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Very Severe Aplastic Anemia appearing after Thymectomy

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Aplastic anemia is a rare complication of thymoma and is extremely infrequent after thymectomy. We present a case of a 60-year-old woman with very severe aplastic anemia appearing sixteen months after thymectomy for a thymoma. She underwent thymectomy for a thymoma in April 2000. Preoperative examination revealed no hematologic abnormality. About sixteen months after the operation, she was readmitted because of pancytopenia with cough and fever. Bone marrow aspiration revealed a very severe hypoplasia in all the three cell lines with over 80% fatty tissue, and chest CT revealed no recurrence of thymoma. Her aplastic anemia had responded to cyclosporine A and granulocyte-colony stimulating factor (G-CSF).

Key Words: Aplastic anemia, Thymoma, Thymectomy, Cyclosporine A

INTRODUCTION

Some hematologic dyscrasias have been associated with thymoma. About 5% of patients with thymoma develop pure red cell aplasia (PRCA)[1]. Other hematologic complications occur far less frequently and include autoimmune hemolytic anemia, pernicious anemia, peripheral neutropenia, agranulocytosis, thrombocytopenia and hypogamma-globulinemia. PRCA disappear after thymectomy but reappear after a latency period even without recurrence of thymoma[2]. Aplastic anemia is a rare complication of thymoma and is properly documented in only a few cases. It is exceedingly uncommon following the surgical removal of a thymoma[3-5]. As thymoma-associated hematologic dyscrasias are likewise supposed to be of immunologic origin, we report here a case of very severe aplastic anemia following thymectomy, which was successfully treated with immunosuppressants such as cyclosporine A and G-CSF.

CASE

A 60-year-old woman who complained of cough and dyspnea visited the Pulmonary Department in April 2000. Chest radiography and computed tomography (CT) showed a large mass in the anterior mediastinum, compatible with a thymoma (Figure 1). A well-capsulated mediastinal tumor was totally removed by thoracotomy. Histopathological examination revealed a lymphocytic thymoma. An initial workup then revealed no abnormal results on the routine hematological examinations. About sixteen months after the operation, a non-productive cough and high fever developed. Chest radiography and CT revealed no recurrence of thymoma. A routine hematologic feature was as follows; Hb 5.9 g/dL; Hct 16.9%; WBC 0.8×10^9/L, absolute neutrophil count 0.2×10^9/L; platelets 86×10^9/L. There was no recent antecedent exposure to chemicals and drugs, and serology for hepatitis A, B, C, parvovirus and HIV infection was negative. Cytomegalovirus

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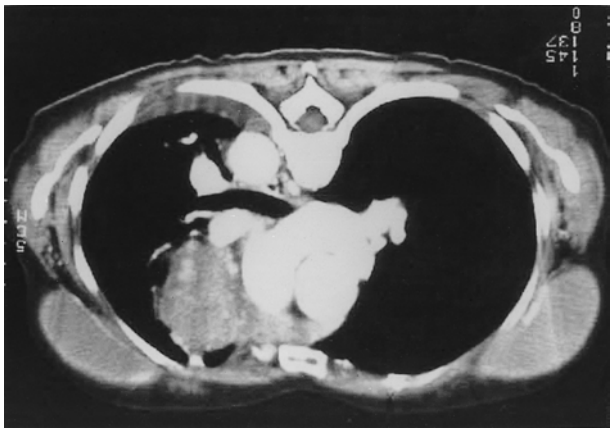

Figure 1. Chest computed tomography showed a large mass in the anterior mediastinum, compatible with a thymoma.

and Epstein-Barr virus serology was consistent with previous viral exposure. With a high suspicion of aplastic anemia, multiple bone marrow aspirations and biopsy were performed. Histopathological examination of the bone marrow disclosed extremely low marrow cellularity with increased fatty areas. The patient received transfusions of platelet concentrate and empiric antibiotic therapy for fever and neutropenia during her hospital course. G-CSF was administered as much as 5 μg/ kg/day. After her neutropenic fever subsided, oral cyclosporine A (5 mg/kg/day) was administered. Three months after this treatment, she is clinically stable with no transfusion requirement and without any signs of infection.

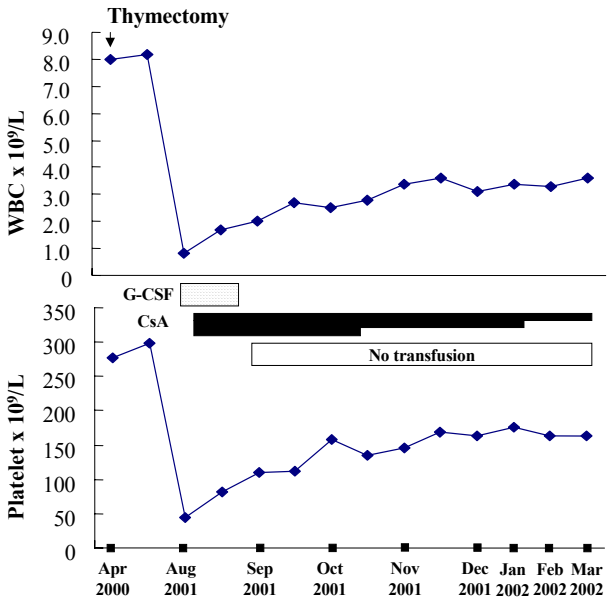

Figure 2. Clinical course of the patient with thymoma and aplastic anemia. CsA, cyclosporine A.

Peripheral blood counts were as follows: Hb 10.3 g/dL; Hct 30.2%; WBC 3.5×10^9/L, absolute neutrophil count 1.9×10^9/L; platelets 164×10^9/L. From then to March, 2002, the patient remained in complete remission with low doses of cyclosporine alone. No side effects have been observed during treatment (Figure 2).

DISCUSSION

Thymoma is the most common tumor of the anterior mediastinum and is often associated with autoimmune diseases, including myasthenia gravis, polymyositis, hypogammaglobulinemia and various cytopenia[6, 7]. These cytopenias include agranulocytosis, PRCA and aplastic anemia. In fact, the overall long-term survival of patients with thymoma is poor once cytopenias occur. Although thymectomy is indicated in thymomas with blood dyscrasia, a permanent hematologic remission can be expected in less than 30% of patients with thymoma-associated PRCA[7-9]. Often, the immunoassociated symptoms like PRCA disappear after thymectomy but reappear after a latency period, even without recurrence of thymoma, and there is no codified therapy for surgically resistant or relapse cases. In aplastic anemia, thymectomy may fail to resolve aplastic cytopenias as in the case presented by Liozon et al[10]. Çöplü et al presented a patient with aplastic cytopenia-associated thymoma in whom complete remission was achieved with surgical removal of the thymoma[11]. The second major approach to treat thymoma-associated PRCA is immunosuppressive therapy. ALG and cyclosporin, often successful in primary as well as secondary PRCA and idiopathic AA, should be proposed in unresponsive cases[6, 12, 13]. Giovannella et al. reported that the combination of octreotide and prednisone produced a complete clinical response in a patient with malignant thymoma and pure red cell aplasia[14].

We reviewed several reports of thymoma-associated aplastic anemia, including our case. Aplastic anemia is a rare complication of thymoma and is extremely infrequent after thymectomy. In large series, the incidence of AA with thymoma is 0~1.4%[8, 15]. To our knowledge, this is the fourth report of aplastic anemia following thymectomy[2, 3, 5].

Many pathogenetic mechanisms have been suggested to explain the bone marrow failure seen in aplastic anemia[16]. The pathogenesis of some types of aplastic anemia clearly display an immunological basis. Especially, the role of suppressor T lymphocytes is considered important in the development of aplastic anemia. Similarly, thymoma associated with aplastic anemia seems to be caused by the suppression of the bone marrow due to an unbalanced

regulation and the inhibitory effects of T lymphocytes on BFU-E and CFU-E as demonstrated in previous reports[4, 10].

Because immune mechanisms appear to play an important part in the maintenance and/or progression of thymoma-associated aplastic anemia, this is the rationale for the use of immunosuppressive therapy as one option in the treatment of the disease[3, 4, 10]. Cyclosporine A has been associated with good responses in cases of thymoma-associated PRCA and aplastic anemia, so we decided to treat the patient with cyclosporine A and G-CSF. Thus, our case seems to be an example for the development of very severe AA, following surgical removal of a thymoma, in which an immunosuppressive agent like cyclosporine A has been efficient.

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