Review Article

Inherited Bone Marrow Failure Syndromes – Challenges and Updates

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Abstract: Congenital or inherited bone marrow failure syndromes are hereditary syndromes of diverse nature which are characterized by inadequate production of blood cells causing cytopenias. Failure of bone marrow can be limited to one or more lineages of blood cells, along with symptoms specified to lineage, through it can affect all cell lineages leading to clinical picture like aplastic anemia. These syndromes are genetic diseases of heterogenous nature caused by germline mutations affecting basic pathways of cell including telomerase biology, biogenesis of ribosomes, structural proteins, and repair of DNA. Common inherited bone marrow failure syndromes consist of Schwachman – Diamond syndrome, Diamond – Blackfan anemia, Fanconi anemia, and Dyskeratosis Congenita. These syndromes have different prognosis and tendency to develop solid or hematological malignancies. Therefore, the adequate diagnosis of these disorders and their differentiation from other bone marrow failure syndromes and/or other etiologies of the bone marrow failure is very significant for surveillance and management of patients. Acquired causes may also lead to bone marrow failure including radiations, chemicals, drugs, immune diseases, viral infections, myelodysplastic syndromes, large granular lymphocytic leukemia, or paroxysmal nocturnal hemoglobinuria (PNH). Inherited bone marrow failure syndromes are heritable and affects family members as well, therefore need genetic counselling. In this review, differential diagnosis, various causes, and their pathogenesis are discussed for better understanding of inherited bone marrow failure syndromes.

Keywords: Bone marrow failure, Cytopenia, Inherited, Pathogenesis, Blood Cells, Syndromes.

INTRODUCTION

The Bone Marrow Failure (BMF) is uncommon and life – threatening state, occurs due to defective/ineffective hematopoiesis in bone marrow leading to cytopenias in blood, and decreased production of one or more cell lineages of hematopoiesis in bone marrow [1, 2]. BMF can be classified as inherited or acquired. Both phenomena can be seen in adults and children, though Inherited Bone Marrow Failure Syndromes (IBMF) are more frequent in children. IBMF are genetic disorders defined by failure of bone marrow, physical abnormalities, and genetic predisposition to develop malignancies. Common IBMF syndromes include Diamond – Blackfan anemia, Fanconi anemia, Dyskeratosis Congenita and Schwachman – Diamond syndrome. The overlaps are seen in their hematological and clinical manifestations. Although, various syndromes have different prognosis and risks to develop solid or hematological malignancies [3]. Therefore, adequate diagnosis of each disease is important for surveillance and management of disease in patients [4]. In this review, pathophysiology, differential diagnosis, and various approaches have been discussed in terms of IBMF.

IBMF syndromes are genetic diseases of heterogenous nature which are caused by germline mutations affecting primary pathways within cell including telomerase biology, synthesis of ribosomes, structural proteins, and repair of DNA [3]. Among these IMBF, no phenotypic-genotypic correlation is found e.g., mutations affect same pathways in cell leading to various phenotypes, as pure red cell aplasia (PRCA) in Diamond – Blackfan anemia, neutropenia in Schwachman – Diamond syndrome, or continuous and progressive failure of marrow in patients with Dyskeratosis Congenita [3]. Moreover, similar phenotype e.g., anemia along with reticulocytopenia may be caused by mutations that affect protein liable for synthesis of ribosomes such as in Diamond – Blackfan anemia or structural protein mutations in Congenital Dyserythropoietic anemia [3].

BONE MARROW FAILURE SYNDROMES CAUSING PURE RED CELL APLASIA

Diamond – Blackfan Anemia (DBA)

DBA is commonest reason for isolated failure of production of red cells. Most patients present clinically in 1st year of life in form of anemia dependent on transfusion. Though, patients may present in late years, as in non – classical DBA [4]. 7 per million births are affected by classical DBA. Congenital manifestations include short stature, dysmorphic faces, abnormalities of hand, kidney, and eye, in half of the patients [5]. This syndrome has tendency to transform into various malignancies i.e., acute myeloid leukemia, myelodysplastic syndrome, female genital malignancies, colon cancers and bone malignancies [6]. The incidence for development of

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solid tumors by 70 years is about 50%, although hematological malignancies are 5% by 50 years [6, 7]. The mean age for diagnosis is 3 months. These patients typically present clinically with macrocytic anemia and reticulocytopenia. There may be increased HbF, adenosine deaminase activity, strong antigen expressions on RBCs, increased folate, and vitamin B12 levels. The median survival age for these patients is 67 years [7]. The major causes for death in patients include infections, iron – overload complications etc. [4].

In DBA, in contrast to other IBMF syndromes, the bone marrow is mostly normocellular. Irrespective of normocellular bone marrow, the erythroid hypoplasia is evident. There is either absence or decrease in erythroid precursor cells [5]. Erythroid precursor cells are sparingly dispersed, although, in few patients, small clusters comprising of pro-erythroblasts may be seen. CD71 immunohistochemical marker can be used to identify these precursor cells [8]. In erythroid cell series, megaloblastic changes, resembling large pro-erythroblasts observed in infection with Parvovirus B19 [2]. Few dysplastic changes may be seen in erythropoiesis and granulopoiesis. Physiological increase in lymphocytes may also be seen [9]. There may also be increased in hematogones. TdT and CD34 expressed premature cells may be increased [10]. In one patient, p53 staining in erythroid precursor cells is reported. Variable patterns of staining is seen depending on status of disease and p53 mutation [11].

In elder children, differential diagnosis includes acquired causes of red cell aplasia e.g., infection with HIV or Parvovirus B19 transient erythroblastopenia of childhood (TEC), drug-induced or immune-mediated red cell aplasia. In acquired causes, there should not be history of anemia before disease onset [3]. Transient erythroblastopenia of childhood usually presents between 3 months to 4 years and continues for a month [12, 13]. Although the etiology of TEC is now known, a transient autoimmune process activated by infection or unknown factor in genetically predisposed individual is assumed [12-14]. Similar morphological features in DBA and TEC remain a challenge in diagnosis. Both diseases present clinically with erythroid hypoplasia, reduced or absent erythroid precursor cells and normal megakaryopoiesis and granulopoeisis. Although, it is seen that bone marrow in patients with DBA has increased cellularity as compared to TEC, perhaps due to earlier evaluation in early age in DBA. In TEC, a noticeable erythroid hyperplasia or lymphocytosis is seen in recovery phase which is not common in DBA [15, 16].

A careful approach should be taken while making diagnosis of dangerous conditions e.g., AML/MDS secondary to DBA because these entities show lower incidence and present in late stage [6, 7]. Bone marrow biopsies are commonly performed in neonates for diagnosis of DBA, and histological features resembling clonal evaluation are shown including hypercellularity of bone marrow, mild dyshematopoiesis and blast cells proliferation. For an accurate diagnosis, histological evaluations in combination with bone marrow and chromosomal studies should be performed [5]. When known abnormalities of chromosomes related to sporadic AML/MDS or multiple abnormalities of chromosomes are demonstrated, they are considered as warning characteristics [17, 18].

The differential diagnosis in first year of life include congenital dyserythropoietic anemia (CDA), hemoglobinopathies, Pearson syndrome, immune – mediated hemolytic anemia and hereditary hemolytic anemias. In patients of Pearson syndrome, bone marrow shows vacuolation within precursor cells along with high number of ringed sideroblasts are obvious and are not evident in patients with DBA. In hemolytic anemia, increased degradation products of hemoglobin along with splenomegaly is seen [3].

DBA is genetic disorder and have mixed patterns such as AD, AR, and X-linked patterns of inheritance [19]. In DBA, the anemia is severe requiring transfusion. Steroids are used for its management. In refractory cases, allogeneic hematopoietic stem cell transplant may be curable.

BONE MARROW FAILURE SYNDROMES CAUSING MULTIPLE CYTOPENIAS

Fanconi Anemia (FA)

Fanconi Anemia (FA) is the most common inherited bone marrow syndrome which is defined by progressive failure of bone marrow, congenital anomalies, fragility of chromosomes and tendency to develop malignancy [20]. Common congenital anomalies include short stature, lesions of skin e.g., hypopigmentation, hyperpigmentation, café au lait spots, and upper limb anomalies. In one-fourth cases, microphthalmia, microcephaly, hypogonadism and anomalies of renal system may be seen.

Fanconi Anemia usually presents clinically as failure of bone marrow between 5 to 15 years of age with 6.5 years as mean age of presentation [20]. Most common presentation is pancytopenia, although HbF persistence and macrocytosis may be seen. The bone marrow failure frequency by 40 years is 90% [21]. In patients with birth defects, the bone marrow failure frequency is more common, whereas in patients with no birth defects, there is higher chance for development of solid tumors and acute leukemia in late life. In patients with FA, the chance for development of acute myeloid leukemia is 600 times and head and neck squamous cell carcinoma is 500 times higher than general population [3]. In patients with FA, frequency of solid tumors is 20% by 65 years, leukemia and MDS is 50% by 50 years and 5% by 30 years [7]. 29 years is the median age for survival and patients usually die by complications from bone marrow failure, malignancies and HSCT.

In patients with FA, cellularity of bone marrow is hypoplastic [22]. Depending upon the disease stage and biopsy time, the cellularity may be variable. Butturini *et al*. showed in his study that examination of bone marrow at initial identification of hematological abnormality revealed hypocellularity in 75%, increased or normal cellularity in 13%, AML or MDS in 12% cases [23]. In early stage, the cellularity of bone marrow may be normal; though with increasing disease severity, it become hypoplastic or aplasic [2]. About 80% of patients develop bone marrow failure by 10 years [21]. In aplastic phase, the bone marrow may show severe hypocellular marrow or fatty marrow along with loss of erythroid, myeloid and megakaryocytic precursor cells. Histologically, these features cannot be differentiated from other causes of aplasia [2]. For accurate diagnosis, complete clinical evaluation is needed, and chromosomal breakage analysis may be required.

Dyserythropoiesis including immature components of erythroid precursors along with megaloblastic changes and/or atypical or abnormal erythropoiesis localization is seen [24]. Decreased megakaryocytes along with dysplastic changes i.e., micromegakaryocytes, may be seen which can be recognized by CD42b and CD61 IHC markers [22]. Sometimes decreased granulopoiesis along with dysplastic change may be seen [24]. Though detection of dysgranulopoiesis is not easy on bone marrow biopsy, left – shift usually accompany such findings [4]. On these findings, difference between FA and hypocellular RCC cannot be made on isolated histology. In FA and hypocellular RCC, mild dyshematopoeisis and absence of blast cells are overlapping findings [24]. Yoshimi et al. showed in one study diagnosed FA in 14.5% patients having consistent histological findings with hypocellular and normocellular RCC [25]. Few patients did not have physical abnormalities and family history. A chromosomal breakage analysis is mandatory is useful in such conditions to distinguish these two etiologies.

MDS related to FA mostly undergoes a phase of aplasia or hypoplasia followed by progressive development of abnormal clones in cytogenetics [24]. Cioc *et al*. explored the association between myelodysplastic syndrome and abnormalities in cytogenetics varied according to findings on morphology. They showed that cytogenetic abnormalities were seen in 100% patients with dysgranulopoiesis and increased blast cells, whereas in patients with dysmegakaryopoiesis, only 83% patients and in dysgranulopoiesis, only 33% patients showed cytogenetic abnormalities. They determined that adequate criteria for diagnosis for MDS related to FA were dysgranulopoiesis and increased blast cells, followed by dysmegakaryopoiesis [24]. In patients with FA, specific genomic and chromosomal abnormality pattern is related which progression to MDS [26]. In AML/MDS, 21q/RUNX1, 3q+, 1q+, 11q- and -7/7q abnormalities are seen. 21q/RUNX1, -7/7q and 3q+ are seen only in AML/MDS stage, while 1q+ may be seen in all stages [24]. In patients of FA with 1q+ abnormality only, there may be very delay or no progression in disease to AML/MDS.

In bone marrow of FA, p53+ cells are identical to that in AML/MDS not related to FA, but higher as compared to aplastic anemia or normal control [27]. The expression of p53 is found in patients of AML/MDS [28]. Therefore, a mutual process between AML/MDS of both FA related and unrelated is accountable for leukemic or pre-leukemic processes is present [27]. Although, it is not clear whether IHC staining of p53 can distinguish between FA from other causes of bone marrow failure, or either it can be used as predictor for progression of disease.

Dyskeratosis Congenita (DC)

Clinically, dyskeratosis congenita (DC) is defined by mucocutaneous abnormalities e.g., leukoplakia, abnormal pigmentation of skin and dystrophy of nail, tendency to develop tumors and failure of bone marrow [29]. Mucocutaneous abnormalities usually present before 10 years [3]. Before 30 years, approximately 80% patients show clinical features, and bone marrow failure is main reason of mortality in these patients. Initially only one cell lineage is affected, but with disease progression, pancytopenia may be developed. The histology of bone marrow appears normal or aplastic, like idiopathic aplastic anemia. If no abnormality of DC is present, then diagnosis become very challenging. In 75% patients, at least one physical abnormality is seen [1]. Physical abnormalities are mostly dependent on age, but absence of this does not exclude the diagnosis of DC [1].

14 years is the median age of presentation in DC [4]. Cytopenias may be seen before occurrence of physical problems. Within first decade, thrombocytopenia is first cytopenia to present [30]. The incidence of bone marrow failure is about 45% by 40 years. By 70 years, the incidence of MDS and leukemia is 10%, and by 50 years, the incidence is 20% [7]. Similar to FA, squamous cell carcinoma of head and neck region, tumors of anogenital and gastrointestinal regions are common solid tumors may occur in these patients [1]. The incidence of solid tumors by 65 years is 20%, with 49 years as median age of survival [1, 7]. Major reasons of deaths in these patients include malignancies, failure of bone marrow and pulmonary diseases. Rarely, pulmonary fibrosis may be associated with DC [29].

DC is caused by genetic mutations in genes involved in maintenance of telomerase [29]. An extensive range of diseases are related to biology of defective telomerase, collectively called telomerase diseases [4]. From these diseases, the classic DC characterizes the prototype. Other forms are recognized

including Hoyeraal – Hreidarsson syndrome, which is severe form of DC, in which multiple organs are affected [29]. This form is identified by microcephaly, cerebellar hypoplasia, intrauterine retardation of growth, immunodeficiency, and severe aplastic anemia. Revesz syndrome is also one of severe forms, characterized by bilateral exudative retinopathy along with classic features of DC [31].

Due to primary defect in telomere, higher mortality risk is associated with HSCT. The pattern of inheritance in DC is various including AR, AR or X-linked, along with common de novo mutations. In 70% cases, mutation in one of genes that maintain the telomerase is seen i.e., TERC, DKC1, TINF2, TERT, NOP10, NHP2, CTC1, WRAP53 and RTEL1. The commonest form of inheritance is X-linked recessive related to DKC1 gene which encodes core telomerase protein dyskerin component [3]. Due to abnormal maintenance of telomere, they are shorter, mostly beneath 1st percentile, in patients with DC [32]. In 5% patients of severe idiopathic aplastic anemia, one of the telomere genes associated with phenotype of DC can be seen [33]. Therefore, distinguishing aplastic anemia from DC by telomere length screening is essential before starting treatment. The flow – FISH is most important tool for screening patients of aplastic anemia [5]. Short telomere may also be observed in other syndromes of IBMF, although they exhibit custers of telomere length in lower optimal range [32].

Similar as FA, the cellularity of bone marrow depends upon disease stage and timing of biopsy. Hypocellular bone marrow is commonly observed, though in early stages, hypercellular marrow is evident. As with progression and severity of disease, the bone marrow become more hypocellular [10]. Short telomere length associates with severity of decreased counts, but association between length of telomere and degree of bone marrow aplasia is not clear [32]. In patients with DC, dysplasia may be seen in any cell lineage [29, 30]. Clusters of immature erythroid precursors with megaloblastic changes and irregular localization may be seen. The degree of granulopoiesis may be variable from decreased to normal to high with associated maturation to left shift. Megakaryopoiesis may be decreased with abnormal localization and micromegakaryocytes may also be seen [22]. Similarly, as FA, differentiation of DC from RCC is not possible on isolated morphology. For distinguishing these two conditions, measurement of length of telomere along with complete clinical examination is necessary. In bone marrow, isolated dysplasia is not sufficient to estimate progression to MDS. Abnormalities in morphology such as dysplasia, increased blast cells or cellularity is necessary to diagnose secondary MDS [34]. Additional presence of abnormalities in chromosomes e.g., monosomy 7, or multiple abnormalities in chromosomes increase risk for progression to malignancy [30].

In contrast to other IBMF syndromes, there is negative correlation between Ki-67 or survivin values and expression of p53, although the data is limited [27]. These findings suggest that pathway mediated by p53 is activated in DC, while there is impaired survivin and Ki-67 compensatory expression, thought the reason is not known.

Schwachman – Diamond Syndrome (SDS)

SDS is a disease associated with defect in ribosomes, characterized by bone marrow failure, neutropenia, associated insufficiency of exocrine pancreas, metaphyseal dysostosis and tendency to develop AML/MDS [35-37]. In majority of patients, biallelic mutations of SBDS gene that functions in biogenesis of ribosomes are seen [38]. Various systems may be involved such as cardiac, skeletal, neurocognitive, immune, and gastrointestinal. Physical abnormalities may be seen in half patients, including metaphyseal dysostosis, short stature, abnormalities in thorax, and developmental delay [1]. Dysfunction of exocrine pancreas with/without malabsorption is the hallmark of this disease [37]. Dysfunction of pancreas is seen in more than 90% patients, typically presents clinically as steatorrhea in first 6 months [36, 37]. Median age of presentation of these patients is 2 weeks, with reduced proteolytic enzymes secretion leading to steatorrhea [1, 37]. In biopsies of pancreas, replacement of fatty acinar cells, dilated ductules and increased interstitial connective tissue are evident [39]. In 50% patients, improvement in pancreatic function by age is seen, however the reason is not clear [40].

In approximately all patients, the commonest hematological abnormality includes neutropenia, either persistent or intermittent [41]. Though neutropenia is obvious in neonatal period, it presents usually after malabsorption. Chemotaxis of neutrophils is also impaired. In two-third patients, anemia is seen, and one-third shows thrombocytopenia. In contrast to other BMF syndromes, anemia in this condition is linked with adequate response of bone marrow and reticulocytosis. Macrocytosis and high HbF levels are seen in majority of patients. By age of 50, the incidence of bone marrow failure is around 40% and AML/MDS is 65% [7]. Cohort studies on SDS are not sufficient to assess risk of tumor development. In few patients, solid tumors are also reported [42, 43]. By age of 45 years, the incidence of solid tumors is 40%, with median survival age is 41 years [7]. Infections e.g., pneumonia or sepsis, myocardial necrosis and AML are major etiologies for mortality [1].

The diagnosis of SDS depends upon clinical features, followed by confirmation by genetic testing [37]. 50% of patients usually presents with neutropenia along with diarrhea [44]. Pancreatic isoamylase and trypsinogen are sensitive tests for dysfunction of pancreas [37]. On imaging studies, pancre-

atic fatty replacement and decreased fecal pancreatic concentration of enzymes supports the diagnosis. 90% of patients with SDS are diagnosed by detection of SBDS gene biallelic mutations [38]. DNAJC21 biallelic mutations is recently identified in patients of SDS [45].

The findings on bone marrow are not specific. The cellularity of variable; hypocellular, normocellular or hypercellular. The reason for hypercellularity may be because of increased B-cell progenitors, called hematogones [5]. The severity of peripheral cytopenias is poorly linked with cellularity [46]. Although, the hypocellularity in bone marrow is due to reduced granulopoiesis, a reduction in megakaryopoiesis and erythropoiesis may also be seen [37]. As in RCC, patchily hematopoiesis distribution is seen in hypocellular bone marrow. Dysgranulopoiesis is seen with maturation arrest to left shift. Dyserythropoiesis includes megaloblastic changes and/or presence of proerythroblasts with abnormal localization. Dysmegakaryopoiesis may also show micromegakaryopoeisis. If multilineage dysplasia is seen in SDS, it is indicative of development of malignancy [37].

There is higher risk for development of aplasia, MDS and AML in SDS. Secondary AML usually presents as AML with MDS-related changes (i.e., M2, M4, M6, M0) [47]. In SDS, secondary MDS differentiation is a problem as mild changes are common, therefore isolated mild dysplastic changes does not specify secondary MDS. Additionally, not all abnormalities in cytogenetics are suggestive for malignant transformation. The abnormalities in cytogenetic connected with SDS consist of i(7)(q10) and del(20)(q11). For diagnosis of SDS-associated AML/MDS, cytogenetic abnormalities in combination with bone marrow histology is necessary [37, 47].

In SDS, positivity with p53 is observed [48]. There is correlation of SDS with expression of Ki-67, p53 and survivin [27]. This shows that survivin is increased for overcoming of p53-associated apoptosis and for promotion of cell proliferation, presenting as increased Ki-67. Decreased marrow failure in SDS is due to this function that compensates for p53-associated apoptosis. Osteoporosis is defined as decreased volume of bone trabeculae, decreased osteoblasts and osteoclasts, and decreased osteoid amount in bone in patients of SDS [49]. There may be association of osteoporosis with neutropenia and dysfunction of bone marrow, or it may indicate primary bone metabolism defect.

In SDS, differential diagnosis includes other IBMF syndromes related to myelopoiesis failure and neutropenia e.g., severe congenital neutropenia syndrome (SCN). DC and FA should be excluded in case of aplasia and pancytopenia [5]. The SCN presents in early age with infections and severe neutropenia. SCN can be diagnosed as severe persistent neutropenia associated with eosinophilia and monocytosis along with normocellular marrow which demonstrate maturation of granulocyte lineage at myelocyte/promyelocyte level [50]. Other causes of neutropenia should be ruled out to establish this diagnosis.

CONCLUSION

The assessment of suspected patients with inherited bone marrow failure may be difficult and challenging. Complete assessment and approach of bone marrow as well as clinical features, additional abnormalities and genetic or laboratory findings is necessary for adequate diagnosis. Additional testing such as chromosome breakage analysis, cytogenetics, flow cytometry and measurement of telomere length may be required. Furthermore, inherited bone marrow failure syndromes are genetic, which affect other members of family, therefore requires genetic counselling.

CONFLICT OF INTEREST

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