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The influence of the platelet count on the incidence of thrombotic and haemorrhagic complications in polycythaemia vera

AUDREY A. DAWSON
M.D., M.R.C.P. (Ed.)
Senior Lecturer in Haematology

D. OGSTON
M.D., Ph.D., M.R.C.P. (Lond. & Ed.)
Lecturer in Medicine

Department of Medicine, University of Aberdeen

Summary

In polycythaemia vera, those patients who have an elevated platelet count develop more thrombotic and more haemorrhagic complications than those with a normal count, even when the haematocrit is maintained by therapy within the normal range.

Introduction

Thrombosis is a common complication of polycythaemia vera and the most frequent cause of death (Chievitz & Thiede, 1962). The authors of some standard haematological textbooks imply that the raised red blood cell volume is the major contributor to the thrombotic tendency of polycythaemia vera (Miale, 1967; Wintrobe, 1967) and recommendations for therapy take account of this view. De Gruchy (1964) and Britton (1969), however, consider that a raised platelet count is an additional important cause of thrombosis, and suggest that treatment be also directed to reduction of the number of platelets.

We have examined the case-records of a group of patients with polycythaemia vera in an attempt to assess the relationship of the circulating platelet level to thrombotic and haemorrhagic complications.

Patients and methods

We examined the records of the forty-six patients with polycythaemia vera admitted to the Aberdeen General Hospitals in the last decade who had had at least one platelet count performed. The majority of these patients were treated by at least one of the authors. The diagnosis was made after exclusion of secondary or relative polycythaemia by history, physical examination and conventional blood counts. In some cases, the red blood cell volume was measured by the use of chromium-51(^{51}Cr) labelled cells. Patients with clinical and laboratory evidence of other myeloproliferative disease at the time of presentation were excluded.

Thirty-six patients were treated by venesection and periodic intravenous injections of radioactive phosphorus (^{32}P) in a dosage of 4–6 mCi. The frequency of this therapy was adjusted to maintain the haematocrit in the normal range. In addition to this treatment, three patients had a course of busulphan, two had pyrimethamine, and two had radiotherapy to the spleen. Ten patients had no therapy other than venesection.

Platelet counts were performed by the method of Oettle & Spriggs (1951) on capillary blood. The normal range of the platelet count by this technique in this laboratory is 150–270,000/mm^3.

The other haematological techniques were carried out by the methods described by Dacie & Lewis (1963).

Results

Relationship of platelet count to mode of presentation

A platelet count was performed in thirty-eight of the forty-six patients at the time of initial presentation and before the start of treatment. These thirty-eight patients have been analysed separately.

Nineteen patients presented with symptoms of occlusive vascular disease; sixteen had an arterial occlusion, seven in a cerebral vessel, four in a major limb vessel, and two in digital arteries. Two patients had myocardial infarction and one had multiple arterial occlusions. Four patients presented with gastro-intestinal haemorrhage; in three this was associated with proven peptic ulceration. The remaining fifteen patients had neither haemorrhagic nor thrombotic complications at the time of presentation. The details of these three groups of patients are summarized in Table 1, and the individual platelet counts illustrated in Fig. 1.

The mean platelet count of the patients presenting with thrombosis was higher than in those without thrombotic or haemorrhagic complications but this difference was not statistically significant ($P > 0{\cdot}1$).

TABLE 1. Data on patients with polycythaemia at time of presentation

Mode of presentation	No.	Age (years) Mean	Age (years) SD	Haematocrit (%) Mean	Haematocrit (%) SD	White blood cell count (per mm³) Mean	White blood cell count (per mm³) SD	Platelet count (per mm³) Mean	Platelet count (per mm³) SD
With haemorrhage	4	64·3	4·0	—	—	25,300	18,970	699,000	219,800
With thrombosis	19	64·1	11·7	64·9	5·8	11,760	2,640	285,300	118,300
Without haemorrhage or thrombosis	15	61·0	9·6	64·7	6·2	9,190	2,850	236,100	53,500

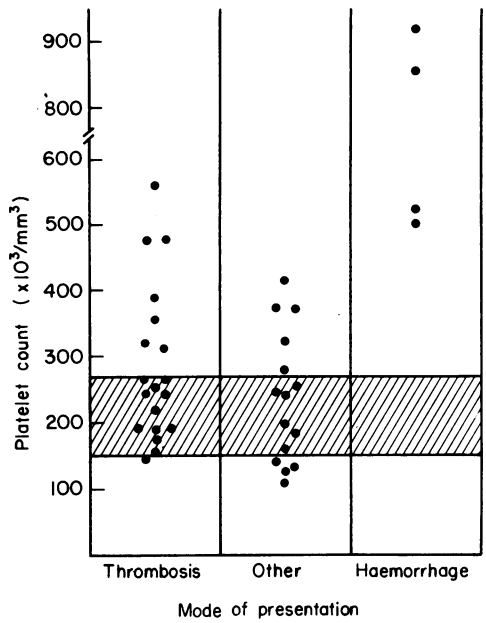

FIG. 1. Platelet counts at time of presentation.

The platelet count of the patients with recent thrombosis was not apparently related to the site of thrombosis. The mean haematocrit was no higher in the patients presenting with a thrombotic complication, and the correlation between the haematocrit and the platelet level in the thirty-four patients without recent haemorrhage was not significant ($r = -0{\cdot}13, P > 0{\cdot}1$).

The platelet count was elevated in the four patients presenting with bleeding. Massive gastrointestinal haemorrhage has been shown to be associated with a fall in the platelet count during, and for several days after, the haemorrhage, followed by a transient elevation during convalescence (Desforges, Bigelow & Chalmers, 1954). The raised platelet counts in our four patients with gastrointestinal haemorrhage did not appear to be related solely to the effect of haemorrhage since subsequent platelet counts in the three survivors of this group, performed at times when no recent haemorrhage had occurred, were also elevated.

Relationship of platelet count to thrombotic and haemorrhagic episodes during follow-up study

Twenty-five patients had regular platelet counts performed over many months, or years. Review of these counts showed that, if platelet levels during maximum haematological response to radioactive phosphorus or during busulphan or pyrimethamine therapy were excluded, most patients' platelet counts throughout the period of follow-up remained relatively constant. Thus, the initially elevated platelet counts showed no tendency to spontaneous reduction, while the platelet counts in the normal range showed no tendency to rise. In only two patients was there marked variability in the level of the platelets and both had persistently high counts. For the purposes of analysis, we have divided the patients into two groups; those with a platelet count in the normal range, and those with an elevated count (over 270,000/mm³). The incidence of thrombosis in those patients with a persistently raised platelet count was much higher than in the patients with a normal count (Table 2).

Accepting the relative stability of the platelet count in patients with polycythaemia, we have analysed the whole group of forty-six patients in relation to the available platelet counts with respect

TABLE 2. Relationship of incidence of thrombotic and haemorrhagic episodes to the platelet count (patients with regular platelet counts)

	No.	Time followed-up (months) mean	Thrombosis Episodes	Thrombosis Patients	Haemorrhage Episodes	Haemorrhage Patients
Repeatedly normal platelet counts	15	66·4	3	3	1	1
Repeatedly high platelet counts (over 270,000/mm³)	10	43·4	8	6	2	2

TABLE 3. Relationship of incidence of thrombosis and haemorrhagic episodes to the platelet count (all patients)

	No.	Mean time followed-up (months)	Thrombosis		Haemorrhage		Deaths
			Episodes	Patients	Episodes	Patients	
Normal platelet count	29	54·8	21	15*	4	3	7‡
High platelet count (over 270,000/mm³)	17	28·5	18	13†	7	6	4

* One had multiple thromboses at autopsy.
† Three had multiple thromboses at autopsy.
‡ One died of carcinoma of uterus, one died of acute myeloid leukaemia.

to the incidence of thrombotic and haemorrhagic episodes and the mortality during the period under surveillance.

The results summarized in Table 3 demonstrate the higher incidence of thrombosis in patients with high platelet counts in polycythaemia vera, and also shows an increase in the number of haemorrhagic incidents in that group. The death-rate is not greatly different, but the time of follow-up is considerably shorter. Nine of the eleven deaths resulted from a vascular thrombosis.

Discussion

Increased blood viscosity, secondary to the increase in the haematocrit, is generally considered to be the most important factor in the increased thrombotic tendency of patients with polycythaemia vera. Some believe that an increase in the platelet count may also be important. In the present study of patients with polycythaemia vera we have found that patients with an elevated platelet count developed, in the months and years after presentation, substantially more thrombotic complications than those with a normal count. This study, therefore, provides some evidence that a raised platelet count has an important role in the production of thrombotic lesions in polycythaemia vera.

The death-rate in this series was high—eleven out of the forty-six patients died (24%); in only two patients was death not the direct result of thrombosis, and five of these died within a month of presentation. In contrast only one patient developed acute myeloid leukaemia.

In planning therapy for patients with polycythaemia vera, attention has been focused in recent years on the risks of the late development of acute leukaemia as a result of administration of radioactive phosphorus (Perkins, Israels & Wilkinson, 1964; Modan & Lilienfeld, 1965); it seems salutary to stress again the more immediate dangers of thrombosis. This study points to the importance of a raised platelet count in the genesis of thrombosis in polycythaemia, and suggests that reduction of the haematocrit should be accompanied by measures directed to control of the platelet count.

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