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Letters to the Editor

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Successful treatment of hepatitis B-associated vasculitis using lamivudine as the sole therapeutic agent

SIR, We read with interest the report by MacLachlan *et al.* [1] describing a patient with hepatitis B virus (HBV)-associated polyarteritis nodosa (PAN) treated with lamivudine and immunosuppression. Another recent report described the successful use of lamivudine and interferon alpha (IFNα) [2]. We report a patient with vasculitis associated with chronic HBV antigenaemia whose disease was successfully managed with lamivudine alone.

A 52-yr-old hospital porter was admitted to hospital in December 1998 with a 10-month history of intermittent, purpuric rash affecting his legs and buttocks. He had paraesthesiae of his legs with numbness of the left foot, intermittent polyarthritis, mild weight loss and an altered bowel habit. His ability to work was hampered by the recent onset of intermittent claudication. There was no history of needle stick injury or drug abuse, but he had been tattooed in the 1960s. There was no history of symptomatic hepatitis.

He had diminished sensation below the mid-shin, especially on the left, and hyperaesthesia of his feet. A purpuric rash was noted around the dorsum of the feet and ankles. General examination was satisfactory. Laboratory tests showed normal full blood count, renal function, liver function, thyroid function, cholesterol, plasma glucose, angiotensin-converting enzyme and a negative myeloma screen. Erythrocyte sedimentation rate (ESR) was 60 mm/h, C-reactive protein (CRP) was 21 mg/l. Immunoglobulin G (IgG) and IgA were raised at 22.9 g/l (8–14.5) and 4.38 g/l (0.7–3.8), respectively. Immunology results were as follows: antinuclear antibodies (ANA) 1:1600, myeloperoxidase antibodies 19 EU/ml (0–8) (indirect immunofluorescence negative), proteinase 3 negative, von Willebrand factor 222 (50–200). Anti-DNA, extractable nuclear antigens, C_3, C_4 and coeliac autoantibodies were negative or normal. The rheumatoid latex test was positive, with a negative Rose-Waaler test. Hepatitis B surface antigen (HBs Ag), HBe Ag and hepatitis B core antibody (HBc Ab) IgG were positive with HBs Ab, HBe Ab and HBc Ab IgM negative, confirming past exposure and lack of immunity to HBV. HBV DNA was measured at 12 pg/ml by radioimmunoassay. Hepatitis C antibody and cryoglobulins were negative. Abdominal ultrasound was normal, but colonoscopy revealed widespread mucosal hyperaemia with large punched out ulcers throughout the transverse colon. Biopsy showed a non-specific chronic colitis with severe active inflammation and crypt abscesses. Neurophysiology confirmed axonal polyneuropathy with absent sensory and reduced motor conduction in both legs. Skin biopsy showed a leucocytoclastic vasculitis. Subsequent magnetic resonance examination of the upper abdomen found no evidence of aneurysmal dilatation involving the upper abdominal aorta, coeliac axis vessels or superior mesenteric artery. Doppler studies confirmed normal peripheral pulse pressures.

HBV-associated vasculitis was diagnosed. He was commenced on lamivudine 100 mg daily in February 1999. Effective suppression of viral replication was achieved after 1 month; by 4 months, HBV DNA was undetectable by radioimmunoassay. During this time his general health improved, arthralgia resolved, as did abdominal and claudication symptoms, and the vasculitic rash gradually cleared. There was a slow recovery of his sensory neuropathy and only small areas of reduced sensation around the toes remained at his 11-month review, in which he reported no new symptoms. However, there was no evidence of seroconversion in terms of loss of HBe Ag; indeed the subsequent introduction of polymerase chain reaction (PCR) assays for viral DNA at our reference laboratory demonstrated HBV DNA copies in the patient's circulation 11 months after commencing treatment.

What can we tell such a patient about his prognosis? An earlier report suggests that seroconversion may lead to complete disease remission [2]. Evidence in the literature shows that lamivudine alone is effective in active hepatitis and cirrhosis due to HBV. In chronic HBV, viral replication can be suppressed in up to 97% of patients. Seroconversion defined by loss of HBe Ag can be achieved in up to 17% at 1 yr and 27% after 2 yr [3], and is generally permanent [4]. Control of disease is therefore likely to be achieved in a majority, but on drug withdrawal both clinical and serological relapse may occur [5]. Resistant strains emerge in a proportion of patients after several months of monotherapy. However, the development of resistance may not imply relapse of the disease, and impact may be limited in those who seroconvert, as HBV DNA typically remains suppressed [6]. Combined therapy using IFNα and lamivudine may result in seroconversion [2], but the use of IFN is associated with considerable side-effects and may carry risks for those in whom hepatic decompensation occurs [7]. Severe or rapidly progressive disease may necessitate the use of immunosuppression, which is associated with possible acceleration of viral replication [8], although concurrent use of lamivudine may prevent this [1].

Our patient exhibited features common to the spectrum of HBV-associated disease from immune complex vasculitis to polyarteritis, illustrating that it is possible to control HBV-associated vasculitis by suppressing viral replication without the use of steroids or

other immunosuppressive agents. Studies in hepatitis suggest that continued treatment might increase the probability of seroconversion and possibly induce permanent remission. This strengthens the argument that pathological immune responses resulting from a defined aetiological agent may be modified if that agent is accurately targeted.

A. Filer, A. Hughes[1], K. Kane[2], D. Mutimer[1], P. Jobanputra[3]

Department of Rheumatology, University of Birmingham, [1]Liver and Hepatobiliary Unit, Queen Elizabeth Hospital, Birmingham, [2]Department of Gastroenterology and [3]Department of Rheumatology, Selly Oak Hospital, Birmingham, UK

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Correspondence to: A. Filer, Department of Rheumatology, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK

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Reply

We read with interest the contribution of Filer *et al.* [1] which reports a patient with a hepatitis B-associated vasculitis who responded to treatment with lamivudine alone.

In contradistinction to the patient we described [2] who had 'full-blown' classical polyarteritis nodosa which easily fulfilled the 1990 American College of Rheumatology criteria [3] and was associated with microaneurysms, histological evidence of chronic active hepatitis and a very high viral load, the current patient had a fairly mild leucocytoclastic vasculitis associated with a relatively low viral load.

This probably explains why this patient responded to simple removal of the antigen, whereas our patient initially deteriorated on a regime of lamivudine and steroids, despite a marked decrease in the viral load, and only improved when cyclophosphamide was added. It seems that although the viral antigen may be involved in the initiation of the vasculitis, the process becomes self-sustaining by the time that full-blown polyarteritis nodosa develops, which would explain why simple removal of the antigen may be insufficient in such cases.

Our patient remained in remission, although he had residual neurological deficits, despite stopping cyclophosphamide after 5 months and steroids after 11 months. Viral load was by then undetectable in the quantitative polymerase chain reaction but seroconversion had not yet occurred. After 12 weeks of α-interferon, he had seroconverted for both hepatitis B surface and 'e' antigens and remained seroconverted 3 months later. A similar strategy might be beneficial in the current case as an alternative to long-term viral suppression with lamivudine.

D. Maclachlan, M. Battegay[1], A. L. Jacob[2], A. Tyndall

University Department of Rheumatology, Felix Platter Spital, Burgfelder Strasse 101, CH-4055 Basel, [1]University Medical Outpatient Department, Kantonsspital Basel, Petersgraben 4, Basel and [2]University Institute of Diagnostic Radiology, Kantonsspital Basel, Petersgraben 4, Basel, Switzerland

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Correspondence to: D. Maclachlan.

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