

Case report

Long-term efficacy of intravenous immunoglobulin in a case of polymyositis with limited application of steroid therapy

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Running title: IVIG in a case of PM with limited steroid therapy

Abstract

A 72-year-old man who had been diagnosed with polymyositis (PM) was admitted to our hospital for pneumonia with exacerbation of muscle weakness, elevation of muscle enzymes, and positive MRI findings. The patient had been refractory to cyclosporine A or azathioprine and hoped to avoid administration of high-dose steroids; intravenous immunoglobulin (IVIG) was therefore administered after improvement of the pneumonia. Two weeks after the IVIG therapy, muscle test scores, activities of daily living, and muscle enzymes were drastically improved. Twenty months after IVIG, no relapse of PM was observed.

Key words: intravenous immunoglobulin, polymyositis, immunosuppressive therapy, prednisolone

Introduction

Polymyositis (PM) is classified as an inflammatory myopathy and is usually responsive to corticosteroid monotherapy (1). Various immunosuppressive agents such as azathioprine or methotrexate are used (2) on occasions when responsiveness to corticosteroid therapy is poor. In addition to these agents, calcineurin inhibitors including cyclosporine A (CyA) and tacrolimus can also be applied (3). Wiendl (1) recommends corticosteroids as the first line of defense against PM, and intravenously administered immunoglobulin (IVIG) therapy should be employed when patients show no response to corticosteroids/azathioprine (AZP). In the case of difficulties with immunosuppressive agents, IVIG therapy is often performed as an alternative therapy, although there has been no prospective, doubleblind, placebo-control study of PM. In this case, we show the long-term efficacy of IVIG in a patient in whom increased corticosteroids therapy could not be applied.

Case report

A 72-year-old man who had been diagnosed with PM in 2004 was treated with 10 mg of prednisolone and 150 mg of CyA daily in an outpatient setting. Since May 2007, elevated creatinine kinase (CK) and aldolase (ALD) levels had been observed; the CyA dose was therefore increased to 175 mg daily, with a trough level of 92.57 ng/ml (50-150 ng/ml). Azathioprine (AZP) was added to the CyA in October 2007 because no apparent inhibition of muscle enzymes had occurred. On 26 December 2007, the patient was admitted to our hospital with high fever, cough, and sputum, resulting in a diagnosis of pneumonia. Although he was admitted due to pneumonia, proximal muscle weakness was simultaneously observed without Gottron's sign or heliotrope rash. The patient did not use statins, and redbrown urine that indicates the existence of rhabdomyolysis was not observed. He had also been diagnosed with normal-tension glaucoma and optic atrophy.

Laboratory findings showed an elevated total leukocyte count of 12,000/mm³ and a platelet count of 17.1 x 10⁴/mm³. Aspartate aminotransferase (AST), CK, C-reactive protein (CRP) levels, and KL-6 were elevated to 64 IU/l (normal range <33), 1,193 IU/l (normal range <287), 2.11 mg/dl (normal

range<0.17), and 331 U/ml (normal range<500), respectively. Anti-Jo-1 antibody was negative. Chest X-ray showed consolidation in the right lower lung field without evidence of interstitial pneumonia. Magnetic resonance imaging (MRI) of the lower legs showed high intensity in short tau inversion recovery (STIR), which is consistent with active PM lesion (Fig. 1).

Regarding pneumonia, the responsible bacteria could not be determined via sputum culture and sensitivity. Polymerase chain reaction (PCR) for non-tuberculous mycobacteriosis was negative. Furthermore, beta-D glucan and a test for cytomegalovirus antigen were negative. However, respiratory symptoms, chest X-ray findings, and CRP level were improved by the administration of sulbactam/ cefoperazone.

Because the CK level had increased from 270 to 514 IU/l in May 2007, the dose of CyA was increased from 150 to 175 mg daily, with a trough level of 92.57 ng/ml in June 2008. However, 50 mg of AZP was added when the CK level was increased to 960 IU/l in October 2007. Furthermore, CyA was increased to 200 mg daily in November 2007 because the CK level was elevated to 1207 IU/l. The patient had been suffering from active PM despite administration of 200 mg of CyA for 2 months, with an effective trough level of 116.49 ng/ml and 50 mg

of AZP, leading us to initially consider the use of high-dose corticosteroids. However, he refused the increased dose of corticosteroids or methylprednisolone pulse therapy because he worried about the exacerbation of glaucoma and a subsequent exacerbation of poor visual acuity. On 2 February 2008, IVIG of 30 g (400 mg/kg) a day for 5 days was administered with a continuation of 6 mg of orally administered prednisolone after approval of the ethics committee in our institution and after informed consent from the patient. After IVIG, manual muscle test scores (MMT) (85–88 points; normal: 90 points), activities of daily living (ADL) (36–43; normal: 45 points), and CK levels (CK; 529 IU/l on 12 February 2008) rapidly improved within 2 weeks without any adverse event. In the outpatient setting, CK (CK; 278 IU/l on 26 March 2008) and aldolase levels normalized within a month, and MRI findings were also normal in March 2008 (Fig. 2). Twenty months after IVIG, the muscle enzymes remain in the normal range.

Discussion

Dalakas et al. [4, 5] reported a double-blind, placebocontrolled study of IVIG for dermatomyositis (DM) patients in whom the efficacy and safety of IVIG were clearly determined. For PM, however, there have been only a few retrospective studies with a small number of patients. Recently, Saito et al. [6] demonstrated the efficacy of IVIG for Japanese patients with PM and DM. In this first prospective study, the efficacy of IVIG was shown for both PM and DM without serious adverse events. Serum CK levels were reported to be significantly reduced at 1 month after IVIG administration, a finding that is consistent with our case. Furthermore, long-term effects on CK levels after IVIG were reported, with 50% of patients achieving normal CK levels for more than 300 days. With regard to the longterm effects of IVIG in PM, Cherin et al. [7] previously reported 35 chronic refractory cases of PM. In this study, 12 out of 25 responders to IVIG maintained full remission for 51.4 ± 13.1 months after the initial IVIG. Interestingly, 5 of these 12 patients needed no immunosuppressive agents, whereas 7 patients used a low-dose steroid, implying that one fifth of patients could attain long-term remission by IVIG only. Genevay et al. [8] also reported the efficacy of IVIG for at least 10 months in a case of refractory PM.

They initially used AZP or MTX in the presence of 30 mg/day of orally administered prednisolone; however, these medications were discontinued due to adverse events or inefficiency. Subsequent IVIG induction with 0.8 g/kg per day for 5 days dramatically improved myositis for at least 10 months, suggesting that IVIG could be an optional therapy with long-term efficacy.

Accordingly, a fairly large dose of glucocorticoid has been concomitantly administered in previous studies or reports of IVIG therapy in PM [1–3]. From this perspective, our case can be considered exceptional, as we could not administer high doses of glucocorticoid according to the patient's request. Certainly, an increase of the steroid dose brings clinically significant adverse reactions. Although osteoporosis, diabetes, and hypertension are important events, repeated infection and exacerbation of glaucoma in our patient are noteworthy clinical conditions. Our case may provide novel insight into the use of IVIG therapy for PM patients for whom glucocorticoid treatment may be problematic. However, the efficacy of IVIG in this case should be considered in the presence of CyA and AZP.

In summary, we report a case showing the long-term effects of IVIG in the treatment of PM without relying on high-dose steroids. On occasions when

high-dose steroid therapy is not allowed in an intractable case of immunosuppressant-resistant PM, IVIG can be used as an alternative regime to suppress disease activity.

The authors declare no conflict of interest.

Abbreviations; ADL: activities of daily living, ALD: aldolase, AST: aspartate aminotransferase, AZP: azathioprine, CK: creatinine kinase, CyA: cyclosporine A, DM: dermatomyositis, IVIG: intravenous immunoglobulin, MMT: manual muscle test scores, MRI: magnetic resonance imaging, PM: polymyositis, STIR: slow tau inversion recovery

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Figure legends

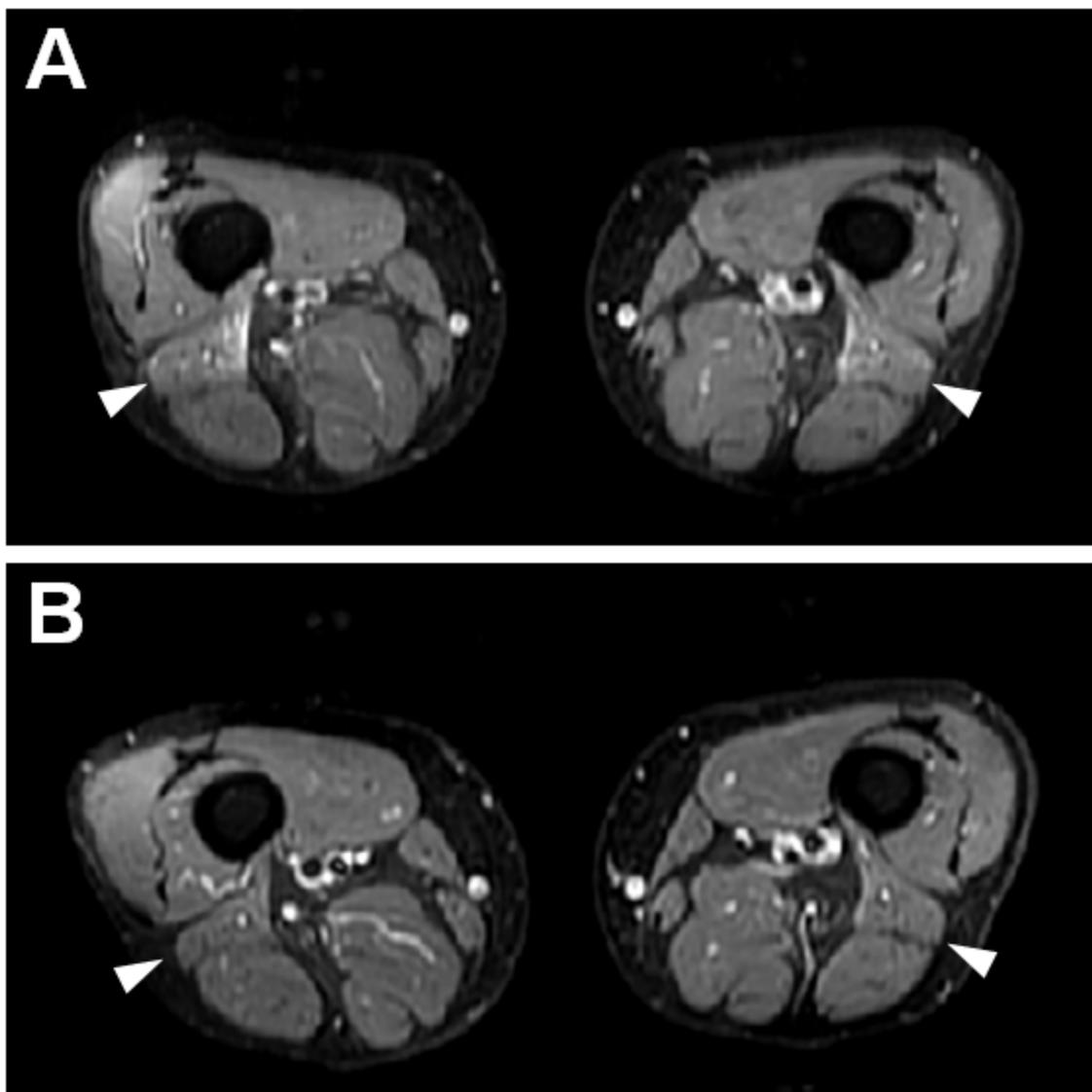


Figure 1

A Magnetic resonance imaging of the biceps femoris muscles (arrowhead) on admission showed high intensity in short tau inversion recovery (STIR), which is consistent with active polymyositis lesion. B After intravenously administered immunoglobulin therapy, high intensity in STIR image was improved

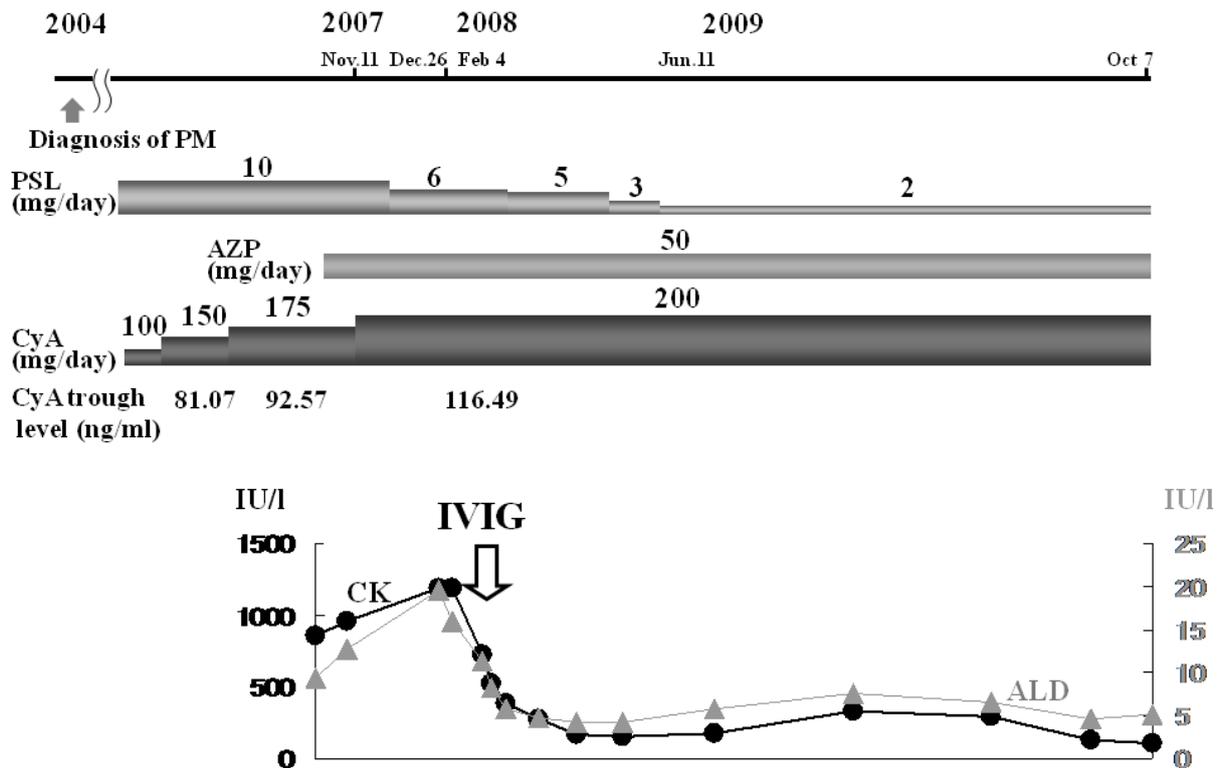


Figure 2

Clinical course during therapy: after diagnosis of polymyositis (PM), 10 mg of orally administered prednisolone and cyclosporine A (CyA) were given. The trough level of CyA was increased from 81.07 to 92.57 ng/ml by administration of 175 mg of CyA daily. As muscle weakness and elevation of muscle enzymes were exacerbated in November 2007, the patient was admitted to our hospital at that time with pneumonia. When 200 mg of CyA with a trough level of 116.49 ng/ml and azathioprine were not effective in treating the PM, intravenously administered immunoglobulin (IVIG) was used without a dose up of corticosteroids (6 mg daily). After IVIG, long-term improvement was achieved, as confirmed by muscle enzymes and magnetic resonance imaging (MRI) 20 months later. AZP azathioprine, PSL prednisolone, STIR short tau inversion recovery