Unexpected Multiple Organ Infarctions in a Poisoned Patient

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Predisposing factors for venous thrombosis can be identified in the majority of patients with established venous thromboembolism (VTE). However, an obvious precipitant may not be identified during the initial evaluation of such patients. In the present case, a 47-year-old female presented to the emergency department of our hospital after ingesting multiple drugs. She had no VTE-related risk factors or previous episodes, nor any family history of VTE. After admission to the intensive care unit sudden hypoxemia developed, and during the evaluation cerebral, renal, and splenic infarctions with pulmonary embolisms were diagnosed. However, the sources of the emboli could not be identified by transthoracic echocardiography or computed tomography angiography. Protein C deficiency was identified several days later. We recommend that hypercoagulable states be taken into consideration, especially when unexplained thromboembolic events develop in multiple or unusual venous sites.

Key Words: infarction; thrombophilia; venous thromboembolism.

Venous thromboembolism (VTE) usually manifests as deep vein thrombosis (DVT) of the lower extremities and pulmonary embolism (PE). Predisposing factors should be investigated in patients with documented VTE to establish a treatment plan. Recent trauma and surgery, immobilization, malignancy, a previous thrombotic episode, pregnancy, and certain medications are well-known predisposing factors for VTE that can be identified by taking a clinical history and performing a physical examination. However, approximately 50% of patients have no clear precipitant for VTE.[1,2] In these patients, it is important to consider inherited or acquired hypercoagulable states (also referred as thrombophilia). Here, we report a rare case in which life-threatening multiple organ infarctions and PE developed. The patient had no underlying risk factors for VTE and was diagnosed as having protein C deficiency.

Case Report

A 47-year-old female with a history of treated bipolar disorder was brought to the emergency department (ED) of our hospital

by emergency medical service personnel. Approximately 40 minutes prior to her arrival, her son had found her unconscious at home with almost 30 empty packets of drugs prescribed by her psychiatrist. Her son stated that he argued with his mother several hours before presentation to the ED. One of the patient's medication packets presented by her son included lithium (300 mg, one tablet), lamotrigine (100 mg, one tablet), escitalopram

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Fig. 1. Computed tomography (CT) of head and CT angiography. (A) Pulmonary emboli in right main and lower left lobar artery (arrows). (B) Left kidney and splenic infarctions. (C) Right kidney infarction. (D) Large low-density and sulcal effacement in middle left cerebral artery territory indicating acute infarction. Left lateral ventricle effacement and slight midline shift is also shown.

(15 mg, one tablet), quetiapine (600 mg, one tablet), lorazepam (3 mg, one tablet), and propranolol (40 mg, one tablet). On arrival in the ED, she was stuporous and her vital signs were as follows: blood pressure, 90/60 mmHg; pulse rate, 87 beats/min; respiratory rate, 40 breaths/min; and oxygen saturation of 14% on room air. Mechanical ventilation (MV) was applied and arterial blood gas analysis (ABGA) performed one hour after MV showed pH, 7.311; PaCO₂, 46.4 mmHg; PaO₂, 125.5 mmHg; and oxygen saturation, 98.8%. Electrocardiography (ECG) revealed normal sinus rhythm. Norepinephrine was started to support decreasing blood pressure. She was admitted to the intensive care unit (ICU) with continuous infusion of remifentanyl and cisatracurium for ventilator synchrony.

Approximately four hours after ICU admission, her monitored oxygen saturation fell below 90%, and a fraction of inspired oxygen of 1.0 was required to maintain oxygen saturation over 90%. Hypoxemia was observed by ABGA (PaO₂, 49.2 mmHg; oxygen saturation, 78.7%) and her serum d-dimer concentration was 9.22 mcg/mL. Her prothrombin and activated partial thromboplastin times were within the normal range. Under suspicion of PE, computed tomography (CT) angiography was performed, and emboli in her right main pulmonary artery, right upper lobar pulmonary artery, left lower lobar pulmonary artery, and left upper segmental pulmonary artery were detected (Fig. 1A). In addition, wedge-shaped low-density lesions in her spleen and bilateral kidneys were observed, suggesting acute infarction

(Fig. 1B, 1C). However, there were no findings suggestive of DVT. Transthoracic echocardiography (TTE) was performed to detect intracardiac sources of embolism; focal hypokinesia of basal inferior segment and scanty pericardial effusion were observed. However, there was no suspected cardiac source of emboli. After heparin (4,000 units initial dose, then 12 units/kg/h) was administered intravenously, head CT revealed diffuse low density and sulcal effacement in the left middle cerebral artery territory, suggesting acute cerebral infarction (Fig. 1D). Mannitol was administered to prevent aggravation of cerebral edema, and heparin was discontinued because of the possibility of hemorrhagic transformation in areas of acute cerebral infarction. On hospital day (HD) 2, extracorporeal membrane oxygenation (ECMO) was considered because of sustained hypoxemia; however, her husband deferred the decision. Fortunately, her hypoxemia improved gradually without ECMO. On HD 4, immunological studies for hypercoagulable states were performed. Conservative management with MV therapy was continued without intravenous heparin or oral anticoagulants. Five days later, the results of her immunological studies were as follows: negative anti-cardiolipin antibody; negative phospholipid antibody; negative anti-dsDNA; weakly positive lupus anticoagulant (LA), 1.22 (normal 0.8-1.2); protein C activity, 39% (normal 73-142%); and protein S activity, 58% (normal 65-140%). At HD 11 a decrease in the extent of PE was observed on follow-up CT angiography, along with a continuous improvement in renal and splenic infarct. However, head CT showed no decrease in the extent of cerebral edema. On HD 13, tracheostomy was performed because the patient remained in a stuporous state and tachypnea was frequently observed following discontinuation of remifentanyl and cisatracurium. Six days after tracheostomy she was weaned off the ventilator, and transferred to a rehabilitation hospital in a deep-drowsy state with an antiplatelet medication (clopidogrel 75 mg daily) on HD 25.

Discussion

Protein C, protein S, and antithrombin III (AT III) are natural anticoagulants. A hypercoagulable state occurs when coagulation activities surpass anticoagulation activities, resulting in an increased propensity for abnormal blood clot

development. A hypercoagulable condition can result from antiphospholipid syndrome or a deficiency in one of the natural anticoagulants.

Our patient developed severe hypoxemia after admission to the ICU as a result of multidrug poisoning. While PE was initially suspected; cerebral, renal, and splenic infarctions as well as PE were detected during the evaluation. However, the sources of emboli were not identified in the CT angiography and TTE. The cause of the patient's multiple organ infarctions was not ascertained for several days.

In clinical practice, hypercoagulable states should be suspected in patients with thrombi of multiple or unusual venous sites, such as the hepatic, portal, mesenteric, and cerebral veins. However, in the present case we focused solely on the patient's medical and family history and the association between ingested drugs and thromboembolism. Consideration of the hypercoagulable disorders was limited initially. Clinical findings such as thrombosis at age <45 years, family history of thrombosis, recurrent idiopathic thrombosis, and unexplained spontaneous abortions also suggest a hypercoagulable state.

When hypercoagulable states are suspected, functional and immunological assays—including protein C and S, AT III, activated protein C resistance—and testing for antiphospholipid syndrome including anticardiolipin antibody and lupus anticoagulant should be performed. Decreased protein C and S activities, and increased LA level, were observed in the present case. Protein C deficiency was thought to be the main factor contributing to the multiple organ infarctions in this patient because her protein S activity and LA level were only slightly lower or higher than the normal range, respectively.

Protein C is vitamin K-dependent protein that exerts its anticoagulant effect by inactivating coagulation factors Va and VIIIa, which are necessary for thrombin generation.[3] The prevalence of protein C deficiency is 0.2-0.5%.[4,5] In one study, patients with this disorder had a sevenfold increased risk of venous thrombosis.[6] In most patients thrombosis is rare until their early 20s, with increasing numbers experiencing thrombotic events as they reach the age of 50 years. Cases of cerebral[7,8], myocardial[7,9], and mesenteric[10] infarction caused by protein C deficiency have been reported.

The present case has some notable issues. First, long-term ECG monitoring and transesophageal echocardiography

(TEE), if TTE is negative, may be necessary to capture paroxysmal atrial fibrillation and to exclude a cardioembolic source. In this patient, atrial fibrillation was not monitored in the ICU. However, TEE was not performed for fear of aggravation of cerebral edema.

Second, acquired causes of low protein C should be considered. Protein C levels can decrease due to secondary consumption during the initial phase of VTE.[11] In addition, oral anticoagulants, liver disease, and vitamin K deficiency can cause lower protein C levels. Laboratory tests and a repeated measurement of protein C level may be used to rule out these conditions. In our patient, we were unable to measure the patient's protein C activity repeatedly because she did not present to our hospital again. If protein C deficiency was not the cause of the multiple organ infarctions in this patient, in the absence of other identified causative factors she may be diagnosed as having idiopathic VTE.

In conclusion, life-threatening thromboembolic events may develop as a result of hypercoagulable disorders. Although suspicion of the hypercoagulable disorders in the absence of a patient or family history of VTE is unlikely, they should be suspected when unexplained thromboembolic events develop in multiple or unusual venous sites.

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