De novo pancytopaenia in an older adult with severe COVID-19 infection

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SUMMARY

During the COVID-19 pandemic, it was recognised that SARS-CoV-2 can cause multisystem illness. Non-respiratory complications observed early in the pandemic were haematological in nature. A rare but serious haematological complication of COVID-19 infection is pancytopaenia. We describe a case of an older adult without pre-existing haematological disease or risk factors for cell dyscrasia with severe pancytopaenia induced by COVID-19, who developed critical illness requiring respiratory support in intensive care and died. Our case report highlights that de novo pancytopaenia may only present with mild dermatological manifestations and may indicate severe COVID-19 infection. Management is primarily supportive and early involvement of haematology should be sought.

BACKGROUND

Since the start of the COVID-19 pandemic, there are over 591 million confirmed cases and 6.4 million deaths from SARS-CoV-2.[1] SARS-CoV-2 has a predilection for the respiratory system but can also cause multisystem illness.[2] Non-respiratory complications observed early in the pandemic were haematological in nature—namely lymphopaenia and thrombosis.[3 4] A rare but serious haematological complication of COVID-19 is pancytopaenia—the reduction of all three haematological cell types.[4 5] We describe a case of an older adult without pre-existing haematological disease or risk factors for cell dyscrasia found to have severe pancytopaenia induced by COVID-19.

CASE PRESENTATION

A Caucasian man in his late 60s was brought in by ambulance to the Resuscitation area of an Accident and Emergency department 6 days after testing positive for COVID-19 on a lateral flow test. His presenting complaint was worsening shortness of breath over the past few days. He denied chest pain, vomiting, diarrhoea, weight loss, bruising or bleeding. His wife reported intermittent confusion at home. He had a previous medical history of hypothyroidism, hypercholesterolaemia and hypertension which were all well-controlled. There was no history of haematological disease or risk factors for blood dyscrasias. He had received two doses of the AstraZeneca (ChAdOx1) vaccination prior to hospital admission (the first dose was administered at 9 months and the second dose at 6 months prior to hospital admission), which constituted the full SARS-CoV-2 immunisation regimen in the UK at the time. He was usually very fit and well and regularly did gardening and household DIY (do-it-yourself) jobs (Clinical Frailty Scale 2—Well).

Initial observations are listed in table 1. He was able to talk in full sentences and was not in respiratory distress. Chest auscultation demonstrated bilateral fine crepitations and wheezing. There was no bruising; however, small petechial rashes were noted on the groin and right shin.

INVESTIGATIONS

Admission blood test results are listed in table 1. Blood film demonstrated red cell anisocytosis, left-shifted neutrophils with toxic granulations and some vacuolations, and reduced platelet count with anisocytosis. Chest radiograph showed multifocal opacities in the mid and lower zones bilaterally with ground-glass peripheral involvement, most pronounced on the right side. Arterial blood gas demonstrated severe type 1 respiratory failure. PCR for SARS-CoV-2 and SARS-CoV-2 spike antibodies were both positive.

DIFFERENTIAL DIAGNOSIS

The main differential diagnoses to consider were those of bone marrow failure, peripheral destruction of haematopoietic cells and infection.[6] The role of SARS-CoV-2 vaccination also cannot be ruled out.

Bone marrow failure: acute myeloid leukaemia (AML)

AML is the most common leukaemia in adults, with increasing incidence in those over 65s.[7] Presenting features include fatigue, anorexia and weight loss which reflect bone marrow failure.[7] Bone marrow failure arises due to the accumulation of immature myeloid cells within the bone marrow, resulting in a blood profile demonstrating leucocytosis, anaemia or thrombocytopaenia; however, depletion of all three cell lines can occur.[7 8] The presence of blast cells ≥20% in peripheral blood film or bone marrow aspirate confirms the diagnosis.[9] AML can arise in the presence of haematological disorder, previous chemotherapy or radiotherapy, or de novo in a previously healthy individual.[7 8] The presence of new pancytopaenia in our patient with well-controlled comorbidities could support the diagnosis of AML. However, toxic left-shifted neutrophils and the absence of blast cells on the blood film favour infection rather than malignancy as the underlying aetiological process. In addition, the patient did not have any constitutional symptoms consistent with AML and no exposure to cytotoxics.

Table 1 Admission blood test results and observations

Blood results		Observations	
Haemoglobin (g/L)	69	Oxygen saturations (%)	96
White cell count (10^9/L)	3.4	Supplemental oxygen (L/min)	10
Platelets (10^9/L)	29	Respiratory rate (breaths/min)	23
Lymphocytes (10^9/L)	0.7	Heart rate (beats/min)	90
Fibrinogen (g/L)	8.3	Blood pressure (mm Hg)	110/40
Renal and liver function	Normal	Temperature (°C)	37.8
Ferritin (µg/L)	2703		
Haematinics	Normal		
Prothrombin time (s)	15.3		
INR	1.1		
Activated partial thromboplastin time (s)	38.9		
CRP (mg/L)	211		

Results above the reference range are shown in red and those below in blue.
CRP, C reactive protein; INR, international normalised ratio.

Peripheral destruction of haematopoietic cells: disseminated intravascular coagulation (DIC)

DIC is a syndrome characterised by paradoxical simultaneous clotting and bleeding tendencies due to the abnormal systemic activation of coagulation pathways.[10] Intravascular deposition of fibrin, reduction of antithrombin III and protein C and insufficient fibrinolysis result from systemic proinflammatory cytokine release.[11] DIC is not an isolated diagnosis but is secondary to an aetiological process that generates systemic inflammatory responses which should be investigated for—these include sepsis, malignancy, organ necrosis (liver or pancreas) and trauma.[10 11] DIC is a recognised complication of severe COVID-19 infection.[12] The characteristic blood picture of DIC is thrombocytopaenia, elevated fibrin degradation products (such as D-dimer), prolonged prothrombin time and activated partial thromboplastin time and low fibrinogen (however, fibrinogen can be normal).[10] D-dimers were not performed in this patient; however, a high result would have been expected due to severe infection. The presence of severe infection with the patient's clotting parameters generally supports DIC; however, high fibrinogen counters the diagnosis.

Infection: COVID-19-induced pancytopaenia

Viruses are a recognised cause of panctyopaenia.[6] Examples include parvovirus B19, hepatitis, cytomegalovirus, Epstein-Barr virus and HIV.[6] It is proposed SARS-CoV-2 could induce pancytopaenia via similar mechanisms to the viruses listed above, where myelosuppression arises from direct viral entry and infection of haematopoetic stem cells.[13] Positive PCR results for SARS-CoV-2, in conjunction with the blood film appearance of toxic left-shifted neutrophils, and absence of the previous history of haematological disease or risk factors for cell dyscrasia resulted in SARS-CoV-2-induced pancytopaenia being the favoured diagnosis.

SARS-CoV-2 vaccination: both mRNA (BNT162b2, mRNA-1273) and adenovirus vector (ChAdOx1) vaccinations have been reported with haematological disorders such as thrombocytopaenia.[14 15] The ChAdOx1 vaccine is associated with thrombotic thrombocytopaenia; however, this condition tends to develop 1 to 3 weeks after vaccination in women under 50 years of age.[15] Given this patient's demographics (man over 60 years old) and the timeframe of his presentation, it is less likely that the AstraZeneca vaccine was a contributing factor.

TREATMENT

Initial management comprised high-flow oxygen therapy and proning to reduce V/Q (ventilation–perfusion) mismatch. Intravenous antibiotics (co-amoxiclav and clarithromycin), dexamethasone, intravenous fluids and carbocisteine were all commenced as part of the hospital's COVID-19 treatment bundle. One unit of red cells and 3 units of platelets were administered after a discussion with the on-call haematologist. In view of thrombocytopaenia, mechanical thromboprophylaxis was commenced instead of subcutaneous low-molecular-weight heparin.

Within a few hours, the patient was transferred to the intensive care unit to commence continuous positive airway pressure due to increased respiratory effort and persistent hypoxia despite high-flow oxygen therapy. Over the next 24 hours, the patient's breathing deteriorated to the point of tiring; therefore, the decision was made to intubate and start invasive ventilation under sedation.

Over the next 48 hours, little improvement was seen in oxygenation and blood results showed evidence of worsening infection (C reactive protein increase to 248 mg/L, worsening lymphopaenia 0.5×10^9/L, procalcitonin 3.73 ng/mL). After discussion with the microbiologist on-duty, it was decided to switch antibiotic treatment to piperacillin–tazobactam to empirically cover for ventilator-associated pneumonia. Interleukin 6 (IL-6) inhibitors (tocilizumab and sarilumab) were considered in view of the early stages of critical illness requiring respiratory support. However, these were not commenced due to a persistently low platelet count $<150\times10^9$/L, IL-6 inhibitors being a contraindication as per the NHS Clinical Commissioning Policy for IL-6 inhibitors in hospitalised patients with COVID-19.[16] Due to overwhelming bed pressures in the hospital, the patient was transferred out of the hospital to another intensive care unit within the region.

OUTCOME AND FOLLOW-UP

Despite intermittent red cell and platelet transfusions throughout the intensive care unit admission, a persistently low platelet count $<150\times10^9$/L meant that IL-6 inhibitors could not be commenced. There were no signs of bleeding throughout admission.

Despite 15 days of invasive ventilatory support, proning and optimal medical management, the patient's respiratory function deteriorated. The patient's wife was informed and a shared decision between her and the intensive care team was made that in the event of a cardiac arrest cardiopulmonary resuscitation would not be performed, which was in keeping with his wishes. Unfortunately after 15 days in intensive care, the patient died.

DISCUSSION

Our report of de novo COVID-induced pancytopaenia is not unique. Several cases have been reported throughout the pandemic of de novo pancytopaenia in adults with no haematological conditions or risk factors for cytopaenia.[17–20] Two cases of spontaneous bleeding (premacular subhyaloid haemorrhage[20] and spontaneous haemoperitoneum[21]) in healthy male patients with no comorbidities have been reported as presenting symptoms of COVID-19-induced pancytopaenia. However, most cases of pancytopaenia in the presence of COVID-19 infection concern patients with an underlying haematological condition[22–24] and/or risk factors for cytopaenias such as chemotherapy,[25 26] methotrexate[27] and other immunosuppressant therapy.[28] The trajectory of COVID-induced pancytopaenia can range from being self-limiting[18 20–22] to worsening of blood

parameters and clinical deterioration despite the use of blood products and optimal treatment of COVID-19[17 19] as seen in the case of our patient.

The mechanism of COVID-19-induced pancytopaenia is not fully known. However, it is recognised that severe COVID-19 is characterised by a hyperinflammatory state and cytokine storm (the overwhelming release of proinflammatory cytokines).[29 30] In a normal immune response to viral infection, proinflammatory cytokines (such as tumour necrosis factor-α, IL-1 and IL-6) are released which stimulates haematopoietic stem cell differentiation into mature leucocytes, erythrocytes and platelets.[31] Immune cells, natural killer (NK) and cytotoxic T lymphocytes induce enzyme-mediated lysis of virus-infected cells, with apoptosis of antigen-presenting cells to clear the virus.[29 31] In COVID-19 infection, viral clearance does not occur as previously described due to the defective lymphocytic activity means and instead recruitment of the whole immune system occurs.[29] Immune system overactivity and cytokine storm contribute to sequelae of acute respiratory distress syndrome and multiorgan failure seen in severe COVID-19 infection.[29] The rationale for using IL-6 inhibitors is to ameliorate this proinflammatory state and has demonstrated survival benefits for patients with severe COVID-19 infection requiring organ support.[32] In the presence of pancytopaenia, the benefits of IL-6 blockade must be cautiously weighed up against the risk of absolute immunosuppression.[16]

The only clinical signs of pancytopaenia in our patient were small petechial rashes, with no overt bruising or bleeding. This dermatological manifestation has been reported in another case of COVID-induced panctyopaenia;[21] however, although a rare presenting symptom, spontaneous bleeding in an otherwise healthy individual can also be the first presentation.[20] Pancytopaenia can create dilemmas in the clinical management of COVID-19 particularly around interventions with increased bleeding risk, such as venous thromboembolism prophylaxis and performing invasive procedures such as arterial line and central venous cannulation where covered with blood products is likely to be required. As described in the literature, and this case report, management of COVID-19-induced pancytopaenia is primarily supportive. Early discussion with haematology should be sought.

Patient's perspective

Before my husband was diagnosed with COVID-19, his colour was very grey and pale. He was also very quiet (not his usual self at all)—enough for myself and the family to notice and try to persuade him to see a doctor which he always replied "I'm OK." On one occasion, he held his head in his hands and said "I think I'm dying" to which I replied "you need to go to A&E," but again he refused.

Once he was diagnosed with COVID-19, that's when the coughing and lethargy started. During the early hours, I awoke from the sounds of my husband talking to himself but not making any sense. He felt very hot and that is when I rang for the ambulance. I think he was frightened of the outcome with how ill he felt. I felt OK in myself—I had my booster vaccine last month which I think stopped me from catching COVID-19 from my husband.

I would like to thank all the staff for their care and how they tried so much to save him.

Learning points

- Pancytopaenia is a rare but serious haematological consequence of viral infections which may only present with mild dermatological manifestations. As future waves of COVID-19 are expected, clinicians need to be vigilant of this haematological complication in the presence of severe SARS-CoV-2 infection.
- COVID-19-induced pancytopaenia can occur in previously healthy individuals with no haematological conditions or risk factors for cytopaenia.
- In a previously healthy individual, presentations can range from no signs of bleeding or immunocompromise to spontaneous bleeding and severe infection.
- Consider acute myeloid leukaemia and disseminated intravascular coagulation as differential diagnoses.
- Management of COVID-19-induced pancytopaenia is primarily supportive. Early discussion with haematology should be sought.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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