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The Di Guglielmo Syndrome

IN 1923, under the designation of "erythremic myelosis,"1 Di Guglielmo described a “new” form of proliferative blood disease involving not the white cells but the nucleated red cells. His initial conceptions of an erythroblastic proliferation akin to leukemia were apparently derived from a case of mixed white cell-red cell disorder which he described in 1917 as "erythroleukemia."2 Although Di Guglielmo emphasized that "erythremic myelosis" was an acute, highly specific pathologic entity, his later publications have indicated not only some modification of his original views but a growing complexity of classification, particularly for so-called "mixed" forms.3 In the meantime, prolongation of the usual course of the disease by the use of such therapeutic methods as transfusions, antibiotics, etc., has revealed that the end-result of most cases is an acute leukemic process.4 It is time, therefore, to re-assess this condition which, in all its variations, we call the Di Guglielmo syndrome.

Di Guglielmo continually stressed the “purity” of the disorder as “an autonomous pathologic entity” of the erythropoietic tissue. Our own studies indicate that this concept is in need of revision. The pure erythroblastic proliferation must be extraordinarily rare, only a few unequivocal cases having thus far been reported. Our studies indicate that after six months or six years of striking proliferation of nucleated red cells, myeloblasts gradually increase and eventually become the predominant cells. At the end, an almost “pure” myeloblastic proliferation (acute granulocytic or myeloblastic leukemia) is present.

It becomes clear that the disease, if it runs out its full course, passes through several stages: 1) preponderant erythroblastic proliferation in the bone marrow; 2) mixed erythroblastic-myeloblastic growth; and finally, 3) preponderant myeloblastic proliferation. This is in keeping with the thought, previously expressed, that the Di Guglielmo syndrome is one of the several myeloproliferative disorders.5 Because the entire bone marrow participates to greater or lesser degree, highly variable pictures result not only from patient to patient but in the same patient as well. Parenthetically, it should be stated that our attempts to classify diseases into neat packages are so often imperfect because the diseases have their own (to us) confusing ways of behavior. If one conceives of the Di Guglielmo syndrome as a proliferative disease of the entire bone marrow, it becomes easier to realize that at any one time either one, two, or three of the bone marrow cells may be proliferating excessively, or that the proliferations may be hopelessly mixed.

We have used the term Di Guglielmo “syndrome” to encompass all the several variations one may see in the condition, ranging from the “pure” red cell proliferation to the “pure” myeloblastic form, although the term is not used if only myeloblasts are present as the first manifestation. “Erythremic myelosis” may be observed as the first and perhaps the only phase of the disease, but by dint of transfusions, etc., the patient may be “saved” to continue through the other stages. “Erythroleukemia” is in some respects a good
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term, embracing both concepts and features, but it fails to honor the pioneer contributions of Di Guglielmo.

Once one realizes that (a) the red cell proliferation may be simply the first stage of the larger, more complex syndrome and (b) that large numbers of nucleated red cells in the peripheral blood are by no means essential for the diagnosis (i.e., “anerythroblastic” forms may occur), it becomes apparent that some cases of “refractory anemia” and of “aplastic anemia with hyperplastic marrow” are in reality examples of the Di Guglielmo syndrome. How, then, is the definitive diagnosis actually made in such cases? We have found the following features helpful:

1. The anemia is of the normocytic, normochromic type, but with certain indices suggesting macrocytosis.
2. The bone marrow shows an extraordinary erythroblastic hyperplasia, suggesting hemolytic disease, but the reticulocytes of the blood are only slightly elevated (ineffective erythropoiesis).
3. The nucleated red cells of the marrow usually show many bizarre forms with polyploid types and megaloblastoid forms. However, the B12 concentration of the serum is normal or elevated, and there is no response to the administration of vitamin B12.
4. The fecal urobilinogen output in the feces may be quite high—indicative of increased hemolysis— but the Cr red cell survival time may be only slightly reduced. This may indicate “heme pigment diversion” as seen in pernicious anemia. Here, too, the fecal urobilinogen output is high in the presence of low reticulocyte level and, presumably, because of the lack of B12. This results in a condition of maturation arrest and of ineffective erythropoiesis, with “diversion” of heme pigment from its usual channels within the developing red cell to bile pigment production.
5. The bone marrow and blood smears show upon very careful inspection, even in the “pure” red cell proliferations, a fair number of myeloblasts sufficient to make the diagnosis of a myeloblastic, as well as of an erythroblastic, proliferation.

Recognition of the Di Guglielmo syndrome begins with study of the acute forms, where the large number of nucleated red cells in the blood and the highly abnormal marrow picture are quite characteristic. “Quieter” forms may then be recognized, in which only a few nucleated red cells in the blood are seen, but with a fairly characteristic marrow picture. If splenectomy is done in such cases, a great increase in nucleated red cells of the blood usually takes place without any apparent beneficial effect. Once diagnosis of the acute forms has been mastered, the chronic forms may be recognized. Here, the process may take years for its final development, up to 10 years in one of our unusually well documented cases, that of an army colonel. In such cases, the bone marrow shows erythroblastic hyperplasia—the anemia is “refractory”; there may be an occasional nucleated red cell or myeloblast in the blood, i.e., the “preleukemic status” of some authors. This probably represents the rather slow development of a proliferative process of the entire bone marrow in which the myeloblastosis may at first be so slight as to have little if any effect on the
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patient. Later, and presumably because of the ineffective erythropoiesis, the anemia becomes more marked. Eventually, despite the use of various therapeutic procedures, the course is one of progressive deterioration, usually with outspoken leukemia as the terminal manifestation. It is hoped that recognition of the several features of the Di Guglielmo syndrome will reduce still further the use of the rather meaningless term “refractory anemia” and will improve our understanding of the rather broad concept of the myeloproliferative syndrome.

WILLIAM DAMESHEK
MARIO BALDINI

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WILLIAM DAMESHEK and MARIO BALDINI

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