Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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LETTER TO THE EDITOR

Clinical and radiological improvement of protracted COVID-19 and Good syndrome secondary to advanced thymoma

Good's syndrome (GS) is a rare clinical entity that affects both sexes over 40 years of age. GS is characterized by the presence of thymoma associated with hypogammaglobulinemia with loss of B cells in most cases. In addition, altered T cell function in the presence of normal or elevated T cell counts has been reported. This disease produces severe immunodeficiency, and an increased incidence of opportunistic and viral infections may complicate the clinical course of affected patients. Few cases of SARS-CoV-2 infection and GS have been reported with different outcomes.[1,2] Although immunocompromised patients are prone to prolonged COVID-19 courses, however, at the same time they might be protected from severe disease mediated by an overstimulation of the immune system.[3] We report a prolonged COVID-19 infection with SARS-CoV-2 viremia in a GS patient who recovered after standard treatment concomitant with convalescent plasma.

The index patient was a 44-year-old male diagnosed with advanced thymoma (type B1) who in the past 6 years had undergone surgical excision and adjuvant mediastinal radiotherapy. After 2 years of stable results, he developed recurrent metastatic disease in multiple sites, for which he underwent multiple surgeries and radiotherapy. On presentation, he was on systemic treatment with gemcitabine and capecitabine for 5 months. The patient was admitted to our institution due to worsening dyspnea, non-productive cough and nasopharyngeal swab indicating positive for SARS-CoV-2 by polymerase chain reaction (PCR). He also reported a SARS-CoV-2 infection 8 months before, with no residual symptoms. Mild hypoxemia (PaO_2 56 mmHg) with hypocapnia ($PaCO_2$ 32 mmHg) and respiratory alkalosis (pH 7.48) were present. While a moderate increase in CRP (3.37 mg/dl; normal values $<$ 0.3 mg/dl) was noted, D-dimer levels (289 ng/mL; normal values $<$500), LDH, CK, renal and liver function were within normal range. Low flow O_2 with nasal cannula (FiO_2 24%) was started for normalization of hypoxemia and hypocapnia.

Chest computed tomography (CT) showed chronic actinic alterations in the mediastinum and left lung, with architectural distortion (unchanged in comparison to previous exams), and ground-glass opacities distributed in the medullary and peripheral regions of the lungs. Compared to the CT performed 8 months before (during the first COVID-19 diagnosis), the pulmonary changes were present in distinct lung fields and with greater extension (Fig. 1). A diagnostic workup was started to rule out infectious causes. Drug pneumonitis was deemed unlikely as the lung parenchymal changes preceded acute onset.

A bronchoscopy with bronchoalveolar lavage (BAL) was performed with positive SARS-CoV2 PCR. BAL cellularity demonstrated 5% macrophages, 92% neutrophils, 3% lymphocytes, 0% eosinophils. Multiplex PCR for other respiratory viruses, Pneumocystis *jiroveci* PCR, bacteria culture, acid-fast bacilli smear and galactomannan on BAL were negative. Additionally, cytomegalovirus (CMV) PCR was positive (viral load of 2350 IU/mL). Gancyclovir was initiated for suspected superimposed CMV pneumonitis and an immunodeficiency screening was ordered. Serologic test for SARS-Cov-2 antibodies was negative. The first immunological evaluation showed a reduction of the gamma-globulin peak in serum electrophoresis with reduced immunoglobulin serum levels. The evaluation of peripheral lymphocyte subsets showed inversion of the CD4/CD8 ratio with no peripheral B cells. Immunoglobulin serum levels were extremely low for all classes. The immunological work-up is summarized in Table 1. With these immunological findings associated with thymoma, the patient was diagnosed with GS and was put on facilitated subcutaneous immunoglobulin replacement treatment. Additionally, dexamethasone 6 mg every 24 h was initiated due to hypoxemia and accompanying COVID-19 infection.

The patient's symptoms and hypoxemia improved with this referred treatment. However, after seven days, the symptoms worsened, with CT showing an increase in the ground glass and reticular opacifications and consolidations (Fig. 2A). A new BAL was performed, which revealed cellularity of 4% macrophages, 92% neutrophils, 4% lymphocytes, 0% eosinophils, besides persistence of SARS-CoV-2 PCR with low cycle threshold value (CT=13), suggesting high viral load. CMV BAL PCR remained positive (11600 IU/mL). Unexpectedly, *Pneumocystis jiroveci* PCR was positive (334,000 copies/mL). Sulfamethoxazole/trimethoprim was initiated to treat Pneumocystis pneumonia (PCP) and was later replaced by primaquine plus clindamycin due to hepatotoxicity. Corticosteroid therapy was maintained throughout the treatment.

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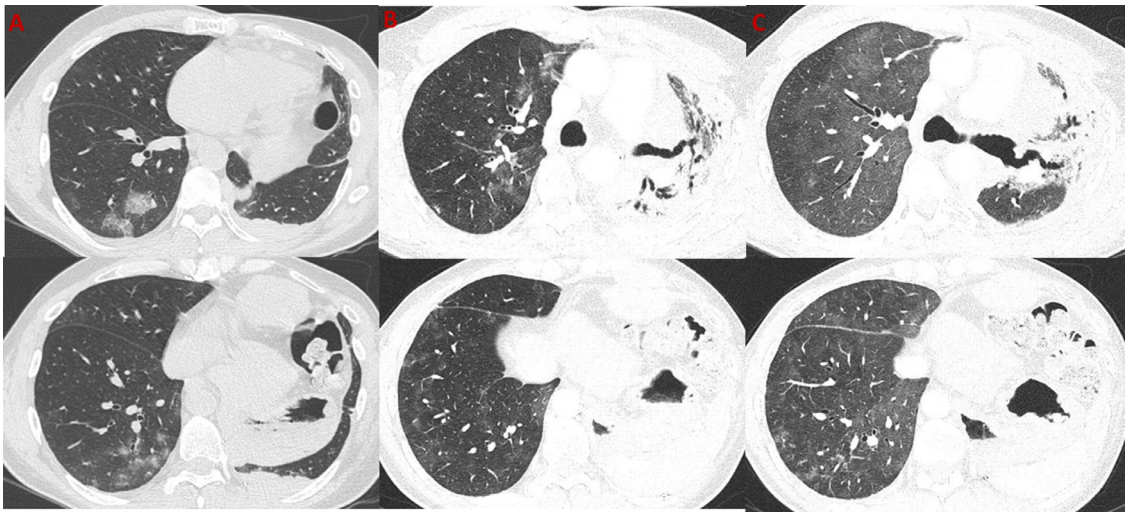

Fig. 1 CT axial slices during the evolution of the case. **(A *first column*)** CT image from the first diagnosis of SARS-CoV-2 infection 8 months before showing ground glass opacities in the right lower lobe. **(B *middle column*)** CT image two months later, before the chemotherapy started, showing ground glass opacities in distinct lung fields. **(C *third column*)** CT image revealing persistent ground glass opacities with greater extension on patient's presentation to emergency care.

After 21 days of treatment for PCP and CMV, the patient's symptoms improved and O_2 saturation returned to 94% in ambient air. However, a repeat CT revealed new ground-glass opacities in the right lower lobe. A third BAL was performed, demonstrating cellularity of 53% macrophages, 31% neutrophils, 16% lymphocytes, 0% eosinophils, negative CMV and Pneumocystis PCR; COVID-19 PCR remained positive, with a persistent low cycle threshold. Based on clinical stability, the patient was followed up on conservative management with a gradual taper of steroids.

Table 1 Patient's immunological evaluation for diagnosis of GS.

	Index patient	Normal range for age
WBC (cells/mm3)	9540 (cells/mm3)	4500-10800 (cells/mm3)
ANC (cells/mm3)	5370 (cells/mm3)	1500-8000 (cells/mm3)
ALC (cells/mm3)	3590 (cells/mm3)	1000-5200 (cells/mm3)
Hb (g/dL)	11.2 (g/dL)	12.0-16.0 (g/dL)
PLTs (cells/mm3)	360000 (cells/mm3)	100000-400000 (cells/mm3)
B cells (CD20+)	0%	8-18%
T cells (CD4+)	22.9%	31-56%
T cells (CD8+)	72.8%	17-41%
CD4+/CD8+	0.3	0.9-2.6
T cells (CD3+)	97%	59-81%
IgA	5 mg/dL	50-400 mg/dL
IgG	151 mg/dL	600-1500 mg/dL
IgM	4 mg/dL	50-300 mg/dL
SARS-CoV-2 IgG antibody test	0.1	$<$ 0.6 = negative
SARS-CoV-2 IgM antibody test	0.1	$<$ 0.6 = negative

Five days after the last bronchoscopy, the patient presented with new-onset hypoxemia, PaO_2/FiO_2 was 170, requiring oxygen through a high-flow nasal catheter. Repeat chest CT angiography showed small subsegmental thromboembolism and revealed new ground-glass opacities and consolidation (Fig. 2B). A diagnosis of protracted COVID-19 was considered. The patient was treated with four units of convalescent COVID-19 donor plasma over 48 h. Corticosteroid tapering was reversed, and its dosage increased. Additionally, anticoagulation therapy was started due to pulmonary embolism. Over the next 24 h, the patient showed substantial clinical improvement with gradual resolution of the hypoxemia, with no requirement for oxygen support four days after the first plasma infusion. A new CT demonstrated a significant reduction of pulmonary compromise (Fig. 2C).

Although not universally, most recent studies define protracted COVID as a disease course with a duration of symptoms beyond the usual natural history (i.e. more than 4 weeks) accompanied by positive respiratory sample PCR as evidence of persistent viral shedding.[1—4] Protracted COVID-19 with viral RNA shedding over 15 days has been described in elderly or immunocompromised patients and severe cases.[4—7] Convalescent plasma therapy (CPT) is a passive polyclonal antibody administration to provide immediate immunity in an attempt to improve the survival rates in severe acute respiratory syndromes of viral etiology (including COVID-19).[4,5] According to some reports, CPT with anti—SARS-CoV-2 antibodies could be a promising approach in the context of protracted COVID-19 in individuals unable to mount a specific humoral response to SARS-CoV-2.[5,6] On the contrary, a randomized trial demonstrated that CPT in hospitalized patients with COVID-19 pneumonia overall did not reduce the progression to severe respiratory failure or death within 30 days.[8]

The present case constitutes the second case report in literature showing prolonged SARS-CoV-2 infection due to GS, and the first one demonstrating clinical and radiological response following a treatment plan that also included CPT infusion. London et al.[9] presented a 41-year-old woman with thymoma and GS, and reported improved COVID-19

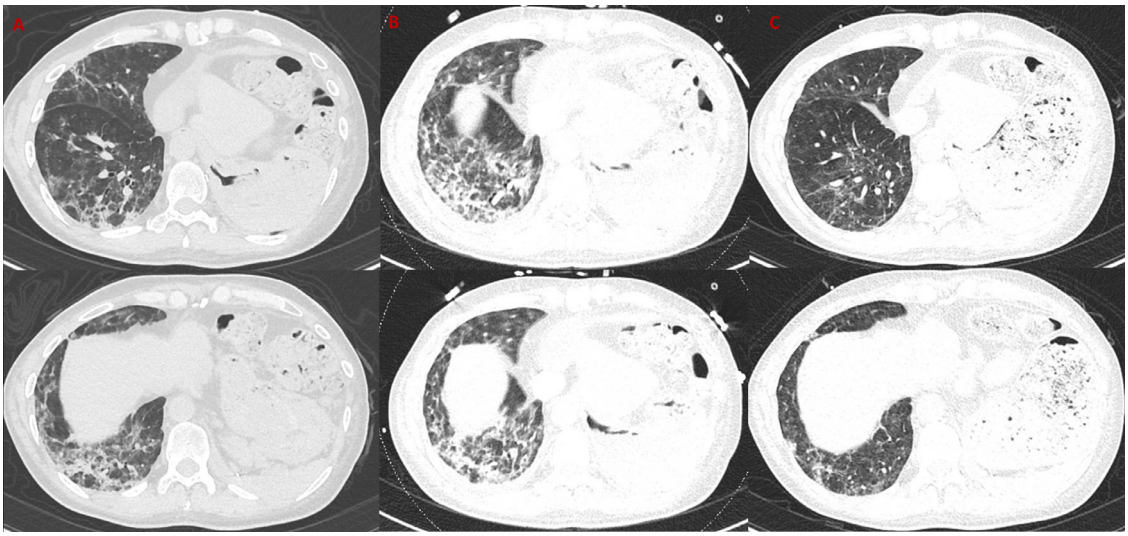

Fig. 2 CT axial slices during the evolution of the case. **(A *first column*)** CT after treatment for CMV and intravenous immunoglobulin demonstrating new ground glass opacities along with consolidations and reticular opacities. **(B *middle column*)** Despite treatment for both CMV and PCP, CT image reveals worsening in pulmonary compromise. **(C *third column*)** CT demonstrating significant radiological improvement after CPT followed by substantial clinical improvement in a short period of time.

symptoms after 4 days of therapy and negative nasopharyngeal PCR following CPT. Our case demonstrates the imaging response in serial CT scans, with significant reduction of ground-glass opacities with standard treatment concomitant with CPT reinforcing the role of ineffective humoral response in protracted forms of COVID-19.

Authors contributions

Milena Tenorio Cerezoli and Felipe Marques da Costa were the pulmonologists conducting the clinical case. João Antônio Gonçalves Garreta Prats was the collaborator infectologist. William Nassib William Junior and Diego Vinícius Gonçalves Santana were the consultant oncologists. Augusto Kreling Medeiros and Ulysses S. Torres were the clinical radiologists accompanying the case. This very complex case demanded a multidisciplinary approach. All the authors, in conjunction, after a meeting of the multidisciplinary team, opted for conceiving this clinical case study and submitting it to Pulmonology. The preliminary draft was written by Augusto Kreling Medeiros, followed by revision and proofreading by all authors, who added insights/ corrections regarding their area of expertise. A final revision was performed by Ulysses S. Torres, with approvation by all authors.

Conflicts of interest

None.

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