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Case Report

Pulmonary Embolism as a Complication of Sars-Cov-2 Infection and Complement Mediated Autoimmune Hemolytic Anemia

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Abstract

SARS-Cov2 infection, especially in the acute phase, has been in many cases associated to the development of hypercoagulable states and a subsequent increased risk of venous thromboembolism [1]. The prevalence of pulmonary embolism (PE) has been shown to be higher in COVID-19 hospitalized patients compared to critically ill ones who test negative for the viral infection [2]. This is the reason why current guidelines of the International Society of Thrombosis and Haemostasis recommend the administration of thromboembolic prophylaxis in all hospitalized patients with SARS-CoV-2 infection or the use of a therapeutic dose of anticoagulant in the most critical cases. Although the pathophysiology underlying the onset of hypercoagulability during SARS-CoV-2 infection is yet not fully understood, the triggering of a powerful inflammatory response together with the role of cytokines and angiotensin converting enzyme 2 (ACE2) receptor, have shown to be able to induce endothelial cell dysfunction and damage with the subsequent onset of hypercoagulability [1]. The presence of activated neutrophils and macrophages in the target tissues has been associated with the induction of neutrophil extracellular traps (NETs) and thrombocytogenesis, promoting vascular collapse, respiratory distress up to a stage of multiorgan failure [3]. Several studies analysing the potential role of SARS-Cov-2 have shown that viral infection can induce immune system dysregulation through phenomena of epitope spreading, bystander activation, cross-reaction or molecular mimicry [4]. In particular, a limited number of autoimmune haemolytic anaemia (AIHA) cases have been reported in patients with SARS-CoV-2 infection, especially in those presenting with a severe clinical displays [5]. Here we report the case of a patient who was admitted to our Internal Medicine Ward diagnosed with warm autoimmune haemolytic anaemia (wAIHA) and pulmonary embolism (PE) with a recent COVID-19 infection.

Keywords: Autoimmune Hemolytic Anemia; Pulmonary Embolism; SARS-Cov-2

Introduction

Autoimmune haemolytic anaemia (AIHA) is a rare condition, with an estimated incidence of 1 to 3 adults in the 6th/7th decade of life every 100.000 individuals per year [6]. It is associated to the development of autoantibodies directed against self-RBC's antigens, with or without complement activation. The clinical display of this disease is heterogeneous ranging from a mild to a life-threatening condition, depending on several determining factors such as antibody thermal amplitude, complement involvement and bone marrow underlining characteristics and compensation. About 50% of AIHA are idiopathic, while 50% may be secondary to lymphoproliferative syndromes, solid tumours, other autoimmune disorders, drugs or infectious agents. Roughly 60-70% of AIHA are classified as warm autoimmune haemolytic anaemias (wAIHA) typically detecting a positive Coombs test (positive direct antiglobulin test, DAT+) associated to the presence of IgG and complement (C3c and C3d). On the other hand 20-25% of cases define cold agglutinin disease (CAD) typically related to the presence of IgM [7]. The therapeutic intervention depends on the severity of the clinical picture and patient's characteristics. Although the use of corticosteroids is extensively recognized as a 1st line treatment, it might be associated to the use of intravenous immunoglobulins, especially in acute severe onset, immunosuppressant drugs and plasma exchange [8]. Growing evidence suggests the use of rituximab in steroid resistant AIHA. Splenectomy is also considered in the absence of a prompt response to medical therapy and is described in literature to be as effective as rituximab in clinical outcomes, with a lower rate of relapse in the long term. Numerous experimental immunomodulation therapies based on targeting of the complement, and various kinases are subject of promising scientific researches [9,10]. Pulmonary embolism (PE) is a clinical presentation of venous thromboembolism (VTE), representing the third most frequent acute cardiovascular syndrome behind myocardial infarction and stroke. It is caused by the generation of thrombi, often in the deep venous compartments, which can travel up to the lung vessels and lodge at the level of the main or lobar pulmonary arteries interfering with both blood circulation and gas exchange. There are several predisposing factors to the development of VTE such as major trauma and surgery, myocardial infarction, spinal cord injuries. Among moderate risk factors, we also find autoimmune disorders, drugs, paraneoplastic syndromes, pregnancy and infectious diseases [11,12].

Investigation

A 60-year-old man was admitted to our Internal Medicine Ward "Cesare Frugoni" Policlinico Hospital of Bari (Italy) for fatigue associated to worsening dyspnoea in the last 10 days. The patient also reported two pre-syncopal episodes in the week prior to admission. At the time of hospital admission physical examination was unremarkable. The patient's past medical history was only positive for hypertension. He was a former smoker, with no familiarity for autoimmune or other relevant diseases. One month prior to the development of symptoms, he reported an infection with SARS-CoV-2, which resolved with no need for therapeutic interventions or hospitalization. The patient underwent a full vaccination cycle for SARS-Cov2. Laboratory tests were carried out showing an alteration of haemoglobin (Hb) at the time of admission 8.4 g/dL, an increased reticulocyte count and DDmer level : 2442 µg/L (n.r.<500 µg/L), bilirubin level (3.2 mg/dL, n.r. 0.2-1 mg/dL - indirect 2.38 mg/dL, n.r. 0-0.75 mg/dL), AST 131 U/L (n.r. 15-37 U/L), ALT 242 U/L (n.r. 12-78 U/L). Detection of a reduction in Haptoglobin content : <0.08 g/dL, (n.r. 0.3-2 g/dL) as well as an increased level of LDH: 798 U/L (n.r. 87-241 U/L) raised the suspicion of a haemolytic process underlining the anaemia. A positive direct antiglobuilin test (DAT+) confirmed the suspicion and identified the presence of IgG/C3d complexes leading to the diagnosis of Warm Autoimmune Haemolytic Anaemia (wAIHA). Given the increased Dimer value and the reported dyspnoea several investigation were carried out such as compression ultrasonography (CUS) of the lower limbs which was negative for deep venous thrombosis (DVT). Echocardiography showed signs of right ventricular overload (TAPSE 20mmHg, PAPS 50mmHg) without left ventricular dysfunction. The presence of dyspnoea associated to laboratory and echocardiographic findings suggested the need to perform a pulmonary angio-CT scan with consequent finding of bilateral subsegmentary pulmonary embolism (PE). In order to assess the AIHA and PE, infectious and other autoimmune causes were ruled out by serology and quantification of autoantibodies. Other laboratory tests performed such as oncology related biomarkers, and lymphocyte subset determination yielded negative results. Methylprednisolone (1mg/kg/day) was started to treat wAIHA. Given the hemodynamic stability the patient, he did not require any blood transfusions. As far as PE is concerned treatment with Enoxaparin (Clexane - Sanofi) 8000 UI/twice a day was started with no complications associated to the therapy. In the first week after initiation of the therapeutic interventions, the symptoms such as fatigue and dyspnoea improved as well as the Hb trend, which showed a progressive increase. The patient was discharged 10 days after admission with the following therapy: Apixaban (Eliquis - Bristol-Myers Squibb) 5 mg/ twice a day, Prednisone 75mg/a day (with progressive dosage tapering) and addressed to outpatient follow-up. Follow-up at 6 months showed a stable clinical picture with no disease relapse upon discontinuation of the therapy.

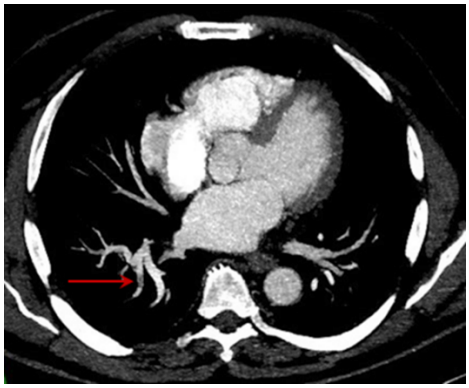

Figure 1: Chest CT scan, mediastinal window taken at the level of the inferior pulmonary lobes (arrow showing right lower pulmonary embolism).

Discussion and Conclusions

This clinical case shows a reasonable double correlation in between Covid-19 infection and wAIHA as potential risk factors to the development of pulmonary embolism. There are indeed scientific evidences, which underline the role of SARS-CoV-2-initiated inflammatory response and endothelial injury in activating the coagulation cascade with the subsequent generation of venous thromboembolism [13,14]. Growing evidence suggests that the role of endothelial cell damage-induced hypercoagulation may be caused by the alteration of different factors such as plasminogen activator inhibitor 1 (PAI-1), von Will brand factor (vWF), soluble thrombomodulin, and tissue factor pathway inhibitor (TFPI) [15]. Recent systematic reviews shed a light on the possible interaction between COVID-19 Vaccines and the pathogenesis of thrombotic events based on the possible interaction of free DNA in vaccines which can bind to platelet factor 4 (PF4) and the subsequent generation of PF4-reactive autoantibodies associated to the setting of thrombosis and even more complex clinical displays such as that of vaccine induced thrombotic thrombocytopenia (VITT) [16-18]. When it comes to AIHA, several evidences highlight its role as a predisposing factor for the development of VTE and subsequently PE. In AIHA, even though the exact pathophysiological mechanisms are yet to be identified, several hypothesis have been proposed involving the role of erythrocytes membranes alterations due to antibody related triggers, oxidative stress and the presence of cell-free haemoglobin leading to the assembly of enzymatic complexes and increased adhesion molecules expression (ICAM-1 and VCAM-1), thus enhancing coagulation [19-21]. PE in these patients is likely to be characterized by a multifactorial genesis due to the coexistence of both autoimmune haemolytic anaemia and Covid-19 infection and subsequent inflammatory response. Although SARS-CoV2 vaccinations have been linked to coagulopathies, we believe that the temporal relation between the onset of the Covid-19 infection and the diagnosis of wAIHA and the negative work-up for underlining disorders, suggests that, although mild in clinical display, the infection might have been the trigger for the development of autoimmune complications [22,23]. The association between AIHA and VTE is increasingly recognized in literature particularly within 90 days from disease onset and up to around 15-30% of adult patients presenting with wAIHA develop VTE, around 50% of which will develop PE. The frequency of occurrence has not been yet significantly linked to primary or secondary causes of AIHA. As we have seen in this case the thrombotic risk in this patient with wAIHA, prior to the diagnosis of PE, does not correlate with the traditional risk factors and does not yield positive results with the commonly used scores for VTE risk assessment. That is why anticoagulant therapy in patients with autoimmune haemolytic anaemia, especially if severe, is often delayed. Although understandable, delaying anticoagulant treatment may lead to a more complicated clinical scenario. Given the lack of specific indications for treatment timing and approach, we believe that, in patients with a diagnosis of AIHA, screening for VTE and immediate prophylaxis with anticoagulant therapy should be initiated regardless of the assessment of thrombotic risk factors.

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