Combined treatment with prednisolone and tacrolimus for myasthenia gravis with invasive thymoma

Shiroh Miura¹, Koichi Azuma¹, Kazuhiko Yamada¹, Sinzo Takamori², Akihiko Kawahara¹, Kazuhiro Noda¹, Mitsuyoshi Ayabe¹, Masayoshi Kage³, Hisamichi Aizawa¹ and Takayuki Taniwaki⁴

¹Division of Respiratory, Neurology and Rheumatology, Department of Medicine; ²Department of Surgery; ³Department of Pathology, Kurume University School of Medicine, Kurume, Fukuoka, Japan

Abstract

We describe a case of recurrent invasive thymoma associated with myasthenia gravis that responded to combined treatment with prednisolone and tacrolimus. The patient suffered from a myasthenic crisis and received methylprednisolone pulse therapy and partial thymectomy. Low maintenance doses of prednisolone and tacrolimus shrank the size of the invasive thymoma and maintained the patient without any myasthenic symptoms. We stress the usefulness of combined treatment with tacrolimus and prednisolone for invasive thymoma, especially for unresectable tumors.

Key words: Myasthenia gravis (MG); invasive thymoma; tacrolimus; steroid.

Introduction

Thymoma and thymic carcinoma are epithelial thymic neoplasms that account for approximately 30% of anterior mediastinal masses in adults and are most commonly seen in the fifth and sixth decades of life (Casey et al., 2008). Overall, 9.5% of patients with myasthenia gravis (MG) have thymoma (Pascuzzi et al., 1984). Corticosteroids and tacrolimus are effective against MG (Pascuzzi et al., 1984; Tsukaguchi et al., 2005; Taguchi et al., 2006; Ponseti et al., 2007; Ponseti et al., 2008). However, combined administration of these drugs for the treatment of invasive thymoma is not currently established. Here, we report a case of MG associated with invasive thymoma. We discuss the possibility of using this combined therapy for invasive thymoma.

Case report

A 60-year-old man diagnosed as MG (Ossermann Stage IIb) with invasive thymoma (Masaoka Stage IVa) had undergone extended thymectomy, partial pneumonectomy and radiotherapy at 55 years of age. His serum anti-acetylcholine-receptor antibody (AChR Ab) titer was 110 nmol/l (normal, < 0.3 nmol/l). Histological examination revealed a mixed thymoma (Fig. 1A, B). Although a transient myasthenic crisis developed, his symptoms were controlled for approximately 3 years by oral administration of prednisolone (70 mg/2 days) and tacrolimus (3 mg/day). The daily doses of the drugs were tapered off to 1 mg/2 days for prednisolone and 2 mg/day for tacrolimus as maintenance doses. After 1 month of taking these maintenance doses, at the age of 58 years, the patient had a myasthenic crisis and local recurrence of the tumor (Fig. 2; -1 month). His serum AChR Ab titer was 8.9 nmol/l. The patient received methylprednisolone pulse therapy (1000 mg/day for 3 days) and tumor reduction surgery. Histological examination revealed a Type B3 thymoma (Fig. 1C). After the surgery, a regimen of oral prednisolone (30 mg/day) and tacrolimus (3 mg/day) was started. After 2 months, the myasthenic symptoms disappeared. After this combined treatment, the daily dose of prednisolone was tapered off to 3 mg/2 days and a shrinkage of the tumor was observed (Fig. 2). The serum AChR Ab titer decreased to 1.9 nmol/l. The patient remains in remission with low-dose combined administration of prednisolone and tacrolimus.

Discussion

We describe a case suffering from systemic MG with recurrent invasive thymoma. The patient underwent partial tumorectomy for the invasive thymoma, followed by maintenance therapy using a low dose...
of tacrolimus in addition to a low dose of corticosteroids, which resulted in both remission of the myasthenic symptoms and a reduction in the tumor size.

Corticosteroids are effective against myasthenic symptoms, and their major effects are anti-inflammation and induction of apoptosis in immune cells (Pascuzzi et al., 1984; Ponseti et al., 2007). Tacrolimus also leads to a reduction in myasthenic symptoms (Utsugisawa et al., 2003; Ponseti et al., 2008). Tacrolimus exerts its immunosuppressive effects by inhibiting the expressions of cytokines in activated T cells through binding to FK-binding protein and blocking calcineurin phosphatase (Liu et al., 1991; Schreiber and Crabtree, 1992; McCaffrey et al., 1993). Moreover, early post-thymectomy administration of tacrolimus combined with prednisone is more effective than prednisone alone for the consolidation of complete stable remission in a shorter period of time in patients with MG (Ponseti et al., 2007). On the other hand, no significant difference in the clinical severity scores was observed between MG patients taking or not taking oral prednisolone before receiving tacrolimus (Utsugisawa et al., 2003). In our case, the myasthenic symptoms gradually improved with combined treatment of low, but certain, doses of prednisolone and tacrolimus.

A multimodality therapy, including neoadjuvant chemotherapy, surgery, adjuvant radiation therapy and chemotherapy, should be considered in patients
who have locally advanced and unresectable thymoma (Casey et al., 2008). Although the exact treatment regimen for thymic carcinoma is unclear, platinum- and doxorubicin-based regimens are currently the standard care for advanced-stage thymoma (Casey et al., 2008; Girard et al., 2009). In our case, combined treatment with prednisolone and tacrolimus induced shrinkage of an unresectable invasive thymoma. Corticosteroids for the treatment of thymoma are not currently the standard care (Casey et al., 2008). However, corticosteroid doses of ≥ 30 mg/day lead to a reduction in the tumor size of invasive thymoma (Kirkove et al., 1992; Taguchi et al., 2006). The effects of tacrolimus on oncogenesis are complex, and there are some cases which tacrolimus induces tumor progression. Conversely, tacrolimus was found to both prevent angiogenesis, which may limit tumor invasion and dissemination, and induce apoptosis (Buell et al., 2005). Only one case was previously described in which combined corticosteroid and tacrolimus therapy induced invasive thymoma regression (Taguchi et al., 2006). In the previously described case and the present case, recurrence happened during either monotherapy of prednisolone (20 mg/2 days) or combined therapy of prednisolone (1 mg/2 days) and tacrolimus (2 mg/day). On the contrary, remission could be obtained by the combined therapy of prednisolone (either 15 mg/day or 3 mg/2 days) associated with tacrolimus (3 mg/day), respectively. These findings suggest that combined low, but certain, doses of prednisolone and tacrolimus are necessary to control invasive thymoma in MG.

In conclusion, combined therapy with prednisolone and tacrolimus is suggested to be useful for the treatment of invasive thymoma. Further studies are needed to clarify the effective doses for invasive thymoma.

REFERENCES


Shiroh Miura
Division of Respiratory, Neurology and Rheumatology,
Department of Medicine,
Kurume University School of Medicine,
67 Asahi-machi, Kurume,
Fukuoka, 830-0011 (Japan).
E-mail: shiroh46@med.kurume-u.ac.jp

COMBINED TREATMENT WITH PREDNISOLONE AND TACROLIMUS FOR MYASTHENIA GRAVIS                   109