Complex Situations in Patients with Adult-Onset Still's Disease

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Abstract Adult-onset Still's disease (AOSD) is a rare systemic inflammatory disorder of unknown etiology, characterized by quotidian or double quotidian fever, a peri-febrile cutaneous eruption, polyarthritis, and multiorgan involvement. AOSD is a challenging disease with protean disease manifestations and rare, albeit potentially life-threatening, complications. In such cases, prompt diagnosis and treatment may prove life-saving.

The purpose of this chapter is to review the diagnosis and management of challenging clinical situations in AOSD patients that are associated with significant morbidity and mortality and to provide the readers with information that could aid their decision-making process.

Keywords Adult-Onset Still's Disease (AOSD) • Complications • Interleukin (IL)-1 • Reactive hemophagocytic syndrome (RHS) • Still's arthritis • Still's rash

14.1
Introduction

Adult-onset Still's disease (AOSD) is a rare systemic inflammatory disorder of unknown etiology with a protean clinical presentation. Symptoms include a quotidian or double quotidian fever, a peri-febrile cutaneous eruption, polyarthritis and, in severe cases, multiorgan involvement. Pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, and IL-18, interferon (IFN)-γ, tumor necrosis factor (TNF), and macrophage colony–stimulating factor are elevated in patients with AOSD and are thought to have a major role in the pathogenesis of the disease.[1] High index of clinical suspicion and careful investigation are required to make an early diagnosis so that aggressive treatment can be initiated. There is no single diagnostic test for AOSD; rather, the diagnosis is based on sets of clinical and laboratory criteria. Several

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sets of classification criteria have been published for AOSD. They have all been developed from retrospective data and classify criteria as major or minor. Table 14.1 compares the most recent Fautrel criteria[3] with the widely used original Yamaguchi's criteria.[2]

Diagnosis of AOSD usually necessitates the exclusion of infectious, neoplastic, and other autoimmune diseases. The diseases to exclude have been described in Table 14.2.

AOSD management greatly depends on the severity and chronicity of symptoms and the predominant disease pattern, systemic, or arthritic. Initial attacks may be effectively treated with short courses of systemic corticosteroids and may never recur. Persistent

Table 14.1 AOSD diagnostic criteria

Yamaguchi et al.[2]	Fautrel et al.[3]
Major Arthralgia >2 weeks Fever >39°, intermittent ≥1 week Typical rash WBC ≥10,000 (≥80,000 granulocytes)	 Spiking fever >39° Arthralgia Transient erythema Pharyngitis PMNs ≥80% Glycosylated ferritin ≤20%
Minor Sore throat Lymphadenopathy and/or splenomegaly Abnormal Liver function tests (−)ve RF and ANA	 Maculopapular rash Leucocytes $>10 \times 10^9$ /L
Diagnostic combination Exclusion criteria – Infections – Malignancies – Other rheumatic diseases	
Diagnosis: 5 criteria (at least 2 major)	4 major or 3 major + 2 minor

Table 14.2 Diagnostic guidelines for hemophagocytic lymphohistiocytosis (HLH) aka hemophagocytic syndrome

Clinical criteria	Fever
	Splenomegaly
Laboratory criteria	Cytopenia (affecting >2 of 3 lineages in the peripheral blood) Hemoglobin <90 g/l Platelets $<100 \times 109$/l Neutrophils $<1.0 \times 109$/l Hypertriglyceridemia and/or hypofibrinogenemia (fasting triglycerides ≥2.0 mmol/l or ≥3 SD of the normal value for age, fibrinogen ≤1.5 g/l or ≤3 SD)
Histopathologic criteria	Hemophagocytosis in bone marrow or spleen or lymph nodes. No evidence of malignancy

disease with frequent recurrent attacks with systemic symptoms (fever, rash) or differentiation into the chronic articular pattern is associated with significant morbidity and requires chronic suppressive treatment with systemic corticosteroids, often in combination with traditional Disease-Modifying anti-Rheumatic Drugs (DMARDS) or the newer biologic agents that offer a more targeted approach.

The purpose of this chapter is to review the management of challenging clinical situations in AOSD patients that may be associated with significant morbidity and mortality and to provide the readers with information that may aid their decision-making process.

14.2
Reactive Hemophagocytic Syndrome (RHS)

RHS, otherwise known as macrophage activation syndrome (MAS), is a rare but potentially fatal condition, which is characterized by acute fever; hepatosplenomegaly; lymphadenopathy; pancytopenia; and raised levels of serum ferritin, triglycerides, and liver enzymes (Table 14.3). The prevalence of RHS in AOSD may be as high as 12%, as suggested by

Table 14.3 Complications of AOSD

Pulmonary   • Pleural effusion   • Transient pulmonary infiltrates   • Interstitial lung disease   • Acute respiratory distress syndrome   • Diffuse alveolar hemorrhage
Cardiovascular   • Pericarditis   • Myocarditis   • Pulmonary artery hypertension
Reticuloendothelial system (*RES*)   • Macrophage activation syndrome   • Autoimmune hepatitis   • Acute liver failure
Vasculopathy   • Cutaneous Polyarteritis nodosa   • Thrombotic microangiopathy
Coagulopathy   • Portal vein thrombosis   • Thrombotic thrombocytopenic purpura   • Disseminated intravascular coagulation
Neurological   • Miller Fisher syndrome   • Peripheral neuropathy

Arlet et al.[4] The possible triggering factors for RHS include drugs, viruses [Epstein Barr Virus (EBV), cytomegalovirus (CMV), parvovirus], autoimmune disorders [rheumatoid arthritis (RA), systemic lupus erythematosus], lymphomas, and leukemias.[5] The hallmark of this syndrome is excessive activation and proliferation of T lymphocytes and macrophages with massive hypercytokinemia with high levels of interleukin-1β, interleukin-6, interferon-γ, and TNF-α. This activation cascade produces an overwhelming inflammatory reaction. RHS can occur at any time during the course of AOSD. Moreover, a simultaneous diagnosis of AOSD and RHS is not uncommon. Flares of AOSD and RHS may be clinically indistinguishable, with the exception of a higher frequency of pleuritis and ARDS in RHS. Biological findings are certainly more sensitive in evoking the diagnosis of RHS during flares of AOSD. Leucopenia or thrombocytopenia is uncommon in AOSD and hence can serve as an alert. Raised serum triglyceride level is considered to be a good marker of the hemophagocytic syndrome,[6] but it has not been specifically analyzed in flares of AOSD.

The treatment of secondary RHS has included a variety of chemotherapeutic and immunosuppressive agents including corticosteroids, cyclosporine, and intravenous gamma-globulin (IVIG).[7] In the absence of controlled studies, case reports and small series have been used for insight in the management of MAS. Treatment with high-dose steroids is effective in most patients. Immunosuppressants may cause a reduction in mortality in patients where RHS was precipitated by an underlying autoimmune process. It has been reported that cyclosporine or etoposide would be effective in steroid-refractory cases. Etanercept has been reported as an alternative for RHS patients refractory to steroids, cyclosporine-A, and IVIG therapy.[8]

The similarity in presentations and the high frequency of RHS in patients with AOSD have prompted experts to consider these conditions as the two ends of the spectrum, with classic AOSD being the mild form and RHS with multiorgan involvement the most severe, life-threatening one. A common pathogenetic link, that is, IL18, a pivotal AOSD cytokine, has been suggested in a recent study. A study of 20 patients, with 21 separate hemophagocytic episodes meeting the International Histiocyte Society criteria, showed that serum IL-18 concentrations were significantly higher in the affected population when compared to healthy controls.[9] In addition, investigators observed an imbalance between IL-18 and IL-18-binding peptide (BP is IL18's natural inhibitor), where concentrations of IL-18BP were insufficient to bind the entire amount of circulating IL-18. A paradoxical decrease of natural killer (NK) cell numbers and cytotoxic functions in secondary RHS was also observed. Based on this study, the authors proposed the potential use of exogenous recombinant IL-18BP, in addition to traditional therapy, for the treatment of severe cases of RHS.

14.3
Severe Destructive Arthritis

The evolution of AOSD from the acute syndrome, where often systemic complaints such as fever and rash predominate, into the chronic articular pattern is a negative prognostic sign. There is less of a chance for spontaneous remission, and the associated polyarthritis can be destructive if left untreated and lead to increased morbidity and disability. Fortunately, in most cases of AOSD, polyarthritis methotrexate (MTX), with or without

small doses of oral corticosteroids, can be very effective in controlling the symptoms and preventing radiographic progression.[10] However, MTX refractoriness has been frequently documented and alternative therapies have been sought. In the prebiologic era, alternative DMARDs were tried, alone or in combination. In a small series where cyclosporin-A was tried, remission in 66% of cases and improvement in the other 33% were reported.[11] Sulfasalazine should be avoided in treatment of AOSD as multiple studies proved low efficacy and high drug toxicity (60% vs. 15% of other drugs) related to treatment with sulfasalazine.[12] CD34-selected autologous peripheral blood stem cell transplantation was attempted in some cases of refractory disease and prolonged remission was achieved after transplantation.[13] Other less studied agents include hydrochloroquine, gold, penicillamin, leflunomide, azathioprine, tacrolimus, and cyclophosphamide. Recent advances in the immunopathogenesis of AOSD and the availability of biologic DMARDs for the treatment of RA has led to their off-label use in refractory AOSD with variable success. In particular, pro-inflammatory cytokines such as TNFα, IL-1, and IL-6 were targeted.

The first group of biologic agents clinically used was the TNF-α inhibitors. Multiple case reports and small series suggested that infliximab, etanercept, and adalimumab may have a role in refractory cases.[1] In an observational series of 12 patients, addition of etanercept to the pre-study regimens of prednisone, MTX, and NSAIDs leads to an improvement in the number of tender and swollen joints count higher than 63%.[14] A European study of eight patients attempted to evaluate the long-term outcome of patients treated with infliximab (a monoclonal chimeric anti-TNF antibody) after the failure of treatments with corticosteroids and DMARDs: The clinical and serological responses improved rapidly in seven out of eight patients, and five of them went into long-term remission even after discontinuation of therapy.[10,15]

IL-1 inhibition has emerged as an even more promising therapeutic strategy, based on our understanding of the role of the NALP-3 inflammasome and IL-1 in inflammation and anakinra; a recombinant competitive IL-1 receptor antagonist has recently emerged as a promising new therapeutic option.[16] In 2008, Lequerre et al.[17] reported 20 cases of SoJIA and 15 cases of AOSD treated with anakinra. Seventy-three percent of the cases of AOSD demonstrated prompt and dramatic improvement in their arthritis and disease activity markers, while allowing for a dramatic decrease of the administered corticosteroid dose.

IL-6 represents an important inflammatory cytokine involved in the pathogenesis of AODS, and it may be a promising target, especially with the development of anti-human IL-6 receptor monoclonal antibody tocilizumab.[17] A case of refractory AOSD successfully treated with rituximab (chimeric anti CD-20 monoclonal antibody) has also been described.[18]

14.4
Cardiac Complications

AOSD commonly involves the pericardium, although the presence of pericarditis in Still's disease does not seem to negatively affect prognosis in the absence of tamponade, since it is usually mild or even asymptomatic. Nonetheless, the clinician should keep in mind that adults with known cardiac involvement may be at a higher risk of developing cardiac decompensation, especially in the acute systemic subgroup of AOSD. Pouchot et al. described series of 23 cases of pericarditis in their 62 cases of AOSD (37%), 3 of which developed tamponade.[19]

The optimal treatment for AOSD-associated pericarditis has not been defined due to the rarity of its occurrence and the lack of controlled studies. Individual approach should be used in treatment of patients with pericarditis and cardiac tamponade. In cases of mild pericarditis, NSAIDs alone may suffice. Systemic use of steroids remains controversial. Lietman and Bywaters[20] in their series of patients with pericarditis did not demonstrate efficacy of steroids in altering the course of pericarditis. However, steroids may be useful in the presence of massive effusion, evidence of cardiac compromise, or progression of effusions not responding to NSAIDs. Drainage of pericardial fluid remains the cornerstone of therapy in the presence of significant cardiac compromise.

Myocardial involvement in adult-onset Still's disease is reportedly low, although likely to be underdiagnosed. Data concerning the clinical course of Sill's myocarditis are lacking, and there is no clear recommendation for the follow-up of myocardial function in similar conditions. Usually Still's disease–related myocarditis has rapid onset and readily responds to prompt corticosteroid treatment, resulting in quick normalization of myocardial function. Regular follow-up of myocardial function is recommended even if clinical symptoms and inflammatory markers have normalized.

14.5
Pulmonary Complications

In contrast to other autoimmune systemic diseases, little attention has been paid to the pulmonary complications of AOSD. Most common pulmonary manifestations of AOSD include pleurisy, acute and chronic pneumonitis, diaphragmatic dysfunction, and drug-induced lung disease.[21] While most cases with acute pneumonitis respond favorably to systemic corticosteroids, there are rare instances where these abnormalities progress to severe respiratory failure requiring mechanical ventilation, pulse corticosteroids, and/or aggressive immunosuppressive therapy. The most characteristic paradigm of such severe life-threatening complication with significant morbidity and mortality would be the adult respiratory distress syndrome (ARDS). ARDS development has been reported in several patients with AOSD, often complicated by multiorgan involvement and disseminated intravascular coagulation (DIC).[22,23]

More recently, Sari et al. presented a case of chronic AOSD complicated with diffuse alveolar hemorrhage (DAH) during an acute flare of the disease.[24] It is not known whether the association between AOSD and DAH is coincidental or whether there is a common pathophysiologic link.

14.6
Hepatic Involvement

Liver dysfunction in AOSD has been well described, ranging from asymptomatic liver function test (LFT) abnormalities to overt liver failure. Andres et al. retrospectively reviewed data from 17 patients with AOSD and found abnormalities in liver biochemistry in 76% of the subjects.[25] However, it is often difficult to differentiate liver dysfunction due to AOSD per se from drug-induced liver dysfunction, since most of the reported cases

occurred during treatment with potentially hepatotoxic drugs. Recently, Chen et al. described high levels of soluble intercellular adhesion molecule 1 (sICAM-1) in patients with active untreated AOSD and proposed that elevated serum sICAM-1 level may be a predictor of liver dysfunction in AOSD. Moreover, serum sICAM-1 levels significantly correlated with disease activity and serum ferritin levels which have also been utilized to monitor disease activity in adult Still's.[26] In any case, close monitoring of LFTs is warranted in AOSD patients, especially early in the disease course, since it often parallels disease activity and abnormalities have been shown to respond to successful treatment.

Fulminant hepatitis or hepatic failure is extremely rare, and most of the reported cases occurred during treatment with hepatotoxic drugs.[27-29] Experimental and clinical data suggest a critical role for cytokines in the development of fulminant hepatic failure. Sekiyana et al. have observed higher serum levels of IL-1β and a significantly reduced ratio of IL-1Ra to IL-1β (IL-1Ra/IL-1β) in patients with fulminant hepatic failure who subsequently died when compared with survivors.[30] In 2007, Mylona et al. presented a case of fulminant hepatic failure in AOSD that was successfully treated with anakinra, a recombinant interleukin-1 receptor antagonist (IL-1Ra), which also supports a possible role for IL-1 inhibition in fulminant hepatic failure.[31]

Autoimmune hepatitis (AIH) is a rare complication of AOSD. In 2010, Liu et al.[32] reported a refractory case of AIH during an AOSD relapse, successfully treated with plasma exchange after other treatment options were exhausted. After five plasmapheresis sessions, autoantibody titers were normalized, as well as serum IgG, LDH, and serum ferritin. Furthermore, leukocytosis and LFT abnormalities resolved. This case was in sharp contrast to other AIH cases, reported by the same authors that had fatal outcomes after treatment with systemic corticosteroids and intravenous immunoglobulin alone. Therefore, AIH may be an indicator for poor prognosis in AOSD, and plasma exchange therapy should be considered, especially in severe cases of liver injury, in combination with high-dose corticosteroids and other immunomodulatory treatments.

Lastly, in exceptionally rare cases, AOSD liver involvement can present with very atypical features. In 2009, Sari et al.[33] presented a case of hepatomegaly in AOSD where liver biopsy histology revealed a ground-glass like hepatocyte inclusion. Ground-glass hepatocytes (GGH) are live cells with a glassy-granular, eosinophilic cytoplasm on light microscopy.[34] GGH represents a histological hallmark of chronic Hepatitis B virus (HBV) infection and is an occasional finding in some noninfectious chronic inflammatory hepatopathies. In such cases, LFTs continue to rise, despite active treatment, with AST levels occasionally exceeding 1,000 IU/L in the absence of viral infection. GGH are revealed on biopsy along with signs of steatohepatitis, and it is unclear at present time whether this finding represents hepatocyte adaptation or injury.[35]

14.7
Oculomotor Disorders

In rare cases, AOSD patients may develop periodic horizontal micro-saccadic oscillations and rapid clockwise torsional eye movements followed by counterclockwise torsional drifts. It has been hypothesized that saccadic burst neurons, excitatory burst neurons

(EBN), and inhibitory burst neurons (IBN) comprise a reciprocally innervated premotor circuit. The neuron membranes contain ion channels that are important for the rebound increase in neural firing after transient external inhibition—post-inhibitory rebound (PIR).[36] Inflammation may alter the fine balance between EBNs and IBNs and produce clinical symptoms.

In 2009, Shaikh et al presented such a case with bursts of horizontal saccadic oscillations, without intersaccadic intervals, and clockwise rapid torsional eye movement that had the same peak velocity–amplitude relationship as torsional quick phases of nystagmus. They suggested that this could be attributed to an immune-mediated alteration in the midbrain neurons of the reciprocally innervated premotor circuit. In such patients, medications that reduce central excitability—for example, antiepileptics such as levetiracetam, gabapentine, and clonazepam—might be useful.

14.8
Leukocytoclastic Vasculitis

Leukocytoclastic vasculitis is characterized by angiocentric segmental inflammation, fibrinoid necrosis, and a neutrophilic infiltrate around the vessel walls with erythrocyte extravasation. Leukocytoclastic vasculitis has been observed in Henoch–Schonlein purpura, Wegener's granulomatosis, and microscopic polyangiitis; however, it had not, until recently, been reported in AOSD.[37] In 2009, Hidekatsu Yanai et al. described a case of AOSD with atypical rash, which skin biopsy revealed to be due to leukocytoclastic vasculitis. Elevated blood vWF - Von Willebrand factor and VEGF - Vascular Endotelial Growth Factor levels in given AOSD patient suggest a potential association between AOSD and vasculitis. Immunologic testing with a negative PR3-proteinase 3 and MPO-ANCA is Myeloperoxidase- Anti-neutrophil cytoplasmic antibodies help rule out Wegener's granulomatosis or microscopic polyangiitis, respectively, in cases of atypical Still's rash.

14.9
Renal Involvement

Recently, Babacan et al.[38] presented a case of AOSD-associated membranous glomerulonephritis successfully treated with Infliximab. Notably, the same patient also suffered from a severe inflammatory polyarthritis, unresponsive to high-dose steroids and DMARDs for a period of 5 years.

Glomerulonephritis (GN) is a rare complication of AOSD. However, its importance for prognosis and therapy is such that it should be considered in the presence of proteinuria. Thonhofer et al. described a case of mesangio-proliferative immunocomplex-based GN accompanied by proteinuria in 2006.[39] While GN has been reported at other instances as the cause of proteinuria,[40,41] other AOSD-associated complications such as collapsing glomerulopathy[42] and thrombotic microangiopathy,[43] however rare, cannot be excluded

Table 14.4 Comparison of amyloidosis in patients with AOSD

First author	Age of disease onset/sex	Number of years before amyloidosis onset	Drug therapy for renal amyloidosis
Fautrel[44]	32/M	ND	PD, MTX
Rivera[45]	26/M	16	PD, AZA
Hashimoto[46]	25/F, 26/M	ND, ND	PD, PD
Ishii[47]	32/F	7	PD, CTX
Bambery[48]	36/F	8	Steroid, dialysis
Wendling[49]	57/F	4	ND
Vingeron[50]	23/F, 27/F	1.5, 4	PD, dialysis both cases
Harrington[51]	26/F	30	PD, COL

ND non- described, *PD* prednisone, *MTX* methotrexate, *AZA* azathioprine, *CTX* cyclophosphamide, *COL* colchicine

and should be ruled out. A hypothesis by Elkon in 1982 that a smoldering vasculitis, mediated by non-necrotizing immune complexes, may support the hypothesis that GN is part of the disease. The possibility of a more active renal process can be supported by the significant decrease in proteinuria after anti-inflammatory treatment. In general, aggressive immunosuppression is recommended in patients with proliferative forms of GN, with a high histological score for active lesions and a low score for chronic lesions. Biologic agents, such as TNF-α blockers, have been suggested as an alternative in AOSD-associated GN refractory to standard immunosuppressants.[14]

Amyloidosis may be a more common AOSD-related renal complication leading to proteinuria and has been described in several case reports and series. (Table 14.4) It can develop as soon as 18 months or as late as 30 years after the diagnosis of AOSD with an incidence of 4.7–14.3%.[44] The majority of the patients developing renal amyloidosis will require treatment with systemic corticosteroids and/or cytotoxic agents.[44,52] In severe cases complicated with renal failure, treatment with hemodialysis in addition to prednisone therapy was administered with good outcomes.[48,51] In new era of biologics, better control of the underlying chronic inflammation by judicious use of these potent medications may prevent the appearance of amyloidosis and/or improve its management.

14.10
Conclusion

AOSD is a rare, auto-inflammatory systemic disorder with significant phenotypic variability that often makes diagnosis difficult. The majority of the cases can be readily managed after proper diagnosis. However, the disease has been associated with rare but serious complications that are associated with significant morbidity and, even, mortality.

The clinician should be aware of such complications and be able to recognize them and refer appropriately for specialized care. Significant advances in our understanding of the disease pathophysiology and the recent availability of targeted biologic treatments have enhanced our ability to intervene therapeutically.

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