Case Reports

Hypereosinophilia associated with intrahepatic cholestasis in early infancy

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ABSTRACT

A male infant presented with intrahepatic cholestasis due to idiopathic eosinophilia damaging the biliary epithelium. No other etiological agent or cause could be identified. He responded well to prednisone therapy.

Keywords: Hypereosinophilia, cholestasis, prednisone.

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Cholestasis has a wide range of causes in children. Among the rare causes of cholestasis in early infancy is idiopathic hypereosinophilic syndrome. This syndrome has been reported in few pediatric cases as well as in adult literature. This is a case of hypereosinophilia with intrahepatic cholestasis in early infancy, that has showed complete recovery with prednisone therapy. We are reporting this case to emphasize the importance of this clinical entity and to alert physicians about such a rare cause of cholestatic jaundice.

Case Report. The patient was a 42-day old boy who was admitted to our hospital because of jaundice. The history started on the first day of life with progressive jaundice, yellowish stool and dark urine. He was exclusively on breast-feeding with good intake. This infant was a product of cesarean section at term because of cephalo-pelvic disproportion after an uneventful pregnancy with good antenatal care to non-consanguineous parents. No medications were used during the pregnancy. He is the first baby for this young couple and no family history of liver diseases, neonatal deaths or endocrinological disorders. No family history of asthma, eczema or hay fever.

On physical examination, the baby was well looking, normal vital signs with obvious jaundice involving the skin and sclerae. No dysmorphic features and his anthropometric measurements were within normal limits. He had distended abdomen, liver was 5-6 cm below the costal margin, smooth and firm, and liver span was 8 cm. Spleen was also palpable 4 cm below the left costal margin, with smooth and firm margins. Examination of other systems was essentially normal as well as his developmental milestone.

Investigations. Hemoglobin of 101 gm/L (10.1 mg/dl), white blood cell count (WBC) 11400/mm3, with 63% lymphocytes, 10% neutrophils, 4% monocytes and 23% eosinophils, and normal platelet count. Liver function test showed alanin aminotransferase (ALT) of 260 U/L (0 – 60), Aspartate aminotransferase (AST) was 680 U/L (0 – 110). Total bilirubin was 11.8 mg/dl (0.2-1mg/dl) [201.8 umol/L (3.4-17.1umol/l)] with a direct bilirubin of 8 mg/dl (0-0.2mg/dl) [136.8 umol/L(0-3.4umol/l)]. Alkaline phosphatase was 2590 U/L (175 – 600), Prothrombin time (PT) 24/17 second and Partial prothrombin time (PTT) 42/36 second. Total protein and albumin were within normal limits. Serum immunoglobulins were within normal limits

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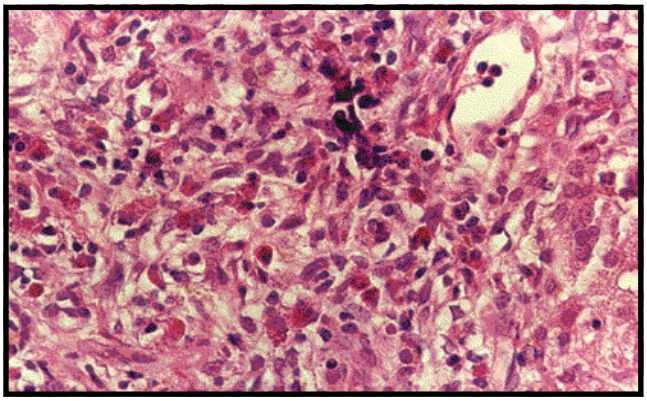

Figure 1 - High power photomicrograph x 280, showing a portal tract area heavily infiltrated by eosinophils with paucity of the bile duct (Hematoxylin and Eosin stain).

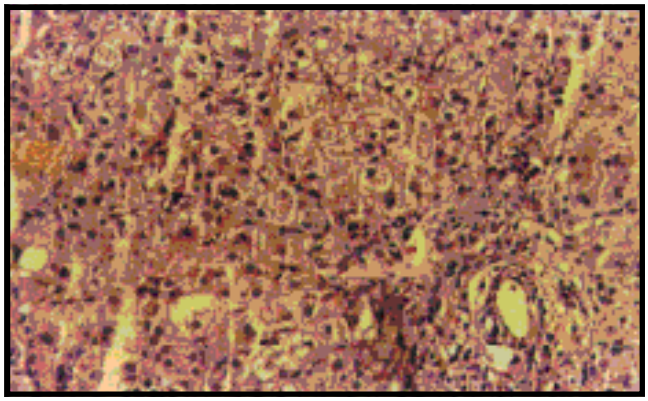

Figure 2 - A photomicrograph of post treatment liver biopsy x 160, showing marked reduction of the inflammatory cells within the portal area and moderate improvement of the lobular disarray of hepatocyte (hematoxylin and eosin stain).

for age except IgE which was 50 KIU(<10). Toxoplasma IgM and IgG of both mother and the infant were negative. Hepatitis serology for A, B, and C were negative. Alpha-1-Antitrypsin: 178 mg/dL (200-366 mg/dL) (1.78g/L). Stool for ova and parasites were negative on 3 consecutive samples. Urine for reducing substance was negative. Urea, creatinine and electrolytes were normal. Bone marrow examination showed active bone marrow with increase in the mature and immature eosinophils, however blast cells were within normal limits. Liver biopsy showed mild to moderate biliary tract expansion by fibrosis and inflammatory reaction rich in eosinophils with hepatocellular cholestasis. The striking histologic finding in this biopsy was the absence of bile ducts in several portal tracts examined (Figure 1). Abdominal ultrasound revealed normal liver and spleen. The gall bladder was not visualized and there was no evidence of intrahepatic bile duct dilatation. The gall bladder was again not visualized on HIDA scan after 5 days of phenobarbitone. Echocardiography and chest radiography were normal. Ophthalmological examination was within normal limits. Repeated investigations showed persistent high bilirubin and liver function tests for the first few weeks while investigating this infant. The patient was treated with phenobarbitone daily. A trial of Progestemil for 10 days did not show any change in his clinical status. Because of the presence of hypereosinophilia with cholestasis, the findings on bone marrow and liver biopsies together with the absence of identifiable causative agents, the patient was presumed to have idiopathic hypereosinophilic cholestasis. He was started on prednisone 2mg/kg/day for one month, then tapered over another month. Eight weeks after starting therapy total and direct bilirubin and liver enzymes became normal as well as eosinophil count in the peripheral blood smear. His 2nd liver biopsy that was carried out at the end of the course showed significant improvement, with major decrease in the eosinophil count, inflammatory reaction and regeneration of the bile ducts (Figure 2). No adverse effect was encountered during the course of treatment. He remained well at 8 months follow up with normal growth and development. He is off all medications at the time of writing this report.

Discussion. Since the discovery of eosinophils by Paul Ehrlich in 1987, the precise function of this cell eludes us even today. The presence of circulating eosinophils in allergic and parasitic diseases is a well-known phenomenon. Some mechanisms have been postulated, the most predominant of these mechanisms are antibody-dependent cellular cytotoxicity and the complement-dependent cellular killing activity. Another potentially important mechanism is a direct increase in bone marrow production of eosinophils. Lastly, there may be prolongation of eosinophil half-life.[1] The empiric threefold criteria have been established for idiopathic hypereosinophilic syndrome (HES): persistence of eosinophilia of 1500 eosinophils/mm3 for at least 6 months or death before 6 months with signs and symptoms of HES disease; lack of evidence of parasitic, allergic, or other recognized causes of eosinophilia and signs and symptoms of organ system involvement or dysfunction either directly related to eosinophilia or unexplained in a given clinical setting.[1] Clearly, eosinophils can infiltrate virtually any organ system that is involved in HES. The 2 organ systems that are severely involved in the syndrome, are namely the heart and the central nervous systems.[1] Hepatic involvement was typified by hepatomegaly and minor abnormality of liver enzyme and the spectrum of pathological findings include congested sinusoids, chronic hepatitis without cirrhosis, and peripheral inflammation.[1] The hypereosinophilic syndrome has been reported in

adult literature. This syndrome has different clinical presentations.[2] This syndrome is not a common problem in the pediatric age group. To our knowledge, no report of this syndrome as young as our patient has been sited in the literature. Spry reported in his series among others,[2] a 14 year old boy who presented with diarrhea, excessive sweating, fever and lower abdominal pain. He responded initially to steroids, but had subsequent relapse and responded to salazopyrine. Foong et al also reported a 19 year old boy who presented with features suggestive of chronic hepatitis. He was treated with prednisone with good response at 7 years follow up.[3] Alfaham further reported a 14-year-old girl who presented with mouth ulcers, blisters of hands and feet, nausea and anorexia. She had history of asthma, eosinophil count of 39% with cardiomegaly and pleural effusion on chest x-ray. The patient was treated with steroids and had a good response.[4] Chusid et al reviewed 14 patients in their series. Only one case was 5 years old and he presented with fever, rash, diarrhea and angioedema. He had peripheral eosinophilia of 60% and WBC of 41,000/mm3. He was treated with prednisone with favorable response. Liver biopsy showed eosinophilic triaditis. In their series only 3 patients had mild abnormality of their liver function test. However, each of the 6 patients whose liver tissue was obtained had abnormal numbers of eosinophils. Hepatic architecture was maintained, but a large number of eosinophils was found in the periportal area. Hepatic involvement was in 43% of their patients including elevation of the liver enzymes and histological abnormality. However, hepatomegaly was found in 85%. The ultimate cause of death was usually related to cardiac involvement.[5] Rickles et al reported a 5 month old female child whom during routine examination was found to be pale and had hepatosplenomegaly. Her WBC was 179,000/mm3 with 86% eosinophils. She was treated as eosinophilic leukemia with prednisone and 6-mercaptopurine. Initial bone marrow examination was normal however, repeat aspirate after 4 months of therapy showed increase in the myeloblast of 6%. The presumptive diagnosis of the author was eosinophilic leukemoid reaction.[6] He also reported 16 other patients in his review between the age of 1.3 and 15 years. Most of the patients died during the follow up and some of them progressed to leukemia either (acute myeloid leukemia) AML or Chronic myeloid leukemia (CML). All the patients presented with hepatomegaly or hepatosplenomegaly plus other systemic manifestations. No patient presented with jaundice as the sole presentation.[6] Olson et al reported a 9 year old boy with hypereosinophilia, who died 9 months later with cardiac complication.[7] They also reviewed another 12 patients with hypereosinophilia and all of them died as a consequence of cardiac derangement. Some of them were included in Rickles's review.[6] Dillon and Finlayson reported a 58-year-old male, who presented with lethargy and jaundice. White blood cell count was 11500/mm3 with 31% eosinophils. Liver biopsy showed marked eosinophilia infiltrate within the portal triads surrounding the bile duct.[8] Rickles et al suggested the following criteria for diagnosing eosinophilic leukemia: (1) pronounced persistent eosinophilia associated with immature forms, either in peripheral blood or bone marrow, (2) greater than 5% blast forms in the bone marrow, (3) tissue infiltration by immature cells of predominantly eosinophilic type, and (4) an acute clinical course measured in months, accompanied by anemia, thrombocytopenia, increased susceptibility to infection, or hemorrhage or both.[6] We think our case supports the idea of differentiating between eosinophilic leukemia and hypereosinophilia syndrome. The criteria set by Rickles et al[6] should be applied in the case of eosinophilic leukemia. These criteria will help the physician in counseling the parents and will also give an idea about the choice of treatment. It seems that steroids are the drug of choice in hypereosinophlic syndrome. However, the bone marrow examination must be carried out before starting the treatment to exclude malignancy. The duration of therapy is not very clear at this stage. The treating physician should try to wean steroids as soon as the clinical status permits.

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