



Case report

Reactivation of hepatitis B in a patient with spondyloarthritis after the suspension of methotrexate and efficacy of treatment with antivirals in association to adalimumab

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ABSTRACT

We report the case of a male chronic hepatitis B virus (HBV) carrier with HLA-B27 spondyloarthritis who developed fulminant hepatitis after discontinuation of methotrexate (MTX). Full recovery after therapy with lamivudine and adefovir allowed treatment with adalimumab which was well tolerated.

Reactivation of hepatitis B after MTX withdrawal is a very rare complication, which can also occur in association with anti-TNF agents. In patients with positive serology for HBV prophylactic antiviral therapy is recommended.

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Reactivación de hepatitis B en un paciente con espondiloartritis tras suspender metotrexato y eficacia del tratamiento con antivirales en asociación con adalimumab

RESUMEN

Comunicamos el caso de un varón portador crónico de virus de hepatitis B (VHB) con espondiloartritis B27 positivo que desarrolló una hepatitis fulminante tras la suspensión del tratamiento con metotrexato (MTX). Una total recuperación tras terapia con lamivudina y adefovir permitió un tratamiento con adalimumab sin otras complicaciones y buena tolerancia.

La reactivación de hepatitis B tras suspensión de MTX es una complicación muy poco frecuente, que también puede ocurrir con los anti-TNF. En pacientes con serología positiva de VHB se recomienda tratamiento profiláctico con antivirales.

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Introduction

Infection by hepatitis B virus (HBV) is a global health problem despite the implementation of vaccination and post-exposure programmes. It is estimated that there are more than 350 million HBV

carriers in the world, with a prevalence in Mediterranean countries of between 1% and 8%.¹

Hepatitis B reactivation is a well known fact for patients with chronic HBV infection who are submitted to immunosuppressive chemotherapy treatment with monoclonal antibodies and in hematopoietic transplant recipients. It can appear either as an asymptomatic form or as fulminant hepatitis having elevated mortality.¹

Methotrexate (MTX) is a widely-used immunomodulator in Rheumatology and is currently the first choice treatment in many diseases. Despite its widespread use, its immunosuppressive action

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Table 1
Compilation of HBV reactivation cases after suspension of MTX

Case	Reference	Age	Gender	Dose	Duration	Prednisone	Evolution
1	2	57	F	7.5-10 mg/week	3 years	ND	Liver transplant
2	3	67	M	7.5 mg/week	2 years	5 mg/day	Death
3	4	74	F	5-7.5 mg/week	3 years	5 mg/day	Death
4	5	72	F	4 mg/week	2 years	5 mg/day	Death
5	6	58	F	15 mg/week	2 years	<7.5 mg/day	Lamivudine and later infliximab and etanercept
6	7	59	F	10 mg/week	7 years	5 mg/day	Lamivudine and death
7	8	67	F	ND	ND	5 mg/day	Lamivudine
8	9	56	M	10 mg/day	ND	4 mg/day	Lamivudine

F indicates female; M, male; ND, not determined.

and the high prevalence of HBV infection, there are very few cases published on the reactivation of hepatitis B in patients who have received treatment with low weekly doses of MTX.²⁻⁹

The reactivation of hepatitis B has also been reported in patients with rheumatic diseases treated with anti-TNF treatment, mainly with infliximab.^{10,11}

Lamivudine has shown to be effective in the treatment and prophylaxis of the reactivation of hepatitis B in patients treated with chemotherapy, immunosuppressors or biological therapy.¹¹⁰⁻¹³ However, due to the high resistance rates in long-term treatments, the latest clinical guidelines recommend the use of new anti-virals.¹⁴

We report the case of a male chronic HBV carrier with HLA-B27 spondyloarthritis with axial and peripheral involvement who developed fulminant hepatitis after discontinuation of methotrexate (MTX). He completely recovered with lamivudine and later in association with adefovir, which allowed the start of treatment with adalimumab, without presenting any new complications a year after follow-up.

Clinical observation

This case involves a 41-year-old male, a plumber, with a clinical history of hypertension from the age of 21, probable allergy to sulphonamides, acute hepatitis B episode 8 years earlier and surgery to the second hammer toe of his left foot. Paternal and maternal hypertension, together with his mother being a HBV carrier, is relevant in the family history.

In July 2005, after an episode of urethritis with sterile urethral secretion for which he was treated with ciprofloxacin, a month later he presented arthritis in his ankle and left wrist with fever. In the medical history, he reported having outbreaks of low back pain and occasional inflammatory heel pain for about 7 years. He denied ocular or skin rashes and intestinal or family history of spondyloarthritis. After admittance to hospital, the examination confirmed oligoarthritis, as well as pain in 2nd hammer toe of the left foot and sacroiliac. Cultures of urethral discharge, stools, urine and blood cultures were negative. The blood count was normal. He showed a marked high level of ESR (98) and PCR (74 mg/l). Biochemistry was normal except for GGT: 117 IU/l and IgA of 610. Serologic tests for syphilis, HIV, HCV, *Salmonella*, *Yersinia* and *Chlamydia* were negative. HBV serology was as follows: HbsAg (+), HBeAg (-), anti-HBc (+), HBc IgM (-) and anti-HBe (+), compatible with the status of chronic HBV carrier. No viral load was determined. The HLA typing was: A1 A24 B27 B8 Bw4 Bw6 Cw2. Imaging studies showed bilateral sacroiliitis grade 3 and impingement of the 2nd left hammertoe, possibly postoperative. Treatment with naproxen 500 mg/12 h and prednisone 15 mg/day was started. There was improvement in the joints and he was discharged from hospital.

In his follow-up, each attempt to reduce the dose of prednisone below 10mg/day was accompanied with new outbreaks of arthritis in the ankles. Due to his history of allergy to sulphonamides that contraindicated sulfasalazine, we started treatment at 6 months

with 10 mg per week of subcutaneous MTX, which we raised to 15 mg a month later. The liver biology remained normal until 3 months later, when it presented: 144 UI/l, GPT: 215 UI/l, GGT: 144 UI/l in an analytical GOT control. We therefore suspended MTX. Fifteen days later, he was admitted to A & E with jaundice, nausea and diarrhoea. He was diagnosed with fulminant hepatitis with cytolysis (GOT: 1,039; GPT: 1,085; GGT: 1,510) and cholestasis (total bilirubin 26.4 mg/l), homogeneous hepatomegaly detected by ultrasound, coagulation disorder (prothrombin activity 39%) and mild renal insufficiency with creatinine of 1.6 mg/l. HBV serology was: HbsAg (+), HBe (+), anti-HBe (+) and 110,000,000 HBV DNA copies/ml. Other causes of viral or autoimmune hepatitis were eliminated. He was treated with lamivudine 100mg/day; prednisone 12.5 mg/day was maintained with a progressive clinical and analytical improvement until complete normalisation of liver and renal function was obtained after 5 months with HBV DNA of 671 copies.

After an allergy study, tolerance to sulfasalazine was found, so treatment was started at 2 g/day with a progressive reduction of prednisone because the arthritis in the heels and Achilles tendinitis persisted. Four months later, a new increase in viral load was discovered, which was controlled by adding 10mg/day of adefovir. A year later, he still had arthritis in his heels and bilateral Achilles tendinitis with radiological tarsal left involvement, grade 4 bilateral sacroiliitis and Achilles enthesophytes, BASDAI 6.9 and BASFI 4.5; liver function was normal and viral load negative. We stopped treatment with sulfasalazine and started treatment with adalimumab every 2 weeks. After a year of follow-up, he has not had any further joint outbreaks, he continues treatment with adalimumab, lamivudine and adefovir, liver function is normal and viral load is negative.

Discussion

Fulminant hepatitis due to the reactivation of hepatitis B after the suspension of low weekly doses of MTX was first described in 1990.² Since then and despite the more frequent use of MTX in Rheumatology, very few cases of this complication having a high mortality have been reported (Table 1). In some cases, the reactivation has been attributed to a mutation in the precore and core promoter regions.²⁻⁴ In another two cases of HLA-B27 spondyloarthritis, MTX contribution was speculated for the reactivation of HBV.¹³

The reactivation of hepatitis B is widely known in oncohematologic patients submitted to treatments with different chemotherapy treatments, aggressive immunosuppression, glucocorticoids, monoclonal antibodies and hematopoietic stem cell transplantation.¹ A series of risk factors that favour this complication are known (Table 2), which nearly always occur after the suspension of immunosuppression when the cellular immune response is restored and is directed against the infected hepatocytes.^{1,10,12}

The reactivation of HBV has also been reported in patients treated with biological therapies (infliximab, etanercept and rituximab) for rheumatology pathologies, inflammatory bowel or lymphomas. Consequently, screening strategies for the prevention and treatment

Table 2
Risk factors for hepatitis B reactivation

Risk factors for hepatitis B reactivation
Male sex
Young age
High doses of chemotherapy or immunosuppressors
Chemotherapy with anthracycline or glucocorticoids
Allogeneic hematopoietic stem cell transplant
Treatment with monoclonal antibodies, rituximab, Alemtuzumab, infliximab
Treatment with MTX or leflunomide
HBV serological profile: HBsAg (+), HBeAg (+), anti-HBc (+) in the absence of HbsAg and anti-HBs, viral load >3×10 ⁵ copies/ml

of HBV reactivation have been published for patients who are about to receive treatment with chemotherapy, immunosuppressors and biological therapy.^{1,10,12}

Prophylaxis and treatment of choice is lamivudine, a nucleoside analogue DNA polymerase, due to its speed in action, safety and cost. However, after several months of treatment, it can produce resistance due to the appearance of mutations; adefovir or new antiviral agents (tenofovir and entecavir) are then recommended.^{1,10,12,14}

Conclusions

We consider that all patients who are going to receive MTX treatment, other immunosuppressors or biological treatments should receive a HBV screening. If HBsAg positive is detected, HBV DNA must be determined and treatment started with antiviral agents independently of whether the virus replicates or not. The recommended antivirals are tenofovir or entecavir; as the treatment normally lasts more than 12 months, these will be maintained during the entire time of treatment duration and up to 6-12 months after suspension, depending on the viral load.^{1,10,14}

Written informed consent was obtained from the patient to administer adalimumab together with antiviral treatment.

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