Presence of antiphospholipid antibodies in COVID-19: case series study

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and its associated coagulopathy are particularly worrisome in patients with systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS), as these diseases carry an increased risk of thrombotic complications. Mathian et al recently reported the clinical course of COVID-19 in a series of 17 patients with SLE under chronic hydroxychloroquine therapy.1 Of note, only one patient (6%) presented thrombosis despite the fact that four patients (24%) had a history of secondary APS, and five patients (29%) were receiving oral anticoagulants. Antiphospholipid (aPL) antibodies were not measured in these patients during active SARS-CoV-2 infection.1

The American Society of Hematology recently stated that ‘at the current time, there are only very limited data on aPL antibodies in COVID-19 and it is unclear if they represent an epiphenomenon or are actually involved in any haemostatic abnormalities seen in COVID-19 disease’.2 Furthermore, almost all the available information refers to the lupus anticoagulant, with frequencies ranging from 45% to 87%.3–4 This paucity of data led us to test a panel of aPL antibodies in blood specimens from 21 patients hospitalised in the intensive care unit between 12 and 19 April, due to severe or critical COVID-19, and received at our laboratory on 20 April to measure interleukin-6 levels. Anticardiolipin, anti-β 2 glycoprotein I, antiprothrombin, antiphosphatidylserine, antiphosphatidylinositol and antianiannexin V antibodies were measured, each in IgM and IgG isotypes. Subsequently, demographic and clinical data were obtained from electronic medical records. Sera collected before the SARS-CoV-2 pandemic from 12 healthy individuals, matched for age and sex, were tested as controls.

Pertinent results are summarised in table 1. The median age of patients was 62 years; 43% were men; and a high number of comorbidities were observed (median Charlson Comorbidity Index of 3). A total of 19 patients (90%) had shortness of breath on admission, and 12 (57%) eventually required invasive mechanical ventilation during hospitalisation. Elevated levels of D-dimer, ferritin and C reactive protein were found at presentation.

Of the 21 patients with COVID-19 studied, 12 had at least one circulating aPL antibody, whereas only 1 of the 12 controls yielded a positive result (57% vs 8%; Fisher’s exact test, p=0.009). The most frequently detected aPL antibodies were antianiannexin V IgM (19%), anticardiolipin IgM (14%), antiphosphatidylserine IgM (14%), anticardiolipin IgG (10%) and antiphosphatidylserine IgG (10%) antibodies. One patient had triple positivity (8%); three patients had double positivity (25%); and the remaining eight had a single positivity (67%). Age and number of comorbidities tended to be lower in patients with aPL antibodies. In contrast, levels of D-dimer, ferritin and C reactive protein were higher both on admission and throughout the hospital stay in these patients. Elevated levels of interleukin-6 (>40 pg/mL) were found only in patients with aPL antibodies. The type of therapies administered in both groups was similar, except for a greater number of patients with aPL antibodies who received glucocorticoids (50% vs 0; Fisher’s exact test, p=0.018).

The occurrence of hospital outcomes was followed up to 30 days after aPL antibody measurement. Two patients presented pulmonary thromboembolism despite being on heparin: a 28-year-old man with a previous diagnosis of

![Table 1: Main clinical and laboratory data of 21 patients with severe or critical COVID-19](image)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Total (N=21)</th>
<th>Positive aPL antibodies (n=12)</th>
<th>Negative aPL antibodies (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, n (%)</td>
<td>9 (43)</td>
<td>3 (25)</td>
<td>6 (50)</td>
</tr>
<tr>
<td>Days of symptom onset</td>
<td>7 (5–9)</td>
<td>7 (5–9)</td>
<td>7 (5–8)</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td>3.0 (1.0–4.0)</td>
<td>1.0 (0.0–3.0)</td>
<td>4.0 (2.0–5.0)</td>
</tr>
<tr>
<td>Coexisting conditions, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>12 (57)</td>
<td>5 (42)</td>
<td>7 (78)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>8 (38)</td>
<td>3 (25)</td>
<td>5 (44)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>7 (33)</td>
<td>3 (25)</td>
<td>4 (44)</td>
</tr>
<tr>
<td>Obesity</td>
<td>7 (33)</td>
<td>5 (42)</td>
<td>2 (22)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>3 (14)</td>
<td>2 (17)</td>
<td>1 (11)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1 (5)</td>
<td>0</td>
<td>1 (11)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>2 (10)</td>
<td>2 (17)</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>2 (10)</td>
<td>2 (17)</td>
<td>0</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>3 (14)</td>
<td>1 (8)</td>
<td>2 (22)</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>2 (10)</td>
<td>0</td>
<td>2 (22)</td>
</tr>
<tr>
<td>Cancer</td>
<td>1 (5)</td>
<td>0</td>
<td>1 (11)</td>
</tr>
</tbody>
</table>

Main findings at hospital admission

- Fever, n (%) | 13 (62) | 7 (58) | 6 (67)
- Shortness of breath/respiratory distress, n (%) | 19 (90) | 12 (100) | 7 (78)
- White cell count (<10 3 per mm 3) | | |
  | 6.5 (4.9–10.4) | 7.0 (5.4–12.1) | 6.2 (4.9–9.6)
- Platelet count (<10 3 per mm 3) | | |
  | 179 (146–198) | 179 (156–193) | 171 (143–240)
- D-dimer (ng/mL) | 339 (177–484) | 387 (207–484) | 303 (132–446)
- Ferritin (μg/L) | 557 (156–882) | 677 (490–1249) | 199 (112–326)
- C reactive protein (mg/L) | 139 (57–210) | 200 (95–256) | 86 (57–144)
- Intubation, n (%) | 12 (57) | 7 (58) | 5 (54)

Laboratory values at the time of aPL measurements

- White cell count (<10 3 per mm 3) | | |
  | 7.8 (6.9–10.6) | 8.6 (6.7–13.2) | 6.4 (5.7–9.8)
- Platelet count (<10 3 per mm 3) | | |
  | 260 (212–349) | 262 (207–332) | 259 (229–349)
- D-dimer (ng/mL) | 417 (216–613) | 437 (206–601) | 403 (278–621)
- Ferritin (μg/L) | 604 (265–1353) | 1038 (580–1392) | 443 (237–547)
- C reactive protein (mg/L) | 90 (71–219) | 140 (80–279) | 39 (17–129)
- Serum interleukin-6 levels>40pg/ ml, n (%) | 2 (10) | 2 (17) | 0

Treatment, n (%) | | |

- Heparin | 18 (86) | 9 (75) | 9 (100)
- Glucocorticoids | 6 (29) | 6 (50) | 0
- Hydroxychloroquine | 15 (71) | 9 (75) | 6 (67)
- Azithromycin | 18 (86) | 10 (84) | 8 (89)
- Lopinavir plus ritonavir | 11 (52) | 6 (50) | 5 (54)

Positive aPL antibodies, n (%) | | | |

- Anticardiolipin IgM | 3 (14) | 3 (25) | 0
- Anticardiolipin IgG | 2 (10) | 2 (17) | 0
- Anti-β 2 glycoprotein I IgM | 0 | 0 | 0
- Anti-β 2 glycoprotein I IgG | 1 (5) | 1 (8) | 0
- Antiprothrombin IgM | 1 (5) | 1 (8) | 0
- Antiprothrombin IgG | 0 | 0 | 0
- Antiphosphatidylserine IgM | 3 (14) | 3 (25) | 0
- Antiphosphatidylserine IgG | 2 (10) | 2 (17) | 0
- Antiphosphatidylinositol IgM | 0 | 0 | 0
- Antiphosphatidylinositol IgG | 0 | 0 | 0
- Antianiannexin V IgM | 4 (19) | 4 (33) | 0
- Antianiannexin V IgG | 1 (5) | 1 (8) | 0
- Pulmonary thromboembolism | 2 (10) | 2 (17) | 0
- Major bleeding, n (%) | 1 (5) | 1 (8) | 0
- Ventilator-associated pneumonia, n (%) | 3 (14) | 1 (8) | 2 (22)
- In-hospital deaths, n (%) | 4 (19) | 2 (17) | 2 (22)
- Discharged, n (%) | 13 (62) | 9 (75) | 4 (44)

Data are presented as median (IQR) unless otherwise specified. aPL, antiphospholipid.
idiopathic pulmonary hypertension who had anticardiolipin IgG antibodies and a 63-year-old woman with a history of Fahr syndrome and hypoparathyroidism who had antianiannxin V IgM antibodies. Both patients had extremely high levels of D-dimer and C reactive protein throughout the follow-up and eventually died of haemodynamic complications. Necropsy studies were not performed. Despite the fact that most patients received heparin, the only clinically significant bleeding was spontaneous retroperitoneal haematoma in a 44-year-old man with antiphosphatidylserine IgM and antianiannxin V IgM antibodies who recovered with conservative management. Two patients in whom no aPL antibodies were observed eventually died of multisystem organ failure. As of 18 May, 13 patients (62%) had been discharged from the hospital; 4 (19%) remained hospitalised; and 4 (19%) died.

In this case series study, a high frequency (57%) of both ‘criteria and non-criteria’ aPL antibodies was found in patients with severe and critical COVID-19. These aPL antibodies appear to be associated with a hyperinflammatory state characterised by extremely high levels of ferritin, C reactive protein and interleukin-6; meanwhile, an association with pulmonary thromboembolism may be suggested. During acute infection, thrombosis or inflammation, different aPL antibodies may transiently arise, and it should not be assumed that a patient with COVID-19-associated coagulopathy and aPL antibodies has catastrophic APS. Indeed, although COVID-19-associated coagulopathy and catastrophic APS may share clinical and laboratory features, both diseases are likely to have a different underlying pathophysiology. However, the high frequency and wide variety of aPL antibodies observed in patients with COVID-19 cannot be ignored.

Currently, there are limited data on the occurrence of aPL antibodies during SARS-CoV-2 infection, and further studies are required to determine whether these represent a simple epiphenomenon or are actually involved in COVID-19-associated coagulopathy.

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