Cyclic thrombocytopenia: A thrombopoietin deficiency?

M. L. LEWIS

From the Department of Haematology, King’s College Hospital Medical School, London

SYNOPSIS Severe cyclic thrombocytopenia is reported in a young woman. This rare phenomenon is of considerable theoretical interest in relation to platelet kinetics. In this patient platelet and fibrinogen survival times exclude the possibility of excessive peripheral platelet destruction. Serial plasma thrombopoietin levels suggest that a deficiency of this protein may be the underlying factor. As a result platelet production may fall to a very low level. The megakaryocyte, however, remains responsive and the hypothesis advanced is that under these circumstances the intermenstrual platelet increase, normally caused by the interplay of the sex hormones, becomes grossly exaggerated.

At least 10 patients with cyclic thrombocytopenia have been reported in the English language literature in the last 50 years. Some observers have suggested that the primary defect is an accelerated loss of platelets from the blood stream (Morley, King-Smith, and Stohlman, 1970), and Brey, Garner, and Wells (1969) have considered it to be merely a variant of immune thrombocytopenic purpura. Many reports have concluded that the phenomenon is a pathological exaggeration of the cyclic platelet variation to be found in a substantial proportion of healthy men and women (Morley, 1969). However, even in the more recently reported cases, no attempt has been made to substantiate the suggested pathogenesis by adequate evaluation of the platelet kinetics. In the present patient, platelet and fibrinogen turnover studies have been performed, together with serial plasma thrombopoietin assays and a trial of normal plasma infusion. The result of these investigations suggests the mechanism underlying this fascinating haematological phenomenon.

Case Report

The patient, a native of Barbados, came to England in 1963 and since then has been employed as a GPO telephonist. She was first seen in May 1969, when 31 years old, with a 20-month history of premenstrual bruising and excessive menstrual losses. Recently, she had completed a course of parenteral iron therapy (1700 mg of Jectofer, Astra Chemicals).

She gave birth to her fourth child in August 1966 and the baby was not reported to have bled or bruised excessively. Subsequently, her menstrual losses became heavy and prolonged and she was admitted to hospital in September 1967, with symptoms of anaemia. The haemoglobin was 4.4 g/100 ml, and the MCHC only 26%. A blood film showed hypochromasia with normal numbers of platelets. Haemoglobin electrophoresis was normal. She was transfused 6 units of stored whole blood before uterine curettage. The curettings showed a normal endometrium. A few days later, the patient noted bruises on her legs for the first time, but unfortunately she failed to attend for follow up as an outpatient.

In the succeeding 20 months, her periods remained heavy although regular. Seven to ten days before each period, she noted a fine red rash on the lips, face, and upper chest, and bruises on the legs. These gradually faded towards the end of menstruation. Apart from a slight epistaxis on one occasion, there was no evidence of blood loss from any other site.

At the time of her referral, menstruation was due in six days and on physical examination, she had a petechial rash on her face and a number of bruises, 5-10 cm in diameter, on her thighs. There were no other abnormal physical findings. Investigation showed a haemoglobin of 12.3 g/100 ml and a mixed red cell population indicating a satisfactory response to the iron therapy. Glucose-6-phosphate dehydrogenase screening was normal. The ESR (Westergren) was 10 mm in one hour. The total and differential white cell counts were normal but the
platelet count was only 14 000/μl. In the bone marrow there was a mild excess of megakaryocytes actively producing platelets. The patient made only irregular follow-up attendances as menorrhagia was apparently controlled by the administration of the antifibrinolytic agent epsilon-amino-caproic acid. However, in January 1970, she returned with a haemoglobin of 6·3 g/100 ml and was admitted to hospital. Then, for the first time, it was possible to study the variation in the platelet count and show that there was a remarkably wide but smooth fluctuation from high-normal to very low levels during her monthly cycle (fig 1). Two days after admission, she was given 2 g of iron dextran intravenously (Imferon, Fisons) and the haemoglobin rose steadily. Twelve days later, when the platelet count had fallen to 6000/μl, a second bone marrow examination still showed active megakaryocytes.

This rhythmical intermenstrual platelet fluctuation has persisted, usually with the highest count in the second week and the lowest in the fourth (fig 2). No history of any drug ingestion has been obtained and, in particular, she has never taken the contraceptive pill. Investigation for platelet autoantibodies by agglutination and antiglobulin consumption tests have been negative. No red cell antibodies, anti-nuclear factor, rheumatoid factor, or Rose Waaler antibodies have been detected. In October 1971, she underwent a right salpingo-oophorectomy for an ectopic pregnancy. The operation was performed without complications at a time when her platelet count was 95 000/μl. It rose to 126 000/μl on the first postoperative day. The following month she was readmitted to hospital because of seven days of unremitting, heavy vaginal bleeding. She was found to have a haemoglobin of 5·5 g/100 ml and only 12 000 platelets/μl. In view of her long history of menorrhagia a hysterectomy was performed 10 days later when her platelet count had risen to 410 000/μl. The postoperative course was again unremarkable. She has not returned for follow up since the last period in hospital. Her general practitioner states, however, that apart from one episode of haematuria she has had no further complaints.

Special Investigations

PLATELET COUNTS
These were performed by the method of Bull, Schneiderman, and Brecher (1965) using a Coulter counter (model F).

51CR-LABELLED PLATELET SURVIVAL STUDIES

Homologous platelets
One unit of ABO compatible blood was drawn from a regular donor into a plastic double pack (Baxter J2) and immediately centrifuged at 200 g for 20 minutes. The platelet-rich plasma thus obtained was manipulated and the platelets labelled with 51chromium by a standard technique (Dacie and
Lewis, 1968). Platelets from the post-infusion blood samples were separated for scintillation counting using the method described by the same authors. Radioactivity was measured in a well-type scintillation counter with a 5 cm crystal, and body-surface scanning was performed using an adequately shielded 8 cm sodium iodide crystal.

**Autologous platelets**

These were obtained at a time when the patient's platelet count was 250,000/µl. After centrifugation, the red cells were reinfused in order to avoid stimulating platelet production through blood loss. Cell labelling and determination of the half-life and body surface activity were carried out as for the homologous platelets.

**Assay for plasma thromopoietic activity**

The method was essentially that of Penington (1970) except that the animals used were not pretreated with antiplatelet serum. Inbred male white mice weighing between 20 and 25 g were used. Citrated plasma samples were obtained at approximately weekly intervals from the patient and a normal female control of the same age. These were stored at −70°C for up to five weeks until the assay was performed. On an average four mice were used for each sample, and 0.5 ml was injected subcutaneously twice daily for two days. On the third day 2μCi of (75Se) selenomethionine (Radiochemical Centre, Amersham) was injected into the tail vein of each mouse. Blood was taken by cardiac puncture on the fourth day and the platelets were separated and radioactivity was counted as described by Penington (1969). The platelet radioactivity incorporation value of a control set of mice given only the (75Se) selenomethionine was subtracted from each test activity and the results were expressed as platelet radioactivity per 0.5 ml of mouse whole blood per 100 s.

**125I-labelled fibrinogen survival**

Homologous fibrinogen (Kabi Pharmaceuticals Ltd) was labelled by the method of McFarlane (1963) and the survival in vivo and half-life were measured as described by Regoczi (1971).

**Normal plasma infusion**

Six hundred ml of plasma was obtained from two regular male donors and infused within six hours of donation.

**Results**

**Platelet survival**

In both the homologous and autologous studies the maximum circulating platelet radioactivity represen-

ted approximately 70% of the infused labelled cells, indicating a normal degree of splenic platelet pooling (Harker and Finch, 1969).

The survival of donor platelets was carried out when the patient's own platelet count was falling rapidly (fig 3). The initial rise in activity to a maximum at 24 hours suggests some transient platelet sequestration. Thereafter the half-survival of approximately four days was within the normal limits for this laboratory. Surface scanning during this time demonstrated no abnormal platelet uptake in the liver or spleen.

![Fig 3 Homologous platelet survival performed during January 1970. The broken line depicts the fall in total platelet count over the same period.](image)

The autologous platelet survival was performed during February 1971, 12 months after the first survival study. Figure 4 shows that the half-life was

![Fig 4 Autologous platelet turnover during February 1971. The peripheral platelet count is shown by a broken line.](image)
again within normal limits (5-5 days) at a time when her platelet count was falling from 250 000/µl. Body surface counting again showed a normal pattern.

ASSAY FOR THROMBOPOIETIC ACTIVITY
No attempt was made to measure the blood volume of the mice used and therefore thrombopoietic activity has been expressed as counts/100s/0.5 ml of mouse whole blood (fig 5). The platelet count of the control subject fluctuated mildly, being at its lowest, 250 000/µl, just premenstrually and at its highest, 330 000/µl, in the third week of her next menstrual cycle. The thrombopoietic activity in the control appeared to be directly related to her platelet count. The patient, on the other hand, showed a low level of activity throughout the study.

Fig 5  Plasma thrombopoietin activity, as determined by mouse bioassay, during the menstrual cycle in the patient and a normal control.

FIBRINOGEN SURVIVAL
The 125I-labelled fibrinogen study, carried out over the same period as the second platelet survival, demonstrated a normal half-life of 100 hours. During the study other coagulation parameters, including the one-stage prothrombin time, thrombin clotting time, kaolin partial thromboplastin time, and the one-stage factor VIII assay, also remained within normal limits.

FRESH PLASMA TRANSFUSION
The infusion of fresh plasma appeared to halt the characteristic fall in her platelet count abruptly. This was followed by a slight rise over the next few days (fig 2). Although the effect on the platelet count was not particularly striking, none of the usual bruising occurred during that month and the subsequent menstrual loss was less than normal. Unfortunately assessment of this response was complicated by the ectopic pregnancy, first causing symptoms only a week after the plasma transfusion and resected three weeks later.

Discussion
Morley et al (1969) suggested that platelet formation is under the control of two feed-back loops. One regulates the production rate and the other the release rate. The 'production rate loop' controls the activity of the primitive megakaryocytes, possibly even at their stem cell stage (Ebbe, 1968), and incorporates a substantial time delay. The mild periodic fluctuation often seen in serial platelet counts may reflect this control mechanism (Morley, 1969). The 'release rate loop' on the other hand is believed to control the marrow transit time and thereby determine the rate of platelet release.

Three possible explanations for an excessive cyclic platelet fluctuation were suggested by Morley et al (1970). They favoured an increased rate of platelet clearance from the peripheral blood. This could be secondary to platelet autoantibody production (Brey et al, 1969), or the result of trapping of platelets in the proliferated uterine capillaries during the week before menstruation (Harrington, 1971). In the present study, however, no autoantibodies were detected and a normal fibrinogen survival excluded a periodic consumptive coagulopathy. Even more important, the platelet survival was normal during phases when the count was falling rapidly.

The second mechanism suggested was a partial production failure at the stem cell stage. On the two occasions when the marrow was examined in our patient, although there was severe thrombocytopenia at the time, megakaryocyte proliferation was noted. However, the platelet count began to rise rapidly within two or three days, and therefore the appearances are probably not a true reflection of overall marrow activity. Morley et al (1970), using a computer simulation, showed that a mild failure of neutrophil production would result in cyclic neutropenia, whereas a severe failure would produce a chronic non-cyclic white cell depletion. Subsequent animal experiments appeared to confirm this hypothesis and the results resembled those in the present case, and in others reported in women, where the mean platelet count was reduced to about one-third of the normal (see table).

If the findings in our patient are the result of a partial failure of platelet production, its cause remains to be elucidated. There is no history of exposure to drugs or other toxic materials likely to depress the marrow, but the relatively low thrombopoietin levels (fig 5) may be significant. Caution must
be observed when interpreting the assay findings for it is difficult to establish precisely the normal range in women and even with weekly blood examinations a spike of high activity could be missed. However, thrombopoietin has been considered an important link in the ‘production rate loop’ and in most forms of thrombocytopenia, including that secondary to excessive platelet destruction, an increased level of thrombopoietin would be expected (Penington, 1970).

The third mechanism postulated by Morley and his coworkers (1970) is a failure of the ‘release rate loop’, possibly from a hormone deficiency. The hormonal fluctuations taking place normally in young women almost certainly play a part in the mild cylical variation in the platelet numbers. To avoid this mechanism, the fresh plasma infused into our subject to provide exogenous thrombopoietin was taken from a male donor. The results of the infusion were interesting but not dramatic. The platelet count ceased to fall, and, indeed, a slight rise was observed. This could be due to a mild hormonal effect on the ‘platelet release loop’. The subsequent plateau, which was sustained for several days, was considered more important and has been taken to implicate involvement of the ‘production rate loop’.

Although no definitive conclusions can be drawn it seems that our patient may have acquired a mild thrombopoietin deficiency. The source of thrombopoietin in the body is not known and therefore any explanation for a loss of production must be purely speculative. It is postulated that in this patient the deficiency of thrombopoietin has resulted in a relative megakaryocyte failure and has coarsened the delayed feedback control mechanism. As a result the mean platelet level has been reduced and the normal intermenstrual platelet fluctuation, presumably determined by the sex hormones, has become pathologically exaggerated.

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References


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M. L. Lewis

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