

A Young Man with Pyrexia of Unknown Origin A Case of Hepatic Granuloma

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HISTORY

A twenty-two years old machine operator was admitted to Shaikh Zayed Hospital Lahore on 27-12-1986 with history of

Fever	40 days
Vomiting	40 days
Headache	3 days

This young man started having continuous fever of moderate intensity with a feeling of chills forty days ago. It was accompanied by vomiting. He had vomiting after each meal, usual frequency was 5-6 times daily. There was no sore throat, dysuria, joint pain, headache, cough or expectoration. He started treatment of general practitioner and continued for one month but there was no improvement, instead the intensity of fever had gradually increased. He started having intractable vomiting and on two occasions had blood stained vomiting. Three days prior to admission he started having continuous headache of moderate intensity. The headache was generalized and did not increase by coughing or straining. During the illness he had lost 4-5 kg. of wt. and complained of weakness.

History of past illness, family history and personal history were not significant.

Family history	Not contributory
Personal history	Not contributory

GENERAL PHYSICAL EXAMINATION

A young man of average frame, looking ill, distressed and withdrawn.

Temp:	102.2°F
Pulse:	120 per minute
BP:	120/70 m.m. Hg

He was dehydrated. There was no jaundice, oedema, lymphadenopathy, clubbing or rash.

SYSTEMIC EXAMINATION:

Abdomen soft, non-tender, liver, spleen, kidneys not enlarged. No shifting dullness.

Nervous System, Higher mental functions, cranial nerves intact, No sensory or motor deficit, reflexes were normal. No neck rigidity or kerning's sign.

Fundoscopy examination was normal

Respiratory system was normal

Cardiovascular system was normal.

In view of above history and physical examination following possibilities were considered

1. Tuberculosis
2. Atypical presentation of enteric fever
3. Malaria
4. Meningitis
5. Encephalitis
6. Systemic infection
7. Abscess

Following investigations were requested

CBC on 28.12.86, W.B.C. 56,000/cmm, Hb 13 G/dl, Hct 39% Poly 64%, Lymphocytes 30% Monocytes 02%, Eosinophils 4%, Platelet count 150,000. ESR 50.

Urinalysis was normal. X-ray chest was normal. Ultrasound abdomen was normal.

Liver function tests showed bilirubin was 0.4 mg/dl, SGOT 30 i.v. (5-40), SPT 38 i.v. (6-45), protein 8.9 gm (6-8.0 gm) albumin 4.4 gm, alkaline phosphatase 460 i.v. Blood culture, no growth after 03 days Widal test non-significant titers, blood for malaria parasite negative. BUN 12 mg/dl, serum creatinine 0.6 mg/dl, blood glucose 85 mg/dl.

Blood CBC was repeated on 30-12-86 & 31-12-86 was normal. C.S.F. on 30-12-86 showed 1.5 ml in volume, clear in appearance. Glucose was 87 mg/dl, Protein was 26 mg/dl, Chloride was 100 mg/dl, cells, W.B.C. were 32 /cu mm, poly 2%, lympho 89%, R.B.C. 16/cu mm. No organisms seen. Montoux was + ve, Gastric washing for AFB was negative.

C.T. Scan of abdomen was normal.

Blood Culture repeated twice - No Growth.

LIVER BIOPSY

Section reveals a fragment of liver with partial loss of lobular architecture by numerous granulomas, composed of epithelioid cells and lymphocytes. Numerous Langhans type of giant cells are also seen.

Conclusion: Chronic granulomatous inflammation, compatible with tuberculosis.

Fever of unknown Origin

I. INFECTIONS

A. Granulomatous

1. Tuberculosis
2. Coccidioidomycosis
3. Histoplasmosis
4. Sarcoidosis
5. Nocardiosis

B. Pyogenic Infections

- 1: Right Upper Quadrant Infections
 - a. Cholangitis
 - b. Cholecystitis
 - c. Liver abscess
 - d. Subphrenic abscess
 - e. Subhepatic abscess
 - f. Diverticulitis
 - g. Appendicitis

2. Pelvic Inflammatory disease
3. Renal infections
 - a. Pyelonephritis
 - b. Perinephric abscess
 - c. Intrarenal abscess
 - d. Ureteral obstruction with infection

C. Subacute bacterial endocarditis

D. Other bacteremias

1. Meningococemia
2. Vibriosis
3. Listeriosis
4. Brucellosis

E. Miscellaneous

1. Malaria
2. Infectious mononucleosis.
3. Cytomegalovirus disease.
4. Coxsackie B disease.
5. Amoebiasis.
6. Leptospirosis.
7. Q. fever.

II NEOPLASTIC DISEASE

A. Tumors of reticuloendothelial system

1. Leukemia
2. Lymphoma, Hodgkin's disease
3. Multiple myeloma

B. Metastatic tumors

1. From Gastrointestinal tract
2. From lungs, kidney, bone
3. Melanoma

C. Solid localized tumors

1. Kidney
2. Liver
3. Lung
4. Pancreas
5. Atrial Myxoma

III Connective tissue diseases

Rheumatic fever
S.L.E.
Rheumatoid arthritis
Giant cell arteritis

Rare causes

- Scleroderma
Dermatomyositis
Polyarteritis
- IV Unclassified**
- Drug fever
Multiple pulmonary emboli
Thyroiditis
Hemolytic anemia
Regional enteritis
Granulomatous hepatitis
- V Psychogenic fevers**
- a. Habitual hyperthermia
b. Factitious fever
- VI Undiagnosed etiology**
- Detailed work up of a patient with F.U.O.**
- A. Routine Laboratory**
- Blood CBC, ESR, urine culture, stools for ova cysts, occult blood, stool culture. Blood cultures, malarial parasite film.
- B. Serologic studies**
- A.S.O. titer, R A factor, FANA⁺ Monotest, heterophil agglutination, Epstein Barr virus titer, Cytomegalovirus titer.
- C. Blood chemistry**
- Sugar, urea, creatinine, calcium, alkaline phosphatase, acid phosphatase, thyroid functions.
- D. Serum protein electrophoresis**
- E. Skin tests**
- Tuberculin, histoplasmin, coccidioidin.
- F. Radiographic procedures**
- X-ray chest, I.V.P., barium enema upper G.I. series and small bowel study, bone films for multiple myeloma, C.T. Scan (for suspected intraabdominal or retroperitoneal disease).

G. Ultrasound**H. Radioisotope studies**

Bone scan, liver scan.

I. Tissue examination

Lymph node or other accessible tumour biopsy, liver biopsy, temporal artery biopsy for giant cell arteritis.

J. Angiography

Lymphangiography for evaluation of lymphoma, angio-cardiography for bacterial vegetations, pulmonary angiography for infarction of lung.

K. Miscellaneous tests

Bone marrow biopsy culture, gastric aspirate for AFB smear.

L Surgical procedures

Peritoneoscopy for evaluation of lymphoma, or tuberculosis, exploratory laparotomy, bronchoscopy.

M Therapeutic trials.**DR. KHURRAM HANIF**

We had this male with 40 days H/O fever and vomiting, he was appropriately labelled as case of P.U.O. In any case of P.U.O. we do repeated history and physical examination, relevant investigation. Out of the extensive list of lab investigation, we elected to do liver biopsy and we found hepatic granulomas. The granuloma can be non specific finding in the liver. It is a compact lesion found in the liver which is well circumscribed from the adjacent normal tissue, it consists primarily of mononuclear inflammatory cells which are phagocytic in nature and called macrophages. When granulomas mature, mononuclear cells change into epitheloid cells. You can see these findings in the transparency made from the tissue of our patient. You can also see Langhan type of giant cells in our preparation. Pathophysiological significance of granuloma is that which shows that the liver is locked in a battle against invading micro-organisms, foreign body or immune complex or parasite. It tells us that liver is trying to contain the infection. It does not have much influence on the hepatic functions, as was the case in this patient. However, in certain cases e.g. in primary biliary cirrhosis, there may be enough

granulomas to cause portal hypertension. The causes of granulomas provide us clue to systemic illness. The causes of granulomas are numerous but among the top two causes are tuberculosis and sarcoidosis. More than 75 % of cases belong to these two categories.

In 10-15 % of cases no cause can be found L.F.T may be normal or there may be marginal elevation of alkaline phosphatase or enzymes. Bilirubin stays in normal range most of the time. In context to today's patient we thought it was tuberculosis.

This patient has no pulmonary symptoms and we feel that his hepatic findings are part of miliary spread, signs and symptoms can be non-specific as in this case. Involvement of bone marrow can present as anemia, neutropenia, polycythemia or even a leukemoid reaction. Tuberculous granulomas are usually located in portal areas as you have seen in the slides.

DR. IQBAL (Dental Surgeon)

I want to stress only one point that chronic gingivitis is also an important cause of P.U.O. and we have a case on record in this hospital as well.

DR. AZIZ (Pathologist)

I want to highlight that granuloma is not a non specific finding as pointed out by Dr. Khurram Hanif but it is many times a specific finding and points towards a disease or group of diseases.

DR. PERVIAZ (A/E Department)

No comment has been made regarding treatment of patient.

DR. KHURRAM HANIF (Gastroenterologist)

We were coming to that in a moment. Anyhow patient has responded to anti-tuberculous treatment and he

became afebrile after two week therapy. The temperature started receding after a week. He is afebrile now.

DR. JAVAID WAHID (Histopathologist)

We received the biopsy specimen of a needle biopsy and slides were prepared after relevant staining. You can see the changes in the micrographs. We found a lot of macrophages, hepatic necrosis and Langhan type of giant cells. We could not find A.F.B. In differential diagnosis sarcoid granulomas are very important. They are discrete and contain foreign body type of giant cells and contain asteroid bodies in the cytoplasm. In case of schistosomiasis, syphilis and actionomycosisthe granulomas are different.

DR. ANWAAR A. KHAN (Gastroenterologist)

This young man had 40 days of fever and central nervous symptoms were not prominent. We did not suspect pyogenic meningitis, there may be an acute progression into a catastrophic end, but instead we considered slowly progressive disease like tuberculosis. When we have a case of P.U.O. we do consider common conditions, most of viral conditions are self limiting within two weeks time. Out of chronic conditions one third are due to infections. Tuberculosis is common even in western countries. Other conditions of significance are lympho-reticular disorders. We must also consider fungal infections like coccidiomycosis, histoplasmosis. One should always try his best to find the cause of P.U.O. I have seen cases of Listerosis abscess in brain to present as P.U.O. Silent lesion may be due to occult abscess or SBE. In making a diagnosis, bone marrow and liver biopsy have almost similar yield. Culture of these tissues is also very useful. Our patient had elevated alkaline phosphatase and granuloma in the liver. Montoux test was positive. All these facts lead to the diagnosis of tuberculosis. He was started on tripple drug regimen and has responded well with normalization of temperature in one week.