TEACHING FILE

GRAND ROUNDS

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FEVER, PANCYTOPENIA, HEPATITIS

Clinical Problem : A 2 months old boy born of non-consanguineous marriage presented with fever for a week. There was no cough, vomiting, convulsions or bowel complaints. He was 3rd of 3 siblings. First child had died due to fever and anemia at one and a half months of age. Second child was alive and well. The patient was born full term without any complications and pregnancy was uneventful. He was on exclusive breast feeds. On examination, the child had hepatosplenomegaly and anemia. Other examination findings were normal. On investigation:

- Hemoglobin = 3.8 gm/dl, WBC = 3,300/cumm, Platelets = 82,000/cumm
- Reticulocyte count = 1.2 percent
- Bilirubin = 0.9 mg/dl, SGOT = 240 IU/L, SGPT = 320 IU/L, Total proteins = 6 gm percent, Albumin = 3.2 gm percent
- Renal function tests, serum electrolytes = Normal
- Chest X-Ray = Normal
- USG Abdomen = Hepatosplenomegaly
- Blood culture = No growth
- Urine and stool examination = Normal
- TORCH titres = Elevated CMV IgG. Rest all normal
- Fundus examination = Normal
- HIV ELISA, VDRL, Parvovirus IgM = Negative
- OptiMAL for malaria and dengue IgM = Negative
- CMV PCR = Negative

What is the diagnosis?

Expert's opinion: This child has fever, pancytopenia and hepatosplenomegaly. Thus one would consider a differential diagnosis of
• Congenital infections
• Malignancy
• Hemolymphohistiocystosis (HLH)

Most of the congenital infections have been ruled out in the child. Malignancy would not cause deranged liver enzymes in the child. This child has involvement of bone marrow (pancytopenia with low reticulocyte count), liver (elevated liver enzymes) and fever. Thus HLH is a possibility in the child. HLH is characterized by fever, splenomegaly, liver dysfunction, and the pathologic finding of hemophagocytosis in bone marrow and other tissues. The diagnostic criteria for HLH in children laid down by the Histiocyte Society includes fever for seven or more days, splenomegaly, cytopenia (absolute neutrophils less than 1000/µL, platelets less than 100,000/µL, hemoglobin less than 9.0 g/dL- of these atleast 2 conditions should be fulfilled), hypofibrinogenemia (less than 250mg, dl) or hypertriglyceridemia (greater than 160 mg, dl), hemophagocytosis (demonstrated in a bone marrow, lymph node or spleen biopsy), rashes and other symptoms like abdominal pain, weight loss and feeding problems which is very common in infants (1). Our patient underwent a bone marrow examination and it showed presence of hemophagocytes and serum ferritin was elevated with low serum fibrinogen suggesting HLH. His serum perforin levels were very low.

HLH is of two main etiological types: familial or primary and secondary HLH. Primary HLH is an autosomal recessive disorder more common with parents' consanguinity. Secondary HLH usually occurs due to strong immunological activation like in immunodeficiency or due to infections. In both of these forms of HLH there is an overwhelming increase in T cell and macrophage activity. Death usually occurs if prompt treatment is not given. Initial therapy of HLH consists of steroids and cyclosporine for 8 weeks regardless of infection. Hematopoietic stem cell transplantation should be performed as early as possible when a suitable donor is available in cases of primary HLH. Our patient subsequently succumbed to his illness.

Reference:

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PULMONARY TUBERCULOSIS AND HEPATITIS

Clinical Problem: A 5½ years old girl presented with fever, jaundice and loss of appetite for 4 days. She was antituberculous therapy (ATT) consisting of Isoniazid (H) and Rifampicin (R) for past 10 months of view of pulmonary TB. On examination, she had jaundice, hepatomegaly. Other systems were normal. Her investigations showed:

• Bilirubin = 3.9 mg/dl

• SGOT = 245 IU/L, SGPT = 225 IU/L

• Total proteins = 7.8 gm/dl, albumin of 3.2 gm/dl

What is the cause of hepatitis?

Expert's opinion: The single biggest problem in the treatment of TB is drug induced liver dysfunction, which has a mortality of upto 13 percent (1,2). Pyrazinamide (PZA), Isoniazid (INH) and Rifampicin (RIF) are hepatotoxic drugs in decreasing toxicity(3). Isoniazid causes hepatitis due to the formation of hydrazines. They are formed by the action of P450 on acetylhydrazine, a product of isoniazid metabolism in the liver. The hydrazines get covalently bound to liver proteins thus damaging the cells. (4) Rifampicin induces P450 enzymes and therefore increases the risk of hepatotoxicity when given with Isoniazid. (5)

Pyrazinamide on the other hand causes direct liver toxicity which is dose related. (5) However, ATT induced drug toxicity is seen more in the intensive phase and less commonly in the continuation phase. (6) Though this child has hepatitis, and is on ATT, drugs may not be the cause of jaundice as the child has been on treatment for the past 10 months. Thus, one should also keep-in-mind, other causes of acute hepatitis such as Hepatitis A and Hepatitis E before this is considered as drug induced hepatitis. In this child, Hepatitis A IgM was positive and child improved gradually. Thus, this was Hepatitis A and not drug induced hepatitis.

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