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CASE REPORT

A Rare Case of Life-Threatening Jaundice Caused by Epstein-Barr Virus Infection and Secondary Cold Agglutinin Syndrome Successfully Treated with Rituximab

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Background: Jaundice and hyperbilirubinemia are common clinical problems characterized by the presence of bile pigments in the blood and their deposition in body tissues. This clinical condition can be associated with a broad spectrum of potential benign and malignant causes, including hepatic inflammation, biliary obstruction, impaired bilirubin conjugation and bilirubin overproduction Therefore, the hyperbilirubinemia diagnostic work-up sometimes can be highly challenging and its therapeutic management can require a multidisciplinary approach.

Case Report: We report on a unique case of life-threatening jaundice and hepatic failure in a 20-year-old female who presented to the emergency room with complaints of fever, constant left abdominal pain and generalized profuse fatigue. A complete and detailed medical history, multiple tests for various infection, radiologic investigations and histological tests were performed in order to clarify the etiology of that rapidly progressive clinical condition. Based on the results, the patient jaundice was caused by an Epstein-Barr virus (EBV) infection and secondary cold agglutinin syndrome. Given the rare and complex diagnosis, multiple clinical specialists were asked to carry out the best patient management.

Conclusion: This rare case highlights how challenging the differential diagnosis and treatment of hyperbilirubinemia can be, presenting a unique case of life-threatening multifactorial hepatic failure treated successfully with rituximab.

Keywords: jaundice, Epstein-Barr virus infection, secondary cold agglutinin syndrome, rituximab

Introduction

Jaundice is a clinical condition associated with yellow color of skin and mucous membranes due to presence of bile pigments in the blood and their deposition in body tissues.[1,2] It occurs when the liver is unable to properly metabolize or excrete bilirubin, a breakdown product of hemoglobin (Hb).[1,3,4] Classically, this state of hyperbilirubinemia is defined by having bilirubin levels greater than 3 mg/dL, and it should be typically considered a sign of an underlying disease condition.

Hyperbilirubinemia, the condition in focus, can result from a wide variety of benign or life-threatening disorders,[5–7] including bilirubin overproduction, impaired bilirubin conjugation, biliary obstruction, and hepatic inflammation.[4,8–12] Because of this broad spectrum of potential causes, both diagnosis and therapeutic management can be challenging, often involving multiple interacting factors.[11,13,14]

This case study presents a rare instance of life-threatening jaundice and hepatic failure in a 20-year-old female, resulting from a complex interplay of Epstein-Barr virus (EBV) infection, secondary cold agglutinin syndrome (CAS) and a possible drug injury.

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Case Presentation

A 20-year-old Caucasian female visited the Emergency Department (ED) with complaints of fever, constant left abdominal pain and generalized profuse fatigue. These symptoms had occurred at rest few days before the ED admission. She also mentioned an episode of dysuria and fever ten days before, which had been treated with ciprofloxacin in the suspect of cystitis. Moreover, she reported having assumed three oral contraceptive pills containing ulipristal acetate in the 30 days before the symptom onset. At the time of presentation, she denied nausea, diarrhea, or constipation, contact with animals, trips abroad, insect, or tick bites.

In January 2022, the patient had had SARS-CoV2 infection which had required anti-inflammatory therapy with ibuprofen and paracetamol without hospitalization need. She denied previous surgical interventions, autoimmune diseases, or chronic disease for which any chronic therapy was required. She reported no allergy toward drug and environmental allergens. Her relatives had never suffered from liver or biliary disease. In addition, she denied any relationship with hematologic disorders such as hemolytic anemia. Regarding her social habits, she confirmed no excessive assumption of alcohol, and she denied smoking cigarettes. However, she reported a minimal physical activity as well as a high intake of sugar-containing beverages and food.

On admission, the patient's initial vitals included blood pressure 100/60 mm Hg, pulse 75 beats per minute, respirations 15 breaths per minute, temperature 37.5°C and an oxygen saturation of 98% on room air. Physical examination revealed an alert, oriented female with grade III obesity (weight 115 kg, height 160 cm). Physical examination revealed severe jaundice involving the muco-cutaneous surfaces and the sclerae. No lymphadenopathies were palpable superficially. Head, ears, eyes, nose, throat (HEENT), neck, cardiovascular, respiratory, musculoskeletal, and neurological examinations were all grossly unremarkable. The abdominal examination revealed mild upper left abdominal pain exacerbated by deep palpation, without tenderness. Murphy and Courvoisier signs were absent. No flapping tremor was elicited.

Initial blood tests indicated leukocytosis with white blood cell (WBC) count 28460/mm^3, normochromic normocytic anemia with hemoglobin 7.9 g/dL, platelets count (PLT) 212000/mm^3, hyperbilirubinemia with total serum bilirubin 23.11 mg/dL composed prevalently of direct bilirubin 19.36 mg/dL, elevated liver function tests (ALT 244 U/L, AST 202 U/L), cholestasis index (GGT 372 U/L, ALP 300 U/L), and C-reactive protein (CRP) 17 mg/dL. Haptoglobin was depleted and Lactate DeHydrogenase (LDH) was significantly elevated (3190 U/L).

To better clarify the etiology of these findings, the patient was tested for various infections, including HIV, hepatitis A, E, B, C viruses, cytomegalovirus, syphilis, West Nile virus, *Plasmodium malariae*, all returning negative results. Furthermore, abdominal ultrasonography and CT scan ruled out biliary obstruction or pancreatic disorders. No evidence of autoimmune hepatitis was found. Interestingly, EBV serology test showed a probable acute infection phase: Virus Capsid Antigen IgM (VCAM) > 160 UI/mL, Early Antigen (D) IgG (EAG) 45.9 UI/mL, Virus Capsid Antigen IgG (VCAG) 47.4 UI/mL and Epstein-Barr Nuclear Antigen (EBNA1) 8.1 UI/mL. The infection acuity was confirmed by EBV DNA titer which was extremely high (123600 copies/mL). Moreover, the direct antiglobulin test for Complement 3 Factor (C3) and cold agglutinin test were positive. Lastly, liver and bone marrow biopsies revealed ring granulomas consistent with EBV infection (Figures 1–4) and a pattern of acute intrahepatic cholestasis indicative of potential drug-induced liver injury.

These findings suggested liver failure due to EBV infection, CAS and a possible oral contraceptive pill toxicity.

Disease Management and Outcome

Based on her diagnosis, the patient was admitted to the Hematology ward. For her hemolytic anemia, she underwent a first-line treatment with high dose methylprednisolone 1 mg/kg intravenously daily and immunoglobulin 1 g/kg intravenously for two days. However, a progressive worsening of general conditions occurred during hospitalization, developing hepatic failure with bilirubin levels rising to 43 mg/dL, hyperbilirubinemia-associated acute kidney injury, and respiratory failure requiring high-flow-nasal-cannula support. Consequently, she was transferred to the Intensive Care Unit (ICU), where she underwent central venous catheter placement due to poor venous access and her critical condition.

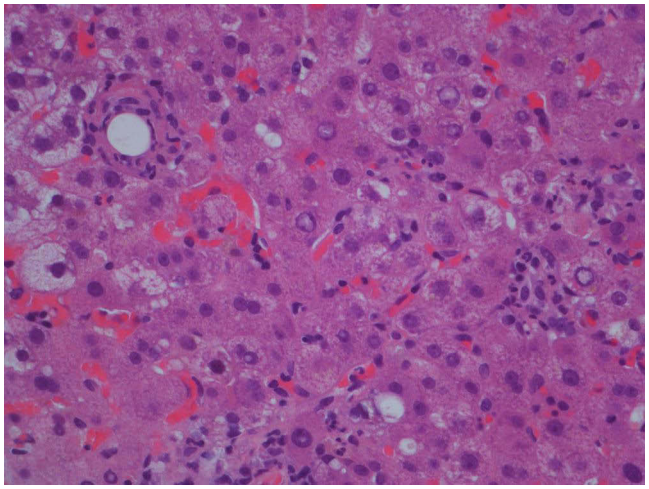

Figure 1 Hematoxylin-Eosin histopathological image of liver biopsy (resolution power 40x) of a 20-year-old female diagnosed with hepatic failure caused by EBV infection and secondary cold agglutinin syndrome. The image reveals a single ring granuloma associated with portal space inflammation and cholestasis. This histopathological pattern is coherent with EBV infection.

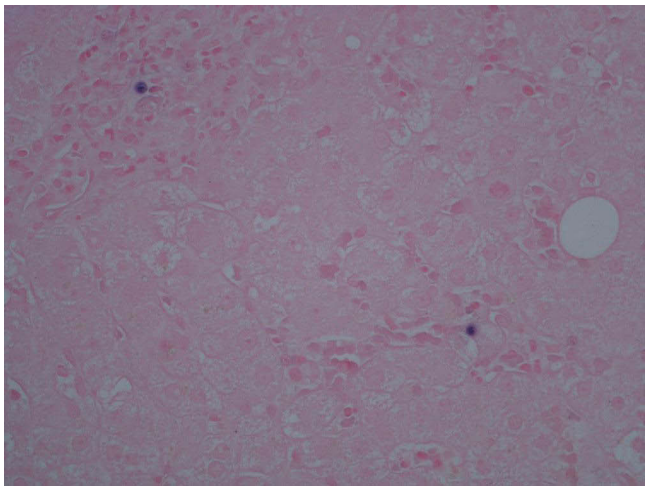

Figure 2 Histopathological image of liver biopsy (resolution power 40x) of Epstein-Barr-Virus-Encoded-RNA (EBER) detected by in situ hybridization in a 20-year-old female diagnosed with hepatic failure caused by EBV infection and secondary cold agglutinin syndrome. The image reveals sporadic EBER – positive cellular elements coherent with EBV infection.

Given the complexity and the multifactorial etiology of the case, multiple clinical specialists were asked to carry out the best patient management (Figure 5). Initially, the patient was subjected to Plasorba BR-350 treatment, a selective adsorption mechanism for bilirubin and bile acid exceeding in plasma. Then, in consultation with nephrologists, continuous veno-venous hemofiltration (CVVH) was initiated to gradually improve kidney function.

She also started hepatoprotective therapy with ursodeoxycholic acid 300 mg orally twice daily, lactulose orally and K vitamin 10 mg intravenously daily.

Given her unresponsiveness to steroid therapy for hemolytic anemia and the concomitant EBV infection, in the context of secondary cold agglutinin syndrome, the patient received rituximab (375 mg/m^2 weekly), a chimeric anti-CD20 monoclonal antibody effective against both disorders.[15,16] Rituximab treatment proved effective in depleting EBV-infected B-lymphocytes and those involved in hemolytic pathogenesis.

After a few weeks and four rituximab administrations, we observed a progressive amelioration of the patient clinical condition, with no more need of dialytic and respiratory support. She was gradually weaned off oxygen therapy, and her

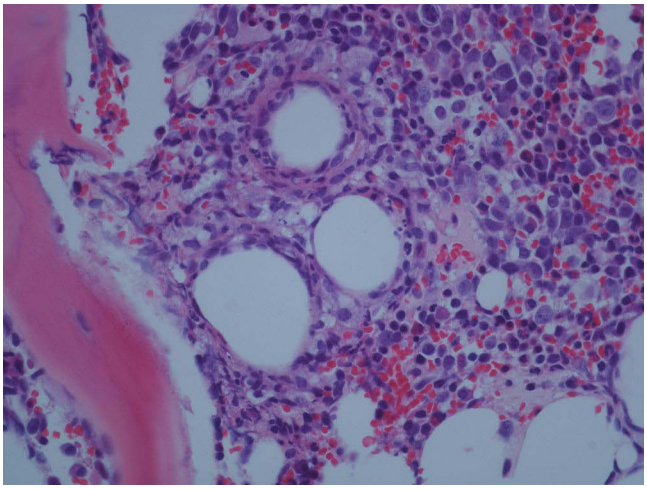

Figure 3 Hematoxylin-Eosin histopathological image of bone marrow biopsy (resolution power 40x) of a 20-year-old female diagnosed with hepatic failure caused by EBV infection and secondary cold agglutinin syndrome. The image reveals ring granulomas coherent with EBV infection.

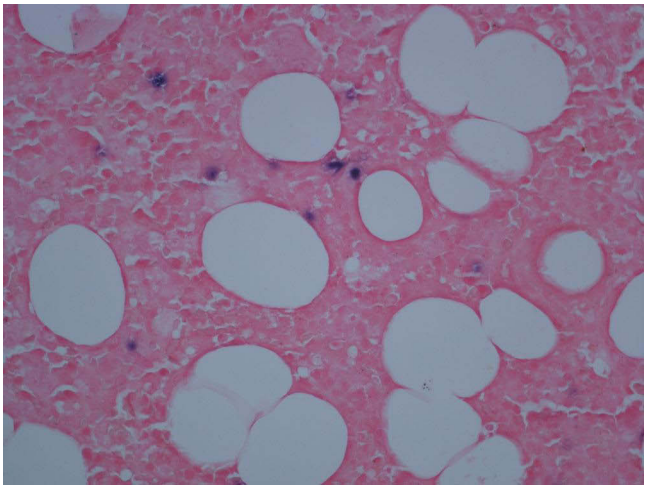

Figure 4 Histopathological image of bone marrow biopsy (resolution power 40x) of Epstein-Barr-Virus-Encoded-RNA (EBER) detected by in situ hybridization in a 20-year-old female diagnosed with hepatic failure caused by EBV infection and secondary cold agglutinin syndrome. The image reveals sporadic EBER – positive cellular elements coherent with EBV infection.

jaundice resolved along with normalization of liver function tests. After rituximab therapy, the EBV-DNA titer resulted negative, as also were cold agglutinin levels. Her hemoglobin level gradually returned to normal values.

Finally, after one month of hospitalization, the patient was discharged in good general condition, with normal liver, renal and hemoglobin values.

Discussion and Conclusion

This rare case of a 20-year-old female with life-threatening jaundice and hepatic failure highlights how challenging the differential diagnosis and treatment of hyperbilirubinemia can be. According to some recent studies, overall survival rates in patients treated for acute liver failure are greater than 60%.[17,18] Approximately 55% of these patients will survive without needing a liver transplantation.[18] As for the EBV infection, a parenchymal injury of the liver tissue is common with about 75% of patients exhibiting a two-to-three-fold increase in liver function tests during the acute phase of infection with levels returning to normal after three weeks. The hepatic changes are therefore usually transient and self-limiting, but cases of liver failure with fatal outcomes have been reported.[19,20] The uniqueness of this case stems from the jaundice diagnostic and therapeutic complexity involving pharmacological, infectious, and hematologic etiologies. To the

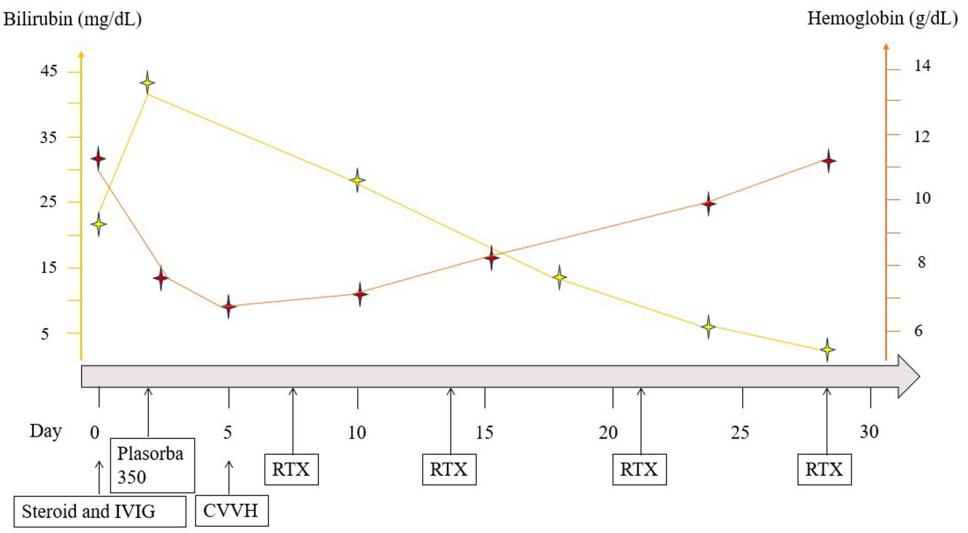

Figure 5 Timeline in days depicting clinical care of a 20-year-old female diagnosed with hepatic failure caused by EBV infection and secondary cold agglutinin syndrome. The day 0 corresponds to patient hospitalization. The variation of patient bilirubin and hemoglobin values are presented in relation to the clinical management.
Abbreviations: IVIG, intravenously immunoglobulin; Plasorba 350, a selective adsorption mechanism for plasmatic bilirubin filtration; CVVH, continuous veno-venous hemofiltration; RTX, Rituximab 375 mg/m^2.

best of our knowledge, this is the first evidence of hepatic failure triggered by a combination of EBV infection, secondary cold agglutinin hemolytic anemia, and a potential oral contraceptive pill toxicity successfully treated with rituximab.

This case study reinforces the notion that accurately diagnosing hyperbilirubinemia requires a comprehensive medical history and a detailed physical examination, with particular attention to drug use and potential sources of liver infection. Moreover, it underscores the importance of performing extensive laboratory and imaging analyses in order to evaluate potential causes of liver dysfunction, such as hematologic and infectious disease. Finally, it highlights the role of rituximab as possible therapeutic option in case of severe EBV infection.

In conclusions, our findings further corroborate the complexity of hyperbilirubinemia differential diagnosis and present a unique case of life-threatening multifactorial hepatic failure successfully treated with rituximab.

Abbreviations

Hb, hemoglobin; EBV, Epstein-Barr virus; CAS, cold agglutinin syndrome; ED, emergency department; WBC, white blood cell; PLT, platelet count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma glutamyl transferase; ALP, alkaline phosphatase; CRP, C-reactive protein; LDH, lactate deHydrogenase; VCAM, Virus Capsid Antigen IgM; EAG, Early Antigen (D) IgG; VCAG, Virus Capsid Antigen IgG; EBNA1, Epstein-Barr Nuclear Antigen; ICU, intensive care unit; CVVH, continuous veno-venous hemofiltration.

Consent

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Prof. Dr. Gianluca Gaidano reports personal fees from AbbVie, Astra Zeneca, BeiGene, Hikma, Johnson and Johnson, and Lilly, outside the submitted work. The authors have no other competing interests or other interests that might be perceived to influence the results and/or discussion reported in this paper.

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