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Internal Medicine

A RARE CASE OF HETEROPHILE NEGATIVE EBV VCA IGM POSITIVE INFECTIOUS MONONUCLEOSIS COMPLICATED BY COLD AUTOIMMUNE HEMOLYTIC ANEMIA

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ABSTRACT Infectious mononucleosis (IM) is often an uncomplicated self-limited illness resulting from Epstein-Barr virus (EBV) in 90% cases. This is a case report of 21-year-old female whose initial clinical and laboratory presentation suggested Heterophile antibody negative Epstein–Barr Viral capsid Antigen (VCA) IgM positive infectious Mononucleosis. Our case was complicated by biliary stasis, cold autoimmune hemolytic anemia with acrocyanosis, thrombocytopenia and some of the features of hemophagocytic lymphohistiocytosis (HLH). Following symptomatic management patient recovered. Physicians should routinely counsel their patients with IM for these complications and should avoid overzealous treatment.

KEYWORDS : cold autoimmune hemolytic anemia; biliary stasis; cold agglutinin disease; Epstein–Barr virus, infectious mononucleosis, hemophagocytic lymphohistiocytosis

BACKGROUND

Epstein-Barr virus (EBV) is a double-stranded DNA virus that is a member of the γ-herpesvirus family. In the United States, by the age of 40 as many as 95 % of adults have been infected with EBV , which manifest in children and infants as asymptomatic or mild disease and in adolescence or young adults as infectious mononucleosis in up to 50 %(1). Infectious mononucleosis(IM) is a clinical syndrome is characterized by fever, tonsillar-pharyngitis, lymphadenopathy and atypical lymphocytes(2). Complications are uncommon in a case of IM.

we describe here a case of IM complicated by cold type autoimmune hemolytic anemia, thrombocytopenia and biliary stasis.

Case report

21-year-old female, presented with a complaint of fever, abdominal pain, difficulty in swallowing, nausea, vomiting and jaundice. She had high grade intermittent daily fever since last 2 weeks. She also had right hypochondriacal abdominal pain past one week prior to presentation, which was constant and non-radiating. She also had decreased appetite, difficulty in swallowing and nausea and vomiting. The patient consulted a nearby hospital and was given tab amoxicillin following which patient developed itchy rash all over the body. She presented to us with above complaints clinical examination on admission revealed fever pallor, icterus and bilateral tender, discrete and mobile anterior and posterior cervical lymphadenopathy and bilateral tonsillitis with tonsillar exudates and pharyngitis.

Because of typical presentation of fever, pharyngitis, cervical lymph node enlargement, amoxicillin induced rash and atypical lymphocytosis a clinical diagnosis of IMN was made Morbilliform form rash was present on lower limbs and abdomen (figure 1).

Figure 1: morbilliform rash on left lower limb

CBC at admission revealed leukocytosis (24,800 cells/mm^3) decreased red cell count of 2.97×10^{12}/l, hemoglobin of 8.3 g/dl and thrombocytopenia (83×10^9/l). Initial peripheral blood smear revealed a similar picture with leukocytosis with neutrophils 50% and lymphocytes 45 %, 2-3 nucleated RBCs per 100 WBCs and 23 % activated lymphocytes and thrombocytopenia. Direct coombs test was also positive. Raised reticulocyte count (35.2%) along with low Haptoglobin (6mg/dl) and raised LDH (2634 U /l) revealed an ongoing intravascular hemolysis due to AIHA and thrombocytopenia.

LFT upon admission revealed conjugated hyperbilirubinemia (direct bilirubin of 8.2 mg/dl with total bilirubin of 11.4 mg/dl), GGT of 194 U/L, ALP of 588 U/l, ALT of 422 U/l , AST of 411 U/l, and albumin of 2.1 g/dl .USG abdomen was normal.

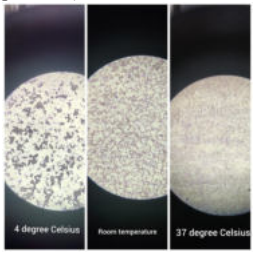
Viral hepatitis serologies and HIV were negative. INR was 1.78.
For this presentation of acute hemolysis and biliary stasis of unknown etiology, the patient was admitted for further evaluation.

Heterophile antibody test was done which came out to be negative. Epstein Barr Virus (viral capsid antigen) IgM was positive. Cytomegalovirus IgM titer was negative. IgG Antibody for CMV also was also positive. Toxoplasma gondii – IgM and IgG were negative Serum ferritin was raised 797 ug/L. Serum triglyceride 556 mg/dl (normal 40-160mg/dl)

After 4 days of admission patient developed acrocyanosis of both lower limbs (figure 2). Bilateral lower limb doppler was done and was normal

Figure 2: showing acrocyanosis

Peripheral smear was done after onset of acrocyanosis was consistent with cold autoimmune hemolytic anemia, with strong auto-agglutination at 40C and room temperature and minimal auto-agglutination at 370C (as shown in figure 4). The cold agglutinin titer was 1:256 (normal up to 1:32).



Therefore, the diagnosis of cold autoimmune hemolytic anemia complicating heterophile antibody negative EBV IM was made. With supportive treatment and steroids, the patient's jaundice, laboratory derangements, and clinical symptoms all improved and the patient was discharged from hospital day 8. The patient's follow-up appointment approximately 3 weeks later showed complete clinical improvement and near complete resolution of all abnormal measurements in the laboratory workup.

Her anti-nuclear antibody was positive (1:80) and rheumatoid factor were negative.

The patient's CBC and hepatic panel slowly improved throughout hospitalization.

DISCUSSION

IMN is an acute self-limiting disease primarily caused by Epstein-Barr virus (EBV) which characterized by its acute presentation of malaise, headache, and fever before developing tonsillitis and pharyngitis. They can progress to high grade fever and cervical lymph node enlargement with tenderness, in addition to severe fatigue. Jaundice is uncommon(3). EBV is the primary agent in IM, and it persists asymptomatically for life in nearly all adults. Treatment is primarily symptomatic and requires supportive care with nonsteroidal anti-inflammatory drugs, acetaminophen, and adequate fluids.((4)(5)). Morbilliform rashes sometimes follow the administration of amoxicillin in patients with IM.

Cold type autoimmune hemolytic anemia (AIHA) is a rare complication of infectious mononucleosis (IM) (2). The exact pathogenesis of IMN causing cold type AIHA is poorly understood. But according to suggested mechanisms initially there is formation of IgM antibodies to EBV. Then due to the molecular mimicry, IgM antibodies cross react with RBC polysaccharide antigens and result in formation of antigen-antibody complexes. This will activate the complement system(6). Diagnosis of cold type AIHA due to IMN is confirmed by demonstrating red cell aggregates in a peripheral blood smear, presence of high titers of cold antibodies, positive direct antiglobulin test with serological evidence of recent IMN infection(2).

Our patient had acquired autoimmune hemolytic anemia in the form of Cold type autoimmune hemolytic anemia (AIHA) with associated thrombocytopenia, both of which are uncommon complication of EBV infection. This case shows secondary cold agglutinin syndrome because it was the result of a separate medical condition or infection(7). Primary cold agglutinin disease (idiopathic cold agglutinin disease), describes the same process but occurring in the absence of an underlying disorder. The GGT and ALP elevations with the AST/ALT elevations, and USG findings consistent of acute hepatitis without biliary dilatation confirm cholestatic hepatitis. The low haemoglobin, high LDH, low haptoglobin, and high Cold Agglutinin titer confirms clinically significant autoimmune hemolytic anemia (AIHA). Both cholestatic hepatitis and clinically significant AIHA are rarely seen in EBV IM. EBV infection complicated by hemolytic anemia has been described in other case reports; however, our patient also experienced severe biliary stasis with direct bilirubin >8.2 mg/dL. This is unusual because biliary stasis typically occurs in the setting of an obstructive processes or critical illness(8). Recognizing that these are two complications of EBV IM can help avoid unnecessary testing.

Our patient also had some of the features hemophagocytic lymphohistiocytosis (HLH), which is a rare complication of rare complication of EBV IM similar complication was also observed by Abdul Siddiqui et al (9). It is caused by excess immune activation. At least 5/8 of the following are needed for HLH diagnosis: Temperature>38.5^{0}C, splenomegaly, cytopenia (at least 2/3 lineages), hypertriglyceridemia (fasting, >265 mg/dL), hemophagocytosis, low Natural Killer cell activity, elevated sCD25, and ferritin>500 mcg/L(9). Our patient met some of these values, but not 5. It is vital for the clinician to be aware of this entity as HLH can range from self-limiting to very aggressive, and may require corticosteroids, immunochemotherapy, or hematopoietic cell transplantation.

In Our patient, CMV was also positive which could be a false positive finding as concluded by by Sohn et al (10). They concluded that serum EBV and CMV IgM dual positivity represents a false-positive finding, as opposed to an actual CMV coinfection, possibly due to antigenic cross-reactivity.

Summary

EBV IM is a seemingly common diseases were complicated by rare complications like cold autoimmune hemolytic anemia, thrombocytopenia, biliary stasis and HLH. Cold type autoimmune hemolytic anemia should be considered in infectious mononucleosis patients who are presenting with anemia. Recognizing uncommon findings like cholestatic hepatitis and AIHA can help avoid unnecessary testing. Recognizing more life-threatening and critical complications like HLH, can expedite initiation of treatment.

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