Congenital Agranulocytosis: Prolonged Survival and Terminal Acute Leukemia

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Three unrelated, Caucasian patients with a disorder resembling infantile genetic agranulocytosis have been studied. There was no history of consanguinity. Parents and siblings were normal. Onset occurred before 3 weeks of age and persisted throughout life. All had severe neutropenia, myeloid arrest pattern of the bone marrow, eosinophilia, monocytosis and hyperglobulinemia. Other congenital anomalies were not present. Their clinical courses were characterized by recurrent, severe bacterial infections particularly of the skin, mouth and lungs but without bacteremia. The infections responded to, but were not prevented by antibiotics, which were administered almost continuously. Fungal infections did not occur and viral infections were not severe. Splenectomy and corticosteroids were without apparent benefit. Relative, though transient, neutrophilia occurred during a few episodes of infection. Chromosome analysis was normal in two of the patients. In one, maturation of neutrophilic leukocytes was not observed in cultures of bone marrow to which normal serum or cysteine was added. One boy is living at 14 10/12 years of age, and one died at 13 3/4 years of disseminated infection. A unique occurrence was the development of terminal acute leukemia (monocytic) in the third patient, a girl at the age of 14 1/4 years.

In 1956, Kostmann introduced the term infantile genetic agranulocytosis to describe a condition seen in 14 children from nine families in a small parish in Northern Sweden. The disorder was characterized by the early onset of severe, recurrent infections particularly of the skin. Twelve of these 14 children died of infection before the age of 6 months. All of the patients had severe neutropenia. Examination of the bone marrows showed maturation arrest of the neutrophilic precursors at the stage of promyelocytes or myelocytes, and abnormalities of the myelocytic nuclei were described. At least 22 additional cases in 18 families have been reported. Sixteen of these patients died of infection prior to the age of 3 years.
The present report describes three patients with congenital agranulocytosis whose clinical courses resembled those described in patients with infantile genetic agranulocytosis. One patient is living at 14 $10/12$ years of age; and one died of infection at 13$1/2$ years of age. The third patient developed acute monocytic leukemia at 14$3/4$ years of age and died 7 months later. The occurrence of acute leukemia in this patient is particularly noteworthy in view of the increasing number of reports of leukemia or lymphoma in patients with other congenital or inherited disorders of the hematologic or immunologic systems.$^{13-19}$

**Case Summaries**

The clinical courses of three, unrelated, Caucasian patients are summarized in Figs. 1, 3 and 4. Onset of the disorder in these patients was a birth or within 3 weeks of life with no known prior exposure to toxic agents. There was no history of consanguinity, congenital anomalies, blood diseases or malignancies in other members of the families. Total and differential white blood cell counts on the parents and siblings (i.e. a sister of Case 1, a brother of Case 2, and three sisters of Case 3) have been normal.

The three patients had severe neutropenia but no other congenital abnormalities. All had monocytosis and eosinophilia. Anemia was present only during some episodes of severe infection and after the onset of leukemia in Case 1. Platelet counts have been normal or elevated, except after the onset of leukemia in Case 1 and during one episode of a coliform abscess of the thigh in Case 2. Repeated examinations of the bone marrow, with the exceptions noted below in Cases 1 and 3, have revealed: cellular specimens with adequate megalakocytes, no increase in blast cells, an increased proportion of undifferentiated myeloid precursors with a marked reduction of differentiated neutrophilic cells, an increased proportion of maturing eosinophilic cells and a normal proportion of maturing basophilic cells. Chromosome analysis of bone marrow from Cases 2 and 3 revealed a normal karyotype. Bone marrow aspirated from Case 3 at the age of 8 years was grown in tissue culture$^*$. Maturation of neutrophilic leukocytes was not observed in culture media to which the following had been added: (a) serum from cord blood of a normal newborn, (b) serum from the patient's blood, (c) serum from the patient's blood to which L-cystine, L-cysteine, glutathione or reduced glutathione had been added. Blood chemistries have been normal except for persistent elevation of the $a$ and $y$ globulins. Urinary amino acid excretion in Case 2, and measurement of chlorides in sweat of Case 3 were normal. Moderate retardation of growth was noted in the three patients, but onset of puberty was not delayed in Cases 1 and 2.

All three patients had recurrent, severe bacterial infections of the skin, mouth and respiratory tract, but without bacteremia. Organisms cultured from skin lesions were *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas* or paracolon species. During infections of the nasopharynx and throat, cultures from these sites usually revealed *Staphylococcus aureus* or Group A, $\beta$ hemolytic streptococci. Fungi, St. Vincent's spirochetes, or specific bacteria could not be identified in the oral lesions. Pulmonary infections usually were attributable to *Staphylococcus aureus*, *Proteus mirabilis*, *Escherichia coli*, or paracolon species. Infections of the urinary tract and bacterial meningitis have not occurred. Fungal infections were not seen; and viral infections including rubella, varicella and mumps were not severe.

Microscopic examination of exudates from skin abscesses and bronchoscopic aspirates in Cases 2 and 3 revealed bacteria, amorphous material, rare monocytes and lymphocytes but no polymorphonuclear neutrophils. A skin window study performed in Case 2 at the age of 8 years was abnormal. At 2 hours, there was no cellular response; at 8 hours, 96 per cent of the cells present were mononuclear; and at 8 hours, a large amount of exudate was present and the cells were primarily mononuclear cells with a rare eosinophil but no basophils or neutrophils. Pathologic examination of the tonsils (Cases 2 and 3) and appendix
Fig. 1.—Congenital agranulocytosis with terminal acute leukemia. Clinical course of Case 1.

(Cases 1 and 2) revealed lymphoid hyperplasia but only rare polymorphonuclear neutrophils. Pathologic sections of the right middle lobe of the lung of Case 3 revealed chronic bronchitis and severe bronchiectasis. There was prominent lymphoid hyperplasia with follicle formation and areas of dense focal eosinophilia but no polymorphonuclear neutrophils were seen. The small arteries and arterioles showed marked intimal thickening.

The principal form of therapy has been the use of antibiotics. Bacterial infections have responded to appropriate antibiotics which have been administered promptly with the many episodes of infection. Prophylactic administration of antibiotics did not appear to prevent infections in Cases 2 and 3. Splenectomy was without apparent benefit in Cases 1 and 2. Corticosteroids (Cases 2 and 3), ACTH (Case 1) and testosterone (Case 1) also were without apparent benefit. Details regarding these three patients are summarized below:

Case 1

F.T. was born August 8, 1948. Recurrent skin infections began at 3 weeks of age, and neutropenia was noted at 9 weeks of age. Her total white blood cell count usually ranged between 8–15,000 per cu.mm. with a total neutrophil count between 250–1000 per cu.mm. (Fig. 1). The total neutrophil count occasionally rose as high as 4–5000 per cu.mm. in association with severe infections (Fig. 1). There was no improvement in the degree of neutropenia following administration of testosterone or adrenocorticotropic hormone (ACTH) for 10 days. At 2 11/12 years of age an 82 Gm. spleen and a small accessory spleen were removed. Pathologic examination of the two specimens showed active and passive congestion, without evidence of phagocytic activity. At 3 10/12 years of age, a ruptured appendix was removed. During the next 3 years she continued to develop recurrent infections of the skin, mouth and respiratory tract. Bronchiectasis of the right upper lobe of the lung was
diagnosed at 7½ years of age. Over the next 5 years, the frequency of the skin and pulmonary infections decreased. Intermittent febrile episodes were treated at home with broad spectrum antibiotics.

At 13 years of age, the patient was first seen at The Johns Hopkins Hospital because of recurrent stomatitis and gingivitis. Bilateral cervical lymphadenopathy was present. Biopsy of the gums revealed edema, hyperplasia of the epithelium and infiltration with lymphocytes and plasma cells, but no neutrophils were seen. Examination of aspirated bone marrow (Fig. 2) confirmed observations during her early childhood* and revealed an increase in the proportion of undifferentiated myeloid precursors with a marked reduction in differentiated neutrophilic cells but no increase in blast cells (i.e. blast cells<5%).

At 14½ years of age, blast cells (8%) were noted in the differential white blood cell count for the first time (Fig. 1). Four months later she remained asymptomatic except for the gingivitis. She was afebrile, and hepatomegaly was not present. The abnormal gums and minimal lymphadenopathy were unchanged. Repeat examination of the blood revealed anemia, thrombocytopenia and an increase in leukocyte count. Approximately 50 per cent of the white cells on smears of blood were blast cells, many of which had morphologic features suggestive of monoblasts, and an additional 30–40 per cent of the cells were monocytes and young monocytes. Many of these cells were actively phagocytic as demonstrated by incubation of blood with India ink. Smears of aspirated bone marrow (Fig. 2) revealed a marked increase in blast cells to 73 per cent, thereby establishing the diagnosis of acute leukemia, probably acute monocytic leukemia. Admission to the hospital was refused. Ten days later she developed severe pain and swelling of the ankles which subsided over the next week. Subsequently, she developed severe anemia and thrombocytopenia and the white blood cell count increased markedly (Fig. 1). Therapy with 6-mercaptopurine produced an initial fall in peripheral white blood cell count. However, remission was not obtained by therapy with 6-mercaptopurine, multiple transfusions, prednisone and methotrexate (Fig. 1). She died 4 months later, with a rapidly rising white blood cell count and severe hemorrhage. Permission for autopsy was not obtained.

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*Fig. 2.—Morphology of bone marrow (original magnification 1000 ×) in Case 1. (A) At the age of 13 years before the onset of acute leukemia. (B) At the age of 14½ years after the onset of acute leukemia.
Case 2

F.H. was born March 4, 1954. The first of many skin infections developed at 10 days of age, at which time neutropenia was noted. His total white blood cell count usually was slightly elevated (Fig. 3) but with severe neutropenia (neutrophils 0–275 per cu.mm.). Marked though transient increases in neutrophils occurred during two episodes of infection involving extensive necrosis of tissue (Fig. 3). At the age of 6½ months he developed a large perianal, coliform abscess and peritonitis. On admission to The Johns Hopkins Hospital, his neutrophil count was 950 per cu.mm. The neutrophil count was 10,800 per cu.mm. 14 days after a transfusion of whole blood (9.0 ml per Kg.) and 7 days after initiation of treatment with cortisone. One week later it was 0 per cu.mm. One week after admission, the anus and perianal tissue spontaneously sloughed. The perianal lesion slowly improved and 3 months later, normal bowel function had returned. A 40 Gm. spleen was removed at 8 months of age. Wright stained smears of touch preparations of the splenic pulp revealed many mononuclear cells but only rare polymorphonuclear neutrophils. Sections of the spleen showed changes of acute splenic tumor but only rare neutrophils.

During episodes of pneumonia at 11 and 11½ months of age, he received transfusions of whole blood (9.0 and 12.0 ml per Kg.), and 10 days after these transfusions, his neutrophil counts were 167 and 1300 per cu.mm., respectively. At 17½ months of age, the neutrophil count increased to 10,200 per cu.mm. in association with a coliform abscess of the thigh and staphylococcal pneumonia. Seven days prior to this blood count he had received a transfusion of packed red blood cells (8.0 ml per Kg.) and the dose of cortisone had been increased. The neutrophil count was 0 per cu.mm. 3 weeks after the transfusion despite continued administration of large doses of cortisone. One month later, a neutrophil count was 1030 per cu.mm. during an episode of pneumonia, although he received no additional transfusions. During many other infections, the number of circulating neutrophils did not increase or rose only to 500–750 per cu.mm.

At the age of 18 months, he was started on a regimen of room isolation; skin care with potassium permanganate; and daily multiple vitamins, ferrous sulfate, cortisone, chloramphenicol and erythromycin. During the next 8 years he did reasonably well and was admitted only for regular evaluation. Periodic infections were treated at home with short courses of more intensive antibiotic therapy. Oral nystatin and monthly injections of gamma globulin were added to the regimen at the age of 4 years, and oxytetracycline was
substituted for chloramphenicol in the prophylactic regimen. Mental retardation was apparent at this time. Extraction of carious teeth resulted in improvement in gingivitis but did not affect the occurrence of cyclic stomatitis. At 9 11/12 years of age he developed an appendiceal abscess which responded well to therapy with chloramphenicol. Appendectomy was performed 6 weeks later. Probable bronchiectasis was noted at this time on chest Xray. The patient was last seen at this hospital at 12 1/2 years of age.

At 13 3/12 years of age he expired 20 hours after the onset of fever, abdominal pain and coma. Autopsy* revealed free air and foul smelling fluid in the peritoneal cavity, as well as extensive fibrinous peritoneal adhesions. There was extensive coagulation necrosis of the cecum and ileum with perforation of the appendiceal stump. Bacteria were noted in the wall of the cecum, but there was no thrombosis of the mesenteric or intestinal vessels. The changes in the intestinal tract were interpreted as indicating inflammation rather than infarction, although acute inflammatory cells were not found in either the bowel or the peritoneal fluid. The pancreas was normal. Severe bilateral pneumonia and pleuritis were noted. Extensive exudate in the bronchi, alveolar and pleural spaces consisted of proteinaceous material and mononuclear cells, but no polymorphonuclear neutrophils were seen. Smears of the bone marrow revealed considerable autolysis. The only segmented cells seen appeared to be eosinophils, and many chains of large bacilli and a few gram positive cocci were noted.

Case 3

M.W. was born April 29, 1955. Neutropenia was noted on the day of birth, and the first of many skin infections occurred at the age of 7 days. His total white blood cell count usually has been < 6000 per cu.mm, and has never been > 10,000 per cu.mm. (Fig. 4). Marked neutropenia (neutrophils 0-450 per cu.mm.) usually was present. The patient was admitted to The Johns Hopkins Hospital for the first time at the age of 2 1/2 years with multiple infections. The liver and spleen were palpable 2-3 cm. beneath the costal margins but there was no lymphadenopathy. The number of neutrophils did not increase following a transfusion of whole blood (18.0 ml per Kg.) which was administered after tonsillectomy. Between the ages of 2 5/12 years and 7 9/12 years, he was hospitalized elsewhere on 30 intensive antibiotic therapy. A bronchiectatic right middle lobe was removed at 9 1/2 years of age.

At the age of 8 years, he was started on a regimen of isolation at home; skin care with gentian violet; daily multiple vitamins, ferrous sulfate, tetracycline and novobiocin; nystatin 3 times a week and monthly injections of gamma globulin. The cyclic pattern of the oral lesions was not altered by administration of prednisone and chloramphenicol for 1 week of each month. Exacerbations of chronic pneumonia responded to short courses of more intensive antibiotic therapy. A bronchiectatic right middle lobe was removed at 9 1/2 years of age.

The number of circulating neutrophils increased transiently to 2210 and 1640 per cu.mm at 10% and 12% years of age during episodes of pneumonia with lung abscess and severe, acute mastoiditis (Fig. 4). Both infections were due to Gram-negative organisms, and both responded to intensive antibiotic therapy. He was not transfused on either of these occasions. Examination of the bone marrow during the episode of mastoiditis showed maturing neutrophilic precursors, i.e. 16.0 per cent juvenile neutrophils and 3.0 per cent segmented neutrophils, but on numerous other occasions maturing neutrophilic precursors were markedly decreased (i.e. < 5%).

Subsequently, the patient has been maintained on a regimen of continuous but alternating therapy with penicillin, chloramphenicol, ampicillin, tetracycline and novobiocin; each drug being given for 1 week and then alternating with the next. He has continued to have recurrent infections but none severe enough to require hospitalization. Clubbing of the fingers and toes, hyperplasia of the gums and minimal hepatosplenomegaly have persisted. Generalized lymphadenopathy has not been noted. He remains under observation.
DISCUSSION

The various types of congenital disorders of leukocytes have been reviewed recently by Kauder and Mauer and Davidson. The three patients described in this report had disorders which resemble that known as infantile genetic agranulocytosis. Kostmann’s original 14 cases occurred in 9 families in an isolated area. There was a high incidence of consanguinity in these families, and an autosomal recessive pattern of inheritance was suggested. There was no history of consanguinity of our patients’ families. Parents and siblings were normal, although the number of siblings was small. Of 22 additional cases in the literature only two of the 18 families had more than one affected child. One family had two affected children and one had four. In two other families, siblings died of severe infections. A sister of one case died of meningitis at 2 months of age, but blood counts were not recorded. The fraternal twin brother of another case died at 5½ months of age with meningococcemia, at which time his white blood cell count was 18,000 per cu.mm. with 82 per cent neutrophils.

The etiology of infantile genetic agranulocytosis is unknown. Chromosomal abnormalities have been described in one case, but analysis of chromosomes in three other cases (9, Cases 1 and 2) were normal. Deficiency of a plasma or serum factor(s) has been suggested by some observations. Cultures of bone marrow cells from several of the patients in the patient’s own serum revealed no maturation of myelopoietic cells, (Case 3) and decreased erythropoiesis. Cultures of normal bone marrow cells in the patient’s sera showed decreased erythropoiesis. Plum noted improvement in maturation of myeloid cells and erythropoiesis in the cultures after addition of normal serum, cysteine or pyridoxine; but tyrosine and liver extract were without effect. However, improvement in maturation of myeloid cells in cultures of bone marrow from other cases was not observed following addition of normal serum (Case 3), cysteine (Case 3) or cystine (Case 3). Administration of cysteine to three patients effected no improvement.

Bjure, Nilsson and Plum described two brothers with multiple congenital anomalies and neutropenia possibly caused by deficiency of a plasma factor. The authors felt that these brothers did not have infantile genetic agranulocytosis since they survived to the age of 10 and 13 years and since there was no improvement in maturation of cells following addition of amino acids or liver extracts to cultures of bone marrow. Cultures of the patients’ bone marrow...
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cells in normal sera showed some improvement in erythropoiesis and maturation of myeloid cells. Mature neutrophils were noted in the bone marrow and peripheral blood of one of these patients approximately 1 week after infusion of normal plasma. However, this patient developed an upper respiratory tract infection at about this time. Transient increase in neutrophils, not associated with transfusion, occurred with some infections in two of our patients (Cases 2 and 3) and in one instance (Case 3) the bone marrow also revealed transient improvement in maturation of the neutrophilic precursors. Infusion of normal plasma into another patient with infantile genetic agranulocytosis did not result in improved maturation of myeloid cells in the bone marrow, increase in the mitotic index or the percentage of cells that incorporated tritiated thymidine. Thus, it is not clear whether the neutrophilia observed by Bjure, Nilsson and Plum was related to the transfusion or the infection, and whether or not their patients had infantile genetic agranulocytosis.

The types of infections seen in our patients were similar to those described in other patients with congenital agranulocytosis. The infections were controlled by therapy with appropriate antibiotics even in the absence of a neutrophilic response. The use of prophylactic antibiotics is more difficult to evaluate. The possibility of developing a resistant bacterial flora certainly is undesirable. Our Cases 2 and 3 have received prophylactic antibiotics and have not developed superinfections with resistant organisms or fungal infections. Case 1 was not on a regimen of prophylactic antibiotics, but she did receive frequent courses of antibiotics during episodes of fever. Therapy which has been without apparent benefit has included splenectomy (Cases 1 and 2), ACTH (Case 1), corticosteroids (Cases 2 and 3) and testosterone (Case 1).

The occurrence of acute monocytic leukemia in Case 1 deserves special comment. Many of the reported cases of infantile genetic agranulocytosis initially were thought to have aleukemic leukemia or monocytic leukemia because of the hypertrophied gums, monocytosis, neutropenia and skin changes. However, their laboratory findings and subsequent courses were not those of a leukemic process. In our Case 1, the terminal clinical course was that of unresponsive and uncontrolled acute leukemia. This course, together with the diagnostic findings in her blood and bone marrow, clearly separated the terminal acute leukemic phase from the previous 14 years of neutropenia.

Certain other congenital hematologic or immunologic disorders have been associated with an increased incidence of leukemia. Four of 80 patients with Fanconi's anemia and five close relatives of the remaining 76 patients have died with acute leukemia. Three of 25 patients with Bruton's type agammaglobulinemia have developed leukemia or lymphoma, and one of these who developed chronic myelomonocytic leukemia had had cyclic neutropenia. Familial neutropenia, usually an asymptomatic or relatively benign disorder with a dominant pattern of inheritance, has been described. A Jewish woman with neutropenia developed acute myeloblastic leukemia. She was noted to have neutropenia approximately 18 months prior
to the definite diagnosis of leukemia. She had had no previously recorded blood counts, but had had two severe abscesses 13 and 8 years prior to the onset of leukemia. Her mother, sister and two nieces had familial neutropenia but her daughter's blood counts were normal. An increased incidence of malignancies also has been noted in patients with Chediak-Higashi syndrome, Wiskott-Aldrich syndrome and ataxia telangiectasia.

Case 1 represents the first recorded instance of acute leukemia in a patient with infantile genetic agranulocytosis. Miller noted the association of leukemia and infantile genetic agranulocytosis in one case. This patient (Case 62 in reference 19) is the same as Case 1 in the present report. Of the 36 previously reported cases of infantile genetic agranulocytosis, only seven (19%) have survived past 3 years of age. Perhaps as more of these children with this rare condition survive longer, other similar terminal episodes will be seen.

It is well recognized that chronic, acquired hematologic abnormalities also may antedate the onset of leukemia for several months to many years. One is reluctant to dismiss the development of terminal leukemia in patients with various congenital and acquired hematologic disorders as a chance occurrence. It is not known whether these antecedent hematologic disorders represent early (i.e. preleukemic) manifestations of an underlying leukemic process or whether they represent primary dysfunctions of bone marrow which then evolve into leukemia.

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