PAROXYSMAL NOCTURNAL HAEMOGLOBINURIA

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PAROXYSMAL nocturnal haemoglobinuria (P.N.H.) is an uncommon disorder of uncertain aetiology characterised by chronic haemolytic anaemia with constant haemosiderinuria and occasionally with bouts of haemoglobinuria which are classically nocturnal. During the past thirteen years we have had four cases under our care. As these patients were under review from diagnosis to death we have been able to carry out a long term study of the clinical course and the problems involved in management.

CASE 1: A male of thirty-nine years was admitted to the Royal Victoria Hospital, Belfast, in April, 1957, complaining of lassitude and increasing shortness of breath for one year. On physical examination there was pallor of mucous membranes, but no other abnormality. Laboratory studies revealed a haemoglobin of 9.6 gm. per 100 ml., P.C.V. 30 per cent, M.C.H.C. 32 per cent, reticulocytes 6 per cent, platelets 130,000 per cu. mm., leucocytes 3,500 per cu. mm., with 67 per cent neutrophils, 1 per cent eosinophils, 26 per cent lymphocytes and 6 per cent monocytes. Peripheral blood smears showed moderate erythrocyte anisocytosis and macrocytosis. Erythrocyte osmotic fragility of fresh blood normal. Aspirate of sternal marrow showed erythropoietic hyperplasia with normoblastic development; no abnormality in either granulopoiesis or thrombopoiesis noted. Serum bilirubin 1.2 mgm. per 100 ml. Acidified-serum (Ham's) test positive; cold-hot lysis (Donath-Landsteiner) test negative. Direct anti-globulin (Coombs) test and serological tests for syphilis negative. No protein, sugar, bile or blood detected in urine, but urobilinogen present in excess; when examined microscopically, the urinary deposit was found to contain large quantities of haemosiderin which gave the characteristic Prussian blue (Perl's) reaction. No free acid detected in gastric juice following histamine stimulation. Stools did not contain occult blood; analysis of a three-day collection showed normal fat excretion. The haematological findings pointed to a diagnosis of haemolytic anaemia with haemosiderinuria; laboratory studies established the presence of a P.N.H. erythrocyte defect. The patient was started on a blood transfusion programme and was given packed cells at intervals of six to ten weeks for a period of two years. During the early part of the transfusion programme local venous thrombosis developed at the site of infusion and consequently all subsequent transfusions were given under oral anticoagulant cover.

In August, 1959, when the patient had received a total of fifty-two units of blood he was re-admitted to hospital for further transfusion. The first unit of compatible packed cells was transfused without reaction but, when about 100 ml. of the second unit had been given, the pulse rate and the body temperature began to rise and the transfusion was discontinued. Laboratory investigations revealed no red-cell incompatibility or evidence of intra-vascular haemolysis. Further blood was prepared by removing the plasma and washing the cells with saline, but transfusion of this produced a similar pyrexial reaction which was not prevented by anti-histamine drugs. At this stage the presence of leuco-agglutinins in the serum was detected by the method of Dausset et al. (1954). Compatible leucocyte-poor washed cells were then prepared and transfused without any pyrexial reaction. From October, 1959, until February, 1961, the patient received transfusions of leucocyte-poor washed cells at intervals of six to eight weeks without reaction.

In February, 1961, the patient was admitted seriously ill following an attack which was called influenza. On physical examination he was found to have evidence of a severe respiratory tract infection with consolidation in the lower lobes of both lungs. An intensive course of antibiotic therapy was given over a period of two weeks with little improvement. Blood cultures were consistently sterile. On admission the patient had a leucocytosis of 13,400 per cu. mm. but this fell to 1,400 per cu. mm.; the reticulocyte count which was 10 per cent on admission fell to less than 1 per cent over the same period. The platelets did not exceed 80,000 per cu. mm. on any occasion. These findings suggested a period of myelo-suppression. This was confirmed when an aspirate of bone
marrow revealed hypoplasia of all three prime elements. An infusion of haemopoietic
tissue produced no rise in the peripheral cell count and the clinical condition of the
patient gradually deteriorated until his death in April, 1961.

Autopsy revealed the presence of broncho-pneumonia with abscess formation and
hypoplastic bone marrow. The kidneys showed striking cortical haemosiderosis. In
spite of the transfusion of more than ninety units of blood there were no deposits of
haemosiderin in the phagocytic cells of the liver, spleen or bone marrow.

CASE 2: A man of thirty-eight years was admitted to the Royal Victoria Hospital,
Belfast, in April, 1952, complaining of general lassitude for seven years with transient
periods of jaundice during the previous three years. Clinically he appeared slightly
anaemic, but no physical abnormalities were detected. The results of the laboratory
investigations are not available; however, it is stated that he had a mild anaemia, the
cause of which was not determined. During the following six years he remained clinically
well on regular injections of purified liver extract.

In 1958 the patient required blood transfusion on two occasions. In March, 1959, the
patient was admitted to hospital, where investigations revealed the presence of
haemolytic anaemia and he was transferred to the Royal Victoria Hospital, Belfast, for
further investigations. On physical examination pallor and icterus were noted, no
splenomegaly or other abnormality. Laboratory studies revealed a haemoglobin of 6.3
gm. per 100 ml., P.C.V. 30 per cent, reticulocytes 8 per cent, platelets 75,000 per cent
cu. mm., leucocytes 3,400 per cu. mm., with 58 per cent neutrophils, 39 per cent lymphocytes, and 3 per cent monocytes. Peripheral blood smears showed moderate erythrocyte anisocytosis and when stained by the method of
Hayhoe and Quaglino (1958) reticulocytosis, phagocytosis, was noted. Erythrocyte osmotic fragility on fresh blood normal. Sternal marrow aspirate showed hyperplasia with normoblastic development; no abnormality in either
granulopoiesis or thrombopoiesis detected. Serum bilirubin 1.3 mgm. per 100 ml. Ham's
test positive; Donath-Landsteiner test negative. Coombs test and serological tests for
syphilis negative. Urine did not contain protein, sugar, bile or blood, but urobilinogen
was present in excess; on microscopical examination the urinary deposit was found to
contain considerable quantities of haemosiderin. These findings showed the presence of
chronic haemolytic anaemia with haemosiderinuria, and this, taken with the character-
istic erythrocyte defect, confirmed the diagnosis of paroxysmal nocturnal
haemoglobinuria.

The patient was started on a blood transfusion programme and was given packed
cells at intervals of approximately six to twelve weeks for a period of twenty-seven
months.

In May, 1961, when the patient had received a total of thirty units of blood he was
re-admitted for further transfusion. After about 200 ml. of the first unit of compatible
packed cells had been transfused the patient's body temperature began to rise. The
transfusion was continued, but when all of this unit had been given he had a rigor and
the body temperature reached 103.6°F. The transfusion was discontinued and within
twelve hours the body temperature had returned to normal. Laboratory investigations
revealed no erythrocyte incompatibility or evidence of intra-vascular haemolysis.
Leuco-agglutinins were detected in the serum. Consequently, leucocyte-poor washed
cells were prepared and transfused without reaction.

From May, 1961, until March, 1964, the patient was successfully transfused with
leucocyte-poor washed cells at intervals of six to eight weeks without any reactions.
The last transfusion in the Royal Victoria Hospital, Belfast, was in March, 1964.

In April, 1964, he was admitted to another hospital with severe anaemia and died
following a blood transfusion. No post-mortem examination was carried out.

CASE 3: A woman of sixty-two years was investigated in another hospital in
November, 1960, because of weakness which had been present for six months. Physical
examination revealed pallor and icterus, without splenomegaly or other abnormality.
Laboratory studies revealed a haemoglobin of 7.6 gm. per 100 ml., P.C.V. 22 per cent,
M.C.H.C. 34 per cent, reticulocytes 9.6 per cent, leucocytes 4,050 per cu. mm., with
63 per cent neutrophils, 2 per cent eosinophils, 32 per cent lymphocytes and 3 per cent
monocytes. Stained smears showed moderate erythrocyte anisocytosis and some
macrocytosis. Sternal marrow aspirate was diluted with peripheral blood but erythro-
poiesis was normoblastic. Serum bilirubin 1.2 mgm. per 100 ml. Direct Coombs test and
serological tests for syphilis negative. Neither Ham's test nor the Donath-
Landsteiner test was carried out at this time. Urine did not contain protein, bile, sugar
or blood; urobilinogen was present in excess. Chemical analysis of gastric juice revealed
the presence of free acid. Stools contained no occult blood. The presence of a haemolytic
anaemia was indicated by the normochromic anaemia associated with reticulocytosis,
elevated serum bilirubin level and increased urinary urobilinogen and the patient was
transferred to the Royal Victoria Hospital, Belfast, for further investigation.

The general haematological and other laboratory findings as above were confirmed
and further studies carried out. Leucocyte alkaline phosphatase reduced. Erythrocyte