Gold-Induced Thrombocytopenia

A Clinical and Immunogenetic Study of Twenty-three Patients

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Thrombocytopenia developed in 23 patients with rheumatoid arthritis treated with gold salts over 25 years. All patients recovered, and there were no episodes of life-threatening hemorrhage; four patients eventually needed splenectomy. The clinical presentation of gold-induced thrombocytopenia and its treatment and outcome are reviewed. Because gold-induced thrombocytopenia is believed to have an immunologic basis, we sought an association between this complication and antigens of the human leukocyte antigen (HLA) region. The most significant finding was the association of the HLA-DR3 alloantigen in 12 of 15 of these patients compared with 26 of 84 in a control population ($\chi^2 = 12.9, p < 0.001$). This study provides further evidence that gold-induced thrombocytopenia is immunologically mediated and that genes of the major histocompatibility complex are involved.

Gold salts are a well-established treatment for rheumatoid arthritis (1, 2). Side effects include stomatitis, dermatitis, proteinuria, nephropathy, and thrombocytopenia, which is estimated to occur in 1% to 3% of patients given this form of therapy (3). Although life-threatening hemorrhage has rarely occurred in patients with thrombocytopenia, splenectomy has been needed in some (4). Gold-induced thrombocytopenia is not simply due to a toxic effect on the bone marrow; the demonstration of adequate to increased numbers of megakaryocytes in the bone marrow (4, 5) and shortened platelet survival time (4) suggests that thrombocytopenia due to gold may be immunologically mediated. Wooley and colleagues (6) recently have shown that patients with definite or classical rheumatoid arthritis who have the human leukocyte antigen (HLA) DR3 have an increased risk of developing proteinuria, but they did not show an increase in this antigen in patients with thrombocytopenia (6). We reviewed the cases of 23 patients admitted to the Brigham and Women's Hospital with gold-induced thrombocytopenia and analyzed their clinical presentation, treatment, outcome, and distribution of HLA-DR antigens.

Methods

Twenty-three patients were admitted to the Brigham and Women's Hospital with gold-induced thrombocytopenia over 25 years. This group was drawn from approximately 4000 patients similarly treated over the same time. Patients with pancytopenia were excluded from this study. All patients had definite or classical rheumatoid arthritis according to the criteria of the American Rheumatism Association (7); 17 were women and six, men, with an age range of 28 to 72 years. In all patients platelet counts were less than 50,000/mm$^3$; all but one had received gold sodium thiomalate (75 to 3500 mg). The abrupt onset of thrombocytopenia was defined as a platelet count less than 50,000/mm$^3$ with the last normal count having been recorded a maximum of 1 month earlier. In addition, patients with a sudden onset of petechiae were classified as having abrupt thrombocytopenia. Gradual onset of thrombocytopenia was defined as onset over 2 months. When neither of the above...
criteria could be fulfilled, the patient was classified as having indeterminate thrombocytopenia. Clinical manifestations, concurrent toxicity, laboratory findings, treatment, and subsequent outcome were tabulated. Control data for HLA-DR typing were obtained from 84 healthy hospital personnel. All patients and controls were white.

Peripheral blood mononuclear leukocytes were obtained by density gradient centrifugation through Ficoll-Hypaque (Phar-...
present in three of six tested, and only three patients had positive antinuclear antibodies (1:320 or less).

All patients received at least 60 mg of prednisone, and 10 of 23 received concomitant treatment with dimercaprol. Nineteen patients completely recovered, with platelet counts returning to normal (more than 150,000/mm$^3$) in 5 to 30 days. Four of these patients experienced relapse as prednisone was tapered; all responded to a repeat course of corticosteroids. Four other patients who did not respond to medical therapy eventually needed splenectomy, and all recovered (Table 1).

Two HLA-DR antigens, DR3 and DR4, were found with increased frequency in the patients with rheumatoid arthritis and gold-associated thrombocytopenia (Table 2). The most significant finding was the association of the HLA-DR3 alloantigen in 12 of 15 of the patients compared with 26 of 84 in a healthy control population ($x^2$, 12.9, $p < 0.001$, $p < 0.008$ corrected). Relative risk for HLA-DR3 was 8.9. There was also an increased frequency of the HLA-DR4 alloantigen in eight of 15 of the patients compared with 21 of 84 in a healthy control population ($x^2$, 4.9, $p < 0.05$).

**Discussion**

Gold compounds have been used in the treatment of rheumatoid arthritis since the 1920s. It was not until 1960, however, that the British Empire Rheumatism Council showed in a controlled study that chrysotherapy was clinically effective (1). This report and others (2, 14) confirmed the clinical efficacy of gold and established it as a major form of therapy in rheumatoid arthritis. The frequent occurrence of side effects is a major problem with chrysotherapy. Thrombocytopenia has been estimated to occur in 1% to 3% of treated patients and has been suggested in at least one review to be a fatal complication in a significant number of patients (3). Our study of 23 patients represents the largest reported series of cases in which this complication developed. There were no episodes of life-threatening hemorrhage, and the major morbidity was related to splenectomy done in four patients as a therapeutic intervention.

The clinical profile of these patients is presented in Table 1. All but two patients were latex positive, and the onset of thrombocytopenia was abrupt in at least 17 of the cases. Bone marrow examinations were done in 16 of the patients and showed normal to increased numbers of megakaryocytes in all. That all patients but one received gold sodium thiomalate rather than aurothioglucose probably reflects institutional preference, but an increased risk of thrombocytopenia with gold sodium thiomalate cannot be excluded. No clinical datum, be it age, sex, gold dosage or other side effect, could be discerned that would enable the clinician to predict who would develop thrombocytopenia.

Treatment of gold-associated thrombocytopenia has included steroid therapy, dimercaprol therapy, cytotoxic agents, and splenectomy (4, 5, 15). In our series all patients received prednisone, and 10 of 23 also received dimercaprol during the initial treatment course. All the patients who received steroids alone recovered; three of 10 patients who had received dimercaprol needed splenectomy as the final intervention. Only one patient was treated with a cytotoxic agent (cyclophosphamide), and he eventually needed splenectomy. Of the seven patients who received dimercaprol and did not need splenectomy, one was recovering when dimercaprol was started (Patient 1) and another (Patient 6) had no improvement until prednisone was also given. Thus only in five of 23 patients could dimercaprol be implicated in the successful treatment of this complication; in all five patients prednisone therapy was started in parallel with dimercaprol. From these data we would recommend prednisone alone as the initial treatment of gold-associated thrombocytopenia, as dimercaprol does not appear to offer any additional therapeutic advantage. The dose of prednisone used most commonly in this series was 60 mg daily.

The pathogenesis of gold-associated thrombocytopenia is unknown. Although a direct toxic effect on the marrow cannot be excluded, the presence of normal to increased megakaryocytes suggests peripheral destruction of platelets. To further support the idea that the thrombocytopenia is a result of peripheral destruction and not a toxic effect of gold on the marrow, Levin and associates (4) have shown shortened platelet survival and platelet phagocytosis by splenic macrophages in a patient with gold-associated thrombocytopenia. However, serum platelet antibodies could not be shown in this patient nor in patients tested by others (5).

The impression that gold-associated thrombocytopenia is caused by immunologic mechanisms, as in idiopathic thrombocytopenia purpura, is supported by our data. All our patients who had bone marrow aspirations had normal or increased megakaryocyte levels, as is found in idiopathic thrombocytopenia purpura. Moreover, the response to prednisone therapy was generally successful, although four patients needed splenectomies. Both idiopathic thrombocytopenia purpura and gold-induced thrombocytopenia appear to be associated with a specific HLA-DR alloantigen, suggesting that immunogenetic factors are relevant to pathogenesis. Idiopathic thrombocytopenia purpura has been shown to be associated with

<table>
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<th>HLA-DR Specificity</th>
<th>Control Subjects ($n = 84$)</th>
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* $p < 0.001$.
† $p < 0.05$.
‡ Sixty control subjects.
the HLA-DR2 allantigen in a population primarily consisting of Ashkenazi Jews (16), and our data suggest that gold-associated thrombocytopenia is associated with the HLA-DR3 allantigen. Only one of our patients had the allantigen DR2 (Table 2). Our data are in agreement with the 14 series published to date of cases of white patients with rheumatoid arthritis, all of which have associations with HLA-DR4 or HLA-Dw4 and not with HLA-DR3 (17–19). This suggests that the primary association with HLA-DR3 in this study is with thrombocytopenia and not rheumatoid arthritis.

The HLA associations reported with gold toxicity may be of more than theoretic interest. There are no previous clinical grounds for ascertaining which rheumatoid arthritis patients treated with gold salts will develop complications. These tests are at present applied to all persons receiving gold salts, and the cost effectiveness of this screening process has been a cause for concern (20). The association between HLA-DR3 and both nephropathy and thrombocytopenia could be clinically useful in selecting those patients in whom it is appropriate to monitor especially if gold-induced leukopenia and aplastic anemia also proved to be HLA related. A prospective study might help define a role for HLA typing in management of the renal and platelet toxicities complicating gold salt therapy.


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References