EDITORIAL

Riddle: What Do Aplastic Anemia, Paroxysmal Nocturnal Hemoglobinuria (PNH) and “Hypoplastic” Leukemia Have in Common?

By WILLIAM DAMESHEK

IN 1961, WE REPORTED 20 cases of severe aplastic anemia in which infusions of allogenic (homologous) bone marrow had been used as one of the therapeutic methods. Seven of these patients made apparently complete recoveries; whether coincidentally or in relationship to the marrow infusions is not clear. Since then, the use of allogeneic bone marrow infusions has been well-nigh discarded for the induction of transplantation, chiefly because of the difficulties involved with suppression of the rejection phenomenon, as well as for the possibility of development of the graft-vs.-host reaction. Of the recovered cases referred to above, three patients have subsequently (as of June 1967) developed the characteristic features of PNH. Originally it occurred to us that this unusually high incidence of PNH might have some obscure relationship to the infused allogenic marrow, but since PNH may follow aplastic anemia without the mediation of introduced marrow, this idea did not appear very likely.

During a recent trip to the Far East where aplastic anemia appears to be unduly prevalent (perhaps because the use of chloramphenicol is relatively uninhibited), it was evident that the incidence of PNH was also unduly high. Thus, in Manila, the Philippines, Dr. Allen Caviles of the Philippines General Hospital informed me that he had observed 71 cases of aplastic anemia in three years, 53 of which had been subject to follow-up; one of these had developed PNH. In the same period, nine cases of PNH had also been observed, five of them having been previously diagnosed as aplastic anemia. Dr. Tien-tse Hwang in Taipei, Taiwan, reported that he had observed 10–14 new cases of aplastic anemia annually, as well as seven cases of PNH at the two hospitals where he worked, one of them the large National Defense Hospital. Among the first 10 cases of hypoplastic anemia he had seen in 1966, one of them subsequently developed PNH. From these several observations, the factor of coincidence for the two apparently disparate conditions of aplastic anemia and PNH seems unlikely.

Dacie and Gilpin were the first to broach the possibility that PNH and aplastic anemia might be related. This was subsequently further emphasized by Dacie and particularly in Lewis and Dacie’s recent paper. Of 46 cases of aplastic anemia, seven had a positive Ham test for PNH and two actually developed clinical evidence of the disease. Conversely, of 60 patients with PNH, 15 showed aplastic anemia sometime during their course. In two such
cases of PNH we observed, the acid hemolysis tests became negative when aplastic anemia developed. In the cases presenting first as pancytopenia-hypoplasia, then later developing hemoglobinuria, it has been customary to stress PNH as the real or fundamental condition and the previously apparent hypoplasia as simply a pre-PNH manifestation.

Names are important chiefly from the symbolic standpoint; they project images! They might be described as “bullets” profoundly affecting our response to a given set of circumstances. Thus, the term “PNH” invokes the concept of a peculiar form of hemolytic anemia in which hemoglobinemia (and hemoglobinuria) develop nocturnally. This puts the disease into the category of the various hemolytic anemias and the hemoglobinurias, which are characterized (among other features) by shortening of the red cell survival time, an active bone marrow with blood reticulocytosis, hemoglobinemia, and bilirubinemia. It has been shown that the shortened red cell survival in PNH is due to an intrinsic defect of the red cell. Such defects are almost always of genetic origin. However, in PNH there is every indication that the disorder is an acquired one. How then can aplastic anemia and PNH be related?

Pancytopenia in PNH has been noted since the early writings on this disease. Thus Crosby, pointing to the usual leukopenia and thrombocytopenia—i.e., pancytopenia—suggested that all the bone marrow cells were involved in the disease. It is the red cell defect, however, that gives this condition its distinctive quality. Surely, the various factors in plasma which could be implicated in the actual hemolysis of the red cells (complement, “properdin,” etc.) are of little importance as compared with the red cell defect. Actually, PNH may be thought of as an acquired defect of the erythron occurring in a previously healthy individual. Once having developed, this defect is apparently self-perpetuating and ecologically advantageous. Indications of the defect are present, not only in the undue hemolysis in the presence of dilute acid, but by a great reduction in red cell cholinesterase, a striking sensitivity to complement and immune antibodies, a morphologic abnormality as seen by electron microscopy, and by the presence of a shortened red cell survival time when the red cells of the patient are injected into a normal individual. Thus, a certain proportion of the nucleated red cells of the bone marrow may be said to have developed an acquired, self-perpetuating abnormality which is sufficient to result in hemoglobinemia and/or hemoglobinuria. Stated in this way, PNH may be considered as a growth disturbance of the erythroblastic component of the marrow. Conceivably, it could be called “neoplastic,” a new kind of growth.

Why should a previously healthy individual develop this defect involving at least a portion of his red cell series? Why should leukopenia and thrombocytopenia be so commonly present? This brings us squarely to the heart of the matter. The more than coincidental relationship of PNH to aplastic anemia and the fact that the latter disease has been commonly associated with exposure to various chemicals or ionizing radiation suggest the possibility that the same agent which results in total marrow destruction may result in injury but not total destruction of one or another component of the marrow. Thus, one may speculate that certain chemicals, which in large dosage may destroy
APLASTIC ANEMIA, PNH AND "HYPOPLASTIC" LEUKEMIA

all the elements of the marrow, may in smaller amounts result in "selective" destruction of one of the marrow components or perhaps only in the loss of a key enzyme of some cells. Such injured cells might retain the capacity to reproduce themselves despite this deletion, and in this manner the formation of a self-replicating clone of abnormal cells might be induced. PNH could thus be a form of neoplasia—of the red cell series—developing, at least in some cases, as the result of an insult to the marrow. Similar reasoning has been applied to the development of leukemia.

As cases of aplastic anemia are followed, whether these are chemically or radiologically induced, or in association with congenital defects (Fanconi syndrome, the Werner syndrome*), it becomes evident that a number of them eventually develop increasing groups of primitive leukocytes in the marrow—i.e., "acute" or primitive cell leukemia. It is conceivable that this type of leukemia is based upon the initial development of a small clone of primitive leukocytes with defective maturation; eventually such a clone may gain ecologic dominance. Thus it is evident that marrow hypoplasia may be followed in some cases by "hypoplastic" primitive cell leukemia, in others by the development of a new type of (defective) red cell growth—i.e., PNH. From this, one may infer that a sufficiently severe "insult" to the marrow—whether chemical, ionizing radiation, or viral—may result in a variable degree of injury with a variable degree of hypoplasia (hypoplastic anemia). In some cases, abnormal clones of either leukocytes or red cells could conceivably arise during the process of repair. If the preponderance of bizarre cells were of the white cell type, "leukemia" would be diagnosed; if, on the other hand, the red cell injury were sufficiently marked as to result in hemoglobinuria, then the diagnosis of PNH would necessarily be made. Thus, at least some examples of the apparently different conditions of PNH, aplastic anemia, and "hypoplastic" leukemia might have a common denominator in the form of an "insult" to the marrow. As a correlative statement, what looks like "aplastic anemia" today might be either "acute leukemia" or PNH two years from now. It is conceivable that such a time lag might be essential to establish a sufficient mass of abnormal cells to result in clinical evidence of one or the other disease.

This attempt to put together in one pathogenetic package such apparently diverse abnormalities as aplastic anemia, PNH, and a form of leukemia is not meant to tear asunder the neat compartmentalization by which we, as physicians, tend to classify disease. Certainly, these "pigeonholes" have merit. On the other hand, in some circumstances they may impede at least conceptual progress. The usual tendency is to refer to the sequence of aplastic anemia-PNH as coincidental disorders, or perhaps as one condition "masquerading" for a time as another. It is conceivable that "lumping," as opposed to "splitting," might be better here. Thus, as in the myeloproliferative disorders and now

* With Dr. E. Perez-Santiago and Dr. Norman Maldonado, I have recently observed, at the Centro Medico of the University of Puerto Rico, a fascinating case of pancytopenia-hypoplastic anemia occurring in a young woman with the Werner syndrome (progeria). Subsequently, she developed increasing numbers of plasma cells in the bone marrow, and the previously diffuse hypergammaglobulinemia had begun a "monoclonal" spike. It was evident that she was now developing multiple myeloma.
perhaps in the field of aplastic anemia, PNH, and "hypoplastic" leukemia, a "vague" approach, as opposed to strict categorization, may have much in its favor. That a single "insult" to the marrow may be responsible for bringing about different kinds of abnormalities, sometimes occurring together, sometimes sequentially, deserves consideration, not only from the conceptual standpoint but from the experimental approach as well.

REFERENCES


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