# Severe acquired haemophilia associated with asymptomatic SARS-CoV-2 infection

Kevin Y Wang,[1] Pratik Shah,[1] Dennis T Roarke,[2] Shams A Shakil[3]

[1]Department of Internal Medicine, NSLIJ Health System, New Hyde Park, New York, USA
[2]Department of Internal Medicine, Northwell Health, New Hyde Park, New York, USA
[3]Department of Hematology Oncology, Northwell Health, New Hyde Park, New York, USA

**Correspondence to**
Dr Kevin Y Wang;
Kevwangyu@gmail.com

Accepted 22 June 2021

## SUMMARY

A 65-year-old man presented with symptoms of severe subcutaneous bleeding in his arm, which led to compartment syndrome requiring fasciotomy and massive blood transfusion protocol. Medical history was significant for history of autoimmune thyroid disease. Workup revealed elevated partial thromboplastin time, decreased factor VIII levels and elevated factor VIII inhibitor levels. He was worked up for causes of acquired haemophilia A and was found to have an elevated SARS-CoV-2 antibody level. Given his negative workup for other secondary aetiologies, we suspect that the cause of his haemophilia A was from his SARS-CoV-2 infection, which has been observed previously in various case reports.

## BACKGROUND

Haemophilia A can present in patients as either congenital or acquired. While the differences in pathophysiology are intuitive, patients with congenital haemophilia A have a 20%–40% chance of developing antibodies to factor VIII during their lifetime usually in the setting of treatment. Contrasting this are patients who develop acquired haemophilia A, which is a rare disorder involving spontaneous development of these autoantibodies, which occur at a rate of one case/million/year.[1] With the novel SARS-CoV-2 virus, there is often a predilection for prothrombotic states; however, it has also been rarely associated with acquired haemophilia A.[2–7] Here, we present a case of severe acquired haemophilia A requiring massive blood transfusions in a patient who had an otherwise asymptomatic SARS-CoV-2 infection.

## CASE PRESENTATION

We are presenting a case of a 65-year-old man who presented to the hospital with acute shortness of breath, chest pain, and a 1-week history of atraumatic painful bruising underneath the skin. No history of prior respiratory infection was reported.

Medical history was significant for congestive heart failure (New York Heart Association stage 1), sick sinus syndrome with permanent pacemaker, chronic obstructive pulmonary disease and Hashimoto thyroiditis status post thyroidectomy around 30 years ago with postsurgical hypothyroidism on levothyroxine. The patient's social history was significant for former polysubstance abuse (former cocaine and heroin use, last use in 2019) and former smoking. Physical examination revealed a large, tense ecchymotic/purpuric plaque on the right upper arm, an oedematous right hand, paresthesias, diminished sensation of the fingers of the right hand, ecchymotic/purpuric plaques in the arm and forearm bilaterally and bleeding from his peripheral intravenous catheters.

## INVESTIGATIONS

Punch biopsy of the ecchymotic plaques of the left forearm revealed extravasation of erythrocytes consistent with haemorrhage in the dermis, no vasculitis or vasculopathic changes were seen. ECG was without acute ischaemic changes and high sensitivity troponin peaked at 597 ng/L (reference range <14 ng/L). Urine drug screen was negative.

The patient's haematological workup with initial blood tests and subsequent workup are referenced in table 1. Workup was significant for normocytic anaemia with haemoglobin level of 50 g/L on presentation with an elevated partial thromboplastin time (PTT) to 85 s with normal values of prothrombin time and international normalised ratio. Given the patient's elevated activated PTT (aPTT) levels, factor levels were checked and were significant for a factor VIII level <1. To see if this was due to a deficiency of factor VIII versus inhibition of the factor, mixing studies were conducted, which did not result in normalisation of PTT, indicating the presence of an inhibitor. Bethesda assay revealed factor VIII inhibitor levels of 176 Bethesda units. Bethesda unit levels and factor VIII assay were trended with treatment until Bethesda inhibitor reached 0 and factor VIII normalised after around 1 month from initial presentation. Blood tests were trended, white blood cell count and platelet count reached normal limits while haemoglobin stabilised at around 110 g/L.

CT chest, abdomen and pelvis revealed diffuse bilateral paraseptal pulmonary emphysema, a 4 mm right upper lobe nodule, right upper extremity 3.5×2.1 cm soft tissue collection suggestive of haematoma and a nodular contour of the liver suggestive of cirrhosis. Repeat CT chest, abdomen and pelvis with intravenous contrast 10 days after initial testing revealed unchanged findings with no evidence of thromboembolic disease in the pulmonary vasculature.

Other workup throughout the hospital stay included SARS-CoV-2 nasopharyngeal PCR test, which was negative on admission, and a Roche total SARS-CoV-2 antibody test, which was positive with a titre of 5.28 (negative ≤0.99 index). Thyroid stimulating hormone (TSH) was elevated at 45.9 mIU/mL (reference range 0.5–5) and free thyroxine (T4) was normal at 1 ng/dL (reference range 0.9–1.8). Autoimmune workup was negative, including antithyroid peroxidase antibody



**To cite:** Wang KY, Shah P, Roarke DT, *et al*. *BMJ Case Rep* 2021;**14**:e242884. doi:10.1136/bcr-2021-242884

**Table 1** Haematological workup

| Lab indices | Range | On admission | On discharge |
|---|---|---|---|
| White blood cell count | 3.8–10.5 x$10^9$/L | 27.39 | 7.15 |
| Red blood cell count | 4.2–5.8 x$10^{12}$/L | 2.22 | 3.5 |
| Haemoglobin | 130.0–170.0 g/L | 50 | 110 |
| Haematocrit | 39.0%–50.0% | 15.1 | 33.6 |
| Mean cell volume | 80.0–100.0 fl | 90.5 | 96 |
| Red cell distribution width | 10.3%–14.5% | 14.5 | 16 |
| Platelet Count | 150–400 x$10^9$/L | 127 | 281 |
| Prothrombin time | 10.6–13.6 s | 12.2 | 11.3 |
| International normalised ratio | 0.88–1.16 | 1.02 | 0.98 |
| Activated partial thromboplastin time (aPTT) | 27.5–35.5 s | 63.6 | 32.6 |
| D-dimer | <229 ng/mL | 672 | |
| aPTT 100% | 27.5–35.5 s | 74 | |
| aPTT 50/50 2-hour Incubation | 27.5–35.5 s | 71.9 | |
| aPTT 50/50 | 27.5–35.5 s | 44.1 | |
| Diluted thrombin time | 16.0–25.0 s | 24.7 | |
| Factor V level | 50%–150% | 114 | |
| Factor IX level | Report | Normal activity | |
| Factor II level | 80%–135% | 66 | |
| Factor VII level | 50%–165% | 77 | |
| Factor X level | 70%–170% | 77 | |
| Factor XI level | 70%–145% | 30 | |
| Factor XII level | 45%–150% | 36 | |
| Factor XIII level | 51%–163% | 37 | |
| Factor VIII assay | 60–125 | <1 | 96 |
| Inhibitor assay (Factor VIII) | 0.0–0.5 Bethesda unit | 176 | 0 |

(anti-TPO), antinuclear antibody, rheumatoid factor, cytoplasmic antineutrophil cytoplasmic antibody, perinuclear anti-neutrophil cytoplasmic antibody, antiSjogren Ro and La antibodies (SS-A, SS-B), histone antibody, anticardiolipin (IgM and IgG) antibody, beta 2 glycoprotein antibody, Jo-1 antibody, double-stranded DNA antibody and liver kidney microsomal antibody.

Malignancy serological workup revealed negative carcinoembryonic antigen, alpha-fetoprotein (AFP), prostate-specific antigen, kappa/lambda free light chain ratio, and anti-RI paraneoplastic antibody. Infectious workup revealed negative blood cultures and negative urine cultures. Hepatitis workup revealed negative hepatitis C antibody and virus RNA by PCR, negative hepatitis B core IgM antibody, negative hepatitis B surface antigen, reactive hepatitis B surface antibody, reactive hepatitis B core antibody, negative hepatitis B DNA by PCR, and negative hepatitis A IgM antibody. The patient was also negative for HIV-1/2 antigen/antibody screen, negative for cytomegalovirus (CMV) by PCR, positive for CMV IgG antibody, negative for CMV IgM antibody, positive for Epstein-Barr virus (EBV) capsid antigen IgG, positive EBV nuclear antigen, negative for EBV IgM antibody, positive for EBV early antigen and negative for herpes simplex 1 and 2 DNA by PCR.

## DIFFERENTIAL DIAGNOSIS

Based on the elevated PTT, low factor VIII levels, mixing study without correction and Bethesda inhibitor assay positive, a diagnosis of factor VIII inhibitor/acquired haemophilia A was made. This was believed to be the cause of the patient's spontaneous and traumatic haematomas and compartment syndrome as well as shortness of breath and chest pain secondary to symptomatic anaemia. The differential for the possible cause of the factor inhibitor, however, is wide and includes autoimmune disease-induced, malignancy-induced, idiopathic, infections and drug-induced.

Given the positive SARS-CoV-2 antibodies found in the patient's serum, with negative SARS-CoV-2 PCR test, we reasonably assumed that the patient suffered a previous SARS-CoV-2 infection prior to his current admission and this was perhaps the trigger for the production of factor inhibitor, especially with his underlying predisposition for autoimmunity given his history of autoimmune thyroiditis. While autoimmune Hashimoto thyroiditis may also trigger acquired haemophilia A,[8] it was treated with thyroidectomy around 30 years ago as well as continued levothyroxine and he appeared to be euthyroid on clinical examination. The patient also had negative anti-TPO antibody suggestive of inactive disease, and while the patient did have an elevated TSH, his normal free T4 was more suggestive of subclinical hypothyroidism, for which the patient's levothyroxine dose was adjusted. Otherwise, the patient's other autoimmune workup was extensive and negative for conditions such as lupus, rheumatoid arthritis, Sjogren's syndrome, systemic sclerosis, inflammatory myopathy, autoimmune hepatitis and vasculitis.

In terms of cancer workup, the patient was up-to-date with his age-appropriate cancer screening. In the hospital, CT scan of his chest, abdomen and pelvis revealed no signs of malignancy and a stable small pulmonary nodule. Of note, the patient's hepatitis testing revealed history of a prior hepatitis B infection and signs of cirrhosis on CT scan, but there were no signs to suggest hepatocellular carcinoma on imaging. AFP levels were also normal and neither ultrasound nor CT scan of the abdomen revealed any discrete liver lesions. Other infectious aetiologies which have been linked to haemophilia A were negative, including HIV, hepatitis C and tuberculosis, given an indeterminate interferon gamma release assay and negative symptoms or imaging findings of tuberculosis (TB). Infectious workup was also significant for a prior resolved EBV and CMV infection. In terms of drugs, the patient was not treated with any common medications associated with acquired factor VIII inhibitor production.

## TREATMENT

Surgical evaluation was concerning for compartment syndrome in the right upper extremity and the patient was treated with emergent fasciotomy. The patient's right upper extremity post fasciotomy wound was complicated by failed haemostasis and persistent extravasation of blood requiring eventual vacuum-assisted closure with continued drainage of blood throughout hospital stay. Three days post fasciotomy, the patient required massive transfusion protocol with a total of 22 units of packed red blood cells (pRBCs), 16 units of fresh frozen plasma (FFP), 7 units of platelets, 2 units of cryoprecipitate, and 3 units of factor VIII to stabilise his blood cell counts from blood loss through his right arm. The patient became acutely hypoxic secondary to his profound anaemia, and after transfusions, the patient's respiratory status improved and he no longer required supplemental oxygen as his acute hypoxic respiratory failure resolved. Treatment for the patient's haemorrhagic shock was initiated with activated recombinant human coagulation factor VII (Novo7), a factor VIII bypassing agent, every 3–4 hours at 90 mcg/kg for total dose of 707 mg until the patient's bleeding stabilised and he had stable haemoglobin counts, intravenous immunoglobulin 1 g/kg/day for a 2-day course, cryoprecipitate when needed for fibrinogen <150, and two units of cryoprecipitate with each factor VII injection to provide fibrinogen for factor VII to act

on, for a total of 161 units of cryoprecipitate. For elimination of the factor inhibitor, the patient was given methylprednisolone IV 1 mg/kg and transitioned to an oral prednisone taper, weekly rituximab for a 4-week course, and a 5-day course of cyclophosphamide 300 mg intravenously daily followed by an oral cyclophosphamide taper. On this regimen, the patient's factor VIII levels improved, but inhibitor levels remained high, and patient was then given factor VIII inhibitor bypass activity (FEIBA), another factor VIII bypassing agent, at 50 units/kg every other day until inhibitor levels reached 0 and the patient ceased having active bleeding (dosing was every other day to maintain haemostasis while balancing possible prothrombotic state). The patient received a total of two doses of FEIBA. For the rest of the hospital stay, the patient received an additional 16 units of pRBCs, 9 units of FFP, 9 units of platelets, and was continued on cyclophosphamide and prednisone taper on discharge to rehabilitation facility.

## OUTCOME AND FOLLOW-UP

The patient was seen in rehabilitation and found to be free of spontaneous bleeding and with a repeat factor inhibitor level of 0 and normal factor VIII level around 3 weeks from discharge.

## DISCUSSION

SARS-CoV-2, is commonly associated with thromboembolic complications with studies showing development of pulmonary embolism in 30% of cases, deep venous thrombosis in 47% of patients admitted to the intensive care unit after 14 days and acute ischaemic stroke in 4.6% of cases.[1–3] This association, while partly linked with sepsis-induced coagulopathy and disseminated intravascular coagulation (DIC), also has features similar to antiphospholipid syndrome with reported presence of antiphospholipid antibodies, such as anticardiolipin IgA and anti–β2-glycoprotein IgA and IgG as well as lupus anticoagulant.[9 10] Other autoimmune conditions induced by SARS-CoV-2 within the haematologic system include autoimmune haemolytic anaemia (AIHA) as well as Evan's syndrome, an antibody-mediated response causing both AIHA and immune thrombocytopenic purpura.[11 12] Autoantibodies may also provide the basis for the effects of SARS-CoV-2-induced coagulopathy causing conditions, which increase the risk of bleeding.

One such condition is acquired haemophilia A. Acquired haemophilia A, which is secondary to the development of an antibody, which inhibits factor VIII, can often be fatal with a mortality rate of 8%–22% and is characterised clinically by spontaneous bleeding, most often in the skin manifesting as purpura or soft tissue bleeding with an isolated elevated PTT.[13] Acquired haemophilia A can have a variety of causes. It is most commonly associated with autoimmunity, which make up about 17%–18% of cases, with the most common being systemic lupus erythematosus, rheumatoid arthritis or Sjogren's syndrome.[14] Another frequent association is in patients with either solid or liquid lymphoproliferative malignancies.[14] Other conditions that are associated are skin disorders, such as pemphigus and epidermolysis bullosa, postpartum, infections (specifically hepatitis C, HIV, TB, urinary tract infection and influenza A), drugs (specifically factor VIII; antibiotics, such as penicillin, sulfonamides and chloramphenicol; anticonvulsants, such as phenytoin; and immunomodulators, such as fludarabine and interferon-alpha) and chronic graft versus host disease.[14–18] Idiopathic aetiology makes up the remaining 50% of cases.[13]

As of this case report writing, there have also been three cases of SARS-CoV-2 infection associated with acquired haemophilia A being described in the literature.[5–7] Two cases presented with severe SARS-CoV-2 infection, which required intubation and non-invasive mechanical ventilation.[5 6] The last case described a case of mild SARS-CoV-2 infection associated with ageusia that recovered without therapy or hospitalisation in an elderly woman with subsequent development of acquired haemophilia A 3 weeks later.[7] Our case is similar to the last case, but uniquely, our patient was asymptomatic and was not aware of SARS-CoV-2 infection at all. We have also performed an extensive workup and ruled out other potential causes through laboratory and imaging studies. This leaves us with asymptomatic SARS-CoV-2 as a potential culprit, with the patient's predisposition to autoimmunity given his remote history of autoimmune thyroid disease.

One possible concern is that the SARS-CoV-2 antibody test may have produced a false positive result. However, a study showed that the Roche total SARS-CoV-2 antibody assay, the assay used in our case, is highly specific. This study involved 667 samples (103 from confirmed SARS-CoV-2 and 564 from non-SARS-CoV-2 patients) and out of the 564 specimens, none were found to be reactive on the Roche total antibody test, generating a specificity of 100% (95% CI, 99.32 to 100), although sensitivity ranged from 75% to 85% 3 days post positive PCR.[19]

One key point to be mentioned is that asymptomatic SARS-CoV-2 infections, which are estimated to occur about 40% of the time, are not without risk. In children, SARS-CoV-2 infection both symptomatic and asymptomatic can be associated with later development of multisystem inflammatory syndrome with features that overlap with Kawasaki's disease.[20] This can also be seen in adults as well.[21] SARS-CoV-2 vaccines, such as from Pfizer and Moderna, are currently being deployed. However, while clinical trials show they are efficacious, it is still unknown how effective they will be with new SARS-CoV-2 variant strains.[22] While they may be potentially effective in reducing the risk of severe infection, as this case highlighted, there may still be risks with even mild or asymptomatic SARS-CoV-2 infection. Therefore, the authors caution the need to continue isolation precautions, such as wearing masks and appropriate social distancing. Also, while our case suggests an association between acquired haemophilia A and asymptomatic SARS-CoV-2 infection, the association does not imply causation. It can be argued that given SARS-CoV-2 antibodies have been shown to be positive even 6 months removed from an active SARS-CoV-2 infection, causation of SARS-CoV-2 infection with production of factor inhibitor is difficult as the patient did not have any symptoms of SARS-CoV-2 or a positive nasopharyngeal PCR to correlate

### Learning points

- Acquired haemophilia A is a rare, but serious condition involving autoantibodies to factor VIII, which can be caused by infections, autoimmune diseases, malignancies and drugs.
- Our case suggests that asymptomatic SARS-CoV-2 infections, and their potential for associated autoimmune phenomena, can be associated with acquired haemophilia A and checking serology for SARS-CoV-2 may be helpful to elucidate potential causes.
- Patients with a history of autoimmune conditions may be more predisposed to some of the autoimmune phenomena seen in SARS-CoV-2 infections.

with his haemophilia A.[23] As a result, while we think that SARS-CoV-2 may be the potential aetiology for the patient's factor inhibitor production, we cannot rule out an idiopathic cause as well given that the majority of cases of haemophilia A are idiopathic. A case series of similar presentations, or a presentation of increasing incidence of acquired haemophilia A in current/post SARS-CoV-2 pandemic compared with prepandemic time would add strength to our theory of causation, but this will require more time and investigation to determine given the rarity of acquired haemophilia A.

More studies are needed to better elucidate the mechanisms of the potential effects of SARS-CoV-2 in coagulopathy and their prevalence.

**Contributors** KW wrote the initial draft and edited draft. PS assisted in editing the draft and contributing ideas. DTR assisted in editing the draft and contributing ideas. SAS assisted in editing the draft and contributing ideas.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient consent for publication** Obtained.

**Provenance and peer review** Not commissioned; externally peer-reviewed.



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