# Thymoma followed by aplastic anemia – two different responses to immunosuppressive therapy

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*Aplastic anemia is an uncommon complication of thymoma and is extremely infrequent after the surgical removal of a thymic tumor. Aplastic anemia is a result of marrow failure and is characterized by peripheral pancytopenia and severely depressed marrow cellularity; it may be an autoimmune manifestation of thymoma. As thymoma-associated hematological dyscrasias, which include pure red cell aplasia, aplastic anemia and myasthenia gravis, are supposed to be of immunologic origin, two cases of very severe aplastic anemia following the resection of lymphocytic thymomas treated with immunosuppression are herein presented.*

***Keywords:*** *Anemia, aplastic; Thymus neoplasms; Immunosuppression; Thymectomy; Myastenia gravis/drug therapy; Cyclosporine/therapeutic use; Human; Male; Aged; Case reports*

## Introduction

Aplastic anemia (AA) is characterized by bone marrow failure; its pathophysiology is mediated by immune response in most cases with the involvement of type 1 activated cytotoxic T cells.(1)

Thymomas are tumors that can be associated with many autoimmune diseases, including pure red cell aplasia (PRCA), myasthenia gravis (MG) and AA.(2) AA is an uncommon complication of thymic tumors; hematological recovery may not be attained even with thymectomy.(2)

Patient 1, a 69-year-old male had been complaining of dyspnea after vigorous effort for six months. He progressed to feeling the same condition after moderate exertion. He was admitted to the Emergency Department with symptoms of angina pectoris and was diagnosed with severe anemia and thrombocytopenia. He had a history of the excision of an anterior mediastinum tumor three years previously. A histopathology examination concluded that the patient had a mixed lymphoid and epithelial thymoma (immunohistochemical study: $CD5^+$ and cytokeratin $19^+$). Patient 2, a 59-year-old female reported progressive weakness associated with bruises and gingival bleeding occurring for about two weeks prior to her visit. She had a history of mediastinal tumor resection two years previously, followed by radiotherapy with remission of the tumor. The histopathology of the tumor identified a thymic neoplasia with lobulated aspect due to a thick fibrous septa associated with polyhedral cells, vesicular nuclei, large numbers of lymphoid cells involving tumor cells and follicular areas, compatible with thymoma. Both patients were in remission from the thymic tumors and their bone marrow biopsy showed cellularity < 5% without fibrosis. In both patients the karyotype of bone marrow did not show mitosis and an investigation of paroxysmal nocturnal hemoglobinuria clones proved negative. Both were treated with immunosuppressive drugs. Patient 1 was treated with adjusted doses of cyclosporine because of liver toxicity. Patient 2 was treated with cyclosporine and prednisone (12.5 mg/kg and 2 mg/kg, respectively), but without hematological response. She evolved with a diffuse alveolar hemorrhage and died. Patient 1 had a satisfactory hematological response. He is alive and is not receiving any blood transfusions or immunosuppressive medication at 49 months of follow-up. He is in remission from the thymoma. Hematological parameters of both patients are shown in Table 1.

Thymoma, characterized by a remarkable morphological heterogeneity, is the most common tumor of the mediastinum; it is associated with autoimmune diseases, such as PRCA, an autoimmune syndrome characterized by the selective inhibition of erythroid lineage hematopoiesis.(3) There are reports that demonstrate the presence of T cell clonal expansion in PRCA corroborating its autoimmune cause.(3,4) However, the role of the thymus

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Table 1 - Hematological data before and after treatment

| Hematological parameters | Patient 1 | | Patient 2 | |
|---|---|---|---|---|
| | Before | After | Before | After |
| Hemoglobin (g/dL) | 5.0 | 12.9 | 6.2 | 5.5 |
| Leucocytes (x $10^9$/L) | 1.4 | 2.7 | 1.1 | 0.9 |
| Neutrophils (x $10^9$/L) | 0.8 | 1.16 | 0.4 | 0.3 |
| Platelets (x $10^9$/L) | 14 | 95 | 8 | 2 |

remains uncertain.[3] It is thought that these associations are the result of the clonal production of self-reactive T cells by the thymic epithelium.[4]

AA is an uncommon complication of thymoma and its occurrence is even more uncommon after the resection of this tumor.[5] The immune disorder caused by thymomas increases the ability to generate mature $CD4^+/CD8^+$ T cells from immature precursor cells, which produce clones of self-reactive T cells responsible for humoral and cytotoxic autoimmune diseases.[4] The pathogenesis of AA associated with thymoma seems to be explained by bone marrow suppression related to unbalanced T cell regulation with inverted $CD4^+/CD8^+$ or an increase in cytotoxic/suppressive cells.[1,2]

The identification of a clonal population of T cells, despite of intense immunosuppression, supports the hypothesis that self-reactive T cells are exported from the thymoma to the periphery, where they are still capable of causing self-immunity at a later date. Thus, resection of the thymoma has no impact on the clinical course of AA. In fact, this highlights the necessity of immunosuppressants during therapy, with the aim of changing the clinical course of the disease and achieving satisfying results.[4]

Immunosuppression is the treatment of choice in elderly patients, as well as in patients without HLA compatible donors. Anti-thymocyte globulin is the most effective immunosuppressive drug in the treatment of severe AA,[1,5,6] and a combination of anti-thymocyte globulin and cyclosporin A is recommended.[6] In cases of the association of thymoma with AA, this therapy and methylprednisolone have been used with some success.[7]

In one of our patients, immunosuppressive therapy with adjusted doses of cyclosporin A gave a considerable hematological response, with the patient not requiring transfusions. On the other hand, despite using dual immunosuppression with conventional doses of cyclosporine A and prednisone, the other patient did not achieve hematological remission and progressed to death in a short time.

In conclusion, the recovery of one patient after immunosuppressive therapy corroborates the probable immune genesis of the pathological process of both diseases. However, AA is a severe and often fatal disease despite early and proper treatment. The increase in self-reactive circulating T cells caused by the thymoma and the surgical removal of the main organ of central control of immune tolerance probably generate more self-reactive T lymphocytes, thus perpetuating the autoimmune phenomenon.

## References


1. Bacigalupo A. Aplastic anemia: pathogenesis and treatment. Hematology Am Soc Hematol Educ Program. 2007:23-8.
2. Koizumi K, Nakau S, Haseyama Y, Kato H, Ohi M, Motohara T, et al. Severe aplastic anemia associated with thymic carcinoma and partial recovery of hematopoiesis after thymectomy. Ann Hematol. 2003;82(6):367-70.
3. Fujishima N, Hirokawa M, Fujishima M, Wada C, Toyoshima I, Watanabe S, et al. Oligoclonal T cell expansion in blood but not in the thymus from a patient with thymoma-associated pure red cell aplasia. Haematologica. 2006;91(Suppl 12):ECR47.
4. Ritchie DS, Underhill C, Grigg AP. Aplastic anemia as a late complication of thymoma in remission. Eur J Haematol. 2002; 68(6):389-91.
5. Locasciulli A, Bruno B, Rambaldi A, Saracco P, Dufour C, Finelli C, Sica S, Varotto S, Arcese W, Locatelli F, Soligo D, Bacigalupo A; GITMO prospective randomized study. Treatment of severe aplastic anemia with antilymphocyte globulin, cyclosporine and two different granulocyte colony-stimulating factors regimens: a GITMO prospective randomized study. Haematologica. 2004;89 (9):1054-61.
6. Marsh JC, Ball SE, Cavenagh J, Darbyshire P, Dokal I, Gordon-Smith EC, Keidan J, Laurie A, Martin A, Mercieca J, Killick SB, Stewart R, Yin JA; British Committee for Standards in Haematology. Guidelines for the diagnosis and management of aplastic anaemia. Br J Haematol. 2009;147(1):43-70.
7. Kojima S, Hibi S, Kosaka Y, Yamamoto M, Tsuchida M, Mugishima H, et al. Immunosuppressive therapy using antithymocyte globulin, cyclosporine, and danazol with or without human granulocyte colony-stimulating factor in children with acquired aplastic anemia. Blood. 2000;96(6):2049-54.


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