Brief Report

Successful Treatment of a Patient with a Thymoma and Pure Red-Cell Aplasia with Octreotide and Prednisone

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THYMOMAS are rare epithelial neoplasms frequently associated with myasthenia gravis, hypogammaglobulinemia, and pure red-cell aplasia.[1-11] In pure red-cell aplasia, autoantibodies against early and late erythroid-cell progenitors or erythropoietin, as well as inhibitory cellular immune mechanisms, have been implicated.[9-11] Limited information suggests that patients with pure red-cell aplasia and thymoma have a poor prognosis.[6,7,10]

We recently demonstrated a high uptake of indium-labeled octreotide (^{111}In-DTPA-D-Phe^1-octreotide) in thymomas, a phenomenon related to the high content of somatostatin receptors in these tumors.[12] The same labeling method has been successful in imaging a wide variety of neuroendocrine tumors.[13,14] Sixteen of 17 thymomas we tested were scintigraphically positive with this method, whereas 4 of 4 cases of thymic hyperplasia were scintigraphically negative (unpublished data). Reubi et al.,[15] using in vitro quantitative autoradiography, found somatostatin receptors in normal thymic tissue but not in four thymomas of undefined histologic subtype.

Our results with scintigraphy of thymomas were the rationale for using octreotide to treat a patient with an inoperable thymoma and pure red-cell aplasia. In this patient chemotherapy had produced only a partial response of the thymoma, and corticosteroids failed to control the anemia. Concomitant hepatic and renal failure contraindicated treatment with cyclosporine.

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CASE REPORT

A 56-year-old woman presented with cough and dyspnea in October 1992. Chest radiography and computed tomography (CT) showed a large mass (13 by 8 by 7.5 cm) in the upper anterior mediastinum, with invasion of the adjacent pericardium, pleura, lungs, and inferior vena cava. These findings contraindicated extirpative surgery. A biopsy during thoracotomy revealed a mixed thymoma, consisting of epithelial cells and lymphoid cells positive for leukocyte common antigen (CD45). After diagnosis, three courses of cisplatin (70 mg per square meter of body-surface area on day 1), cyclophosphamide (700 mg per square meter on day 1), and prednisone (100 mg daily for five days) at three-week intervals were given. The patient's symptoms improved. However, the sudden onset of severe anemia, which responded poorly to blood transfusions, forced the cessation of chemotherapy. A bone marrow aspirate disclosed severe erythroblastopenia (less than 0.4 percent erythroblasts), a finding consistent with pure red-cell aplasia. Colony-forming assays[16] of marrow cells obtained during the active phase of the disease showed reduced growth of erythroid burst-forming unit but not of granulocyte–macrophage colony-forming unit progenitors (Table 1).

In coculture experiments, carried out by adding the patient's serum or lymphocytes to a culture of normal bone marrow cells, the growth of erythroid burst-forming units was inhibited by the patient's serum but not by normal serum (Table 1). During the active phase of the disease, the CD4:CD8 ratio was decreased (0.96; normal range, 1.3 to 2.3) in the patient's peripheral blood because of an increased number of CD8 T lymphocytes, which may have been suppressor T cells.

After therapy with prednisone (1 mg per kilogram of body weight per day) for one month, the hemoglobin level increased from 5.8 to 7.8 g per deciliter, but transfusions were still required (Fig. 1). In April 1993, a chest CT scan showed a large residual mediastinal thymoma (Fig. 2A). Three additional courses of chemotherapy were then given, but the anemia worsened and hepatic and renal failure supervened (bilirubin, 3 g per deciliter [51 μmol per liter]; blood urea nitrogen, 1 g per deciliter [3.6 mmol per liter]; creatinine, 3.5 g per deciliter [3100 μmol per liter]).

In June 1993, the patient was evaluated by ^{111}In-DTPA-D-Phe^1-octreotide scintigraphy (3 mCi [111 MBq] per 10 μg of peptide; Mallinckrodt, Patten, the Netherlands), which showed intense uptake in the residual mass (Fig. 2B). This evidence prompted us to consider treatment with octreotide. After the patient's informed consent had been obtained, octreotide (Sandostatina, Sandoz, Milan, Italy) was administered subcutaneously at a dose of 0.5 mg every eight hours (1.5 mg per day) along with prednisone (0.6 mg per kilogram per day).

After one month of this treatment, improvement was evident. The hemoglobin concentration increased, and blood transfusions were no longer necessary (Fig. 1). After three months, considerable shrinkage of the thymoma was found by CT examination (Fig. 3A) and corroborated by the lack of uptake of ^{111}In-DTPA-D-Phe^1-octreotide in the mediastinum (Fig. 3B). When the daily dose of prednisone was reduced by 50 percent for two weeks, the anemia worsened. The anemia continued to worsen during a four-week pause in octreotide treatment beginning one month after the reduction in the dose of prednisone (Fig. 1). After 15 months of treatment with octreotide and prednisone, the patient was in complete remission, with no radiographic or scintigraphic evidence of thymoma.

As of August 1996, the patient remained in complete remission while continuing to receive small doses of octreotide (0.5 mg twice daily) and prednisone (0.2 mg per kilogram per day). No side effects have been reported during treatment, with the exception of mild hyperadrenocorticism.

DISCUSSION

The combination of octreotide and prednisone produced a complete clinical response in a patient

TABLE 1. EFFECTS OF THE PATIENT'S LYMPHOCYTES AND SERUM ON COLONY FORMATION BY NORMAL BONE MARROW CELLS BEFORE AND FIVE MONTHS AFTER THE BEGINNING OF TREATMENT WITH OCTREOTIDE AND PREDNISONE.*

CULTURE	BEFORE TREATMENT		AFTER TREATMENT	
	CFU-GM	BFU-E	CFU-GM	BFU-E
	number of units			
Patient	63±3	23±4†	55±2	31±2
Control	65±12	70±5‡	50±5	35±7
Control with patient's lymphocytes	60±7	72±8	53±3	30±3
Control with patient's serum	70±5	3±4	49±2	35±4
Control with control lymphocytes	69±12	78±4	55±7	38±2
Control with normal serum	61±8	65±7	55±8	42±6

*Values shown are the means (±SD) of triplicate samples. CFU-GM denotes granulocyte–macrophage colony-forming units, and BFU-E erythroid burst-forming units.

†$P<0.05$ for the comparison with control BFU-E before treatment.

‡$P<0.01$ for the comparison with control BFU-E with the patient's serum before treatment.

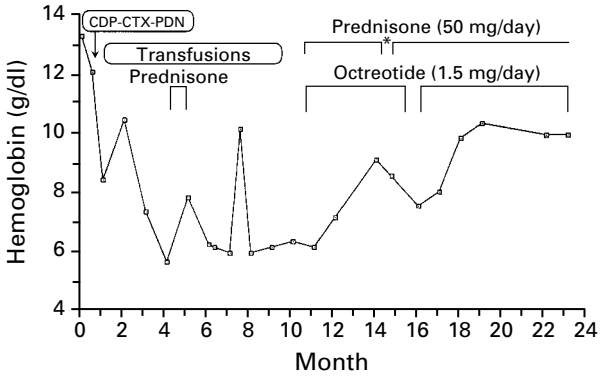
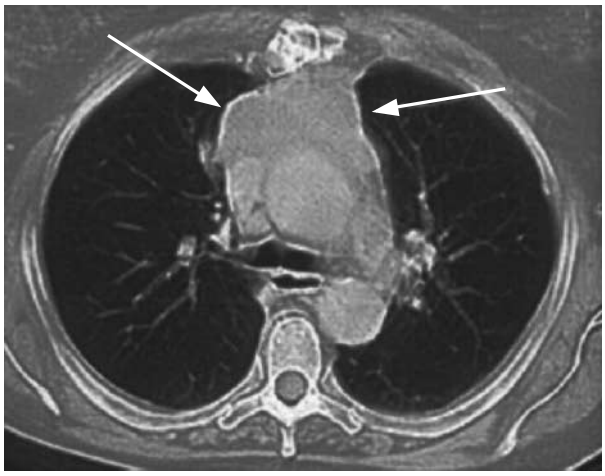


Figure 1. Clinical Course of a Patient with a Thymoma and Pure Red-Cell Aplasia.

CDP denotes cisplatin, CTX cyclophosphamide, and PDN prednisone. The asterisk indicates a reduction of 50 percent in the daily dose of prednisone.



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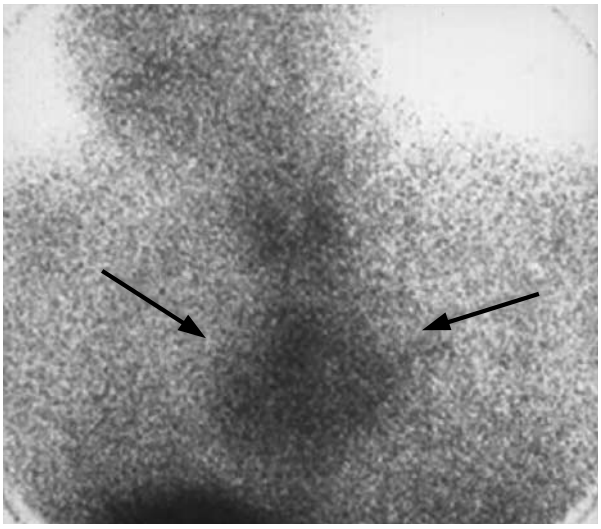

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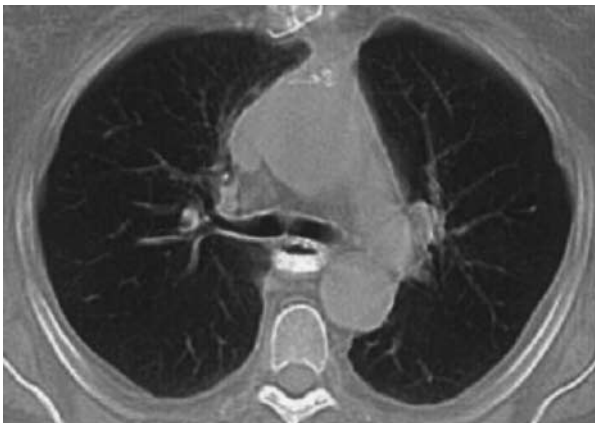
Figure 2. Chest CT Scan (Panel A) and Anterior Chest View of ^{111}In-DTPA-D-Phe^{1}-Octreotide Scintigraphic Scan 24 Hours after Injection of the Labeled Octreotide (Panel B), before the Beginning of Therapy with Octreotide and Prednisone.

The arrows indicate the extent of the thymoma in the CT scan and the peptide uptake in the scintigraphic scan.

with a malignant thymoma and pure red-cell aplasia. Given this unusual combination of disorders, the standard therapeutic options range from radical surgery (with or without radiotherapy) for early-stage thymoma to chemotherapy, radiotherapy, or both for advanced disease.[17,18] Some patients with a malignant thymoma that resists standard chemotherapy can respond to prednisone.[19] Corticosteroids exert effects against tumors by inducing apoptosis[20]; it is relevant here that dexamethasone induces apoptosis in thymoma cell lines.[21] Nevertheless, high doses of prednisone, either alone or in combination with cisplatin and cyclophosphamide, failed to cause remission of either the thymoma or the pure red-cell aplasia in our patient.

In vitro and in vivo studies have documented that octreotide inhibits hypersecretion of hormones and peptides such as growth hormone, thyrotropin, and vasoactive intestinal peptide and causes regression of pituitary adenomas and carcinoids.[13,14] Furthermore, octreotide, like somatostatin, is produced by lymphocytes and monocytes and released by nerve end-



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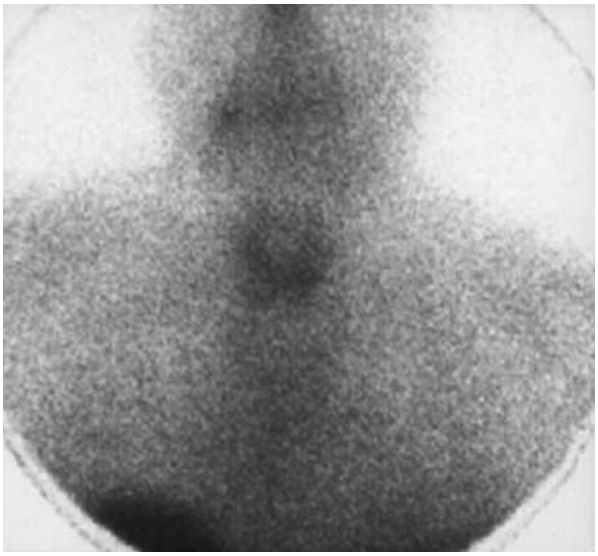

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Figure 3. Chest CT Scan (Panel A) and Anterior Chest View of ^{111}In-DTPA-D-Phe^{1}-Octreotide Scintigraphic Scan 24 Hours after Injection of the Labeled Octreotide (Panel B) after Three Months of Therapy with Octreotide and Prednisone.

The tumor has receded, and there is no evidence of peptide uptake.

ings,[22,23] and it may inhibit the function of activated immune cells. The response in our patient may have been due to the apoptotic effects of corticosteroids (primarily on the lymphocytic component of the mass) and the growth-inhibiting action of octreotide (mainly on the neoplastic thymic cells). This synergistic effect against the thymoma may also have inhibited the synthesis or the release of one or more serum factors responsible for the immune mechanisms in pure red-cell aplasia. It is notable that after treatment with corticosteroids and octreotide, the patient's serum no longer inhibited the formation of erythroid burst-forming units by normal bone marrow cells.

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