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SUCCESSFUL TREATMENT OF THROMBOTIC THROMBOCYTOPENIC PURPURA WITH PLASMAPHERESIS AND RITUXIMAB-A CASE SERIES

Immuno Hematology

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ABSTRACT

Thrombotic thrombocytopenic purpura is a haematological disorder which affects the arterioles and capillaries of multiple organs.We report three cases of TTP successfully treated with plasmapheresis & low dosage rituximab.All three cases were diagnosed according to diagnostic criteria of TTP.A Weekly doses of 100 mg rituximab was given for four week(on day 1,day 8, day15 ,day22).Resolution of clinical symptoms and hemotological abnormalities after completion of treatment, all three patient achieved complete Response. The duration of complete response was 5-27 months. During the treatment course, All three patients were treated with plasmapheresis at different times, the recommended quantity of plasmapheresis was 40 ml/kg once a day and the plasmapheresis was stopped when platelet dose went up to $150x10^9$. This case series indicates that plasmapheresis may positively support early salvage therapy in both acute/refractory and relapsing cases and its combination with rituximab exhibits short and long term favorable effects for the treatment of TTP.

KEYWORDS

Thrombotic Thrombocytopenic purpura,Plasmapheresis and Rituximab

INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is a haematological disorder characterized by pentad of fever, neurological abnormalities, microangiopathic hemolytic anemia, renal failure and thrombo cytopenia [1].This disorder is a rare life threatening disorder that occurs due to deficiency of ADAMTS 13 (a disintegrin and metalloproteinase with thrombospondin type 1 motif ,member 13)which is a von Willebrand factor cleaving protein.TTP can affect the arterioles and capillaries of multiple organs [2].For diagnosis the symptoms of fever, microangiopathic hemolytic anemia and thrombocytopenia are necessary [3].As there is clinical over- lap with haemolytic uraemic syndrome, autoimmune disease and a spectrum of pregnancy- related problems, the diagnosis of TTP is difficult[4].The current frontline treatment is still plasmapheresis and steroids [5].Therefore, it is important to make differential diagnosis with these diseases that evolve with microangiopathic hemolytic anemia Within a short time so that the plasmapheresis can be initiated[6]. Although plasmapheresis can effectively reduce the mortality to approximately 20% [7], there is a significant subset of patients with either delayed or absent responses, requiring protracted courses of plasmapheresis with a high rate for the associated complications [8].

Rituximab is a chimeric monoclonal antibody against the CD20 antigen expressed on B lymphocytes. The proposed mechanism of action of this drug in the treatment of this condition is its clearance of CD20-positive B cells. It has been used for relapsing or refractory TTP, which leads to high-rate and durable remission [8-11]. Here, we reported three cases with TTP that were successfully treated with rituximab combined with plasmapheresis.

We present 3 cases which diagnosed with TTP from January 2020 to December 2020 at our institutes. The diagnosis was established by the presence of many clinical findings of classic pentad.Written informed consent was obtained from all patients.

Case series:-

Case 1:

In March 2020, A 45-year-old, female presented with fever,lethargy and Mucocutaneous bleeding in our hospital. On admission the patient was semiconscious, minimally responsive to deep pain, and febrile with a temperature of 102°F; no movement of his right arm or leg was noted.

A blood count revealed a hemoglobin of 8.0 g/dl and a platelet count of 7000/cu mm. Her blood urea nitrogen (BUN) was 40 mg /dl and creatinine was 1.08 mg/dl. The partial thromboplastin time was 33 sec and prothrombin time 13 sec. A peripheral smear showed marked red blood cell fragmentation and multiple nucleated red blood cells, compatible with a microangiopathic type of anemia. No improvement following 5 units of blood, 14 units of platelets. Laboratory data Hematological, biochemical, and blood film morphology confirmed the diagnosis of TTP

Plasmapheresis using Frecinius kabi were started.Subsequently,7 plasmapheresis cycles were performed & replaced by fresh frozen plasma.Prednisolone was started at dose of 40 mg and Rituximab was administered at a weekly dose of 100 mg through intravenous for 4 weeks (on day 1,day 8, day15 and day 22).After the initial plasmapheresis, the patient became conscious and was able to respond to simple commands.neurological status became normal after the 6^{th} cycle. The morphologic appearance of her peripheral smear was normal following Seven plasmapheresis. she has remained well 9 months after the onset of her illness and no any further treatment was required. The patient's hematologic values during the plasmapheresis are shown in

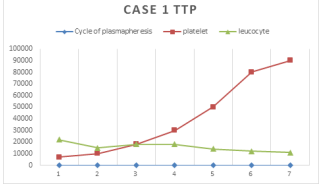

Fig. I. Graphic illustration of the heamatological values in case 1,demonstrating temporal relationship of their recovery to normal following serial plasmapheresis

Case 2:
In august 2020, a 32-year-old male patient with left sided upper limb weakness , mucocutaneous bleeding, abdominal pain for 4 days was admitted.

The peripheral blood examination revealed the presence of abundant schistocytes. Hematological, biochemical, and blood film morphology confirmed the diagnosis of TTP. TTP was diagnosed and underlying 11-year TTP history was ruled out. It was considered as a relapse TTP. He was treated with plasmapheresis, steroids and rituximab (100 mg weekly) for 4 weeks. On admission revealed a hemoglobin of 8.6 g/dl, and platelet count of 9000/cu mm. His blood urea nitrogen (BUN) was 43 mg /dl and creatinine was 0.70mg/dl.The partial thromboplastin time was 35 sec and prothrombin time 16 sec. Laboratory data Hematological, biochemical, and blood film morphology confirmed the diagnosis of TTP.

The treatment with plasmapheresis using Frecinius kabi and steroids was started, after more than 1 week of Plasmapheresis,Plt count still $<20^{x}10^{9}$/l suggesting poor efficacy so we then used Plasmapheresis combined with rituximab, as a result platelet count returned to normal suggesting that rituximab improve curative efficiency of Plasmapheresis in refractory TTP. and the progressive improvement was obtained.Subsequently, 10 plasmapheresis procedures were performed & replaced by fresh frozen plasma. The patient's hematologic values during the plasmapheresis are detailed in Fig. II. He has remained well 6 months after the onset of his illness and has required no further treatment.

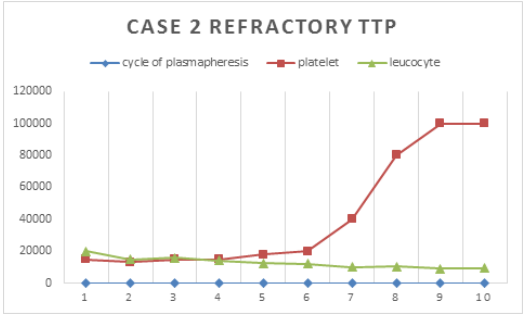

Fig.2. Graphic illustration of the heamatological values in case 2,demonstrating temporal relationship of their recovery to normal following serial plasmapheresis

Case 3: In may 2020, a 25-year-old female presented with an anuria and bilateral pedal edema and four day complaint of abdominal pain & fever with altered behaviour & a complain of six-day mucocutaneous bleeding was admitted.

A diagnosis of TTP was supported by laboratory findings and the plasmapheresis was initiated, followed by using low-dose rituximab.

She completed 5 cycles of plasmapheresis and immediately before the second dose of rituximab, a lowering in her hemoglobin and platelet count was documented, without clinical deterioration . No additional therapy was initiated and her hemoglobin and platelet count gradually increased until reaching normal parameters. The fourth and last dose of rituximab was administered.

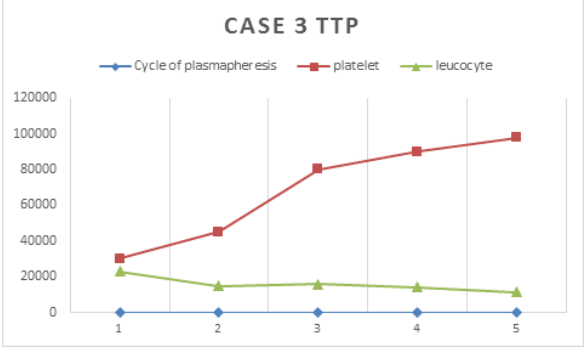

Fig.3.Graphic illustration of the heamatological values in case 3,demonstrating temporal relationship of their recovery to normal following serial plasmapheresis

Table 1: Clinical & laboratory features of Patient at presentation and treatment outcome

Feature	Case 1	Case 2	Case 3
Age(year)/gender	45y/female	32y/male	25y/female
Underlying condition	No	TTP	No
Neurological manifestation	Yes	Yes	Yes
Laboratory parameter at onset	Hb 8 g/dl, Plt $7x10^{9}$/L LDH 1600IU/L	Hb 8.6g/dl, Plt 9 x 10^{9}/L LDH 375 IU/L	Hb 7 g/dl, Plt $30x10^{9}$/L LDH 900 IU/L
Direct or Indirect coomb test	Negative	Negative	Negative
Creatinine(umol/L)	1.08	0.70	7.30
Schistocytes	YES	YES	NO
Rituximab indication (mg)	100MG	100 MG	100MG
Concomitant treatment	PREDNISOLONE	PREDNISOLONE	PREDNISOLONE
Number of plasmapheresis	7(Daily)	10(Daily)	5(Daily)
Duration of CR(Month)	9	6	12
Laboratory parameter at Discharge	Hb 10.6 g/dl, Plt 98 $x10^{9}$/L LDH 320 IU/L	Hb 11 g/dl, Plt $100x10^{9}$/L LDH 220 IU/L	Hb 10 g/dl, Plt $96x\ 10^{9}$/L LDH 340 IU/L

DISCUSSION:
In this study, we present three cases of TTP including two cases with primary TTP and one case with eleven-year history of TTP, concerning a relapse and refractory TTP. The three patients presented with a clearly suspicious clinical course, with the manifestation of severe microangiopathic anemia and thrombocytopenia on admission. Owing to laboratory restrictions presence of an ADAMTS-13-directed antibody or low activity of the cleavage protein could not be documented. In the case 1 and case 2, the clinical, hematological, and biochemical data were clear enough to justify the start of treatment, due to a severe and typical presentation.

TTP is a rare but life-threatening autoimmune disorder [12, 13]. Despite the use of the well-known and established treatment for TTP, the disease relapse occurs in 30-50% of cases [14]. Plasmapheresis was initated owing to a presumptive diagnosis of TTP Because of the associated high mortality of up to 90% in untreated patients [16].Plasmapheresis is mainstay of treatment in TTP as it reduces mortality from 90% to 10-20%[9]. This modality of treatment depletes the circulating antibodies against ADAMTS 13 and the very high molecular weight von Willebrand factor multipers, Plasmapheresis also replaces missing von Willebrand cleaving protease the condition of disease is improved at about 1 week and Plasmapheresis Combined with prednisolone at conventional doses as first line therapy reduces mortality of TTP around 10-15%[17]Relapse was defined as platelet count less than $50x10^{9}$/l after minimum of seven procedure of Plasmapheresis, In case 2,after more than 1 week of Plasmaphresis,Platelet count still <40x109/l suggesting poor efficacy so we then used plasmapheresis combined with prednisolone and rituximab was used as a result platelet count returned to normal suggesting that rituximab improve curative efficiency of Plasmapheresis in refractory TTP.

To meet the standards, rituximab has been reported to be applied in refractory or relapsed cases of TTP with success [15]. Depletion of B-cells can prevent synthesis of this antibody and presumably induce remission of the disease [12, 13].The dose of rituximab had been used successfully in other autoimmune diseases. However, it had rarely been previously reported for the treatment of TTP.We administered a rituximab dose of 100 mg weekly and last 4 weeks, The three patients in this presentation received low-dose rituximab along with plasmapheresis with a remarkably good outcome. It is particularly important to address the markedly good and sustained response in cases 2 (a relapsed and refractory case), usually considered challenging case. Up to now, there is no evidence of relapse in any of the three cases during a follow-up of 9,6,-and 12months, and it may support the low-dose rituximab benefit to our patients shown by the depletion of lymphocyte count during treatment.

CONCLUSION:
Three TTP patients have achieved a complete and sustained response after treating plasmapheresis, with rituximab, Plasmapheresis Can

cure most patients,but relapse rate can be upto 50%-60%. Plasmapheresis Combined with rituximab can improve efficacy of Plasmapheresis in refractory TTP and prevent disease relapse, therefore plasmapheresis combined with rituximab is an effective and safe treatment for TTP and refractory relapse TTP.

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