DIAGNOSIS AND TREATMENT OF MACROCYTOSIS

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MACROCYTOSIS is present in any condition in which there is an outpouring of immature red blood cells or in which there may be faulty absorption, utilization, or storage of the erythrocyte-maturing factor (E.M.F.). It may be suspected on routine examination of the stained blood smear, but an accurate diagnosis must await the actual measurement of the mean cell diameter by means of an erythrocytometer or the calculation of the volume index. The volume index is determined by dividing the per cent normal red blood count into the per cent normal hematocrit reading. A volume index of 1.08 or above indicates macrocytosis.

With any sudden demand upon the hematopoietic system precipitated by an acute loss of blood, the bone marrow endeavors to compensate by releasing immature red blood cells, or reticulocytes, which are larger than mature erythrocytes. This results in reticulocytosis, which may at times reach levels as high as 45 or 50 per cent.

An example of this condition was found in a 24-year-old girl with portal hypertension. During the preceding ten years she had had repeated episodes of hematemesis, for which 81 transfusions had been given. Two years after the onset of bleeding a splenectomy had been performed at another institution, and this was followed by multiple injections of esophageal varices. During the course of several hospitalizations a devascularization of the stomach and several esophagoscopies were carried out in an effort to control bleeding points. She had recently been hospitalized for a recurrence of severe hematemesis, at which time her blood count had reached 2,970,000 red cells, hemoglobin 49 per cent, volume index 1.28, color index 0.83, and a reticulocyte count of 20.5 per cent. Examination of the bone marrow at this time revealed an extremely erythroblastic marrow.

In this case, in an effort to compensate for repeated and massive blood loss, the bone marrow had released many cells which were not completely matured, producing reticulocytosis and resulting in macrocytosis. When the blood picture returned to normal following repeated transfusions and cessation of bleeding, the macrocytosis disappeared.

The most common cause of an increase in volume index with an apparent macrocytosis is pernicious anemia, in which the large cells are due to the absence of the erythrocyte-maturing factor. The bone marrow demonstrates an almost complete megaloblastic arrest, with a resultant inadequacy of proper maturation. The erythrocyte-maturing factor depends upon the interaction of the intrinsic factor of Castle, secreted by the gastric glands, and the extrinsic factor, supplied by the diet. Absence of this factor arrests maturation

of the red blood cells and causes the subsequent outpouring of relatively immature cells. As soon as the intrinsic factor is supplied by substitution of parenteral liver extract, maturation of the megaloblast proceeds normally.

One such patient, a 49-year-old housewife, sought medical advice because of "weakness and acid condition" of ten months' duration. When she was seen first her tongue was red and atrophic, but no icterus, splenomegaly, or alteration in sensation was apparent. No free hydrochloric acid was present in the stomach. Blood count was 1,350,000 red blood cells, hemoglobin 35 per cent, 3850 white blood cells, with 72 per cent neutrophils. The volume index was 1.44 and the color index 1.29. The patient responded satisfactorily to parenteral liver therapy, and in a period of several months her blood had returned entirely to normal.

If there is inadequate absorption of the erythrocyte-maturing factor, similar difficulties may be experienced. In sprue, because of the associated diarrhea, proper absorption is lacking, so that once again the erythrocyte-maturing factor is not present in adequate amounts for complete maturation of the red blood cell. An example was a 39-year-old housewife who, for two and a half years preceding admission at the Cleveland Clinic, had experienced varying degrees of diarrhea, at times reaching 15 to 20 stools daily. The stools would invariably be frothy, yellow, bulky, greasy, and foul-smelling. Complete gastrointestinal x-ray examination elsewhere failed to reveal any organic basis for the diarrhea. Severe weight loss had occurred. Atrophy of the tongue was not noted, and no splenomegaly or alteration in vibratory sense was apparent. There was no free hydrochloric acid in the stomach; total acidity was 10 units. A stool specimen revealed large amounts of neutral fatty acids and many fatty acid crystals. The glucose tolerance test was of the diabetic type. A roentgenogram of the small bowel revealed a deficiency pattern. Initial blood count revealed 3,770,000 red blood cells, 68 per cent hemoglobin, 4600 white blood cells, and 8 per cent eosinophilia. The volume index was 1.09. Under parenteral liver therapy combined with oral folic acid and vitamin and dietary management, symptoms quickly subsided, and a rapid gain in weight ensued. The blood count returned to normal.

Inadequate absorption of E.M.F. was encountered in a 50-year-old housewife with anemia and numbness of the finger tips. This patient had had a hysterectomy at the age of 31, a laparotomy for questionable intestinal obstruction at the age of 36, and another operation at the age of 46 because of "acute intestinal obstruction." Physical examination was normal except for impairment of the vibratory sense in the toes. An Ewald test upon two occasions revealed 40 units of free hydrochloric acid, with a total acidity of 60 units. Roentgenograms of the small bowel demonstrated an obstructing lesion in the proximal ileum probably secondary to previous surgery. The initial blood count revealed 2,910,000 red cells, 68 per cent hemoglobin, 5700 white cells, with a normal differential distribution. The volume index was 1.31. The patient responded slowly to the less refined parenteral crude liver extract, but she became symptom-free and her blood count returned to normal. Recently, because of fear of any future bowel obstruction, another laparotomy has been

performed, sidetracking an almost complete stenosis of the ileum associated with an ileocolic fistula which had prevented complete obstruction. She has remained entirely symptom-free, receiving liver extract every other week.

This case represents a different type of failure of absorption of the E.M.F. which may produce macrocytosis.

Still another cause of macrocytosis is that found in liver disease, in which, although an adequate amount of E.M.F. is present, improper utilization and storage takes place. In one case, a 50-year-old man with cirrhosis of the liver had experienced repeated hematemesis and tarry stools six weeks prior to admission. He had been a moderately heavy drinker of alcoholic beverages for some time, with a restricted dietary intake. His complexion was sallow, and several areas of telangiectasia were noted on the nose. The liver edge was palpable 2 fingers' breadth below the right costal margin. The bromsulfalein retention test revealed 32 per cent retention of the dye at the end of thirty minutes. The Takata-Ara test was positive. Roentgenograms of the esophagus did not demonstrate esophageal varices. Blood count revealed 2,760,000 red blood cells, 58 per cent hemoglobin, and 4500 white cells, with a normal differential distribution. The volume index was 1.29, icteric index 15. Unfortunately, this patient died following a severe episode of hematemesis before an opportunity for adequate therapy was possible.

If the liver disease is not too severe, and if excessive scar tissue is not present, a satisfactory response may usually be expected with supportive management and liver extract injections, with subsequent return of the blood picture to normal. Of course, absence of macrocytosis does not preclude the presence of liver disease.

Aplastic anemia is one of the more rare causes of macrocytosis and is believed to be secondary to failure of maturation in red cell development. The reason for such failure is not understood. The bone marrow is aplastic as in the following case: A 67-year-old man who had been engaged in the rubber industry and at times had been exposed to the fumes of benzol, had become short of breath and had developed anemia several years prior to admission. Other than considerable pallor and hepatomegaly, physical examination was negative. An Ewald test, bromsulfalein retention test, urea clearance, and roentgenograms of the chest were within normal limits. The bone marrow was completely aplastic upon two occasions and the blood count revealed 2,200,000 red blood cells, 44 per cent hemoglobin, and 1150 white blood cells with a volume index of 1.11. Therapy is of no avail in such cases.

A normal volume index can be present in pernicious anemia under certain circumstances, such as in the case of a 50-year-old colored truck driver who initially complained of epigastric pain and the passage of tarry stools intermittently for five years. Physical examination revealed a severe blood loss; the blood pressure was 84 systolic, 50 diastolic. There was diffuse tenderness throughout the abdomen. Examination of the stool was negative for occult blood three days after admission. No abnormalities were demonstrable by roentgenogram of the gastrointestinal tract. An Ewald test revealed an absence of free hydrochloric acid, with a total acidity of 12 units. The blood count

revealed 2,230,000 red blood cells, 40 per cent hemoglobin, 6450 white blood cells, and an icteric index of 15. The reticulocyte count was 1.8 per cent, with 10 nucleated red blood cells per 100 white cells. The volume index was 0.98. Study of the bone marrow revealed a megaloblastic marrow.

This patient failed to demonstrate an increase in volume index, because the microcytosis from repeated gastrointestinal hemorrhages had offset the macrocytosis of pernicious anemia. Under management by repeated transfusions and parenteral liver therapy, the patient has made an uneventful recovery.

Conclusions

Macrocytosis may be due to any one or a combination of several factors. These include lack of the E.M.F., failure of its absorption, failure of its proper utilization, or sudden release of immature cells from the bone marrow secondary to acute blood loss. The management of macrocytosis depends upon its etiology, but an effort should always be made to supply parenterally an adequate amount of E.M.F. to assure its presence in proper amounts. When macrocytosis is due to aplastic anemia, no type of therapy is of avail.