ATYPICAL COGAN’S SYNDROME SUCCESSFULLY TREATED WITH CORTICOSTEROIDS AND PULSE CYCLOPHOSPHAMIDE THERAPY

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Abstract: An 18-year-old woman was admitted to the medical center near her home with complaints of high fever and severe headache in June 1995. A diagnosis of adult-onset Still’s disease was suspected and 50 mg/day of prednisolone was orally administered. In early April 1997, the patient suffered from sudden bilateral hearing loss and high fever. Pure tone audiogram taken at the same time showed an asymmetric bilateral neurosensorial hearing loss. A diagnosis of Cogan’s syndrome was made. Administration of 60 mg prednisolone daily improved fever. Audiogram taken one month after administration of prednisolone showed improvement in the right ear. Monthly cyclophosphamide pulse therapy 700 mg combined with oral prednisolone was instituted. This combination therapy enabled the successful tapering of prednisolone without recurrence of hearing loss. Combined corticosteroid and pulse cyclophosphamide therapy would appear to be one effective regimen for Cogan’s syndrome.

Key words: Cogan’s syndrome, corticosteroids, cyclophosphamide, neurosensorial hearing loss.

INTRODUCTION

Cogan’s syndrome is an uncommon disorder characterized by nonsyphilitic interstitial keratitis and vestibuloauditory dysfunction1). In addition to the inflammatory eye and ear lesions, approximately 15% of cases of Cogan’s syndrome are associated with systemic vasculitis of small to large vessels2). The cause of
Cogan's syndrome is unknown. However, positive antibodies against inner ear and corneal antigens suggests an autoimmune nature of this disease\textsuperscript{3-4}. For treatment of Cogan's syndrome, the favorable effect of corticosteroid\textsuperscript{5} with or without immunosuppressants including cyclophosphamide\textsuperscript{6}, methotrexate\textsuperscript{7}, or FK 506\textsuperscript{8} has been reported. However, an established regimen for successfully treating this rare disorder has not been established.

We here report successful treatment for sudden hearing loss in a patient with atypical Cogan’s syndrome by administration of corticosteroid and pulse cyclophosphamide therapy.

CASE REPORT

An 18-year-old woman with a negative medical history was admitted to the medical center near her home with complaints of high fever, nausea, vomiting, polyarthralgia and severe headache in June 1995. Meningitis was suspected because of meningeal irritation signs with CSF pleocytosis of consisting of 30% polymorphonuclear cells; peripheral blood leukocytosis of 23,600/\mu l; and positive CRP of 21.4 mg/dl. No bacteria or fungus was detected in the CSF. On the 3rd day of admission, urticarial eruption without itching was noticed on the hands, feet and lower abdomen. Ultrasound sonography revealed mild hepatosplenomegaly, but serum transaminases were normal. The clinical course of this patient is shown in Fig. 1.

Based on these clinical and laboratory findings, a diagnosis of adult-onset Still’s disease was suspected and 50 mg/day of prednisolone was orally administered. After two mild exacerbations on rapid tapering of prednisolone, all symptoms

\begin{center}
\begin{tabular}{c|c|c|c|c|c|c|c}
& 1995.6 & 9 & 1997.4 & 5 & 6 & 7 & 8 \\
\hline
PSL & \begin{tabular}{c}
50 30 20 \\
50 30 20 \\
50 60 50 30 30
\end{tabular} & off & CPA (750 mg) iv & & & & \\
Fever & \begin{tabular}{c}
80 60 50 30 30 \\
80 60 50 30 30
\end{tabular} & & & & & & \\
Arthralgia & \begin{tabular}{c}
80 60 50 30 30 \\
80 60 50 30 30
\end{tabular} & & & & & & \\
Headache & \begin{tabular}{c}
80 60 50 30 30 \\
80 60 50 30 30
\end{tabular} & & & & & & \\
WBC (\mu l) & 23,600 & 8,700 & 7,400 \\
CRP (mg/dl) & 21.4 & 16.9 & <0.1 \\
\end{tabular}
\end{center}

Fig. 1. The clinical course of this patient
Fig. 2. Spontaneous hearing acuity fluctuations documented on pure tone audiograms in this patient. A) Audiogram taken in April 1997 at the onset of the disease. B) taken in May 1997, one month after the onset while she was treated with 60 mg/day of prednisolone. (o-o, right ear, x-x, left ear)
disappeared and all drugs including prednisolone were discontinued by October, 1995. In early April 1997, the patient was re-admitted to the hospital due to sudden bilateral hearing loss and high fever. Headache, nausea, polyarthralgia and skin rash present in the previous episodes were not found at this time. Laboratory examination revealed elevated levels of CRP and ESR with a normal WBC. Administration of 60 mg prednisolone daily improved fever and normalized the elevated CRP and ESR. Then, the patient was transferred to our department in May 1997.

Upon admission to our department, routine laboratory data were normal. Serological tests were all negative, including anti-DNA antibodies, anti-extractable nuclear antigen antibodies, anticardiolipin antibodies, rheumatoid factor, and P- and C- ANCA. Serological tests for syphilis were also negative, and total hemolytic complement level and serum immune complexes were within normal range.

Pure tone audiogram taken in May (Fig. 2B) showed improvement in the right ear compared with that taken in April (Fig. 2A) which showed an asymmetric bilateral neurosensorial hearing loss, moderate in the right ear and mild in the left ear. Tympanic membranes were normal. Brain magnetic resonance imaging with contrast enhancement was also normal. Eye examination disclosed bilateral cataracts probably induced by corticosteroid, but no corneal abnormalities. Monthly cyclophosphamide pulse therapy 700 mg combined with oral prednisolone was instituted since the patient had relapsed several times. This combination therapy enabled the successful tapering of prednisolone without recurrence of hearing loss at last follow up one year later.

DISCUSSION

Although the present case is somewhat atypical, a diagnosis of Cogan’s syndrome was made based on the presence of bilateral neurosensorial hearing loss of unknown etiology in association with high fever, headache, polyarthralgia and skin rash. Reversal of neurosensorial hearing loss with corticosteroids and combined pulse cyclophosphamide therapy support the diagnosis. Cogan’s syndrome is usually characterized by the presence of both nonsyphilitic interstitial keratitis and neurosensorial hearing loss. Initial symptoms of typical Cogan’s syndrome may be either ocular or vestibular, and in the majority of patients both organs are affected within one year of onset. In addition to involvement of the eyes and ears, some patients with Cogan’s syndrome develop systemic, neurologic, and vasculitic complications. Systemic complications including fever, fatigue, arthralgia, myalgia, rashes, headache and gastrointestinal symptoms develop in 70% of patients, more frequently in atypical Cogan’s syndrome. Neurologic complications including headache, seizure, strokes, and coma occur in about 10% of patients, and are considered to be caused by vasculitis. Vasculitis affecting various sizes of vessels occurs in 10% of patients, and aortic insufficiency is the most serious complication
of Cogan’s syndrome. Based on these reported clinical characteristics, the present case was diagnosed as an atypical Cogan’s syndrome, beginning with systemic complications and followed by neurosensory hearing loss. Systemic complications and laboratory findings of Cogan’s syndrome resemble adult-onset Still’s disease which, therefore, should be distinguished from atypical Cogan’s syndrome.

Previous reports have suggested autoimmune mechanisms for the pathogenesis of Cogan’s syndrome, since lymphocyte infiltration in the affected tissues and serum antibodies against inner ear and corneal antigens are often found. Successful treatment for Cogan’s syndrome with high-dose corticosteroids has been achieved, while additional immunosuppressive agents including azathioprine, cyclophosphamide, cyclosporine, FK506, and methotrexate have been used in severe cases. To improve hearing loss or to prevent deafness, early start of treatment with high-dose corticosteroids has been recommended. In our case, early treatment with prednisolone, 60 mg/day (1.2 mg/kg body weight), successfully improved hearing loss, and combined monthly pulse cyclophosphamide enabled successful tapering and discontinuance of prednisolone. Establishing the best therapeutic regimen for Cogan’s syndrome will be difficult since randomization for the treatment of this rare and serious syndrome could not be done. Combined corticosteroid and pulse cyclophosphamide therapy, as has been used for generalized vasculitis, would appear to be one effective regimen for Cogan’s syndrome, although one case with lack of response to combination therapy has been reported.

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REFERENCES

7. Richardson B, Methotrexate therapy for hearing loss in Cogan’s syndrome. Arthritis