Pure Red Cell Aplasia and Myasthenia Gravis with Recurrent Thymoma

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ABSTRACT. In 1995, a 42-year-old male underwent thymothymectomy for thymoma (Masaoka stage Ⅲ) followed by 50-Gy irradiation to the mediastinum. One year after the operation, the patient was diagnosed with post-thymectomy myasthenia gravis (MG). The thymoma recurred in this patient, and he underwent tumor extirpation for recurrent thymomas in 2001 and 2006. He also underwent adjuvant chemotherapy after the operation in 2006. Approximately two months after the last administration of anticancer drugs, the patient presented with shortness of breath on effort and palpitation, and consulted at our hospital outpatient clinic. His hemoglobin concentration was 6.2 g/dl, and his reticulocyte count was 0.1%. His white blood cell and platelet levels were, however, within normal range. A bone marrow biopsy revealed severe erythroid hypoplasia with normal myeloid and megakaryocytic lineage. Based on these findings, pure red cell aplasia (PRCA) was diagnosed. Oral administration of cyclosporin A (350 mg/day (5 mg/kg)) was started after a final diagnosis. Six months after the initiation of treatment with this immunosuppressant drug, the patient required no additional transfusion with a normal hemoglobin concentration.

Key words ① **Pure red cell aplasia** ② **myasthenia gravis** ③ **thymoma** ④ **cyclosporin A**

Clinical summary

In 1995, a 42-year-old male underwent thymothymectomy for thymoma followed by 50-Gy irradiation to the mediastinum. Pathological examination of the resected specimen revealed, that according to the WHO classification, the tumor was a B2 type thymoma (Fig. 1a, 1b). It had invaded the left lung, left phrenic nerve, and pericardium (Masaoka stage III). One year after the operation, the patient experienced ptosis and was diagnosed with post-thymectomy myasthenia gravis (MG). This symptom is usually well controlled by oral prednisolone (5 mg) administration. However, the thymoma recurred in this patient, and he underwent tumor extirpation for recurrent thymomas in 2001 and 2006. He also underwent adjuvant chemotherapy

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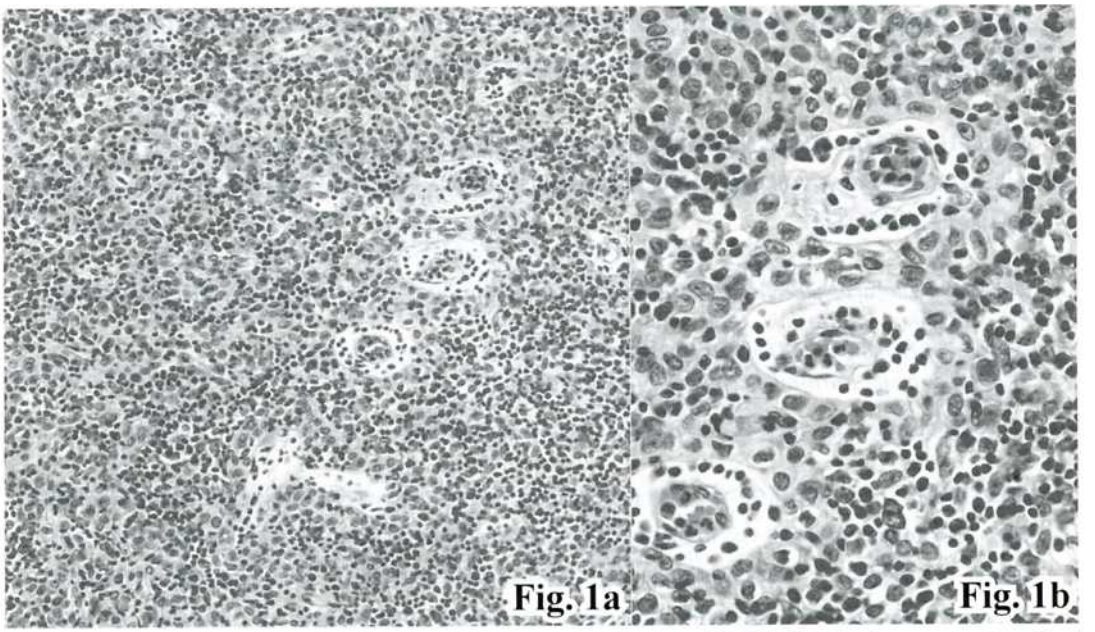

Fig. 1. Pathological finding of the resected specimen (H.E. stain ×100: Fig. 1a, ×200: Fig. 1b). The thymoma consists of both round epithelial cells and lymphocytes (B2 type thymoma according to WHO classification.).

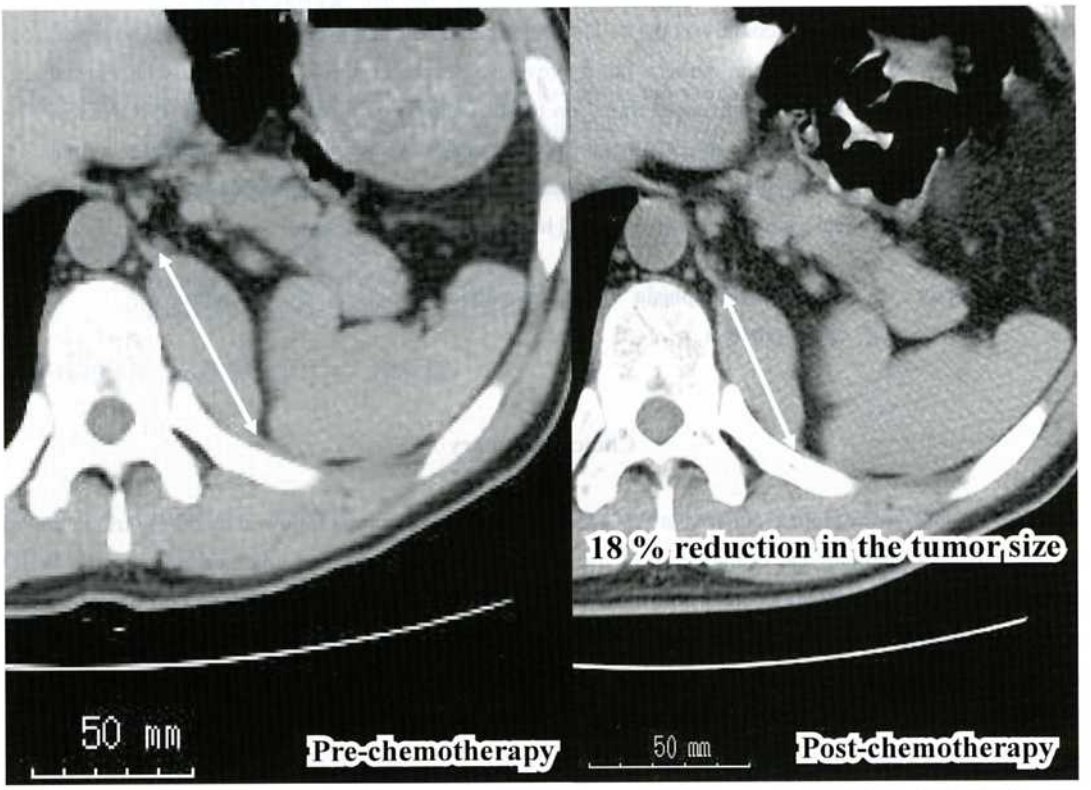

Fig. 2. Chest computed tomography shows the response to the chemotherapy was stable disease (SD, 18% reduction in the tumor size) according to Response Evaluation Criteria in Solid Tumors (RECIST).

(Carboplatin AUC5 + Paclitaxel 200 mg/m^2 × 4 courses) after the operation in 2006 because the operation resulted in a macroscopically incomplete resection. The response to the chemotherapy was stable disease (SD, 18% reduction in the tumor size) according to Response Evaluation Criteria in Solid Tumors (RECIST) (Fig. 2). Approximately two months after the last administration of anticancer drugs, the patient presented with shortness of breath on effort and palpitation, and consulted at our hospital outpatient clinic. Blood examination revealed severe anemia, as shown in table 1. His hematocrit was 17.7% with a hemoglobin concentration of 6.2 g/dl, and his reticulocyte count was 0.1%. His white blood cell and platelet levels were, however, within normal range. His erythropoietin level was 2,740 mU/ml (normal range: 8~36 mU/ml). A bone marrow biopsy revealed severe erythroid hypoplasia with normal myeloid and megakaryocytic lineage (Fig. 3). Based on these findings, pure red cell aplasia (PRCA) was diagnosed. Severe anemia due to PRCA was initially treated by transfusion of eight units of RBC, and oral administration of cyclosporin A (350 mg/day (5 mg/kg)) was started after a final diagnosis (Fig. 4). Six months after the initiation of treatment with this immunosuppressant drug, the patient required no additional transfusion; his hemoglobin value was 11.7 g/dl and his reticulocyte count was 1.9%. MG is well controlled by administration of 5 mg oral prednisolone without any change in the size of the remaining thymoma.

Pure red cell aplasia (PRCA), a disorder first reported in 1922[1], is described as an anemia wherein red cell precursors are almost completely absent in the bone marrow, but granulopoiesis and megakaryopoiesis is essentially normal[2]. PRCA is associated with various conditions such as viral infections, immune disorders, ABO-incompatible hematopoietic stem cell transplantation, and malignancies, including a well-described association with thymomas[2]. Approximately 8% of patients with PRCA have thymomas according to previous literatures[3),4)]. However, Kondo K *et al*[5] reported that of 1089 thymoma patients, 28 (2.6%) presented with PRCA, whereas in 270 (24.8%) patients, the thymomas were associated with myasthenia gravis (MG). A thymoma patient presenting with PRCA and MG is extremely rare. To our knowledge, since 1939[6], only 35 patients[7)~11)] with thymomas presenting with PRCA and MG, including our patient, have been reported. Suzuki *et al*[8] reported that 4 (2.9%) out of 135 MG patients developed PRCA 11.5 years (on average) after the occurrence of MG, and all of these patients had thymomas. This might indicate that the occurrence of thymomas with PRCA and MG is more frequent than reported previously.

Regarding the effect of thymothymectomy on PRCA, Masaoka *et al*[12] reported that it was effective in only 6 (37.5%) out of 16 thymoma patients with PRCA. Other reports[13),14)] have also noted unsatisfactory results of thymothymectomy for a thymoma with PRCA. On the other hand, the effectiveness of thymothymectomy for MG with a thymoma is approximately 80%, with remission and improvement[15]. Despite these inconsistent results, surgical resection of a thymoma for PRCA is still recommended as the primary treatment[14]. In our patient, since a thymothymectomy was performed 11 years ago, and the recurrent tumor of pleural dissemination was unresectable, we decided to administer cyclosporin A to treat PRCA. At present, cyclosporin A has a higher response rate for PRCA (80%~82%)[3),16)] than other treatment agents such as corticosteroids, antithymocyte globulin (ATG), and cytotoxic drugs. In particular, cyclosporine A has been highly effective even when administered as a second- or third-line therapy following non-responsiveness of PRCA to corticosteroids or cytotoxic agents[3]. Regarding the adverse effects of cyclosporine, although immunosuppressants such as cyclosporine and tacrolimus are believed to be involved in tumor development through various mechanisms[17], short-term follow-up has not revealed thymoma regrowth after the initiation

Table 1. Laboratory examination of peripheral blood.

RBC	205x10^4	/μl	(410-540)
Hemoglobin	6.2	g/dl	(13.0-16.5)
Hematocrit	17.7	%	(39.0-48.0)
WBC	4,230	/μl	(3500-9500)
Platelet	27.1x10^4	/μl	(15.0-35.0)
Reticulocyte	0.1	%	(0.5-2.0)
Fe	259	μg/dl	(79-235)
TIBC	265	μg/dl	(248-395)
Ferritin	1,026	ng/ml	(10-240)
Haptoglobin	86.3	mg/dl	(25-145)
erythropoietin	2,740	mU/ml	(8-36)
anti-acetylcholine receptor antibody	16	nmol/l	(≦0.2)

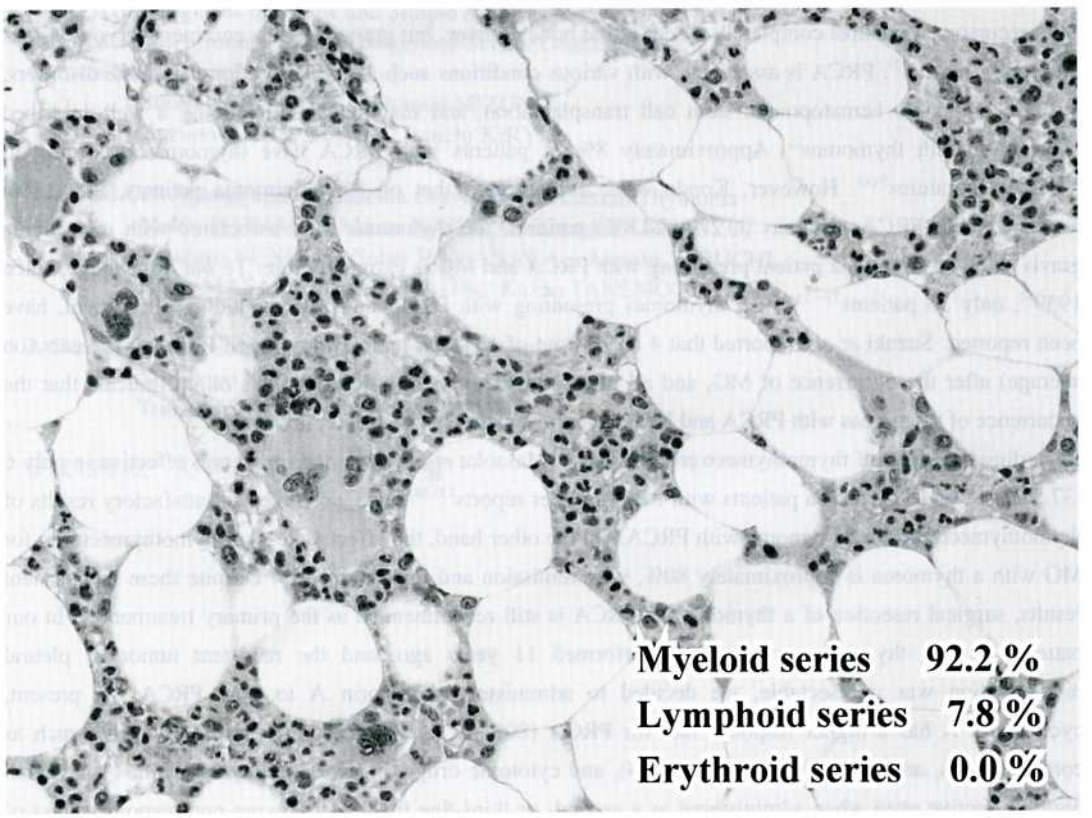

Fig. 3. Pathological finding of bone marrow biopsy (H.E. stain ×200). This examination revealed severe erythroid hypoplasia with normal myeloid and megakaryocytic lineage (myeloid series: 92.2%, lymphoid series: 7.8%, and erythroid series 0.0%).

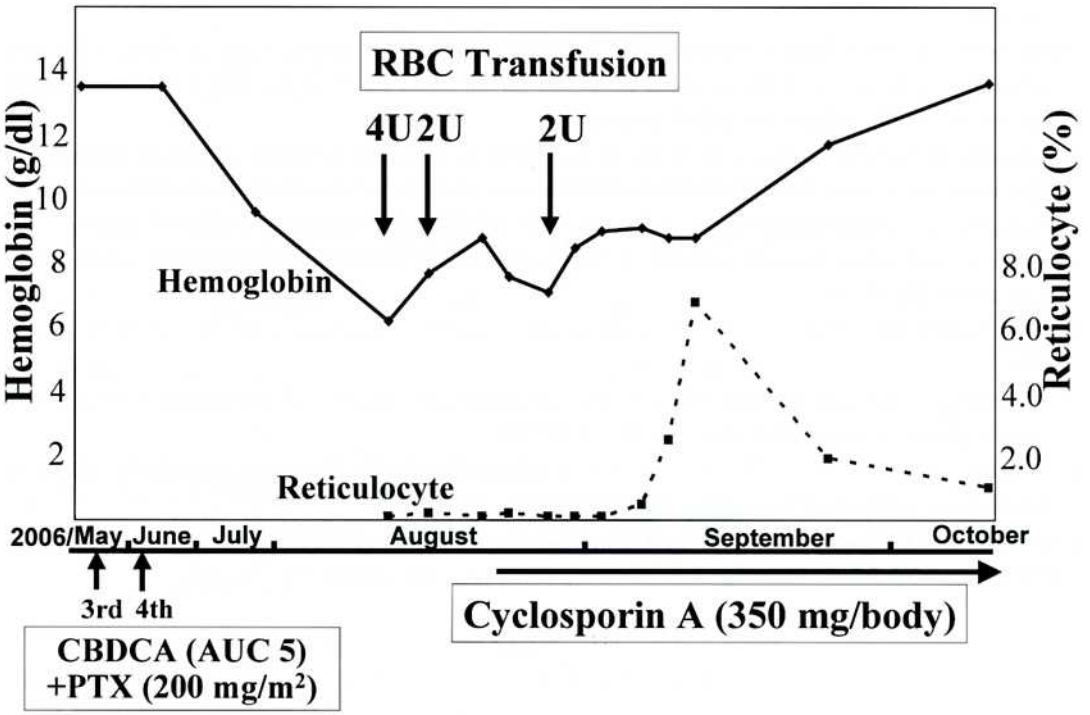

Fig. 4. Clinical course. CBDCA= Carboplatin, PTX= Paclitaxel, AUC= Area under the curve, RBC=Red Blood Cell.

of cyclosporin A administration in our patient.

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