THE NATURAL HISTORY OF TRILINEAR MYELODYSPLASTIC SYNDROME AND ERYTHROLEUKEMIA

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ABSTRACT

A case of Di Guglielmo's syndrome passed through the three stages of chronic erythromyelosis, erythroleukemia and acute myeloid leukemia (AML). According to the FAB classification the subsequent stages of this syndrome were refractory anemia (RA), RA with excess of blasts (RAEB), AML-M6, AML-M2 and undifferentiated AML-M0 as the end-stage disease. Light- and electronmicroscopic findings on peripheral blood and bone marrow slides showed a pronounced trilineage myelodysplastic syndrome (MDS) during the RA, RAEB, AML-M6 and M2 phases of the disease, i.e. dysplastic erythropoiesis with PAS-positive erythroblasts, agranular and hypogranular neutrophils and dysplastic megakaryocytes. It is concluded that this case of Di Guglielmo's syndrome with chronic erythromyelosis, erythroleukemia and AML appears to be a continuum of trilineage MDS, AML-M6 and M2 with dyserythropoiesis which evolved into AML-M0.

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Key words: erythroleukemia, trilineage myelodysplastic syndrome, acute leukemia, FAB classification, electron microscopy

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The term erythroleukemia originates from the observation of both erythroblasts and myeloblasts in peripheral blood and bone marrow smears.1 Dameshek reassessed all variations of chronic and acute erythroleukemias and called it the Di Guglielmo syndrome.2 We prospectively studied a well-documented case of this syndrome and classified the subsequent stages of chronic erythromyelosis, erythroleukemia and pure acute leukemia according to the FAB classification for myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML).3,4

Case Report

A 36-year-old woman presented in 1984 with progressive fatigue, pallor and easy bruisingability. At the time of referral in July 1985, the hemoglobin level had fallen to 3.8 g/dL hematocrit 19%, erythrocytes 1.9×10¹²/L, reticulocytes 9.1%, MCV 110 fl, platelets 34×10⁹/L and white blood cells 8.4×10⁹/L. Differential count showed 6% band forms and 71% segmented neutrophils, 17% lymphocytes, 5% monocytes, a few pseudo Pelger neutrophils, 3 polychromatic and 174 orthochromatic dysplastic erythroblasts per 100 leukocytes. Erythroblasts in peripheral blood and bone marrow morphology were extremely abnormal with giant and multinuclear forms and nuclear budding and fragmentation. Several early and intermediate erythroblasts were as intensely positive with the PAS stain as the segmented neutrophils. The cytoplasm of the majority of neutrophils at different maturation stages was markedly hypogranular. The chronic erythremic myelosis progressively evolved into a mixed dyserythropoietic and myeloblastic proliferation of classical erythroleukemia, which subsequently progressed to acute leukemia after 18 months of follow-up (Table 1). The initial increase in mononucleated and binucleated abnormal micromegakaryocytes diminished. The majority of blasts (78%) were positive for peroxidase and negative for α-naphthyl acetate esterase, PAS, and acid phosphatase stains.

Two courses of intensive chemotherapy (daunorubicin, vincristine, and Ara-C) induced a reappearance of the erythroleukemic picture followed by acute myeloid leukemia. After a third and fourth course of chemotherapy (amsacrine, Ara-C, mitoxantrone) the disease terminated in a pure undifferentiated myeloblastic leukemia. The blasts were positive for the peroxidase stain.

Electron microscope studies of peripheral blood were performed after 1 year of follow-up at the time of erythroleukemia or blast transformation of RAEB, with dyserythropoietic peripheral blood and bone marrow (Table 1). Ultrastructurally the early and late erythroblasts and the reticulocytes displayed blebbing or an invaginated plasma mem-
brane (Figure 1, above). Platelets (Figure 1, above) showed a ruffled plasma membrane and micromegakaryocytes showed disordered demarcating membrane system (Figure 1, left). About half of the peripheral white blood cells were neutrophils, some of which possessed a labyrinth. The morphology and the number of granules varied considerably. The (crystalline-core) nucleated granule, which is first formed during granulopoiesis, is the predominant type of granule (see ref. #5). Aberrant forms as well as normal forms of nucleated granules were evident (Figure 1, right). Azurophil granules and specific granules were relatively rare. Auer bodies were also occasionally seen. Among the myeloblasts (18%) a distinct minor population of blast cells presented a crescent-shaped nucleus with one or two nucleoli and moderately condensed chromatin. In the cytoplasm, small and large granules and a relatively high number of mitochondria were present. At the time of end-stage disease one and a half years later, the ultrastructural picture of the peripheral blood consisted largely of such undifferentiated blast cells (Figure 1, below), which appeared to be peroxidase negative.5 Chromosome analysis of bone marrow nucleated cells at the time of chronic erythromyelosis and erythroleukemia metaphases revealed a normal 46,XX pattern. During the episode of RAEB-T/AML-M2, trisomy 8 was found in 10% of 45 cells analyzed as a transient minor

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<th>Table 1. Peripheral blood and bone marrow findings in a case of Di Guglielmo’s syndrome.</th>
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<tr>
<td>Time lapse in months after diagnosis</td>
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<tr>
<td>Leukocytes x10^9/L</td>
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<tr>
<td>Myeloblasts %</td>
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<td>Peroxidase stain</td>
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<td>Erythroblasts x 100 leukocytes</td>
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<td>Chemotherapy (CT)</td>
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clone during the early evolution of the disease. At time of end-stage myeloid leukemia, complex chromosomal abnormalities were found in 73% of 26 metaphases analyzed from peripheral blood cell cultures. The karyotype was 46,XX, del(2)(p21 or p22), t(4;5)(q28;ql5?), t(6; 19) (q22;q12), t(7; 10)(q21; p12).

### Discussion

Di Guglielmo's concept of erythroleukemia and acute erythremic myelosis is that of rather fulminating mixed forms of dual proliferation of erythroblasts at different maturation stages and immature myeloblasts in the bone marrow but initially often not in the peripheral blood. Chronic erythromyelosis is a slowly progressive refractory anemia and thrombocytopenia with dyserythroblasts in the peripheral blood and bone marrow without excess of blasts. The Di Guglielmo syndrome, if it runs its full course, passes through three subsequent stages of refractory anemia with dyserythropoiesis, gradual transition into mixed dyserythropoietic/myeloblastic proliferation and pure acute myeloid leukemia.

The subsequent stages of chronic erythromyelosis, erythroleukemia and acute leukemia in the Di Guglielmo syndrome presented here could be classified as refractory anemia (RA) with dyserythropoiesis, RA with excess of blasts (RAEB) and erythroblasts, AML-M2 with dyserythropoiesis followed by pure AML-M2. The light- and electron microscope findings in our case are typical of trilineage myelodysplasia with a slowly progressive increase of myeloblasts in the bone marrow. After chemotherapy a transient phase of AML-M6 reappeared and was followed by undifferentiated AML-MO in the end-stage disease.

Cuneo et al. documented various degrees of MDS involving multiple cell lineages in initial bone marrow smears in 20 patients with de novo or therapy related AML-M6. The myeloblasts were classified as undifferentiated MO in 8, M1 or M2 in 7 and M4 in 1. Kowal-Vern et al. distinguished two distinct morphological entities within erythroleukemia AML M6. One of these, with relatively preserved maturation of dysplastic erythropoiesis, originates from trilineage MDS and is incorporated in the FAB classification (AML-M6A). The other, with a preponderance of immature pro-erythroblasts in excess of 30% of the total erythroblastic population, is designated as acute erythroleukemia (AML-M6B). Cuneo et al. recognized two cytogenetic, clinicopathological pictures: the first, with major karyotypic abnormalities (MAKA) and maturation arrest of erythroblasts, involved 14 patients; the second, with minor karyotypic abnormalities (MIKA) and preserved maturation of erythroblasts, 6 patients. Olepade found no correlation between the degree of maturation arrest and atypia of erythroid precursors and the cytogenetic findings and prognosis in 26 cases of de novo AML-M6.

However, AML-M6 with complex cytogenetic abnormalities, especially of chromosome 5 and/or 7, is associated with unfavorable biological and clinical features, while AML-M6 with simple or no detectable cytogenetic abnormalities shows a more favorable clinical outcome after chemotherapy. Davey et al. distinguished two morphological groups of AML-M6 based solely on the ratio of proerythroblasts and basophilic erythroblasts to the total number of erythroblasts. Group 1, with proerythroblasts and basophilic erythroblasts in excess of 25% of total bone marrow erythroblasts, accounted for one fourth of the patients and group 2 comprised the remainder of the 52 cases of AML M6. Group 2 exhibited more karyotypic abnormalities and a lower rate of complete remission than group 1. This study confirms the strong relationship between response to therapy and chromosomal abnormalities.

The case presented here does not belong to the category of fulminating, acute onset erythroleukemias with immature erythroblasts, major cytogenetic abnormalities and very short survival. No or minor cytogenetic abnormalities were seen at onset of the disease. The acquisition of chromosomal abnormalities during clinical progression of myeloblastic transformation is well documented in all types of MDS. AML-M6 usually is unstable, clearly between trilineage MDS and AML and rapidly evolves to frank AML-M0, -M1, -M2, -M4 or -M7.

### References