Intracardiac thrombi and skin necrosis in a young female patient

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Peripartum cardiomyopathy (PPCM) is a rare cause of heart failure which usually develops between 4 weeks prepartum and 5 months postpartum in women without previously known cardiac disease. Intracardiac thrombi are not uncommon in patients with PPCM [1]. But other factors such as protein C deficiency may aggravate the hypercoagulable state caused by PPCM. In patients with protein C deficiency, oral anticoagulant therapy with warfarin may cause severe skin necrosis known as warfarin-induced skin necrosis (WISN) [2]. In these patients, re-introduction of therapy with warfarin has produced variable results: with recurrence/worsening of the skin necrosis, or without recurrent thrombosis [2–4]. Here we present a young female PPCM patient with protein C deficiency and WISN; warfarin was reintroduced and no skin necrosis occurred again.

A 27-year-old female patient was referred to Peking Union Medical College Hospital in May, 2010, with a 3-year history of breathlessness. The symptoms developed 12 weeks after an uncomplicated pregnancy with normal vaginal delivery. Her past medical history was unremarkable. Echocardiography performed 16 weeks after the delivery showed dilated left atrium (LA) and ventricle with left ventricular ejection fraction (LVEF) of 21% and multiple intracardiac thrombi. She was started on warfarin 4.5 mg daily covered with subcutaneous low molecular weight heparin (LMWH). Four days later, painful purpuric lesions and subsequently full thickness skin necrosis occurred in the abdomen. Both LMWH and warfarin were withheld and the abdominal skin necrosis healed gradually with formation of a large scar (Figure 1 C). Three months later, new ecchymotic skin plaques appeared on her arms and legs that progressed to painful necrotic ulcers, and she was referred to our hospital for further management.

Her initial blood tests including full blood count, renal and liver function tests, antinuclear antibodies, anticardiolipin antibodies, and lupus anticoagulant were unremarkable. Repeated echocardiography revealed dilated LA (47 mm) and LV (LVEDD = 71 mm) with LVEF of 30%, multiple intracardiac thrombi and the cardiac magnetic resonance showing similar findings (Figures 1 A and 1 B). The levels of protein S, activated protein C resistance and antithrombin III were normal, but the level of protein C decreased (50% activity; normal range: 69–151%). The biopsy of the skin...
plaque showed lymphocytic infiltration in the dermis, without vasculitis manifestation. The diagnosis of PPCM complicated by WISN in presence of protein C deficiency was established. Because the oral anticoagulant therapy was indispensable for the patient, warfarin was reintroduced starting at a very low dose (1.5 mg/day) and titrating gradually with co-administration of intravenous unfractionated heparin (UFH), which was adjusted to maintain the activated partial thromboplastin time between 1.5 and 2.0 times the baseline value until a therapeutic international normalized ratio (INR) $\geq 2.0$ had been reached. During the anticoagulant therapy, no further skin necrosis developed and the original lesions healed. On discharge, she was taking warfarin 4.5 mg daily and the INR was 2.33. Her breathlessness was resolved after diuretic therapy. Carvedilol and enalapril were titrated gradually to 25 mg q12h and 10 mg q12h respectively. During the 9-month follow-up period, she remained asymptomatic except fatigue on heavy physical exertion, and no new skin lesion was observed. Repeated echocardiography at 9 months after discharge showed nearly normal LVEF (47%) and decreased LV (LVEDD = 63 mm).

To our knowledge, this is the first report presenting PPCM with protein C deficiency and subsequent development of WISN. This case fulfilled the diagnostic criteria of PPCM [5]. The etiology of PPCM is not well understood. Potential causal mechanisms include viral infection [6], autoimmune disease, and abnormal response to the hemodynamic stress of pregnancy. Recently a myocardial tissue study in PPCM revealed ultrastructural remodeling of small capillaries with the presence of endothelial cell apoptosis and impairment of the microcirculation [7]. In our case, the multiple intracardiac thrombi suggested that there may have been another factor aggravating the hypercoagulable state caused by PPCM. This was later proved to be a decreased level of protein C.

Figure 1. A – Echocardiogram showing multiple intracardiac thrombi (indicated by arrowheads). B – Cardiac magnetic resonance showing similar findings to echocardiogram. C – Large scar in the abdomen after the WISN healed.
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The abdominal skin necrosis was closely related to the use of warfarin, which was diagnosed as Warfarin-induced skin necrosis. Warfarin-induced skin necrosis is a rare disease which affects 0.01% to 0.1% of patients treated with the oral anticoagulant. The most common predisposing factor of WISN is protein C deficiency, as illustrated in this case. The mechanism is thought to be that the protein C level drops rapidly after the intake of warfarin because of its short half-life, so administration of warfarin to protein C-deficient individuals causes a paradoxical hypercoagulable state at the start of treatment. This leads to thrombotic occlusions of the microvasculature with resulting necrosis [8].

In the patients suffering from protein C deficiency, skin necrosis may occur even without warfarin use because of the hypercoagulable state, and histological examination typically shows presence of fibrin thrombi filling the vessel lumen in the superficial dermis [9, 10]. The absence of vascular thrombi in our case was probably due to prior anticoagulant use for 10 days before the skin biopsy.

Our case serves to alert physicians to perform prompt investigation of possible underlying thrombophilia in PPCM patients presenting with multiple intracardiac thrombi and unexplained skin lesions. Recently we have had several alternative anticoagulation medicines, such as oral factor II antagonist (dabigatran) or factor Xa antagonist (rivaroxaban). However, their use in WISN has not been proven by evidence-based medicine. Our case suggests that successful re-administration of warfarin in patients with a history of WISN is possible by starting at a low dose with gradual dose adjustment, as demonstrated in our case.

Written informed consent was provided by this patient.

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