10.1 Introduction

Among acquired stem cell disorders aetiopathological links have been established between hypoplastic MDS, aplastic anemia (AA), paroxysmal nocturnal hemoglobinuria (PNH) and T-cell large granular lymphocytic leukemia (T-LGL) (see Fig. 10.1). All these entities are bone marrow failure disorders\(^1\) in which oligoclonal T-cell-mediated immune responses are without doubt pathophysiologically relevant. These overlap syndromes seem to form some kind of disease-continuum, whereby each entity can occur on its own, or arise in the background of any of the other above-mentioned diseases. As an example, PNH may follow, or precede MDS, and MDS-clones as well as PNH-clones are often detectable in patients with aplastic anemia. It may well be that T-LGL represents one extreme end of this spectrum, characterized by maximal clonal/oligoclonal T-cell proliferation, as LGL-like immunodominant cytotoxic lymphocyte (CTL) clonotypes are found within the whole spectrum of this continuum of overlap syndromes [2].

It is generally accepted that T-cell-mediated immune attack is involved in the pathophysiology of bone marrow failure syndromes including LGL, AA, MDS and PNH, although it is currently unclear, whether this reflects an autoimmune attack directed against normal hematopoiesis, or an immune surveillance reaction instigated by dysplastic myeloid cells. These bone marrow failure syndromes are characterized by polyclonal CTL expansions, as well as immunodominant clonotypes, as determined by TCR (T-cell receptor) variable beta-chain CD3 region analysis. CTL expansions, leading to TCR V\(\beta\) skewing, in bone marrow biopsy specimen are found in

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\(^1\)Nishimura and colleagues used the following scoring system to define bone marrow failure: each cytopenia was given one point; an additional point was added for severity if Hb was <10 g/dl, WBC <3,000/\(\mu\)l or PLT <60,000/\(\mu\)l; two additional points were added for Hb <6 g/dl, WBC <1,000/\(\mu\)l or PLT <20,000/\(\mu\)l; Total scores \(\geq 4\) points were classified as bone marrow failure [1].
81% of patients with aplastic anemia and 97% of MDS patients, including both hypo- and hypercellular variants, respectively [3–5]. Although no correlation could be determined between clonality and disease severity, the decline of pathogenic CTL clones may be used as markers of disease activity as well as to monitor hematologic decline of pathogenic CTL clones determined between clonality and disease severity, the respective [3–5]. Although no correlation could be found in patients, including both hypo- and hypercellular variants, as well as to monitor hematologic decline of pathogenic CTL clones 

It has been suggested that the high rate of emergence of PNH clones in bone marrow failure syndromes is related to a relative growth advantage conferred by disturbed immune function. In fact, certain GPI-anchored proteins function as receptors for growth inhibitory cytokines such as TGF-β, IFN-γ, or TNF-α, which play well recognized pathophysiologic roles in AA as well as MDS (see Chaps. 10.3 and 6.3, respectively). Therefore GPI-anchor protein deficiency would confer a further indirect growth advantage, as growth inhibitory cytokines would no longer be able to exert their function in the absence of their GPI-linked receptor (summarized in [9]).

Additionally, an elevated incidence of HLA-DR2 has been found in PNH, AA/PNH and MDS/PNH, and both the presence of HLA-DR2 and a PNH-clone has been identified as an independent predictor of response to immunosuppressive therapy [10]. This further solidifies the notion that clonal expansion of GPI-deficient cells is likely related to an immune mechanism.

10.2 MDS/PNH Overlap Syndromes

While PNH can occur on its own (“classic” PNH), it can also precede, or evolve in the setting of, another bone marrow disorder. However, evidence is accumulating that there is always an underlying bone marrow disorder, which does not necessarily have to be clinically apparent, even in the case of “classic” PNH.

Approximately 10–23% of MDS patients have erythroidic and granulocytic PNH clones negative for decay accelerating factor (DAF, CD55) and/or CD59 [11]. Whereas exogeneic permissive factors are required for the dominance of the abnormal clone in PNH, which is basically a benign clonal myelopathy, MDS stem cells eventually undergo transformation steps resulting in growth and survival advantages. PNH may follow, or precede MDS. These far, the appearance of PNH clones per se has not been shown to increase the risk of transformation to AML. Thus the GPI-deficient phenotype does not seem to be leukemogenic in a myelodysplastic background.

Many patients with MDS/PNH have more than one PNH clone with different types and seemingly random