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Clinical characteristics, management and outcome of COVID-19-associated immune thrombocytopenia: a French multicentre series

The causes of secondary immune thrombocytopenia (ITP), which account for approximately 18–20% of all adult ITP cases, include some viral infections.[1,2] Indeed, ITP can be triggered by or associated with many viruses including hepatitis C virus, human immunodeficiency virus, cytomegalovirus, Epstein–Barr virus and others like severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1).[1,3–5] Among the suspected mechanisms, antibodies directed against virus glycoproteins may cross-react with platelet surface integrins like glycoprotein IIb/IIIa (GPIIb/IIIa) or GPIb-IX-V.[6]

Mild thrombocytopenia has been observed in approximately 5–10% of patients with symptomatic SARS-CoV-2 infection.[7] Various mechanisms have been suggested, including decreased platelet production and enhanced platelet destruction, as for other viral infections.[5,8] Recently, a member of our network reported the first case of severe ITP associated with coronavirus disease 2019 (COVID-19).[9] Three

Table I. Characteristics and outcomes of the 14 COVID-19-induced immune thrombocytopenia patients.

Patient	Age (years), sex	COVID-19 symptoms	Time from 1st COVID-19 signs to ITP, days	Time from COVID-19 RT-PCR to ITP, days	Severity of COVID-19 (WHO score)	Lowest platelet count, $\times 10^9$/l	Bleeding	ITP treatment	ITP outcome	COVID-19 outcome	Follow-up, days
#1	58, F	Fever, cough	10	8	4	2	Purpura, epistaxis, oral haemorrhagic bullae	IVIg (D1, D5) then eltrombopag until D28	Complete response	Recovery	40
#2	66, M	Fever, cough, anosmia, dyspnoea, hypoxaemia, moderate pneumonia on CT-scan	13	3	5	1	Epistaxis	IVIg (D1, D3) then eltrombopag until D15	Complete response	Recovery	52
#3	62, F	Fever, cough, moderate pneumonia on CT-scan	5	9	4	9	No	Prednisone 5 days	Response then relapse (D58)	Recovery	60
#4	62, M	Dyspnoea, minor pneumonia on CT-scan	2	Concomitant	3	<10	No	Prednisone 3 days	Complete response	Recovery	60
#5	74, M	Fever, cough pneumonia on CT-scan	12	6	5	<1	Purpura, mucosal bleeding, gastrointestinal bleeding	Prednisone 10 days	Complete response	Recovery	50
#6	63, M	Fever, cough, dyspnoea, hypoxaemia, moderate pneumonia on CT-scan	23	12	5	10	No	Prednisone 3 weeks	Complete Response	Recovery	60
#7	65, M	Fever, minor pneumonia on CT-scan	22	1	4	17	0	Dexamethasone (D1–D4)	Complete response then relapse (D30)	Recovery	60
#8	66, F	Fever, cough, dyspnoea, hypoxemia, moderate pneumonia on CT-scan	8	5	5	8	Purpura, epistaxis, intracranial bleeding	Methylprednisolone + IVIg (D1–D3) + eltrombopag until D15	Complete response	Recovery	60
#9	79, F	Fever, cough, dyspnoea, hypoxaemia, moderate pneumonia on CT-scan	16	5	5	9	Purpura	IVIg (D1–D3)	Response	Recovery	30
#10	59, F	Fever, cough, dyspnea, moderate pneumonia on CT-scan	30	Negative RT-PCR	4	1	Purpura, mucosal bleeding	IVIg (D1–D3)	Response	Recovery	45
#11	61, F	Fever, cough, anosmia, dysgeusia, moderate pneumonia on CT-scan	25	12	5	21	Purpura	IVIg (D1–D3)	Response	Recovery	45

Table I. (*Continued*)

Patient	Age (years), sex	COVID-19 symptoms	Time from 1st COVID-19 signs to ITP, days	Time from COVID-19 RT-PCR to ITP, days	Severity of COVID-19 (WHO score)	Lowest platelet count, $\times 10^9$/l	Bleeding	ITP treatment	ITP outcome	COVID-19 outcome	Follow-up, days
#12	69, F	Fever, cough, dyspnoea, hypoxaemia, moderate pneumonia on CT-scan	14	8	4	<10	Purpura, epistaxis, subcutaneous haematomas, gross haematuria	IVIg (D1–D2) then			
Romiplostim on D2 and D8	Complete response	Recovery	63								
#13	53, M	Fever, cough, dyspnoea, Moderate pneumonia on CT-scan	27	Negative RT-PCR	3	19	Purpura	Prednisone 3 weeks IVIg (D1–D3)	Complete response then relapse (D35)	Recovery	50
#14	72, M	Fever, cough, dyspnoea, hypoxaemia, diarrhoea, moderate pneumonia on CT-scan	15	13	7	8	No	IVIg (D1–D3)	Complete response	Recovery	60

Abbreviations: CT, computed tomography; D, day; ITP, immune thrombocytopenia; IVIg, intravenous immunoglobulin; RT-PCR, reverse transcription-polymerase chain reaction.

other cases have been reported subsequently.[10,11] These single observations limit the interpretation of data, due to possible publication bias. To better characterise the clinical course, management and response to therapy of *de novo* ITPs occurring after SARS-CoV-2 infection, we recorded the incident cases that occurred up to 30 April 2020 in France in centres belonging to the French Reference Network for Adult Autoimmune Cytopenias (Table SI. ITP was defined according to the International Working Group definition with no evidence of any other cause of thrombocytopenia such as disseminated intravascular coagulation.[12] We focussed on patients with profound thrombocytopenia, that is: a platelets count nadir of $<30 \times 10^9$/l during the course of the disease to reduce the potential number of sepsis-induced thrombocytopenia.[13] Response and complete response (CR) were defined according to standardised international criteria: platelet count of $>30 \times 10^9$/l with at least a doubling of the baseline value, and platelet count of $>100 \times 10^9$/l respectively. According to French law and European Union general data protection regulations, all patients were informed about the study and data collection by a written letter detailing their rights.

We included 14 patients with a reverse transcriptase-polymerase chain reaction (RT-PCR)-confirmed SARS-CoV-2 infection on a nasopharyngeal swab ($n = 12$) or a highly suggestive feature of COVID-19 on chest computed tomography (CT)-scan with compatible clinical symptoms ($n = 2$). Patients' characteristics are described in **Table I**. The median (range) age was 64 (53–79) years and seven patients (50%) were women. The median (range) time from first COVID-19 manifestations to first ITP manifestation was 14 (2–30) days; it was >7 days in 12 (86%) cases. In four patients (#3, #4, #10 and #12), a SARS-CoV-2 RT-PCR was performed at the time of ITP onset: it was positive in two of them, demonstrating an active viral shedding, and negative in the two others, including one with a previous positive RT-PCR at the time of infection (patient #12). Seven patients (50%) had a hypoxaemic pneumonia corresponding to a World Health Organization (WHO) progression score of ≥5. The outcome of COVID-19 was favourable in all cases. Only one patient was admitted to the Intensive Care Unit (ICU) due to acute respiratory failure (patient #14). No deaths occurred.

Regarding ITP, all patients but one had initial a platelet count of $<20 \times 10^9$/l and 11 patients had a platelet count of $\leq 10 \times 10^9$/l. In all cases, either a previous normal platelet count was obtained or the patient had no previous history of bleeding. Haemorrhagic manifestations were heterogeneous. Noteworthy, four patients had severe bleeding symptoms, including intracranial haemorrhage, gastrointestinal, severe metrorrhagia and gross haematuria (one of each). Of note, three other patients had mucosal bleeding. One patient (#4) was diagnosed concomitantly with chronic lymphocytic leukaemia. First-line treatment consisted of corticosteroids alone (i.e. prednisone 1 mg/kg/day) for four patients who achieved an initial response after a median (range) of 10 (5–21) days. One patient who received 40 mg of dexamethasone for 4 days also achieved CR on Day 5. Importantly, none of these five patients had a worsening of COVID-19 pneumonia. Intravenous immunoglobulin (IVIg; 1–2 g/kg) was administered to nine patients, alone in four patients, or associated with a thrombopoietin receptor agonist (romiplostim, $n = 1$; eltrombopag, $n = 2$; eltrombopag + methylprednisolone, $n = 1$) or with prednisone ($n = 1$). All achieved a rapid initial response. After a median (range) follow-up of 60 (30–63) days, all patients achieved at least a response (nine CR and three response), but three had relapsed. No thrombosis was observed.

This first multicentre series reveals that COVID-19-associated ITP occurs mostly during the second phase (after 1 week of evolution) of SARS-CoV-2 infection, with significant bleeding and a favourable outcome. In all patients, an immune mechanism was suspected because of the exclusion of alternative causes, in particular no evidence of sepsis-induced thrombocytopenia (the only patient in ICU dramatically responded to IVIg) and disseminated intravascular coagulation. Post-infectious ITP has been described in many infectious contexts after the first week of infection.[1,3–5] Importantly, we have excluded other viral causes of ITP, and the occurrence of other viruses, such as influenzae, have been dramatically reduced during the containment in France as in other countries.[14]

Here, the causal relationship between SARS-CoV-2 infection and ITP was supported by several points: 1) the time of occurrence (after the first week of infection as reported for other virus-induced ITPs); 2) the exclusion of alternative causes, in particular no evidence of sepsis-induced thrombocytopenia (the only patient in ICU dramatically responded to IVIg) and disseminated intravascular coagulation; 3) the dramatic response to steroids or IVIg; 4) the low rate of recurrence as usually observed in ITP triggered by acute viral infections; 5) the very low number of newly diagnosed ITP during the lockdown in France.

Interestingly, it has been recently shown that patients with severe COVID-19 pneumonia produce a very large quantity of antibody secreting cells during the second week after first symptoms, in contrast to patients with few symptoms who did not.[15,16] The short time between COVID-19 first symptoms and ITP onset in some patients of our present series suggests the presence of extrafollicular B-cell generating cross-reactive antibodies against platelets. In contrast, delayed ITP and ITP relapses evoke a germinal centre response resulting in persistent pathogenic antibodies secretion.[17] Thus, like other viruses, COVID-19 may be responsible for transient resolutive ITP, but also for triggering a tolerance breakdown potentially leading to persistent or chronic ITP. Indeed, three patients relapsed during follow-up. The exact causative mechanism of thrombocytopenia remains speculative, and needs further experimental studies.

Because of the high incidence of thromboembolic events in patients with severe COVID-19,[18] it is reassuring that we did not observe any thrombosis, including in patients

receiving corticosteroids, IVIg and thrombopoietin receptor agonists during the first 2 months of follow-up. Similarly, no patient treated with corticosteroids had worsening of COVID-19 pneumonia. Altogether, these findings sustain recent British guidance that recommend first-line treatment with corticosteroids for SARS-CoV-2-associated ITP.[19]

The present retrospective study has some limitations. Two patients had a negative SARS-CoV-2 RT-PCR. However, the sensitivity of nasopharyngeal swab RT-PCR is only approximately 70% and these two patients had clinical symptoms and a CT-scan pattern of COVID-19.[20] Albeit using the National Reference Centre Network for Adult Immune Cytopenias that covers the whole French territory, we cannot ensure completeness of case recording. Moreover, because the defined platelet-count threshold was $<30 \times 10^9$/l to be included in this series, the number of COVID-19-associated ITP may have been underestimated. Nevertheless, the prevalence of COVID-19-associated ITP is probably rare. Indeed, a mathematical model estimated that 3·7 million (range 2·3–6·7) people have been infected in France.[21]

Altogether, this series highlights that COVID-19-associated ITP can cause profound thrombocytopenia and severe bleeding manifestations occurring mostly during the second phase of the infection, but has a favourable outcome in most cases. Initial response to standard ITP treatments seems very good, with no strong safety signal and especially in regard to the risks of thrombosis and of bacterial infection.

Conflict of interest

Matthieu Mahévas received research grants from GSK, and meeting attendance grants from GSK and Amgen. Guillaume Moulis received research grants form CSL Behring, Novartis, Grifols, and meeting attendance grants from Amgen and Novartis. Lionel Galicier participated to educational boards for GSK. Bertrand Godeau received research grant from Amgen, and Bertrand Godeau served as an expert for Amgen, Novartis, LFB and Roche. Mikael Ebbo has participated in advisory boards for Amgen, Grifols GSK and Novartis.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table SI. Number of patients recorded in this series by participating centres in the network.

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Single-cell oxygen saturation imaging shows that gas exchange by red blood cells is not impaired in COVID-19 patients

SARS-CoV-2 coronavirus infection is characterised by a marked inflammatory state and viral pneumonitis. A striking clinical feature is severe hypoxaemia, often in the presence of near-normal lung mechanics. Several hypotheses have been put forward to explain these findings,[1,2] including pulmonary microvascular thrombosis, dysregulated hypoxic pulmonary vasoconstriction and dysfunctional gas transport by red blood cells (RBCs). Derangement in convective O_2 transport is an attractive hypothesis as this would explain why COVID-19 hypoxaemia is often refractory to supplemental oxygen. A controversial *in silico* prediction postulated that the virus attacks haemoglobin (Hb),[3] and despite subsequent criticism,[4] a number of hypotheses have emerged linking Hb with COVID-19, such as the association between thalassaemias or fetal Hb with disease severity.[5–7] Notwithstanding these opinions, studies in China have confirmed modestly lower Hb levels in severe COVID-19[8,9] and greater heterogeneity in terms of RBC volume, quantified as RBC Distribution Width-Standard Deviation (RDW-SD).[10]

In a recent letter to this Journal, Hb oxygen affinity was shown to be unaltered in a cohort of 14 patients infected with SARS-CoV-2.[11] However, steady-state measurements of affinity cannot predict the kinetics of gas exchange by RBCs, which may become rate-limiting in COVID-19 due to impaired perfusion of the injured lung and inflammation-triggered RBC deformations that expand intracellular diffusion path length. Moreover, measurements on whole blood report an ensemble population average, which cannot resolve the presence of small subpopulations of dysfunctional RBCs, if these emerge in COVID-19. Indeed, given that RDW-SD increases in COVID-19, O_2 handling must be interrogated with cellular resolution.

We recently designed single-cell oxygen saturation imaging to assess O_2 unloading kinetics and O_2 storage capacity on a cell-by-cell basis.[12] We now applied this technique to study blood from COVID-19 patients at the John Radcliffe Hospital, Oxford, UK. Ten SARS-CoV-2-positive patients [9/10 confirmed by polymerase chain reaction (PCR) result, remaining patient diagnosed clinically] were recruited to this study through the Oxford GI Biobank (ethics 16/YH/0247). In half of the patients, blood was sampled within the first two weeks of diagnosis, and for the other half, sampling was in the subsequent fortnight. Three patients were asymptomatic healthcare workers, identified by voluntary PCR testing, and the