3. McFadden, J.P. Hypothermia-induced thrombocytopenia (letter). *J R Soc Med* 1988, **81**: 677.
4. Brien, H., Amess, J.A. & Mollin, D.L. Recurrent thrombocytopenia, erythroid hypoplasia and sideroblastic anaemia associated with hypothermia. *Br J Haematol* 1982, **51**: 451–456.
5. Villalobos, T.J., Adelson, E., Riley, P.A. & Crosby, W.H. A cause of the thrombocytopenia and leukopenia that occur in dogs during deep hypothermia. *J Clin Invest* 1958, **37**: 1–7.
6. Hessel, E.A., Schmer, G. & Dillard, D.H. Platelet kinetics during deep hypothermia. *J Surg Res* 1980, **28**: 23–34.
7. Pina-Cabran, J.M. Hepatic and splenic platelet sequestration during deep hypothermia in the dog. *Haemostasis* 1974, **2**: 235.

Postgrad Med J (1993) **69**, 229–231

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Thrombotic thrombocytopenic purpura associated with pregnancy in two sisters

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Summary: Two sisters suffered from thrombotic thrombocytopenic purpura late in their first pregnancies. HLA typing of the patients and their immediate family members demonstrated no obvious relationship. Hereditary aspects, association with pregnancy, prognosis and management of pregnant women with TTP are discussed.

Introduction

Thrombotic thrombocytopenic purpura (TTP) is a serious multisystem disease characterized pathologically by widespread intraluminal and sub-endothelial hyaline thrombi which involve the capillary and precapillary arterioles.¹ Clinically, 74% of patients manifest, at any given time during the illness, the triad of thrombocytopenia, micro-angiopathic haemolytic anaemia and neurological symptoms. Only 40% of patients present with the classic pentad of renal impairment, high temperature and the triad.² Pregnancy is a well-recognized condition associated with TTP.³ Familial occurrence of TTP is rare, but well documented.⁴ There is one previous report of two sisters who developed TTP during pregnancy.⁵ We report two further similar cases.

Case reports

The patients are members of a family of eight siblings, one male and seven females, the offsprings

of non-related Palestinian parents. The first patient, at age 29 years, was in the 38th week of her first pregnancy when she had induction of labour at another hospital in May 1983. The patient was febrile, jaundiced and thrombocytopenic with platelet count $9.0 \times 10^9/l$. She also had Coombs negative haemolytic anaemia. ANA test was negative. She delivered a healthy male baby. Haemolytic anaemia and thrombocytopenia persisted after delivery and failed to respond to steroid therapy. In July 1983 the patient was transferred to a hospital in London. The initial blood count there showed a white blood cell count of $10.4 \times 10^9/l$, platelets $13.0 \times 10^9/l$ and haemoglobin 9.3 g/dl. Peripheral blood smear showed spherocytes, fragmented and nucleated red blood cells. Bone marrow examination showed increased megakaryocytes. TTP was diagnosed and the patient was started on aspirin, dipyridamole and daily plasma exchange. Her blood count became normal 5 days later, but she relapsed shortly after plasma exchange was discontinued. Subsequently she received plasma infusion and achieved a second remission. The patient was maintained on aspirin and dipyridamole. She has been followed at

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Accepted: 20 August 1992

Hamad General Hospital since September 1983. She developed three additional relapses between November 1983 and November 1984. Plasma infusion on each occasion resulted in full recovery. There has been no additional relapse of TTP since the last episode in November 1984. The patient has not had a second pregnancy.

The second patient is a previously healthy female, sister of the first patient. She was in the 23rd week of her first pregnancy when she was admitted to Hamad General Hospital with a 2 day history of epistaxis and spontaneous skin bruises. Physical examination revealed generalized purpuric rash and several skin bruises. She was normotensive. Laboratory investigations showed a white blood cell count of $16.8 \times 10^9/l$, haemoglobin 8.7 g/dl, platelets $9.0 \times 10^9/l$, reticulocytes 5.0%. A peripheral blood smear showed thrombocytopenia, neutrophilic leucocytosis, a fair number of fragmented red blood cells, and occasional nucleated red blood cells. Bone marrow examination showed no abnormalities. Lactic dehydrogenase was 1655 U/l. Blood urea nitrogen, serum creatinine, total bilirubin, liver enzymes and anti-thrombin III levels were within normal limits. Direct Coombs test was negative. The prothrombin time and the partial thromboplastin time were normal. Urine analysis showed more than 300 red blood cells/high power field. TTP was diagnosed. The patient was started on aspirin, dipyridamole and received plasma exchange for 10 days. Serial blood counts showed gradual improvement, and, on the sixth hospital day, the white blood cell count was $14.9 \times 10^9/l$, haemoglobin was 11 g/dl and platelets were $267 \times 10^9/l$. The patient was in the 25th week of gestation when she was discharged on aspirin, dipyridamole and periodic prophylactic fresh frozen plasma infusions at gradually increased intervals. Vaginal delivery was induced in the 34th week of gestation due to significant intrauterine fetal growth retardation. The 1800 g baby died 3 days later of sepsis. Pathological examination of the placenta showed multiple vascular infarcts. Prophylactic fresh frozen plasma

infusion was discontinued 4 months after delivery. Follow-up after the initial remission of TTP showed no evidence of relapse and currently she is fully asymptomatic and maintains normal blood count.

Figure 1 shows the HLA types of our patients and their immediate family members. There seems to be no association between the HLA pattern and the development of TTP in our patients. Four other sisters of the patients had normal pregnancies without haematological complications.

Discussion

The familial occurrence of TTP is rare. Five families affected with TTP in addition to three families affected with haemolytic uraemic syndrome, a closely related disorder, have been reported in the English literature.^{6,7} An autosomal recessive pattern of inheritance has been suggested since in all reported families only siblings were involved, except for one family in which mother and daughter were affected.⁶ Specific genetic markers have not been identified. TTP and haemolytic uraemic syndrome developed in two HLA identical siblings 6½ years apart⁸ but HLA studies were unremarkable in the present cases.

Pregnancy is a well-recognized condition predisposing to TTP,³ but there is only one report in the literature of two sisters who developed TTP during pregnancy.⁵ The nature of the association between pregnancy and TTP is unclear. In Weiner's review the mean maternal age was 23.3 ± 6.8 years and the mean gestational age at the onset of symptoms was 23.5 ± 10.4 weeks.³ The mortality rate was 68% for those who did not receive plasma therapy whereas no deaths occurred among those who received plasma therapy. Eighty per cent of infants died as a direct or indirect result of the maternal disease. The cause of infant death appears to be intrauterine growth retardation due to placental infarction.⁹

The prognosis of patients with TTP has improved considerably during the past two decades.

Figure 1 HLA types of patients, parents and siblings. ● = patients with thrombotic thrombocytopenic purpura.

This coincided with the introduction of plasma therapy for this serious disease. The mortality rate of 95%, reported in 1966 by Amorosi *et al.*¹⁰ is in sharp contrast with the 18% mortality rate of 46 TTP patients who were diagnosed between 1964 and 1980.² In the past few years, several pregnant women with TTP were successfully managed with either plasma infusion or plasma exchange and delivered healthy babies.^{11,12}

TTP and severe pre-eclampsia shares many clinical and laboratory manifestations. It is important to differentiate between these two entities since termination of pregnancy which is therapeutic in pre-eclampsia was not shown to be helpful in TTP complicating pregnancy.³ Determination of anti-thrombin III level, which was shown to be low in pre-eclampsia and normal in TTP, is helpful in the differentiation between the two conditions.³

Larger than usual von Willebrand factor multimers were found in the plasma of patients with chronic relapsing TTP.¹³ Recently Thorp *et al.* found a normal von Willebrand factor (vWF)

multimeric pattern in six women with severe pre-eclampsia while larger than usual multimers of von Willebrand factor were present in plasma of a pregnant patient with chronic relapsing TTP.¹⁴ They suggested that determination of the vWF multimeric pattern is useful in the differentiation between TTP and severe pre-eclampsia.

Despite the dramatic improvement in the prognosis of TTP as a result of modern therapy, patients who recover from the initial episode of TTP are at considerable risk of relapse in the future.¹⁵ Precipitating factors include infection, surgery and pregnancy. Based on this, women with a previous history of TTP, who wish to become pregnant, should have close follow-up during pregnancy with frequent monitoring of platelet count, haemoglobin, lactic dehydrogenase and blood film. Plasma therapy should be initiated at the earliest evidence of relapse of TTP. Consideration, as well, should be given to prophylactic plasma infusion for pregnant women with a history of relapsing TTP.

References

1. Kwaan, H.C. Clinicopathologic features of thrombotic thrombocytopenic purpura. *Semin Haematol* 1987, **24**: 71–79.
2. Ridoffi, R.L. & Bell, W.R. Thrombotic thrombocytopenic purpura: report of 25 cases and review of the literature. *Medicine (Baltimore)* 1981, **60**: 413–428.
3. Weiner, C.P. Thrombotic microangiopathy in pregnancy and the postpartum period. *Semin Haematol* 1987, **24**: 119–128.
4. Ruggeri, P. & Remuzzi, G. Thrombotic thrombocytopenic purpura and related disorders. *Haematol Oncol Clin North Am* 1990, **4**: 219–241.
5. Fuchs, W.E., George, J.N., Dotin, L.N. *et al.* Thrombotic thrombocytopenic purpura: occurrence two years apart during late pregnancy in two sisters. *JAMA* 1976, **235**: 2126–2127.
6. Lian, E.C.-Y. Pathogenesis of thrombotic thrombocytopenic purpura. *Semin Haematol* 1987, **24**: 82–100.
7. Elias, M., Horowitz, J., Taf, I., Kohn, D. & Flatau, E. Thrombotic thrombocytopenic purpura and haemolytic uremic syndrome in three siblings. *Arch Dis Child* 1988, **63**: 644–646.
8. Helman, R.M., Jackson, D.V. & Buss, D.H. Thrombotic thrombocytopenic purpura and haemolytic uremic syndrome in HLA identical siblings. *Ann Intern Med* 1980, **93**: 283–284.
9. Wurzel, J.M. TTP lesions in placenta but not fetus. *N Engl J Med* 1979, **301**: 503–504.
10. Amorosi, E.L. & Uttman, J.E. Thrombotic thrombocytopenic purpura: report of 16 cases and review of the literature. *Medicine* 1966, **45**: 139–145.
11. Erza, Y., Mordel, N., Sadovsky, E., Schenker, J.C. & Eldor, A. Successful pregnancies of two patients with relapsing thrombotic thrombocytopenic purpura. *Int J Gynaecol Obstet* 1989, **29**: 359–363.
12. Maina, A., Donvito, V., Giachino, O., Stratta, P. & Camaschella, C. Thrombotic thrombocytopenic purpura in pregnancy with maternal and fetal survival: case report. *Br J Obstet Gynaecol* 1990, **97**: 443–445.
13. Moake, J.L., Rudy, C.K., Troll, J.H. *et al.* Unusually large plasma Factor VIII: von Willebrand factor multimers in chronic relapsing thrombotic thrombocytopenic purpura. *N Engl J Med* 1982, **307**: 1432–1435.
14. Thorp, J.M., White, G.C., II, Moake, J.L. *et al.* von Willebrand factor multimeric levels and patterns in patients with severe preeclampsia. *Obstet Gynecol* 1990, **75**: 163–167.
15. Rose, M. & Eldor, A. High incidence of relapses in thrombotic thrombocytopenic purpura. *Am J Med* 1987, **83**: 437–444.