

Fulminant hepatitis in an asymptomatic chronic carrier of hepatitis B virus mutant after withdrawal of low-dose methotrexate therapy for rheumatoid arthritis

Sirs,

Regarding the liver toxicity of low-dose methotrexate (MTX) therapy for rheumatoid arthritis (RA), it has been argued that development of cirrhosis is possible after high cumulative doses (1); however, it remains uncertain whether this regimen results in reactivation of hepatitis viruses. A 72-year-old Japanese woman, who was an asymptomatic chronic hepatitis B virus (HBV) carrier, was admitted to our hospital on July 31, 2002, because of general malaise and abnormal liver function tests. She had a 15-year history of RA, and had been receiving MTX (4 mg/week) since July 2000. In May 2002, she was observed to have elevated transaminase levels; aspartate aminotransferase (AST) 222 IU/l, alanine aminotransferase (ALT) 246 IU/l, both of which had been within normal ranges until March 2002. At this point, HBe antigen was negative and anti-HBe antibody was positive, along with positive HBs antigen and negative anti-HBs antibody. MTX was discontinued because other potentially hepatotoxic drugs were excluded. Transaminase levels decreased only slightly for the following 2 months, but in July her AST and ALT rose even further and she was referred to our hospital.

On admission, the patient had a mild hepatomegaly as well as several swollen and tender joints of the extremities. AST was 765 IU/l, ALT 569 IU/l, albumin 2.7 g/dl, and the prothrombin time was slightly prolonged (64.5%). HBe antigen turned out to be positive, but IgM anti-HBc antibody was negative. Mutations in the core promoter and the precore regions were detected in HBV-DNA from her serum, the level of which was found to be remarkably high (7.5 LGE/ml). No evidence of other hepatotoxic

virus infection (hepatitis A, C, and D virus, cytomegalovirus, or EBV) was detected by serological tests. Because of the diagnosis of hepatitis as a consequence of reactivation of HBV, therapy with lamivudine and interferon was started. In addition, high-dose corticosteroid and cyclosporine were simultaneously given to control the severe hepatitis. Although the HBV-DNA level decreased due to these treatments, liver function deteriorated gradually, and she fell into a state of fulminant hepatitis and eventually died of fungal pneumonia. Autopsy revealed massive hepatocellular necrosis. It is known that reactivation of HBV can be induced after intensive immunosuppressive therapy with cytotoxic agents used for various neoplastic disorders (2-4); however, it has not yet been clearly established that a low-dose MTX regimen for RA also has the potential to reactivate HBV in asymptomatic carriers. We have found in the literature only 3 other cases of fulminant hepatitis in a HBV carrier after cessation of low-dose MTX therapy (5-7) (Table I). Notably, the precore mutant virus was detected in both case #3 and in our case, and additionally the core promoter mutation was detected in the present case. Since both of these mutations are known to be associated with fulminant hepatitis (8-10), it is hypothesized that the mutations and the immunosuppressive effect of low-dose MTX may have led to widespread HBV infection to hepatocytes. Thus, after withdrawal of the drug several weeks later, the restoration of immunocompetency could lead to a rigorous immunologic attack against the infected hepatocytes.

The treatment of RA with MTX was officially approved in Japan in 1999 and the number of prescriptions of this drug has recently been increasing. It is also notable that approximately 1% of Japanese adults are estimated to be HBV carriers. As MTX therapy becomes more widely prescribed in the areas with relatively high rates of chronic HBV infection, there is much concern for an increase in similar events. We propose that MTX should not be given to carriers of

HBV even when the liver function tests are normal. If MTX has already been given, serum HBV-DNA should be monitored. Use of anti-viral agents should also be considered without delay.

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References

1. KREMER JM, ALARCÓN GS, LIGHTFOOT RW JR *et al.*: Methotrexate for rheumatoid arthritis. Suggested guidelines for monitoring liver toxicity. *Arthritis Rheum* 1994; 37: 316-28.
2. GALBRAITH RM, EDDLESTON AL, WILLIAMS R, ZUCKERMAN AJ: Fulminant hepatic failure in leukaemia and choriocarcinoma related to withdrawal of cytotoxic drug therapy. *Lancet* 1975; 2: 528-30.
3. WANDS JR: Subacute and chronic active hepatitis after withdrawal of chemotherapy. *Lancet* 1975; 2: 979.
4. LOK AS, LIANG RH, CHIU EK, WONG KL, CHAN TK, TODD D: Reactivation of hepatitis B virus replication in patients receiving cytotoxic therapy. Report of a prospective study. *Gastroenterology* 1991; 100: 182-8.
5. FLOWERS MA, HEATHCOTE J, WANLESS IR *et al.*: Fulminant hepatitis as a consequence of reactivation of hepatitis B virus infection after discontinuation of low-dose methotrexate therapy. *Ann Intern Med* 1990; 112: 381-2.
6. NARVÁEZ J, RODRIGUEZ-MORENO J, MARTÍNEZ-AGUILÁ MD, CLAVAGUERA MT: Severe hepatitis linked to B virus infection after withdrawal of low dose methotrexate therapy. *J Rheumatol* 1998; 25: 2037-8.
7. ITO S, NAKAZONO K, MURASAWA *et al.*:

Table I. Review of the literature on severe/fulminant HBV hepatitis after withdrawal of low-dose MTX for RA.

Case no.	Author	Age / Sex	Dosage and duration of MTX	Reason for cessation of MTX	Other DMARDs or steroids	Time lag between MTX cessation and hepatitis	Outcome
1.	Flowers <i>et al.</i> (5)	57 / F	7.5 – 10 mg/week 3 years	Interstitial pneumonia	Not described	41 days	Rescued by liver transplantation
2.	Narváez <i>et al.</i> (6)	67 / M	7.5 mg/week 2 years	Interstitial pneumonia	PSL 5 mg/day	~21 days	Died
3.	Ito <i>et al.</i> (7)	75 / F	5 – 7.5 mg/week 3 years	Elevation of liver enzymes	PSL 5 mg/day bucillamine	15 days	Died
4.	Present case	72 / F	4 mg/week 2 years	Elevation of liver enzymes	PSL 5 mg/day bucillamine	~60 days	Died

HBV: hepatitis B virus, MTX: methotrexate, RA: rheumatoid arthritis, DMARD: disease-modifying antirheumatic drug, PSL: prednisolone or prednisone.

Letters to the Editor

Development of fulminant hepatitis B (precore variant mutant type) after the discontinuation of low-dose methotrexate therapy in a rheumatoid arthritis patient. *Arthritis Rheum* 2001; 44: 339-42.

8. CARMAN WF, JACYNAMR, HADZIYANNIS S *et al.*: Mutation preventing formation of hepatitis B e antigen in patients with chronic hepatitis B infection. *Lancet* 1989; 2: 588-91.
9. BUCKWOLD VE, XU Z, CHEN M, YEN TSB, OU J: Effects of a naturally occurring mutation in the hepatitis B virus basal core promoter on precore gene expression and viral replication. *J Virol* 1996; 70: 5845-51.
10. SATO S, SUZUKI K, AKAHANE Y *et al.*: Hepatitis B virus strains with mutations in the core promoter in patients with fulminant hepatitis. *Ann Intern Med* 1995; 122: 241-8.

Silicone gel filled breast implants and dermatomyositis

Sirs,

Several studies have investigated the possible relationship between silicone gel-filled breast implants and autoimmune or connective tissue diseases (1-4). From a public health perspective, there appears to be no significant evidence that such a relation exists (5). Nevertheless, the coexistence of breast implants and connective tissue disease in a number of individuals points to a causal relationship; silicone bleeding from silicone-gel filled breast implants could act as a precipitating factor for the development of these diseases (6). We report herein two women with common HLA alleles, who presented with dermatomyositis and anti-synthetase antibodies after the implantation of silicone-gel-filled breast prostheses. This association has rarely been reported previously (7, 8).

Case 1. A 40-year-old white woman presented with symmetrical proximal muscle weakness of the limb girdles and neck in September 1997. Six months earlier the patient had undergone surgical breast augmentation for cosmetic reasons, with the implantation of bilateral silicone gel-filled breast prostheses. A left deltoid muscle biopsy showed perifascicular atrophy, necrosis and inflammatory infiltrate. Anti-synthetase (anti-Jo-1) antibodies were found by ELISA and confirmed by immunoprecipitation of RNAs from ³²P-labeled HeLa extracts. The patient was treated with prednisone (1mg/kg/day) with mild improvement, but elevated creatine phosphokinase persisted over the next 8 months; azathioprine (1.5 mg/kg/d) initially and later cyclosporine (5 mg/kg/d) had to be added to the patient's treatment. Despite this drug therapy, mild weakness and high creatine phosphokinase level persisted, so the prostheses were

replaced on July 1999. The patient is now being treated with cyclosporine (3 mg/kg/d) and prednisone 5 mg/d and is asymptomatic. High-resolution computerized tomography (HRCT) has detected no lung involvement and pulmonary function tests are normal. The patient's HLA was HLA-A [1, 23]; HLA-B [8(Bw6), 44(Bw4)]; HLA-Cw [07, 04]; HLA-DRB1* [0301(HLA-DRB3* 0101), 07(HLA-DRB4*)]; HLA-DQB1* [0201, 0202].

Case 2. A 51-year-old woman was admitted for evaluation of arthralgia and erratic arthritis of the metacarpophalangeal joints, asthenia and myalgia. Eight years before she had undergone breast augmentation with silicone-gel filled implants for cosmetic reasons. Gottron papules were observed on the skin of the hands and elbows and a periorbital edema with heliotrope rash of the eyelids was also noted. Skin retraction and local changes at the implantation site with contracture around the implant were observed on physical examination of the breast region. Muscle biopsy showed characteristic findings of dermatomyositis. Anti-synthetase (anti-Jo-1) antibodies were positive. The patient's HLA was HLA-A [1, 24]; HLA-B [8(Bw6), 39(Bw6)]; HLA-Cw [07, 12]; HLA-DRB1* [0301 (HLA-DRB3* 0101), 16 (HLA-DRB5*)]; HLA-DQB1* [0201, 0502]. Corticosteroid treatment (1 mg/kg/d) was initiated, but azathioprine at a dose of 1.5 mg/kg/d had to be added to improve clinical status. She was counseled to undergo explantation of the breast prostheses, but she repeatedly refused. Aggressive treatment with prednisone boluses (1 g/day, for 3 days) and the first of a series of 6 monthly cyclophosphamide boluses (750 mg) was initiated with apparent good response. At this time HRCT showed calcification and retraction of the prosthesis and mild lung fibrosis. Respiratory function tests disclosed a moderate restrictive pattern.

Silicone gel breast prostheses are extensively utilized for breast augmentation or reconstruction. We have had the opportunity to diagnose and attend two patients with silicone-gel filled breast implants who developed full-blown dermatomyositis after breast augmentation. Both tested positive to anti-synthetase antibody, a specific myositis antibody, but only the patient who refused prosthesis explantation developed a full-blown anti-synthetase syndrome with interstitial lung disease.

The HLA status of these patients showed that class II HLA(DR, DQ) was identical in one of two haplotypes. On the basis of the combination of factors found in the study of these two patients, we speculate that the identical class II HLA alleles resulted in a reaction to silicone that triggered a humoral

autoimmune response and the development of full-blown dermatomyositis with anti-synthetase antibodies.

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References

1. BRIDGES AJ, CONLEY C, WANG G, BURNS DE, VASEY FB: A clinical and immunologic evaluation of women with silicone breast implants and symptoms of rheumatic disease. *Ann Intern Med* 1993; 118: 929-36.
2. GABRIEL SE, O'FALLON M, KURLAND LT, BEARD CM, WOODS JE, MELTON J: Risk of connective-tissue diseases and other disorders after breast implantation. *N Engl J Med* 1994; 330: 1697-702.
3. SÁNCHEZ-GUERRERO J, COLDITZ GA, KARLSON EW, HUNTER D, SPEIZER FE, LIANGMH: Silicone breast implants and the risk of connective-tissue diseases and symptoms. *N Engl J Med* 1995; 332: 1666-70.
4. NYRÉN O, YIN L, JOSEFSSON S *et al.*: Risk of connective tissue disease and related disorders among women with breast implants: a nation-wide retrospective cohort study in Sweden. *BMJ* 1998; 316: 417-22.
5. JANOWSKY EC, KUPPER LL, HULKAS BS: Meta-analysis of the relation between silicone breast implants and the risk of connective tissue diseases. *N Engl J Med* 2000; 342: 781-90.
6. GAUBITZ M, JACKISCH C, DOMSCHKE W, HEINDEL W, PFLEIDERER B: Silicone breast implants: correlation between implant ruptures, magnetic resonance spectroscopically estimated silicone presence in the liver, antibody status and clinical symptoms. *Rheumatology* 2002; 41: 129-35.
7. HOOT HR, SONTHEIMER RD: Autoimmune connective tissue disease and connective tissue disease illness after silicone gel augmentation mammoplasty. *J Am Acad Dermatol* 1994; 31: 626-42.
8. MEYER DR, BUI HX, CARLSON JA *et al.*: Silicon granulomas and dermatomyositis-like changes associated with chronic eyelid edema after silicone breast implants. *Ophthal Plast Reconstr Surg* 1998; 14: 182-8.