INFANTILE CONGENITAL ANEUTROCYTOSIS

BY

DAGFINN AARSKOG

From the School of Medicine, Paediatric Department, University of Bergen, Norway

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In 1956 Kostmann reported a new disease of infancy which he termed 'infantile genetic agranulocytosis'. He described 14 children of both sexes in nine families. All but two of the children died as a result of the disease. For six of them detailed clinical and histological data were reported. The disease occurs during early infancy with infections particularly of the skin. There is a complete or almost complete lack of polymorphonuclear neutrophil leucocytes in the peripheral blood, and the bone marrow shows a marked retardation or block in the maturation of the myelopoietic cells. All of the affected children in his report lived in the northern part of Sweden. Close consanguinity between the parents was established in five of the nine families. Kostmann presented a genetic analysis which supported the conclusion that the disease was primarily caused by a single recessive autosomal gene (a simple recessive mutation).

Since Kostmann's original report three additional cases belonging to the same families have been examined (Kostmann, 1960).

Hedenberg (1959) described a case of agranulocytosis discovered in a girl at the age of 1 week. He found good agreement with infantile genetic agranulocytosis. In his case there was no consanguinity between the parents. The family lived in the southern part of Sweden, and there was no relationship to the families described by Kostmann.

Outside Sweden, Luhby, Speer, Lee and Shapiro (1957) described an infant who presented with agranulocytosis at 2 weeks of age; it persisted until the child died of an overwhelming infection when 7 months old. The authors concluded that the case represented a congenital genetic agranulocytosis due to an inborn error of development and maturation of the neutrophils. They found the condition apparently identical to that described by Kostmann. Kniker and Panos (1957) studied two infants aged 7 and 30 months, both of whom had fatal agranulocytosis. They stated that the clinical, laboratory and pathological features closely fitted the syndrome described by Kostmann. However, all cases on

record outside those belonging to the families reported by Kostmann have failed to show hereditary or genetic factors.

The number of reported cases of this syndrome is still small, although this deleterious mutation seems now to occur in different areas. The purpose of this paper is to present a further case with typical clinical and laboratory findings.

Case Report

The patient was a 2-month-old girl admitted to the Children's Hospital, Bergen, on June 4, 1960, because of jaundice, pyoderma and otitis.

There was no consanguinity between the parents, and the patient was the fourth child. A sister died of meningitis at the age of 2 months. There was no known case of blood disorder in the family.

The mother did not use any medicaments during the pregnancy which was uneventful. The delivery was spontaneous at term on April 4, 1960, and the child's birth weight was 2,870 g.

At the age of 1 week she developed pyoderma, and when 10 days old a slight jaundice was observed. At the age of 6 weeks she had an otitis and was treated with aureomycin, 120 mg. daily.

Upon admission to the Children's Hospital she looked ill, but her general condition was not severely affected. She was thin, pale and slightly icteric. Temperature 37.7° C. On the abdomen she had several pea-sized, bluish-red infiltrations. The liver was felt about 2 cm. below the right costal margin and the spleen just below the left. She had signs of an otitis with a clear, viscid discharge. The blood examinations are summarized in Table 1. Examination of the bone marrow by needle aspiration revealed a cellular marrow with a striking absence of neutrophilic myeloid elements (Table 2). The total serum protein was 6 g. per 100 ml. with decreased albumin fraction and elevated gamma-globulin level. Examination of the serum for leucocyte antibodies was negative.

A blood culture was negative. Cultures from the ear revealed coagulase positive *Staphylococcus aureus*, and from the cutaneous infiltrations there was growth of *Escherichia coli*, *Proteus vulgaris* and *Enterococcus*.

She was treated with large doses of penicillin and with streptomycin, erythromycin, chloramphenicol and

TABLE 1
BLOOD EXAMINATIONS

Date (1960)	Hb (%)	R.B.C. (million/mm. ³)	W.B.C. (per mm. ³)	Stab Cells (%)	Poly-morpho-nuclear Neutrophils (%)	Eosino-phils (%)	Baso-phils (%)	Lympho-cytes (%)	Mono-cytes (%)	Platelets (per mm. ³ × 10 ⁹)	Reticulo-cytes (per 1,000)	Sedimen-tation Rate
4/6	62	4.01	13,300	—	—	2	—	46	52	92	24	125
6/6			20,800	—	—	1.5	0.5	63	31			
13/6	48	2.92	17,800	0.5	0.5	4.5		82	12.5	170		50
13/6	Blood transfusion											
20/6	71	3.82	14,700	—	—	9.5	1	41.5	48	142	52	
27/6	69	3.36	18,700	—	—	8.5	0.5	77	14		12	126
4/7	68	3.38	11,800	—	—	3	1	77	19		10	
7/7											54	
9/7			16,200	—	—	9.5		52.5	38			
23/7	Blood transfusion											
27/7	78									315		
29/7	65	3.82	30,800	—	—	2	0.5	63.5	34		28	
8/8	65	3.80	15,300	—	—	12	1	52	35	248	30	
15/8	63	3.53	36,100	—	—	8	1	50.5	40.5		36	
29/8	Blood transfusion											
9/9	85	4.87	23,800	—	—	9.5		41	49.5		12	
14/9	Blood transfusion											
15/9	87	4.82	18,000	—	—	8.5		66	25.5		6	
19/9			18,000	—	—	2	0.5	72	25.5			

vancomycin in appropriate doses. She also received repeated blood transfusions. However, the clinical course was marked by intermittent fever and a new outbreak of cutaneous infiltrations. Smears of the latter showed the cellular reaction to be monocytic and lymphoid. Throughout the whole course only occasional

neutrophilic granulocytes were found in smears from the peripheral blood. Platelet and reticulocyte counts were within normal limits (Table 1). Attempts to improve the bone marrow with vitamin B₁₂ and folic acid were of no effect.

On August 30, 1960, physical examination revealed signs of pneumonia, and a radiograph showed massive consolidations in both lungs. Despite massive antibiotic therapy she died on September 19, 1960, of an overwhelming lung infection.

Autopsy. At autopsy scattered pleural adhesions were found. In the right lung there were two large abscesses, and in the left lung several bronchopneumonic foci. Microscopically the wall of the lung abscesses was infiltrated by mononuclear cells with many plasma cells. The spleen was also rich in plasma cells and contained large amounts of haemosiderin. The bone marrow showed pronounced myelofibrosis with deposits of haemosiderin. It contained many eosinophilic granulocytes and plasma cells. In the kidneys there were scattered foci of cellular infiltrations containing mainly lymphoid cells, but also many plasma cells and some eosinophilic granulocytes.

Definite polymorphonuclear neutrophilic leucocytes were not found.

Discussion

Agranulocytosis after drug therapy is a well-known feature in adults, and is also known as a rare complication in infancy and childhood. The present patient did not receive medicaments known to cause agranulocytosis, neither did the mother use any drug during the pregnancy.

It is also a well-known clinical fact that severe infections, especially sepsis, may be associated with

TABLE 2
BONE MARROW EXAMINATION*

Blood basophils	0.8
Basophilic myelocytes	0.6
Segmented basophils	0.2
Eosinophils	9.8
Eosinophilic myelocytes	3.0
Eosinophilic metamyelocytes	1.6
Stab eosinophils	5.2
Neutrophils	0.8
Neutrophilic promyelocytes II	0.8
Monocytes	26.8
Monoblasts	0.4
Promonocytes	3.4
Monocytes	22.8
Athrophagocytes	0.2
Lymphocytes	44.8
Plasma cells	17.0
Plasmoblasts	1.2
Proplasmocytes	9.2
Plasmocytes	6.6
Megakaryocyte-platelet system	0.4
Megakaryocytes	0.4
Normocytes	8.0
Basophilic normoblasts	1.6
Polychromatophilic normoblasts	3.0
Oxyphilic normoblasts I	2.4
Oxyphilic normoblasts II	1.0
Non-haemopoietic cells	0.4
Osteoblasts	0.4

* Examination carried out on August 8, 1960 (500 cells were counted).

leucopenia and a relative granulocytopenia. However, leucopenia is not a common feature in sepsis. Recently Nyhan and Fousek (1958) reported a series of 106 newborn infants with sepsis. Leucopenia was noted in five infants. Persistent absence of polymorphonuclear neutrophil leucocytes similar to that observed in this patient hardly occurs in sepsis.

During the past few decades a number of other conditions occurring in infancy and childhood have been observed in which there is an isolated reduction or complete absence of polymorphonuclear neutrophil leucocytes. Transitory granulocytopenia of the newborn was described by Slobody, Abramson and Loizeaux (1950) and Lehndorff (1951). In this condition there is a pronounced granulocytopenia with a duration of several days up to four weeks. During the granulocytopenic phase there is a pattern of maturation arrest at the neutrophil myelocyte stage in the bone marrow. The persistent nature of the aneutrocytosis in the present case rules out this possibility.

Chronic granulocytopenia in children was first described by Fanconi (1941), but Salomonsen (1948) first put forward the opinion that the syndrome represented a distinct clinical entity. Stahlie (1956) reported a case and collected 15 cases from the literature. The syndrome is characterized by a chronic, marked, selective granulocytopenia with a corresponding leucopenia. The bone marrow is normal. The disease usually starts after the age of 6 months, runs a benign protracted course with a tendency to infections and spontaneous cure. This clinical entity differs from the case reported in the patient's age at onset, the pathological bone marrow, the grave course and fatal outcome.

The present case seems to correspond closely with Kostmann's syndrome. However, there was no consanguinity between the parents and to date no other conclusive case of the disease has been found in the family. It is noteworthy that the patient had a sister who died of meningitis at the age of 2 months. Unfortunately her blood was not examined. The early onset in the neonatal period with skin manifestations, the relentless clinical course as well as the findings in the peripheral blood and bone marrow are in good agreement with the findings in Kostmann's cases.

The monocytosis accompanying the aneutrocytosis in the patient resembles that seen in several previously reported cases. In two of Kostmann's cases the monocytes made up 50% of the total number of white cells. Monocytosis of moderate degree was also observed in another case. A moderate increase in the total number of monocytes

was noted in the case reported by Luhby *et al.* (1957). Hedenberg also noted monocytosis, and in his case a varying connexion between the infections and monocytosis could be observed. Tobler and Buser-Plüss (1942) demonstrated experimentally that the monocytes in a patient with agranulocytosis had a considerably stronger phagocytic function than those of controls. The monocytosis may therefore represent a compensatory mechanism for the impaired phagocytic function in this patient. The elevated serum gamma-globulin level found in the present patient may also be compensatory as an attempt to raise the immunobiological protective mechanisms against infection. Hypergammaglobulinaemia was also noted by Kostmann in one case and was marked in both cases reported by Kniker and Panos (1957). The latter authors also found eosinophilia and plasmocytosis in the bone marrow, findings similar to those in the present patient. In view of the role played by plasma and eosinophilic cells in the immunobiological response to infection, it seems justifiable to look upon the plasmocytosis and eosinophilia also as secondary phenomena.

Considering the terminology of this syndrome it seems more reasonable to use the term aneutrocytosis than agranulocytosis, since only the polymorphonuclear neutrophilic leucocytes are affected. The eosinophilic and basophilic leucocytes may actually be increased.

Summary

A case of infantile congenital aneutrocytosis is presented. A 2-month-old girl who suffered from infections starting soon after birth, revealed an almost complete absence of neutrophilic myelogenous elements in the peripheral blood and bone marrow. This persisted until she died at the age of 5 months of an overwhelming pulmonary infection. The case seemed to correspond closely with Kostmann's syndrome, but there was no evidence of genetic background.

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