Partial Immunologic Reconstitution of a Patient with Acquired Agammaglobulinemia: A Transient Phenomenon Accompanying Therapeutic Plasmapheresis

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A patient with acquired agammaglobulinemia was treated with plasmapheresis. The rationale for this procedure was based on the presence of a cytotoxic autoantibody with specificity for helper (TH2) T lymphocytes. Plasmapheresis reduced the autoantibody concentration to undetectable levels, which resulted in an increase number of helper T cells. These T cells provided normal in vitro helper activity. Plasmapheresis did not correct a concomitant suppressor T-cell defect, and the clinical remission ended during the fifth month of exchange therapy.

ACQUIRED agammaglobulinemia (AAG) or common variable immunodeficiency disease (CVID) is a disorder characterized by a diminished quantity of circulating immunoglobulin, qualitatively abnormal B lymphocytes, and impaired cell-mediated immunity. Although individuals afflicted with AAG have a more favorable prognosis than those with other pathophysiologically related disorders, life-threatening infection and premature death are the ultimate sequela of the disease. The use of prophylactic antibiotics is of no avail. Temporizing measures, such as the administration of gammaglobulin, frequently improve the quality of life. Successful bone marrow transplantation offers the most definitive therapeutic results.

During the past 7 yr, we had the opportunity to care for a patient with AAG. In addition to the customary immunologic deficiencies, the patient produced a cytotoxic antibody that reacted with autologous and histoidentical helper T lymphocytes. The presence of this potentially pathogenic immunoglobulin provided a rationale for the use of plasma exchange therapy.

PATIENT HISTORY AND IMMUNOLOGIC STATUS

D.L. was a 17-yr-old white male with confirmed AAG. Details of his medical history and clinical course have been reported previously. His early childhood was complicated by recurrent episodes of dacrocystitis, conjunctivitis, upper respiratory tract infections, and pneumonia. Pulmonary infections eventually progressed to bronchiectasis. Immunoglobulins were measured in early childhood and throughout adolescence. IgG levels averaged 34 mg/dl and never exceeded 70 mg/dl. Levels of IgM and IgA were consistently below detectable limits. He was anergic to Candida albicans, streptokinase-streptodornase, and dinitrochlorobenzene. His peripheral blood lymphocytes averaged 1200/cu mm, ranging from 800 to 2200/cu mm. T cells constituted 70% of the total lymphocyte count. His TH2 cell population (helper T cells) was 25%-30% of normal. Phytohemagglutinin, concanavalin-A, pokeweed mitogen, Candida albicans, staphylococcus protein A, and streptokinase-streptodornase failed to stimulate his lymphocytes in short-term culture. Coculture experiments using the patient's T lymphocytes proved that these cells suppressed the secretion of immunoglobulins by both autologous and normal donor B lymphocytes. His serum was shown to contain an IgG globulin that was cytotoxic to autologous and histoidentical helper T cells.

The patient's clinical condition failed to improve with conventional therapy, including periodic administrations of gammaglobulin and fresh frozen plasma. Thymosin and transfer factor therapy were begun at age 13 with transient clinical improvement. Unfortunately, this favorable response lasted less than a year, terminating in repetitive episodes of severe pulmonary infection and supplicative otitis media.

The sustained reduction of TH2 lymphocytes and the presence of a circulating lymphocytotoxic immunoglobulin with autologous reactivity, provided rationale for the use of plasma exchange therapy. Plasmapheresis was performed every 2 wk for a total of 5 mo.

MATERIALS AND METHODS

Peripheral blood lymphocytes were quantitated by conventional differential counting and with a Technicon Hemalog D, which uses spectrophotometric principles. Immunoglobulins were detected by immunoelectrophoresis and quantitated by radial immunodiffusion. T and B lymphocytes were identified by sheep red blood cell (SRBC) rosette formation employing E and EAC cells. T cells were determined by rosetting with IgM-coated SRBC, as reported previously. Suspensions of T lymphocytes obtained by SRBC rosetting were incubated with horse anti-human thymocyte globulin, washed and reincubated with fluorescein-conjugated rabbit F(ab')2, antiserum to horse globulin, and analyzed with a fluorescence activated cell sorter (FACS II). The response of lymphocytes to mitogens was measured by the incorporation of tritiated thymidine into stimulated cells. Immunoglobulin secretion by B lymphocytes was measured by the double antibody precipitation technique of Litwin. Suppressor T cells were identified by the reverse plaque assay and by coculture experiments with homologous B-cell preparations in the presence of pokeweed mitogen. The lymphocytotoxic factor in the patient's serum was assessed by the Trypan blue dye exclusion technique of James et al. and the 51Cr-microcytotoxicity method of Brunner et al. Cell pellets containing either 106 peripheral blood lymphocytes or 107 T cells obtained by rosetting with sheep red blood cells were incubated for 1 hr at 37°C with 0.2-ml aliquots of the patient's serum or 0.2 ml of a purified IgG fraction of his serum obtained by ammonium sulfate precipitation followed by DE-52 ion exchange chromatography. The cells were washed free of the serum or the IgG-containing fraction and incubated with guinea pig...
pig complement for 18 hr at 37°C. Lymphocytotoxicity was consid-
ered significant at the 15% level. The effect of the patient’s cytotoxic
antibody on helper T-cell function was assessed in coculture experi-
ments employing mixtures of B lymphocytes and T cells that had
been irradiated to eliminate suppressor cell activity.6 Fluorescent-
labeled anti-human IgG was used to enumerate the binding of the
lymphocytotoxic autoantibody to T cells.

Plasmapheresis was performed on the Haemonetics Model 30
(discontinuous) blood processor. During each procedure, 650 ml of
plasma, approximately 20 ml/kg, were removed and replaced with
an equal amount of normal serum albumin (5%). Anticoagulant
ACD formula B was used throughout the exchange procedures.
Lymphocytapheresis was not performed during any of the proce-
dures.

RESULTS

Following the first plasma exchange, a decrease in
the activity of the cytotoxic autoantibody was
observed. A decrease in antibody activity, as measured
by indirect immunofluorescence, followed each subse-
cquent procedure. Prior to plasmapheresis, the patient’s
serum reacted with 39% of histoidentical T cells.
Reactivity was reduced to 16% following the second
plasmapheresis and by the fifth procedure was no
longer evident by fluorescence microscopy or FACS II
analysis.

The fall in antibody concentration was accompa-
nied by an increase in the patient’s total lymphocyte count
and an absolute increase in the Tμ and TH2- (helper)
cell populations (Fig. 1). The absolute lymphocyte
count rose from a nadir of 800–5000/μl. TH2- cells
increased from 20% to 42% of the total T-cell popu-
lation. Prior to plasma exchange, Tμ cells constituted
8%–16% of the lymphocyte population. Following the
exchange procedures, this subset increased to 79%.

Prior to plasmapheresis, the patient’s serum blocked
the helper T-cell–B-cell interaction necessary for
immunoglobulin secretion in vitro. This blocking
activity was eliminated by the first plasma exchange.
Both the serologic and the cytologic improvements
persisted throughout the period of plasma exchange.
However, 48 days after plasmapheresis therapy was
discontinued, the TH2- lymphocyte antibody was
again detectable in the patient’s serum, binding to
42% of the histoidentical helper T cells. This activity
was not influenced by any subsequent therapy.

Clinical improvement was evident during the first 4
mo of plasmapheresis therapy, but terminated in the
fifth month with recurrent bouts of pneumonia and
suppurative otitis media. A thymectomy was per-
fomed. The postoperative course was complicated by
osteomyelitis of the sternum. The infection did not
clear with intensive specific antimicrobial therapy. A
bone marrow transplant was performed using a histo-
dentical sibling as the donor, but the patient died of
sepsis shortly afterwards.

DISCUSSION

Acquired agammaglobulinemia is a heterologous

FIG. 1. Quantitative and pheno-
typic changes in the patient’s lympho-

cyte population that occurred during
the initial 2.5 mo of plasmapheresis.
Arrow (I) denotes single plasmaphere-
sis. (O—O) Total lymphocytes;
(Δ—Δ) Tμ cells; (O—O) TH2- cells.
The patient's B cells secreted gammaglobulin when cocultured with histoidentical T cells obtained from a sibling. Similarly, the addition of autologous helper T cells to a culture of the patient's B cells initiated the secretion of gammaglobulin. These in vitro observations suggested that the patient's helper T-cell defect was a quantitative and not a qualitative problem, and that this problem, at least in part, was attributable to the circulating anti-TH2 lymphocytotoxic autoantibody. Pathophysiologically, the patient's disease could be considered an autoimmune disorder. It was therefore of great interest to ascertain what effect the elimination of the autoantibody would exert on the helper T-cell population. Extrapolating from the in vitro data, restoration of a phenotypic balance between the T-cell subsets could alleviate the agammaglobulinemia.

Plasma exchange has been used in the supportive therapy of a variety of autoimmune disorders, including Goodpasture's syndrome, myasthenia gravis, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, and "acquired" hemophilia. In most instances a direct relationship has been noted between the level of circulating autoantibody and the clinical response. Although plasmapheresis is neither specific nor definitive, it provides sufficient time to initiate a more conventional form of therapy.

The diminished activity of the autologous TH1 antibody and the accompanying cytotoxic and immunologic responses observed during D.L.'s plasma exchange therapy resemble those reported in other similarly treated autoimmune diseases. Reduction of the lymphocyte antibody was accompanied by an increase in the number of circulating helper T cells as determined by their T\(\mu\) and TH1 markers. These cells provided normal helper function. His B lymphocytes regained the in vitro capacity to produce and secrete immunoglobulin in the presence of an adequate number of autologous helper T cells. Unfortunately, plasmapheresis did not improve the patient's B-cell function in vivo. The increased population of activated (Ia\(^+\) suppressor (TH2\(^+\)) T cells was not influenced by the exchange procedures. Accordingly, the ability of his B lymphocytes to secrete immunoglobulins remained impaired. A block at this level of immunoglobulin production has been documented in other cases of AAG.

It is apparent that the plasma exchange did not influence the patient's prognosis. It is speculative but conceivable that such therapy may exert a favorable long-term effect in immunodeficiencies that are a result of autologous cytotoxic activity. Confirmation of such an effect can only be obtained through future studies.

REFERENCES

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