

Hepatitis B reactivation in a chronic hepatitis B surface antigen carrier with rheumatoid arthritis treated with infliximab and low dose methotrexate

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Infliximab, a humanised, mouse derived, genetically engineered, monoclonal antibody to tumour necrosis factor α (TNF α), is successfully used in association with low dose methotrexate in the treatment of rheumatoid arthritis (RA).¹ Serious infections have been reported to be associated with infliximab treatment.^{1,2} However, the safety of infliximab is unknown or has not been yet established in chronic viral infections, including human immunodeficiency virus, hepatitis B virus (HBV) or hepatitis C virus infections. We describe a case, from our cohort of 102 patients treated with infliximab plus methotrexate, who carried hepatitis B surface antigen (HBsAg) and subsequently developed acute hepatitis due to HBV reactivation after 16 months of treatment with infliximab.

CASE REPORT

A 49 year old man was diagnosed as having RA in January 1990. HBsAg, and HBe and HBe antibodies were positive, while HBe antigen and HBs antibodies were negative. From January 1990 to May 2000 he received several treatments consisting of different disease modifying antirheumatic drugs (DMARDs) (hydroxychloroquine, sulfasalazine, sodium aurothiomalate, and cyclosporin A) in addition to oral steroids (<10 mg/day of prednisone) and non-steroidal anti-inflammatory drugs. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) remained persistently normal. However, response to these treatments was poor, and peripheral arthritis persisted. In June 2000 he began treatment with infliximab (6 mg/kg every eight weeks) associated with methotrexate (10 mg/week), with a good response of the joint signs and symptoms, as well as the inflammatory indices. In January 2002 he developed malaise, anorexia, fatigue, increased levels of AST (97 IU/l) and ALT (176 IU/l), and then he was admitted to our division.

Hepatomegaly was evident on the physical examination. Serum AST, ALT, and total bilirubin were further raised to 336 IU/l, 573 IU/l, and 22.6 μ mol/l, respectively. Hypoalbuminaemia and prolongation of the prothrombin time were also found. Abdominal ultrasonography showed ascites. There was no evidence of hepatitis A and C virus, Epstein-Barr virus, cytomegalovirus, or herpes simplex virus infection. IgM HBe antibodies, and high serum HBV/DNA polymerase levels (1492 pg/ml) were detected, and acute hepatitis caused by HBV reactivation was diagnosed. Infliximab and methotrexate were stopped, while prednisone (8 mg/day) was continued. Lamivudine at a daily dose of 100 mg was started, and, after two months, serum AST and ALT returned to normal (30 and 40 IU/l, respectively) and HBV/DNA polymerase levels dropped (9 pg/ml).

DISCUSSION

Hepatitis B reactivation is a well known adverse event in patients with chronic HBV infection receiving cytotoxic or immunosuppressive treatment.³

Inhibition of TNF α might lead to additional advantages for viral replication owing to escape from host antiviral mechanisms. The antiviral activity of TNF α has long been

recognised.⁴ Indeed, synergistic activity of interferon γ (INF γ) and TNF α has been shown to affect early steps in herpes simplex virus replication at the level of early gene transcription and translation,⁵ while these cytokines inhibit murine cytomegalovirus late gene transcription and DNA replication.⁶

Data from animal models indicate that INF γ and TNF α may also synergistically inhibit HBV gene expression and replication, leading to a reduction in the intracellular level of HBV transcripts.^{7,8} Moreover, TNF α , which is induced by HBV antigens, is supposed to be beneficial for viral clearance.⁹ On the other hand, methotrexate might reduce the clearance of intra-hepatic HBV depleting specific cytotoxic cells.¹⁰

Despite the wide use of methotrexate in the treatment of RA and the high prevalence of HBV infections in some countries, to our knowledge, only two other cases^{11,12} with fulminant hepatitis B (precore variant mutant type) after two years' treatment and concomitant discontinuation of methotrexate have been reported.

So far, no reports have described an association between HBV hepatitis and conventional DMARDs such as D-penicillamine or sulfasalazine. Instead, a case with both Crohn's disease and ongoing active hepatitis C infection has been reported. The patient underwent infliximab treatment with no worsening of his liver function or polymerase chain reaction status during a 16 week follow up period.¹³

Our case suggests that serological assay for hepatitis B should be performed before treatment with infliximab. If immunosuppressive drugs must be used in patients with RA and chronic infection with HBV, then liver function and HBV/DNA polymerase levels should be closely monitored.

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Anticardiolipin antibodies in acute multifocal posterior placoid pigment epitheliopathy

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Acute multifocal posterior placoid pigment epitheliopathy (AMPPPE) is a disorder of otherwise healthy young adults. A possible thrombotic process involving the choroid has been suggested in the pathogenesis of this condition. We report a case of AMPPPE and anticardiolipin antibodies (aCL).

CASE REPORT

A 32 year old woman presented because of sudden onset of bilateral decrease in visual acuity. Her past medical history was negative. One week before the decrease in vision, the patient had been complaining of headaches associated with fever, chills, and a rash on her neck and lower extremities.

The initial ocular examination showed a visual acuity of 20/200 in the right eye and 20/30 in the left eye. Fundus examination disclosed bilateral multiple yellow-white placoid lesions in the posterior pole at the level of the retinal pigment epithelium (RPE). Serous detachment of the right macula was also noted. Fluorescein angiography showed early hypofluorescence of the lesions with staining in the late phases of the angiogram. Based on the clinical and fluorescein angiogram findings, the diagnosis of AMPPPE was made.

Physical examination showed a temperature of 38.5°C, tender posterior cervical lymphadenopathy, as well as skin lesions affecting both legs. Biopsy of the lesions was compatible with erythema nodosum. Extensive fever investigation was negative. The erythrocyte sedimentation rate was 69 mm/1st h, and IgG aCL was 78 GPL (normal <15.0 GPL); IgM aCL was negative.

Over a period of two weeks, the fever resolved and the patient's vision started to improve without any treatment. The fundus lesions disappeared leaving irregular RPE pigmentation. One month later her vision had recovered to 20/30 in the right eye and 20/25 in the left eye. There was total resolution of the serous detachment in the right eye. Two, four, and six months after presentation, the IgG aCL were 63, 57, and 52 GPL, respectively. One year later, the aCL titres were normal. The eye and systemic examination remained normal throughout this period.

DISCUSSION

AMPPPE has been associated with a wide variety of disorders, including viral infections (adenovirus), streptococcal infections, vasculitides (cerebral vasculitis and Wegener's granulo-

matosis), post-hepatitis B vaccination, Lyme disease, tuberculosis, and sarcoidosis.¹⁻³ Few reports have suggested an immunological mechanism.

The pathogenesis of AMPPPE remains obscure.⁴ AMPPPE has been associated with retinal vascular occlusive disease. Charteris *et al* reported a case of AMPPPE complicated by a central retinal vein occlusion.⁵ The occurrence of these two conditions at the same time may imply that AMPPPE is part of a wider thrombotic disease. Furthermore, the presence of a serous macular detachment further supports injury to the choriocapillaris and RPE. Serous macular and retinal detachment are often seen in occlusive diseases of the choriocapillaris (for example, toxemia of pregnancy, disseminated intravascular coagulopathy).⁶

Antiphospholipid antibodies (aPL) have been reported in various ophthalmological conditions, including amaurosis fugax, retinal arterial and venous occlusion, and transient diplopia as well as in recurrent ischaemic optic neuropathy.⁷ They have not been previously described in association with AMPPPE. The aPL have been frequently detected in patients with various infectious diseases.⁸ Although aPL associated with infections were initially thought to be non-pathogenic and not associated with thrombotic complications,⁸ recent data uncovered a possible pathogenic role for these antibodies in precipitating thrombosis.⁸ Lupus anticoagulant or aCL, or both, were associated with a number of viral infections like hepatitis C virus, human immunodeficiency virus, cytomegalovirus, varicella zoster, Epstein B virus, adenovirus, and parvovirus B. In many instances the presence of these antibodies was associated with thrombosis.⁸

The presentation and course of our patient suggest a possible role for aCL in the pathogenesis of AMPPPE.

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