

SPLENIC LEUCEMIA ASSOCIATED WITH PREGNANCY

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LEUCEMIA is defined by Delafield and Prudden¹ as a disease in which the characteristic changes are an alteration in the relative proportions of the different leucocytes of the blood with, usually, an increase in their number, and the appearance of certain forms not seen in the circulation under normal conditions. The red cells are diminished in number and abnormal in form. Accompanying these alterations in the circulating blood are changes in the bone-marrow, spleen and lymph nodes.

Leucemia is usually classified in four types which are determined by fairly well defined clinical and morphological characteristics. These four types are designed as acute and chronic lymphatic leucemia, and acute and chronic myelogenous or splenomedullary leucemia. The latter type we find, in very rare instances, associated with pregnancy; but whether any direct connection exists is still undetermined. Obstetric text books afford us very little satisfaction. Aside from the general statement that the disease occurs and is made worse during pregnancy, no further information is presented. Most authors regard it as a rare complication, and only a comparatively small number of cases have been described.

It is unnecessary in this paper to consider in detail the signs and symptoms of leucemia. The essential point in the diagnosis is the occurrence of a very great increase in the leucocytes, not at all uncommonly up to 200,000, or more. The large number of myelocytes, from 30 to 50 per cent of all the leucocytes present, serves to distinguish the splenomedullary from the lymphatic type of the disease. In the latter the striking feature is the enormous relative increase in the small lymphocytes, often from 90 to 95 per cent, the myelocytes, on the other hand, being very scanty.

The occurrence in the writer's experience within a comparatively short interval of time of two well developed and subsequently fatal cases of leucemia associated with pregnancy, has prompted the brief clinical study of the subject herewith presented. Before proceeding with the recital of cases, a review of the literature may be of interest. No satisfactory references to this subject antedate the year 1888, and since then scattered cases have been reported totalling only about twenty.

J. Whitridge Williams² comments on the rarity of leucemia as a complication of pregnancy and advocates termination of the latter in

serious cases, as good results have been known to follow this course. He refers to the statistics of Hermann and Schroeder.

Edgar³ states that women affected with leucemia seldom become pregnant and in the few recorded cases the infant was sound.

Other standard textbooks either fail to mention the complication or dismiss the subject in a similar fashion. An examination of the journal literature affords us good descriptions of several cases, but leaves no doubt of its rarity.

In an analysis of 60,000 labors occurring in the service of the New York Lying-in Hospital during a period of twenty years, from 1890 to 1910, J. W. Markoe⁴ does not include a single case of leucemia complicating pregnancy and diagnosticated as such.

A single case of Hodgkin's disease or pseudoleucemia occurring in this institution was published by A. B. Davis⁵ in which the characteristic pathologic changes were present. The patient died about three months after delivery and autopsy confirmed the diagnosis. The blood examinations in this case showed the usual picture associated with this disease without any evidence of the characteristic leucocytosis associated with true leucemia.

Another case of interest in this connection is the report of a successful splenectomy by Dr. A. B. Davis⁶ in which the enlarged and wandering spleen found, was probably due to a long standing malarial infection and no characteristic leucocytosis was present.

Of the undoubted cases of true leucemia complicating pregnancy, the first mentioned is that of Greene,⁷ of which the original reference unfortunately has not been accessible. The reports which have been obtainable include the following cases arranged chronologically:

J. C. Cameron.⁸ Patient aged thirty-six; para vii; seen in the seventh month of her pregnancy with a history of having been under treatment for leucemia for the previous year. A tumor had developed in the left hypochondrium during the sixth pregnancy. Children all normal. Patient had been losing flesh for three years, with occasional attacks of icterus. She was delivered spontaneously of a four and one-half pound child, which was apparently well, in good condition, but died on the fourth day. Autopsy on baby negative as to leucemia. Blood counts practically normal; no leucocytosis. Mother's blood showed the characteristic changes.

The point of interest in this case is the hereditary tendency as a possible factor in the disease. The grandmother and mother apparently had symptoms pointing to leucemia. Two of her children developed leucemia and all had attacks of jaundice at intervals. The most marked symptoms, namely edema and dyspnea, rapidly subsided after labor and the disease ran an apparently chronic course. In this case three recurrent pregnancies took place after the splenic enlargement was noted. Disastrous effects on the nursing child were noted; but the case seems to show that a leucemic mother can bear a nonleucemic child.

In a subsequent paper⁹ the author presents a supplementary report on this case. The patient again became pregnant⁸ with exacerbation of symptoms, including edema, dyspnea, loss of weight, and weakness. She went to term and had a rapid delivery, with slight bleeding, which was followed by early relief of symptoms. The child suffered from malnutrition and died during the fifth month. Convalescence of the mother was slow. Menstruation returned, but was painful and the dizziness and dyspnea remained. The patient again became pregnant⁹ and was made much worse; so that labor was induced at the seventh month. The woman almost collapsed during the delivery of a dead and poorly nourished fetus. The recovery was very slow, and the spleen remained large. In this case the leucemia of the mother did not prevent a recurrence of pregnancy or limit its frequency.

W. W. Jaggard:¹⁰ Patient thirty-four years of age, para vi. Regular menstrual history. Family and past history negative. Had five full-term, normal, and one premature, deliveries. Labors quick and easy. A rapidly growing tumor in left hypochondrium began eight weeks after the last labor and was accompanied by rapid loss in weight and marked malaise. Blood showed characteristic picture of the splenomedullary type of leucemia with a ratio of white to red cells as 1 to 2.7; hemoglobin about 50 per cent. Emaciation progressed rapidly, and was accompanied by severe abdominal pains and edema of the extremities. Death supervened eleven months after labor. No autopsy. The writer believes that the disease began during the sixth month of pregnancy at the time when the blood glandular organs are most affected by the influence of gestation.

Stillman (included in a report by Jaggard): Patient para iv, age thirty-four years; apparently went through one pregnancy with a healthy child and recovered, but died one month after the last confinement. A diagnosis of splenomedullary leucemia was made, but no further details of the case are presented.

Hilbert:¹¹ Patient age thirty-seven years; para viii; previously well. During the eighth month of her last pregnancy she suddenly developed severe headaches, general weakness with slight rise of temperature and, several weeks later, an extensive sloughing of the mucous membrane of the gums. Blood examination showed a leucemia. Characteristic petechial spots appeared. Spontaneous labor resulted in the birth of a macerated fetus. Very slight bleeding, followed by collapse and death in ten hours postpartum. Autopsy showed a medullary leucemia with the spleen and lymph glands slightly enlarged. Cultures sterile. The author distinguished in this case a prodromal stage, lasting five weeks, followed by the true leucemic period which ended fatally. He thinks the gingivitis quite diagnostic.

C. E. Laubenburg:¹² Patient thirty-two years of age; very anemic; history of three previous miscarriages. Family history good. Menstrual history normal. Six living healthy children. A gradual decline in health during the previous six or seven years was noted, marked by weakness, malaise, cardiac distress, dyspnea, and edema of the extremities. This condition was usually worse during her pregnancies, but improved after labor. The three miscarriages were not accompanied by severe hemorrhages. A gradually increasing mass had been observed in the left side of the abdomen which, on admission to the hospital during her tenth pregnancy, extended downward to the fundus of the five months' uterus. Blood examination showed characteristic leucemia. A spontaneous labor occurred with the birth of a macerated five months' fetus. The patient went into coma during labor with marked dyspnea and rapidly progressing pulmonary edema, followed by death forty

hours after delivery. The diagnosis was confirmed by autopsy; the splenomedullary type of the disease being present. Extensive bacterial cultures were negative.

This case with those of Sanger, Cameron and Green are the only ones reported in which pregnancy occurred repeatedly in a woman already sick with leucemia.

H. Schroder:¹³ Patient twenty-five years of age; always sickly. Had five labors and two miscarriages in a period of seven years. Labor spontaneous; one living child; others died at varying intervals from intercurrent diseases. No suspicion of blood disorder, although the patient noticed a splenic enlargement after her fifth labor. During the sixth pregnancy her previously noted symptoms of dyspnea, malaise, weakness, loss of weight, etc., grew worse and, when admitted to the hospital in the sixth month, blood examination showed the characteristic picture of splenic leucemia. Labor induced with delivery of a recently dead six months' fetus. No marked improvement followed. Autopsy on the child negative.

In this case the patient probably went through a full term pregnancy during the period in which her leucemia was already developed and after the second pregnancy, notwithstanding the induction of labor, no marked improvement resulted.

Hermann,¹⁴ reported a case of leucemia at a meeting of the London Obstetrical Society and included in the paper were references to twelve cases published elsewhere. He found only eight cases sufficiently described from which to draw conclusions to the mutual influences of pregnancy and leucemia. Dr. Hermann concluded that the termination of pregnancy was indicated whenever the diagnosis of leucemia was made.

Melinkow and Zomakion¹⁵ report 15 cases from the literature, including one personal case. This patient presented a leucocyte count of 220,000 and had been under treatment for a long time with the x-rays. Labor normal with slight atonic hemorrhage. During pregnancy the hemoglobin content sank from 65 to 45 per cent, red cells from 4,000,000 to 280,000. During the puerperium the hemoglobin sank to 21 per cent, red cells to 180,000. Microscopic examination of the placenta showed that the vessels of the fetal villi contained normal blood; that in the intervillous spaces were leucemic to a high degree, showing a complete anatomic separation between the two bloods. (Original not accessible, no details.)

Thaler:¹⁶ Patient forty years of age; para ix; near term; developed an acute febrile angina followed by epistaxis and anemia. Labor with a dead fetus which, at autopsy, was found to have a hydrothorax, numerous ecchymoses, renal congestion, etc., but no evidence of leucemia. The mother's blood count at the time of labor showed 2,055,000 red cells, color index 0.87, 175,000 leucocytes. The author considers the disease in his case to have been due to the influence of an unknown toxin on predisposed abnormal blood-forming organs.

Peterson¹⁷ reports the following well studied case which was fatal a few hours after labor. A primipara, age 24, gave a history of marked anemia extending over a period of seven years. She was admitted to the Breslau Maternity as the first case of leucemia in about 20,000 labor cases. At the time she was about seven and one-half months' pregnant, extremely anemic and with enlargement of both liver and spleen. The blood examinations seemed to contradict the diagnosis of leucemia based on other symptoms. The red cells, 1,800,000; no increase in the white cells noted; hemoglobin 25 per cent. Picture resembled that of a severe secondary anemia. A rapid spontaneous labor took place and a healthy vigorous child with normal placenta was delivered, the process lasting about eight hours. An hour and a half

later the woman went into sudden collapse without any response to treatment. Autopsy showed a marked anemia of all the internal organs with no lymph-node enlargement. Sections of liver, spleen and bone-marrow showed undoubted myelogenous leucemia in which the suddenly developing acute exacerbation during pregnancy in a predisposed person did not permit of sufficient time for the invasion of the circulation by the characteristic new cell forms.

PERSONAL CASES

CASE 1.—Mrs. A. L.; Italian; para iii; two children alive and well. Admitted to the Lying-in Hospital February 3, 1920, with a history of having last menstruated three months previously. Her physician had been taking care of her for the past month for a dyspnea which began about three months previously and was getting progressively worse. An edema of the legs had been coming on gradually, which was always worse in the evening. The patient complained of constipation. Examination on admission showed a well-nourished middle-aged woman, acutely ill, presenting a condition of moderate dyspnea, edema of the lower extremities, with no cyanosis, jaundice or rash. A marked odor of acetone in the breath was noticed. The tongue was coated; lips dry; lungs negative; heart slightly enlarged with the apex beat in the sixth interspace. Pulse 120. A faint systolic murmur at the apex was transmitted to the back. The abdomen was markedly distended so that no masses or areas of tenderness could be determined. No vaginal examination was made. During the night, after admission, the patient seemed in fair condition and apparently rational. Her general condition became worse towards morning. The pulse increased to 180, was of poor quality, and an examination of the chest at this time seemed to show a beginning pulmonary edema. No response to stimulating treatment noted. The patient began to vomit without apparent cause and then rapidly grew worse, dying at 10 A.M. February 4th, without regaining consciousness. The blood count showed a marked anemia and in addition a very high leucocyte count, 472,000; red cells, 1,090,000; hemoglobin 20 per cent; color index 0.2; polynuclears 5 per cent; small lymphocytes 88 per cent; large lymphocytes 9 per cent. Diagnosis of acute lymphatic leucemia was made. Urine examination negative. Abortion was indicated in this case and was to have been done the morning after admission, but the rapid progress of the symptoms terminated in a fatal issue before the uterus could be emptied. No clue was at hand of the patient's previous condition which, from the statement of her doctor, seemed to be quite normal. Her general appearance and good nutrition did not point to the presence of the disease for any considerable length of time.

The single blood count shows such a preponderance in the proportion of small lymphocytes, about 88 per cent with a total white cell count of 472,000, that one is inclined to regard this case as one of lymphatic leucemia, in contrast to the more commonly reported splenomedullary form. Unfortunately the rapidly progressing illness and failure to obtain an autopsy prevented a satisfactory diagnosis. No enlarged lymphatic glands were noted and the abdominal distention interfered with palpation of the spleen. It is possible that we had here an instance of the so-called mixed leucemia.

Comment.—This case demonstrates a rapidly progressing illness apparently coincident with the development of the pregnancy.

CASE 2.—Mrs. Lily D.; para iv; age thirty-five; Russian; admitted to the Lying-in Hospital, March 31, 1920. Patient gave a history of three normal deliveries, the last three and one-half years ago. The family history was negative in so far as could be ascertained. The patient had always been in good health; no definite history

of previous illness until after the birth of the last child. Since then she noticed a shortness of breath on slight exertion and was told she had heart trouble. Menstrual history apparently normal. Her last period began October 29, 1919. She stated that she felt sick soon after her pregnancy began, presenting a series of indefinite complaints, the most marked being dyspnea and weakness. She was referred to the hospital with a diagnosis of endocarditis, and the suggestion that the uterus be emptied.

Physical examination on admission showed a moderately well nourished woman with subcutaneous fat slightly developed; complexion rather pale and sallow; marked dyspnea present.

The heart showed a systolic murmur at the fourth interspace, transmitted to the left. An increased fremitus was noted over the apex of the right lung with harsh breathing over the left lung and signs of fluid at the base of the right lung. There was no edema or varicosities of the extremities. The abdomen was soft, thin-walled, and presented an area of moderate tenderness and swelling over the left hypochondrium extending downward. The globular, movable uterus reached about half way to the umbilicus. The blood examination, after admission, showed a marked anemia with greatly increased leucocyte count. A diagnosis of acute leucemia being made, probably of the splenomedullary type. The urine showed traces of albumen and a few granular casts. The patient's general condition seemed to grow rapidly worse after admission to the hospital. The dyspnea was marked, even when sitting up; the pulse was rather weak and irregular. The abdomen became considerably distended and slight elevations of temperature were present. Induction of abortion was done on April 4th, with a medium size Voorhees' bag, and a small living fetus of about five months' size delivered within a few hours. After labor the patient's condition grew worse. She was troubled with a continuous cough and expectorated abundant thick white mucus. The abdominal distention continued and did not respond satisfactorily to the usual treatment with irrigations, enemas, etc. Stimulation with digitalis and strychnia failed. The patient grew steadily weaker, was unable to take nourishment, became more cyanotic and, finally, sank into a condition of coma in which she died, April 18, about two weeks after delivery. Another blood count made April 7 showed a further diminution in the red cells and coloring matter with an increase in the leucocytes. The details of the blood and urine examinations follow:

April 2. Erythrocytes 3,350,000; hemoglobin 65 per cent; color index 0.9; leucocytes 106,000; polynuclears 8 per cent; small lymphocytes 11 per cent; large lymphocytes 81 per cent.

April 7. Erythrocytes 2,820,000; hemoglobin 55 per cent; leucocytes 120,000; color index 0.9; polynuclear 5 per cent; small lymphocytes 10 per cent; large lymphocytes 85 per cent.

Urine Examination.—Specific gravity 1.020-1.030; small amount of pus; trace of albumin; few granular casts; abundant urates.

Comment.—In addition to the blood condition, this patient presented undoubted evidences of cardiac and pulmonary disease; but the leucemia may be regarded as the terminal condition. The rapid progress of the illness during the pregnancy seems to point to a decided influence of this process on the blood dyscrasia. Nothing in the family or personal history, in so far as this could be obtained, was of note. Her other children were perfectly well. The premature fetus was alive at the time of delivery and normal. Wassermann was negative. No autopsy permitted.

SUMMARY

A survey of the reported cases of leucemia complicating pregnancy in which a fairly definite diagnosis from the blood picture was made discloses a total of 12 cases, including two of the writer. The ages of the patients varied from twenty-four to forty; the majority being between thirty-two and thirty-six. With the exception of Peterson's case, all were multiparæ. A possible hereditary history is mentioned in only one case. The parity varied from three to nine. In most of the cases we get a history of living children that showed no tendency to the disease up to the time of the report but, in a few instances, we are told that the babies died at varying periods from a few days to five months, after labor. In four cases mention is made of the birth of macerated or stillborn fetuses. Among twelve cases the mother survived in but two, but how long these mothers lived is not stated, neither is the subsequent course of the disease given. In the majority of cases we find that the woman survived but a short time after labor. One of the writer's patients died before delivery took place. In Peterson's case death came on an hour after labor; in Hilbert's case death took place in ten hours, and in Laubenburg's case death occurred forty hours after labor. There is a record of death in Stillman's case one month after delivery; my second case died in two weeks, and Jaggard's case died eleven months after delivery. In every instance but one (my own case) in which the definite diagnosis is presented, the splenomedullary type of the disease was observed. It will be noted that in many cases the authors mention a prodromal period in which progressive emaciation, anemia, and loss of strength were noted soon after pregnancy, from which no recovery resulted and during which period the woman again became pregnant. The leucemia itself does not therefore appear to be a deterrent factor to conception.

Although the presence of a true leucemia as a complication of pregnancy is from all available records a very rare condition, nevertheless we ought to be on our guard against it. Probably a considerable number of cases of marked anemia in which no satisfactory blood count has been made may have been true instances of this disease. In any case where an anemic patient fails to recover under proper treatment, a more minute and detailed examination of her blood should be made with reference to the possible diagnosis of leucemia. The occurrence of pregnancy in this disease indicates a most unfavorable outlook for the mother and conception must, therefore, not be allowed to take place where the condition is suspected. The prognosis is undoubtedly worse in the pregnant than in the nonpregnant state; and whether the association is accidental or not, is immaterial. Where the disease is already present abortion seems to be indicated, with a rapidly progressing course and a fatal issue. The presence of an enlarged spleen is an almost constant factor in the disease and should lead one to look

for this sign in every anemic patient. The value of the x-ray in leucemia has been brought forward; but, in the event of a pregnancy, its application as a cure for the disease may work an undoubted harm on the fetus and the induction of labor should be done before radiation is begun.

It is necessary to distinguish between the acute and chronic forms of leucemia. Pregnant women may contract a rapidly fatal leucemia if we are to believe the evidence of the cases thus far reported, although it seems possible that the disease was present in a milder form in many of these patients before their last and usually fatal pregnancy occurred. It will be noted that there are apparently cases of chronic leucemia in this series in which pregnancy and labor occurred, and for this reason conservative treatment has been advised under such circumstances. In view of the rapidly fatal ending during the puerperium it would appear that this advice is not justifiable and that in order to avoid such an outcome labor had better be induced in all cases.

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Owing to war interruptions, much of the recent Continental literature was not available for reference.

DISCUSSION

DR. WILLIAM M. BROWN, ROCHESTER, NEW YORK.—In all of the cases reported by Dr. Kosmak I take it that the life of the child was of very little value, on account of its prematurity. Why delay radiation, because apparently delivery hastened the end or exaggerated the condition? Why not disregard the child *in utero* and get the benefit of the radiation if there is benefit, and take care of the contents of the uterus afterward if you can improve the patient before you empty the uterus?

DR. JAMES E. DAVIS, DETROIT, MICHIGAN.—It would seem that if one viewed this disease, according to the fundamentals that underlie malignancy, the condition ought to be improved under pregnant conditions, excepting that there is a greater call upon the blood elements. A parallel between a leucemia and any malignancy of tissue is very close, and many pathologists place the leucemias in the class of malignant disease. You have cells that have deviated from

the normal proportions, to each other, cells that have become anaplastic; that are perverted from their normal condition, and there is the same general physiologic effect upon the body as we find in the fixed tissue malignancies. I cannot see why there is any advantage in bringing on a delivery or an abortion. I have no doubt that all of these cases begin before the pregnancy and because during the pregnancy there was a cause for a larger amount of blood, and this being a disease involving fundamentally the hematopoietic organs, the call involved exhaustion of these organs before pregnancy could be completed. As I have said, I cannot possibly see any therapeutic value in terminating the pregnancy.

DR. KOSMAK (closing the discussion).—Answering Dr. Brown, I want to say I have had no personal experience with x-rays in cases of this kind, and as to the time of application, I can only reply that few of these women went to term, or they were not brought under observation until they were almost at term. For lack of time details of previously reported cases were not stated, but they are too insufficient in number to formulate any distinct directions as to the course to be pursued. In both of my cases the condition of the patient was so serious that the induction of abortion did contribute to the well-being of these particular women. There is one case reported of three successive pregnancies where the diagnosis was undoubted, and one pregnancy went to the sixth, another to the seventh, and a third one to the eighth month, but there was only one live child out of the three.

In view of the extreme emaciation and distress that most of these patients develop, I cannot see why we should not give them a chance if we can bring about relief by the induction of abortion or premature labor.

You will note in the summary that many of these women gave birth to macerated fetuses. In view of that fact, we can reduce the element of danger by emptying the uterus. There was no difficulty in doing this in one patient I referred to. In this case we put in a bag and in a few hours she was delivered.

I was much interested in Dr. Davis' remarks about the supposed malignant tendency in these cases of leucemia. That has been mentioned several times and undoubtedly there is a good deal of truth in it. In view of that fact, if we assume this is a malignant disease, we ought to pursue the same course we pursue in any other kind of malignancy during pregnancy, namely, empty the uterus. It seems to me, that is the consensus of opinion. What we do in the presence of malignancy in other parts of the body, we should do in that of the blood-forming organs.

I desire above all to call attention to the necessity of thoroughly examining all cases of marked anemia associated with pregnancy. We ought to make a careful white cell count and look for any tendency to leucemia, for many writers have noted a prodromal period marked by progressive emaciation, by dyspnea, etc., in addition to the changed blood.