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

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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 thymomectomy. 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, pericardiectomy, partial right pneumonectomy and radiotherapy at 55 years of age. His serum anti-acetylcholine-receptor antibody (AChRAb) 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 AChRAb 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/2days and a shrinkage of the tumor was observed (Fig. 2). The serum AChRAb 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

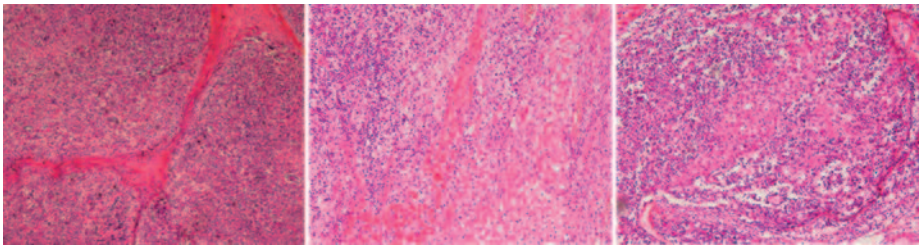

FIG. 1. — (A) Histologically, the tumor shows a typical appearance with a predominant lymphoid component and lobulation separated by fibrosis (original magnification × 40). (B) The tumor has a biphasic cell population, comprising small round lymphocytes mixed with epithelial cells (original magnification × 100). (C) The recurrent thymoma has a biphasic cell population with necrosis (original magnification × 100).

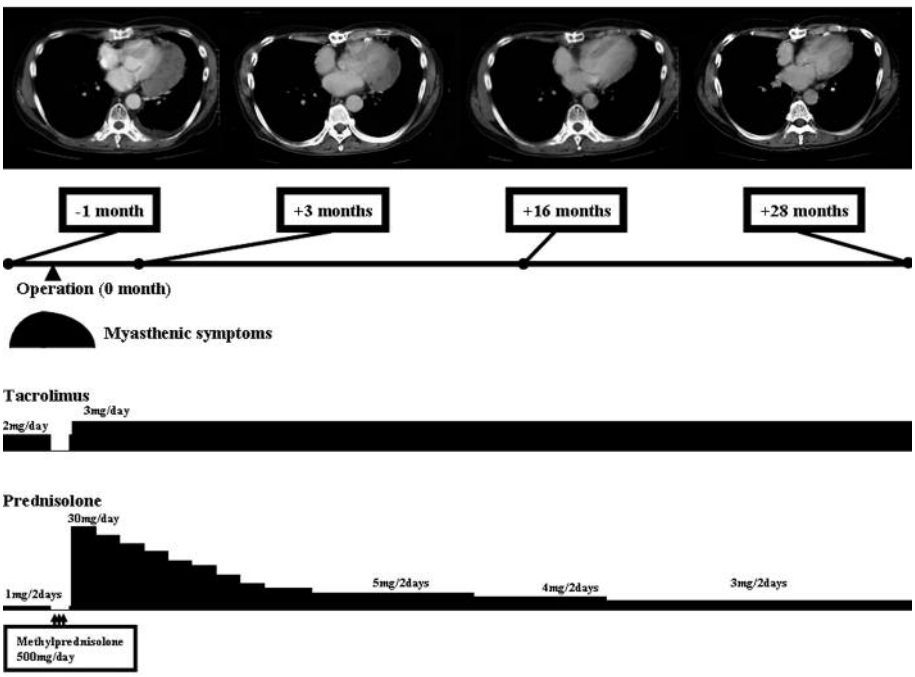

FIG. 2. — Clinical course. Serial computed tomography scans of the chest show that the left paracardiac invasive thymoma has almost disappeared after combined therapy with prednisolone and tacrolimus.

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 tecrolimus 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 $\geq$ 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 angioinvasion, 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.

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