A case of recurrent severe pre-eclampsia associated with essential cryofibrinogenaemia

Katrina Chau¹, Christopher Henderson², Alan Adno³, Timothy Spicer¹, Bruce Cleland¹ and Angela Makris¹

Abstract

Essential cryofibrinogenaemia is a rare disorder characterized by cryofibrinogens without cryoglobulins. Connective tissue disorders and thrombophilia are known to increase risk of pre-eclampsia, but pre-eclampsia has not previously been reported in association with cryofibrinogenaemia. We report the case of a 32-year-old woman with recurrent severe pre-eclampsia diagnosed with essential cryofibrinogenaemia.

Keywords

Severe pre-eclampsia, cryofibrinogenaemia, eosinophilic/T-cell vasculitis

Introduction

Cryofibrinogens were first described in 1955 and are a complex of proteins including fibrin, fibrinogen and fibronectin that precipitate in plasma when cooled to 4°C¹ as opposed to cryoglobulins that precipitate in serum. Cryofibrinogenaemia may be primary (essential) or secondary to malignancy, connective tissue disorders or infection. Manifestations include livedo reticularis, digital ulceration and gangrene. We describe a case of recurrent episodes of severe pre-eclampsia associated with cryofibrinogenaemia.

Case report

A 32-year-old Arabic woman had previously developed severe pre-eclampsia requiring delivery at 27 (1998) and 26 weeks gestation (2003). The 2003 pregnancy was complicated by a cerebrovascular accident. She had been admitted from 21 weeks of gestation with difficult to control hypertension associated with headache and visual disturbances. There was no haematologic or other biochemical derangement. Ultrasound confirmed placental insufficiency with fetal growth on the fifth centile. She developed headache and drowsiness and proceeded to emergency caesarean section. Magnetic resonance imaging showed ischaemic changes with increased signal intensity in the right basal ganglia and subcortical white matter of the right frontal lobe. A thrombophilic and autoimmune disorder such as antiphospholipid syndrome was considered. Investigation identified her to be heterozygous for Factor V Leiden mutation but no other prothrombotic or autoimmune tendency was found on repeated testing. Transoesophageal echocardiogram revealed a small patent foramen ovale but Doppler ultrasound did not reveal any deep vein thrombosis. She was anticoagulated with warfarin but had difficulty achieving the therapeutic range and this was discontinued.

She developed chronic hypertension prior to her recent pregnancy in winter 2010. Despite treatment with aspirin, calcium supplementation and prophylactic low-molecular-weight heparin she developed severe pre-eclampsia necessitating delivery at 25 weeks of gestation. During this pregnancy she was noted to have widespread livedo reticularis (Figure 1) and on further questioning had longstanding Raynaud's phenomenon. Further investigation revealed the presence of cryofibrinogens and methylene tetrahydrofolate reductase polymorphism. Histology of the placenta suggested eosinophilic/T-cell vasculitis (Figure 2). The cryofibrinogenaemia persists two months post delivery as does her Raynaud's phenomenon and livedo reticularis.

Investigations of underlying causes of her cryofibrinogenaemia were negative.

The fetus weighed 531 g at birth and survived. The baby had hyaline membrane disease, pulmonary haemorrhage, sepsis and physiological jaundice but was discharged from hospital at the corrected age of 39 weeks.

Discussion

The pathogenesis of cryofibrinogenaemia is poorly understood. Cryofibrinogenaemia in itself is not necessarily pathogenic as cryofibrinogens have been found in plasma of otherwise healthy blood donors.² Manifestations secondary to cutaneous ischaemia in the peripheries can be explained by cryofibrinogens and there is often a temporal relationship between cold exposure and onset of symptoms. However, other venous and arterial thrombotic events have been reported including pulmonary emboli, cerebro- and cardio-vascular ischaemia and mesenteric artery thrombosis.¹ The most likely hypothesis for the pathogenesis of cryofibrinogens is a defect in fibrinolysis, supported by high levels of protease inhibitors and cases where fibrinolytics have resulted in significant improvement of symptoms.³

Cryofibrinogenaemia is a rare disorder that may contribute to the development of pre-eclampsia. The manifestations of essential cryofibrinogenaemia may be more obvious in pregnancy because pregnancy induced increase in fibrinolysis inhibitor activity. The frequency of cryofibrinogens has been demonstrated to be higher in healthy pregnant women⁴ compared with non-pregnant. This may be due to the effect of hormones, as women using oral contraceptives in the 1960s had significantly higher incidence of cryofibrinogenaemia.⁵ Impaired fibrinolytic function may cause, or be an effect of, endothelial dysfunction precipitating pre-eclampsia. Placental insufficiency may be caused by thromboses. The finding of eosinophilic/T-cell vasculitis in the

¹Renal Unit

²Department of Anatomical Pathology, Sydney South West Pathology Service

³Department of Obstetrics and Gynaecology, Liverpool Hospital, Elizabeth Street, Liverpool, Sydney, New South Wales 2170, Australia

Corresponding author:

Katrina Chau, Liverpool Hospital, Elizabeth Street, Liverpool, Sydney, 2170, Australia.

Email: dr.katrina.chau@gmail.com

Figure 1. Livedo reticularis of the hands and lower limbs. Note: hyperaemia of the digits. The photographs were taken in an air-conditioned clinic room at 22°C.

Figure 2. Eosinophilic/T-cell vasculitis of the placenta. (A) Low power showing crescentic area of deeper pink staining in the superior aspect of a chorionic vessel, corresponding to a site of vasculitic damage with deposition of fibrinoid material. (B) High power of the area of fibrinoid degeneration, demonstrating a significant inflammatory infiltrate of eosinophils (dark red cytoplasm) and lymphocytes and (at the bottom of the image) loss of integrity of the endothelial layer.

placenta is of uncertain significance. It is possibly associated with fetal vascular thrombo-occlusive disease.⁶ This patient also had prothrombotic genotypes which may have further increased the risk of pre-eclampsia.

It is unclear as to whether any treatment could have altered the outcome. Treatment in early pregnancy may have modulated abnormal placental development but fibrinolytic therapy such as stanozol and tissue plasminogen activators are contraindicated. The use of steroids, immunosuppressants and plasmapheresis has limited evidence¹ and may have exposed the patient to risk with uncertain benefit.

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Declaration of conflicting interests

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Ethical approval

The authors obtained written patient consent to publish this case report.

Guarantor

KC.

Contributorship

KC wrote the first draft of the manuscript. AM presided over the case. AA, TS and BC assisted in the clinical management of the patient. CH provided a pathological diagnosis and figure legend. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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