Acute autoimmune hepatitis presenting with peripheral blood eosinophilia

Shoket Chowdry,* Erin Rubin,** David A. Sass***

* Division of Gastroenterology, Hepatology and Nutrition, Department of Medicine, University of Pittsburgh.
** Division of Transplantation Pathology, Department of Pathology, University of Pittsburgh.
*** Division of Gastroenterology and Hepatology, Department of Medicine, Drexel University College of Medicine.

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.1 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.

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 x 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 x 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, Ebstein-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 (MHAII) 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. He was initiated on an immunosuppressive regimen with prednisone 40 mg/day initially. The dose was gradually titrated 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”, 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). 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).

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Day 1</th>
<th>Day 3</th>
<th>Day 10</th>
<th>Day 16</th>
<th>Day 45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Bili 0.3-1.5 mg/dL</td>
<td>8.8</td>
<td>9.2</td>
<td>3</td>
<td>2.2</td>
<td>1.1</td>
</tr>
<tr>
<td>AST &lt; 40 IU/L</td>
<td>955</td>
<td>876</td>
<td>240</td>
<td>124</td>
<td>37</td>
</tr>
<tr>
<td>ALT &lt; 40 IU/L</td>
<td>1194</td>
<td>883</td>
<td>544</td>
<td>357</td>
<td>83</td>
</tr>
<tr>
<td>ALP 40-125 IU/L</td>
<td>121</td>
<td>106</td>
<td>118</td>
<td>84</td>
<td>83</td>
</tr>
<tr>
<td>GGT &lt; 65 IU/L</td>
<td>150</td>
<td>131</td>
<td>185</td>
<td>206</td>
<td></td>
</tr>
<tr>
<td>WBC 4-11x10⁹/L</td>
<td>8.5</td>
<td>6.8</td>
<td>-</td>
<td>13.6</td>
<td>3.7</td>
</tr>
<tr>
<td>% Eos 0-6%</td>
<td>39%</td>
<td>37%</td>
<td>-</td>
<td>1.70%</td>
<td>3.10%</td>
</tr>
<tr>
<td>Abs Eos 0-0.4x10⁹/L</td>
<td>3.3</td>
<td>2.6</td>
<td>-</td>
<td>0.2</td>
<td>0.1</td>
</tr>
</tbody>
</table>

The hepatic lobule was markedly regenerative with hepatocyte rosettes, in which hepatocytes form a ring around the bile canaliculus (Figure 1D). Rosettes of hepatocytes are common in the periportal region and this finding in conjunction with portal plasma cell infiltration enhances the diagnostic score that has been promulgated by the International Autoimmune Hepatitis Group. 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. 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. Causes of secondary (reactive) eosinophilia include tissue-invasive
Table 2. Reported cases of AIH associated with peripheral blood eosinophilia.

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>14</td>
<td>41</td>
<td>16</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Peak transaminase (IU/L)</td>
<td>ALT: 1,560</td>
<td>ALT: NR</td>
<td>ALT: 320</td>
</tr>
<tr>
<td></td>
<td>AST: 700</td>
<td>AST 200</td>
<td>AST 200</td>
</tr>
<tr>
<td>Peak eosinophil count (x 10^9/L)</td>
<td>7.437</td>
<td>2.64</td>
<td>63.2</td>
</tr>
<tr>
<td>IgG level (mg/dL)</td>
<td>2,300</td>
<td>2,600</td>
<td>NR</td>
</tr>
<tr>
<td>AIH-related antibodies</td>
<td>SMA (+)</td>
<td>SMA (++)</td>
<td>SMA (+): 1:800</td>
</tr>
<tr>
<td>Liver histology: specific inflammatory infiltrate</td>
<td>Lymphs</td>
<td>Plasma cells, lymphs, eos</td>
<td>Lobular hepatitis inflammatory cell: NR</td>
</tr>
<tr>
<td>Autoimmune disease associations</td>
<td>Coombs’ (+) HA</td>
<td>UC, AI</td>
<td>UC, HES</td>
</tr>
</tbody>
</table>


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 x 10^9/L), he did have a moderate peripheral blood eosinophilia of 39% (absolute count of 3.3 x 10^9/L).

Tissue eosinophilia has been described with a number of gastrointestinal and hepatobiliary disorders. Gastrointestinal disorders include eosinophilic gastroenteritis,8 eosinophilic esophagitis, gastroesophageal reflux disease,9 Helicobacter pylori infection,10 inflammatory bowel disease,11 celiac disease and collagenous colitis.12 Hepatic eosinophilia has been described in association with AIH,6 various medications, e.g. anti-seizure medications13 and antibiotics,14 helminthic parasites, hypereosinophilic syndrome,15 primary biliary cirrhosis,16 sclerosing cholangitis,17 eosinophilic cholangitis18 and eosinophilic cholecystitis.19

Peripheral blood eosinophilia is present much less frequently in these conditions and has never previously 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,20 ulcerative colitis20,21 and Coombs’-positive hemolytic anemia22 (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.

REFERENCES

1. Weller PF. Approach to the patient with eosinophilia. 2011 UpToDate.