

## Rituximab in a child with autoimmune thrombotic thrombocytopenic purpura refractory to plasma exchange

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**Abstract** A nine-year-old girl presented with headache, purpura and mild left hemiparesis. Laboratory evaluation revealed thrombotic microangiopathy with ADAMTS13 deficiency, with auto-antibodies to ADAMTS13. She was treated with plasma exchange and steroids, following which she improved transiently, relapsing within 2 months. The relapse was refractory to conventional therapy and rituximab was tried. She had good response to rituximab and has been in remission for the past 12 months. Rituximab may be a promising option for children with acquired TTP refractory to plasma exchange and steroids.

**Keywords** Thrombotic thrombocytopenic purpura · TTP · Rituximab · ADAMTS13

### Case report

A nine-year-old girl was referred to us with a 2-month history of purpura and recurrent headache. Her illness started as sudden onset reddish-purple lesions in both the lower limbs. There was no history of preceding fever, exanthem, abdominal pain, loose stools or jaundice. Her general and systemic examination including blood pressure

was normal. Urine analysis showed multiple RBCs and mild proteinuria and peripheral smear revealed a mild anemia with fragmented RBCs and thrombocytopenia. Immunological workup for ANA, dsDNA, C3, C4, c-ANCA and p-ANCA was negative. The patient had been started on empiric therapy with Tab.prednisolone at 1 mg/kg/day by her family physician to which she had responded with rapid clearance of the purpuric lesions in a week. Following this, the steroid dose was tapered and stopped. However, over the next 2 weeks, she developed recurrent severe headache, vomiting and resurgence of the purpuric spots. The physician also noted left-sided facial palsy. The peripheral smear again revealed schistocytes and thrombocytopenia. MRI of the brain showed an infarct in the right frontal area, a small left hemispheric subdural hematoma, bilateral minimal subarachnoid hemorrhage and petechial hemorrhage in the right internal capsule and basal ganglia (Fig. 1). C3, C4 assay was repeated and found to be normal. The physician referred the child to another hospital, where a diagnosis of SLE was considered and she was administered 2 pulses of intravenous methyl prednisolone. She was then referred to our centre for further management. When she presented to us, the child was alert, oriented and comfortable at rest. Her pulse and blood pressure (110/70 mmHg) were stable. She had mild pallor, icterus and a few flat purpuric spots. Nervous system examination showed a mild left hemiparesis. She had no palpable liver or spleen enlargement; respiratory and cardiovascular systems were normal. Investigations revealed moderate anemia (Hb 8.5 g) with several fragmented RBCs and severe thrombocytopenia ( $10000/\text{mm}^3$ ); FDP was negative. Serum LDH was elevated (1224 IU/L). Liver function tests showed bilirubin: 2.6 mg/dL, ALT:31 IU/L, AST:68 IU/L and renal function was within normal limits (Serum creatinine 0.5 mg/dL). Urine microscopy revealed

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600 RBC/mm<sup>3</sup> with no casts and transient moderate proteinuria (3+). The immunological workup (ANA, ds DNA and antiphospholipid antibody, DCT) was repeated and confirmed to be negative. Serology for HIV was nonreactive. A bone marrow aspiration study showed florid normoblastic erythroid hyperplasia with normal megakaryopoiesis; no atypical cells were seen. The diagnosis of idiopathic thrombotic thrombocytopenic purpura (TTP) was considered and she was started on plasma exchange along with oral steroids. During each cycle, 40 ml/kg (1000 ml) of plasma was removed and replaced with 600–1000 ml of FFP depending on availability. The deficit in plasma was replaced with human albumin. After a total of seven cycles of plasma exchange, her hemoglobin improved from 8.4 to 11.8 g/dL with a normal peripheral smear. She was discharged and followed up at 2 weekly intervals for 2 months during which period steroids were tapered and stopped completely.

The child was in remission for 2 months, following which she relapsed with worsening of anemia and thrombocytopenia. She was readmitted and plasma exchange was started again. This time, however, she did not respond despite nineteen cycles of plasma exchange and oral prednisolone. During this admission, we could get her ADAMTS13 levels done. The results showed low levels of the enzyme (ADAMTS13 activity <5 %, normal range 60–123 %) with presence of antibodies to it (IgG anti-ADAMTS13 assay 22 %, normal value <6.1 %). The ADAMTS13 activity was measured using the Fret substrate assay, and IgG anti-ADAMTS13 was measured using an in-house ELISA method at Haemostasis Research Unit,

Department of Haematology, University College London [1, 2]. Thus, a diagnosis of acquired TTP was made. As she was refractory to plasmapheresis and steroids, we decided to start her on rituximab. After four cycles of weekly rituximab therapy (375 mg/m<sup>2</sup> per dose), she attained complete remission. Oral steroids were tapered over the next 3 months and she was maintained on low dose alternate day steroids (0.5 mg/kg/day). She is currently on follow-up and is asymptomatic with normal platelet counts, no evidence of hemolysis on the peripheral smear and a normal LDH value for the last 12 months. Repeat ADAMTS13 levels could not be done due to logistical reasons.

## Discussion

Thrombotic microangiopathy (TMA) is a relatively common feature of several systemic diseases. It is seen in sepsis, disseminated intravascular coagulation, both D+ and D– hemolytic uremic syndrome, as an adverse effect of several drugs like clopidogrel, ticlopidine, quinine and mitomycin C. The condition can also be secondary to certain malignancies, following hematopoietic stem cell transplant and also in patients infected by the human immunodeficiency virus [3]. The most common thrombotic microangiopathy encountered in children is hemolytic uremic syndrome in which renal failure dominates the clinical picture [4]. Conventionally, TTP has been considered a disease of adults with a predilection of CNS symptoms. Clinical differentiation between HUS and TTP is difficult due to considerable overlap of features. After the discovery of ADAMTS (A Disintegrin And Metalloprotease with ThromboSpondin type 1 repeats) 13, TTP was shown to be due to a severe deficiency of ADAMTS13 activity [4].

It has been found that patients with TTP have a more than normal concentration of circulating ultra large von Willebrand factor (vWF) multimers which mediate platelet adhesion to the endothelium in large numbers. These patients lack a protease (ADAMTS13) which in normal individuals cleaves the vWfmultimers. The ADAMTS13 deficient state can be either congenital or acquired due to antibodies to the enzyme. Antibody-mediated TTP could be one of the many manifestations of a systemic autoimmune disorder or due to autoimmunity directed against the enzyme alone [5].

Congenital TTP usually presents early in life. About 75 % of children present soon after birth, whereas 25 % have the first episode later during childhood, usually between the age of 2 months and 4 years [4]. Treatment for this condition aims at replenishing the deficient ADAMTS13 which is satisfactorily achieved by regular infusions of fresh frozen plasma. Plasma therapy for TTP, introduced



**Fig. 1** Contrast-enhanced T1-weighted axial MRI of the patient showing a non-enhancing hypointense area in the right frontal lobe consistent with infarct (black arrow)

in the 1970s, marked the first breakthrough in the treatment of TTP, which improved the survival rate dramatically from <10 to >60–90 % [5].

Autoimmune or acquired TTP usually presents in adolescence or adulthood with the characteristic clinical features of headache, fleeting neurological signs (due to the reversible CNS ischemia) and bleeding manifestations. Intracranial bleeds as we observed in our patient are unusual in TTP and rarely reported in the literature [6]. Low levels of the enzyme ADAMTS13 (<5 %) in the presence of autoantibodies to it establish the diagnosis. First-line management of this condition is plasma exchange therapy and steroids [7]. Plasma exchange removes the inhibitors to ADAMTS13 and other cytokines that stimulate the endothelium to release the ultra large VWF multimers. It also supplies the deficient enzyme. However, patients with acquired TTP may fail to respond to plasmapheresis and steroids, which was the case in our patient when she presented with relapse.

In recent years, in the management of acquired TTP in adult patients, the role of the anti-CD20 monoclonal antibody rituximab has appeared crucial both as a first-line treatment combined with plasma exchanges and as a potential prophylaxis against relapses [8, 9]. Adults who failed to respond after 7–14 days of plasmapheresis were considered for rituximab therapy [8]. However, there are only few anecdotal reports of the use of rituximab in children with acquired TTP [10–14]. All the reported cases are from the developed world, and sustained remission up to 12 months has been reported only in 4 pediatric patients till date [10, 11, 14]. Ours is the first report from the developing world of successful treatment of pediatric TTP by rituximab with sustained remission for a period of 1 year. The duration of remission after rituximab is not yet clearly known in children with TTP. Used at a dose of 375 mg/m<sup>2</sup> weekly for 4 weeks, rituximab is fairly well tolerated, the usual adverse effects being nausea, vomiting and, occasional hypotension. Rituximab depletes antibody-producing B cells (CD20 positive) for 3–9 months. Normalization of platelet counts and LDH has been reported to occur within 1–4 weeks of the first dose and relapses after rituximab have been reported in ~10 % [13, 14]. In our child, platelet count normalized within 2 weeks of the first dose of rituximab. Once the platelet count was normal, the steroids were tapered. Currently, she remains in remission for the last 12 months with normal platelet count, peripheral smear and LDH levels.

In children with TMA and CNS features, measurement of ADAMTS13 activity and antibodies helps not only to confirm the diagnosis of TTP, but also to differentiate the congenital and acquired forms. In cases refractory to

plasmapheresis and steroids, rituximab can induce remission. The duration of remission and relapse rate with rituximab therapy needs further study.

**Conflict of interest** None.

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