

Pulmonary arterial hypertension and acute respiratory distress syndrome in a patient with adult-onset stills disease

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Abstract

Adult-onset Still's disease (AOSD) is an inflammatory disorder characterized by recurrent fevers, arthralgia, leukocytosis, and a salmon-colored rash. Diagnosis is made based on the Yamaguchi criteria. Various cardiac and pulmonary manifestations have been described in association with AOSD, including acute respiratory distress syndrome (ARDS) and pulmonary arterial hypertension (PAH). We describe the first case of both PAH and ARDS in a patient with AOSD who, despite aggressive therapy, declined rapidly and ultimately died. There was concern for pulmonary veno-occlusive disease given the rate of her decompensation, but this was found not to be the case on autopsy. Treatment of AOSD with cardiopulmonary involvement requires rapid identification of AOSD followed by aggressive immunosuppression.

Keywords

pulmonary arterial hypertension, adult-onset Still's disease, acute respiratory distress syndrome, pulmonary veno-occlusive disease

Date received: 13 December 2016; accepted: 8 May 2017

Pulmonary Circulation 2017; 7(4) 797–802

DOI: 10.1177/2045893217712710

Introduction

Adult-onset Still's disease (AOSD) is an inflammatory disorder characterized by recurrent fevers, arthralgia, leukocytosis, and a salmon-colored rash. Diagnosis is made based on the Yamaguchi criteria.¹ Various cardiac and pulmonary manifestations have been described in association with AOSD, including acute respiratory distress syndrome (ARDS) and pulmonary arterial hypertension (PAH).^{2–5} We present a case of a young woman who developed PAH and ARDS as a consequence of her AOSD, where her clinical course was initially concerning for pulmonary veno-occlusive disease (PVOD), which was ruled out on autopsy.

Case presentation

A 31-year-old African American woman presented with a two-week history of rapidly progressive shortness of breath on exertion and leg swelling. Prior to her presentation, she could complete activities of daily living without any difficulty but experienced dyspnea while climbing stairs and lifting heavy objects for the last year. Despite multiple

hospitalizations for these issues at an outside community institution, an etiology for these symptoms was never fully evaluated or determined. The patient was diagnosed with AOSD at the age of 24 years and had previously been managed with various immunosuppressive therapies including prednisone and mycophenolate mofetil. Upon presentation to our institution, she was receiving prednisone and methotrexate for the management of her AOSD symptoms and was prescribed trimethoprim-sulfamethoxazole for prophylaxis. Physical examination was notable for hyperpigmented macules of the bilateral upper arms, lower extremity pitting edema, distended jugular venous pulse with accentuated hepatojugular reflex, and a loud P2 on cardiac auscultation.

Her chest radiograph (CXR) is shown in Fig. 1. A trans-thoracic echocardiogram showed normal left ventricular size

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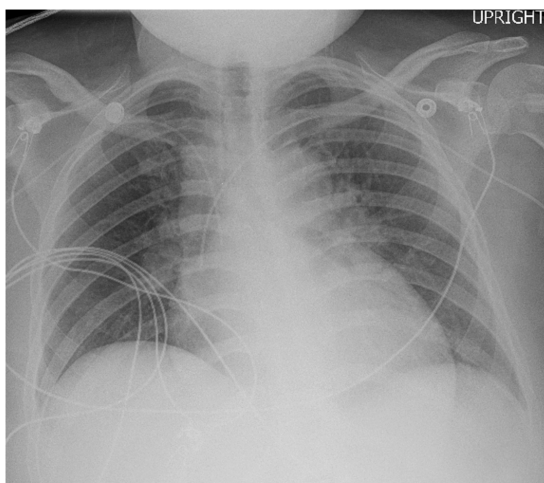


Fig. 1 CXR on day of admission showing clear lung fields, cardiomegaly, and a slightly widened mediastinum.



Fig. 2 Apical four-chamber view showing right atrial and ventricle dilation and a small pericardial effusion.

and function with an ejection fraction of 55–60%, severe enlargement of the right ventricle and atrium, flattening of the interventricular septum in systole and diastole, and severe tricuspid regurgitation (Fig. 2). Right ventricular systolic pressure was estimated at 70–80 mmHg and there was evidence of a small pericardial effusion. A non-contrast CT of the chest on admission revealed extensive mediastinal and hilar lymphadenopathy with some axillary lymphadenopathy, an enlarged pulmonary artery of approximately 39 mm, and extensive mosaic attenuation throughout the bilateral lungs (Fig. 3) with no evidence of pulmonary embolism.

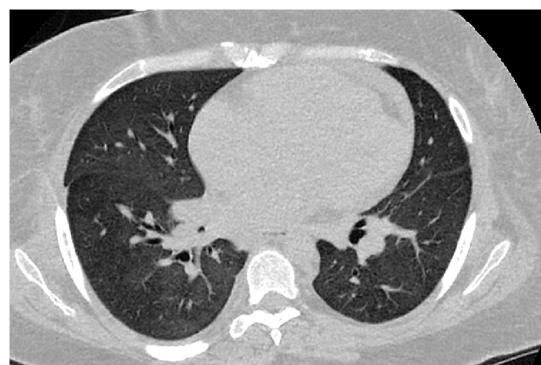


Fig. 3 Chest CT without contrast performed on day of admission showing evidence of mild bilateral mosaic attenuation throughout the lungs.

Table 1 Right heart catheterization.

Measurement	Value
Right atrium	23 mmHg
Right ventricle	50/21 mmHg
Pulmonary artery	52/30 mmHg
Mean pulmonary artery pressure	38 mmHg
Pulmonary artery occlusion pressure	8 mmHg
Cardiac output (thermodilution)	2.9 L/min
Cardiac index (thermodilution)	1.6 L/min/m ²
Pulmonary vascular resistance	10.3 Woods Units
Pulmonary arterial oxygen saturation	97%
Pulmonary venous oxygen saturation	40%
Hemoglobin	9.5 g/dL

The patient was clinically fluid overloaded on presentation (elevated jugular venous pulsation, bilateral lower extremity edema) requiring diuresis to optimize her fluid status prior to right heart catheterization (RHC). Laboratory evaluation revealed an elevated NT-pro-BNP of 1566 pg/mL, transaminitis (AST and ALT were 790 and 697 U/L, respectively, total bilirubin 1.0 mg/dL and alkaline phosphatase 81 U/L), elevated C-reactive protein (105.2 mg/L), and a leukocytosis (16.9 thou/cu mm with 90% PMNs). The patient's transaminitis was new when compared with values from a few months prior. An ANA titer was positive at 1:160; however, the rest of her autoimmune workup and HIV status were negative. Right upper quadrant ultrasound showed mild hepatomegaly without cirrhosis consistent with hepatic congestion. Her RHC findings were consistent with pre-capillary PAH. Pulmonary artery pressures were measured to be 52/30 mmHg with a mean of 38 mmHg. Her pulmonary artery occlusion pressure was normal at 8 mmHg (Table 1). Given that the patient was functional class IV and had a high-risk hemodynamic pulmonary

profile according to 2015 ESC/ERS guidelines for the diagnosis of pulmonary hypertension,⁶ given the high right atrial pressure, low cardiac index, and low mixed venous oxygen saturation, she was initiated on intravenous epoprostenol and oral tadalafil, with plans to add an endothelial receptor blocker as a third agent. Additionally, as she continued diuresis, she experienced hypotension with systolic pressures as low as 70 mmHg with a lactic acidosis as high as 4.9 mmol/L (which later resolved with the addition of a dobutamine infusion).

Over the subsequent three days, the patient began to decline, exhibiting symptoms of right ventricular failure. Inhaled epoprostenol at 50 ng/kg/min was initiated and epoprostenol infusion was gradually increased to a rate of 8 ng/kg/min. Despite this, she exhibited worsening hypoxia on serial arterial blood gas measurements despite increasing her inhaled FiO₂. Due to her hemodynamic instability, the patient was worked up for an infectious etiology and broad-spectrum antimicrobial coverage was initiated.

Despite these interventions, the patient continued to deteriorate. She ultimately required endotracheal intubation and mechanical ventilation due to her worsening hypoxia (desaturations as low as 70% on 100% inhaled FiO₂ non-rebreather mask) in conjunction with tachycardia to 160 beats per minute. Her lactic acidosis returned as well, peaking at 3.6 mmol/L. Complete blood count revealed a worsening leukocytosis 24.9 thou/cu mm with 15% bands. The patient's CXR prior to intubation (Fig. 4) and clinical picture at the time of this decompensation was consistent with ARDS. Shortly after intubation, the patient experienced pulseless electrical activity and despite advanced cardiovascular life support she ultimately died. The rapid decline after initiating pulmonary arterial hypertension therapy was concerning for possible underlying pulmonary veno-occlusive disease (PVOD) or pulmonary capillary hemangiomatosis (PCH). Additionally, her rapid decline precluded the possibility of any repeat imaging or advanced monitoring of cardiac output.

Autopsy revealed right ventricular hypertrophy and moderately dilated right ventricle and right atrium. Additionally, the patient's lungs were significant for diffuse alveolar damage with prominent hyaline membrane formation with edema and a prominent neutrophilic alveolar infiltrate. There was both intimal thickening of the pulmonary arteries and arterioles (Fig. 5). Features suggestive of the presence of PVOD and PCH were not present on pathological examination. Pathology slides were sent out for a second opinion that confirmed the initial report. Regardless, all cultures and staining performed on lung samples did not identify any infectious organisms. The final diagnosis was PAH and ARDS in the setting of AOSD. Considering the right ventricular hypertrophy present on autopsy and her report of dyspnea on exertion for the year prior to her decompensation, it is likely the patient's PAH had been present for some time and not recognized during her previous hospitalizations.

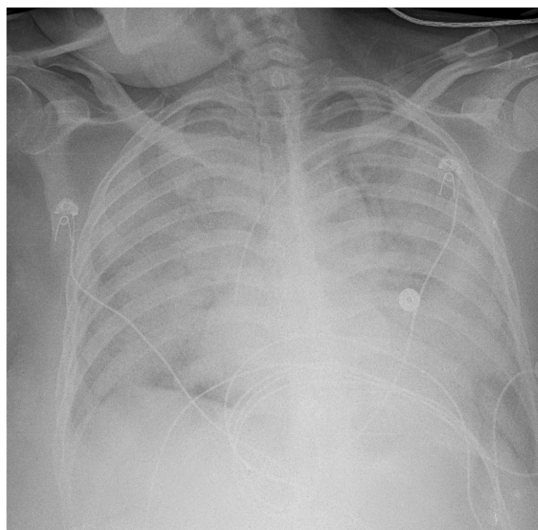


Fig. 4 CXR three days after admission revealing diffuse bilateral infiltrates.

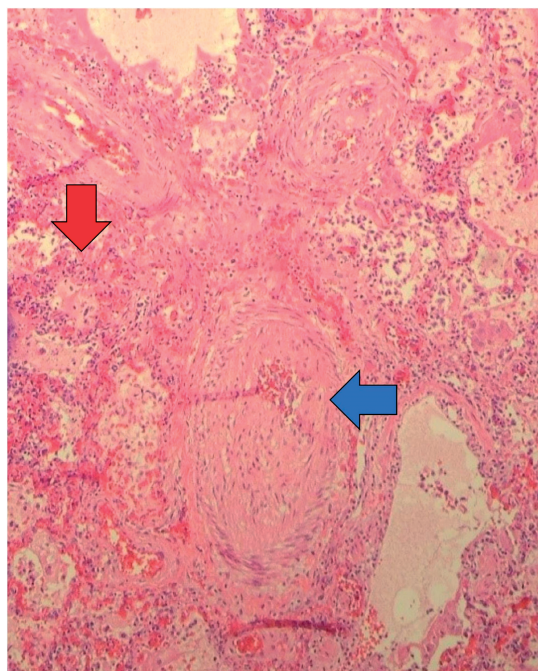


Fig. 5 Pulmonary histology showing evidence of pulmonary arteriole intimal thickening (blue arrow) and hypertrophy as well as prominent alveolar edema and neutrophilic alveolar infiltrate (red arrow).

Discussion

AOSD is a rare systemic autoinflammatory disease whose prevalence is roughly 0.16/100,000.⁷ The disease usually presents in young individuals, but there is a degree of bimodality to the age distribution.^{8,9} AOSD with PAH typically occurs in young women and to date 12 cases have been published (Table 2).

Table 2 Cases of AOSD and PAH.

Authors	Age	Sex	Fever	WBC (thou/mm ³)	Arthralgia	Rash	Therapy for PH/AOSD	Outcome
Zen et al., 1990 ¹⁸	29	F	+	Elevated	+	+	None/none	Died
Chen et al., 2006 ¹⁹	41	F	NA	NA	NA	NA	None/none	Survived
Chen et al., 2006 ¹⁹	27	F	NA	NA	NA	NA	None/none	Survived
Mubashir et al., 2007 ²⁰	29	F	+	Elevated	+	+	Nifedipine 60 mg daily/ corticosteroids, anakinra	Died
de Siqueira et al., 2009 ²¹	18	F	+	32.6	+	+	None/indomethacin, cortico- steroids, methotrexate	Survived
Khattari et al., 2011 ²²	26	F	+	16.3 (87% PMNs)	+	+	None/corticosteroids, naproxen	Survived
Campos et al., 2012 ¹²	27	F	+	Elevated	+	+	Amlodipine/corticosteroids, azathioprine, anakinra	Survived
Ibarra et al., 2013 ²³	43	F	–	11.8	–	+	Sildenafil/corticosteroids, cyclophosphamide, rituximab	Survived
Thakare et al., 2013 ⁵	18	F	+	23.2	–	+	None/none	NA
Kadavath et al., 2014 ²⁴	38	F	+	27.1	+	+	None/corticosteroids, tocilizumab	Survived
Guillemineault et al., 2016 ³	19	F	+	“Normal”	+	+	Ambrisentan, tadalafil/ corticosteroids, methotrexate, anakinra	Died
Wong et al., 2016 ¹³	24	F	+	NA	+	+	Epoprostenol, tadalafil, treprostinil, ambrisentan, tadalafil/corticosteroids, methotrexate	Survived
Our case	31	F	+	16.9 (90% PMNs)	+	+	Epoprostenol, tadalafil/ corticosteroids, methotrexate	Died

F, female; +, present; –, not present; NA, not available.

Although the mortality in AOSD is low,¹⁰ it increases dramatically in cases where the disease is complicated by cardiopulmonary abnormalities.¹¹ PAH and ARDS are rare complications of AOSD. We report the first case where both complications occurred in a patient with AOSD. The presence of mediastinal adenopathy on chest imaging and the patient's clinical decline after initiation of PAH-specific therapy was concerning for PVOD/PCH. However, autopsy failed to show evidence suggestive of either. To date, there have been no cases of PVOD/PCH reported in association with AOSD.

The exact pathophysiology of AOSD is unknown, but much of the disease seems to involve macrophage and neutrophil activation. Furthermore, therapy for AOSD can involve inhibition of IL-1, IL-18, and TNF α , implicating their role in the disease.^{12–14} With regards to PAH, there is a consensus that dysregulation of these cytokines plays a role in the remodeling of the pulmonary vasculature via recruiting of inflammatory cells. It seems reasonable to conclude that this similarity between AOSD and PAH could represent a reasonable mechanism for the pathophysiology of the disease; however, more research is necessary.

The mainstay of treatment of AOSD involves immunosuppression. Specifically, inhibition of IL-1 with anakinra

has been associated with improved outcomes in AOSD and PAH.^{12,14} In this case, the patient was continued on her prior immunosuppressive regimen for AOSD. Escalation of her immunosuppressive therapy was considered; however, due to her rapid hemodynamic decline and the possibility of an infectious etiology, we decided the benefit did not outweigh the risk at that time. Furthermore, the choice was made to prioritize treatment of the patient's right-sided heart failure as a consequence of her PAH given her rapidly progressing hemodynamic instability and eventual hypoxic respiratory failure.

AOSD does have an established relationship with ARDS (Table 3), having now been published in 18 cases. ARDS is known to occur because of the pathogenic production of cytokines, such as TNF α and IL-1.^{15–17} This has been established in the context of sepsis, but as previously mentioned, these cytokines are implicated in the development of PAH from AOSD. It stands to reason that the pathogenic release of these cytokines from AOSD could also result in ARDS and PAH, such as in this case.

What is not clear is why, exactly, ARDS and PAH tends to be so fulminant in cases of AOSD. It has been noted that any pulmonary complication has been associated with a poorer outcome and our patient experienced two concomitant severe

Table 3 Cases of AOSD and ARDS.

Authors	Age, years	Sex	Fever	WBC (thou/mm ³)	Arthralgia	Rash	Therapy for AOSD	Outcome
Hirohata et al., 1986 ⁴	65	F	+	14	+	–	Corticosteroids, cyclophosphamide	Died
Pederson et al., 1991 ²⁵	40	M	+	33	+	+	Corticosteroids, azathioprine	Survived
Gibbs et al., 1993 ²⁶	21	F	+	NA	+	–	Corticosteroids	Survived
Yokoyama et al., 1995 ²⁷	71	M	+	NA	–	+	Corticosteroids, nafamostat mesilate	Survived
Iglesias et al., 1999 ²⁸	29	F	+	16.6	+	–	Corticosteroids	Survived
Shinohara et al., 1999 ²⁹	54	F	+	17.7 (84% PMNs)	+	+	Corticosteroids	Survived
Mito et al., 2002 ³⁰	24	F	+	NA	–	+	Corticosteroids, cyclosporine	Survived
Suleiman et al., 2002 ³¹	36	F	+	30.9	–	–	Corticosteroids, methotrexate	Survived
Hagiyama et al., 2003 ³²	24	F	+	12.9 (95% PMNs)	–	–	Corticosteroids, cyclophosphamide	Survived
Hagiyama et al., 2003 ³²	20	M	+	12.2 (88% pmns)	–	+	Corticosteroids	Survived
Manganelli et al., 2003 ³³	17	F	+	NA	–	+	Corticosteroids, 6-mercaptopurine, cyclosporine, IVIG	Died
Biron et al., 2006 ³⁴	39	F	+	22 (90% PMNs)	+	+	Corticosteroids	Survived
Biron et al., 2006 ³⁴	68	F	+	28 (88% PMNs)	+	+	Corticosteroids	Survived
Biron et al., 2006 ³⁴	43	M	+	15.6 (91% PMNs)	–	–	Corticosteroids, IVIG	Survived
Guignard et al., 2007 ¹⁴	23	M	+	21	–	+	Corticosteroids, methotrexate	Survived
Chvojka et al., 2009 ³⁵	24	M	+	NA	–	–	Corticosteroids	Died
Dua et al., 2013 ²	26	F	+	20 (92% PMNs)	–	–	Corticosteroids	Died
Our case, 2016	31	F	+	16.9 (90% PMNs)	+	+	Corticosteroids, methotrexate	Died

F, female; M, male; +, present; –, not present; NA, not available.

pulmonary complications.¹¹ Considering the pathophysiology of extremely rapid decline is unclear, it perhaps highlights avenues for further research to elucidate a mechanism beyond that of the release of cytokines.

As in our case, patients with AOSD are frequently empirically treated with broad-spectrum antimicrobial therapy, but tend to ultimately be transitioned to aggressive immunosuppression. Our case differs in that the patient's clinical status was more fulminant given her severe right heart failure due to PAH. This precluded the possibility of definitively excluding infectious etiologies and allowing for adequate and timely treatment with immunosuppression.

Conclusion

We describe the first case of both PAH and ARDS in a patient with AOSD who, despite aggressive therapy, declined rapidly and ultimately died. Treatment of AOSD with cardiopulmonary involvement requires rapid identification of AOSD as the etiology for decompensation followed by aggressive immunosuppression. Considering this, we

recommend early involvement of rheumatology specialists in cases where patients present with new onset respiratory failure with a history of rheumatologic disease in which pulmonary hypertension is in the differential diagnosis. This case also highlights how the concomitant presentation of these two conditions may be mimicking the clinical presentation of PVOD or PCH. No standard of care for the management of these conditions currently exist.

Conflict of interest

The author(s) declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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