UNUSUAL RETICULOCYTOSIS IN AN UNTREATED CASE OF PERNICIOUS ANAEMIA

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The following case caused some difficulty in diagnosis owing to the finding of reticulocytosis of more than 30% in the presence of severe anaemia and a recent history of jaundice.

Case Report

Mrs. X., aged 30, had always been perfectly well until February, 1939, when she complained of feeling run down, with loss of appetite and energy. She had also lost some weight. Her private doctor, having treated her symptomatically with an iron mixture without response, referred her to hospital. There, no history could be elicited to account for her symptoms, while it was noted that she looked sallow and pale, although her mucous membranes were of a good colour. There was also marked pyorrhoea. Radiographs of her chest were normal, while a blood count showed a moderate anaemia: red cells, 2,570,000; Hb, 49%; colour index, 0.95; white cells, 12,000—polymorphs 72%, eosinophils 1.5%, lymphocytes 24.5%, mononuclears 2.5%. The red cells showed some anisocytosis and poikilocytosis. On account of these findings and because there had been no response to iron therapy, hepamult was prescribed in addition, and she was advised to have her teeth extracted. This was done, and she next attended the hospital two months later, feeling very much better. A blood count on this occasion showed: red cells, 4,600,000; white cells, 9,600; Hb, 92%; colour index, 1.

Shortly after this she married and moved to the Birmingham district, where she was well until March, 1940, when she again became pale and nauseated. She improved with some medicine from her doctor, but again relapsed at the beginning of July. She then became very nauseated and developed epigastric pain and jaundice—so much so that the jaundice was commented upon by her friends. She lost weight again and a great deal of energy. Headaches were very severe. She had had no haematemesis and no upset in her menstrual functions, but some slight bleeding from the rectum had occurred. There was no family history of any blood disorder. She was referred to the General Hospital for further advice one month after the onset of her most recent attack.

She was there noted to be very pale—on first appearances suggestive of a patient with a bleeding duodenal ulcer. She had a smooth tongue, a marked haemic murmur, and slight tenderness in the epigastrium. Vaginal and rectal examinations were negative. Investigations showed a macrocytic type of anaemia with 42% haemoglobin and a positive indirect and slight direct van den Bergh test (serum bilirubin, 1 unit). She was therefore admitted to the Queen Elizabeth Hospital (August 6) for further investigation. Physical examination was essentially the same as that in the out-patient department, although there was divergence of opinion as to the presence of splenic enlargement. Her faeces were benzidine-negative.

The blood examination on admission showed marked reticulocytosis (red cells, 1,420,000; *reticulocytes*, 33.4%; Hb, 34%; colour index, 1.21; white cells, 4,600—polymorphonuclears 21.25%, eosinophils 1.25%, lymphocytes 74.5%, monocytes 2.7%, neutrophil myelocytes 5.25%), while the stained films revealed great anisocytosis, slight poikilocytosis, and marked polychromasia, the platelets appearing normal.

Inquiry into her dietetic habits disclosed that she did not eat excessive amounts of meat, that she was accustomed to have liver regularly once a week, and that she had had no liver therapy from her doctor. A diagnosis of chronic haemolytic anaemia appeared probable, and Dr. T. W. Lloyd was asked to carry out investigations with this in view. On August 9 his examination with heparinized blood gave the following results:

Red cells		2,110,000
Haemoglobin		51%
Colour index		1.2
Haematocrit		21.7%
Mean cell volume		103 cubic microns
Mean cell haemoglobin concentration		32.4%
<i>Reticulocytes</i>		31%
White cells		1,900 per c.mm.
Polymorph neutrophils		25.5%
Eosinophils		0.5%
Premyelocytes		1%
Lymphocytes		72%
Monocytes		1%
Normoblasts		2%

A striking feature of the neutropenia, which in itself was unusual in the presence of such active red cell regeneration, was the absence of non-segmented forms, all the polymorphs being heavily segmented.

The fragility began in 0.45% and was complete in 0.25% saline, a slight increase as compared with normal. The lecithin resistance was greatly increased, thus:

Concentration of Lysolecithin	Haemolysis of Patient's Cells	Haemolysis of Control Cells
1/32	100%	100%
1/64	52%	100%
1/128	0	15%
1/256	0	0

This test was considered to exclude acholuric family jaundice. The Price-Jones curve (250 cells) showed very marked macrocytosis, mean diameter 8.78 μ . It was a homogeneous curve, and when decomposed by the method of Mogenes the main component had a mean diameter of 8.75 μ and contained 100% of the cells drawn.

The serum was examined for haematin (methaemalbumin) by Schumm's method and by spectroscopic analysis. Tests that proved to be negative were also carried out by the method of Damashek for the presence of isohaemolysins. The Donath-Landsteiner test for paroxysmal (cold) haemoglobinuria was also negative.

In the meantime the patient was improving on a normal hospital diet without any medication. A fractional test meal showed the presence of achlorhydria, and a laevulose-tolerance test gave a normal result. On admission the van den Bergh test had shown a positive biphasic reaction and a positive indirect reaction with an icterus index of 10. One month later the indirect test was still faintly positive with the icterus index at 7.4 units, while eight weeks after admission both the direct and indirect tests were negative.

In view of these findings the diagnosis of pernicious anaemia was put forward. Accordingly a test dose of liver extract

Chart showing the blood counts during stay in hospital and the response to liver therapy

(anahaemin 2 c.cm. intramuscularly) was given when the red cells were 2,300,000 and the reticulocytes had fallen to less than 1%. A reticulocyte response of 10% was obtained on the sixth day following, falling to normal six days later. The achlorhydria was shown to be absolute, no HCl being secreted in response to 1.5 mg. of histamine. Liver extract was continued with complete relief of her symptoms and restoration of the blood picture to normal (see Chart).

The patient has maintained good health for fourteen months on a fortnightly dose of 2 c.cm. of anahaemin. The most recent blood count showed: red cells 4,640,000, Hb 98%, and colour

index 1.05; the van den Bergh test was negative. The Price-Jones curve is now within normal limits, with a mean diameter of 7.014 μ .

Discussion

The striking feature of this case was the persistence of a reticulocytosis of over 30% for at least forty-eight hours in a patient who had received no treatment and the difficulty in diagnosis that this finding caused. Such a reticulocytosis, taken in conjunction with the apparently rapid onset and a history of other attacks and of jaundice, seemed to indicate haemolytic anaemia. Against this the presence of glossitis was one small point, but the negative findings of the special investigations and the subsequent findings of complete achlorhydria threw further doubt on the original diagnosis. Finally, the reticulocyte response to a test dose of liver extract associated with a rise of red cell content indicated an absence of haemopoietic factor. Such a response would be exceptional in any of the haemolytic types of anaemia. In fact, all the findings seem to indicate a diagnosis of pernicious anaemia in spite of such an unusual reticulocytosis.

Little mention is made in the literature regarding the number of reticulocytes present during the relapse phase. Sturgis and Isaacs (1938) state that spontaneous crises are sometimes seen with 7 to 8% of reticulocytes. Whitby and Britton (1939) note that occasionally pronounced reticulocytosis is present, but do not give figures. A rapid survey of other relevant publications failed to throw any light on the problem. The marked reticulocytosis in this case, following a submaximal dose of the intrinsic factor, should be due to the reaction of a young and comparatively healthy bone marrow, which has not yet become exhausted in the effort to keep up the supply of corpuscles from inadequate material. The same amount in an older person would, no doubt, only have given the reticulocytosis that is usually noted during remissions (7 to 10%).

It is interesting to speculate on the reason why this patient, accustomed to a regular and adequate diet, should suddenly relapse and with apparently equal rapidity begin to regenerate her red blood corpuscles. While we know that absence of the intrinsic factor leads to the development of pernicious anaemia, there is no definite knowledge as to the factors that lead to its disappearance. It is frequently suggested that the stomach in persons completely achlorhydric is especially disposed to gastritis, which will eventually lead to the suppression of the intrinsic factor. The history in this case supports such an idea. Dental sepsis, often put forward as an aetiological factor in earlier days, no doubt caused some degree of gastritis to initiate the first relapse. The last relapse, ushered in as it was by nausea, vomiting, epigastric pain, and jaundice, is very suggestive of gastritis with an associated "duodenitis." The relapses would then be due to a suppression of the intrinsic factor and the remissions be due to improvement in the gastritis, with a consequent return to a more normal diet and the reappearance of a small amount of intrinsic factor (cf. pernicious anaemia of pregnancy). The diagnosis of gastritis is not altogether unjustified, as for a short period after starting liver therapy the patient had nausea, vomiting, and epigastric discomfort which were relieved by a simple bismuth mixture, and also on one or two occasions since her discharge from hospital she has had short bouts of epigastric discomfort.

Summary

A case of pernicious anaemia in a young married woman aged 30 is reported. The patient presented the unusual feature of reticulocytosis of 33.4% in the absence of any previous treatment.

Administration of liver extract gave complete relief of symptoms and restored the blood picture to normal.

Good health has been maintained on a fortnightly dose of 2 c.cm. of anahaemin.

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Medical Memoranda

Acquired Immunity to Blood Transfusion Reactions: A New Phenomenon

Reactions occurring during the transfusion of blood are for clinical purposes commonly divided into two main groups: haemolytic and non-haemolytic. The onset of the reactions is similar, but as a rule the former becomes progressively worse for hours or days, and often ends fatally; while the latter, alarming though it may appear, usually expends itself within an hour, leaving no observable evidence of permanent damage. It is with the latter type that this paper is concerned.

It has been our experience that the recipient, having suffered this reaction, is for some time immune to further reaction to the same blood. Hence the transfusion may with complete safety be resumed soon after subsidence of the response.

FIRST OBSERVATIONS

Our first observation of this kind was made on a male Hindu aged 18 to whom a transfusion was given following amputation of a leg after a crush injury. Fifty c.cm. or so of 5% glucose solution alone was first used, and then the blood was started at the rate of about 50 drops a minute. When 150 c.cm. of blood had run in, the patient developed a severe chill, the pulse became rapid and thready, and there was marked pallor. The transfusion was discontinued promptly, the foot of the bed was elevated on shock-blocks, and hot-water bags and blankets were applied. One c.cm. of adrenaline was injected intramuscularly. The reaction, which was most violent, ran its course and subsided completely within an hour. A careful check was made of the blood, but no error was found either in the grouping or in the cross-agglutination tests. Also, the citrate solution had to be considered, although our intravenous solutions had produced no such symptoms in some hundreds of administrations. Accordingly, 50 c.cm. of the glucose-saline solution was given by vein to each of three otherwise healthy fracture patients, and 20 c.cm. of 3.8% citrate solution was injected intravenously in two other afebrile individuals. None of these subjects developed chills or fever, nor was there any significant variation in the pulse rate as a result of the injections. The reaction observed in our patient was therefore purely from the blood, and was characteristic of the non-haemolytic type, being in general essentially the same as the others of this type which we had seen here and elsewhere.

THE HYPOTHESIS OF ANAPHYLAXIS

Because of its typical character this case was chosen to test a hypothesis which had occurred to us: that the reaction is anaphylactic in nature. If this were an anaphylactic response the patient had very likely become desensitized, and it should be possible, therefore, to continue the transfusion without further response. Accordingly, some five hours after the patient's recovery the transfusion was resumed, the blood being run into the vein very slowly, while careful watch was kept for any untoward symptoms. The transfusion was completed without the slightest reaction.