

Unusual Presentation of Epstein-Barr Virus Hepatitis with Cholestatic Jaundice and Hyperferritinaemia

Ahmed Osman*, Wimal Nettikumara, Lalani Heva, Salah Mansy and Guna Sameera Chevireddy

Department of Paediatrics, East Sussex Healthcare NHS Trust, United Kingdom

***Corresponding Author:** Abdul Gatrad, Consultant Paediatrician and Honorary Professor, Manor Hospital, Walsall, UK and University of Kentucky, Lexington, KY, USA.

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Abstract

Epstein-Barr virus (EBV) infection is common in children and usually presents as infectious mononucleosis with fever, sore throat and lymphadenopathy. Although mild liver involvement is frequently seen, cholestatic jaundice is rare in paediatric patients. Marked hyperferritinaemia is also uncommon and may raise concern for serious inflammatory, hepatic or haematological disease. We describe a child who presented with fever, jaundice, dark urine and abdominal pain. Blood tests showed cholestatic hepatitis with significantly elevated liver enzymes and ferritin levels. Further investigations excluded hepatitis A-E, autoimmune liver disease, metabolic causes and haemophagocytic lymphohistiocytosis. EBV serology confirmed acute primary infection. The patient was managed conservatively with supportive care and showed gradual clinical and biochemical improvement without complications. This case highlights the importance of considering EBV infection in children presenting with cholestatic jaundice and hyperferritinaemia, particularly when the initial presentation suggests more severe liver or systemic inflammatory disease.

Keywords: Epstein-Barr Virus (EBV); Cholestatic Jaundice; Hyperferritinaemia; Haemophagocytic Lymphohistiocytosis (HLH)

Background

Epstein-Barr virus (EBV) infection is common in children and adolescents and most often presents as infectious mononucleosis. Liver involvement during acute infection is frequently seen, but it is usually mild, self-limiting and clinically silent. In contrast, cholestatic hepatitis with jaundice is rare in paediatric patients and can resemble autoimmune, metabolic or obstructive hepatobiliary disease, making diagnosis more challenging [1].

The mechanism of liver injury in EBV infection is not fully understood and is believed to result mainly from an exaggerated immune response rather than direct viral damage to hepatocytes. Previous paediatric studies have shown that cholestatic liver dysfunction is more commonly reported in older children and adolescents and may occasionally be accompanied by marked inflammatory markers and hyperferritinaemia [2,3].

Marked hyperferritinaemia may raise concern for serious inflammatory conditions such as haemophagocytic lymphohistiocytosis (HLH), sepsis or autoimmune hepatitis, often leading to extensive investigations. Early recognition of EBV-associated hepatitis is important to avoid unnecessary invasive tests and to guide appropriate supportive management and follow-up [4].

Case Presentation and Discussion

A previously well female adolescent presented with a 3-week history of progressive systemic and upper respiratory symptoms. During the first week of illness, she developed sore throat and nasal congestion, followed in the second week by a persistent dry cough. In the third week, she experienced intermittent fevers occurring every few days, night sweats, nausea, reduced appetite, reduced oral intake and generalized myalgia. Bowel motions remained daily with no change in stool colour or consistency.

Over the preceding 48 hours, her symptoms worsened with repeated episodes of non-bilious vomiting, marked reduction in oral intake and fluid consumption, and progressive lethargy. She had initially been reviewed by her general practitioner and managed as a presumed viral illness. On the day of presentation, she developed new jaundice involving the skin and sclera, dark concentrated urine, reduced urine output and postural light-headedness, prompting attendance to the emergency department.

Her past medical history was unremarkable. She was born following an uncomplicated term pregnancy and normal vaginal delivery and had achieved normal developmental milestones. Immunisations were up to date. She was not taking regular medications and had no known drug allergies. There was no history of recent travel, animal exposure, recreational drug use, alcohol intake, medication overdose or use of herbal remedies. Menstrual history was normal, and she denied sexual activity. She lived with her parents and younger sibling, all of whom were well. There was no significant family history of liver, autoimmune or metabolic disease.

On examination, she appeared unwell and visibly jaundiced but remained alert and oriented without evidence of encephalopathy. Temperature was 38.8°C, heart rate 108-118 beats/min, blood pressure 101/67 mmHg, respiratory rate 20-21 breaths/min and oxygen saturation 98% in room air. She had mild dehydration with dry mucous membranes. Abdominal examination demonstrated mild right upper quadrant tenderness with a palpable liver edge. There were no signs of chronic liver disease or ascites. No splenomegaly was palpable clinically, although mild splenomegaly was later identified on abdominal ultrasound. Neurological examination was normal. Mild tonsillar enlargement was noted without exudate or cervical lymphadenopathy. The remainder of the systemic examination was unremarkable.

Investigations

Definitions: cholestatic hepatitis refers to acute hepatic inflammation with a predominantly cholestatic biochemical pattern, characterised here by conjugated hyperbilirubinaemia with disproportionate elevation of alkaline phosphatase and gamma-glutamyl transferase. Conjugated hyperbilirubinaemia denotes an increased direct bilirubin fraction, typically >20% of total bilirubin when total bilirubin is >85 µmol/L. Hyperferritinaemia means a ferritin concentration above the age- and sex-appropriate upper reference limit; ferritin is also an acute-phase reactant and is therefore non-specific.

A summary of the principal investigations and their interpretation is provided in table 1. The chronological biochemical and haematological course is shown in table 2. Follow-up abdominal ultrasound demonstrated resolution of splenomegaly, hepatomegaly, lymphadenopathy and gallbladder oedema (Figure 1).

Category	Key findings	Reference range
Haematology	Mild normocytic anaemia (Hb 105 g/L), persistent lymphocytosis (peak 5.55×10^9 /L), reactive lymphocytes and atypical mononuclear cells on blood film.	Hb 120–160 g/L; lymphocytes 1.0–4.8 $\times 10^9$ /L
Paul–Bunnell test	Positive heterophile antibody test.	Qualitative: negative
Coagulation	INR 1.1, PT 11.6 s, APT ratio 0.92.	INR 0.9–1.2; PT 10–14 s; APT ratio 0.8–1.2

Liver function tests	Peak bilirubin 188 µmol/L (conjugated 115 µmol/L), ALT 172 U/L, GGT 320 U/L, ALP 680 U/L, albumin nadir 31 g/L.	Total bilirubin <20 µmol/L; conjugated <5 µmol/L; ALT 10–40 U/L; GGT 5–35 U/L; ALP ~50–150 U/L; albumin 35–50 g/L
Inflammatory markers	CRP peaked at 19 mg/L; ferritin peaked at 1241 µg/L.	CRP <6 mg/L; ferritin 15–150 µg/L
Renal and metabolic tests	Renal function, ammonia, glucose, thyroid function, CK, vitamin B12 and folate were normal.	Age/assay dependent; local paediatric laboratory ranges
EBV testing	EBV VCA IgM and IgG positive, equivocal EBNA antibodies, EBV DNA PCR detectable at 138,269 copies/mL.	Age/assay dependent
Other viral testing	CMV, hepatitis A–E, HSV, adenovirus, enterovirus, parvovirus B19 and VZV negative.	Qualitative: negative
Autoimmune screen	Negative anti-smooth muscle, liver–kidney micro-somal, ANCA, connective tissue disease and coeliac serology. Weakly positive anti-mitochondrial antibody (1:160) with negative M2-specific antibodies.	Qualitative: negative
Initial ultrasound	Hepatosplenomegaly (liver 18.4 cm; spleen 14.2 cm), gallbladder wall oedema, echogenic portal vein walls and reactive porta hepatis/aortocaval lymphadenopathy.	Normal liver span up to 17 cm; spleen span up to 12 cm
Follow-up ultrasound	Resolution of splenomegaly, hepatomegaly, lymphadenopathy and gallbladder oedema (Figure 1).	Normal liver span up to 17 cm; spleen span up to 12 cm

Table 1: Summary of investigations with interpretation.

Date	Total bilirubin	ALT	ALP	Albumin	CRP	Ferritin	Other findings	Clinical interpretation
03/03/26	168↑	172↑	511↑	40	19↑	1241↑	GGT 241; conjugated bilirubin 115; INR 1.1; lymphocytosis	Marked cholestatic hepatitis
04/03/26	188↑	157↑	484↑	38	17↑	940↑	Persistent lymphocytosis	Peak cholestatic hepatitis
05/03/26	170↑	136↑	444↑	33↓	14↑	—	Hb 105 g/L	Early biochemical improvement
06/03/26	154↑	131↑	422	31↓	11↑	805↑	Anaemia, hypoalbuminaemia	Improving cholestasis
07/03/26	140↑	149↑	432↑	32↓	6↑	—	Persistent lymphocytosis	Continued recovery
09/03/26	122↑	130↑	680↑	31↓	4	620↑	Hb 101 g/L	Transient ALP rise
12/03/26	50↑	74↑	574↑	38	—	—	Improving counts	Significant recovery
23/03/26	38↑	37	369	41	—	62	Hb 116 g/L; conjugated bilirubin 33	Near-complete resolution
10/04/26	13	27	107	49	—	50	Hb 131 g/L; conjugated bilirubin 9	Complete recovery

Table 2: Chronological investigation summary.

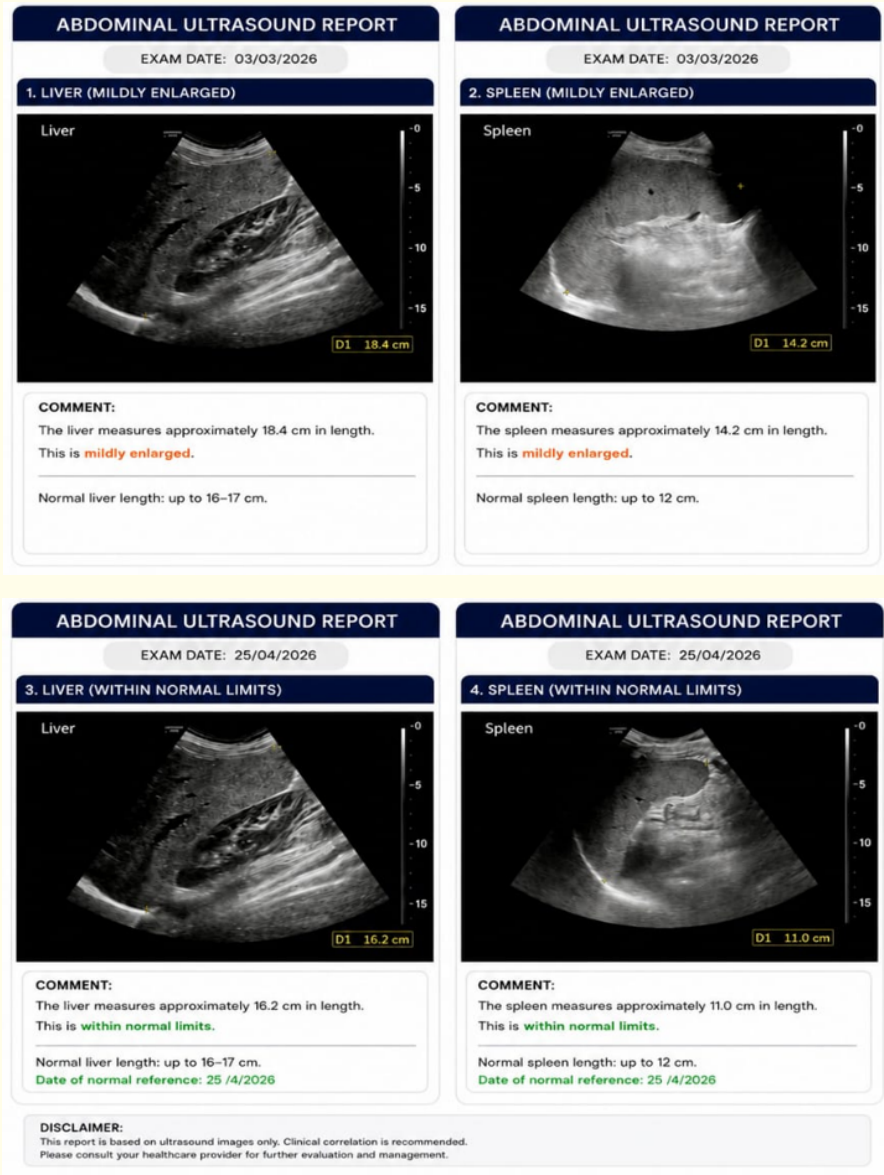


Figure 1: Abdominal ultrasound showing improvement in the size of the liver and spleen, created by Ahmed Osman, Wimal Nettikumara, Lalani Heva, Salah Mansy and Guna Sameera Chevireddy.

Differential diagnosis

The main conditions considered and the reasons for exclusion are summarised in table 3. Acute viral hepatitis, autoimmune hepatitis, Wilson disease, HLH and drug-induced liver injury were considered before EBV was established as the most coherent diagnosis [5-8].

Treatment

After confirmation of the diagnosis, the case was discussed with the tertiary paediatric liver team. As Epstein-Barr virus (EBV) infection is usually self-limiting, they recommended supportive management including adequate hydration and a short course of ursodeoxycholic

Differential diagnosis	Features supporting diagnosis	Features excluding diagnosis in this case
Acute viral hepatitis (HAV, HBV, HCV, HEV, CMV)	Fever, jaundice, transaminitis, hepatomegaly	Negative serology/PCR for hepatitis A, B, C, E and CMV
Autoimmune hepatitis	Raised transaminases, cholestatic jaundice, hypergammaglobulinaemia	Negative ANA, SMA and LKM antibodies; coagulation remained normal
Wilson disease	Adolescent hepatitis with hepatic or neuropsychiatric manifestations	No neurological signs, no evidence of haemolysis, and clinical course inconsistent with Wilson disease
Haemophagocytic lymphohistiocytosis (HLH)	Fever, hepatitis and marked hyperferritinaemia	Fever, transient splenomegaly and ferritin >500 µg/L, but no pancytopenia, progressive splenomegaly, organ failure or reported haemophagocytosis; clinical improvement without HLH-directed therapy
Drug-induced liver injury	Cholestatic hepatitis may occur with medications or herbal agents	No history of regular medications, overdose, supplements or toxin exposure
Epstein-Barr virus hepatitis	Positive EBV VCA IgM, positive EBV PCR, lymphocytosis, hepatosplenomegaly and cholestatic hepatitis	Findings strongly supported EBV-associated hepatitis after exclusion of alternative causes

Table 3: Conditions considered in the differential diagnosis and reasons for exclusion.

acid at a dose of 5 mg/kg and fat-soluble vitamins for about 1 month until conjugated bilirubin normalised. Recent paediatric data also support spontaneous biochemical recovery in EBV-associated hepatic involvement [9].

Outcome and follow-up

Following diagnosis, the patient remained clinically stable and did not require invasive intervention or antiviral therapy. Arrangements were made for regular follow-up with both the tertiary liver team and the local paediatric team to monitor clinical recovery and serial liver function tests.

During follow-up, her mum reported that the patient was doing well overall, with complete clinical improvement. On follow-up, her blood tests gradually returned to normal, and repeat abdominal ultrasound demonstrated significant improvement with resolution of the previous splenomegaly and lymphadenopathy and only mild hepatomegaly (Figure 1).

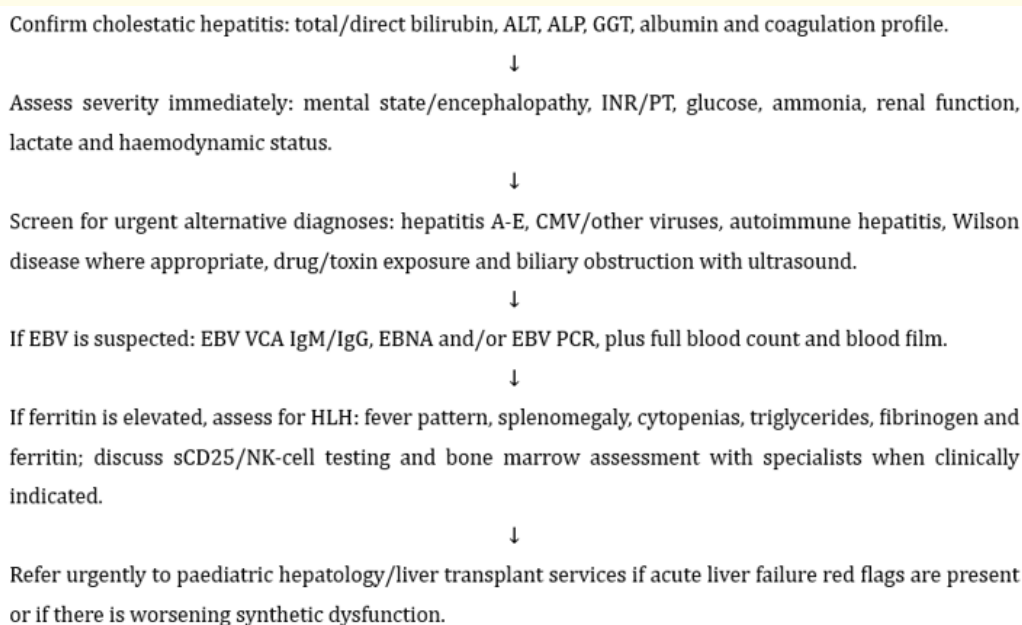
Several differential diagnoses were considered. Acute viral hepatitis due to hepatitis A, B, C, E and cytomegalovirus was initially suspected because of the fever, jaundice, transaminitis and hepatomegaly; however, serology and PCR testing were negative. Autoimmune hepatitis was considered given the cholestatic liver dysfunction, but autoimmune serology including antinuclear, anti-smooth muscle and liver-kidney microsomal antibodies were negative, coagulation remained normal, and liver function improved spontaneously within weeks. Wilson disease was considered because of the patient's age and hepatic presentation, although there were no neurological features, haemolysis or clinical findings suggestive of Wilson disease. HLH was also considered because of the elevated ferritin level, splenomegaly and hepatitis; however, the patient did not meet the diagnostic criteria, with no pancytopenia, organ failure or progressive splenomegaly. Drug-induced liver injury was unlikely as there was no history of medication use, toxin exposure, supplements or herbal remedies [5-8].

The diagnostic approach to cholestatic hepatitis requires exclusion of other important causes before attributing the presentation to EBV. Hepatitis A-E, CMV and other viral causes were excluded, autoimmune serology was unrevealing, and the clinical context did not support drug-induced liver injury or Wilson disease. Ultrasound excluded mechanical biliary obstruction. Therefore, EBV was considered the most coherent diagnosis in the context of positive VCA IgM, detectable EBV DNA, atypical lymphocytosis and spontaneous recovery. This reinforces that hyperferritinaemia alone should never be used to establish EBV hepatitis or HLH.

The present case also illustrates the importance of distinguishing EBV hepatitis from acute liver failure. Paediatric acute liver failure is characterised by acute liver injury with significant coagulopathy, generally INR ≥ 1.5 with encephalopathy or INR ≥ 2.0 without encephalopathy after exclusion of vitamin K deficiency [10]. Our patient remained alert without encephalopathy and had an INR of 1.1, supporting significant hepatitis/cholestasis without acute liver failure. Hepatology referral is appropriate when there is worsening synthetic dysfunction, rising INR, encephalopathy, hypoglycaemia, hyperammonaemia, rapidly progressive jaundice, significant diagnostic uncertainty or other evidence of acute liver failure.

Ferritin should be interpreted as a general marker of inflammation rather than a disease-specific marker. In this case, ferritin peaked at 1241 $\mu\text{g/L}$ (reference 15-150 $\mu\text{g/L}$), which appropriately prompted consideration of HLH but was not, by itself, diagnostic. HLH-2004 requires five of eight criteria: fever, splenomegaly, cytopenias affecting at least two lineages, hypertriglyceridaemia and/or hypofibrinogenaemia, haemophagocytosis, low or absent natural killer-cell activity, ferritin $> 500 \mu\text{g/L}$ and elevated soluble interleukin-2 receptor (sCD25) [11]. The available clinical data in this patient did not show pancytopenia, progressive splenomegaly, organ failure or reported haemophagocytosis. Triglyceride, fibrinogen, NK-cell activity and sCD25 testing were not pursued, and bone marrow examination was not performed, because the patient remained clinically stable and demonstrated rapid spontaneous biochemical improvement. This approach should not be interpreted as excluding HLH solely on the basis of ferritin; persistent fever, progressive splenomegaly, new cytopenias, coagulopathy, hypofibrinogenaemia, hypertriglyceridaemia, neurological symptoms or organ dysfunction should prompt urgent reassessment and specialist discussion.

Suggested diagnostic algorithm for an adolescent with fever and cholestatic jaundice:



Figure

Red flags for acute liver failure include INR ≥ 1.5 with encephalopathy or ≥ 2.0 without encephalopathy, rising INR despite vitamin K, encephalopathy, hypoglycaemia, rising ammonia, severe acidosis or lactatemia, renal dysfunction, haemodynamic instability or rapidly progressive jaundice [10].

HLH should be suspected with persistent or recurrent fever, splenomegaly, cytopenias in ≥ 2 lineages, triglycerides ≥ 3.0 mmol/L, fibrinogen ≤ 1.5 g/L, ferritin > 500 $\mu\text{g/L}$, haemophagocytosis, reduced NK-cell activity or raised soluble CD25; diagnosis generally requires five of eight HLH-2004 criteria unless a molecular/familial diagnosis is established [11]. Follow-up should include clinical review and serial liver biochemistry and synthetic function until symptoms and laboratory abnormalities resolve, with repeat ferritin if initially markedly elevated or systemic inflammation persists. Persistent cholestasis, rising INR, encephalopathy, recurrent fever, worsening cytopenias or diagnostic uncertainty should prompt early paediatric hepatology review. Where splenomegaly is documented, strenuous exercise and contact or collision sports should be avoided during the acute illness and while the spleen remains enlarged. Return to full activity should be individualised after recovery; routine serial ultrasound is not required for all patients but may be considered when splenomegaly persists and return-to-sport decisions remain uncertain.

In this case, the patient was managed conservatively with hydration, monitoring and symptomatic treatment, together with a short course of ursodeoxycholic acid (5 mg/kg). Serial liver function tests and ferritin levels improved gradually and normalised within weeks, and follow-up abdominal ultrasound demonstrated significant radiological improvement (Figure 1). The overall prognosis of EBV hepatitis is favourable in immunocompetent patients, with spontaneous recovery expected in most cases. Severe complications such as fulminant hepatic failure, chronic active EBV infection and HLH remain rare [12].

Learning Points/Take Home Messages

- Cholestatic jaundice is an uncommon presentation of primary Epstein-Barr virus (EBV) infection and should be included in the differential diagnosis of paediatric cholestatic hepatitis.
- Hyperferritinaemia is a non-specific marker of inflammation and should not be interpreted in isolation as evidence of haemophagocytic lymphohistiocytosis (HLH).
- Most uncomplicated EBV hepatitis in clinically stable immunocompetent patients is self-limiting and is managed primarily with supportive care.
- Patients with EBV and hyperferritinaemia should be assessed for HLH and acute liver failure, with hepatology referral when there are clinical or biochemical red flags.
- In EBV infection, consider HLH when fever is persistent or recurrent with splenomegaly, cytopenias, coagulopathy, hypertriglyceridaemia, hypofibrinogenaemia, rapidly rising ferritin or organ dysfunction.
- Acute liver failure is suggested by worsening coagulopathy (INR ≥ 1.5 with encephalopathy or INR ≥ 2.0 without encephalopathy), encephalopathy, hypoglycaemia, rising ammonia or other evidence of rapidly progressive hepatic dysfunction.
- Supportive management is the mainstay of uncomplicated EBV hepatitis; refer to a paediatric hepatology service for significant cholestasis, worsening synthetic function, diagnostic uncertainty or acute liver failure red flags.

Patient's Perspective

Seeing my child develop jaundice and persistent fever was frightening, especially while serious liver and inflammatory conditions were being investigated. The uncertainty during the investigations was very stressful for our family. Once Epstein-Barr virus infection was confirmed, we felt relieved to have an explanation and reassured that the illness would improve with supportive care.

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