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CASE REPORTS

Autoimmune Hepatitis with Autoimmune Haemolytic Anemia Triggered by Varicella - a Rare Presentation

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ABSTRACT

Varicella is a common infectious exanthematous disease of children. Infection manifests as polymorphic maculopapulovesicular along with low grade fever, malaise and headache. Adults are less likely to be infected with varicella infection but once infected suffer disproportionately from serious complications like pneumonia, encephalitis, hepatitis and thrombocytopenia. Varicella hepatitis is generally a self-limiting disease with only a temporary subclinical rise in hepatic enzymes and are usually encountered however autoimmune hepatitis (AIH) which is an autoimmune disorder of unknown etiology affecting the liver is a very rare association of Varicella infection .similarly autoimmune haemolytic anaemia (AIHA) affecting the erythrocytes which is also rarely associated with varicella infection limited to few case reports. We report a rare triplex of acute varicella infection with AIHA and AIH in a young female patient.

Keywords: Varicella, autoimmune hepatitis, autoimmune haemolytic anaemia

INTRODUCTION

Varicella is a common infectious exanthematous disease which generally affects children. It commonly presents as pleomorphic skin eruptions sometimes complicated by pneumonia, ataxia, arthritis or thrombocytopenia (1). Autoimmune hepatitis (AIH) which is an autoimmune disorder of unknown etiology affecting the liver is a very rare association of Varicella infection (2). Autoimmune haemolytic anaemia (AIHA) is another autoimmune disease affecting the erythrocytes which is also rarely associated with varicella infection and only a few cases have been reported (1). We report a rare triplex of acute varicella infection with AIHA and AIH in a young patient admitted with us. ❑

CASE REPORT

An 18-year-old female, not a known case of any chronic illness, presented to PGIMS, Rohtak with history of healed pleomorphic skin lesions and mild fever 10 days back, followed by yellowish discoloration of skin and eyes for 4 to 5 days. Her initial physical examination showed severe pallor with jaundice and hepatomegaly 1cm below right costal margin along with healed skin lesions. Her baseline investigations showed hae-

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moglobin (Hb) level 3.6 g/dl, total leucocyte count 9800/cu mm (78% neutrophils, 20% lymphocytes and 2% eosinophils), platelets 333 x 10^9 /L and a corrected reticulocyte count of 1.25%. The red blood cells (RBC) indices were normal and the peripheral blood showed normocytic normochromic anemia. The direct Coombs test was positive. The antinuclear antibody (ANA) was also positive (1:160 titres) with homogenous pattern. Her other laboratory findings included raised aspartate aminotransferase (AST), alanine aminotransferase (ALT) (494 U/L, 618 U/L respectively), serum alkaline phosphatase 179 U/L, serum bilirubin. 12.6 mg/dl (direct 4.6 mg/dl, indirect 8.0 mg/dl), serum LDH 1372 U/L [Normal 230-460 U/L]. S. Proteins level was 7.6 g/L with mildly increased globulins (4.6 g/L) and decreased albumin (3.0 g/L). Her coagulation profile was normal. All serology tests for hepatitis (IgM anti HAV, HbsAg, Anti HCV, Anti HEV) and HIV were negative, but showed positive result for IgM Varicella. Widal test and Quantitative Buffy coat smear for malarial parasites and IgM for Leptospira and scurb typhus were also negative. Haemoglobin electrophoresis and glucose-6-phosphate-dehydogenase (G6PD) estimation were normal. Other tests including anti-smooth muscle anti double stranded antibodies (anti dsDNA), anti-mitochondrial (AMA) and anti-liver/kidney microsomes (anti LKM-1) autoantibodies were negative. Serum ferritin, serum copper and ceruloplasmin level were normal. Renal function tests, thyroid function test and blood sugar were within normal limits. Urine examination was also normal. Liver biopsy was done which showed interface hepatitis with predominant lymphocytic infiltration, and the presence of plasma cells (Figure 1).

In view of patient having pallor, jaundice, a positive DCT and ANA, increased LDH level, positive liver biopsy and elevated liver enzymes a possibility of Varicella induced AIHA with AIH (pre-treatment score of >17 according to the revised International Autoimmune Hepatitis Group system) was made and patient was put on oral steroids with 3 units erythrocytes packed cells. The patient responded with improvement of anaemia and liver functions. The Hb level was 9.6 g/dl, AST/ ALT were 49U/L and 76U/L respectively, serum bilirubin level was 2.2mg/dl and serum LDH was within normal range Patient was discharged with tapering dose of steroid for 4 weeks and planed for a repeat liver biopsy at 6-8 week for further management plan but unfortunately patient did not turned up for follow up. ❑

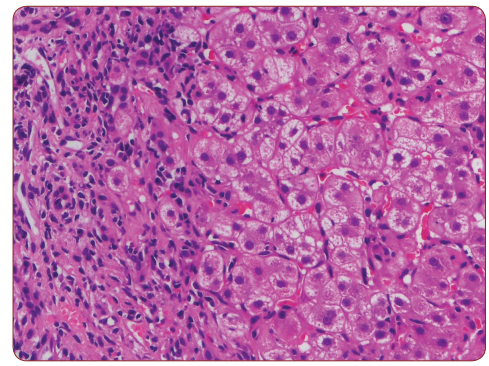

FIGURE 1. Liver biopsy showing interface hepatitis with predominant lymphocytic infiltration, and the presence of plasma cells.

DISCUSSION

Varicella is a linear double stranded deoxyribonucleic acid (DNA) virus causing Chicken Pox in susceptible host. Primary infection with the varicella-zoster virus (VZV) is most commonly a childhood event. 92% of adults are estimated to be immune. Infection manifests as maculopapulovesicular rash in various stages of development accompanied by a low grade fever, malaise, and headache and usually runs a benign course. More serious complications such as pneumonia, encephalitis, hepatitis and thrombocytopenia are known to occur rarely. Adults suffer disproportionately from these complications. Although constituting only 1.5% of the total cases of primary varicella, they account for 17% of all hospitalizations for varicella (3). The reason for the higher rate of complications in adults is not understood, but it is known that cell mediated immunity plays a crucial role in controlling the infection.

Varicella hepatitis is generally a self limiting disease with only a temporary subclinical rise in hepatic enzymes. Mild and transient liver enzyme abnormalities can occur in up to one fourth of children with varicella and rarely acute fulminant hepatitis can be seen in immunocompetant adults with more than tenfold rise in transaminases. However liver involvement in primary varicella infection in setting of immunocompromised and organ transplant patients can be very aggressive and result in fatal fulminant hepatitis. Early institution of acyclovir can be lifesaving (4-6). On the other hand as in our case autoimmune hepatitis triggered by varicella has only once reported by Al Hamoudi (2).

The pathophysiology of AIH is unknown and genetic/other causative factors singly or overlapping have been implicated including viral infec-

tions like cytomegalovirus (CMV), herpes simplex virus (HSV), Ebstein Barr virus (EBV) and hepatitis viruses. Role of VZV is likely to be similar as other virus infections in pathophysiology of AIH. It is postulated that molecular mimicry between viral proteins and different auto antigens in the liver may be responsible for the immune cross reactions that damages the liver tissues. One such protein that has been implicated includes the asialoglycoprotein receptor, found in the periportal hepatocytes and is thought to play in the immunological reactions in AIH (7). Along with that a defective T-cell response to asialoglycoprotein has been detected in patients following viral infections (8). In addition to the above mentioned pathogenic mechanisms modification//s of sequestrated intracellular proteins by the virus and release of variety of cytokines by activated T cells has also been implicated.

Varicella induced AIHA is an uncommon complication of Varicella (1). AIHA in general is characterized by increased destruction and decreased life span of erythrocytes due to autoantibodies of IgG and IgM directed to red cell antigen. In a study series of 865 patients of AIHA cases only one was due to Varicella (9). Rarely Paroxysmal cold hemoglobinuria also has also been reported during varicella infection especially adolescent. Our case developed hemolysis in the second week following acute chicken pox and a similar trend was noticed in a review of 6 cases of AIHA due to varicella where 4 of them developed it within 2 weeks (10). The normal reticulocyte count in our patient despite hemolysis could be explained on the basis of haemolytic process affecting them also.

According to evidence we treated our patient with 1mg/kg of prednisolone and the patient responded by improving haemoglobin levels and no further need for blood transfusion. The mechanism of action of steroids is probably down regulation of Fc receptors on phagocytes, reduced interleukin 2 (IL-2) production, suppression of sequestration of opsonized red cells by splenic macrophages and reduction in the binding affinity of autoantibodies for red cells Other drugs like intravenous immunoglobulin (IVIG), azathioprine, cyclosporine A, cyclophosphamide and rituximab could also be used in case the patient doesn't responds to oral steroids but the data is limited (11).

There is an increased risk of VZV infections in patients with underlying autoimmune disease. But can recent infection further triggers autoimmune process to cause autoimmune haemolytic anaemia and autoimmune hepatitis, very scanty literature is available limited to few case reports only. The sequence of events already described and positive IgM Varicella strongly indicated that AIHA and AIH were triggered by preceding Varicella infection in our patient and responded to oral steroids treatment. The presence of these two rare associations in the same patient opens up new scope for research in finding the common pathogenesis explaining these two disorders. Further follow up of patients of AIHA and AIH should be undertaken to provide some light on the same. In addition patients of AIHA and AIH should be screened both clinically and serologically for a viral etiology. ❑

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