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, × 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, dysnoea, 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 | 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, dysnoea, 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 | Recovery | 60            |
| #8      | 66, F             | Fever, cough, dysnoea, hypoxaemia, 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, dysnoea, hypoxaemia, moderate pneumonia on CT-scan | 16                                       | 5                                      | 5                               | 9                               | Purpura | IVIg (D1–D3) | Response | Recovery | 30            |
| #10     | 59, F             | Fever, cough, dysnea, 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, x 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 haematoma, gross haematuria | IVIg (D1–D2) then |
|         |                  |                    |                                           |                                        |                                 |                                  |          |                |              |                 |                 |
| #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. 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 de novo definition. Cases that occurred up to 30 April 2020 in France in centres 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. 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. 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. 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. 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, it is reassuring that we did not observe any thrombosis, including in patients
receiving corticosteroids, IVlg 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 × 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 CSL Behring, Novartis, LFB and Roche. Mikael Ebbo has participated in advisory boards for Amgen, and Bertrand Godeau served as an expert for Amgen, for GSK. Bertrand Godeau received research grant from Novartis. Lionel Galicier participated to educational boards for Grifols, and meeting attendance grants from Amgen 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, 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), and despite subsequent criticism, a number of hypotheses have emerged linking Hb with COVID-19, such as the association between thalassaemias or fetal Hb with disease severity. Notwithstanding these opinions, studies in China have confirmed modestly lower Hb levels in severe COVID-19 and greater heterogeneity in terms of RBC volume, quantified as RBC Distribution Width-Standard Deviation (RDW-SD).

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. 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$_2$ transport 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. 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 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