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Case Report

Internal Medicine Section

Refractory Thrombotic Thrombocytopenic Purpura: A Case Report

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ABSTRACT

Thrombotic Thrombocytopenic Purpura (TTP) is a thrombotic microangiopathy. Clinical manifestations occur due to decreased perfusion to the internal organs. Usually it responds to pulse steroids and plasma exchange. Various therapies are available for refractory cases which respond to N-Acetyl cysteine, cyclosporin, rituximab, bortezomib and caplacizumab. We report a case of refractory TTP in a 29-year-old female, showed improvement with the use of rituximab (anti-CD 20 monoclonal antibody), who presented with history of fever and one episode of seizure.

Keywords: N-Acetyl cysteine, Rituximab, Splenectomy

CASE REPORT

A 29-year-old female without any comorbidities came to emergency department with history of high grade fever and one episode of seizure. She had no history of weight loss and loss of appetite. She was not on any long term medications. Clinically she had pallor. Blood investigations showed anaemia (Haemoglobin-4 gm/dL) and thrombocytopenia (Platelet count-10,000/cmm) with ESR of 110 mm/hour. Peripheral smear showed fragmented red blood cells (Schistocytes). Serum Lactate dehydrogenase (LDH-907 IU/L) was elevated. ANA was 2+ positive. Anti ds-DNA, ANCA were negative. C3 and C4 were within normal range. She was kept in intensive care unit (ICU). Blood products transfusion was done to prevent bleeding and for severe anaemia. The MRI brain with contrast showed multiple small infarcts in posterior inferior cerebellar arterial territory and chronic small vessel ischaemic changes in cerebral hemispheres. She was started on Pulse Methylprednisolone (1 gm IV once daily for three days) therapy along with plasma exchange. But she had epistaxsis due to persistent thrombocytopenia. Due to unresponsiveness to plasma exchange, other therapies were discussed with the patient like rituximab and bortezomib. However, patient could not afford those treatments. In view of some evidence regarding the use of N-Acetyl cysteine as adjunctive therapy in TTP, it was given for three days. She continued to have thrombocytopenia and she was discharged. Rituximab was arranged and she was admitted again for rituximab infusion. After four doses of rituximab 500 mg (on day 0, 5, 9 and 16), she had platelet count of 2,01,000/cmm (on day 23) with normal LDH level. Peripheral smear did not show fragmented red blood cell. She was put on oral steroid. Subsequently the patient was lost to follow up.

DISCUSSION

Acquired TTP is a thrombotic microangiopathy characterised by pentad of fever, thrombocytopenia, microangiopathic haemolytic anaemia, renal failure and neurological manifestations [1]. This classic pentad of clinical features is seen only in 5% patients [2]. It is due to a deficiency of the Von Willebrand factor cleaving metalloprotease, called ADAMTS 13 (a disintegrin and metalloproteinase, with a thrombospondin type 1 motif, member 13). Antibodies against this ADAMTS 13 contribute to the pathogenesis [3,4]. TTP is associated with autoimmune diseases like Systemic Lupus Erythematosus (SLE), Sjogren syndrome and mixed connective tissue disease [5]. Malignancies particularly adenocarcinomas are associated with TTP and most often due to malignancies of stomach, breast, prostate and lung [6,7]. Various drugs like clopidogrel, ticlopidine, cyclosporin, tacrolimus, estrogen/progesterone, gemcitabine, interferons, mitomycin, quinine have been implicated in causation of TTP [8].

In our patient ADAMTS 13 level was not assessed. We tried pulse methylprednisolone and plasma exchange, but patient had no response. Due to cost issues, she was started on N-Acetyl cysteine infusion. There are some evidences supporting the use of N-Acetyl cysteine in refractory TTP [9,10]. Even after the use of N-Acetyl cysteine, she had no response. Finally it was decided to start on injection rituximab. We arranged four doses of injection rituximab. She showed dramatic response to rituximab therapy. Among nine patients with refractory TTP treated with rituximab, eight patients showed remission after a median follow up of 30 months in a retrospective review [11]. Weekly rituximab (375 mg/m^2) for four weeks is the most frequently used dose [12]. Different dosing regimen was also tried (Rituximab 375 mg/m^2 on days 0, 3, 7, and 14). Rituximab is useful in refractory TTP and addition of rituximab to plasma exchange and corticosteroids improves the platelet counts in >80% of patients [13,14].

There are evidences in favour of twice daily plasma exchange [15]. However, it was not tried in our patient. Other therapies like cyclosporin, cyclophosphamide, vincristine and eculizumab are useful in TTP. Cyclosporin along with plasma exchange shows improvement in ADAMTS 13 activity [16]. An interesting fact that, Cyclosporin itself can cause TTP [8]. Patients who are not responding to plasma exchange and steroids, cyclophosphamide is an another option [17]. Combination of vincristine and plasma exchange as initial therapy in TTP shows better response [18]. Seven of eight patients (87%) with refractory TTP showed complete response to Vincristine (1.4 mg/m^2 on day one, followed by 1 mg on days four and seven) [19]. Vincristine was the most useful drug for refractory TTP prior to rituximab era. Refractory TTP responding to eculizumab-an anti C5 monoclonal antibody has been reported in literature [20]. Five out of six patients received bortezomib showed complete remission in refractory TTP [21]. Bortezomib is an emerging therapy for refractory TTP [22]. Compared to rituximab, bortezomib has many advantages like subcutaneous administration, cost effective and no need for hospitalisation. However, many trials are needed to prove its efficacy. Caplacizumab-anti Von

Willebrand Factor humanised immunoglobulin is an another option which induces a faster resolution in acute TTP with increased risk of bleeding [23]. Splenectomy is a surgical option for refractory cases. It is a better option to achieve long term remissions and to prevent future relapses [24]. Among 74 patients with refractory TTP, only 8% of patients failed to respond to splenectomy [25]. It is useful where newer therapies are not available. Newer therapy like recombinant ADMATS 13 shows good response in TTP. Recombinant ADAMTS 13 overcomes the neutralising inhibitors and reconstitute ADAMTS 13 activity in acquired TTP. It may have role in refractory TTP also [26].

CONCLUSION

Early recognition and treatment with appropriate available treatment is important to prevent hypoperfusion to organs. Cyclosporin, cyclophosphamide and vincristine are useful in refractory TTP when newer medications are not available. Various newer pharmacological therapies are available for refractory TTP like rituximab, bortezomib, eculizumab, caplacizumab. Surgical option like splenectomy gives long term response with less relapses. Recombinant ADAMTS 13 may have role in refractory TTP. Appropriate available treatment should be used to achieve remission in refractory TTP. However, larger multicenter studies are required to assess the efficacy of various newer therapies in refractory TTP.

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