

A Case Report of Double-Filtration Plasmapheresis for the Resolution of Refractory Chronic Urticaria

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Abstract: A 29-year-old Chinese female was diagnosed with chronic urticaria. Dexamethasone and gamma globulin initially resolved the illness; however, when dexamethasone was decreased and gamma globulin was withdrawn, urticaria emerged again and could not be controlled by any of the medications used. The diagnosis of refractory chronic urticaria was made and double-filtration plasmapheresis (DFPP) was performed. The symptoms were relieved

during the first DFPP procedure and the disease resolved shortly thereafter. DFPP theoretically removes medium to large molecular substances such as IgG and IgE from circulation, and therefore may prove to be an effective treatment for refractory chronic urticaria. **Key Words:** Chronic urticaria, Cyclosporine, Double-filtration plasmapheresis.

Chronic urticaria (CU), defined as recurring attacks of hives lasting longer than 6 weeks, is a common disorder for which a cause is determined in less than 20% of patients (1). One theory is that CU might be autoimmune in origin, at least for a sub-population of patients. Several lines of evidence indicate this concept.

In this article, we describe the case of a patient with refractory chronic urticaria, successfully treated with double-filtration plasmapheresis (DFPP). To our knowledge, no other reports have described DFPP in the treatment of CU. We also discuss the possible mechanism by which DFPP exerts its effect on CU.

CASE REPORT

A 29-year-old Chinese female was admitted to our hospital in July 2005 with a six-year history of chronic urticaria. Approximately six years ago, she suffered from red wheal-like skin rashes and itching over her whole body after a period of fatigue. The rashes dis-

appeared 1–2 days later, but new rashes appeared every day. The rashes grew larger and fused together. The patient also had abdominal pain, but did not have fever, headache, cardiac problems, or dyspnea. The wheals lasted for two months and she was diagnosed with “chronic urticaria” by the dermatology department. After being treated with antihistamine drugs and prednisone, her rashes disappeared; however, the symptoms recurred every one to two years. Antihistamine drugs, gamma globulin, prednisone, dexamethasone and methylprednisolone were used, and then symptoms were controlled.

One week before admission, the patient again suffered from red wheal-like rashes with unbearable pruritus. On admission, the patient was alert, oriented, afebrile (37.1°C) and normotensive (112/76 mm Hg) with a regular heart rate of 72 beats per minute. She appeared to be otherwise normal and healthy. There was no cyanosis or any sign of bleeding or anemia on the skin, and no disk-like erythema or butterfly erythema on her face. Her superficial lymph nodes were not palpable, and her lips and oral mucous membranes were normal; no oral ulcers were found, and her teeth and gums were normal. The tonsils were not enlarged, and no injection or exudates were present on the pharynx. The external canal ear was clear, and there was no tenderness over

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FIG. 1. Before the first double-filtration plasmapheresis procedure there were some wheals on the patient's neck.

the mastoid processes or accessory nasal sinuses. The thyroid gland was normal with no palpable nodules. Her cardiac rhythm was regular and the heart sounds were strong with no splitting or pathological murmurs. Both lungs were resonant and the breath sounds were clear without pathological sounds or rales. Her abdomen was soft and non-distended, with no tenderness, palpable masses, organomegaly, or shifting dullness. Her limbs had free movement, and no peripheral edema was present. There was some erythema (with patches ranging in size from coin-like to the size of an irregular palm) on the neck (Fig. 1), both flanks, forearms, backs of the hands, thighs and lower legs. The majority of the erythema took the form of a half ring and was slightly raised about the surface of the skin. The borders were clear, and some rashes merged into one. There was no effusion, scale, tubercle or haphalgnesia on the erythema.

The laboratory findings were as follows: the complete blood count, routine urine and stool tests, liver and renal function, electrolytes, serum sugar, and thyroid function were normal. The immunoglobulin (Ig) E level was 304.76 U/mL (normal range <165.3 U/mL), IgG was 1840 mg/dL (normal range <1620 mg/dL). The complement results, including C2, C3 and C4, were normal, as were the erythrocyte sedimentation rate and renal function (RF). Anti-nuclear, anti-ds-DNA, anti-Sm, anti-mitochondrial, and antineutrophil cytoplasmic antibodies were negative. Hepatitis indicators and anti-human immunodeficiency virus antibodies were all negative. The chest X-ray and electrocardiography findings were normal.

On day 1 of admission, dexamethasone (5 mg/day), gamma globulin (20 g/day), desloratadine (5 mg/

nocte) and ebastine (10 mg/day) were prescribed. On day 3 of admission, the rashes and pruritus disappeared. On day 6, when gamma globulin was withdrawn and dexamethasone was decreased to 3 mg/day, rashes and pruritus recurred on the whole body. On day 7 desloratadine was stopped and dexamethasone was replaced by methylprednisolone (20 mg/day, orally). Three days later the rashes were still present. On day 10 the dosage of methylprednisolone was increased to 40 mg/day (intravenous infusion) and extra Bacillus Calmette Guerin (0.5 mg/day, intramuscular injection) was started. Until day 15, no curative effects were exhibited. A diagnosis of refractory chronic urticaria was strongly suggested. On day 16 her IgE levels increased to 465.53 U/mL. Because the drugs were inefficient, DFPP was suggested to reduce levels of autoimmune antibodies, IgE and pro-inflammatory cytokines in order to control the disease. On day 17 the first DFPP procedure was performed using a plasauto-IQ machine from Japan. We performed DFPP with a cascade flow filter (the first filter was an Asahi plasma separator, Plasmaflo OP-08W; the second filter was a membrane-type plasma-component separator (Cascadeflo EC-40W; Asahi Medical Co., Tokyo, Japan). A double lumen catheter was inserted into the patient's right femoral vein and the treatment itself was without complications. The replaced plasma volume was 4000 mL. The discarded plasma, which was replaced by 500 mL Ringer's solution plus 100 mL of 20% human serum albumin, was approximately 300 mL. During plasmapheresis, the rashes and pruritus began to ease, and were resolved completely by the completion of DFPP (Fig. 2). The IgE level decreased from 390.9 U/mL to 95.5 U/mL, the serum



FIG. 2. After the first double-filtration plasmapheresis procedure the wheals disappeared.

globulin level decreased from 32.3 g/L to 14.4 g/L, the IgG level decreased from 1840 mg/dL to 626 mg/dL, and the serum albumin level was reduced from 35.4 g/L to 21.8 g/L. In addition, other routine laboratory indices were maintained within normal ranges after DFPP. Thereafter, no new rashes appeared, and subsequently all drugs were withdrawn. On day 19, the second DFPP was performed. On day 23, three coin-sized, half-ring shaped rashes appeared on the patient's neck with slight itching. About 2–3 hours later, the rashes resolved on their own. Oral methylprednisolone (20 mg/day) and cyclosporine A (5 mg/kg-BW, 12 hourly, orally) were initiated and lasted for one year. On day 24, the third DFPP was performed successfully. After this, the rashes did not reappear again and the patient was discharged. Over the next year, urticaria did not recur in this patient.

DISCUSSION

Chronic urticaria is defined as recurring attacks of hives lasting for longer than six weeks (1). Most cases of CU are considered idiopathic, because no exact cause could be identified in >80% of cases. The causes listed in most textbooks include physical factors, chronic infection (such as *Helicobacter pylori* (2,3), or Hepatitis A and B viruses), candidiasis, aeroallergens, internal malignancy and drugs, although in practice none of these can be convincingly incriminated (4,5). Among others, non-allergic intolerance reactions to foods and autoreactivity functional autoantibodies directed against the IgE receptor have been described (5–8). Although the mechanisms responsible for CU are not well known, it has recently been accepted that autoimmunity plays an important role in the pathogenesis of CU for at least a subpopulation of patients. Hide et al. (8), Fiebiger et al. (9) and Tong et al. (10) reported that many CU patients had autoantibodies directed to the Fc ϵ RI α subunit. These autoantibodies could stimulate human basophils to release histamine (the major mediator in urticaria) (10). They were also able to activate rat basophil leukemia cells that were transfected with the α subunit of Fc ϵ RI (10). Dalal et al. (11) reported two CU cases that expanded the spectrum of autoimmune disease associated with CU in children, emphasizing the importance of autoimmunity as a possible cause, both in adults and the pediatric population. Leznoff and Sussman (12), Rumbly et al. (13), Gallo et al. (14) and Liutu et al. (15) reported that CU was associated with a variety of autoimmune diseases. The severe CU patients with autoantibodies could benefit from immunoregulation treatment, such as

intravenous immunoglobulin (16), cyclosporine (17) and plasmapheresis (18), when antihistamine drugs were not effective or dependent on oral steroid. The theory that some cases of CU are an autoimmune disease was the basis for using DFPP and cyclosporine to treat our patient.

The major mode of action of plasmapheresis is rapid depletion of special disease-associated plasma factors (19). In DFPP, we use two membranes with different pore sizes as a plasma separator and a plasma cascade flow (20). The pore size of the plasma cascade flow is smaller than that of the plasma separator; thus, the first filter, the plasma separator, separates blood cells from plasma components, and the plasma cascade flow (the second filter) then divides smaller molecular components (proteins) beneficial to patients, such as albumin, from larger molecular ingredients, including pathogenic substances, in a size-dependent manner (20,21). The larger molecular ingredients are then abandoned, and the smaller molecular components containing albumin are mixed with blood cells and infused back to the patient. DFPP has the ability to remove medium to large molecules, including various antibodies such as autoantibodies directed to the Fc ϵ RI α subunit, from the plasma protein fraction of the treated patients.

None of the medications had an effect on our patient; however, the disease began to resolve soon after the first DFPP procedure, suggesting that rapid depletion of autoantibodies against Fc ϵ RI α might occur during DFPP. The autoantibodies were IgG and their weights were approximately 150 kDa; therefore, DFPP could theoretically remove autoantibodies in a size-dependent manner. After the first DFPP procedure, our patient's IgG level decreased from 1840 mg/dL to 626 mg/dL, and the descending amplitude was almost 65%. Because DFPP treated this CU patient successfully, it suggested that this case of CU might belong to the group of autoimmune disease, with autoantibodies playing an important role in its pathogenesis. Grattan (18) reported eight severe, unremitting chronic urticaria patients undergoing plasmapheresis (plasma exchange, PE). The symptoms were abolished for 2 months in one patient and for 3 weeks in another; two patients showed an almost complete resolution of symptoms, two had temporary relief, and the other two showed little change. This was the only report we found about the use of plasmapheresis in the treatment of CU. Considering our patient, the therapeutic effects of DFPP plus immunosuppression treatment might be better than that of PE only.

DFPP can clear autoantibodies, but it does not have the ability to inhibit formation of autoanti-

bodies, so that immunosuppressive drugs such as cyclosporine A must be used following DFPP. In our patient, the chronic urticaria was rapidly resolved by DFPP and controlled for one year by cyclosporine A. As the treatment was successful, this suggests that some CU cases may be an autoimmune disease and that DFPP combined with immunomodulatory treatment is useful in the treatment of CU.

CONCLUSION

DFPP appears to be effective for the treatment of refractory chronic urticaria; however, future studies are warranted for further investigation.

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