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An adult onset Still's disease in a young man within waves of dengue fever syndromes

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Abstract: We describe the first case report of an Adult Onset Still's Disease (AOSD) in a previously healthy young man from Jazan, Saudi Arabia in the summer of 2017. The patient symptoms, signs and investigations fulfilled Yamaguchi's criteria for the diagnosis of Adult Onset Still's disease [1]. The patient experienced a sore throat, high grade fever, right knee arthralgia, left knee arthritis, a generalized salmon colored rash, leukocytosis, elevation of liver transaminases, high LDH, high ferritin, absence of ANA, RF, AMA, ASMA and DNA and reactive bone marrow aspiration and biopsy without any evidence of infectious diseases etiologies or malignancies that were satisfactory to confirm the diagnosis of AOSD. We have observed an evidence of two different bacterial sources simultaneously as triggering etiologies; positive ASO titer and positive blood culture for E. Coli where the clinical features and laboratories investigations derangement post antibiotics treatment have remained. The patient has responded to the pulse methylprednisolone and tapering doses of prednisolone. Our successful clinical experience in the case is that the prednisolone lower doses combined with NSAID (voltaren) to minimizing the steroid adverse effects was sufficiently effective to maintaining remission.

Keywords: AOSD, LDH, ANA, RF, AMA, ASMA, DNA, NSAID, prednisolone

INTRODUCTION

The Adult Onset Still's Disease (AOSD) is a very rare multisystem autoimmune inflammatory disorder of unknown pathogenesis and etiologies; which mimics clinical signs and symptoms of several well-known diseases including infectious diseases, connective tissue diseases and malignancies [1,2,3]. AOSD incidence approximately is 0.5 (0.14 to 0.40) per 100 000 where the prevalence of the diseases approximately is 1 in 300,000 to 1 in 1000,000 (1 -34 per 10000000) [4]. The insidious presentation of AOSD may delay the diagnosis or labeled patient with a wrong diagnosis as ta negative rheumatoid factor rheumatoid arthritis. However, the key point is that, it requires a low threshold of clinical suspicion to reach diagnosis at the glance of the presentation. The typical salmon colored rash is the most unique clinical characteristic sign in reaching the diagnosis of AOSD if appreciated at the occurrence or recurrence of the typical rash and may differentiate it from other diseases categories and their overlapping symptoms and signs at the presentation. In the absence of a diagnostic test to confirm AOSD to date, the clinical features and laboratories investigations are required to delineate the AOSD diagnosis as described in Yamaguchi's classification criteria [1]. However, bone marrow aspiration and biopsy is mandatory to be normal in order to rule out the possibility of infectious diseases; tuberculosis, brucellosis, malignancies or infiltrative diseases.

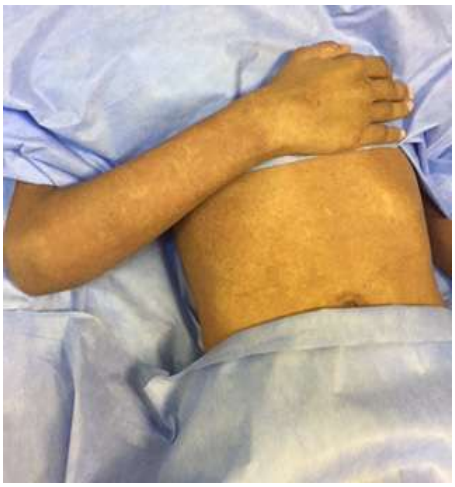
CASE REPORT

22 years old year young man presented to emergency department with fever for two weeks. His symptoms started initially with a sore throat for three days where he received cefuroxime for seven days with minuscule improvement. The fever was controlled with paracetamol as needed in the first week then his fever was persisting throughout the days up to three to four days at a time in a row, then slowed down to normal and recurred again with the same intensity and similar duration. He was seen in emergency department twice, four days apart where he received injection of non-steroidal anti-inflammatory (Voltaren) with good improvement for the day. By the end of the first week of the illness, he experienced a rash that distributed all over his body including his trunk, abdomen and all extremities but without itching for seven days before it faded away. These symptoms were associated with nausea and vomiting without diarrhea or constipation. Furthermore, the patient experienced a significant decreased in appetite where he lost about three

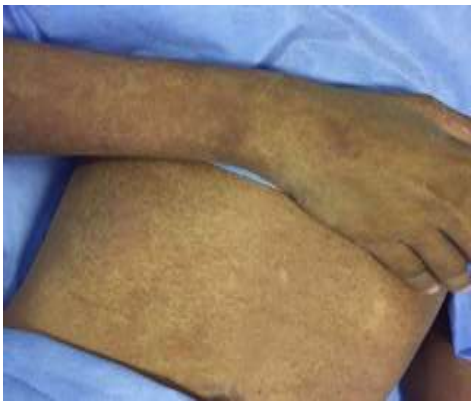
kilograms in weight at the end of second week of the illness. He had no headache, visual complains, shortness of breath. He has no raw milk ingestion or eating undercooked meat, and no travel abroad or visits to any diseases endemic areas. He is not sexual active and has or had any urinary symptoms, drinking alcohol, smoking, or abused or used drugs. No history of contact with tuberculosis patient. Patient did not experience a malaria or dengue infection historically. The rest of the history is non-contributory.

On examination showed a slim, colored-skin young male in his estimated age and height. Vitals signs disclosed a temperature is 39.4° C, respiratory rate is 18 breath per minute, pulse is 120 beats per minute, blood pressure is 130/75 mmHg and oxygen saturation is 96 % in room air. He is oriented to time, place and person, jugular venous pressure is 4 centimeters above sternal angle and normal hepato-jugular reflux. He is not pale or jaundiced and no lymphadenopathies enlargement. The chest and cardiovascular examination systems are normal. The Abdomen examination revealed scaphoid abdomen with no scars, organomegly or ascites. The neurological, the peripheral vascular and the locomotor examinations are normal. Skin examination revealed macular popular rash all over his abdomen, trunk, back, all extremities sparing the palms and the soles. Genitourinary system examination is normal.

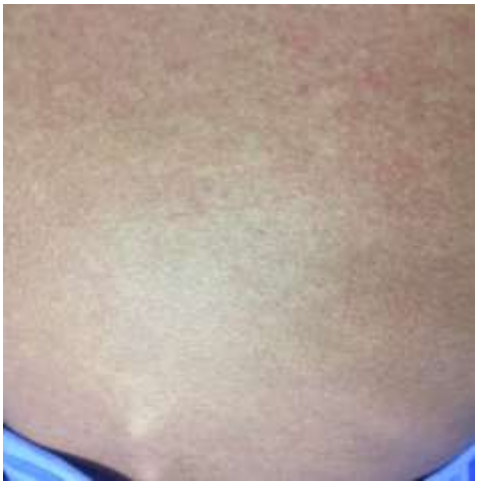
Investigation showed WBC 20.86 × 10^9/L (normal 4.5 to 11.0 × 10^9/L) with 89.0% neutrophil and hemoglobin 12.4 gram/dl (normal 14-18 gram/dl) with normal platelets. The kidney function test is normal. The liver function test revealed Aspartate transaminase (AST) 540 (normal up to U/L), Alanine transaminase (ALT) 590, (normal up to 40 U/L), Alkaline phosphatase (ALP) (normal 39-112 U/L), total bilirubin 9.2 (normal up to 17 mmol/L) , direct bilirubin 4.1 (up to 4.5mmol/L) lactate dehydrogenase (LDH) 377 (normal 72-182 U/L), Albumin 16 (normal up to 38-50g/L), calcium 1.87(Normal 2.0-2.6 mmol/L) and total protein 68(normal up to 66-87g/L) whereas Total bilirubin direct bilirubin, lipid profiles, phosphate, magnesium, Prothromin time, Partial thromboplastin time, and bleeding time were within normal limit. The electrocardiography, chest X-ray and transthoracic echocardiography are normal. Abdominal ultrasound with renal duplex showed mild heptosplneomegaly with normal kidney sizes and the rest of the abdominal examination are normal.



Picture-1: Photography of the the Abdomen and the right forarm

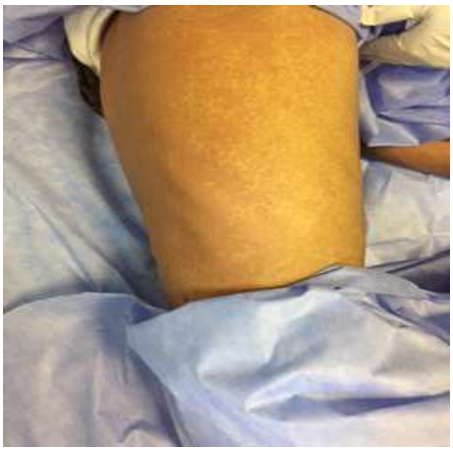


Picture-2: Photography of the the Abdomen and the right forarm (closer view)

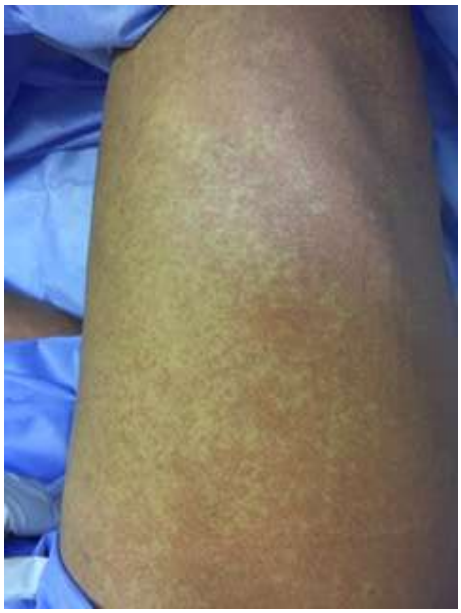


Picture-3: Photography of the back of the patient

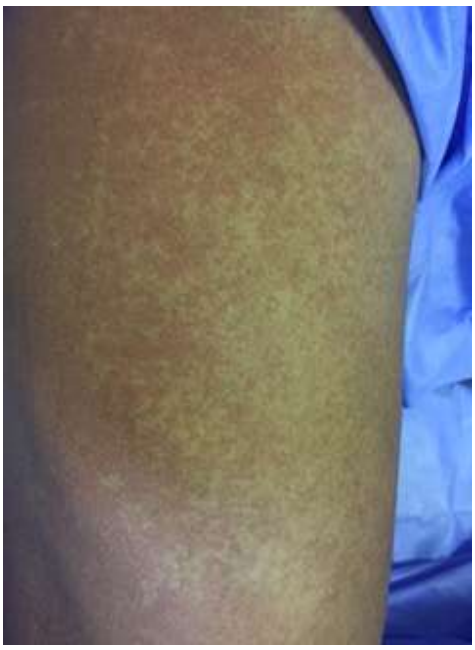
Picture-4: Photography of the patient abdomen right side



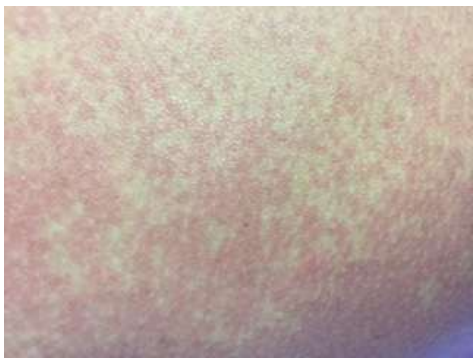
Picture-5: Photography of the patient back side



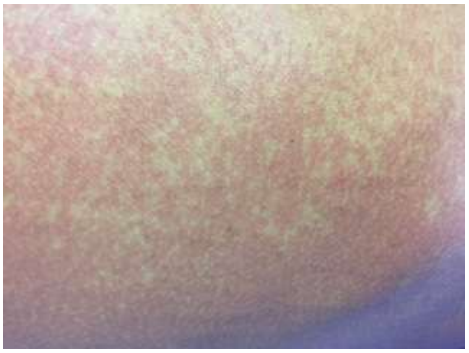
Picture-6: Photography of the patient back right side



Picture-7: Photography of the patient back right side



Picture-8: Photography of the patient back right side



Picture-9: Photography of the patient back right side

DISCUSSION

Adult onset Stills Disease (AOSD) is know to present in three different clinical presentation; mild, moderate, or severe clinical features manifestation that mimicking several and wide varieties diseases including infectious diseases; dengue fever, malaria, meningococcal meningitis and Rocky mountain spotting fever (RMSF), connective tissue diseases; rheumatoid arthritis diseases, mixed connective tissue diseases and systemic lupus erythematous, and malignancies; leukemia, lymphoma and other solid tumor [2,3].

ASOD express its clinical features as monophasic, intermittent and chronic forms with overlapping of these features over the course of the AOSD manifestation. The mild form AOSD may take weeks to a year to resolve where the course of the other two forms varies in severity and relapse, however, all the forms may relapse with milder intensity compare to the initial presentation irrespective of the modalities of therapy that may be used to manage specific form [2,3].

Our patient initial presentation started with a sore throat associated with high fever for three days where he used cefuroxime empirically without alleviation of the sore throat symptom. However, his high fever was controlled reasonably well with acetaminophen in the first week of the illness. The patient visited emergency department within the second and third week twice where his fever required non-steroidal anti-inflammatory drugs; voltaren injection to have a good response for 8 to 12 hours then, continued to have fever off NSAIDS. However, he was admitted for further evaluation where temperature was continued to reach up to 39.4C with tachycardia and macular-popular rash that was noticed over his body. The rash was thought to be a viral or dengue fever rash with dermatography appearance in emergency department, being living in an endemic area of dengue fever [5].

The initial laboratories work up including complete blood count demonstrates high leukocytosis with predominantly neutrophil and continued to be almost daily for three weeks of admission. The AST and ALT were up to three to four folds initially and reach 10 to 12 folds respectively during his hospital course. The elevated ESR was more than 100, C-reactive protein more than 6 mg/L that is positive. The renal function was normal however, albumin reached as low as 16 g/L (normal 35-50g/L) with normal corrected calcium. Urine analysis and culture were negative.

However, the patient lives in area where people are commonly exposed to Anopheles and Aedes aegypti mosquitos' victors bites, where malaria thin and think films that was performed twice, and dengue serology and Polymerase chain reaction (PCR) are negative. Throat swab ASO titer was positive. The blood culture was taken and patient was started on ceftriaxone 2 grams intravenously daily empirically however, the patient continued to be febrile with tachycardia but hemodynamically stable. Then, ceftriaxone was change to ciprofloxacin 400 mg twice a day intravenously when blood culture was available which showed Escherichia coli that was susceptible to Amoxicillin/Calvulanic acid, ciprofloxacin and trimethoprim Sulfamethoxazole, Tigecycline, Gentamicin Amikacin Meropenem, and Imipenem, but resistance to Ampicillin, Cefazolin, Cefoxitin, Ceftriaxone and Nitrofurantion.

However, his high-grade fever persisted with appropriate dose and sensitive antibiotics into the 2nd week of admission and 4th week of the illness. The patient clinical manifestation of the symptoms continued to be worsening on antibiotics and developed a right knee arthralgia followed the left knee arthritis; redness, swelling with limited range of mobility. However, in the absence of diagnosis at this point of time a trail of prednisolone 30 milligram orally once a day for two days was given where arthritis and arthralgia improved but not resolved completely. He continued to have a low-grade fever that persisted. A significant improvement in the leukocytosis and transaminases; AST and ALT were seen, however, these parameters were elevated within two days to the range before prednisolone treatment trail.

A high grade of fever continued on the 3rd week of hospitalization; 5th week of illness where bone marrow aspiration and biopsy was done to role out deep seated infection and malignancies. However, the next day, the patient developed a rash that declared as a

macular popular rash non-itchy, which is typical of a salmon-colored rash appearance on the truck, body extremities as demonstrated in the pictures (1,2,3,4,5,6,7,8,9).

Furthermore, in the presence of reactive bone marrow aspiration and biopsy that has confirmed no hematological malignancies including the macrophage activation syndrome (MAS) , infiltrative diseases or granuloma [6]. Additionally, a ferritin level was done to reveal a high level of 1500 ug/L, which require to be confirmed by diluting of the serum ferritin sample further that showed a very high level up to 10500 ug/L (normal 11-336) that settled the challenges of the case.

Acknowledging the rarity of AOSD, but the persistence presence of leukocytosis, persistence of fever, Escherichia coli septicemia, positive ASO titer as triggering association in addition to salmon colored rash and high ferritin that excluded other diseases have led us to confirm the diagnosis of our patient with Adult Onset Still's Disease (AOSD) [5].

Retrospectively, It is obviously clear now that the rashes during his presentation was a salmon colored rash that was over sighted in emergency at the time, as a dengue fever rash. However, in the absence of photography of the rash at the first occurrence to demonstrate the type of the rash, we left only to postulate at this point but with high clinical confident that the rash was unrelated to dengue fever syndrome in the presence of negative dengue serology and PCR but salmon colored rash which characteristic of AOSD [5].

The diagnosis of AOSD was reached by the presence of almost all major and minor criteria that were documented in the case; the persistence of high fever up to 39.6 C , arthralgia and arthritis, leukocytosis with predominant neutrophil, increase level of aspartate (AST) ,alanine aminotransferase (ALT) , lactate dehydrogenase for more and a typical salmon colored rash as in the Pictures (1,2,3,4,5,6,7.8.9). The absence of antinuclear antibody (ANA) and rheumatoid factor (RF) in addition to ultrasonography that showing hepatomegaly and splenomegaly and the high ferritin that was strikingly high, that all satisfied the Yamaguchi criteria for the diagnosis of AOSD [1]. However, in our patient the lymphadenopathies were observed as the only clinical feature that was not existed, which excluded Kikuchi's disease [7].

The management of the patient started with pulse steroid where methylprednisolone one gram intravenously daily for three days followed by prednisolone 1 milligram per kilogram where the patient received 40 milligram orally daily. The patient showed a significant improvement within the first 24 hour, where fever subsided, and within three days the liver enzymes; transaminases AST and ALT declined from 10 and 12 folds to 1 fold respectively. The serum albumin improved from 16 to 27 with normal corrected calcium. However, white blood count decline from 23.8 to 8.89 with 71.4 neutrophil where hemoglobin was 8.5-9.0 and the salmon colored rash cleared [8].

We observed that patient started to developed proximal myopathies clinically in the upper and lower extremities due to methylprednisolone in the first ten days of treatment. We decreased the dose of prednisolone to 0.5 milligram per kilogram for a week however; we observe that the proximal myopathies in both upper and lower extremities have improved with mild increase in transaminases less than two folds and low albumin to 16 g/L.

We added non-steroidal anti-inflammatories drug (NSAID) in form of Voltaren 50 mg twice a day where patient responded within a week time and able to do his daily activities as needed and his transaminase reflect one fold increase and albumin became 22 g/L, however, a white blood count was elevated with predominantly high neutrophil which may be explained by steroid demargination in the view of clinical and biochemical improvement.

We observe a combination of lower dose of prednisolone and NSAID will be a way to manage AOSD if mild to moderate however, where in severe cases is worth trying to avoid high steroid doses and long-term adverse effects. The management of AOSD remains a challenge and a unique experience to share in order to have a collective experience worldwide.

CONCLUSION

We report the first case of Adult Onset Still's Disease (AOSD) in a young man from Jazan, Saudi Arabia in the summer of 2017. AOSD is a quite uncommon and may present insidiously mimicking common or uncommon features of several diseases. In spite of that our patients' presentation fulfilled the Yamagoshi's criteria overtime to confirm diagnosis AOSD. However, the diagnosis AOSD among waves of dengue fever syndrome cases is a quite challenging clinical association to be appreciated at the glance. The reoccurrence of salmon colored rash and high ferritin is a quite characteristic toward diagnoses.

Patient was able to respond to pulse therapy of methylprednisolone within less than 24 hours and was maintained on prednisolone 1 milligram per kilogram orally daily. An adverse effect was developed in form of a proximal myopathies in all extremities that managed with a lower dose of prednisolone 0.5 milligram and low dose of NSAID where he continued to improved clinically and biochemically

A low dose of prednisolone and NSAID are a promising approach to manage a patient with mild to moderate AOSD and to be tapered slowly over several weeks to months in order to reach a satisfactory

recovery. Finally, we share this case challenging diagnosis and management issues to increase the awareness of such rare disease in an endemic area of dengue fever syndromes at this point and the response to rapid tapering of the prednisolone with NSAIDs as in our patient. However, close monitoring of patient is in place if further intervention may be required.

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