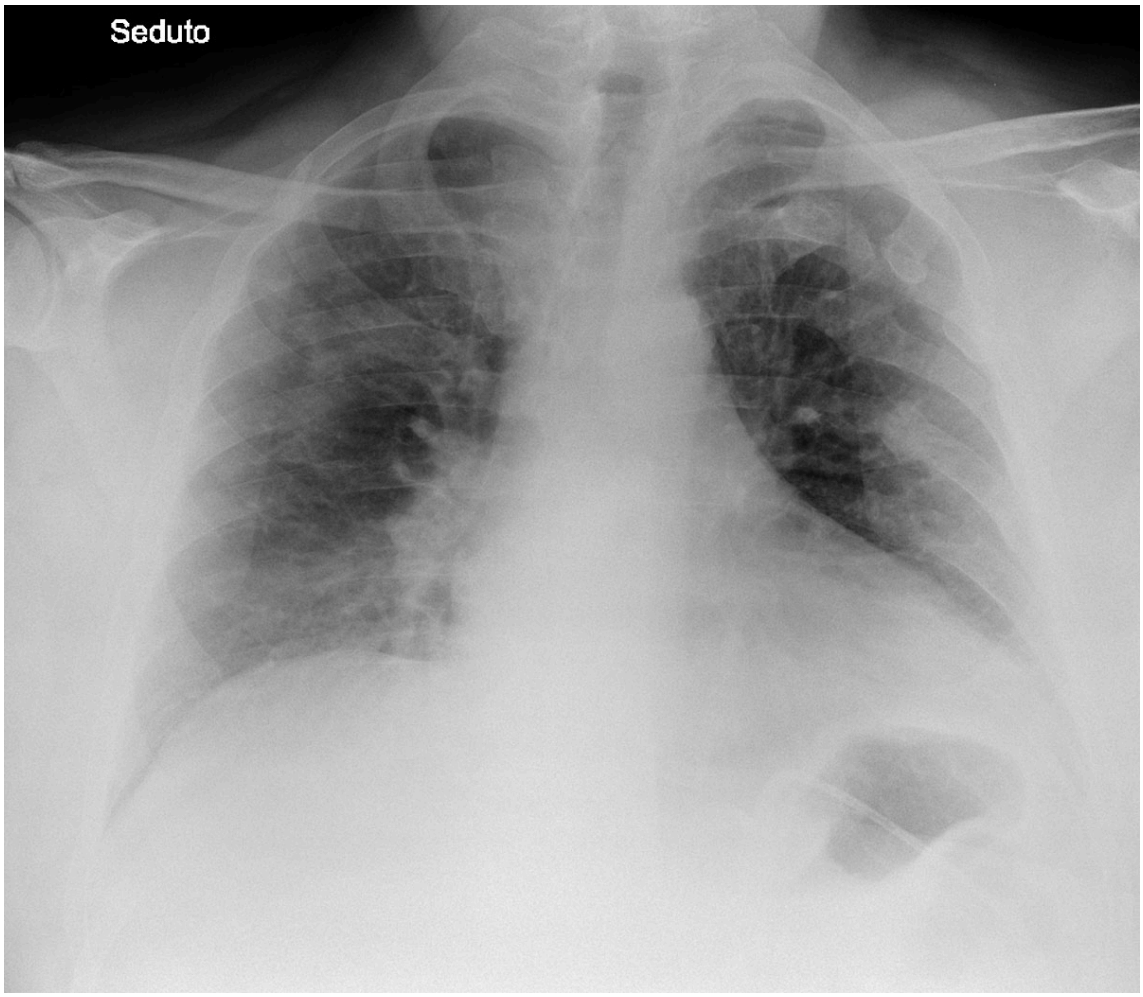


Table 1: Medications taken by the patients before and during COVID-19.

Treatment period	**Patient 1 female**	**Patient 2 male**
Pre-COVID-19 Starting 17 February 2020	Fulvestrant	Losartan
	Abemaciclid	Hydrochlorothiazide
During COVID-19 Starting 10 March 2020	Fligrastim	–
	Darunavir	**Darunavir**
	Cobicistat	**Cobicistat**
	Hydroxychloroquine	**Hydroxychloroquine**
	Levofloxacin	Cetriaxon
	Piperacillin	Azithromycin
	Tazobactam	–
Intensive care	No	Yes
Dismissed from Hospital	16 March 2020	2 April 2020

in a transplant patient under long-term immunosuppression has been published recently by Zhu [31]);

– to demonstrate that a single causal explanation for the course of events (recovery, severe complications, death) in COVID-19 is not at hand;

– to invite to a comprehensive approach to the study of the immune cascade and to the interferences of the drugs involved in its modulation, leading to recovery or fatal outcome.

The suggestion by Mehta [7] to consider active immunosuppression as a strategic tool to combat or prevent cytokine storm in COVID-19 has been commented on by Ritchie and Siganayagam [32], with a warning that this might be a "double-edged sword". Therefore, we conclude that it is imperative to take a closer look into interactions of drugs on the molecular level that can trigger different immune responses and inflammatory processes responsible for the most severe complications of COVID-19.

This could be done, for example, by studying the potential role of P-glycoprotein (Pgp), a transmembrane ABC transporter, in cytokine extrusion by immune cells. The activity of Pgp and thus the extrusion of cytokines can be modulated by inhibitors (as demonstrated for verapamil by Wyska [33]) and by inducers of Pgp (for modulators and inhibitors of Pgp cf. Seelig [34]).

Patient perspective

The patients have indicated an interest in a scientific discussion of their cases and in the conclusions resulting from it.

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Disclosure statement

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