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Case Reports

Neonatal Leukemia

Detection of Herpes Virus in the Mother and Child

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LEUKEMIA in the newborn is unusual. It may be readily confused with leukemoid reactions complicating mongolism, congenital syphilis, viremia, septicemia, toxoplasmosis, hemolytic anemia, thrombocytopenic purpura, erythroblastosis fetalis, and cytomegalic inclusion disease.[1-3] The leukocytosis, the presence of blast-like cells, and the predominance of myelocytes and promyelocytes which may be seen in the forementioned diseases present a problem in the differential diagnosis of leukemia in this age group.

Granulocytic leukemia is reported to be seven or eight times as frequent as the lymphatic type in the neonate [2] and this is at variance with the generally accepted predominance of the lymphoblastic type in childhood. Further confusion arises in the alleged association of granulocytic leukemia with mongolism in which the hematologic changes may undergo spontaneous remission or resolution. In fact, some investigators [4] designate the hematologic component in the mongoloid as labile granulopoiesis rather than leukemia.

Recently an infant presented with leukemia in which the diagnosis was established by the presence of lymphoblasts in the peripheral blood and confirmed at necropsy by the infiltration and replacement of the bone marrow and visceral organs by the leukemic process. It is our purpose to report this case because of the rarity of leukemia in the neonate, to relate clinical and hematological findings, and finally to record observations of viral detection studies.

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Report of a Case

A full-term white female infant was born to a gravida 6, para 3, 39-year-old mother on Oct 29, 1966. Pregnancy and delivery were uneventful. The condition of the child was good at birth with an Apgar rating of nine. The child's birthweight was 7 lb 3 oz (3,260 gm) and her length, 19½ inches. The child's hospital course was unremarkable. There was no evidence of purpura or hepatosplenomegaly.

During a routine check up at 4 weeks of age it was noted that the abdomen was large and lymph node enlargement in the groin and neck was present. At this time the mother stated that there were purple spots on the baby's face and over the left foot at 8 days of age.

Physical examination revealed a very pale, well-nourished infant in no distress. The weight was 9 lb 9 oz (4,338 gm). There were a few purpuric areas measuring 3 × 6 mm on the face, back, and left foot. Enlarged nodular lymph glands were present in the groin and anterior and posterior cervical chains. The liver was enlarged 3.5 cm below the right costal margin and the spleen was palpated 6.5 cm below the left costal margin. The heart rate was 160 beats/min, but no murmurs were heard. The remainder of the physical examination was normal.

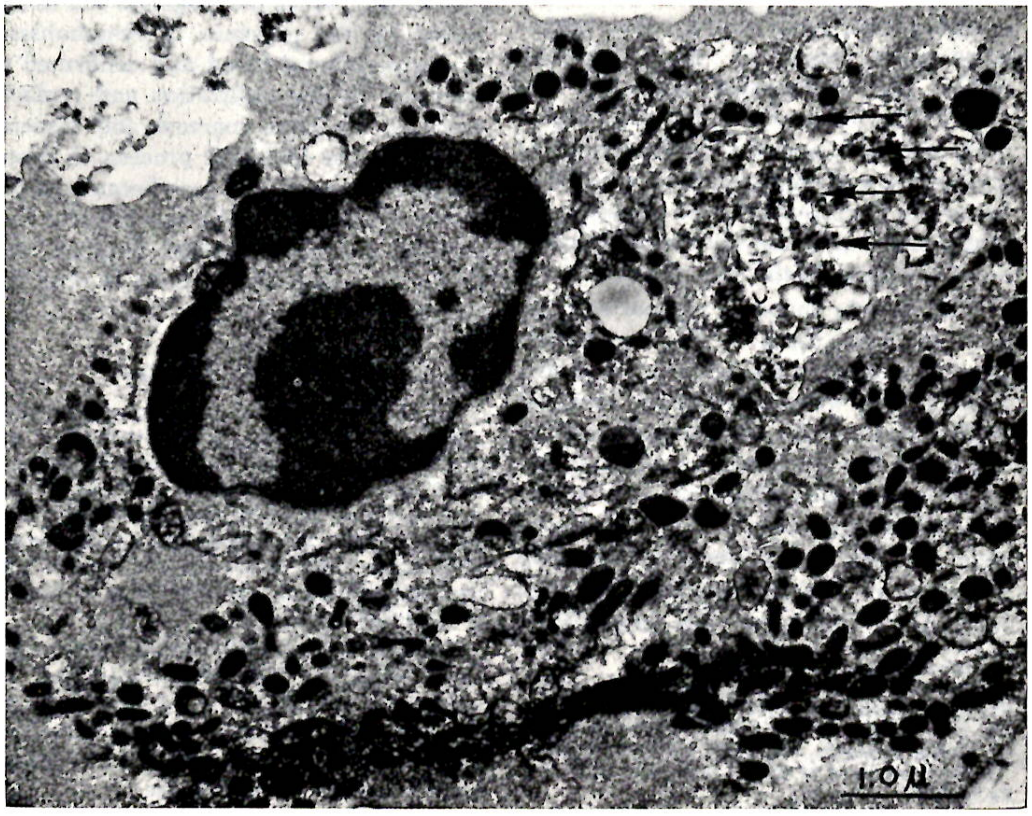
The laboratory work done in the hospital disclosed the following: Hemoglobin, 5.1 gm; hematocrit, 13.5; leukocyte count, 1,300,000/cu mm. Examination of the stained smear showed all the cells to be in the lymphatic series and 71% were classified as lymphoblasts. About 10% of the leukocytes were smudge cells. No platelets were seen. The erythrocytes were normocytic and normochromic. A diagnosis of acute lymphoblastic leukemia was made. Urinalysis was normal. No inclusion bodies were seen in a stained smear of the urinary sediment. The total bilirubin was 1.1 mg/100 cc and the direct phase was 0.5 mg.

The infant's condition remained unchanged during her hospital stay of 12 days. Two days before discharge it was apparent that the inguinal lymph nodes had regressed in size. However, the hepatosplenomegaly persisted. Repeat laboratory studies prior to discharge from the hospital revealed a hemoglobin of 4.8 gm and a white cell count of 610,000/cu mm.

At the request of the parents no therapy was instituted. The child was seen daily at her home until her death at the age of 7 weeks. Except for a respiratory infection there was very little change in her condition. Two days prior to her death the inguinal lymph nodes were considered to be as large as at the time of her hospital admission. Three ecchymotic areas 5 × 6 mm were seen over the back, and she had developed a low grade fever. The purpuric areas were the only hemorrhagic manifestations even though no platelets were seen in the peripheral blood. Jaundice never appeared and the child had no clinical features to suggest Down's syndrome.

The mother was always in good health and at the time of delivery her hemoglobin, total white cell count, and differential were within normal

Fig 1.—Neutrophil from the peripheral blood of the mother. This cell contains herpesvirus-type particles (**arrows**) which may have been phagocytized (× 15,000).



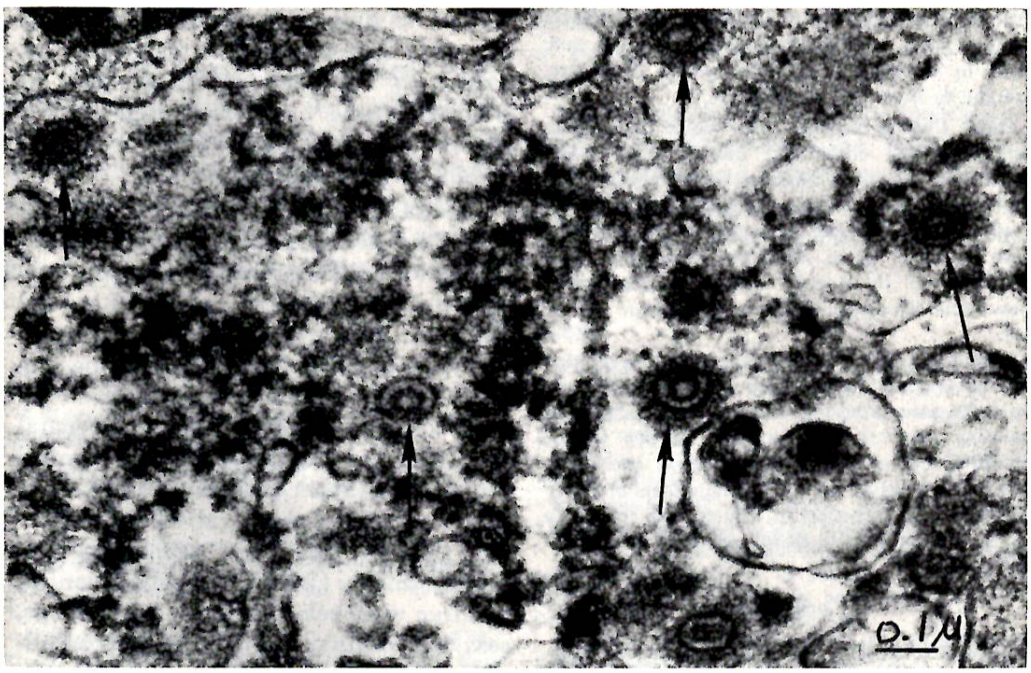


Fig 2.—An enlargement of the area of Fig 1 containing the virus particles (× 78,000).

limits. Serologic tests for syphilis were negative. She had no herpetic lesions .

Postmortem Examination.—*Gross Findings.*—The child's body length was 22 inches and the weight 9 lb, 8 oz (4,309 gm). On external examination a few pale petechial hemorrhagic markings were seen in the skin of the anterior abdominal wall. Several inguinal lymph nodes were palpable bilaterally. The liver was enlarged, weighing 250 gm. It was uniform and pale brown. The spleen weighed 100 gm and had a pale pink cut surface. Many enlarged, discrete, pale, gray-white mesenteric and retroperitoneal lymph nodes were seen. No gastrointestinal bleeding was evident. Both kidneys had a combined weight of 135 gm and the pale gray-white parenchyma showed poor corticomedullary differentiation. Extensive diffuse petechial hemorrhages were present in the epicardium. The heart weighed 50 gm and was pale gray-tan. Extensive subserosal petechial hemorrhages were seen in the lungs. The remainder of the gross study was not remarkable, except for the pale pink marrow seen in ribs and sternum.

Microscopic Examination.—Microscopic study disclosed extensive leukemic infiltration of kidneys, spleen, bone marrow, and lymph nodes. The leukemic cells were large with a fairly uniform distribution of the nuclear chromatin and a scant cytoplasm. Leukemic cell infiltrates were seen in the epicardium, the interstitial portion of the myocardium, the liver sinusoids and portal areas, the alveolar walls of the lungs, and the medulla of the adrenal glands.

Essential anatomic diagnoses included the following: acute lymphoblastic leukemia; leukemic infiltrations of the bone marrow, spleen, liver, kidneys, pancreas, lymph nodes, adrenal glands, heart, and lungs; petechial hemorrhages in the epicardium, visceral pleura and skin; and moderate hepatosplenomegaly.

Electron Microscopic Examination.—Due to the current interest in the viral cause of leukemia, the blood of the child and of both parents was examined using the whole cell negative technique (J. H. Monroe, G. Schidlovsky, and S. Chandra, personal communication) and subsequent electron microscopic examination performed. Identical herpesvirus-type particles were found in the peripheral blood leukocytes of the child and the mother, but no virus particles could be identified in the father's blood. A pellet of leukocytes from the mother's blood was also examined using standard thin-section techniques for electron microscopy, but no such study could be done on the infant's blood due to insufficient material. Figure 1 shows a neutrophil from the mother's blood which contains virus particles (**arrows**). These particles appear to have been phagocytized by the cell. When the virus particles are viewed at a somewhat higher magnification (Fig 2) they are seen to be morphologically identical to those seen by Epstein, et al[6] in

culture cells derived from Burkitt tumors. Such particles have been studied in great detail and found to belong to the herpes group. They are thought to have 162 capsomeres.[6,7]

Tissue Culture Studies.—The white blood cells from both the child and mother have been established as free-floating lymphoblast-type cell lines similar to those described by Epstein et al.[5] These cultures have not been passaged more than 100 times. Electron microscopic examination of these cell lines has consistently shown the presence of herpesvirus-type particles.

Inoculation of virus particles into several tissue culture cell lines which are susceptible to the known members of the herpesvirus groups infecting man (herpes simplex, herpes zoster, human cytomegalic inclusion disease, and varicella) has revealed no cytopathic effects or other indications of infection in any of the cell lines (E. M. Jensen and W. Korol, personal communication).

Comment

The infant first exhibited clinical evidence of the leukemic state eight days after birth, when the mother noted the petechial hemorrhages in the skin. On this basis we considered the leukemia to be neonatal rather than congenital. In our patient the usual clinical manifestations of neonatal leukemia were observed, ie, petechiae, pallor, and hepatosplenomegaly. The absence of jaundice was unusual, as was the moderate cervical and inguinal lymphadenopathy, because the latter is an uncommon finding in the neonatal form.[8] This rarity of enlarged lymph nodes may be related to the infrequency of the lymphatic type which is responsible for only 12% of leukemia in the newborn. Since our patient had lymphatic leukemia, the same explanation would account for the lymphadenopathy found here. The leukocytosis of 1,300,000/cu mm is the highest recorded in leukemia in a newborn. It was of interest that normoblastemia was not seen and only an occasional granulocyte was found in the peripheral smears. The fulminating leukemia involving the lymphatic series almost completely precluded erythropoiesis and granulopoiesis in the bone marrow.

There was no known exposure of the mother to diagnostic x-rays during this gestation. Nor was there a history of exposure to benzene[9] or drugs such as phenylbutazone[10] or chloramphenicol[11] which have been implicated as having a possible leukemogenic role.

There is clinical information which suggests that mothers of leukemic children tended to suffer more viral infections during pregnancy than did a group of control mothers. Stewart,[12] in a retrospective study of children who died during the years 1953-55 of leukemia or cancer before the age of 10, compared their prenatal and postnatal experience with a control group of healthy children. Of 1,416 cases surveyed, 677 of the children had leukemia and 739 had other neoplasms. The same number (1,416) of healthy control children were selected on the basis of age, sex, and locality. Ten mothers whose offspring developed neoplasms suffered severe viral infections during the relevant pregnancy: rubella, 3; mumps, 2; infectious hepatitis, 2; herpes zoster,3. Four of the children in this group had leukemia. Only one mother in the control group had a viral infection (herpes zoster) during gestation. Although the number of cases studied was small, the author thought that mothers with severe prenatal viral infections had an increased liability to produce offspring who developed neoplasms. The mother of our patient did not have a clinically recognizable viral infection during this pregnancy; however, particles belonging to the herpesvirus group were found in her "buffy coat" cells.

While there is no proof that leukemia in man is of viral cause, it is interesting to speculate that the herpesvirus particles seen in our infant may be related to the disease. This premise is conditioned by the lack of knowledge at this time as to whether herpes-type viruses isolated from many patients with leukemia or lymphomas (and from an increasingly large number of "normal" humans) are oncogenic or harmless passengers in the lymphatic cells.

Summary

A case of rapidly progressive acute lymphoblastic leukemia in a neonate is described. The onset occurred with purpura on the eighth day followed by hepatosplenomegaly and pallor. An unusual feature was the moderate cervical and inguinal lymphadenopathy. The leukocytosis of 1,300,000 cells/cu mm is the highest on record in leukemia seen in the newborn.

The demonstration of virus particles of the herpesvirus group in the "buffy coats" of the mother and infant was of interest, but their biologic activity and cancer-producing capability is a matter of speculation.

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