International Journal of Health Sciences and Research
www.ijhsr.org ISSN: 2249-9571

Case Report

Unusual Presentation of an Uncommon Disease: It can be Adult-Onset Still's Disease

Abdul S. Mohammed, Prajwal Boddu, Abdalla Hassan, Catherine Kallal

Advocate Illinois Masonic Medical Center, Department of Internal Medicine,
836 W Wellington Ave, Chicago, IL 60657

Corresponding Author: Abdalla Hassan

Received: 04/10/2015 *Revised: 15/12/2015* *Accepted: 18/12/2015*

ABSTRACT

Adult onset Still's disease (AOSD) is a rare systemic inflammatory disorder characterized by fever, arthritis or arthralgia and rash. We present the case of a 23 year old male who presented to the emergency department with complains of fever, sore throat, rash, chest and right knee pain for one week. Patient was febrile with temperature of 39.2^{o}C and pulse of 110/min. Erythematous maculopapular rash was observed on the arms, chest and lower extremities with axillary lymphadenopathy and hepatomegaly. Laboratory studies showed CRP of 6.8 mg/dl, ferritin of 3948 mg/ml, LDH of 741 U/l, AST was 561 U/l and ALT was 522 U/l. Skin biopsy revealed non-specific inflammation with predominance of lymphocytes. Patient was meeting Yamaguchi criteria for Adult onset Still's disease and was subsequently started on Naproxen with complete resolution of fever, rash, knee pain and resolution of AST and ALT elevation.

Keywords: AOSD, NSAIDS, ferritin, chest pain.

INTRODUCTION

Adult onset Still's disease is a systemic inflammatory disorder that usually presents with fever, arthritis or arthralgia and rash. It is an often a diagnosis of exclusion with an incidence of approximately 0.16 cases per 100000 and there is a bimodal age distribution with peaks between ages 15 to 25 and 35 to 46. [(1)] The etiology of AOSD, while uncommon, has been postulated to be a combination of genetic and infectious factors in the setting of immune dysregulation and alteration in cytokine production in favor of Th1 predominance. [(2)] AOSD frequently presents a diagnostic challenge, requiring serial assessments and extensive laboratory work up to exclude other diseases. We present a case of AOSD that exemplifies the challenges clinicians encounter in establishing the diagnosis.

CASE REPORT

23 year old man with no significant past medical history presented to our emergency department with complains of fever, sore throat, rash, chest pain, right knee pain, lower abdominal pain and chills for one week. The chest pain was particularly severe and he noted that it was worse with leaning forwards and taking deep breaths.

On admission, the patient had a temperature of 39.2^{o}C, blood pressure of 117/99 mm Hg, pulse of 110/min and respiratory rate of 18/min. An erythematous maculopapular rash was observed on the arms, chest and lower extremities. Physical exam was also

significant for axillary lymphadenopathy, lower abdomen tenderness and hepatomegaly. However, pericardial friction rub was not elicited. Chest X-ray, EKG and Echocardiogram showed no evidence of pericarditis. Initial laboratory studies showed a CRP of 6.8 mg/dl, ESR of 11 mm/hr, leukocytes of 4000/mm^3, hemoglobin of 12 g/dl, platelet of 164 x $10^3/mm^3$, LDH of 741 U/l, AST was 561 U/l and ALT was 522 U/l with normal bilirubin.

Our patient continued to spike fevers with no response to acetaminophen. Infectious disease and hematology-oncology consults were obtained. Blood and urine cultures were negative. Additional diagnostic work up was negative for HIV, RPR, Blastomycosis, CMV, EBV, HSV, Lyme, Brucella, Coxiella and Viral hepatitis. Rheumatologic work up included ANA, RF and ANCA which were normal. Serum electrophoresis was normal. Ferritin was elevated at 3948 mg/ml. Blood and urine cultures were negative.

Ultrasound of Abdomen demonstrated hepatomegaly and splenomegaly which was confirmed on CT abdomen and pelvis (figures 1&2) which also revealed mesenteric and retroperitoneal lymph node enlargement. Skin biopsy showed non-specific inflammation with predominance of lymphocytes (figure 3).

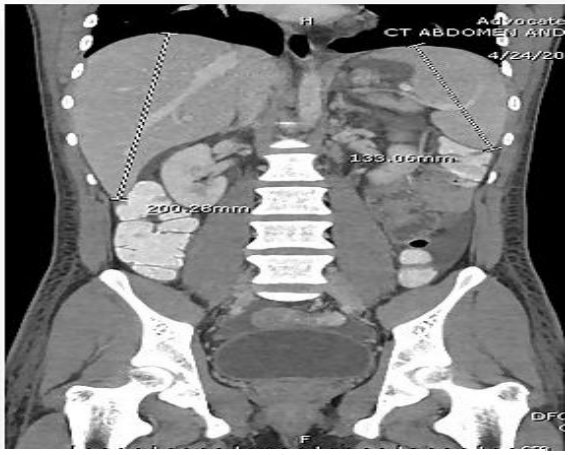

Figure 1: Coronal section of CT abdomen and pelvis demonstrating hepato-splenomegaly

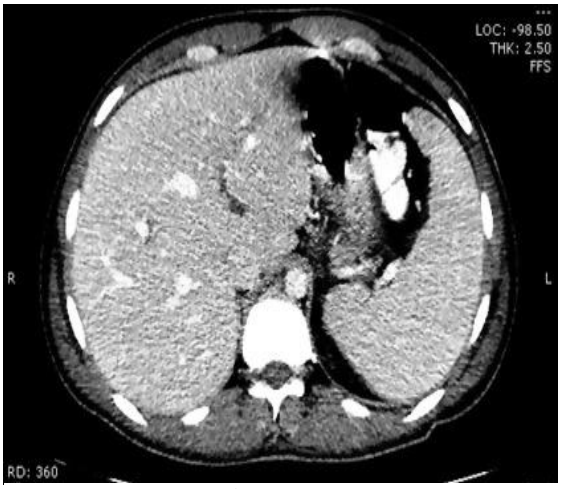

Figure 2: Axial section of CT abdomen demonstrating hepato-splenomegaly

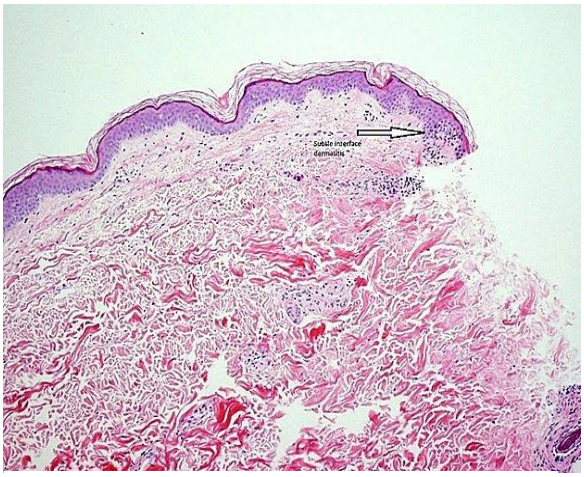

Figure 3: Micrograph of skin biopsy demonstrating interface dermatitis (Hematoxylin &Eosin, x 40)

Table 1: Yamaguchi criteria for Adult onset Still's disease

Major Criteria	***Minor Criteria***	***Our Patient***
Fever ≥ 39 x 1 Week		*x*
Leukocytosis		
Rash		*x*
Arthralgia ≥ 2 weeks		*x*
	Sore Throat	*x*
	Lymphadenopathy	*x*
	Hepato OR Splenomegaly	*x*
	Abnormal LFT's	*x*
	Negative ANA	*x*
	Negative RF	*x*

LFT – liver function test, ANA – anti nuclear antibody, RF-rheumatoid factor

On the seventh day of hospitalization, a Rheumatology consult was obtained. It was determined that the patient met the Yamaguchi criteria [(3)] (table 1) for Adult onset Still's disease. The patient was subsequently started on an oral NSAID with rapid resolution of fever, rash, knee pain as well as normalization of

his liver functions. The decision to start Naproxen was made after a careful evaluation of disease severity to be mild and obviate the use of steroidal therapy with its anticipated side effects.

DISCUSSION

Due to the low incidence of AOSD, it presents with a diagnostic challenge particularly for primary care physicians. AOSD can easily be missed, despite extensive work, if the diagnosis is not considered in febrile patients who appear to have infectious or neoplastic conditions. Many patients might be undiagnosed if extensive work up is not done. AOSD frequently relapses in individual patients and may cause life threatening complications such as the macrophage activation syndrome, cardiac tamponade and ARDS. [4,5] While several clinical features of our patient were atypical for the diagnosis of AOSD, several were classic. Unusual features included the prominence of chest pain, the relative paucity of joint symptoms and the dramatic response to naproxen. In contrast, the positive diagnostic (Yamaguchi) criteria as well as select laboratory findings were highly consistent with the diagnosis. Attention to the variety of clinical presentations of AOSD will assist the clinician in consideration of this disease entity.

A unique feature of our case was its presentation with chest pain that had pleuritic and positional components. This raised a concern for cardiopulmonary involvement and warranted exclusion of pericarditis. Although our patient did not have EKG or echocardiographic evidence of pericarditis, we suspect that some degree of inflammatory serositis was present as an explanation for the patient's chest symptoms.

Another peculiar feature of our case was the relative paucity of joint symptoms. While the patient did not note mild unilateral knee pain, this complaint was less significant to the patient than the chest pain and abdominal symptomatology. While atypical, this presentation is well documented. [6]

From a diagnostic standpoint, utilizing the Yamaguchi criteria offers both high sensitivity and specificity to establish the diagnosis of AOSD. Our patient exceeded the minimum number of criteria (total of eight criteria fulfilled including three major criteria (please see table 1)). Several other diagnostic markers in our patient were consistent with the expected findings in AOSD. These included elevations in CRP, LDH, liver enzymes and a high serum ferritin. Serum ferritin, generally considered a marker of iron storage, is also an acute phase reactant. Nearly 70% of patients with AOSD have increased levels of serum ferritin. [7] Some studies have shown that ferritin may serve as a prognostic marker in AOSD. Ferritin levels often correlate with disease activity and may normalize during remission. [8]

Cutaneous manifestations are a part of the diagnostic criteria for AOSD. Skin biopsy findings in AOSD usually have nonspecific findings, including dermal edema and mild perivascular inflammation in superficial dermis, consisting primarily of lymphocytes and histiocytes. Immunofluorescence of skin biopsy might show sight complement C3 deposition in blood vessel wall. [9]

Three different patterns have been described in AOSD with variable prognosis. The first category of patients tends to have monocyclic or self-limited pattern with complete remission within a year. The second group have intermittent or polycyclic pattern with recurrence of systemic and articular flares separated by periods of remission. The final group shows chronic joint problems and is prone to joint destruction. [10] The patient reported above would require close follow up to determine the progression of his disease and monitoring for life threatening

complication of AOSD known as Macrophage Activation Syndrome.

Lastly, our patient's prompt response to naproxen with resolution of fever, rash and joint pains was uncharacteristic. While NSIAD's are recommended as initial treatment for mild disease, fewer than 20% of patients will experience complete resolution of symptoms with this therapeutic modality, [(11)] however vigilance is needed in these patients because NSAIDS can trigger Macrophage activation syndrome and it can be difficult to distinguish it from the underlying AOSD. [(12)]

Prednisolone should be started for patients not responding to NSAIDS or suffering from pericarditis, serositis, persistent anemia or markedly elevated liver enzymes. Disease modifying anti rheumatic drugs such as methotrexate have been used to control acute symptoms and it is suggested that at least 6 months of therapy should be given to allow ample time for the assessment of therapeutic effect. [(13)] For patients who do not respond to conventional medications, biologic agents targeting IL 1, IL 6 and TNF alpha have been effective.

CONCLUSION

In conclusion, AOSD is an important diagnosis to consider in febrile adults. While infections and neoplastic conditions must always be excluded in a patient with unexplained fever, a consideration by clinicians of AOSD as an alternative causative pathology is imperative.

ACKNOWLEDGEMENTS

Dr. David Mael, Department of Rheumatology, Advocate Illinois Masonic Medical Center. Department of Radiology, Advocate Illinois Masonic Medical Center for providing images for the case report. Dr. Becky John, Department of Pathology, Advocate Illinois Masonic Medical Center for providing pathology images.

Conflict of interest: The authors have no financial, commercial, or non-commercial interest to disclose.

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How to cite this article: Mohammed AS, Boddu P, Hassan A et al. Unusual presentation of an uncommon disease: it can be adult-onset still's disease. Int J Health Sci Res. 2016; 6(1):540-544.

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