CASE OF THE MONTH

B Cell ALL with Pyrexia of Unknown Origin, Masquerading as Inflammatory Arthritis

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Abstract

We present a young male, with long standing fever, weight loss, bone pains, hepatosplenomegaly, cytopenias and severe joint pains. With normal peripheral smear and predominant joints involvement, he was started on corticosteroids. The partial response prompted the physician to continue the steroids. After some time, however, joints and bony pains worsened.

After referral to us, he was found to have multiple bony lytic lesions and peripheral smear suggested B cell ALL. So, presentation predominantly with musculoskeletal symptoms, a normal peripheral smear and a partial therapeutic response to steroids as treatment of Systemic Juvenile Idiopathic Arthritis, delayed the diagnosis significantly leading to complications.

So through our report we would like to stress that suspecting and diagnosing leukaemia early is important to prevent complications and resistance to treatment. An early bone marrow examination should also be instituted as a standard of care in peripheral smear negative patients.

Case Summary

A 17 year old male patient resident of Bihar presented to us with high grade continuous fever, joint pains and weight loss since 1½ years. Joint pains involved large joints of all the limbs, migratory type, asymmetrical with night time exacerbations without any associated redness or swelling. With these complaints he was diagnosed outside as a case of Juvenile Idiopathic Arthritis (JRA). Erythrocyte sedimentation rate (ESR) and C Reactive protein (CRP) were elevated but RF and ANA were negative. He has been receiving Disease modifying anti rheumatic drugs (DMARDS) and steroids with intermittent improvement in fever but the joint pains persisted. After investigations like Computed tomography scans, Ultrasonography etc, he was started on empirical ATT for Pyrexia of unknown origin (PUO) based on prevalence of Tuberculosis in our country and as the most common cause of PUO. Peripheral smear during all this time was normal except for pancytopenia.

Table 1: Investigations relevant to evaluation of fever. (Abbreviations: mg – milligram, g – gram, ng – nanogram, mm – millimeter, U – Units, dl – deciliter, L – Liter, RF- Rheumatoid factor, ANA- Anti nuclear antibody)

Parameter	Value
Haemoglobin	4 g/dl
TLC	2500 /dl
Platelet	102000 /dl
ESR	60 mm in the first hour
CRP	172.8 mg/L
LDH	2664 U/L
Ferritin	2095 ng/ml
Fibrinogen	670 mg/dl
Triglycerides	232 mg/dl
rK 39	Negative
RF	16
ANA	1:80

On examination, he had severe pallor, hepatosplenomegaly and tender joints with no generalized lymphadenopathy. With these findings we kept the differentials of Adult onset still disease (AOSD), Lymphoma/ Leukaemia, Kala Azar, Secondary Macrophage activation Syndrome and TB. Important investigations are mentioned in Table 1.

Peripheral smear showed pancytopenia. With these lab investigations we also thought it to be a case of Adult Onset Stills Disease (AOSD) with Macrophage activation syndrome (MAS) and treated with DMARDs. But since the case was not completely fitting into AOSD criteria (Patient had leucopenia in contrast to expected leukocytosis) and previously treated on similar lines with no improvement and severe weight loss, anorexia,symptoms of joint pains out of propotion to signs with severe pancytopenia, organomegaly and elevated LDH , our suspicion for haematological malignancy was still high, so we did not start the patient on steroids.

We did a CECT chest and abdomen which revealed hepatosplenomegaly with hypodense cortical lesions bilateral kidney. Multiple lytic/sclerotic lesions were present in pelvic bones, bilateral femur and multiple ribs. This radiological finding strengthened our suspiscion for haematological malignancy. Bone marrow touch smear showed near total replacement by blasts which were MPO negative, Peripheral smear showed 70% blast (Figure 1). Flow cytometry analysis of the bone marrow aspirate revealed CD 45 dim blasts which were CD 34 +, CD 19 +, cCD 79a dim +, CD 81+, CD 58+, HLA DR +, CD 10 +, CD 123+, CD 38+, and negative for cMPO, sCD 3, cCD 3, CD 7, CD 20, CD 22, and CD 117 (Table 2). Thus diagnosed as B cell ALL. He was put on standard B ALL chemotherapy protocol. The patient has completed the induction phase of treatment with oral Prednisolone (60 mg/m^2), intravenous Vincristine (1.5 mg/m^2), L-Asparginase 10000 IU/m^2 and is doing well. He is planned to be shifted on to consolidation and maintenance phase.

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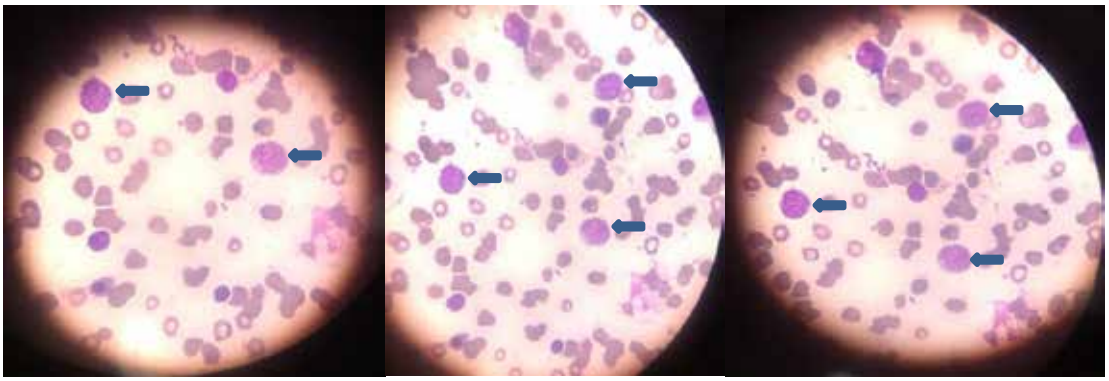

Fig. 1: Peripheral smear showing multiple lymphoblasts – large cells with rounded nucleus, homogenous thick chromatin with increased N:C ratio. Scanty agranular cytoplasm

Table 2: Flowcytometric analysis of the bone marrow aspirate

Positive	Negative
CD 34	cMPO
CD 19	sCD 3
CD 79a	CD 7
CD 81	CD 20
CD 58	CD 22
CD 10	CD 117
CD 123	
CD 38	

Discussion

The usual clinical features suggesting ALL are a young patient presenting with fever, weight loss, night sweats with pancytopenia, lymphadenopathy and hepatospleenomegaly.[1,2] This patient had symptoms of fever, joint pains and weight loss with joint pains as predominant manifestation. Common clinical differentials of such patients include haematological malignancy, Tuberculosis, Leishmaniasis, Hemophagocytic lymphohistiocytosis (HLH), Systemic Juvenile Rheumatoid arthritis and adult onset stills disease.

Arthralgia or even signs of arthritis is a frequent finding in ALL ranging from (18.5%-20%).[3,4] Malignancies are to be suspected when pain is disproportionately severe compared to the physical examination findings, and when pancytopenia, and an elevated LDH level are present. Joint pain being the predominant complaint in our patient diverted the attention to a rheumatological diagnosis. Few studies have shown that osteoarthalgia ranges from 8.4 to 35 %[5,6] in pediatric acute leukaemias. Osteoarthralgia in leukemic patients tends to be migratory, asymmetric, mono- or oligoarthralgia and poor inflammatory findings for their severe pain[6,7] but often indistinguishable from early stage of JIA. Unlike JRA, pain from leukemia may, but not always, be point tenderness over the diaphysis rather than diffusely over the joint(s). Our patient also had diffuse pain. Such presentation can occur in 15% to 30% of ALL cases at disease onset, when peripheral blood changes are subtle or even absent.

Infact we also initially thought it could be a case of AOSD as he was partially fitting in the Yamaguchi criteria.[5] He did not have the typical rash or leukocytosis. In the background of pancytopenia, we suspected Macrophage activation syndrome (MAS) secondary to AOSD. Although our working diagnosis was AOSD with MAS, we did not initiate steroids because to make a diagnosis of AOSD we hadn't excluded infection or malignancy which is an important prerequisite in this diagnosis. Also, since we had suspicion of haematological malignancy which would partially respond to steroids and mask the diagnosis. Earlier too, probably the diagnosis of Systemic Juvenile Rheumatoid arthritis was rushed into without adequately ruling out malignancy.

There was clearly a delay in the diagnosis – 1.5 yrs in our case. The mean Symptom Presentation Interval(SPI) in a study by Marwaha et al was 91 days (range: 30- 365 days) while the mean presentation diagnosis interval was 7.6 days (range : 2- 18 days).[6] Thus, even after admission there was an average diagnostic delay of about a week underscoring the importance of appropriate investigations to rule out ALL in patients with atypical features of JIA. Other investigators have also reported a mean SDI of 3–5 months with a range of up to18 months. Why this delay occurs is probably due to the close mimic of symptoms, the negative peripheral smear in early cases, partial response to steroids.

Study by Jones et al has shown that 75% of children with ALL did not have blasts in the peripheral blood at the time of evaluation by pediatric rheumatologists.[8] Thus underscoring the importance of bone marrow examination in such patients. Our case also had repeated peripheral smears negative for blasts leading to a possible delay in the diagnosis.

The 3 most important factors that predicted a diagnosis of ALL in the study by Jones et al were low white blood cell count (< 4 x 10(9)/L), low-normal platelet count (150-250 x 10(9)/L), and history of night time pain, which were all present in our patient. In the presence of all 3, the sensitivity and specificity for a diagnosis of ALL were 100% and 85%, respectively. Rheumatologists usually anticipate increased, not decreased, WBC and platelet counts when considering a diagnosis of systemic JRA, and increased platelet counts are not unusual for any type of JRA.

ANA as a test is not a good test to rule in a diagnosis of a rheumatological condition as it can be positive in ALL as well. A twofold or above increase of LDH is almost exclusively seen among children with ALL.[9] Although the frequency of finding an abnormal radiograph was similar between ALL and JRA, presence of radiolucent bands, lytic lesions, and sclerotic lesions should alert the physician to consider malignancy until proven otherwise. Our patient too had an elevated LDH and bony lytic lesions.

There were multiple observations which were made as to where the

diagnosis was missed. If we look at his clinical presentation it is important to note that it was not just joint pains but he had bone pains with nocturnal exacerbations which was missed and the significant weight loss was never explained. His pancytopenia was not worked up, although a peripheral smear was always normal. The probable hypothesis for this could be a partial response of ALL to steroids. Before labelling the patient as AOSD or JIA and starting on steroids, malignancy was not excluded despite persistent pancytopenia. Thus bone marrow examination is important in every patient presenting with atypical features of JIA and a normal peripheral smear to rule out an underlying haematological malignancy.

Conclusion

We presented here a case of B cell ALL which was for more than a year treated AOSD with steroids. So we would like to conclude by emphasising that before labelling a patient as AOSD, a bone marrow examination is important in every patient presenting with atypical features of JIA and a normal peripheral smear to rule out an underlying haematological malignancy. Because the treatment of the condition with steroids might mask the diagnosis of an underlying haematological malignancy further delaying the diagnosis and later the malignancy may become steroid resistant.

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