Autoimmune Hemolytic Anemia and Myasthenia Gravis

Junichi KAMEOKA, Kazuyasu ENDO, Tomohiro SUGAWARA, Kyoko KANEDA,
Osamu FUKUHARA, Kuniaki MEGURO, Tadami SAKURAI, Akira MIURA,
Kumiko NAITO, Kaoru YOSHINAGA, Shozo NAKAMURA* and Masahiro OUCHI**

A case of autoimmune hemolytic anemia associated with myasthenia gravis in a 33-year-old female is presented. The association of autoimmune hemolytic anemia and myasthenia gravis is a very rare event, with only eight cases reported. The known association of these two diseases is reviewed. To our knowledge, this is the first reported case in which autoimmune hemolytic anemia preceded systemic myasthenia gravis.

Key words: Thymectomy, Prednisolone, Anti-acetylcholine receptor antibody

Autoimmune hemolytic anemia (AIHA) and myasthenia gravis (MG) are disorders in which autoimmune mechanisms are believed to be responsible for their pathogenesis. Both diseases have been reported to occur in patients with other autoimmune diseases. However, the association of AIHA and MG is rare. As far as we know, only eight cases have been reported (1–8). In seven of the eight previous cases, MG preceded the development of AIHA. Here we report a case in which MG developed during the remission period of AIHA.

CASE REPORT

A 33-year-old woman was found to have anemia during her first pregnancy, which had not been relieved by the administration of iron. In December 1981, she delivered a mature baby. After delivery she developed a rapidly progressive anemia and was referred to our hospital for clinical evaluation. She had received no specific medication except for oral iron and antacids. She had no significant past history or family history.

Physical examination revealed pallor, mild jaundice, and moderate hepatosplenomegaly. Laboratory investigations showed the following

values: the red blood cell count was $120 \times 10^4/\mu\text{l}$, hemoglobin 4.0 g/dl, platelet count $31 \times 10^4/\mu\text{l}$ and the reticulocyte count 17.3%. The white blood cell count was $9,400/\mu\text{l}$ with 71% neutrophils, 22% lymphocytes and 6% monocytes. The level of total serum bilirubin was elevated at 2.9 mg/dl (conjugated 0.8 mg/dl), LDH 721 IU/l and ESR was 185 mm in 1h. The serum immunoglobulin levels were as follows: IgG 1,500 mg/dl, IgA 184 mg/dl and IgM 67 mg/dl. The direct Coombs test was positive for IgG and C₃, while the indirect Coombs test was negative; antibodies showed no specificity against Rh or any other blood group antigens. The anti-nuclear antibody test and anti-DNA antibody test were negative. Bone marrow examination disclosed only erythroid hyperplasia with a myeloid to erythroid ratio of 0.39. ⁵¹Cr red blood cell survival studies revealed a half-life of 5.5 days.

A diagnosis of AIHA was made, and treatment with 40 mg/day of prednisolone was initiated. The hemoglobin level rose steadily to 10.3 g/dl after 2 wk. Reticulocyte count, total bilirubin level, and LDH level were returned to normal. The direct Coombs test, however, remained positive. She was discharged in February 1982.

From Second Department of Internal Medicine, *Department of Neurology, Tohoku University School of Medicine, Sendai and **Department of Surgery, National Sendai Hospital, Sendai

Received for publication April 18, 1990; Accepted for publication October 31, 1990

Reprint requests should be addressed to Junichi Kameoka, MD, The Second Department of Internal Medicine, Tohoku University School of Medicine, 1-1 Seiryō-cho, Sendai 980, Japan

During the subsequent 2 yr, prednisolone treatment was tapered to a maintenance dose of 10 mg every other day. From May 1985 the platelet count decreased gradually and the indirect Coombs test, as well as the direct Coombs test, were positive.

She was well until May 1986, when she complained of muscle fatigue and intermittent slurred speech. Result of an edrophonium chloride (Tensilon) test was positive. On suspicion of MG, she was admitted to the National Sendai Hospital in July 1986. Laboratory findings showed the following: RBC $365 \times 10^4/\mu\text{l}$, Hb 8.3 g/dl, platelet $9.3 \times 10^4/\mu\text{l}$ and WBC $2,700/\mu\text{l}$ (neutrophils 82%, lymphocytes 16% and monocytes 2%). Serological test showed an IgG level of 2,494 mg/dl, IgA level of 244 mg/dl and IgM 69 mg/dl; the antinuclear antibody test was positive at a serum dilution of 1:320, and the anti-DNA antibody test was negative. Both the direct and indirect Coombs test were positive. Anti-acetylcholine receptor antibody levels were measured at 308 pmol/ml (N; < 0.6 pmol/ml). Thyroid function was normal and antithyroglobulin and antimicrosome antibodies were negative. Urinalysis showed no proteinuria and the sediment was normal. Electromyogram of hypothenar muscles by repetitive stimulation at low frequency (5 Hz) disclosed a 26.9% decrement between the first and the fifth potential. Chest X-rays showed no evidence of thymoma.

MG was diagnosed and the patient was given 15 mg/day of ambenonium chloride, resulting in symptomatic improvement. In July 1986, she underwent thymectomy. The thymus weighed 25 g and the histologic specimens showed hyperplasia with germinal centers (Fig. 1). Postoperatively, the patient showed improvement in muscle strength and anti-acetylcholine receptor antibody levels fell to 127 pmol/ml. The decremental response by repetitive nerve stimulation also fell to 14.0% on electromyogram. AIHA was controlled well and platelet count returned to the normal range. She was discharged, receiving 10 mg/day of prednisolone and 15 mg of ambenonium chloride.

At the 3-yr follow-up evaluation in July 1989, the patient remained well on maintenance therapy with 7.5 mg/day of prednisolone alone. Hematological findings were as follows: RBC $394 \times 10^4/\mu\text{l}$, Hb 11.2g/dl, platelet $24.9 \times 10^4/\mu\text{l}$,

Fig. 1. Thymus with germinal center. HE $\times 100$.

WBC $5,200/\mu\text{l}$, and the reticulocyte count was 3.0%. There has been no recurrence of MG.

DISCUSSION

In our review of the literature, there have been only eight reported cases of coexisting AIHA and MG (1–8). We analyzed the reports of the nine cases, including the present case. The ages of these patients ranged from 25 to 62 yr, six of them were female and three were male. In seven of the eight previous cases, the onset of MG preceded the onset of AIHA by 2 months to 34 yr. In our case, AIHA preceded MG by 5 yr. AIHA preceded MG in another previous case, in which MG was the ocular type, the anti-acetylcholine receptor antibody was not increased, and the interval between the diseases was 3 yr (7). Microscopic descriptions of the thymus were available in seven cases (either by thymectomy or at autopsy), one of which showed thymoma, three disclosed hyperplasia with germinal centers, and the remaining three were normal.

It is of interest to note that AIHA developed after thymectomy for MG in three of the eight cases. The association of autoimmune diseases is well studied in MG and systemic lupus erythematosus (SLE). The development of SLE after thymectomy for MG has been reported in several cases, and reduced thymic factors has been speculated as the pathogenesis of SLE in these patients (9–12).

In contrast to SLE, there have been only a few studies on the thymic role in AIHA. Jenkinson and East injected splenocytes from NZB mice, a strain which develops AIHA spontaneously, into adult normal mice in two groups (13). Neonatally thymectomized mice developed AIHA, while intact

mice did not, suggesting that thymic cells may suppress autoimmune hemolysis. These experimental findings imply that thymectomy might induce AIHA. On the other hand, in a few cases of AIHA with thymoma, thymectomy has resulted in clinical improvement (14, 15). In one case of coexisting AIHA and MG, removal of a "normal" thymus brought about a remission of AIHA after 1 yr (5).

In the review of these reports, the relationship between AIHA and MG is still uncertain. We believe that the present case is well worth reporting because this is the first case of AIHA preceding systemic MG, which demonstrates that AIHA can occur in the absence of treatment for MG, particularly thymectomy. Further observations are necessary to clarify these associations.

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