

Supplemental Table 1. Diagnostic criteria for acute vs remote EBV infection.

	VCA IgG	VCA IgM	EA ^a	EBNA ^b
Negative-Susceptible	-	-	-	-
Acute Primary Infection	+	+	+	-
Recent Primary Infection	+	+/-	+	-/+
Past (remote) Infection	+	-	-/+	+
Reactivated Infection	+	-	+/-	+

Adapted from the University of Michigan Pathology Department

^aEarly antigen ^bEpstein-Barr nuclear antigen

Supplemental Table 2. EBV serologies at admission, 1 week, and 5 months after presentation in patient #1.

	Admit	1 week later	Month 5 postLT
VCA IgM	+	-	+
VCA IgG	+	+	+
NA IgG	-	+	+
EA IgG	-	-	-
EBV DNA *	< 2000 copies/ml	-	-

* By PCR with range of detection of <500 copies/mL- 2×10^8 copies/mL

Supplemental Material: Case Vignettes

Patient #1: A previously healthy 44 year old Caucasian woman presented with a 10 day history of jaundice and dark urine. She had been taking over-the-counter omeprazole for several months, fish oil and a multivitamin. She rapidly progressed to grade III hepatic encephalopathy on hospital day #3 which subsequently worsened to grade IV encephalopathy on hospital day #4 necessitating intubation. She underwent emergency LT on hospital day #5 and her explant pathology showed massive hepatic necrosis (**Figure 1**). She had an uncomplicated hospital course and was discharged on hospital day #18. Of note, repeat EBV serologies performed 1 week after initial studies showed transition from positive to negative VCA IgM and negative to positive EBV NA IgG (**see Supplemental Table 2**).

After establishing a diagnosis of EBV-related ALF, acyclovir 325 mg IV every 8 hours for 2 days was initiated on hospital day #3 followed by ganciclovir 300 mg IV every 12 hours for 2 days and then acyclovir 500 mg IV every 12 hours for one day. The dose of acyclovir was changed to 500 mg IV every 24 hours for 3 days, then to 500 mg IV every 12 hours for 4 days. At day 8 after transplantation, she was transitioned to valacyclovir 1000 mg by mouth twice daily which was continued for 90 days. She was discharged on tacrolimus 3 mg twice daily, mycophenolate mofetil 1000 mg twice daily, and prednisone 30 mg daily. At 6 weeks post-transplant, she had a biliary anastomotic stricture that was successfully treated with ERCP. At 3 1/2 months post-transplant, she developed CMV colitis with a serum CMV DNA level of 794 copies/ml due to her donor-positive/recipient-negative status. She was restarted on valacyclovir and completed a 5 week course of treatment. She improved quickly and subsequent CMV PCR tests showed no detectable virus. At 18 months of follow-up, she is doing well and has normal liver biochemistries with no evidence of recurrent disease while receiving maintenance tacrolimus and mycophenolate mofetil.

Patient #2: A previously healthy 21 year old Caucasian male presented with a 2 week history of abdominal pain, malaise, fever and chills, rash, joint pains, sore throat, facial swelling, and melena. The patient denied a history of alcohol, illicit drug use, or recent travel and only reported taking ibuprofen for 4 days prior to admission. At presentation, he was in stage IV hepatic encephalopathy with peripheral edema, diffuse hyperreflexia, and splenomegaly and cervical lymphadenopathy. EBV VCA IgM was positive at 6.44, but a quantitative viral load was not performed. All other viral and diagnostic serologies were unremarkable. He was initially treated with acyclovir 340 mg IV every 12 hours for 24 hours and then with methylprednisolone 40 mg IV for one day beginning on hospital day #3. He died on hospital day #4 from cerebral herniation. No liver tissue was available to confirm the diagnosis and an autopsy was not performed.

Patient #3: A 38 year old Asian male presented with 2 weeks of nausea, vomiting, headache, malaise, fever, myalgias, and loose stools. Four days prior to this admission, he had been hospitalized for an acute febrile illness which was subsequently diagnosed as acute EBV infection based upon a positive heterophile antibody test. He was receiving chronic thyroid replacement and also reported taking acetaminophen 4000 mg daily for 5 days and amoxicillin for 6 days prior to admission. On admission, he had grade 1 encephalopathy, a temperature of 39.0° C, and cervical lymphadenopathy. His admission labs revealed a cholestatic liver injury profile with a serum alkaline phosphatase of 715 IU/ml and INR of 1.6. Liver imaging demonstrated splenomegaly. One week later, repeat EBV serologies demonstrated the EBV NA IgG had become positive and serum EBV DNA was positive. A liver biopsy showed mild portal and sinusoidal lymphocytosis and PCR of liver tissue showed that EBV DNA was present. He received famciclovir 1500 mg for 11 days, prednisone 60 mg daily starting on hospital day #8 and lasting for 6 days and Neupogen for a total of 4 days. He was also treated with n-acetylcysteine, ursodiol and vitamin K. His liver biochemistries trended downward and he was discharged three weeks later.

He was never listed for transplant, and at 5 years follow-up, he is doing well with no evidence of residual liver disease.

Patient #4: An 18 year old immunosuppressed Caucasian male with active Crohn's ileocolitis as well as psoriasis presented with a 3 week history of nausea, vomiting, headache, malaise, fever, chills, sore throat, and myalgias. He had been on 6-mercaptopurine for approximately four years at a dose of 50 mg daily, but 1 month prior to admission, the dosage was increased to 100 mg daily due to endoscopic evidence of moderately active Crohn's ileocolitis. His thiopurine methyltransferase genetic assessment showed alleles consistent with normal activity. He had not taken any oral steroids for several months prior to admission and denied illicit drug use, alcohol use, or recent travel. One week prior to admission, a Monospot was positive. On admission, he had grade 1 hepatic encephalopathy and a cholestatic liver injury with evidence of liver failure (**Table 2**). A liver biopsy showed focal microvesicular steatosis, chronic interlobular inflammation, and patchy necrosis. This was felt to be more consistent with EBV hepatitis than drug toxicity due to mercaptopurine. The patient died on hospital day #12 from multi-organ failure. An autopsy showed ascites (1400 ml), hepatomegaly (2840 g), and splenomegaly (1600 g). Florid lymphoid hyperplasia was noted throughout the liver, spleen, lymph nodes, bone marrow, right and left lungs, right and left kidneys, colon and pituitary which consisted of collections of immunoblasts, large and small lymphocytes, plasma cells, and reactive T cells. EBER stain was focally positive (**Figure 2**), and these findings were felt to be consistent with infectious mononucleosis and extensive EBV-associated extranodal lymphoproliferative disorder (LPD).

