CASE REPORT

Accelerated arterial and venous clots in a young pregnant woman: a saga of thrombotic storm

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aryal.madan@gmail.com**SUMMARY**

Thrombotic storm is a rare condition, characterised by serial thrombotic events, which escalates rapidly within a few days to a few weeks involving multiple and unusual sites. Since it usually responds to anticoagulation and is often lethal if not treated promptly, early diagnosis is crucial. We describe a case of a young pregnant woman with multiple acute arterial and venous thrombotic events including stroke and myocardial infarction, who successfully recovered with continued anticoagulation therapy.

BACKGROUND

Recurrent arterial and venous clots in a short period of time are rare in young patients, particularly those without high-risk thrombophilia or other acquired risk factors for clotting. The differential diagnosis of such hypercoagulable state is relatively short and includes heparin-induced thrombocytopenia (HIT), disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP) and disseminated malignancy.¹ We describe a case of a young pregnant woman who developed multiple acute arterial and venous thrombotic events within 4 days.

CASE PRESENTATION

A 28-year-old African-American woman, 14 weeks pregnant, presented to the emergency department with nausea, abdominal pain and elevated blood glucose. Her medical history was significant of long-standing diabetes mellitus type I on insulin glargine, poorly controlled hypertension and non-compliance to her medications. Her personal and family history was negative for thrombophilia and connective tissue disorders. She was a current smoker with a 7 pack-year history of smoking. She denied any alcohol intake and drug abuse. On examination, she was afebrile and had a blood pressure 160/90 mm Hg. An examination of the chest, the cardiovascular system, the abdomen and the neurological examination were normal.

INVESTIGATIONS

Laboratory test results revealed: white cell count 11 300/mm³, haemoglobin 9.4 g/dl, haematocrit 26.5%, platelet 194 000/mm³, blood urea nitrogen 14 mg/dl, creatine 1.06 mg/dl and prothrombin time 10.2 s. Urine analysis showed ketones (40 mg/dl). Her chest x-ray was normal. A diagnosis of diabetic ketoacidosis (DKA) was made.

TREATMENT

She was treated with infusion of regular insulin and normal saline. Heparin (5 000 U subcutaneous

every 8 h) for deep vein thrombosis prophylaxis was started on the day of admission. Her hypertension was treated with hydralazine.

OUTCOME AND FOLLOW-UP

On day 2 of hospitalisation, she developed shortness of breath. Her chest x-ray showed bilateral chest infiltrates consistent with atypical pneumonia. She was treated with ceftriaxone and azithromycin. However, she developed progressive hypoxic respiratory failure requiring continuous positive airway pressure and was transferred to intensive care unit.

On day 4, she delivered non-viable fetus. Hospital stay was further complicated by the development of inferior wall myocardial infarction leading to pulmonary oedema. Cardiac catheterisation revealed right coronary artery clot without any significant coronary atherosclerosis. Transthoracic echocardiogram showed a mass in the mitral valve concerning for vegetation or thrombus. The blood cultures, sputum cultures and urine cultures were all negative, thus suggesting against vegetation from bacterial endocarditis. HIV serology was negative. She subsequently developed thrombocytopenia (nadir platelet count 51 000/mm³) and renal failure (peak creatine level 2.2 mg/dl). Haemolytic panel including reticulocyte count, peripheral blood smear, haptoglobin and lactate dehydrogenase levels were normal. D-Dimer and fibrinogen were elevated at 1715 ng/ml and 528 mg/dl, respectively. Coagulation profile (prothrombin time and partial thromboplastin time) was normal. Tests for HIT antibodies and serotonin release assay were sent; prophylactic heparin was stopped and argatroban drip was started. With negative test results for HIT antibodies and serotonin release assay, argatroban infusion was subsequently switched to heparin drip.

On day 5, she developed left upper-quadrant abdominal pain. CT scan of the abdomen and pelvis revealed splenic infarct and bilateral iliac vein thrombi. An extensive workup including lupus anticoagulant, anticardiolipin antibody, β -2-glycoprotein, factor V Leiden mutation, prothrombin gene mutation, antithrombin III, protein C, protein S, flow cytometry for CD 55/CD 59 assays and homocysteine level were unremarkable. Evaluation for connective tissue disease including antinuclear antibody, antimitochondrial antibody, antiproteinase-3 antibody and anti-glomerular membrane antibody were also normal.

On day 8, she was found to have clonus of bilateral feet while on mechanical ventilation and sedation. MRI of the head showed multiple embolic stroke in bilateral cortices and cerebellum in numerous vascular territories. Given her young age and recurrent

To cite: Aryal MR, Badal M, Bhandari N, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-009776

thrombosis in coronary, splenic, iliac and cerebral vessels, a diagnosis of thrombotic storm (TS) was considered. She was maintained on unfractionated heparin. Despite the rapidly progressive clinical course, she responded to aggressive uninterrupted anticoagulation with heparin which was switched to warfarin on discharge. Continued anticoagulation for 3 months led to recovery of symptoms with minimal residual neurological deficit.

DISCUSSION

TS is a rare entity characterised by excessive and accelerated course of acute to subacute thrombosis in unusual sites involving multiple organs. Although not fully known, the postulated triggers include pregnancy, inflammation, trauma, surgery and infection.^{1 2} Despite its occasional association with known hypercoagulable conditions such as antiphospholipid syndrome, factor V Leiden mutation and protein C deficiency, the exact aetiology for the fulminant course of TS remains largely unclear. Possible explanations include variable phenotypic expression of coagulation disorders or the presence of yet-to-be-determined novel hypercoagulable disorders. A subset of patients with TS have positive antiphospholipid antibodies and share clinical features with catastrophic antiphospholipid antibody syndrome (CAPS).²

The diagnostic criteria of TS includes younger age (less than 38-year-old) plus two or more of the clinical criteria (Box 1).¹

The criteria establish the diagnosis of TS not by any specific test or pattern of hypercoagulable state or thrombophilia marker but by its stereotypic clinical behaviour.¹ The clues that TS may be impending in an otherwise routine case of thrombosis include rapid development of thrombosis in multiple and unusual sites even while primary site is being evaluated.

TS shares many features with haemolysis with elevated liver enzymes and low platelets (HELLP) syndrome,^{1 3 4} pre-eclampsia,⁵ antiphospholipid syndrome,⁶ TTP⁷ and HIT.⁸ TS may be seen in association with and be superimposed upon the above-mentioned conditions. It has been argued that the combination and rapidity of multiple thromboembolic events at unusual sites distinguishes TS which might be regarded as extreme rather than distinct free-standing entity. It is important to distinguish TS from HIT in patients with multiple thromboembolic episodes because of the difference in the choice of the anticoagulant. The response of TS to intravenous and then oral anticoagulant agents differentiates it from Trousseau's

syndrome⁹ and DIC.¹⁰ Unlike DIC, TS is not necessarily associated with coagulopathy. TTP can be differentiated by the presence of microangiopathic haemolytic anaemia, thrombocytopenia and renal failure. However, the distinction can be difficult in certain patients. We hypothesise that there might be some role of inflammatory cascade in intensifying this process in predisposed patients.

Our patient was pregnant and went on to have fetal abortion; however, the clinical and laboratory parameters for HELLP syndrome, pre-eclampsia, HIT, DIC and TTP were not met. The absence of antiphospholipid antibody rules out the diagnosis of CAPS. The presence of multiple hypercoagulable conditions such as DKA, pneumonia and respiratory failure, pregnancy as well as cardiovascular risk factors likely predisposed the patient to TS. The Thrombotic Storm Study Group criteria were used to establish the diagnosis of TS.

Prompt diagnosis and therapy with aggressive anticoagulation is the key to control TS.¹ TS responds very well to continuous anticoagulant therapy.² Since fresh clots are known to contain and release thrombin, TS may exacerbate explosively with cessation or even brief interruption in anticoagulation therapy.² In the event of recurrent thrombosis despite anticoagulation or anticoagulation failure the need for insertion of a vena caval filter is often considered by physicians. However, in TS, insertion of a vena caval filter is not recommended, as these filters may further increase the coagulation.¹¹ In paediatric population pharmacomechanical thrombolysis via an interventional radiological approach, local catheter-directed tissue plasminogen activator (tPA) administration, systemic intravenous tPA administration, surgical thrombectomy or a combination of these have been used. Immunomodulatory therapies including steroids, intravenous immunoglobulin and/or plasmapheresis have also been tried. Rituximab and cyclophosphamide have been used in children with persistent evidence of inflammation. The long-term prognosis with resolution of acute TS is generally excellent but in one instance, paroxysmal nocturnal haemoglobinuria developed during 10 years follow-up. It is important to note that paediatric population tends to do worse in the long term with recurrent persistent thrombosis and post-thrombotic syndrome despite treatment.^{1 12} Our case highlights a good approach to recurrent thromboembolism in young patients: the need to exclude congenital thrombophilia as well as acquired conditions such as antiphospholipid syndrome, DIC, HIT and TTP; early diagnosis of TS using Thrombotic Storm Study Group criteria, avoidance of vena caval filter and continued uninterrupted anticoagulation.

Box 1 Thrombotic Storm Study Group diagnostic criteria of thrombotic storm¹

- ▶ Acute, two or more arterial or venous thromboemboli, with or without thrombotic microangiopathy, typically in a compressed period of time (1–2 weeks) yet may recur from time to time over years
- ▶ Unusual location (other than pulmonary embolism, lower extremity deep venous thrombosis, myocardial infarction and stroke) such as thrombosis of hepatic, cerebral, portal, or renal veins, skin (purpura fulminans) and adrenal glands
- ▶ Progressive/recent unexplained recurrence
- ▶ Refractory to acute therapy or atypical response to therapy
- ▶ Exacerbated by inadequate or interrupted treatment
- ▶ Frequently preceded by an initiating event (pregnancy, inflammation, trauma, surgery and infection)

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Learning points

- ▶ Thrombotic storm is an acute hypercoagulable syndrome with rapidly escalating course of acute serial thrombotic event in unusual location.
- ▶ Thrombotic Storm Study Group criteria, which include those of age less than 38 years, thrombotic events in unusual sites, unexplained recurrence and possible triggering events should be utilised for early diagnosis.
- ▶ Rarity of the disease, reliance on clinical syndrome and lack of specific tests can result in the delay of diagnosis; physicians' awareness and suspicion are important for prompt diagnosis.
- ▶ Continuous anticoagulation remains the mainstay of treatment; vena caval filter should be avoided.

Contributors MRA and MB wrote the initial version of the manuscript. NB and VRB made the initial edits. MRA, NB and VRB contributed to final revision of the manuscript. MB obtained patient consent.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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