Levamisole Aids in Treatment of Refractory Oral Candidiasis in Two Patients with Thymoma Associated with Myasthenia Gravis: Report of Two Cases

Wei-Hao Lai, DDS; Shin-Yu Lu, DDS; Hock-Liew Eng¹, MD

Oral candidiasis is associated with defects in cell-mediated immunity and is common among patients undergoing cytotoxic chemotherapy, or corticosteroid or antibiotic therapy, and those patients seropositive for AIDS and HIV (human immunodeficiency virus). This paper demonstrates the important role of cell-mediated immunity in oral candidiasis in 2 cases of thymoma associated with myasthenia gravis. Both suffered from recurrent oral candidiasis after a thymectomy, radiotherapy, and chemotherapy. There was an initial good response to conventional antifungal therapy, which later became refractory. Lymphocyte subset quantitation showed a T cell deficiency and a decreased CD4/CD8 ratio. Levamisole, an immunomodulator, or an immunopotentiating drug was added as adjunctive therapy in combination with oral nystatin treatment. Oral candidiasis responded favorably, and substantial relief was obtained with a concurrent increase in T cells and the CD4/CD8 ratio. These findings clearly demonstrate a significant role of cell-mediated immunity in oral candidiasis, and that eradication of infection is dependent on the host defense mechanism. (Chang Gung Med J 2002;25:606-11)

Key words: thymoma, myasthenia gravis, oral candidiasis, levamisole.

Opportunistic fungal infections are the major clinical manifestations in immunocompromised hosts.⁴ The thymus gland is the master gland of immunity. Lymphocyte precursors that populate the thymus can develop into various T lymphocytes responsible for cellular immunity. A thymectomy weakens the body's ability to fight infections.⁵ This paper describes 2 patients with malignant thymoma associated with myasthenia gravis who suffered from serious depression of cellular immunity and recurrent oral candidiasis after a thymectomy, chemotherapy, and chest radiotherapy. They initially showed a good response to numerous antifungal medications, including nystatin, ketoconazole, clotrimazole, and fluconazole, but later showed very slow and decreased response to them. For such patients, treatment options are limited because cross-resistance to other available systemic azoles may occur. Intravenous amphotericin B is the only licensed preparation available for this purpose. The obvious disadvantages of amphotericin B, its toxicity and inconvenience of intravenous administration, make the option of an effective orally active agent an attractive one.⁶ These patients' serious intractable causes of severe deficiency of T cells warranted a trial administration of levamisole to promote the number and function of the T cells. They were given levamisole at 150 mg/day for 3 days each week and oral nystatin tablets 1 × 10⁶ U t.i.d. every day. Unexpectedly, they showed dramatic improvement.
within 3–4 weeks of initiation of the 2-drug regimen, and complete remission of signs and symptoms of oral candidiasis occurred within 2 months.

Levamisole, an antihelmintic drug, has attracted interest as an effective agent in diseases in which cellular immune deficiency is suspected. The findings of an increase in helper T cells or in the CD4/CD8 ratio after levamisole treatment can aid in the control of oral candidiasis and restore the efficacy of nystatin. It clearly demonstrates a significant role for cell immunity in oral candidiasis.

CASE REPORT

Case 1

A 32-year-old man visited the Oral Medicine Clinic of Chang Gung Memorial Hospital, Kaohsiung Medical Center in February 1994 because of painful lips, mouth, and throat, and difficulty in swallowing. A review of his medical history revealed that he had been treated for a malignant thymoma associated with myasthenia gravis by undergoing a thymectomy and chest radiotherapy 4 years previously in another hospital. In late 1993, diffuse painful oral mucosa developed and demonstrated no response or became worse to topical steroid or systemic prednisolone therapy in another hospital. Oral examination showed diffuse erosive and erythematous lesion over the panoral mucosa with a few white plaques that could be scrubbed with a cotton roll. Smear study, positive smear culture, and lip biopsy confirmed a chronic ulcer with fungal infection. It responded favorably to nystatin tablets. From 1994 to 1998, he was treated with numerous antifungal medications for recurrent oral candidiasis, including oral nystatin tablets, clotrimazole paste, and ketoconazole tablets. At the beginning of treatment, he responded favorably. After cessation of the medication, he soon experienced another worsening of the oral candidiasis. In early 1998, the signs and symptoms of oral candidiasis remained unchanged (Fig. 1A-D). Comparing his lymphocyte subset populations between Feb. 1994 and Feb. 1998, total T cells had decreased from 56% to 17%, T-helper cells from 26% to 2%, T-suppressor cells from 50% to 7%, and the CD4/CD8 ratio from 0.5 to 0.29, conditions even worse than those commonly found in AIDS patients (Table 1). This fact warranted our trial administration of levamisole to promote the number and function of T cells. He was then given levamisole at 150 mg/day for 3 days each week and oral nystatin tablets 10^6 U t.i.d. Unexpectedly, he showed dramatic improvement within 4 weeks of the initiation of the 2-drug regimen, and complete remission of signs and symptoms of oral candidiasis was seen within 2 months (Fig. 1E-H). After 2 months of lev-
amisole therapy, his total T cells had increased from 17% to 61%, T helper cells (CD4+) from 2% to 22%, T-suppressor cells (CD8+) from 7% to 38%, and the CD4/CD8 ratio from 0.29 to 0.58 (Table 1). The obvious restoration in function and number of T cells made oral nystatin therapy again possible.

### Table 1. Change in Lymphocyte Subset Populations after Levamisole Therapy

<table>
<thead>
<tr>
<th>Levamisole Therapy</th>
<th>Date</th>
<th>CD3+</th>
<th>CD4+</th>
<th>CD8+</th>
<th>CD4/CD8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1 before therapy</td>
<td>Feb. 1994</td>
<td>56%</td>
<td>26%</td>
<td>50%</td>
<td>0.52</td>
</tr>
<tr>
<td></td>
<td>Feb. 1998</td>
<td>17%</td>
<td>2%</td>
<td>7%</td>
<td>0.29</td>
</tr>
<tr>
<td>after therapy</td>
<td>Apr. 1998</td>
<td>61%</td>
<td>22%</td>
<td>38%</td>
<td>0.58</td>
</tr>
<tr>
<td>Case 2 before therapy</td>
<td>Apr. 1999</td>
<td>62%</td>
<td>18%</td>
<td>46%</td>
<td>0.39</td>
</tr>
<tr>
<td>after therapy</td>
<td>Jun. 1999</td>
<td>66%</td>
<td>18%</td>
<td>32%</td>
<td>0.56</td>
</tr>
</tbody>
</table>

However in August 2000, he suffered an attack of recurrent spontaneous pneumothorax, and had progressive dyspnea and dysphagia. The chest CT examination and biopsy confirmed local recurrence of a malignant thymoma with lung and pleural metastases. He was admitted to the Oncology Department for chemotherapy, and a tracheostomy was performed to improve respiration and plasmapheresis for myasthenia gravis. His oral condition remained stable under supplemental therapy with levamisole and nystatin.

### Case 2

A 56-year-old man visited the Oral Medicine Clinic of Chang Gung Memorial Hospital, Kaohsiung Medical Center in April 1999 because of persistent oral candidiasis with pain even after continuous therapy with ketoconazole for 6 months from his primary care physician. A review of his medical history revealed that he had had a malignant thymoma with encasement of a major vessel associated with myasthenia gravis. He had been treated with radiotherapy and chemotherapy following a thymectomy from July to December 1998. The oral candidiasis had developed in October 1998, and antifungal therapy with ketoconazole was given after a smear study and a positive culture. At the start of therapy, the response was dramatic, but poor efficacy was noted 6 months later. Then he was treated with fluconazole for 1 week without improvement. He was referred to the Oral Medicine Clinic for persistent pseudomembranous and erosive candidiasis of the tongue. The diagnosis of oral candidiasis was further confirmed by tongue biopsy. We prescribed levamisole plus nystatin from April 1999. The response was favorable, and substantial relief was obtained after 3 weeks of medication (Fig. 2).

Comparing his lymphocyte subset populations between April and June 1999, the total T cells had increased from 62% to 66%, T-helper cells (CD4+) had remained unchanged (18%), T-suppressor cells (CD8+) had decreased from 46% to 32%, and the CD4/CD8 ratio had increased from 0.39 to 0.56 (Table 1). With intermittent levamisole plus oral nystatin tablet therapy, the patient’s oral candidiasis has been controlled for approximately a year.

**DISCUSSION**

Clinical resolution of refractory oral candidiasis by levamisole plus nystatin has not previously been documented in any paper. This report presents observations in 2 cases of a thymoma associated with myasthenia gravis (MG) who developed severe cell-mediated immunodeficiency after a thymectomy, radiotherapy, and chemotherapy. MG is an autoim-
immune disease that is characterized by anti-acetylcholine receptor antibodies causing episodic muscle weakness and fatigue. MG occurs at all ages, but usually between the ages of 20 and 40 years, when it is often associated with thymic hyperplasia; but it is associated with thymomas in older patients. Some 22.4% of thymoma patients have MG, and 24% of myasthenic patients have thymomas. This high coincidence indicates that thymomas are the main cause of MG. Cholinesterase inhibitors can improve muscle weakness but not the underlying disease, which often progresses unless definitive treatment is provided. So a thymectomy has become a common treatment modality for patients with or without a thymoma.

Thymomas are tumors derived from the epithelial cells of the thymus and are contained in abnormalities like germinal centers. The presence of germinal centers is related to the production of anti-acetylcholine receptor antibodies responsible for the pathogenesis in the thymus of MG patients. If most of the thymus is removed, symptoms in MG patients usually lessen, and in some individuals, disappear completely. Most people, even medical doctors, incorrectly believe that the thymus has finished its role and has become a fat-like disused tissue by the time one becomes an adult. In fact, it is still the cornerstone for modulation of T-lymphocyte maturation even to a very old age. Obviously, this report is an extension of such an observation.

The 2 cases also provide evidence of levamisole efficacy in cellular immune mechanisms by restoring the normal functioning of T lymphocytes, and increasing the ratio of CD4/CD8 by increasing the numbers of T4 lymphocytes (CD4+) or by decreasing the number of T8 lymphocytes (CD8+) in immunocompromised hosts. The improvement in T cell subset populations may explain why the combination of levamisole and nystatin can produce improved results in the management of troublesome oral candidiasis in thymectomized MG patients. It is quite clear that oral candidiasis is strongly associated with defects in cell-mediated immunity, and the final eradication of an infection is dependent on the host defense mechanism.

Candidiasis is an almost universal finding in the patients with severe immunodeficiency of the T cell type. It is, however, not seen in patients with B-cell defects in the absence of concomitant T cell defects. So, Candida infections are found in nearly all AIDS patients with a low CD4+ count. Klein in 1984 reported that candidiasis developed in 12 of 15 patients with AIDS and a CD4/CD8 ratio of less than or equal to 0.51, as compared with none of 4 patients with ratios equal to or greater than 0.60. This phenomenon is in accord with our findings in that the 2 cases in this report had CD4/CD8 ratios of 0.29 and 0.39 and presented with severe refractory oral candidiasis. But their response to an antifungal drug turned out favorably when their CD4/CD8 ratios had increased to 0.58 and 0.56, respectively. This report provides evidence of levamisole efficacy in restoring T cell immunity and helping control oral candidiasis in thymectomy patients.

REFERENCES

Levamisole輔助治療胸腺瘤合併重症肌無力患者之
復發性口腔念珠菌感染：二例報告

賴維顯、盧心玉、邢福柳

口腔念珠菌病是一種機會感染的疾病，可能因局部或全身性抵抗力降低而發病。尤其當人體的細胞免疫能力嚴重缺陷時會導致長期反覆感染。本文所提出的二位胸腺瘤合併重症肌無力患者，在胸腺切除後，都受到復發性口腔念珠菌病的困擾。在單獨使用抗黴菌藥物的前1到3年反應不錯，之後則療效不佳。經評估後發現患者的T細胞有嚴重缺陷，且CD4/CD8比例降低。在投與Levamisole後，患者的T細胞增加，CD4/CD8比例上升，再合併Nystatin的使用得以迅速改善口內症狀。這項發現顯示細胞性免疫力在口腔念珠菌病上扮演重要角色，感染最後的根除並非單靠抗生素，而是靠患者的免疫能力。本文提供Levamisole修復T細胞免疫力的部分證據，並對胸腺切除患者的口腔念珠菌病有效控制。這種合併的治療方式未見於以往的文獻，特此提出報告。(長庚醫誌 2002;25:606-11)

關鍵字：胸腺瘤、重症肌無力、口腔念珠菌感染、Levamisole。