



# Adult Onset Still's Disease Complicated by the Acute Respiratory Distress Syndrome

Michael S. Putman<sup>1</sup> and Anisha B. Dua<sup>2\*</sup>

<sup>1</sup>Department of Medicine, University of Chicago, Chicago, USA

<sup>2</sup>Department of Rheumatology, University of Chicago, Chicago, USA

\*Corresponding author: Anisha B. Dua, Assistant Professor, Program Director, Division of Rheumatology, University of Chicago Medical Center, Chicago, USA, Tel: +1 773 702 6119; Fax: +1 773 834 7065; E-mail: [adua@uchicago.edu](mailto:adua@uchicago.edu)

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## Adult Onset Still's Disease

Characterized by high spiking fevers, an evanescent rash, pharyngitis, and hyperferritinemia, Adult onset Still's disease (AOSD) primarily affects the joints and skin. As many as one in four patients, however, also display pulmonary manifestations of disease. One of the most devastating of these, the acute respiratory distress syndrome (ARDS), is diagnosed when patients develop new or worsening acute hypoxemia within one week of a known clinical insult and display bilateral non-cardiogenic opacities on pulmonary imaging [1]. Diagnosing AOSD in patients presenting with ARDS may be difficult given many shared clinical characteristics and the lack of clear pathognomonic radiographic or laboratory findings. Subsequent delays in the initiation of appropriate immunosuppression may place patients at a higher risk of mortality. Providers should be aware of the potential for ARDS to complicate AOSD, as expedient diagnosis and treatment of the underlying disease process may result in better outcomes.

The reported prevalence of pulmonary complications in AOSD varies. A widely cited retrospective review of 62 patients by Pouchot et al. reported a 53% prevalence of pleuritis and pulmonary effusion [2] but multiple other large case series have reported rates of 4-22% for pleuritis [3-8] 9%-30.5% for pleural effusion [3,9,10] and 3%-15% for interstitial pneumonia [4,6-8]. Though less common, cases of diffuse alveolar haemorrhage, [11] organizing pneumonia [12] and diffuse pulmonary nodules [13] have all been reported. Pulmonary involvement in AOSD is associated with higher rates of relapse and death [4]. Thus, prompt diagnosis of AOSD with pulmonary manifestations is critical in initiating appropriate therapy.

We previously reported a case of AOSD presenting as ARDS and performed a literature review, identifying 18 additional cases [14]. A PubMed search for AOSD and a review of articles that report concurrent cases of ARDS revealed no new cases from January 1st 2012 to January 1st 2016. Patients in our prior series ranged from 17-71 years of age and when data was available all met the Yamaguchi criteria for AOSD [15]. Patients initially received antibiotics but developed progressive respiratory failure and required intubation. Once the diagnosis of AOSD was made, antibiotics were discontinued and high dose corticosteroids were initiated. While the majority of patients responded well within hours to days, 4 out of 19 failed treatment and eventually died [14,16-18]. Imaging findings of ARDS in these case reports were described as dense, diffuse, bilateral infiltrates. Unfortunately, these could not be radiographically differentiated from other more common etiologies of ARDS, such as infection, inhalation, or lung contusion [19].

The lack of pathognomonic radiographic findings in AOSD and the overlap of clinical features between AOSD and infection may make timely diagnosis difficult. Diagnostic delays in AOSD are already common, with a median time to diagnosis of 3 months [3]. Moreover, both AOSD and infections share many clinical features, such as fevers and leukocytosis. Other primary features of AOSD are nonspecific, such as rash, lymphadenopathy, and arthralgias. Even hyperferritinemia, a common feature in AOSD, [20] can be found in other conditions such as renal failure, hepatocellular injury, infections, and malignancies [21]. Prompt diagnosis of AOSD presenting with or complicated by ARDS may therefore require a high level of clinical suspicion based on presentation and history. Moving forward, greater use of diagnostic markers with higher specificity for AOSD, such as the glycosylated ferritin, [20] and further development of experimental biomarkers, such as serum S100A8/A9 [22] or calprotectin levels, [23] may improve diagnostic specificity. At a minimum, AOSD should be considered when patients with ARDS also exhibit an evanescent rash or persistent fevers despite appropriate antimicrobial coverage.

Expedient diagnosis of AOSD presenting as ARDS may be especially important, as the shift from antimicrobial therapy to immunosuppression may improve outcomes. In our review of prior cases, ferritin levels and clinical status improved after treatment with methylprednisolone [14]. Though corticosteroids remain the first line agents for AOSD, case series of patients receiving biologic therapies have been promising [24]. In particular, biologics targeting IL-1, such as anakinra, canakinumab, and riloncept, have been recommended as first line therapy for patients who fail corticosteroids [24-26]. These agents have a faster onset of action than TNF agents or methotrexate and may be more efficacious, though head to head trials have not been performed [25]. Even in cases of ARDS, where patients are often critically ill, there may be an emerging role for anakinra. In three recent case reports, patients presented with pulmonary disease and decompensated shortly thereafter, with two requiring vasopressors and all three requiring mechanical intubation. All three patients were subsequently diagnosed with AOSD and received anakinra, either after failing conventional therapy or in conjunction with corticosteroids, and all three recovered rapidly [27-29].

In addition to the macrophage activation syndrome, disseminated intravascular coagulopathy, thrombotic thrombocytopenic purpura, and pulmonary arterial hypertension, ARDS represents a life threatening complication of AOSD [30]. Though it remains a rare manifestation, patients with AOSD complicated by ARDS require prompt diagnosis and immunosuppressive treatment. This can be difficult given the lack of pathognomonic features; clinicians should consider AOSD when patients with ARDS develop persistent fevers or an evanescent rash. As novel diagnostic biomarkers and fast acting

targeted therapies become available, patients afflicted with AOSD could experience a welcome decline in treatment delay and associated morbidity.

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