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CASE REPORT

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# A case of pure red cell aplasia complicated by Evans syndrome

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**Abstract** A 33-year-old woman complaining of severe anemia was admitted to our hospital for polyclonal hyperglobulinemia. She was diagnosed with pure red cell aplasia (PRCA) associated with Evans syndrome. Initially, the presence of human parvovirus B19 (HPV B19) IgM appeared to indicate that the cause of PRCA was HPV B19 infection. Evans syndrome improved with steroid therapy, but PRCA was refractory. Cyclosporine was administered; consequently, the patient markedly recovered from PRCA and was discharged. PRCA complicated by Evans syndrome occurred during the course of polyclonal hyperglobulinemia. The most direct etiology for the onset of PRCA was unclear; however, immunological disorders such as polyclonal hyperglobulinemia, in addition to HPV B19 infection, may have been partly responsible for the etiology of PRCA.

**Key words** Cyclosporine · Evans syndrome · Human parvovirus B19 · Polyclonal hyperglobulinemia · Pure red cell aplasia

## Introduction

Pure red cell aplasia (PRCA) is a disease state in which erythroid hematopoiesis is reduced. The causes of PRCA include infectious diseases associated with human parvovirus (HPV) B19, thymoma, drug and lymphoproliferative disorders, and autoimmune diseases. The usual course of HPV B19-related PRCA is spontaneous resolution within 2–3 weeks. However, if the patient is an immunocompromised host, HPV B19 infection often persists for 3 weeks.[1] In this setting, intravenous immunoglobulin (IVIg), which contains antibodies to HPV B19, is often effective. In cases of autoimmune disease-related PRCA, treatment generally comprises steroid and cyclophosphamide, but patients resistant to these drugs are often administered cyclosporine. It has been reported that 65% of otherwise refractory patients respond to cyclosporine.[2] PRCA is often complicated by autoimmune hemolytic anemia (AIHA) and is classified under severe combined anemias.[3,4]

Here, we discuss a case in which PRCA was complicated by Evans syndrome, which is characterized by AIHA and thrombocytopenia.

## Case report

A 33-year-old woman with complaints of fever and dizziness was admitted to our hospital on June 30, 2003. In 1993, she had presented with swollen cervical lymph nodes, a neck rash, and pyrexia. At that time, she was suspected to have collagen disease and was referred to our department. Oral prednisolone (30 mg) was administered and then gradually tapered off and stopped in June 2001. However, in November 2001, she was again hospitalized for fever, parotid swelling, and swollen cervical lymph nodes, but her condition improved and she was discharged. From the beginning of October 2002, she experienced thirst, low-grade fever, and arthralgia. She was diagnosed with type I diabetes mellitus (DM) and diabetic ketoacidosis with a blood sugar concentration of 345 mg/dl, a hemoglobin A1c (HbA1c) concentration of 10.29%, urine ketone bodies (++), and she was positive for anti-glutamic acid decarboxylase antibody. Insulin therapy was initiated at this time. From May 2003, she experienced dizziness, palpitations, and body weight loss (10 kg per month). On June 8, 2003, she experienced sudden abdominal pain and was transported by an ambulance to a nearby emergency hospital.

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She was diagnosed with diabetic ketoacidosis, but she had also a markedly decreased Hb level (1.8 g/dl) and was diagnosed with PRCA by bone marrow biopsy. Further, she displayed signs of shock with blood pressure at 85/48 mmHg and facial pallor. Her body temperature was very low at 34.7°C, and the plasma adrenocorticotropic hormone (ACTH) level was high at 143 pg/ml (normal range 7.4–55.7 pg/ml). Hence, a complication of acute adrenal failure was suspected. Shock and severe anemia improved after blood transfusions and fluid replacement therapy, and she was discharged on June 23, 2003. However, she once again developed fever from June 27, 2003, and subsequently experienced dizziness and aggravated symptoms; she was once again referred to our department on June 30, 2003. She was hospitalized for further evaluation on the same day. She had a past medical history of vitiligo vulgaris at the age of 31 and amenorrhea at the age of 32.

On examination, the palpebral conjunctiva was apparently anemic. Lymph nodes on the neck, axilla, and inguinal region were swollen. Vitiligo was present on the neck. The spleen was palpable for one fingerbreadth on the left costal margin and was tender. No neurological findings were noted. Laboratory findings on admission were as follows (Table 1). The Hb level was very low at 4.8 g/dl; the reticulocyte count was also low at $0.326 \times 10^4$ per microliter. A direct Coombs' test was positive, indirect bilirubin was dominant, the aspartate transaminase (AST) and lactic dehydrogenase (LDH) levels were increased, and the haptoglobin level was decreased to less than 10 mg/dl. These findings suggested the presence of AIHA. In addition, the platelet count was also low at $9.0 \times 10^4$ per microliter, and the platelet-associated IgG level was very high. The patient was diagnosed with Evans syndrome on the basis of the presence of AIHA and thrombocytopenia. Regarding endocrine function, both the anti-thyroid peroxidase antibody and anti-thyroglobulin antibody were positive, and the ACTH and cortisol levels were both decreased. The thyroid-stimulating hormone level was increased; free triiodothyronine (T3) and free thyroxine (T4) levels were depressed. Immunological tests were positive for the anti-nuclear antibody and anti-Smith antibody; the patient was suspected to have systemic lupus erythematosus (SLE) with hemolytic anemia. However, there were no other signs of SLE, including malar rash, discoid rash, photosensitivity, oral ulcer, arthritis, serositis, renal disorder, and neurologic disorder, throughout the course from 1993. These findings did not fall under the SLE classification criteria proposed by the American College of Rheumatology in 1982.[5] A virus examination showed that HPV B19 IgM was equivocal and IgG was positive (HPV B19 IgM was increased to 1.33 in an earlier test conducted at another hospital). A bone marrow biopsy did not show any particular anomalies in granulocytes and megakaryocytes, but erythroblasts were markedly decreased in number, a finding consistent with PRCA.

After admission, methylprednisolone pulse therapy was initiated, and subsequently, 60 mg prednisolone for Evans syndrome was orally administered. In addition, mannitol–adenine–phosphate-added red cell concentrate (MAP) was transfused when appropriate. The AST, LDH, and bilirubin levels decreased, and Evans syndrome improved. However, the patient did not respond to steroid administration at all and the reticulocyte count remained low. Therefore, the oral administration of cyclosporine at 75 mg/day was initiated on the 26th hospital day. Subsequently, the reticulo-

**Table 1.** Laboratory findings on admission

| | |
|---|---|
| *CBC* | C3 90 mg/dl |
| WBC 4100 per microliter | C4 19 mg/dl |
| RBC $163 \times 10^4$ per microliter | CH50 40.4 U/ml |
| Hb 4.8 g/dl | TSH 8.73 IU/ml |
| Hct 13.8% | FT3 1.36 pg/ml |
| Platelets $9.0 \times 10^4$ per microliter | FT4 0.71 ng/ml |
| Reticulocytes $0.326 \times 10^4$ per microliter | Anti-Tg Ab 135 U/ml |
| | Anti-TPO Ab 2.0 U/ml |
| | ACTH 5.0 pg/ml |
| *Coagulation* | Cortisol 1.7 μg/dl |
| PT 71% | Anti-adrenal cortex Ab (–) |
| APTT 46.6 s | PA-IgG 255.8 ng/$10^7$ cells |
| FBG 296 mg/dl | Cold agglutinin ×2048 |
| FDP 13 μg/ml | Direct Coombs' test |
| D dimer 12 μg/ml | Anti IgG (+) |
| | Anti C3b/C3d (–) |
| *Blood chemistry and serology* | Indirect Coombs' test (+) |
| TP 8.9 g/dl | ANA (EIA) 55.4 |
| Alb 3.3 g/dl | Anti-ds-DNA Ab 5 U/ml |
| AST 46 IU/l | Anti-Sm Ab 67.5 U/ml |
| ALT 20 IU/l | Anti-RNP Ab ≤ 7.0 U/ml |
| LDH 1246 IU/l | Anti-SS-A Ab ≤ 7.0 U/ml |
| TB 2.8 mg/dl | Anti-SS-B Ab ≤ 7.0 U/ml |
| 2.7 mg/dl | Anti-CL β2GPI Ab 1.2 U/mlIB |
| ALP 180 IU/l | LAC (dRVVT) 1.04 |
| γ-GT 41 IU/l | HPV B19 IgM 0.97 (±) |
| BUN 11 mg/dl | IgG 10.07 (+) |
| Cr 0.4 mg/dl | |
| Na 131 mmol/l | *Urinalysis* |
| K 4.0 mmol/l | SG 1.007 |
| Cl 97 mmol/l | PH 5.5 |
| FPG 159 mg/dl | Protein (±) |
| CRP 8.47 mg/dl | Glucose (–) |
| Fe 170 μg/dl | Urobilinogen (±) |
| UIBC 6 μg/dl | Acetone (–) |
| Ferritin 8301 ng/ml | Bilirubin (–) |
| Haptoglobin <10 mg/dl | Occult blood (–) |
| IgG 3999 mg/dl | RBC 0 ~ 1/HPF |
| IgA 242 mg/dl | WBC 0 ~ 1/HPF |
| IgM 402 mg/dl | CPR 1.7 g/day |

CBC, complete blood count; WBC, white blood cells; RBC, red blood cells; Hb, hemoglobin; Hct, hematocrit; PT, prothrombin time; APTT, activated partial thromboplastin time; FBG, fibrinogen; FDP, fibrin degradation product; TP, total protein; Alb, albumin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; TB, total bilirubin; IB, indirect bilirubin; ALP, alkaline phosphatase; γ-GT, γ-glutamyl transpeptidase; BUN, blood urea nitrogen; Cr, creatinine; FPG, fasting plasma glucose; CRP, C-reactive protein; UIBC, unsaturated iron-binding capacity; Ig, immunoglobulin; TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; Anti-Tg Ab, anti-thyroglobulin antibody; Anti-TPO Ab, anti-thyroid peroxidase antibody; ACTH, adrenocorticotropic hormone; Anti-adrenal cortex Ab, anti-adrenal cortex antibody; PA-IgG, platelet-associated IgG; ANA, anti-nuclear antibody; Anti-ds-DNA Ab, anti-double strand-DNA antibody; Anti-Sm Ab, anti-Smith antibody; Anti-RNP Ab, anti-ribonucleoprotein antibody; Anti-SS-A Ab, anti-Sjogren syndrome A antibody; Anti-SS-B Ab, anti-Sjogren syndrome B antibody; Anti-CL β2GPI Ab, anti-cardiolipin β2 glycoprotein I antibody; LAC (dRVVT), lupus anti-coagulant (dilute Russell Viper venom time); HPV B19, human parvovirus B19; SG, specific gravity; HPF, high-power field; CPR, C-peptide immunoreactivity

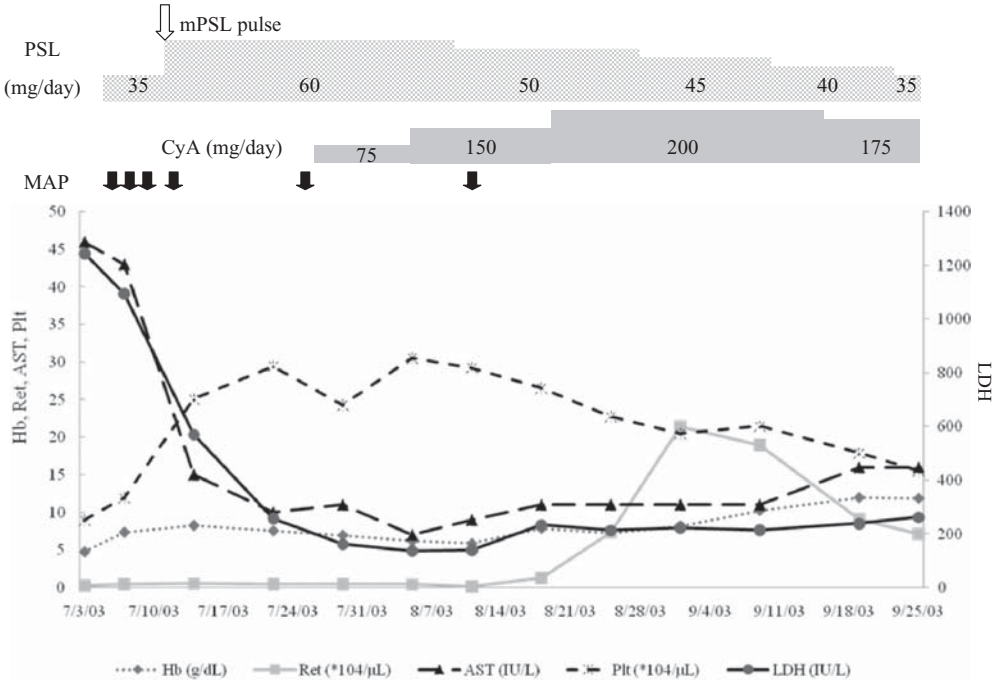


**Fig. 1.** Clinical course during admission. Hemolysis was improved by mPSL pulse therapy and the oral administration of 60 mg prednisolone. However, the reticulocyte count did not increase and anemia persisted. Therefore, cyclosporine was initiated on the 27th day, and as a result, the reticulocyte count began to increase and anemia improved. *PSL*, prednisolone; *mPSL*, methylprednisolone; *CyA*, cyclosporine; *MAP*, mannitol–adenine–phosphate-added red cell concentrate; *Hb*, hemoglobin; *Ret*, reticulocyte; *AST*, aspartate transaminase; *Plt*, platelet; *LDH*, lactate dehydrogenase

**Table 2.** Reported cases of pure red cell aplasia complicated by Evans syndrome

| Case | Country | Age/sex | Association | HPV B19 | Polyclonal hyperglobulinemia | ANA | Therapy | Outcome | First author |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Japan | 15/M | Hypoglobulinemia | + | – | Unknown | PSL | Alive | Oikawa[8] |
| 2 | Japan | 71/M | IBL | – | ± | Unknown | PSL 60 mg/day, CHOP | Alive | Tsukamoto[7] |
| 3 | Japan | Unknown | MPGN, Hypoglobulinemia | + | – | – | PSL 1 mg/kg/day, IVIG, splenectomy | Unknown | Katori et al.[9] |
| Present case | Japan | 33/W | DM, Hashimoto disease | + | + | + | mPSL pulse, PSL 60 mg/day, cyclosporine | Alive | |

IBL, immunoblastic lymphadenopathy; MPGN, membranous proliferative glomerulonephritis; DM, diabetes mellitus; PSL, prednisolone; IVIg, intravenous immunoglobulin; mPSL, methylprednisolone; M, man; W, woman

cyte count began to increase around the middle of August, and the Hb level also improved with an increase in the reticulocyte count. Because the course of DM was brittle, the dosage of insulin was adjusted for her blood glucose level; consequently, the blood glucose level was stable before her discharge. She was finally discharged after the 89th day of admission (Fig. 1).

## Discussion

In 1951, Evans et al.[6] reported cases of AIHA associated with complicated thrombocytopenia. Cases of PRCA complicated by Evans syndrome are very rare, and only three cases have thus far been reported in Japan (Table 2). One case revealed hyperglobulinemia[7] and the two other cases were associated with hypoglobulinemia;[8,9] the latter cases were diagnosed as acute PRCA caused by HPV B19 infection. It is thought that HPV B19 attacks and destroys proerythroblasts directly through the blood group P antigen (globoside) receptor.[10,11] In a normal immune response, aplastic crisis induced by HPV B19 is temporary and resolves spontaneously as a consequence of a rise in the virus antibody titer. However, an immunologically deficient status such as hypoglobulinemia does not permit viral elimination and results in persistent viral infection and finally in the development of PRCA.[1] HPV B19 often causes AIHA besides PRCA.[12] The persistent HPV B19 infection in cases associated with hypoglobulinemia may have caused PRCA complicated by Evans syndrome.

In addition, Tsukamoto reported a case associated with hyperglobulinemia complicated by immunoblastic lymphadenopathy (IBL).[7] IBL is characterized by systemic lymphadenopathy, hepatosplenomegaly, polyclonal hyperglobulinemia, and as specific findings of histology, the growth of mature or immature plasma cells and large juvenile lymphoblasts called immunoblasts.[13] Occasionally, in IBL, the anti-nuclear antibody becomes positive and SLE-like symptoms are observed.[14] Moreover, IBL often complicates hemolytic anemia and PRCA.[15,16]

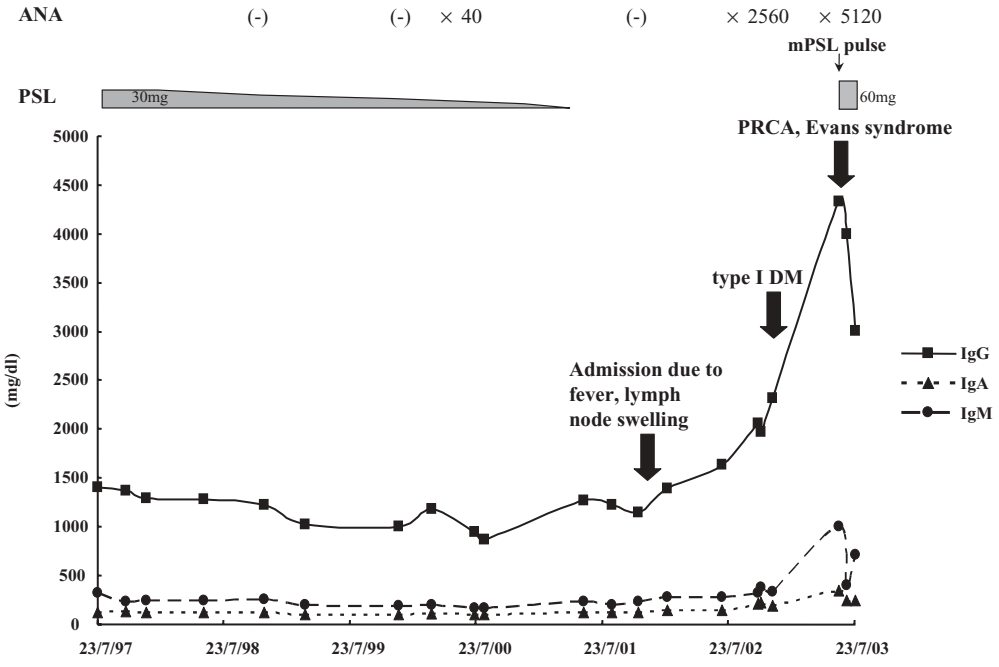


**Fig. 2.** Pre-hospitalization course. After discontinuation of predonisolone, serum IgG and IgM levels increased significantly, and subsequently various autoimmune diseases occurred. *ANA*, anti-nuclear antibody; *PSL*, prednisolone; *mPSL*, methylprednisolone; *PRCA*, pure red cell aplasia; *DM*, diabetes mellitus; *Ig*, immunoglobulin

In our patient, HPV B19 IgM was positive in an earlier test conducted at another hospital and was initially suspected to be the cause of PRCA. However, although the antibody titer of HPV B19 decreased, anemia did not improve. Therefore, when the administration of cyclosporine was initiated, PRCA markedly improved. The patient was previously administered prednisolone for repeated fever and lymph node swelling. However, when prednisolone was discontinued, the serum gamma globulin level increased significantly; subsequently, the anti-nuclear antibody became positive, and the patient developed type I DM, PRCA, and Evans syndrome (Fig. 2). Therefore, in addition to HPV B19 infection, immunological disorders such as polyclonal hyperglobulinemia may have been partly responsible for the onset of PRCA; but the most direct etiology for the onset of PRCA is unclear.

Autoimmune hemolytic anemia in the case of Evans syndrome is originally diagnosed as hemolytic anemia by a warm IgG antibody. However, in our patient, mixed-type AIHA, which Sokol et al.[17] proposed in 1981, was suspected because cold agglutinin was positive before hemolytic anemia developed. In the case of cold agglutinin disease, the complement is generally attached to the erythrocyte membrane, and the cold agglutinin adheres to the membrane for complement fixation and causes hemolysis. However, in our case, the adhesion of C3b/C3d to the erythrocyte membrane was not observed in the direct Coombs' test. Therefore, it was thought that the warm IgG antibody caused AIHA directly, and the cold agglutinin did not contribute to hemolytic anemia.

Regarding endocrine abnormalities, Anderson et al.[18] proposed that such abnormalities were characterized by autoimmune lesions. Thereafter, Neufeld et al.[19,20] suggested polyglandular autoimmune syndrome (PGA) to be an endocrine abnormality and classified the condition into two types. PGA type II includes type I DM and autoimmune-related thyroid disease and primary adrenal insufficiency. Our patient had a past medical history of type I DM and vitiligo vulgaris, and amenorrhea. In addition, at the onset of PRCA, the patient showed loss of weight, hypothermia, hypotension, increased level of ACTH, and suspected acute adrenal insufficiency besides diabetic ketoacidosis. At the time of admission, the patient had also chronic thyroiditis. Therefore, the patient may have had complications owing to PGA type II at the onset of PRCA. Occasionally, PGA type II also complicates vitiligo vulgaris and amenorrhea.[20] Complications of PRCA and PGA have been reported earlier to lead to the rearrangement of T cell receptors.[21,22]

In our patient, PRCA with HPV B19 infection occurred and was subsequently complicated by the Evans syndrome. Initially, it appeared that only HPV B19 infection was responsible for the onset of PRCA; however, immunological disorders caused by polyclonal hyperglobulinemia may have also contributed partly to the onset of PRCA. However, the most direct etiology for the onset of PRCA was unclear.

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