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Case Report

Adult onset still's disease: a rare disorder

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ABSTRACT

Adult onset disease is a variant of systemic onset juvenile idiopatic arthritis characterised by seronegative poly arthritis in association with multi systemic inflammation. it is often seen in young adults. Authors have report a case of a 28 year old male who presented to us with a predominantly systemic symptoms. patient presented with a 6 month history of high grade fever, with associated recurrent joint pains, sore throat, generalized tonic-clonic seizures and skin rashes. Patient remained markedly ill for most of his in-patient stay. Aesilogy is unknown, though it is currently thought that there is interplay between a genetic predisposition, an immune dysregulation and environmental play mainly infectious. Therapeutic decisions should be based on the extent and severity of organ involvement.

Keywords: Adult onset still's disease, Joint symptoms, Lymphadenopathy, Persistent high fever

INTRODUCTION

Adult onset Still disease (AOSD) is an uncommon autoimmune inflammatory disease most often seen in young adults.[1,2] It is a variant of systemic onset juvenile idiopathic arthritis characterized by seronegative polyarthritis in association with multi systemic inflammation.[3]

Clinical findings consist of a combination of systemic manifestations (mostly persistent high spiking fevers, evanescent rash, and lymphadenopathy) and joint symptoms ranging from arthralgia to aggressive arthritis.[1] The aetiology is still unknown though it is currently thought that there is interplay between a genetic predisposition, exposure to an infectious component and an immune dysregulation.[1] There is no specific serological bio marker for diagnosis; the clinical diagnosis is based on pattern recognition and exclusion of other diseases thus often leading to delay in diagnosis.[1,4,5] Therapeutic decisions should be based on the extent and severity of organ involvement.[1] Nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin are useful in limiting the intensity of symptoms of the disease, while glucocorticoids, methotrexate, and tumour necrotic inhibitors (TNFα) are good options for correcting the disease evolution. Patients have a favorable outcome.[1,6] There is a lack of clinical trials on AOSD and therefore a lot still unknown.[1]

We report a case of AOSD which presented to us with predominantly systemic symptoms. Patient remained markedly ill for most of his in-patient stay, such that there was hardly any clinical sub specialty whose input was not sort for, nor was there any call shift that was not called in because of an emergency related to the patient's critical state.

CASE REPORT

A 28-year old male patient presented with recurrent fever of 6-month duration, which was high grade, intermittent, not worse at any time of the day and temporary relieved by acetaminophen. Present episode of fever started 2weeks prior to presentation. There was an associated history of recurrent joint pain and swelling for 6months.

Joint pain involved the knee, ankle, digits of hands, elbows, neck and back. Patient had difficulty walking and

Grasping object during episodes of joint pains was relieved by ibuprofen. Two hours prior to presentation he developed generalized tonic clonic seizures. Each episode lased about 1-2mins, resolving spontaneously with no postictal sleep. There was a preceding history of a rash the abated before presentation to the hospital. He also complained of a persistent sore throat, a frontal headache and two episodes of non-projectile vomiting. He had lost weight remarkably, was generally weak and admitted to anorexia, malaise and easy fatigability. His drugs history included chronic use of non-steroidal anti-inflammatory drugs.

Examination findings were an acutely ill looking male, febrile (T: 38°c), pale, anicteric, presence of cervical lymphadenopathy, Glasgow coma scale of 9/15 with presence of neck stiffness, negative kerning's and Brudzinski sign. There were hypopigmented macules over the fore head and posterior neck. There was swelling of distal interphalangeal joint of the small, ring and middle fingers of his left hand. He had a hepatomegaly of 6cm, pulse rate was 102 beats per minute, blood pressure was normal. He was suspected to have mixed connective tissue disease, possibly SLE with rheumatoid arthritis to rule out cerebrospinal meningitis and retroviral disease.

Investigations showed a haemoglobin count of 6.9g/dl, white blood count of $13.58x10^9$/I, neutrophils were 85%, platelets 318 $x10^9$/I. A blood film showed lysed red cells, leucocytosis with neutrophilia. Neutrophils show toxic granules, most are mature and fully segmented. Lymphocytes are mostly reactive, small and intermediate sized cell with open chromatin irregular nodules, some with deep blue cytoplasm. Platelets are moderately increased with numerous platelets aggregate. Serum electrolytes, urea and creatinine showed urea of 15.5mmol/l, creatinine of 355umol/l (normal range on repeat E/U/Cr), other indices were within normal limits. Serum trans aminases were elevated, serum albumin was reduced, and a random blood sugar was 6.7mmol/l. Urinalysis showed a proteinuria of 30mg/dl, subsequent analysis had negative findings.

Blood culture result yielded no growth. A chest radiography, an electrocardiography and a magnetic resonance imaging of the brain showed a normal study. Abdominal ultra sound scan showed a liver of 20.63cm, its echotexture was homogenous with no focal Hypo/hyperechoic masses, no intra or extra hepatic biliary and vascular change. Result of Immunology was negative for dsDNA, ANA, RF, Anti CCP and Anti Sm antigen. C reactive protein was 32ug/ml (1.0-3.0UG/l) and ESR was >150mm/hr. He was negative to HIV 1and 2, HBsAg and HCVAb.

He was placed on intra veinous broad spectrum antibiotics, intra veinous infusion, oral levetiracetam, diazepam, ibuprofen, hydroxychlorpquine, vit B complex. About 2 days on admission, patient became unconscious with GCS 3/15. He was nursed as an unconscious patient, a naso gastric tube was passed, intravenous meropenem, oral prednisolone was Commenced. He regained consciousness after about 36 hours.

Fever spikes of about 39-40°c persisted for 2 weeks of inpatient care and an impression of pyrexia of unknown origin was entertained. At this point, a diagnosis if AOSD was suspected and he was asked to assay for serum ferritin levels. He requested a referral to another specialist centre for further care but presented back to our centre after 9months, symptoms were persistent and a diagnosis was yet to be made. He subsequently assayed serum ferritin, level was 7408ug/i. He was then managed for AOSD with oral methotrexate, oral prednisone and short course of NSAIDs.

He soon became lost to follow up for 2months, representing with worsening symptoms He Had stopped oral methotrexate because he felt better.

DISCUSSION

Adult-onset Still disease (AOSD) is a rare autoimmune inflammatory disease of unknown aetiology, which was initially described in adult by Eric Bywaters in 1971.[1,7] There are sporadic, cases of AOSD documented before 1971.[8] Eric Bywaters described 14 cases of an illness starting in adult life that resemble still's disease (systemic juvenile idiopathic arthritis (JIA) and coined the term AOSD due to the disease's close resemblance to a paediatric syndrome described by Dr George still in 1897.[1] Currently, systemic JIA and AOSD are considered the same entity.[1] AOSD occurs worldwide but there is no consensus on its incidence and prevalence as additional studies and data on the epidemiology are needed.[1] There annual incidence estimated in retrospective European studies is 0.1 to 0.4 per 100,000 inhabitants.[1] In Japan and France, the incidence is said to about 1-3 new cases per million inhabitants per year.[6] It is to affect women > men, with onset of the disease between 16 and 35 years although it has been reported amongst the geriatric age group.[1,4]

This case illustrates the typical presentation of the classic symptoms of AOSD as the 28-year-old male in this case presented with intermittent fever spikes (temperature >39° C), arthralgia and a prior history a rash. In a compilation of cohort studies done over 7 years in various parts of the world, fever was found to be the presenting symptom in 95% of cases.[1] pyrexia of unknown origin is said to be the major reason why a patient with new onset AOSD seeks help.[1] Symptoms that occasionally precede the fever and should raise suspicion for AOSD include; a sore throat (usually a non suppurative pharyngitis), constitutional symptoms such as anorexia, myalgia, fatigue.[5] these pharyngitis in AOSD is

proposed to be from underlying cricothyroid perichndritis. These symptoms were also found in the case illustrated. The series of cohort study showed that patients with AOSD at onset and often worse during periods of fever, complain of myalgia (13% to 70%) arthralgia (80% to 100%), and arthritis (18% to 100%).[1,6] Joints affected most frequently are the knees, Wrists, and kneels, although involvement occurs in 2/3^{rds} of patients.[4] The illustrated case presented with typical joint involvement and had normal radiographic findings as normally seen in early cases. Joint involvement could progress to severe destructive polyarthritis in AOSD.

Other frequent findings are lymphadenopathy, (33% to 73%) especially of cervical chain, splenogaly (17% to 64%) and hepatomegaly.[1] These were all seen in the illustrated case except for a splenomegaly. The patient also had several episodes of tonic clonic seizures, which is documented to occur rarely. Other Rare presentations are pericarditis, pleural effusions, myocarditis and cardic tamponade, aseptic meningitis and encephaditis, cranial neural palsies, uveitis, interstitial nephritis, collapsing glomerulopathy and renal amyloidosis.[1] It is therefore clear that the manifestations of AOSD are pleotropic and often lead to delay in diagnosis and treatment.[1]

The aetiology is still unknown and suspected to be multifaceted. Interplay between being genetically predisposed, the presence of an infectious component and immune dysregulation has been suspected to play a causative role.[1] this is relevant to our patient as a full blood count suggested a possible infection but available investigation with blood culture done had no growth. Absences of identified infectious agent have been reported on some studies.[5] numerous case reports of AOSD following viral infectious have been documented.[4,9] One of which the patient presented 2 month after being managed for infectious mononucleosis.[9] A temporal relationship between disease onset and viral or bacterial syndromes is documented to occur with parvovirus B19, rubella virus, mumps, echovirus 7, human herpes virus 6, parainfluenza virus, Epstein-Barr virus, cytomegalovirus, coxsackievirus B4, adenovirus).[9] some bacterial infections such as *Chlamydia pneumonia*, *Yersinia enterocolitica*, *Brucella abortus*, and *Borrelia burgdorferi*.[1] Thus the triggering of symptoms of AOSD is not directly linked to the aggression itself (infection), but to the reactions that is mounted against it.[6] It must be said here that proof of an infectious aetiology is not established.[1,9]

There has been no consistent association between AOSD and a particular HLA locus.[1] HLA antigens said to be associated with susceptibility to AOSD in a Korean study are HLA DRB1*15 and DRB1*12 in Korean while HLA associated with clinical prognosis is HLA B35 with self-limited disease and DR2 and DR5 with a chronic course based on a study in japan.[1,6] other studies have not confirmed these findings.[1,9]

Currently, it is thought that both the innate and adaptive immune response is dysregulated in patients with AOSD.[1,9] An important step in the pathogenesis of AOSD is stimulation of innate immunity with macrophage and neutrophil activation (evidenced by elevation of CD 64 in patients with active disease) and a raised IL-18 level.[5,9] IL-18 is also implicated in hepatotoxicity, joint disease and is possibly responsible for the cause of liver enzyme derangement typical in AOSD, as it facilitates the TH1 response and induces IL-1β, TNFα and IFNγ.[9] IL-1β seem to be emerging as a key regulator in the pathogenesis of AOSD.[5] it is involved in proliferation of neutrophils and diapedesis.[5] several molecular studies have also shown that elevated levels of IL-1β are associated with active and severe disease.[5] these cytokines also appear to share a role in increasing the production of ferritin, with IL-18 level correlating significantly with serum ferritin level.[9] These pro inflammatory cytokines increase the expression of Toll-like receptors (TLR are sensitive to microbial or viral peptides), thus creating a vicious cycle of inflammatory response and augmentation.[9]

The role of Th17 responses is emerging, since level of Th17-related cytokines, including IL-1β, IL-6 are elevated.[1] This has shown that in the adaptive immunity side of the pathogenesis, dysregulated production of Th17 cells and secretion of IL-17 are seen in patients with AOSD.[9] significantly higher levels of IL-17 have also been implicated in the pathogenesis of autoimmune disorder (SLE), with a parallel correlation between clinical remission of disease and decreases in its level.[9] patients with AOSD show hypercomplementaemia and serum levels of IL-1β, IL-6 IL-17, IL-18, IL-21, IL-23, TNFα, IFNγ, soluble IL-2 receptor and M-CSF that are considerably higher compared to controls.[5,9] these therefore augment and maintain the inflammatory cascade.

Macrophage activation syndrome (MAS) is a life-threatening complication seen in AOSD as well as systemic onset juvenile idiopathic arthritis.[5] Its pathogenesis though not clearly understood, is said to involve cytokine induced hyperproliferatio of activated CD8+ T lymphocytes and macrophages in the reticuloendothelial system.[5] It should be suspected when AOSD patients present with fever, hepatosplenomegaly, lymphadenopathy, pancytopaenia, transamintis, coagulopathy CNS, pulmonary, renal involvement, Diagnosis of MAS is by bone marrow aspiration and biopsy which show hemophagocytosis.[5] In our patient, the unique laboratory picture of AOSD was chanced upon while investigating the causes of fever of unknown origin. Note that the characteristic laboratory findings of AOSD are not pathognomonic, but its presence plus the clinical manifestations should help clinicians establish its diagnosis by excluding other possible conditions such as rheumatoid arthritis, systemic lupus erythematosis, vacuities, polymyosistis, malignancies and infection.[1,6]

Eight different sets of Fautrel criteria has been proposed for diagnosis of AOSD and based on the Yamaguchi criteria Yamaguchi criteria and Fautrel criteria (Table 1), our patient diagnosed.[1,4,10] The Yamaguchi criteria is a mostly widely cited criteria and found to be the most sensitive (93%).[5] The illustrated case scored 8 and 5 of the Yamaguchi and Fautrel criteria respectively.

Table 1: Yamaguchi and Fautrel criteria.

Criteria	Yamaguchi et al	Fautrel et al
	Major: Fever ≥39° C for >1 wk, Arthralgia >2wk, Maculopapular nonpruritic salmon-Pink rash, leucocytosis ≥10,000/mm^3 with ≥80% Neutrophils	Major: spiking fever ≥39°C, arthralgia, transient erythema, pharyngitis, neutrophils >80%, glycosylated ferritin fraction <20%
	Minor: pharyngitis or sore throat, Lymphadenopathy and/or Hepatomegaly, splenomegaly, abnormal aminotransferases, negative rheumatoid factor or ANA assay	Minor: Typical rash, leukocytosis ≥10,000/mm^3
Required	At least 5 criteria, including 2 major	Four major criteria or 3 major and 2 minor criteria
Exclusion needed	Infections, malignancies, vasculitides	Four major criteria or 3 major and 2 minor criteria
Case in discuss	Met criteria	Met criteria

Other investigations specific to the symptoms complex are an erythrocyte sedimentation rate and C-reactive protein that are almost invariably elevated.[1,6] serum ferritin that is markedly elevated and higher than five times the upper limits of normal (40 to 200ng/mL), may suggest the presence of the disease with 80% sensitivity and 46% specificity; when combined with a decrease in the proportion of glycosylated ferritin (<20%), the specificity rises to 93%.[1,5] AOSD is one of the most common causes of markedly elevated serum ferritin levels.[11] These findings were illustrated in this case report.[1] Skin biopsy can be an important investigation as it aids in differentiating this disorder from vasculitis and Sweet syndrome.[1] First-line treatment is said to be with nonsteriodal anti-inflammatory drugs and glucocorticoids.[1] Patient with severe symptoms should be treated with glucocorticoids from the outset of therapy.[1] The usual prednisolone dose is 0.5 to 1mg/kg/day.[1] Intravenous pulse methylprednisolone (1000mg/day times three) is reserved for life-threatening disease such as severe hepatic involvement, dissemination intravascular coagulation, cardiac tamponed.[1] No consensus has been reached on a therapeutic tapering scheme once clinical remission is achieved.[1] No consensus has been reached on a therapeutic tapering scheme once clinical remission is achieved.[1] The illustrated case has NSAID and oral glucocorticoids as first-line therapy as he presented with predominantly arthralgia. There was a need to move to 2nd line drugs because he had possible NSAID induce gastritis and a nephropathy with episode of impaired fasting glucose.

Highlighting the potentiation of disease by cytokines, there is also the need to initiate targeted therapies such as is seen in the 2nd and 3rd line therapies. Second-line therapy includes immunosuppressant and DMARDs such as methotrexate (indirect action on the TNF, IL-6), cyclosporine, azathioprine, cyclophosphamide and tacrolimus.[1,9] DMARDs are initiated for maintenance therapy.[5] The case illustrated was placed on methotrexate following complaints of persistence of fever, arthralgia including episodes of impaired glucose tolerance. He was admitted to resolution of arthralgia till date after 2 months of methotrexate. In a retrospective study of 13 Japanese patients placed on methotrexate, 8 patients were found to be in remission between 3-13 weeks of commencing methotrexate.[12] There-line therapy includes biologic agents such as the Tumor necrosis factor inhibitors infliximab and etanercept. Inhibition of IL-1β and IL-6 are more effective than TNF.[13] Anakinra, a recombinant IL-1 receptor antagonist is said to show positive results in ameliorating the disease at a clinical, haematological, biochemical and cytokine level.[5,9] Other IL-1β inhibitions available are canakinumab (a human monoclonal antibody directed against IL-1β) and rilonacept (a soluble IL-1 trap fusion protein).[5] Interleukin 1β inhibition is useful as the mainstay of treatment for refractory AOSD.[5]

The prognosis of AOSD is determined by its clinical pattern. This could range from a monocyclic or self-limiting systemic group that is seen in 60% of cases, manifesting with only one episode of systemic manifestations, with disease course that usually lasts less than 1 year, with complete resolution of symptoms.[4,9] The second group is polycyclic systemic or intermittent pattern whom experience more than one episode followed by partial or total remission.[4,9] The 3rd group is the

chronic articular pattern: patients with chronic AOSD have persistently active disease associated with persistent polyarthritis lasting for 6months progressing to destructive arthritis.[4,9]

Baseline risk factors for an unfavourable outcome include occurrence of polyarthritis early, hip and shoulder involvement, and the need of glucocorticoid therapy for more than 2 years.[1] The articular prognosis is based on the clinical profile, diagnostic delay and therapeutic efficiency and the illustrated case falls into the 2nd group of AOSD.[14] The functional status of patients with AOSD is generally good.

In 1991, from a study on 62 patients, Pouchot et al, proposed a 'systemic score' reaching up to 12 points, and assigning one point to each of the following manifestation: fever, skin rash, pleuritis, pneumonia, pericarditis, liver involvement, spleen involvement, lymphadenopathy, leukocytosis >15,000/mm³, sore throat, myalgia, and abdominal pain.[15] it is reported recently that this score successfully predicts a poor outcome for AOSD.[15] A systemic score >/=7 or >6 plus MAS, kidney failure or myocarditis at diagnosis is associated with mortality.[15]

CONCLUSION

In conclusion, we happened on a case of Adult-onset Still disease while investigating a fever of unknown origin. This is because for over 40 decades, AOSD is a diagnostic difficulty. The persistence of symptoms and the rigors in diagnosing the patient spanned about 18monthhs and show the difficulty in entertaining such a rare diagnosis and the financial difficulties seen in our area of practice. Clinical findings consisting of a combination of systemic manifestations (mostly spiking fever, evanescent rash, and lymphadenopathy) and joint symptoms ranging from arthralgia to aggressive arthritis including a raised serum ferritin, negative RF and ANA are important in making a diagnosis. The patient made good improvement on steroids and methotrexate but this has been marred by financial difficulties and a state of denial which is common in our area of practice. More clinical trials on adult-onset still disease is needed to improve on the knowledge of this condition.

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