

# Fever of Unknown Origin due to Liver Tuberculosis

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## ABSTRACT

*Infection, especially extra pulmonary tuberculosis, remain the leading cause of fever of unknown origin (FUO). FUO is defined as temperature higher than 38.3 °C with duration of fever of more than 3 weeks. We reported a case of liver tuberculosis, whose had fever more than 38.3 °C in 2 months. A liver biopsy and histology evaluation have performed revealing liver tuberculosis. The patient received oral anti-tuberculosis agents. But after three days of anti-tuberculosis treatment, the patient experience jaundice. The patient was diagnosed as a drug induced hepatitis. After adjusted regimen of oral anti-tuberculosis, the patient's condition improved. The patient was back home with good conditions.*

**Keywords:** fever of unknown origin – liver tuberculosis

## INTRODUCTION

Fever of unknown origin is a condition where a patient suffers from continuous fever for 3 weeks with a temperature of over 38.3°C with an uncertain cause even after one week of intensive laboratory and other medical investigation.<sup>1,2,3</sup>

Other terms used for this condition include *febris et causa ignota*, fever of obscure origin, fever of undetermined origin, unexplained fever, prolonged fever, pyrexia of unknown origin, and fever of unknown origin (FUO). The cause of FUO according to the type of illness is classified into the following six groups:<sup>1,2</sup>

### 1. Infection (45-55%)

Important infectious causes of FUO include tuberculosis, sepsis, systemic bacterial infections (such as salmonellosis and brucellosis), Bacterial endocarditis, mononucleosis, toxoplasmosis and fungal disease.

### 2. Neoplasm (12-20%)

Important neoplastic causes of FUO include Hodgkin's and non-Hodgkin's diseases, Leukemia,

histiocytosis (particularly in children), Renal cell carcinoma and Hepatoma.

### 3. Collagen disease (10-15%)

FUO may be caused by Sarcoidosis, Polyarthritis nodosa, Wegener's granulomatosis, Juvenile Rheumatoid Arthritis and dermatomyocitis.

### 4. Hypersensitivity disorder

FUO due to hypersensitivity is chiefly a reaction to drugs such as sulphonamide, penicillin, rifampicin, isoniazid, phenytoin, or methyldopa.

### 5. Metabolic disorder

Important metabolic causes of FUO are porphyria metabolic disorder, polyserocytis (Familial Mediterranean Fever) and Type V hypertriglyceridemia.

### 6. Factitious Fever

Examinations such as blood test, microbiological culture from body fluids/surface lesions, seroimmunological testing, or routine x-ray could be used prior to resorting to available advanced examination modalities such as the ultrasound, endoscopy, or CT-scan/MRI.<sup>4</sup>

At the next phase, consider making a closer diagnosis through biopsy of suspected sites. Examinations such as angiography, aortography, or lymphangiography could also be performed.

Serological testing is actually very beneficial for patients with FUO.<sup>1</sup> Two blood specimens are usually required for the test. Efforts should be made to ensure the availability of the two specimens to facilitate the interpretation of the serological titer results. A titer increase of four times or more has a very significant meaning to determine the possible cause of disease. It is important to master the art of interpretation, since results may not be as apparent.

Isolation of the microorganism causing the disease is the chief diagnostic criteria in patients suspected of infectious fever. A common examination is blood, urine, and stool culture as well as viral isolation.<sup>1</sup>

With the wider spectrum of viral disease and the influence of urbanization, globalization as well as inadequate environment, there is a greater possibility of patients suffering from viral infection. At this moment, there needs to be guidelines to differentiate a patient with viral or bacterial disease, which entail a totally different treatment approach. An examination that could be performed at the initial phase is hematological evaluation, where acute bacterial infection would produce a shift to the left, with or without leukocytosis.

If such condition is not found and we still need to differentiate viral and bacterial infection, C-reactive protein (CRP) may be examined. CRP may increase over tenfolds in acute bacterial infection.<sup>1,4</sup>

X-ray photo is a vital medical examination modality, particularly for diagnosing renal and pulmonary disorders. The bone marrow and joints are also ideal sites for x-ray evaluation.<sup>1,4</sup>

Biopsy plays a great role in determining the cause of FUO, and could be performed where modern medical support facilities are unavailable. It is important for the diagnosis of diseases such as lymphoma, malignant metastasis, tuberculosis, or fungal infection, particularly in enlarged glands.<sup>1,4</sup>

Considering the fact that the ultrasound is very easy to use, the association between a disorder in the field of internal medicine, it use has increased and is more widespread, particularly for evaluation of the heart or abdomen. This examination method is especially useful for conditions such as atrial myxoma or vegetations on the heart valves.

Abdominal ultrasound can detect disorders in the liver, kidneys, retroperitoneal space, and pelvis. Bear in mind

that false positives may be obtained, and ultrasound should always be considered a supportive examination, taking into consideration the totality of the disease.<sup>1,4</sup>

In the future, CT-scan is expected to greatly facilitate diagnosis, by demonstrating body abnormalities through horizontal sections of body organ anatomy. It is the ideal examination modality to evaluate retroperitoneal abnormalities.<sup>1</sup>

Efforts to treat undiagnosed fever with adjuvant therapy, and is only justified when all methods to achieve diagnostic certainty has been attempted.<sup>1,5</sup> The principle is that drugs should be used with the proper indication according to local knowledge and should be specific in nature.

## CASE REPORT

Mrs. R, 42 years, was admitted to Cipto Mangunkusumo General Hospital with a chief complaint of fever since 2 months prior to admission. The fever was fluctuating, and was sometimes accompanied by chills in the mornings or afternoons. There was no cough or running nose. The fever responded to medication but would reemerge after the medication wears out. The patient had a loss of appetite.

Six weeks prior to admission at Cipto Mangunkusumo General Hospital, the patient had been admitted to another hospital for 6 weeks. During 1 week of hospitalization, the patient's fever dropped and then rose, never to fall again. At other hospital, the patient had undergone a series of examination, with results as follows: normal chest x-ray; ultrasound revealing a normal liver and bile duct, a slightly enlarged spleen, and no enlargement of paraaortic lymph nodes. The patient had also undergone blood testing for malaria and widal, both turning out negative. C3, C4, and DsDNA testing also came out normal.

There was no problem urinating or with bowel movements. Because the patient felt no improvement, she came to Cipto Mangunkusumo General National Hospital.

Prior history revealed no history of jaundice, heart disease or epigastric pain.

From physical examination at admission we found the following: the patient was moderately ill, fully conscious, with a blood pressure of 110/70 mmHg, pulse rate of 110 x/minute, body temperature of 38°C, and respiratory rate of 28 x/minute. Her conjunctiva were pale, her sclera not jaundiced. Her jugular venous pressure was 5 – 2 cm H<sub>2</sub>O. Heart evaluation revealed normal first and second heart sounds without murmur or

gallop. Lung examination demonstrated a vesicular breath sound without rales or wheezing.

Abdominal evaluation results were as follows: the abdomen was flat, not distended, without tenderness. The heart and spleen were not palpable. The extremities were warm and not edematous.

The results of laboratory examination during admission were as follows: Hemoglobin level 5.5 g%, white blood cell count 3800/ml, platelet count 150,000/ml, ureum level 13 mg/dl, creatinine level 0.9 mg/dl, sodium level 130 meq/l, potassium level 3.6 meq/l, SGOT = 39 U/l, SGPT = 35 U/l. HIV testing was negative and there was no signs of fungus in the patient's blood.

On the seventh day, bone marrow puncture was performed, revealing histoplasma. The diagnosis was thus histoplasmosis. The patient was immediately scheduled to take Amphotericin B according to hospital protocol, which is as follows:

- Day 1, administration of a test dose of 5 mg of Amphotericin B
- Day 2, administration of 10 mg of Amphotericin B
- Day 3, administration of 15 mg of Amphotericin B
- Day 4, administration of 20 mg of Amphotericin B
- Day 5, administration of 25 mg of Amphotericin B
- And so on.

Note that Amphotericin B was added to 500 cc of 5% Dextrose to be administered within 6 hours, and that 1 vial of Dexamethasone and 1 tablet of Paracetamol was administered prior to that.

After the seventh day of Amphotericin B administration, the patient was still feverish with a body temperature of 38-41°C. Amphotericin B was still administered, suspecting that the patient suffered from histoplasmosis that had not responded to treatment.

On the 12<sup>th</sup> day of treatment with Amphotericin B, the patient and family refused to continue treatment, signing a refusal letter. Since the patient needed treatment, she was given 2 x 200 mg of Itraconazole (Sporanox).

On the 37<sup>th</sup> day, the patient underwent a repeat abdominal ultrasound as a preparation for biopsy, since hepatosplenomegaly was found during physical examination. Ultrasound revealed hepatosplenomegaly and enlarged paraaortic and hepatic parahilar lymph nodes. The patient immediately underwent liver biopsy.

There was a suspicion that the prolonged fever in this patient might be due to tuberculosis. A Mantoux test was thus performed for screening, and a repeat chest x-ray taken. The Mantoux test revealed negative findings, while the chest x-ray was normal.

On the 42<sup>nd</sup> day of hospitalization, the liver biopsy pathology evaluation revealed liver tuberculosis with caseation.

On the 43<sup>rd</sup> day of treatment, the patient received the following oral anti-tuberculosis drugs: rifampisin 1 x 450 mg, INH 1 x 300 mg, Pirazinamid 3 x 500 mg, Etambutol 2 x 250 mg dan Vit B6 3 x 10 mg. Her fever fell to 37.5°C.

On the 45<sup>th</sup> day of hospitalization, which was the third day of anti-tuberculosis treatment, the patient's sclera became jaundiced. The patient's SGOT and SGPT were then examined, turning out to be 182 U/l and 157 U/l respectively.

Oral anti-tuberculosis was continued, with the following regimen:

• Ethambutol	2 x 250 mg
• Streptomycin	1 x 750 mg
• Ofloxacin	1 x 400 mg

The patient was scheduled for a rifampycin trial, but the test was not performed due to financial constraints.

Repeat ultrasound examination did not find signs of obstruction.

On the 45<sup>th</sup> day, the subdivision of Hepatology agreed to continue oral anti-tuberculosis agents with SGOT, SGPT, and bilirubin monitoring twice weekly. If the patient's condition improves, the previous drugs may be reused with the smallest most effective dose.

On the 65<sup>th</sup> day of treatment, the patient was released free of fever and in a better condition. Treatment with Isoniazid was reestablished gradually, starting with a dose of 1 x 100 mg for 3 days then increased to 2 x 100 mg, while all other treatments continued as usual.

Rifampycin was no longer administered to this patient.

## DISCUSSION

At the time of admission into Cipto Mangunkusumo General Hospital, the patient was diagnosed with prolonged fever, since she has had a fever since 2 months prior to admission and had undergone various examinations with normal result. This is in accordance with the definition stated in various literature.<sup>1,2,3</sup>

Various causes of fever has been eliminated from laboratory examinations, such as negative Widal test results, negative malaria test results, negative HIV test results, a normal chest x-ray, and a generally normal ultrasound finding.

Since the examinations had not provided optimal results, a bone marrow puncture was performed, firstly suggesting chronic granulomatous leukemia. Since there

was no leukocytosis in the patient's peripheral blood and histoplasm was found, the diagnosis was histoplasmosis. The patient immediately received treatment for histoplasmosis with Amphoterycin B, which was in accordance with literature stating Amphoterycin B as the drug of choice for histoplasmosis.<sup>6,7</sup>

After administration of Amphoterycin B for 12 days according to protocol, the patient remained feverish. Due to the lack of improvement, a repeat chest x-ray and a Mantoux test were performed to find possible cryptic tuberculosis. The chest x-ray turned out normal, and the Mantoux test negative.

The patient then underwent a repeat abdominal ultrasound, revealing hepatosplenomegaly and enlarged paraaortic lymph nodes. A liver biopsy and histopathology evaluation were then performed, revealing liver tuberculosis. The patient immediately received the following oral anti-tuberculosis agents:

- Rifampycin 1 x 450 mg,
- Isoniazid 1 x 300 mg,
- Pyrazinamid 3 x 500 mg,
- Ethambutol 2 x 250 mg, and
- Vitamin B6 3 x 10 mg.

After three days of anti-tuberculosis treatment, the patient's eyes became jaundiced, and liver function testing revealed an SGOT of 182 U/l and SGPT of 157 U/l. The patient was thus suspected to have suffered drug-induced hepatitis.

Oral anti-tuberculosis agents were still administered with an adjusted dose, where rifampycin was replaced with streptomycin. The following regimen was thus administered: 1 x 750 mg of Streptomycin, 2 x 250 mg of Ethambutol, 1 x 400 mg of Ofloxacyne. Isoniazid was temporarily terminated. This was in accordance with literature, stating that oral anti-tuberculosis agents are the choice treatment for hepatic tuberculosis.<sup>8,9</sup> Literature also states that rifampycin could disturb liver function.<sup>10</sup>

With an adjusted regimen of oral anti-tuberculosis, the patient's condition improved, the fever subsided, and the patient's eyes were no longer jaundiced.

From abdominal ultrasound on the 13<sup>th</sup> of September 2001 at Cipto Mangunkusumo Hospital, it was concluded that the patient suffered from hepatosplenomegaly and enlarged paraaortic and parahilar hepatic lymph nodes.

The results of histopathology evaluation of the patient's liver biopsy were as follows: numerous granulomatous lesions were found, a large one demonstrating caseous necrosis, epitheloid cells, and 1-2 Langhan datia cells. The findings were found to be in accordance with liver tuberculosis with casseation.

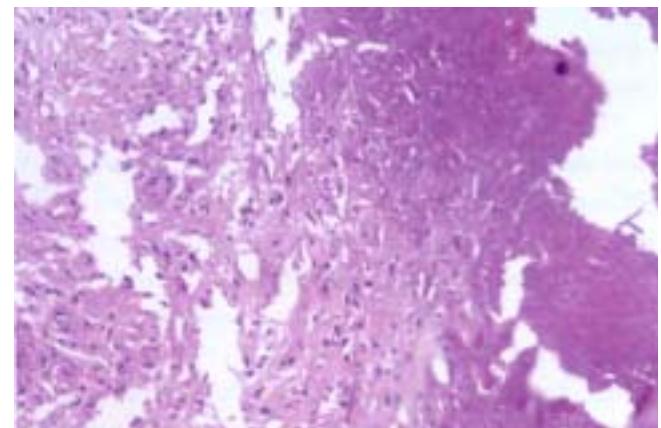


Figure 1. Histology Evaluation from Liver Biopsy Show Numerous Granulomatous Lesions, Epitheloid Cells and Langhan Datia Cells.

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