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MYELODYSPLASTIC SYNDROME (MDS) AS A LATE STAGE OF SUBCLINICAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH): A PUTATIVE ROLE FOR *LEPTOSPIRA* INFECTION. A HYPOTHESIS

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It is proposed that hemophagocytic lymphohistiocytosis (HLH) and myelodysplastic syndromes (MDS) may be temporally distinct phases of pathophysiologically related disease processes. A significant subgroup of MDS may develop from subclinical HLH. In that case, HLH-like disease would chronically proceed with little disease activity or under occasional flares only, until it first becomes clinically apparent at the MDS stage. At the MDS stage, however, HLH activity may be easily overlooked by histological or cytogenetic means, since hemophagocytosis has fallen already largely silent. Current treatment options for HLH, like high-dose intravenous immunoglobulins (IVIG), may turn out to be helpful in MDS patients as well.

In rare and extreme cases, *Leptospira* infection causes severe and life-threatening HLH. Thus, this proposal also implies that an insufficient, dysfunctional or misdirected immunological response to *Leptospira* infection may lead to MDS in the long run in a significant number of cases, which have not been recognized as *Leptospira*-triggered events in the first place. Infections by agents other than *Leptospira* may lead to subclinical HLH-like disease with MDS as a late stage as well.

Keywords: malignancy, hematology, acute myeloid leukemia (AML), immunomodulation, autoimmune disease, microbiology, Epstein-Barr virus (EBV), epigenetic

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Hemophagocytic lymphohistiocytosis. HLH, which is synonymously sometimes called hemophagocytic syndrome or macrophage activation syndrome, occurs predominantly in children. HLH may represent a primary congenital immune disorder, or it may develop secondary to infection, autoimmune disease or malignancy [1]. Some HLH occur on the basis of hematological diseases, among them MDS [2]. HLH secondary to infection may be triggered by Epstein-Barr virus [3], *Plasmodium falciparum* [4], mycobacteria [5], or unidentified viruses [6]. *Leptospira* infection is part of the differential diagnosis of HLH, too [7, 8]. HLH in general is accompanied by a massive immune attack on the hematopoietic system. In the case of *Leptospira*-triggered HLH, this may be related to the genetic composition of *Leptospira* spp., which codes for the enzymes of a complete heme biosynthetic pathway and can perfectly utilize exogenous heme sources [9]. For *Leptospira*-triggered HLH, solely antibiotic treatment is not sufficient. For HLH in general, immunosuppressive treatment containing corticosteroids, high-dose IVIG or etoposide may be used, depending on the specific molecular background and risk profile [1, 3, 10]. The risk to develop AML or MDS has been reported to increase after etoposide treatment of hematological disease [11–14]. However, the risk to develop AML or MDS after suffering an HLH may already be increased through the condition of past HLH, without etoposide treatment.

Myelodysplastic syndrome

MDS are a collection of hematological diseases, mostly of the elderly, with currently unclear etiology and overall poor prognosis. MDS are characterized by a dysfunctional clonal hematopoiesis, bone marrow cell dysplasia, and refractory cytopenia. Most patients present with anemia. The median survival time is 2.5 years. Currently, stem cell transplantation is considered the only potential cure [15, 16]. Like for HLH, immunomodulation or immunosuppression may be used as a conservative treatment option for MDS, e.g. through lenalidomide, antithymocyte-globulin (ATG) or cyclosporin [16]. Since MDS frequently comes along with immunosuppression, the success of immunosuppressive treatment for MDS seems paradoxical at first and is not entirely understood. However, if MDS is viewed as the result of a lowly smoldering or burnt-out HLH, then the relative success of immunomodulatory or immunosuppressive treatment for MDS may become comprehensible. In addition, treatment options that are currently reserved

for HLH, like high-dose IVIG, may become available for the treatment of MDS in the future.

Clonality of erythropoiesis in MDS

According to my hypothesis, the clonal hematopoiesis, which characterizes MDS, may first have originated as a reactive pan- or polyclonal proliferation, in order to counteract low grade and hence stealthy hemophagocytosis. Later on, most of the erythropoietic clones may already have been phagocytosed, died of apoptosis, or silenced by other means, e.g. epigenetic alterations. Therefore, epigenetic therapy through hypomethylating agents, e.g. azacitidine or decitabine may also be used in MDS [16]. In the later phases of symptomatic MDS, hematopoiesis may have turned oligo- or even monoclonal and become more malignant. Epstein-Barr virus-driven post-transplant lymphoproliferative disease (PTLD) may pose an analogy. Early-onset PTLD is frequently polyclonal at first and responds to a timely recovery of the immune system. If not caught in time, PTLD may turn monoclonal and more malignant, and does not respond to the withdrawal of immunosuppressive drugs anymore [17]. A strong hemophagocytic activity is usually not observed in the bone marrow of MDS patients. In our view, however, the HLH-like early phase has for the most part already ended at the late MDS phase of the disease process. Therefore, typical macrophages in the act of digesting erythrocytes may be spotted only occasionally in MDS bone marrow when deliberately searching for them.

Specific HLH and MDS subtypes

Ethnic differences both among HLH and MDS subtypes may be a case in point for the proposed pathophysiological connection between HLH and MDS. A subtype of acute HLH of children and adolescents, often associated with EBV-infection, occurs more frequently in Japan and other parts of Asia than in Europe and the US [3, 10]. Accordingly, a low risk MDS subgroup with a better prognosis occurs more frequently in Japan than in Germany [18]. The subgroup frequencies of both HLH and MDS might be different due to the same underlying genetic traits.

Case report collection

A couple of case reports in the order of their appearance may illustrate the proposed pathophysiological cohesion between HLH and MDS:

1. An MDS case turned into an HLH after three years. The histiocytes in this case did not show any signs of malignancy [19].
2. A 68 years old male MDS patient developed a mononuclear cell infiltrate with a prominent erythrophagocytic activity in the skin. Curiously, his hematologic condition did not deteriorate in consequence [20].
3. Platelet phagocytosis was not discovered by light microscopy, but only by electron microscopy in 2 of 26 MDS cases. This suggests that phagocytosis may be generally underdiagnosed in MDS by standard histology [21].
4. In the uncommon case of splenomegaly, MDS patients have sometimes been splenectomized in order to improve their severe cytopenia. In a series of 13 splenectomy cases, monocytic proliferation or erythrophagocytosis were regularly found in the splenic tissue [22].
5. A 56 years old female MDS patient suffered additional chronic kidney disease and tuberculosis. The patient´s condition was complicated by a hemophagocytic syndrome, which was refractory to corticosteroids. After plasmapheresis her MDS began responding to corticosteroids again [5].
6. The reactive hemophagocytic syndrome of an adult patient was accompanied by an MDS. Although the patient was treated with immunosuppressive therapy including etoposide, his condition progressed. After syngeneic bone marrow transplantation he recovered and, at the time of publication, had lived without relapse for more than 2 years [23].
7. The bone marrow histology of six Japanese HLH cases showed a similar picture as it is observed in MDS at the disease onset. The observed pancytopenia and MDS-like morphological abnormalities were attributed to the abundant hemophagocytosis and cellular damage due to cytokine induction [24].
8. The MDS of a 75 years old man was associated with hemophagocytosis through the myelomonocytic bone marrow lineage. Phagocytic activity was increased upon therapy with the growth factors G-CSF and GM-CSF [25].
9. On the basis of a recurrent AML/MDS disease, the development of an acute HLH was observed. This HLH was presumably triggered by a viral pneumonia and was only discovered at autopsy [6].

All these case reports support the notion that there may be a pathophysiological connection between HLH and MDS. The overall rarity of such reports, however, and especially the paper by Imashuku et al. [24] may indicate that the regular order of events is not HLH on the basis of an already existing MDS, but an MDS developing out of a prior subclinical HLH-like disease.

Therapy options and note of caution

Before active vaccination against hepatitis A became available, travellers to tropical countries were regularly given low dose intramuscular immunoglobulins (IMIG) as a prophylaxis against hepatitis. Travel and family physicians may search their records, whether low dose IMIG has caused small, but significant rises of hemoglobin levels in some MDS patients in the past. If my working hypothesis bears out, plasmapheresis or immunoglobulins may become additional treatment options for suitable MDS subgroups. Low dose IMIG or high dose IVIG might even be tried *ex iuvantibus* in suitable patients. However, currently this would be experimental and, in the case of high dose IVIG, rather expensive therapy. Thus, such therapeutic experiments should be left to the specialized physician, e.g. the experienced hematologist, in the framework of a clinical study, and only after the informed consent of the patient on the experimental nature and the potential side-effects of this treatment has been obtained.

Leptospirosis

Most healthy and well-fed individuals develop immunity against most infectious agents without subsequent damage and frequently even without experiencing any clinical symptoms. The same is true for *Leptospira* infection, and only a minority of those with a positive serum IgG titer against *Leptospira* has suffered acute leptospirosis (Morbus Weil). Intermediate or mild clinical pictures exist, even among immune suppressed individuals [26]. Accordingly, IgG antibodies against *Leptospira* are, at a low prevalence, common among different, mainly rural populations [27–30]. Furthermore, while renal carriage and leptospiruria is a well-known phenomenon in rats [31], asymptomatic renal colonization has only recently been described in humans [32]. A significant proportion of individuals who asymptomatically shed the DNA of pathogenic or intermediate-pathogenic *Leptospira* strains have not developed antibody titers [32]. In general, a negative

IgG titer after bacterial contact may be due to the insufficient sensitivity or quality of the respective serological test, the decline of the antibody titer over time, or a functionally insufficient immune response to the infectious agent. Acute or generalized leptospirosis is not so much dominated by typical symptoms of infection, but by symptoms of immune pathology [31]. Activation of the coagulation system and thrombocytopenia are common features [33]. Unique and unusual symptoms frequently impede the correct diagnosis [34–36]. Generalized leptospirosis may even mimic leukemic disease or concur with an MDS [37]. Reports of chronic human disease are scarce [35, 38]. However, I propose that, besides an acute immune pathology, a long-lasting subclinical or chronic immune pathology may be triggered by *Leptospira* infection, too. For this slowly progressing immune pathology to turn into symptomatic disease, *Leptospira* may or may not stick around until disease onset, and antibody titers may or may not be positive. On the one hand, this would resemble "hit and run" pathogenesis, as it has been discussed for Epstein-Barr virus and other viruses [39, 40]. On the other hand, chronic *Leptospira* infection may remain well below the detection limits of current PCR and serological test procedures. Nevertheless, I suggest that MDS patients should be systematically screened for antibodies against *Leptospira* spp. Furthermore, the development of diagnostic systems for testing the specific cellular immunity against *Leptospira* spp. would be helpful.

Our working hypothesis of a cohesion between subclinical HLH-like disease and a considerable subgroup of MDS, with infectious disease as a trigger, may contribute to understanding the pathophysiology of MDS and expand future therapy options.

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