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Case Report

Scleroderma-like Manifestation in a Patient with Primary Systemic Amyloidosis: Response to High-dose Intravenous Immunoglobulin and Plasma Exchange

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A 54-year-old Korean male with scleroderma-like manifestation of primary systemic amyloidosis presented with firm cutaneous induration of face and distal extremities, subcutaneous induration of the trunk and proximal extremities, limited range of motion in all joints, hoarseness, and dysphagia. Monthly high-dose intravenous immunoglobulin (hdIVIg) was given (three treatments, each time administering 0.4 g/kg per day for five days), and both signs and symptoms began to improve. However, the quantitative analyses of serum protein did not improve. Therapeutic plasma exchange (TPE) was performed monthly to clear the elevated serum immunoglobulin, and after several treatments, their levels normalized and symptoms were maintained in the improved state for more than two years. To summarize, hdIVIg and TPE combination therapy may be used as a safe first-line treatment for patients with primary systemic amyloidosis presenting with symptomatic monoclonal gammopathy.

Key Words: Amyloidosis, plasma exchange

INTRODUCTION

Amyloidosis refers to a heterogeneous group of disorders characterized by extracellular deposition of proteinaceous fibrillar materials (termed amyloid) in various tissues and organs.[1] It can be divided into two major forms: amyloid light chain (AL) amyloidosis and amyloid A amyloidosis.[2] Clinical skin involvement occurs in approximately 25% of patients with AL amyloidosis,[3] and common manifestations include petechiae, purpura, ecchymoses, papules, nodules, plaques, and tumefactive lesions; a scleroderma-like manifestation is rarely seen.[4,5]

Therapeutic plasma exchange (TPE) has been proven to be an effective treatment in patients showing monoclonal gammopathy.[6] We applied TPE to treat an AL amyloidosis patient with scleroderma-like manifestations because the amyloids in AL amyloidosis are derived from the monoclonal immunoglobulin light chains produced by plasma cells.

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CASE REPORT

A 54-year-old Korean male was first referred to our department on October 4, 2001, with a history of hoarseness, difficulty in swallowing, and progressive generalized hardening of the body that had progressed over the past two years. The skin on his face and distal extremities was indurated, and several brownish and shiny papules were noted on the forehead and perioral area. On the trunk and proximal extremities, the skin was normal in elasticity, but the underlying muscles were indurated, and almost all of the joints were restricted in motion (Fig. 1A, Table 1). Quantitative analyses of serum protein revealed concentrations of immunoglobulin G (IgG) of 1,780 mg/dl and kappa (κ) light chain of 532 mg/dl (the normal ranges are 700-1,600 mg/dl and 170-370 mg/dl, respectively). Serum immunofixation showed a

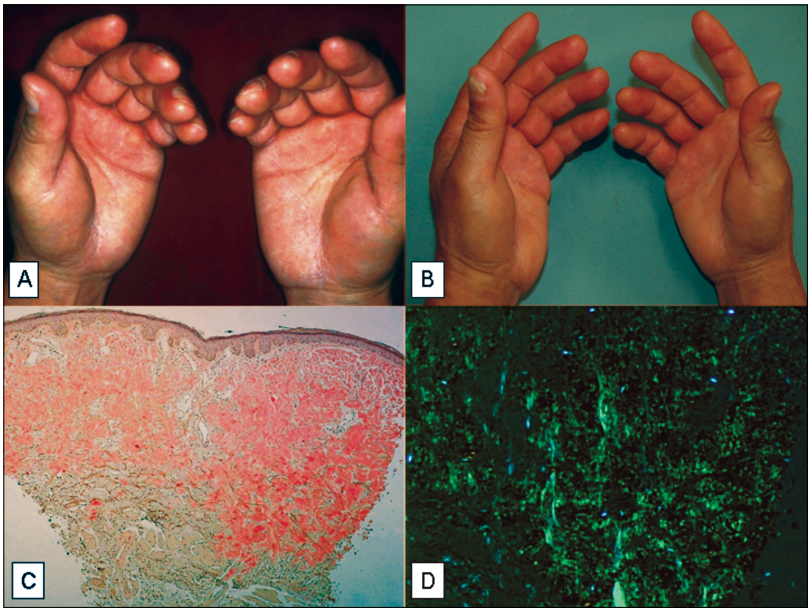

Fig. 1. (A) Joints are severely restricted in motion when fingers are fully extended. (B) Marked improvement in the range of motion three weeks after the 3rd hdIVIg therapy. (C) Biopsy from the lip shows pinkish amorphous homogeneous masses of amyloid in dermis, subcutaneous tissue, and muscle (Congo red stain; original magnification × 40). (D) Congo red stain produces apple-green birefringence under a polarized light microscope (original magnification× 40).

characteristic pattern of monoclonal IgG gammopathy, particularly of κ paraprotein. Laryngoscopic examinations revealed granulomatous materials deposited in the vocal cords, and nerve conduction studies showed polyneuropathy of the sensory nerves. Impaired left ventricular systolic function and thickening of the left ventricular walls with restrictive filling were noted upon echocardiography. There were no remarkable findings in various studies, including a bone marrow aspiration study, abdominal ultrasonography, and esophagography. The skin biopsy specimens showed a deposition of amyloid materials in the dermis, subcutaneous tissues, and in the connective tissue septae of the skeletal muscle by Congo-red stain (Fig. 1C), and it produced a characteristic apple-green birefringence when viewed under a polarized light source (Fig. 1D).

After failure to control the symptoms with systemic steroids, colchicine, or cyclophosphamide, monthly high-dose intravenous immunoglobulin (hdIVIg) was infused for three courses of treatment (each time giving 0.4 g/kg/day for five days); the patient noted improvement in subjective symptoms such as tightness of legs and dysphagia, and the range of motion of his joints began to improve as early as three weeks after the first treatment (Fig. 1B, Table 1). However, the elevated IgG and κ light chain levels did not decrease, despite the symptomatic changes, and the symptoms progressed with the discontinuation of hdIVIg therapy. Although the patient had no apparent renal dysfunction, the concern of potential renal involvement in systemic amyloidosis and the possibility that hdIVIg would enhance that risk made us decide to discontinue further hdIVIg therapy. To clear the excess serum immunoglobulin, which was constantly elevated despite the hdIVIg therapy, monthly TPE was performed, and the normalized serum immunoglobulin levels and the symptoms and signs, including dysphagia, tightness of legs, induration of skin, and the limited range of motion, were maintained in an improved state for more than two years.

DISCUSSION

Most reports on the treatment of primary and myeloma-associated systemic amyloidosis have been anecdotal, and responses to treatment are difficult to assess because of the poor correlation between amyloid load and organ dysfunction.[7] Cytotoxic chemotherapy is the mainstay of treatment, and melphalan, prednisone, colchicine, penicillamine, azathioprine, vincristine, and cyclophosphamide have been used in the treatment of systemic amyloidosis. Cohen et al.[8] reported that

Table 1. Estimated Range of Motion of the Joints under Passive Movement

Joints	Motion of joints	Range of motion (°)		Normal range
		Before treatment	Three weeks after the 3rd administration	
Elbow	Flexion	0 - 120	10 - 120	0 - 150
	Extension	- 30	- 5	0 - 10
Hand	Flexion of MPJ	30 - 90	0 - 90	0 - 90
	Flexion of PIP	0 - 80	0 - 90	0 - 100
Thumb	Flexion of IP	0 - 50	0 - 50	0 - 80
Hip	Flexion	0 - 105	0 - 110	0 - 120
Knee	Flexion	0 - 120	0 - 125	0 - 135
	Extension	- 20	- 5	0 - 10
Ankle	Dorsiflexion	0 - 10	0 - 10	0 - 20
	Plantar flexion	0 - 15	0 - 30	0 - 50

Data are given in degrees unless otherwise indicated.
MPJ, Metacarpophalangeal joint; PIP, Proximal interphalangeal joint; IP, Interphalangeal joint.

colchicine was found to improve life expectancy in 53 patients with AL amyloidosis. Erikkson et al.[9] proposed the therapeutic implications of α1-antitrypsin. More aggressive chemotherapy, myeloablation, and autologous bone marrow transplantation have been proposed as novel therapeutic approaches.[10,11] Immunotoxins directed against the precursors of the amyloidogenic plasma cells are under investigation.[9] Conflicting evidence exists concerning vitamin C and vitamin E.[7] Merlini et al.[10] showed that doxorubicin derivatives play a role in enhancing the resorption of AL amyloid *in vitro* and in murine models.

HdIVIg has increasingly been used for the treatment of certain dermatoses, such as bullous autoimmune diseases and erythema multiforme.[12] Lister et al.[13] reported two patients with scleromyxedema who showed a dramatic response to treatment with hdIVIg. Krastev et al.[14] reported a case of gastrointestinal amyloidosis showing clinical improvement with hdIVIg treatment, as in our case.

Although the majority of cases reported to date show an absence of or only slight adverse side-effects with hdIVIg, it is suggested that hdIVIg therapy may enhance the risk of adverse side-effects, and should be carefully considered in patients with pre-existent diseases such as congestive heart failure, immobilization, or renal insufficiency.[15] In addition, dysproteinemia due to hdIVIg therapy itself may result in cast nephropathy and renal failure. Although the patient had no apparent renal dysfunction, to avoid potential renal involvement in systemic amyloidosis and other possible risks of hdIVIg, we decided against further hdIVIg therapy. Also, considering that hdIVIg could not effectively reduce the level of serum paraprotein, TPE seemed to be an effective and safe alternative for removing the paraproteins, which is ultimately necessary to prevent disease progression. TPE is regarded as being less effective than hdIVIg therapy for the treatment of amyloidosis. However, it is effective in patients with symptomatic monoclonal gammopathy because it removes the paraproteins very efficiently, particularly in patients who do not respond to drug therapy.[4]

In conclusion, hdIVIg and TPE combination therapy may be used as a safe first-line treatment for patients with primary systemic amyloidosis presenting symptomatic monoclonal gammopathy. However, long term follow-up is needed to fully elucidate the effects of combination therapy, and the application of these treatments in a larger group of patients is necessary.

REFERENCES

1. Husby G. Nomenclature and classification of amyloid and amyloidoses. J Intern Med 1992;232:511-2.
2. Kyle RA, Greipp PR. Amyloidosis (AL). Clinical and laboratory features in 229 cases. Mayo Clin Proc 1983; 58:665-83.
3. Kyle RA, Bayrd ED. Amyloidosis: review of 236 cases. Medicine (Baltimore) 1975;54:271-99.
4. Breathnach SM. Amyloidosis of the skin. In: Freedberg IM, Eisen AZ, Wolff K, Austen KF, Goldsmith LA, Katz SI, editors. Fitzpatrick's dermatology in general medicine. 6th ed. Vol. 2. New York: McGraw-Hill Companies; 1993. p.1428-35.
5. Lee DD, Huang CY, Wong CK. Dermatopathologic findings in 20 cases of systemic amyloidosis. Am J Dermatopathol 1998;20:438-42.
6. Drew MJ. Plasmapheresis in the dysproteinemias. Ther Apher 2002;6:45-52.
7. Gertz MA, Kyle RA. Amyloidosis: prognosis and treatment. Semin Arthritis Rheum 1994;24:124-38.
8. Cohen AS, Rubinow A, Anderson JJ, Skinner M, Mason JH, Libbey C, et al. Survival of patients with primary (AL) amyloidosis. Colchicine-treated cases from 1976 to 1983 compared with cases seen in previous years (1961 to 1973). Am J Med 1987;82:1182-90.
9. Eriksson S, Janciauskiene S, Merlini G. The putative role of alpha-1-antitrypsin in the disaggregation of amyloid lambda fibrils. J Intern Med 1995;237:143-9.
10. Merlini G. Treatment of primary amyloidosis. Semin Hematol 1995;32:60-79.
11. Comenzo RL, Gertz MA. Autologous stem cell transplantation for primary systemic amyloidosis. Blood 2002;99:4276-82.
12. Schofield JK, Tatnall FM, Leigh IM. Recurrent erythema multiforme: clinical features and treatment in a large series of patients. Br J Dermatol 1993;128:542-5.
13. Lister RK, Jolles S, Whittaker S, Black C, Forgacs I, Cramp M, et al. Scleromyxedema: response to high-dose intravenous immunoglobulin (hdIVIg). J Am Acad Dermatol 2000;43:403-8.
14. Krastev Z, Vassilev M. GI amyloidosis treated with megadoses of i.v. gammaglobulin. Hepatogastroenterology 1994;41:204-5.
15. Wittstock M, Benecke R, Zettl UK. Therapy with intravenous immunoglobulins: complications and side-effects. Eur Neurol 2003;50:172-5.