

Idiopathic Granulomatous Hepatitis Presented as Fever of Unknown Origin

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Abstract: *Granulomatous hepatitis is a well-known cause of fever of unknown origin [1, 2, 3]. This syndrome is characterized by hepatic granulomas and nonspecific flu-like symptoms, fever, and weight loss, or by asymptomatic liver function abnormalities [4]. Most common causes include viral hepatitis, Mycobacterial infections, Q fever and histoplasmosis. Certain malignancies e.g. lymphomas and drugs/ toxins are also associated with the development of granulomatous hepatitis. Recent studies have shown that in 5-30 of cases, granulomatous hepatitis is idiopathic with no obvious secondary cause [5]. Steroids are very safe and effective for symptomatic treatment in most cases. Moreover, in some cases, like ours, long-term steroid treatment is needed [6]. We are introducing an interesting case of 45-year-old female presented with fever of unknown origin and worsening jaundice. On investigations she was found to have hepatic and bone marrow granulomas without any obvious secondary cause and diagnosed with idiopathic granulomatous hepatitis as the cause of her symptoms.*

Keywords: MCV (Mean cell corpuscular volume), ACE (Angiotensin converting enzyme), IVC (Inferior vena cava), AST (Aspartate aminotransferase), ALT, (Alanine aminotransferase), HIV (Human Immunodeficiency virus), LFT (Liver function tests), PBC (Primary biliary cirrhosis).

1. Case Report

A 45-year-old, female presented with fever of unknown origin (temperature varying from 37.5 to 38.3) and worsening abdominal pain for 2 months. Patient also complains of, mild confusion, fatigue, chronic dry cough, weight loss for two months. Past medical history is significant for bilateral lung atelectasis and macrocytic anemia. Further history exploration reveals that the patient has been done extensive work up for jaundice two years ago and found to have high bilirubin level of 5.0. Her other pertinent lab included high alkaline phosphate at that time. She had never been a smoker and denies alcohol abuse. Patient also denies use of any intravenous recreational drug and herbal medication lately.

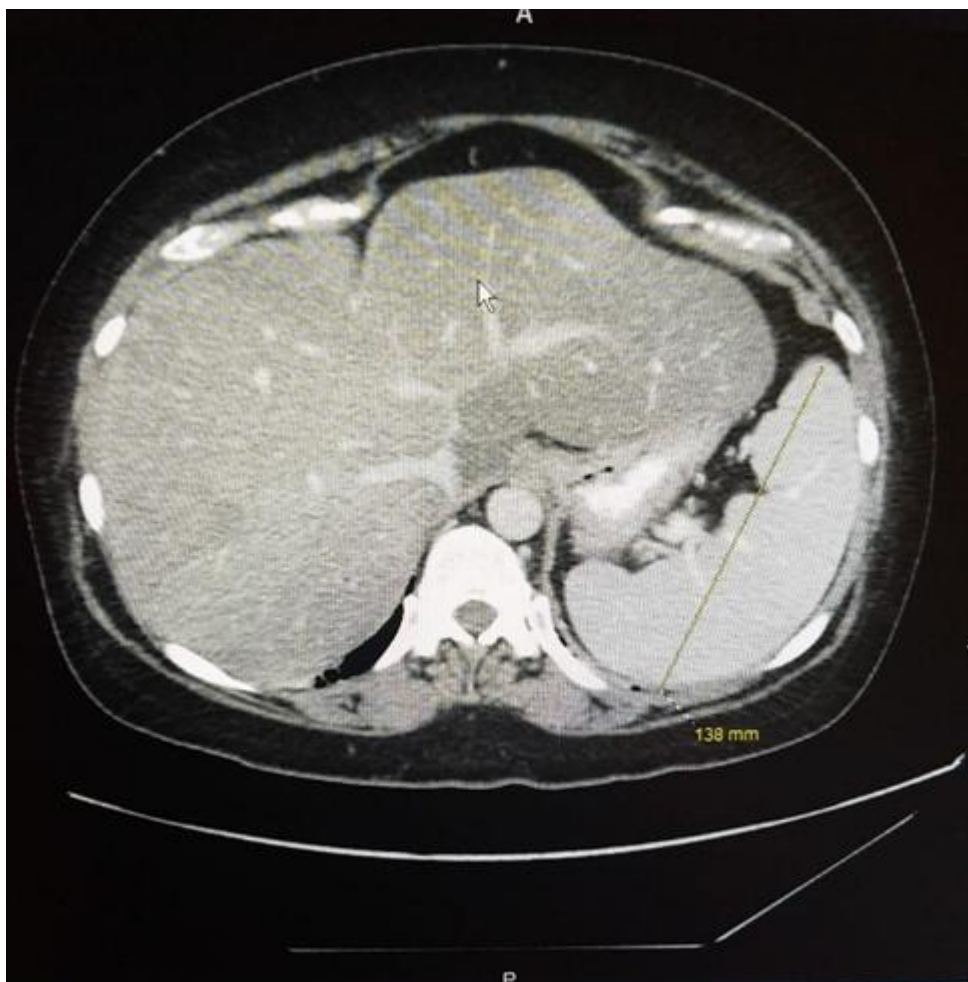
At the time of presentation, she has mild confusion and alert to time and person only. On physical examination she had non-tender hepatosplenomegaly. There are no palpable lymph nodes. Throughout the course of disease there was no rash on the body and basic laboratory blood work showed baseline Hemoglobin of 10-11, with MCV of 110 with increased RDW [red cell distribution width]. Peripheral blood smear showed macrocytic anemia with target cells and polychromasia. There is no morphological evidence of hemolysis. Serum calcium is within normal range, but she had raised ACE level of 80. Serum hepatitis panel for hep A, B, C, cytomegalovirus, abstain barr virus, herpes virus is negative. Blood test for Mycobacterium tuberculosis and sputum smear and culture is also negative. Blood culture is also negative for bacteria and fungus. Her thyroid test panel is also within normal limits. Hepatic enzymes are slightly raised, ALT 80, AST 64 and Alkaline phosphate 124. Bone

marrow biopsy is consistent with normal cell count and morphology. Chest x-ray revealed opacities in the lung basis suggestive of chronic atelectasis but negative for hilar lymphadenopathy.

Certain other investigations include ultrasound of Abdomen, which showed marked hepatosplenomegaly with the liver at 22 cm with increased echogenicity. MRI with MRC showed almost the similar picture with liver at 25 cm with diffuse steatosis. It also showed narrowing of IVC and hepatic veins. CT scan showed liver at 27 cm with effacement of hepatic veins. Liver biopsy showed METALS 3 septal fibrosis. It is also positive for findings consistent with both steatohepatitis and granulomatous hepatitis.

Patient was started on solumedrol and ursodiol 600mg BID and her Bilirubin down-trended and LFTS became stable. Repeated liver biopsy showed the same results consistent with steatohepatitis and granulomatous hepatitis. Patient found to have liver granulomas which are causing her symptoms and her MELD (Model for end-stage liver disease) score was 20. After four days of hospital treatment, the patient sent home on prednisone and asked to taper treatment in two weeks.

After two weeks of tapered prednisone treatment, she developed fever again and admitted to the hospital. This time she was treated with high dose steroids and was asked to continue it for long duration of time. She was also advised for regular follow up for any side effect of steroids. This time she was treated for 08 weeks with tapering the treatment. She reported no fever after completion of treatment.



Picture 1: CT Abdomen shows granulomas in liver and large spleen



Picture 2: CT Abdomen shows granulomas involving the surrounding structures of liver

2. Discussion

Differential diagnosis of Granulomatous hepatitis is enormously broad and includes infections, inflammation, malignancy and certain medications/toxins use. However, in many cases there is no definitive cause found and is called idiopathic Granulomatous hepatitis. Recent studies recommend the work up for granulomatous hepatitis which includes, chest radiography, serology for hepatitis B, and C, Brucella antigen, Q fever and syphilis, cultures for mycobacteria and fungi, assay for serum anti-mitochondrial

antibodies and tuberculin skin test. Idiopathic granulomatous hepatitis is the term used in cases where no discernible cause is found even after liver biopsy [7, 8, 9]. In the absence of signs and symptoms of secondary disease, it is difficult to classify the liver granulomas for etiology only on histological basis [10]. Moreover, it's difficult to find out mycobacteria and fungi on special tissue biopsy stains.

The proposed pathophysiology for fever in idiopathic granulomatous hepatitis is the release of Interleukin-1 and other inflammatory markers [11]. These markers act on

hypothalamus thermoregulatory set point and lead to fever. Fever in most cases is usually relapsing in character like in this very case, but in some cases, it can be continuous or remittent [12]. Immunopathogenesis for granuloma formation is explained by the fact that all the aforementioned pathogenic antigens act on the hepatic tissue and trigger granulomatous reaction in both liver and bone marrow [13].

Infections are well-known cause of Granulomatous hepatitis. Mycobacteria, coxiella Burnetti and Brucella are the most commonly reported bacterial pathogens [19]. Common Viral causes include, hepatitis B and C viruses, herpes simplex virus, Epstein Barr virus, cytomegalovirus and HIV [17]. Most common drugs associated with granulomatous hepatitis include Methyldopa, Quinine, hydrochlorothiazide, benzodiazepines, and in some cases Allopurinol etc. [14]. Granulomas have also been found in certain malignancies which include lymphoma etc.

Among the Inflammatory causes, sarcoidosis is ruled out in the absence of adenopathy, rash, iritis, arthropathy, pulmonary infiltrates, hypercalcemia and eosinophilia. Furthermore, serum ACE inhibitor level has no positive or negative predictive values for the diagnosis of sarcoidosis. Although in our case, serum ACE inhibitor level is slightly elevated but, without any other concrete evidence, it is not attributed to sarcoidosis. Primary biliary cirrhosis has also been reported linked to granulomatous hepatitis [18]. Although, in some cases primary biliary cirrhosis granulomas are similar to the granulomatous granulomas but PBC is primarily diagnosed by the presence of anti-mitochondrial antibodies in serum. In our case serum test for anti-mitochondrial antibodies is also negative.

Steroids are the mainstay of treatment for fever of unknown origin due granulomatous hepatitis with excellent prognosis [15, 16]. Usually, low dose steroids are used for short duration of time but in some cases long-term steroid treatment is recommended especially in those where patients remain symptomatic even after steroid treatment. According to some studies, this treatment could be as long as 33.1 weeks [16]. It is recommended that patients should also be monitored for side effects in such cases. Among other treatment options, Indomethacin has also been used in some cases for idiopathic granulomatous hepatitis [16]. Indomethacin has certain advantages over steroids as it is not immunosuppressive and has less side effects profile.

3. Conclusion

Idiopathic granulomatous hepatitis causes relapsing fever, and corticosteroids are the best treatment option. In certain cases, steroids are used for long-term especially when fever persists. However, with the long-term steroids use, one should also keep in mind the side effects of steroids especially, the essentially of metabolic syndrome.

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