

## Acute autoimmune hepatitis presenting with peripheral blood eosinophilia

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### ABSTRACT

Peripheral blood eosinophilia has been described in a broad variety of allergic, infectious, neoplastic and autoimmune diseases. To the best of our knowledge blood eosinophilia has never previously been reported in association with isolated autoimmune hepatitis (AIH) in the absence of other autoimmune conditions. Herein we report an interesting case of an 18 year old man who presented to our hospital with an acute autoimmune hepatitis diagnosed on the basis of clinical features, serology and histopathology. He was noted to have a moderate peripheral eosinophilia at diagnosis which resolved within days of initiation of corticosteroids for treatment of the AIH. Given the absence of other systemic conditions or drugs which may have produced the eosinophilia and its rapid resolution with treatment of the underlying liver disease, we wished to highlight this rather novel presentation of AIH.

**Key words.** Autoimmune hepatitis. Jaundice. Eosinophilia.

### CASE REPORT

An 18 year old African American man presented to our medical center with a four day history of progressive jaundice. He denied any history suggestive of viral prodrome, recent travel, sick contacts, exposure to well water, medication ingestion (including herbal or over-the-counter), exposure to recreational drugs, alcohol, tattoos, blood transfusions or high risk sexual behavior. There was no abdominal pain, pruritus, alteration in bowel habit, weight loss, gastrointestinal bleeding or mental confusion.<sup>1</sup> Pertinent family history included a mother with Hashimoto's thyroiditis and a father with type 2 diabetes mellitus. Physical examination revealed icteric sclera with no hepatosplenomegaly nor stigmata of chronic liver disease. There was no clinical ascites nor asterixis.

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Initial laboratory data revealed a hepatocellular liver injury pattern:

- Total bilirubin 8.8 mg/dL (normal 0.3-1.5).
- Conjugated bilirubin 5.2 mg/dL (normal 0-0.3).
- Alanine aminotransferase (ALT) 1,194 IU/ L (normal < 40).
- Aspartate aminotransferase (AST) 955 IU/ L (normal < 40).
- Alkaline phosphatase 121 IU/L (normal 40-125).
- Gamma glutamyl transferase (GGT) 150 IU/L (normal 7-51).
- Albumin 4.1 g/dL (normal 3.7-5.1), and
- INR 1.2.

Abdominal ultrasound examination exhibited a normal appearing liver with no intra- or extrahepatic biliary ductal dilation.

Interestingly, his complete blood count (CBC) revealed an absolute white blood cell count of  $8.5 \times 10^9/L$  (normal 3.8-10.6) with the differential count indicating a 39% eosinophilia (normal 0-6%) and an absolute eosinophil count of  $3.3 \times 10^9/L$  (normal 0-0.4).

Serologic work-up revealed negative drug and toxicology screens, negative testing for acute viral hepatitis [including hepatitis A, B, C, Epstein-Barr

virus, cytomegalovirus (CMV) and herpes simplex virus (HSV)]. A normal ceruloplasmin of 56.4 mg/dL excluded acute Wilson's disease. Immunological testing yielded a positive antinuclear antibody (ANA) test to a titer 1:640 (homogenous pattern), a strongly positive anti-smooth muscle antibody (SMA) test of 170 EU (normal < 20) and a markedly elevated quantitative serum IgG 2,760 mg/dL (normal 751-1,560).

We thus had a strong suspicion for AIH and a percutaneous liver biopsy revealed moderate to severely active hepatitis with hepatocyte dropout, central venulitis (Figure 1), a modified hepatitis activity index (MHAi) grading of 10/18 and a fibrosis stage of 1/6. The liver architecture was distorted by regenerative lobular changes with rosetting of hepatocytes. There was marked lymphoplasmacytic interface hepatitis with the inflammatory infiltrate including eosinophils. Hepatocanalicular cholestasis was seen. The interlobular bile ducts appeared intact and no florid duct lesions were appreciated. There was a notable absence of portal or periportal granulomas, ground glass cells, viral inclusions, Mallory's hyaline or other pigment depositions. The trichrome stain showed central venular and marked perisinusoidal fibrosis. PAS/D, iron and copper stains were negative. Immunohistochemical stains for CMV, HSV1 and 2, hepatitis B surface and core antigens were all negative.

Based on the above clinical, serologic and histopathologic parameters, our patient met criteria for 'definite AIH' as defined by the revised diagnostic scoring system for AIH in adults.<sup>2</sup> He was initiated on an immunosuppressive regimen with prednisone at 40 mg/day initially. The dose was gradually titra-

ted and azathioprine added after a few weeks. His jaundice and eosinophilia resolved within 2 weeks of starting corticosteroids and he is completely asymptomatic. The trend of his liver enzymes and CBC (with differential) are seen in table 1. The patient is currently taking low dose prednisone and azathioprine 75 mg/day.

## DISCUSSION

The classic histologic picture of autoimmune hepatitis (AIH) includes the *sine qua non* "interface hepatitis",<sup>3</sup> lymphoplasmacytic portal tract inflammation, apoptotic hepatocytes, ballooning degeneration and hepatic rosette formation. AIH is a clinicopathologic diagnosis as no one particular histologic feature is pathognomonic.

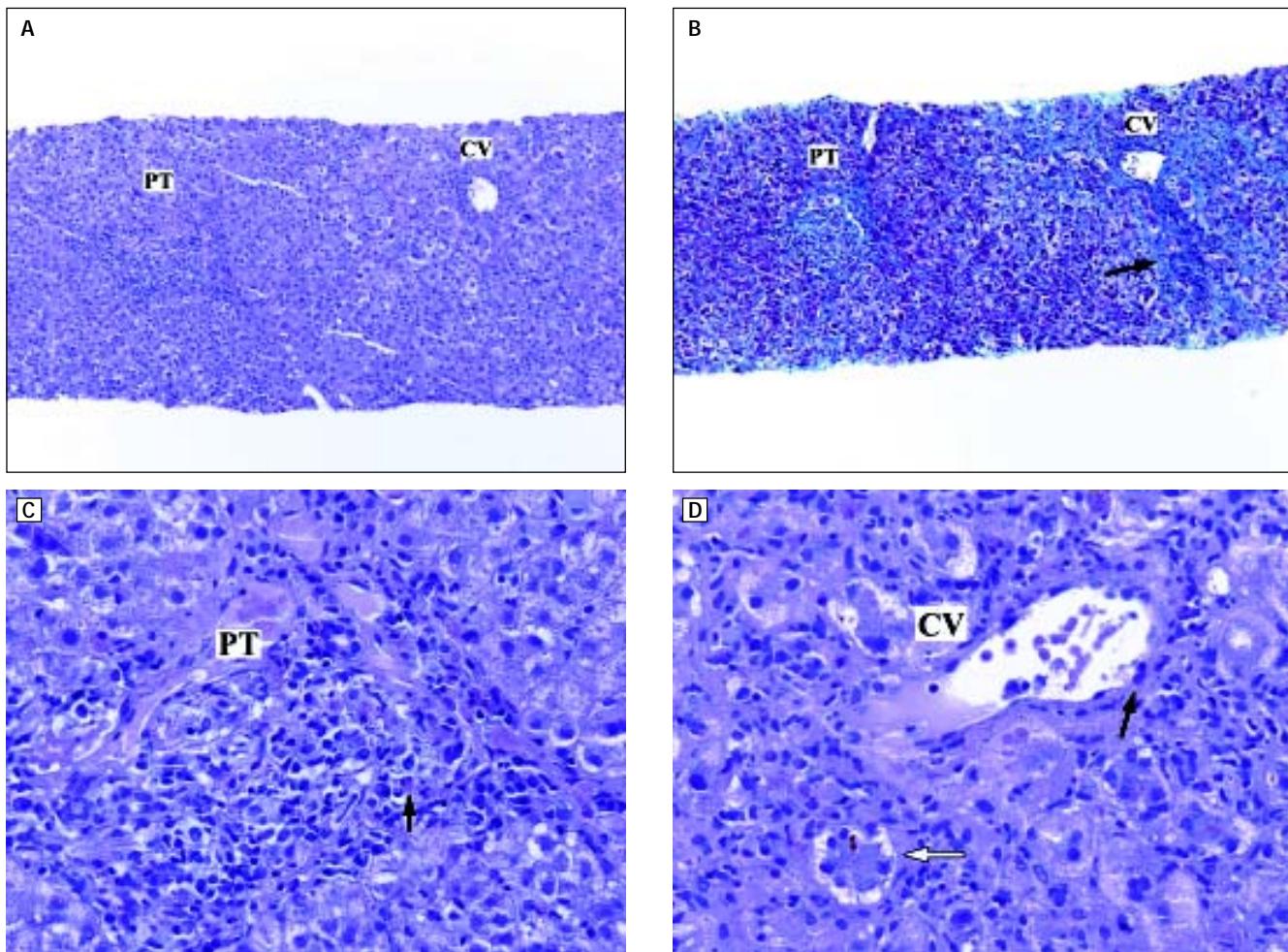
Our patient's biopsy showed active disease with much hepatocellular damage and regeneration (Figure 1A). Lymphocytic, often lymphoplasmacytic, infiltrates usually extend from portal tracts into acinar tissue where they are associated with hepatocyte injury. Acinar inflammation may be limited to the periportal regions (interface hepatitis) or involve the entire acinus (panacinar or lobular hepatitis).<sup>4</sup> Trichrome stain revealed prominent zone 3 perisinusoidal fibrosis and centrovenular fibrosis (Figure 1B). These features suggest a component of chronicity as repeated episodes of hepatic injury and repair lead to fibrosis. The conjunction of plasma cells in the portal tract with a brisk interface hepatitis (Figure 1C) strongly supports a diagnosis of AIH. The finding of inflammatory cells surrounding the central vein with undermining of the endothelium or "centrovenulitis" is also characteristic (Figure 1D).

**Table 1.** Laboratory trend pre/post steroid treatment.

Day	Day 1	Day 3	Day 10	Day 16	Day 45
Total Bili 0.3-1.5 mg/dL	8.8	9.2	3	2.2	1.1
AST < 40 IU/L	955	876	240	124	37
ALT < 40 IU/L	1194	883	544	357	83
ALP 40-125 IU/L	121	106	118	84	83
GGT < 65 IU/L	150	131	185	206	
WBC 4-11x10 <sup>9</sup> /L	8.5	6.8	-	13.6	3.7
% Eos 0-6%	39%	37%	-	1.70%	3.10%
Abs Eos 0-0.4x10 <sup>9</sup> /L	3.3	2.6	-	0.2	0.1

↑ Immunosuppressive treatment initiated

Each parameter is listed with its normal range below. Total Bili: total bilirubin. AST: aspartate aminotransferase. ALT: alanine aminotransferase. ALP: alkaline phosphatase. GGT: gamma glutamyltransferase. WBC: white blood cell. % Eos: percentage eosinophilia. Abs Eos: absolute eosinophil count.



**Figure 1.** Histology slide(s): **A.** Histologic examination revealed features of an AIH with lymphoplasmacytic portal tract (PT) inflammatory infiltrate with interface hepatitis, marked lobular activity with rosetting and ballooning of hepatocytes. CV is the central vein (H&E stain, 10x). **B.** The central vein (CV) is accentuated with fibrosis. Marked perisinusoidal fibrosis is particularly prominent in the zone 3 region (black arrow). PT is the portal tract (trichrome stain, 10x). **C.** Portal tract (PT) showing scattered eosinophils (black arrow) with lymphoplasmacytic infiltrate. An active interface hepatitis is present with plasma cells extending from the PT into the hepatic parenchyma (H&E stain, 40x). **D.** Central vein (CV)/Zone 3 region: The histologic findings of hepatic rosette formation (white arrow) is a strong indicator of AIH. Other histologic manifestations of AIH include perivenular inflammation (black arrow), ballooned and syncytial giant hepatocytes. Scattered eosinophils were also present (H&E stain, 40x).

The hepatic lobule was markedly regenerative with hepatocyte rosettes, in which hepatocytes form a ring around the bile canalculus (Figure 1D). Rosettes of hepatocytes are common in the periportal region<sup>5</sup> and this finding in conjunction with portal plasma cell infiltration enhances the diagnostic score that has been promulgated by the International Autoimmune Hepatitis Group.<sup>2</sup> In addition to these findings, scattered eosinophils were present. In a recent study describing the use of liver biopsy evaluation in the discrimination of idiopathic autoimmune hepatitis (AIH) versus drug-induced liver injury

(DILI), Suzuki, *et al.* found that portal tract eosinophils were found 60.7% of the time and intra-acinar eosinophils 32.1% of the time in AIH cases, both more frequent than in cases of DILI.<sup>6</sup> Thus the finding of hepatic eosinophils (although not the predominant inflammatory cell type) further supports a diagnosis of AIH in our case. Moreover, no offending pharmaceutical agents could be identified either.

Acquired blood eosinophilia is considered either a primary or a secondary phenomenon.<sup>7</sup> Causes of secondary (reactive) eosinophilia include tissue-invasive

**Table 2.** Reported cases of AIH associated with peripheral blood eosinophilia.

	Case 1	Case 2	Case 3	Case 4
Age/14	41	16	18	
Sex	Male	Female	Male	Male
Peak transaminase (IU/L)	ALT 1,560 AST 700	ALT: NR AST 200	ALT: 320 AST 200	ALT: 1,194 AST: 955
Peak eosinophil count ( $\times 10^9/L$ )	7.437	2.64	63.2	3.3
IgG level (mg/dL)	2,300	2,600	NR	2,760
AIH-related antibodies	SMA (+) ANA (+) 1:160	SMA (++) ANA: NR	SMA (+) 1:800 ANA: NR	SMA (++) 1: 170 ANA (+): 1: 640
Liver histology: specific inflammatory infiltrate	Lymphs	Plasma cells, lymphs, eos	Lobular hepatitis inflammatory cell: NR	Interface hepatitis with lymphs, plasma cells, and some eos
Autoimmune disease associations	Coombs' (+) HA	UC, AI thyroid disease	UC, HES	None
Reference (year of publication)	22 (1973)	20 (1977)	21 (2007)	Current report (2012)

AIH: autoimmune hepatitis. NR: not reported. AST: aspartate aminotransferase. ALT: alanine aminotransferase. IgG: immunoglobulin G. SMA: anti-smooth muscle antibody. ANA: anti-nuclear antibody. AI: autoimmune. Lymphs: lymphocytes. Eos: eosinophils. HA: hemolytic anemia. UC: ulcerative colitis. HES: hypereosinophilic syndrome.

parasitosis, medications, allergic or inflammatory conditions and malignancies in which eosinophilia is not considered part of the neoplastic process. Primary eosinophilia, on the other hand, is classified into the subcategories 'clonal' and 'idiopathic'. Clonal eosinophilia usually occurs in the context of hematologic malignancies where there is cytogenetic or bone marrow histologic evidence of a clonal expansion of these cells of the leukocyte lineage. Idiopathic eosinophilia is a diagnosis of exclusion where a thorough evaluation for primary or secondary causes is unrevealing. Although, on presentation, our patient did not have a leukocytosis (absolute white cell count was  $8.5 \times 10^9/L$ ), he did have a moderate peripheral blood eosinophilia of 39% (absolute count of  $3.3 \times 10^9/L$ ).

Tissue eosinophilia has been described with a number of gastrointestinal and hepatobiliary disorders. Gastrointestinal disorders include eosinophilic gastroenteritis,<sup>8</sup> eosinophilic esophagitis, gastroesophageal reflux disease,<sup>9</sup> *Helicobacter pylori* infection,<sup>10</sup> inflammatory bowel disease,<sup>11</sup> celiac disease and collagenous colitis.<sup>12</sup> Hepatic eosinophilia has been described in association with AIH,<sup>6</sup> various medications, e.g. anti-seizure medications<sup>13</sup> and antibiotics,<sup>14</sup> helminthic parasites, hypereosinophilic syndrome,<sup>15</sup> primary biliary cirrhosis,<sup>16</sup> sclerosing cholangitis,<sup>17</sup> eosinophilic cholangitis<sup>18</sup> and eosinophilic cholecystitis.<sup>19</sup>

Peripheral blood eosinophilia is present much less frequently in these conditions and has never previ-

ously been reported as a manifestation of isolated acute autoimmune hepatitis. It has, however, been described in cases of AIH associated with other autoimmune conditions, e.g. autoimmune thyroid disease,<sup>20</sup> ulcerative colitis<sup>20,21</sup> and Coombs'-positive hemolytic anemia<sup>22</sup> (Table 2). The purpose of the present report is to make physicians aware of this association so as to consider the diagnosis in an individual presenting with markedly elevated transaminases in concert with a high eosinophil count. This hematologic characteristic, when present, may allow the treating physician to narrow the differential diagnosis before embarking on more specialized testing.

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