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Recurrent infection-induced autoimmune haemolytic anaemia complicated by pulmonary embolism: a case report and literature review

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ABSTRACT

A 73-year-old woman presented with progressive dyspnoea up to type 1 respiratory failure. Laboratory values showed leucocytosis, reduced haemoglobin to 71 g/L, elevated indirect serum bilirubin and lactic dehydrogenase. Computed tomography pulmonary angiography (CTPA) revealed peripheral pulmonary embolism (PE). Echocardiography showed enlarged right ventricle, elevated estimated pulmonary arterial systolic pressure (57.2 mmHg) and normal left ventricular ejection fraction. The patient was diagnosed with autoimmune haemolytic anaemia (AIHA), which was induced by recurrent infections without standard treatment in the past year. AIHA is the cause of PE due to the absence of common predisposing factors and other thrombophilia. The patient became better after administration of glucocorticoids, intravenous immunoglobulin and rivaroxaban.

KEYWORDS: autoimmune haemolytic anaemia, pulmonary embolism, infection

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Case presentation

A 73-year-old woman was referred to the emergency department (ED) with progressive dyspnoea, weakness and dark urine for about 10 days. She complained of recurrent fever for 1 year due to pneumonia or urinary tract infection (UTI). She presented to local hospital and was diagnosed with suspicious infection due to leucocytosis. Although treating with moxifloxacin, her symptoms failed to relieve. Past medical history included reflux oesophagitis for many years and was treated with omeprazole. She has no history of illicit substance use.

Vital signs were blood pressure at 116/62 mmHg, heart rate of 90 beats/min, respiratory rate of 26 breaths/min and oxygen saturation of 85% on room air. Physical examination showed high-pitched P2, no crackles and rhonchi in both lungs, no peripheral oedema, no erythema and no palpable cords. The initial significant findings revealed type 1 respiratory failure, haemoglobin (Hb) was 71 g/L with white cell count of 23.01 $\times$ 10^9/L, neutrophils of 74.2% and platelet count of 241 $\times$ 10^9/L; a high level of D-dimer (2.78 mg/L); troponin I (cTNI) was 0.091 ng/mL and brain natriuretic peptide (BNP) was 236 pg/mL. A 12-lead electrocardiography (ECG) showed no abnormalities in ST segment and T wave (Fig 1). Emergent computed tomography pulmonary angiography (CTPA) showed bilateral subsegmental and segmental pulmonary emboli (Fig 2a).

Initial management

The patient was sent to the cardiac care unit (CCU). Echocardiography showed enlarged right ventricle and elevated estimated pulmonary arterial systolic pressure (57.2 mmHg) and normal left ventricular ejection fraction (81.2%). Dynamic changes of laboratory results are summarised in supplementary material S1. We exclude common predisposing factors and other thrombophilia for pulmonary embolism (PE) by a detailed history and laboratory test (cardiolipin anti-antibody, anti-β2-glycoprotein 1 antibody, lupus anticoagulant, protein C or S were normal). The patient suffered from haemolytic anaemia as judged by elevated reticulocyte and serum bilirubin. Further tests showed peripheral blood smears, paroxysmal nocturnal haemoglobinuria (PNH) clone, haemoglobin electrophoresis, erythrocyte penetration fragility test, G6PD activity, complement H factor concentration, complement H factor antibody and ADAMTS13 were all normal. Coombs test was positive, and resulted in the diagnosis of autoimmune haemolytic anaemia

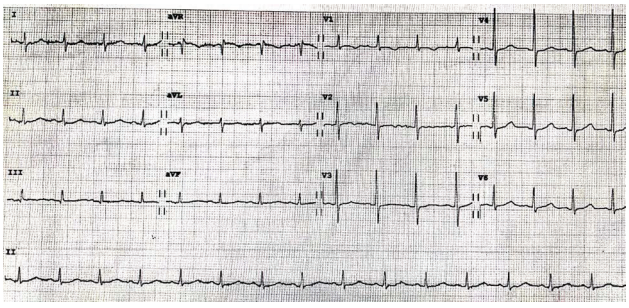

Fig 1. Electrocardiography on admission.

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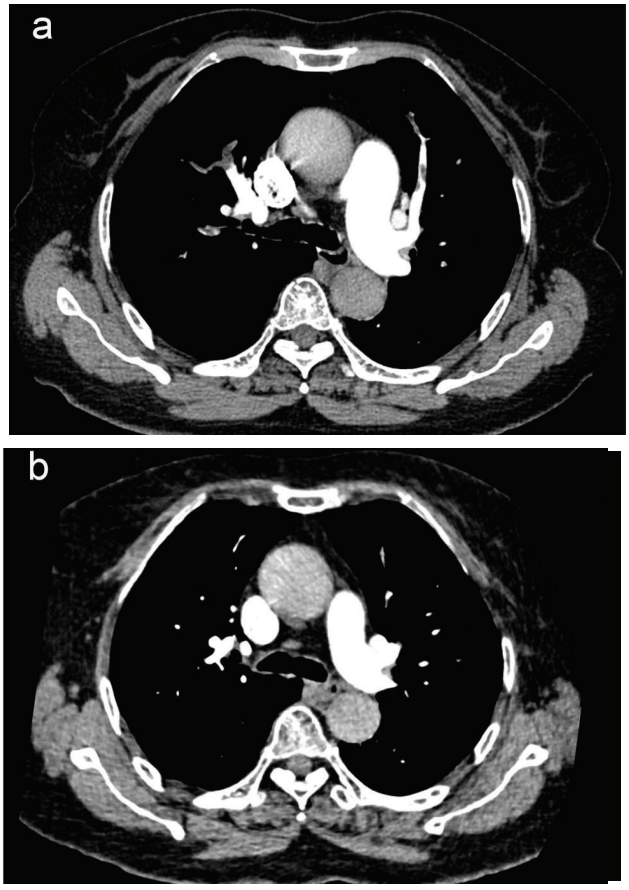

Fig 2. Comparison of computed tomography pulmonary angiography. a) Image on admission showing bilateral subsegmental and segmental pulmonary embolism. b) Image at 3 months after discharge showing no pulmonary embolism.

(AIHA). The works for secondary AIHA included other autoimmune diseases (antinuclear antibody, anti-dsDNA were negative), serum immunofixation electrophoresis (no monoclonal band) and a computed tomography to exclude lymphoma and solid tumours. In addition, T-SPOT.TB, the immunoglobulin M of mycoplasma, Epstein–Barr virus (EBV), cytomegalovirus (CMV), influenza virus, rubella virus, measles, adenovirus and parvovirus B19, hepatitis B surface antigen (HBsAg) and HIV antibodies were all negative. Finally, PE attributed to AIHA was considered due to no common aetiology of PE.

According to guidelines, the patient was stratified as Pulmonary Embolism Severity Index (PESI) class IV, simplified PESI (sPESI) ≥1, the risk of early death is intermediate–high.[1] She received low-molecular weight heparin (LMWH) and discontinued other suspicious drugs. During hospitalisation, she once received intravenous methylprednisolone sodium succinate 40 mg once daily (od)) and intravenous immunoglobulin 10 g od for 7 days. The patient didn't receive anti-infective nor blood transfusion therapy.

Case progression and outcome

The patient was discharged after 3 weeks with oral prednisolone 40 mg qd and rivaroxaban 15 mg twice daily (bid). At 3-month follow up, reinspection of CTPA revealed disappearance of thrombosis (Fig 2b). At the recent follow-up, 12 months after the initial presentation, she required 5 mg od of prednisolone and 20 mg od of rivaroxaban to keep her haemoglobin (Hb) over 10 g/dL and had no thromboembolic episodes.

Discussion

Autoimmune haemolytic anaemia (AIHA) is a rare and heterogeneous disorders characterised by the destruction of red blood cells through warm or cold autoantibodies.[2] The overall estimated incidence in adults is 0.8–3 per 100,000/year, a prevalence of 17:100,000 and a mortality rate of 3–4%.[3,4] AIHA is the higher risk for thromboembolism due to hypercoagulability.[2] AIHA occur in systemic lupus erythematosus (SLE), chronic lymphocytic leukaemia (CLL), infection, drug exposure and other mixed disorders.[2,5,6] As early as 1967, Allgood *et al* reported that pulmonary embolism (PE) was the most common cause of death in AIHA, and revealed the association between PE and AIHA.[7] Patients with AIHA have 2.6-fold higher risk of venous thromboembolism (VTE) compared with non-AIHA.[8] In two large studies, the prevalence of thromboembolism in AIHA patients was recorded up to 15%.[4,9] Anticoagulant prophylaxis can effectively reduce the occurrence of a thromboembolic episode in acute exacerbation of AIHA (4.7% vs 33.3%).[10] The reasons for patients with AIHA were at an increased risk of VTE remain unclear, which may include the increased expression of phosphatidylserine, microparticles and cytokine-induced monocytes or endothelial tissue factors.[8,11] Thromboembolic episodes are relatively common during active phases of the disease, but also occur during disease maintenance therapy.[12] High leucocyte count and severe anaemia were associated with VTE.[9] PE is a life-threatening complication of AIHA. Clinical manifestations of PE include sudden dyspnoea, hypoxaemia, and chest pain, which can easily be masked by severe anaemia caused by AIHA, leading to delayed diagnosis.[13] Therefore, close attention as well as timely treatment plays a crucial role.

The causes of AIHA and PE are complex and varied, which need comprehensive evaluation in patients with PE at the first occurrence.[1,2] In our case, considering that the patient had suffered recurrent infection without sufficiently effective treatment and haemoglobin gradually decreased in the past year, which strongly suggested that the prodromal infection induced AIHA. Previous literature reported that infection associated AIHA is not rare, accounting for 14% of all patients.[11] Drug-related AIHA was excluded because the anaemia did not worsen after taking drugs such as moxifloxacin.

The first-line therapy for AIHA is glucocorticoids and approximately 80% of patients would respond to the therapy. There are no studies in comparing tapering regimens, where long duration and slow reduction are recommended. No response to steroids after 21 days or relapse during/after a steroid wean is an indication for the second-line therapy.[2,3] This patient was administered with rivaroxaban sequent to LMWH, although there was insufficient evidence-based practice in the alternative of novel oral anticoagulants to vitamin K antagonists. Direct oral anticoagulants (DOACs) are not recommended in antiphospholipid syndrome (APS)-induced VTE.[14] Notably, numbers of AIHA patients complicated with thromboembolism were reported with positive antiphospholipid antibodies.[11] The thrombotic risk is reported to not correlate with traditional risk factors during AIHA.[13]

Vitamin K antagonists reduce functional coagulation factors in the extrinsic and intrinsic pathways of coagulation, which showed a stronger anticoagulant effect.[15] Thus, it is uncertain that DOACs may be a perfect substitute to warfarin in VTE, especially attributed to thrombophilia or autoimmune diseases. In our case, DOACs are safe and effective for this patient, which providing a clinical evidence for anticoagulant therapy of AIHA-induced PE. Given the higher risk of thrombosis, long-term anticoagulation and follow-up should be recommended.[12]

Key points

- AIHA is a hypercoagulable disorder, requiring vigilance against the complication of deep vein thrombosis.
- Consider a wide range of differentials when patients present with PE attributed to AIHA.
- No guidelines to recommend anticoagulant therapy for AIHA induced PE. DOACs may be effective and safe in APS-negative AIHA. ■

Supplementary material

Additional supplementary material may be found in the online version of this article at www.rcpjournals.org/clinmedicine:
S1 – Dynamic changes of laboratory results and process of diagnosis and treatment from the initial infection to follow-up.

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