Low- and intermediate-risk myelodysplastic syndrome with pure red cell aplasia

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ABSTRACT
Objectives: Our aim is to investigate the clinical characteristics of low- and intermediate-risk myelodysplastic syndrome (MDS) with pure red cell aplasia (PRCA).
Methods: We retrospectively reviewed the patients of low- and intermediate-risk MDS patients who had been diagnosed with PRCA in our hospital between January 2010 and December 2019.
Results: There were 6 low- and intermediate-risk MDS patients with PRCA in our study, 1 male and 5 females, with a median age of 63.5 (50-75) years. It accounted for 7.7% (6/78) of all diagnosed PRCA cases and 1.67% (6/359) of diagnosed MDS cases during the same period. All patients were treated with multiple drugs, including recombinant human erythropoietin, cyclosporine, glucocorticoids, androgen, sirolimus, intravenous immunoglobulin and decitabine. Two patients achieved complete remission, two patients achieved partial remission and became blood transfusion independent. Two patients had no response and one patient died.
Conclusion: Low- and intermediate-risk MDS with PRCA was difficult to treat, but the prognosis was good.

KEYWORDS
Myelodysplastic syndrome; pure red cell aplasia; diagnosis; prognosis; drug therapy; cyclosporine; glucocorticoids; androgen; sirolimus

Introduction
Pure red cell aplasia (PRCA) is a rare bone marrow failure syndrome only involving erythrocytes. Its clinical features include severe anemia, reduced reticulocytes, absence or severe reduction of bone marrow erythroid precursors, and normal white blood cells and platelets [1]. Myelodysplastic syndrome (MDS) is a group of heterogeneous malignant clonal hematopoietic stem cell diseases, with dysplasia in one or multiple lineage of myeloid blood cells, ineffective hematopoiesis, and high risk of transformation to acute myeloid leukemia (AML) [2]. Erythroid dysplasia is one of the distinctive features of MDS. Absence or extreme reduction of erythroid precursors is a rare form of erythroid dysplasia. A very small number of patients with MDS onset in the form of PRCA [3]. The differential diagnosis of low- and intermediate-risk MDS and PRCA is very difficult, especially for MDS without blasts.

Methods
We retrospectively reviewed 6 patients of low- and intermediate-risk MDS patients who had been diagnosed with PRCA in our hospital between January 2010 and December 2019. The diagnostic criteria of MDS and PRCA are based on literature [1,2].

Results and discussion
Our study found that there were 6 low- and intermediate-risk MDS patients with PRCA, 1 male and 5 females, with a median age of 63.5 (50-75) years. It accounted for 7.7% (6/78) of all diagnosed PRCA cases and 1.67% (6/359) of diagnosed MDS cases during the same period. All patients had severe anemia and were red blood cell (RBC) transfusion dependence. The median RBC transfusion was 4 (2-8) U /8 weeks. The reticulocytes are severely reduced. The number of white blood cells and platelets were normal. The bone marrow erythroid precursors were severely reduced, with a median of 1.25 (0.5-2.0) %. Serum erythropoietin (EPO) and ferritin levels were significantly increased. One patient had a 5q- and 20q- chromosome karyotype, and one patient had a 20q-chromosome karyotype during follow-up, one patient had 1q21. TET2, GATA2, KRAS and DNMT3A mutations were found in the patients. None of the 6 patients was positive for STAT mutations. According to the WHO 2016 MDS diagnostic criteria, one patient was 5q syndrome, and five patients had MDS-MLD (Tables 1 and 2).

All patients were treated with recombinant human erythropoietin, 5 patients were treated with cyclosporine, 5 patients were treated with glucocorticoids, 4 patients were treated with androgen, 2 patients were...
treated with sirolimus, and 1 patient was treated with hypomethylating agent (decitabine). Two patients achieved complete remission (CR), two patients achieved partial remission (PR) and became blood transfusion independent. Two patients had no response and one patient died (Table 3).

The causes of PRCA include that autoantibodies or autoreactive immune cells kill bone marrow erythroid precursors, viruses attack erythroid precursors, or defective hematopoietic stem and progenitor cells prevent differentiation into erythroid precursors [4].

Immunosuppressive agents such as glucocorticoids and cyclosporine are effective for PRCA caused by immune factors [5]. The majority of parvovirus B19-related PRCA responds well to intravenous immunoglobulin (IVIgG). However, PRCA caused by defective hematopoietic stem and progenitor cells has poor response, rapid progress and short survival time [4].

PRCA appeared in 1.6%-4.0% of patients with MDS [1,6,7]. The abnormal differentiation of MDS clonal stem cells and immune abnormalities are the main causes of PRCA. The higher risk group of MDS patients with MDS clonal stem cell differentiation dominates, while lower risk group MDS patients with immune abnormalities cause the destruction of erythroid precursors [4].

The differential diagnosis of PRCA and MDS is sometimes difficult. Patients with higher risk MDS have more blasts, which is relatively easy to distinguish from PRCA. However, in low- and intermediate-risk MDS, there are no blasts, which makes it difficult to identify. We found that neutrophils and megakaryocytes had dysplasia in lower risk MDS patients with PRCA including neutrophils with nuclear hyposegmentation and decreased cytoplasmic granules and micromegakaryocytes. During the follow-up, the quantities of white blood cells and platelets became abnormal. Although MDS-PRCA was significantly reduced in peripheral blood reticulocytes, it was significantly higher than that of immune PRCA. The bone marrow

Table 1. Clinical characteristics of low- and intermediate-risk MDS with PRCA.

| No. | sex | age (y) | TD | WBC (10^9/L) | Neutrophils (%) | platelet (10^9/L) | RBC (10^12/L) | Hb (g/L) | RET (%) | EPO (IU/L) | Ferritin (μg/L) | BMEP | marrow cellularity |
|-----|-----|---------|----|--------------|-----------------|------------------|---------------|----------|---------|------------|-----------------|------|------------------|
| 1   | F   | 65      | Yes| 6.65         | 65              | 280              | 1.26          | 63       | 0.12    | 714        | >2000           | 0.5  | normal           |
| 2   | F   | 50      | Yes| 7.18         | 53.4            | 281              | 1.22          | 45       | 0.6     | >750       | 662             | 1    | normal           |
| 3   | F   | 62      | Yes| 4.55         | 59              | 228              | 0.78          | 32       | 0.16    | >750       | >2000           | 1    | normal           |
| 4   | F   | 68      | Yes| 6.19         | 67              | 179              | 1.96          | 62       | 0.17    | >750       | >2000           | 1.5  | normal           |
| 5   | M   | 75      | Yes| 8.83         | 63.7            | 122              | 2.05          | 62       | 0.09    | >750       | >2000           | 2    | normal           |
| 6   | F   | 59      | Yes| 6.2          | 48.1            | 382              | 2.61          | 74       | 0.12    | >750       | >2000           | 2    | normal           |

MDS: myelodysplastic syndrome. PRCA: pure red cell aplasia. TD: transfusion dependent. WBC: white blood count. RBC: red blood cell. Hb: hemoglobin. RET: reticulocyte. EPO: erythropoietin. BMEP: bone marrow erythroid precursors.

Table 2. Cytogenetics, molecular abnormalities and subtype of low- and intermediate-risk MDS with PRCA.

| No. | Karyotype | Molecular abnormalities | MDS subtype (WHO 2016) | IPSS | R-IPSS |
|-----|-----------|-------------------------|------------------------|------|--------|
| 1   | Normal    | 1q21                    | NA                     | MDS-MLD | 0.5 INT-1 |
| 2   | 20q-      | 20q-,5q-                | NA                     | 5q-syndrome | 0 LR 2.5 |
| 3   | Normal    | Normal                  | NA                     | MDS-MLD | 0 LR 2.5 |
| 4   | Normal    | Normal                  | NA                     | MDS-MLD | 0 LR 2.5 |
| 5   | Normal    | Normal                  | NA                     | MDS-MLD | 0 LR 2.5 |
| 6   | Normal    | 20q-                    | KRAS, CARD11, KMT2D, FAT1 | MDS-MLD | 0 LR 2.5 |

MDS: myelodysplastic syndrome. PRCA: pure red cell aplasia. NA: Not available. IPSS: international prognostic scoring system. R-IPSS: revised international prognostic scoring system. LR: low risk. INT: intermediate.

Table 3. Treatment and prognosis of low- and intermediate-risk MDS with PRCA.

| No. | Therapy | Response | Death | Cause of Death | AML transformation | MDS progression | Follow up (months) |
|-----|---------|----------|-------|----------------|-------------------|-----------------|-------------------|
| 1   | EPO/CSA/CS/IVIgG | CR     | No    | -              | No                | No              | 22                |
| 2   | EPO/CSA/CS/Androgen/Tha | PR  | No    | -              | No                | No              | 30                |
| 3   | EPO/CS/ Androgen | PR     | No    | -              | No                | Yes             | 6                 |
| 4   | Androgen/EPO/RAP | CR     | No    | -              | No                | No              | 109               |
| 5   | EPO/CSA/CS/Androgen | NR    | No    | -              | No                | No              | 132               |
| 6   | EPO/CSA/CS/RAP/HMA | NR    | Yes   | Lung infection, sepsis | No  | Yes | 18      |

MDS: myelodysplastic syndrome. PRCA: pure red cell aplasia. EPO: recombinant human erythropoietin. CSA: cyclosporine. CS: glucocorticoids. IVIgG: intravenous immunoglobulin. Tha: Thalidomide. RAP: sirolimus; HMA: Hypomethylating drugs. CR: complete response. PR:part response. NR: no response. AML: acute myeloid leukemia.
erythroid precursors were significantly reduced, but most of them can still be seen in MDS-PRCA, while absent in the majority of immune PRCA. Chromosomal abnormalities and MDS related gene mutations can help diagnose MDS-PRCA.

The treatment of lower risk MDS-PRCA is less effective than immune PRCA, but overall survival is not significantly different from other low-risk MDS. Of our 6 patients, except for one patient who died at 18 months, the other 5 patients survived during the follow-up period without AML transformation, which were significantly better than high-risk MDS-PRCA patients [6,7]. Because anemia was the only symptom of all these patients, and EPO was the first-line drug for MDS anemia. All 6 patients were treated with EPO, 1 case was PR (patient 3), and 5 cases were no response. This may be related to the significant increase in the level of plasma EPO in patients [8]. One 5q-patient (patient 2) was treated with thalidomide after EPO failed. Cerchione et al. [9] used lenalidomide to treat 3 cases of 5q-PRCA, 1 case had response and 2 cases had no response. Although thalidomide is less effective than lenalidomide in 5q- syndrome, it was also effective in some patients [10]. Lenalidomide was not available at the time in China, thalidomide was chosen for the patient, but there was no response. Five patients received combined cyclosporine and glucocorticoids, two patients were PR, and three patients were NR. During the follow-up of one PR patient (patient 1), the parvovirus B19-IgM was positive, and the patient was CR after IVIgG treatment. One patient (patient 6) was refractory to EPO, cyclosporine, glucocorticoid therapy and sirolimus. She developed a 20q-chromosome abnormality and was treated with decitabine, but it was still ineffective and eventually died of severe infection. Hypomethylating drugs had no obvious effect in patients with low-risk MDS-PRCA, but had severe side effects, including neutropenia and infection. One patient (patient 3) was initially treated with androgen for CR. Relapse after 1 year, the patient had no response to EPO, but got CR after switching to sirolimus treatment. Sirolimus has good effect in the refractory and relapsed PRCA, with controllable side effects [11]. We used sirolimus to treat 2 cases of lower risk MDS-PRCA, 1 case of CR, and 1 case of NR.

Because the low incidence of low- and intermediate-risk MDS-PRCA, our report has only 6 cases, and further study is needed.

**Compliance with ethical standards**

**Ethical approval:** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent:** Informed consent was obtained from the patient included in the study.

**Disclosure statement**

No potential conflict of interest was reported by the author(s).

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