**CASE REPORT**

**Strongyloides** infection manifested during immunosuppressive therapy for SARS-CoV-2 pneumonia

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Received: 28 July 2020 / Accepted: 1 September 2020 / Published online: 10 September 2020 © The Author(s) 2020

**Abstract**

**Background** SARS-CoV-2 pandemic has posed formidable public health and clinical challenges. The use of immunosuppressive agents, such as high dose corticosteroids and cytokine inhibitors (e.g., Tocilizumab) has been suggested to contrast the hyperinflammatory process involved in the pathogenesis of the severe disease, with conflicting evidence. Among the drawbacks of immunosuppressive therapy, the risk of reactivation of latent infections, including parasitic infestations, is to be considered.

**Case presentation** We report a case of a 59-year-old Italian patient treated with high dose intravenous dexamethasone and two intravenous doses of Tocilizumab for interstitial bilateral pneumonia associated with SARS-CoV-2 infection who developed itching, abdominal pain, and an increased eosinophil count. Stool examination confirmed the presence of *S. stercoralis* larvae. The patient was treated with a 4-day course of Ivermectin with full recovery.

**Discussion** We report the first case of *S. stercoralis* infection following an 11-day treatment with high-dose steroids and Tocilizumab for severe COVID-19. Clinicians should be aware of the risk of strongyloidiasis as a complication of the treatment for severe COVID-19.

**Keywords** *Strongyloides stercoralis* · Tocilizumab · SARS-CoV-2 · Immunosuppression

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**Background**

The recent emergence of SARS-CoV-2 and its rapid spread throughout all continents has become a global concern [1]. Many studies have recently been conducted to identify the molecular pathway leading to alveolar damage in moderate and severe Coronavirus disease 2019 (COVID-19), and have shown the pivotal role of the hyperinflammatory response of the patients’ immune system to the virus in determining alveolar destruction [2]. This is the rationale for the use of corticosteroids, to counteract respiratory failure in severely ill patients, along with oxygen supply [3]. Clinical observational studies have described an improvement in clinical symptoms and oxygenation after steroid administration in patients with severe COVID-19 [4–7]. Moreover, one randomized clinical trial has been recently published to support a survival benefit (the RECOVERY trial) [8]. This controlled, open-label randomized trial provides evidence that treatment with dexamethasone at a dose of 6 mg once daily for up to 10 days reduces 28-day mortality in hospitalized patients with COVID-19 who are receiving oxygen supply, but not
among those receiving no respiratory support. On the other hand, IL-6 has been implicated in the pathogenesis of the disease, causing what is known as “cytokine release syndrome” (CRS), contributing to the development of ARDS. Tocilizumab, an IL-6 inhibitor that has been approved for the treatment of rheumatoid arthritis, has been suggested to reduce ARDS-related complications in patients affected by COVID-19 [9, 10].

Previous experiences with tocilizumab suggest an increased risk of opportunistic and bacterial infection similar to anti-TNF-α agents. When using this drug, continuous clinical monitoring is recommended, as secondary infections might arise [11].

Strongyloidiasis is a parasitic disease widely distributed in tropical and subtropical regions [12]. It is mainly caused by Strongyloides stercoralis (seldom by other Strongyloides species), a soil-transmitted helminth that spread primarily through contaminated soil. The presence of this helminth has been well documented in some temperate countries, especially in the past, like the Mediterranean basin [13].

Rhabditiform larvae are eliminated through the stool in soil, where they can develop either infective filariform larvae directly, or free-living adult male and female worms, which mate and develop eggs, rhabditiform larvae and eventually infective filariform larvae. Infective filariform (L3) larvae penetrate the human host skin and migrate to the small intestine, where they become adult female worms, which produce eggs via parthenogenesis and new rhabditiform larvae. These can either be eliminated through stool or can become infective filariform larvae, penetrating either the intestinal mucosa or the skin of the perianal area, resulting in autoinfection [14]. By this peculiar auto-infective cycle, untreated cases can generate persistent, lifelong infections, and represent a risk factor for a potentially fatal hyperinfection syndrome or disseminated infection [15].

So far, only a few reports describe exacerbation of S. stercoralis infection in patients treated with either tocilizumab or anti-TNF-α agents [16, 17].

Case report

A 59-year-old woman born in Southern Italy was admitted to our ward in March 2020 after experiencing malaise, nausea, vomiting and fever lasting about a week. Chest x-ray showed bilateral basilar interstitial pneumonia and SARS-CoV-2 RT-PCR in a oropharyngeal/nasal swab resulted positive. Since arterial pO2 was 57 mmHg, she was started on high-flow supplemental oxygen support. The patient reported chronic treatment with low dose prednisone for adult Still’s disease since 2010 and atenolol for hypertension.

Treatment with hydroxychloroquine, lopinavir/ritonavir, and dexamethasone was started together with enoxaparin prophylaxis. On the 5th day of hospitalization due to severe hypoxia and worsening of respiratory performance, she underwent non-invasive mechanical ventilation with continuous positive airway pressure (CPAP), which was continued for a total of 11 days. On day 7th she was treated with two doses of tocilizumab 8 mg/kg 12 h apart. Dexamethasone treatment was given at the dose of 20 mg/day for 5 days, followed by 10 mg/day for other 6 days. During the hospitalization, she presented an episode of atrial fibrillation, which was successfully reverted by amiodarone, and hyperglycemia, for which she started insulin-based treatment, later switched to oral hypoglycemic agents. Overall her clinical condition gradually improved, and she completed oxygen weaning on day 27th of hospitalization.

On day 25th her eosinophil absolute count (EAC) increased up to 5540 cell/µL and the patient reported abdominal pain and itching. Stool examination revealed the presence of rhabditiform larvae of S. stercoralis, while IFAT serology tested positive at a titre of 1:640. A 4-day oral treatment with ivermectin (200 mcg/kg) was administered, with a rapid decrease of eosinophil cell count and symptom improvement. She was discharged and a follow-up visit 1 month later was scheduled to check EAC, serology for S. stercoralis and stool examination.

The patient did not develop fever or worsening clinical condition concomitant to EAC rising. She denied travelling to tropical or subtropical areas and revealed recent moving to Lombardia region from Calabria region (Southern Italy). She reported repeated episodes of diffuse itching in the last 10 years, treated with topical steroids with partial improvement.

Discussion

To date, no case of strongyloidiasis related to severe COVID-19 treatment has been reported. Nevertheless, based on the experiences from the use of steroids and tocilizumab in other diseases, it is conceivable that exacerbation of S. stercoralis infestation may occur [18]. Efficacy of immunosuppressive treatments for severe COVID-19 is still debated. In particular for tocilizumab, a recent meta-analysis did not show any additional benefit for patients with severe COVID-19 [19]. The authors concluded that further recommendations on tocilizumab should wait results from ongoing clinical trials, due to the low quality of evidence of the available studies. Nevertheless, despite the promising preliminary data of RECOVERY trial on steroid administration [8], some concerns have been raised about the applicability of these results in different settings, such as in low-income, African countries [20]. Authors highlighted the risk of harms rather than benefits from steroid administration as a consequence of the different epidemiology of other infectious diseases.
like tuberculosis or strongyloidiasis (which may be reacti-
vated or worsened).

Strongyloidiasis is mainly an asymptomatic or mildly
symptomatic disease [21], often only accompanied by a
moderate increased EAC. In a recent study conducted in
Northern Italy the prevalence of infection was 8% in Italian
patients with EAC ≥ 500 cells/µL, especially in those born
before 1947 and originating from rural areas surrounding the
Po river, regardless of symptoms. The prevalence of stron-
yloidiasis was even higher (17%) in immigrants originating
from endemic areas with eosinophilia [13]. Our patient had
only recently moved to Lombardy: her 10-year history of
itching suggests that she might have acquired the infection
in Southern Italy.

In case of immunosuppression, strongyloidiasis can deter-
mine an hyperinfection syndrome or disseminated infection,
with fatality rates up to 70–100% [15]. In Strongyloides
hyperinfection syndrome an acceleration in the parasite
life cycle leads to excessive reproduction rates within the
traditional reproductive sites of the worm (skin, guts and
lungs). The number of larvae increases in stools and/or sput-
um along with clinical manifestations to the respiratory,
gastrointestinal system and peritoneum. Disseminated stron-
yloidiasis is a severe infection which results from massive
dissemination to body districts the parasite does not nor-
mally reach and colonise, such as the liver, heart, brain and
the urinary tract [22].

Hyperinfection or disseminated strongyloidiasis are rarely
reported in patients treated with tocilizumab. To date, only
one case report described the onset of haemorrhagic alveolitis
following combined steroid and tocilizumab treatment [17],
while sporadic cases following anti TNF-α or high dose cor-
ticosteroid treatments have been reported [16, 23].

Given these high fatality rates, a screening process should
be performed when using such therapies in patients with risk
of exposure to Strongyloides, and, if diagnostic test is not
available, pre-emptive treatment with ivermectin should be
considered [24]. The use of Tocilizumab for COVID-19 is
limited to a short-term treatment course, which includes a
few doses (generally 2 or 3). If compared to the long treat-
ment course which is licensed for rheumatological diseases,
the risk for opportunistic disease reactivation should be lim-
ited, though no specific studies have yet been conducted.

Our patient did not present increased EAC on admission,
which suggests that the worsening of patient’s strongyloidiasis
was associated with the use of tocilizumab and high-dose
corticosteroids. Our patient did not develop an hyperinfection
syndrome or a disseminated infection, possibly due to the
rapid detection of the infection and its prompt treatment.
It is also possible that the leukocyte formula alterations in
the course of COVID-19 could have masked a pre-existing
mild hypereosinophilia, as a consequence of the hyperin-
flammatory response to SARS-CoV-2 infection.

A dedicated strategy based on epidemiological risk stratifi-
cation has been recently proposed to prevent Strongyloi-
des hyperinfection/disseminated infection for COVID-19
patients undergoing steroids [25]. In inpatient clinical set-
tings, presumptive ivermectin treatment is proposed for at-
risk patients who initiate or are candidates for steroids, as
well as in case of invasive gram-negative rod infection while
waiting for diagnostic tests. Even in outpatient setting, in
presence of risk factor for strongyloidiasis, a presumptive
therapy (usually one dose) should be considered, if it is not
contraindicated and serology is not available.

In confirmed uncomplicated infection the efficacy of a
single-dose treatment has been well established [26], longer
treatment being suggested in hyperinfection/dissemination
[27]. In our case the underlying immunosuppressive treat-
ment prompted us to adopt a treatment longer than that pro-
posed for uncomplicated infection.

In conclusion, we report the first case of strongyloidiasis
following high-dose steroid and tocilizumab treatment
for severe COVID-19. Risk assessment for strongyloidiasis
should be performed for people who live or have visited
areas, where the organism is endemic. Similarly, we suggest
considering this helminth in case of unexplained appearance
of hypereosinophilia. When a prompt diagnosis is not feasi-
ble, due to the urgency of treatment and the risk of fatal out-
come either for COVID-19 or Strongyloides hyperinfection/
dissemination syndrome, empirical pre-emptive single-dose
ivermectin therapy must be considered.

Author contributions VM, VC, MG, F Castelnuovo, CG, AM, F Cas-
telli drafted the text; VM and VC performed data analysis and literature
research; VM, MG contributed to the conception and design of the
manuscript; F Castelnuovo and GC contributed to the acquisition of
data; FC and AM substantively revised the text.

Funding Open access funding provided by Università degli Studi di
Brescia within the CRUI-CARE Agreement. This research received
no specific grant from any funding agency in the public, commercial,
or not-for-profit sectors.

Compliance with ethical standards

Conflict of interest All authors had no financial or other conflicts of
interest to disclose.

Ethics declarations Informed consent was obtained from the subject.

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