Refractory Recurrent Thymoma Successfully Treated with Long-acting Somatostatin Analogue and Prednisolone

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Abstract

The patient was 54-year-old woman diagnosed as recurrent invasive thymoma (type B3; WHO classification). Although partial response was obtained by systemic chemotherapy (PAC: cisplatin, doxorubicin, cyclophosphamide), the tumor started to become enlarged after cessation of chemotherapy. Combined treatment of octreotide and prednisolone was administered because various chemotherapies, including PAC, were not effective. After seven months, the tumor size was markedly decreased. The combination of octreotide and prednisolone should be considered as one of the choices of treatment in patients with recurrent thymoma.

Key words: octreotide, prednisolone, somatostatin analogue, thymoma

(Inter Med 48: 1061-1064, 2009)
(DOI: 10.2169/internalmedicine.48.1922)

Introduction

It has been reported that several combination chemotherapies, such as PAC (cisplatin, doxorubicin, and cyclophosphamide) (1) and ADOC (doxorubicin, cisplatin, vincristine, and cyclophosphamide) (2, 3), are effective for patients with locally advanced or recurrent thymomas. However, the standard treatment for recurrent cases already treated with PAC and ADOC remain controversial. Although there has been a few cases successfully treated with newly developed anticancer agents, such as paclitaxel (4) and docetaxel (5), there is not enough data to analyze whether or not these regimens can be justified as the standard treatment for patients with recurrent thymoma.

Recently, it has been reported that combined treatment with somatostatin (SST) analogue and prednisolone is effective for patients with recurrent thymoma (6-9). However, there are no cases reported for thymoma treated with octreotide in Asian countries. We herein present a case with refractory recurrent thymoma, which was successfully treated with the combination therapy of octreotide, somatostatin analogue, and prednisolone.

Case Report

A 54-year-old woman presented with left ptosis, articulation disturbances and muscle weakness of right upper extremity in October 1981. After undergoing several examinations, she was diagnosed as myasthenia gravis (MG) at a different institution. Thoracic computed tomography (CT) revealed an anterior mediastinal tumor suggestive of thymoma. However, surgical resection was not performed due to refusal to consent for surgery. On March 1991, she was referred to our hospital for surgical resection of the thymoma. Extended thymectomy with partial resection of left upper lobe, S3, was performed. The diagnosis for invasive thymoma, WHO classification type B3, was established and clinical stage was classified as III according to the Masaoka staging system. Then, she received postoperative thoracic radiotherapy consisting of a total dose of 50 Gy. During the follow-up period, she was readmitted and referred to our department due to exacerbation of dyspnea on exertion and orthopnea in February 2004. A chest radiograph revealed increased left pleural and pericardial effusion. Furthermore, a thoracic CT identified the presence of multiple pleural nodules and mediastinal lymphadenopathy. We performed a nee-

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Received for publication December 6, 2008; Accepted for publication February 20, 2009
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Figure 1. Pathological finding of the disseminated pleural nodule revealing the polygonal-shaped epithelial cells (Hematoxylin and Eosin staining, ×100).

Figure 2. Chest radiograph revealed multiple nodular lesions in the left lung field (2A). Thoracic computed tomography (CT) revealed multiple disseminated pleural nodules (2B).

Figure 3. Chest radiograph revealed multiple nodular lesions in the left lung field (3A). Thoracic computed tomography (CT) revealed multiple disseminated pleural nodules (3B).

Discussion

Octreotide is a synthetic octapeptide SST analogue, which acts for a longer period compared to the naturally occurring SST. SST is polypeptide hormone consisting of 14 amino acids and its receptors are expressed in various tissues, including hypothalamus, cerebral cortex, gastrointestinal tracts, pancreas, as well as the thymus (9-11). SST inhibits the release of the following hormones: growth hormone from the pituitary gland, glucagon and insulin from the pancreas, and gastrin, VIP (vasoactive intestinal polypeptide), and secretin from the gastrointestinal tracts, thyroid releasing hormone and so on. Among the five kinds of SST receptors (SST1 to 5), SST2 is generally identified in various human tumor tissues (12, 13). Additionally, octreotide is known to have strong affinity to SST2 and SST5 receptors. Secretion of SST is result of the binding of octreotide to the SST receptor, however, it does not bind to the receptors of the normal thymic epithelial cells. To support this, octreotide has a direct anti-tumor effect for several cancer cell lines, including breast cancer and gastric cancer (14).

Although the detailed mechanism of the anti-tumor effect...
of octreotide for thymomas is not fully understood, it has been reported that SST has antiproliferative effects associated with 1) inhibition of growth factors, such as insulin-like growth factor-1 (IGF-1) and epidermal growth factor (EGF), 2) activation of immunity and 3) inhibition of tumor vessel angiogenesis (14).

Since Palmieri G et al first reported the effectiveness of the combined treatment of octreotide with prednisolone in 1997 (15), several similar cases have been reported in the literature (6, 8). However, the detailed mechanism of the synergy effect of prednisolone with octreotide remains unclear. In the present case, anti-tumor effect of octreotide was not sufficient and an additional administration of prednisolone appeared to be effective. Most cases describing the dramatic response of thymomas to glucocorticoid alone are classified B1 subtype, which contain numerous lymphocytes (16, 17). The present case was classified as WHO classification B3, containing few lymphocytes. Therefore, steroid therapy generally is not speculated to be effective in our case. Why was octreotide effective in our case? It has been revealed that human thymic epithelial cells have glucocorticoid receptors in vitro (18) and apoptosis is induced in thymic epithelial cells as well as in lymphocytes as a consequence of steroid pulse therapy (19). Moreover, it has been reported that administration of low-dose dexamethasone increases the expression of SST gene in the thymus (20). On the basis of above findings, steroid therapy may have modulated the proliferation of epithelial cells and secretion of hormones from the thymus in our case. However, the patient had already taken prednisolone to treat coexisting MG before commencing octreotide. Therefore, it was difficult to evaluate anti-tumor effect of octreotide alone. Further study to compare prednisolone alone vs. prednisolone plus octreotide is necessary.

In the present case, the dosage of both of octreotide and prednisolone was lower than that used in the previous phase II study (6). When we decided the dosage of octreotide, we took into account her physical size that is apparently smaller than Western people. Moreover, the treatment with octreotide is very expensive because it is not covered by medical insurance in Japan. The present case suggests that the dosage of octreotide can be reduced according to patient’s physical size. Further study to investigate an adequate dosage of octreotide for Asian patients is also needed.

The present case did not undergo octreotide (111-In- diethylenetriamine, pentaacetic acid (DTPA)-D-Phe1-octreotide) scintigraphy to evaluate whether the SST receptors are present or not prior to the commencement of octreotide treatment since this scintigraphy examination is not available in our country. To our knowledge, reported cases treated with octreotide were all examined with this scintigraphy examination and positive uptake of octreotide by the thymic tumors was confirmed (6-9). However, it has been shown that 92.9-100% (21) of these patients with thymoma revealed positive uptake with SST receptor scintigraphy. Moreover, findings of the scintigraphy would be independent of the subtypes of thymic tumors (7, 20). The usefulness of the scintigraphy in predicting the clinical response to octreotide treatment is still controversial in patients with various tumors, including malignant neuroendocrine tumors, pituitary adenoma, and pancreatic carcinoma (22). The response rate of octreotide has not been reported in patients with thymoma, revealing negative uptake with SST receptor scintigraphy. Thus, considering the present situation in Japan, we commenced octreotide therapy without performing SST receptor scintigraphy after obtaining informed consent since it is difficult for the patient to undergo further systemic chemotherapy.

In conclusion, the present case demonstrated that combined therapy with octreotide and prednisolone is to be considered as an effective and tolerable treatment in patients with refractory recurrent thymoma.

### References

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Figure 3. After seven months of treatment with octreotide and prednisolone, both chest radiograph (3A) and CT (3B) revealed a marked decrease in size of the pleural tumors.