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# Pure red cell aplasia: Clinical features and treatment results in 16 cases

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**Abstract** Pure red cell aplasia (PRCA) is a rare hematological disease characterized by selective marrow erythroid aplasia. We report the clinical features and treatment results of 16 Chinese patients with PRCA. Nine (56%) cases were not associated with any underlying disorders and were considered idiopathic, while seven patients (44%) had associated diseases, three involving the thymus, two with T large granular lymphocyte leukemia (T-LGLL), and one each with Stevens-Johnson syndrome and acute hepatitis A. Conventional-dose corticosteroid therapy resulted in complete remission in three of 13 patients. Cyclosporin A was used in six patients. There were three complete and one partial remissions. High-dose methylprednisolone was ineffective in four patients who failed conventional-dose corticosteroids but achieved complete remission in one patient with thymoma who did not respond to thymectomy. Antithymocyte globulin was used in four patients, resulting in partial remission in only one patient with concomitant T-LGLL. Intravenous gamma globulin and danazol were ineffective in three patients. Thymectomy was performed in two patients, with one patient remitting. This is the largest series of PRCA reported in an oriental population. Our results indicate that treatment of PRCA may still be problematic and better therapeutic strategy will have to be defined.

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## Introduction

Acquired pure red cell aplasia (PRCA) is a rare hematological condition, characterized by severe anemia and reticulocytopenia, with normal white cell and platelet counts, and selective aplasia of the erythroid cell line in the marrow [6]. PRCA can be a primary hematological disorder in the absence of any other associated diseases. However, it may also be secondary to a wide variety of underlying disorders, including thymoma [10, 30], hematological malignancies such as chronic lymphocytic leukemia [1, 4], solid tumors [7], autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis [3, 5, 7], viral infections, particularly due to parvovirus B19 [33], and drugs [7].

Primary (or idiopathic) PRCA is considered an autoimmune disorder. Antibodies directed against heme synthesis or erythroid progenitors have been described [15, 23]. However, it can also be cell mediated. T lymphocytes, including cytotoxic T cells and T cells or T$\gamma$ cells of the large granular lymphocyte type, have been shown to specifically suppress erythropoiesis [12, 21, 24]. Owing to the autoimmune nature of PRCA, a variety of immunomodulatory agents and methods, including corticosteroids, cytotoxic drugs, antithymocyte globulin, intravenous immunoglobulin, and plasmapheresis [22], have been used to treat this disorder. However, the optimal therapeutic strategy has not been defined. We report our experience of 16 Chinese patients with PRCA and discuss the therapeutic strategy adopted.

## Patients and methods

*Patients.* Between 1989 and 1994, 16 consecutive Chinese patients with PRCA were seen at two regional hospitals in Hong Kong, which served a population of 3 million. The diagnosis of PRCA

was based on the findings of anemia, reticulocytopenia (<0.1%), and selective erythroid hypoplasia/aplasia in a normocellular marrow with normal myeloid and megakaryocytic cell lines. Vitamin $B_{12}$, folate and iron deficiencies were excluded. Both the peripheral blood and marrow were carefully scrutinized for evidence of lymphoproliferative disorders or increase in large granular lymphocytes. Immunophenotyping of peripheral blood lymphocytes was performed when there was evidence of an underlying lymphoproliferative disorder. Computerized axial tomographic (CAT) scan of the thorax was performed in 12 patients irrespective of the appearance of the chest X-rays, but it was not done in four other patients who had normal chest X-rays. Cases with no demonstrable underlying diseases were classified as idiopathic PRCA. Those with a demonstrable underlying disorder, including thymoma, were classified as secondary PRCA.

*Treatment.* Regular transfusions to keep the hemoglobin above 10 g/dl were given to all patients. Surgery was offered to patients with a thymic lesion demonstrated by CAT scan. In the other patients, first-line therapy was conventional-dose corticosteroids (prednisone at 1 mg/kg/day, tailing when a response occurred). When a response was not observed, second-line therapies were used, including cyclosporin A (CsA, 8 mg/kg/day, initial serum level 200–400 ng/ml, tailing when a response occurred), "pulse" methylprednisolone (1 g/day for 3 days, then 0.5 g/day for 3 days), antithymocyte globulin (Atgam, Upjohn, 25 mg/kg/day), intravenous gamma globulin (IvIg, 400 mg/kg/day for 5 days) , and danazol (200 mg three times daily). Complete response was defined as return to normal hemoglobin level (>11 g/dl), re-establishment of erythropoiesis (erythroid precusors >10% of marrow nucleated cells), and independence from transfusion. Partial response was as above, but with hemoglobin less than 11 g/dl.

## Results

*Patients.* The clinical features of the patients are summarized in Table 1. Nine patients (56%) had no demonstrable associated diseases, and their PRCA was classified as idiopathic. Three patients (19%) had thymic enlargement demonstrated on CAT scan. Two patients underwent thymectomy, one showing an epithelial thymoma and the other thymic lymphoid hyperplasia. Two patients (12%) had underlying T-large granular lymphocyte leukemia (T-LGLL), both showing CD3+ CD4− CD8+ CD16− CD56− LGLL in the circulation, one of whom had been reported previously [17]. In the other patients, careful scrutiny of the peripheral blood and bone marrow did not reveal evidence of a lymphoproliferative disorder. PRCA was concomitant with drug-induced Stevens-Johnson syndrome in one patient. Another patient developed PRCA after an episode of acute hepatitis A infection, as shown by positive anti-hepatitis A IgM antibody and absence of antibodies against hepatitis B and C viruses. Twelve of the 16 patients had their serum immunoglobulin level tested at diagnosis, and all showed normal results.

*Response to corticosteroids.* First-line immunosuppression with conventional-dose steroids was given to all patients, except those with thymic lesions and one patient (patient 12) who died before commencement of therapy. Three patients had a complete response (two idiopathic and one post-hepatitis A). Steroids were successfully tailed off in all cases, and remission has been maintained for 18, 48, and 68 months. No relapse has been observed.

*Response to CsA.* CsA was used in seven patients (cases 5, 6, 7, 10, 11, 13, and 16). Prior therapies in these pa-

**Table 1** Clinical features and response to therapy of 16 patients with PRCA (*Hb* hemoglobin (g/dl), *WBC* white cell count ($\times 10^9$/l), *Plat* platelet count ($\times 19^9$/l), *Ster* prednisone, *HDM* high-dose methylprednisolone, *CsA* cyclosporin A, *ATG* antithymocyte globulin, *IvIg* intravenous gamma globulin, *CR* complete response, *PR* partial response, *NR* no response)

| Case | Sex/ age | Hb | WBC | Plat | Associated disease | Response to therapy (months given) | | | | | Outcome (months) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Ster | HDM | CsA | ATG | Others | |
| 1 | M/76 | 2.7 | 4.8 | 227 | Nil | NR (l) | — | — | — | — | Transfusion dependent (67) |
| 2 | F/23 | 3.9 | 4.4 | 216 | Nil | CR (8) | — | — | — | — | CR (68) |
| 3 | F/76 | 6.0 | 5.0 | 265 | Nil | NR (5) | — | — | — | Androgens; NR (5) | Transusion dependent (37) |
| 4 | F/56 | 7.3 | 7.2 | 519 | Nil | CR (3) | — | — | — | — | CR (48) |
| 5 | M/72 | 3.5 | 4.0 | 160 | Nil | NR (6) | — | CR (l2) | — | — | CR (24) |
| 6 | M/34 | 6.5 | 5.2 | 185 | Nil | NR (6) | NR (1) | CR (16) | NR (1) | Androgens; NR (4) | CR (28) |
| 7 | F/73 | 5.8 | 4.0 | 150 | Nil | NR (6) | NR (1) | NR (3) | NR (1) | IvIg; NR (1) | Transfusion dependent (24) |
| 8 | F/65 | 2.6 | 9.4 | 360 | Thymoma[a] | — | — | — | — | — | Refused therapy, transfusion dependent (60) |
| 9 | M/60 | 4.0 | 6.0 | 206 | Thymoma | NR (2) | CR (1) | — | — | Thymectomy; NR | CR (15), died of emphysema |
| 10 | M/52 | 6.0 | 20.0 | 360 | LGLL | NR (4) | NR (1) | NR (6) | NR (1) | Myleran NR (6) | Transfusion dependent (28) |
| 11 | M/48 | 6.5 | 15.0 | 145 | LGLL | NR (4) | NR (1) | NR (6) | PR (1) | Myleran NR (6) | Transfusion independent (18) |
| 12 | M/26 | 7.8 | 6.6 | 92 | Stevens-Johnson syndrome | — | — | — | — | — | Died of complications of Stevens-Johnson syndrome |
| 13 | F/62 | 3.8 | 4.2 | 211 | Nil | NR (24) | — | CR (9) | — | — | CR (21) |
| 14 | F/28 | 3.6 | 5.0 | 200 | Thymic lymphoid hyperplasia | — | — | — | — | Thymectomy; CR | CR (33) |
| 15 | M/35 | 7.0 | 8.3 | 839 | Hepatitis A | CR (2) | — | — | — | — | CR (18) |
| 16 | M/60 | 7.6 | 4.1 | 288 | Nil | NR (8) | — | PR (3) | — | — | Transfusion independent (18) |

[a] Diagnosis based on CAT scan appearance and not confirmed by histology

tients included steroids, high-dose pulse methylprednisolone, and ATG. One patient (patient 7) developed impairment of renal function early on after CsA therapy, which necessitated its cessation. Of the other six evaluable patients, therapeutic benefit was seen in all the idiopathic cases (cases 5, 6, 13, and 16), with complete response in three cases (patient 5, 6, and 13) and partial response in one case (patient 16). Low-dose CsA (100–150 mg/day) was necessary to maintain the remission in these patients. Two patients (cases 10 and 11) with T-LGLL-associated PRCA showed no response.

*Response to other second-line therapies.* High-dose pulse methylprednisolone was used in five patients (cases 6, 7, 9, 10, and 11) after failure of conventional-dose steroids. There was one complete response in a patient (case 9) with thymoma who did not respond to thymectomy. Antithymocyte globulin (ATG) was administered to four patients (patients 6, 7, 10, and 11). Only one patient with T-LGLL (case 11) showed a partial response. He is currently transfusion independent with a baseline hemoglobin of 9 g/dl, but with no apparent improvement of his LGLL status. Two patients (cases 3 and 6) were given danazol (200 mg three times per day). No response was observed. One patient (case 7) was given IvIg without any response.

*Response to thymectomy.* Of the three patients with demonstrable thymic enlargement, one patient (case 8) had psychosis and refused any therapy except transfusion. Patient 9 showed a thymoma consisting of spindle cells mixed with ovoid cells, which was classifed as a mixed-type thymoma. No response was seen after surgery. He was given high-dose pulse methylprednisolone 9 months after surgery and was able to achieve a complete remission. Patient 14 had thymic follicular lymphoid hyperplasia, and complete remission occurred after thymectomy. She had been briefly reported previously [32].

*Transfusion dependence.* Five patients in our series became transfusion dependent. Aside from one patient who refused specific treatment, none of the other four patients had responded to steroids. Two patients (cases 1 and 3) did not receive further treatment because of their old age and concomitant systemic medical diseases. One patient (case 7) received multiple forms of treatment with no response. The subsequent development of diabetes mellitus and hypertension made the patient reluctant to accept further treatment. The final patient with T-LGLL (case 10) was refractory to multiple treatments and developed fulminant pulmonary tuberculosis while on ATG. He refused further immunosuppression.

## Discussion

This is the largest series of patients with PRCA reported in an Oriental population. Similar to other large Western series, the majority (56%) of patients had idiopathic PRCA. This series identified three (19%) patients with underlying thymic pathology, a frequency which is also similar to those reported in the West [6]. An interesting observation is the high incidence of T-LGLL (2/16, 12%) in our patients. In the West, PRCA is very rarely associated with T-LGLL, and only sporadic cases have been reported [7, 18]. However, the incidence of PRCA among T-LGLL in Japanese patients has been reported to be as high as 64% [26]. Thus, it appears that PRCA and T-LGLL may be commonly associated in Oriental populations. This is contrary to the West, where the most common lymphoproliferative disorder associated with PRCA is B-cell chronic lymphocytic leukemia (B-CLL). We have not seen this complication in our B-CLL patients during the study period (unpublished observation). The implication is that for oriental patients presenting with PRCA, a diligent search for an underlying T-lymphoproliferative disorder is warranted.

Our strategy has been to use conventional-dose steroids as the first-line therapy. However, conventional-dose steroids resulted in a response rate of only 23% (3/13). None of the patients who failed conventional-dose corticosteroids responded to high-dose "pulse" methylprednisolone [27], although one patient who failed thymectomy responded to it. Of note was the good response seen in the patient with PRCA complicating hepatitis A. Three similar cases showing good response to steroids have also been reported in the English literature [13, 31]. Thus, conventional-dose corticosteroids appear to be particularly effective for post-hepatitis A PRCA.

Of the second-line therapies, CsA was the most efficacious, achieving a complete response in four of six patients (66%). Therapeutic benefit was obtained at the lowest end (8 mg/kg/day) of the dose range of 8–12 mg/kg/day as recommended [16, 22]. All responders had failad previous therapies with steroids and/or androgens and ATG. In fact, the overall response rate of PRCA to CsA has been reported to be around 65% [28]. Although CsA works against T lymphocytes by a variety of actions, both patients with T-LGLL showed no response.

ATG has also been reported to be a useful modality in treating PRCA [2, 9, 20, 22]. Although none of our idiopathic cases responded to ATG, one of our two T-LGLL cases achieved a partial response. One similar case had been previously reported in the literature [11], although the response was unsustained. The mechanism of action of ATG in T-LGLL-associated PRCA remains unknown [14]. As direct inhibiton of erythropoiesis by leukemic LGL had been demonstrated [25], we postulate that only a subclone of the LGL leukemia was responsible for inhibiting erythropoiesis, so that its

suppression/elimination by ATG resulted in remission of PRCA but not the LGLL. Although intravenous gamma globulin and danazol have been reported to be useful in some patients [19], we have not observed any response in our patients.

Cytotoxic agents, including methotrexate [29], azathioprine [8], and cyclophosphamide [8, 16, 22, 23], have been reported to be useful in PRCA, particularly when combined with corticosteroids. Cyclophosphamide has been the main cytotoxic agent used, with a response rate reported to be as high as 55–80% [16, 22]. Unfortunately, we have not been able to test the use of cytotoxic agents in the treatment of our transfusion-dependent patients.

We conclude that conventional-dose steroids and CsA were both effective treatments. However, with a smaller dose, fewer side effects, and an apparently high efficacy, CsA may be the initial treatment of choice. For patients failing steroids and CsA, there remains the choice of ATG and IvIg, although responses are unpredictable. Cytotoxic immunosuppressive agents may be associated with long-term side effects and should probably be reserved for older patients [16]. However, despite these treatments, there may still be patients who are transfusion dependent. Thus, newer modalities of treatment will have to be developed for treatment of PRCA, to avoid the side effects of long-term transfusion.

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