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Review

Bone Marrow Failure Syndromes*

Blanche P. ALTER

The Polly Annenberg Levee Hematology Center, Departments of Medicine and Pediatrics, Mount Sinai Medical Center

Abstract The inherited marrow failure syndromes are a heterogeneous group, with all types of genetic patterns, and the entire gamut of symptoms and physical findings. The only condition which can be diagnosed with certainty is FA, because of the chromosome breakage ; even this diagnosis requires thinking of it first. Many of the patients with these syndromes are not properly diagnosed initially; since treatment depends on diagnosis, it is important that these conditions be considered for every patient with single or pancytopenia. Hematopoietic cultures may be useful for defining the diagnosis or determining the prognosis. Many of these syndromes can be detected in utero in subsequent preg-nancies, and thus there is an additional reason for early diagnosis of the propositus. Since at least heterozygotes for some of these conditions may be common (e.g. FA 1/200), it is reasonable to suggest that aplastic anemia genes may be sufficiently prevalent to explain even "acquired" aplastic anemia.

I. Introduction

My hypothesis is that what we call "ac-

quired" aplastic anemia (AA) occurs on a
background of either homozygosity or at least
heterozygosity for genes for bone marrow
failure. This discussion will describe the

phenotype of patients who are homozygous or hemizygous for some of those genes. Tables 1 and 2 outline the acquired and the inherited aplastic anemias, and Table 3 the single cytopenias.l," Many of the acquired aplasias that are secondary to a known insult such as drugs, chemicals, or viruses may occur as a "second hit" on a genetic background of

aplasia genes. Those that are called "idio-

pathic" may also have one or more bone marrow failure genes which we cannot yet identify. The single cytopenias can also occur as acquired or inherited conditions, and here too the relevant genes have not yet been identified.

In a 20-year interval at Boston Children's Hospital (from 1950 to 1970), there were 134

patients with aplastic anemia under age 20, of which 40 had some form of an inherited dis-order. Most of these were Fanconi's anemia

(FA), some were familial but not Fanconi's, and 4 of them were amegakaryocytic throm-bocytopenia who went on to AA. These numbers suggest that probably 30% of pe-diatric AA is inherited. In fact, this is not restricted to pediatrics. In an ongoing study of patients over 16 years of age referred to the National Institutes of Health for antithymo-cyte globulin or cyclosporine treatment (Dr. Neal Young, personal communication), 5 to 10% were found to have Fanconi's anemia by chromosome breakage, despite normal physical examinations. Those of us who learned in

medical school that patients with Fanconi's anemia have physical anomalies must now learn that they may be physically normal (see below).

II. Fanconi's Anemia (FA) (Table 4)

Patients with FA may range in appearance from multiple anomalies to totally normal. The oldest living patient is now 38, and is short, hyperpigmented, with microphthalmia, absent thenar muscles, hypoplastic thumbs,

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Reprint requests to Blanche P. Alter, Box 1079, Division of Hematology, Mount Sinai Medical Center, One Gustave L. Levy Place, New York, NY 10029, USA

138 The Japanese Journal of Pediatric Hematology Vol. 5 No. 2 (June 1991)

clinodactyly, and cafe au lait spots. The
"classical" patient is short
, microcephalic,
microphthalmic, with a broad nasal base, and
epicanthal folds. Thumb anomalies are seen
in almost 50% of patients, with radial hypo-

plasia not uncommon. Structural renal anom-
alies are found in •`25%. There are a
variety of other birth defects which occur less
frequently.1) In addition, however, as many
as 25% of FA homozygotes (proven by chro-
mosomal breakage, see below) may have
entirely normal physical appearances (the
so-called "Estren-Dameshek" patients), or may
have short stature and/or cafe au lait spots as
the only manifestations.
There are •`700 Fanconi's anemia patients
reported with this clearly autosomal recessive
disorder. The mean age at diagnosis was
around age 8, but at least 10% were older than
16, and 5% were less than 1 year. The male:
female ratio was 1.3 : 1.

Table 1 Acquired aplastic anemias

Modified from 1) and 2).

Table 2 Inherited aplastic anemias

Modified from 1) and 2).

Table 4 Fanconi's anemia

Modified from 1) and 2).

Table 3 Classification of the single cytopenias

Modified from 1) and 2).

Bone Marrow Failure Syndromes 139

The specific chromosome breakage analysis is done using peripheral blood" which is cul-tured for 3 days with phytohemagglutinin. For the last 24 hours, a DNA cross-linking agent such as diepoxybutane (DEB) or mitomycin C (MMC) is added to the culture. Patients with Fanconi's anemia are unable to repair crosslink damage, and so their mitotic figures following this treatment show numerous breaks, gaps, and rearrangements, as well as quadriradial figures. Although breakage may be increased spontaneously it is much magnified with these agents. The other chromosome breakage syndromes, Bloom's syndrome, xeroderma pig-mentosa, and ataxia telangiectasia, share with Fanconi's anemia an increase in spontaneous chromosome breakage, but the further increase with DEB or MMC is specific for FA. Prenatal diagnosis of FA has been done using chorionic villus or amniotic fluid cells, and examining for spontaneous and DEB- or MMC-induced breaks.

The hematologic problems in FA are often not noted until middle childhood. In retro-

spect, however, macrocytosis, increased fetal hemoglobin, and developing thrombocyto-penia may have been present long before the correct diagnosis was made. Erythro-poietin is usually substantially elevated. When aplastic anemia is present, the bone marrow is very hypocellular.
The first line of treatment of aplastic anemia in FA is usually androgens, if they can be used before the patient is totally aplastic. We usually use an oral androgen just because it is easier to manage, particularly in thrombo-cytopenic patients. It does have a risk of liver toxicity, and we monitor liver function very carefully. Androgens are combined with a little corticosteroid, since androgens will ac-celerate growth, and steroids may delay it. In addition, patients receiving steroids may bleed less at a given platelet count, because steroids may improve vascular integrity. Androgens prolong the projected survival by about 4 years, although they do not cure the patient. I have a patient now who has been on androgens for 8 years, and the 38-year-old man discussed above has been on androgens for more than 20 years. These are examples of those who can get long-term benefit. The

overall projected median survival is age 16 from the literature, including androgen-re-sponders, nonresponders, and untreated pa-tients.

Curative bone marrow transplant has been performed using an HLA-matched sibling, with approximately 70% projected survival. Standard preparation for marrow transplant for aplastic anemia uses 200 mg/kg cyclo-phosphamide. When that protocol was used in Fanconi's anemia, there was a high mor-tality rate, with only a 40% chance of survival, because cyclophosphamide damages DNA, and in these patients DNA of all cells, not just that of their bone marrow, is subject to a problem with chromosome breakage and repair. Dr. Eliane Gluckman in Paris recognized this, reduced the cyclophosphamide to one tenth of the normal dose, coupled with 600 Gy of irra-diation, and has achieved an approximately-70% disease-free survival rate in FA." Ad-

mittedly, most transplanted Fanconi's anemia patients are not beyond 5 years yet, and there are perhaps only a hundred Fanconi's anemia patients who have had marrow transplants worldwide. Although marrow transplant may be the cure for aplastic anemia in FA, I am not sure we know quite how to do it right yet. As in acquired aplastic anemia, mismatched or unrelated donor transplants are not any better in FA, and have a less than 25% survival rate. The most recent approach was described by Gluckman et al" : Chorionic villus cells were

obtained prenatally, DEB-induced chromo-some breakage was normal, indicating that the fetus was not FA, and HLA-typing indicated that the fetus matched the patient. Umbilical cord placental blood was collected at delivery, cryopreserved, and later used to reconstitute the patient. This approach permits the use of reconstituting material at a time when the donor may be too young to have general anesthesia for bone marrow harvesting.
FA patients have additional complications besides aplastic anemia. There is approxi-mately a 10% risk of leukemia, which may be prevented with marrow transplant. Approxi-mately 10% get other cancers, half of which are liver cancers, and the rest are usually squamous carcinomas. Half of these were in females involving the gynecologic system, and

140 The Japanese Journal of Pediatric Hematology Vol. 5 No. 2 (June 1991)

most of the others involved the GI tract, from
tongue to esophagus to stomach to colon to
anus. How does one treat these patients ?
The same agents used for treatment of their
malignancy will interrupt their DNA. The
leukemias are myeloid, and treatment is very difficult because normally treatment is to aplasia. Non-FA patients recover, but FA anemia patients may not, because they do lack residual normal stem cells.

Androgens have been implicated as causing the complications. Perhaps they cause some of the liver cancers, but there are a lot of patients who die of leukemia or other cancers who never had androgens, and many who never had aplastic anemia. Cancer is the complica-tion of the older patient, and cancers are the things we now warn the marrow transplant patients about, because they will live longer and may get cancer. The immunosuppressive preparation for transplant might actually ex-acerbate this tendency.
Older FA patients now enquire about the possibility of having children. Although male fertility is clearly decreased, often associated with hypogonadism or hypospermia, female fertility may not be substantially decreased. Among 110 FA females who survived to at least 16 years of age, there were 17 who be-came pregnant (15%), with a total of 26 preg-nancies (24 per hundred), resulting in 7 spontaneous abortions, 19 deliveries, and 18 living children. Although aplastic anemia often worsened during the pregnancy, almost all patients subsequently improved, and none died of hematologic complications in the peri-partum period."
Another major concern in many families, particularly those with young children, is the development of aplastic anemia. My labora-tory has performed in vitro erythroid cultures from the peripheral blood of more than 2 dozen FA patients. The development of burst-forming unit-erythroid (BFU-E)-derived colonies correlated to some extent with the

clinical status of the patient. Those few who had normal blood counts, including normal red cell mean cell volumes (MCV) and normal levels of fetal hemoglobin, had normal numbers of BFU-E, with a normal increase in low oxygen or with added hematopoietic growth

factors. Those whose in vivo hematopoiesis was only slightly impaired, such as those with increased fetal hemoglobin, macrocytosis, and/ or mild thrombocytopenia, had some BFU-E, but in reduced numbers. Most of the other

patients, including several with good clinical responses to androgens, had decreased or zero BFU-E." Thus it may be possible to predict hematologic outcome based on blood (or marrow) erythroid progenitor assays.

III. Dyskeratosis Congenita (DC)
(Table 5)
The next most frequent inherited marrow failure syndrome after FA is DC. More than 150 patients have been reported with this condition, of which three-fourths appear to have X-linked recessive inheritane, with the other cases divided between apparent auto-somal recessive and autosomal dominant."

The diagnosis of DC requires the triad of dyskeratotic nails, lacy reticular skin pig-mentation, and mucous membrane leuko-plakia ; the median age for this diagnosis was 20 years. Approximately half of the patients developed aplastic anemia, at a median of 15 years, and 10% developed cancer, in the third and fourth decades. Many patients were called "acquired" aplastic anemia until the diagnosis of DC was considered.
The category of X-linked recessives includes single case males, or male-only families, with maternal transmittance. Autosomal recessive

cases are those with sporadic females, con-sanguinity, and brother-sister sets. The auto-somal dominant cases are in 4 families with 2

or 3 generations of males and females. The assignment of a case to a category is a bit arbitrary ; for example, a single male case might be autosomal, not X-linked; a sporadic female could be autosomal recessive, dominant, or X-linked and Lyonized.
There may be other physical abnormalities in addition to the diagnostic triad. Epiphora is common, as is early loss of teeth and hair, hyperhidrosis of palms and soles, and gastro-intestinal problems. Patients with DC and aplastic anemia have at times been misdiag-nosed as FA. However, chromosome break-age is probably normal in DC, and is not in-creased with DEB or MMC. There is an

Bone Marrow Failure Syndromes 141

Xq28 restriction fragment length polymor-phism which may be useful for confirmation of some cases, as well as for prenatal diagnosis. The prognosis is not good in DC, with a projected median survival age of 33 years. The cancers are predominantly squamous cell, with a median survival of 35 years of age. Treat-ment of the aplastic anemia is not very suc-cessful, with death occurring at a median of 4 years after marrow failure. Androgens pro-duced only temporary respites, as in FA. Bone marrow transplant has been disappoint-ing, with only 1 survivor out of 5 2 deaths were at 2 and 7 years from venoocclusive dis-ease. Modifications of the preparations are needed, but it is not clear what these should be.

IV. Diamond Blackfan Anemia (DB)
(Table 6)
Inherited pure red cell aplasia has been re-ported in close to 400 cases, with a ratio of males : females of 1.1: 1. The median age at diagnosis was 3 months, with 10% diagnosed between 1 and 6 years. The diagnostic cri-teria include normochromic, usually macro-cytic anemia, reticulocytopenia, marrow eryth-roblastopenia although 10% may have normal or hyperplastic erythroid series, and usually normal white cell and platelet counts. Al-though most cases are sporadic, 14 families had dominant inheritance, and another 30 appear to be autosomal recessive, including 7 with consanguinity.
Thirty percent of the patients had some physical abnormality, usually less obvious than in FA. Low birth weight, short stature,

abnormal head or face, flat thenars, triphalan-geal thumbs, and other anomalies have been described. There is no correlation between the

physical examination and outcome.
Red cell adenosine deaminase is usually elevated,9) while macrocytosis, increased fetal hemoglobin, and increased levels of antigen-i and erythropoietin are almost always found. Chromosomes are usually normal, and break-age is not increased. Prenatal diagnosis has not yet been done prospectively.
Cultures of erythroid progenitors from blood or marrow show decreased numbers of colonies, with an increased requirement for erythro-poietin and/or IL-3 or other growth factors. Early suggestions that DB might be due to serum or cellular inhibitors of erythropoiesis have not been substantiated.

Patients were initially treated with trans-fusions, for which they had an absolute re-quirement. The usual therapy now is with prednisone or other corticosteroids, given daily or on alternate days. More than half the patients respond to this, and avoid routine transfusions. Up to 20% may have a spon-

Table 5 Dyskeratosis congenita

Modified from 1) and 2).

Table 6 Diamond Blackfan anemia

Modified from 1) and 2).

142 The Japanese Journal of Pediatric Hematology Vol. 5 No. 2 (June 1991)

taneous remission at any age. A few may
respond to Cyclosporine A, but the response is
usually transient. The projected median sur-
vival is 31 years of age, and only the group who
respond to steroids demonstrate a plateau in
the survival curve. Bone marrow transplant was successful in 10 of 13 reported cases, but not everyone agrees that DB is an indication for transplant. Leukemia was reported in 7 patients, indicating that DB is a premalignant condition, although less so than FA. There are no bona fide reports of aplastic anemia in DB patients.
Patients with transient erythroblastopenia of childhood (TEC) must be distinguished from those with DB. The former have a median

age of 2 years, with more than 90% beyond the first year of age at diagnosis. They usually have a history of an antecedent viral illness. At the time of diagnosis, they are anemic, with normal MCV and fetal hemo-globin. Most patients improve within 1 to 2 months, receiving either no specific treatment or 1 or 2 transfusions. The most prevalent in vitro finding is a serum-mediated inhibitor of erythropoiesis.

V. Amegakaryocytic Thrombocytopenia (Amega) (Table 7)
Patients with amega often present in the neonatal period with hemorrhagic symptoms and thrombocytopenia. There are 21 reports of such children, with normal physical ex-aminations, as well as 15 other patients with neurological or cardiac anomalies. Both types

of amegas have an excess of males, suggesting that some may be X-linked recessives, and other autosomal. In addition to thrombo-

cytopenia, red cell macrocytosis and elevated fetal hemoglobins were observed. Bone mar-rows were normocellular, with decreased or absent megakaryocytes. Half died from thrombocytopenic bleeding. Almost all of the rest developed pancytopenia, and most of these died. One patient evolved beyond aplasia to acute myeloid leukemia and then died, and another had a preleukemic myelodysplastic marrow with clonal aberrations of chromosome

19. Steroids alone or with androgens were only temporarily useful; one patient is a long-term survivor following bone marrow trans-plantation. Amega is a single cytopenia which does develop aplastic anemia, and is also a premalignant condition. It can be diagnosed prenatally by performing a platelet count on a sample of fetal blood obtained in the midtri-
mester.

VI. Thrombocytopenia Absent
Radii (TAR) (Table 8)
More than 150 patients have been reported with TAR. The diagnosis is usually made at birth, because of the bilateral absence of radii

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with thumbs present (a distinction from FA, where thumbs are absent if radii are absent). The condition appears to be an autosomal recessive, although there are only 2 reports of consanguinity. Most of the babies had bloody diarrhea, thought to be related to a milk allergy. In addition to the radial anomalies, half had abnormal hands, 40% abnormal lower limbs, 10% heart disease, and 10% hemangio-mas. Transient leukocytosis occurred in 70% of the patients. Bone marrows are normo-

Table 7 Amegakaryocytic thrombocytopenia

Modified from 1) and 2).

Table 8 .Thrombocytopenia absent radii

Modified from 1) and 2).

Bone Marrow Failure Syndromes 143

cellular, with decreased or absent megakaryo-
cytes.
Twenty-five percent of patients died from
bleeding in the first year. The current re-
commendation is to transfuse with single donor

platelets ; after the first year the platelet count
spontaneously improves and the children are
out of danger. There are no reports of evolu-
tion to aplastic anemia or leukemia in TAR,
and thus it is a true single cytopenia. Prenatal
diagnosis of the radial ray anomalies can be
done by ultrasound, and of the thrombo-
cytopenia by a fetal blood platelet count.

VII. Schwachman-Diamond Syndrome

(SD) (Table 9)
This syndrome consists of patients with
pancreatic insufficiency and neutropenia. More
than 150 have been reported; despite the
excess of males it is an autosomal recessive
disorder. Metaphyseal dysostosis and short
stature are common. Malabsorption is usually
diagnosed in infancy, as is the neutropenia; the
latter may be chronic, cyclic or intermittent.
The malabsorption responds to treatment
with pancreatic enzymes. Twenty percent
went on to develop aplastic anemia, and 5%
leukemia ; most of these died from infection or
bleeding, with a median age at death of 3 years
for those who died, and a median projected
survival overall of age 35. Treatment with
hematopoietic growth factors such as G-CSF
may offer hope for these patients.

VIII. Kostmann's Syndrome (KS)
(Table 10)
Infantile genetic agranulocytosis, or severe
chronic neutropenia, was reported in more than
100 patients, and is an autosomal recessive
disorder. The neutropenia is diagnosed early
in infancy, because of infections. KS is a
single cytopenia, with an absolute neutrophil
count below 200/ƒÊl. The bone marrow cellu-
larity is normal, with decreased mature myeloid
precursors, and often a maturation arrest. In
vitro colonies do grow, but do not contain
mature granulocytes, unless GM-CSF or G-
CSF is added.
The prognosis was poor for KS, with a
median projected survival of 3 years until
recently. G-CSF is now an excellent therapy

for KS, with improvement of neutrophil counts and alleviation of infections in treated pa-tients.10) Two patients were reported to
develop leukemia in the pre-G-CSF era.
Prenatal diagnosis may be possible using fetal blood for a neutrophil count.

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Table 9 Schwachman-Diamond syndrome

Modified from 1) and 2).

Table 10 Kostmann's syndrome

Modified from 1) and 2).

144 The Japanese Journal of Pediatric Hematology Vol. 5 No. 2 (June 1991)

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