Cerebral Vasospasm and Intracerebral Haemorrhage in a Case of Pregnancy-Related Thrombotic Thrombocytopenic Purpura / Haemolytic Uraemic Syndrome

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Summary

We report a case of a woman with pregnancy-related thrombotic thrombocytopenic purpura / haemolytic uraemic syndrome (TTP/HUS) who developed cerebral vasospasm similar to that seen in the other pregnancy-related thrombotic microangiopathic syndromes of eclampsia and HELLP syndrome. A further complication in this case was the development of a focal intracerebral haemorrhage necessitating surgical removal. Despite a successful evacuation of the haematoma and several plasma exchange treatments she developed recurrent haemolysis and thrombocytopenia with an eventual fatal outcome due to severe pulmonary and gastrointestinal haemorrhage.

Introduction

Pre-eclampsia, eclampsia and Haemolysis, Elevated Liver enzymes and Low Platelets, or HELLP syndrome, form a spectrum of related thrombotic microangiopathic disorders of pregnancy^{1,2,3}. The development of neurological complications in these cases is often associated with the presence of cerebral vasospasm^{1,2,4-7}. Yet another rare pregnancy-related thrombotic microangiopathic disorder is the Thrombotic Thrombocytopenic Purpura/Haemolytic Uraemic Syndrome (TTP/HUS)^{2,8}. TTP/HUS is as-

sociated with renal and neurological dysfunction. We have found no evidence to date of cerebral vasospasm being documented radiologically in a case of pregnancy-induced TTP/HUS.

Case Report

A 27-year-old previously healthy gravida III, para I woman with a previous normal first delivery and second mid-trimester abortion was admitted at 28 weeks of pregnancy with antepartum haemorrhage and evidence of premature labour. She was initially managed conservatively with bed-rest but five days later developed acute pulmonary oedema and pneumonia, treated with antibiotics, diuretics and oxygen supplementation.

At this stage she had a mild anaemia with a prepartum haemoglobin level of 10.5 g/dl and a platelet count of 172,000/ml. Three days after this she developed worsened bleeding per vaginum with slowing of the foetal heart rate. An emergency caesarian section was performed during which an 80% placental abruption was diagnosed. During the following two days after delivery her platelet count fell to 17,000/ml. She also developed acute respiratory failure possibly on the basis of pulmonary haemorrhage requiring mechanical ventilation. Her blood pressure was not elevated at any

Figure 1 Unenhanced axial CT scan showing the left frontal intracerebral haemorrhage.

stage during this postpartum period. Her renal function also progressively deteriorated (urea 21.7 mmol/L and creatinine 142 μ mol/L) with proteinuria of more than 3g/L, and her haemoglobin level fell to 6.5 g/dl. Her liver function tests remained normal and the lactate dehydrogenase (LDH) levels rose to a high of 2169 IU/L due to the haemolysis.

The prothrombin and partial thromboplastin-times were within normal limits. At this stage no assay for ADAMTS-13 activity was available locally. She was treated with plasmapheresis with a transient improvement in the platelet count to 59,000/ml and fall in LDH levels to 541 IU/L. She relapsed again despite daily plasmapheresis and blood and platelet transfusions. After several more days she improved yet again and the decision was taken to stop the sedation and to wean her from the ventilatory support. As she was being awoken she was found to have a right-sided hemiparesis. An unenhanced CT scan showed a large left frontal intracerebral haemorrhage with no cerebral oedema noted in the parietal or occipital lobes (figure 1). At this stage her platelet count had

improved to a level of 136,000 /ml. Wishing to exclude possible anatomical cerebrovascular abnormality prior to surgical evacuation of the haematoma the attending neurosurgeon requested a cerebral arteriogram. Digital subtraction arteriography showed multifocal areas of stenosis in various central and peripheral intracranial arteries suggestive of an arteritis or diffuse vasospasm (figure 2A-D). With no supportive clinical or serological data to support the diagnosis of a systemic arteritis and given the earlier complicated pregnancy it was decided that the arteriographic findings did indeed represent diffuse vasospasm. The haematoma was duly evacuated without complication. Despite some initial improvement in renal function and a haemoglobin level of 11.4 g/dl and platelet count of 196,000 she deteriorated yet again several days later with worsening renal function and fall of the haemoglobin level to 6.6 g/dl and platelet count to 66,000/ml. At this stage she developed severe uncontrollable pulmonary and gastrointestinal haemorrhage and despite further plasmapheresis therapy she developed refractory shock and died.

Discussion

For many years both thrombotic thrombocytopenic purpura (TTP) and haemolytic uraemic syndrome (HUS) were considered separate clinical syndromes, with TTP being characterized by fever, fluctuating neurological manifestations, renal impairment, microangiopathic haemolytic anaemia (MAHA) and thrombocytopenia, and HUS by fever, acute renal failure, MAHA and thrombocytopenia⁹. More recently both TTP and HUS have been recognized as parts of a spectrum of overlapping conditions whose fundamental abnormalities are related to microvascular occlusions, and whose clinical manifestations depend upon the organ or organs most affected by this occlusive microangiopathy. The clinical spectrum is now termed TTP/HUS⁸.

The basic pathogenetic mechanism is endothelial cell damage probably caused by circulating factors toxic to the endothelial cell, and possibly even in some cases via an auto-immune mechanism although TTP/HUS is not classified primarily as an auto-immune disorder. Among the various substances released into the circulation by the damaged endothelial cells are ultra-large multimeric molecules of

Figure 2 A) Selective left vertebral digital subtraction arteriogram, lateral projection, showing spasm in the posterior inferior cerebellar artery (arrow) B) Selective right internal carotid DSA, Townes projection, showing severe spasm in the anterior and proximal middle cerebral arteries. C) Selective left internal carotid DSA, LAO projection, showing spasm in the supraclinoid ICA (white arrow) and pericallosal artery (double arrow). An "aneurysm" at the A1-A2 junction was originally suspected but disproven with 3D rotational arteriography.

the von Willebrand factor (VWF). These VWF multimers play an important role in stimulating platelet aggregation particularly in the microcirculation^{9,10}. ADAMTS-13 is a metalloprotease responsible for in-vivo degradation of circulating VWF multimers. A severe deficiency (?5% normal activity) of ADAMTS-13 has

been detected in some, but not all, patients suffering from TTP/HUS suggesting that there are other factors responsible for the pathogenesis and development of the clinical features¹¹. Certainly cases of pregnancy-induced TTP/HUS have been shown to have markedly reduced ADAMTS-13 levels, often on the basis of a

congenital enzyme deficiency^{2,8}. After platelet activation, fibrin-platelet microaggregates form which mechanically occlude the microvessels not only producing tissue ischaemia but also resulting in fragmentation of erythrocytes as they are forced through the partly obstructed arterioles. This leads to the development of a microangiopathic haemolytic anaemia (MAHA)^{9,10}. The formation of the platelet aggregates (microthrombi) results in accelerated platelet consumption and thrombocytopenia with a secondary bleeding tendency. In addition to familial and idiopathic forms of TTP/HUS as well as those cases related to pregnancy, other cases are related to cancer and chemotherapy, bone-marrow transplantation and immunosuppressive therapy.

Pregnancy-related TTP/HUS shares common clinical and pathophysiological features with the other pregnancy-related thrombotic microangiopathic complications including severe pre-eclampsia, eclampsia and the Haemolysis, Elevated Liver enzymes, Low Platelets (HELLP) syndrome. The important clinical features of TTP/HUS include the hematologic abnormalities (being thrombocytopenia and MAHA), fever, neurological symptoms such as diffuse mental status abnormalities, focal neurological deficits and seizures, and acute oliguric renal failure. Pre-eclampsia consists of the combination of hypertension and proteinuria whereas severe pre-eclampsia involves a wider spectrum of abnormalities including severe hypertension, neurologic abnormalities, renal dysfunction, thrombocytopenia, MAHA and hepatocellular abnormalities.

Eclampsia is pre-eclampsia with the development of seizures. HELLP syndrome is considered to be severe pre-eclampsia with prominent MAHA, thrombocytopenia and liver function abnormalities. Unlike in pre-eclampsia and eclampsia, hypertension is not a feature of TTP/HUS, as in our case. Similarly the liver function abnormalities seen in HELLP syndrome are not characteristic of TTP/HUS. Mild thrombocytopenia is common in pre-eclampsia although MAHA is not. A somewhat simplistic view is that HELLP syndrome predominantly affects the liver whereas TTP/HUS affects the kidneys and central nervous system. There is thus much overlap between these various syndromes and their differentiation can be difficult. It is critical, however, to try and diagnose TTP/HUS as the treatment of choice for

this condition is plasma exchange which is of no benefit in the treatment of pre-eclampsia, eclampsia or HELLP syndrome^{2,10}. Plasma exchange is thought to help by replacing the deficient ADAMTS-13 enzymes or other factors necessary for reversal of the syndrome, as well as removing any relevant active auto-antibodies from the patient's circulation^{2,9}. Not all cases of TTP/HUS respond to plasma exchange, however. Our patient was assessed as having TTP/HUS by virtue of the severe thrombocytopenia, haemolytic anaemia, renal dysfunction, and lack of hypertension and hepatic function abnormalities. Being initially sedated and ventilated the neurological problems only became apparent at a much later stage.

Both systemic and cerebral vasospasm are well-described features of pre-eclampsia, eclampsia, delayed eclampsia, and HELLP syndrome^{1,3-7}. Common to all of these syndromes is the initial development of endothelial cell injury, possibly triggered by the release of circulating toxic factors from the foetal-placental unit, with varying degrees of associated haemolysis, platelet activation and consumption and capillary leakage. The endothelial cell injury, in addition to triggering platelet aggregation, is also thought to lead to altered vessel wall regulation and response to circulating systemic vasoactive substances (e.g. angiotensin II), as well as the release of local vasoactive substances within the endothelium (e.g. nitric oxide)⁷. It is the combination of enhanced vascular sensitivity to local and systemic pressor agents, microthrombosis and loss of intravascular volume due to capillary leakage that leads to vasospasm and reduced tissue perfusion thereby causing the various clinical manifestations of these syndromes.

Diffuse vasospasm may thus account for the hypertension seen in pre-eclampsia or eclampsia. Hypertension is usually not a feature of either HELLP or TTP/HUS unless there is associated pre-eclampsia.

Cerebral vasospasm is most commonly seen following aneurysmal subarachnoid haemorrhage (SAH), and uncommonly related to SAH from vascular malformations, tumours or trauma¹². The exact pathogenesis of cerebral vasospasm following SAH is poorly understood, but has been shown to be related to the presence of blood/clot in the subarachnoid space. The development of vasospasm appears

to be related to both the volume of and duration of exposure to the blood around the cerebral arteries^{12,13,14}. The development of vasospasm is thought to be related to the release of spasmogenic substances from the perivascular clot that then gain access to the inner layers of the vessel through a porous adventitia¹⁵. The chief suspect for the stimulation of cerebral vasospasm is oxyhaemoglobin (OxyHb)¹⁶. The time of onset of vasospasm following aneurysmal SAH is related to the onset of lysis of red cells within the perivascular clot, i.e. at 3-5 days post haemorrhage, with the subsequent release of free OxyHb into the perivascular environment. Again the exact mechanism by which the OxyHb produces vasospasm is unknown, but is thought to be possibly mediated by a number of potential mechanisms including altered eicosanoid production, generation of free radicals, stimulation of cellular vasoconstrictors and inhibition of nitric oxide and other cellular vasodilatory substances. After penetration of the adventitia the OxyHb acts on both mural smooth muscle and endothelial cells, although there may be an additional role played by the adventitia itself in the development of the vasospasm^{17,18}.

The cerebral arterial vasospasm seen in the pregnancy-related microangiopathies differs in its pathogenesis from that occurring after aneurysmal SAH in that the spasmogenic factors exist primarily within the vessel lumen and not in the perivascular space. The spastic response is thus to circulating spasminogens rather than the relatively "static" ones encountered in the perivascular clot after SAH. Again the presence of free OxyHb within the circulating blood is thought to be the principal cause of the cerebral (and systemic) vasoconstriction seen in the pregnancy-related microangiopathies¹⁹. In addition to the effects of free OxyHb, the induction of cerebral vasospasm may also be produced in part to the further effects

of other circulating factors, possibly including those that triggered the systemic endothelial cell damage leading to the development of the microangiopathy in the first place. To date cerebral vasospasm has been described in cases of pre-eclampsia, eclampsia and HELLP syndrome³. Given then the pathophysiological similarities between these syndromes and TTP/HUS it is hardly surprising that cerebral vasospasm would also be seen in the latter syndrome, probably being at least in part responsible for the development of neurological complications. Cerebral oedema often accompanies the cerebral vasospasm in these syndromes, usually affecting the occipital and parietal lobes. This vasogenic-type oedema is usually reversible and this condition has been termed the Posterior Reversible Encephalopathy syndrome or PRES^{7,20}. PRES has also been shown to occur in similar patient populations as non-pregnancy induced TTP/HUS, such as in patients on chemotherapy or immunosuppressive therapy²⁰. Occasionally vasospasm is associated with cerebral infarction or haemorrhage, the latter perhaps being more likely in cases with associated severe hypertension and low platelet count²¹.

Cerebral vasospasm is currently treated with magnesium sulphate (or nimodipine) with a single reported case of successful intracranial angioplasty in an eclamptic woman^{22,23}. Thus the importance of our case lies in the fact that cerebral vasospasm can be seen in association with pregnancy-related or induced TTP/HUS and may in fact be a relatively consistent feature of pregnancy-induced TTP/HUS, particularly in those patients who develop neurological complications. We suspect that similar changes may possibly occur in the intracranial arteries of non-pregnancy-related TTP/HUS patients, particularly those who may develop neurological complications, but this has yet to be demonstrated.

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