CASE REPORT

Successful Management of Refractory Dialysis Independent Wegener's Granulomatosis with Combination of Therapeutic Plasma Exchange and Rituximab

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Abstract Wegener's granulomatosis (WG) is an autoimmune, antineutrophil cytoplasmic antibody mediated necrotizing vasculitis involving renal, and upper and lower respiratory systems. Treatment relies on a combination of immunosuppressive drugs and tapering regimen of glucocorticoids. Therapeutic plasma exchange (TPE) has been recognized as a second line treatment. We report the successful use of TPE in combination with rituximab in achieving remission in a patient with WG (dialysis independent) not responding to conventional therapy.

Keywords Wegener's granulomatosis · Therapeutic plasma exchange · Rituximab

Introduction

Wegener's granulomatosis (WG) is an autoimmune, antineutrophil cytoplasmic antibody (ANCA) mediated necrotizing vasculitis. It classically involves renal, and upper and lower respiratory systems. Mortality rate is around 90 % if left untreated. Treatment relies on a combination of

immunosuppressive drugs and tapering regimen of glucocorticoids. Therapeutic plasma exchange (TPE) has been effectively used in the management of systemic vasculitides and autoimmune disorders based on its principle of removal of pathogenic autoantibodies and immune complexes [1]. Few case reports and randomized controlled trials (RCTs) have demonstrated the use of TPE as a second line treatment for WG. As per ASFA guidelines, TPE is category I indication for ANCA associated WG in dialysis dependent cases and category III indication for dialysis independent cases. We report the successful use of TPE in combination with rituximab in achieving remission in a patient with WG (dialysis independent) not responding to conventional therapy.

Case Report

A 58-year old male, known case of ANCA positive WG for the past 2 years presented with disease exacerbation for the last 3 days. He complained of low grade fever, epistaxis, loss of appetite and decreased urine output and conjunctival bleed in both eyes. There was one episode of malena. A crusting lesion was present on the nose. For the treatment of WG, he had received 18 pulses of high dose cyclophosphamide (500 mg cyclophosphamide in 500 ml of 0.9 % normal saline over 1 h) at every 4 weeks interval, last pulse being 1 month back. During this time, he experienced three relapses in disease activity after initial improvement in clinical symptoms. Patient was dialysis independent. In addition, he was a diagnosed case of pulmonary and abdominal tuberculosis, and was on anti-tubercular therapy for 2 months. Investigations revealed anaemia (6.4 g/dl), leukocytosis (10,600/ul), azotemia (serum urea-84.4 mg % which shot up to 218.1 mg %,

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serum creatinine-7.5 mg %) and mild transaminitis (SGOT-36U/L, SGPT-52.3 U/L).

For managing the current disease exacerbation, TPEs were planned along with intravenous rituximab and oral corticosteroids (prednisolone 80 mg/day). Rituximab infusion in a dose of 1,000 mg (375 mg/m²) was administered once a week for 4 weeks. Simultaneously TPE was started and a total of twelve TPE procedures were performed at one or two day's interval over a month. Due to low hemoglobin, TPE kit was primed with a packed red blood cell unit for the initial five procedures. One plasma volume exchange was done in all the procedures with replacement fluids as 5 % human serum albumin and normal saline. Blood group specific fresh frozen plasma was also used in three of the procedures. The patient had no complications during the procedures except in one in which he had mild shivering at the end of the procedure. It subsided on giving intravenous chlorpheniramine and hydrocortisone.

With treatment, clinical, haematological and biochemical parameters improved substantially. Fever, conjunctival bleed and epistaxis subsided and remission was achieved. Figure 1 shows the serial changes in patient's hemoglobin and serum creatinine. At the time of discharge after 1 month of hospital stay, patient's hemoglobin was 6.2 g/dl, serum urea was 87.31 mg % and serum creatinine was 3.74 mg %. The patient was kept on regular follow up and received another dose of rituximab 1,000 mg after 6 months. After 8 months, he was still dialysis independent and his hematologic and biochemical parameters were as follows—hemoglobin 8.1 g/dl, serum urea 28 mg % and serum creatinine 2.4 mg %.

Discussion

WG, a small vessel vasculitis can lead to early mortality and end stage renal disease. Various treatment modalities have

been employed depending on the extent of involvement of internal organ systems. These include combination of various cytotoxic drugs like cyclophosphamide, cyclosporine A, methotrexate and tapering doses of glucocorticoids [2]. High dose pulse cyclophosphamide forms the mainstay of treatment. TPE is used as an adjunctive therapy, not a first line therapy. In refractory cases, the role of rituximab, a monoclonal antibody which targets CD20 + B-cells is being investigated [3]. It selectively targets mature and pre-B lymphocytes including memory B cells without affecting antibody secreting plasma cells which lack CD20. It is relatively less toxic drug but has low efficacy in patients with predominantly granulomatous disease [4]. Other biologicals which have been tried in WG but require more substantiative evidence include anti TNF- α agents like etanercept, infliximab, alemtuzumab and antithymocyte globulin. Etanercept has been associated with serious adverse events and limited available data suggests increased rate of granulomatous infections with the use of infliximab. Alemtuzumab (humanized monoclonal antibody to CD52) and Leflunomide (isoxazole derivative) are under experimental use only.

The index patient was initially treated conventionally with pulse cyclophosphamide and oral corticosteroids. As the clinical condition of the patient continued to worsen, it was planned to shift the treatment to an alternative agent, that is, rituximab. However since the peak action of rituximab occurs at 3–4 weeks after administration, TPE was started to tide over this critical period. In 2005, Nguyen et al. reported the therapeutic success of TPE in a patient with WG with diffuse alveolar hemorrhage (DAH) refractory to the drug therapy (cyclophosphamide and methylprednisolone). In that report, pulmonary status of the patient markedly improved and he was discharged in stable condition. The author further proposed to include this entity in the therapeutic apheresis guidelines [5]. In the most recent ASFA (American Society for Apheresis) guidelines, use of TPE in WG has been categorized on the basis of dialysis dependence and DAH. In the presence of aforementioned complications, there is a strong evidence to suggest the use TPE as a first line therapy (category I). However if the patient is dialysis independent, the use of TPE needs to be individualized (category III) [6]. Although our patient was dialysis independent, yet he showed refractoriness to the first line therapy and developed progressive renal failure. Hence, TPE was indicated.

Klein et al reported a case of WG in whom extra renal symptoms improved with the immunosuppressive therapy but progressive renal disease persisted. With the addition of TPE therapy, renal functions markedly improved. This suggested the efficacy of TPE when used in addition to conventional therapy in patients with severe renal disease [7]. In a retrospective study assessing the role of TPE in the treatment of vasculitides, it was concluded that the pulse

Table 1- serial changes in patient's hemoglobin and serum creatinine (post the respective TPE)

Fig. 1 Serial changes in patient's hemoglobin and serum creatinine (post the respective TPE)

cyclophosphamide and methylprednisolone followed by their maintenance doses and TPE leads to partial or complete remission and hence may be life-saving [8]. Sugimoto et al. successfully managed a patient with WG complicated with pulmonary haemorrhage and rapidly progressive glomerulonephritis with TPE and intravenous methylprednisolone therapy [9].

In 2007, MEPEX (methyl prednisolone and plasma exchange) trial was undertaken involving 137 patients with severe renal ANCA associated vasculitis with serum creatinine >5.8 mg/dl. It was observed that as compared to intravenous methyl prednisolone, treatment with plasma exchanges was associated with 24 % reduction in the risk of progression to end stage renal disease at 12 months [10]. Several RCTs have been done to study the role of plasma exchange in ANCA associated vasculitis. Earlier it was recommended that TPE is beneficial in severe renal failure with serum creatinine levels >5.8 mg/dl [11]. In a recent randomized controlled trial involving 32 patients of WG, Szpirt et al. recommended that TPE has a definite role even in WG patients with moderately decreased renal functions (serum creatinine >2.85 mg/dl) [12]. PLEXIVAS, an ongoing international RCT on WG patients with moderate renal failure has been started to further ascertain the role of TPE in the management of such patients [11]. Another randomized double-blind controlled trial found that rituximab is equally effective to cyclophosphamide for the treatment of new major renal disease or mild alveolar haemorrhage in ANCA associated vasculitis. In case of a relapsing disease, rituximab was found to be superior to cyclophosphamide [13].

TPE is associated with decreased risk of end stage renal disease (ESRD) as it removes autoantibodies, complements, adhesion molecules, cytokines and by some less defined immunoregulatory effects [11, 12]. Exchange of 1–1.5 plasma volume removes 70–80 % of the desired component and a minimum of 5–7 exchanges are required for removal of three-fourth of the antibody load. In our case, TPE along with rituximab combination therapy was used as the patient was refractory to cyclophosphamide. However, TPE combined with immunosuppressive drugs should be used under close monitoring with proper dose schedule adjustments alternating with TPE procedures.

Conflict of interest None.

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