Clin Rheumatol (2006) 25: 396–398
DOI 10.1007/s10067-005-0015-2

CASE REPORT

Yoshihide Asano · Hironobu Ihn · Takeo Maekawa · Takafumi Kadono · Kunihiko Tamaki

High-dose intravenous immunoglobulin infusion in polyarteritis nodosa

Report on one case and review of the literature

Received: 8 February 2005 / Accepted: 10 March 2005 / Published online: 19 October 2005
© Clinical Rheumatology 2005

Abstract We describe a 58-year-old Japanese female who developed polyarteritis nodosa (PN). Her skin disease and systemic symptoms were resistant to dapsone (1.5 mg kg^{-1} day^{-1}), high-dose oral prednisone (1 mg kg^{-1} day^{-1}) and azathioprine (2 mg kg^{-1} day^{-1}), and intravenous cyclophosphamide pulse therapy (10 mg kg^{-1} day^{-1}). She was ultimately treated with infusion of high-dose intravenous immunoglobulin (IVIG) at a dose of 0.1 g kg^{-1} daily for five consecutive days weekly for a period of 12 weeks, resulting in remission of his cutaneous and systemic symptoms and successful tapering of his prednisone and azathioprine dose. However, 12 months later, relapsing fever and polyarthritis recurred, and eventually, 24 months later, indurated erythema and punched-out ulcers appeared on the lower legs. These symptoms were reduced after increasing the dose of oral prednisone (1 mg kg^{-1} day^{-1}). Our case indicates that the high-dose IVIG infusion therapy may be useful for controlling PN in certain periods since the long-term observation revealed deterioration of symptoms. We review related articles and discuss its effectiveness in PN.

Keywords High-dose intravenous immunoglobulin infusion · Polyarteritis nodosa

Y. Asano · T. Maekawa · T. Kadono · K. Tamaki
Department of Dermatology, Faculty of Medicine,
University of Tokyo,
7-3-1 Hongo, Bunkyo-ku,
Tokyo, 113-8655, Japan

H. Ihn (✉)
Department of Dermatology & Plastic and Reconstructive Surgery, Faculty of Medical and Pharmaceutical Sciences,
Kumamoto University,
1-1-1 Honjo, Kumamoto-city,
Kumamoto, 860-8556, Japan
e-mail: ihn-der@kaiju.medic.kumamoto-u.ac.jp
Tel.: +81-96-3735233
Fax: +81-96-3735235

Introduction

Polyarteritis nodosa (PN) is a rare autoimmune disease characterized by spontaneous inflammation of the arteries of the body. Because arteries are involved, the disease can affect any organ of the body. The most common areas of involvement include the muscles, joints, intestines, nerves, kidneys, and skin. Poor function or pain in any of these organs can be a symptom. Since the disease course is chronic and life-threatening exacerbations are frequent, the prolonged use of immunosuppressive drugs, such as corticosteroids, cyclophosphamide, and azathioprine, has been an established form of therapy [1].

In recent years, the benefits of high-dose intravenous immunoglobulin (IVIG) have been described for a variety of autoimmune diseases, including PN [2–6]. We herein report a case of PN, which we treated with IVIG, with a temporary response. We review related articles and discuss its effectiveness in PN.

Case report

A 58-year-old Japanese female was admitted to our department with nonhealing, punched-out ulcers on the lower legs in January of 1999. She had been treated with oral prednisone for 2 years against pain, burning, paresthesia, and numbness of extremities due to an unclassified vasculitis, which was diagnosed by peripheral nerve biopsy. On physical examination, she presented with fever, polyarthritis, and myalgia in addition to sensory changes. There were lots of livedo reticularis, bean-sized indurated erythema and punched-out ulcers, and scarring on the toes, forefeet, and distal lower legs.

Laboratory investigations revealed a white blood cell count of 8.3×10^4 mm^{-3} (neutrophils 88.0%, basophils 0%, eosinophils 0%, lymphocytes 10.0%, monocytes 2.0%), hemoglobin 12.6 g dl^{-1}, a platelet count of 27.1×10^4 mm^{-3}, an erythrocyte sedimentation rate of 37 mm h^{-1}, and C-reactive protein concentration of 0.9 mg dl^{-1} (normal <0.3). Complement levels were within normal limits. Antinuclear antibody

(ANA) was positive at 1:40 with a speckled pattern. Serum HB_sAg, antineutrophil cytoplasmic antibody, anti-Parvovirus B19 IgM, and antistreptolysin O titer were negative. Liver enzymes were within normal limits. Urine analysis and renal function tests were normal. Coagulation profile including antiphospholipid antibody did not reveal any abnormality. Ultrasonography of the abdomen and echocardiogram were normal. Incisional skin biopsy obtained from indurated erythema revealed a leukocytoclastic vasculitis involving medium size deep dermal arteries, thrombosis of small arterioles, and fibrinoid necrosis. Visceral angiography performed at this point showed multiple microaneurysm and caliber irregularities in the arterial supply of the liver, spleen, pancreas, intestine, and kidneys. Based on these findings, she was diagnosed as having PN.

She was firstly treated with dapsone (1.5 mg kg^{-1} day^{-1}) for 2 weeks with no efficacy. After stopping dapsone, high-dose oral prednisone (1 mg kg^{-1} day^{-1}) was introduced, and 2 months later, oral azathioprine (2 mg kg^{-1} day^{-1}) was added. One month later, in addition to the administration of these drugs, she was treated with two courses of intravenous cyclophosphamide pulse therapy (10 mg kg^{-1} day^{-1}) within a 4-week interval, but new lesions continued to appear during the treatments. In August of 1999, in addition to high-dose oral prednisone and azathioprine, she received infusion of IVIG at a dose of 0.1 g kg^{-1} daily for five consecutive days weekly for a period of 12 weeks. After the completion of first course of IVIG, fever, polyarthritis, and ulcers on lower legs were dramatically improved, and ulcers were completely healed in 4 weeks. After the completion of IVIG therapy, oral prednisone and azathioprine were gradually tapered to 0.2 mg kg^{-1} day^{-1} and 1 mg day^{-1}, respectively. Although sensory changes were persistent, fever, polyarthritis, and new skin lesions were not observed for 2 years in the follow-up periods. However, from January of 2002, relapsing fever and polyarthritis recurred, and eventually in January of 2003, indurated erythema and punched-out ulcers appeared on the lower legs. These symptoms were reduced after increasing the dose of oral prednisone 1 mg kg^{-1} day^{-1}.

Discussion

So far, six cases of PN treated with IVIG have been reported [2–6]. We summarized the clinical features of these cases and our case in Table 1. Four cases including the present case were diagnosed as having systemic PN, and three cases as having cutaneous PN. The possible association between the onset of PN and the persistent bacterial or viral infection was observed in five cases: three cases with Parvovirus B19 infection and two with streptococcal infection. Five cases excluding case no. 4 and no. 6 were resistant to the immunosuppressive treatments. Case no. 4 was not treated with the immunosuppressive reagents, but treated with prophylactic penicillin because this case appeared to associate with streptococcal infection. Case no. 6 was treated only with IVIG. In all cases, the symptoms were rapidly and dramatically improved after the first administration of IVIG. In five cases, no recurrence was observed in the follow-up periods ranging from 12 to 36 months. In contrast, the symptoms recurred in case No. 5 and the present case at 7 and 24 months after the completion of IVIG therapy, respectively. Noticeably, all of five cases with a complete remission had possible association between the onset of PN and bacterial or viral infection.

To date, various mechanisms of action for IVIG in autoimmune disorders have been postulated, such as the blockade of Fcγ receptors on reticuloendothelial cells, alteration of T and/or B cell function, and the provision of anticytokine antibodies that alter the immune response and lead to the down-regulation of the immune response [7]. It

Table 1 Summary of the clinical features of PN treated with intravenous immunoglobulin infusion

Cases	Authors	Age/sex	Diagnosis	Cause	Prognosis	Follow-up (months)	Total dose	Previous treatments
1	Finkel et al. [2]	5 males	PN	Parvovirus B19	CR	36	6 g kg^{-1} (2 g kg^{-1}×3)	Prednisone, azathioprine, cyclophosphamide
2	Finkel et al. [2]	16 females	PN	Parvovirus B19	CR	20	1.2 g kg^{-1} (1.2 g kg^{-1}×1)	Prednisone, cyclophosphamide
3	Gedalia et al. [3]	2 males	PNc	Streptococcal infection	CR	18	2 g kg^{-1} (1 g kg^{-1}×2)	Prednisone
4	Uziel and Silverman [4]	9 males	PNc	Streptococcal nfection	CR	12	4 g kg^{-1} (2 g kg^{-1}×2)	Prophylactic penicillin
5	Kroiss et al. [6]	57 males	PNc	–	Recurrence	8	13 g kg^{-1} (2 g kg^{-1}×6, 1 g kg^{-1}×1)	Prednisone, methotrexate, mycophenolate mofetil
6	Viguier et al. [5]	33 females	PN	Parvovirus B19	CR	36	2 g kg^{-1} (2 g kg^{-1}×1)	None
7	The present case	58 females	PN	–	Recurrence	36	6 g kg^{-1} (0.5 g kg^{-1}×12)	Prednisone, azathioprine, cyclophosphamide

PN Polyarteritis nodosa, *PNc* cutaneous polyarteritis nodosa, *CR* complete remission

is possible that in PN, IVIG prevents vasculitis by binding to the Fcγ receptor, thus preventing immune complex deposition in the vessels, or by neutralization of the anti-endothelial antibodies that may cause the inflamed vasculitis through its anti-idiotypic antibodies. In addition to these immunomodulatory effects, IVIG is an excellent source of Parvovirus B19-specific IgG and antibodies to streptococcal superantigens. As described above, a complete remission was achieved by IVIG therapy in patients with PN associated with Parvovirus B19 infection or streptococcal infection, while its effect was temporary in patients with PN unassociated with these infections. Taken together, it is postulated that the effect of IVIG therapy on PN is temporary, but in situation that PN is induced by infections, IVIG therapy leads to a complete remission of the disease due to the neutralization of immune activation triggers, such as Parvovirus B19 and Streptococcus.

In summary, our case indicates that the IVIG therapy may be useful for controlling PN in certain periods since the long-term observation revealed deterioration of symptoms. Taken together with previous reports, we suggest that IVIG is an important adjunct in selected patients with PN, especially PN associated with bacterial or viral infections.

References

1. Guillevin L, Le Thi Huong D, Godeau P, Jais P, Wechsler B (1988) Clinical findings and prognosis of polyarteritis nodosa and Churg–Strauss angiitis: a study in 165 patients. Br J Rheumatol 27:258–264
2. Finkel TH, Torok TJ, Ferguson PJ, Durigon EL, Zaki SR, Leung DY, Harbeck RJ, Gelfand EW, Saulsbury FT, Hollister JR et al (1994) Chronic parvovirus B19 infection and systemic necrotising vasculitis: opportunistic infection or aetiological agent? Lancet 343:1255–1258
3. Gedalia A, Correa H, Kaiser M, Sorensen R (1995) Case report: steroid sparing effect of intravenous gamma globulin in a child with necrotizing vasculitis. Am J Med Sci 309:226–228
4. Uziel Y, Silverman ED (1998) Intravenous immunoglobulin therapy in a child with cutaneous polyarteritis nodosa. Clin Exp Rheumatol 16:187–189
5. Viguier M, Guillevin L, Laroche L (2001) Treatment of parvovirus B19-associated polyarteritis nodosa with intravenous immune globulin. N Engl J Med 344:1481–1482
6. Kroiss M, Hohenleutner U, Gruss C, Glaessl A, Landthaler M, Stolz W (2001) Transient and partial effect of high-dose intravenous immunoglobulin in polyarteritis nodosa. Dermatology 203:188–189
7. Ballow M (1997) Mechanisms of action of intravenous immune serum globulin in autoimmune and inflammatory diseases. J Allergy Clin Immunol 100:151–157