Chronic hepatitis in hypereosinophilic syndrome: report of an unusual case

Ipereosinofilia ed epatite cronica: descrizione di un caso

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INTRODUCTION

Hypereosinophilic syndrome (HES) is characterized by more than 1500 eosinophils per microlitre of peripheral blood for at least 6 months, lack of evidence for parasitic, allergic or other known causes of eosinophilia, and signs or symptoms of multisystem organ dysfunction. Pulmonary infiltrates with eosinophilia (PIE, eosinophilic pneumonias) include distinct individual syndromes characterized by eosinophilic pulmonary infiltrates and, commonly, peripheral blood eosinophilia. Furthermore, in most patients with HES who displayed hepatic abnormalities as one part of the syndrome, there was liver eosinophilia, occurring as either granulomatous aggregates or sparse lobular infiltration.

We present an unusual case of hypereosinophilic syndrome associated with clinical and histological features of chronic hepatitis, in the absence of a significant number of eosinophils in the inflammatory infiltrate. The disease was successfully controlled by long-term use of glucocorticoids.

CASE REPORT

A 28-year-old woman had a long history of lung and blood eosinophilia detected in May 1992. The syndrome was characterized by biopsy-proven eosinophilic infiltration in the lung, and peripheral blood eosinophilia (55%, 3500 eosinophils per microlitre of peripheral blood) (Figure 1). Recurrent flare up was successfully treated by steroids.

In May 1995 the patient developed an acute hepatitis. Laboratory data showed aspartate aminotransferase [AST] 478 IU/L, alanine aminotransferase [ALT] 935 IU/L (normal values <40 IU/ml); LDH and serum alkaline phosphatase within normal limits; HBsAg and anti-HBs, anti-HCV, IgM anti HAV, IgM anti CMV, IgM anti EBV were negative. ALT levels subsequently remained elevated (maximum 1.5-2 above the normal values). A bone marrow biopsy specimen showed a high eosinophil count (25% of total cells).

She was referred to our Liver Unit in February 2001. Laboratory data showed: AST 58 IU/L, ALT of 91 IU/L, gamma-globulin 1,4 gr./dl. (19.8%), normal alkaline phosphatase (ALP) and bilirubin, erythrocyte sedimentation rate of 30 mm/h. Serum electrophoresis and serum creatine kinase were normal. Antinuclear antibodies (ANA), anti-mitochondrial antibody (AMA), smooth muscle antibodies (ASMA) and LKM-1 were negative. ALT levels subsequently remained elevated (maximum 1.5-2 above the normal values). A bone marrow biopsy specimen showed a high eosinophil count (25% of total cells).
(liver-kidney microsomes) were negative. Eosinophils were $2.1 \times 10^9/L$ (white cell count $8.8/10^9/L$) (24% eosinophilic cells). Bilirubin, prothrombin time, platelet count and serum electrolytes normal. No history of liver disease was noted in the family, of which all members remained well during the patient’s illness. She was otherwise completely well and denied any itching, abdominal discomfort, bleeding or changes in stool or urine. A careful investigation was performed to rule out other causes of eosinophilia. There was no history of allergy, drug intake or heart disease. Electrocardiogram, a cardiac sector scan, and chest X-ray results were all normal. Abdomen physical and US examination showed a slight hepatomegaly. During spring 2001, serum aminotransferases decreased spontaneously (AST 44; ALT 65 IU/L). One year after, she experienced fatigue, 2-kg weight loss in 3 months, nocturnal sweating and coughing. In May 2002 eosinophil count was $2.8 \times 10^9/L$ with a total white cell count of $9.9 \times 10^9/L$ (28% eosinophils). The erythrocyte sedimentation rate rose to 37 mm/h, AST was 58 IU/L, ALT 96 IU/L, ALP 89 IU/L (normal 50 to 190 IU/ml). Serum protein electrophoresis was normal. ANA, AMA and ASMA were negative. The serum caeruloplasmin was 50 mg/dl (normal 20 to 53 mg/dl); also normal were ferritin serum levels, thyroid function tests, cryoglobulins, alpha 1 anti-trypsin; tests for coeliac disease were negative. The serum IgE was 40 IU/ml (normal = 0 to 158 IU/ml), T4/T8 ratio was normal. The C reactive protein was slightly elevated. Tests for Lupus Erythematosus were negative and a slight increase in the concentration of immune complexes in the serum was seen. No fecal parasites were found. Serum antibodies, laboratory examinations and epidemiological data to amoeba, echinococcus, filaria, schistosoma, leishmania, trypanosoma, malaria, toxocara and giardia were negative. Physical investigation showed only slight hepatomegaly (spleen tip 1 cm below the left costal margin); there was no lymphadenopathy or skin changes. An ultrasound of the abdomen displayed slight hepatomegaly with an inhomogeneous structure. Liver was enlarged up to 15 cm; a celiac lymph node of approximately 2 cm in diameter was identified. An echocardiogram and pulmonary function tests were entirely within normal limits. Holter monitoring was within normal limits; echocardiogram showed a resting left ventricular ejection fraction of 67%.

A liver needle biopsy specimen showed foci of piecemeal necrosis (interface hepatitis) and spotty necrosis, occasionally confluent in pericentral fields (Figure 2). Inflammatory infiltrate was mainly made by lymphocytes with scattered eosinophils. Mild portal fibrosis was identified with trichrome staining. Diagnosis of chronic hepatitis was then proposed. Treatment with 20 mg of prednisolone daily was started with dramatic improvement: fatigue disappeared within few days, aminotransferase returned to normal levels within one month. Eosinophilic count fell from $2.8 \times 10^9/L$ to $0.2 \times 10^9/L$ within 2 weeks. During 4 months, the prednisolone dose was tapered to 7.5 mg, this leading to a complete normalization of the eosinophil count. Except for a steroid withdrawal syndrome with myalgias treated with nonsteroidal anti-inflammatory drugs, the patient remained completely free of symptoms.

**DISCUSSION**

Liver involvement is reported to be fairly common in HES. Fauci et al. recorded hepatomegaly and minor abnormalities of liver function tests in 32% of HES patients [1]. The spectrum of pathologic findings included congested sinusoids, chronic hepatitis without cirrhosis, and periportal inflammation, the predominant feature being a marked inflammatory infiltrate by eosinophils. There are few reports of patients with histological features of chronic
hepatitis and associated peripheral blood eosinophilia.
Panush et al. described a boy with chronic hepatitis, eosinophilia and haemolytic anaemia [2]. Four men with HES, in which chronic hepatitis was the only clinical manifestation, are reported by Croffy et al. [3]. In two of them liver biopsy specimens demonstrated large numbers of eosinophils in the portal triads. All were consistent with chronic hepatitis and one showed cirrhosis. In a young man with peripheral blood eosinophilia and liver disease, the initial histological picture of acute hepatitis, progressed towards changes of chronic hepatitis, but with an inflammatory infiltrate predominantly composed of eosinophils [4].
Spry et al. described 15 HES patients, 2 of them having eosinophilic infiltration of many organs, including the liver [5]. Hepatic vein obstruction caused by pancreatitis was reported in one patient and massive hepatomegaly (liver weight 2,250 gm) with eosinophil and lymphocyte infiltration in another [6, 7]. All but one of the reported patients with chronic hepatitis and HES were male and there is a marked male predominance in published series of HES. In the paper by Spry et al. only 2 out of 15 patients were women [5]. Our patient is female and this a rare feature in previous reported cases.
Cytotoxic effects of the so-called major basic protein and other eosinophilic granule proteins have also been described [8, 9]. Foong et al. demonstrated the presence of major basic protein in areas of hepatocyte injury in their patient

Table 1 - Data on present (*) and published cases of HES associated with liver involvement.

<table>
<thead>
<tr>
<th>Gender, Presenting symptoms (age (y), duration)</th>
<th>Associated abnormalities</th>
<th>ANA</th>
<th>SMA</th>
<th>AMA</th>
<th>Ig increase</th>
<th>Maximum PB eosinophil Count x 10^9/L</th>
<th>BM eosinophilia</th>
<th>Hepatic eosinophilia</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>M, 14 Malaise, intermittent fever and headaches</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>IgG+</td>
<td>6.0</td>
<td>+</td>
<td>NS</td>
<td>+</td>
</tr>
<tr>
<td>M, 23 Weight loss</td>
<td>Cervical nodes, HM</td>
<td>+</td>
<td>NS</td>
<td>-</td>
<td>+</td>
<td>3.2</td>
<td>+</td>
<td>NS</td>
<td>+</td>
</tr>
<tr>
<td>M, 20 Fatigue, myalgias, sweats (6 mo)</td>
<td>Periorbital edema (+)</td>
<td>-</td>
<td>NS</td>
<td>-</td>
<td>9.0</td>
<td>+</td>
<td>Portal</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>M, 14 Fatigue, anorexia (1 mo)</td>
<td>HM</td>
<td>-</td>
<td>NS</td>
<td>NS</td>
<td>-</td>
<td>8.7</td>
<td>+</td>
<td>NS</td>
<td>+</td>
</tr>
<tr>
<td>M, 34 Nausea, jaundice (10 d)</td>
<td>Pruritic rash</td>
<td>-</td>
<td>-</td>
<td>NS</td>
<td>?</td>
<td>1.7</td>
<td>NS</td>
<td>Portal</td>
<td>+</td>
</tr>
<tr>
<td>M, 19 Fatigue, occasional headaches (3 mo)</td>
<td>Pruritic rash</td>
<td>-</td>
<td>NS</td>
<td>-</td>
<td>IgE+</td>
<td>11.2</td>
<td>+</td>
<td>Portal, lobular</td>
<td>+</td>
</tr>
<tr>
<td>F, 65 Fatigue, night sweats, night cough (3 mo)</td>
<td>Arthralgias</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>IgG+</td>
<td>6.3</td>
<td>+</td>
<td>Portal, lobular, areas of confluent necrosis</td>
<td>+</td>
</tr>
<tr>
<td>*F, 28 Fatigue, night sweats</td>
<td>HM IgE-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>IgG-</td>
<td>2.8</td>
<td>NS</td>
<td>Scattered eosinophils</td>
<td>+</td>
</tr>
</tbody>
</table>

M, male; F, female; ANA, antinuclear antibodies; SMA, smooth muscle antibodies; PB, peripheral blood; BM, bone marrow; HM, hepatomegaly; NS, not stated
with primary acute, later chronic hepatitis [4]. Positive tests for antinuclear antibodies have been described in two of the patients with chronic hepatitis and eosinophilia [2, 3]. In those reports eosinophilic liver infiltration was observed in the portal tract with no or only mild eosinophilic infiltration of the parenchyma; moreover features of biliary involvement were demonstrated [10-13].

In the present patient, investigation has not detected any of the known causes of persistent hypereosinophilia, thus allowing the diagnosis of HES [7]. Among symptoms commonly occurring in HES, she complained of pulmonary infiltrates, and later nocturnal sweating, coughing attacks, and weight loss [5]. There was no evidence of neurologic, skin, or heart involvement, known to occur in more than 50% of patients [1]. She developed a long-standing liver disease, initially acute then evolving into chronic hepatitis. The possibility of AST increase due to cardiac or skeletal muscle involvement was unlikely in view of the normal sector scan and electrocardiogram investigation and lack of muscle-related symptoms. Liver specimen showed features of chronic hepatitis, without evidence of marked eosinophilic infiltrate; this could support the hypothesis that liver damage can be related to a substance produced by eosinophils and not directly to eosinophilic liver infiltration. Viral hepatitis (Hepatitis A, B, C, EBV, CMV) and other causes of chronic hepatitis were excluded.

In conclusion HES represents a heterogeneous group of disorders with the common features of eosinophilia of unknown cause for over 6 months and multivisceral dysfunction. Circulating immune complexes and elevated IgE levels are often present [7]. Bone marrow involvement occurs in all patients, but the heart and nervous system usually are most severely involved and eosinophils are believed to cause heart disease. Chemotherapeutic lowering of the eosinophil count results in a marked improvement in the manifestations of HES, and functional improvement can occur. Liver involvement is usually in form of chronic necroinflammatory disease with predominant eosinophil infiltrate. Data about liver histological involvement and all available clinical information about patients with HES developing chronic liver disease are summarized in Table 1.

In our case, manifested by a chronic hepatitis without remarkable eosinophilic inflammatory infiltrate, we observed a marked improvement in aminotransferases in conjunction with normalization of the eosinophil count following high-dose steroid therapy. Without adequate treatment, the syndrome has a high morbidity and mortality and aggressive therapy is in order.

**Key words:** Hypereosinophilic syndrome, chronic hepatitis.

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**SUMMARY**

Hypereosinophilic syndrome has been reported to be associated with hepatic dysfunction; liver histology is mainly characterized by a diffuse eosinophilic inflammatory infiltrate. A 28-yr-old women, affected by idiopathic hypereosinophilic syndrome with bone marrow and pulmonary eosinophilic infiltrates associated with peripheral eosinophilia, developed features of chronic hepatitis without a significant eosinophil component. She responded favourably to systemic glucocorticoid therapy with normalization of liver function tests within a few weeks.

This observation could support the hypothesis that liver damage in idiopathic hypereosinophilic syndrome may be due to circulating substances produced by eosinophils rather than direct infiltration of liver by these inflammatory cells.
REFERENCES