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Hepatotoxicity of parenteral gold therapy in rheumatoid arthritis: A case report and review of the literature

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ABSTRACT

We report a case of severe hepatotoxic reaction during gold therapy for rheumatoid arthritis. The previous literature on this condition is reviewed and the possible mechanisms of gold-induced hepatotoxicity are discussed.

Introduction

Gold salts have been used for many years in the treatment of rheumatoid arthritis (RA). The long-term use of gold salts in RA patients is primarily limited by toxicity reactions which are observed in 30% - 40% of patients (1). The most common side effect of gold therapy consists of mucocutaneus reactions, such as stomatitis and dermatitis, which account for 60% - 80% of all gold-associated toxicities (1). Other toxic effects of gold therapy, such as proteinuria and bone marrow depression, have been reported in 2% - 10% and in 1% - 5 % of patients, respectively (1-4).

Hepatotoxic reactions to treatment with parenteral gold are very uncommon. In the present paper, we report one case of gold-associated hepatotoxicity and review the previous literature on the occurrence of this rare side effect.

Case report

In July 1997 a 62-year old Caucasian male known to have rheumatoid factor positive rheumatoid arthritis (RA) since 1991, was admitted to our ward with a two-day history of painless icterus, nausea and vomiting, and discolouration of his stools beginning one day before. The patient's medical history revealed a myocardial infarction in 1982 followed by coronary artery bypass grafting (CABG) one year later. Previous anti-rheumatic therapy had consisted of methotrexate which was stopped because of ineffectiveness. Thereafter, three weeks before admission, aurothioglucose was started at a weekly dose of 50 mg (total cumulative dose 160 mg). During this period, the patient had reported to his general practitioner sweating, fatigue and myalgia shortly after each gold injection. These symptoms were considered mild and had required no additional treatment. On admission, further therapy consisted of prednisone 7.5 mg/day, acetylsalicylic acid 80 mg/day, metoprolol 50 mg/day, and naproxen 500 mg twice daily in stable dosages. The patient denied intravenous drug abuse, promiscuous sexual behaviour or excessive alcohol consumption.

Physical examination revealed a subfebrile (38.4°C), icteric patient with mild synovitis of the finger joints and knees. The liver was tender but not enlarged on examination, and there were no signs of splenomegaly. Discoloured stools were found on rectal examination.

Laboratory examinations showed a erythrocyte sedimentation rate of 22 mm/hr, mild normochromic anemia (hemoglobin concentration 7.3 mmol/L [normal: 8.1 - 10.7 mmol/L], mean corpuscular volume 89 fl), a leukocyte count of 3.8 x 10^9/L (differentiation: 75% granulocytes, 12% lymphocytes, 10% monocytes, 0% eosinophils, 1% basophils, 2% large unstaind cells), and a normal platelet count of 211 x 10^9/L. Liver function tests revealed a cholestatic pattern and predominantly conjugated hyperbilirubinemia (Fig. 1).

The possible diagnoses included drug related hepatotoxicity due to gold salts or non-steroidal anti-inflammatory drugs (NSAIDs), viral or autoimmune hepatitis, biliary obstruction due to tumor or concrements, and Felty's syndrome. Additional laboratory examinations yielded no evidence for hepatitis A, B or C, cytomegaly or Epstein-Barr virus infection. Antinuclear antibodies and liver disease-specific antibodies such as anti-mitochondrial, anti-smooth muscle and anti-liver-kidney microsomal antibodies were absent. HLA genotyping previously performed for other reasons showed HLA-A11, -A32, -B57, -Bw4, -Bw6, -DR4, -DR5, -DR52, and -DR53.

Abdominal ultrasonography and computed tomography of the abdomen showed no evidence for intra- or extra-hepatic cholestasis, biliar concrements or splenomegaly. A liver biopsy was initially planned but was precluded by the onset of prolonged bleeding due to the concomitant use of naproxen and acetylsalicylic acid. Therapy consisted of the discontinuation of any potentially hepatotoxic drug (aurothioglucose, naprosyne and acetylsalicylic acid) and a slight increase in the prednisone dosage to 15 mg/d.

One day after his admission, the patient's

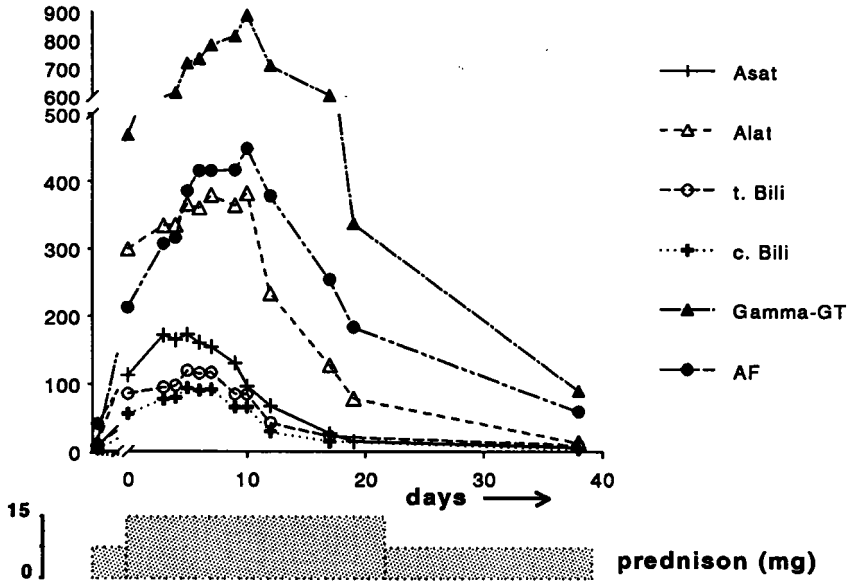

Fig. 1. Evolution of the cholestatic liver function test disturbances in our patient. Day 0 was the day of hospital admission. Abbreviations: Asat: aspartate-amino transferase; Alat: alanine-amino transferase; AF: alkaline phosphatase; Gamma-GT: gamma-glutamyl transpeptidase; t. Bili: total bilirubin; c. Bili: conjugated bilirubin.

subfebrile temperature subsided, and four days later his stool colour normalized. Approximately four weeks after his admission, liver function tests were normalized (Fig. 1) and naproxen was resumed.

Discussion

For several decades parenteral gold salts have been used in the therapy of RA. The most common side effects of chrysotherapy involve the skin, kidney and bone marrow. In contrast, pulmonary, gastrointestinal, and neuromuscular toxicities are rare (1-6). In this paper we report one case of gold salt-related hepatotoxicity, a very rare adverse event, which occurred shortly after the initiation of chrysotherapy. A systematic search of the English literature for the last 30 years yielded only 23 other well-documented cases of gold salt related hepatoxicity, which are summarized in Table I (5-19).

The underlying mechanism of gold-induced hepatotoxicity remains unknown, although two possible mechanisms have been proposed. The first, an idiosyncratic side effect, is sustained by the fact that hepatotoxic reactions are not dose-related and can occur even after small doses of gold salts (7, 8, 12, 14, 16-18). The concomitant skin rash (n = 2), eosinophilia (n = 6), and increased IgE levels (n = 1) seen in some cases (Table I) also support this theory. The second mechanism, suggested by Fleischner *et al.*, is a direct toxicity due to gold accumulation in the lysosomes of hepatic macrophages (19). This mechanism could explain the hepatotoxicity observed after prolonged exposure to parenteral gold. The relevance of this finding is, however, unclear since uncomplicated chrysotherapy also results in gold accumulation in many organs, especially in cells of the reticuloendothelial system in the liver and kidney (20, 21).

In 1977 Davis *et al.* suggested that concomitant treatment with NSAIDs might potentiate liver dysfunction due to parenteral gold salts (22). Among the total group of 24 cases reviewed in the present study, 10 patients used a combination of gold salts and NSAIDs, 6 did not, and in the remaining 8 cases no co-medication was mentioned. The number of observations is therefore too small to allow definite conclusions to be drawn with regard to enhanced hepatotoxicity linked to the concomitant use of NSAID and gold salts.

The presence of an HLA B8/DR3 haplotype has been associated with an increased risk of gold-induced thrombocytopenia and nephrotoxicity, but not with other adverse events related to chrysotherapy (3). Whether this "autoimmune" HLA haplotype is also associated with an increased risk for gold-induced hepatotoxicity has not been addressed. Detailed data on HLA typing was reported only in 3 out of the 24 patients reviewed for this paper (14, 18, and our own observation). These data do not allow us to draw any firm conclusions.

In previous reports, therapy for gold-induced hepatotoxicity has always consisted of discontinuation of the drug. In seven cases, including our own, corticosteroids were started either to minimise the liver damage or to control RA activity (9, 14, 16). British Anti-Lewisite (BAL) and N-acetylcysteine as empirical detoxifying agents were used in two patients (5, 16). The overall outcome in gold-induced hepatotoxicity seems favourable. All except one patient survived and liver function was restored in all cases. The patient with a fatal outcome died of pulmonary insufficiency due to bronchopneumonia and fibrosing alveolitis (15).

In conclusion, hepatotoxicity is a rare, but well-documented side effect of parenteral gold therapy. Discontinuation of gold administration is usually followed by complete recovery. The therapeutic value of corticosteroids or other therapies remains uncertain.

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Table I. Hepatotoxicity induced by parenteral gold therapy: a review of the English literature.

Year of pub.	Ref. no.	Sex/ age (yrs.)	Rheumaroid factor	Cum. gold dose (mg)	Concomitant therapy	Liver biopsy	Eosin-ophilia	IgE (U/L)	HLA-DR3	Outcome
1973	7	M/66	-	150	INH†, acetaminophene	Cholestasis	N.R.	N.R.	N.R.	Recovery (1 year)
		F/34	+	200	Phenylbutazone	Cholestasis				Abnormal liver function test due to other illness.
1977	8	F/50	N.R.	110	N.R.	Cholestasis	+	N.R.	N.R.	Recovery (14 weeks)
		F/59	N.R.	60		Hepatitis	-			N.R.
		F/51	+	37.5		Not performed	+			Recovery (3 weeks with refusal for follow-up)
1978	9	M/8	N.R.	35	N.R.	Cholestasis	N.R.	N.R.	N.R.	Recovery (5 weeks)
1979	10	F/66	+	200	N.R.	Cholestasis	+	N.R.	N.R.	Recovery (9 months)
1982	11	F/3	N.R.	10	Phenobarbital, indomethacin, prednisone	N.R.	-	N.R.	N.R.	Recovery (within 1 year)
1983	12	F/65	-	300	Piroxicam	Cholestasis	+	N.R.	N.R.	Recovery, except for AF‡ (20 weeks)
		F/61	+	600	Aspirin	Cholestasis	-			Recovery, except for AF (13 weeks)
		F/56	+	60	Phenoprofen	N.R.	+			Recovery, except for AF (5 weeks)
1984	13	F/43	+	130	Naprosyne	Non-specific hepatitis	-	N.R.	N.R.	Recovery (2 months)
1984	14	F/56	+	135	None	Not performed	+	N.R.	-	Recovery (1 month)
1984	15	F/53	+	30	None	Necrosis, cholestasis	-	N.R.	N.R.	Death (bronchopneumonia)
1985	16	F/10	N.R.	35	None	N.R.	-	N.R.	N.R.	Recovery (2 weeks)
		M/36		2900	Aspirin, prednisolone	Necrosis	-			Recovery (2 weeks)
		F/30		N.R.	N.R.	Pericholangitis	N.R.			Recovery (2 weeks)
		F/10		225	N.R.	Necrosis	-			Recovery (period N.R.)
1985	17	F/53	+	185	Ibuprofen, synacthen	Cholestasis	N.R.	N.R.	N.R.	Recovery (3 weeks)
1989	18	M/70	+	200	None	Cholestasis	-	130	+	Recovery (12 weeks)
1991	5	M/54	N.R.	160	Prednisone, sucralfate	Cholestatsis	N.R.	N.R.	N.R.	Recovery (10 months)
1991	19	F/56	N.R.	> 2500	N.R.	Necrosis	-	N.R.	N.R.	N.R.
1994	6	F/40	-	160	Ketoprofen	N.R.	N.R.	N.R.	N.R.	Recovery (3 weeks)
Our report 1998		M/62	+	160	Prednisone, metoprolol, naprosyne, acetylsalicylic acid	Not performed	-	N.R.	-	Recovery (4 weeks)

N.R.: not reported; †INH: isoniazide; ‡AF: alkaline phosphatase.
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