

## Rostrum

*Editor's introductory comments: Plasma exchange (pheresis) is being utilized with increasing frequency for a variety of disorders. Although serious reactions are infrequent, the allergist-immunologist may be consulted and should be informed about the problem. The following report reviews the situation based on a case observed by the authors.*

### An approach to immunologic reactions associated with plasma exchange

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Removal, addition, or exchange of blood products has become an important part of the therapy of many diseases. Techniques, such as plasmapheresis, have been used in neurologic diseases, such as myasthenia gravis and Guillain-Barré syndrome, hematologic diseases, such as TTP, and autoimmune diseases, such as systemic lupus erythematosus.<sup>1-3</sup> These procedures are frequently complicated by reactions that are considered immunologic.<sup>4-7</sup> The actual mechanisms governing specific instances may not be identified.

Although most of these reactions are mild, involving urticaria and pruritus, some reactions have been more severe, and fatalities have been reported.<sup>4, 5, 7-10</sup> It is important for the allergist-immunologist to be aware of these reactions; despite limited information regarding pathogenic mechanisms, an approach can be developed for evaluation and treatment of patients developing these complications.

Such a strategy is suggested by the case of a primigravida who at 6 weeks gestation developed thrombocytopenia and hemolytic anemia. Subsequently, during PE, she began to have allergic-type reactions. An approach to the treatment of reactions associated with plasmapheresis and, in particular, FFP infusions is presented. Special attention is focused on the impact of pregnancy in this situation. In addition, what is known about the underlying immunologic mechanisms is reviewed.

#### Abbreviations used

|       |                                     |
|-------|-------------------------------------|
| TTP:  | Thrombotic thrombocytopenic purpura |
| FFP:  | Fresh-frozen plasma                 |
| p.o.: | By mouth                            |
| PE:   | Plasma exchange                     |
| IC:   | Immune complex                      |
| RBC:  | Red blood cell                      |

#### CASE REPORT Initial presentation

A 23-year-old primigravida in her sixth week of what had been an uneventful pregnancy was noted to be jaundiced by her acquaintances. There were no significant past medical problems.

On physical examination, her temperature was 100° F, but other vital signs were normal, including her blood pressure that was 102/60 mm Hg. The remainder of the examination was noteworthy for the obvious jaundice and a few scattered petechial lesions on the lower extremities. There was no evidence of neurologic abnormalities.

Subsequent laboratory evaluation revealed a platelet count of 6000/mm<sup>3</sup>. The hematocrit was 33.4%, the reticulocyte count was 1.2%, and the haptoglobin was <5 mg/dl. The white blood count was 12,600/mm<sup>3</sup>. The total bilirubin was 12.5 mg/dl, and the direct bilirubin was 0.4 mg/dl. The lactate dehydrogenase was 885 U/ml (normal range, 81 to 175 U/ml), but the aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase were normal. A direct Coombs' and an antinuclear antibody test were negative. Blood urea nitrogen and creatinine were unremarkable, but a urinalysis revealed proteinuria, and >100 RBC per high-power field. Complement values were normal. Evidence of RBC fragmentation was observed on inspection of the peripheral blood smear. Schistocytes, spherocytes, a

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few helmet cells, and giant platelets were present. Bone marrow examination disclosed a normocellular marrow with adequate numbers of megakaryocytes.

Taken together, the smear and bone marrow findings were considered to indicate peripheral destruction of both erythrocytes and platelets. With thrombocytopenia, evidence of microangiopathic hemolytic anemia, renal dysfunction, and fever, a tentative diagnosis of TTP was made.

### Subsequent course

Plasmapheresis with FFP replacement was initiated. Toward the end of the first procedure, urticaria and pruritus developed. Diphenhydramine was administered, but shortly afterward, while the patient was walking to the bathroom, she became light-headed. Her blood pressure at that time was 96/68 mm Hg, and her heart rate was 132 beats/min. Normal saline was infused, and her vital signs were stabilized. At the end of a subsequent plasmapheresis, despite antihistamine premedication, the patient reported chest tightness. On another occasion, a physician described the presence of mild wheezes. An IgA level obtained from serum drawn before any therapy was administered was 77 mg/dl (normal range, 75 to 420 mg/dl). Assays for anti-IgA and antiplatelet antibodies were negative.

Initially, plasmapheresis was performed on a daily basis with 10 to 12 U of FFP infused during each treatment. Because of concern of hypotension and bronchospasm, a premedication regimen before PE was instituted. Prednisone, 50 mg p.o., was administered 13, 7, and 1 hour before plasmapheresis. In addition, 1 hour before the procedure, diphenhydramine, 50 mg p.o., and ephedrine, 25 mg p.o., were administered. With these prophylactic medications, the patient never had more than a few hives after plasmapheresis. Her platelet count, the haptoglobin, and bilirubin levels returned to normal; the hematocrit stabilized. The interval between procedures was gradually lengthened. During most of the latter half of her pregnancy, she required plasmapheresis once a week. Attempts were made to reduce the prepheresis doses of corticosteroids and diphenhydramine. Although the prednisone dose was successfully reduced to 40 mg, these efforts were generally unsuccessful. She subsequently delivered a healthy 7 pound 7 ounce male child at 36½ weeks gestation. Apgar scores were 9 and 9.

In the 2 days immediately surrounding delivery, schistocytes were noted on the blood smear, and the platelet count was slightly below normal. Plasmapheresis was reinstituted. Soon afterward, her TTP went into remission and she has not required plasmapheresis since that time. A total of 57 PEs had been performed with infusion of 687 units of FFP.

### DISCUSSION

In summary, this is a case of a primigravida who was considered to have TTP and required extraordinary numbers of PEs. In the course of therapy, she was able to tolerate 687 U of FFP, despite the potential for life-threatening adverse reactions.

The primary processes of thrombocytopenia with microangiopathic hemolytic anemia and visceral or-

gan involvement were manifest, indicating the diagnosis of TTP. Although neurologic symptoms were absent, this was not considered inconsistent with the diagnosis, since 8% to 48% of patients lack these manifestations on presentation.<sup>11</sup> Untreated, TTP has a mortality rate approaching 100%. However, when PE is instituted expeditiously, a vastly improved survival rate of approximately 80% can be achieved.<sup>3, 11</sup>

For the allergist, the events illustrated by this case raise three important questions: (1) What are the immunologic reactions associated with PE? (2) How can these reactions be controlled so that life-threatening episodes are prevented? (3) What are the additional considerations when the patient is pregnant? In most instances the adverse reactions to the plasmapheresis process are mild; however, hypotension and bronchospasm resulting in possible hypoxia for mother and fetus may occur.

### Incidence of immunologic reactions

Although definitions of an "allergic reaction" during plasmapheresis may vary among investigators, the reported incidence appears to range from 6% to 12% (Table I). In our own experience with 699 plasmapheresis procedures using a rotating membrane system,<sup>12</sup> there were 21 immunologic reactions for an incidence of 3%. Of the 21 reactions, five were anaphylactic type and 16 were mild reactions, consisting of pruritus, erythema, or urticaria. All these reactions were limited to the 127 procedures in which FFP was at least part of the replacement fluid. Thus, in PEs involving FFP, the overall reaction rate was 17%, 4% being potentially life-threatening. All the severe reactions occurred in the patient presented in this study.

As suggested by our own experience, the reaction rate is higher when FFP is used as the replacement fluid. Isbister<sup>5</sup> and Isbister and Biggs<sup>13</sup> state that, with repeated exposure to plasma products, the total rate of such reactions as pruritus, erythema, urticaria, or anaphylactic-type reactions in an individual patient may reach 50%. Sutton et al.<sup>4</sup> and Rock and Tricklebank<sup>14</sup> have noted not only the increased rate when the replacement is FFP but also that patients tend to have repeated reactions.

### Immunologic mechanisms related to the plasmapheresis technique

During plasmapheresis, immunologic reactions can be considered as either related to the technique or to the blood product administered. First, consider the plasmapheresis apparatus and technique.

Plasmapheresis involves separation of plasma by either centrifugation or filtration. The method used at the University of Connecticut Health Center involves

filtration.<sup>12</sup> Much of the information on reactions related to membrane filtration comes from the hemodialysis experience. Cuprophane membranes, widely used in hemodialysis, have been associated with hypotension, bronchospasm, flushing, and angioedema in conjunction with complement activation and leukopenia.<sup>15-17</sup> In addition, hemodialysis reactions have been associated with cold sterilization of dialyzers with ethylene oxide.<sup>15, 18, 19</sup> Reprocessing methods, such as the use of bleach, have been demonstrated to influence the frequency of reactions in reused equipment.<sup>20</sup>

Similar reactions linked to ethylene oxide have now been reported with plasmapheresis.<sup>21, 22</sup> Cuprophane membranes are not used for PE. However, a closely related membrane, cellulose acetate, has been used and may cause some complement activation.<sup>23</sup> The onset of all these reactions, unlike the situation described in this study, is generally at the start of the procedure, usually within the first 15 minutes.

In this case report, such mechanisms are unlikely in that the filter was fabricated from a relatively biocompatible polyamide membrane, and sterilization did not involve ethylene oxide. Finally, the delayed time of onset of the reaction would be unusual.<sup>15, 22</sup> In summary, it appears unlikely that this patient's reactions were related to the plasmapheresis apparatus.

### Immunologic mechanisms related to the plasma infusion

It is more likely that the administration of blood products during plasmapheresis was involved. In particular, this patient received PE with infusion of FFP. When the replacement fluid is FFP, allergic-type reactions occur more frequently.<sup>4, 7</sup>

FFP contains such proteins as albumin, immunoglobulins, coagulation and fibrinolytic factors, and complement. One of the commonest, best studied, and most serious immunologic reaction occurs when the recipient is IgA deficient.<sup>7, 10</sup> Approximately half of such IgA-deficient individuals have anti-IgA antibodies.<sup>24</sup> Most of these antibodies are of IgG isotype, although IgE-anti-IgA has been reported.<sup>10, 25</sup> When immunoglobulins, including IgA, are infused, ICs of IgA and IgG-anti-IgA can activate complement. The anaphylatoxins C3a and C5a are generated and trigger mast cell and possibly basophil degranulation. However, this patient was not IgA deficient. In fact, assays of her serum obtained on admission revealed no evidence of anti-IgA antibodies.

Complement activation may occur by the formation of ICs other than those comprised of IgA and antibodies of other immunoglobulin isotypes. ICs introduced by the infusion itself, or ICs formed by the

**TABLE I.** Incidence of allergic reactions in plasmapheresis in representative studies\*

| Primary author                                        | No. of PEs | % Of allergic reactions |
|-------------------------------------------------------|------------|-------------------------|
| Centrifuge plasma separation                          |            |                         |
| Aufeuve <sup>43</sup> , Springer et al. <sup>46</sup> | 3086       | 6                       |
| Fabre <sup>44</sup>                                   | 578        | 12                      |
| Membrane plasma separation                            |            |                         |
| Samtleben <sup>45</sup>                               | 120        | 8.3                     |
| Sprenger <sup>46</sup>                                | 306        | 0.7                     |
| Membrane and centrifuge <sup>†</sup>                  |            |                         |
| Sutton <sup>‡</sup>                                   | 5235       | 3.7‡                    |

\*The different percentages may reflect the variable degree to which plasma containing solutions, such as FFP, were used.

†Both separation systems were used.

‡These episodes were associated with fever, chills, and urticaria, but there were 120 incidents of hypotension and two respiratory arrests not included.

interaction of donor and recipient proteins may activate the alternate pathway of complement. Support for this concept comes from the observation that repeated exposure to plasma may increase the reaction rate to an incidence of 50%.<sup>5, 7</sup> Such infusions of antigenic molecules may result in activation and proliferation of B-lymphocytes with subsequent antibody production.

Whether antibodies are present or newly generated in the recipient, they may be directed at many potential antigens. For example, although there was no evidence of anti-IgA in this patient, small amounts of recipient allotypic antibody to IgA, IgG, an antigenically distinct complement protein or to any infused protein may result in the formation of ICs.<sup>7, 10, 26</sup> Conversely, donor antibodies may be infused that recognize soluble antigens.

There are many antigens on RBC membranes and not all characterized routinely by blood banks before transfusion. Similarly, antigens have been recognized on the membranes of other blood cells, including platelets.<sup>7</sup> Antibodies to such antigens may be present in plasma infusions, and some of these antigens, such as the Lewis antigen, are soluble,<sup>27</sup> but whether this is of significance in terms of allergic-type reactions is unknown. It is also possible that some membrane-associated antigens may be closely related to soluble antigens which the same infused antibody may recognize. There is a study of a severe transfusion reaction occurring in an individual who had been diagnosed to lack an RBC antigen called Rodgers. This patient was also revealed to have IgG directed against C4. The HLA locus coding for the Rodgers antigen and C4 are near each other.<sup>10, 28</sup> A proposed interpre-

**TABLE II.** Reported and hypothesized causes of immunologically based adverse reactions associated with plasmapheresis

| Mechanism                                     | Reference No. |
|-----------------------------------------------|---------------|
| Mast cell and/or basophil degranulation       | 10, 24        |
| Complement Activation                         | 6             |
| IgA, IgG-anti-IgA complexes in IgA deficiency | 7, 10, 24     |
| Membrane incompatibility                      | 23, 47        |
| Other IC formation                            | 7, 10, 24     |
| Blood product antigen                         | 26            |
| IgE-mediated hypersensitivity                 |               |
| Infused IgE and subsequent antigen exposure   | 10, 24, 29    |
| Sensitization with infused antigen            |               |
| Ethylene oxide                                | 21, 22        |
| Antibiotic, food antigen                      | 10            |
| IgA                                           | 25            |
| Direct mast cell degranulation                |               |
| Opiates in infusion                           | 24            |
| Other mediators                               |               |
| Kinin activation or infusion                  | 5, 7, 13      |
| Arachidonic acid product participation        | 7, 10         |
| Platelet-activating factor                    | 10            |
| Failure to inactivate mediators               | 5             |

tation of the events was that previous transfusions sensitized the recipient to Rodgers antigen, resulting in production of an antibody that also cross-reacted with an allotype of C4 introduced in the present infusion.

Mechanisms other than complement activation have been proposed. Mast cell degranulation as a consequence of infused IgE binding to receptors on mast cells followed by antigen exposure is theoretically possible. Transfer of specific IgE to food antigens followed by exposure to relevant antigens has been hypothesized in one case report.<sup>24, 29</sup> It has been suggested that infusion of IgE to penicillin determinants followed by administration of such an antibiotic to the recipient could result in anaphylaxis,<sup>10</sup> but further investigation of this hypothesis is necessary. In reverse, it also has been speculated that mast cell degranulation could occur after an infused antigen, such as penicillin, binds and cross-links IgE already present on mast cells in a penicillin-allergic recipient.<sup>10</sup> Theoretically, direct mast cell degranulation could occur if an opiate is contained in the infusion.

Another proposed explanation is that repeated PE may deplete enzymes, such as histaminases or proteases, which would normally break down the products of immune reaction.<sup>5</sup>

Other cells and mediators may be associated with some of these reactions. Basophil degranulation hypothetically could occur. Production of bradykinin could prove important.<sup>5, 7, 13</sup> Prekallikrein activators

and other components of the kinin system may be infused in the FFP.<sup>13</sup> Arachidonic acid products, such as leukotrienes, may participate,<sup>7</sup> but their roles have not been established. Platelet-activating factor, like the leukotrienes, is a phospholipid and mast cell product that can generate a wheal-and-flare reaction when it is injected into skin, cause hypotension by intravenous injection, and activate eosinophils and neutrophils. These mechanisms are summarized in Table II.

### Diagnostic tests

Given that the mechanisms governing these immediate reactions are not completely understood, what diagnostic tests should be performed? If the suspected problem is related to the plasmapheresis technique, changing the equipment may be the most useful maneuver. However, if changing the technique does not eliminate the problem or, instead, the infusion is implicated, the analysis becomes more difficult. If it is possible, the relevant immunogen should be determined. An assay for anti-IgA should be performed. It may be possible to obtain other *in vitro* tests for specific IgG or IgE, for example, an ELISA for ethylene oxide-human serum albumin. In some cases, the presence of relevant IgE may be identified by skin testing, for example, penicillin skin testing. Blood levels of tryptase may implicate mast cell participation.<sup>30</sup> Prostaglandin D<sub>2</sub> is another mast cell product, but measurement is difficult.<sup>30</sup> Plasma histamine levels

peak within minutes of an anaphylactic event. Histamine is present in the urine somewhat longer and may indicate mast cell or basophil involvement. Unfortunately, these tests may not be readily available, although a test for tryptase levels is becoming more easily obtainable.<sup>31</sup> The assays for the products of complement activation, C3a and C5a, are also difficult and not routinely available but are more sensitive measures of complement activation than measuring C3 or C4 or total hemolytic complement.<sup>32</sup> However, tests of mast cell or complement activation do not identify the specific inciting immunogen and, for that reason, may not be particularly helpful.

### Impact on pregnancy

No matter which mechanisms are pertinent, a clinician must attempt to control serious reactions, particularly when the patient is pregnant. Maternal hypotension or maternal hypoxia that may result from anaphylaxis can compromise fetal oxygenation.<sup>33, 34</sup> Maternal hyperventilation occurring during these reactions and resulting in maternal hypocapnia and alkalemia may also compromise fetal oxygen supply.<sup>34</sup> Chronic oxygen deprivation in the fetus may be associated with reduced fetal growth, prematurity, and low birth weight.<sup>34</sup> However, the critical amount and duration of such oxygen deprivation has not been defined.<sup>34</sup> Nevertheless, disregarding the underlying TTP and borrowing from the experience with asthma in pregnancy, it would appear that, if maternal oxygenation and perfusion can be maintained, maternal-fetal outcome will approach that of the general population.<sup>35, 36</sup>

### Management

Because this pregnant patient required frequent PEs and there was concern of possible bronchospasm and hypotension, a prophylactic premedication regimen was initiated. This protocol is the successful regimen used in the prophylaxis of patients with a history of radiographic contrast media reaction who require readministration of radiographic contrast media.<sup>37, 38</sup> When there is an increased risk of such anaphylactic-like events, this regimen appears to have widespread application. Recently, this premedication has been used in preventing intraoperative anaphylaxis in patients with a history of such events.<sup>39, 40</sup> Furthermore, such pretreatment has been proposed for preventing unexplained allergic-type reactions occurring in required blood product transfusion.<sup>10</sup> The case presented here is the most extensive application of such a regimen in PE. Because a role for corticosteroids in the treatment of TTP has recently been proposed,<sup>41</sup> the use of prednisone in this case is particularly fortuitous. Fi-

nally, these medications are appropriate in pregnancy.<sup>33, 42</sup>

### SUMMARY

Immunologically mediated anaphylactic-type events are not uncommon with PE. The pathogenesis of these reactions is not well understood and demands further investigation. If a technique or equipment-related phenomenon can be identified, it should be addressed (e.g., replace the membrane for a more biocompatible membrane and use better rinsing procedures to eliminate ethylene oxide). Testing for specific relevant immunogen, either by in vivo or in vitro methods, if these methods are available, should be considered. If infusion of essential blood products is the most likely cause, then a premedication regimen may be helpful in preventing such reactions. As the risks and benefits of treatment are weighed, it is important to remember that every hive need not be eliminated. Instead, the goal is to prevent compromise to oxygenation and perfusion in both mother and fetus while comfort is maintained and drug-induced adverse effects are avoided.

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