DR. GEORGE NESR (Orcid ID : 0000-0001-7147-843X)

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Corresponding author mail id : george.nesr@nhs.net

ITP flare with mild COVID-19 infection in pregnancy: A case report

George Nesr[1], Catherine Garnett[1], Chris Bailey[1], and Siamak Arami[1]

1 Haematology Department, Northwick Park Hospital, UK

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the third zoonotic coronavirus to be identified in humans during the twenty-first century, after severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV)(Coronaviridae Study Group of the International Committee on Taxonomy,of Viruses, 2020). The resultant disease, Coronavirus Disease (COVID-19) (WHO, 2020), was first identified in December 2019 in Wuhan, Hubei province, China (WHO, 2020) and rapidly evolved into a pandemic (WHO, 2020) within months. In the UK, the first confirmed case was identified in late January 2020 and the first COVID-19 related death was recorded in March 2020 (UK Government, 2020). The clinical picture of COVID-19 ranges from asymptomatic infection (Nishiura *et al*, 2020) to fatal pneumonia, with the later caused by the "cytokine storm" and the consequent ARDS (Xu, Z. *et al*, 2020). Although SARS-CoV-2 affects the respiratory system primarily; gastrointestinal, genitourinary, nervous and cardiovascular systems' affection was reported (Zhang *et al*, 2020). The hematopoietic system is affected both quantitatively and qualitatively, with some of these changes, namely lymphocyte and platelet counts, bearing prognostic significance in the disease course (Terpos *et al*, 2020; Zini *et al*, 2020).

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Immune thrombocytopenia (ITP) is an autoimmune disease characterized by an isolated low platelet count (< 100 x 10^9/L). The pathophysiology of ITP is complicated; with some aspects yet to be elucidated. Autoantibodies against platelet glycoproteins increases their destruction by macrophages and dendritic cells in the spleen and liver, and decreases their production by megakaryocytes. The initial trigger for the production of autoantibodies remains unknown and about 50% of patients lack these autoantibodies. An abnormal Th1/Th2 ratio, with skew towards Th1 phenotype, and higher levels of Th17, Th22, and splenic follicular Th cells contribute to the autoimmunity. In addition, increased numbers of CD8+ T cells and reduced numbers of Treg cells also play a role (Swinkels *et al*, 2018). Herein, we present a case of a pregnant patient known to have ITP, who sustained a flare after being diagnosed with COVID-19.

A 34-year old lady, pregnant in the second trimester (20/40 weeks; gravida 2 para 1), and known to have ITP since 2013, presented to the A & E department in our hospital with a 1-day history of dry cough, fever, petechiae and gum bleeding. The patient had no other comorbidities and reported no recent change in her medications. Physical examination showed no other bleeding manifestations or respiratory symptoms, with no cardiological or abdominal findings, apart from the known gestation. Initial full blood count (FBC) was remarkable for a platelet count of 13 x 10^9/L (normal range 150 – 450 x 10^9/L). The rest of her blood analyses, including renal and hepatic profiles, C-reactive protein, D-dimer, and clotting screen (prothrombin and activated partial thromboplastin times, and fibrinogen level) were all unremarkable. A blood film did not show red cell fragments. A nasopharyngeal swab for SARS-CoV-2 PCR was taken on admission, and was later found to be positive. A working diagnosis of ITP flare was instated. Given the active bleeding, she was admitted and started on intravenous immunoglobulins (1 g/kg of body weight) and oral prednisolone (1 mg/kg of body weight). Respiratory symptoms and fever were managed conservatively, without the need for supplemental oxygen. On the next day of her admission (Day 1), the patient reported improvement in bleeding per gums and no new petechiae. A repeat FBC revealed an increase in the platelet count to 34 x 10^9/L and consequently the IVIG and prednisolone were both stopped. A drop

in lymphocytes counts to 1.2 x 10^9/L (normal range 1.5-4 x 10^9/L) was also noted. Day 2 showed further improvement in platelet count to 64 x 10^9/L. Based on the clinical improvement and the recovering platelet count, the patient was deemed medically fit for discharge with outpatient follow up. Fig 1 shows the platelet and lymphocytes count before, during and after the admission.

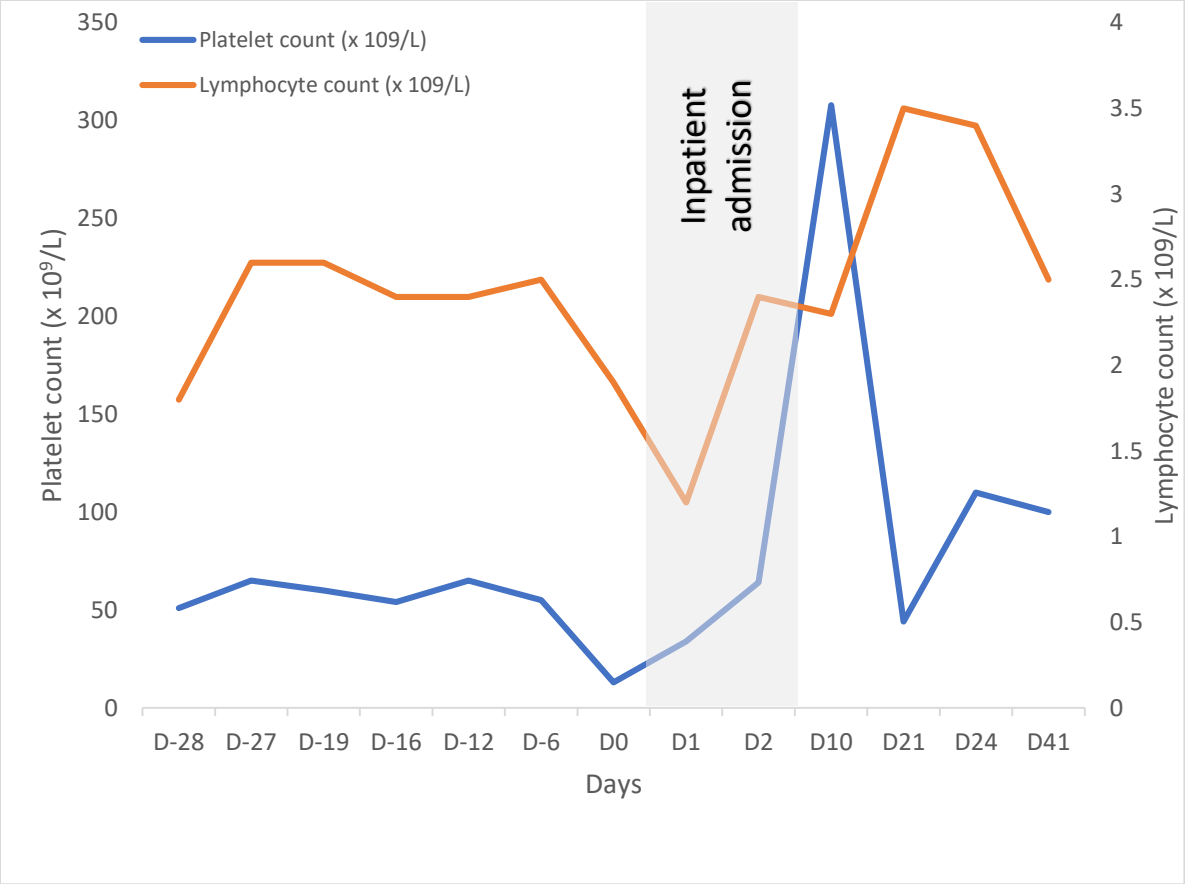

Figure 1. Line chart showing the platelet and lymphocyte counts before, during, and after admission. The grey shaded part highlights the inpatient admission period. D0 denotes the admission day. The patient had frequent full blood counts before and after admission given her pregnancy.

Dysregulated immune response is pivotal in the pathophysiology of ITP (Swinkels *et al*, 2018) and is thought to contribute to thrombocytopenia seen with COVID-19. Mechanisms suggested for the later include (Xu, P. *et al*, 2020)

- Decreased platelet production through direct infection of the bone marrow cells, as part of secondary hemophagocytic lymphohistiocytosis in patients with severe COVID-19, or due to the disruption of platelet release in the pulmonary circulation.
- Increased platelet clearance by the immune system, non-specifically through coating by immune complexes produced as a part of the immune response against SARS-CoV-2, or specifically by platelet antibodies produced through molecular mimicry to SARS-CoV-2.
- Increased consumption secondary to low grade coagulopathy.

Our patient had mild COVID-19 with no coagulopathy, and hence most of the above mechanisms are unlikely to be applicable. The platelet nadir and the response to IVIG and steroids makes a diagnosis of gestational thrombocytopenia unlikely. The normal kidney and liver functions, and absence of red cell fragments, excluded thrombotic microangiopathies. Taking this into consideration, and based on the chronology of events, COVID-19 is likely to be the precipitating factor for the disease flare. One mechanistic explanation, in the context of pre-existing ITP, would be the overactivation of T cells, manifested by increase of Th17 and high cytotoxicity of CD8+ T cells as reported by Xu *et al.*, albeit the fact that their patient developed ARDS and hence had severe COVID-19 (Xu, Z. *et al*, 2020).

Of relevance to our current report is the publication by Zulfiqar *et al.* (Zulfiqar *et al*, 2020) wherein they presented a patient with "de-novo" ITP developing after infection with SARS-CoV-2. It is to be highlighted that the patient in their report had autoimmune hypothyroidism and received low molecular weight heparin, which might have contributed to the thrombocytopenia. Likewise, "de-novo" ITP with COVID-19 infection was diagnosed in recently published case reports, one of whom was a pregnant lady in her 3rd trimester (Bomhof *et al*, 2020; Kim *et al*, 2020). To the best of our knowledge, our report is the first of ITP flare in a patient with COVID-19.

To conclude, we reported a case of a pregnant patient known to have ITP who developed a flare of her disease in the context of mild COVID-19 infection. Although, COVID-19 remains a primarily

respiratory disease, extra-pulmonary manifestations are increasingly recognized and vigilance is needed to detect these in an effort to mitigate complications.

Disclosure and competing interests statement

None

Authors' contributions

GN: collected the data and wrote the manuscript.

CG, CB, SA: critically reviewed the manuscript.