Thrombocytosis following thrombocytopenia in man

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Summary

Observations are presented on the changes in the platelet count of patients during the treatment of Addisonian pernicious anaemia with vitamin B₁₂, of thrombocytopenic purpura with prednisone, and of malignant disease with methotrexate.

In each of these clinical situations, thrombocytopenia was succeeded, after a delay of a number of days, by a phase of thrombocytosis.

Introduction

An elevation in the circulating platelet count has been observed in a variety of physiological and pathological conditions. However, the rise in platelets varies widely in timing and duration. The myeloproliferative diseases are frequently accompanied by a persistent increase in the platelet count which may be of considerable magnitude. Such stresses as exercise are accompanied by a transient and moderate rise in platelets. In a number of circumstances, for example, trauma, the increase in platelets takes place after a delay of a number of days and lasts for a few days. We present observations on further examples of thrombocytosis of this last type occurring during the treatment of Addisonian pernicious anaemia with vitamin B₁₂, of thrombocytopenic purpura with prednisone, and of cancer with methotrexate.

Methods and patients

Platelet counts

These were performed by the method of Oettle & Spriggs (1951). The normal range for healthy adults in this laboratory is 150-270,000/mm³.

Serum vitamin B₁₂ levels

These were assayed microbiologically by the method of Spray (1955) using *Lactobacillus leichmannii*. The lower limit of normal for the laboratory is 160 pg/ml.

Other haematological measurements were performed by the techniques described by Dacie & Lewis (1963).

Patients with Addisonian pernicious anaemia

All fourteen patients had megaloblastic marrow smears, a histamine-fast achlorhydria, serum anti-parietal cell antibodies, and a serum vitamin B₁₂ of less than 160 pg/ml. In some patients a Schilling test, with and without oral intrinsic factor, was performed to confirm the diagnosis of pernicious anaemia.

Patients with thrombocytopenic purpura

This group consisted of patients with thrombocytopenia which appeared to be the direct result of sensitivity to drugs, and of patients with idiopathic thrombocytopenia purpura using the diagnostic criteria given by Doan, Bouroncle & Wiseman (1960) except that histological examination of the spleen was not possible.

Results

Addisonian pernicious anaemia

Fourteen patients with pernicious anaemia had platelet counts performed before and every 2 or 3 days after the start of therapy with intramuscular hydroxycobalamine. Eleven patients were thrombocytopenic before therapy, and nine of these had a rise in the platelet count to above normal levels after starting treatment; the peak platelet count was between 10 and 17 days after the first injection of vitamin B₁₂ (mean 14 days). No such platelet rise was demonstrated in patients starting with a normal platelet count (Table 1). The maximal platelet count occurred some days after the reticulocyte peak. Fig. 1 illustrates this difference in timing between the peak reticulocyte and platelet counts.

Thrombocytopenic purpura

Nine patients with acute thrombocytopenic purpura were studied. None required splenectomy and two recovered spontaneously. Seven were treated with a short course of prednisone. Six of the steroid-treated patients had a phase of thrombocytosis, the peak platelet count being 8-14 days after the start of prednisone (mean 10 days). The

TABLE 1. Platelet counts before and after start of vitamin B₁₂ therapy in patients with Addisonian pernicious anaemia

Patient	Platelet counts (per mm ³)		Time of highest platelet count (days after start of therapy)*
	Before therapy	Highest count after therapy	
1	46,000	331,000	16
2	56,000	168,000	—
3	23,000	385,000	17
4	39,000	376,000	13
5	46,000	321,000	14
6	213,000	261,000	—
7	185,000	248,000	—
8	81,000	426,000	13
9	18,000	298,000	16
10	78,000	555,000	10
11	10,000	230,000	—
12	200,000	208,000	—
13	115,000	564,000	13
14	13,000	520,000	12

*Where in excess of normal platelet count.

FIG. 1. Changes in the platelet (●) and reticulocyte (×) counts following the administration of vitamin B₁₂ (arrows) to a patient with Addisonian pernicious anaemia.

platelet counts of three of these patients are illustrated in Fig. 2. The two patients who received no specific therapy had only a gradual rise in the platelet count without a phase of thrombocytosis. To exclude the possibility that prednisone may induce a thrombocytosis in normal subjects, 40 mg of prednisone daily was taken by two healthy adults for 5 days. Their platelet counts before, during and after this course of prednisone are also illustrated in Fig. 2; no significant alterations in the platelet count took place.

FIG. 2. Response of the platelet count to prednisone in three patients with thrombocytopenic purpura (●) and in two normal subjects (○). Arrow indicates start of prednisone treatment.

Methotrexate therapy

We have reported previously that therapy with methotrexate (amethopterin) is followed, in most patients, by a reduction in the platelet count, and that this period of thrombocytopenia is succeeded by a thrombocytosis, maximal 10–17 days after cessation of the drug (Ogston, Dawson & Philip, 1968). This sequence of changes in the platelet count is illustrated in Fig. 3 from data obtained from three further patients given an intra-arterial infusion of methotrexate for the treatment of malignant disease. It can be seen that the peak platelet count occurred around 10 days after the time of the lowest platelet count.

FIG. 3. Changes in the platelet count during and following the administration of intra-arterial methotrexate to three patients.

Discussion

There is now considerable evidence from animal experiments that the level of circulating platelets influences their production by megakaryocytes. This evidence had been reviewed recently by Abildgaard & Simone (1967) and by Ebbe (1968). It is widely believed that a feedback mechanism is mediated by a humoral factor termed 'thrombopoietin' which is released in response to thrombocytopenia (De Gabriele & Penington, 1967a), and experimental thrombocytopenia in rats stimulates an increased production of platelets with a phase of thrombocytosis (Matter *et al.*, 1960; Odell, McDonald & Asano, 1962; De Gabriele & Penington, 1967b).

The thrombocytopenia of untreated pernicious anaemia is well established (Paddock & Smith, 1939), but we have been able to find only one previous study which draws attention to the moderate thrombocytosis occurring some 2 weeks after the start of therapy with vitamin B₁₂ (Rak *et al.*, 1967). The thrombocytopenia secondary to vitamin B₁₂ deficiency and to methotrexate therapy presumably results from interference with normal megakaryocyte metabolism.

Most investigators consider that the deficiency of platelets in idiopathic thrombocytopenic purpura results from accelerated destruction of platelets by antibodies rather than from a primary deficit in production (Davey, 1966; Najean *et al.*, 1967). Thrombocytopenia due to drug sensitivity is probably also secondary to antibody formation. In both types of thrombocytopenia the rationale of prednisone therapy is to diminish the damaging effect of antigen-antibody reactions at the surface of platelets.

We have illustrated three situations in man where thrombocytopenia, produced by different mechanisms, is commonly succeeded by thrombocytosis some 10-14 days after the elimination of factors

depressing platelet production or destroying formed platelets. These clinical observations favour the view, therefore, that thrombocytopenia in man, as in experimental animals, induces the release of a substance which stimulates platelet production.

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