Fig S2. Patients without CVD at time of treatment initiation developing a CVD 1–5 years after therapy initiation. Separated on type of therapy. A. Total numbers and B. CI for each type of therapy.

Table S1. ICD diagnoses according to ICD-10.

Table S2. History of CVD at time of CLL diagnosis and start of first-line therapy

Table S3. Number of patients without previous history of CVD, who were diagnosed with a new CVD within 5 years after start of first-line therapy for CLL. Each year and in total after 5 years.

Table S4. Number of patients with previous history of CVD who were diagnosed with a new CVD within 5 years after start of first-line therapy for CLL. Each year and in total after 5 years.

Table S5. Type of first-line therapy and baseline characteristics of patients each group.

Table S6. Patients without CVD at treatment initiation developing a CVD. Separated on type of therapy.

Table S7. CVD as cause of death within 5 years after CLL diagnosis.

Table S8. CVD as cause of death within 5 years after initiating CLL therapy.

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Acute promyelocytic leukaemia lying under the mask of COVID-19-a diagnostic and therapeutic conundrum

The diagnosis and management of acute promyelocytic leukaemia (APML) in the context COVID-19 poses a challenge for clinicians. We present a case illustrating this due to the masking of the typical laboratory pattern of APML coagulopathy and the potential heightened risks of thrombosis and differentiation syndrome (DS) when the two conditions are combined.

A 36-year-old man was admitted in April 2020 with fever, cough and sweats. Examination revealed a fever of 38·4°C, heart rate of 116 bpm, normal blood pressure, respiratory rate of 19, saturations of 95% on air and bilateral crepitations up to the mid-zone. There was no bruising, petechiae, hepatosplenomegaly or lymphadenopathy.

The blood count showed haemoglobin 95 g/l, total white cell count $1{\cdot}0 \times 10^9$/l, neutrophil count $0{\cdot}5 \times 10^9$/l, lymphocyte count $0{\cdot}4 \times 10^9$/l, platelet count 69×10^9/l. Blood film revealed teardrop poikilocytes, left-shifted neutrophils with vacuolation and plasmacytoid lymphocytes. Prothrombin time (PT) was 18.5 s [normal range (NR) 9·1–12.5], activated partial thromboplastin time (APTT) 31 s (NR 26–40), D-dimer 43 246 ng/ml (NR 0–230), Clauss fibrinogen >5·00 g/l (NR 1·8–3·6) and ferritin 4073 µg/l (NR 30–400). His creatinine was 193 µmol/l (NR 62–106), lactate dehydrogenase 452 iu/l (NR 135–225) and C-reactive protein 382 mg/l (NR 0–5).

A nasopharyngeal swab detected SARS-CoV-2 RNA. His computed-tomography pulmonary angiogram was negative

for pulmonary embolus but showed extensive, predominantly peripheral, consolidative changes consistent with moderate/severe COVID-19 (Fig 1). His clinical status including coagulopathy improved rapidly with antibiotics but neutrophils remained low, prompting an urgent bone marrow examination. Bone marrow aspirate was a dry tap but the trephine roll had bilobed, hypergranular mononuclear cells highly suggestive of APML. Peripheral blood fluorescence *in situ* hybridisation detected the presence of a low level *PML-RARA* rearrangement. The bone marrow trephine biopsy became available two days later and showed 75% infiltration by promyelocytes (Fig 2).

He was commenced on all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) at 50% doses due to the risk of DS sequelae in the context of COVID-19 lung disease. Intermediate dose enoxaparin was initiated to minimise thrombotic complications.

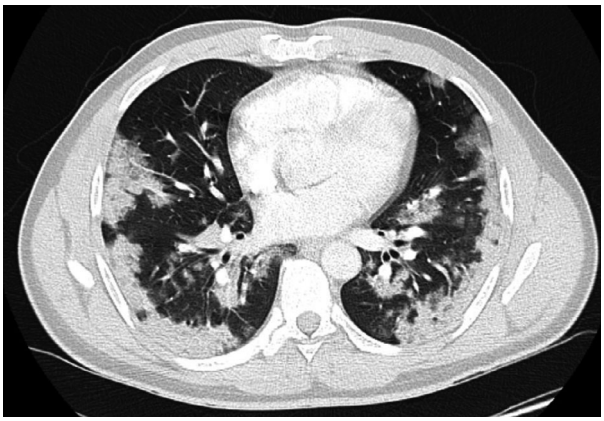

Fig 1. CT chest axial slice demonstrating extensive bilateral patchy, peripheral consolidative changes throughout the lungs.

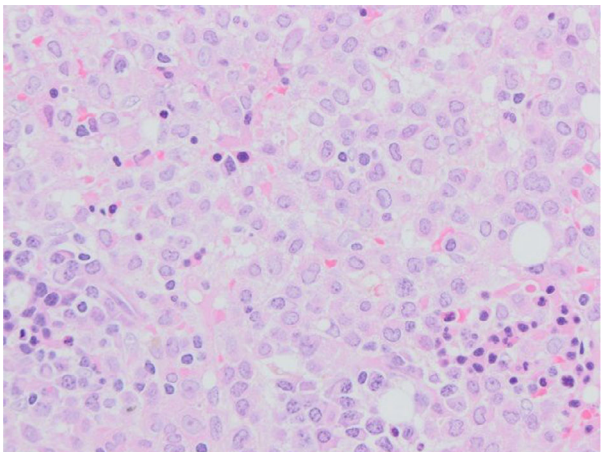

Fig 2. Bone marrow trephine biopsy: Bone marrow biopsy showing numerous blasts, many with bilobate/reniform nuclei and cytoplasmic granules. The background shows dysplastic erythropoiesis and scattered plasma cells. Haematoxylin and eosin staining, ×20.

Our case remains clinically well following initial dose-reduced ATRA/ATO treatment with slow titration to near full doses. He had sustained resolution of coagulopathy with no bleeding or thrombotic complications.

Coagulopathy is the leading cause of fatality in APML. Typically, due to a combination of disseminated intravascular coagulopathy, hyperfibrinolysis and thrombocytopenia, patients usually present with low platelet count, prolonged PT and APTT, elevated D-dimers and low fibrinogen levels.[1,2] Survival rates have markedly improved with prompt initiation of ATRA/ATO and supportive measures addressing the coagulopathy.

COVID-19 is also associated with coagulopathy, denoted the coagulopathy of COVID (CAC).[3,4] CAC is due to the inflammatory response to SARS-CoV-2 which results in thrombo-inflammation and drives thrombosis.[3] Abnormal coagulation parameters in COVID-19 include prolonged PT and APTT, raised D-dimers (associated with increased mortality) and high fibrinogen, with thrombocytopenia uncommonly reported.[3–5]

Although our case had features of APML, the concomitant diagnosis of COVID-19 raised diagnostic and therapeutic challenges. Firstly he had no bleeding manifestations, reported in up to 76% of APML patients.[1] Furthermore, his fibrinogen was consistently raised and thrombocytopenia mild, discordant with the usual pattern in APML. His abnormal coagulation parameters largely corrected with supportive management for COVID-19 prior to the initiation of ATRA, suggesting his coagulopathy was more consistent with CAC.

Whilst viral infection-associated haemophagocytic lymphohistiocytosis can lead to pancytopenia, this is uncommon in COVID-19. The main full blood count abnormality reported in COVID-19 is lymphopenia, associated with worse prognosis.[6] The significant neutropenia in our case prompted us to conduct an urgent bone marrow examination. Although we were unable to attain an aspirate, the trephine roll was helpful and raised the suspicion of APML. Suspicion of APML would lead to prompt initiation of ATRA and help reduce mortality. DS, a complication of ATRA, which presents with fever, weight gain, dyspnoea, pulmonary infiltrates and pleuro-pericardial effusions has a mortality rate of up to 30% due to hypoxic respiratory failure if untreated.[7,8] As our patient had respiratory compromise due to COVID-19, we were reluctant to commence ATRA based on suspicion of APML diagnosis due to the risk of further respiratory compromise from DS. Furthermore, the atypical pattern of coagulation derangement and the improving trend of both platelet count and coagulation studies raised diagnostic uncertainty.

Once the diagnosis was confirmed with the presence of *PML/RARA* translocation in peripheral blood, the choice of appropriate treatment was the next dilemma. Given the low white cell count at presentation our case fell into the low–intermediate risk group and thus was a candidate for ATRA/ATO combination with associated survival rates of >90%.[9] Due to the perceived risk of DS on our patients' COVID-19-compromised lung, we cautiously initiated treatment with

ATRA and ATO at 50% doses. Whilst the benefit of prophylactic corticosteroids in prevention of DS is uncertain and mainly reserved for patients presenting with a white cell count >5 × 10^9/l, we used prophylactic low dose dexamethasone.[9]

Although haemorrhagic complications of APML predominate and are reduced by ATRA, thrombosis is not uncommon; however, this risk is not reduced by ATRA.[1,2] The acute inflammatory state in COVID-19, in addition to the known thrombotic risk of hospitalisation, results in a highly pro-thrombotic state. This, when combined with APML thrombotic complications were felt to warrant intermediate dose enoxaparin prophylaxis in our case.

This case presented challenges due to atypical coagulation studies in the context of COVID-19. Laboratory findings of APML can be disguised in the context of COVID-19, thus stressing the need to suspect a potential acute leukaemia in COVID-19 presenting with neutropenia. The complexities of balancing risk of DS on the background of already severely inflamed lungs and the risk/benefit of prophylaxis with steroids made it necessary to consider treatment alterations.

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Rapid diagnosis of hereditary haemolytic anaemias using automated rheoscopy and supervised machine learning

Haemolytic anaemias arise when red blood cell (RBC) integrity is compromised, eventually resulting in premature clearance or lysis and leading to anaemia when these effects cannot be sufficiently compensated by the capacity of the bone marrow to produce new cells.[1] Hereditary anaemia occurs as a consequence of genetic mutation[2] (e.g. affecting membrane complex or cytoskeletal proteins, haemoglobin or metabolic enzymes), and diagnosing affected patients is a complex process since, given the wide variety of possible genetic causes, multiple examinations must be performed and an unambiguous result is usually reached only after DNA sequencing.[3] Furthermore, phenotypic severity can vary widely not just among individuals with different mutations but also among individuals suffering from the same mutation, thereby complicating diagnosis.[4]

While molecular diagnoses have become increasingly easier, cheaper and faster to perform in recent years, constraints on their use still exist,[5] and phenotype-based diagnostic methods still constitute an important proposition.