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TITLE:
Life-threatening complications of adult-onset Still's disease

ABSTRACT:
Adult-onset Still's Disease (AOSD) since its description in 1971 has proven to be a very complex and challenging disease entity. This rare auto-inflammatory disease is classically described by the "Still's triad" of fever, rash, and arthritis, although the atypical cases frequently outnumber the typical ones. The exact pathogenesis and etiologic factors responsible for the clinical features remain largely obscure, despite recent suggestive cytokine biology findings. Diagnosis is made on clinical grounds, following the exclusion of mimickers of infectious, autoimmune or neoplastic etiology, with the additional consideration of non-specific laboratory abnormalities such as peripheral leukocytosis and elevation of serum ferritin and other acute phase reactants. The disease manifestations are protean and can include diverse complications, affecting multiple organ systems. Moreover, the severity of the organ involvement can vary considerably, representing a wide spectrum from the self-limited to severe. The mainstay of therapy has evolved from the traditional use of corticosteroids and oral immunosupressants to the newer targeted treatments with biologic agents. The scope of this review is to alert the clinician to the existence of life-threatening AOSD complications, namely the macrophage activation syndrome, disseminated intravascular coagulopathy, thrombotic thrombocytopenic purpura, diffuse alveolar hemorrhage, and pulmonary arterial hypertension. Such knowledge may lead in earlier recognition, prompt treatment, and, ideally, improved patient outcomes.

Introduction:
Adult-onset Still's disease (AOSD) is a systemic inflammatory disorder analogous to the systemic form of juvenile idiopathic arthritis (sJIA). The clinical manifestations of this disease range from spiking fevers, arthritis, evanescent rash, elevated liver enzymes, lymphadenopathy, hepatosplenomegaly, and serositis [1–3]. While it is not possible to make an accurate prognosis during the initial presentation of the disease, several clinical characteristics, identified in large patient cohorts, may hint toward a more complicated course (Table 1).

The pathogenetic mechanism for this condition has yet to be ascertained. Involvement of an infectious agent, as suggested by the reported temporal relationship between disease onset and prior exposure to viral, bacterial, and other pathogenic organisms has been suspected. This hypothesis is consistent with the pre-eminent role played by innate immunity in this disease. A predisposing genetic background has also been suggested, although no consistent associations with HLA haplotypes or other non-HLA genes has been confirmed [4]. Several proinflammatory cytokines have been implicated in the pathogenesis; high levels of interleukin (IL)-1, IL-6, and IL-18; macrophage colony-stimulating factor; interferon-γ; and tumor necrosis factor (TNF-α) have been detected in sera from patients with AOSD [5]. The clinical response to the empirical use of biologic medications that were originally developed for the treatment of rheumatoid arthritis (RA; Table 2) and target these inflammatory mediators has shown promise, thus pointing towards their role in the disease pathogenesis [6–9]. Prognosis depends on the course of the disease and tends to be more favorable when systemic symptoms predominate and the disease does not evolve into its chronic articular sub-type. Laboratory abnormalities including neutrophil leukocytosis, abnormal liver function tests, and increased ferritin levels.

Diseases that often need to be excluded, before the diagnosis of AOSD can be safely made, include infectious, neoplastic, and autoimmune disorders. However, lack of disease specificity for the symptoms and the laboratory markers hinders the diagnosis and the absence of established disease activity markers makes determination of treatment efficacy problematic [10–13]. More than one-third of patients' progress into chronic disease where complications such as pericarditis, cardiac tamponade, disseminated intravascular coagulation, and hepatic and respiratory failure are associated with untoward morbidity and mortality [14, 15].
AOSD treatment has evolved and largely abandoned the use of non-steroidal anti-inflammatory drugs (NSAIDs). Systemic corticosteroids are used, predominantly during the initial presentation, where the systemic symptoms predominate and often in combination with immunosuppressants (e.g., methotrexate) [16]. Biological agents (mainly IL-1 and IL-6 inhibitors) have been successfully used in refractory cases [5].

The goal of this article is to discuss some of the most severe AOSD-related complications and review the literature for the collective experience relating to their clinical presentation, management, and prognosis.

Macrophage activation syndrome ::: Macrophage activation syndrome:
or reactive hemophagocytic syndrome (RHS) is a life-threatening complication of AOSD, with a reported mortality rate ranging between 10 and 22 % [17–20]. It is characterized by an uncontrollable activation of the reticulo-endothelial system within the bone marrow, reticuloendothelial system and central nervous system, with subsequent phagocytosis of hematopoetic cells by tissue macrophages (histiocytes) [20, 21]. Its clinical picture consists of acute high fever, lymphadenopathy, and hepatosplenomegaly (Table 3). Laboratory findings include pancytopenia and high serum levels of ferritin, triglycerides, and liver enzymes, while, paradoxically, demonstrating a normal erythrocyte sedimentation rate (ESR). Although macrophage activation syndrome (MAS) is, overall, a very rare condition, it is not uncommon in AOSD, with an incidence of 12–14 % in two recent series, a rate higher than other rheumatic diseases [22, 23]. Clinical and biological features of MAS closely resemble reactive hemophagocytic lymphohistocytosis (HLH) and the disease is in fact considered today as a subclass of HLH (secondary), which is induced by heterogeneous disorders including infections, malignant tumors, and medications [24]. HLH criteria include a decrease in white blood cell count, platelets, or fibrinogen and the demonstration of low or absent natural killer cell activity or soluble IL-2 receptor. However, the minimum threshold level for hyperferritinemia required for the diagnosis of HLH (500 μg/l) is not useful in detecting MAS, with the ferritin level generally peaking to more than 5,000 μg/l in the latter condition [25].

Hypofibrinogenemia is one of the most important clues for the diagnosis of MAS since patients usually have high fibrinogen levels due to their underlying inflammatory disease. An increased fibrinolysis is most probably due to the uncontrolled activation of the macrophages and plasminogen overproduction. A decrease in factor II and factor VII + X values has also been observed in some reports [26].
The most frequently implicated triggering factors include infections, medications, and disease flare ups [24, 27]. Patients with MAS have a decreased natural capacity to eradicate infected cells and to eliminate antigen stimulation. This in turn induces T cell activation and proliferation with cytokine secretion (interferon-gamma and granulocyte macrophage colony-stimulating factor) and macrophage hyper-activation. The end result is an uncontrollable increase in TNFα, interleukin-1, and interleukin-6 production with a severe systemic inflammatory reaction, i.e., “cytokine storm” [20].
The immunodeficiency state induced by the treatment of AOSD may lead to reactivation of latent viruses, such as Epstein-Barr virus or cytomegalovirus, which could, theoretically, trigger MAS. There is also a suggestion that certain therapeutic agents, such as non-steroidal anti-inflammatory drugs, methotrexate, sulfasalazine, penicillamine, and lately TNF-α, IL-1, and IL-6 inhibitors may be capable of provoking MAS, often complicating their therapeutic use [23].
Preliminary diagnostic guideline used in MAS complicating sJIA was based on a set of laboratory and clinical criteria [27]. The clinical criteria include central nervous system dysfunction, hemorrhage, and hepatomegaly while the laboratory criteria consisted of a low platelet and white cell count, hypofibrinogenemia and elevated AST (Table 4). Early suspicion of MAS is most commonly raised by the detection of subtle laboratory changes, whereas clinical symptoms may be delayed. A recent international effort to identify candidate markers using an expert consensus process identified nine criteria that included a falling platelet count, hyperferritinemia, evidence of macrophage hemophagocytosis in the bone marrow, increased liver enzymes, falling leukocyte count, a persistent continuous fever ≥38 °C, a falling erythrocyte sedimentation rate, hypofibrinogenemia, and hypertriglyceridemia [25]. Hemophagocytosis, seen in bone marrow aspiration and biopsy establishes the diagnosis, even though hemophagocytosis could be seen more frequently in biopsies from the liver, spleen, and/or lymph nodes. Bone marrow aspiration is considered the gold standard and is usually required in atypical cases where there may be a diagnostic dilemma. There is significant overlap between AOSD and MAS and these two conditions are often thought to be anchoring the same disease spectrum, with AOSD representing the milder form. Moreover, it may be a two-way street, with the individual patients’ clinical manifestations fluctuating between those two phenotypes, throughout the disease’s lifespan [22]. It is not unusual for a patient to simultaneously carry both diagnoses, i.e., AOSD and concurrent mild MAS. The similarities in clinical presentation may reflect overlapping pathophysiologic

mechanisms. Less severe or “subclinical” cases of MAS may not be diagnosed if they respond to immunosuppressive treatments given for a presumed flare of AOSD [28–30]. In 2005, Mazodier et al. published the results of a study showing significantly elevated serum IL-18 concentrations and decreased levels of IL-18 binding protein (IL-18BP) in the population affected with MAS, when compared to healthy controls [31]. Interestingly, IL-18 has been repeatedly shown to play a major role in the pathogenesis of AOSD and IL-18 inhibition may prove to be a desirable future approach for both entities. A case of AOSD-associated thrombotic microangiopathy (TMA) has also been reported suggesting the association of IL-18, high levels were seen at onset of disease which dramatically decreased with TMA resolution suggesting the antiangiogenic effect of IL18 [32].

Empiric treatment of MAS traditionally consisted of the following agents alone or in combination: intravenous pulse corticosteroids, immune gamma globulin (IVIG), and cyclosporine A (CyA). Mizrahi et al. described a patient with relapsing MAS successfully treated with CyA and mycofenolate mofetil (MMF) [33].
There are several reports of the use of IL-1 inhibitors in the management of MAS. Kelly et al. described a case of successful use of anakinra in management of MAS in a 13-year-old patient with sJIA [34]. Two more cases of MAS associated with sJIA reported symptoms promptly resolving after anakinra initiation. In addition to the reported efficacy, the authors marveled at the avoidance of the potentially toxic immunosuppressant cyclosporine A and/or the antineoplastic agent etoposide [35]. SJIA-associated MAS has required anakinra doses as high as 10 mg/kg/day and, in one published report, combination with abatacept [36]. Recently, a case of AOSD-associated MAS that was complicated by a history of active spinal tuberculosis responded favorably within 48 h to the addition of anakinra to her corticosteroid regimen. Furthermore, there was no tuberculosis reactivation after 10 months of anakinra treatment [37].
Anti-cytokine therapies are finding a niche in the treatment of MAS that complicates sJIA. TNF inhibitors, despite some early anecdotal reports of efficacy, are currently considered ineffective or even harmful. Temporal association of anti-TNFα therapy and bacterial infection has been suggested to play a catalytic role in the deregulation of macrophage–lymphocyte interactions in MAS [38]. There are several cases of MAS following the use of etanercept in patients with AOSD [37, 39]. In such cases, the observed decreases in ESR and WBC counts may be erroneously interpreted as response to treatment, while in reality they may signify the beginning of MAS. Therefore, MAS should always be considered in the differential diagnosis of AOSD patients with low WBC and platelet counts lacking clinical improvement after etanercept use.
Tocilizumab, a humanized anti-interleukin-6 receptor monoclonal antibody, was reported to be effective in the management of AOSD that involved MAS during the induction therapy, although its efficacy is unclear for the highly active phase of the disease [40].
Future therapeutic protocols for the treatment of MAS may include different combinations of pulse corticosteroids, CyA or etoposide, and anti-cytokine treatment, such as blockade of IL-1 and/or IL-6.

Disseminated intravascular coagulopathy ::: Disseminated intravascular coagulopathy:
is a life-threatening complication caused by an uninhibited activation of the coagulation system. This severe complication has been reported to occur in AOSD and its diagnosis can be challenging, even for seasoned clinicians [41]. Eight disseminated intravascular coagulopathy (DIC) cases, some associated with hepatopathy have been reported in the literature to date [42]. The clinical presentation of a patient with AOSD complicated by coagulopathy and the patient becoming acutely ill may closely mimic sepsis, leading to treatment with antimicrobials only and delaying management with immunomodulators.
To further complicate diagnosis, DIC and multi-organ failure may also occur as a complication of AOSD-related MAS [43]. However, patterns of non-remitting fever and purpuric or petechial rash that accompany DIC can be differentiated from the remitting high-spiking fever and evanescent maculopapular rash of AOSD. The precipitous fall of ESR in the context of worsening clinical condition and persistent hyper-ferritinemia should be a red flag and raise the index of suspicion for the presence of DIC. High titers of serum-soluble adhesion molecules and soluble thrombomodulin have also been noted during the first episode of DIC which indicate endothelial cell damage in AOSD complicated by DIC [44].
Interestingly, there have been reports of patients developing acute myocarditis during DIC attacks in AOSD, potentially implicating a, yet unidentified, infectious trigger [45]. Treatment with immunomodulators, together with supportive measures, can be effective in even some of the

most severe cases, as it was in a case complicated with concomittant acute respiratory distress syndrome (ARDS) and DIC successfully managed with prednisolone therapy [46].
The efficacy of anakinra has also been advocated patients with severe flare of AOSD and DIC [47]. Some experts have even suggested it should be first line therapy in life-threatening DIC [43, 48]. More recently, a case of glucocorticoid and cyclosporine refractory AOSD complicated by DIC was successfully managed with tocilizumab, a humanized anti-IL-6 receptor monoclonal antibody. IL-6 inhibition led to a rapid response, symptomatic improvement, and corticosteroid sparing [49].

Thrombotic thrombocytopenic purpura:
Thrombotic thrombocytopenic purpura (TTP) associated with AOSD has been documented with nine published cases in the literature and is invariably associated with significant morbidity and mortality [50]. TTP is more common and more severe in African Americans compared to other races and ethnicities [51]. ADAMTS13 activity and inhibition have been found to be important predictors of disease outcome [52]. An early sign that should raise the index of suspicion for TTP is development of acute vision impairment. In extreme cases, multiple thrombi formation and massive cytokine release causing progressive vascular permeability, worsening brain edema and, ultimately, rapid death may also occur [53].
The dual diagnosis of AOSD and TTP has interested scientists and physicians alike since its first description, since there has always been hope of discovery of a common pathogenetic path. However, no mechanism, so far, has been able to sufficiently explain their coexistence. It has been suggested that autoantibodies to CD36 (glycoprotein IV) may play a dual role in the pathogenesis of TTP and AOSD, since CD36 is important in the clearance of inflammatory cells and T-cell activation [54]. Alternatively, decreased activity of von Willebrand factor-cleaving protease (a disintegrin and metalloproteinase with thrombospondin type 1 motif), member 13 (ADAMTS-13) may play a prominent role in the pathogenesis of TTP [55]. In the presence of ADAMTS-13 inhibitors (e.g., antibodies against ADAMTS-13), intravascular platelet thrombi develop [56]. The characteristic pathologic findings in TTP include hyalinized thrombi in the vascular beds of the brain, pancreas, heart, and kidneys. TTP is a medical emergency, since the outcome of untreated TTP is renal failure and death [57]. There have been at least 11 published cases of TTP/HUS associated with AOSD, five of which with presenting renal failure [56]. Masuyama et al. reported a case of AOSD complicated by TTP that resulted in retinal microangiopathy and rapidly fatal cerebral edema [53].
TTP is often diagnosed on the basis of thrombocytopenia and microangiopathic hemolytic anemia that cannot be explained otherwise, so that treatment can be begun early to lower mortality rates in this often fatal disease [58]. Lack of treatment results in a mortality rate of about 90 %, but even with treatment the mortality rate can be as high as 20 %. The current mainstay of treatment is plasma exchange because of its efficacy in randomized clinical trials, and relapsing episodes can be managed successfully with additional plasma exchange, aspirin, vincristine, hemodialysis, corticosteroids, intravenous immunoglobulins, azathioprine, cyclophosphomide, rituximab, and/or splenectomy [50, 56]. There are only rare reports of treatment of patients with TTP and AOSD with biologic agents. In 2010, Sumida et al. presented a case of TTP in multi-drug-resistant Still's successfully treated with tocilizumab that seemed to be successful in treating both the TTP and the underlying treatment-refractory AOSD [59].

Diffuse alveolar hemorrhage:
Pulmonary involvement is well-known in AOSD and is seen in up to 53 % of AOSD cases, with the most common pulmonary diseases being pleural effusion and transient pulmonary infiltrates [60]. Life-threatening pulmonary complications of AOSD include respiratory distress syndrome, and diffuse alveolar hemorrhage. It is still a matter of speculation whether the association between AOSD and diffuse alveolar hemorrhage (DAH) is coincidental or if it can be attributed to some common pathogenic link. The first case of chronic AOSD complicated with diffuse alveolar hemorrhage during the acute flare of the disease has been reported by Sari et al. in 2009 [61]. Several studies suggest that alterations in pro-inflammatory cytokine production play an important role in the pathogenesis of AOSD.
Interleukin-18 (IL-18) appears to be an anchor cytokine in AOSD pathogenesis, as it is overproduced in the acute phase of the disease and is believed to be the cytokine initiating the inflammatory cascade that includes interferon gamma, IL-6, and TNF-a [62]. DAH is a medical emergency characterized by the accumulation of red blood cells in the alveolar spaces. Hemoptysis, coughing, and progressive dyspnea are common initial symptoms, and the disease may progress to acute respiratory failure. Hemoptysis is not a sine qua non symptom, and may be

even absent. Chest radiography is nonspecific and commonly shows new patchy or diffuse alveolar opacities. Characteristic laboratory features of DAH include decreasing hemoglobin and hemorrhagic bronchoalveolar lavage fluid [63, 64]. Treatment modalities in DAH include pulse steroids administered at a dose of 1,000 mg/day for 5 days [61], plasma exchange, and intravenous cyclophosphamide.

Pulmonary arterial hypertension:
Cardiopulmonary disease has been described in 30–40 % of patients with AOSD. Pulmonary manifestations include aseptic pneumonitis, interstitial lung disease, serositis with accompanying pleural effusion, and rarely ARDS [65]. Affected patients may complain of cough, pleuritic chest pain, and dyspnea. The association of pulmonary arterial hypertension (PAH) with connective tissue diseases has been well characterized in autoimmune diseases such as systemic sclerosis and systemic lupus erythematosus. We are aware of only six published cases to date [66].
It was in 1990 that the first case was reported in Japan of a 29-year-old woman who had developed progressive, pre-capillary severe hypertension 2.5 years after the diagnosis of AOSD was established [67]. Two additional cases were reported in northern Taiwan [68], in a single-center case series of 19 patients with co-prevalence of PAH and various connective tissue diseases. Another case reported from the USA was that of a 29-year-old woman with a 9-year history of AOSD who developed the characteristic clinical and hemodynamic findings of PAH and despite treatment, including anakinra 100 mg/day SQ, died 2.5 months after the diagnosis of PAH [69]. In 2009, a case was reported in an 18-year-old female from India with new onset AOSD who quickly developed severe PAH (mean PAP of 65 mmHg) in the absence of other causes [70]. Campos et al. reported a case of PAH responsive to anakinra in a 27-year-old woman with a 7-year history of AOSD [66].
PAH is diagnosed when the resting mean pulmonary artery pressure (PAPm) is greater than 25 mmHg, in the setting of pulmonary capillary wedge pressure <15 mmHg, based on right heart catheterization and after exclusion of conditions like left heart and thromboembolic disease [71]. Pulmonary microangiopathy, which may also cause renal involvement and thrombotic thrombocytopenic purpura in AOSD patients, has been implicated. Inflammatory mechanisms appear to play a significant role in autoimmune rheumatic-disease-associated PAH, although the mechanisms may differ significantly in AOSD where innate immunity mechanisms have a predominant role. In autoimmune-disease-associated PAH, the presence of antinuclear antibodies, rheumatoid factor, IgG, and complement fraction deposits in the walls of pulmonary vessels are characteristic [72]. It is believed that the regulatory T-cells play a role in preventing B-cell activity, and lead to the severe angioproliferative changes. Veno-occlusive disease, formation of microthrombi, and pulmonary fibrosis are also frequently seen. The key histological findings are intimal thickening and media hypertrophy of the small- and medium-sized pulmonary arteries and formation of plexiform lesions. Both the sporadic forms of PAH and those associated with rheumatic diseases are characterized by endothelial proliferation [73].
The treatment modality for PAH in AOSD aims to target the inflammatory component. Survival in CTD-associated PAH (CTD-PAH) has been observed to be shorter than in idiopathic PAH (IPAH) [74]. The dearth of available data on this complication, the rarity of reported cases and the subsequent absence of randomized control trials, has lead to management of this condition with empirical therapy centered around the use of immunosuppressive therapy in conjunction with vasodilator therapy. Several case reports describe regression of PAH with immunosuppressive therapy in patients with rheumatic diseases [75]. All three groups of advanced therapies; prostanoids, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors used in idiopathic PAH have also been shown to improve pulmonary hemodynamics and functional status in patients with CTD-PAH [76–80]. Biologic agents have been explored as an important avenue in patients, especially in steroid-resistant cases [81]. Anakinra, a recombinant human IL-1 receptor antagonist, has been shown to reduce the systemic inflammatory reactions [82]. Newer approaches, including tocilizumab, an anti-IL-6 receptor monoclonal antibody have also been proposed to target the IL6 dysregulation [83–85].
Early diagnosis, classification, and initiation of a disease-specific treatment algorithm might improve survival in these patients.

Liver involvement:
Liver involvement in AOSD patients can range from mild to severe. They can present with no symptom or with hepatomegaly, icterus, loss of appetite, fatigue, and right abdominal pain. In a series studying liver involvement in 77 patients with AOSD, clinical and laboratory features were

compared with previously published data [86–88]. Hepatomegaly was reported in nearly half of the AOSD patients while transient elevation of liver enzymes was seen in three quarter of the cases. Hepatic failure, however, is a rare complication of adult Still's disease and it has been suggested that it may be associated with hematophagocytic syndrome [89].
In a 10-year retrospective study of 12 patients who satisfied the diagnostic criteria for adult Still's disease, severe liver abnormalities were noted. One hundred percent of patients presented with fever, and 41 % with hepatomegaly. Abnormalities in liver function tests were seen in 92 % of patients, wherein 17 % of patients presented with serum aminotransferase levels five times the normal level and 83 % of patients with levels that were between two and five times normal [90]. The pathophysiology of liver involvement is not known. Cytokine production and sustained macrophage activation have been implicated to play a role in the liver manifestations [87, 91]. Previous descriptions of hepatic histopathology in AOSD consist of portal inflammatory infiltrates in most cases [92], mild interstitial hepatitis [93], mild portal fibrosis, focal hepatitis with necrosis [94], and mild chronic necro-inflammatory change [95].
NSAIDS and MTX may also contribute to the liver damage of AOSD. Remission with the use of these drugs has been observed to even normalize the level of transaminase [85–87]. Severe liver disease however may not respond to anti-inflammatory or immunosuppressive therapy. There are reports of two patients with adult Still's disease-related liver failure who required liver transplantation, one of whom died [96, 97].

Discussion:
AOSD is a systemic auto-inflammatory disease that may be infrequently associated with significant morbidity and life-threatening manifestations. Although the prognosis of AOSD is generally favorable, death may occur in some patients due to overwhelming infection, hepatic failure, amyloidosis, adult respiratory distress syndrome, heart failure, macrophage activation syndrome, and pulmonary hypertension [69, 98–101]. Clinicians should be aware of those complications, since early recognition and prompt management in a monitored setting can significantly decrease morbidity and mortality. Treatment efforts should include both supportive measure and coordinated efforts to control the underlying systemic inflammation. High doses of systemic glucocorticoids combined with immunosuppressive agents are usually recommended [102–104]. Targeted therapy with biologic agents, in particular with anti-IL1 and anti-IL6 inhibitors has enhanced our ability to manage refractory AOSD and its associated severe complications [105]. However, the rarity of the disease, diversity of clinical presentation, and lack of controlled studies (especially in AOSD) has limited our knowledge of the exact efficacy and safety of our interventions. For example, novel treatments for AOSD and its pediatric counterpart sJIA have been reported to both effectively treat and potentially induce severe complications such as MAS. This gap in knowledge could be potentially filled by information gathered by prospective, disease specific, registries, and an international collaborative effort.