CASE REPORT

Adult Onset Still's Disease: A Case Report in Hospital Kuala Lumpur

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Summary

Adult onset Still's disease (AOSD) is a rare systemic autoinflammatory disorder of unknown etiology characterized by a clinical triads of daily spiking high fever, evanescent rash and arthritis; with laboratory findings of hyperferritinemia, neutrophilic leucocytosis and negative autoantibodies of rheumatoid factor and antinuclear antibody. Diagnosis is made after exclusion of infections, autoimmune diseases and malignancy. Here we illustrate a case of AOSD with prolonged high fever, evanescent rash presenting as scattered erythematous patches, polyarthritis, lymphadenopathy, serositis, anemia, leukocytosis, hyperferritinemia and hepatitis. It was complicated by crico-arytenoid arthritis, acute interstitial nephritis with nephrogenic diabetes insipidus. Skin biopsy showed distinctive dyskeratotic keratinocytes at the upper epidermis. Diagnosis of AOSD was made at 6 weeks from the onset of fever. She responded partially to high dose of systemic corticosteroids, intravenous immunoglobulin, methotrexate and anakinra.

Key words: *Adult onset Still's disease, autoinflammatory disorder, dyskeratotic keratinocytes*

Introduction

Adult onset Still's disease (AOSD) is a sporadic complex autoinflammatory syndrome first described in 1971.[1] It is characterised by high spiking fever, polyarthritis, sore throat, lymphadenopathy, hepatosplenomegaly, serositis, and evanescent skin eruptions.[1,2] It is associated with life-threatening complications too. Diagnosis of AOSD is laborious as it requires extensive investigations to exclude infections, autoimmune diseases and malignancy. Here we illustrate a young female who exhibited a turbulent presentation of ASOD.

Case Report

A 30-year-old Chinese female presented with 2 weeks of fever, chills, rigors, sore throat, and dry cough associated with polyarthalgia at proximal interphalangeal joints, wrists, elbows, shoulders, ankles and knees. There were no oral ulcers, photosensitivity, alopecia, weight loss, abdominal pain, diarrhea, heat intolerance and palpitation. There was also no prior new medication or history of travelling. She did not respond to antibiotics and

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paracetamol given at a private health care facility. She was then hospitalized in Hospital Kuala Lumpur in September of 2018 after 3 weeks of prolonged and persistent high fever.

She was pale, blood pressure was low to normal and tachycardic. Her weight on admission was 42kg. Her fever was spiking at 40°C every night. This was associated with evanescent erythematous patches over the knuckles which resolved when fever subsided. She also had pruritic erythematous patches at the upper anterior chest as shown in Figure 1(a). Her condition deteriorated with dyspnoea requiring non-invasive ventilation at high dependency unit.

Laboratory tests revealed normocytic normochromic anemia (Hb 7.5g/dL) and leucocytosis (highest white blood cells count 44.4 x 10^9/L, 88-93% neutrophils). The acute phase reactants were elevated with erythrocyte sedimentation rate (ESR): 65 mm/hr; highest C-reactive protein (CRP): 288 mg/L; and highest ferritin: 36,737µg/L. She had mild transaminitis (highest aspartate transaminase: 90U/L; highest alanine transaminase: 848U/L; and alkaline phosphatase: 204U/L) and hypoalbuminemia (lowest albumin 14g/L). Viral screening including HIV and Hepatitis A IgM, anti Hep BsAg antibody, anti HepB core antibody and anti Hep C virus antibody were negative. VDRL titre was 1:4 and TPHA was negative. Her Mantoux test was 0mm, and the Quanteron gold (performed twice with 2 weeks apart) were indeterminate. Leptospira serology, mycoplasma serology, melioidosis serology, blood films for malaria parasites, Widal Weil Felix (WWF) test, sputum acid fast bacilli (AFB) were all non-reactive. Anti-nuclear antibody (ANA), rheumatoid factor (RF), anti-cyclic citrullinated peptide (Anti-CCP), anti-smooth muscle antibodies (ASMA), anti-mitochondrial antibodies (AMA) antibody and Anti-Liver Kidney Microsomal (LKM) antibodies were negative. Complement level C3, C4, were within normal range. Chest radiography showed bilateral pleural effusion.

There was pericardial effusion on her echocardiogram with free wall of the right atrium and posterior left ventricle which ranged between 1.4-1.6cm. Apart from mild mitral and tricuspid regurgitation, her ejection fraction was between 58-60% without any thrombus and vegetations. Computed tomography (CT) of her brain was normal. Her CT thorax, abdomen and pelvis revealed bilateral hilar mediastinal lymph node enlargement and hepatomegaly. No paraprotein was detected from serum and urine electrophoresis. Apart from increased granulocytic series especially the granulocyte precursor, her bone marrow aspiration and trephine biopsy did not detect any hemophagocytic lymphohistiocytosis (HLH), acute leukemia or lymphoma. Cultures (bacterial fungal and mycobacterium) from the bone marrow biopsy were negative.

Ten days into hospitalization, a referral was made to the Department of Dermatology for her rash. She was tachypnoeic, hypotensive and febrile. There were persistent erythematous patches noted at the neck (Figure 1a), erythematous patches over the knuckles of fingers with tender swollen proximal interphalangeal joints bilaterally. There were bilateral pedal edema. Breath sound was reduced at the base of the lungs. There were however no murmur, lymphadenopathy, hepatomegaly, splenomegaly or ascites.

Skin biopsy at the erythematous patch of the anterior chest showed spongiotic epidermis with presence of dyskeratotic keratinocytes at the stratum granulosum. The upper dermis showed perivascular eosinophils and neutrophils infiltration. (Figure 2a, H&E, x200). There were no interface changes, vasculitis or mucin deposition. Clinical pathological correlation with the skin histological findings were consistent with Still's Disease.

The diagnosis of Adult Onset Still's Disease (AOSD) was finally made nearly 6 weeks after the onset of fever. She was started on IV Hydrocortisone 100mg 8 hourly. During the same admission, she received intravenous ceftriazone (2 days), intravenous tazobactam + piperacillin (2 courses at different occasions, total 12 days), intravenous meropenem (2 courses at different occasion, total 3 weeks), oral doxycycline (1 week), intravenous augmentin (7 days) and oral cloxacillin (7 days). The antibiotics were given for presumed sepsis initially and subsequently positive blood and urine cultures of *Acinetobacter baumanii* and *Enterococcus species* respectively. Despite the concomitant systemic corticosteroids and antibiotics, her fever did not resolve.

Three weeks after intravenous hydrocortisone was initiated, she developed scattered vesicular eruptions involving the right temple, oral cavity, upper limbs and trunk. A repeated skin biopsy showed intraepidermal blister containing numerous

viral cytopathic effect cells exhibiting very large nuclei with multiple inclusions and nuclear clearing (Figure 2b, H&E, x100). This was suggestive of herpes infection. Herpes simplex virus 1 & 2 DNA PCR were not detected probably due to a late sampling from the lesions. However, herpes simplex virus 1 & 2 IgM was detected. Other human herpes virus screenings (CMV and EBV) were negative. A diagnosis of disseminated herpes infection was made. She was treated with IV Acyclovir 500md 8-hourly for a week.

Subsequently, she developed dysphagia and phonatory gap with vocal cords paralysis. Extensive investigations including abnormal flexible endoscopic examinations of swallowing, a non-reactive anti–acetylcholine receptor (AChR) antibody and a normal Magnetic Resonance Imaging (MRI) with angiography of the brain had concluded that these were the complications of ASOD due to the arthritis of the crico-arytenoid joints. Her symptoms responded to IV methylprednisolone 500mg od for 3 days. Apart from that, she received 2 units of packed cell transfusion. She improved finally and then was discharged with oral prednisolone 30mg daily, oral pantoprazole, cholecalciferol, calcium supplements, ferrous fumarate and vitamins after 3 months of hospital stay.

Unfortunately, she was readmitted to the hospital twice in January 2019 for severe hepatitis (highest level of ALT=1,372U/L and AST=1,351U/L) with persistent high fever. Her serum ferritin peaked at 64,114ug/L. Her serum fibrinogen was normal and D-dimer was slightly raised at 7.2ug/ml (<0.5). Repeated bone marrow aspiration in February 2019 showed no evidence of acute leukaemia nor haemophagocytosis. Liver biopsy showed mild to moderate interface hepatitis with inflammatory infiltrates consisted of lymphocytes, plasma cells and neutrophils. Mild focal hepatocellular cholestasis, mild cytoplasmic vacuolation of some bile duct lining and lymphocytic lobular inflammation was observed. There was no intraepithelial fibrosis and granuloma. She was given intravenous immunoglobulin 2g/kg twice (3 weeks apart) and a course of intravenous methylprednisolone 500mg daily for 3 days. Her hepatitis improved and she was discharged with oral prednisolone 40mg daily with vitamins, cholecalciferol and calcium supplements.

Subcutaneous Anakinra 90mg daily was initiated end of February 2019 while the dose of oral prednisolone was taper down slowly. Two weeks after the initiation of anakinra, she was readmitted with high fever and cough. She was diagnosed with hospital acquired pneumonia based on the appearance of infective changes at the right middle lobe on her chest radiograph. Her liver enzymes were almost normalized with serum ferritin of 6,891μg/L. Anankira was withheld, intravenous tazocin was initiated and oral prednisolone was maintained at 15mg daily. Cloxacillin was added on day 6 of tazocin for five days for cellulitis of her right hand. She then developed new cutaneous reactions. Firstly, she presented with persistent periorbital swelling followed with Stevens Johnson Syndrome (SJS) like lesions. She had severe oral and genitalia erosions, conjunctivitis and blanchable maculopapular eruptions on her face, body and limbs with less than 10% body surface area of detached skin. Based on the algorithm of drug causality for epidermal necolysis (ALDEN)[3], both tazocin and cloxacillin scored 3 out of 10, which means they were only "possible" culprits, neither "probably" nor "very probable". This is mainly because they were given in her previous admission (twice for tazocin and once for cloxacillin) without any reactions documented. Both tazocin and cloxacillin were withheld. Her skin lesions gradually resolved in 2 weeks with supportive skin care treatment and intravenous hydrocortisone 50mg 8hourly.

Unfortunately, she had hospital acquired infections with right mid lobar pneumonia (broncho-alveolar lavage culture grew methicillin-resistant *Staphylococcus aureus [MRSA])*, urine culture grew *MRSA* and *Escherichia coli*, blood culture grew coagulase-negative *Staphylococci*). She was then given intravenous meropenem (total 10 days) and vancomycin (total 14 days). While receiving these antibiotics and systemic corticosteroids (equivalent of prednisolone dose 15mg to 50mg daily) she developed periorbital swelling with heliotrope like rash, mildly scaly malar erythema sparing the infraorbital and nasolabial fold, mildly scaly scalp together with non-pruritic purpuric to brown macules over trunk, upper and lower limbs including the palms without any mucosal erosions (Figure 1b-e). Her high fever persisted despite antibiotics. She had thrombocytopenia (lowest platelet count of $67x10^9$), low fibrinogen, raised D-dimer and mildly prolonged prothrombin time. Her ferritin was again raised at 12,444 μg/L, liver enzymes raised at ALT: 570U/L, AST:1773U/L signifying the active AOSD. Skin biopsy was also performed on a lesion on her palm and showed singly apoptotic keratinocytes at the upper epidermis, similar to the findings of the

Figure 1. a. Persistent pruritic erythematous patches at the upper anterior chest and neck in September 2018, b-e. Periorbital swelling with heliotrope-like rash, mildly scaly malar erythema sparing the infraorbital and nasolabial fold, non-pruritic purpuric macules on the palms, brown macules over trunk, and dorsum of feet in April 2019.

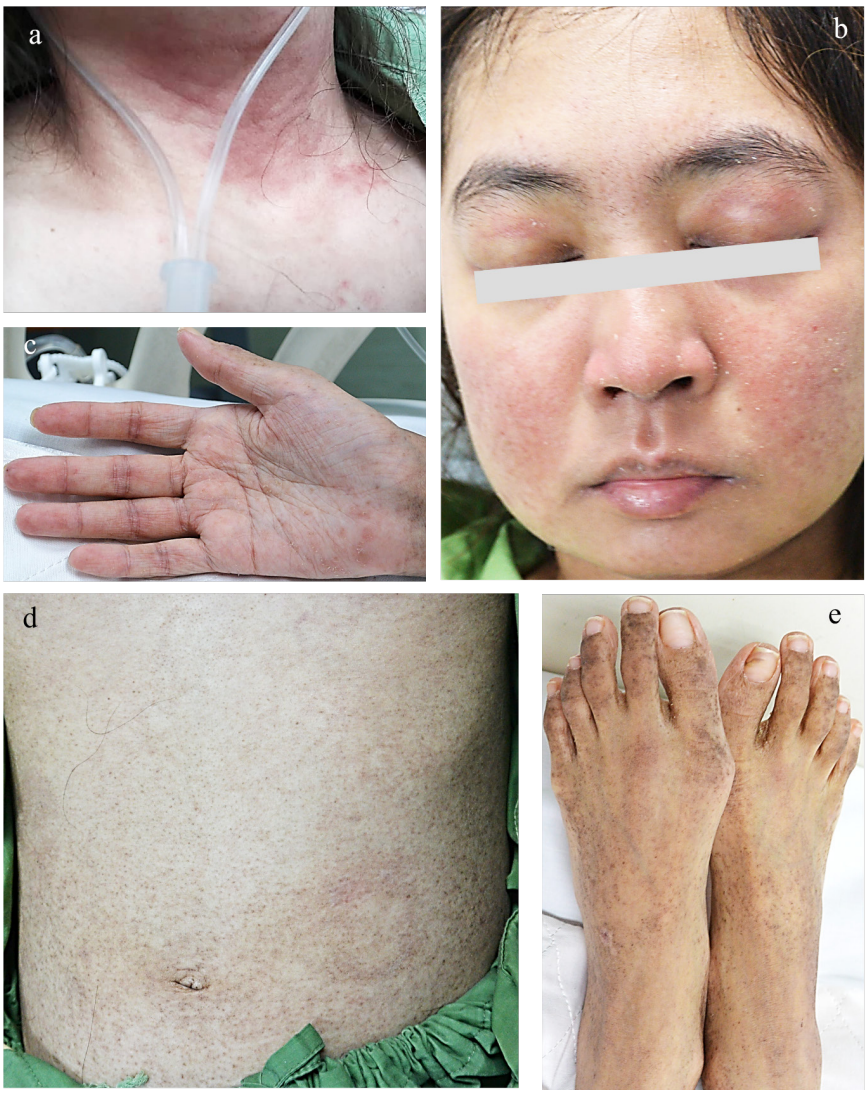
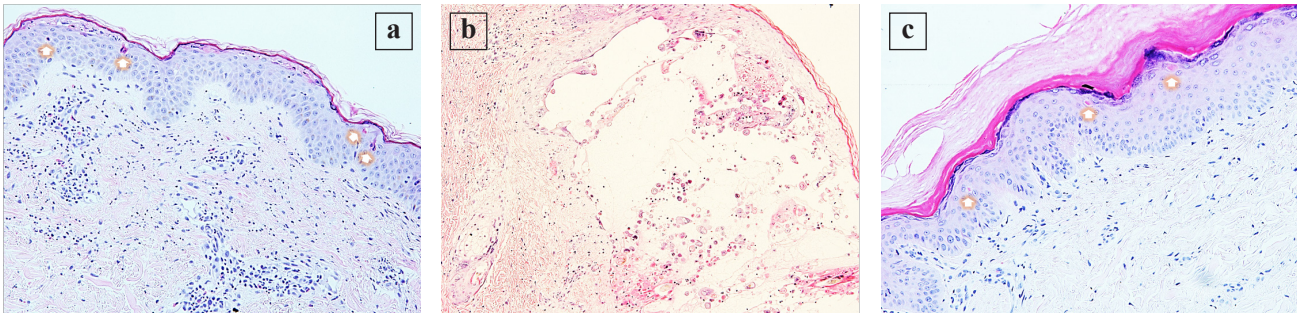


Figure 2. a. Skin biopsy on the erythematous patch of the anterior chest in September 2018 showed spongiotic epidermis with presence of dyskeratotic keratinocytes (arrow) at the stratum granulosum. The upper dermis showed perivascular eosinophils and neutrophils infiltration. (H&E, x200); b. A repeated skin biopsy in October 2018 done on a vesicle showed intraepidermal blister containing numerous viral cytopathic effect cells exhibiting very large nuclei with multiple inclusions and nuclear clearing (H&E, x100); c. Another skin biopsy on her left palm showed singly apoptotic keratinocytes (arrow) at the upper epidermis (H&E, x200)



first skin biopsy, which was suggestive of AOSD (Figure 2c, H&E, x200), rather than cutaneous adverse drug reactions. She also developed polyuria as a sign of nephrogenic diabetes insipidus resulted from acute interstitial nephritis. Her antibiotics was changed to intravenous colistin for 7 days. A course of oral oseltamivir was also prescribed. Intravenous immunoglobulin (IVIg) 0.4g/kg/ day for 5 days was administered and subcutaneous anakinra 90mg was resumed. Her diabetes insipidus was controlled by desmopressin and later replaced with fludrocortisone treatment. She improved clinically and was finally discharged with oral prednisolone 10mg daily, subcutaneous anakinra 90mg daily, fluodrocortisone 0.1mg daily, cholecalciferol, calcium supplements and vitamins.

Her subsequent outpatient follow-ups with rheumatologist showed that her disease activity was sub-optimally controlled. She was still experiencing fever almost every day. Apart from that she had generalized lymphadenopathy (size ranged from subcentimeter to 2.4cm) demonstrated on repeated CT scan. Her latest ferritin level was 1820 μg/L with normalized liver enzymes. Lymph node biopsy showed reactive hyperplasia and had excluded lymphoma. Her latest medications included subcutaneous anakinra 200mg daily and oral methotrexate 20mg weekly together with calcium supplements and vitamins.

Discussion

ASOD is phenotypically likened to childhood-onset Still's disease, which is now known as systemic juvenile idiopathic arthritis (sJIA). sJIA occurs in children less than 16 years-old. sJIA is more common in children with the worldwide incidence ranges between 0.4 to 0.8 per 100,000 children.[4] Both male and female children are affected equally.[4] sJIA is reported to affect children of all ethnic backgrounds.[4] The incidence of ASOD worldwide is much lower incidence as compared to sJIA i.e. 0.16 to 0.4 per 100,000 adults.[4] Like sJIA, ASOD has equal gender distribution[2,6-7] in most reports but there is a female preponderance in the Japanese, Korean and Chinese studies.[6] Although ASOD may present for the first time in adults above 65 years old[8,9] (reported to be between 5-23%), it usually affects younger people, with bimodal peak at 15-25 years and 36-46 years.[2,6-7]

Being a multigenic autoinflammatory disease involving mainly the innate immune system, AOSD is believed to be triggered by some factors (viral or bacterial infections, malignancies and possibly other environmental elements) in a genetically susceptible individual.[5-7] No definite trigger has been identified. AOSD has been associated with HLA-B17, -B18, -B35, -DR2 and -DR4, DRB1*12, DRB1*15, Bw35 and DRB1*14. HLA-BRB1*1501 (DR2) and DRB1*1201 (DR5) were associated with chronic disease course of AOSD and HLA-DQB1*0602 (DQ1) was associated with chronic and systemic disease.[6,10] Polymorphisms in both interleukin (IL)-18 gene and macrophage migration inhibitory factor (MIF) gene were associated with AOSD. In addition, gain-of-function mutation of the MEFV, a hereditary periodic fever syndrome gene was identified with severe form of AOSD.[6,10] Dramatic activation of the inflammatory cells of the innate immunity is the hallmark of AOSD. Toll-like receptor (TLR) 7 ligation is up-regulated in the dendritic cells.[6,10] Recruitment of neutrophils and macrophages are heightened, resulting in pro-inflammatory responses and cytokine "storm". Amplified production of IL-1β, IL-6 and IL-18 was studied extensively in AOSD.[6,10] Anti-IL-1 treatment has been shown to be useful in treating AOSD. Interestingly, the cytotoxic functions of NK cells were impaired in AOSD. Besides, the circulating $CD4^{+}CD25^{high}$ Treg cells, serum transforming growth factor β (TGF- β) and IL-10 were found to be low in severe AOSD which allow unhindered inflammation in AOSD.[5,9] Other cytokines including IL-17, IL-23, TNF, CXCL9,10,11, and 13 were also found to be raised in AOSD, albeit undetermined significance.[10]

AOSD typically present with a clinical triad of high spiking fever of at least 39°C, joint involvement and typical evanescent erythema.[5-7] The fever is abrupt, once or twice a day, highest in the evening and lasts less than 4 hours. The joint involvement is usually symmetrical polyarthritis, mainly affecting the wrists, knees and ankles.[5-7] In about a third of arthritis, joint becomes erosive where patients may develop isolated bilateral carpal ankylosis.[5-7]

Cutaneous manifestation is one of the major diagnostic criteria for AOSD. It is described in 58-87% of patients with ASOD.[5] Our patient has demonstrated a few types of cutaneous manifestations with different morphology at different stages of disease activity. She had the classical evanescent erythematous patches over her knuckles during her febrile attack before the diagnosis of AOSD. Classical evanescent rash has been described in the literature as salmon-pink, maculopapular eruption accompanied by fever, predominantly found on

Table 1. Yamaguchi et al[20] and Fautrel et al[21] Classification criteria for adult onset Still's Disease

Criteria	Yamaguchi et al[20], 1992	Fautrel et al[21], 2002
Major criteria	• Fever =39 °C lasting 1 week or more • Arthralgia lasting 2 weeks or more • Typical skin rash: maculopapular, nonpruritic, salmon-pink rash with concomitant fever • Leukocytosis =10,000/mm^3 with neutrophil polymorphonuclear proportion =80%	• Spiking fever =39 °C • Arthralgia • Transient erythema • Pharyngitis • Neutrophil polymorphonuclear proportion =80% • GF proportion =20%
Minor criteria	• Pharyngitis or sore throat • Lymphadenopathy and/or splenomegaly • Liver enzyme abnormalities (aminotransferases) • Negative for rheumatoid factor or antinuclear antibodies	• Typical rash • Leukocytosis =10,000/mm^3
Exclusion criteria	• Absence of infection, especially sepsis and Epstein–Barr viral infection • Absence of malignant diseases, especiallylymphomas • Absence of inflammatory disease, especially polyarteritis nodosa	None
Requirement	At least five criteria, including two major criteria and no exclusion criteria	Four major criteria or three major criteria and two minor criteria

the extremities and trunk.[11-14] Histological findings of these lesions usually show a normal epidermis with mild perivascular lymphocytes and neutrophils infiltration at superficial dermis.[11-14]

Our patient also presented atypical eruption of AOSD which was the persistent mildly pruritic erythematous patch on her neck and anterior chest. The presence of the unique histology of the skin lesion i.e. distinctive distribution of dyskeratotic keratinocytes at the upper epidermis as well as cornified layers[11-14] expedited the diagnosis of AOSD in our patient. Interestingly our patient had presented with SJS-like eruption preceded by persistent periorbital swellings. SJS and/or toxic epidermal necrolysis-like eruption, apart from drug induced, has been associated with infections (especially herpes simplex and mycoplasma infection), systemic lupus erythematosus, graft-versus-host disease (GVHD) and pseudoporphyria in haemodialysis patients.[15] Although antibiotics could possibly be implicated in our patient, the likelihood was perhaps low based on low ALDEN scores. Regrettably, a skin biopsy was not performed while she had the SJS-like eruption. The incidence of drug eruption has been reported is significant among AOSD patients ranging from 8-92% and mostly described as urticaria and maculopapular eruptions.[12]

The true incidence of cutaneous adverse drug reactions is probably questionable as they could be the atypical eruption of AOSD. AOSD presenting as SJS-like eruption has not been described before. However GVHD-like skin reaction has been described in a patient with AOSD presenting as immune reconstitution inflammatory syndrome (IRIS) during steroid tapering.[16] Our patient was only given minimal immunosuppressants (low dose of oral prednisolone 15mg daily and anakinra was withheld) for her AOSD while she developed SJS-like eruption. Hence, the SJS-like eruption that she experienced may not be drug related but could be the presenting feature of GVHD like reaction as part of her AOSD. The skin lesions improved when her corticosteroids increased to a higher dose.

Furthermore, our patient also presented with dermatomyositis-like persistent eruptions together with purpuric and brown macules over her trunk, hands, palms and feet after resolution of the SJS-like eruption. A repeated biopsy again demonstrated the unique features of AOSD. The manifestations of atypical or persistent AOSD-related cutaneous eruptions include persistent urticaria, persistent pruritic papules and plaques, erythematous to violaceous or pigmented lichenoid papules, dermatomyositis-like, cutaneous GVHD, lichen amyloidosis, prurigo pigmentosa like, maculopapular or lichenoid eruptions, peau d'orange like, vesiculo-pustular eruptions of the limbs and lichen simplex chronicus.[11-14] The presentation may appear as the earlier presentation of AOSD or as a cutaneous marker of disease activity. Hence a high index of clinical suspicious is needed in order to avoid delay in diagnosis or introducing aggressive treatment.

Other clinical manifestations such as odynophagia and pharyngitis, generalized lymphadenopathy, pericarditis (pericardial effusion), hepatomegaly, interstitial nephritis (diabetes insipidus), pleuritis

(pleural effusion) were all present in our patients. Other clinical involvement such as subacute glomerulitis, collapsing gloerulopathy, pancreatitis, meningitis, cranial nerves paralysis and seizures which have been reported in AOSD,[5-7] were, fortunately not present in our patient.

A significant leucocytosis (>10x10^9/L) with neurophilia (>80%) is another hallmark of AOSD. The highest documented leucocyte count in our patient was 44.4x10^9/L with 88-93% neutrophils.[5-7] Neutropenia, in the presence of anemia and/or thrombocytopenia may indicate reactive hemophagocytic syndrome.[5-7] Raised liver enzymes are very common and it was observed in our patient.[5-7] Being an autoinflammatory disease, all the auto-antibodies especially rheumatic factor and antinuclear antibodies are typically non-reactive.[5-7] Not surprisingly, acute phase reactants such as ESR and CRP are substantially increase in AOSD.[5-7]

Serum ferritin, an indicator of macrophage activation, is raised in many inflammatory conditions including AOSD.[10] Several cytokines mentioned earlier such as IL-1β, IL-6, IL-18 and TNFα appeared to drive the production of ferritin.[10] It is observed that the serum ferritin levels in AOSD were much higher than many other autoimmune, inflammatory, infectious and neoplastic diseases, usually >1000ng/ml (normal between 40-200).[10,17,18] This was seen in our patient with the highest ferritin level above 64,000). The specificity of serum ferritin level alone in the diagnosis of AOSD was however reported to be low, between 41 and 46%.[10,17,18] Glycosylated fraction of ferritin (GF) has been described as a more specific diagnostic marker for AOSD, where the GF is typically <20% (50-80% of ferritin in healthy subjects is glycosylated).[10,17,18] The AOSD diagnostic sensitivity and specificity improved to 70.5% and 92.9% respectively when there is at-least five-fold rise in serum ferritin combined with GF≤20%. Nevertheless, total serum ferritin appears to be a more useful marker in terms of disease activity monitoring.[10,17,18] It often normalises when the disease goes into remission. GF however remained low despite disease remission, and hence cannot be used to monitor disease activity of response to treatment.[19] Other potential markers such as procalcitonin, calpotectin, serum IL-1, IL-6, IL-18, CD163, CXCL 10, CXCL13, MIF are again not specific to AOSD and have not been recommended for routine investigation for AOSD.[10]

Diagnosing AOSD is extremely challenging as illustrated in our patient. The lack of diagnostic biomarkers and non-specific clinical presentations often result in a significant delay in the diagnosis and treatment in this rare condition. A few classification criteria have been developed but the Yamaguchi diagnostic criteria[20] (1992, Table 1) for AOSD is the most widely used. It however requires exclusion of infections, malignancies and other autoimmune diseases. The Fautrel criteria[21] (2002, Table 1) on the other hand, included ferritin and GF levels as diagnostic biomarkers. The latest validation study showed that both sets of criteria yield high sensitivity and specificity.[22] Although we could not determine the GF in our patient, she fulfilled both diagnostic criteria for AOSD.

The course of AOSD is unpredictable. Our patient was probably has a chronic and progressive course. Since the onset of symptoms, she appeared to have regular systemic flares of AOSD for at least 18 months despite on various immune-modulatory agents. A monocyclic course is described to be self-limited disease or being able to achieve drug-free remission without relapses.[5-7] A recurrent or polycyclic course is featured by AOSD relapses after a period (months or years) of disease control with or without immune-modulatory agents.[5-7]

Management of AOSD is extremely challenging too. Non-steroidal anti-inflammatory drugs (NSAIDs), systemic corticosteroids, immunosuppressive agents such as methotrexate, leflunomide, gold, azathioprine, ciclosporin A, hydroxychloroquin and cyclophosphamide as well as intravenous immunoglobulin have been described as helpful.[5-7,23] The use of NSAIDs and sulfasalazine have been associated with macrophage activation syndrome (MAS).[24] Biologic agents such as IL-1 inhibitors (anakinra and canakinumab), IL-6 inhibitors (tocilizumab), TNF-inhibitors (infliximab, etanercept and adalimumab) are indicated for severe form of AOSD.[5-7] Anti-TNF-α appeared to be useful in controlling the joint symptoms of AOSD, but less effective on other systemic symptoms.[5-7] An agent under development includes IL-18 inhibitor (Tadekinig alpha).[5-7]

The objective of aggressive treatment of AOSD aims to induce remission of disease and also prevent complications and end-organ damage. The well-known serious complications of AOSD include reactive hemophagocytic lymphohistiocytosis (HLH), coagulation disorders (disseminated intravascular coagulation ad thrombotic

microangiopathy), fulminant hepatitis, pericarditis, cardiac tamponade, myocarditis, endocarditis, pulmonary arterial hypertension, pleuritis, interstitial lung disease, aseptic empyema, diffuse alveolar haemorrhage and amyloid A amyloidosis.[24] HLH, also known as macrophage activation syndrome is the most feared deadly complications of AOSD with a reported mortality rate of between 10-20%.[24] It is characterized by persistent high fever, hepatosplenomegaly and cytopenia with the presence of activated macrophages in hematopoeietic organs.[24] It has been considered in our patient and repeated bone marrow aspiration had excluded HLH. In addition, patients may suffer from complications from the treatment of AOSD such as bacterial and viral infections. This happened in our patient. She developed herpes simplex viral infection and pneumonia while receiving systemic corticosteroids. Furthermore, delayed association with malignancy has been described in AOSD including lymphoma, myelodysplastic syndrome, leukemia, breast cancer, thyroid cancer, lung cancer, esophageal cancer, rectal cancer, cholangiocarcinoma and etc.[25] Hence, long term follow up of patients with AOSD is mandatory.

Conclusion

We described a young female with AOSD with several severe complications. She presented with both classical and non-classical cutaneous manifestations. Her skin biopsy on the persistent erythematous patch demonstrated distinctive features of AOSD which had enabled the clinician to achieve the diagnosis. Unfortunately, she had a chronic and progressive disease and more aggressive treatment options may need to be considered for her.

Conflict of Interest Declaration

All authors have no financial/conflict of interest to disclose.

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