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CASE REPORT

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A case of life-threatening refractory polychondritis successfully treated with combined intensive immunosuppressive therapy with methotrexate

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Abstract Relapsing polychondritis (RP) is a rare disease of unknown etiology causing systematic inflammation and resulting in destruction of cartilaginous tissues. We describe here an 18-year-old Japanese woman who developed severe airway stenosis as the initial symptom with auricular, nasal, and ocular inflammation. The effect of high dose oral steroid, methylprednisolone pulse therapy, and cyclophosphamide was temporary and her conditioning was worsening. Finally we added methotrexate to the immunosuppressive treatment and achieved reduction of disease activity. This case illustrates the potentially fatal sudden onset of airway inflammation that can occur with this disorder, and the effectiveness of methotrexate.

Key words Airway stenosis · Cyclophosphamide · Methotrexate · Relapsing polychondritis

Introduction

Relapsing polychondritis (RP) is an uncommon disease characterized by episodic inflammation of cartilaginous structures resulting in tissue destruction. The target of inflammation is proteoglycan-rich structures, whose pathogenesis is believed to involve an immunologic mechanism with antibodies against type II collagen, where 60% of cases are reported to be positive.[1] More recently, an increase in HLA-DR4 antigen was detected in patients with RP.[2] Rheumatic disease or autoimmune disease coexist in up to 30% of cases.[3–5]

In a report by McAdam et al.,[4] nearly 50% of patients had laryngotracheobronchial involvement; however, only 12% had initial airway involvement. Generally, patients with signs of acute inflammation are usually treated with prednisolone, in a dose of 0.5 to 1.0 mg/kg. Patients with severe manifestations, such as airway compromise, in the setting of active inflammation have often been treated traditionally with methylprednisolone pulse therapy. However, there are cases resistant to steroid pulse therapy and treatment for those cases has not been established. Here, we report a patient with sudden onset of RP who developed progressive laryngotracheal involvement, with auricular, nasal, and ocular inflammation later, which led to severe stenosis of the trachea that required intensive combined therapy with steroid, cyclophosphamide, and weekly methotrexate.

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Case report

An 18-year-old female patient had been well until March 2006, when she became aware of low-grade fever with saddle nose, hoarseness, and ear pain with redness. She was treated as suffering a common cold without significant improvement, which led her to visit an otolaryngologist. Treatment with betamethasone (1.5 mg/day) was effective although withdrawal led to relapse of her symptoms. In addition, she developed acute progressive dyspnea and stridor, and visited our emergency unit on April 3, 2006. Bronchoscopy revealed severe bilateral vocal cord and trachea lumen swelling. Intravenous administration of dexamethasone 8 mg was performed for 3 days followed by prednisolone 40 mg/day. Her symptoms improved except for hoarseness. However, 10 days later dyspnea with stridor redeveloped, and severe stenosis and swelling at the glottis, subglottis, and main bronchus were observed under X-ray and three-dimensional computed tomography (CT) (Fig. 1a,b). Emergency tracheostomy was performed to keep the airway clear. Seven days after tracheostomy, swelling, tenderness, and erythematous changes in her right ear were noted with high-grade fever. Inflammation of the pinna persisted, in spite of treatment with prednisolone 40 mg/day for

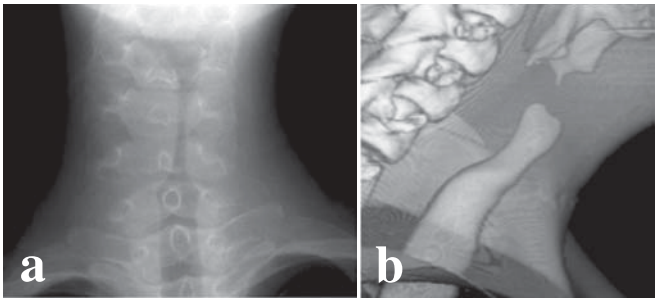

Fig. 1. Neck X-ray showing narrow main bronchus (**a**) and three-dimensional reconstruction of the patient's computed tomography (CT) scan (**b**)

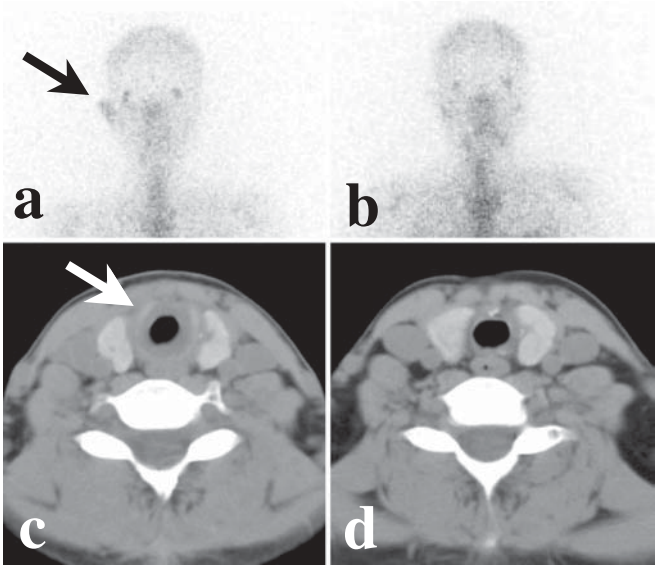

Fig. 2. Gallium scan showing increased uptake in the right ear (**a;** *arrow*) and CT scan showing swelling of the tracheal mucosa (**c**) with improvement after treatment (**b** and **d**)

3 weeks. Therefore, she was referred to our department of internal medicine to consider other immunological complications and further treatment with immunosuppressants. Laboratory data revealed hemoglobin 10.7 g/dl, white blood cell count of 15200/μl, platelet count of 59.6×10^3/μl, and increased concentration of C-reactive protein (CRP): 11.4 mg/dl. Left shift of the white blood cell count was not observed and physical examination did not show evidence of recent infections. Renal and liver function tests and immunoglobulin (Ig) levels, including IgG, IgM, and IgA, were all within normal limits. Antinuclear antibody and rheumatic factor were negative although antineutrophil cytoplasmic antibody (PR3-ANCA) was positive (16 EU). Computed tomography of the chest showed marked swelling of cartilages and lumen of the trachea and severe stenosis above the tracheostomy (Fig. 2c). No abnormality was observed in the lung field. She developed bilateral auricular, nasal, and respiratory tract chondritis, and we diagnosed her as having relapsing polychondritis based on the criteria proposed by McAdam et al.[4] She was treated with methylprednisolone pulse therapy (1000 mg/day × 3), which decreased the level of CRP to 0.74 mg/dl and improved her symptoms. However, its effect lasted only a few days and her right ear redness reappeared, and increased CRP (2.69 mg/dl) was observed; cyclophosphamide (15 mg/kg) was administered intravenously. On the next day, redness in both eyes suddenly appeared with high fever. She was diagnosed as having bilateral scleritis, and weekly methylprednisolone pulse therapy was performed for another 2 weeks with biweekly cyclophosphamide administration. After each treatment with methylprednisolone or cyclophosphamide, those effects lasted only a couple of days and mainly her scleritis reappeared with increased CRP. Because her scleritis worsened in the morning, methylprednisolone was switched to betamethasone, considering its half-life, and weekly methotrexate (8 mg) was started. Her symptoms improved dramatically and CRP turned negative 10 days after she started to receive methotrexate and betamethasone (Fig. 3). Significant improvement on Ga scintigram, uptake to her right ear (Fig. 2a,b) and bronchus swelling were notable (Fig. 2c,d). Throughout the clinical course she did not show any symptoms suggesting arthritis, which was also confirmed by negative uptake in the joints on Ga scintigram.

Discussion

This case study demonstrates the possibility of acute airway involvement as the initial symptom of RP and the importance of aggressive therapy with steroid and immunosuppressive drugs to control this life-threatening condition.

Refractory polychondritis is a rare disease whose cause remains unknown. The diagnosis of RP usually is made based on the criteria proposed by McAdam et al. in 1976.[4] Our patient's symptoms included auricular, nasal, and laryngeal chondritis with scleritis, and a definite diagnosis of RP was established. Refractory polychondritis has been known to be frequently associated with the presence of other multisystem diseases, of which vasculitis is the most common.[4,6,7] Antinuclear antibodies can be detected in 5%–20% and antineutrophil cytoplasmic antibody (ANCA) can be found in 25% of patients with RP.[8] However, only 10% of patients in this group have clinical symptoms of vasculitis. In our patient, PR3-ANCA was positive although her symptoms and clinical findings did not satisfy the diagnostic criteria of Wegener's granulomatosis.

Organs involved in RP include ears (85%), nose (59%), eyes (52%), and joints (50%–75%). The airway is affected in about 50%–70%, but its involvement as the initial presentation was evident in only 12% of cases in the report of McAdam et al.[4] Among the patients with airway involvement, 80% with initial involvement required tracheostomy, contrasting with 25% who developed respiratory tract involvement later in the disease course.[4] Airway stenosis can occur for one or a combination of reasons: (1) localized fibrous mass within the airway, (2) airway collapse because of wall destruction, and (3) airway wall thickening due to inflammation. Indications for tracheostomy early in RP are

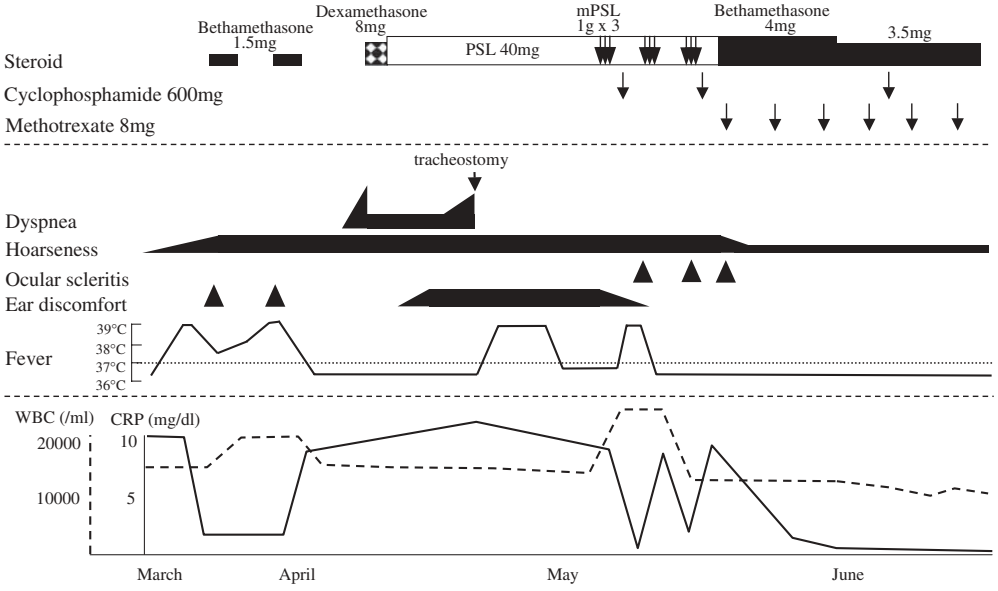

Fig. 3. Clinical course. Prominent effect of methotrexate to ocular scleritis and chondritis of the airway. *mPSL*, methylprednisolone; *PSL*, prednisolone; *WBC*, white blood cells; *CRP*, C-reactive protein

Table 1. Summary of cases with involvement of the eye and/or the airway successfully treated with immunosuppressants

Year	First author	Site of symptoms	Treatment	Reference
2006	Yu	Eye	MTX	14
2005	Tesche	Eye, ear	MTX, steroid	15
2005	Ogawa	Airway, eye, ear, kidney	CY, steroid	16
2005	Chang	Airway	AZA, steroid	17
2003	Hellmich	Airway	CY	18
1991	Lipnick	Airway	CY, AZA, dapsone, steroid	9
1990	Hoang	Eye	CY, AZA, steroid	19
1984	Svenson	Airway	CY, AZA, cyclosporin, steroid	11
1981	Adler	Airway, nose, ear, joint	CY, steroid	20
1981	Ruhlen	Airway, kidney	CY, steroid	10

MTX, methotrexate; CY, cyclophosphamide; SASP, salazosulfapyridine; AZA, azathioprine

usually not the collapse of laryngeal or tracheal cartilaginous rings, but, rather, severe glottic, laryngeal, and subglottic inflammation and edema, leading to airway obstruction.

Airway involvement is one of the most serious manifestations of RP, which remains the most challenging long-term management problem in this disorder. There is as yet no single uniformly effective treatment. It is empirically known that systemic corticosteroids[9] and other immunosuppressants are required. A standard therapy for RP remains to be established; however, corticosteroids are the agents of choice for active inflammation. Nevertheless, corticosteroids do not stop disease progression in severe cases.[4] Methotrexate, cyclosporine, azathioprine, and cyclophosphamide have all been used to treat RP, either because of their steroid-sparing effects or for use in patients with life-threatening disease.[10–13] Reviewing the literature, among the cases successfully treated with immunosuppressants, all cases with airway involvement have been treated with cyclophosphamide and recently cases with eye involvement have been treated with methotrexate, showing high efficacy (Table 1). In our patient, the effect of cyclophosphamide was temporary although methotrexate showed a prominent effect on both ocular scleritis and bronchial chondritis (Fig. 3). In theory, the choice of methotrexate is reasonable since chondral destruction is the common pathology with rheumatoid arthritis. However, we cannot exclude the possibility that cyclophosphamide showed its effect when methotrexate was added. Based on our experience reported here, we propose the use of methotrexate for RP that is resistant to steroids, not only because of its effectiveness but also its low toxicity compared to other immunosuppressants, especially in young patients with bronchial involvement. Recently, tumor necrosis factor blockade and interleukin-1 receptor blocker have been used successfully to treat refractory cases of RP.[22–24] Biological products may be useful for RP resistant to treatment although further study is needed.

Initially, mortality in RP patients with respiratory tract involvement was almost 50%.[4] However, recent reports estimate the mortality to be 6%, suggesting infection as the most common cause of death with corticosteroids and airway collapse as a contributing factor. Decrease in mortality was suggested to be due to earlier diagnosis and therapy.[2] Early respiratory tract involvement and age of 50 years or younger with strictures contribute to greater risk, and our

patient had these characteristics. Despite initial treatment with high-dose corticosteroid, she developed life-threatening acute airway obstruction which was also resistant to methylprednisolone pulse therapy and cyclophosphamide. Additional treatment with weekly methotrexate (8 mg/week) finally improved her symptoms, with serological decrease of inflammation. With acute airway involvement in RP, such aggressive therapy, especially the addition of methotrexate, should be considered in order to prevent death.

In summary, RP is a systemic disease that can be associated with airway involvement as an initial symptom. In addition, there are an increasing number of case reports by multiple specialists, establishing RP as a systemic disease that is also related to autoimmune disease. In particular, younger patients with early respiratory tract involvement are predicted to have a poor general outcome; therefore, aggressive therapy with steroid pulse therapy followed with oral high-dose steroid and/or intensive immunosuppressive drugs including methotrexate without delay appears to be very important.

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