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 Editors-in-Chief

Covid-19 associated autoimmune thrombotic thrombocytopenic purpura: Report of a case

Dear Editor:

At the end of 2019, a novel pneumonia syndrome was identified in Wuhan, a city in the Hubei Province of China [1]. In February 2020, the World Health Organization designated the disease Covid-19, which stands for coronavirus disease 2019 [2]. While the majority of patients have mild symptoms without pneumonia or mild pneumonia, the clinical spectrum of symptomatic Covid-19 cases ranges from mild to critically ill [3]. As previously reported, patients with Covid-19 may show a range of immune complications, such as autoimmune hemolytic anemia (OIHA), immune thrombocytopenia (ITP), Guillain-Barré and antiphospholipid syndrome (APS) [4–8]. Here we present a confirmed case of Covid-19 presenting with autoimmune thrombotic thrombocytopenic purpura (TTP). We propose that autoimmune TTP, can be a severe autoimmune complication in Covid-19 patients and should be considered in the differential diagnosis of thrombotic microangiopathies (TMA).

A 74-year-old woman with a history of hypertension presented with a five-day history of progressive fatigue and dry cough. On physical examination, she was pale, slightly subicteric and she had apathic confusion. Her body temperature was 37.6 °C. Lung auscultation revealed fine bibasilar crackles. Contrast enhanced magnetic resonance imaging of the brain was normal. Reverse transcriptase PCR assay detected the presence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA in the nasopharyngeal swab. Chest computed tomography (CT) showed patchy peripheral bibasilar ground glass opacities in both lungs, findings compatible with mild Coronavirus Disease 2019 (Covid-19) pneumonia (Fig. 1). Favipiravir, hydroxychloroquine and azithromycin were initiated to treat Covid-19. Her complete blood count (CBC) at admission showed the following: Hgb 6,6 g/dl, MCV 102 fl, Htc 19%, total leukocyte count 3700/mm^3, neutrophil 1960/mm^3, lymphocyte: 15,900/mm^3 and platelet count 48,000/mm^3. Prothrombin and activated partial thromboplastin time were normal. Fibrinogen level was 300 mg/dl (normal range, 200 to 400) and D-Dimer was slightly elevated (1.2 μg/ml; normal range, 0 to 0.5). On biochemical tests, the following were abnormal: lactate dehydrogenase (LDH) 1108 U/l(135–248), serum ferritin level 666 μg/l (23–336), total bilirubin 2,6 mg/dl (0–1,2), unconjugated bilirubin 2,2 mg/dl (0–1,2) and haptoglobin 8 mg/dl (30–200). Our patient had a reticulocytosis of 8% (0.60%–1.83%), with an absolute reticulocyte count of 150 × 10^9/l (29.5–87.3 × 10^9/l). Her direct Coombs test was negative. Peripheral blood smear showed polychromasia and increase in schistocytes (Fig. 2). Taking into account the presence of lethargy concomitantly with thrombocytopenia and microangiopathic hemolytic anemia, a presumptive diagnosis of autoimmune TTP was made. After obtaining blood sample for ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) activity and ADAMTS-13 inhibitor, which is an autoantibody to ADAMTS-13, central venous catheter was placed and daily therapeutic single volume plasma exchange (PE) was begun along with methylprednisolone 1 mg/kg/day and folic acid. By the 3rd day of consecutive therapeutic PE, her platelet count rose to 130,000/mm^3 and LDH level decreased to 525 IU/l and the patient was fully conscious. Acetylsalicylic acid was added to the treatment. ADAMTS-13 activity and inhibitor were reported to be 0,2% (normal range: 40–130%) and > 90 U/ml (normal range: < 12 U/ml), which confirmed the diagnosis of autoimmune TTP. Other viral, autoimmune and malignant diseases associated with autoimmune TTP were screened and found to be negative. By the 7th day of PE after LDH levels were normal and platelet count remained over 150,000/mm^3 for two consecutive days, the frequency of plasma exchange was decreased and MP was started to be tapered. After a total of 11 of PE sessions, PE was terminated. At discharge on 21st day of admission, her CBC was as follows: Hgb 10,6 g/dl, Htc 31%, total leukocyte count 11,670/mm^3, neutrophil 7920/mm^3, lymphocyte: 2300/mm^3 and platelet count 398,000/mm^3. Her absolute reticulocyte count was 80 × 10^9/l and biochemical tests showed normal LDH and bilirubin levels.

TMA encompass a group of disorders characterized by microangiopathic hemolytic anemia, thrombocytopenia, in which many primary and secondary etiological predisposing factors have been described—namely autoimmune disorders, pregnancy, cancer, drugs and antineoplastic therapy, bone marrow/solid organ transplantation, and infections [9]. Recently, an increasing evidence suggests that viruses may also play an important role as trigger factors in the pathogenesis of thrombotic microangiopathies.

The exact pathophysiology of viral-associated TMA remains to be explained. While direct endothelial cell injury appears to play an important role, cytokine storm endothelial injury, immune complex mediated events and ADAMTS13 inhibitors had been reported to be associated with the pathophysiology of virus triggered TTP [10]. Host genetic or ambient susceptibility factors may create a favorable ground for the viruses to trigger the cascade of events that eventuates in the clinical manifestations of TMA.

Autoimmune disorders including Guillain-Barré and APS have been described in the course of Covid-19 infection [4,5]. OIHA and ITP associated with Covid-19 have also been reported [6–8]. Common conditions associated with secondary TTP including lymphoproliferative disorders, other autoimmune disorders and collagen vascular diseases were excluded in our patient, which suggests that acquired TTP was driven by Covid-19 infection. Albiol et al. reported the single case in the literature of a 57-year-old woman diagnosed with acquired autoimmune TTP following the diagnosis of Covid-19 [11]. To the best of our knowledge, this is the second case of acquired autoimmune TTP diagnosed concomitantly with Covid-19 infection. We suggest that Covid-19 induced ADAMTS13 inhibitors contribute to the TMA and hence to the neurologic symptom in this patient. Although the copresence of Covid-19 and autoimmune TTP may be considered anecdotal, one cannot reject the possibility of such an association. More cases must be reported to reinforce the causal relationship in such circumstances.

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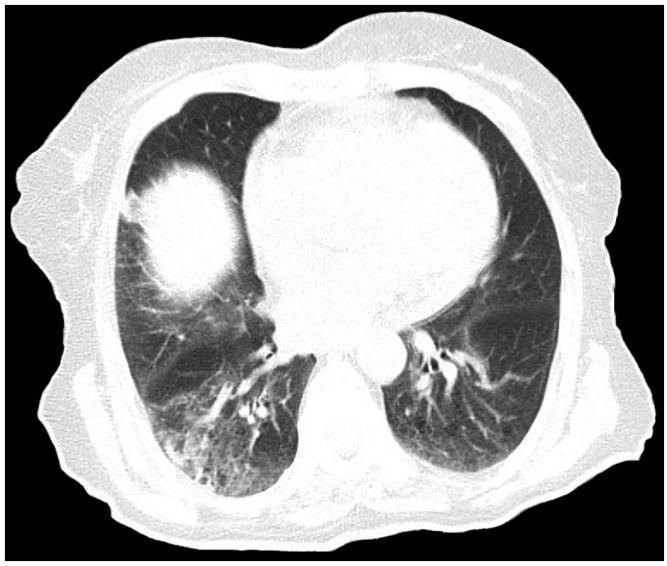

Fig. 1. Chest computed tomography (CT) showed patchy peripheral bibasilar ground glass opacities in both lungs, findings compatible with mild Coronavirus Disease 2019 (Covid-19) pneumonia.

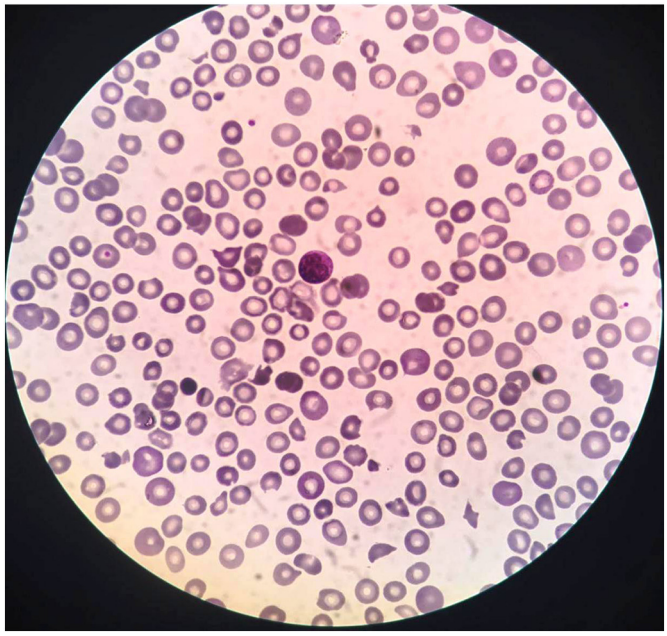

Fig. 2. Peripheral blood smear showed polychromasia and increase in schistocytes.

In conclusion, viral associated endothelial stimulation and damage could ultimately lead to the development of this life-threatening multisystemic disorder. Clinician awareness is crucial when TMA occurs in the context of a viral infection in the absence or even in the presence of confusing initiating factors, since prompt recognition of the clinical picture may be life-saving. Our case highlights the increased importance of the recognition of different immune mediated hematological complications associated with Covid-19.

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