Case report

Extensive cerebral venous sinus thrombosis: a potential complication in a patient with COVID-19 disease

Paul Bolaji, Babatunde Kukoiyi, Nasar Ahmad, Chris Wharton

SUMMARY

A 63-year-old man was admitted with left-sided weakness and subsequent focal seizures following a recent diagnosis of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia in a nearby hospital. He developed status epilepticus and became comatose, requiring intensive care unit admission for invasive ventilation. Imaging done at admission confirmed extensive cerebral venous sinus thrombosis (CVST) with bilateral venous cortical infarcts and acute cortical haemorrhage. No known risk factor for CVST could be identified. He improved with anticoagulation and antiepileptic therapy. He was subsequently transferred to an inpatient rehabilitation facility. Although Coronavirus disease 19 (COVID-19) infection has been previously associated with thrombotic complications, these mostly relate to the pulmonary vasculature. We present this case as a potential association between CVST and COVID-19 infection.

BACKGROUND

COVID-19 disease is a worldwide pandemic that has affected over 8 million people globally as of 18 June 2020. Severe disease is associated mainly with pneumonia, but several non-respiratory complications have been observed in case series and reports. COVID-19 disease has been associated with ischaemic stroke, seizures and encephalopathy. However there are very few reports of COVID-19 associated cerebral venous sinus thrombosis (CVST) in the published literature.

CVST is a rare disease. There are several known genetic and acquired risk factors for CVST. CVST has a good prognosis when treated promptly but can be fatal when not treated.

INVESTIGATIONS

The patient had brain imaging with plain CT and CT venogram (figures 1 and 2, respectively) at admission that revealed extensive venous sinus thrombosis with bilateral venous cortical infarcts and acute cortical haemorrhage.

D-dimers were significantly elevated. Protein C, S and antithrombin III levels were reported as normal. Factor V Leiden mutation was negative, however, anticardiolipin IgG antibodies were positive. Lupus anticoagulant was moderately positive, however, antiphospholipid IgG antibodies were normal in room air. The antinuclear antibody was negative (table 1). Alanine transaminase was initially elevated at admission (table 1). However, it normalised before discharge. Other components of the liver function tests, electrolytes, urea and creatinine were within normal limits.

He was rescreened for COVID-19 infection in our hospital and the SARS-CoV-2 virus was detected from nasopharyngeal swab sampling. Repeat chest X-ray at admission showed patchy bilateral ground-glass consolidation consistent with COVID-19 pneumonia. Chest X-ray, routine blood tests and other clinical findings were not suggestive of malignancy.

TREATMENT

Therapeutic doses of low-molecular-weight heparin and levetiracetam were commenced at admission.
A few hours later, he developed convulsus status epilepticus which was treated with intravenous lorazepam and intravenous phenytoin. He required intubation and was managed in the intensive care unit. He did not have any further seizure episodes and we were able to extube him after 4 days. He was then transferred to the stroke unit for further management.

In the stroke unit, he was managed by a multidisciplinary stroke team with inpatient rehabilitation including speech and language therapy, physiotherapy and occupational therapy. He made steady improvement and low-molecular-weight heparin was continued for therapeutic anticoagulation. This was subsequently changed to edoxaban as advised by the haematologist while he was at the rehabilitation facility.

OUTCOME AND FOLLOW-UP
He was transferred to continue further inpatient treatment in a rehabilitation centre closer to his primary residence with a plan to continue anticoagulation for 6 months. His mobility and ability to perform activities of daily living improved and he was able to walk with a cane in the rehabilitation centre. He was discharged home from the rehabilitation centre about 3 weeks after his initial presentation in our hospital.

DISCUSSION
CVST is an uncommon condition.3 The annual incidence in studies ranges between 1.32 and 1.57 per 100 000.4 5 It is more common in the younger population and more prevalent in women than men.7 CVST can present broadly as three clinical syndromes: isolated intracranial hypertension (headache, papilloedema and visual problems), encephalopathy (mental status change, widespread neurological signs and coma) and focal syndrome (with seizures reported in 39.3%, paresis in 37.2% and aphasia in 19.1%).3–6 CVST can cause stroke due to focal cerebral infarction and haemorrhage that is seen on brain imaging in 46.5% and 39.3% of presentations, respectively.7 Urgent neuroimaging with cranial CT and CT venography or magnetic resonance venography are recommended for diagnosis, and initial treatment with heparin anticoagulation favoured (even in the presence of intracerebral haemorrhage), resulting in a good outcome for 80% and mortality of <5% in the Western world.8

The risk factors that predispose individuals to CVST are also seen in other forms of venous thromboembolism. Risk factors like oral contraceptive use, pregnancy and puerperium might explain the increased prevalence of CVST in women in comparison with men.2 Genetic predisposition to thrombophilia might also be detected in people with CVST like protein C, S and antithrombin III deficiency, factor V Leiden and prothrombin G20210A gene mutations.9 Other risk factors are connective tissue disease, local infections of the head, neck and sinuses and malignancy especially in the older population.10 However, a study showed that in up to 12.5% of cases, no risk factor is identified.7 The absence of an established risk factor makes COVID-19 disease a strong potential aetiological factor for developing CVST in our patient presented in this case.

COVID-19 disease has multi-systemic manifestations, one of which includes a high prevalence of venous thromboembolism. In some case series, the incidence of venous thromboembolism ranged between 25% and 27% of patients with severe COVID-19 infection.11 12 This prothrombotic state is not only limited to severe COVID-19 disease. In a recent retrospective study conducted by Han et al,13 coagulation parameters like raised D-dimers, fibrin degradation products and high fibrinogen were found to be correlated with the severity of the COVID-19 infection. These coagulation parameters were also noted to be raised in milder infection compared with healthy controls.

The mechanism of this thrombophilic state in SARS-CoV-2 infection has not been fully elucidated. However, several putative mechanisms have been proposed. The cytokine storm in

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**Table 1** Summary of blood tests requested during admission

| Blood tests                  | Value  | Reference range |
|------------------------------|--------|-----------------|
| Haemoglobin (g/L)            | 130    | 130–180         |
| White cell count (x10⁹/L)    | 8.0    | 4.0–11.0        |
| Lymphocyte count (x10⁹/L)    | 1.1    | 1.5–4.5         |
| C-reactive protein (mg/dL)   | 60     | 0–5             |
| ALT (IU/L)                   | 91     | <56             |
| International normalised ratio | 1.1 |             |
| Fibrinogen (g/L)             | 5.68   | 1.50–4.5        |
| D-dimers (mg/L, FEU)         | 4.77   | 0.15–0.45       |
| Ferritin (ng/mL)             | 610.0  | 22–275          |
| Protein S (IU/mL)            | 134    | 60–140          |
| Protein C (IU/mL)            | 84     | 70–130          |
| Antithrombin III (IU/mL)     | 116    | 80–120          |
| Factor V Leiden mutation     | Absent |                     |
| Prothrombin gene mutation (G20210A) | Absent |                     |
| Antinuclear antibody         | Negative |                                      |
| Lupus anticoagulant          | Moderately present |                     |
| Anticardiolipin IgG (GPL)    | 4.1    | 0–10            |

ALT, alanine transaminase; IgG, immunoglobulin G.
Unusual association of diseases/symptoms

severe inflammatory response syndrome seen in COVID-19 disease can induce a procoagulable state. It is also considered that SARS-CoV-2 could have some specific procoagulant effects independent of the cytokine storm, especially with its tropism for angiotensin converting enzyme 2 (ACE2) receptor that is present in the endothelium of blood vessels. A case series has also reported the association of COVID-19 disease with cerebral infarction and raised antiphospholipid antibodies, which was similarly noticed in the blood profile of our patient. Such a link between antiphospholipid antibodies and thrombotic complications of SARS-CoV-2 could also explain the prothrombotic state in COVID-19 disease, but transient rises in antiphospholipid antibodies in acute illness are known to cause false positives.

There have been a few specifically reported cases of CVST and COVID-19 disease in literature apart from the more published associations with pulmonary embolism and deep venous thrombosis. initially reported CVST in a 59-year-old man who was COVID-19 positive. In a more recent case series of three patients, Calvacanti et al. reported CVST in patients younger than 41 years of age with COVID-19 disease. However, these patients were not reported to have been screened for genetic thrombophilia, and one of them was on oestrogen replacement therapy. The extensive thrombophilia screening for conditions associated with CVST and their absence in our patient goes further to validate the association between COVID-19 and CVST in our patient.

It is plausible that cases could have been under-reported as clinicians may not have considered CVST as a cause of neurological symptoms in patients with COVID-19 disease. The neurological presentations of CVST are not specific to the condition. It is the presence of a known risk factor with either the insidious presentation of significant headache or encephalopathy or with sudden onset seizure or stroke symptoms that often prompt more focused investigation for CVST. For primary care and ED professionals, these neurological symptoms may serve as a red flag for requesting advanced neuroimaging beyond plain CT scans for patients with COVID-19 disease.

In conclusion, we suggest that clinicians consider the possibility of CVST in patients with neurological symptoms who test positive for SARS-CoV-2 to expedite prompt recognition and management of this condition.

Contributors PB: managed the patient, conceived the idea of the case report, was involved in planning, literature search and referencing for the case report, wrote the initial draft of the case report, revised the case report and approved the final draft of the case report; is the guarantor. BK: managed the patient, conceived the idea of the case report, was involved in planning the case report, wrote the initial draft of case report, took consent from the patient, revised the case report and approved the final draft of the case report. NA: managed the patient, was involved in planning the case report, revised, critically analysed the initial draft, did literature search and approved the final draft of the case report. CW: managed the patient, was involved in planning the case report, revised, critically analysed the initial draft and approved the final draft of the case report.

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Patient perspective

Honestly, it all seemed like a blur to me. I do not remember being in ICU.

It was only 5 or 6 days later I realised where I was. It just started coming back to me a little bit at a time.

I think I have done quite well from where I was, my left side is a bit weak but it is all working, so I am glad about that.

The nurses said I have done well because I beat COVID-19 and more or less beat the stroke as well.

Learning points

- COVID-19 disease can present with thrombotic complications including cerebral venous sinus thrombosis (CVST).
- SARS-CoV-2 infection may cause CVST and other venous thromboembolism either through increased cytokine and clotting factors production or direct endothelial injury through binding to the ACE2 receptor.
- Neurological symptoms like headaches, seizures and focal neurological deficits in patients with COVID-19 disease should be considered as red flags for CVST.
- Clinicians should have a low threshold for requesting advanced neuroimaging beyond a plain CT scan to aid prompt diagnosis of CVST.
- CVST is associated with the good functional outcome despite the severity of neurological deficit if patient are treated early with anticoagulation and complications like status epilepticus are addressed.

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