

Two Approaches to the Clinical Dilemma of Treating TTP with Therapeutic Plasma Exchange in Patients with a History of Anaphylactic Reactions to Plasma

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Background: Thrombotic thrombocytopenic purpura (TTP) is a rare but serious disease caused by autoantibody-mediated deficiency in von Willebrand factor (VWF) cleaving protease, ADAMTS-13. The primary acute treatment is therapeutic plasma exchange (TPE). However, some patients can develop allergic/anaphylactic reactions to the replacement (i.e., donor) plasma over time. Two potential treatment strategies for patients with TTP who demonstrate severe allergic reactions to plasma used for exchange were examined. **Methods:** Two patients with TTP exacerbations who developed severe allergic reactions to donor plasma were identified. One patient's TPE was re-initiated with Octaplas, a lot-batched solvent and detergent treated, type-specific, pooled donor plasma product. The other patient was exchanged with primarily albumin, followed by slow incremental exposures to donor plasma to mitigate exposures and allergic risks. Both patients were assessed for anaphylaxis. **Results:** Both treatment strategies were successful in preventing any further clinically significant allergic/anaphylactic reactions and facilitated both patients' TTP remissions. **Conclusions:** Based on our experience with two similar patients with TTP exacerbations and history of anaphylactic reactions to plasma during TPE, we have identified two possible treatment protocols to achieve remission in this clinical dilemma. Substituting Octaplas for standard plasma or, alternatively, using albumin with slowly increasing amounts of standard plasma may help to mitigate the risk of further anaphylactic adverse events. *J. Clin. Apheresis* 00:000–000, 2016. © 2016 Wiley Periodicals, Inc.

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INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) has been historically diagnosed as a pentad of symptoms, most often manifesting as hemolytic anemia, thrombocytopenia, neurological symptoms and less commonly fever and renal impairment [1]. Alternatively, TTP can be minimally defined as microangiopathic hemolytic anemia (MAHA) with thrombocytopenia ($<150,000/\mu\text{L}$), neurological symptoms and decreased levels of the metalloprotease, ADAMTS-13. In fact, most patients with a clinical diagnosis of inherited (Upshaw–Schulman syndrome) or acquired TTP demonstrate less than 10% ADAMTS-13 activity [1]. Acquired or idiopathic TTP has been associated with the presence of an inhibitory IgG autoantibody leading to a functional deficiency of ADAMTS-13. In contrast, a wide variety of conditions including metastatic cancer, neonatal age, serious infections, hemolysis with elevated liver enzymes and low platelets (HELLP) associated with pregnancy, and cirrhosis of the liver can give moderately decreased ADAMTS-13 levels, but are not defined as idiopathic TTP [2,3].

Therapeutic plasma exchange (TPE) is a mainstay of therapy for individuals with a new diagnosis of

idiopathic TTP [4]. In this procedure, ADAMTS-13 inhibitors are removed by the apheresis device, with the simultaneous replacement of the protease via donor plasma. One potential complication of such procedures is allergic or anaphylactic reactions to the plasma infusion. Severe allergic transfusion reactions (including anaphylactic reactions) are most often attributable to deficiency of IgA with resultant production of anti-IgA antibodies in an exposed host [5,6]. Without a baseline IgA level prior to initiation of TPE one cannot exclude the possibility of severe IgA deficiency driving the allergic reactions; the differential diagnosis would also

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TABLE I. Summary of Patient Demographics and Test Results Performed at our Institution

Patient characteristic/result	Patient 1	Patient 2
Age	40 years old	40 years old
Gender	Female	Female
Presenting platelet count	32,000/ μ L	5,000/ μ L
ADAMTS-13% Activity	<30%	11%
ADAMTS-13 Inhibitor %	>70%	30%
TPE replacement fluid	Octaplas	5% Albumin, Plasma ^a
Total # of TPE treatments	5	15

^aPatient 2 therapeutic plasma exchanges (TPEs) were performed with varying ratios of 5% albumin with increasing amounts of donor plasma. See text for details.

include allergic reactions to other, non-immunoglobulin plasma proteins such as haptoglobin [5].

Herein we present two cases of idiopathic TTP exacerbations where TPE was complicated by severe allergic reactions to the standard donor plasma used for initial exchanges. When we consulted the literature on how best to proceed with apheresis therapy in our cases, there was a dearth of recommendations for this particular scenario. As such, and given: (1) the relative lack of clinical management guidance for severe allergic reactions to plasma associated with TPE for TTP, (2) the frequency with which allergic reactions to plasma are reported [5], and (3) the fact that TPE remains the optimal therapy for TTP [4], we felt the approaches we adopted in these cases would serve as practical guidance for providers who may have to deal with similar circumstances at their own facilities.

MATERIAL AND METHODS

We identified two patients with idiopathic TTP who developed anaphylaxis to donor plasma during their initial TPE regimens. One patient's TPE was re-initiated with a lot-batched solvent-detergent plasma, (Octaplas, Octapharma USA Inc, Hoboken, NJ). The other patient was re-exchanged initially with only 5% albumin replacement solution, with the slow integration of donor plasma to mitigate exposure and allergic risks. Both patients were assessed for signs and symptoms of severe allergic reaction. TPEs for patients 1 and 2 at our institution were performed via central line double lumen catheters using the COBE Spectra Apheresis System (Terumo BCT, Lakewood CO). All procedures were performed with calcium gluconate repletion. Patient demographics and laboratory results from the treatment course at our institution are summarized in Table I.

Typically, at our facility, we perform 1.0 plasma volume exchanges for patients with idiopathic TTP. Such exchanges are performed daily using donor plasma (either standard donor plasma, or plasma-

cryoprecipitate reduced) with goals being normalization of platelet count to $>150,000/\mu$ L as well as correction of lactate dehydrogenase (LDH) to within normal reference range (currently, at our facility, that is LDH levels <243 U/L). In most cases, one to three additional TPE procedures are performed on patients after normalization of platelet counts and LDH (every other day, rather than daily); such a "tapered TPE" approach is anecdotal, but in our experience helps to assure a durable TTP remission. For our TPE procedures in the setting of TTP, patients are routinely treated with diphenhydramine (even in the absence of a history of allergic transfusion reactions). Again, while an anecdotal practice, this is done to help ensure tolerance of the TPE without allergic sequelae.

CASE REPORTS

Patient 1

Patient 1 is a 40-year-old female with a past medical history of hypertension and type 2 diabetes mellitus (non-insulin dependent) who initially presented to an outside hospital with a 3-week history of progressive headache, confusion, and dizziness. She underwent a head MRI given her headache; it was negative for an acute process. She had also had noticed bruising along her arms and initial laboratory results from an outside hospital (and prior to transfer to our facility) revealed severe thrombocytopenia with platelets of $10,000/\mu$ L (ref $150\text{--}350 \times 1,000/\mu$ L), lactate dehydrogenase (LDH) >800 U/L; ref $118\text{--}242$ U/L), fibrinogen 419 mg/dL (ref $159\text{--}439$ mg/dL) and evidence of microangiopathic hemolytic anemia (significant schistocytes on peripheral blood smear). A disseminated intravascular coagulation (DIC) panel (fibrinogen, hematocrit, INR, PT, PTT) was ordered which showed all results within normal range; however, total bilirubin was elevated to 2.2 mg/dL (ref <1.20 mg/dL) with no significant renal involvement by laboratory parameters [BUN 12 mg/dL (ref $7\text{--}20$ mg/dL) and creatinine 0.9 mg/dL (ref $0.5\text{--}1.2$ mg/dL)]. ADAMTS-13 levels were less than 10% (ref $>67\%$ activity) with 67% inhibition. IgA levels were in the normal range on historic testing.

Prior to her transfer to our facility, Patient 1 underwent a total of four TPEs with plasma as the replacement fluid; however, she was noted to have progressively severe allergic symptoms during each treatment beginning with mild pruritus on initial TPE, evolving to urticaria involving the upper chest and then her face during the second and third. During the final treatment at the outside hospital, and despite premedication with diphenhydramine (dose unknown), she experienced shortness of breath, chest pain and throat swelling which necessitated treatment with epinephrine. Further TPE sessions were halted. The patient's

platelets had risen to 280,000/ μ L but immediately began to decline and the patient was transferred to our institution with presumed TTP exacerbation for further management as the transferring facility was unsure how to best proceed given the severity of the allergic reactions when treating with plasma. On arrival at our institution, platelets had dropped to 91,000/ μ L, ADAMTS-13 activity was less than 30% with greater than 70% inhibition. LDH was 219 U/L and coagulation factor activities were all normal. Repeat peripheral blood smear showed normocytic normochromic anemia with mild thrombocytopenia and occasional giant platelets, increased spherocytosis, anisocytosis, and schistocytes (1–2/hpf, >1% increasing to 6–7/hpf on follow up peripheral blood smear interpretation).

Given Patient 1's initial diagnosis of TTP and evidence for disease exacerbation, emergent TPE was planned at our institution. The decision was made to use a modified plasma product (Octaplas, as discussed in the "Materials and Methods" section) as the replacement fluid for the TPE procedure with the concomitant application of anti-histamine and anti-inflammatory medications (diphenhydramine 25 mg by mouth before each procedure and methylprednisolone via the intravenous route 250 mg once daily). At the time TPE was initiated the patient's platelets had further dropped to 32,000/ μ L. The patient underwent five consecutive days of TPE with 4 L using Octaplas only as the replacement fluid; no incidents of severe allergic symptoms were noted during or after any of the exchanges. The patient's final sustained platelet count at discontinuation of TPE was 173,000/ μ L. There have been no reports of disease recurrence since the completion of this second course of TPE.

Patient 2

Patient 2 is a 40-year-old female with no significant past medical history who also presented to an outside hospital with a week long history of blurred vision and dysarthria with numbness of the tongue reported. Laboratory testing at an outside facility prior to transfer to our hospital revealed: thrombocytopenia with platelets at 24,000/ μ L, minimal renal involvement by laboratory criteria with mildly elevated BUN 30 mg/dL and creatinine 1.5 mg/dL. LDH was 612 U/L, haptoglobin less than 10 mg/dL (ref 30–200 mg/dL) and a total bilirubin of 1.52 mg/dL. Peripheral blood smears revealed microangiopathic hemolytic anemia showing marked thrombocytopenia with occasional giant platelet forms, increased schistocytes and occasional microspherocytes. ADAMTS-13 activity levels were 5% with an inhibitor reported (but level unknown). A head CT at the time of presentation did not reveal an acute ischemic process. Reticulated platelet count was 71%, which

was markedly elevated (reference range is up to 20% for patients with thrombocytopenia in this range).

Prior to transfer to our facility, Patient 2 underwent three consecutive TPEs with plasma replacement with significant improvement of her platelet count from 27,000/ μ L to 321,000/ μ L. She developed what was described as an anaphylactic reaction midway through her third apheresis session with hypotension, profound hives, shortness of breath and a brief loss of consciousness, and the procedure was subsequently stopped with no further procedures attempted; the patient was then started on oral prednisone (dose unknown). Note that despite the history of a severe allergic reaction prior to transfer, IgA levels using a pre-TPE specimen were not done on this patient. The patient maintained platelet counts greater than 187,000/ μ L for 3 days on this regimen and was discharged home with plans to start outpatient rituximab therapy. On return to clinic five days after discharge to begin rituximab, her platelets had dropped to 21,000/ μ L and she was transferred to our institution with a diagnosis of TTP exacerbation. This patient was transferred to our hospital as the initial facility was unsure how to best proceed given the severity of the allergic reactions when treating with TPE and plasma. Upon transfer, and prior to initiation of TPE, the platelet count was 5,000/ μ L with mildly elevated BUN (23 mg/dL) and a creatinine of 1.0 mg/dL. LDH was 566 U/L, haptoglobin less than 10 mg/dL and a total bilirubin of 1.52 mg/dL. In addition to thrombocytopenia, the laboratory workup showed ADAMTS-13 activity level of 11%, with 30% inhibition.

In light of Patient 2's severe TTP exacerbation, emergent TPE was planned. We elected to not measure IgA levels at that time due to the earlier receipt of plasma at the transferring facility; our reasoning was that any IgA measurement at that time would not be representative of the patient's actual baseline IgA levels and would be non-contributory to care. Given the unclear etiology of her allergic transfusion reactions, her initial 3.5 L TPE was done completely with 5% albumin as a replacement fluid in order to avoid provocation of another anaphylactic event. Five further consecutive daily TPEs were performed with escalating use of plasma and diphenhydramine (25 mg by mouth immediately prior to each procedure); she was also carefully monitored for allergic symptoms as plasma replacement was initiated. Her second exchange was done with 2.5 L of 5% albumin followed by 1 L of plasma. Her third exchange was 50% albumin and 50% plasma. After the completion of each of the first three procedures, the patient also received plasma infusion overnight by slow drip in a monitored setting. Procedures four, five, and six used 1 L of 5% albumin and 2.5 L of plasma with diphenhydramine as described above. Ultimately the patient underwent a total of 15 plasma exchanges (treatments 7–15 were done

consecutively with full plasma) with no severe allergic symptoms throughout her treatment course and achieved remission as defined in our Methods section. There have been no reports of relapse since the completion of this second course of TPE.

DISCUSSION

Since the average TTP patient requires approximately 40 L of plasma replacement (equating to an average of 200 donor exposures) over a treatment course [6], there is the significant potential for sensitization and subsequent allergic reactions during care. Despite these repeated exposures, severe allergic adverse events (such as bronchospasm or anaphylaxis) in TPE in general, and for TTP in particular, are actually quite rare [7–9]. Given this rarity, there are virtually no guidelines on how best to proceed with TPE in patients with TTP who demonstrate anaphylactic reactions to the primary, empiric therapy. Some considerations (as were undertaken in our case) for replacement fluid include albumin and solvent-detergent plasma. Replacement with albumin almost never causes similar severe allergic reactions in most standard TPE procedures [7–9] and therefore has been proposed for many years as reasonable treatment modality for TTP [10]. Octaplas, a more novel therapeutic option, has been shown to have nearly half the allergic reaction rate when compared with plasma in regular transfusion practice and thus presents a potentially useful option for treating patients with a history of severe allergic reactions to traditional plasma products [11].

Another approach to mitigate the possibility for adverse TPE events in TTP would be shortening the overall course of therapy and/or reducing risks for relapse. For instance, Som et al. identified a decline in overall TPE related complications in TTP patients which they attributed to more consistent use of adjuvant corticosteroids and rituximab (anti-CD-20 monoclonal antibody). Their approach resulted in fewer relapses and exacerbations, thereby limiting further plasma exposure and sensitization potential [12]. One other option in this regard is the immediate discontinuation of TPE, as opposed to approaches at tapering treatment (as has been practiced at our facility as described in “Materials and Methods” section); this approach also limits donor exposures and may help mitigate allergic adverse events.

Regarding our specific approaches, a significant concern for Patient 1 was triggering a severe allergic reaction with re-initiation of TPE using standard donor plasma. As such, pre-medication regimens consisted of diphenhydramine and IV methylprednisone, while epinephrine was on hand at all times. Of equal importance was the selection of replacement fluid for TPE. Alter-

natives to plasma were considered and, ultimately based on the normal historical IgA level, we felt that proceeding with a plasma product would not be overly risky. Nonetheless, to mitigate the chances for an allergic response, we choose Octaplas as a replacement fluid. As a lot-batched solvent-detergent treated plasma product, Octaplas has the potential advantage continually selecting for lot batches to which the patient has shown no past reaction. This was done in our case and, as such, we felt that this plasma product gave us the best option for avoiding the triggering of a severe allergic event in our patient. Moreover, ADAMTS-13 levels in Octaplas are comparable to that of normal plasma, as has been previously reported [13]. Therefore, we felt that we were maximizing the potential for ADAMTS-13 replacement, while minimizing (to the best of our ability) potential allergic side effects.

Regarding Patient 2, there were also significant concerns on how best to proceed with TPE given her history of severe reactions to plasma infusion. Because historical IgA levels were unavailable, we were concerned about the use of any plasma-containing products for replacement fluid, especially during her first set of TPEs; therefore, we did not consider even solvent-detergent treated plasma for this patient. As albumin is a common replacement fluid in TPE, limits exposure to plasma proteins, maintains oncotic pressure, and (in our experience) has been much less allergenic than plasma, we chose to initially proceed with albumin-based exchange only. A major disadvantage of albumin in TTP is that it fails to replete ADAMTS-13 levels. Interestingly, despite this limitation, some studies have also demonstrated no significant differences in the average number of TPE procedures done for patients receiving partial albumin exchange when compared with studies using full plasma exchange in the setting of TTP [14]. Nonetheless, in order to provide the patient with some ADAMTS-13 replacement during “albumin-predominant” exchanges, we worked closely with the clinical team to insure that the patient underwent slow infusion of plasma after each of these earliest apheresis procedures. Our thinking was that a slow plasma infusion rate in a monitored setting, with concomitant administration of anti-histamine medications, would allow for a rapid intervention should the patient manifest signs/symptoms of anaphylaxis, while also being an *in vivo* test of her tolerance of plasma exposure. Since the patient did very well with these slow plasma infusions, we felt confident about steadily increasing the amounts of plasma that we introduced into each subsequent plasma exchange.

There are several limitations to our study. While there is extensive literature for various fluid replacement strategies in TPE treatment of TTP patients, essentially no studies have specifically focused on the TTP patient subpopulation with a history of severe

allergic reactions to standard plasma. As a case series with only two patients we are limited by virtue of the study size and cannot control for underlying conditions or treatment differences in TPE frequency, duration, replacement rate and vascular access from the outside hospitals that may have contributed to the patients' allergic symptoms. We also cannot exclude the possibility that aggressive pre-medication prior to the TPEs at our facility was the most important cause for tolerance of subsequent exchanges, particularly for Patient 1 in whom plasma was used from the very first TPE. However given the rarity of severe allergic reactions in an already rare disease such as TTP, our report, combined with others that have shown solvent-detergent plasma as a practical replacement fluid for TPE in the setting of TTP [15,16], should be useful of information for practical information on allergic-risk mitigation. It is also important to note that our case series relied on reported "anaphylactic" reactions from outside institutions that may have used differing clinical criteria to make this diagnosis. Finally, due to the recent TPE treatments we were unable to get a baseline IgA level on Patient 2 to exclude the possibility of IgA deficiency mediated anaphylaxis, although her ultimate tolerance of numerous plasma-based exchanges late in the course of therapy at our facility make IgA deficiency an unlikely possibility.

CONCLUSIONS

Based on our limited experience with two similar patients with idiopathic TTP and history of anaphylactic reactions to plasma during TPE, we have identified two possible treatment protocols to achieve remission in this difficult clinical dilemma. Substituting Octaplas for plasma, or alternatively using albumin with slowly increasing amounts of plasma in this patient population, and strict monitoring for severe allergic reactions may mitigate the risk of further anaphylactic reactions.

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