Case Reports

Fever of unknown origin

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ABSTRACT

This report describes a 3-year-old female child with prolonged fever in which a very extensive work-up resulted in the discovery of the underlying congenital anomaly causing her symptom.

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Fever of unknown origin (FUO) refers to a fever of one week or more, in which the basic examination and investigations fail to determine its nature. The following criteria are used to define this problem in children and adolescents: (i) a history of fever of more than one week duration (2–3 week for adolescents), (ii) documentation of fever by a health care provider, and (iii) no apparent diagnosis one week after investigation was begun in either an inpatient or outpatient setting.[1] The principal causes of FUO in children are infections and connective tissue (autoimmune) diseases. Neoplastic disorders should also be seriously considered, although it is rare to cause fever alone.[2] Drugs can also result in fever. When factitious fever (inoculation of pyogenic material or manipulation of the thermometer by the patient or parent is suspected, fever should be documented in the hospital by an individual who remains with the patient while the temperature is taken. Prolonged and continuous observation of the patient is imperative. Fever of unknown origin lasting more than 6 month is uncommon in children and should suggest granulomatosis or autoimmune disease.[3] Repetitive evaluation including history, physical examination, and radiographic studies, may be required.

Case Report. A 3-year-old female presented to a local hospital complaining of fever for 9 days, which comes daily, no associated chills, rigors or sweating. There was a history of generalized tonic clonic convulsion for 5 minutes when she was febrile on the day of presentation. The patient had decreased appetite and mild weight loss. There was also a history of skin rash and loose bowel movements, no mucus or blood in the stool. No history of dysuria, discoloration of the urine and no history of animal contact or recent travel. Her past history was significant for simple febrile convulsion. Her systemic review, vaccinations, development were unremarkable. The patient is living with her mother with reasonable socio-economic status. Physical examination revealed a very stable child with normal vital signs including blood pressure, and normal growth parameters. Systemic examination was remarkable for a functional murmur grade 2/6 at the left upper sternal boarder, liver of 3 cm below the right costal margin which is soft and smooth, spleen was 2 cm below the left costal margin. She had no joint or skin involvement. Central nervous system examination was normal. Patient was admitted to the hospital and a work up showed a white cell count of 7000 with 80% lymphocytes, 20% polymorphs. Hemoglobin was 10.7 mg/dl, platelets 250, sedimentation rate (ESR): 10mm per first hour. Blood film for malaria was negative. *Brucella and Leishmania* serologies were negative as well as the blood culture. Blood chemistry including calcium, renal function was within normal. Chest radiograph was normal. Urine analysis showed a pH of 5, pus cells 18-20/high power field (hpf), red blood cell (RBC) 2-4/hpf, and trace of proteins. Urine culture

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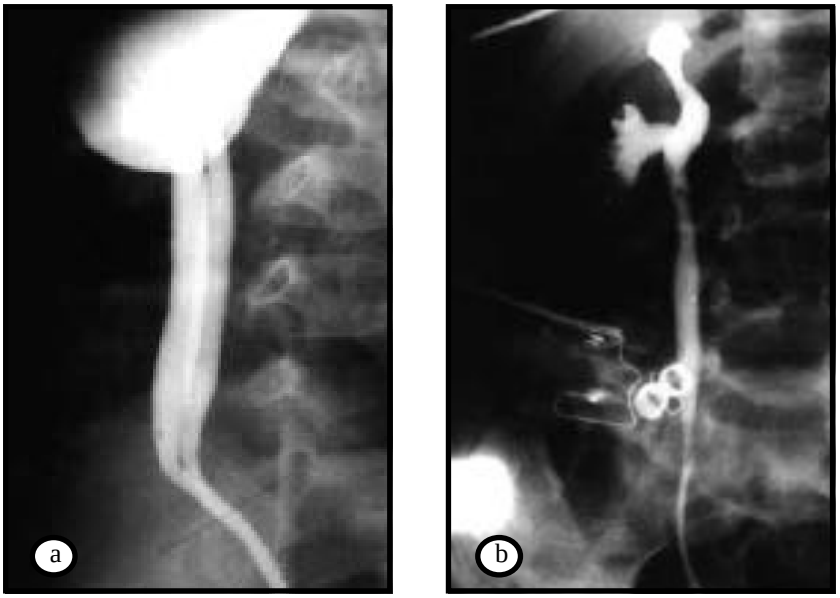

Figure 1 - Intravenous pyelogram showing **a)** duplicated collecting system on the right side that joins at the lower third of the ureter and **b)** after surgical intervention and excision of the duplicated system.

obtained at the same time was sterile. Peripheral blood smear showed a mild hypochromic microcytic anemia but otherwise normal. Monospot and widal tests were negative. Ultrasound of the abdomen confirmed the presence of hepatosplenomegaly, but there were no other positive findings. Patient was observed; no fever was documented during the admission and she was discharged to come back for a follow-up. Prior to her discharge, her organomegaly regressed and the tentative diagnosis was viral infection. Four months later, she was referred to us from her local hospital due to the recurrence of fever that persisted for more than one week, with no other systemic complaints. Temperature was documented at our hospital. There was no associated rigors, chills, sweating or headache. No urinary symptoms, but she was complaining of lower abdominal pain, which is peri-umbilical, of mild intensity with no other associated gastrointestinal tract symptoms. While obtaining further information, a history of pulmonary tuberculosis in the grand father was given. He died one year back while on treatment. Physical examination revealed a highly febrile child, but other vital signs were normal. Her weight was 15 kg, which is within normal. No lymphadenopathy, mouth ulcers or pharyngitis. Her systemic examination was negative apart from minimal limping to the right side. Her investigations showed hemoglobin similar to her previous reading. Sedimentation rate of 2 mm per first hour. Blood culture was sterile. Urine analysis showed pus cells of 14-16/hpf and negative RBCs and protein. Urine culture was reported as contaminated specimen. Blood film for malaria was negative, monospot test and widal were negative. Complement 3 (C3)and complement 4 (C4) were normal, antinuclear antibody was negative. Peripheral smear was reported as hypochromic microcytic anemia. Chest radiograph was normal. Mantoux test performed using 5 units purified protein derivative intradermally was negative, gastric aspirate for acid fast bacilli (AFB) was negative. Urine for AFB stain was negative as well as the culture. Twenty-four hours urine collection for AFB was negative. Ultrasound of the abdomen was normal. Bone marrow aspiration showed no evidence of malignancy, *Leishmania donovani* bodies or malaria parasite. Cultures were negative for *Brucella* and tuberculosis. Human immunodeficiency virus, hepatitis serology for B, and hepatitis serology for C were negative. Immunoglobulins assay were normal. Serum cholesterol and triglycerides were within normal. Magnetic resonance imaging of the abdomen and bone scan were normal. Echocardiography was performed and was normal. Repeated urine culture showed *Escherichia coli* (*E coli*) 100,000 coloni per ml and her ESR increased to 52 mm per first hour, patient was started on gentamycin for a total of 10 days. Repeated urine culture was negative. Fever subsided over one week and her general condition improved. At this stage, she was discharged with follow-up visit for further evaluation and investigations. Three weeks after discharge, the patient was readmitted with the complaint of irregular fever and red urine of one-week duration. No history of dysuria or polyuria. Urine frequencies as well as the amount did not change. This discoloration was in all urine samples. No leg edema or joint swelling, but she had mild left knee arthralgia. Her physical examination including blood pressure was normal. Her complete blood count,

chemistry including calcium and renal function did not change. Sedimentation rate of 3 mm per first hour. C-reactive protein was negative. Urine analysis showed trace of protein, numerous RBC, no cast. Urine culture and urine for bilharesiasis as well as blood culture were negative. Calcium to creatinine ratio was normal. Twenty-four hour urine collection for protein was normal. Antinuclear antibody, rheumatoid factor, C3, and C4 were within normal. Abdominal ultrasound showed normal kidneys size and echogenicity. Hematuria cleared and patient was discharged with a follow-up. Two weeks after, she presented again with hematuria and fever. Her examination was positive only for acute tonsillitis. Initial blood work was normal, urine analysis showed numerous RBCs with 2-4 pus cells, protein 3+ and pH of 6. Urine culture showed *E coli* of significant growth. The patient was started on gentamycin and ampicillin. Repeated urine culture was sterile. Child became afebrile, hematuria improved over a few days. Micturating cycto-urethrogram showed normal bladder outline with no evidence of vesico-ureteric reflux. Intravenous pyelogram showed a ureteral duplication on the right side (**Figure 1**). Cystoscopy showed a ureteric duplication on the right side that joined at the lower third at the level of sacro-iliac joint with intra renal reflux. Dimercaptosuccinic acid (DMSA) scan was normal. The diagnosis at this point was duplication of the right collecting system with intra renal reflux and recurrent urinary tract infections presenting as FUO. Surgical intervention was performed in which the upper ureter was dissected at both ends. Patient postoperative period was smooth and she recovered fully. There were neither fever nor hematuria after 6 months of follow-up.

Discussion. To reach to the specific diagnosis in the case of fever of unknown origin is not usually easy and straightforward.[2] As there is no single aspect in the history, physical examination or laboratory investigation that can predict who is at the greater risk, some investigators use a special criteria for identifying infants and children with high and low risk of serious diseases.[2] In a review by Majeed,[3] the author tried to divide the FUO into 2 main types: Type 1 fever of unknown origin, which is a daily fever for more than 3 weeks. In this type, the main causes are infectious, connective tissue diseases and malignancy. Type 2 is a chronic episodic fever of unknown origin in which there is fever for few days followed by fever free interval and well-being. In this type a more rare causes are usually present such as familial Mediterranean fever, the hyper-immunoglobulin D syndrome and cyclic neutropenia. It is of great importance to rule out life threatening conditions such as invasive infections and malignancies for which a delay in diagnosis may jeopardize the prognosis. Hidden infections should be looked for as dental, hepatic or renal abscesses.[2,4] When searching for rare causes in such a patient, the approach should be systematic. The understanding of the condition by the parents help the physician to guide investigations in a reasonable order. The discomfort on the child and the cost of investigations should be considered. Repeated history and physical examination of the patient is of great importance as new information or signs may be helpful in directing the physician. This would not have been possible without being patient, both on the parents and physicians. Fever can also result from medications and this should be considered if the patient is receiving drugs. Drug fever is not usually associated with other symptoms, and temperature remains elevated at a relatively constant level.[5] Withdrawal of the drug is associated with resolution of the fever, generally within 72 hours.[5]

In our case, initially there was an abnormal cell count on few urinary samples inspite of negative cultures; this raised the suspicion of sterile pyuria or a congenital renal anomaly. The changes in the presentation over time were very helpful in redirecting our differential diagnosis and investigations. This patient demonstrates an unusual case of FUO and how extensive was the work up in order to find the cause of fever. We encourage physicians to be patient and through where facilities and time allow them to do so.

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