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CASE REPORT

Childhood fever of unknown origin (FUO) – A Pandora box

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Abstract

Rheumatological illnesses are common differential diagnosis in the evaluation of childhood fever of unknown origin (FUO). We report an 11-year-old female child referred as FUO for eight months, possibly sarcoidosis. Her past records showed treatment for UTI, enteric fever in initial two months of fever. She was referred to tertiary institute due to recurrence of fever, multiple joint pain, right eye pain where she underwent evaluation for FUO. Investigation showed positive anti-nuclear antibody (ANA), elevated ESR. She was diagnosed as a case of juvenile idiopathic arthritis (JIA) with uveitis and treated with steroids, disease-modifying anti-rheumatic drugs (DMARDs). Two months later, she developed fever, multiple joint pain and worsening right eye visual acuity. Ophthalmic reevaluation revealed panuveitis and periphlebitis. CT chest showed mediastinal lymphadenopathy. With the above features, childhood sarcoidosis was suspected and treated with T. Azathioprine. Child was referred to our institute due to return of fever spikes. On examination, she had intermittent fever, plaque like lesion in cheeks? lupus pernio,, but skin biopsy was suggestive of SLE. Investigations showed positive ANA by indirect immunofluorescence (IIF), positive anti dsDNA (IIF), low complement (C3), positive immunoblot for SmD1, U1RNP, SSA/Ro60. Diagnosis was revised as childhood SLE with one clinical and three immunological criteria. She responded to steroids and immunosuppression. We report this case of childhood lupus presenting as FUO, multiple joint pain, uveitis, periphlebitis, without specific skin lesions, renal and hematological manifestations. We emphasize the need for meticulous evaluation and long term follow up for children with FUO diagnosed as rheumatological illness. The slow evolution of disease process and atypical presentation of common illnesses may lead to diagnostic dilemma.

Keywords: juvenile idiopathic arthritis; sarcoidosis; lupus pernio; childhood lupus; childhood FUO

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Introduction

Children presenting with fever of unknown origin (FUO) need meticulous clinical and laboratory evaluation. The diagnostic evaluation of a child with a prolonged fever of uncertain cause may be taxing and perplexing. Most serious infections rapidly declare themselves through clinical course and routine laboratory studies, culture. After excluding common childhood infections, the differential diagnosis to be considered includes tuberculosis, malignancies, rheumatological illness, immunodeficiency, drug fever etc. [1]. The workup of these illnesses involves a holistic approach involving various subspecialties and, often requiring an array of laboratory investigations.

Rheumatological illnesses common in Indian children includes juvenile idiopathic arthritis, childhood lupus and vasculitis (most often Henoch schonlein purpura) [2]. These conditions may mimic each other and may present together also as overlapping condition. We present a case of childhood FUO, labelled with multiple diagnoses and over the course of time evolving into a defined rheumatological condition.

Case presentation

We report an 11-year-old female child from rural background referred to our tertiary institute as FUO for eight months, possibly childhood sarcoidosis. We tried to elicit the past history of the child from parents and analyse the previous records of the child. In the initial two months of fever, the child was managed as E.coli culture positive urinary tract infection, and later as widal positive (1:80) enteric fever by a nearby general practitioner. Due to recurrence of fever in the next two months, child was referred to a tertiary hospital as fever of unknown origin. She also developed multiple joint pain and right eye pain during the course of this illness. Extensive investigations done in the tertiary hospital for tuberculosis, rheumatic heart disease, malignancy and immunodeficiency were negative. Ophthalmic evaluation was suggestive of right eye uveitis. Anti-nuclear antibody (ANA) done in this child was positive. She was diagnosed as undifferentiated juvenile idiopathic arthritis (JIA) (fever, polyarticular, ANA positivity & uveitis) and started on bridge therapy with steroids, disease-modifying anti-rheumatic drugs (DMARDs). After an initial phase of improvement in symptoms for two months, child developed fever spikes again with decreasing visual acuity in right eye. Ophthalmological reevaluation suggested progression of right eye uveitis to panuveitis with retinal periphlebitis. CT chest done in this child showed mediastinal lymphadenopathy. In view of panuveitis, periphlebitis and mediastinal nodes, diagnosis was revised as childhood sarcoidosis. She was started on steroids and azathioprine. She was advised follow up in outpatient department of tertiary care hospital.

Child was referred to our rheumatology institute due to return of fever spikes, with referral diagnosis of FUO, possibly sarcoidosis. Clinical examination was normal except for intermittent fever spikes, new onset plaque like lesion over cheeks, reduced right eye visual acuity. There was no history of photosensitivity, oral ulcers & bleeding manifestations. There was no history of loss of appetite or loss of weight. There was no active arthritis during the time of admission at our institute. Due to plaque like lesion in cheeks (Figure 1) without classical maculopapular rash or photosensitivity, lupus pernio was suspected. Dermatologist opinion obtained also echoed the same suspicion, but skin biopsy (Figure 2) was suggestive of SLE. She underwent an array of immunological investigations which showed positive ANA (IIF), positive anti dsDNA (IIF) with low complement C3 and normal C4. ANA profile showed positivity for SmD1 (3+), U1RNP (3+), SSA/Ro60 (3+). Investigations done to rule out secondary APLA, coombs test were negative. Patient's serum ACE levels were normal and repeat CT chest done in our institute showed normal lung fields and mediastinum. Patient's complete hemogram, renal function test, liver function test, urine PCR were within normal limits. Routine cultures of blood, urine were negative. The diagnosis in our case was finally revised as childhood SLE, with1 clinical (skin) and 3 immunological criteria (as per SLICC criteria). She had a SLEDAI score of 19 and was started on steroids & planned for immunosuppression. The child showed good response with remission of symptoms. She was advised FFA for fundus evaluation and advised follow up in lupus clinic.

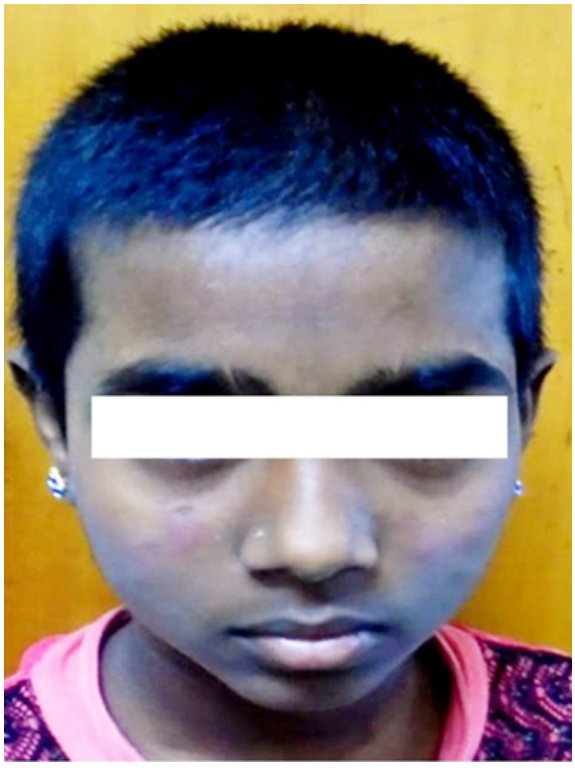

Figure 1: Plaque like lesion over face.

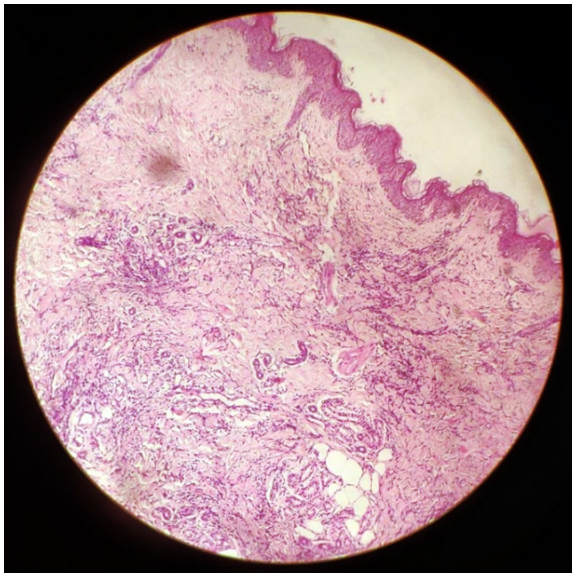

Figure 2: Skin biopsy showing flaky hyperkeratosis, acanthosis, follicular plugging, inflammatory infiltrate consisting of lymphocytes, histiocytes throughout dermis, around blood vessels and hair follicle.

Discussion

The evaluation of childhood FUO requires extensive clinical evaluation and laboratory support, which may be limited in rural settings. Further there may be lack of specialist availability hampering the management of such children in this part of the country. Our patient initially presented with fever and was managed as urinary tract infection based on urine culture showing 10^5CFU/ml E.coli. She was later diagnosed as enteric fever based on widal (1:80) positivity. E.coli growth in urine may occur because of poor technique of sample collection and widal (1:80) may occur due to anamnestic response. Alternatively child with connective tissue disease may be predisposed to such illness because of immunosuppression due to disease per se [3].

Child was referred to tertiary care centre due to persistence of fever along with appearance of new symptoms of multiple joint pain and eye pain. She was diagnosed as a case of JIA and started on steroids, DMARDS. The arthritis in lupus is predominantly non erosive type, often showing good response to steroids. In our case, the patient might have had temporary remission of symptoms due to use of steroids and DMARDS. A study from tertiary hospital in India showed that the most common cause of children presenting with FUO was rheumatological diseases, preceded only by infections [4]. In a study done by Dayal et al., JIA was the most common connective tissue disease frequently associated with FUO [5]. Ina multicentre study by Ana Paulo Sakamoto et al. in 852 childhood lupus patients, chronic arthritis was an early manifestation of childhood SLE, frequently mimicking JIA at the onset. Moreover it is predominantly polyarticular, often involving hands and ankles. Chronic arthritis as an isolated was observed at disease onset in 13/32(41%) childhood SLE patients and JIA was the first diagnosis in 18/32(56%). Chronic arthritis can mislead and delay the diagnosis of lupus since JIA was the first diagnosis in more than half of these patients [6]. In a retrospective study done by Jeamsripong et al., in children presenting with musculoskeletal complaints to rheumatology OPD, JIA was the diagnosis in 25.6% patients. The other conditions diagnosed in these children included Henoch-Schönlein purpura (16.1%), reactive arthritis (14.2%), and systemic lupus erythematosus (13.7%) [7].

The diagnosis was revised as childhood sarcoidosis as the patient developed progressive eye involvement in the form of panuveitis and periphlebitis along with recurrence of fever and mediastinal lymphadenopathy. Panuvetis and periphlebitis may occur as ocular manifestations

in sarcoidosis [8, 9]. But Sen DK observed that, sarcoidosis is notably absent as a cause of uveitis among 94 childhood cases of endogenous uveitis [10]. Childhood sarcoidosis frequently involved the lungs, lymph nodes (mediastinal lymphadenopathy) but may also involve eyes, skin, liver and spleen. Tuberculosis is the most common cause of mediastinal lymphadenopathy in this part of country. SLE may also cause lymphadenopathy commonly involving cervical, axillary, inguinal region. Hilar and mediastinal lymph node enlargement due to SLE is very rare [11, 12]. Mediastinal lymphadenopathy in lupus patients may respond to immunosuppression. This may be the reason for absent mediastinal nodes in repeat CT chest done in our case.

Child was referred to our rheumatology institute due to reappearance of fever along with plaque like skin lesion over cheeks, possibly lupus pernio. Her immunological profile and skin biopsy supported the diagnosis of childhood lupus. SLE may also present with many atypical skin lesions, apart from the classical maculopapular malar rash. Lupus pernio like skin lesion may also occur in 10.3% lupus patients [13]. Also clinical features of childhood onset lupus may vary from that of adults. Fever, hematological, seizures, ocular, renal involvement may be common in children, compared to adults presenting with malar rash, photosensitivity, and pleuritic [14]. Among the ocular manifestations in childhood SLE, uveitis is a rare entity. In a study by Gallagher et al., SLE as a cause of uveitis is estimated to be 0.47% (95% CI, 0.41% - 0.53%) [15]. In another study, uveitis is observed in 7/852 childhood SLE patients [16]. Perivascular sheathing is also rarely observed in SLE [17]. Uveitis may occur in lupus as an atypical manifestation due to vasculitis.

From the patient perspective, the chronicity of illness may demand economic and social support to the parents of such children, in addition to medical management of the child. In our case, the child presenting from rural background required frequent referral to tertiary hospital. This may result in displacement of family's home, workplace and bring in immense stress to the family.

Conclusion

We report this case of childhood lupus presenting as FUO, multiple joint pain, uveitis and periphlebitis, without common manifestations like malar rash, renal and hematological manifestations. The slow evolution of disease process and atypical presentation of common illness may lead to diagnostic dilemma. The treating physician may need to be alert in recognizing the atypical manifestations of common rheumatological illness. Also the treatment of rheumatological conditions may overlap, which may mask the real underlying problem. We emphasize the need for meticulous evaluation and long term follow up for children with FUO, diagnosed as rheumatological illness. The treating physician may consider revising the diagnosis based on the response to initial treatment and evolution of disease process during follow up. Repeated clinical evaluation, prudent utilization of laboratory tests, and post-discharge follow up remains the cornerstone of safe management of febrile children with rheumatological diagnosis.

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Conflict of interest

Authors declare no conflict of interest.

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