We investigated the mechanism for isolated agranulocytosis and marrow pure white cell aplasia in an elderly man receiving 0.5 to 1.0 g per day of chlorpropamide (Chl) without other toxic drug exposure or overt systemic illness. Patient marrow revealed an absence of recognizable granulocytic precursors; megakaryocytes and erythroid precursors were normal. The WBC count was 1800/mm³ on admission with only 2% neutrophils; the absolute neutrophil count first exceeded 500/mm³ on the 17th day following cessation of Chl. A serum Chl level on admission was 100μg/mL (acute phase, AP); no Chl was detected in serum (convalescent phase, CP) assessed on the 22nd hospital day. Antineutrophil antibodies were not detected, and T cell depletion failed to augment patient in vitro granulopoiesis. Patient AP serum produced potent complement-mediated inhibition (87% ± 7%) of autologous granulocyte progenitors (CFU-GM) with minimal inhibition of erythroid (11% ± 5%) or multipotent (5% ± 4%) progenitor cells. Selective inhibition by patient AP serum of CFU-GM (74% ± 11%) was also seen against two allogeneic marrows. Patient CP serum no longer inhibited (6% ± 4%) autologous CFU-GM. Addition of Chl (5 to 120 μg/mL) to CP serum but not to control serum resulted in potent drug concentration-dependent complement-mediated inhibition of autologous and allogeneic CFU-GM.

Inhibition of CFU-GM in the presence of Chl had limited activity against morphologically recognizable marrow granulocytic precursors in a microimmunofluorescence assay. These results are most consistent with the development of Chl-dependent, selective antibody-mediated immune inhibition of granulopoiesis.

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We have previously reported the occurrence of spontaneously arising selective autoantibody-mediated immune inhibition of granulopoiesis in a patient with agranulocytosis and profound marrow granulocytic hypoplasia (primary pure white cell aplasia). In this report we investigated the mechanism for acquired neutropenia and marrow pure white cell aplasia in an elderly man receiving high doses of chlorpropamide (Chl) with no other history of toxic drug exposure or overt systemic illness.

CASE REPORT

An 81-year-old man was admitted to the hospital in May 1985 for fever and severe neutropenia. A routine hemogram performed in March 1985 had demonstrated a normal WBC count. The patient was subsequently admitted to Stanford Hospital with fever, otalgia, and neutropenia. He had a prior history of adult onset (Type II) diabetes mellitus treated with dietary restriction and for the last three months had taken 500 to 1,000mg PO daily of Chl. The patient was also taking occasional acetaminophen and oxycodone, and there was no family history of blood dyscrasias. On physical examination he was febrile with a left otitis externa. Phimosis and balanitis were present. The nodes, spleen, and liver were not palpable, and the remainder of the examination was unremarkable. Routine serum chemistries were normal except for a creatinine of 2.7mg/dL. The hematocrit was 35%, the platelets were 486,000/μL, and the WBC count was 1,800/μL with 2% neutrophils, 93% lymphocytes, 3% monocytes, and 2% eosinophils. Direct and indirect (with and without 100μg/mL Chl) Coombs' tests were negative. The reticulocyte count was 1.0%. A bone marrow aspirate and biopsy revealed a mild decrease in overall cellularity (35%). There was virtually a complete absence of granulocytes and all morphologically recognizable myeloid precursors. Erythroid maturation was normal, and megakaryocytes appeared increased in number. No evidence for a thymoma was detected on chest roentgenograms. The patient had a normal serum B₁₂ and folate level and an unremarkable serum immunoelectrophoresis. A serum Chl level obtained on the second hospital day was 100μg/mL (average plasma Chl concentrations following ingestion of 250 mg; range from 19-114 μg/mL, with the variation most dependent upon differences in drug half-life and variations in the volume of distribution). Chlorpropamide was not detectable when the level was again assessed on the 22nd hospital day. The patient was begun on tobramycin and cefoperazone, and his Chl was discontinued. His fever gradually defervesced over the ensuing seven days with a gradual improvement in his balanitis and otitis. The patient’s absolute neutrophil count slowly increased and first exceeded 500/μL on the 17th hospital day. A repeat bone
marrow aspirate performed on the 25th hospital day demonstrated reconstitution of marrow myeloid precursors with normal maturation and a myeloid:erythroid (M:E) ratio of approximately 2:1.

METHODS

Assay systems for hematopoietic progenitors. Two to four milliliters of marrow aspirate from normal adult bone donors were drawn into heparinized syringes, layered over Ficoll-Hypaque (Pharmacia, Piscataway, NJ) gradients, and interface mononuclear cells collected. All donors gave fully informed consent prior to marrow aspiration, and all studies were approved by the Stanford University Human Experimentation Committee. Marrow mononuclear cells (5 to 15 x 10^6/mL) were cultured in the presence or absence of 0.5 IU of purified human urinary erythropoietin (1,140 U/mg of protein, National Institutes of Health) in triplicate 0.25-ml aliquots in methylcellulose microwell cultures containing 1% Mo-conditioned medium (MoCM, a medium conditioned by a T lymphoblast cell line containing both myeloid colony-stimulating activity and erythroid burst-promoting activity^8,9). Committed erythroid progenitors (burst-forming units-erythroid [BFU-E]) and granulocyte-macrophage progenitors (colony-forming units-granulocyte-macrophage [CFU-GM]), as well as multipotent hematopoietic stem cells (colony-forming units giving rise to mixed colonies containing granulocytic, erythroid, macrophage, and megakaryocytic cells [CFU-GEMM]), were enumerated by in situ observation containing granulocytic, erythroid, macrophage, and megakaryocytic cells [CFU-GEMM]) were enumerated by in situ observation containing granulocytic, erythroid, macrophage, and megakaryocytic cells (CFU-GEMM)) were enumerated by in situ observation after 10 to 14 days of incubation at 37 °C as previously described.6,8,11 Marrow CFU-GM were also independently assessed in cultures containing 15% human placental conditioned medium, in place of MoCM, as a source of myeloid colony-stimulating activity.3 In some experiments marrow cells were further fractionated by double-adherence monocyte depletion (less than 2% residual monocytes) and/or solid-phase immunoabsorption with pan-T Leu-1 monoclonal antibody to deplete T lymphocytes (less than 1% to 2% residual normal marrow T cells) as previously described.11

Cytotoxicity and immunoabsorption studies. Antibody and drug-dependent complement-mediated cytotoxicity against human hematopoietic progenitors was assessed as previously described.4 Suspensions of 2 x 10^5 nonadherent buoyant marrow cells per milliliter were prepared in Iscove's modified Dulbecco's medium. Test sera (patients acute [day 2] and recovery [day 25] serum or control AB serum) were preincubated with saline or diluent controls or varying concentrations of Chl (8 to 120 µg/mL final concentration) for 30 minutes at 37 °C. Chlorpropamide (Diabinese, Pfizer Pharmaceuticals, New York) was dissolved in either 100% ethanol or in 0.15 mol/L sodium hydroxide with heating and subsequent neutralization with 0.15 mol/L hydrochloric acid; appropriate diluent controls were used in all experiments. One quarter milliliter of the drug-serum mixture was incubated with an equal volume of the marrow cell suspension with or without tested rabbit complement (Pel-Freeze Biological, Rogers, AR) for 30 to 60 minutes at 37 °C. After incubation, marrow cells were washed twice, and aliquots were plated in methylcellulose. No decreases in colony formation were noted after cell incubation with complement, control human AB serum, or drug diluent alone at appropriate final concentrations. In some experiments, marrow cells, patient or control serum, drug suspension, and fresh rabbit complement were combined and incubated together at 37 °C for 60 minutes prior to washing and plating. In other experiments, drug suspensions were preincubated with marrow cells with or without control sera for 30 minutes at 37 °C; the cells were then washed twice and incubated with test sera with or without a source of fresh complement prior to plating.

Serum antineutrophil activity was independently assessed by a modified granulocyte-microagglutination technique9 and by a granulocyte cytotoxicity assay^8 against a panel of granulocytes from ten normal donors in the presence and in the absence of 20 to 100 µg/mL chlorpropamide. Patient antineutrophil activity was also assessed by a Cowan I staphylococcal slide test; the latter includes both direct and indirect tests for detection of cell-bound antibody and allows direct visualization of small numbers of autologous granulocytes during periods of severe granulocytopenia.12 A fluorochromatic modification of the Terasaki micromethod was used to assay for lymphocyte cytotoxicity against a panel of lymphocytes from 19 normal donors.14 Patient serum activity against morphologically recognizable marrow granulocytic precursors was assessed via an indirect immunofluorescence technique as previously described: marrow cell pellets were treated with test serum with or without varying concentrations of Chl (20 to 110 µg/mL final concentration) or with 80H.5 monoclonal antibody (an IgM complement-fixing murine hybridoma antibody specifically recognizing an antigen on mature granulocytes and on immature marrow myeloid precursor cells)15. Following incubation at 4 °C for 20 minutes, cell suspensions were washed with phosphate-buffered saline and were then incubated with either goat antihuman fluorescein isothiocyanate (FITC)-labeled anti-IgG antibody or goat antimouse FITC-labeled anti-IgM antibody (Tago, Burlingame, CA) prior to examination by phase and fluorescence microscopy.

Absorption of IgG from test sera was performed using protein A-sepharose CL-4B affinity chromatography before and after treatment with either rabbit or goat anti-IgG.1 Absorbed samples were assessed for adequacy of separation by immunoelectrophoresis; virtually all IgG in the absorbed sera was removed by the immunoabsorbent procedure. Patient's serum was also absorbed with pooled platelets from 14 random donors to remove possible class I (but not class II) anti-HLA alloantibodies as previously described.5,16

RESULTS

Patient marrow obtained on the first and third days of hospitalization was cultured separately in methylcellulose to enumerate marrow multipotent (CFU-GEMM) and committed granulocyte-macrophage (CFU-GM) and erythroid (BFU-E) progenitor cells. Patient colony yield per 2 x 10^5 buoyant marrow cells included 158 ± 26 (mean ± SEM) BFU-E, 67 ± 9 CFU-GM, and 4.0 ± 1.8 CFU-GEMM. These results are comparable to those obtained from prior and/or concurrent culture of ten normal human marrows in our laboratory (Table 1). Colony cytologic composition, examined after micropipette selection and histochemical staining, did not differ between patient and control marrows after assessment of individual CFU-GM and CFU-GEMM from each experiment. Independent assessment of patient CFU-GM, using placental-conditioned medium rather than Mo-conditioned medium as a source of myeloid colony-stimulating activity, yielded colony numbers comparable to those obtained after plating of normal human marrow. No increment in patient marrow CFU-GM was seen following marrow T cell depletion by immunoabsorption using a pan-T Leu-1 monoclonal antibody (data not shown). These data together indicate that neither a deficiency of marrow granulocyte-macrophage or multipotent progenitors nor qualitative changes in patient colony cytologic composition could explain the patient's agranulocytosis and marrow white cell aplasia. These results also provide no evidence for autologous T cell inhibition of granulopoiesis.
Table 1. Inhibitory Effect of Patient Acute-Phase Serum on Growth of Autologous Marrow Hematopoietic Progenitors

<table>
<thead>
<tr>
<th></th>
<th>CFU-GM</th>
<th>BFU-E</th>
<th>CFU-GEMM</th>
<th>Percent CFU-GM Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control BM*</td>
<td>55 ± 8</td>
<td>145 ± 22</td>
<td>3.5 ± 2.0</td>
<td>—</td>
</tr>
<tr>
<td>Patient BM†</td>
<td>67 ± 9</td>
<td>158 ± 26</td>
<td>4.0 ± 2.8</td>
<td>—</td>
</tr>
<tr>
<td>Patient BM + AB Serum + C †</td>
<td>63 ± 7</td>
<td>143 ± 19</td>
<td>3.2 ± 2.0</td>
<td>6</td>
</tr>
<tr>
<td>Patient BM + Patient Serum†</td>
<td>59 ± 81</td>
<td>149 ± 23</td>
<td>3.0 ± 1.7</td>
<td>12</td>
</tr>
<tr>
<td>Patient BM + Patient Serum + C †</td>
<td>9 ± 4</td>
<td>141 ± 18</td>
<td>3.7 ± 2.5</td>
<td>87</td>
</tr>
</tbody>
</table>

*Mean ± SEM from ten separate experiments, each plated in duplicate in methylcellulose cultures.
†Mean ± SEM from two separate experiments, each plated in triplicate in methylcellulose cultures. Mo-conditioned medium was used as a source of myeloid colony-stimulating activity in both patient and control cultures. Marrow was obtained on two separate occasions during the first five days of hospitalization while the patient was still neutropenic.

Patient AP serum was next examined for antineutrophil activity. Both the direct and the indirect Cowan I staphylococcal slide tests performed to detect antineutrophil antibodies were negative. Serum granulocyte cytotoxicity and granulocyte agglutinating activity were assessed against a panel of ten normal donors. Neither the cytotoxicity nor the microagglutination assay detected antineutrophil activity in patient serum. The patient's acute and chronic-phase sera were cytotoxic for lymphocytes derived from only three of 19 normal blood donors.

We next examined patient AP serum (obtained on the second hospital day) for its effect on autologous marrow hematopoietic progenitors. In two separate experiments using MoCM as a source of myeloid colony-stimulating activity, patient heat-inactivated serum in the presence of complement produced potent (mean 87%) inhibition of autologous marrow CFU-GM with minimal inhibition of either BFU-E or CFU-GEMM (Table 1). Similarly, patient AP serum produced potent complement-mediated inhibition of autologous marrow CFU-GM when patient granulocyte macrophage progenitors were cultured in the presence of placental conditioned medium (Fig 1). The further addition of as much as 120 μg/mL of Chl to patient AP serum was not associated with any further significant decrement in autologous marrow CFU-GM. Similar selective inhibition of CFU-GM was noted against two separate allogeneic human marrows after treatment with patient serum plus complement (Fig 1). Patient serum did not demonstrate cytotoxicity for lymphocytes derived from either of the two allogeneic marrow donors. Minimal inhibition (12%) of allogeneic BFU-E or CFU-GEMM was noted after treatment of marrow with patient serum plus complement. Patient serum in the absence of complement had little inhibitory effect on allogeneic hematopoietic progenitors.

The effect of patient acute (day 2, containing 100 μg/mL Chl) and convalescent (day 25, containing no detectable Chl)-phase serum with and without exogenous Chl was next assessed on growth of autologous marrow CFU-GM. Patient marrow was obtained for this set of experiments upon recovery of the WBC count to 6,800 per μL, four weeks following cessation of Chl. Previously frozen patient AP serum in the presence of complement again selectively inhibited autologous marrow CFU-GM (Fig 2). However, patient convalescent-phase serum in the presence of complement failed to inhibit either autologous or allogeneic marrow granulocyte-macrophage progenitors. Patient convalescent-phase serum in the presence of Chl (60 μg/mL final concentration) did inhibit (79% ± 21%) autologous CFU-GM (Fig 2). Inhibition of autologous CFU-GM by patient convalescent-phase serum was seen when the previously prepared drug-serum mixture was incubated with marrow plus complement. Inhibition was also noted when marrow, serum, drug suspension, and complement were incubated together simultaneously (88% ± 26%). Autologous CFU-GM inhibition was not seen, however, when the drug suspension was preincubated with marrow, after which marrow cells were washed and then incubated with serum plus complement prior to plating (11% ± 7%). No inhibition was noted after marrow cell incubation with AB serum plus 60 μg/mL Chl plus complement (Fig 2).

Inhibition of patient CFU-GM colony growth by convalescent-phase serum was drug-concentration dependent (Fig 3).

![Figure 1](https://www.bloodjournal.org)
with demonstrable progenitor inhibition occurring at Chl concentrations of 30 to 120 µg/mL (the patient’s AP serum Chl level on the second hospital day was 100 µg/mL). Patient serum plus Chl in the absence of complement had little demonstrable inhibitory activity against autologous CFU-GM (Fig 3). Patient convalescent-phase serum plus Chl with or without complement had little inhibitory activity against autologous BFU-E.

Absorption studies of patient serum were next performed utilizing protein A-sepharose affinity chromatography to deplete patient serum of IgG immunoglobulin. As demonstrated in Fig 4, inhibition of allogeneic CFU-GM in the presence of 100µg/mL Chl could no longer be demonstrated following immunoabsorbent removal of IgG from patient convalescent-phase serum. Absorption of patient’s serum with pooled platelets from 14 random donors to remove possible anti-HLA antibody activity did not affect the inhibitory activity of patient convalescent-phase serum plus Chl against allogeneic CFU-GM.

Patient serum was next assessed for activity against morphologically recognizable marrow myeloid precursors utilizing an indirect immunofluorescent assay. Results were compared with similar assays on the same allogeneic target marrow population using an antihuman IgM monoclonal antibody termed 80H.5. This antibody recognizes an antigen common to mature granulocytes and immature marrow granulocytic cells and was positive by immunofluorescence for 54% ± 9% of nonadherent allogeneic marrow mononuclear cells. This percentage corresponded to the number of morphologically recognizable granulocytic precursors as assessed by Wright-Giemsa staining of marrow target cell cytacentrifuged preparations. Patient convalescent-phase serum in the presence or absence of 100µg/mL Chl was positive for 9% ± 3% of allogeneic marrow cells (n = 3). These results were not different from those obtained after incubation with allogeneic marrow and AB serum with or without Chl (11% ± 4%). The results suggest that patient serum in the presence or absence of Chl had limited immunofluorescent activity against morphologically recognizable allogeneic marrow granulocytic precursors.

**DISCUSSION**

This patient’s severe neutropenia and marrow pure white cell aplasia completely resolved following discontinuation of Chl and in the absence of immunosuppressive therapy. Patient AP serum (containing 100µg/mL Chl) produced potent complement-mediated inhibition of both autologous and allogeneic granulocyte-macrophage (CFU-GM) hematopoietic progenitors with little demonstrable cytotoxic activity against autologous or allogeneic erythroid (BFU-E) and multipotent (CFU-GEMM) progenitors. Patient serum also possessed little activity against autologous and allogeneic lymphocytes, granulocytes, or morphologically identifiable marrow granulocytic precursors. Patient convalescent-phase serum (obtained after recovery of marrow and peripheral
blood granulocytopenia and four weeks following cessation of Chl) no longer inhibited autologous or allogeneic CFU-GM. However, the addition of Chl to patient convalescent-phase serum resulted in potent drug concentration-dependent, complement-mediated selective inhibition of autologous and allogeneic CFU-GM. Inhibition of allogeneic CFU-GM was no longer demonstrable following protein A-sepharose immunoabsorbent removal of IgG from patient serum. These results are most consistent with the development of Chl-dependent selective antibody-mediated immune inhibition of granulopoiesis.

The etiology and pathogenesis of marrow pure white cell aplasia appear in many ways analogous to the previously described syndrome of acquired pure red cell aplasia. Primary chronic pure red cell aplasia has been associated in about 50% of cases with IgG autoantibodies causing either complement-dependent erythroblast lysis, complement-independent inhibition of erythroid progenitor colony growth, or, rarely, inhibition of endogenous circulating erythropoietin. We have previously described a patient with pure white cell aplasia associated with a spontaneously arising (non-drug-dependent) complement-fixing IgG autoantibody that selectively inhibited autologous and allogeneic CFU-GM proliferation. Thymomas have also been reported in association with both acquired pure red cell aplasia and with acquired marrow granulocytic hypoplasia. At least four cases of Chl-associated pure red cell aplasia have been previously reported. Agranulocytosis has also been described as a rare complication of Chl administration; marrow smears in these patients have revealed varying degrees of hypocellularity and only partial preservation of erythroid elements and megakaryocytes. Stein et al have described a female patient with fatal agranulocytosis associated with Chl therapy and the presence of serum leukoagglutinins. Stein et al have described a female patient with fatal agranulocytosis associated with Chl therapy and the presence of serum leukoagglutinins. The marrow in this case was described as hypocellular with “profound depression of myeloid cells” but with normal erythroid cells and megakaryocytes. No further studies were undertaken to evaluate the mechanism of the selective marrow myeloid hypoplasia.

A number of mechanisms have been postulated to explain the pathogenesis of drug-induced immune cytolysis. In penicillin-induced hemolytic anemia, the drug is tightly bound to erythrocytes in vitro and in vivo; inhibition of autologous CFU-GM was not seen in our patient, however, when Chl was preincubated with target marrow mononuclear cells prior to washing and incubation with patient serum plus complement, thus making a drug-adsorption mechanism unlikely. An “innocent bystander” mechanism has been described in a case of Chl-induced immune hemolytic anemia in which the causal antibody was found to be a complement-requiring IgG immunoglobulin. Alternatively, drugs may in some patients lead to the production of “autoantibodies” directed against intrinsic red cell antigens. In this instance, however, antibodies are usually demonstrable in the absence of drug, and cell cytolysis usually persists for several weeks to months following cessation of drug therapy.

The explanation regarding cellular specificity of drug-induced immune cytolysis remains to be elucidated. Recent evidence suggests, however, that target cells may have receptors for some drugs or drug-antibody complexes. Chlorpromamide-induced immune hemolytic anemia has been described in at least one instance to be associated with an antibody directed against Jk<sup>a</sup> antigenic determinants. Human red blood cell surface antigenic determinants have not, however, been found on hematopoietic progenitor cells. Claas et al have provided evidence that certain drugs may induce autoantibody formation by reacting with restricted non-HLA polymorphic determinants present on the surface of either platelets or granulocytes. Cellular specificity in drug-antibody reactions may also be conferred as a consequence of alternative mechanisms of drug-antibody binding to target cell determinants: binding of antidrug antibody to target cells, which occurs only in the presence of drug, has been shown in preliminary experiments utilizing quinidine-dependent antiplatelet antibodies to be mediated by the Fab domain of the antibody rather than the Fc portion of the immunoglobulin. Our data seem most consistent with the hypothesis that binding of patient drug-antibody complex occurs via an antigenic determinant or receptor that is relatively restricted in expression to the surface of human CFU-GM and which appears to be lost during the early stages of progenitor cell differentiation.

Granulocyte-macrophage progenitors, obtained from the patient during a time of profound neutropenia, grew normally in the absence of patient serum or drug. These observations suggest that the assayed colonies may have arisen from primitive precursors that did not bind the patient’s drug-antibody complex. Erythroid colonies are often similarly present in normal or increased numbers in the marrow of patients with antibody-mediated inhibition of erythropoiesis and pure red cell aplasia. Marrow colony growth in patients with humoral inhibitors of autologous hematopoiesis has also been described in spontaneously arising pure white cell aplasia and in patients with antibody-mediated aplastic anemia. Normal growth of patient CFU-GM may, alternatively, reflect differences in vivo and in vitro in the kinetics of drug-antibody receptor binding and cytolysis.

Drug-associated inhibition of granulocyte-macrophage progenitor growth has been described infrequently in patients with agranulocytosis. Bone marrow smears, however, in a number of these patients have demonstrated coexistent suppression of erythroid and megakaryocytic activity or, alternatively, considerable preservation of myeloid activity with a relative paucity of only the more mature granulocytic elements. In some cases of purported drug-induced suppression of marrow colony formation, the drug inhibited growth of normal allogeneic myeloid colonies but did not suppress growth of patient recovery marrow colonies. Taele et al have described two patients with diphenyldihydantoin-associated antibody-mediated inhibition of granulopoiesis; sera from these patients, however, also appeared capable of mediating destruction of polymorphonuclear leukocytes. Kelton et al have reported a patient with quinidine-induced pancytopenia and marrow hypoplasia; quinidine plus patient serum inhibited growth of both autologous and allogeneic erythroid and granulocytic progenitor cells.
cells. Very recently Mamus et al have described the development of reversible marrow granulocytic aplasia in association with ingestion of ibuprofen. Inhibition of in vitro granulopoiesis in this instance was observed only in the presence of patient serum or IgG plus ibuprofen plus complement.

Further investigations of patients with drug-induced immune suppression of hematopoiesis should provide a better understanding of the mechanisms underlying drug-induced myelosuppression and may identify either surface antigenic determinants or antibodies which would prove useful in the recognition and purification of early hematopoietic progenitor cells.

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Chlorpropamide-induced pure white cell aplasia

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