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A Case of Adult Onset Still's Disease with Severe Pneumonitis Treated with Anakinra

Soung Ha Cho, One Zoong Kim, Sang Woo Cho, Dong Min Lim, Su Kyoung An, and Choon Kwan Kim

Department of Internal Medicine, VHC Medical Center, Seoul, Korea

Adult onset Still's disease (AOSD) is a systemic autoinflammatory disorder that presents with recurrent fever, extreme fatigue, and joint pain. Pulmonary involvement is not uncommon and, although rare, severe pneumonitis can progress to respiratory failure. Still's disease-associated pneumonitis is generally treated with immunosuppressive agents, but improvement in our understanding of systemic inflammatory processes led us to explore alternative agents. Anakinra is an interleukin-1 receptor antagonist used to treat autoinflammatory disorders resistant to immunosuppressive therapy. Several case reports have demonstrated efficacy of anakinra in treating AOSD, but its relevance in cases complicated with severe pneumonitis has not been examined. Our patient's disease activity was not controlled with systemic steroids and cyclophosphamide. Treatment with anakinra led to a dramatic clinical response. This is the first reported case of AOSD with severe pneumonitis refractory to conventional therapy successfully treated with anakinra. (Korean J Med 2014;87:245-250)

Keywords: Adult onset Still's disease; Pneumonitis; Anakinra

INTRODUCTION

Adult-onset Still's disease (AOSD) is a systemic inflammatory disorder of unknown etiology. AOSD is characterized by repeated fever, joint pain, pharyngitis, hepatosplenomegaly, enlargement of lymph nodes, and a variable degree of pneumonitis. Multiple organ systems are frequently involved, and in rare cases, AOSD can manifest as severe pneumonitis [1]. Although treatment usually commences with the application of non-steroidal anti-inflammatory drugs (NSAIDs), the addition of systemic glucocorticoids, disease-modifying antirheumatic drugs (DMARDs), and biologic agents such as tumor necrosis factor (TNF) inhibitors usually proves necessary [2]. However, certain cases of AOSD are refractory to these

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Correspondence to Choon Kwan Kim, M.D.
Department of Internal Medicine, VHC Medical Center, 53 Jinhwang-doro 61-gil, Gangdong-gu, Seoul 134-791, Korea
Tel: +82-2-2225-1491, Fax: +82-2-2225-4374, E-mail: schenics@naver.com

conventional agents. Anakinra, a recombinant human interleukin-1 (IL-1) receptor antagonist, demonstrates promising utility in such instances [2]. We report the first case, of AOSD with severe pneumonitis that failed to respond to steroids and cyclophosphamide but exhibited rapid clinical improvement following application of anakinra.

CASE REPORT

A 68-year-old Asian male presented to the emergency department complaining of episodes of fever that had occurred daily for more than 1 week and did not respond to NSAIDS. He reported that his fever occurred principally in the afternoon, persisted for 2-4 hours, and then subsided following a period of mild sweating. Associated symptoms included malaise, headache, sore throat, muscle ache, nausea, and vomiting. The patient had experienced an episode of AOSD 5 years previously that involved recurrent daily spiking fever, evanescent rash, and high ferritin levels. He was treated with a short course of steroids and has subsequently been afebrile.

During initial evaluation, the patient was thin and exhibited mild respiratory distress. His blood pressure was 140/80 mmHg, his pulse rate was 90 beats per minute, his respiratory rate was 20 breaths per minute, and his body temperature was 39℃. Emergency blood counts revealed leukocytosis with a left shift. Blood cultures were obtained, following which empiric antibiotics were initiated; the patient was then admitted for further evaluation.

Further physical examination revealed a mild inspiratory crackle over the area of the right lower lung. There was no evidence of hepatosplenomegaly or arthritis. Multiple areas of salmon-colored, macular and non-pruritic rash were observed across the anterior chest, lower back, and upper limbs. The rash was most prominent at the height of each fever.

Hematologic evaluation revealed a white blood cell count of 16,000/mm^3 with 92% neutrophils, hemoglobin concentration of 11.7 g/dL, and platelet count of 120,000/mm^3. Blood smear revealed normocytic normochromic anemia with a left shift and toxic alterations in neutrophils.

Blood chemistry analysis revealed aspartate aminotransferase of 50 U/L, alkaline phosphatase of 144 U/L, total bilirubin of 1.0 mg/dL, lactate dehydrogenase of 903 U/L, blood natriuretic peptide of 391 pg/mL, and creatinine of 1.2 mg/dL. Total protein and albumin levels were mildly decreased.

The acute-phase reactants CRP and ESR were elevated, at 482 mg/L and 87 mm/hr, respectively; procalcitonin was elevated, at 16.2 ng/mL; and serum ferritin was markedly increased, at 20,000 ng/mL. Anti-nuclear antibody, anti-nuclear cytoplasmic antibody, anti-cardiolipin antibody, anti-phospholipid immunoglobulins, and rheumatoid factor were not detected. Hepatitis B and C serologies were negative. A chest radiograph demonstrated mild peribronchial thickening in the right perihilar area.

During the fourth day of admission, the patient complained of progressive dyspnea; his O_2 saturation, measured by pulse oximetry in room air, dropped to 78%. A simple chest radiograph revealed diffuse bilateral infiltrations and pleural effusion (Fig. 1). A facial mask with 6 L/min O_2 was provided to maintain oxygen saturation above 90%.

Two days later, computed tomography (CT) of the chest revealed findings consistent with severe pneumonitis with reactive bilateral pleural effusion (Fig. 1). CT scans of the abdomen and pelvis were negative for abscess or mass. Transthoracic echocardiography results were unremarkable. Thoracentesis revealed an exudate with 95% segmented neutrophils and no evidence of pulmonary tuberculosis or malignancy. Bronchoscopic alveolar lavage was negative for viral and pneumocystis pneumonia, and transbronchial lung biopsy revealed no diagnostic parenchymal abnormality. Serum tests for legionella and mycoplasma were also negative. Bone marrow biopsy revealed no evidence of hematologic malignancy, but reactive hyperplasia of granulocytic cells was detected.

Because follow-up tests for serum ferritin levels yielded values exceeding 10,000 ng/mL, with a maximum value of 70,000 ng/mL, a diagnosis of AOSD was entertained. Although evidence of arthralgias, lymphadenopathy, and hepatospleno-

megaly were lacking, the presence of sore throat, fever exceeding 39℃ for more than 1 week, a rash typical of febrile episodes, leukocytosis with > 90% granulocytes, abnormal liver function tests, and negative antinuclear antibody and rheumatoid factors were consistent with three of the major and three of the minor criteria for AOSD diagnosis. Accordingly, intravenous (IV) prednisone at 1 mg/kg/day was initiated. Because blood and sputum cultures had returned no clinically relevant results, antibiotics were substituted to cover atypical organisms.

Continued therapy with antibiotics and systemic corticosteroids and application of IV gamma globulin for 7 days failed to result in clinical improvement. The patient's condition deteriorated further, with worsening dyspnea. Follow-up chest CT demonstrated increased bilateral diffuse infiltrates with pleural effusion. The patient's vital signs became unstable, with blood pressure of 60/35 mm/Hg, heart rate of 134 beats per minute, respiratory rate of 36 breaths per minute, and body temperature of 38℃. Fluid resuscitation and IV dopamine were initiated, and the patient was transferred to the intensive care unit for mechanical ventilation.

On the day of transfer, a pulse of 1,000 mg IV cyclo-

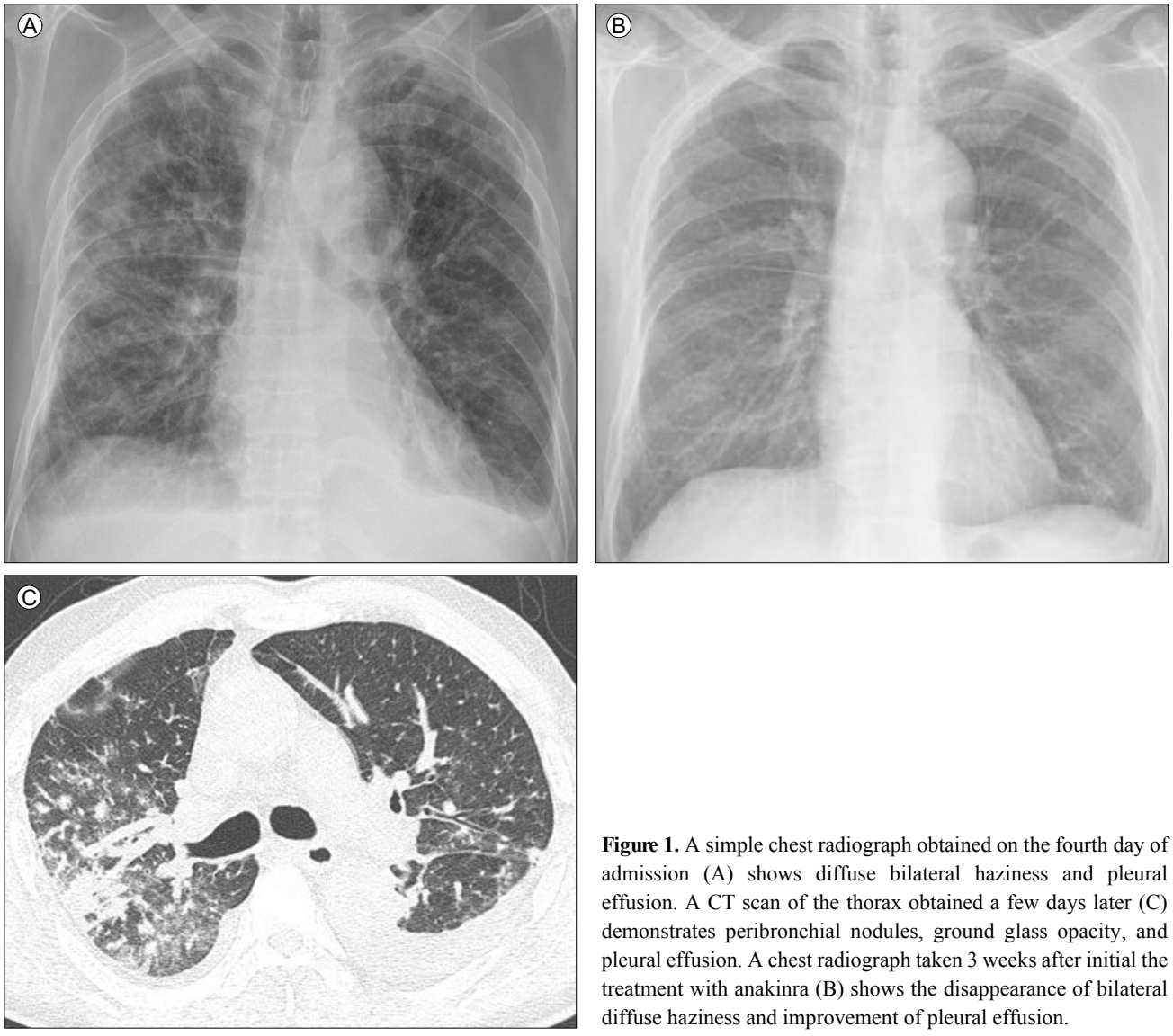

Figure 1. A simple chest radiograph obtained on the fourth day of admission (A) shows diffuse bilateral haziness and pleural effusion. A CT scan of the thorax obtained a few days later (C) demonstrates peribronchial nodules, ground glass opacity, and pleural effusion. A chest radiograph taken 3 weeks after initial the treatment with anakinra (B) shows the disappearance of bilateral diffuse haziness and improvement of pleural effusion.

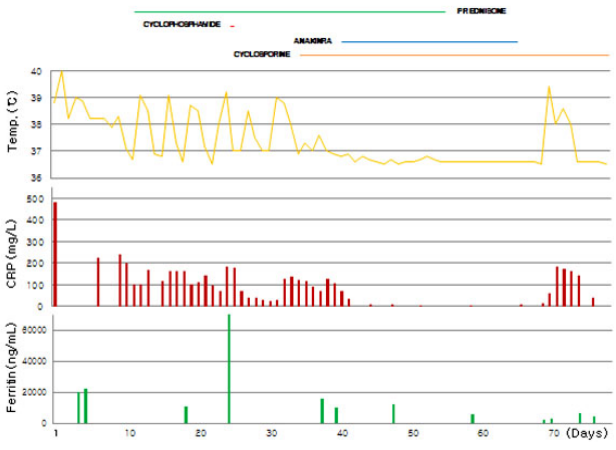

Figure 2. Variations in temperature, CRP, and ferritin levels in association with treatment periods of prednisone, cyclosporine, cyclophosphamide, and anakinra. CRP, creactive protein.

phosphamide was administered, in accordance with its frequent use for systemic autoimmune disorders. Application of cyclophosphamide was followed by cyclosporine at 4 mg/kg/day. However, fever and dyspnea could not be brought under control, and WBC, CRP, ESR, and ferritin levels all remained at elevated levels. Starting 3 days after cyclophosphamide infusion, the patient was subcutaneously administered anakinra daily at 100 mg in addition to cyclosporine and corticosteroids.

The patient's condition improved dramatically following only 1 day of anakinra treatment. Ferritin levels returned to normal, and pulmonary infiltrates cleared rapidly. Over the following days, the steroids were tapered off, while anakinra and cyclosporine were maintained for a total of 30 days. Because it was unclear whether the patient's clinical improvement was attributable to cyclosporine or to anakinra, the latter was withheld to allow for observation of clinical changes. Two days later, daily fever returned, the salmon-colored rash reappeared, and ferritin levels rose again (Fig. 2). However, these symptoms disappeared immediately following reinstatement of anakinra. The patient was eventually discharged with anakinra and cyclosporine; treatment responsiveness was confirmed during outpatient follow-up following the tapering-off of cyclosporine.

DISCUSSION

The prevalence of pulmonary involvement in AOSD varies markedly across cases, ranging between 0 and 53% [1]. Pleurisy represents the most common pulmonary manifestation and can present alone or in addition to transient pulmonary infiltrates that frequently resolve without complication. Acute pulmonary abnormalities usually respond well to systemic steroids, but in certain cases, these abnormalities may progress to life-threateningly severe respiratory failure that requires mechanical ventilation [1].

The similarities between clinical and laboratory presentations of AOSD and those of infectious diseases suggest a role for infectious agents in AOSD pathogenesis [3]. However, definitive evidence is currently lacking. Although genetic, environmental, and immunologic factors have also been implicated, conclusive evidence has not been forthcoming; reports that specific HLA alleles are associated with AOSD still require corroboration [4].

Although there are no definitive laboratory tests for AOSD, biomarkers can aid in differentiation of AOSD from infectious diseases. Serum ferritin levels ≥ 2,500 ng/mL appear to be highly specific to AOSD [5]. However, autoimmune disorders, inflammatory solid tumors, and hematologic malignancies can also express hyperferritinemia, albeit usually at lower levels [5]. Despite elevated inflammatory markers, culture results are negative, and antimicrobials have no effect on the clinical course. The pathognomonic rash observed in Still's Disease is fleeting, and it can be easily mistaken for a trivial skin disorder. Moreover, lung biopsy has not proven illuminating in the context of AOSD complicated by acute pneumonitis. Hyaline membrane formation and type II pneumocyte hyperplasia indicate adult respiratory distress syndrome but do not contribute to the diagnosis of AOSD [1].

AOSD is a diagnosis of exclusion, necessitating that a wide variety of similarly presenting disorders also be considered, including malignancies, vasculitides, granulomatous diseases, and connective tissue disorders. Because diagnosis is based primarily on clinical grounds, several diagnostic

criteria have been proposed. Among these, the Yamaguchi criteria are the most widely cited, and exhibit the highest sensitivity [1]. The major Yamaguchi criteria are as follows: (1) fever (body temperature > 39℃, intermittently for ≥ 1 week); (2) arthralgia for > 2 weeks; (3) typical rash; and (4) WBC > 10,000/mm^3 (> 80% granulocytes). The minor criteria are: (1) sore throat; (2) lymphadenopathy and/or splenomegaly; (3) abnormal liver function tests; and (4) negative RF and ANA. The presence of five of these criteria, of which at least two are major, is required for diagnosis of AOSD. It has been reported that a combination of the Yamaguchi criteria and hyperferritinemia offers superior results in AOSD diagnosis [5].

Treatment of AOSD has long been empirical due to a lack of concrete data from randomized controlled clinical trials. NSAIDs were once considered the first-line medication, but these have been largely replaced by corticosteroids due to low response rates, only 7-15%. Steroids are effective in approximately 75% of AOSD cases. Nevertheless, the adverse effects inherent to chronic steroid therapy, the relapses frequently seen in response to tapering, and resistance to their effects have all been of concern. Steroid-resistant AOSD is currently treated with DMARDs, with a response rate of nearly 60% [6].

Evidence that cytokines play a central role in the pathogenesis of AOSD has led to the application of several different biologic agents. Activation of neutrophil and macrophages and up-regulation of T-cell activity have been observed in the context of AOSD. Recently, the role of several proinflammatory cytokines, including TNF-α, IL-1, IL-6, IL-8, IL-17, and IL-18, has been elucidated with respect to AOSD pathogenesis. Although cytokine profiles have not proven instructive in differentiating AOSD from sepsis, they have sometimes been shown to be elevated in conjunction with serum CRP and ferritin levels. IL-6 is purportedly responsible for increased production of ferritin and CRP by the liver. Elevated levels of different cytokines can serve as potential markers of disease activity and may prove useful in determining prognosis [3].

Although IFN-γ levels are also reportedly elevated in AOSD, this cytokine was not associated with disease activity [4]. Therefore, in contrast to rheumatoid arthritis, in which anti-TNF agents play an important therapeutic role, they have been used with only modest success in AOSD [4].

The serum concentration of IL-1 level is markedly elevated in AOSD and is implicated in its pathogenesis. Recent studies suggest that dysregulation of IL-1 production resulting from an interplay of extrinsic and intrinsic factors is responsible for the maintenance of disease activity in AOSD [7].

It has been suggested that anakinra may be an effective alternative therapy for AOSD patients. Anakinra is a recombinant version of a human IL-1 receptor antagonist that is administered subcutaneously at a dosage of 100 mg/day. Possible adverse reactions include headache, fever, nausea, arthralgia, nasopharyngitis, and increased risk of infection [2], although none of these reactions was observed in our patient.

Patients treated with anakinra demonstrate rapid resolution of clinical and laboratory markers. Indeed, several authors have reported dramatic clinical improvements in response to its use [2,4]. The effectiveness of anakinra and its corticosteroid sparing effect have been well documented in a case series of refractory AOSD reported by Oh et al. [8] In a study by Kontzias et al. canakinumab, a monoclonal antibody for IL-1 with a longer half-life, successfully controlled disease activity in anakinra-refractive cases [9]. Furthermore, because IL-6 shares an important pathogenetic role with IL-1, the IL-6 antagonist tocilizumab also has demonstrable effectiveness in anakinra-refractive AOSD [10].

Withholding anakinra can result in clinical flare-ups and re-elevation of inflammatory markers. The relapse rate associated with anakinra therapy has not yet been determined, but long-lasting clinical remission is possible in response to tapering [3]. This suggests that IL-1 activity is responsible for the main inflammatory process observable in certain AOSD patients.

To the best of our knowledge, this is the first reported case of successful treatment of AOSD with severe pneumonitis using anakinra. Our study demonstrates that anakinra is

an effective therapy even in cases of refractory AOSD with severe pneumonitis.

중심 단어: 성인형 스틸병; 폐렴; 아나킨라

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