ADULT ONSET STILL'S DISEASE: A DIAGNOSTIC DILEMMA

Koirala D, Pathak UN, Adhikari P, Shrestha R, Neupane C

Department of Internal Medicine, Nepal Medical College Teaching Hospital, Attarkhel, Gokarneshwor-8, Kathmandu, Nepal

ABSTRACT

Adult-onset Still's disease (ASD) is a rare clinical entity with unknown etiology, characterized by arthritis, fever, evanescent rash and other systemic presentations. This case report describes a 19-year-old male who presented with sore throat, fever, arthritis, evanescent rash, raised liver enzymes and hyperferritinemia. It also reveals the diagnostic dilemma faced during the diagnosis of the disease. He was diagnosed to have ASD based on Yamuguchi criteria after the exclusion of other potential diagnoses. Patient was treated with prednisolone and there was a good response with improvement in symptoms and laboratory indices.

KEYWORDS

Adult onset Still's disease, arthritis, fever, evanescent rash, Prednisolone

CORRESPONDING AUTHOR

Dr. Dinesh Koirala,
Department of Gastroenterology
Maharajgunj Medical Campus, Tribhuvan University Teaching Hospital, Kathmandu, Nepal
Email: destinydins@gmail.com
Orcid No: https://orcid.org/0000-0002-5556-2786
DOI: https://www.doi.org/10.3126/nmcj.v23i1.36240

INTRODUCTION

Adult Still's disease (ASD) is an inflammatory disorder characterized by quotidian (daily) fever, arthritis, and an evanescent rash. First described in children by George Still in 1896, "Still's disease" has become the eponymous term for systemic juvenile idiopathic arthritis.[1] In 1971, the term "adult Still's disease" was used to describe a series of adult patients who had features similar to the children with systemic juvenile idiopathic arthritis and did not fulfill criteria for classic rheumatoid arthritis (RA).[2] ASD is characterized by the classic triad of persistent high spiking fever, arthralgia, and salmon colored skin rash. However, diagnosing ASD is often difficult due to the presence of several nonspecific symptoms and the absence of characteristic serological biomarkers.[3] None of the above signs is sufficient to establish the diagnosis, and several other diseases (notably infectious or neoplastic diseases) may produce similar symptoms. Thus, ASD often corresponds to a "diagnosis of exclusion", meaning that the diagnosis is retained when the other possible diagnoses have been completely ruled out.[4] The evolution of the disease is difficult to predict; it may be limited to only one flare or may recur over a period of several months or years.

CASE REPORT

Nineteen years old boy from Kathmandu at first noticed pruritic and localized rashes on bilateral forearm and abdomen 5 months back. There was no fever, joint pain and sore throat. There was no history of intake of any drugs and no history of allergy to any substances or drugs. Gradually the severity of itching increased so he went to a nearby hospital and consulted with a Dermatologist. He was managed with a provisional diagnosis of acute dermatitis. He was given injection methylprednisolone 125 mg intramuscular single dose, steroid cream to apply topically and tablet Fexofenadine for 5 days. But the rashes did not subside. Instead it progressed to the back and abdomen. He also developed sore throat and difficulty in swallowing after 10 days of developing the rash. But there was no history of fever, cough, breathlessness, palpitation, joint pain, skin nodules, black colored urine, limb swelling, facial puffiness and ear discharge. Then he again consulted in the previous hospital. He was then advised to take prednisolone, cetirizine and azithromycin for 5 days. Following the intake of these drugs, sore throat subsided and skin rashes decreased.

After 1 month, he developed similar rashes all over the body starting from previous sites and spreading to the limbs along with severe joint pain, redness, swelling at both knees and elbows along with morning stiffness for 10-15 minutes. Arthritis was non migratory and symmetrical. Small finger joints were not involved. He also developed fever ranging from 103- 105°F once daily (quotidian in nature) without chills, rigor and sweating. Then he took some analgesics from a nearby clinic. Gradually, the fever, rashes and joint pain decreased in severity.

Again, after few days he re-developed throat pain, joint pain, rashes and fever which was similar in nature as previous which subsided after taking some oral antibiotics. After 2 weeks, he developed similar symptoms which subsided after admitting and treating with injection ceftriaxone. He again presented after 10 days with similar high spike fever once daily and joint pain. He was given chloroquine empirically in view of clinical malaria. After that fever and joint pain subsided for about 2 weeks; only to re-develop similar symptoms again. He had lost 4 kg in last 4 months.

On examination, patient had fever which was present once daily about 102-103°F. Rest of the day he was afebrile. Vitals were normal. There was no pallor, icterus, cyanosis, clubbing and edema. Multiple discrete lymph nodes were palpable in the cervical chain ranging from 0.5-1 cm in size, non-tender, soft, mobile with intact overlying skin. Axillary and inguinal lymph nodes were not palpable. Rashes were seen over the abdomen, arms and thighs. These were bluish, grouped, confluent, non-blanching and maculopapular. Throat examination was normal. Respiratory, cardiovascular examination was normal. On abdomen examination spleen was palpable 1 cm below the left subcostal margin which was non tender. Liver was not palpable.

Investigations were done. Complete blood count showed leukocytosis (15,300/cumm) with neutrophilia (N, 79%) and thrombocytosis (6,03,000/cumm). Kidney function test was normal. Liver function test, ALT was 141 U/L and AST was 86 U/L. ESR was 60 mm in first hour and CRP was positive. LDH was 1835 U/L. However, Direct Coombs test, Rheumatoid factor, ANA, dsDNA was negative. ASO titer, CPK total, lipid profile, thyroid function test, uric acid, chest X-ray and ECG was within normal limits. Skin scraping from the rash showed no fungal elements. Blood culture also showed no growth. Serology was non-reactive. Iron profile showed elevated ferritin 20,945 ng/ml (Normal value=30-400 ng/ml). There was splenomegaly on USG. Cervical lymphadenopathy was there but revealed no material on fine needle aspiration (FNA). Ophthalmological examination showed soft exudate and choroiditis in left eye and vitritis in bilateral eyes.

A provisional diagnosis of ASD was made and the patient was started on oral prednisolone. The symptoms gradually improved. Clinical symptoms like throat pain, rashes, joint pain, eye signs, lymphadenopathy, splenomegaly gradually

resolved and the lab parameters were also within normal limits in a period of 2 months of follow up.

DISCUSSION

Adult Still's disease is an uncommon clinical entity which usually presents as fever of unknown origin.[5] Many other systemic manifestations such as lymphadenopathy, serositis, pericarditis, endocarditis, myocarditis and organomegaly may occur, along with laboratory test abnormalities including leukocytosis, high serum ferritin levels and elevated liver enzymes. ASD is a rare disease that affects younger people, the majority presenting between 16 and 35 years of age.[6] The precise etiology of ASD is unknown. However, many hypotheses have been proposed in the pathogenesis of ASD. Chen *et al.* demonstrated a predominance of T helper cell (Th1) cytokines in patients with active untreated ASD. Disease susceptibility correlates with particular alleles of each serologically or cellularly defined specificity, such as HLA-DRB1*0801 of DR8 and HLA-DPB1*0201 of DPw2.[7] The prevalence of the disease is 0.16 cases per 100,000 people, with an equal distribution between the sexes. It has bimodal age distribution, with one peak between 15-25 years and the second between the ages of 36-46 years.[8]

Clinically, the most classic manifestations of ASD are fever, rash, sore throat, and arthralgia with fever and arthralgia being the most common among them.[9] The fever is usually a high spiking quotidian fever (≥39 °C) that occurs in the evening with return of normal temperature the next day morning. The fever is often accompanied by other symptoms or could present as pyrexia of unknown origin alone. Non suppurative pharyngitis is one of the common earlier findings in ASD and can either precede the development of fever or can occur along with other symptoms. The pharyngitis in ASD patients is proposed to be from underlying cricothyroid perichondritis. The characteristic rash in Still's disease is a transient, non-pruritic, salmon colored, macular, or maculopapular lesion often observed during febrile episodes. The most common locations of the rash include the trunk and proximal extremities. In one-third of patients, the rash may be mildly pruritic and can develop at sites of cutaneous injury due to pressure or trauma, which is referred to as Koebner's phenomenon.[3] Intense arthralgia is ubiquitously seen in all ASD patients. The most commonly involved joints are the knees, wrists, ankles, and elbows. ASD often involves the distal interphalangeal joints of the hand, which are commonly spared in inflammatory joint disease of the young adults (e.g., SLE and rheumatoid arthritis) with the exception of psoriatic arthritis.[10]

In all ASD patients, throat culture and viral serology are negative and, therefore, antibiotic therapy is ineffective. Lymphadenopathy develops in 44–90.0% of ASD patients and may raise the suspicion of lymphoma initially.[11] Hepatosplenomegaly can be a common manifestation in the early phase of the disease.[12] In one study from Japan, which included 71 patients who satisfied criteria for ASD, 16 of 71 patients (23.0%) subsequently met the American College of Rheumatology (ACR) classification criteria for RA after a median follow-up of 18 months (range: 6-132 months).[6]

The laboratory findings include rise in acute phase reactants like leukocytosis, neutrophilia, thrombocytosis with a rise in ESR, CRP and ferritin. Serum ferritin is markedly elevated i.e. >3000 ng/mL (N: 40-200 ng/mL) in 70.0% of patients (elevations correlate with disease activity so suggested as a marker to monitor the response to treatment.[9] Bone marrow aspiration shows hyperplasia of granulocytic precursors, hypercellularity (75.0%), increased histiocytes (25.0%), and the presence of hemophagocytosis (17.0%).[13]

Japanese criteria, often termed the Yamaguchi criteria, have the highest sensitivity in patients with a definite diagnosis of ASD.[14] Yamaguchi criteria requires the presence of 5 features, with at least 2 being major diagnostic criteria. Infection, malignancy, or other rheumatic disorder known to mimic ASD should be ruled out first prior to considering ASD as a diagnosis.

Yamaguchi Criteria for Adult Onset Still's Disease

Major criteria	Minor criteria
Fever of at least 39°C (102.2°F) lasting at least one week	Sore throat
Arthralgia or arthritis lasting 2 weeks or longer	Lymphadenopathy
A non-pruritic macular or maculopapular skin rash that is salmon-colored in appearance and usually found over the trunk or extremities during febrile episodes	Hepatomegaly or splenomegaly
Leukocytosis (>10,000/microL), with at least 80.0% granulocytes	Abnormal LFT, particularly elevations in AST, ALT and LDH
	Negative tests for antinuclear antibody (ANA) and rheumatoid factor (RF)

The goals of therapy are to control physical signs and symptoms of inflammation (e.g. fever, rash, morning stiffness, joint pain, and swelling) and, secondarily, controlling laboratory indices of inflammation (e.g. elevations in ESR and CRP), preventing end organ damage, minimizing risk of adverse effects of therapy, including long-term effects of glucocorticoids.[9] NSAIDs and steroids form the base of treatment in mild to moderate disease whereas DMARD is required for severe disease.[4] We have to initiate prednisolone at 0.5 to 1 mg/kg/day, depending upon the severity of disease. Approximately 70.0% respond to glucocorticoids alone within hours to a few days. Once symptoms controlled for at least 1 month and laboratory indices normalized, rapidly taper to a low maintenance dose for 2-3 months to maintain control of signs and symptoms of disease. If unable to progressively taper glucocorticoids to an acceptable level (e.g. less than 10 mg daily), treatment with a traditional or biologic DMARD should be initiated. The DMARD of choice depend on the predominant manifestation of the disease. For arthritis predominant, methotrexate or a TNF inhibitor (similar to RA) are used. For systemic inflammation predominant anakinra (IL-1 inhibitor), tocilizumab, or canakinumab are preferred.[15] If the disease is severe i.e. presence of life-threatening organ involvement such as severe hepatic involvement, cardiac tamponade, and/or DIC, pulse therapy with high-dose intravenous glucocorticoids is followed first by combination therapy consisting of oral glucocorticoids plus anakinra.[4]

In our case on reviewing the history, examination and investigation, and then excluding the other differential diagnosis, we came to a conclusion of ASD as the final diagnosis. Patient was started on steroids which alleviated all the symptoms and the lab parameters as well.

In conclusion, ASD is a diagnostic dilemma for physicians as it presents with a combination of nonspecific symptoms that can be caused by a wide variety of diseases. However, the key point to remember is that, for patients who present with prolonged and unexplained fever combined with musculoskeletal symptoms and macular rash, the differential diagnoses should always include ASD. Timely diagnosis and treatment of the disease can prevent complications and lead to a favorable prognosis with improved quality of life.

REFERENCES

1. Still GF. On a form of chronic joint disease in children. *Arch Dis Child* 1941; 16: 156–65.
2. Bywaters EGL. Still's disease in the adult. *Ann rheum Dis* 1971; 30: 121–33.
3. Garcia FJN, Pascual M, López De Recalde M *et al.* Adult-onset Still's disease with atypical cutaneous manifestations. *Medicine (Baltimore)* 2017; 96: 1–8.
4. Gopalarathinam R, Orlowsky E, Kesavalu R, Yelaminchili S. Adult Onset Still's Disease: A Review on Diagnostic Workup and Treatment Options. *Case Rep Rheumatol* 2016; 2016: 1–6.
5. Mert A, Ozaras R, Tabak F, Bilir M, Ozturk R, Ozdogan H, *et al.* Fever of unknown origin: A review of 20 patients with adult-onset Still's disease. *Clin Rheumatol* 2003; 22: 89–93.
6. Sakata N, Shimizu S, Hirano F, Fushimi K. Epidemiological study of adult-onset Still's disease using a Japanese administrative database. *Rheumatol Int'l* 2016; 36: 1399–405.
7. Arlet JB, Boutin-Le Thi Huong D, Pouchot J, Piette JC. Current concepts on the pathogenesis of adult-onset Still's disease. *Revue de Medecine Interne* 2005; 26: 549–56.
8. Sanchez Loria DM, Moreno Alvarez MJ, Maldonado Cocco JA, Scheines ODM EJ. Adult Onset Still's Disease Clinical Features and Course. *Clin Rheumatol* 1992; 11: 516–20.
9. Cush JJ, Medsger TA, Christy WC, Herbert DC, Cooperstein LA. Adult-onset still's disease. *Arthritis Rheum* 1987; 30: 186–94.
10. Owlia M, Mehrpoor G. Adult- Onset Still's disease : AA review. *Indian J Med Sci* 2009; 63: 207–21.
11. Jeon YK, Paik JH, Park S-S *et al.* Spectrum of lymph node pathology in adult onset Still's disease; analysis of 12 patients with one follow up biopsy. *J Clin Pathol* 2004; 57: 1052–6.
12. Kieron B. L. Lim TDS. Still disease and the liver-an underappreciated association. *Gastroenterol Hepatol* (NY) 2011; 7: 844–6.
13. Min JK, Cho CS, Kim HY, Oh EJ. Bone marrow findings in patients with adult Still's disease. *Scand J Rheumatol* 2003; 32: 119–21.
14. Bhagat S, Dhobale VK. Adult Onset Still's Disease-Diagnosis on a Stand Still. *Gen Med Open Access* 2015; 3: 185.
15. Al-Homood IA. Biologic treatments for adult-onset Still's disease. *Rheumatol* 2014; 53: 32–8.