Chronic Hepatitis with Eosinophilic Infiltration Associated with Asthma

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Abstract

A 49-year-old asthmatic woman with a history of drug allergy to aspirin and penicillin presented to the hospital with fever, dark urine, general exanthema and fatigue. Physical examination revealed jaundice. She had been taking four different over-the-counter drugs. Laboratory examination showed eosinophilia, elevated Ig E, hyperbilirubinemia and elevated liver function tests. HBs Ag, anti-HCV Ab and Ig M anti-HA were negative. She was initially diagnosed with drug-induced hepatitis and was treated with steroids. However, liver dysfunction with eosinophilia relapsed after discontinuing steroids. Liver biopsy revealed eosinophilic infiltration. Steroids were discontinued after the start of 6-mercaptopurine.

Key words: chronic hepatitis, eosinophilia, autoimmune hepatitis, drug-induced hepatitis, steroids, azathioprine, 6-mercaptopurine, hypereosinophilic syndrome, asthma

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Introduction

Drug-induced hepatitis should resolve with or without steroids by cessation of the offending drug (1). On the other hand, autoimmune hepatitis (AIH) is a self-perpetuating hepatocellular inflammation of unknown cause. It is characterized by the presence of interface hepatitis on histologic examination, hypergammaglobulinemia, and autoantibodies in the serum (2). The diagnosis is often based on the scoring system codified by an international panel (3, 4) and there is no consensus on a gold standard for making the diagnosis. We report an asthmatic woman with many features of acute drug-induced hepatitis. The pathology findings from liver biopsy were compatible with autoimmune hepatitis with eosinophilic infiltration. Her overall clinical presentation, however, was not entirely compatible with either drug-induced hepatitis or AIH.

Case Report

A 49-year-old woman developed dark urine and fatigue

towards the end of March 2002 and presented to the hospital with a general skin eruption on April 2. She had been taking four different over-the-counter (OTC) medications and two different dietary supplements. She had a history of drug allergy to aspirin and penicillin. Her past medical history revealed asymptomatic gallstones, asthma and duodenal ulcer, all under good control. On physical examination, scattered erythematous maculopapular lesions were noted on her trunk and extremities. Her physical exam was otherwise unremarkable. Laboratory examination revealed normocytic anemia with eosinophilia, elevated liver function tests, and hyperbilirubinemia. There was no evidence of hepatitis A, B, C or Epstein Barr virus infection. Serum immunoglobulin G was normal. Autoantibodies such as anti-nuclear antibody (ANA), anti-smooth muscle cell (SM) antibody, anti-liver/kidney microsome (LKM) type 1 antibody, anti-mitochondrial antibody and anti-M2 antibody were negative (Table 1). Drug lymphocyte stimulation tests (DLST) for all OTC drugs and supplements which she had been taking were negative. There were no pulmonary infiltrates to suggest allergic bronchopulmonary mycoses, eosinophilia-myalgia syndrome, Loeffler's syndrome, eosinophilic pneu-

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Table 1. Laboratory Values at Initial Presentation

CBC	
Hb (g/dL)	11.2
MCV (fl)	88.4
Platelet (X104/ μ L)	21.1
WBC (/ μ L)	5300
Differentials (%)	
Band	14
Seg	20
Lymphocyte	35
Monocyte	5
Eosinophil	22
Basophil	2
Coagulation	
PT (sec)	12 (9-13)
APTT (sec)	33.8 (25-45)
Blood biochemistry	
Albumin (g/dL)	3.3
AST (IU/L)	1019
ALT (IU/L)	772
ALP (IU/L)	345
Total bilirubin (mg/dL)	8.5
Direct bilirubin (mg/dL)	7.2
LDH (IU/L)	1029
γ -GTP (IU/L)	195
IgG (mg/dL)	1930
IgA (mg/dL)	816
IgM (mg/dL)	122
IgE (mg/dL)	3500
HBs Ag	Neg
IgM HBc Ab	Neg
Anti-HCV Ab	Neg
IgM Anti HA	Neg
EBVCAIgM	Neg
ANA	Neg
AMA (M2)	Neg
Anti-SM Ab	Neg
Anti-LKM1 Ab*	Neg
HLA typing	A2(A*02), A11(A*11), B38(B*38), B39(B*39), DR4 (DRB1*04), DR8 (DRB1*08)

MCV, mean corpuscular volume; PT, prothrombin time; APTT, activated; Neg, negative; HA, hepatitis A virus; EBVCA, Epstein Barr virus capsid antigen; ANA, anti-nuclear antibody, SM, smooth muscle; LKM1, liver kidney microsome type 1, HLA, human leukocyte antigen

* Measured on Nov 11, 2003

monia or allergic granulomatosis (Churg-Strauss Syndrome). She did not have any history of traveling abroad. Intestinal parasite infections (tapeworms, flukes and roundworms) were excluded by appropriate fecal tests. Her asthma was under control with scheduled use of inhaled steroids. The diagnosis of drug-induced hepatitis was made and oral prednisolone (PSL) was initiated at the dosage of 30 mg/day on April 13. Based on a return of measured AST and ALT to within normal ranges, her liver injury was resolved in mid-May 2002.

Her healthcare team strongly recommended that she avoid OTC medication and supplement use. However, she developed similar episodes of liver dysfunction as detected by

routine monitoring of AST and ALT with skin lesion (Fig. 1) in July 2002, in December 2002 and in June 2003, all of which resolved after administration of a few weeks of PSL. Percutaneous liver biopsy was performed in June 2003 for tissue diagnosis. Pathology findings suggested eosinophilic infiltration in the portal and central vein areas, with focal necrosis around the central vein (Fig. 2). These findings were compatible with the diagnosis of AIH except for the presence of eosinophilic infiltration. She was started on azathioprine in July 2003 to prevent recurrent hepatic injury, however she developed nausea so the drug was discontinued. We then started alternate day therapy with PSL (5 mg every other day) in August 2003. Despite continuous steroids therapy, she experienced a fifth episode of liver injury (AST 103 IU/L, ALT 166 IU/L) at the beginning of February 2004. We subsequently increased the dosage of PSL to 20 mg/d temporarily and started azathioprine again in late February 2004. She developed nausea again and we switched from azathioprine to 6-mercaptopurine. PSL dose was tapered then discontinued. From that time to the present (4 year interval), her liver function tests have been normal and there has been no recurrence of skin lesions (Fig. 3).

Discussion

We treated a 49-year-old woman with recurrent chronic liver inflammation involving eosinophilic infiltration of the liver. Her chronic liver inflammation was ameliorated temporarily with steroid treatment. We could discontinue the use of steroids by treating her with 6-mercaptopurine. The differential diagnosis included drug-induced hepatitis, AIH, liver injury associated with hypereosinophilic syndrome and eosinophilic cholangiopathy.

Drug-induced liver disease manifests as various types of liver injury including acute hepatitis, chronic hepatitis and granulomatous hepatitis. Drug-induced acute hepatitis is classified as either immunoallergic or metabolic idiosyncratic type. The immunoallergic type is associated with eosinophilia in 33 to 67% of cases as well as skin lesions. Both types of drug-induced hepatitis should resolve after discontinuing the offending drug (1). The present case was distinct from either type of drug-induced liver disease because the liver injury recurred even after stopping all drugs and there was no pathology finding of vasculitis to suggest drug-induced liver disease.

Another disease in the differential diagnosis of this case is AIH. There are two scoring systems used to aid in the diagnosis of AIH. One is the revised original pretreatment scoring system of the International AIH Group (3) while the other uses simplified diagnostic criteria (4). The former scoring system has been reported to have greater sensitivity; the latter scoring system has been reported to have greater specificity (5). In the present case, the score was 16 using the revised original scoring system, which was categorized as definite AIH. However, the score was 3 using the simplified scoring system, which was classified as neither definite

Figure 1. Elevation of liver function test was associated with erythematous maculopapular lesion. These pictures were taken in June 2003.

Figure 2. Liver biopsy was performed in June 2003. The infiltration of chronic inflammatory cells and mild fibrosis were noted in the portal area (a) where there were eosinophils and plasma cells (b). Inflammatory cells infiltrated around the central venule (c) and these cells included eosinophils and plasma cells (d).

nor probable in the diagnosis of AIH. The results of two scoring systems were therefore unhelpful in establishing a definitive diagnosis.

Punush et al (6) reported the case of a 14-year-old boy diagnosed with chronic active hepatitis with eosinophilia and autoimmune hemolytic anemia. His ANA and anti-SM antibody were positive. Neither bone marrow examination nor

percutaneous liver biopsy showed eosinophilic infiltration. The cause of eosinophilia was not clarified.

Another disease entity in our differential diagnosis for the present case is idiopathic hypereosinophilic syndrome (HES), which represents a heterogeneous group of disorders with the common feature of prolonged eosinophilia of unknown cause and organ system dysfunction. Organs may in-

Figure 3. Liver function tests were simultaneously elevated with serum Ig E. Liver function tests improved with the administration of prednisolone. Prednisolone was successfully discontinued after the start of 6-mercaptopurine.

clude the heart, central nervous system, kidneys, lungs, gastrointestinal tract, and skin. Bone marrow is involved in all affected individuals (7). A presumptive diagnosis of idiopathic HES can be made if all three of the following criteria are met: 1) persistent eosinophilia of 1,500 eosinophils/ μ L for at least 6 months or death before 6 months with signs and symptoms of HES; 2) lack of evidence of parasitic, allergic, or other recognized causes of eosinophilia; and 3) signs and symptoms of organ system involvement or dysfunction either directly related to eosinophilia or unexplained in the given clinical setting (8).

Minola and Sonzogni (9) reported a 28-year-old woman with a long history of lung and blood eosinophilia treated successfully by steroids who developed chronic hepatitis. Her autoantibodies (such as ANA, anti-SM antibody and anti-LKM type 1 antibody) were negative. Liver biopsy revealed hepatic inflammatory infiltrate due mainly to lymphocytes with scattered eosinophils.

Terrier et al (10) also reported a 16-year-old boy diagnosed with AIH, HES and ulcerative colitis, successfully treated with steroids and azathioprine. The present case was also not diagnosed as idiopathic HES because her eosinophilia was not unexplained given that she had a long history of asthma. The eosinophilia and elevated Ig E were associated not with exacerbation of asthma but rather with elevated liver function tests.

We thought that eosinophilic cholangiopathy (11) was unlikely because she did not have any symptom of cholangitis or cholecystitis. In addition, the rise of her aminotransferases was more remarkable compared to those of her biliary enzymes.

Croffy et al reported four man cases of idiopathic (auto-

immune) chronic active hepatitis associated with significant eosinophilia (12). One of these four patients also suffered from maculopapular rash. The findings of bone marrow biopsy for three of the four patients were described; two of these three showed increased eosinophils in the bone marrow. Only one of the four reported patients had high titers of autoantibodies. All four patients responded to corticosteroids. The authors suggested that these four cases should be categorized as a different entity than classic autoimmune hepatitis.

There is another case report of chronic liver injury other than classic AIH associated with eosinophilia. Foong et al reported a 19-year-old Japanese man who had features of chronic hepatitis with piecemeal necrosis as the sole clinical feature of idiopathic HES (13). Bone marrow aspirate showed a marked increase in normal appearing cells of the eosinophil series, ranging from eosinophilic myelocytes through metamyelocytes to mature bilobed eosinophils. Liver biopsy showed moderately heavy mixed inflammatory infiltrate containing many eosinophils. His liver injury resolved with alternate day therapy of PSL and was followed up for seven years.

There are published reports of eosinophilic disorders in the esophagus, stomach, small intestine and colon. Case reports and case series support potentially effective agents including special diets, glucocorticoids, mast cell inhibitors, antihistamines, and leukotriene antagonists (14). Netzer et al reported that immunomodulatory treatment with purine analogues is a promising therapeutic approach for corticosteroid-dependent eosinophilic esophagitis (15).

Interestingly, the present patient was able to discontinue steroid treatment after the administration of a purine ana-

logue. It appears that eosinophilia and the elevation of IgE are part of the pathognomonic process in the present case. Eosinophilic infiltration was confirmed in liver tissue biopsies, and her eosinophilia and elevation of IgE were observed simultaneously with evidence of liver damage (elevation of serum liver function tests).

In conclusion, we encountered a 49-year-old asthmatic woman who suffered from cryptogenic chronic hepatitis with hepatic eosinophilic infiltration. Her absolute eosinophilic count and IgE fluctuated in positive association with her liver function tests. She was successfully treated with 6-mercaptopurine. Our patient's clinical features and course

along with our review of the literature suggest that this patient was suffering from chronic hepatitis as a sole clinical feature of asthma-related allergic state or a heretofore-unnamed atypical AIH or AIH variant, which could be designated as "eosinophilic hepatitis".

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