

Chrysotherapy and thrombocytopenia

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SUMMARY In a study of the clinical and immunogenetic profiles of 17 patients with rheumatoid arthritis and thrombocytopenia (platelet count $<150\,000/\text{mm}^3$ ($150 \times 10^9/\text{l}$)) due to gold therapy two clinical patterns were distinguished without knowledge of HLA type: group I, an early precipitous thrombocytopenia (10 patients), and group II, a less dramatic fluctuant fall (seven patients). In group I patients the clinical and laboratory features suggested an immune mediated, peripheral destruction of platelets, and all patients in this group were found to be HLA-DR3 positive. Two patients subsequently received penicillamine without toxicity. In group II the basis of thrombocytopenia appeared to be different, and only two patients in this group were HLA-DR3 positive. All group II patients had received penicillamine; four developed a thrombocytopenia. Mechanisms of toxicity in both groups are discussed. It would appear that HLA typing is unlikely to help in predicting all those patients at risk of toxicity during chrysotherapy.

Gold therapy carries with it a risk of a life threatening toxic reaction.^{1–4} Blood dyscrasias, especially thrombocytopenia, are not uncommon. Gold induced thrombocytopenia is alarming: it is frequently sudden, severe, and unpredictable but may occur more gradually and does not appear to be dose related.⁵ The mechanism of thrombocytopenia remains uncertain but may be due to direct marrow suppression or to specific antiplatelet antibody production. An association with the class II B cell isoantigen HLA-DR3 and with the class I antigen HLA-B8 has previously been found in patients with a profound thrombocytopenia.⁶

In order to determine whether this marker can help in predicting all those at risk of developing a thrombocytopenia the clinical features and outcome of 17 patients with gold induced thrombocytopenia with respect to class II antigen type have been compared.

Patients and methods

CLINICAL REVIEW

The case notes of 17 patients with classical or definite rheumatoid arthritis (RA) in whom sodium

aurothiomalate (GST) therapy was discontinued due to persistent thrombocytopenia (platelet count $<150\,000/\text{mm}^3$ ($150 \times 10^9/\text{l}$)) on more than three occasions) were reviewed. The association with GST was confirmed by an independent observer (HC) unaware of the HLA typing results. The information sought in the case notes included: (a) total dose of GST; (b) mode of onset, pattern, and outcome of thrombocytopenia; (c) subsequent or prior penicillamine therapy; and (d) bone marrow morphological features and the presence or absence of antiplatelet antibodies.

HLA TYPING

Human leucocyte antigens (HLA) were identified by a standard microcytotoxicity technique covering 51 antigens of the A, B, and C loci and eight DR specificities (DR1–8 inclusive).

ANTIPLATELET ANTIBODIES

Platelet antibodies were sought by the suspended immunofluorescence test⁸ and platelet associated immunoglobulin by an enzyme-linked immunosorbent assay.⁹

Results

CLINICAL

All patients developed thrombocytopenia while

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receiving gold. Two kinds of clinical presentation were obvious with no prior knowledge of HLA antigen status.

GROUP I

In 10 patients there was a precipitous early thrombocytopenia: eight patients had platelet counts $<5000/\text{mm}^3$ ($5 \times 10^9/\text{l}$) (median $5000/\text{mm}^3$ ($5 \times 10^9/\text{l}$), range $5000\text{--}67\,000/\text{mm}^3$ ($5\text{--}67 \times 10^9/\text{l}$)). Median duration of GST treatment was three months (range one to eight months), and median total dose of GST was 675 mg (range 200–1020 mg). Sternal marrow aspirates in nine patients showed megakaryocytosis in eight. Antiplatelet antibodies were present in five of six patients tested. High titres of platelet associated immunoglobulin were present in three patients. All patients recovered uneventfully, and no life threatening haemorrhagic complications were encountered. The platelet count in all patients returned to $>150\,000/\text{mm}^3$ ($150 \times 10^9/\text{l}$) within 15 weeks of stopping GST (median nine days; range four days to 15 weeks). Corticosteroid therapy was used in six patients, and the maximum duration of corticosteroid therapy was 12 months. Two patients subsequently received D-penicillamine with no toxicity.

GROUP II

Seven patients had a gradual onset of thrombocytopenia. Median duration of GST therapy was five months (range three to 46 months), and median total dose of GST was 810 mg (range 300–3750 mg). Median lowest platelet count was $123\,000/\text{mm}^3$ ($123 \times 10^9/\text{l}$) (range $65\,000\text{--}132\,000/\text{mm}^3$ ($65\text{--}132 \times 10^9/\text{l}$)). In one of three sternal marrow examinations megakaryocytes were reduced. Antiplatelet antibodies were not detected in four of the patients tested. No patient received corticosteroid therapy. Platelet counts returned to $>150\,000/\text{mm}^3$ ($150 \times 10^9/\text{l}$) within four weeks of stopping GST (median 14 days; range seven to 28 days). All patients within this group had received D-penicillamine (three before and four after GST), and four developed a thrombocytopenia, but no other toxic reactions occurred.

HLA TYPE

All 10 (100%) group I patients were HLA-DR3 antigen positive, and HLA-B8 which is commonly present with DR3 due to linkage disequilibrium was present in nine. Only two (29%) of the group II patients were HLA-DR3 antigen positive (group I significant $p < 0.05$ Fisher's exact probability test). As expected HLA-DR4 was equally common in both groups. (DR4 occurs in 56% (range 33–71%)

of patients with RA and in 26% (range 20–33%) of controls.⁷)

Discussion

This study identifies two distinct subtypes of GST induced thrombocytopenia, suggesting different underlying mechanisms. The clinical pattern, marrow megakaryocytosis, and presence of antiplatelet antibodies in group I suggest an autologous antibody mediated peripheral destruction of platelets, and it appears unlikely that in this group gold has a direct suppressive effect on the marrow. Other workers^{10,11} have shown that platelet survival is reduced and that phagocytosis by splenic macrophages occurs in gold induced thrombocytopenia.¹² It is possible that GST may stimulate antiplatelet antibodies by several mechanisms: (1) It may bind irreversibly to the platelet membrane, and subsequently either gold or the thiol moiety may act as haptens. (2) Alternatively, GST may act as a hapten bound to a plasma protein macromolecule, which then acts as the immunogen, the platelets being innocent bystanders which non-specifically adsorb the resulting immune complexes. It has been shown that the HLA-DR3 phenotype is associated with delayed Fc receptor mediated clearance of IgG sensitised autologous erythrocytes.¹³ GST accumulates in the mononuclear-phagocyte system¹⁴ and might therefore enhance this effect.

The HLA-B8, DR3 phenotype is strongly associated with autoimmune diseases. The aberrant expression of class II major histocompatibility antigens by several cell lines is established^{15–18} and is one postulated mechanism for the development of autoimmune phenomena.¹⁹ The finding in the present study that all group I patients are HLA-DR3 positive raises the possibility that exposure to gold may result in the aberrant expression of this antigen on the megakaryocyte or earlier progenitor cell.

The features observed in the second group with a more gradual onset of thrombocytopenia and absent antiplatelet antibodies are not so readily explained. The clinical findings are more in keeping with a direct selective suppression of thrombopoiesis. Both marrow aplasia and granulocytopenia due to GST are recognised.⁵ GST in vitro inhibits the formation of granulocyte macrophage colonies in a dose dependent manner in concentrations that are achieved in vivo,²⁰ but the exact mechanism by which gold compounds induce cellular toxicity is not known. The interaction of GST with sulphhydryl groups is one postulated mechanism of gold toxicity²¹ and of its therapeutic effect.²² It is therefore of interest that four group II patients have

also developed a thrombocytopenia on penicillamine, another thiol containing compound.

The strong association in group I with the presence of HLA-DR3 raises the question whether GST should be withheld in DR3 positive patients. Prospective studies to determine the risk of toxicity in this subset have been suggested, but this approach would represent a considerable financial undertaking.²³ Approximately 26% of patients with RA possess HLA-DR3, and the highest estimated incidence of GST thrombocytopenia is 8% (more commonly around 3%). In our study 60% of patients with thrombocytopenia belonged to group I, therefore less than 5% (probably less than 2%) of gold treated patients are liable to develop a sudden, precipitous thrombocytopenia. If prior HLA typing dictated choice of therapy, four out of five DR3 positive patients would be unnecessarily denied the potential benefits of GST therapy. At present the HLA association with gold induced thrombocytopenia is more of theoretical than practical interest.

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