Successful management of recurrent pregnancy-related thrombotic thrombocytopenia purpura in a renal transplant recipient

Kimberly Lam¹, Vanessa Martlew², Steve Walkinshaw³, Zarko Alfirevic⁴ and Matthew Howse¹

¹Department of Nephrology, Royal Liverpool and Broadgreen University Hospital, NHS Trust, Liverpool, UK, ²Department of Haematology, Royal Liverpool and Broadgreen University Hospital, NHS Trust, Liverpool, UK, ³Department of Obstetrics, Liverpool Women’s Hospital NHS Trust, Liverpool, UK and ⁴Department of Reproductive and Developmental Medicine, University of Liverpool, Liverpool, UK

Correspondence and offprint requests to: Matthew Howse; E-mail: matthew.howse@rlbuh.nhs.uk

Abstract
Thrombotic thrombocytopenic purpura (TTP) is a rare but potentially devastating complication of pregnancy. We report the first documented case of a successful treatment of recurrent TTP complicating pregnancy in a renal transplant patient.

Keywords: ADAMTS-13; pregnancy; renal transplant; thrombotic thrombocytopenia purpura

In 2003, a 31-year-old nulliparous patient, with end-stage kidney disease secondary to chronic pyelonephritis, received a living-related transplant from her sister; immunosuppression was tacrolimus and mycophenolate mofetil (MMF). Graft function was excellent with a serum creatinine between 100 and 120 µmol/L. She subsequently requested preconception counselling. This included converting MMF to azathioprine 125 mg. She soon became pregnant. At the 22nd week of gestation, she presented with new-onset hypertension and proteinuria. Investigations showed haemolytic anaemia (Hb 7.7 g/dL, LDH 1047 U/L) and thrombocytopenia (47 × 10⁹/mL). Microangiopathic haemolytic anaemia (MAHA) was confirmed on the blood film. Liver enzymes were normal, but there was renal graft dysfunction (creatinine 145 µmol/L). The diagnoses of thrombotic thrombocytopenic purpura (TTP) and pre-eclampsia were made. Plasma exchange (PEX) was commenced using solvent–detergent virally inactivated fresh-frozen plasma (Octaplas) as replacement fluid. Tacro-

References


Received for publication: 21.3.10; Accepted in revised form: 31.3.10

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limus was withdrawn to prevent TTP progression, and prednisolone 20 mg substituted. Subsequent scanning confirmed fetal death, and the pregnancy was terminated.

The patient was very keen for a further pregnancy. She continued to take prednisolone 5 mg and azathioprine 125 mg as tacrolimus may have contributed to the development of TTP. Five months post-termination, she suffered an acute rejection of the renal allograft treated, with good response, with methylprednisolone. Subsequently, tacrolimus was re-introduced to prevent a further rejection.

In May 2007, a second pregnancy was confirmed. The patient was monitored weekly from the 12th week of gestation including her ADAMTS-13 levels (Figure 1). We extrapolated experience from pregnancy in patients without transplants and planned to use a threshold of <15% to electively start PEX. The levels remained above this threshold. Fetal movements were felt from the 21st week of gestation.

At the 28th week of gestation, she presented with a nose bleed. Thrombocytopenia was confirmed with a platelet count of $41 \times 10^9$/mL compared to 221 the week previously, as was MAHA (Hb 5.9 g/dL, LDH 1360 U/L). Her ADAMTS-13 activity was 6%. She received two units of Octaplas. The cardiotocograph indicated fetal distress, and an emergency caesarean section was performed. We avoided platelet infusions because of the risk that these would precipitate worsening disease and a cerebrovascular event.

A baby girl was delivered. She required care on the Special Care Baby Unit but is now healthy. Blood losses during the caesarean section were minimal.

ADAMTS-13 immunoglobulin G (IgG) antibodies were measured at 10.5% prior to the initiation of PEX (laboratory reference range for a negative result <11%). When the patient’s serum was mixed 50:50 with control serum, no inhibition of ADAMTS-13 activity was observed. This suggests that the patient’s serum contained no inhibitors of ADAMTS-13 activity.

Post-operatively, the patient was treated with 20 PEX procedures with Octaplas. Renal function was well preserved throughout, her platelet count improved to $149 \times 10^9$/L. Haemoglobin and LDH levels returned to normal. When the patient recovered, complement C3 and C4 were shown to be within the laboratory reference range. Factor H levels were mildly elevated (0.74 g/L, laboratory range 0.35–0.59 g/L) as was the factor I level (64 mg/L, range 38–58 mg/L). A mutation search for genes encoding factors H and I and the membrane co-factor protein CD46 showed no mutations.

**Discussion**

The differential diagnosis of acute renal failure with associated with MAHA in pregnancy includes TTP, haemolytic–uraemic syndrome (HUS), haemolysis, elevated liver enzymes and low platelets syndrome (HELLP), and pre-eclampsia toxaemia (PET). In the current case, HELLP syndrome can be discounted as the liver enzymes were not elevated. TTP and HUS may form part of the same syndrome, but the low levels of ADAMTS-13 and normal/elevated levels of factor H suggested that TTP predominated in this case. Such low levels of ADAMTS-13 are not characteristic of PET [1], although the patient’s new-onset hypertension and oedema suggest that, in addition to TTP, some PET may have been super-imposed.

TTP is a potentially life-threatening disorder characterized by microangiopathic haemolytic anaemia, thrombocytopenia, and thrombi formation in arteries and capillaries resulting in organ ischaemia. Our understanding, diagnosis and management of the disease have been greatly enhanced by its association with ADAMTS-13 deficiency [2]. ADAMTS-13 is a metalloprotease that cleaves unusually large von Willebrand factor (vWF) multimers and prevents their accumulation causing platelet aggregation and microvascular thrombosis. Acquired ADAMTS-13 deficiency is often associated with circulating anti-ADAMTS-13 antibodies. PEX, which replaces...
the deficient ADAMTS-13 and removes the antibodies, has reduced the mortality of patients with idiopathic TTP from >90% to 25% [3].

TTP in pregnancy is rare; however, patients who have experienced one episode of pregnancy-related TTP are at increased risk in future pregnancies. The condition usually occurs during the second trimester. ADAMTS-13 assays may assist in the diagnosis of TTP and in particular facilitate its distinction from pre-eclampsia and HELLP syndrome. There is a physiological decrease in ADAMTS-13 levels during the second and third trimesters of normal pregnancy, and levels may be as low as 25% of normal [4]. However, when TTP complicates pregnancy, levels are characteristically <5% of normal [5]. Scully et al. [5] have successfully used ADAMTS-13 monitoring to predict recurrent pregnancy-associated TTP and institute prophylactic PEX.

Treatment of TTP in pregnancy with PEX can produce similar outcomes to that of non-pregnant population as pregnancy does not impair the response to PEX [6]. Untreated TTP not only results in poor maternal outcomes, but also fetal death and intraterine growth restriction due to placental infarcts [7]. Successful treatment can result in the delivery of a normal sized infant, and successful pregnancies have occurred in women receiving maintenance plasma infusions preconception. Delivery is recommended only for patients who do not respond to PEX. Guidelines have been developed for the optimal PEX regime, and these include recommendations for diagnosis and treatment of TTP in pregnancy [8]. Octaplas reduces the risk of allergic reactions.

This is the first documented case of a successful treatment of a renal transplant patient with recurrent TTP. Despite the satisfactory outcome, the case raises a number of questions that are discussed.

The patient had two potential causes: tacrolimus therapy and pregnancy. Tacrolimus-associated thrombotic microangiopathy in a renal transplant recipient was first described by Schmidt et al. in 1991 [9]. Tacrolimus is a direct endothelin-1-mediated vasoconstrictor causing tissue ischaemia and endothelial cell injury. This, coupled with abnormally large vWFs due to ADAMTS-13 deficiency, leads to microthrombi formation. Once TTP has occurred, tacrolimus dose reduction or withdrawal alone is effective in <50% at reversing TTP without therapeutic PEX [10]. We attempted to withdraw tacrolimus in this patient prior to the second pregnancy but acute rejection occurred, and the drug was therefore re instituted. An alternate might have been to replace tacrolimus with sirolimus, but TTP has also been reported with sirolimus [11] whose safety in pregnancy has not been established. We speculate that tacrolimus therapy meant this patient had a predisposition to TTP, and this was triggered by pregnancy. The cause of the profoundly suppressed ADAMTS-13 levels is unknown; as the patient had normal levels at the start of pregnancy, there was no congenital deficiency of this protease. No antibodies to, or inhibitors of, ADAMTS-13 were detected at the time of TTP. Therefore, the patient had an acquired deficiency of ADAMTS-13, and the cause of which is unknown, although abnormalities of turnover (i.e. reduced production or increased consumption) are possible explanations.

In view of the work of Scully [5], we had elected to start PEX prophylactically if the ADAMTS-13 levels fell below 15% in the second pregnancy. TTP did indeed occur when the levels fell below this level, but before, we had the opportunity to institute prophylactic PEX.

In conclusion, this case shows that management of recurrent pregnancy and renal transplant-associated TTP is possible with a good outcome, and it is possible to predict the disease using monitoring of ADAMTS-13 levels.

Conflict of interest statement. None declared.

References


Received for publication: 5.1.10; Accepted in revised form: 6.4.10