Cryosupernatant and Immunosuppression as Effective Alternative Therapies for TTP in Three Pediatric SLE Patients

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Abstract Thrombotic thrombocytopenic purpura (TTP) and systemic lupus erythematosus (SLE) very rarely present simultaneously and pose a diagnostic and therapeutic dilemma to the physician. Prompt diagnosis and management with plasma exchange and immunosuppression is life-saving. To describe the effectiveness of cryosupernatant and steroids in pediatric SLE with TTP. We describe three children aged 12–14 years with SLE who were diagnosed with TTP based on fever, CNS manifestations, ANA, anti-dsDNA, anti-sm positivity, hypocomplementemia, and microangiopathic anemia with thrombocytopenia. All three children were managed with cryosupernatant and steroids without plasmapheresis. All children improved with cryosupernatant and steroids. All attained remission within 10 days. They were doing well at last follow up without relapse or flare. Cryosupernatant and steroids may be an effective therapy for Thrombotic thrombocytopenic purpura with systemic lupus erythematosus

Keywords Pediatric systemic lupus erythematosus · Thrombotic thrombocytopenic purpura · Cryosupernatant

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disorder with protean manifestations. One among them is thrombotic thrombocytopenic purpura (TTP). TTP is classically characterized by the pentad of fever, microangiopathy anemia, thrombocytopenic purpura, neurological abnormalities and renal disease with neurological and renal manifestations occurring later in the course of the disease. TTP, an uncommon life threatening disease, can present in approximately 2 % of the patients with SLE. Very rarely TTP presents simultaneously with SLE [1]. Moreover waiting for complete evolution of pentad features significantly delays treatment and worsens the outcome [2]. The treatment options include plasma exchange using fresh frozen plasma (FFP)/cryosupernatant (CSP) and immunosuppressive therapy [3]. Cryosupernatant is the remnant after removing cryoprecipitate [which is rich in *von Willebrand factor* (vWF) multimers]. We describe three children with TTP as the initial presentation of SLE and their laboratory reports at presentation in Table 1. We treated them with steroids and cryosupernatant transfusion instead of plasma exchange. All three children responded well to the treatment without any relapse.

Case Reports

About 250 children with SLE are followed in Pediatric Rheumatology Clinic in Christian Medical College, Vellore since July 2009. All children presented with SLE and TTP were included in this study. Eventhough plasmapheresis is available in our center; all children with SLE and TTP were treated with cryosupernatant and steroids in view of patient's non affordability for plasmapheresis. Informed

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Table 1 Laboratory findings at admission in all children who presented with SLE and TTP

Laboratory test	Case 1	Case 2	Case 3
Haemoglobin (g %)	7.3	7.8	7.8
Total count (cu mm)	4,700	10,864	6,250
Differential count	N70 %, L20 %, M10 %	N54 %, L26 %, M10 %, myelocytes 4 %, band 6 %	N52 %, L38 %, M 10 %
Platelets(cu.mm)	10,000	25,000	12,000
Reticulocytes (%)	8	11	7
Blood picture—schistocytes/high power field	10–12/field	8–10/field	9–11/field
Coagulation parameters	Normal	Normal	Normal
Creatinine (mg %)	0.8	0.8	0.6
Urine protein/creatinine ratio (normal <0.35 mg protein/mg creatinine)	7.5	1.52	13.9 (done at a later date; 2 days after 1st cycle of CPP)
LDH (U/L)	2,933	4,590	2,009
Direct Coombs test (DCT)	Negative	Negative	Negative
Complements			
C3 (Normal 90–180 mg/dl)	80	36.8	87
C4 (Normal 10–40 mg/dl)	10	<6.93	<8
ANA	Speckled	Speckled	+
DsDNA (normal <100 IU/ml)	160	296	382
Anti-sm (normal <20 RU/ml)	32	2	3
Anticardiolipin	Negative	Negative	Negative
Lupus anticoagulant	Negative	Negative	Negative
Renal biopsy with Immunofluorescence ^a	Class II <i>IgG 2+, C₃ 1+</i>	Class III <i>IgG 2+, IgA 2+, IgM 3+, C₃ 3+</i>	Class I <i>Negative</i>

Italics indicates immunofluorescence results

^a Renal biopsy performed after normalization of platelet count

consent from parents was taken in all children before commencing treatment.

Case 1

14 year old boy presented with history of fever for 6 days, altered sensorium and yellowish discoloration of the eyes for 4 days. There was no past history of jaundice, renal dysfunction, blood transfusion or seizures. On examination he was pale and icteric. His Glasgow Coma Score was 12/15. Investigations revealed anemia with haemoglobin of 7.3 g %, total WBC count was 4,700/cu.mm with differential of L20 %, N70 %, M10 %, platelet count was 10,000/cc.mm, reticulocytes were 8 %, LDH was 2,933 U/L and creatinine was 0.8 mg %. Peripheral blood smear showed 10–12 schistocytes/oil immersion field. Total bilirubin was 1.8 mg/dl, direct bilirubin was 0.8 mg/dl, liver enzymes were normal and Direct Coombs test was negative. In view of non-immune hemolytic anemia with thrombocytopenia, he was diagnosed to have microangiopathic anemia. Urine analysis showed no hematuria with 2 + proteinuria. ANA, DsDNA and Anti SM were positive. Anticardiolipin and

lupus anticoagulant were negative. C3 and C4 levels were low. Urine protein creatinine ratio was 7.5. Renal biopsy showed mesangioproliferative glomerulonephritis with IF positive for IgG and IgM. His A Disintegrin and Metalloproteinase with thrombospondin *Motifs* (ADAMTS 13) activity level was 62.15 % (normal range 50–150 %); Antigen: 0.82 µg/ml (normal range 0.60–1.60 µg/ml). He was diagnosed to have SLE with TTP based on fever, CNS manifestations, ANA, Anti-DsDNA, Anti-Sm positivity, hypocomplementemia, and microangiopathic anemia with thrombocytopenia.

He was started on pulse steroids (Inj. Methylprednisolone 30 mg/kg IV once daily) for 3 days and then changed to oral prednisolone 2 mg/kg/day along with cryosupernatant transfusion (10 ml/kg/day). He received 60 ml/kg of cryosupernatant cumulatively over a period of 6 days. His haemoglobin and platelet count normalized (haemoglobin was 9.6 g % and platelet count was 330,000/cu mm) within 6 days. He symptomatically improved and was discharged on oral steroids. At the last follow up after 16 months, his complements remained normal, DSDNA levels was low, and Anti-phospholipid antibody also

remained negative. There was no evidence of relapse or flare during the follow up period.

Case 2

12 year old girl presented with menorrhagia for 7 days. She had attained menarche 1 year ago and had normal menses since then. There was no past history of jaundice, prolonged bleeding, renal dysfunction, blood transfusion or seizures. On examination she was drowsy and pale. Investigations revealed anemia with haemoglobin of 7.8 g % with normal total and differential count. Her platelet count was 25,000/cc.mm, LDH was 4,590 U/L and S. Creatinine was 0.8 mg %. Peripheral blood smear showed schistocytes. Total bilirubin was 2 mg/dl, direct bilirubin was 0.7 mg/dl, liver enzymes were normal and Direct Coombs test was negative. In view of non-immune hemolytic anemia with thrombocytopenia, she was diagnosed to have microangiopathic anemia. Her prothrombin and activated partial thromboplastin time were within normal limits. Urine analysis showed 20–25 RBCs per high power field. ANA, DSDNA and Anti SM were positive. C3 and C4 levels were low. Urine protein creatinine ratio was 1.52. Renal biopsy showed focal proliferative glomerulonephritis with IF positive for IgG, IgM and IgA. She was diagnosed as SLE with TTP based on ANA positivity, hypocomplementemia, microangiopathic anemia with thrombocytopenia and lupus nephritis Class III.

She was started on pulse steroids (Inj. Methylprednisolone 30 mg/kg IV once daily) for 3 days followed by prednisolone (2 mg/kg/day) along with cryosupernatant transfusion (10 ml/kg/day). She received 70 ml/kg of cryosupernatant cumulatively over a period of 7 days. With above measures, her haemoglobin and platelet count normalized (haemoglobin was 10.6 g % and platelet count was 119,000/cu mm) after 7 days. She symptomatically improved and was discharged on oral steroids and mycophenolate mofetil. At the last follow up after 15 months, her complements remained normal, DSDNA levels was low, and Anti-phospholipid antibody also remained negative. There was no evidence of relapse or flare during the follow up period.

Case 3

14 year old girl presented with fever for 10 days associated with petechiae and purpura. She had one episode of passing tarry stools with one episode of fresh blood in stool. There was history of jaundice over last 4–5 days associated with passage of dark colored urine. There was no history of seizures or altered sensorium. There was no past history of jaundice, renal dysfunction, blood transfusion or seizures. On examination, she was pale and icteric. Her liver was

palpable 5 cm below the right costal margin and spleen was palpable 3 cm below the left costal margin. Her neurological examination was within normal limits. Investigations revealed anemia with haemoglobin of 7.8 g % with normal total and differential count. Her platelet count was 12,000/cc mm, LDH was 2,009 U/L and S. Creatinine was 0.6 mg %. Peripheral blood smear showed schistocytes. Total bilirubin was 2.5 mg/dl, direct bilirubin was 1 mg/dl, liver enzymes were normal and Direct Coombs test was negative. In view of non-immune hemolytic anemia with thrombocytopenia, she was diagnosed to have microangiopathic anemia. Her prothrombin and activated partial thromboplastin time were within normal limits. Urine analysis showed proteinuria (albumin 4+) and hematuria (>200 RBC's per high power field). ANA and DsDNA and were positive. C3 and C4 levels were low. Urine protein creatinine ratio was 13.9. Renal biopsy showed minimal mesangial lupus nephritis with IgG and IgM positive on immunofluorescence. She was diagnosed as SLE with TTP based on ANA/DsDNA positivity hypocomplementemia, microangiopathic anemia with thrombocytopenia and minimal change lupus nephritis.

She was started on pulse steroids (Inj. Methylprednisolone 30 mg/kg IV once daily) for 3 days and followed by prednisolone (2 mg/kg/day) along with cryosupernatant transfusion (10 ml/kg/day). She received 40 ml/kg of cryosupernatant cumulatively over a period of 4 days. Her Haemoglobin and platelet count normalized (Haemoglobin was 9.3 g % and platelet count was 100,000/cu mm) after 4 days. She symptomatically improved and was discharged on oral steroids. At the last follow up after 9 months, her complements remained normal, DSDNA levels was low, and Anti-phospholipid antibody also remained negative. There was no evidence of relapse or flare during the follow up period.

Discussion

The coexistence of SLE and TTP, although rare, has been reported to be more common in children with SLE than in adults [4.]The diagnostic criteria for TTP have changed significantly from the original pentad of thrombocytopenia, microangiopathic hemolytic anemia, neurological abnormalities, renal abnormalities, and fever, [5] to the dyad of thrombocytopenia and microangiopathic hemolytic anemia [6]. The coexistence of 5 symptoms, typical of TTP and often described in textbooks, is not frequent in clinical practice. It is clear from the series of cases that microangiopathic hemolytic anemia and thrombocytopenia occur in 100 % of patients and CNS symptoms in 60–88 % of cases, whereas renal function disorder (18–76 %) and fever (22–86 %) are less frequent [7].

The underlying reason exact mechanism of association of TTP with SLE is unclear. There is still considerable debate whether certain antiphospholipid antibodies or lupus anticoagulant play a pathogenetic role in triggering TTP in SLE patients, although neither of these antibodies is essential to develop TTP [8]. In addition the relationship between the ADAMTS-13 inhibitor and SLE also needs to be further investigated. In the absence of ADAMTS13, vWF multimers facilitate platelet activation and aggregation which leads to microvascular thrombosis. *Possible mechanisms* by which TTP occurs in SLE include inhibitory/neutralizing antibodies against ADAMTS13, complement mediated endothelial injury, increased release of reactive oxygen species and free radicals which oxidizes vWF rendering it resistant to ADAMTS13 [8].

Although plasmapheresis remains the treatment of choice, the exorbitant cost of the procedure remains the biggest challenge in resource poor nations. None of our children described in this series could afford Plasmapheresis. Cryosupernatant is the blood product which is the remnant after separating cryoprecipitate. Cryosupernatant is deficient in vWF and rich in ADAMTS13, so theoretically plasma exchange using cryosupernatant is better than plasma exchange with FFP, however large clinical trials are needed to prove its practical effectiveness [9]. All the children in this series responded well to treatment with cryosupernatant. *At last follow up, Complements increased and DsDNA decreased. Antiphospholipid antibody was negative at follow up for all children.*

Though there is few trials available comparing plasma exchange using FFP with plasma exchange using cryosupernatant [10]. In a meta-analysis Michael et al. [11] found that Plasma exchange with FFP is still the most effective treatment available for TTP. Scully et al. [12] reviewed the treatment of 50 cases of TTP where they found no difference in number of plasma exchange to remission with cryosupernatant and solvent/detergent fresh-frozen plasma. However, allergic/urticarial and citrate reactions were more common with cryosupernatant.

Due to financial constraints, we treated all three patients with CSP transfusion (10 ml/kg/day) and steroids. Steroids suppress the ongoing inflammation while the cryosupernatant is rich in ADAMTS13. Treatment was initiated with pulse steroids for 3 days and oral steroids thereafter. Cryosupernatant transfusion was continued for minimum of 2 days after attaining remission. Remission is defined as attaining normal neurological status, platelet count >150,000/cu.mm, LDH <1.5 times the normal and improving haemoglobin level [10]. All the three patients in our series attained remission within 10 days. They were discharged on oral steroids and followed up for 3–10 months. All children underwent renal biopsy only after normalization of platelet count. There were no signs of relapse during the follow up period.

In refractory cases, the use of rituximab may be a costly option, although currently its use is limited to a few cases [13]. Mortality rate of TTP in patients with SLE has been reported to be 46–50 % and was associated with the presence of concomitant infections and the delay in the initiation of plasma exchange therapy [14].

Conclusion

Consider SLE in any child who presents with TTP and evaluate accordingly. Cryosupernatant transfusion along with steroids is a cost effective alternative to plasmapheresis especially in developing countries and is shown in this series to attain remission within 2 weeks. Large clinical trials are needed to prove the superiority or equivalence of cryosupernatant transfusion over plasma exchange. Rheumatologists, haematologists and critical care specialists need to evolve an urgent multidisciplinary approach which emphasizes the early recognition of this complication and early initiation of treatment to improve the outcome of this potentially life threatening condition.

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