Thrombocytopenia due to aurothioglucose, sulphasalazine, and hydroxychloroquine

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Abstract

A 56 year old woman with rheumatoid arthritis developed relapsing thrombocytopenia during successive treatments with aurothioglucose, sulphasalazine, and hydroxychloroquine. The presence of IgM or IgG antibodies or immune complexes reactive with autologous platelets could not be shown. Relapsing thrombocytopenia may indicate a genetically determined HLA-DR3 and B8 aberrant immunological response to stimuli such as certain second line drugs.

Treatment with second line antirheumatic drugs often produces side effects. In this report we describe an exceptional patient with rheumatoid arthritis who developed isolated thrombocytopenia during successive treatments with aurothioglucose, sulphasalazine, and hydroxychloroquine. Although thrombocytopenia is a common side effect of parenteral gold, it is very rare during treatment with sulphasalazine and has only once been reported to be caused by hydroxychloroquine.

Case report

A 56 year old woman had had seropositive rheumatoid arthritis since January 1986. Initial treatment consisted of non-steroidal anti-inflammatory drugs. Because of persistent disease activity, parenteral gold (aurothioglucose 50 mg weekly) was added. After five months this effective treatment had to be discontinued because of dermatitis and proteinuria. Parenteral gold treatment was reinstated after one year in a very low dose (5 mg monthly). During the four months that this low dose treatment was given, the patient reported neither improvement nor side effects.

In August 1988 the patient visited our hospital for the first time. Physical examination showed active polyarthritis of the hands, wrists, elbows, and forefeet. Laboratory investigations showed an increased erythrocyte sedimentation rate (ESR) of 89 mm in the first hour; a haemoglobin concentration of 98 g/l; a white cell count of $5.7 \times 10^9/l$ with a normal differential; a platelet count of $85 \times 10^9/l$; no antinuclear antibodies. A Rose-Waaler test gave a result of 320 IU, and the latex reaction was 50 IU. There was no proteinuria. HLA typing was done and showed the presence of HLA-B8 and HLA-DR3 antigens. Because of the thrombocytopenia the platelet count was repeated after a few days; it then amounted to $150 \times 10^9/l$. A month later the platelet count was $186 \times 10^9/l$ and parenteral

gold was resumed, now in the usual dose of 50 mg. After a single intramuscular injection severe thrombocytopenia with a platelet count of $5 \times 10^9/l$ occurred. Physical examination yielded normal results, in particular, no signs of bleeding or enlargement of the spleen were found. All drug treatment, including parenteral gold, naproxen, and paracetamol, except temazepam, was discontinued. Treatment consisted of an infusion of 6 units of thrombocyte concentrate and prednisone 40 mg daily. The patient's previous drugs, except aurothioglucose, were subsequently reinstated. A fast recovery of the platelet count occurred (figure) and the prednisone was tapered off. After discontinuation of the corticosteroids a flare-up of the disease occurred and sulphasalazine was prescribed. The patient responded very well to this, but again the platelet count dropped to 35×10^9 platelets/l. Physical examination showed no signs of bleeding, but there was a slight erythema on the back and mild arthritis of some finger joints and the right knee. Laboratory tests showed an ESR of 57 mm in the first hour; a haemoglobin concentration of 119 g/l; a white cell count of $5.2 \times 10^9/l$, with a normal differential; a C3 of 1726 mg/l; C4 of 275 mg/l; C1q binding assay of 5%; circulating immune complexes containing IgM and small amounts of IgG. Immune complexes containing IgA were not found; IgM was 1.09 g/l; IgG was 11.3 g/l; and IgA was slightly increased to 2.63 g/l. Bone marrow examination showed megakaryocytosis and no signs of increased intramedullary activity of the mononuclear phagocyte system. Sulphasalazine was stopped and spontaneous recovery of the thrombocyte count was noticed. The patient sustained another flare-up of the disease and hydroxychloroquine treatment was started. After two and a half months the thrombocyte count fell again to 70×10^9 platelets/l. The thrombocyte count rose to nearly normal values within two weeks of discontinuing the hydroxychloroquine. Low dose corticosteroids were given because of persistent disease activity. Since then the patient has had a normal thrombocyte count.

Serum samples obtained in October, November, and twice in February were fractionated by isokinetic sucrose gradient centrifugation as described by Faaber *et al.*¹ Undiluted serum fractions were tested for IgM and IgG reactivity in an enzyme linked immunosorbent assay (ELISA) as described by Sintnicolaas *et al.*² The reactivity of the patient's serum fractions with autologous platelets indicates that no IgG or IgM autoreactive platelet antibodies were present. The reactivity patterns of patient

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and control sera were identical. No auto- or alloreactive IgM or IgG immune complexes were present, which could be concluded from the data obtained with the 'pellet or bottom' fractions in the ELISA. IgG alloreactivity was clearly shown in the serum sample obtained in November four weeks after the platelet transfusion. The serum sample obtained four months later showed hardly any IgG alloreactivity.

Discussion

Thrombocytopenia as a result of drug treatment is a rather common feature, occurring in 1–3% of patients treated with parenteral gold.³ Two different types of thrombocytopenia have been distinguished^{4–6}: the 'toxic' type and the more common 'immune mediated' type. With respect to the latter, a strong correlation with the presence of the HLA-B8 and HLA-DR3 antigens has been found.^{7–11}

The fact that we could not show the presence of autoreactive antibodies or immune complexes in the patient reported, not even in the serum sample obtained during severe thrombocytopenia, does not necessarily mean that autoreactive antibodies or immune complexes could not have been responsible for the severe thrombocytopenia. In retrospect, the thrombocytopenia noted in our patient at the initial visit might have been caused by the low dose gold given before referral to our hospital. In about 30% of patients with drug induced thrombocytopenia antibodies reactive with autologous thrombocytes¹² cannot be found in *in vitro* tests. Sometimes the binding of antibodies or immune complexes to platelets can be observed only when the suspected drug—or one of its metabolites—is added.^{13–16} We screened the sera without additions. An alternative explanation for why autoreactivity was not detected may be that autoreactive antibodies might have been of low titres, adsorbed to the platelets, and cleared from the blood. Because of the high sensitivity of the ELISA we reject lack of sensitivity as an explanation; we also reject the dilution introduced by the fractionation (less

than 1/10) as an explanation, for the signals of unfractionated sera did not exceed the signals of the fractionated sera (data not shown).

The alloreactivity found in the serum sample taken in November can most likely be explained as being due to a secondary response provoked by the transfusion, because the patient had been pregnant in the past.

To our knowledge, an isolated thrombocytopenia resulting from treatment with sulphasalazine has not been described either in patients with inflammatory bowel disease, or in rheumatoid arthritis. Only cases of thrombocytopenia associated with concomitant leucopenia,^{17,18} hypogammaglobulinaemia,¹⁹ and erythroid aplasia²⁰ have been reported.

Antimalarial drugs such as quinine and quinidine are notorious for inducing thrombocytopenia. Chloroquine has also been reported to possess such properties.²¹ Although hydroxychloroquine is regularly prescribed for patients with rheumatoid arthritis, and in large quantities, occurrence of thrombocytopenia induced by this drug has been reported only once.²²

It is not known whether previous thrombocytopenia during chrysotherapy increases the risk of recurrence of a fall in platelet count during subsequent treatment with sulphasalazine or hydroxychloroquine, as has been suggested by Bliddal *et al.*^{23,24} The relapsing thrombocytopenia, however, may indicate a genetically determined HLA-DR3 and B8 aberrant immunological response to stimuli such as certain second line drugs.

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