From the Case Records of Kanchi Kamakoti CHILDS Trust Hospital: An Unusual Infection Presenting as Pyrexia of Unknown Origin

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Dr Silky

Sir today we would like to discuss with you, the clinical data of a girl who has been suffering from fever for more than 2 months, admitted today in KKCTH.

A 6-year-old girl had been brought by her mother with high-grade intermittent fever ($T_{max}$ around 102°F), for nearly 60 days. She also has vague mild abdominal pain more in the upper abdomen. On further probing, there was history of few episodes of nonbilious vomiting and significant weight loss of 3 kg in 2 months. There is no history of abdominal pain/alteration bowel habits/abdominal distension/jaundice/pallor/rash or joint pain. There is no history of any travel or contact with tuberculosis. There has been no consumption of unpasteurized milk.

Dr Lakshan Raj

I went through all the previous records of illness and treatment and investigation details and present them now.

Day 1–4 of Illness

Fever started with abdominal pain more in the left upper quadrant. On day 4, basic investigations were done (CBC: Hb, 10.3 g/dL, TLC, 9900 cells/mm³ with platelet count 4.7 lakhs/mm³ and CRP—17 mg/L). She received oral amoxyclav for 5 days as outpatient basis.

Day 10 of Illness

She was admitted for the same in an outside hospital. Workup done was suggestive of mild leukocytosis (18,500 cells/mm³) with normal platelet count (4.67 lakhs/mm³) and CRP—17 mg/L; CXR—normal; widal (negative) and urine and blood c/s—sterile. She was treated with IV ceftriaxone and amikacin for 6 days. In view of persistent fever, antibiotics were escalated to piperacillin-tazobactam, doxycycline, and linezolid, and chloroquine was added empirically.

Day 23 of Illness

She developed jugulodigastric lymphadenopathy of the left side (3 × 3 cm) and had persistent high-grade fever in spite of 12 days of broad-spectrum antibiotics.

Day 30 of Illness

In view of persistent fever spikes, she was readmitted in an another hospital. Repeat CBC showed: Hb—9 g/dL; mild leukocytosis (18,500 cells/mm³) with normal platelet count (3.87 lakhs/mm³), and CRP—31 mg/L; ESR—96, blood c/s—sterile. USG neck was done and reported to reveal multiple bilateral lymphadenopathy, with maximum of 4.7 cm × 1.6 cm. FNAC of LN was done and reported as acute suppurative lymphadenitis. USG abdomen was done and it showed multiple small hypoechoic focal lesions (0.3–0.5 cm in spleen).

Antibiotics were escalated to meropenem (from piperacillin-tazobactam) and linezolid was continued for nearly 3 weeks. Repeat USG abdomen after 14 days, two cystic lesions in spleen (2.1 cm × 1.6 cm × 1.8 cm and 2.2 × 1.6 cm × 1.5 cm). Repeat USG neck showed upper deep cervical lymph nodes (2.4 × 0.9 cm). On administration of meropenem and linezolid, fever spikes seemed to be spacing out. She was discharged on oral linezolid. She was at home for nearly a week with low-grade intermittent fever spikes (one to two spikes per day with a $T_{max}$—101°F).

Day 52 of Illness

She again started having high-grade fever >103°F with abdominal pain and vomiting, hence was referred to us on day 59 of illness.

In spite of 60 days of fever, she looked nontoxic, ambulant, and cheerful, though she resented frequent venipuncture and tests. She was not jaundiced or anemic. There was no clubbing. She had tender bilateral posterior cervical nodes (2–3 nodes bilateral)—2 × 2 cm, tender, firm without matting. Liver and spleen were not palpable. On deep palpation, she had significant tenderness at the left costal margin. The cardiovascular and respiratory system examination revealed no abnormalities. Fundus examination was normal [as part of Pyrexia of Unknown Origin (PUO)]. There were no rashes and musculoskeletal system examination was normal. There were no meningeal signs or neurological abnormalities.

Dr K Dhanalakshmi

Summarizing the details available so far, the issues are as follows:

- Fever >2 months
- Left upper quadrant abdominal pain
Dr Silky

Why you are thinking of atypical infections? Can it be a connective tissue disorder or immunodeficiency?

Dr K. Dhanalakshmi

The organisms known to cause splenic lesion in tropical countries include salmonella and other enteric group of organisms. This child has received multiple antibiotics in the last 2 months with reasonable coverage against the above-mentioned organisms. Immunodeficiency, even though we need to consider it in the differential diagnosis because of the receipt of multiple intravenous antibiotics, the chance is less likely because the child is absolutely well before and has had no serious illness in the past requiring hospitalization. But I would like to keep in mind the possibility of chronic granulomatous disease (CGD) and acquired immunodeficiency syndromes.

With regard to connective tissue disorders, it seems to be less likely because of the age and no clinical pointers toward the same (rash/joint pains) and in investigations also there is no marked thrombocytosis and acute-phase reactants are only mildly elevated.

Second-line investigations for PUO—ECHO and fundus examination need to be done and we will plan for bone marrow aspiration and culture.

Dr S Balasubramanian

Yes … agreed. This child has had prolonged fever with hypoechoic lesions in the spleen and weight loss. The diagnosis at this point of time favors infection such as splenic abscess of bacterial or fungal vs. tuberculous. Dr Silky, please review the differential diagnosis of hypoechoic lesions in the spleen.

Dr Silky

On reviewing literature, the differential diagnosis for focal lesions of spleen is divided into several categories. They include cystic lesions, infective or inflammatory processes, lymphoproliferative disorders, and metastasis. Different splenic diseases may present with a similar echostructure (Table 1).

Among them infectious etiologies encompass bacterial, fungal, and mycobacterial abscesses. The classic triad of findings for a splenic abscess is fever, left upper quadrant pain, and splenomegaly. It is reported that an abscess in the spleen can develop by four ways:

- Hematogenous: Spread is usually by hematogenous seeding from other sites of infection. The two most common sources are the heart in endocarditis and blood by direct introduction of bacteria into the blood with intravenous drug use.
- Trauma and subsequent ischemia create an environment for bacteria to grow. Overt trauma is through external forces or microscopic trauma due to hemoglobinopathies.
- Contiguous focus of infection like pancreatic or subphrenic abscess, or from adjacent infected segments of bowel.
- Immunocompromised state like human immunodeficiency virus (HIV) infection or diabetes mellitus or transplant or neoplasia.

Infection is rarely isolated to the spleen, but most commonly seen with concurrent hepatic abscesses. Streptococcus, staphylococcus, salmonella, and E. coli are the major causative agents of splenic abscess in the last century. However with increased number of immunocompromised patients, recent series have shown increased number of fungal isolates including Candidiasis, Aspergillus, Cryptococcus, and Histoplasmosis. Splenic tuberculosis is characterized by irregular miliary disease or coalescent micronodules, which become focal masses as they increase in size. In a series from Thailand, the agent of melioidosis, Burkholderiapseudomallei, was the cause of splenic abscess in 24 of 41 cases from which a pathogen was isolated.

Dr S Lakshan Raj

The preliminary investigations are available now sir. Complete blood count is showing mild leukocytosis and anemia (Hb—8.8 g/dL; TC—19,000 cells/mm³; DC—N73/L23/M3/E1, platelets 4.90 lakhs cells/mm³), LFT and RFT is normal. CRP—Positive 31.7 mg/L and ESR—100 mm/hour. ECHO and fundus examination are normal. Blood culture is sterile so far.

USG neck—bilateral upper cervical lymphadenopathy, no abscess collection. USG abdomen has shown moderate hepatosplenomegaly with a hypoechoic lesion in the spleen. Sir, she is still having high nearly continuous fever; should we consider empirical antibiotics after doing bone marrow aspiration and culture? Do we need to do tuberculosis workup and immunodeficiency workup?

Dr S Balasubramanian

I think we should start on meropenem and doxycycline as they would cover all common and unusual pathogens including anaerobes. Meanwhile, we will complete the workup for tuberculosis and get bone marrow aspiration done. I think we should do whole body positron emission tomography-computed tomography (PET-CT) to try to identify foci of infection.

Dr Dhanalakshmi, can you review the role of PET-CT in PUO?
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Dr K Dhanalakshmi

Nuclear medicine methods are generally categorized as secondary diagnostic methods in PUO diagnosis. Morphological changes may not occur at early periods of infections and inflammation, both of which constitute the bulk of the PUO etiology. Because of this, sensitivities of anatomical imaging and modalities such as USG, CT, and MRI can be low.

Fluorodeoxyglucose positron emission tomography (FDG-PET) is a valuable imaging method for its success in demonstrating both neoplasms and infection-inflammation foci. Since the most common three etiologies of FUO are known to be infections, noninfectious inflammatory events, and neoplasms, the FDG-PET scan appears to be a valuable modality in diagnosing the etiology of PUO. Increased FDG uptake is present in all activated leukocytes (granulocytes, monocytes, as well as lymphocytes), which enable imaging of acute and chronic inflammatory processes. 1,2,3

The study of Lorenzen et al. 9 is one of the first studies using FDG-PET in diagnosis of FUO, and they reported the contribution of FDG-PET to establishment of diagnosis in a group of 16 patients as 69%. They noted the absence of a pathological focus, which could be the underlying cause for fever among patients with negative FDG-PET results, and reported a high negative predictive value for FDG-PET. Bleeker-Rovers and colleagues reported sensitivity, specificity, positive predictive value, and negative predictive value of FDG-PET as 93, 90, 87, and 95%, respectively.

PET/CT with 18-fluorodeoxyglucose (FDG) has a role for evaluating focal splenic lesions, especially in patients with a history of malignancy. In a patient with known malignancy, FDG PET/CT can be useful in differentiating malignant from benign lesions. 3 If the mass is hypermetabolic, it should be considered malignant. Conversely, if the mass is non-FDG-avid, it is likely benign and may be followed with CT or MRI to assess stability. However, in a patient without a known malignancy, FDG-PET has virtually no utility in differentiating benign from malignant lesions. In these scenarios, FDG-PET could be helpful if the splenic mass increases in size. If the enlarging mass is hypermetabolic, tissue sampling is recommended. If not, careful inspection of the companion CT should be undertaken to look for non-FDG-avid lesions elsewhere to suggest a disseminated process, in which case biopsy of any lesion is recommended. If no additional CT findings are identified, continued follow-up is considered appropriate.

Dr Silky

Sir, we have started her on meropenem and doxycycline. Tuberculosis workup (CXR—normal, Mantoux—negative; resting gastric juice gene expert and AFB smear is negative) is negative. Primary immunodeficiency workup (NBT, IgProfile, flow cytometry for T-cell subset analysis) is also normal. Bone marrow aspiration revealed reactive marrow with trilineage hematopoiesis. Bone marrow culture also did not yield any growth so far. We are still clueless at this point of time about the etiology of fever.

Dr S Balasubramanian

We will do a PET–CT as it will help us in evaluation of PUO especially with splenic lesion as the only focus, as all the above second-line investigations of PUO have not given us a clue so far. FDG PET-CT is better than CECT in making a specific diagnosis in the evaluation of PUO and it will also help in deciding the best possible site for biopsy.

Dr S Lakshan Raj

Sir, we got a PET-CT done as you advised and guess what? It revealed multiple hot spots in liver and large lesions in the spleen, suggestive of early, evolving microabscesses in the liver and multiple large splenic abscesses. Radiology consult has been obtained from Dr Gopinath, our interventional radiologist, who carried out aspiration under USG guidance. About 10 mL of pus was drained from one of the hypoechoic lesions in the spleen and we have sent it for aerobic and anaerobic culture (Figs 1 and 2).

Dr S Balasubramanian

I just now got a report from the microbiology team that the pus culture is growing Burkholderia pseudomallei sensitive to imipenem, ceftazidime, and cotrimoxazole. We can now switch to ceftazidime alone, thus finally confirming a diagnosis of melioidosis, which was elusive so long. It is time for us to review melioidosis in children.

Dr K Dhanalakshmi

Melioidosis is an endemic disease in Southeast Asia and Australia but is commonly underdiagnosed and underreported in the Indian subcontinent. The southern part of India is apparently a new “hot spot” in the global map of melioidosis. Childhood infections are now increasingly being recognized, even in immunocompetent population. Pediatric melioidosis is reported to be between 5 and 15% of all melioidosis cases. 10

Acute infections were defined as those presenting symptoms for less than 2 months and within 2 months of inoculation. Chronic infections are those presenting with symptoms for 2 or more months with infection acquired in the recent or remote past. It may present as a localized disease involving a single anatomic focus or disseminated disease involving two or more anatomic areas and/ or bacteremia.

Clinical presentations were classified into the following primary diagnostic groups: 

• Pneumonia—including associated complications such as pleural effusion, lung abscess.
• Soft tissue infections—infections of nonskeletal tissue surrounding or supporting organs and other structures including subcutaneous tissue, muscle, lymph nodes, blood vessels, and soft tissue organs, namely, the liver or spleen.
• Osteomyelitis/septic arthritis—infection of bones, joints, ligaments, or cartilage.
• Neurological—brain and spinal cord including meninges and the peripheral nervous system.
• Genitourinary—infection of the urinary and genital systems including the kidneys.
• Skin.
• No evident focus.

In all series, pneumonia is the most common presentation of melioidosis and is involved in approximately half of all cases. Skin and soft tissue infections are a common manifestation of melioidosis and may be the source of systemic infection or result from hematogenous spread. Presentations may be rapidly progressive, similar to necrotizing fasciitis from other organisms. Infections involving many other sites have been described, including hepatosplenic abscess, mycotic aneurysms, mediastinal infection, and thyroid and scrotal abscesses.
Children with localized melioidosis present primarily with cervical node swelling, subcutaneous abscesses, suppurative parotitis, or lacrimal gland infections. Acute suppurative parotitis accounts for up to 40% of pediatric cases but only small numbers of adult cases.11

Immune suppression is recognized as a risk factor for clinical melioidosis and is present in up to 80% of adults—most commonly, diabetes, renal disease, hazardous alcohol use, and immune suppression states. In contrast, only 25% of children have an associated underlying chronic disease (particularly thalassemia) or immune suppression. Recently, cystic fibrosis has also been recognized as a particular risk for melioidosis in young travelers and residents of endemic regions (Fig. 3).10

The current convention is to view the treatment of melioidosis as comprising of two phases: the first is the acute phase, the aim of which is to stop patients from dying of overwhelming sepsis; the second is the eradication phase, the aim of which is to kill any residual bacteria and to minimize the risk of the infection relapsing (Table 2).6

Adding trimethoprim/sulfamethoxazole (co-trimoxazole) for patients with severe infection involving the brain, prostate, or other privileged site (same dosing as described for eradication therapy) can be considered. If co-trimoxazole is included, it should be continued for the entire duration of the acute phase (Table 3).

**Dr S Balasubramanian**

We will continue IV antibiotics for a minimum of 2 weeks and then switch over to eradication therapy with co-trimoxazole for 12 weeks.

**Dr Lakshan Raj**

She has come for follow-up after 2 weeks. She is clinically well with a weight gain of 1 kg in 2 weeks. Repeat USG abdomen was done and it was completely normal. Sir, why did not she respond to meropenem, which was given in an outside hospital for nearly 2 weeks?

**Dr S Balasubramanian**

The possible explanation for lack of remission to meropenem could be the underlying abscess in the spleen. Once the abscess was...
Aspirated and appropriate antibiotics were started, she responded well.

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Aspirated and appropriate antibiotics were started, she responded well.

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Fig. 3: Clinical manifestations of melioidosis

Table 2: Initial acute-phase therapy for melioidosis

| Patient                          | Drug          | Dosage/route | Frequency |
|----------------------------------|---------------|--------------|-----------|
| With no complications            | Ceftazidime   | 50 mg/kg (up to 2 g) intravenous | Every 8 hours, or 6 g/day by continuous infusion after a 2 g bolus |
| With neuromelioidosis or persistent bacteremia or in intensive care unit | Meropenem | 25 mg/kg (up to 1 g) intravenous | Every 8 hours |

Duration of acute-phase therapy is generally 10–14 days; however, >4 weeks of parenteral therapy may be necessary in cases of more severe disease, e.g., septic shock, deep-seated or organ abscesses, extensive lung disease, osteomyelitis, septic arthritis, or neurological melioidosis.

Table 3: Oral eradication-phase therapy for melioidosis

| Drug                                | Recommended dosage/frequency |
|-------------------------------------|------------------------------|
| Trimethoprim/sulfamethoxazoleb      | 8 mg/40 mg per kg; maximum dose 320 mg/1600 mg every 12 hours |
| OR Amoxicillin/clavulanic acid (co-amoxiclav) | 20 mg/5 mg per kg every 8 hours; maximum dose 1000 mg/250 mg every 8 hours |

Recommended duration of therapy is a minimum of 12 weeks.

If the organism is susceptible and the patient does not have a documented allergy to it, oral co-trimoxazole is the agent of first choice. If the organism is resistant to co-trimoxazole or the patient is intolerant, the second-line choice is co-amoxiclav.

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