Idiopathic Granulomatous Hepatitis

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A 12-year-old male child reported with history of fever for last seven years. Hepatosplenomegaly, hepatic and bone marrow granulomas were the main features. Idiopathic Granulomatous Hepatitis (IGH), a rare syndrome amenable to immunosuppressive therapy was diagnosed.

Key words: Granulomatous Hepatitis

Idiopathic Granulomatous Hepatitis (IGH) is a rare cause of pyrexia of uncertain origin (PUO). Generally reported to affect middle aged adults, IGH is uncommon in children. We report a child with IGH who became symptomatic at the age of 5 years and was diagnosed and treated successfully with immunosuppressive drugs at 12 years of age.

Case report

This male child first presented at the age of 5 years with high grade fever and hepatosplenomegaly. Investigations for PUO were inconclusive. The child responded to an empirical course of antimalarials. During the subsequent seven years, the child was repeatedly hospitalized with recurrent episodes of high grade fever almost every year. Each febrile episode lasted for 2 to 12 weeks and was associated with massive hepatosplenomegaly. Defervescence, either spontaneous or induced by empirical therapy was associated each time with regression of liver and spleen sizes. Additional clinical features and investigations done over the period of illness are outlined in Table I. Bone marrow and liver showed presence of non-caseating granulomas with epitheloid cells. These were diffusely scattered in the bone marrow, while in the liver, they were mainly
TABLE I—Clinical and Investigative Profile of the Case.

<table>
<thead>
<tr>
<th>No of admission</th>
<th>Month/year of admission</th>
<th>Duration</th>
<th>Principal clinical findings</th>
<th>Investigations</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Feb'95</td>
<td>30 days</td>
<td>High grade fever, Hepatosplenomegaly</td>
<td>Positive Mantoux Doubtful hilar lymphadenopathy</td>
<td>ATT (EHRZ × 2 months +HR × 4 months)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Blood counts, Widal, Cultures, peripheral smear, LET</td>
<td></td>
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<td>2.</td>
<td>Oct'96</td>
<td>15 days</td>
<td>- do - Pallor additionally</td>
<td>Non-caseating granulomas in liver biopsy</td>
<td>ATT (SHRZ × 2 months +HR × 10 months)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Bone marrow aspiration, ANA Rheumatoid factor, splenic puncture, ELISA and Aldehyde tests for Kala Azar, HIV</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Jul'97</td>
<td>20 days</td>
<td>-do-</td>
<td>Nil</td>
<td>Empirical antimalarials, antibiotics</td>
</tr>
<tr>
<td>4.</td>
<td>Sep'98</td>
<td>15 days</td>
<td>-do-</td>
<td>Nil</td>
<td>Spontaneous defervescence</td>
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<tr>
<td>5.</td>
<td>Sep'99</td>
<td>90 days</td>
<td>Progressive pallor and petechiae. Generalized seizures and coma for 2 weeks following a cardiac arrest during antimalarial treatment</td>
<td>Non-caseating granulomas in bone marrow-AFB and fungus-negative Pancreaticia with reticulocytosis. CT scan abdomen-retroperitoneal lymphadenopathy.</td>
<td>FNAC axillary lymph node, CSF and bone marrow PCR for tuberculosis, DsDNA, Brucella (2ME), TORCH titers, Serum Calcium, Serum LDH, Splenic biopsy, Angiotensin Converting Enzyme (ACE).</td>
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<td></td>
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<td>CSF studies, ELISA for Tuberculosis, Immunoglobulin profile</td>
<td>Antimalarials</td>
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<td></td>
<td></td>
<td></td>
<td>Spontaneous defervescence</td>
<td>Splenectomy</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>ATT (SHRZE+Oflaoxacin × 2 months, HR + Oflaoxacin × 10 months)</td>
</tr>
<tr>
<td>6.</td>
<td>Jul'01</td>
<td>90 days</td>
<td>Abscess nose, massive hepatomegaly, dysuria, external hemorrhoids</td>
<td>pancytopenia Serum bilirubin 7 mg/dL (Direct Positive) Serum Alk Phosphatase 3290 IU/L SGPT 233 IU/L Gamma GT 556 IU/L Serum Cholesterol 475 mg/dL Liver biopsy-non-caseating granulomas Bone marrow-non-caseating granulomas</td>
<td>Platelet counts, DCT, prothrombin time, USG abdomen KUB, CT chest and abdomen, DTPA scan, viral markers for hepatitis, CD4/CD8 counts, 2D Echo, ANCA, Anti Sm antibody, Anti LKM, antibody, Colonoscopy, Barium enema.</td>
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<td>Urine culture-Candida</td>
<td>Amphotericin for urinary infection.</td>
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<td>Prednisolone (60mg/day) tapered to 10 mg/ alternate day)</td>
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</tbody>
</table>

LFT-Liver function test, ANA-Anti nuclear antibody, FNAC-Fine needle aspiration cytology, PCR-Polymerase chain reaction, DsDNA-Anti Double stranded DNA antibody, HIV-Antibody to Human immunodeficiency virus, 2ME-2 Mercapto ethanol, LDH-Lactate dehydrogenase, DCT-Direct Coomb's test, USG KUB-Ultrasound scan KUB area, ANCA-Anti neutrophil cytoplasmic antibody, LKM-Anti liver kidney, mitochondrial antibody, AFB-Acid fast bacillus, ATT-Antitubercular therapy, DTPA-Diethylamine penta acetic acid scan, CSF-Cerebrospinal fluid.
located in the periportal regions. Initially, the granulomas were attributed to tuberculosis and the child was given three courses of antitubercular therapy (including the multi-drug resistant regime) over the course of the illness. He underwent splenectomy during his fifth hospitalization due to features of hypersplenism. Splenic histology was normal.

During his last hospitalization, the child weighed 38 kg on admission. He had massive hepatomegaly and obstructive jaundice. There was no lymphadenopathy or bony tenderness. He remained febrile for a period of 90 days during which he suffered a weight loss of 12 kg, developed anemia and neutropenia. The liver and bone marrow continued to show granulomas without any evidence of pathogens or malignancy on special staining studies. Investigations to look for other causes of hepatic granulomas were negative. There was no improvement in the fever despite empirical therapy. The child was diagnosed as a case of idiopathic granulomatous hepatitis and put on prednisolone (2 mg/kg/day) and methotrexate (7.5 mg per week).

Thereafter, the child improved with regression of jaundice and hepatomegaly, waning of biochemical and hematological abnormalities and weight gain. Prednisolone was gradually tapered to a dose of 10 mg on alternate days over the next four months and methotrexate was continued. Follow up liver and bone marrow biopsies showed regression in granulomas. Steroids were discontinued successfully and low dose methotrexate was continued.

**Discussion**

Idiopathic granulomatous hepatitis is a condition characterized by recurrent fever and granulomas in the liver and other organs when other causes of hepatic granulomas have been excluded(1,2).

Hepatic granulomas are not uncommon, seen in up to 30% of routine liver biopsy specimens and can result from a number of infective and non-infective conditions. Of these, tuberculosis and sarcoidosis together account for 50 -65% of cases. 26-50% of cases remain undiagnosed despite extensive investigations(3,4). A thorough search for the common etiologies must be carried out before the diagnosis of idiopathic granulomatous hepatitis is made. However, the very existence of this condition has been disputed as extra abdominal investigation may prove sarcoidosis as the cause of febrile hepatic granulomatosis(5). Our patient was extensively evaluated and empirically treated for mycobacterial and fungal disease. Classic sarcoidosis was unlikely in the absence of significant lymphadenopathy, iritis, rash, arthropathy, pulmonary infiltrates, eosinophilia, hypercalcemia or elevated angiotensin converting enzyme levels. Other causes of hepatic granuloma were ruled out by extensive investigations.

The age of patients reported with this condition usually varies from 16 to 60 years. In their series of 88 patients, Sartin and Walker(4) found the mean age to be 54.2 years. The prominent symptom is fever, which is often relapsing in character although continuous and remittent fever patterns have also been described(1). Forty four per cent of patients first presented as PUO in one series(4). Other symptoms, all of which were present in our patient, include malaise, chills, weight loss, abdominal pain, anorexia, night sweats, nausea, jaundice, diarrhea and abdominal distension.

There are no typical biochemical, hematologic or immunologic abnormalities. Most investigations help to rule out other conditions. Common laboratory abnormalities include a raised ESR, positive C-reactive
protein, hypergammaglobulinemia, hypalbuminemia, normocytic anemia and neutrophilic leucocytosis(6). Liver function tests show raised bilirubin, alkaline phosphatase and a variable, often mild rise of aminotransferases. Hepatic histology reveals granulomas in all cases. The commonest finding is of multiple lesions consisting of typical focal nodular aggregations of lymphocytes, mononuclear cells and epitheloid cells. Caseation is absent as a rule. Most granulomas are distributed randomly throughout the hepatic parenchyma although periportal granulomas are also seen(1). Our patient had predominantly periportal granulomas. Other organs such as the kidney, lymph node, spleen, bone marrow, skin, muscle and lung may also show the presence of granulomas(1,6-8). Our search for extrahepatic granulomas yielded positive results in the bone marrow.

The natural history of the disease is long, with multiple remissions and exacerbations. Occasional episodes, particularly with renal involvement can be serious and often life threatening. Response to corticosteroids is usually dramatic(1,9,10). Our patient did not respond to prednisolone alone and required addition of methotrexate. Response to immunosuppressants such as methotrexate or cyclophosphamide in patients resistant or intolerant to steroids has been earlier reported(1,11).

In a case of prolonged PUO with organomegaly and histological evidence of granulomatous lesions, the possibility of IGH must be borne in mind, when thorough search fails to reveal an etiology. The case also suggests that IGH can rarely occur at a much younger age than commonly reported in the literature. The disease is amenable to immunosuppressive therapy and has a good prognosis.

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REFERENCES