

CASE REPORT

Two patients with acute thrombocytopenia following gold administration and five-year follow-up

M-D. Levin^{1*}, M.B. van 't Veer², J.C. de Veld², H.M. Markusse^{3†}

¹Department of Haematology, Erasmus Medical Centre, Dr. Molewaterplein 40, 3015 GD Rotterdam, the Netherlands, tel.: +31 (0)10-463 92 22, fax: +31 (0)10-463 58 14, e-mail: Levin@xs4all.nl,

²Department of Haematology, Erasmus MC-Daniel den Hoed, ³Department of Rheumatology, Rijnmond Zuid Medical Centre, * corresponding author, † deceased 5 May 2002

ABSTRACT

Thrombocytopenia is a well-known side effect following intramuscular gold therapy in patients with rheumatoid arthritis. Thrombocytopenia may occur at any time and it can be irreversible and sometimes fatal despite cytotoxic or immunosuppressive therapy.

We describe two patients who presented with haemorrhagic diathesis on the day after the administration of aurothioglucose. The thrombocytopenia in these patients was caused by aurothioglucose-induced antibody-mediated platelet destruction. Both patients made an uneventful recovery and the platelet count returned to normal within several weeks without further treatment. Antibody-detecting tests were repeated five years later and could not demonstrate the presence of antibodies. Also after incubation with aurothioglucose no antibodies could be demonstrated.

INTRODUCTION

Haematological abnormalities are well-known complications following intramuscular gold therapy in patients with rheumatoid arthritis¹⁻³ with an incidence of 1 to 3% in most series. The occurrence of thrombocytopenia during gold therapy is unpredictable and may occur at any time during treatment. Development of thrombocytopenia may be insidious or acute and the cause can be diverse and sometimes difficult to assess. Both bone marrow depression and antibody-mediated platelet destruction have been described.^{4,7} The course of thrombocytopenia can be irreversible and sometimes fatal despite cytotoxic or immunosuppressive therapy. Long-term follow-up after thrombocytopenia caused by antibodies directed against

platelets in the presence of gold is unknown.

We studied the cause of thrombocytopenia in two patients who presented on the day after the administration of aurothioglucose with severe haemorrhagic diathesis.

CASE REPORTS

Patient 1

A 51-year-old woman was seen in our outpatient clinic because of a seropositive, erosive and nodular rheumatoid arthritis (RA) since 1991. After initial treatment with sulphasalazine, intramuscular aurothioglucose was started at 100 mg weekly until a cumulative dose of 1000 mg. While receiving a dose of 50 mg aurothioglucose once every two weeks, to a cumulative dose of 1350 mg, she mentioned that she was developing haematomas on the day after the aurothioglucose injection. During outpatient follow-up no haematomas and normal platelet counts ($192\text{--}320 \times 10^9/l$) were found on the day the aurothioglucose was given. Clinical examination one day after the aurothioglucose injection showed petechiae and haematomas and the platelet count had fallen from $238 \times 10^9/l$ to $6 \times 10^9/l$ in two days. Indomethacin, calcium and vitamin D were stopped and prednisone 7.5 mg daily was continued. A bone marrow biopsy showed normocellular bone marrow with normal megakaryopoiesis. Immunoglobulin G (IgG) could be demonstrated on the patient's platelets by the direct platelet immunofluorescence test and the ether-eluate made of the patient's own platelets reacted positively to donor platelets (table 1). Also IgG was demonstrated on donor platelets after incubating with the patient's serum.⁸ No binding of

immunoglobulin of the IgM class was observed on the platelets.⁹ With no additional treatment her platelet count gradually returned to normal in three weeks (*figure 1*) and no further aurothioglucose was given.

Five years later all tests were repeated without aurothioglucose and with four different aurothioglucose concentrations (*table 1*).¹⁰⁻¹⁵ All tests showed no detectable IgG on donor and patient's platelets.

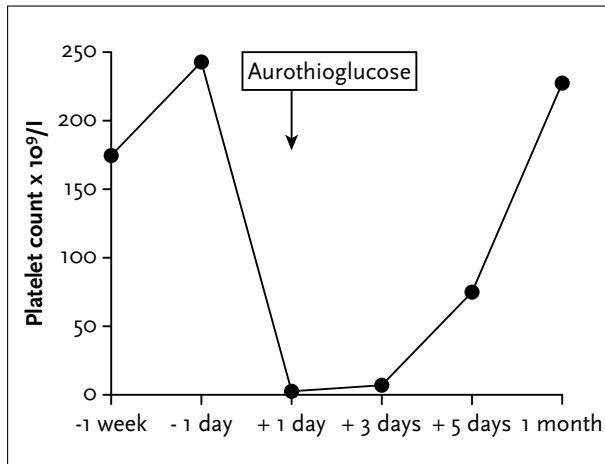


Figure 1
Platelet count of patient 1 during aurothioglucose-induced thrombocytopenia

Table 1
Tests measuring antibodies against platelets of both patients during five-year follow-up

TESTS	PATIENT 1	PATIENT 2
Indirect PIFT during admission ¹	+	+
Direct PIFT during admission ²	+	+
Ether-eluate test during admission ³	+	+
Indirect PIFT after five years	-	-
Indirect PIFT after five years with aurothioglucose ⁴	-	-
Direct PIFT after five years	-	-
Ether-eluate after five years	-	-

¹ Indirect Platelet Immunofluorescence Test: incubation of donor platelets, patient's serum and anti-IgG-FITC. ² Direct Platelet Immunofluorescence Test: incubation of patient's platelets and anti-IgG-FITC. ³ Eluate: reincubation of ether-eluated patient platelets to donor platelets and anti-IgG-FITC. ⁴ Indirect PIFT after *in vitro* incubation with four concentrations of aurothioglucose.

Patient 2

A 47-year-old woman was seen in our outpatient clinic because of a seropositive and erosive RA since 1989. After treatment with sulphasalazine, intramuscular aurothioglucose was given at a dose of 50 mg weekly until a cumulative

dose of 1000 mg was reached. After a cumulative dose of 2700 mg, while receiving aurothioglucose injections of 25 mg every third week, she mentioned that haematomas had started to develop the day after the aurothioglucose injection. No skin abnormalities, however, were noticed during outpatient follow-up and the platelet counts were repeatedly normal ($260-330 \times 10^9/l$) before the next injection. However, the clinical examination three days after the injection revealed petechiae and haematomas and the platelet count had fallen from $280 \times 10^9/l$ to $18 \times 10^9/l$. The bone marrow biopsy showed normal megakaryopoiesis and normocellularity. Immunofluorescence tests demonstrated IgG on patient's own platelets and on donor platelets after incubating with patient's serum. An eluate made from patient's platelets reacted positively with donor platelets (*table 1*). No IgM antibodies could be demonstrated. aurothioglucose injections were stopped and without additional treatment her platelet count returned to normal (*figure 2*). Five years later all tests were repeated with serum alone and with four different concentrations of aurothioglucose (*table 1*). All tests showed no IgG on the patient's platelets (direct immunofluorescence test). Platelets from one of three donors showed binding of IgG to platelets after incubation with patient's serum without aurothioglucose, probably caused by HLA antibodies.

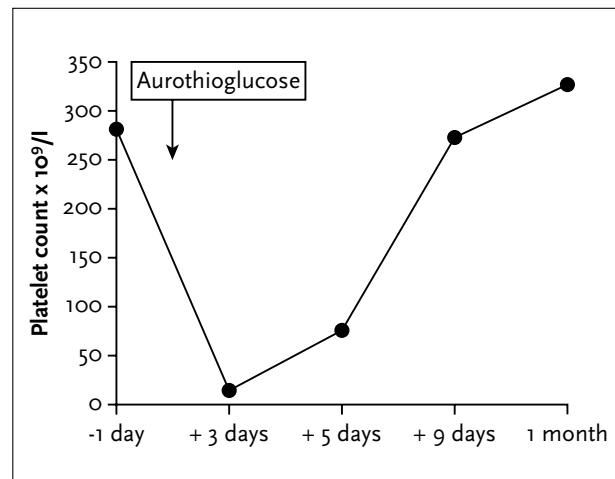


Figure 2
Platelet count of patient 2 during aurothioglucose-induced thrombocytopenia

DISCUSSION

In patients with RA, thrombocytopenia can be caused by decreased thrombopoiesis, increased platelet destruction and platelet pooling. Increased platelet destruction is regularly encountered, caused by autoantibody-mediated destruction on the basis of concomitant diseases (e.g. Felty's syndrome) or medication. Gold, as has been

described in several case reports,¹ can cause thrombocytopenia by bone marrow aplasia^{4,5} or antibody-mediated platelet destruction.^{6,7} Gold-induced aplasia is often refractory to treatment. Most patients die of septic shock before or after receiving immunosuppressive or cytoreductive therapy or even bone marrow transplantation.^{4,5} Gold-induced antibody-mediated platelet destruction has been described by several authors in case reports or small case series.²⁻⁵ Some studies showed HLA-DR3 positivity in 68 to 100% (normal prevalence 23%) of the patients.^{3,16,17}

The positive direct and indirect platelet immunofluorescence tests (positive tests to donor and patient platelets together with positive eluate reactions) can point to antibodies directed against platelet-specific antigens (e.g. idiopathic thrombocytopenia, Aldomet), against hidden antigens exposed in the presence of aurothioglucose (as seen in EDTA-dependent thrombocytopenia), or against aurothioglucose itself, the platelet being destroyed by the antibody-antigen complex as an innocent bystander. The positive reaction of the eluate with donor platelets, however, excluded antibody-antigen complexes. The negative tests five years later with incubation of aurothioglucose made the mechanism with a hidden antigen unlikely. The tests point to a true autoantibody character of the antibodies directed against a platelet-specific antigen, but induced by aurothioglucose. The rapid resolution of the thrombocytopenia points to a dose-dependent reaction of this autoantibody induction. Gold administration can induce acute autoantibody-mediated platelet destruction that is completely reversible without treatment. Serious attention should be paid to patients who report haemorrhagic diathesis in the days following drug administration of any kind.

NOTE

Case histories and data were presented at the HOVON continuous medical education day 2002 in Rotterdam.

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