Isolated Isochromosome 17q in Myelodysplastic Syndromes with Pure Red Cell Aplasia and Basophilia

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Abstract

Myelodysplastic syndromes (MDS) with pure red cell aplasia (PRCA) have been shown to be a rare form of MDS. A 35-year-old man presented with pancytopenia: hemoglobin 59 g/L, reticulocytes 2×10⁹/L, platelets 33×10⁹/L, and leukocytes 1.8×10⁹/L with 1% blasts. Bone marrow was hypercellular with 50.4% myeloid cells, 0.0% erythroblasts, 25.4% basophils, and 5.6% myeloblasts. Dysplastic changes including pseudo-Pelger-Huët anomaly of neutrophils and mononuclear micromegakaryocytes were found. Immunohistochemistry with glycoporphin C confirmed erythroid aplasia. Cytogenetic analysis showed 46,XY,i(17)(q10)[18]/47,XY,+8[2]. Considering two reported cases, these findings indicate that isolated i(17q) may be implicated in the pathogenesis of MDS with PRCA as a recurrent cytogenetic aberration.

Key words: isolated isochromosome 17q, myelodysplastic syndromes, pure red cell aplasia, basophilia

Introduction

An isochromosome of the long arm of chromosome 17, i(17q), is frequently observed in accelerated and blast phases of Philadelphia (Ph) chromosome-positive chronic myeloid leukemia (1). In addition, i(17q) is occasionally detected as a sole abnormality in Ph-negative myeloid malignancies including myeloproliferative neoplasms (MPN), myelodysplastic syndromes (MDS), MDS/MPN, and their transformation to acute myeloid leukemia (AML) (2-8). It has been shown that isolated i(17q) is associated with marked granulocytic and megakaryocytic dysplasia and severe anemia in these myeloid malignancies (3-8).

MDS associated with pure red cell aplasia (PRCA), or with erythroid hypoplasia/aplasia, are rare forms of myelodysplasia, and characterized by moderate to severe anemia, reticulocytopenia, and profound reduction of erythroblasts in the bone marrow (9, 10). Approximately 50 cases have been reported in the literature, although the definitions of erythroid hypoplasia were heterogeneous: erythroblasts were 1% or fewer, or less than 5% of bone marrow cells (9-21).

These patients were predominantly elderly males, required regular red cell transfusions, and had poor prognoses mainly because of acute transformation (9). Thus, MDS with PRCA are thought to represent a distinct clinicopathological entity (10, 19). However, cytogenetic findings in MDS with PRCA have not been fully characterized. Here, we describe a new case of MDS with PRCA, which also demonstrated an isolated i(17q) and bone marrow basophilia.

Case Report

A 35-year-old man was admitted to another hospital because of general malaise and fever. Initial peripheral blood examination showed severe anemia: hemoglobin 41 g/L, platelets 138×10⁹/L and white blood cells (WBC) 5.2×10⁹/L. After repeated transfusions, the patient was transferred to our hospital for precise examination of anemia. On admission, peripheral blood values were hemoglobin 41 g/L, platelets 138×10⁹/L and WBC 12.3×10⁹/L with 2% blasts and 91% neutrophils. Serum level of C-reactive protein (CRP) was 30.68 mg/dL (normal range, <0.3). Computed tomography (CT) scans disclosed severe bilateral pneumonia.

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but not thymoma. After treatment with antibiotics and antifungal agents for one month, pneumonia was relieved and CRP decreased to 0.02 mg/dL. At this time, peripheral blood values were hemoglobin 59 g/L, reticulocytes 2×10^9/L, platelets 33×10^9/L and WBC 1.8×10^9/L with 1% blasts, 1% metamyelocytes, 1% band forms, 23% segmented neutrophils, 1% eosinophils, 27% basophils, 1% monocytes, and 45% lymphocytes. Serum levels of ferritin and erythropoietin were markedly elevated to 6,826 ng/mL (25-280) and 4,062 mIU/mL (0-29), respectively. Serum IgM antibody for parvovirus B19 was negative.

Bone marrow examination showed relative myeloid hyperplasia, erythroid aplasia and an increased number of megakaryocytes (Fig. 1A, B). Differential counts were 0.0% erythroblasts, 5.6% myeloblasts, 1.4% promyelocytes, 8.6% myelocytes, 22.2% metamyelocytes, 3.6% band forms, 14.6% segmented neutrophils, 2.8% monocytes, 4.6% eosinophils, 25.4% basophils, and 10.4% lymphocytes. Bilineal dysplastic changes, such as pseudo-Pelger-Huët anomaly of neutrophils and mononuclear micromegakaryocytes, were observed (Fig. 1C-G). Bone marrow biopsy revealed hypercellular marrow with myeloid hyperplasia and myelofibrosis (Fig. 2A, B). Immunohistochemistry showed that only a few cells were positive for glycophorin C, confirming erythroid aplasia, whereas almost all cells were positive for myeloperoxidase (Fig. 2C, D).

Immunophenotyping by three-color flow cytometry demonstrated that blasts were positive for CD13, CD16, CD33, CD41, and HLA-DR. The CD4/CD8 ratio in the T-cell population of bone marrow was inverted (0.49). G-banding analysis showed unrelated clones as follows: 46,XX,i(17)(q10)[18]/47,XX,+8[2] (Fig. 3A). Fluorescence in situ hybridization (FISH) with TP53/CEP 17 probes showed that one TP53 signal was deleted in 84 of 100 interphase nuclei (Fig. 3B). FISH with CEP 8 probe confirmed three CEP 8 signals in 6 of 100 cells (Fig. 3C). We next performed bone marrow scintigraphy with indium chloride (111In), because 111In is selectively incorporated into erythroid precursors after binding to transferrin (22). The scintigraphy exhibited a marked decrease of activity in the central bone marrow (Fig. 4).

We made a diagnosis of MDS, refractory anemia with excess of blasts (RAEB)-1, according to the World Health Organization (WHO) classification. There was no effect of pneumonia when the diagnosis of MDS was made. The association with PRCA was also confirmed by these laboratory findings. The disease was classified as intermediate-2 in the International Prognostic Scoring System (IPSS) and high in the WHO classification-based prognostic scoring system (WPSS) (23). Then, two months later after admission, the patient underwent myeloablative cord blood transplantation (CBT) from an human leukocyte antigen (HLA) one locus mismatched unrelated female donor. Before CBT, there was no significant change of hematological data: hemoglobin 64 g/L, reticulocytes 2×10^9/L, platelets 58×10^9/L and WBC 1.4×10^9/L with 2% blasts, 10% segmented neutro-
phils, and 22% basophils. CBT was performed after conditioning regimen with total body irradiation and high-dose cyclophosphamide. Tacrolimus and mycophenolate mofetil were used for graft-versus-host disease prophylaxis. He obtained hematological and cytogenetic complete remission (CR) and complete chimerism on day 28 after CBT. At the time of writing, he has been in CR for more than 21 months.

Discussion

We have presented an unusual case of MDS with PRCA, isolated i(17q), and basophilia. PRCA was characterized by bone marrow biopsy, immunohistochemistry, high levels of ferritin and erythropoietin, and a decrease of activity in the bone marrow scintigraphy as well as bone marrow smear. Granulocytic and megakaryocytic dysplasia and basophilia possibly due to i(17)(q10) were also found in the bone marrow. In spite of poor prognostic factors, the patient remains in CR after receiving CBT.

Isolated i(17q) is observed in approximately 1% of patients with MDS (4, 6). MDS with i(17q) appear to have several common clinical features: male predominance, advanced age, severe anemia, hypercellular bone marrow, eosinophilia/basophilia, increased micromegakaryocytes, hyposegmentation and hypogranularity of neutrophils, and poor prognosis (4). Among these, bone marrow eosinophilia and basophilia were shown to be specifically and most frequently associated with i(17q) (24). Thus, similar to MDS with PRCA, MDS with i(17q) also represent a unique subset.

With regard to cytogenetic findings in MDS with PRCA, results from a total of 37 cases are available (9-21). Twenty-six cases showed normal karyotypes, whereas 11 cases had acquired clonal abnormalities: add(1)(q42),-2,-18,-19,+2mar (1 case), del(5)(q13q33) (2 cases), del(5)(q14q34) (2 cases), t(6;8)(p15;q22) (1 case), +8 (1 case), i(17)(q10)/i(17q) (2 cases), and del(20)(q11q13) (2 cases). Together with the present case, i(17q) was found in 3 of 12 cases with cytogenetic abnormalities (4, 12), indicating that i(17q) as well as del(5q) are recurrent cytogenetic aberrations in MDS with PRCA (13).

Clinical information of MDS with PRCA and i(17q) is summarized in Table 1. The subtypes were classified as RAEB in all cases. Bone marrow erythroblasts ranged from 0% to 2%. All cases showed marked anemia, granulocytic and megakaryocytic dysplasia, and basophilia and/or eosinophilia. Cytogenetically, i(17q) was found as a sole abnormality in all stem lines, and trisomy 8 was found to accompany as an unrelated clone in two cases. These common findings suggest that MDS harboring isolated i(17q) and PRCA might constitute a novel clinical entity. Interestingly, in spite of severe anemia, dysplastic erythropoiesis has been hardly described in MDS with i(17q) (2-8). Thus, PRCA
Figure 3. Cytogenetic findings of the bone marrow cells at the diagnosis. (A) G-banded karyotype is 46,XY,i(17)(q10). An arrow indicates the i(17)(q10). (B) FISH with TP53/CEP 17 probe on interphase nuclei. One TP53 signal (red) and two CEP 17 signals (blue) are observed. (C) FISH with CEP 8 probe. Three CEP 8 signals (green) are confirmed.

Figure 4. Bone marrow scintigraphy with $^{111}$In shows a marked decrease of activity in the central bone marrow. Only intense renal activity is observed.

may be one of the mechanisms responsible for severe anemia in MDS with i(17q).

Isolated i(17q) results in monosomy 17p and trisomy 17q. We performed FISH with TP53 and confirmed the loss of 17p, which could be associated with pseudo-Pelger-Huët anomaly of neutrophils as reported in 17p- syndrome (25). On the other hand, trisomy 17q leads to the gain of myeloid-associated genes such as CSF3 (GCSF) and MPO located at 17q11.2-12 and 17q21.3-23, respectively (2). Molecular mechanisms of i(17q) in myeloid malignancies remain to be elucidated, but the existence of unrelated minor clones with trisomy 8 in two cases suggests that cytogenetically undetectable primary genetic events may precede isolated i(17q) (26).

MDS with PRCA seem to be divided into two subtypes: one with an increasing percentage of blasts in the bone marrow, and the other with no evidence of proliferative or blas-
tic change (11). The former is presumably due to an intrinsic defect of maturation and proliferation of erythroid precursors as a part of MDS, whereas the latter may have a possibly autoimmune etiology and a favorable response to immunosuppressive therapy. In fact, MDS patients successfully treated with cyclosporine were classified as RA, and T-cell receptor gene rearrangements with an inverted CD4/CD8 ratio were demonstrated (14, 19). In contrast, MDS with PRCA and i(17q)/del(5q) may belong to the former type because these cases were correlated with high percentages of blasts (4, 12, 13).

Treatment regimens for MDS with PRCA were varied: prednisolone, erythropoietin, cyclosporine, G-CSF, and azacitidine (9-21). Only one patient underwent allogeneic bone marrow transplantation after transformation to AML, and died at 57 months after the diagnosis (19). The low frequency of allogeneic stem cell transplantation (allo-SCT) in MDS with PRCA in spite of unfavorable cytogenetic abnormalities. Accumulation of more cases will be necessary to clarify the appropriate treatment for MDS with PRCA.

**The authors state that they have no Conflict of Interest (COI).**

**References**


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**Table 1.** Reported Cases of MDS Associated with PRCA and Isochromosome 17q

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age/ Sex</th>
<th>Dx (WHO)</th>
<th>WBC (×10^9/L)</th>
<th>Hb (g/dL)</th>
<th>Plt (×10^9/L)</th>
<th>EPO (mU/mL)</th>
<th>Mbl in BM (%)</th>
<th>Ebl in BM (%)</th>
<th>Eos in BM (%)</th>
<th>Dys-myo in BM (%)</th>
<th>Dys-mgk in BM (%)</th>
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<td>1</td>
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<td>2</td>
<td>13</td>
<td>7</td>
<td>pP, hy</td>
<td>mon</td>
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<td>33</td>
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