Idiopathic Immunoneutropenia

Report of a Case with a Leukocyte Agglutinating Factor in the Serum

By Johan Märtensson, M.D. and Inga Vikbladh, M.D.

IMMUNOHEMOLYTIC ANEMIA and immunothrombocytopenic purpura are now common terms to designate conditions in which the red blood cells or the platelets are destroyed by immune mechanisms. We have studied a case that showed analogous changes regarding the neutrophil leukocytes and which we therefore classed as immunoneutropenia. The case is considered of general interest, because it shows that similar mechanisms may be involved in so-called idiopathic affections not only of the erythrocytes and thrombocytes, but also of the leukocytes.

SURVEY OF THE LITERATURE

A review of earlier experiments with leukotoxic or leukocytolytic sera was presented in 1927 by Lindström,7 who also tried such sera in the treatment of myelocytic leukemias. In 1926, Doan7 described a leukotoxic substance. He found that 5 per cent of a series of normal persons had white blood cells that are disintegrated by all sera and that 5 per cent had sera toxic to all white blood cells. This observation was substantiated by Tullis8 in 1953, who also showed that human leukocytes can be grouped according to the A-B-O system.

The findings made in agranulocytosis vary: Roberts, et al.14 did not find such patients' sera to exert any effect on normal leukocytes, while other workers12, 24 reported such sera to cause a decrease in the vitality or phagocytic power of the leukocytes or complete leukocytolysis. In the discussion of chronic hypoplastic neutropenia, Spaet, et al.28 suggested that the blood may contain a substance noxious to mature leukocytes and at the same time capable of inhibiting the formation of their precursors.

Evans, et al.9 stressed that acquired hemolytic anemia is often associated with thrombocytopenia and leukopenia, probably due to the presence of separate immune substances more specific for platelet and white cell tissue. They expressed the opinion that such immune substances could probably be found in thrombocytopenia and in splenic neutropenia without associated changes of the other cell elements. Evans found platelet agglutinin18 and this finding has been repeatedly observed in idiopathic thrombocytopenia and in sedormid and quinidine purpura. The platelet depressing component is a globulin that agglutinates the thrombocytes and is probably also capable of damaging the megakaryocytes.12

Recently, Moeschlin, et al.19 reported that blood from a patient with experimental, acute pyrimidin agranulocytosis caused granulocytopenia within 10 to 20 minutes, when transferred to healthy volunteers. The patient's serum did not cause increased lysis but a greatly increased agglutination of both normal leukocytes and of the patient's own leukocytes collected during a remission. The authors offered the following explanation for the development of granulocytosis. Antibodies are fixed to the surface of the leukocytes, which are thereby agglutinated and then removed from the circulation, probably in the lungs, which transfusion and isotope studies have shown to be the main site of elimination of the white blood cells.14, 15 Of particular interest is their view that the enormously increased demand on the granulocytes, through peripheral destruction of these cells, exhausts the bone marrow of them and probably of their precursors and that this explains the cytologic picture usually

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called "inhibition of maturation of the bone marrow," a term that should perhaps be revised.

Tullis mentions that a potent leukotoxin can occasionally be demonstrated in patients with spontaneous agranulocytosis and aleukemic leukemia and speculates on the possibility of a leukotoxin being able to explain the paradoxical coexistence of peripheral leukopenia and extremely proliferant leukemic bone marrow.

Bent Hansen reported a case of granulocytopenia with increased erythrocyte sedimentation rate and markedly increased γ-globulin. Medication with ACTH resulted in an increase of the granulocytes and a decrease of the γ-globulin. The author stressed the similarity with acquired hemolytic anemia and suggested that the condition might be the leukocytic variant of this disease.

Moeschlin thought it likely that the immunologic mechanism demonstrated by him might explain not only acute anaphylactic agranulocytosis, but also other previously unexplainable leukopenias, perhaps also the group termed splenic neutropenia. There are also recurrent granulocytopenias in which the blood picture is normal between seizures. Sometimes the attacks recur at fairly regular intervals, so called periodic or cyclic neutropenia. Such cases have also been seen in Scandinavia. In some cases neutropenia may persist for many years without signs of increased splenic activity. Adams and Witts described five such cases, but regarded them as a variant of aplastic anemia that had involved the white blood cells only. Spaet, et al. offered a similar explanation for four cases which were nonsplenic, nonecyclic, completely obscure as to etiology, and apparently due to a specific inability of the bone marrow to elaborate granulocyte precursors. These chronic neutropenias often produce only mild symptoms, but the patient is disposed to infections. However, with adequate treatment the prognosis is usually good. Splenectomy has proved of no real value.

Case Report

In the case we studied, the clinical picture most closely resembled that of the last-mentioned group of granulocytopenias. The patient was a primipara, aged 49, with no personal or familial history of blood disease. In 1948 she had thyrotoxicosis, for which she was successfully operated on. At that time she had slight, relative neutropenia and a moderate anemia. In December 1951 she caught a cold after which she felt tired and had colds repeatedly. In April 1952 she had joint pain, and in May she was treated with salicylic acid and streptomycin, twelve 0.5 Gm. injections in the course of a week. The joint pain disappeared, but the patient, who was doing her own housework, reported increasing fatigability. Examination of the blood showed leukopenia and extreme neutropenia, which has now, more than one year later, persisted practically unchanged. (Unfortunately the blood had not been examined before the institution of streptomycin therapy.) In addition to the blood changes the erythrocyte sedimentation rate was increased and the formol-gel reaction was positive, thus indicating increased serum globulin. Sternal puncture showed a certain inhibition of myelopoiesis. She received a few blood transfusions, without any side reactions and then liver preparations, after which she was followed up at the outpatient department. Vitamin tablets given periodically and some B₁₂ injections, because of acne rosacea, were the only treatment the patient had received and she had taken no other medicine, nor had she been exposed to any chemical agents. As her condition persisted unchanged, she was again admitted to the Medical Clinic in February 1953.

Observations on Admission

The patient was in a good general condition. No icterus. The lymph nodes, liver, and spleen were not enlarged. Abdominal x-ray: normal-sized spleen. Parodontosis and tartar. Slightly increased temperature. Antistreptolysin titer normal, no streptococcal agglutination of L or O antigen. Usual tests for allergy showed no hypersensitivity of the skin. Coombs test was negative. Urobilin in feces was 120 mg./24 hours. Examination for the L. E. phenomenon was negative. Erythrocyte sedimentation rate 88 mm. per hour. Formol-gel reaction was positive after 1 hour. Thymol turbidity test 10 U. Zinc turbidity test 17 U. Electro-
IDIOPATHIC IMMUNONEUTROPENIA

Table 1.—Blood Findings

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<tr>
<th>Date</th>
<th>Hgb (%)</th>
<th>RBC</th>
<th>WBC</th>
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<th>E</th>
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<td>0</td>
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<td>2200</td>
<td>7</td>
<td>10</td>
<td>1</td>
<td>66</td>
<td>16 1 normoblast/200 WBC</td>
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<td>11</td>
<td>1</td>
<td>1</td>
<td>61</td>
<td>27 Aniso-poikilocytosis</td>
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Phoretic studies: decreased albumin, increased globulins, especially γ-globulin. At cross-matching, pronounced rouleaux formation was observed. Thrombocytes 194,000 and 247,000. Reticulocytes: 0.7, 1.1, and 1.5 per cent red cells. Blood group 0 Rh+. Representative blood findings are given in table 1.

Sternal Marrow

Relative increase in the myeloid series suggestive of increased production in this group. The cells matured, but there was a steep fall between the number of stab forms and segmented forms. (The appearance of the preparation did not permit any conclusion as to whether this was due to inhibited maturation at this level or to increased destruction in the circulation.) There was a slight relative decrease of the erythroblasts, mostly small forms, a few larger but no distinct megaloblasts. There was also a slight relative decrease of the lymphocytes.

Differential Count*

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</tr>
<tr>
<td>Promyelocytes</td>
<td>0.8</td>
</tr>
<tr>
<td>Myelocytes, neut.</td>
<td>24.4</td>
</tr>
<tr>
<td>Metamyelocytes</td>
<td>12.4</td>
</tr>
<tr>
<td>Leukocytes, neut.</td>
<td>100.0</td>
</tr>
<tr>
<td></td>
<td>21.2</td>
</tr>
<tr>
<td></td>
<td>200.0</td>
</tr>
<tr>
<td></td>
<td>0.8</td>
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</table>

SERUM STUDIES

The patient thus had persistent neutropenia without associated splenomegaly with increased sedimentation rate and increased γ-globulin. This might suggest the existence of some immunooactivity. The serum was therefore studied for such activity on normal leukocytes in vitro.

Interactions of the Blood Serum with Normal Leukocytes

In order to avoid spontaneous agglutination of the leukocytes we used silicone treated glass. Venous blood from a healthy person belonging to the same blood

* The differential count was performed by Hans Hellsten, M.D.
group as that of the patient was tapped directly into a large centrifuge tube
containing heparin, where it was allowed to stand for 2 to 3 hours at room tem-
perature and then centrifuged for about 3 minutes at approximately 500 rpm.
The leukocytes in the layer between the plasma and the erythrocytes were then
removed. The concentration of the specimen thus collected was 15 to 30,000 per
cu.mm., which was sufficient. One ml. of the leukocyte suspension was mixed
with 1 ml. of the patient’s serum. A similar quantity of the suspension and of
normal plasma respectively were used for a control test. Agglutination was
observed almost immediately after mixing. However, the mixture was allowed
to stand at room temperature for 1 to 2 hours, after which it was gently stirred
and part of it was stained in the usual way with methyl violet for determining
the number of white cells and studied in a Bürker’s chamber, while the remainder
was used for making ordinary blood smears, which were stained according to
May-Grünwald-Giemsa. Distinct agglutination was regularly demonstrated in
the patient’s serum. In the smears the agglutinates arranged themselves like a
string of beads along the longitudinal margins. These beads consisted of clusters
of 5 to 100 neutrophile leukocytes or more (fig. 1). Isolated eosinophils were also
sometimes seen. The central part of the smear contained only a few polynuclear
cells. There, the mononuclear cells were preponderant. In the control test the
cells were distributed fairly equally throughout the entire smear. However,
single, small agglutinates of a few cells were seen in the control tests, too.

In order to estimate the agglutinin titer, we diluted the patient’s serum with
0.9 per cent sodium chloride before mixing it with the leukocyte suspension.
Specimens collected during cortisone therapy gave definite agglutination in a
dilution of 1:20, but not of 1:40. In a test using a 1:40 dilution and performed six
weeks after cortisone therapy it was found that of 2000 counted cells along the
longitudinal margins of the preparation, 83 per cent of the neutrophile leukocytes
had arranged themselves in groups of 5 to 50 cells or more. The corresponding
figure for a dilution of 1:120 was 25 per cent, for 1:240 it was 16 per cent, while
with the dilution of 1:480 only 6 per cent of the neutrophils lay in groups of 5
to 8 cells, i.e. the same values as found in control tests using saline only.

Fig. 1.—Normal leukocytes agglutinated in the patient’s serum.
Electrophoretic Studies

The total protein concentration of the patient’s serum was 6.5 Gm. per 100 ml., of which 37.2 per cent was represented by albumin and α1-globulin, 6.5 per cent by α2-globulin, 13.5 per cent by β-globulin, and 40.8 per cent by γ-globulin (fig. 2). As the normal amount of γ-globulin ranges between 10 and 12 per cent, it may be concluded that the patient’s serum contained a pathologic protein fraction representing some 30 per cent of the total protein and migrating at the same rate as the γ-globulin.

As it was expected a priori that the agglutinating factor in the serum was probably to be found in the γ-fraction, we separated the serum by zone electrophoresis in a filter paper medium (see Kunkel and Slater3). From ten sheets of filter paper (Munktel Nr. 20, 150) measuring 60 x 10 cm., segments of 1 x 6 cm. were cut out 25 cm. from the end next to the cathode. The filter papers were then superimposed on one another between two glass plates measuring 50 x 11 cm. in such a manner that the free ends of the papers were of equal length on either side. In order to prevent evaporation, the block of filter paper was wrapped in a thin sheet of plastic material. Barbital buffer solution at pH 8.6, ionic strength 0.1 was used for the separation, which was performed at 4 °C. The filter papers were first allowed to attain equilibrium with the buffer solution before the separation was started. In order to obtain as high as possible a concentration of the various fractions, 1 ml. of the patient’s serum was first placed in a cellophane tube, where it was evaporated to half its original volume by means of a cold current of air. The serum was afterwards applied to the excised segments, which were then replaced in their original position in the block of filter paper. A potential of 240 volts was applied to the electrodes and gave a current of 40 ma. After 42 hours the albumin fraction had migrated about 30 cm. from its point of departure. The uppermost filter paper was dried and stained with brom phenol blue for indentifying the position of the protein fractions. The nine underlying filter papers were cut into strips 2 cm. wide and placed in perforated cylinders in a centrifuge tube, so that all fluid centrifuged off could be recovered. The albumin, β-globulin, and γ-globulin fractions diluted with buffer solution were

Fig. 2.—Electrophoretic pattern of the patient’s serum.
afterward concentrated in the manner described above, so that the final protein concentration was about 0.5 Gm./100 ml. These different protein fractions were afterward mixed with a suspension of leukocytes. It was observed that only the pathologic \( \gamma \)-globulin fraction caused agglutination.

These tests thus showed that the patient's serum agglutinated normal leukocytes, especially the neutrophils, in vitro. The agglutinating factor was contained in the \( \gamma \)-globulin fraction.

Further investigation of the properties of the pathologic \( \gamma \)-globulin fraction is in progress.

Interactions of other Pathologic Sera with Normal Leukocytes

Sera from other patients with granulocytopenia or increased \( \gamma \)-globulin were also studied. However, in none of the cases hitherto studied did the serum agglutinate leukocytes (two patients with granulocytopenia and splenomegaly, two with hemolytic anemia, of which one probably had lupus erythematosus disseminatus, two with multiple myeloma, one with myeloblastleukemia, one with chronic polyarthritis and splenomegaly, and one with increased \( \gamma \)-globulin of unknown cause).

Therapeutic Trials and Clinical Investigations

The value of ACTH and cortisone in the treatment of immunohemolytic anemia has often been confirmed since first reported in 1950. Many authors have also claimed their value in immunothrombocytopenia. In some cases of acute agranulocytosis, ACTH has probably been of decisive therapeutic importance, but failure has also been recorded. The above-mentioned case of granulocytopenia responded favorably. Our patient received, cortisone for one month, in the beginning in a daily dose of 200 mg., which was gradually decreased to 125 mg. This medication produced no definite change in the blood picture (see table 1: March 13 and April 13, 1953) or in the protein reactions (thymol turbidity and zinc turbidity tests, formol-gel reaction, and erythrocyte sedimentation rate) and the serum still agglutinated leukocytes, but the agglutination titer was distinctly lower during cortisone therapy than afterward. On the other hand, the patient felt well during this time and the temperature was practically normal.

After cortisone therapy had been stopped, a blood transfusion was tried. An increase in the number of granulocytes was hardly to be expected. It appears that ordinary blood transfusions are incapable of increasing the white count and that even the administration of concentrated suspensions of leukocytes will produce only a slight increase in the number of white blood cells. Three hundred ml. blood was drawn from the patient, after which she was given 750 ml. fresh blood from two donors. White cell and differential counts of the donors' blood were done immediately before the transfusion, and of the patient's blood before, during and afterwards. The transfusion was, however, followed by a decrease in the white count. No acute symptoms appeared; transfusion of leukemic blood has been known to cause respiratory and circulatory disorders, which are believed to be due to the uptake of an excessive amount of leukocytes by the pulmonary circulation. However, in the course of two days the temperature rose to 39 C.
and then the white count was 900 per cu. mm., the lowest recorded in this case, but 24 per cent of this number consisted of eosinophils. In the course of the following five days the temperature decreased to its previous slightly increased level. It seems reasonable to suppose that in a patient like this with an active immunologic process there may gradually develop a steady state and that this state can be disturbed by transfusion of fresh blood, which may introduce some co-factors capable of rendering the process more active.

It is sometimes possible by means of the adrenalin test to estimate the functional state of the blood forming tissues and of the amount of blood cells stored in the organism. In the present case the administration of 1 mg. adrenalin subcutaneously caused, if anything, a decrease in the white count for the first 35 minutes, but the differential count remained unchanged.

The granulocytopenia was discovered after a short course of streptomycin therapy, but by then the patient had had symptoms for five months, so that it is quite possible that the blood changes had existed just as long. Streptomycin is capable of causing anemia, granulocytopenia, thrombocytopenia, and aplastic anemia, sometimes with a fatal issue. Usually the changes do not appear until after prolonged medication, on withdrawal of which they either progress rapidly or pass off, though sometimes slowly. In the present case the granulocytopenia was fairly stationary after discovery. A patch test with a 25 per cent solution of streptomycin produced no reaction. She then received streptomycin intramuscularly, 1 mg., 1 cg., and 1 dg. at two day intervals. At that time the patient “felt as if she had a cold,” but denied new symptoms. The eosinophils almost completely disappeared, and on one occasion the differential count showed 7 per cent pathologic mononuclear cells (see table 1: May 9, 1953). It is uncertain whether these changes can be ascribed to the streptomycin. One might rather assume some intercurrent virus infection. Bunnel was negative. At check examination one month later, by which time the eosinophil count had returned to its previous level, 0.1 Gm. streptomycin produced no change in the blood picture (see table 1: June 11, 1953). After the initial streptomycin therapy (May 1952) the number of eosinophils was 8 to 9 per cent.

The patient was discharged in unchanged condition. Blood transfusions were obviously unable to produce any improvement, and as the spleen was not enlarged, splenectomy was not indicated. Cortisone in the dose given had produced no definite sign of improvement. It is intended, in the absence of spontaneous improvement, to try ACTH in a large dose. On discharge she was advised to present herself immediately for antibiotic therapy in the event of any infection. As yet the clinical picture has not been so very alarming, so that, judging by earlier reports of cases of chronic neutropenia with a similar clinical picture, the prognosis is favorable.

**Discussion**

It appears that the leukocyte agglutinating factor demonstrated in the patient’s serum may explain the underlying mechanism of the neutropenia in the same way as has been assumed for acute experimental pyramidal agranulocytosis. In vitro studies showed no definite signs of leukocytolysis. Intravascular agglutination of red blood cells in immunohemolytic anemia has been observed in
man and has even been cinematographed in animal experiments.\textsuperscript{23} It is probable that intravascular agglutination of white blood cells plays a corresponding role in the initiation of their elimination from the blood stream. Moeschlin's\textsuperscript{19} assumption that the increased destruction of neutrophile leukocytes in the peripheral blood exhausts the bone marrow of these cells is compatible with the appearance of the sternal marrow in the case under discussion. That the immunologic mechanism demonstrated cannot always explain the granulocytopenia is obvious from the fact that no such agglutination could be shown in sera from two other granulocytopenic patients who had splenomegaly.

Nothing is known of the fundamental cause of the patient's disease, of what can have initiated this autoimmunizing reaction, or of what continues to sustain the formation of agglutinin in the serum. As suggested by Moolten, et al.\textsuperscript{20} as the cause of certain cases of hemolytic anemia, it might be some virus infection. The process might also have been initiated by a drug antigenic factor. In this connection the possibility assumed in so-called idiopathic thrombocytopenia must be borne in mind, namely that the process may be due to immunization against a protein-allergen-complex in which the allergen cannot be demonstrated. It is, however, difficult to explain why the condition should continue without progression or regression long after all medication had been stopped. No definite evidence is available to support the assumption of the streptomycin being the causal agent. We have therefore been obliged to class the case under the heading idiopathic immunoneutropenia, and it appears that, as far as the neutrophile leukocytes are concerned, the disease is analogous with idiopathic immunohemolytic anemia and idiopathic thrombocytopenia. There were no signs of co-existent hemolytic anemia, and the number of thrombocytes lay within a normal range, so that the agglutinating agent acted selectively on the leukocytes, especially on the neutrophils. The number of eosinophils was either normal or increased, i.e. a fairly high percentage, almost throughout the period of observation. It is possible that a more refined technic would be able to demonstrate antibodies on the surfaces of the leukocytes with Coombs' test in similar cases in remission or in cases with less profound granulocytopenia. In a case of idiopathic thrombocytopenia Stefanini, et al.\textsuperscript{21} showed that the thrombocytes were coated by a substance capable of reacting with anti-human globulin rabbit serum.

We have as yet not been able to study the effect of the patient's serum on chronic myelocytic leukemia. It would be of interest to see how less mature myeloid cells react. If such cells were agglutinated selectively, such globulin as that in the patient's serum might be useful for identifying immature cells as belonging to the myeloid series. It would also be of interest to study the effect of a transfusion of the patient's blood on chronic myelocytic leukemia in a patient belonging to the same blood group. One might expect a better and less risky effect than that produced by leukotoxic sera used in the nineteen twenties. However, judging by the sternal marrow of the patient, with its fair abundance of immature myeloid cells, a striking effect can hardly be expected.

**Summary**

A case report is presented of a woman, aged 49, with persistent neutropenia, increased erythrocyte sedimentation rate, a pathologic serum protein fraction...
migrating at the same rate as $\gamma$-globulin representing about 30 per cent of the total protein, and with undue fatigue as the only symptom.

Normal leukocytes, especially neutrophils, were agglutinated by a factor contained in the patient's serum and bound to the pathologic $\gamma$-globulin fraction and active even in a dilution of at least 1:120.

The neutropenia may be explained by the formation, in the patient, of antibodies intravascularly agglutinating her own neutrophile leukocytes, which were then eliminated from the circulating blood. The appearance of the bone marrow did not argue against such an assumption.

It has not been possible to demonstrate any definite causal factor of the disease. As far as the neutrophile leukocytes are concerned, the disease is analogous with idiopathic immune hemolytic anemia and idiopathic immunothrombocytopenia.

No leukocyte agglutination could be demonstrated in sera from two other patients with granulocytopenia or in sera from a number of patients with various diseases and associated increased $\gamma$-globulin.

**SUMMARIO IN INTERLINGUA**

Es presentate le caso de un femina de 49 annos de etate qui exhibiva persistente neutropenia, un elevate rata de sedimentation erythrocytic, e un pathologic fraction del proteina serie le qual migrava al mesme velocitatem como le globulina $\gamma$ e representava circa 30 pro cento del proteina seric total. Le sol symptoma del patiente esseva un fatiga excessive.

Leucocytos normal, specialmente neutrophilos, esseva agglutinate per un factor continite in le sero del patiente. Iste factor esseva ligate al pathologic fraction del globulina $\gamma$. Illo esseva active mesmo in un dilution de al minus 1:120.

On pote explicar le neutropenia del patiente per le formation de anticorpores que agglutinava intra le vasculos le leucocytos neutrophile, le quales esseva tunc eliminate del sanguine circulante. Le apparentia del medulla ossee non argueva contra iste supposition.

Il non ha essite possibile demonstrar un definite factor causal del morbo. Quanto al leucocytos neutrophile, le morbo es analoge a idiopathic anemia immune hemolytic e idiopathic immunothrombocytopenia.

Nulle agglutination del leucocytos esseva demonstrabile in seros ab duo alte patientes con granulocytopenia o in seros ab plure patientes con varie morbos involvente augmentate quantitates de globulina $\gamma$.

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