Reactive thrombocytosis in pulmonary tuberculosis

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SUMMARY The incidence of reactive thrombocytosis in active pulmonary tuberculosis was studied in 122 patients. Thrombocytosis was common, platelet counts often exceeding 1 × 10¹²/l. A significant inverse correlation was noted between the mean platelet volume and the platelet count (r = −0·54, p < 0·0001). Interval estimation suggested that this relation was non-linear. Further studies were done in a small group of six patients. Platelet survival was considerably shortened, the platelets aggregated excessively in vitro, serum concentrations of thrombopoiesis stimulating activity were raised, and serotonin uptake and release were within normal limits. The degree of thrombocytosis correlated significantly with the degree of inflammation measured by the erythrocyte sedimentation rate (r = 0·40, p < 0·003) and serum C-reactive protein concentration (r = 0·35, p < 0·008).

Thrombocytosis occurs in many chronic inflammatory diseases, including tuberculosis.¹⁻⁴ The precise stimulus for increased platelet production in reactive thrombocytosis is not clear, but it is associated with increased numbers of small megakaryocytes in the marrow,⁴⁻⁶ which show reduced nuclear ploidy.⁵ The platelets are also small,⁷⁻⁹ but it has recently been suggested, that this may simply reflect the thrombocytosis, as there is normally an inverse correlation between the number and volume of platelets.¹⁰ The present study was done to define reactive thrombocytosis in acute tuberculosis with particular reference to the association between the volume and number of platelets, their survival, and certain aspects of their function.

Patients and methods

One hundred and twenty two patients with pulmonary tuberculosis were studied; most were of black or mixed racial origin. Twenty were newly diagnosed and about to begin antituberculous treatment, 82 had been diagnosed recently and were already being treated, and 20 were nearing the end of a six month course of treatment. A full blood count was done in all patients. Acute phase markers, including the erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) concentration were measured in 58 subjects, and thrombopoiesis stimulating activity was assessed in six untreated controls. Platelet function tests and platelet survival were also measured in five of these six subjects. Platelet counts were done weekly in a further seven patients to assess the effects of treatment on the reactive thrombocytosis.

Full blood counts, including platelet counts and platelet indices, were performed on a Coulter Model-S-Plus electronic counter (Coulter Electronics, Hialeah, Florida, USA) with standard calibration and quality control. CRP concentrations were measured by an immunoturbidometric method¹¹ on an IL III multistat centrifugal analyser (Instrumentation Laboratory, Lexington, Massachusetts, USA). CRP standards were obtained from Behringwerke (Marburg, West Germany) and antibodies to CRP from Dako (Copenhagen, Denmark). Serum thrombopoiesis stimulating activity was measured in a bioassay system¹² and the results were compared with those from three normal subjects whose activity was assigned the value of 100%. In the platelet survival studies autologous platelets were labelled with ¹¹¹Indium oxine and then reinfused. Survival was evaluated by the method of Thakur et al.,¹³ as modified by Heyns et al.¹⁴ Platelet aggregation was...
measured by the method of Born and Cross\(^1\) using a
Chronolog Dual Channel Aggregometer (Coulter
Electronics, Hialeah, Florida, USA) attached to a
Coulter Electronics OmniscrIBE recorder (Coulter
Electronics, Hialeah, Florida, USA). Platelet uptake
and release of radioactive serotonin were measured
by the method of David and Herion.\(^16\)

The study was approved by the Committee for
Research in Human Subjects of the University of the
Witwatersrand. Subjects were admitted to the study
only after it had been explained to them and their
informed consent obtained.

Linear correlation was determined by the Pearson
product-moment coefficient of correlation. Confi-
dence limits and residuals of the appropriate
regression line were calculated by regression analysis
using the statistical analysis system on an IBM 370
computer. Differences between discrete platelet count
intervals in terms of normal platelet volumes were
determined both by analysis of variance and by
sequential Student's \(t\) tests with a Bonferroni cor-
rection.

**Results**

The mean platelet count in the 20 patients about to
start treatment was 582.6 \(\times 10^9/1\) (SD 194.8), 681.0
\(\times 10^9/1\) (SD 232.0) in the 82 who had just started
treatment, and 292.4 \(\times 10^9/1\) (SD 75.9) in the 20
neighbouring the end of the course. A normal range of
159-415 \(\times 10^9/1\) (mean 283 \(\times 10^9/1\)) was established
in 564 normal subjects of black, white, and mixed
race. There were no statistical differences between
platelet counts in the first two groups but both were
significantly different from the group nearing the end
of the course (\(t = 6.2, p < 0.005\) and \(t = 7.4,\)
\(p < 0.005\), respectively). Seven patients who were
already being treated, and who had reactive thrombo-
cytosis, had platelet counts weekly for 11 weeks.
There was a steady, though modest, drop from the
seventh week onwards, the final mean value being
about 70% of the original.

The mean platelet volume was normally distrib-
uted, with a skewness of 0.3941. There was a
significant inverse correlation between mean platelet
volume and platelet number, with a Pearson prod-
uct-moment coefficient of correlation of \(-0.54\)
\((p < 0.0001)\). Interval analysis suggested that the
inverse correlation was not linear (figure). Platelet
volumes in the lower ranges were significantly
different from those in the higher ones. The fact that
there was no significant difference between mean
platelet volumes for intervals at higher platelet counts
emphasised that the volume number inverse relation
was not linear. In a further analysis the values of
mean platelet volume for the various intervals in the
patients with tuberculosis were compared with those
in the 564 normal subjects. There was no significant
difference between the two groups at any interval over
the normal range (figure).

In vitro platelet aggregation in five of the subjects
suggested that their platelets might aggregate abnor-
malhly; this was best illustrated by the aggregation in
response to arachidonic acid. The minimal doses
inducing full aggregation were 0.4, 0.2, 0.3, 0.3 and
0.3 mmol (normal minimal dose 0.5-1.0 mmol). In
contrast, serotonin uptake and release remained nor-
mal. Platelet survival was reduced and concentrations
of thrombopoiesis stimulating factor were
significantly raised in the five subjects (table).

![Non-linear correlation between mean platelet volume (2 SD) and given platelet intervals in normal subjects (-----) and patients (-----), with reactive thrombocytosis in pulmonary tuberculosis.](http://jcp.bmj.com/)

The relation between the increased platelet count
and the activity of the disease was assessed further in
58 patients receiving treatment. There was a
significant direct correlation between the ESR and the
platelet count \((r = 0.40, p < 0.003)\) and between the
serum CRP concentration and the platelet count
\((r = 0.35, p < 0.008)\). The CRP and ESR correlated
significantly with each other \((r = 0.50; p < 0.0001)\).

**Discussion**

The association between tuberculosis and thrombo-
cytosis has been reported\(^1\) but as an uncommon
occurrence,\(^17\) and in a 1974 review of the haem-
atological complications of tuberculosis it was not
even mentioned.\(^16\) Though our study was not
designed to assess prevalence, it seemed that reactive
thrombocytosis was common in our group of patients
with active pulmonary tuberculosis, and that it could
be severe, with eight (9%) of the 92 having platelet counts of \(> 1000 \times 10^9/\text{l}\).

The present findings have shown an inverse, nonlinear relation between mean platelet volume and platelet count in active tuberculosis, and also that platelet survival is considerably shortened. The correlation between high platelet counts and decreased platelet life span shows that thrombocytosis must be increased. The finding that many of the circulating platelets are both young and small in reactive thrombocytosis runs counter to the hypothesis that young platelets tend to be large.\(^\text{19,20}\) Why they should be small is not known, although it may be associated with the fact that the megakaryocytes in states of reactive thrombocytosis tend to be small.\(^\text{4-6}\)

The possibility that the increased numbers of small young platelets might be a feature of pulmonary tuberculosis was also considered. The pulmonary vasculature is thought to contribute to the production of platelets by fragmenting proplatelets,\(^\text{21}\) and the question arose as to whether a diseased microvasculature in pulmonary tuberculosis might lead to excessive fragmentation and hence smaller platelets. Such an explanation seems untenable, however, as a parallel study on the reactive thrombocytosis of rheumatoid arthritis gave results identical with those in pulmonary tuberculosis (unpublished observations).

The raised concentrations of serum thrombopoiesis stimulating activity in patients with pulmonary tuberculosis suggest the presence of a circulating stimulatory factor, which is in keeping with a previous report of increased thrombopoietin concentrations in patients with tuberculosis.\(^\text{22}\) It must be emphasised, however, that the bioassay used in the present study cannot distinguish between diverse stimulators of different chemical composition. The fact that small platelets are produced in reactive thrombocytosis suggests that the inflammatory mediator is different from the one operating in idiopathic thrombocytopenia, because the platelets are large in this condition. Therefore, the large megakaryocytes of low nuclear ploidy, which are a feature of idiopathic thrombocytopenia,\(^\text{2}\) may be the result of stimulation via a mediator induced by thrombocytopenia, and the small megakaryocytes of low nuclear ploidy, which occur in reactive thrombocytosis,\(^\text{5}\) may result from an inflammation induced stimulator.

Our finding that platelets can aggregate excessively in reactive thrombocytosis in tuberculosis is at variance with the observations of Thompson et al.\(^\text{23}\) It is, however, compatible with a recent report of synergism between platelet agonists and the acute phase reactant, CRP.\(^\text{24}\) In the 58 patients in the present study in whom CRP was evaluated the mean serum concentration was 60.8 (SD 37.2) mg/l (normal values < 12 mg/l). Therefore, the increased quantities of CRP, which were present in the platelet rich plasma, might have been acting in concert with aggregation agonists to produce excessive aggregation.

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**References**

Platelets and tuberculosis


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