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Case Report

Adult onset Still's disease in an elderly patient with fever of unknown origin after multiple trauma: A case report and literature review

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ABSTRACT

We report a 65-year-old Singaporean Chinese woman with Adult-Onset Still's Disease (AOSD) who presented with fever of unknown origin after multiple trauma who was successfully treated with prednisolone and methotrexate. The incidence of AOSD is extremely rare in the elderly population. Elderly patients with AOSD may also have atypical presentations and hence lead to a delay in diagnosis. In elderly patients with fever of unknown origin, particularly in Asians, the diagnosis of AOSD should be considered.

INTRODUCTION

Adult onset Still's disease (AOSD) is a rare inflammatory disorder of unknown etiology that has a bimodal age distribution in all ethnic groups with peaks at 15-25 and 36-46 years of age.[1] The annual incidence of AOSD is estimated to be 0.16 cases per 100,000 people, with an equal distribution among the sexes. Very few patients above the age of 65 have been reported and have occasionally been described in the USA, Europe, China and Japan.[2] In Singapore, a study of 17 patients who were diagnosed over a span of 8 years showed that the median age of presentation was 45 years (range 16-68) with 82.4% being of Chinese ethnicity.[3] Few cases of AOSD have been reported in the literature. A search of MEDLINE revealed 20 case reports of elderly patients (age 65 and above). At least 4 cases had atypical presentations[4-7] and most cases were treated effectively with corticosteroids.

CASE PRESENTATION

We report a 65-year-old Chinese woman who presented to emergency department after a fall from height. She had a past medical history of hypertension, hyperlipidemia and depression. She suffered multiple injuries including fractures to the sternum, ribs, pelvis, and lower limbs with massive internal bleeding. She underwent urgent iliac artery embolization and surgical fixation of the pelvic bone. Her other fractures were treated conservatively. She also received blood transfusions and wound debridement.

She developed a fever on the second day of admission and thereafter received several courses of antibiotics in view of persistent quotidian fever attributed to infections. She was treated with amoxicillin/clavulanate, piperacillin/tazobactam, ciprofloxaxin and cefuroxime for suspected pneumonia, urinary tract infection and foot wound infection. Her other medications included metoprolol, mirtazapine, cholecalciferol, omeprazole and paracetamol.

She did not complain of any symptoms except for occasional lower limb myalgia. Physical examination did not reveal any lymphadenopathy, rash or hepatosplenomegaly.

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Her surgical wounds subsequently healed. She later developed bilateral knee pain and swelling. A comprehensive evaluation was performed for fever of unknown origin (FUO). She had multiple sets of blood cultures which were all negative for bacterial growth. Syphilis, tuberculosis, malaria, hepatitis B, hepatitis C and HIV tests were all negative. Her liver function test, procalcitonin and uric acid level were normal. Peripheral blood film was unremarkable. Ferritin level was 1,349 ug/L. Her autoimmune tests including Anti-CCP, rheumatoid factor, ANCA (Anti-myeloperoxidase, Anti-PR3), SLE panel (C3, C4, Anti-ds-DNA) and Anti-ENA panel (Anti-Ro, Anti-La, Anti-RNP, Anti-Sm, Anti-Jo1, Anti-SCl 70) were negative. Anti-nuclear antibody titer was 1:160 with speckled pattern. Her chest X-ray and echocardiogram were normal. CT scan of thorax, abdomen and pelvis were negative for malignancy but revealed reduction of previous pericardial effusion and pelvic hematoma and resolution of bilateral pleural effusion. X-ray of the knees reported tricompartmental osteoarthritic changes with fluid in bilateral suprapatellar pouches. Arthrocentesis of the left knee was performed revealing 14 ml of straw colored synovial fluid. Examination of the knee fluid showed a nucleated cell count of 6,926/uL (79% were neutrophils). No organisms or crystal were isolated from the knee aspirate. Her myeloma panel results were not suggestive of myeloma.

Despite extensive investigations, she continued to have fever and persistently elevated inflammatory markers. She was assessed by a rheumatologist and a diagnosis of AOSD was made. She was treated with oral prednisolone and with the addition of methotrexate, there was complete resolution of her fever and symptoms, with subsequent down trending of her inflammatory markers.

After treatment with seven weeks of prednisolone and one month of methotrexate, her C-Reactive Protein (CRP) level was 6 mg/L, Erythrocyte Sedimentation Rate (ESR) level was 21 mm/hr and ferritin level decreased to 695 ug/L. Prednisolone dose was subsequently tapered. Figure 1 shows the trend of her inflammatory markers.

DISCUSSION

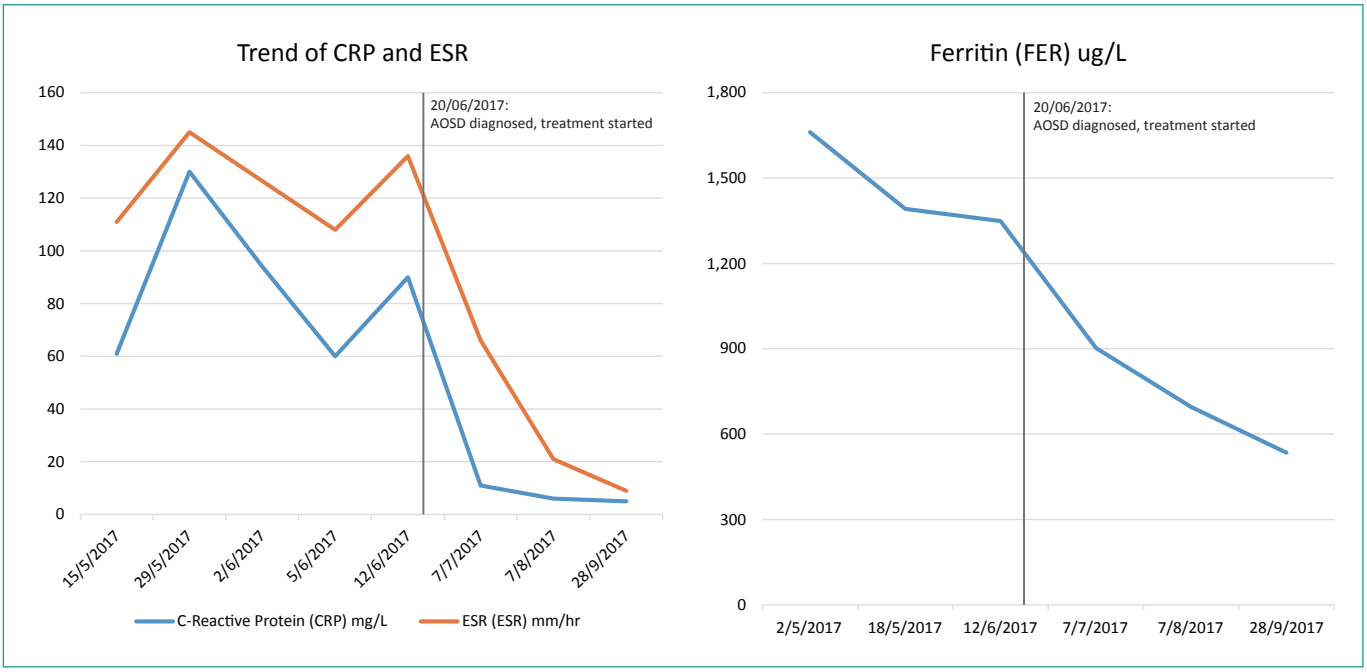
This case demonstrates the complexities in clinching the diagnosis of AOSD in an elderly patient who had FUO after multiple trauma. AOSD is rare in the elderly and is difficult to diagnose in this population. Important categories of conditions to exclude are infections, malignancy, systemic autoimmune diseases, vasculitis, auto-inflammatory diseases, neutrophilic dermatoses and drug reactions.

AOSD is a diagnosis of exclusion and based upon the presence of characteristic clinical and laboratory findings. Fever, rash and arthritis or arthralgia each occur in about 75% to 95% of patients.[8] For older patients with FUO, a rash is a valuable diagnostic sign for AOSD.[9] This, however, was absent in our patient.

Several diagnostic criteria have been proposed, given the lack of a definitive diagnostic test since they lack the combined sensitivity and specificity to be useful for clinical diagnosis. Nonetheless, their utility guides the diagnostic evaluation and in identifying patients more likely to have AOSD. Most of them rely upon the exclusion of other conditions.

Ferritin levels of 1,000 ng/mL and above in combination with other clinical criteria have been used to imply the diagnosis of AOSD. Glycosylated ferritin fraction has been reported to be an even more specific marker of disease than ferritin and the level of glycosylated ferritin usually drops to <20% in patients with AOSD.[7,10,11]

Figure 1. Trend of CRP, ESR and Ferritin



The Yamaguchi criteria[9] appears to have the highest sensitivity in patients with a definite diagnosis of AOSD.[12] The Fautrel criteria[13] appears to have the highest specificity, although not commonly used as glycosylated ferritin is not widely available. While our patient did not fulfil either the Yamaguchi or Fautrel criteria, the case met the criteria of Cush,[14] Reginato[15] and Kahn[16] (fever, leukocytosis, negative RF, arthralgia/arthritis, pleuritic/pericarditis, myalgia).

The etiology of AOSD is unknown although both genetic factors and infectious triggers have been suggested as important. Numerous viruses and bacterial pathogens have been proposed and this may have been a potential trigger for our patient who was treated for pneumonia and urinary tract infection in the initial post-operative period.

Immune dysfunction has also been proposed to contribute to the pathogenesis of AOSD. Patients with active and untreated disease have higher levels of interleukin-6 (IL-6), IL-8, IL-18 and tumor necrosis factor-α than healthy controls.[17] In a South Korean study, the investigators concluded that serum levels of CXCL10 and CXCL13 might be useful markers to assess AOSD activity as they were significantly elevated in patients with active AOSD compared to patients with rheumatoid arthritis and healthy people.[18]

There has not been any previous reports in the literature on whether multiple trauma had any associations with AOSD. Nonetheless, trauma involving high velocity impact often lead to complex fractures and severe injuries of the surrounding soft tissues. Mice models studying cytokine patterns and the evolution of remote organ dysfunction after multiple fractures demonstrate that such trauma initiates a complex systemic inflammatory response in which the pro- and anti-inflammatory cytokines, such as IL-6 and IL-10, play a pivotal role in systemic inflammation.[19,20] This has been attributed to the locally exposed bone components to injured soft tissue[21] and is commonly seen after long bone fractures.[22]

In soft tissue injury, IL-6 has been shown to be have a greater role compared to other cytokines.[23,24] However, both IL-6 and IL-10 correlate with the systemic inflammatory response and injury severity.[25,26]

Moreover, a prospective cohort study analyzing the inflammatory response (IL-6) after primary definitive treatment of femoral fractures and damage control orthopaedic surgery, demonstrated the damage control strategy was associated with sustained inflammatory response.[27]

The Depuy Synthes cannulated screw system was used for surgical fixation of the pelvic fracture in our patient. The material of the cannulated screws and rod used was 316L stainless steel. To date, there have not been any case reports of autoimmune reactions due to pelvic fixation with similar metal implants as regulated by the Health Science Authority of Singapore.

Hence, we speculate that the possible triggers of either the initial trauma, surgery or infection in our patient may have given rise to immune dysregulation and contributed to the pathogenesis of AOSD, although causality cannot be assumed.

There are 3 main patterns to the clinical course of AOSD-monophasic, intermittent and chronic. Approximately one-third of patients fall into each category. A description is shown in Table 1.

Even though the prognosis is generally favorable, cases of AOSD leading to multi-organ failure and death have also been reported. Life threatening complications of AOSD include fulminant hepatic failure, myocarditis, acute respiratory distress syndrome, disseminated intravascular coagulation and Macrophage Activation Syndrome (MAS).

A poor prognosis is also associated with polyarticular onset, proximal joint arthritis, prior episode in childhood, and requirement of systemic steroids for more than 2 years.[28,29] Moreover, polyarticular onset and chronic joint involvement have been associated with a poorer functional outcome, but systemic symptoms have not.[30]

No guidelines for the treatment of AOSD have been established due to the rarity of the condition and the lack of clinical trials. Treatment modalities available include the use of NSAIDs, steroids, immunosuppressants and biological agents.5 There is currently no consensus on the treatment of elderly patients with AOSD. More clinical studies could be useful to increase our knowledge about AOSD therapy in the elderly. TABLE 2 gives an approach to therapy in general but management has to be individualised with close monitoring of adverse drug effects especially in the elderly.

AOSD is an uncommon illness among the general population, especially in the elderly. It often poses a diagnostic challenge and involves excluding other illnesses and extensive evaluation. This case showed that despite the Yamaguchi and Fautrel criteria having the highest sensitivity and specificity respectively, patients with AOSD may still be mistakenly excluded. Moreover, elderly patients may

Table 1. Patterns of AOSD

	Monophasic	Intermittent	Chronic
Description	One disease flare lasting weeks to months, completely resolving within a year	Involves recurrent flares with remission between flares that can last up to several years	Persistently active disease
Key features	Self-limiting Systemic features predominate	Subsequent flares tend to be less severe and shorter duration than initial episode	Articular symptoms predominate Destructive arthritis may occur

Table 2. Approach to therapy

Goals of Therapy		
1. Control physical signs and symptoms of inflammation 2. Control laboratory indices of inflammation 3. Prevent end organ damage, including joint injury and other major organ complications 4. Minimize the risk of adverse effects of therapy, including long-term effects of glucocorticoids		
Targeted Treatment by Disease Severity And Clinical Response to Initial Therapies		
Disease severity	**Features**	**Suggested treatment**
Mild	Fever, rash, arthralgia, mild arthritis. No involvement of internal organs	• Nonsteroidal anti-inflammatory drugs (NSAIDs) – close monitoring required due to potential to trigger MAS • Low-dose glucocorticoids if not controlled with NSAIDs alone
Moderate	High fever, debilitating joint symptoms, or evidence of internal organ involvement that is non-life threatening	• Glucocorticoids • Nonbiologic or biologic disease modifying antirheumatic drugs – methotrexate if predominantly joint disease.
Severe	Life threatening organ involvement and/or conditions	• High-dose or pulse glucocorticoid therapy • Early intervention with biologic agents e.g. IL-1 or IL-6 inhibitors

also display atypical presentations. However, knowledge of the various classification criteria would give the clinician better insight into the myriads of presentations of AOSD. Consequently, identifying the disease severity and instituting early treatment would thus yield a favorable prognosis with the aim of not only controlling inflammation, but also preventing complications especially that of articular destruction and organ damage.

CONFLICTS OF INTEREST STATEMENT

There are no conflicts of interests including financial, consultant, institutional and other relationships that might lead to bias.

REFERENCES

01. Magadur-Joly G, Billaud E, Barrier JH, Pennec YL, Masson C, Renou P, et al. Epidemiology of adult Still's disease: estimate of the incidence by a retrospective study in west France. *Annals of the Rheumatic Diseases.* 1995;**54**(7):587-90.

02. Kurasawa M, Kotani K, Kurasawa G, Shida K, Yamada S, Tago T. Adult-onset Still's disease in a patient over 80 years old successfully treated with low-dose methotrexate therapy. *Age and Ageing.* 2007;**36**(1):104-6.

03. Fong WS, Lui NL. Adult-Onset Still's Disease: A Review. *Proceedings of Singapore Healthcare.* 2013;**22**(1):40-7.

04. Vila LM, Molina MJ. Chronic anemia and thrombocytosis as the initial presentation of Still's disease in an elderly patient. *Gerontology.* 2007;**53**(5):289-92.

05. Apostolova M, Shoib M, Glynn M. A rare presentation of adult onset Still's disease in an elderly patient. *Rheumatology Reports.* 2011;**3**:e10(1):38-9.

06. Kumano T, Ishibashi H, Kubota Y, Ono Y, Tada Y, Nagasawa K, et al. Adult-onset Still's disease in an elderly woman with atypical presentation. *Case Reports in Internal Medicine.* 2014;**1**(2):158-62.

07. Hamidou MA, Denis M, Barbarot S, Boutoille D, Belizna C, Le Moel G. Usefulness of glycosylated ferritin in atypical presentations of adult onset Still's disease. *Annals of the Rheumatic Diseases.* 2004;**63**(5):605.

08. Gerfaud-Valentin M, Jamilloux Y, Iwaz J, Seve P. Adult-onset Still's disease. *Autoimmunity Reviews.* 2014;**13**(7):708-22.

09. Yamaguchi M, Ohta A, Tsunematsu T, Kasukawa R, Mizushima Y, Kashiwagi H, et al. Preliminary criteria for classification of adult Still's disease. *The Journal of Rheumatology.* 1992;**19**(3):424-30.

10. Efthimiou P, Paik PK, Bielory L. Diagnosis and management of adult onset Still's disease. *Annals of the Rheumatic Diseases.* 2006;**65**(5):564-72.

11. Senthilvel E, Papadakis A, McNamara M, Adebambo I. Adult-Onset Still Disease (AOSD). *Journal of the American Board of Family Medicine JABFM.* 2010;**23**(3):418-22.

12. Masson C, Le Loet X, Liote F, Dubost JJ, Boissier MC, Perroux-Goumy L, et al. Comparative study of 6 types of criteria in adult Still's disease. *The Journal of Rheumatology.* 1996;**23**(3):495-7.

13. Fautrel B, Le Moel G, Saint-Marcoux B, Taupin P, Vignes S, Rozenberg S, et al. Diagnostic value of ferritin and glycosylated ferritin in adult onset Still's disease. *The Journal of Rheumatology.* 2001;**28**(2):322-9.

14. Cush JJ. Adult-onset Still's disease. *Bulletin on the Rheumatic Diseases.* 2000;**49**(6):1-4.

15. Reginato AJ, Schumacher HR, Jr., Baker DG, O'Connor CR, Ferreiros J. Adult onset Still's disease: experience in 23 patients and literature review with emphasis on organ failure. *Seminars in Arthritis and Rheumatism.* 1987;**17**(1):39-57.

16. Kahn M, Delaire M. Maladie de Still de l'adulte. In: Kahn M, Peltier A, Meyer O, Piette J, editors. *Les maladies systémiques.* Paris: Flammarion. 1991, p.231-8.

17. Chen DY, Lan JL, Lin FJ, Hsieh TY. Proinflammatory cytokine profiles in sera and pathological tissues of patients with active untreated adult onset Still's disease. *The Journal of Rheumatology.* 2004;**31**(11):2189-98.

18. Han JH, Suh CH, Jung JY, Nam JY, Kwon JE, Yim H, et al. Association of CXCL10 and CXCL13 levels with disease activity and cutaneous manifestation in active adult-onset Still's disease. *Arthritis Research & Therapy.* 2015;**17**:260.

19. Kobbe P, Vodovotz Y, Kaczorowski DJ, Mollen KP, Billiar TR, Pape HC. Patterns of cytokine release and evolution of remote organ dysfunction after bilateral femur fracture. *Shock (Augusta, Ga).* 2008;**30**(1):43-7.

20. Levy RM, Prince JM, Yang R, Mollen KP, Liao H, Watson GA, et al. Systemic inflammation and remote organ damage following bilateral femur fracture requires Toll-like receptor 4. *American Journal of Physiology Regulatory, Integrative and Comparative Physiology.* 2006;**291**(4):R970-6.

21. Kobbe P, Kaczorowski DJ, Vodovotz Y, Tzioupis CH, Mollen KP, Billiar TR, et al. Local exposure of bone components to injured soft tissue induces Toll-like receptor 4-dependent systemic inflammation with acute lung injury. *Shock (Augusta, Ga).* 2008;**30**(6):686-91.

22. Kobbe P, Vodovotz Y, Kaczorowski DJ, Billiar TR, Pape HC. The role of fracture-associated soft tissue injury in the induction of systemic inflammation and remote organ dysfunction after bilateral femur fracture. *Journal of Orthopaedic Trauma.* 2008;**22**(6):385-90.

23. Rose S, Marzi I. Mediators in polytrauma--pathophysiological significance and clinical relevance. *Langenbeck's Archives of Surgery.* 1998;**383**(3-4):199-208.

24. Roumen RM, Hendriks T, van der Ven-Jongekrijg J, Nieuwenhuijzen GA, Sauerwein RW, van der Meer JW, et al. Cytokine patterns in patients after major vascular surgery, hemorrhagic shock, and severe blunt trauma. Relation with subsequent adult respiratory distress syndrome and multiple organ failure. *Annals of Surgery.* 1993;**218**(6):769-76.

25. Gebhard F, Pfetsch H, Steinbach G, Strecker W, Kinzl L, Bruckner UB. Is interleukin 6 an early marker of injury severity following major trauma in humans? *Archives of Surgery (Chicago, Ill : 1960).* 2000;**135**(3):291-5.

26. Neidhardt R, Keel M, Steckholzer U, Safret A, Ungethuem U, Trentz O, et al. Relationship of interleukin-10 plasma levels to severity of injury and clinical outcome in injured patients. *The Journal of Trauma.* 1997;**42**(5):863-70; discussion 70-1.

27. Pape HC, Schmidt RE, Rice J, van Griensven M, das Gupta R, Krettek C, et al. Biochemical changes after trauma and skeletal surgery of the lower extremity: quantification of the operative burden. *Critical Care Medicine.* 2000;**28**(10):3441-8.

28. Pouchot J, Sampalis JS, Beaudet F, Carette S, Decary F, Salusinsky-Sternbach M, et al. Adult Still's disease: manifestations, disease course, and outcome in 62 patients. *Medicine.* 1991;**70**(2):118-36.

29. Wouters JM, van de Putte LB. Adult-onset Still's disease; clinical and laboratory features, treatment and progress of 45 cases. *The Quarterly Journal of Medicine.* 1986;**61**(235):1055-65.

30. Cush JJ, Medsger TA, Jr., Christy WC, Herbert DC, Cooperstein LA. Adult-onset Still's disease. Clinical course and outcome. *Arthritis and Rheumatism.* 1987;**30**(2):186-94.