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Preliminary report

Progressive peripheral CD8$^+$ T lymphocytosis complicated by pure red cell aplasia following immunosuppressive therapy for thymoma-associated myasthenia gravis

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ABSTRACT

We herein report a unique case of type B2 thymoma-associated myasthenia gravis which was ameliorated by immunosuppressive therapy in combination with chemotherapy. However, the patient subsequently developed pure red cell aplasia and marked lymphocytosis after additional chemotherapy aimed at improvement of thymoma. While a separate immunosuppressive regimen was effective for anemia, lymphocytosis was exacerbated. The biopsied thymoma specimen contained CD4$^+$, CD8$^+$, and CD4$^+$/CD8$^+$ T cells, some of which were CD3$^-$, suggesting immature thymocytes. In contrast, majority of the peripheral lymphocytes were polyclonal CD3$^+$/CD8$^+$/T cell receptor (TCR)αβ$^+$ T cells. The CD4/CD8 ratio in the present patient might be affected by immunosuppressive agents, resulting in CD8$^+$ T cell expansion associated with pure red cell aplasia. Although several cases of thymoma accompanied by peripheral T cell lymphocytosis were reported, marked CD8$^+$ T cell proliferation is extremely rare.

1. Introduction

Thymus is the primary site for maturation and education of T cells. CD4$^-$CD8$^-$ T cells, the most immature cells in the thymus, differentiate into CD4$^+$CD8$^+$ T cells. These double-positive cells can express functional αβ T cell receptors (TCRs) which are involved in signaling for differentiation to intermediate (CD4$^+$CD8^{low}) T cells that can in turn differentiate into either CD4$^+$CD8$^-$ or CD4$^-$CD8$^+$ mature T cells.

Although relatively rare, thymoma is one of the most commonly diagnosed tumors of the anterior mediastinum. Complete surgical resection is an important predictor for long-term survival in thymoma patients. However, patients at advanced stages are treated with radiation therapy and/or chemotherapy.

Thymomas frequently associate autoimmune disorders such as myasthenia gravis (MG), pure red cell aplasia (PRCA), and hypogammaglobulinemia. MG is an autoimmune disease mediated by acetylcholine receptor (AChR) autoantibodies. Approximately 30% of MG cases are accompanied by thymomas, and thymectomy results in the reduction of antibodies against AChR.

Here, we report a unique case of thymoma-associated MG accompanied by PRCA in combination with a marked peripheral expansion of mature CD8$^+$ T cells 2 years after the initial diagnosis.

2. Case presentation

A 40-year-old-female was admitted to our hospital for weight loss of 10 kg in 6 months, muscle weakness, and a mass in the mediastinum on chest X-ray. ^{18}F-Fluorodeoxyglucose (FDG)-positron emission tomography (PET) and computed tomography findings (Fig. 1A and B) revealed FDG accumulation within an irregular mass in the anterior mediastinum, which was extending to left posterior thoracic wall with massive pleural effusion. Laboratory findings (Table 1) were as follows: white blood cells, 9.10 × 10^9/L (with 49% lymphocytes); red blood cells, 4.18 × 10^{12}/L; hemoglobin, 13.1 g/dL; and platelets, 275 × 10^9/

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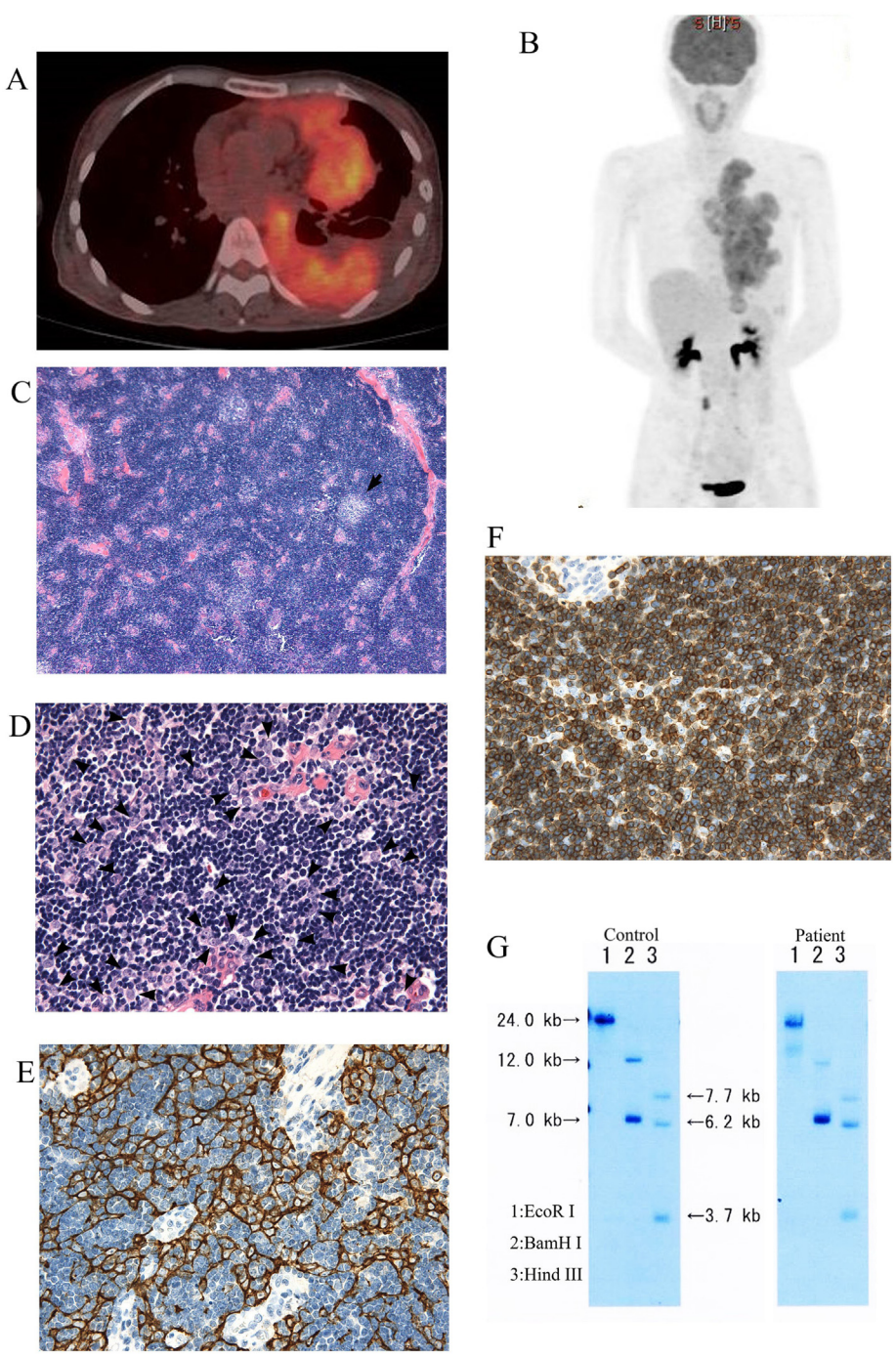

Fig. 1. (A–B) Imaging findings in the present case. ^{18}F-Fluorodeoxyglucose (FDG)-positron emission tomography (PET)/computed tomography findings reveal strong accumulation of FDG in a large, irregular mass (standardized uptake value $[SUV]_{max} = 5.0$) in the anterior mediastinum and the left posterior thoracic wall, with massive pleural effusion. (C–F) Histological and immunohistological examination of the intrapleural mass. (C) Analysis of the intrapleural mass exhibiting prominent large epithelial cells with numerous admixed lymphocytes. Only occasional medullary foci (arrow) are observed (haematoxylin and eosin staining). (D) High-power view showing epithelial cells with large, round, and vesicular nuclei with prominent nucleoli (arrowheads). Mitotic figures in the epithelial cells are rare. (E–F) Immunohistological examination showing CK AE1/AE3-positive epithelial cells (E) and mostly CD3-positive lymphocytes (F). (G) Southern blot analysis for T cell receptor (*TCR*)*β1* gene of the peripheral blood cells did not reveal rearranged bands.

L. Blood chemistry was almost normal, except for lactate dehydrogenase (300 IU/L; normal range, 120–245 IU/L), creatinine phosphokinase (732 IU/L; normal range, 50–210 IU/L), and soluble interleukin (IL)-2 receptor (620 U/mL; normal range, 145–519 IU/L). Elevated anti-AChR antibody levels (21.4 nmol/L; normal range, ≤0.3 nmol/L) were also observed.

Thoracoscopic biopsy of the intrapleural mass led to the diagnosis of type B2 thymoma (Fig. 1C–F) accompanied by MG and myotonic dystrophy. Complete surgical resection could not be performed, and the patient received 4 cycles of ADOC chemotherapy (52 mg doxorubicin, 0.75 mg vincristine sulfate, 920 mg cyclophosphamide, and 65 mg cisplatin), which led to a reduction in the thymoma size. Low-dose prednisolone (tapered from 15 mg/day to 7 mg/day) and tacrolimus (tapered from 1.5 mg/day to 0.5 mg/day) ameliorated the muscular symptoms and reduced AChR antibody levels. However, thymoma gradually worsened, and TS-1 was administered (100 mg orally for 14 days every 3 weeks) 14 months after ADOC chemotherapy.

The patient was referred to the hematology department because of progressive anemia after 4 courses of TS-1 therapy. Laboratory findings (Table 1) were as follows: white blood cells, 11.4×10^9/L (with 71% lymphocytes); red blood cells, 1.67×10^{12}/L; hemoglobin, 5.5 g/dL; and platelets, 172×10^9/L. Blood chemistry was almost normal, including lactate dehydrogenase, creatinine phosphokinase, soluble IL-2 receptor, vitamin B12, folic acid, ferritin, and anti-nuclear antibody levels as well as thyroid function, except for the levels of IgG (418 mg/dL; normal range, 820–1740 mg/dL) and IgM (36.2 mg/dL; normal range, 52.0–270.0 mg/dL). Bone marrow examination revealed hypocellular marrow with a slightly reduced megakaryocyte count.