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CASE REPORT

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Two cases of acute respiratory distress syndrome resulting from adult-onset Still's disease

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Abstract Adult-onset Still's disease (AOSD) is a systemic inflammatory disorder of unknown origin. Acute respiratory distress syndrome (ARDS) is a rare complication of AOSD, with only nine cases having been reported in the literature. Here, we describe two cases of AOSD complicated with ARDS that were successfully treated with immunosuppressive therapy, including corticosteroids. Although ARDS is a life-threatening complication in AOSD, early commencement of high-dose corticosteroids and mechanical ventilation improve the prognosis.

Key words Acute respiratory distress syndrome (ARDS) · Adult-onset Still's disease (AOSD) · High-dose corticosteroids · Systemic inflammatory response syndrome (SIRS)

Introduction

Adult-onset Still's disease (AOSD) is a systemic inflammatory disease of unknown origin characterized by high spiking fever, skin eruption, and arthralgia.[1] The main pulmonary manifestations of AOSD are pleuritis and pneumonitis.[2] Acute respiratory distress syndrome (ARDS) is a rare but life-threatening complication in AOSD.[3–11] ARDS is a process of noncardiogenic pulmonary edema and hypoxemia associated with a variety of etiologies, including septic shock and severe trauma,[12] that carries a high mortality.[13] No standardized treatment protocol has so far been established for ARDS, although supplemental oxygen, mechanical ventilation, and avoidance of fluid overload are recommended. The administration of corticosteroids is sometimes effective, but remains controversial.[13] Here, we report two cases of AOSD complicated with ARDS. Both patients recovered after intensive treatment, i.e., immunosuppressive therapy including high-dose corticosteroids and mechanical ventilation.

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Case 1

A 24-year-old woman presented with repeated high spiking fever for several days from October 1997, and was admitted to hospital on December 10, 1997. At admission, her temperature was 39.1°C, pulse 110/min, and blood pressure 96/60 mmHg. The results of a physical examination were normal except for the presence of Köbner's sign. Laboratory examination revealed erythrocyte sedimentation rate 98 mm/h, C-reactive protein (CRP) 20.4 mg/dl, WBC count 6600/mm^3 with 88% neutrophils, hemoglobin 11.9 g/dl, platelet count 27.1 × 10^4/mm^3, lactate dehydrogenase (LDH) 219 IU/l, aspartate aminotransferase (AST) 24 IU/l, alanine aminotransferase (ALT) 14 IU/l and ferritin 64 ng/ml. Antinuclear antibody (ANA) was positive with a titer of 1:160. Rheumatoid factor (RF) was negative. Repeated blood cultures were negative. On the 3rd hospital day, sore throat, arthritides on bilateral knees, and pink macular rash on the trunk and proximal limbs appeared. The rash only appeared during fever. Subsequently, the WBC count rose to 12 900/mm^3 with 95% neutrophils; CRP also increased to 26.9 mg/dl. Serum ferritin was 103 ng/ml. A diagnosis of AOSD was made according to Yamaguchi's criteria.[14] Loxoprofen sodium was administered, and the patient's temperature fell below 37°C. On the 7th hospital day, however, her temperature rose to 38°C and she complained of slight dyspnea. Her respiratory condition worsened on the 8th hospital day, and a chest X-ray and chest computed tomography revealed bilateral diffuse pulmonary infiltrates, with an air bronchogram consistent with ARDS (Fig. 1). Arterial oxygen pressure was 59.5 Torr with a 100% rebreathing mask. The patient was intubated for mechanical ventilation. The administration of methylprednisolone (1 g on the first day and 0.5 g for 5 days) was initiated,

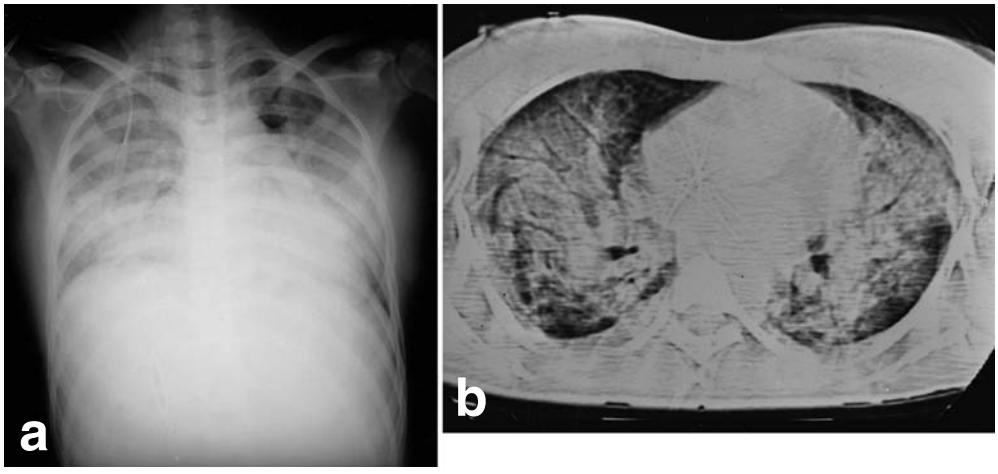

Fig. 1. **a** Chest X-ray obtained on the 8th hospital day, showing diffuse bilateral infiltrates. **b** Chest CT obtained on the 8th hospital day, showing alveolar filling and consolidation

followed by maintenance therapy of 60 mg prednisolone daily. Cyclophosphamide (700 mg) was also given intravenously on the first day. After the start of immunosuppressive therapy, her temperature decreased gradually, oxygenation and the findings on chest roentgenograms improved significantly, and on the 15th hospital day she was extubated. During her clinical course, LDH, AST, and ALT increased to 265 IU/l, 66 IU/l, and 60 IU/l, respectively, on the 10th hospital day, and then gradually improved. No signs of disseminated intravascular coagulation (DIC) were noted. Blood and sputum cultures were negative, as were serological tests for infection. Echocardiography showed normal cardiac function. Prednisolone was tapered to 25 mg daily, and the patient was discharged.

Case 2

A 20-year-old man was admitted to the hospital for evaluation of high spiking fever, skin rash, and bilateral cervical lymphadenopathy on May 18, 2000. In April 2000, he became aware of swelling of the right cervical lymph node. In May, he developed a high spiking fever, and received drugs, including nonsteroidal anti-inflammatory agents and antibiotics, from his physician. However, his condition did not improve and a skin rash appeared on his extremities and trunk. On the day of hospital admission, his temperature was 40.4°C, pulse 100/min, and blood pressure 108/52 mmHg. Physical examination revealed bilateral cervical lymphadenopathy and a pink maculopapular rash on his extremities and trunk. The rash was present irrespective of fever. No arthritides were observed. Laboratory examination revealed CRP 8.3 mg/dl, WBC count 12200/mm^3 with 88% neutrophils, hemoglobin 13.6 g/dl, platelet count 17.0 $\times$ 10^4/mm^3, LDH 1000 IU/l, AST 53 IU/l, ALT 26 IU/l, and ferritin 14455 ng/ml. ANA and RF were negative. A diagnosis of AOSD was made according to Yamaguchi's criteria.[14] Diclofenac sodium was administered, but high spiking fever continued. On the 5th hospital day, the patient complained of dyspnea and became hypotensive. A chest X-ray revealed bilateral diffuse pulmonary infiltrates with an air bronchogram consistent with ARDS (Fig. 2a). Arterial oxygen pressure was 40.9 Torr with a 100% rebreathing mask. LDH, AST, ALT and CRP increased to 2240 IU/l, 139 IU/l, 75 IU/l, and 16.4 mg/dl, respectively. He was intubated for mechanical ventilation. Administration of methylprednisolone (1.5 g on the first day and 1.0 g for 2 days) was started, followed by maintenance therapy of 60 mg prednisolone daily. After the start of corticosteroid therapy, his temperature decreased gradually, and oxygenation and the findings of chest roentgenograms improved (Fig. 2b). The patient was extubated on the 12th hospital day. During his clinical course, his platelet count declined to 8.6 $\times$ 10^4/mm^3 on the 7th hospital day, but returned to 21.3 $\times$ 10^4/mm^3 on the 10th hospital day without any specific therapy for DIC. Blood and sputum cultures, as well as serological tests for infection, were negative. Echocardiography revealed normal cardiac function. Prednisolone was tapered to 30 mg daily, and the patient was discharged.

Discussion

AOSD is a systemic inflammatory disease of unknown origin characterized by high spiking fever, skin eruption, and arthralgia.[1] The prevalence of pulmonary involvement in AOSD ranges from 0% to 53%,[2] with most cases showing pleuritis and pneumonitis. ARDS is a rare complication of AOSD, with only nine cases having been reported in the literature (Table 1).[3–11] Although such cases of AOSD are clinically indistinguishable from AOSD without ARDS, they present two characteristic features at the onset of ARDS. First, in all nine cases, ARDS occurred in the active stage of AOSD, i.e., the presence of high fever, arthralgia, and liver dysfunction. Second, in 6 of 9 cases, ARDS was complicated with DIC.[5–10] Our patients also had fever, arthralgia, and liver dysfunction at the occurrence of ARDS, but did not show features of DIC.

ARDS is characterized by arterial hypoxia and diffuse radiographic infiltrates associated with a variety of etiolo-

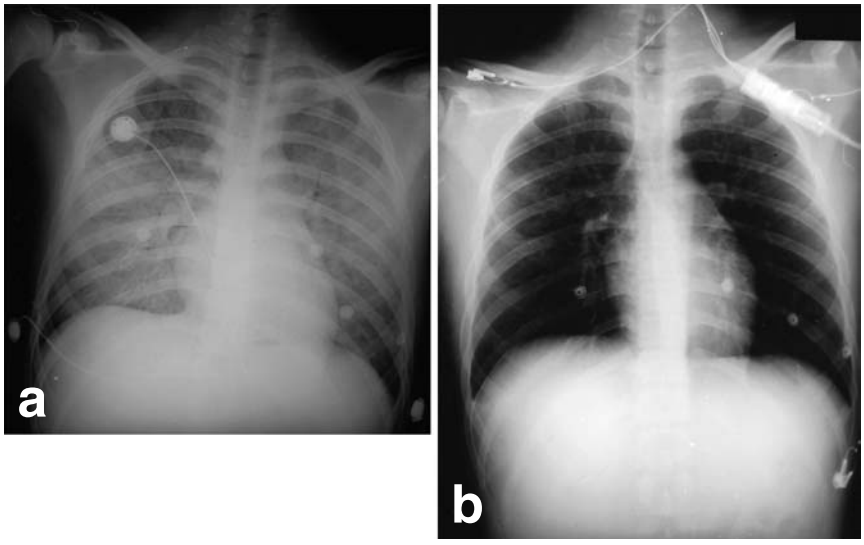

Fig. 2. **a** Chest X-ray obtained on the 5th hospital day, showing diffuse bilateral infiltrates. **b** Chest X-ray obtained on the 12th hospital day, showing a marked improvement of the infiltrative shadows

gies, including pneumonia, septic shock, and severe trauma.[12] Multiple factors are thought to be involved in the pathogenesis of ARDS. Endothelial and epithelial cell injury could be induced by direct damage to the lung resulting from infection or by a neutrophils-dependent process.[13] Furthermore, abundant production of multiple proinflammatory cytokines could initiate and amplify the inflammatory process in ARDS. In fact, many cytokines, including tumor necrosis factor (TNF)-α, macrophage-migration inhibitory factor, interleukin (IL)-1β, and IL-6, have been reported to be elevated in the sera and/or bronchoalveolar lavage fluids of patients,[15–19] and ARDS associated with septic shock and severe trauma is often complicated by disseminated intravascular coagulation (DIC) and multiple organ failure. In this way, ARDS is similar to systemic inflammatory response syndrome (SIRS), and SIRS can lead to ARDS.[20]

AOSD is also considered to be a systemic inflammatory disorder,[1] and cytokines, including TNF-α, interferon (IFN)-γ, IL-6, macrophage-colony stimulating factor, and IL-18, are elevated in the sera of patients.[21–24] Although cytokine profiles were not examined throughout the clinical course of any of nine reported cases, all cases, including ours, had spiking fever and arthralgia at the onset of ARDS, and some cases reported significantly elevated CRP levels. In this regard, Shinohara et al.[10] reported that CRP rose to 22.5 mg/dl at the onset of ARDS. In our cases 1 and 2, the CRP levels rose to 23.2 mg/dl and 16.4 mg/dl, respectively, at the occurrence of ARDS, suggesting excessive cytokine production, since CRP production from hepatocytes is mainly induced by IL-6.[25,26] Recently, serum levels of IL-18 were reported to be higher in AOSD patients than in healthy controls or in other systemic rheumatic disease, including RA.[23,24] Furthermore, serum concentrations of IL-18 correlate with the severity[23] and activity[24] of AOSD. IL-18 is a proinflammatory cytokine that induces production of many other cytokines, including IFN-γ, and enhances not only T cell and NK cell cytotoxicity, but also neutrophil migration and degranulation.[27] Jordan et al.[28] reported that IL-18 is implicated in acute lung inflammation via increasing neutrophil migration and lung vascular permeability. It is therefore possible that IL-18 might be implicated in the pathogenesis of ARDS. The involvement of increased cytokine production in the pathogenesis of DIC has also been reported.[29–31] DIC is observed in some cases of AOSD that show an extensive inflammatory response, and it sometimes results in a poor prognosis.[1,6,8] DIC is also a complication of ARDS and SIRS. In 6 of 9 cases showing ARDS in association with AOSD, DIC occurred simultaneously with ARDS, but the remaining 3 cases did not exhibit DIC. DIC was not associated with our two cases. Although the relationship between ARDS and DIC remains to be clarified,[10] a different mechanism might be operating in the occurrence of ARDS and DIC in AOSD. In addition, Fujii et al.[32] recently reported that cytokine and major histocompatibility complex (MHC) profiles differ between chronic articular AOSD, i.e., having chronic arthritis lasting longer than 6 months, and systemic AOSD, i.e., having no chronic arthritis. It is therefore possible that diverse cytokine and MHC profiles of patients of AOSD may account for the differences in their clinical manifestation.

The treatment of AOSD with severe systemic complications involves systemic administration of corticosteroids, including pulse methylprednisolone, and other immunosuppressive agents such as cyclophosphamide. However, no standardized regimen has been established for the treatment of ARDS as a complication of AOSD. In general, ARDS is a serious clinical situation with a mortality rate of 40%–60%, although a recent study has shown a slightly decreased mortality.[13] In contrast, in 8 of the 9 reported cases and in our two cases of ARDS associated with AOSD, ARDS was controlled with high-dose corticosteroid therapy[4–11] with or without immunosuppressants, although mechanical ventilation might be necessary to improve oxygenation of the arterial blood. Consequently, 10 of a total of 11 cases went into remission. In the remaining

Table 1. Reports of acute respiratory distress syndrome resulting from adult-onset Still's disease

References	Year	Age	Sex	Treatment	Fever	Arthralgia	Liver damage	DIC	Other complications	Activity	Outcome
Hirohata et al.[3]	1986	65	F	CS, CPA	+	+	?	–	–	Active	Death (due to infection)
Reginato et al.[4]	1987	20	F	CS	+	+	+	–	–	Active	Remission
Pederson[5]	1991	40	M	CS, AZP	+	+	+	+	–	Active	Remission
Pouchot et al.[6]	1991	–	–	CS	+	+	?	+	IP	Active	Remission
Gibbs et al.[7]	1993	21	F	None (CS)	+	+	+	+	–	Active	Remission
Yokoyama et al.[8]	1995	71	M	CS	+	+	+	+	–	Active	Remission
Iglesias et al.[9]	1999	29	F	CS	+	+	+	+	–	Active	Remission
Shinohara et al.[10]	1999	54	F	CS	+	+	+	+	–	Active	Remission
Carron et al.[11]	2000	31	M	CS	+	+	+	–	IP	Active	Remission
Our cases		24	F	CS, CPA	+	+	+	–	–	Active	Remission
		20	M	CS	+	+	+	–	–	Active	Remission

CS, corticosteroid; CPA, cyclophosphamide; AZP, azathioprine; DIC, disseminated intravascular coagulation; IP, interstitial pneumonitis

case, cyclophosphamide pulse therapy after the failure of corticosteroid therapy induced severe granulocytopenia, and the patient died of opportunistic infection in spite of extensive treatment.[3] In this respect, ARDS associated with AOSD is different from conventional ARDS, which is considered to be resistant to corticosteroid therapy and carries a high rate of mortality.[13] The better prognosis of ARDS in AOSD can be ascribed to the absence of any severe underlying disease, except for AOSD, and the younger age of the patient population. In addition, early treatment with high-dose corticosteroids with or without immunosuppressants will prevent the initiation of a cytokine cascade, which also contributes to a better prognosis in AOSD.

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