Pathology of bone marrow failure syndromes

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Abstract

Bone marrow failure syndromes encompass a heterogeneous group of disorders, including 'acquired' idiopathic aplastic anaemia and the 'inherited' genetic diseases of bone marrow failure, all unified by the defining feature of failure in haemopoiesis. Idiopathic aplastic anaemia is characterized by depletion in the number of haemopoietic stem cells and resulting cytopenias, associated with a classical immune signature, underlying the pathogenesis in this disease. In contrast, the genetic diseases of bone marrow failure may have non-haematological manifestations, often a prominent family history and predisposition to cancer. Although considered immune in nature, cryptic genetic mutations are increasingly being reported in idiopathic aplastic anaemia, blurring the lines of distinction between the two entities. Likewise, inherited bone marrow failure syndromes with single gene defects are also associated with secondary acquired mutations and interplay with environmental factors for disease manifestation or progression. Immunosuppressive therapy has been the cornerstone of treatment in idiopathic aplastic anaemia and underpins the dysfunctional immune response as the aetio-pathogenesis in idiopathic aplastic anaemia. Genomics is becoming crucial not only for the correct diagnosis and classification in bone marrow failure syndromes but also to screen for secondary acquired mutations which affect disease prognostication and outcomes.

Keywords aplastic anaemia; congenital amegakaryocytic thrombocytopenia; diagnosis; Diamond–Blackfan anaemia; Dyskeratosis Congenita; Fanconi anaemia; genetics; inherited bone marrow failure syndromes; severe congenital neutropenia; Shwachman–Diamond syndrome

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Introduction

Bone marrow failure syndromes (BMFS) are a heterogeneous group of disorders characterized by the inability of the bone marrow to produce an adequate number of circulating blood cells, resulting in cytopenias. The defect maybe quantitative or qualitative or both any may involve any one to some or all of the lineages (erythroid, megakaryocytic or granulocytic/monocytic). Conventionally, these are classified as idiopathic aplastic anemia (AA) (or acquired, unknown primary aetiology but presumed immune), inherited bone marrow failure syndrome (IBMFS) (positive familial history and/or usually a clinical phenotype associated with characteristic pattern in test results) and secondary (bone marrow failure in susceptible individuals due to a precipitating factor). Variation in the manifestation and severity of the disease, irrespective of the classification of its underlying aetiology is considerable, and there is often interplay of genetic and environmental factors, among others. More than two thirds of patients are classified as having idiopathic disease. Within this form, there is a wide variation in disease incidence, based on both geographical region and ethnicity, suggesting environmental and genetic contributions, respectively. The inherited bone marrow failure syndromes (IBMFS) present most commonly in childhood or early adolescence (although late onset cases may present in adulthood often in the absence of typical somatic abnormalities of the syndrome), are often associated with somatic abnormalities and have a predisposition towards cancer. Recent molecular advances are beginning to unravel the pathophysiology where perturbations of key cellular pathways like telomere maintenance, ribosome biogenesis, and DNA damage response/repair all converge downstream to cause cell cycle checkpoint activation and apoptosis of the haematopoietic stem cell (HSC). These advances have provided a better understanding of normal haemopoiesis and how this is disrupted in patients with bone marrow failure. These patients have diverse specialist needs and are best managed at expert centres with access to transplant facilities. Ongoing research has been greatly facilitated by recruiting patients into national and international registries which allows for systematic study of these rare diseases. With the advent of next generation sequencing, new BMFS are being discovered, such as GATA2 deficiency, and it is likely that the molecular basis for many of the previously uncharacterised syndromes will be defined.

Pathogenesis and clinical correlations in bone marrow failure syndromes

Idiopathic aplastic anaemia (AA)

Until the early -70s in the last century, little was understood about AA; transfusion support along with androgens was all that was available for treatment and resulted in a uniformly high mortality rate. The success of bone marrow transplant (BMT) in restoring haemopoiesis in AA patients implicated a deficiency of haemopoietic stem cells (HSC). Haematologic improvement after immunosuppressive therapy (IST), initially in the context of rejected allogeneic grafts and then in patients receiving only IST, implicated the immune system in destruction of marrow stem and progenitor cells. Mouse model studies corroborated the immune picture of HSC destruction in AA, when donor lymphocytes that were mismatched at major and minor loci at the histocompatibility complex were infused and caused HSC depletion in the recipient mouse marrow. Although acquired AA has been causally associated with many agents including virus, drug, benzene and radiation, no aetiological agent has been identified in most cases. About 5—10% of patients with AA have a preceding seronegative hepatitis, usually in younger individuals, but a causative virus has not been isolated. Diverse factors could theoretically be held responsible for bone marrow failure, ranging from immune abnormality, quantitative and qualitative defects in stem/progenitor cells and blocks in differentiation to a lack of stroma support or inadequate cytokine production. However, the disorder in most AA patients can now be ameliorated or cured by BMT and IST, which might be the best evidence of immunologic pathogenesis of acquired AA.[1—3]

Genetics in AA: genetics influence both the immune response and its effects on the haemopoietic compartment. There are histocompatibility gene associations with AA, and some cytokine genes may be more readily activated in patients because of differences in their regulation, as suggested by polymorphisms in promoter regions. An inability to repair telomeres and to maintain the marrow's regenerative capacity, resulting from mutations in the complex of genes responsible for telomere elongation, has been linked to patients with familial or apparently acquired AA, with or without the typical physical stigmata of constitutional AA. These genetic factors are variable in their penetrance, ranging from highly determinant loss-of-function mutations to subtle polymorphisms.

Karyotypic abnormalities are seen in up to 12% of AA patients including trisomy 8; single nucleotide polymorphism array karyotyping (SNP-A) may help predict patients who are at risk of clonal evolution. Recent studies have demonstrated that clonal haemopoiesis is evident in up to 20% of patients with AA. Somatic mutations in genes commonly affected in myeloid neoplasm, such as *ASXL1, DNMT3a, BCOR1* in addition to *PIGA* may help predict patients who are at a higher risk of transformation to myelodysplastic syndromes (MDS).[4]

Idiopathic AA and the role of immune system: there is recent evidence to show that a subset of patients with 'acquired' idiopathic AA, have underlying genetic mutations associated with inherited bone marrow failure syndromes. However, these patients are best regarded as having a cryptic presentation of IBMFS rather than idiopathic AA. The majority of idiopathic AA patients respond to a combination of immunosuppressive therapy (IST) for e.g. anti-thymocyte globulin and cyclosporine (ATG+CsA) which suggest an important role for immune system dysregulation in the pathogenesis of "idiopathic" or acquired AA.

One of the first reports on the immune nature of the insult in idiopathic AA indicated a potential role for $CD8^+$ T cells and the finding of an increase in number of activated cytotoxic lymphocytes (CTLs) in AA patients' bone marrow. This finding has also confirmed by other groups in both MDS and AA. The expanded $CD8^+$ T cells were mainly oligoclonal (based on T cell receptor CDR3 rearrangement studies) and response to IST was correlated with the disappearance of expanded T cell clone. The antigen specificity of the expanded $CD8^+$ T cells has also been suggested by some research groups. However, the role of $CD4^+$ T-cell subsets in the pathogenesis of BMFS has become more apparent in recent years. $CD4^+$ T-cells are a heterogeneous population, ranging from mainly immunosuppressive cells (regulatory T cells or Tregs) to pro-inflammatory $CD4^+$ T helper cells (mainly Th1, Th2, Th9, Th22 and Th17 cells). A fine balance between Tregs and T helpers is crucial for maintaining a healthy immune system. Like several other autoimmune diseases, Tregs dysfunction plays an important role in the pathogenesis of AA. Tregs are not only reduced in AA but are also dysfunctional with an aberrant cytokines profile. There is also a correlation between better response to IST and number of Tregs in these patients. In addition to the reduced number and function of Tregs, there is additional evidence for an increase in the number and function of pro-inflammatory Th17 cells.

Identifying an immune signature that could predict response to IST in AA and *in-vitro* or *in-vivo* polarization of CD4+ T cells as a therapeutic option are current foci of translational research in this field.[5]

Inherited bone marrow failure syndromes (IBMFS)

The IBMFS, although generally rare, have served as a paradigm for understanding the more common and complex acquired disorders. An interesting observation that features prominently across all IBMFS is the greatly increased risk of cancer, including leukaemias and solid tumours, irrespective of the pathway of affliction in the various IBMFS in HSC preservation, maturation and differentiation.[6] Also apparent are individual genetic defects in specific cellular pathways in the different IBMFS. However, there is still considerable cross-talk between these pathways, as evident from the findings of short telomeres not just in the prototype 'telomere disorder' Dyskeratosis Congenita (DKC) but also in other IBMFS such as Fanconi Anaemia (FA) and Diamond —Blackfan Anaemia (DBA).

Fanconi anaemia (FA): FA is a genetic disease of bone marrow failure, characterised by hypersensitivity to cross-linking agents, and high risk of transformation to acute myeloid leukaemia. Prominent somatic abnormalities are seen in up to two thirds of cases and include dermatological (e.g. café au lait spots), skeletal (e.g. hypoplastic thumbs, scoliosis), genitourinary (e.g. horseshoe kidney), gastrointestinal (e.g. duodenal atresia), cardiac and neurological abnormalities. The majority of patients present towards the end of the first decade of life with uni- or bi-lineage cytopenias which usually progress to a global bone marrow