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TEACHING FILES (GRAND ROUNDS)

PYREXIA OF UNKNOWN ORIGIN IN A CHILD: HOW TO APPROACH?

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Clinical Problem:
A 6-year-old boy presented in August 2024 with high-grade fever for 15 days. There was no nausea, vomiting, abdominal pain, loss of weight or appetite. On presentation, weight was 24 kg (between 75th-90th percentile according to Indian Academy of Pediatrics (IAP) charts) and height was 108 cm (between 10th-25th percentile according to IAP charts). On examination, pallor and bilateral inguinal lymphadenopathy (1 x 1cm) was present. Other general and systemic examinations were normal. Investigations are shown in Table 1. He was admitted and empirically started on intravenous cefotaxime. Routine urine examination was normal. Blood and urine cultures were negative. Non-contrast computerized tomography (NCCT) of the chest showed diffuse subtle centrilobular nodules in both lungs without hilar or mediastinal lymphadenopathy. Urine Xpert MTB/Rif and interferon-gamma release assay were negative. Malaria antigen test, dengue NS1, scrub typhus IgM, brucella IgM and HIV ELISA were negative. 2D-echocardiography did not show any vegetations or valvular abnormalities. Abdominal ultrasound showed mild hepatosplenomegaly with multiple liver and spleen lesions, and bilateral bulky kidneys. Oral doxycycline was added. In view of persistent fever, lymphocyte subset analysis was advised which showed low B-cell counts. Total serum IgE was 53.89 IU/mL(normal: <90 IU/mL), serum IgA was 354 mg/dL(normal: 34-305 mg/dL), and serum IgM was 224 mg/dL(normal: 31-208 mg/dL). On day 10 of admission, urine histoplasma antigen was sent and was positive. All antibiotics were stopped and he was started on intravenous liposomal amphotericin-B(L-AMB)(3 mg/kg/day), to which he responded and became afebrile after 2 doses. He received L-AMB for 2 weeks followed by oral itraconazole 100 mg twice a day. Abdominal ultrasound on day 14 of L-AMB showed mild hepatosplenomegaly with complete resolution of liver lesions and reduction in size of splenic lesions. At the 1-month follow-up, abdominal ultrasound showed mild hepatosplenomegaly with no focal lesions in the liver or spleen. Urine histoplasma antigen became negative at 3 months of therapy.

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How to approach Pyrexia of Unknown Origin (PUO) in a child?

Discussion:
The classical Petersdorf and Beeson criteria for PUO defined it as a well-documented fever above 38.3°C for atleast 3 weeks without an apparent source after 3 weeks of outpatient evaluation or 1 week of in-hospital evaluation.[1] Currently, PUO in a child may be defined as a temperature above 38.3°C, atleast once a day, for atleast 8 days with an inconclusive history, physical examination and preliminary investigations, evaluated by a paediatrician out patiently. PUO understandably poses a diagnostic dilemma for clinicians with a wide spectrum of causes including infectious, autoimmune, malignancy, factitious, and iatrogenic[3]. Chien et al.[4] proposed a four-level approach to childhood PUO. The first level involves a detailed history and physical examination, followed by simple screening tests such as complete blood counts, routine biochemistry tests, urinalysis, urine or blood or stool culture, and chest radiographs. The second level involves more specific screening tests including viral cultures, bacterial and viral serology, abdominal or lymph node ultrasonography, and basic autoimmune panels. The third level entails targeted and invasive investigations such as computerized tomography/ magnetic resonance imaging, bone marrow sampling, lumbar puncture, lymph node biopsy, echocardiography, and polymerase chain reaction testing for viruses. The final level, if the cause of PUO is still unknown, advocates for a treat-and-assess approach involving the use of antimicrobial agents, steroids and so forth based on clinical judgement and response to therapy.[4] Most recent studies of PUO in children have found infectious diseases to be the most common cause, followed closely by autoimmune and malignant diseases.[4,5,6,7] While several bacterial, viral, fungal, and parasitological infections may cause PUO in children, in an Indian context it is essential to work-up for bacterial pneumonia, respiratory viral infections, urinary tract infections, vector-borne diseases, scrub typhus, enteric fever, tuberculosis, and brucella.[5,6,7] Autoimmune causes in childhood PUO include systemic lupus erythematosus (SLE), juvenile idiopathic arthritis (JIA), inflammatory bowel disease, sarcoidosis, vasculitis, Kawasaki disease, and Behcet disease.[3] Indian studies have found SLE, JIA, and Kawasaki disease as common causes of childhood PUO.[5,7] Malignancy as a cause of childhood PUO has a somewhat similar

Table 1. Investigations of the patient.

Parameters	At presentation	At follow-up	Reference Ranges
Hemoglobin (gm/dL)	10.8	12.2	11.5-15.5
White blood cell count (cells/cumm)	9670	6230	5000-13,000
Absolute neutrophil count (cells/cumm)	4846	2199	2000-8000
Absolute lymphocyte count (cells/cumm)	4520	2909	1000-5000
Platelets (106 cells/cumm)	5.32	2.70	1.50-4.50
CRP (mg/dL)	67.4	-	-
ESR (mm/hr)	16	-	-
ALT (IU/L)	18	16.4	<41
AST (IU/L)	30	18	<41
ALP (IU/L)	237	-	51-332
Total bilirubin (mg/dL)	0.2	-	0.0-1.10
Direct bilirubin (mg/dL)	0.1	-	0.0-0.60
Indirect bilirubin (mg/dL)	0.1	-	0.10-0.80
BUN (mg/dL)	7	-	5-18
Serum creatinine (mg/dL)	0.51	0.69	0.3-0.59
Serum total protein (gm/dL)	7.3	-	6.00-8.30
Serum albumin (gm/dL)	3.7	-	3.80-5.40

Note : CRP- C-reactive protein, ESR- Erythrocyte sedimentation rate, ALT- Alanine aminotransferase, AST- Aspartate aminotransferase, ALP- Alkaline phosphatase, BUN- Blood urea nitrogen.

prevalence as autoimmune disorders. Common malignant causes include leukemias, lymphomas, neuroblastoma, hemophagocytic lymphohistiocytosis, and Langerhans cell histiocytosis.[3] In Indian children, the common malignancies implicated as etiologies in PUO include acute myeloid leukemia, acute lymphoblastic leukemia, and neuroblastoma.[5,6,7] Additional important causes to keep in mind while evaluating a patient with PUO include pseudo-PUO and iatrogenic fevers. Pseudo-PUO refers to successive episodes of self-limited febrile infections that are perceived by the caregivers as a single prolonged febrile episode. This occurs when a well-defined infection that resolves is followed by other febrile illnesses that are poorly-defined. Ruling out pseudo-PUO required careful history taking, including maintaining a fever diary, in order to avoid an expensive and unneeded workup.[3] Iatrogenic or drug-induced PUO can be caused by any medication including antibiotics, anticonvulsants, chemotherapeutic drugs, non-steroidal anti-inflammatory drugs, and antipyretics, and can manifest at any point after starting the drug. Drug-induced fever can be confirmed by the resolution of fever usually within two half-lives of stopping the offending drug. The first step in the management of PUO is to discontinue all the non-essential medications so as to rule out the possibility of drug fever. If the patient is on multiple medications, the elimination may be done one after the other.[2,3] In healthy-appearing children with PUO, the use of empirical antibiotics or steroids is not recommended. Empirical antibiotics may hinder the detection of common infectious etiologies of PUO and are thus recommended only if the infection or the pathogen is diagnosed or if there is a high clinical suspicion. Similarly, steroids for suspected autoimmune causes of PUO should only be started after confirmation of the diagnosis or if there is a high clinical suspicion for serious inflammatory conditions, and after ruling out malignancies. Further management of PUO will be specific to the underlying cause. Pediatric PUO has a relatively good prognosis even in cases with no identifiable cause.[2,3]

Compliance with ethical standards
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