Mediterranean Anemia in a Negro Complicated by Pernicious Anemia of Pregnancy

Report of a Case

By Melvin A. Goldberg, M.D. and Steven O. Schwartz, M.D.

The development of megaloblastic anemia in patients with Mediterranean anemia is apparently rare. Crosby and Sacks have described the only recorded case of this type. It occurred in a young Sicilian with Mediterranean anemia who developed Addisonian pernicious anemia. The present report is that of a Negro woman with Mediterranean anemia who developed megaloblastic anemia during each of three pregnancies. In addition to this unusual coincidence, three other features of the case are worthy of comment: (1) the occurrence of Mediterranean anemia in a Negro; (2) the development of megaloblastic anemia during administration of liver extract; (3) the changes in the morphology of the red cells when erythropoiesis became megaloblastic.

Report of Case

B. D., a Negro woman, aged 19, was first admitted to the Cook County Hospital on August 9, 1949. She was in the seventh month of her first pregnancy. She was apparently in good health until about one month before admission when there set in progressive weakness, exertional dyspnea, fatigue, and ankle edema. Five days before admission the patient experienced vague abdominal pain in the right lower quadrant which persisted for three days. She vomited once, about a week before admission.

The only illness the patient could recall occurred at the age of 9 and was characterized by fever and fatigue of one month’s duration, for which the patient had been given blood transfusions.

Physical Examination

Examination revealed pallor but no jaundice. An accentuated second pulmonic tone was audible; a systolic murmur was heard at the pulmonic area. The liver was palpated 4 cm. below the right costal margin and the spleen was 5 cm. below the left costal margin. The uterus was 3 cm. above the umbilicus. There was bilateral pretibial edema.

Laboratory Results

The laboratory data were as follows: hemoglobin 3.2 Gm. (21 per cent); red blood cells 2.03; white blood cells 8600; reticulocytes 0.8 per cent; color index 0.5. The blood film revealed 2 plus anisocytosis, 3 plus poikilocytosis, and 3 plus hypochromia. The sickle cell preparation was negative; nonprotein nitrogen 40 mg. per cent; albumin-globulin ratio

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The term Mediterranean anemia is used in this paper to encompass the entire group of diseases characterized by microcytosis, hypochromia, ovalocytosis, anisocytosis and poikilocytosis, and, most prominently, targeting, together with certain familial hereditary patterns and clinical features. It is recognized that this group covers the spectrum from the most benign to the most severe forms clinically, and the range from hypochromatic polycythemia to the severe Cooley's anemia hematologically.
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3.6/2.2 Gm. per cent; cephalin flocculation negative; icterus index 7; blood culture negative. Urinalysis revealed 1 plus albumin and 3 plus urobilinogen. The electrocardiogram was within normal limits. The stool benzidine reaction was negative. Examination of the marrow showed increased cellularity; nucleated RBC:WBC ratio of approximately 2:1; megaloblastic erythropoiesis with a left shift; and a few giant band forms. On gastric analysis free acid was present after histamine administration.

**Hospital Course**

Thirty units of purified liver extract were given twice weekly. Three 500 cc. blood transfusions were given, and ferrous sulfate, 5 gr., was prescribed three times daily. Twelve days after liver therapy, reticulocytes were 17.4 per cent, hemoglobin 6.2 Gm. (40 per cent), and red blood cells 3.26. The patient was discharged from the hospital on August 17, 1949 and followed while under treatment in the out-patient clinic. Thirty units of purified liver extract were given once weekly and 15 gr. of ferrous sulfate were taken by mouth daily. Hemoglobin varied between 6.2 Gm. and 7.3 Gm. (40 and 47 per cent) and red blood cell counts were between 3.91 and 4.39.

The patient returned to the hospital on October 15, 1949 in active labor. Two 500 cc. blood transfusions were given before delivery of a normal infant. She was again followed in the out-patient clinic and both liver and iron therapy were continued. Two weeks after delivery the hemoglobin had risen to 9.5 Gm. (61 per cent) and red cells to 5.72; eight months later the hemoglobin was 10.7 Gm. (69 per cent) and the red blood cells 6.88.

In August of 1950 the patient reported that she was again pregnant, in the fifth month. It was noted that the hemoglobin had fallen to 6.8 Gm. (44 per cent) and the red cell count to 5.17, despite the administration of liver (30 units) at least once monthly, and continuous iron therapy. In the eighth month of this second pregnancy, the hemoglobin had fallen to 5.3 Gm. (34 per cent) and the red blood cells to 3.63. Hospitalization was ordered for further study. During a ten day period, 3300 mg. of iron were given intravenously and liver therapy was continued; notwithstanding there was no significant change in the hemoglobin or red cell count: the hemoglobin was 6.0 Gm. (39 per cent) and the red count 3.67. A repeated gastric analysis again revealed the presence of free acid; sickling preparation was again negative; marrow examination again showed increased cellularity, with a nucleated RBC:WBC ratio of 1:1; erythropoiesis was megaloblastic with a left shift; granulopoiesis was normal. Liver and iron therapy were discontinued. Folic acid (15 mg. daily) was instead prescribed. After ten days of folic acid therapy the hemoglobin had fallen to 5.1 Gm. (33 per cent) but the red blood cell count rose slightly to 3.98. Folic acid was discontinued and vitamin B₁₂ (45 μg.) was given parenterally twice weekly. On the ninth day of vitamin B₁₂ therapy the hemoglobin had risen to 7.6 Gm. (49 per cent) and the red cell count to 5.07, and on the eighteenth day of this therapy the hemoglobin was 9.8 Gm. (63 per cent) and the red blood cell count 5.83. Unfortunately, reticulocyte counts were not made. Because persistent hypochromia did not respond to iron therapy and because chronic blood loss was not suggested, the patient’s family was examined. The results of these examinations are summarized in table 1.

Based on the findings in the family, and the patient’s persistent hypochromia, a diagnosis of Mediterranean anemia was made.

On discharge, vitamin B₁₂ therapy was prescribed. The patient returned to the hospital on January 7, 1951 in active labor and delivered a second normal full term infant. This child (G. D.) was examined at 1 year and was likewise found to have a hypochromic polycythemia (see table 1).

After delivery the patient was again followed in the out-patient clinic but received no specific therapy; fourteen months after delivery she felt well and examination of the blood revealed the following: Hemoglobin 10.4 Gm., (67 per cent); red blood cells 6.93; blood film: 2 plus anisocytosis, 2 plus poikilocytosis, 2 plus hypochromia, and 1 plus microcytosis. She returned to the clinic once more, feeling well and with similar blood findings.

The patient was next seen on January 11, 1953 when she was readmitted to the hospital in the ninth month of her third pregnancy. She had felt well until about one week before this admission when a severe nosebleed required packing for control. Epistaxis was accom-
MEDITERRANEAN ANEMIA COMPLICATED BY PERNICIOUS ANEMIA

Table 1.—Blood Film Studies

<table>
<thead>
<tr>
<th>Relative</th>
<th>Present Age</th>
<th>Hemoglobin</th>
<th>RBC</th>
<th>Hypochromia</th>
<th>Poikilocytosis</th>
<th>Anisocytosis</th>
<th>Targeting</th>
<th>Sickness</th>
<th>Spleen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Father (C. W. 49)</td>
<td>12.5 Gm. (90%)</td>
<td>5.46</td>
<td>2 plus</td>
<td>1 plus</td>
<td>Negative</td>
<td>Not palpable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother (M. W. 45)</td>
<td>7.9 Gm. (51%)</td>
<td>4.36</td>
<td>2 plus</td>
<td>3 plus</td>
<td>Negative</td>
<td>Not palpable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal grandmother (M. C.)</td>
<td>12.5 Gm. (90%)</td>
<td>4.55</td>
<td>1 plus</td>
<td>1 plus</td>
<td>Negative</td>
<td>Not palpable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sister (J. W. 26)</td>
<td>11.4 Gm. (73%)</td>
<td>5.05</td>
<td>2 plus</td>
<td>1 plus</td>
<td>Negative</td>
<td>2 cm. below</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sister (D. W. 19)</td>
<td>9.2 Gm. (59%)</td>
<td>5.45</td>
<td>2 plus</td>
<td>2 plus</td>
<td>Negative</td>
<td>Not palpable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brother (C. W. 24)</td>
<td>14.8 Gm. (95%)</td>
<td>5.66</td>
<td>2 plus</td>
<td>2 plus</td>
<td>Negative</td>
<td>Not palpable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daughter (R. D.) 4 mo.</td>
<td>10.7 Gm. (69%)</td>
<td>5.08</td>
<td>1 plus</td>
<td>1 plus</td>
<td>Negative</td>
<td>Not palpable</td>
<td></td>
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</table>

Pallor was again asymptomatic. The tongue was well coated and papillated, but the edges were red; there were small white elevated patches both on the tongue and on the mucous membrane of the pharynx. The liver and spleen were palpable as on previous occasions. The uterus was 4 cm. above the umbilicus.

Laboratory Studies

Examination of the blood showed hemoglobin 6.2 Gm. (40 per cent); red blood cells 2.18; color index 0.9; white blood cells 3150; platelets 54,140; and reticulocytes 0.8 per cent. Film of the blood revealed 1 plus hypochromia. Gastric analysis demonstrated the presence of free acid after histamine. The marrow was hypercellular. Nucleated RBC:WBC ratio was approximately 2:1. Erythropoiesis was megaloblastic with a left shift and granulopoiesis showed many giant metamyelocytes and band forms.

Treatment

The patient received one 500 cc. blood transfusion after admission. Folic acid (10 mg. daily) was given orally and on the eighth day of this therapy there was a maximum reticulo-erythrocyte response of 22.5 per cent, the hemoglobin was 6.7 Gm. (43 per cent), and red blood cell count 3.59. The color index was 0.6. A film of the blood then revealed 3 plus hypochromia. The platelets had returned to normal levels. Eleven days after admission a normal full term infant was delivered. This infant (D. D.) was examined at 4 months and was also found to have Mediterranean anemia (see table 1).

The patient has been followed in the out-patient clinic and without having received any subsequent specific therapy feels well. The blood count has risen to prepregnancy levels. The marrow continues moderately hypercellular; megakaryocytes are adequate in number and appearance; nucleated RBC:WBC ratio 3:1; normoblastic erythropoiesis; and intact granulopoiesis. On last examination the marrow revealed accelerated but normoblastic erythropoiesis, and the electrophoretic pattern of the hemoglobin was normal.

Discussion

In the case presented the patient developed megaloblastic anemia without achlorhydria or neurologic changes in each of three pregnancies. After each delivery anemia improved dramatically; after the last two pregnancies, improve-
ment occurred without specific treatment. These observations are entirely consistent with the diagnosis of pernicious anemia of pregnancy.

In the first two pregnancies observations of the peripheral blood were consistent with those of hypochromic anemia notwithstanding the presence of megaloblastic erythropoiesis. Hypochromia was intensified after delivery even though the total red cell count rose to polycythemic levels. There was persistent splenomegaly but no evidence of chronic blood loss and no response to either oral or intravenous iron therapy. Similar conditions of the blood were demonstrated in seven members of the patient's immediate family. The electrophoretic pattern of the patient's hemoglobin was normal. This clinical picture is considered typical of Mediterranean anemia. That this disease is familial and hereditary has been well established; the fact that this patient is a Negro does not rule out the diagnosis. The theory of a strict racial latency is no longer valid inasmuch as the disease has been described previously in Negroes as well as in other non-Mediterranean races.

Mediterranean anemia is an uncommon disease; megaloblastic anemia of pregnancy is rare. Davidson reported that of five hundred and thirty-one cases of macrocytic anemia seen in seven years, only thirty-one were associated with pregnancy. In our own material megaloblastic anemia of pregnancy is most unusual. It is interesting to speculate whether the coexistence of these two unusual hematologic diseases is more than mere coincidence. Little evidence for a relationship between the two conditions is found in the literature. There have been no previous reports of megaloblastic anemia of pregnancy complicating Mediterranean anemia and there has been only one report of the coexistence of Addisonian pernicious anemia and Mediterranean disease. Only three instances of family history of anemia have been reported regarding megaloblastic anemia of pregnancy. In each of these a member of the patient's family was said to have had either Addisonian pernicious anemia or megaloblastic anemia of pregnancy. A possible relationship between the two conditions is suggested, however, by one feature in the course of this patient's history: the development of megaloblastic anemia in each of three pregnancies despite an adequate diet. This is unusual. Thompson and Ungley followed sixteen patients with megaloblastic anemia of pregnancy through subsequent pregnancies and observed only one recurrence. There have been several isolated case reports of recurrences and although Callender in her review of twenty-five cases warned of this danger, she reported only two such instances; thus, it appears that recurrences are the exception rather than the rule. It may be that megaloblastic anemia occurred during each pregnancy in this patient because the underlying Mediterranean anemia predisposed to this complication. With the erythroid hyperplasia of Mediterranean anemia there is probably an increased demand for the factors necessary for red cell maturation. The added burden of pregnancy may further increase this demand to the extent where it can no longer be met by a diet considered adequate under ordinary circumstances, with resulting megaloblastic anemia.

The effects of megaloblastic erythropoiesis on red cell morphology are of particular interest in this case. In each pregnancy, when erythropoiesis was megaloblastic, anemia was worsened. In the third pregnancy the reduction in red
cells was out of proportion to the reduction in hemoglobin. As a result, the previously low color index tended to rise and the degree of red cell hypochromia was decreased. In this pregnancy before treatment, the hemoglobin was 6.2 Gm. (40 per cent) and the red cell count 2.18; the color index was 0.9 and the red cells showed only slight hypochromia. After eight days of folic acid therapy, the red cell count rose to 3.59 and the hemoglobin to 6.7 Gm. (43 per cent); the color index was then 0.6 and the pre-existing severe hypochromia again became evident. Similar observations were made by Crosby and Sacks1 in their report of Addisonian pernicious anemia complicating Mediterranean anemia in which observations of the peripheral blood were compatible with anemia before treatment; after treatment, the hypochromic polycythemia of Mediterranean anemia dominated. These findings are not inconsistent with the current concepts of the hemopoietic defect of Mediterranean anemia. Although the target cell was once considered to be the fundamental defect in Mediterranean anemia,15 it is now believed that the target cell is merely the morphologic representation of a cell in which there is a disproportionate reduction in its contents relative to its surface area.16, 17 The primary defect in Mediterranean anemia is apparently an inability to utilize more than a limited quantity of the iron available for hemoglobin synthesis.2, 18, 19 Red cell production is uninhibited as evidenced by the ability to respond to hemorrhage20 and hemolysis21 as well as by the frequent presence of polycythemia. This combination of diminished hemoglobin synthesis with uninhibited red cell production results in the characteristic peripheral blood picture of hypochromia and low color index. Contrariwise the characteristic peripheral blood findings of megaloblastic anemia are an increase in red cell size and hemoglobin content, and a high color index. Thus when megaloblastic erythropoiesis complicates Mediterranean anemia, as observed in the case presented as well as in Crosby's case, the anemia becomes more severe but the red cells need no longer show the characteristic hypochromia of Mediterranean anemia.

Another unusual feature in this case was the development of megaloblastic erythropoiesis while under liver therapy. After the first pregnancy, purified liver extract (30 units) was given parenterally at least once monthly; nevertheless, megaloblastic anemia occurred in the last trimester of the second pregnancy. This has not been reported in human cases before, although it has been observed in animals in which vitamin B12 and liver extract failed to protect against the development of megaloblastic anemia when diets deficient in vitamin C and folic acid were given.22, 23 The fact that purified liver extract did not protect against this type of megaloblastic anemia is not wholly unexpected. Minimal or complete lack of response to liver or vitamin B12 therapy in pernicious anemia of pregnancy has been reported,11, 12, 24-26 whereas response to folic acid has usually been good.13 Cases have been reported in which folic acid therapy was successful after liver, vitamin B12, and B158, therapy failed.10, 28-30 During the second pregnancy, in the case presented here, there was an apparent lack of response to folic acid with a subsequent good response to vitamin B15 therapy. This observation may not be valid because reticulocyte responses were not obtained and because folic acid therapy was probably discontinued too soon. It is our belief that the ultimate improvement was a result of folic acid therapy and was probably unrelated to vitamin B12. The response to folic acid in the third pregnancy was excellent. The
failure of liver to protect against the development of pernicious anemia of pregnancy in this case further emphasizes the difference between this type of megaloblastic anemia and that of Addisonian pernicious anemia.

**Summary**

1. A case is presented of a Negro woman with Mediterranean anemia who developed megaloblastic anemia of pregnancy in each of three pregnancies.
2. The possibility that Mediterranean anemia predisposes to the development of pernicious anemia of pregnancy is discussed.
3. With megaloblastic erythropoiesis, anemia became more severe, but the characteristic red cell hypochromia of Mediterranean disease was masked.
4. Purified liver extract failed to protect against the development of megaloblastic anemia of pregnancy but folic acid produced a satisfactory therapeutic response.

**SUMMARIO IN INTERLINGUA**

1. Es presentate le caso de un negressa con anemia mediterranee qui disveloppava anemia megaloblastic de pregnantia in cata un de tres pregnantias.
2. Es discutite le possibilitate que anemia mediterranee predispone le patiente a disveloppar anemia perniciose de pregnantia.
3. Con erythropoiese megaloblastic, le anemia deveniva plus sever, sed le hypochromia del erythrocytas que es characteristic del morbo mediterranee esseva obscurece.
4. Extracto purificate de hepate non protegeva le patiente contra le disveloppamento de anemia megaloblastic de pregnantia, sed acido folico evocava un satisfacente responsa therapeutic.

**REFERENCES**

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