Experience with Surgery for Thymoma Associated with Pure Red Blood Cell Aplasia*

Report of Three Cases

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We present three cases of thymoma associated with pure red blood cell aplasia in which thymectomy and thymectomy were performed. Case 1, a patient with pure red blood cell aplasia and hypogammaglobulinemia, was treated after surgery with immunosuppressive agents. She died not show any remission and died eight months after the operation. Case 2, a patient with pure red blood cell aplasia alone, showed transient erythropoiesis only in the early postoperative period and died one year and seven months after the operation. Patient 3 had pure red blood cell aplasia alone before surgery and was treated after surgery with prednisolone and fluoxymesterone. He showed good remission from the aplasia after these treatments; however, myasthenia gravis appeared seven months after the operation. These results seem to show that such combined therapy as applied in case 3 may be effective for some of the patients with pure red blood cell aplasia and thymoma; however, the effects of thymectomy or thymectomy (or both) are still controversial for the treatment of pure red blood cell aplasia.

Thymoma often is associated with various autoimmune diseases during its natural history. Among them, myasthenia gravis has been proven to be caused by circulating antibody to the acetylcholine receptor, and the protocol for treatment is being established; however, the causes of other diseases associated with thymoma, such as pure red blood cell aplasia and hypogammaglobulinemia, are not known nor are their effective treatments.

Recently, we had experience with three patients

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FIGURE 1. Preoperative roentgenograms of patients with thymomas associated with pure red blood cell aplasia. Left, Case 1; center, case 2; and right, case 3.
diagnosed as having thymoma, pure red blood cell aplasia and hypogammaglobulinemia. The patient was transferred to our department for surgical treatment on Jan 19, 1981. Since February 1978, she had had stomatitis.

On examination, the patient had a trichophytosis on the nails and hepatosplenomegaly. A chest x-ray film revealed a tumorous mass on the right side behind the sternum (Fig 1).

The results of hematologic examinations in the three patients are summarized in Table 1. In patient 1, there was severe anemia without any reticulocytes in the peripheral blood, and there were no erythroblasts, with relative lymphocytosis, but there was some decrease in nucleated cells, and plasma cells in the bone marrow tended to disappear. Biochemical and immunologic investigations of peripheral blood showed an apparent decrease in the serum γ-globulin level, as well as in serum immunoglobulins. B-lymphocyte composition was also decreased (Table 2). The results of other examinations were reported as decreased lymphocyte blastogenesis to pokeweed mitogen (PWM) and inactive skin tests to purified protein derivative of tuberculin (PPD) and dinitrochlorobenzene.

The patient underwent thymectomy and thymectomy on Feb 10, 1981. The tumorous mass was well encapsulated. The specimen measured 9.8 by 12.1 by 6.7 cm. On cut section, there was a smooth parenchymal surface with soft portions slightly separated by fibrous septa (Fig 2). Histologically, the specimen predominantly contained epithelial cells with spindle-shaped nuclei. Lymphocytes were relatively scant (Fig 3). This spindle-cell thymoma showed no malignant nature histologically.

After surgery the patient was given immunosuppressive agents such as prednisolone, ACTH, and azathioprine. The patient suddenly died eight months after the operation without any improvement in the hematologic findings. At autopsy the bone marrow had no erythroblasts, and abundant fat. There was diffuse hemosiderosis in the liver, spleen, pancreas, and thyroid gland. Brown atrophy of the myocardium was also remarkable.

**Case 2**

A 63-year-old man developed weakness and slight breathlessness in the spring of 1981. An abnormal shadow on the chest x-ray film and anemia were noted in September 1981. The patient was transferred to our department via Tohoku University Medical Center with a diagnosis of thymoma and pure red blood cell aplasia on Jan 5, 1982. Neither the liver nor the spleen was palpable. The chest x-ray film revealed a tumorous mass on the right mediastinal side near the anterior chest wall (Fig 1). A blood cell count showed the erythrocytes to number 304 × 10^6/μl and no reticulocytes (Table 1). On examination, bone marrow revealed no erythroblasts and a decrease in nucleated cells and plasma cell component. Other examinations showed a decrease in surface immunoglobulin-positive lymphocyte levels to 0.2 percent (control, 7.6 percent). Cutaneous reactivity to PPD was normal.

The patient underwent thymectomy and thymectomy on Jan 26, 1982. The tumor was well encapsulated. The specimen measured 3.8 by 7.6 by 4.2 cm. On cut section, it had a parenchymal surface with soft portions grossly separated by thin fibrous septa (Fig 2). Histologically, epithelial cells had spindle-shaped nuclei with scant lymphocyte migration (Fig 4). There were no malignant patterns in these specimens.

The patient received no immunosuppressive therapy after surgery but showed temporary remission in bone marrow findings; the erythroblast level was increased up to 13.2 percent at one month after surgery; however, a decrease in this level began to be progressive thereafter.

Finally, the patient died of cerebral softening one year and seven months after surgery. Autopsy was not performed.

**Case 3**

A 58-year-old man had a history of pneumonia in childhood. Old right-sided pleuritis had been noted roentgenologically for ten years.

The patient presented with loss of appetite and faintness in August 1983, and anemia associated with an abnormal shadow on chest x-ray film was noted. He was admitted into our department on Sept 8, 1983.

Chest roentgenographic examination revealed a large tumorous...
shadow on the left side behind the anterior chest wall, with old pleuritis on the left (Fig 1). Investigations of peripheral blood showed anemia without any reticulocytes (Table 1). There were no erythroblasts but normal findings of granulopoiesis in bone marrow. Biochemical and immunologic examinations showed normal levels of \( \gamma \)-globulins and each kind of immunoglobulin (Table 2). The indirect Coombs' test was positive. There was a relative decrease in the B-

lymphocyte level, but lymphocyte subsets measured by monoclonal anti-T-cell antibodies were within the normal range.

The patient underwent thymectomy and thymectomy on Nov 17, 1983. The tumor had a thickened capsule but seemed to be invasive to the left upper lobe and pericardium; thus, its surgical category was invasive thymoma. The excised specimen measured 8.4 by 11.9 by 7.3 cm and was well encapsulated (Fig 2). Histologically, there were two dominant areas in the specimen; a dark area had collections of lymphocytes, and another light portion had an epithelial dominant pattern with scant lymphocytes. Many epithelial cells had spindle-shaped nuclei (Fig 5). Histologically, there was no tumor cell invasion into the capsule.

After surgery the patient showed rapid improvement in the hematologic findings; peripheral reticulocyte levels were going up to 8 percent and 78 percent on the 12th and 19th postoperative days, respectively; however, this level decreased to 24 percent five weeks after the operation. Bone marrow showed 9.6 percent erythroblasts at this period.

The patient was discharged five weeks after the operation, but was readmitted to our hospital three weeks later, because of progressive breathlessness. On readmission the reticulocyte level was zero, and the red blood cell count was \( 204 \times 10^6/\mu l \) in the peripheral blood.

After readmission, in order to suppress a presumed autoimmune mechanism in the pure red blood cell aplasia and to stimulate bone marrow erythropoiesis simultaneously, we started therapy with
prednisolone in combination with fluoxymesterone (Halotestin). Soon after these treatments began, the patient showed remarkable improvement in the anemic symptoms; the peripheral reticulocyte level became 59 percent, and the bone marrow erythroblast level reached 28.2 percent after one month of the treatment. The patient was discharged from the hospital after 14 weeks, when his reticuloocyte level in the peripheral blood was 27 percent and the bone marrow erythroblast level was 24.6 percent. Continued observations of peripheral blood and bone marrow blood have remained improved; however, seven months after the operation, the patient showed symptoms of myasthenia gravis with a serum anti-acetylcholine receptor antibody level of 5.8 pmoles/ml (normal range, 0–0.3 pmoles/ml). During the past four months since the myasthenia gravis appeared, the antibody level has decreased to 3.8 pmoles/ml. The continued treatment so far has consisted of prednisolone (20 mg every other day) and fluoxymesterone (Halotestin; 30 mg daily).

**DISCUSSION**

Abnormalities of the thymus, including thymoma, have been associated with various immunologic abnormalities, and are regarded as autoimmune diseases. It has been known that approximately 5 percent of thymomas are associated with pure red blood cell aplasia, and 50 percent of the cases of such aplasia are associated with thymoma. Pure red blood cell aplasia is presumably related to an autoimmune mechanism. The disease is known to be associated with other autoimmune diseases, such as myasthenia gravis, systemic lupus erythematosus, and pemphigus foliaceus; the disease is also known to show immunologic abnormalities which are found in autoimmune diseases. Krantz and Kao have found that IgG of the serum from a patient with pure red blood cell aplasia is cytotoxic to erythroblasts under complement interaction; however, it is not commonly possible to detect circulating antibody against erythroblasts routinely so far. On the contrary, it is well known that in the case of myasthenia gravis, the patient frequently has a circulating antibody (anti-acetylcholine receptor antibody) which seems to be widely possible to detect in many institutions. Thus, these situations in pure red blood cell aplasia have made it difficult to establish an exact protocol for treatment of this disease.

For the patient who concomitantly has thymoma and pure red blood cell aplasia, treatment should be scheduled for the thymoma itself and for the aplasia. Of all the treatments for thymoma, it is clear that surgery is the first choice. On the contrary, for patients with pure red blood cell aplasia, surgery has not been widely accepted as the first choice in therapy; however, as it is strongly suggested that the disease has the same etiology as myasthenia gravis, thymectomy or thymectomy (or both) might be considered to be effective for pure red blood cell aplasia. This aplasia is a progressive disease. Hirst and Robertson reported that in approximately 15 percent of the patients with pure red blood cell aplasia, the levels of other elements, including serum globulins, were later depressed.

The three cases in the present study showed some interesting results. The first patient, who had thymoma, pure red blood cell aplasia, and hypogammaglobulinemia, died eight months after surgery without any remission from the hematologic findings and symptoms of immunodeficiency.

There has been no evidence that hypogammaglobulinemia is caused by an autoimmune mechanism. Rather, a recent report suggests that this abnormality is induced by thymoma itself.

There have been no reports showing that thymectomy is effective for hypogammaglobulinemia. Surgery for those patients who have pure red blood cell aplasia with severe immunodeficiency seems to have no efficacy for the marrow depression.

The second case with thymoma and pure red blood cell aplasia showed temporary improvement in the aplasia soon after the operation, but the patient died one year and seven months after surgery. The transient improvement following surgery in this patient may well be related to the surgical stress response and an increase in circulating endogenous corticosteroids.

The third patient, who had thymoma and pure red blood cell aplasia, showed rapid improvement from the aplasia soon after surgery without any other therapy, which can be explained in the same manner as case 2. Symptoms in patient 3 became worse again, but therapy with prednisolone and fluoxymesterone induced remission for more than seven months. It is difficult to explain whether the male hormone has a role in remission from pure red blood cell aplasia, but, rather, it is clear that prednisolone was effective against pure red blood cell aplasia in case 3. In this case an appearance of myasthenia gravis during the course of treatment for pure red blood cell aplasia suggests that the etiology of the aplasia had an autoimmune origin and might have been influenced by the corticosteroid therapy.

To summarize the results of our experience with surgery for thymoma associated with pure red blood cell aplasia, controversy remains about the efficacy of surgery for these situations; however, it may be effective in some cases of pure red blood cell aplasia to treat with prednisolone after surgery. Until the precise mechanism of pure red blood cell aplasia can be revealed, one can regard corticosteroid therapy following surgery as one of the best treatments required in patients with thymoma.

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