CASE REPORT

Intense pruritus in Epstein-Barr virus (EBV) hepatitis treated with naloxone drip

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Accepted 9 January 2015

SUMMARY

Pruritus is a manifestation of chronic liver disease. Epstein-Barr virus (EBV) infection often presents as infectious mononucleosis and mild hepatitis. Severe pruritus in the setting of infectious mononucleosis and persistent marked hyperbilirubinaemia is exceedingly uncommon. To the best of our knowledge, we present the first case of a patient with EBV hepatitis and severe pruritus that was successfully treated with an *ultra-low* dose of intravenous naloxone.

BACKGROUND

Pruritus is a manifestation of chronic liver disease. Among liver diseases in general, the prevalence of pruritus varies from 5% in patients with chronic hepatitis C to 70% in patients with primary biliary cirrhosis.^{1,2} Epstein-Barr virus (EBV) infection often presents as infectious mononucleosis (IM), which is characterised by a constellation of fever, sore throat and adenopathy. Gastrointestinal signs and symptoms such as mild elevations in transaminases (two to three times upper limit of normal), abdominal pain and hepatosplenomegaly, are often unrecognised. While mild to moderate hepatic injury occurs commonly in IM, clinical jaundice with high bilirubin levels (>6 mg/dL) is only occasionally encountered ($<5\%$ of cases).³ Additionally, severe pruritus in the setting of IM and persistent marked hyperbilirubinaemia is exceedingly uncommon.

To the best of our knowledge, this is the first case of a patient with EBV hepatitis and severe pruritus that was treated with an *ultra-low* dose of intravenous naloxone.

CASE PRESENTATION

A 39-year-old Caucasian man with a history of hypothyroidism secondary to a partial thyroidectomy was referred to our hepatology clinic with a 3-week history of generalised weakness, jaundice with worsening liver function tests (LFTs) (table 1) and pruritus. The onset of these symptoms was preceded by 5 days of fever, chills, nausea and vomiting, decreased appetite and diarrhoea, for which he was treated empirically with azithromycin but experienced no symptomatic relief. A trial of hydroxyzine and a selective serotonin reuptake inhibitor by his primary care physician failed to control his pruritus.

INVESTIGATIONS

The patient's physical examination was remarkable for jaundice, an enlarged right anterior cervical lymph node and multiple linear excoriations on his

extremities and trunk from scratching (figure 1). Laboratory tests, obtained prior to the hepatology clinic visit, showed a mixed elevation of transaminases and bilirubin, and a positive Monospot (heterophile antibody) test. There was no evidence of haemolysis or leucocytosis, and the patient was negative for hepatitis A/B/C serology. Initial management included supportive care and ursodiol in addition to antihistamines. Ultrasound of the right upper quadrant was unremarkable. However, the patient returned in 1 week with worsening symptoms, including pruritus severe enough to cause insomnia, lethargy and loss of workdays. EBV serology confirmed the diagnosis of an acute infection; IgM and early antigen were positive, and IgG and antibodies to EBV nuclear antigen (window period) were negative.

TREATMENT

During the next few appointments at the hepatology clinic over a period of 2 weeks, the patient was sequentially prescribed rifampicin 150 mg twice daily, diphenhydramine 25 mg twice daily, cholestyramine 4 g four times daily and naltrexone 12.5 mg four times daily. However, none of these treatments relieved his pruritus. He stopped naltrexone after the first dose due to development of shakes, numbness and paraesthesias involving the extremities.

Having exhausted most of the treatment options and with the patient reporting worsening pruritus, he was admitted to the hospital for naloxone infusion. The rationale for intravenous infusion of naloxone was to introduce an opiate antagonist slowly so as to prevent a withdrawal reaction. In an effort to be cautious, a bolus of naloxone was omitted, and the patient was started on an ultra-low dose naloxone drip (0.02 $\mu\text{g/kg/min}$), which is 10% of the standard recommended infusion. Over the next 24 h the naloxone drip was titrated up to a rate of 0.8 $\mu\text{g/kg/min}$. He tolerated the treatment without any adverse effects and reported complete relief of pruritus in 36 h.

OUTCOME AND FOLLOW-UP

The patient was discharged home on low-dose naltrexone at 12.5 mg/day with the plan to increase the dose by 12.5 mg every week until the pruritus resolved. He remained asymptomatic from pruritus during follow-up visits over 1 month.

DISCUSSION

EBV infections are a well-known entity associated with mild-to-moderate hepatic dysfunction, which is usually self-limiting. Jaundice occurs in less than

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To cite: Agrawal S, O'Connor R, Aoun E, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-207037

Table 1 Patient's liver function tests during acute EBV infection and pruritus grades before and during treatment

Component	Initial presentation	Week 3, hepatology clinic visit	Week 4, follow-up	Week 5, day of admission	36 h postintravenous naloxone treatment	10 Days oral naltrexone	1 Month oral naltrexone
Total bilirubin (mg/dL)	6.4	19.2	24.3	25.8	25.4	16.3	1.2
Direct bilirubin (mg/dL)	3.7	10.6	15.3	15.3	15.7	9.4	0.5
Alkaline phosphatase (IU/L)	236	229	205	179	175	132	87
ALT (IU/L)	210	87	63	70	68	42	29
AST (IU/L)	135	49	48	62	60	38	27
Haemoglobin (g/dL)	12.8	12.3	11.7	11.9	12.2	12.6	12.5
INR	1.0	1.1	1.4	1.2	1.3	1.1	1.0
Pruritus grade	Moderate	Moderate	Severe	Severe	Mild	None	None

ALT, alanine aminotransaminase; AST, aspartate transaminase; EBV, Epstein-Barr virus; INR, international normalised ratio.

5% of these patients and may be due to either cholestatic hepatitis or haemolytic anaemia. In the presence of indirect hyperbilirubinaemia, a complete blood count and peripheral blood smear are an essential part of the evaluation to exclude haemolysis.⁴ Liver function abnormalities during EBV infection (elevations in aspartate transaminase, alanine aminotransaminase and/or lactate dehydrogenase) occur most often during the second week, and resolve within 2–6 weeks. However, in our patient, symptoms persisted for over 8 weeks.

In a case series, Fuhrman *et al*⁵ reported data on seven patients with marked hyperbilirubinaemia in IM. On review, all patients presented with a viral illness prodrome and abnormal LFTs. All patients tested heterophile-antibody positive and hepatitis A/B/C negative, and no other source of hepatitis was identified in these cases. Antibodies to IgM type to viral capsid antigen were initially demonstrated at a level of 1:40 or greater in all patients. All of these patients had documented cholestasis and jaundice, limited to 2–3 weeks in duration, but none suffered from subsequent pruritus. Supportive care was the mainstay of treatment in all cases.

Infiltration of portal areas with lymphocytes and monocytes is a classic histological finding of EBV hepatitis along with vacuolisation and swelling of hepatocytes. Sinusoids with mononuclear cells in an 'Indian Bead' pattern are also pathognomonic for EBV infections.⁶

Pruritus of cholestasis results from accumulation of bile acids and pruritogens produced by the liver in plasma and other tissues. Increased central neurotransmission via the endogenous opioid system can result in pruritus (eg, pruritus induced by morphine).^{7 8} Increased bile acid levels during cholestasis lead to an increased central opioidergic tone via activation of mu

Figure 1 Excoriations on lower extremities due to intense pruritus.**Table 2** Common medications for pruritus of cholestasis

Drug	Dose recommendations	Adverse events
Rifampicin	10 mg/kg/day orally; typically, 150 mg twice daily	Potential hepatotoxicity
Cholestyramine	4 g 3–4 times/day after meals	Nausea, bloating, constipation
Naltrexone, naloxone	Naltrexone 50 mg/day Naloxone 0.4 mg intravenous bolus followed by infusions of 0.2 µg/kg/min	Opiate withdrawal-like reaction
Selective serotonin reuptake inhibitor (sertraline)	75–100 mg daily	Insomnia
Phenobarbital	10–40 mg orally three times a day	Drowsiness, lethargy, dependence
Diphenhydramine	12.5–25 mg orally daily-twice daily	

opioid receptors, which results in pruritus. Patients with cholestasis can experience symptoms of opiate withdrawal when given opiate antagonists.⁹ Therefore, the pruritus of cholestasis may result from altered opioidergic neurotransmission evident from pruritus being relieved by administering opioid antagonists such as naloxone.¹⁰

Mild hepatitis due to EBV infection is a common finding in IM but persistent hyperbilirubinaemia and pruritus are rare. Multiple oral medications have been indicated for treatment of pruritus of cholestasis and can be tried separately or in combination (table 2). Intravenous use of naloxone to relieve pruritus of chronic cholestasis and to prevent an opiate withdrawal-like syndrome has been described before in controlled studies.^{11 12} This report illustrates a unique presentation and successful treatment of severe pruritus with naloxone drip, in the setting of prolonged cholestatic liver disease secondary to acute EBV infection ultimately requiring hospitalisation after failing all other therapies.

Learning points

- ▶ Epstein-Barr virus hepatitis presenting with persistent hyperbilirubinaemia and pruritus is rare.
- ▶ Multiple medications including oral naltrexone are readily available for treatment of pruritus.
- ▶ Ultra-low dose intravenous naloxone can be used to relieve severe pruritus in an in-patient setting with success.

Contributors SA and MB were involved in the care of the patient. All authors contributed to the writing of this manuscript.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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