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Case Report

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A case of mononucleosis infectiosa presenting with cholemic nephrosis

Obbo W. Bredewold, Johan W. de Fijter and Ton Rabelink

Department of Nephrology, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands

Correspondence and offprint requests to: Obbo Bredewold; E-mail: o.w.bredewold@lumc.nl

Abstract
A 38-year-old male was admitted with fever, progressive jaundice, cervical lymphadenopathy, hepatomegaly and acute oliguric renal failure. Epstein-Barr virus (EBV) infection was diagnosed by detection of EBV-DNA in plasma and confirmed by EBV seroconversion. Kidney biopsy revealed acute tubular necrosis and abundant casts, consisting of bilirubin pigment. With conservative treatment, the patient fully recovered from cholemic nephrosis, an uncommon condition, not described after EBV infection before.

Keywords: acute kidney failure; cholemic nephrosis; Epstein-Barr virus; Fouchet; hyperbilirubinaemia

Introduction

Epstein-Barr virus (EBV) is a member of the family of herpesviridiae and is widely distributed in humans. After transmission, a wide spectrum of disease can become manifest, ranging from asymptomatic seroconversion to nonspecific complaints or the classic 'mononucleosis infectiosa' (mono syndrome). Younger children and older adults usually have a more benign course of disease.

While subclinical renal involvement is relatively common in infected patients, significant parenchymal dysfunction was estimated to be only 1.6% [1]. Renal failure can be caused by interstitial nephritis [2], immune complex glomerulonephritis or rhabdomyolysis.

We present a case of a 38-year-old man with a severe sequela of EBV infection including extreme jaundice and acute oliguric renal failure.

The case

The patient was admitted to the hospital with fever, malaise, nausea, headache and jaundice. The previous 2 weeks, he had a persistent dry cough for which he received amoxicillin. He had no medical history besides mild untreated hypertension. There was no alcohol, nicotine or drug abuse. He had a monogamous relationship with his wife. The family history was negative.

His temperature was 38.6°C, his blood pressure was 108/60 mmHg and his heart rate was 95/min. Physical examination revealed jaundice, besides enlarged and painful cervical lymph nodes. Fine crackles were heard over both lungs, and the spleen was slightly enlarged. The remainder of the investigation was normal. After laboratory examination (Table 1), acute EBV infection with obstructive jaundice and acute renal failure (ARF) was diagnosed. Urinalysis showed hypercellularity, with extensive tubular epithelial cells, granular casts and amorphous material. A bone marrow aspirate ruled out haemophagocytic syndrome. A computed tomography of the chest and abdomen showed bilateral pleural effusion, hepatomegaly (18 cm) and splenomegaly (15 cm), but no hydronephrosis. Because of progressive oliguric renal failure with fluid overload, intermittent haemodialysis was started.

We considered acute interstitial nephritis due to amoxicillin or EBV infection and acute tubular necrosis due to unobserved circulatory insufficiency. A percutaneous renal biopsy was taken, 1 week after admission. (Figure 1)

Light microscopic analysis showed no glomerular abnormalities. The tubular lumina in both the cortex and medulla

Table. 1 Laboratory results on admission

Haemoglobin (mmol/L)	5.5
Leukocytes (10E9/L)	14.7
Thrombocytes (10E9/L)	225
Erythrocyte sedimentation rate (mm/h)	43
Creatinine (mcmol/L)	288
Blood urea nitrogen (mmol/L)	16
Sodium (mmol/L)	141
Potassium (mmol/L)	3.8
Bicarbonate (mmol/L)	16
Bilirubin total (mcmol/L)	616
Bilirubin conjugated (mcmol/L)	488
Alkaline phosphatase (IU/L)	99
Gamma glutaryl transpeptidase (IU/L)	102
Lactate dehydrogenase (IU/L)	806
Alanine aminotransferase (IU/L)	134
Aspartate aminotransferase (IU/L)	178
C-reactive protein (mg/L)	113
Creatin kinase (IU/L)	1350
Albumin (g/L)	27
Ferritin (ng/mL)	8024
Haptoglobin (mg/dL)	2
EBV serology	
IgG	NEG
IgM	POS
EBV-DNA (copies/mL)	3.2 × 10E3

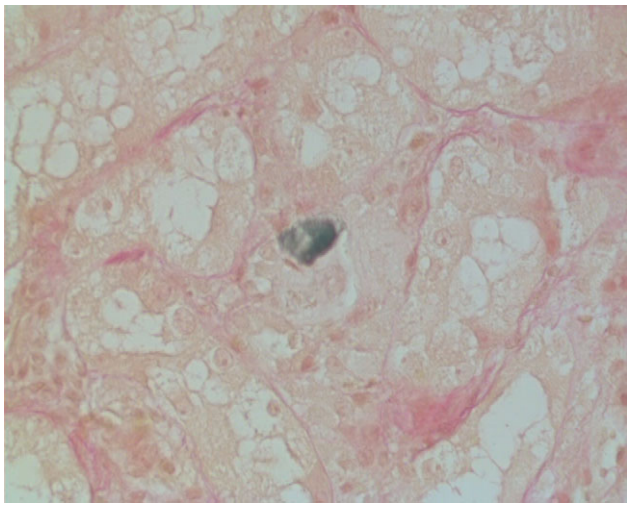

Fig. 1. Fouchet's staining shows marked positivity for bilirubin containing casts.

contained numerous casts, with a course granular, brown appearance. Iron staining of the casts was negative, as was von Kossa's staining for calcium. Fouchet's stain was performed because of the extreme hyperbilirubinaemia and showed marked positive staining for bilirubin in the tubular casts (Figure 1: Fouchet staining). Immunofluorescent staining did not show any depositions of IgA, IgM, IgG, C3, C1q, kappa or lambda.

After 16 days, the fever dissolved. Concomitantly his diuresis increased, lymphadenopathy disappeared and bilirubin levels fell to 35 mmol/L. Dialysis was discontinued. Repeated ultrasound of the abdomen showed normalization of the hepatic and spleen size. The patient was discharged. Six months later, levels of bilirubin and creatinine had normalized. Seroconversion for EBV-IgG was confirmed.

Discussion

Renal failure in this patient was explained by bilirubin-containing tubular cast formation with concomitant acute tubular necrosis, a condition known as cholemic nephrosis (CN) [3]. CN is seldomly reported and has never been described in EBV infection. Tubular toxicity of bilirubin appears to occur only in cases with very high levels of bilirubin [4]. Its pathogenesis is not fully elucidated. Both bilirubin itself as well as elevated levels of bile salts are suggested to have a direct toxic effect on proximal tubular cells [4]. The rarity of the condition and the ill-defined pathophysiology led us to meticulously consider the alternative causes of renal failure in this patient.

The lowest recorded blood pressure was 108/60 mmHg. Even for a patient with prior hypertension, such a severe case of renal failure is unlikely to have been caused by this degree of hypotension. Moreover, there was no history of fluid loss through diarrhoea or vomiting.

High bilirubin levels are frequently seen in cirrhosis and liver failure, which, in its decompensated state, can lead to the hepatorenal syndrome (HRS). Because of the absence of ascites and long-standing liver disease, we considered HRS to be highly unlikely.

Casts may be seen in pigment-induced nephropathy by myoglobin or haemoglobin [5] and in multiple myeloma. Casts of these origins could have been preformed by reacting with tubular-secreted Tamm–Horsfall protein in acidic conditions, and subsequently contaminated with filtered bilirubin. A cast of such consistence would have been hard to distinguish from a true bilirubin cast. However, laboratory examination ruled out either of these conditions.

EBV itself is infrequently known to be involved in ARF [2, 6, 7]. Negative EBER-1-antigen staining in our biopsy makes a direct causative role for EBV in this case unlikely.

Finally, we considered acetaminophen and amoxicillin to have caused drug-induced ARF. Acetaminophen is known for its potential nephrotoxicity, even in the absence of liver failure [8], but was only administered after onset of ARF. Our patient used amoxicillin prior to hospitalization, but the biopsy showed no typical signs of acute interstitial nephritis.

In conditions of extrahepatic cholestasis, renal clearance of bilirubin increases from $<5\%$ of total bilirubin to 90%. Numerous studies point to a renoprotective effect of bilirubin in both rats [9] and humans [10], by exerting vasodilatory effects on renal peritubular endothelium. In the case of extreme jaundice, as we observed in our patient, unknown nephrotoxic effects of bilirubin or bile salts probably outweigh the advantageous effect on vascular endothelium. We hypothesize that there is a limit for proximal tubular bilirubin transport, above which casts may form and obstruct tubular transport.

The search for 'CN' in medline (www.pubmed.org) resulted in 11 publications. However, it is not mentioned in several standard textbooks on nephrology. This striking paucity of data suggests that it is either a very rare condition or that it is frequently overlooked. Especially, when ascites develop in patients with liver disease, it is pragmatic to ascribe kidney failure to HRS. We believe a biopsy with subsequent Fouchet's stain should be considered in atypical cases or in cases refractory to standard therapy.

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Conflict of interest statement. None declared.

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