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Eosinophil-Induced Chronic Hepatitis

Chronic hepatitis associated with hypereosinophilia has been very rarely reported worldwide. A 7-month-old male infant presented with a high fever, cough, non-projectile vomiting and hepatomegaly. The eosinophil count of the peripheral blood increased up to 21,500/mm^3 (49% of WBC). The infant had a history of frequent contact with a neighbor keeping a pigsty. The pathologic examinations of the liver showed severe porto-periportal necroinflammation with marked eosinophilic infiltration, giant cell transformation and ballooning degeneration of hepatocytes, and degranulation of the eosinophils. Bone marrow showed increased eosinophils and decreased myeloid series. Pericardial effusion and bilateral pulmonary consolidation were noted. Corticosteroid aggravated the clinical symptoms of the infant. Anthelmintic treatment significantly normalized the eosinophil count and liver function tests, but cardiopulmonary manifestations continued.

Key Words : *Hypereosinophilic syndrome; Hepatitis chronic*

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INTRODUCTION

Eosinophils have direct cytotoxicity through the intracytoplasmic product, major basic protein and eosinophilic granule proteins. Fauci et al. (1) performed a multicenter study of the hypereosinophilic syndrome, and found that 32% of 50 patients with hypereosinophilic syndrome had hepatic involvement. Croffy et al. (2) reported 4 cases with hypereosinophilic syndrome associated with chronic active hepatitis, and Foong et al. (3) reported eosinophil-induced chronic active hepatitis in idiopathic hypereosinophilic syndrome, those symptoms and the pathology of those patients were improved by corticosteroid therapy. The patient in this report who showed hypereosinophilia, increased bone marrow eosinophils, severe chronic hepatitis, pericardial effusion, and bilateral pulmonary consolidation, may be the first reported infant case of eosinophil-induced chronic hepatitis in Korea.

CASE REPORT

A 7-month-old male infant was admitted due to a fever which had developed 3 days before admission. Activity and feeding were poor, and other symptoms were non-projectile vomiting once per day and a cough. He was born at full term and his birth weight was 4,200 g. His vital signs were normal, growth percentile was 75-90 percentile. He looked ill. There was neither skin rash, nor lymphadenopathy. The lung sound was coarse in both lungs. The heart beat was regular and murmur was not heard. The liver was palpable 5 cm below the right costal margin, the spleen was not palpable. The extremities and neurologic systems were normal.

Laboratory findings were WBC 26,400/mm^3 (neutrophil 17%, lymphocyte 54%, monocyte 3%, eosinophil 26 %), eosinophil count 6,800/mm^3, total protein 5.7 g/dl, albumin 4.0 g/dl, ALT 1,067 units, AST 981 units, alkaline phosphatase 241 units, total bilirubin 2.1 mg/dl, direct bilirubin 0.9 mg/dl, ammonia 96 μg/dl, CRP 0.18 mg/dl, prothrombin time 18.5 sec (45%), aPTT 40 sec (27%). Stool examination for parasites performed 4 times were negative for *Ascaris lumbricoides, Ancylostoma duodenale, Strongyloides stercoralis*. IgE was 22 IU/ml, and T4/T8 ratio was normal. Serologic tests for parasitic infections including *Ascaris suum, Toxocara canis, Capillaria hepatica* were all negative. Serologic studies for viral hepatitis were negative for hepatitis A, hepatitis B, hepatitis C, EBV, and CMV. Anti-nuclear antibody, anti-DNA antibody, anti-mitochondrial antibody, and LE cell were negative. Chest x-ray film showed pneumonia in both lungs. Abdominal ultrasonogram showed mild hepatomegaly, abdominal CT showed hepatomegaly and periportal edema (Fig. 1). Sinus tachycardia was noted on EKG. Echocardiogram showed a moderate amount of pericardial effusion of moderate amount. A needle biopsy

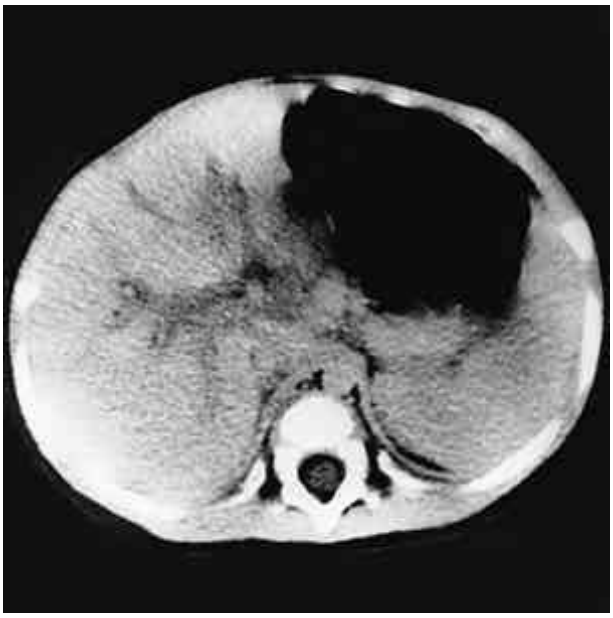

Fig. 1. Abdominal CT showed hepatomegaly and periportal edema.

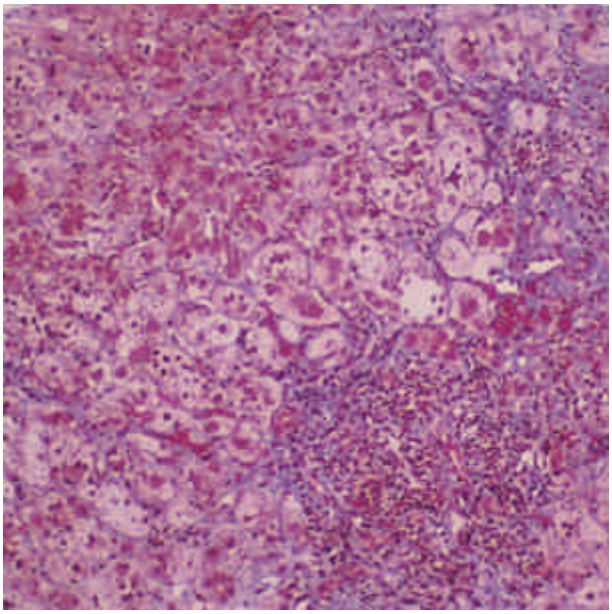

Fig. 2. The liver shows heavy infiltration of inflammatory cells with piecemeal necrosis and mild fibrosis (Masson's trichrome).

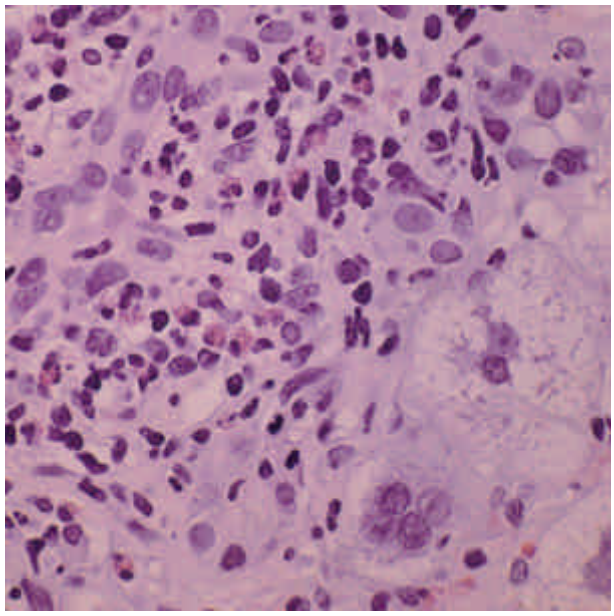

Fig. 3. Many eosinophils are admixed in portal infiltrates. Some are degranulated or degranulating. Giant cell transformation of hepatocytes is seen in the lower right of the figure (H&E).

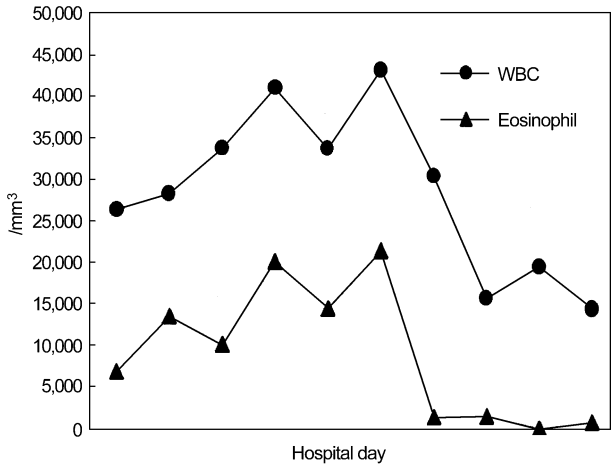

Fig. 4. The initial WBC count was 26,400/mm^3 with 26% eosinophil (6,800/mm^3). The WBC count examined on the 22nd day of admission was 43,300/mm^3 with 49% of eosinophils (21,500/mm^3). The eosinophil count dropped to 40/mm^3 after 17 days of medication with flubendazole.

of the liver was performed. The liver showed marked lobular disarray with ballooning degeneration of hepatocytes. Giant cell transformation was also notable, especially in periportal areas. The portal spaces were widened by heavy infiltration of inflammatory cells (Fig. 2). Fair amounts of eosinophils were infiltrated in the portal spaces, some of which seemed to be degranulated. There was disruption of limiting plates with piecemeal necrosis and creeping fibrosis by these inflammatory cells, resulting in bridging necrosis (Fig. 3). These findings were consistent with chronic hepatitis of moderate severity, with both grade 3 portal and lobular inflammation and stage 3 portal fibrosis. WBC count examined on the 22nd day after admission was 43,300/mm^3 with 49% of eosinophils (21,500/mm^3). Bone marrow aspiration and biopsy specimens showed decreased myeloid series and increased eosinophils with normal maturation and no malignant cells. The clinical manifestations and laboratory findings were

compatible for hypereosinophilic syndrome. Corticosteroid was administered to the infant, but the three times corticosteroid was ingested, high spiking fever developed three times. The infant had a history of frequent contact with a neighbor with pigsty, authors suspected a possible visceral larva migrans, so flubendazole was administered for 3 weeks. The eosinophil count dropped to 40/mm^3 after 17 days of medication with flubendazole (Fig. 4), ALT dropped to 135 units, AST 172 units after 21 days of medication, and the hepatomegaly was improved. Despite the improvement of the eosinophil count, ALT and AST, intermittent mild fever, poor feeding and pericardial effusion continued, and bilateral pulmonary consolidation gradually aggravated. So the authors suspected a possibility of hypereosinophilc syndrome in this case. The patient denied further treatment and self-discharged.

DISCUSSION

This case showed persistent marked eosinophilia, increased bone marrow eosinophils, intermittent mild fever, poor feeding, hepatic dysfunction, porto-periportal necroinflammation with marked eosinophilic infiltration, pericardial effusion and bilateral pulmonary consolidation. Though this case showed improvement of the eosinophil count, ALT and AST after oral medication of anthelmintic drug, the other organic symptoms and signs persisted. So the authors suspected a possible hypereosinophilic syndrome (HES). HES is a disorder with a prolonged hypereosinophilia and multiple organ dysfunction. The diseases associated with a secondary eosinophilia are allergic or hypersensitivity disease, parasitic disease, cutaneous allergic disease, connective disease, lymphoma, T cell leukemia, and immunodeficient states. The diagnostic criteria for idiopathic HES are persistent eosinophilia of 1,500/mm^3, absence of evidence of other causes for eosinophilia, and signs and symptoms of organ involvement. The frequency of organ system involvement in idiopathic HES are hematologic (100%), neurologic (64 %), skin (56%), cardiovascular (54%), pulmonary (40%), liver (32%), nose and sinuses (26%) etc. The presenting symptoms and signs of HES are weakness, fatigue, cough, dyspnea, myalgia, angioedema, rash, fever, and rhinorrhea (1).

There has been few report of HES with chronic hepatitis (2, 3), the presence of eosinophilia in idiopathic chronic active hepatitis is also uncommon, and the maximal eosinophil counts were less than 15% in peripheral blood smears (4-8). The infant reported here may be the first infant case with chronic hepatitis induced by hypereosinophilia in Korea. The diagnosis of chronic hepatitis was made by needle biopsy, the eosinophil count was 49% of the WBC, and he had the clinical symptoms and signs of HES which were described above. The involved organs in this case included the bone marrow, heart, lungs, and liver. As the eosinophil count decreased to normal range, the liver transaminase levels decreased and the hepatomegaly also improved. Even though a study for the detection of the major basic protein of eosinophil was not performed, the clinical course shows that the hepatic lesion was significantly associated with tissue damage by the eosinophils.

Activated eosinophils play a role in the cell damage in the liver (3), skin (9), heart (10), and intestine (11). Eosinophils have direct cytotoxicity through the intracytoplasmic product. The cytotoxic effect of major basic protein and eosinophilic granule protein have been described (1, 3). Degranulated and activated eosinophils were recently detected (12-14). The liver biopsy specimen of this case also showed many degranulated eosinophils. Activated eosinophils predominantly produce leukotriene C_4 with potent smooth muscle spasminogenic and vasoactive properties (15). These eosinophilic products may contribute to the pathophysiology of diseases associated with hypereosinophilia.

The hepatic lesions in HES are usually mild hepatomegaly or mild abnormalities in liver function tests. The pathologic findings of the patients whom Fauci et al. (1) reported were congested sinusoids, hepatitis without cirrhosis or portal inflammation. Croffy et al. (2) reported 4 cases with hypereosinophilia-associated chronic active hepatitis, the pathologic findings of which were mild hepatitis with eosinophilic infiltration, no bridging necrosis and little fibrosis. The case reported by Foong et al. (3) showed chronic active hepatitis with eosinophilic infiltration with degranulation and hepatocytic necrosis. Our case showed severe portal and periportal inflammation with eosinophilic infiltration, the eosinophils were degranulated.

Most patients with HES respond to corticosteroid treatment, but our case developed a high spiking fever whenever corticosteroid was given, and his eosinophil count and liver function tests showed a distinctive response to an antihelminthic drug (flubendazole). The authors suggest that this infant probably had attracted a parasitic infection which induced hepereosinophilia.

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