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**Fibrosing cholestatic hepatitis-like syndrome in an immunocompetent patient with an acute flare of chronic hepatitis B**

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**Abbreviations**

FCH: fibrosing cholestatic hepatitis

HBV: hepatitis B virus

LFTs: liver function tests

INR: international normalized ratio

sAg: surface antigen

Fibrosing cholestatic hepatitis (FCH) is an uncommon form of liver injury that often progresses to fulminant liver failure(1). FCH is well-described in immunosuppressed patients, particularly after transplantation, with chronic hepatitis B virus (HBV) or C

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virus infection. There has been no reported case of FCH occurring in immunocompetence.

We present the case of an immunocompetent patient with acutely decompensated chronic HBV infection, with FCH-like findings on histopathology.

### **Case Report**

A 60-year-old Chinese male was referred to our centre with worsening liver function tests (LFTs). His past history was significant for chronic HBV infection diagnosed in China in 2006, for which he was commenced on adefovir. In 2015 the patient experienced viral breakthrough and telbivudine was added to adefovir. In September 2017 the patient ceased adefovir when his supply ended, remaining on telbivudine. He had no other medical history, took no other regular medications and abstains from alcohol.

On admission in December 2017 LFTs were abnormal with alanine aminotransferase 177IU/L (normal [N], 5-40IU/L), aspartate aminotransferase 245IU/L (N < 40IU/L), gamma-glutamyltransferase 81IU/L (N < 60IU/L), alkaline phosphatase 169IU/L (N, 30-110IU/L), serum bilirubin 54micromol/L (N < 21micromol/L) and international normalized ratio (INR) 1.6. Abdominal ultrasound showed no features of cirrhosis or portal hypertension. Investigations revealed no evidence of metabolic, autoimmune, biliary or vascular pathology.

HBV serology was positive for surface-antigen (sAg), core-antibody and e-antigen, whereas surface-antibody and e-antibody were negative. HBV viral load was above the assay quantifiable threshold (>10<sup>9</sup> IU/ml). All other viral serologies were negative.

Telbivudine was ceased, and entecavir and tenofovir commenced two days after admission, while awaiting sequencing of HBV polymerase. Sequencing detected HBV Genotype-C subtype-C2 with changes in rtL180 and rtM204I, associated with lamivudine and telbivudine resistance, and reduced sensitivity to Entecavir. Entecavir was ceased.

Despite treatment, serum bilirubin continued to increase whereas aminotransferases remained relatively stable.

A liver biopsy performed one week after admission demonstrated widespread hepatocellular ballooning, only mild cholestasis, fibrous septa and portal tracts with mild mononuclear infiltration. HBV immunohistochemistry showed diffuse HBsAg staining of hepatocytes (100%) and extensive nuclear (80+%) and cytoplasmic (100%) HBV core-antigen staining(Fig. 1). Diagnosis was consistent with FCH-like changes occurring in acutely decompensated chronic HBV disease.

Tests to assess for immunosuppression were performed, human immunodeficiency virus serology was negative and T-cell flow cytometry was consistent with immunocompetence.

The patient progressed to fulminant liver failure with worsening hyperbilirubinaemia and hepatic encephalopathy with a Model for End-Stage Liver Disease score of 35 (INR4.1, Creatinine 65micromol/L, Bilirubin 537micromol/L).

He underwent successful liver transplantation 23 days following admission and made an uneventful recovery. The explant showed established mature fibrosis and nodularity, hepatocytes with ground glass cytoplasm, and sanded nuclei, consistent with longstanding chronic HBV. There was extensive widespread hepatocyte ballooning degeneration, with scattered acidophil bodies, minimal inflammation, prominent bile stasis, florid periportal /periseptal ductular reaction, and extensive immature periportal and sinusoidal fibrosis(Fig. 2). The features were in keeping with a severe FCH-like flare due to uncontrolled viral replication, leading to acute decompensation.

## **Discussion**

FCH is a histopathological diagnosis that is characterised by marked hepatocyte ballooning, cholestasis and extensive periportal and/or perisinusoidal fibrosis(1).

There is minimal infiltration of inflammatory cells with an extensive periportal ductal reaction(1).

The hepatocyte damage seen in FCH is likely due to the direct cytopathic effect of high viral loads inducing hepatocyte apoptosis, cellular degeneration and necrosis(1). This differs from an immunocompetent patient with chronic hepatitis B or C infection whereby the hepatocellular damage is secondary to activation of the host's immune system, manifesting as a prominent inflammatory hepatitis on histology.

FCH has been described in immunocompromised patients, particularly following transplantation, and is characterised predominantly by jaundice with a rapidly-rising bilirubin and only mild-to-moderate increases in aminotransferases(1). Features of progressive liver failure, notably encephalopathy and coagulopathy, can develop and death may occur within weeks to months of onset(2).

To our knowledge, this is the first reported case of marked FCH-like changes occurring in the absence of immunosuppression. We postulate that non-compliance/resistance to antiviral medications led to uncontrolled proliferation of HBV. This resulted in significant hepatocyte injury and development of FCH-like changes, with resultant liver failure.

This case illustrates that an FCH-like presentation can occur in immunocompetence in the setting of an overwhelming acute flare of HBV. Clinicians and pathologists should consider this diagnosis in patients who are not overtly immunosuppressed and treat it aggressively when diagnosed.

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#### **Potential conflict of Interest**

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None

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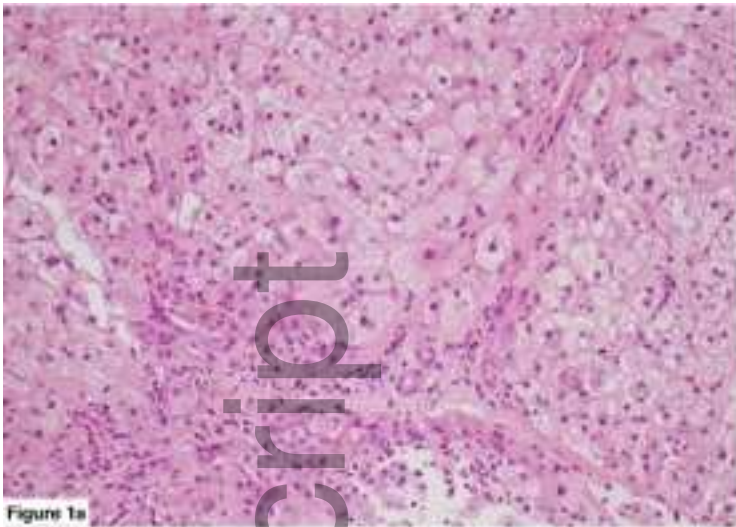


Figure 1a

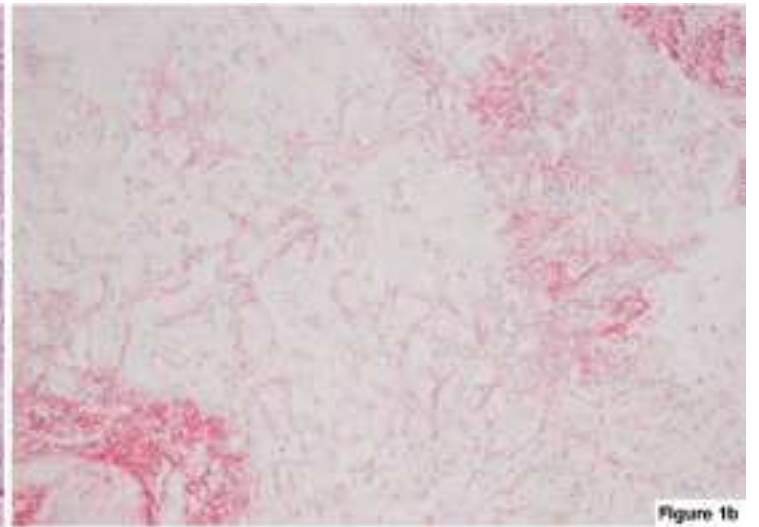


Figure 1b



Figure 1c

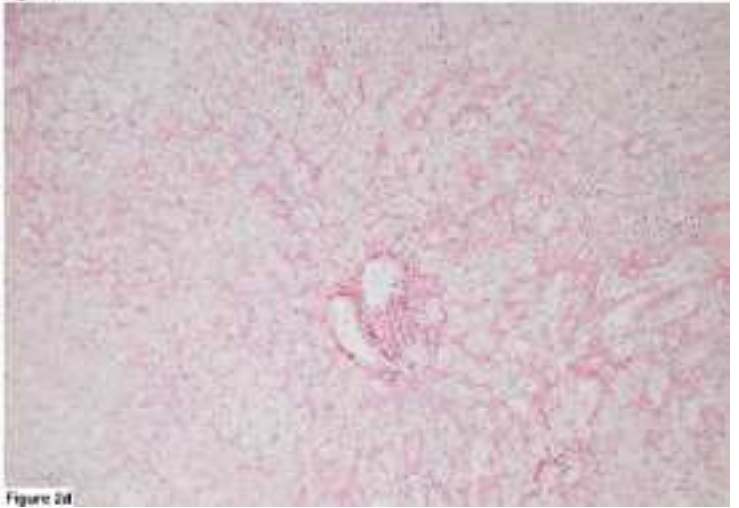
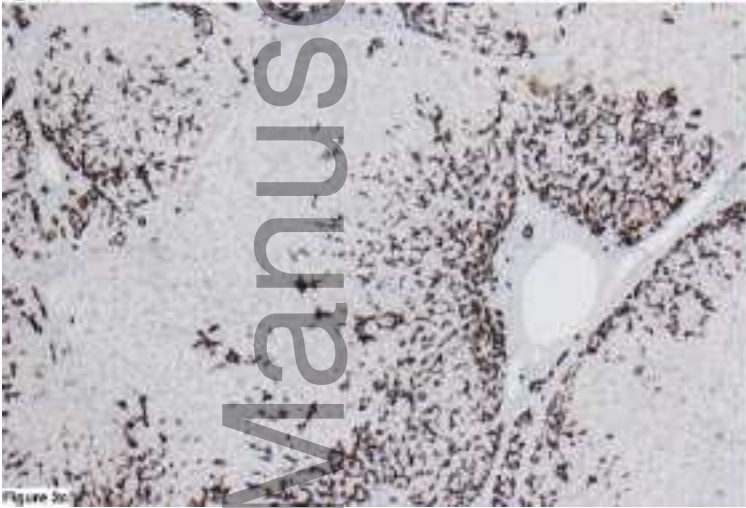
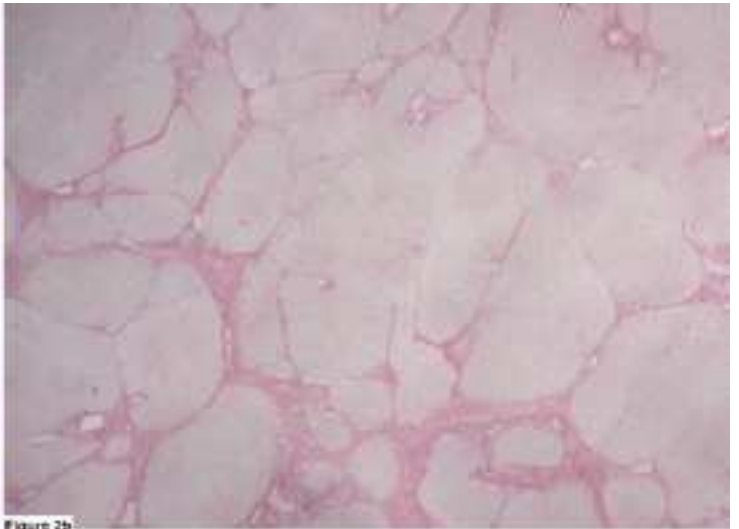
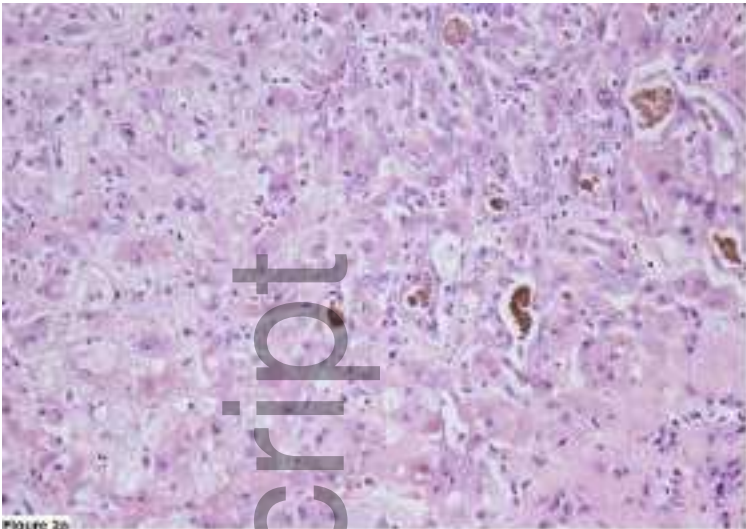


Figure 1d

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