Case report

Thrombocytosis in rheumatoid arthritis

Recurrent arterial thromboembolism and death

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SUMMARY A patient with rheumatoid arthritis complicated by excessive thrombocytosis and recurrent thromboembolic events is presented. The platelet count correlated well with disease activity and thrombosis occurred when thrombocytosis was marked. The patient died from massive thrombosis of the aorta despite treatment with anticoagulants, corticosteroids, and azathioprine.

Thrombocytosis may occur in association with autoimmune, collagen, and malignant diseases (Levin and Conley, 1964; Bean, 1965; Selroos, 1972; Davis and Mendez Ross, 1973). In rheumatoid arthritis a positive correlation has been found between the platelet count and disease activity (Bean, 1965; Selroos, 1972; Hryszko *et al.*, 1975; Hernandez, 1975; Hutchinson *et al.*, 1976). Thrombosis is infrequent in rheumatoid arthritis and when present is usually related to coexisting arteritis. Thromboembolic complications have rarely been related to thrombocytosis (Davis and Mendez Ross, 1973). We report a patient with rheumatoid arthritis complicated by excessive thrombocytosis and recurrent arterial thrombosis who died of massive thrombosis of the aorta despite treatment with anticoagulants, corticosteroids, and azathioprine.

Case report

In 1968 a 38-year-old Jewish female of Ashkenazi origin, married and mother of 2, began to suffer from typical rheumatoid arthritis affecting the joints of the hands, the feet, and the knees. Treatment with aurothioglucose 50 mg per week and prednisone 30 mg daily was started in 1970. The symptoms responded promptly and after 20 injections of gold she was maintained on 50 mg gold once a month and 5 mg prednisone daily. She was in complete clinical and laboratory remission for 4 years. In 1974 she was admitted to another hospital because of a sudden severe pain in the lower part of her left

leg. Femoral arteriography showed a complete high obstruction. Emergency surgery showed 'white' clots in the superficial femoral and the popliteal arteries which were easily removed. The arterial wall appeared normal. No further studies were done and the patient was started on heparin and bishydroxycoumarin.

Two months later severe arthritis recurred. Several days after readmission a sudden episode of right hemiplegia and aphasia occurred which lasted 15 minutes and subsided completely. Platelet count was $800 \times 10^9/l$ ($800\,000/mm^3$) and prothrombin time 27%. She was started on azathioprine 150 mg daily and additional therapy of dipyridamole 225 mg daily, prednisone 15 mg daily, and bishydroxycoumarin as needed. 2 months later while on this treatment the platelet count was $426 \times 10^9/l$, spontaneous platelet aggregation was 86% (normal 35%), and ADP-induced aggregation was 95% (normal $\geq 85\%$). In spite of the treatment, exacerbations of arthritis continued and the platelet count fluctuated together with the erythrocyte sedimentation rate (Fig.). A recurrence of right hemiparesis lasting a few seconds occurred again when the platelet count was $344 \times 10^9/l$.

The last admission took place about 6 months after the first thrombotic episode and was due to another attack of right hemiplegia. Platelet count was again $800 \times 10^9/l$. On the 19th day of admission severe abdominal pain and shock occurred. Exploratory laparotomy showed multiple thrombi in the abdominal aorta and the iliac arteries. Embolectomy was performed but she died in shock shortly thereafter. Permission for autopsy was not granted.

Fig. Relationship between platelet count, erythrocyte sedimentation rate, and thromboembolic events.

Discussion

Our patient had recurrent episodes of major arterial occlusions at different sites. Thrombosis occurred always during exacerbation of arthritis and was associated with marked thrombocytosis. On one occasion a 'white' (platelet) clot was removed from the femoral artery. Exploration of the affected arteries on two occasions showed no evidence of inflammation of the arterial wall. We therefore conclude that in this case thrombosis was related to thrombocytosis and that the latter reflected the activity of the disease.

Thromboembolic phenomena in autoimmune diseases are usually ascribed to a hypercoagulable state (Hollander and McCarty, 1972), vasculitis (McAdam *et al.*, 1975), and presumably to thrombocytosis (Williams *et al.*, 1972). Steroid therapy has been implicated in the pathogenesis of a hypercoagulable state and vasculitis but not in a raised platelet count.

Thrombocytosis has been found in one-third of 115 patients with severe rheumatoid arthritis (Selroos, 1972). Other authors have reported figures like 22% (Hryszko *et al.*, 1975), 12% (Hernandez *et al.*, 1975), and even 52% (Hutchinson *et al.*, 1976). When present, thrombocytosis usually correlates positively with the disease activity as reflected by clinical and other laboratory parameters (Bean, 1964; Selroos, 1972; Hryszko *et al.*, 1975; Hutchinson, 1976). Relapses of arthritis may frequently be associated with the appearance of thrombocytosis, while remissions are usually accompanied by a decreased

platelet count. Hutchinson *et al.* (1976) have noted the association between extreme thrombocytosis and extra-articular manifestations of the disease, in particular pulmonary involvement, peripheral neuropathy, and vasculitis. Hernandez *et al.* (1975) reported acute joint exacerbation in 17 patients and vasculitis in 2 out of 24 patients with rheumatoid arthritis and thrombocytosis.

The association between marked thrombocytosis and thrombosis is well known. Spontaneous hyperaggregation of platelets appears to be the cause of thrombosis leading to painful toes and fingers (Vreeken and Van Aken, 1971). Essential thrombocytosis can cause peripheral gangrene due to vascular thrombosis (Preston *et al.*, 1974) and splenectomy is sometimes followed by thrombosis associated with excessive thrombocytosis (Hayes *et al.*, 1963).

Thromboembolic complications in rheumatoid arthritis require treatment to reduce the raised platelet count. Conventional anticoagulant therapy failed to prevent subsequent thrombotic episodes in our patient and does not decrease platelet aggregation. Since thrombocytosis reflects rheumatoid activity, therapy should aim to suppress concomitantly the inflammatory process and platelet production. Bean (1965) reported 3 patients in whom methotrexate therapy resulted in marked improvement of arthritis and a coincident decrease in the platelet count. A similar effect has been described in 3 patients after treatment with corticosteroids alone (Hutchinson *et al.*, 1976). On the other hand, thrombocytosis was not affected by treatment with

nonsteroid anti-inflammatory agents, gold, D-penicillamine, and in some patients corticosteroids (Hernandez *et al.*, 1975; Hutchinson *et al.*, 1976). As mentioned above, azathioprine had a partial effect on the platelet count in our patient, but thromboembolic episodes were not prevented. Thrombosis seems to be an extremely rare cause of death in rheumatoid arthritis and, to the best of our knowledge, this is the first reported case. Nevertheless, in view of the possible serious complications, thrombocytosis in rheumatoid arthritis should be regarded as an indication for intensive and effective therapy with corticosteroids, immunosuppressive, anticoagulant, and antiplatelet aggregation agents.

References

- Bean, R. H. D. (1965). Thrombocytosis in auto-immune disease. *Bibliotheca Haematologica*, **23**, 43–49.
- Davis, W. M., and Mendez Ross, A. O. (1973). Thrombocytosis and thrombocythemia. *American Journal of Clinical Pathology*, **59**, 243–247.
- Hayes, D. M., Spurr, C. L., Hutaff, L. W., and Sheets, J. A. (1963). Postsplenectomy thrombocytosis. *Annals of Internal Medicine*, **58**, 259–267.
- Hernandez, L. A., Rowan, R. M., Kennedy, A. C., and Buchanan, W. M. (1975). Thrombocytosis in rheumatoid arthritis; a clinical study of 200 patients. *Rheumatology*, **6**, 635–639.
- Hollander, J. L., and McCarty, D. J. (1972). *Arthritis and Allied Conditions. A Textbook of Rheumatology*, 8th ed., p. 510. Lea and Febiger, Philadelphia.
- Hryszko, S., Pietruska, Z., Bernacka, K., and Bogdanikowa, B. (1975). Thrombocytosis in rheumatoid arthritis in the light of observation of 150 patients. *Rheumatologia*, **13**, 255–261.
- Hutchinson, R. M., Davis, P., and Jayson, M. I. V. (1976). Thrombocytosis in rheumatoid arthritis. *Annals of the Rheumatic Diseases*, **35**, 138–142.
- Levin, J., and Conley, C. L. (1964). Thrombocytosis associated with malignant disease. *Archives of Internal Medicine*, **114**, 497–500.
- McAdam, L. P., O'Hanlan, M. A., Pearson, C. M., and Bluestone, R. (1975). Relapsing polychondritis. A steroid responsive disease? *Arthritis and Rheumatism*, **18**, 415.
- Preston, F. E., Emmanuel, I. G., Winfield, D. A., and Malia, R. G. (1974). Essential thrombocythaemia and peripheral gangrene. *British Medical Journal*, **3**, 548–562.
- Selroos, O. (1972). Thrombocytosis in rheumatoid arthritis. *Scandinavian Journal of Rheumatology*, **1**, 136–140.
- Selroos, O. (1973). Thrombocytosis. *Acta Medica Scandinavica*, **193**, 431–436.
- Vreeken, J., and Van Aken, W. G. (1971). Spontaneous aggregation of blood platelets as a cause of idiopathic thrombosis and recurrent painful toes and fingers. *Lancet*, **2**, 1394–1397.
- Williams, W. J., Beutler, E., Erslev, A. J., and Rundles, R. W. (1972). *Hematology*. 1st ed., p. 1163. McGraw-Hill, New York.