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Case-based Reviews in Pediatric Infectious Diseases



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Foreword
YK Amdekar

Contents

1. **A Child with Fever for Three Months 1**
   YK Amdekar

2. **Approach to a Child Having Fever with Coma 10**
   Vipin M Vashishtha

3. **A Child with Recurrent Fever 35**
   Yashwant Rao

4. **Fever with Positive Tuberculin Skin Test 45**
   Ajay Gaur, Prakash Petchimuthu

5. **Fever Beyond One Week 50**
   Arun Shah

6. **Typhoid Fever with Jaundice 56**
   Kheya Ghosh Uttam, Prabhas Prasun Giri

7. **Children with Pyrexia and Unilateral Pleural Effusion 62**
   Rohit Bannerji, Mallar Mukherjee, Monjori Mitra

8. **Prolonged and Confusing Fevers in Children 76**
   Rajesh Rai, Ankita Bhandari

9. **Fever with Splenomegaly 88**
   Dipti Agarwal

10. **An Infant with Deep Jaundice and Acholic Stools 97**
    Alka Agarwal, Nimisha Arora

11. **Child with Unusual Infections 108**
    Vinod Gunasekaran, Anupam Sachdeva

12. **An Infant with Cataract and Positive IgM Rubella 117**
    Bharat Mehra, AJ Chitkara

13. **A Child with Prolonged Diarrhea 122**
    AK Patwari

14. **An Infant with Microcephaly with Recurrent Seizures 129**
    Rekha Mittal, Ridhimaa Jain

15. **Neurocysticercosis in Children 140**
    RK Sabharwal

16. **A Child with Recurrent or Nonresolving Pneumonia 151**
    Vimlesh Soni, Sanjay Verma

17. A Case of Recurrent Jaundice 161
Shrish Bhatnagar

18. Case-based Scenarios in Rickettsial Infection..... 168
Atul Kulkarni, Vikram Hirekerur

19. Case Scenarios on Rational Antibiotic Usage 177
Dhanya Dharmapalan

20. Approach to a Case of Matted Lymphadenopathy 185
Vineet Saxena, Pranjali Saxena

21. A Two-month-old Child with Acute Kidney Injury..... 191
Amit Agarwal

22. Pediatric Septic Shock..... 198
Vivek Saxena

23. Unusual Skin Manifestations of Pediatric Tuberculosis 210
Rajesh Rai, Pallavi Gahlowt

24. Adolescent Immunization 216
Ashok Banga

Index.....231

CHAPTER

4

Fever with Positive Tuberculin Skin Test

Ajay Gaur, Prakash Petchimuthu

INTRODUCTION

The global tuberculosis (TB) report 2018 reports that in India, an estimated 2.2 lakh children become ill with TB each year (22% of global TB burden), with slightly higher burden among males. Pulmonary TB is the most common form in children. It is also known that 10% of cases reported to the NTCP (National Tuberculosis Control Program) are from children under 14 years of age. TB is a formidable problem keeping high suspicion of TB in children presented with persistent fever or cough for more than 2 weeks

Tuberculosis remains a leading cause of morbidity and mortality in the world, especially in developing countries. A combination of factors including high costs, limited resources, and the poor performance of various diagnostic tests make the diagnosis of TB difficult in developing countries. Short of demonstrating viable organisms in body tissues and fluids, the tuberculin skin test (TST) is the only method of detecting *Mycobacterium tuberculosis (MTB)* infection in an individual and is used to diagnose TB in individual patients, as well as in epidemiological settings, and to measure the prevalence of TB infection in populations. The TST is one of the few investigations dating from the 19th century that are still widely used as an important test for diagnosing tuberculosis. Though very commonly used by physicians worldwide, its interpretation always remains difficult and controversial. Various factors such as age, immunological status, and coexisting illness influence its outcome and interpretation.

CASE 1

An 18-month-old child presented with complaints of persistent pneumonia with mild fever and cough lasting for 15 days. The patient has been referred for these complaints. On detailed history, there were no similar episodes before but the patient had episodes of cough and cold for 3–5 days which usually will be relieved by oral medications. This episode started with history of fever for 4–5 days followed by cough and cold without expectoration. The patient was fully vaccinated. There was no history of contact with TB in the family and any foreign body aspiration. On admission, the patient was

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sick and on respiratory distress, so was started on oxygen and antibiotics. Respiratory rate was 48/min and heart rate was 116/min; subcostal retractions were present and bilateral air entry was present. No cyanosis, no anemia, no icterus, no lymphadenopathy, and no edema were present. Head-to-toe examination revealed no positive findings. Anthropometry showed weight for length <–3 SD, weight for age <–3 SD and length for age <–2 SD. Cardiovascular examination was normal. Per abdomen examination showed mild hepatomegaly with palpable liver 2 cm below right costal margin.

Q1. What differential diagnosis should we consider?

Ans. This could be due to bacterial or viral pneumonia but after giving 15 days of antibiotics there is no improvement, so we have to think of other causes also. Other causes could be due to human immunodeficiency virus (HIV), TB, congenital heart disease, chronic foreign body, congenital malformations of lung such as congenital cystic adenomatoid malformations, lung hypoplasia, fungal infections, gastroesophageal reflux disease (GERD), or immunodeficiency disorders.

Q2. What investigations to be done?

Ans. Complete blood count revealed normal values, except mild leukocytosis and normal eosinophil count with raised erythrocyte sedimentation rate (ESR); chest X-ray (CXR) revealed bilateral pneumonitic patches. Mantoux test was done and results after 72 hours showed 10 mm of induration. Blood culture and sensitivity was done before starting antibiotics which revealed no growth of bacterial and fungal organisms. Sputum and gastrointestinal (GI) aspirate for acid-fast bacillus (AFB) and cartridge-based nucleic acid amplification test (CBNAAT) was sent and reports were normal. HIV serology was normal. Diagnostic bronchoscopy was done and no foreign body was found. Serum IgE levels were normal. 2D-ECHO was done and showed no major abnormality. Contrast-enhanced computed tomography (CECT) thorax showed consolidation of the right middle lobe of lung.

Discussion

After all investigations, the patient was diagnosed with TB and ATT (antitubercular therapy) was started after which the child recovered within 15 days. So in this case of TB, only investigations positive were TST and consolidation. According to new guidelines, in case of suspicion of TB in children, CBNAAT sputum is the initial investigation of choice. As this was negative, next investigation to proceed in TB was CXR and TST. If CXR showed highly suggestive lesions, irrespective of Mantoux test, we should do GI aspirate/induced sputum/BAL (bronchoalveolar lavage) for AFB. If AFB is detected in any of the above investigations, then it would be diagnosed as morphologically diagnosed TB. But in this case, no AFB was detected and so we had to label it as clinically diagnosed TB. Now coming to TST, it demonstrates the existence of host hypersensitivity to the tuberculosis bacillus proteins, usually as a result of MTB infection although it can also be induced with

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Bacillus Calmette–Guérin (BCG) vaccine or infection with environmental *Mycobacteria*. The TST only indicates that the person has been infected with TB previously or not, i.e. it gives idea about latent infection. It does not specify that the patient is having the disease. The sensitivity and specificity of TST were 80% and 85% respectively from a recent systematic review, which were similar to the newer serum immune-based diagnostic methods such as interferon gamma release assays (IGRAs). However, the sensitivity of the TST decreases in children of younger age and in HIV-infected children. False-positive results have been a concern with neonatal BCG vaccination and other environmental mycobacteria or incorrect method of administration. The correct method of administration of TST involves intradermal administration of 2 TU PPD-RT23 (properly stored and refrigerated) on the forearm and it is important to raise a wheal of at least 6 mm after the intradermal injection and the test is read 48–72 hours after an injection. Ballpoint or palpatory methods are used to read the induration. The width of reaction (induration) in the horizontal plane is noted for interpretation. Mantoux test or purified protein derivative (PPD) skin test is considered positive if the induration is 10 mm or more. Degree of reaction including necrosis and ulceration may not necessarily differentiate infected from diseased. If the patient returns for reading beyond 72 hours but by 7th day, a positive test can still be read. A repeat test may be needed, if there is an induration less than 10 mm and the suspect reports for reading beyond the stipulated time of 72 hours post injection. Repeat tuberculin test when required should preferably be done on the other arm. Another important cause of false positive tuberculin skin test includes previous BCG vaccine administration. In a meta-analysis of Mantoux test, it was found that patients who had received BCG vaccination were more likely to have a positive result. The relative risk was 2.12 [95% CI (confidence interval): 1.50–3.00] as compared to those without BCG vaccine. The effect of BCG on Mantoux test was less after 15 years of vaccination. The studies also show that 4 years after the neonatal BCG vaccination, there is no difference of TST reaction in the vaccinated and the unvaccinated children. Also it was stated that TST reaction due to BCG vaccination wanes of as age advances and the reaction usually does not exceed 10 mm. But in this case, it is very difficult to report that positive TST was due to BCG vaccination or prior infection. But current recommendation is for patients with a high risk for tuberculosis, the history of BCG vaccination should not be a consideration in the interpretation of the tuberculin test. Also this difference could be evidenced by the IGRA assays which assess the release of interferon-gamma (IFN-γ) to PPD in the peripheral blood. In case, the positive TST was due to BCG, IGRA will be negative, and in case of TB infection, IGRA will be positive. It recognizes *MTB* specifically and eliminates the cross-reactions in patient who have been exposed to atypical organisms as well as those who have received BCG immunizations. But according to our national guidelines, there is no role of immunological assays such as IGRAs. In this case, as it was clinically diagnosed TB, the patient was given ATT and he improved.

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CASE 2

A boy of 3 years of age, for over the past 4 months had evening and nocturnal fever with night sweats, general asthenia, and progressive weight loss. This symptomatology had persisted despite several outpatient treatments with nonspecific antibiotics. He had normal perinatal medical history and a birth weight of 3,100 g. BCG vaccine was administered at birth. He is the youngest of four siblings, all of whom were alive and well. He did not have any family disorder and parental consanguinity. His family had a low socioeconomic status and history of contact with TB (grandfather). At admission, he exhibited alertness, clinical anemia, severe malnutrition with a body weight of 9.1 kg, a height of 85.5 cm with mid-upper arm circumference (MUAC) 11 cm. His anthropometry interpretation was that weight for age <–3 SD and weight for height <–3 SD. He exhibited firm, mobile, confluent, nontender, bilateral, and cervical lymphadenopathy with normal looking skin. General examination showed pallor, not icteric, no cyanosis, and no clubbing. The pulmonary examination was normal as were those of the other organs. Per abdomen examination showed no organomegaly.

Q1. What differential diagnosis would you consider?

Ans. This child has prolonged fever with loss of weight over 3 months. Fever of prolonged duration suggests chronic bacterial infection or systemic inflammatory disorder. But systemic inflammatory disorder would have manifested with skin rash, arthritis, mouth ulcers, or other organ involvement over few weeks and so is unlikely. Other possibility that should be kept in mind are malignancy and collagen vascular diseases, the most common malignancy among children being hematological malignancy. Absence of severe anemia, purpura or bleeding, no organomegaly rules out hematological malignancies such as leukemia and lymphoma. Absence of skin rashes or any cutaneous manifestation, joint pain, and mucosal involvement also rules out collagen vascular diseases. Lymphadenopathy in this case can be related to infectious mononucleosis, cytomegalovirus (CMV), and tuberculosis. Slowly progressive chronic infections include tuberculosis, CMV, malaria, and kala-azar besides fungal infection. Malaria and kala-azar would have severe pallor and large splenomegaly. Primary streptococcal infection may present with prolonged fever but fever may not last for 3 months, and hence unlikely in this child. So, differential diagnosis in this child would include infections such as tuberculosis, CMV, and infectious mononucleosis.

Q2. What laboratory investigations to do?

Ans. Complete blood count with ESR, blood culture, C-reactive protein (CRP), CXR, TST, ultrasound abdomen, fine-needle aspiration cytology (FNAC) of cervical lymph nodes, sputum for AFB, and HIV serology.

Results

The complete blood count revealed hyperleukocytosis of TLC (total leukocyte count)—12,000 (48% neutrophils, 35% lymphocytes, 15% monocytes, and 2%

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eosinophils) and a hypochromic microcytic anemia of 7.3 g/dL. CRP was negative. ESR was raised. The HIV serology was negative. The blood cultures were negative. The intradermal reaction to tuberculin revealed an induration with a diameter of 15 mm. Testing for AFB in the expectorations was negative. The cervical lymph node biopsy with anatomical pathology examination indicated a caseating granuloma. The anteroposterior CXR was normal. The abdominal ultrasound revealed deep mesenteric lymphadenopathy of nonsignificant size. GI aspirate for AFB was negative for two consecutive samples.

Diagnosis of these cases described

A diagnosis of tuberculosis was made. The patient was treated with anti-tuberculosis agents according to RNTCP for 6 months and a nutritional support based on therapeutic milk and enriched local food items. After 6 months, there was a favorable change in his condition, with regression of the lymphadenopathies and a weight gain of 5 kg.

Take Home Message

- Tuberculosis is leading cause of morbidity and mortality in children.
- The presentation and symptomatology is vague, clinician should have high index of suspicion.
- Tuberculin skin test (TST) is one of the oldest method of diagnosis and still relevant, if method of inoculation and reading is correct.
- Various epidemiological factors should be considered in interpretaion of results.

SUGGESTED READING

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- Comprehensive coverage of all aspects of pediatric infectious diseases in a crisp and to-the-point format
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