Autoimmune Hepatitis After Long-Term Methotrexate Therapy for Rheumatoid Arthritis

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Abstract: Methotrexate (MTX) therapy may be effective in patients with rheumatoid arthritis (RA) or psoriasis due to its anti-inflammatory and immunosuppressive properties. Potential liver toxicity of MTX exists, but the incidence of MTX-specific lesions in liver biopsy of patients with RA and elevated serum transaminase levels is rare; however, severe hepatic damage may occur unexpectedly in these patients. We describe the first documented case of an adult patient with RA who developed an acute flare of severe hepatitis after long-term therapy with MTX. Autoantibodies positivity, elevated serum IgG levels and compatible liver biopsy findings prompted us to diagnose autoimmune hepatitis, most probably triggered by a breakdown of immune tolerance induced by MTX. A complete remission was achieved in this patient with corticosteroids therapy.

Keywords: Autoimmune hepatitis, methotrexate, rheumatoid arthritis, drug-induced autoimmunity, immunological tolerance, corticosteroids.

INTRODUCTION

Treatment with methotrexate (MTX), a folic acid antagonist with anti-inflammatory and immunosuppressive properties, has been associated with an improvement in symptoms and a reduction in joint damage in patients with rheumatoid arthritis (RA) [1]. The potential usefulness of MTX in the treatment of RA and psoriasis was first demonstrated in 1951 [2]. Since then MTX has become a first-line therapy for patients with RA [1]. The well-documented toxicities of MTX led the American College of Rheumatology, in 1994, to issue guidelines for monitoring patients treated with MTX [3]. In addition, two British Societies (BSPAR and BSR) published guidelines for the therapeutic use of MTX in rheumatology practice [4,5]. One well-recognized effect of MTX is the induction of hepatic toxicity, which may progress to cirrhosis [6]. Concerns regarding the toxicity of MTX in patients with juvenile idiopathic arthritis prompted Hawley et al. [7] to survey current monitoring for the toxicity of this drug in pediatric rheumatology practice in the British Isles; these and other authors concluded that monitoring of blood tests in pediatric patients when receiving MTX therapy can be safely undertaken less frequently than had previously been recommended [7-9]. In successive studies it has been demonstrated that increased serum levels of aspartate and alanine aminotransferases (AST/ALT) occur commonly during MTX therapy, but serious hepatic toxicity appears to be rare [10] and that a rare incidence of MTX-specific lesions in liver biopsy of patients with RA and elevated liver enzymes exist [11]. Nevertheless, significant hepatic damage may occur unexpectedly in patients receiving MTX. In this report we describe the first documented case of a patient with RA, who was treated with MTX and who subsequently developed severe autoimmune hepatitis (AIH). Recently, a detailed review of the pathogenic mechanisms involved in the mediation of drug-induced autoimmunity has been published [12]. AIH is a chronic, progressive liver disease of unknown aetiology. The clinical manifestations may be diverse and AIH may be associated with other immune-mediated disorders. Factors involved in its pathogenesis appear to include a genetic predisposition, triggering factors such as viral infections or drugs, and altered immune-regulation [12-14]. AIH is characterized by high AST and ALT serum levels, an interface hepatitis associated with an infiltration of plasma cells, hypergammaglobulinemia, elevated serum levels of IgG and the presence of serum autoimmune markers as autoantibodies [13-15]. The phenomena of autoimmune diseases apparently being triggered by specific drugs has become a cause of increasing concern [12, 16]. The patient we report here is an adult with RA, who had received long-term therapy with MTX and subsequently developed an acute flare of severe hepatitis that underwent remission following the administration of corticosteroids.

CASE REPORT

A 57-year-old man was diagnosed with RA in December-2000. As treatment with MTX, 15 mg weekly, was associated with a satisfactory clinical response, the drug was administered long-term. The patient presented in July 2003 with jaundice following the development of asthenia and weight loss. The patient was subsequently transferred to our hospital. Original results of blood tests revealed: prothrombin time (PT) 15 sec. (69.9%), albumin 3.2 g/dl, total bilirubin (TB) 3.3 mg/dl, AST 1242 IU/L, ALT 1715
Current Drug Safety, 2011, Vol. 6, No. 3

IU/L, gamma-glutamyl transpeptidase 196 IU/L and alkaline phosphatase 167 IU/L. Subsequently, there was deterioration in the results of some blood tests: TB 6.8 mg/dl, AST 1175 IU/L, ALT 1746 IU/L, PT 17 sec. and albumin 2.9 g/dl. Serum was positive for antinuclear antibodies (ANA) (titre of 1/160), having previously been negative. Serum gammaglobulin was 2.1 g/dl and IgG 1890 mg/dl. Routine laboratory investigations for infection with the hepatitis A, B and C viruses were negative. The patient denied ingestion of any herbal medicines or drugs other than MTX.

A needle biopsy of the liver was obtained under ultrasound guidance. The histological findings were typical of AIH; they included architectural distortion characterized by perivenular and lobular confluent and bridging necrosis, enlargement of portal tracts, an intense parenchymal infiltration with plasma cells, interface hepatitis characterized by intra-acinar parenchymal hepatocellular damage, and early changes of hepatic regeneration (Fig. 1). The diagnostic score for AIH (>7) was confirmatory [15].

Therapy with methylprednisolone (80 mg/day) was instituted. By day 3 results of blood tests had improved: AST 216 IU/L, ALT 644 IU/L, TB 4.3 mg/dl, PT 13 sec, and albumin 3.3 g/dl. The dose of methylprednisolone was decreased using a tapering dose regimen. By month 5 results of blood tests had normalized: TB 0.6 mg/dL, AST 26 IU/L, ALT 38 IU/L, PT 12 sec, albumin 3.5 g/dl, gammaglobulin 1.7 g/dl and IgG 1670 mg/dl. Throughout 6 years of follow-up results of these blood tests remained consistently normal (Table 1).

DISCUSSION

Liver involvement in RA is usually minimal, although intra-hepatic portal hypertension secondary to nodular regenerative hyperplasia has been described [17-19]. Our patient with RA was treated with MTX and developed severe hepatitis. Hepatic damage associated with MTX therapy may vary from hepatic steatosis to cirrhosis, but acute hepatic necro-inflammatory disease is rare [20]. A relationship between MTX-induced hepatic folate depletion and MTX-associated hepatic damage has not been established, but reduced serum levels of AST and ALT occur after folinic acid supplementation [21]. Before our patient presented normal values for routine serum biochemical liver function tests and serum markers of autoimmunity were negative; after increased AST/ALT serum levels, presentation hepatic histology was diagnostic of AIH. Our patient appears to be the first documented case of AIH occurring after long-term administration of MTX. As AIH developed during MTX therapy and resolved after initiating corticosteroids treatment, the hepatic autoimmune disease may well have been attributable to MTX therapy rather than a complication of RA; however, histological AIH-like lesions, significantly associated with autoimmune markers, has been demonstrated in RA patients [11].

As it has been previously reported [16] immunosuppressive therapy was successfully discontinued in our patient during follow-up without a relapse of the hepatitis occurring. This case suggests that a breakdown of immune tolerance induced by a drug may trigger hepatic auto-reactivity [12, 22-24] that is rapidly suppressed by corticosteroids therapy. It can be estimated that AIH may be triggered by MTX inducing a breakdown of immunological tolerance, by a mechanism that probably has features in common with that described in association with infliximab therapy [25]. In such cases, the major factors that influence progression of hepatic disease appear to be rapid development of AIH and favourable responsiveness to corticosteroids therapy. It would seem that the possibility of drug-induced AIH should always be considered in the differential diagnosis of a patient presenting with evidence consistent with drug-induced liver injury. A recent report has drawn attention to a significant proportion of patients with AIH apparently having a drug implicated in its pathogenesis [26].

![Fig. (1).](image-url) Liver biopsy of the patient showing several findings compatible with autoimmune hepatitis. Upper panel: Distortion of the lobular architecture by confluent and bridging inflammation and necrosis, with inflammatory enlargement of portal tracts (H&E, x40). Lower panel: Inflamed expanded portal tract with plasma cells infiltration and characteristic interface hepatitis (H&E, x100 magnification).
REFERENCES


