Still's Disease–A Case of Diagnostic Dilemma

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Abstract

Still's disease is an auto-inflammatory multisystem disease characterized by high spiking fever, salmon-colored rash that comes and goes, arthritis and other varieties of systemic manifestations. The puzzling fever and leukocytosis and high serum level of procalcitonin mistakenly may lead to diagnosis of severe bacterial infection or sepsis. But use of broad-spectrum antibiotic fails to improve the condition. It may mimic other multisystem autoimmune rheumatic diseases, but autoantibodies are negative. It may resemble the malignancies like leukemia and lymphoma, but lymph node biopsy and bone marrow study does not support. We have reported a case of Still's disease in a 14-year-old young boy. Initially he presented like a viral illness, but high fever persisted for more than 4 weeks associated with body ache and skin rash without any arthritis. He had cervical lymphadenopathy, mild hepatosplenomegaly, pleural and pericardial effusion. He had persistent leukocytosis, high serum procalcitonin and high serum ferritin but low serum iron. Bacterial infection and sepsis were excluded, hematologic malignancy was ruled out by lymph node biopsy and bone marrow examination. There was no conclusive evidence of tuberculosis. Still a therapeutic trial was given but failed to produce any benefit. After exclusion of all the possible differentials and basing on diagnostic criteria he was diagnosed as a case of Still's disease. With the use of steroid and immunosuppressive agent his condition improved dramatically and now he is leading a normal life.

Key-words: Still's disease, Fever of unknown origin, Skin rash, Juvenile Idiopathic Arthritis.

Introduction

Systemic onset Juvenile Idiopathic Arthritis (SoJIA) is one of several rheumatic diseases that affect children below 16 years old. The whole body is affected, not only the joints. It is the rarest form of JIA. It is also called Still's disease or Still's syndrome, after the name of pathologist, Dr. F Still, who first reported the illness[1]. Adult version of the disease is called adult onset Still's disease. Classically the patient present with high spiking fever transient erythematosus skin rash and arthritis. There may be lymphadenopathy, hepatosplenomegaly, serositis. Fatality is due to secondary infection, cardiac complications, amyloidosis and macrophage activation syndrome. It may present as fever of unknown origin (FUO). It may be confused with septicemia, leukemia, lymphoma, disseminated TB, SLE, systemic sclerosis, MCTD and other multisystem diseases[2,3].

Diagnosis is often delayed or missed due to rarity of disease, non-specific clinical manifestation, incomplete form of the disease and lack of specific diagnostic test. It is a diagnosis of exclusion. However, typical clinical presentation along with neutrophilic leukocytosis in absence of bacterial infection and high serum ferritin level in absence of iron overload gives strong clue to the diagnosis. High index of suspicion, adequate knowledge and experience of physician are required to diagnose and manage such cases. During last 9 years we have diagnosed 5 cases of Still's disease and 3 cases of adult onset Still's disease in CMH Dhaka. We are presenting one case on SoJIA which was diagnosed in March 2018. The main aim of reporting the case is to generate awareness amongst the physician regarding diagnosis and treatment of such rare disease, especially in the setting of fever of unknown origin.

Case Report

A 14-year-old boy was admitted to CMH Dhaka on 26 February 2018 with short history of sore throat for 7 days, high grade fever and bodyache for 4 days and erythematous skin rash in chest and abdomen (Figure-1) for 2 days. There was no history of cough, SOB, headache, red eyes, vomiting, arthralgia, dysuria, diarrhea or bleeding manifestation. Past medical history was unremarkable. In addition to fever and skin rash he had 2 enlarged left cervical lymph nodes 1-2 cm in size and mildly congested throat. Examination of chest and precordium was normal and there was no organomegaly. Initially it was thought to be viral origin, but his fever was persisting for more than 4 weeks. His investigation reports showed very high neutrophilic leukocytosis (TLC 19.3 x 10^9/L with 93% neutrophils), ESR 97 mm in first hour and CRP was positive. LFT, RBS, serum creatinine etc were normal. Dengue NS1 antigen was negative. Chest X-ray showed bilateral mild pleural effusion and cardiomegaly (Figure-2). USG of abdomen showed mild hepatosplenomegaly. Blood C/S, urine C/S, throat swab C/S, sputum C/S and AFB were negative. Pleural fluid study revealed exudative fluid with raised ADA but no organism could be isolated. FNAC from cervical lymph node showed reactive hyperplasia. His serum procalcitonin was high (2.43 ng/ml) and repeated blood samples showed rising neutrophilic leukocytosis (up to 36 x 10^9/L with 93% neutrophils) without immature cells in PBF and very high ESR (110 mm in first hour). So empirically he was treated with antibiotics without any benefit. Further investigations were done to find out the underlying cause. His ECG was normal and echocardiogram showed mild pericardial effusion. ANA, anti ds DNA, RA factor, anti CCP antibody, c-ANCA, p-ANCA etc were negative. PT, APTT, fibrinogen, FDP and D-dimer were within normal limit. Bone marrow examination was unremarkable. CT scan of chest revealed bilateral pleural and pericardial effusion (Figure-3) and CT scan of abdomen showed hepatosplenomegaly (Figure-4). Basing on suspicion of disseminated TB, he was also started with ATT and continued for about 2 weeks without any improvement. Meanwhile his iron profile showed low serum iron but very high ferritin level (19300 ng/ml, normal value 22-320 ng/ml) and high LDH (1082 U/L), low serum albumin (24 gm/dl).

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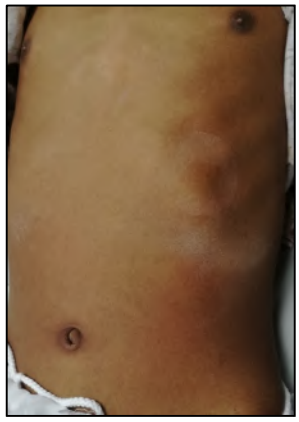

Figure-1: Erythematous rash in chest and abdomen

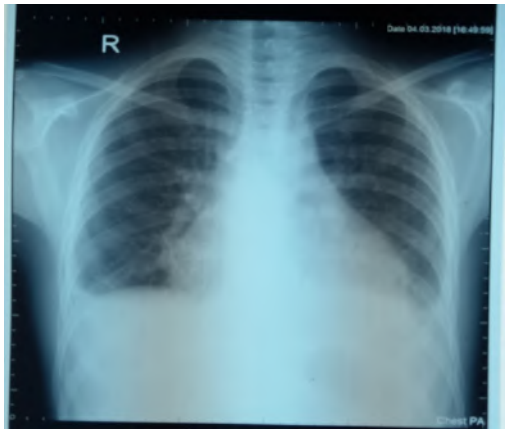

Figure-2: CXR showing bilateral mild pleural effusion and cardiomegaly

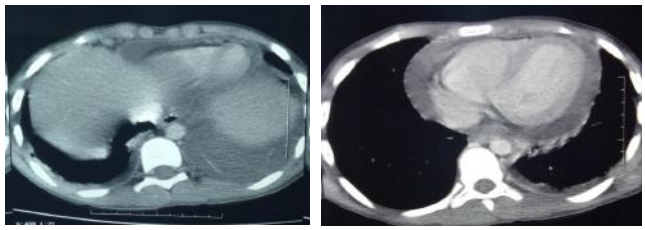

Figure-3: CT scan of chest showing bilateral pleural effusion and pericardial effusion

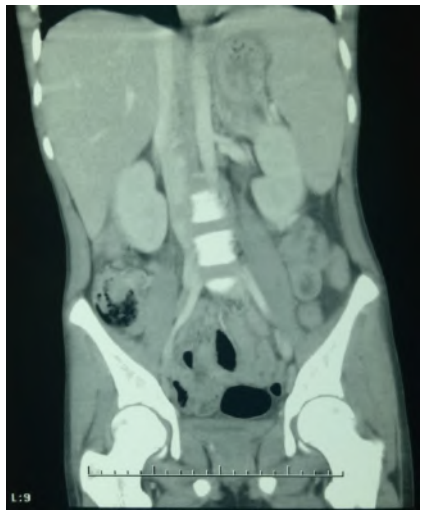

Figure-4: CT scan of abdomen showing hepatosplenomegaly

Therefore, considering the clinical features and investigation reports and after exclusion of all other possible differential diagnoses, he was diagnosed as a case of SoJIA/Still's disease. Accordingly, treatment started with IV Methyl Prednisolone daily for 5 days followed by high dose oral prednisolone. Injection Methotrexate S/C weekly along with Tab Folic acid on following day was given. With this treatment he responded well and became afebrile within 3-4 days and skin rash and pleural effusion disappeared quickly. Lymphadenopathy and hepatosplenomegaly regressed gradually. Leukocytosis became normalized within few weeks and serum ferritin also gradually decreased. Patient was discharged on 10 April 2018 with advice to continue tapered dose of prednisolone along with oral methotrexate and folic acid, iron, calcium and vitamin D supplements. He was followed up at 1, 3, 6 and 12 months. He became symptom free and now he is leading a normal life with minimum maintenance dose of prednisolone and methotrexate.

Discussion

Still's disease is an auto-inflammatory multisystem disease characterized by high spiking fevers, salmon-colored rash that comes and goes, arthritis and other systemic manifestations in a child who is less than 16-year-old[4]. It is diagnosis of exclusion. It makes up 10-20% of Juvenile Idiopathic Arthritis and affects boys more than girls. The ratio is reversed in case of Adult onset Still's disease[5]. The Yamaguchi criteria is used to diagnose this disease (Table-I)[1]. To make a definitive diagnosis, at least 5 or more criteria must be present with at least 2 major criteria. Presences of any infection, malignancy or rheumatic diseases are exclusion criteria.

Table-I: Yamaguchi criteria[1]

Major Criteria	Minor Criteria
Fever >39^{0}C, intermittent, > 1 week	Sore throat
Typical rash	Lymphadenopathy
WBC>10000 /mm^3 (>80% Granulocytes)	Hepatomegaly and/or Splenomegaly
Arthralgia and/or arthritis >2 weeks	Abnormal liver function test
	Negative rheumatoid factor and ANA

Morbiliform, macular, often with central clearing appears on limbs, trunk and less commonly on face, neck, palm and sole[6]. The rashes are evanescent (not fixed), salmon colored, migratory and may be pruritic in 5% cases. Koebner phenomenon may occur[7]. The rashes correlate with the acute febrile illness. Early affected joints include the wrists, knees and ankles. The presentation can be polyarticular (41%), oligoarticular (40%) or monoarticular (7%). It may progress to a chronic progressive state in 33-50% patients[8]. It may present with a wide range of systemic manifestations, starting from lymphadenopathy, splenomegaly, hepatomegaly, serositis (pericarditis, myocarditis), myositis. Neurological manifestations like seizures, meningismus, irritability and decreased level of consciousness may also occur. Still's disease is not associated with uveitis[9].

Since it is a disease of exclusion, a wide range of investigations need to be done. CBC, PBF, CRP, chest x-ray, USG of whole abdomen, liver function, serum ferritin all gives hints towards the diagnosis. Blood and urine C/S, autoantibodies like ANA, Anti ds-DNA, RA, lymph node biopsy and bone marrow study are done to exclude infections, autoimmune diseases hematological diseases[10]. Once

diagnosed, it can be treated adequately with NSAIDs, prednisolone, DMARDs like MTX, Azathiprine, Hydroxychloroquine. Biologics like IL-1 and IL-6 receptor antagonists, Anti TNF alpha and Anti CD-20 are effective options for individuals who can afford. Plasmapheresis, IVIg and autologous stem cell transplantation are some advanced options[11]. Inadequately treated cases may present with joint destructions, hepatitis, pancreatitis, aseptic meningitis, sensory neural deafness, DIC, TTP, Amyloidosis, Macrophage activation syndrome etc. Patient may die from Macrophage activation syndrome, intercurrent infection, amyloidosis, cardiac failure, aseptic meningitis or DIC. 25% cases usually progress to severe destructive arthritis and mortality rate is 4% in USA and Canada, and 2.1% in Europe[12].

Conclusion

Still's disease is a rare disease. High index of suspicion, adequate knowledge and experience is required to diagnose the disease. There is no single test that can confirm the diagnosis of Still's disease. It is a diagnosis of exclusion. Careful clinical history, physical examination, laboratory test and exclusion of all possibilities can help to reach the diagnosis. The treatment is rewarding and can prevent mortality and morbidity. Long term follow-up is required.

References

1. Luthi F, Zufferey P, Hofer MF et al. ""Adolescent-onset Still's disease: Characteristics and outcome in comparison with adult-onset Still's disease". Clin Exp Rheumatol 2002; 20 (3):427–30.

2. De Benedetti F, Meazza C, Vivarelli M et al. Functional and prognostic relevance of the 173 polymorphism of the macrophage migration inhibitory factor gene in systemic-onset juvenile idiopathic arthritis. Arthritis Rheum 2003; 48(5):1398–407.

3. DeWitt EM, Kimura Y, Timothy B et al. Consensus treatment plans for new-onset systemic juvenile idiopathic arthritis. Arthritis Care & Research 2012; 64(7):1001–10.

4. Vastert SJ; Jager WD, Noordman BJ et al. IL-1 receptor antagonist restores IL-18 NK cell axis in systemic JIA. Journal of Translational Medicine 2012; 10(Suppl 3):45.

5. Wulffraat NM; Jager WD, Prakken B et al. Early effects of Anakinra in corticosteroid naïve SOJIA patients. Pediatric Rheumatology 2008; 6 (Suppl 1):29.

6. Gattorno M, Piccini A, Sara DL et al. The pattern of response to anti–interleukin-1 treatment distinguishes two subsets of patients with systemic-onset juvenile idiopathic arthritis. Arthritis & Rheumatism 2008; 58(5):1505–15.

7. Singh-Grewal D, Schneider R, Bayer N et al. Predictors of disease course and remission in systemic juvenile idiopathic arthritis: Significance of early clinical and laboratory features. Arthritis & Rheumatism 2006; 54 (5):1595–1601.

8. Hoffman F. Background Information. Roche Group Media Relations. http://www.roche.com/med-ra-sjia.pdf.pdf

9. Davies R, Southwood T, Kearsley-Fleet L et al. Standardized Mortality Rates are Increased in Patients with Severe Juvenile Idiopathic Arthritis. Oxford Journal of Rheumatology 2015; 54(1):i153.

10. Still GF. A special form of joint disease met with in children. Doctoral dissertation, Cambridge, 1896.

11. Bywaters EG (March 1971). Still's disease in the adult. Ann Rheum Dis 1971; 30(2):121–33.

12. Cimaz R, Scheven AV, Hofer M. Systemic-onset juvenile idiopathic arthritis: The changing life of a rare disease. Swiss Medical Weekly 2012; 142:w13582.