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LETTER TO THE EDITOR

Resolution of thymoma-related pure red cell aplasia after octreotide treatment

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To the Editor

Thymic tumors are often accompanied by paraneoplastic syndromes such as myasthenia gravis (approximately 45%) and, less frequently (<5%), by pure red cell aplasia (PRCA), dermatomyositis, systemic lupus erythematodes, and occasionally Cushing syndrome, syndrome of inappropriate antidiuretic hormone secretion and graft versus host-like skin reaction [1–6]. The pathophysiology of thymoma-associated PRCA is not well understood thus the optimal therapy remains unknown. In one series, surgical resection was reported to induce resolution of PRCA in 25–30% of patients (Zeok et al. 1979), whereas in the most recently published study of 12 patients no complete remission of anemia (defined as Hb >11g/dl without transfusion) following surgery was reported [7,8]. Thus, to ameliorate red blood cell (RBC) transfusion requirements most patients are subsequently treated with danazol, corticosteroids, immunosuppressive or cytotoxic agents (ciclosporin, anti-thymocyte globulin, azathioprine, low dose cyclophosphamide) [1,8]. The efficacy of these treatments is not satisfactory, therefore some investigators have tried other treatment approaches such as octreotide, allogeneic nonmyeloablative hematopietic cell transplantation, cetuximab or rituximab [2,3,9–11]. Here we present a patient with resolution of thymoma-associated PRCA following treatment with a somatostatin analog.

A 35 year old, previously healthy woman was diagnosed with right mediastinal mass and extensive pleural lesions by a routine chest x-ray performed in January 2004. Computed tomography (CT) confirmed the presence of a large (12 × 7 cm) mediastinal mass, infiltrating pleura and perihepatic peritoneum. Metastatic lesions were found in the 3rd right lung segment, 5th liver segment and the diaphragm. Biopsy specimen obtained during thoracotomy showed abundant epithelial and lymphoid cells typical for malignant thymoma. Due to dissemination of the neoplasm surgical resection was not attempted. Instead, standard systemic chemotherapy consisting of doxorubicin, cisplatin, cyclophosphamide and vincristin was administered (ADCO). Treatment was initially well tolerated, however after the 4th cycle a sudden drop in hemoglobin level (from12.5 to 8.2 g/dl) with no thrombopenia, neutropenia, or symptoms of bleeding was noted. Corticosteroid therapy was contraindicated due to acute gastritis diagnosed by gastroscopy. In August 2004, after completing six cycles of chemotherapy a partial tumor remission was achieved without improvement of anemia. Serum level of iron, and the total iron binding capacity and ferritin were within the normal limits. Three months after completion of the first-line treatment CT scans showed progression of the disease. A second-line chemotherapy regimen consisting of cisplatin and etoposide (PE) was initiated in November 2004. Therapy was discontinued after 3 cycles because of poor tolerance. Due to persistent anemia necessitating RBC transfusions every two weeks, treatment with recombinant human erythropoetin was applied, with no response within 4 months. In May 2005 disease progression prompted

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further treatment. After 6 cycles of single-agent ifosfamide, a partial remission was achieved again without improvement of anemia: hemoglobin levels remained between 5.4 and 7.2 g/dl. A further work-up lead to the diagnosis of PRCA. Octreotide scintigraphy performed in June 2004 showed weak tracer uptake, therefore octreotide treatment was not initiated at that time. However, in November 2005, due to the lack of efficacy of prior aggressive therapy and after obtaining informed consent – octreotide treatment was eventually initiated (20 mg intramuscularly every 28 days). Due to high risk of gastrointestinal bleeding octreotide treatment was not combined with prednison. After three months of therapy hemoglobin levels normalized, and the bone marrow biopsy showed erythroid reconstitution and normal megakaryopoiesis and granulopoiesis. One year after the initiation of octreotide treatment the patient remains in good health, with a WHO performance status of 0, without any symptoms of anemia (hemoglobin 12.7 g/dl) and with CT-confirmed maintained partial remission for more than 12 months.

Optimal salvage therapy of advanced chemotherapy-refractory thymoma as well as optimal therapy for thymoma-associated PRCA has not yet been established. Some reports including small numbers of patients suggested a benefit from second-line chemotherapy or different types of immunotherapy [1,9,10,12]. The rationale for somatostatin analog treatment is based on at least two observations. First, the association of many different autoimmunologic paraneoplastic syndromes with thymoma suggests some interactions between neuroendocrine and the immune system. Second, epithelial and lymphoid cells in thymus express several receptors for neuropeptides and hormones including somatostatin receptors, which are known for their antiproliferative function in many human tumors although that mechanism is not fully understood.

At least three reports indicated a beneficial role of sandostatin analogs in the treatment of advanced thymic tumors [2,13]. In 1997 Palmieri et al. reported a complete remission of the tumor and resolution of thymoma-associated PRCA after treatment with sandostatin and prednison in a patient with chemorefractory disease, although the individual contribution of each agent was difficult to assess [3]. According to Loehrer et al., sandostatin monotherapy may induce 10% of objective responses, compared to 38% with sandostatin/prednison combination [2]. In the case presented here, steroid therapy was not attempted due to the patient's history of severe gastritis and concern of steroid-induced bleeding. Although spontaneous remission of PRCA has been reported, the resolution of PRCA with octreotide suggests a pivotal role of neuroendocrine receptor signaling in the pathophysiology of PRCA [12].

In conclusion, octreotide may be an interesting treatment option for patients with thymoma-associated PRCA, although the mechanism of action remains to be established.

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