Findings that shed new light on the possible pathogenesis of a disease or an adverse effect

Adrenalectomy to treat reactivated chronic hepatitis B infection in a patient with a steroid-secreting adrenal tumour

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Summary

We present a case of reactivation of chronic hepatitis B virus (HBV) infection by a steroid-producing adrenal tumour. The tumour caused a reactivation and subsequent flare of the patients' HBV. The adrenal tumour was treated with an adrenalectomy and as a consequence the patients' transaminitis and viral load fell rapidly without the need for any additional hepatitis B treatment. The role of hepatitis B and steroid priming is discussed and the possible immunological mechanisms that underpin this phenomenon.

BACKGROUND

This case report demonstrates that the endogenous production of corticosteroids caused 'priming' of this patients' hepatitis B infection. She developed a flare of her hepatitis B virus (HBV) and alanine aminotransferase (ALT). When the steroids were 'withdrawn' (adrenalectomy), this allowed the host immune response to take over, resulting in control of her HBV. It opens the debate as to the role of 'steroid priming' in those with HBV, indicating there may be a subsection of patients in whom such a treatment could be beneficial. It also gives a useful insight into the interaction of HBV with the immune system. The endogenous nature of the steroid production makes this case distinctly unique with no other similar reports of this phenomenon in the literature.

CASE PRESENTATION

A 52-year-old Ukrainian lady presented to Hepatology out-patients clinic with general malaise and abnormal liver function tests. She had no known risk factors for liver disease. Her medical history included hypertension and renal stones.

INVESTIGATIONS

Her initial bloods showed: bilirubin 7 µmol/l, ALT 279 IU/l, alkaline phosphatase 67 IU/l, albumin 44 g/l and international normalised ratio 1.0. A liver screen showed she had hepatitis B (HBsAg positive, HBeAg negative, anti-HBe positive) with a HBV DNA level of 9.7 million IU/ml. Hepatitis C, ferritin and autoantibody screen were negative. Her α-fetoprotein was 15 KIU/l. Ultrasound scan showed a normal liver appearance. However, it did show an incidental mass on her left kidney. To delineate this further, a CT scan was carried out which confirmed this mass, as well as evidence of chronic pancreatitis, renal cysts and renal stones.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for this renal mass lesion included tuberculosis or a neoplasm. Subsequently, she

developed diabetes mellitus and a psoas muscle abscess, which required draining. The left adrenal mass (see figure 1) was diagnosed as an adrenal adenoma. Endocrine tests confirmed Cushing's syndrome (cortisol 1089 nmol/l and adrenocorticotrophic hormone less than 5 ng/l). She underwent a left adrenalectomy.

TREATMENT

See the following.

OUTCOME AND FOLLOW-UP

After adrenalectomy, her Cushing's syndrome settled. This was associated with her hepatitis B infection becoming inactive. Within 6 months, the ALT returned to normal level and her hepatitis B DNA level dramatically fell to 600 IU/ml without any additional hepatitis B treatment (see figure 2).

This is likely to be a case of reactivation of HBV due to endogenous steroids rather than a de novo infection as she had no risk factors for acute HBV and she comes from an area of moderately high prevalence.

DISCUSSION

Reactivation of HBV by exogenous steroids (such as during chemotherapy) has been well documented.¹⁻³ This is the first case report of reactivation of chronic hepatitis B by a steroid-producing adrenal tumour that was successfully treated by adrenalectomy. The adrenalectomy cured both her Cushing's syndrome and hepatitis B. Tsou *et al*⁴ reported a similar case of hepatitis B and Cushing's syndrome, but the patient died from hepatic failure.

The host immune response is key to controlling HBV infection. The host immune responses to viral antigens displayed on infected hepatocytes are the principal determinants of hepatocellular injury. Indeed, the virions and hepatitis B surface antigen (HBsAg) particles produced in hepatocytes can be taken up by antigen presenting cells,

Figure 1 Transaxial CT scan through the upper abdomen postintravenous contrast demonstrates a mass within the left adrenal gland (marked with an arrow), exhibiting heterogeneous contrast enhancement in keeping with an adrenal tumour.

Figure 2 A rapid decrease in the HBV DNA level and ALT was seen after adrenalectomy (marked with an arrow).

which can then degrade the viral proteins to peptides that can be presented onto the cell surface bound to major histocompatibility complex (MHC) class I or class II molecules. These peptide antigens are then recognised by CD8 or CD4 T lymphocytes, which are then sensitised. Virus-specific CD8 cytotoxic T lymphocyte cells can then recognise viral antigens on MHC class I chains on infected hepatocytes. This recognition reaction can lead to either direct lysis of the infected hepatocyte or the release of interferon- γ and

tumour necrosis factor α , which can downregulate viral replication in surrounding hepatocytes without causing direct cell killing.⁵

Corticosteroids suppress cell-mediated immunity, inhibited genes encoding for proinflammatory cytokines such as interleukin 2 (IL-2) and decreasing T lymphocyte proliferation. Humoral immunity is also suppressed, expressing smaller amounts of IL-2 and IL-2 receptors, hence diminished B cell expansion and antibody synthesis.⁶

Learning points

- ▶ Host immune response is key to control of HBV infection.
- ▶ Steroid priming may help a certain subsection of patients who have HBV infection.
- ▶ Reactivation of HBV is likely to become a more frequent problem and may appear to be a de novo presentation.
- ▶ Screen patients for HBV who are to undergo immunosuppression.

HBV replication is increased by corticosteroids, but serum aminotransferases tend to decline. Once corticosteroids are removed, the opposite occurs and viral replication declines and there is often a flare in aminotransferases.^{7–10} The underlying mechanism behind this phenomenon is not fully understood, but it is thought that the increased viral replication may be partly explained by a steroid responsive element in HBV genome, which stimulates viral transcriptional activity.⁵ The immunological rebound effect following corticosteroid removal has been hypothesised to be secondary to the increased activation of lymphocytes that promote the T-helper 1 cells immune response while there is increased viral antigen expression.¹¹

Initial clinical studies^{12–13} suggested a possible beneficial role for steroids in the treatment of HBV. Steroid priming was hypothesised to induce suppression of the host immune response. On withdrawal, the host would have an enhanced immunoreactivity and subsequently clear the virus. Subsequent clinical studies did not confirm benefit.^{14–15}

This case report demonstrates that the endogenous production of corticosteroids caused ‘priming’ of this patients’ hepatitis B infection. She developed a flare of her HBV and ALT. When the steroids were ‘withdrawn’ (adrenalectomy), this allowed the host immune response to take over resulting in control of her HBV.

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Competing interests None.

Patient consent Obtained.

REFERENCES

1. Yeo W, Chan TC, Leung NW, *et al.* Hepatitis B virus reactivation in lymphoma patients with prior resolved hepatitis B undergoing anticancer therapy with or without rituximab. *J Clin Oncol* 2009;**27**:605–11.
2. Cheng AL, Hsiung CA, Su IJ, *et al.* Steroid-free chemotherapy decreases risk of hepatitis B virus (HBV) reactivation in HBV-carriers with lymphoma. *Hepatology* 2003;**37**:1320–8.
3. Hoofnagle JH, Dusheiko GM, Schafer DF, *et al.* Reactivation of chronic hepatitis B virus infection by cancer chemotherapy. *Ann Intern Med* 1982;**96**:447–9.
4. Tsou PL, Lee HS, Jeng YM, *et al.* Submassive liver necrosis in a hepatitis B carrier with Cushing’s syndrome. *J Formos Med Assoc* 2002;**101**:156–8.
5. Ganem D, Prince AM. Hepatitis B virus infection—natural history and clinical consequences. *N Engl J Med* 2004;**350**:1118–29.
6. Mier JW, Vachino G, Klempner MS, *et al.* Inhibition of interleukin-2-induced tumor necrosis factor release by dexamethasone: prevention of an acquired neutrophil chemotaxis defect and differential suppression of interleukin-2-associated side effects. *Blood* 1990;**76**:1933–40.
7. Chou CK, Wang LH, Lin HM, *et al.* Glucocorticoid stimulates hepatitis B viral gene expression in cultured human hepatoma cells. *Hepatology* 1992;**16**:13–18.
8. Sagnelli E, Manzillo G, Maio G, *et al.* Serum levels of hepatitis B surface and core antigens during immunosuppressive treatment of HBsAg-positive chronic active hepatitis. *Lancet* 1980;**2**:395–7.
9. Nair PV, Tong MJ, Stevenson D, *et al.* Effects of short-term, high-dose prednisone treatment of patients with HBsAg-positive chronic active hepatitis. *Liver* 1985;**5**:8–12.
10. Scullard GH, Smith CI, Merigan TC, *et al.* Effects of immunosuppressive therapy on viral markers in chronic active hepatitis B. *Gastroenterology* 1981;**81**:987–91.
11. Liaw YF, Tsai SL, Chien RN, *et al.* Prednisolone priming enhances Th1 response and efficacy of subsequent lamivudine therapy in patients with chronic hepatitis B. *Hepatology* 2000;**32**:604–9.
12. Müller R, Vido I, Schmidt FW. Rapid withdrawal of immunosuppressive therapy in chronic active hepatitis B infection. *Lancet* 1981;**1**:1323–4.
13. Rakela J, Redeker AG, Weliky B. Effect of short-term prednisone therapy on aminotransferase levels and hepatitis B virus markers in chronic type B hepatitis. *Gastroenterology* 1983;**84**:956–60.
14. Hoofnagle JH, Davis GL, Pappas SC, *et al.* A short course of prednisolone in chronic type B hepatitis. Report of a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1986;**104**:12–17.
15. Lee SD, Tong MJ, Wu JC, *et al.* A randomised double-blind placebo-controlled trial of prednisolone therapy in HBeAg and HBV DNA positive Chinese patients with chronic active hepatitis B. *J Hepatol* 1991;**12**:246–50.

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