Autoimmune Hemolytic Anemia – Fascinating from a Laboratory as well as from a Clinical Point of View

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Clinically the diagnosis of an autoimmune hemolytic anemia (AIHA) often starts with a patient with an unclear anemia, while in the laboratory the first hint is a blood sample with a positive direct antiglobulin test (DAT). Both anemia and positive DAT are non-specific findings that raise many questions. These include a wide range of laboratory characteristics such as immunoglobulin (sub-) class of the red blood cell (RBC) autoantibodies (Au-ab), presence of warm or cold Au-ab, thermal range of cold Au-ab, capability of Au-ab to activate complement, specificity of warm or cold Au-ab, and masking of additional RBC alloantibodies by Au-ab. Moreover, the clinical findings have to be scrutinized critically: Was there a sudden onset or a gradual beginning of hemolytic anemia? Is the hemolysis life-threatening? Does the patient suffer from a persisting systemic autoimmune or tumor disease, in particular a hematological malignancy? Has the patient been transfused within a certain time span before the first occurrence of the anemia symptoms? Was there a recent infection? Does the patient take drugs, newly or regularly?

If a clinician is confronted with a newly diagnosed AIHA, each of these questions has to be answered to distinguish ‘idiopathic AIHA’ as a disorder of its own from ‘secondary AIHA’ as a symptom of a detectable underlying disease (e.g. chronic lymphocytic leukemia, systemic lupus erythematosus, *Mycoplasma pneumoniae* infection). This classification is important for choosing the appropriate medical treatment of AIHA. In idiopathic AIHA that is present in about 45% of the AIHA cases [1] immunosuppressive drugs (corticosteroids and others) are most frequently applied to cope with severe hemolysis [2]. In secondary AIHA the ‘drug of choice’ is governed by the underlying disease and may range from ‘wait and see’ in self-limiting cases of infection-related AIHA, over immunosuppressive drugs in cases with an overt systemic autoimmune disorder to chemotherapy in patients with lymphoproliferative malignancies [2, 3]. Regardless of the clinical background, many AIHA patients have to be transfused, at least temporarily, as

none of the available drugs are able to stop severe hemolysis immediately [4]. In view of these facts, each newly diagnosed ‘AIHA’ may become a challenging experience for the doctor who is responsible for the patient for several reasons: i) There is no close relationship between the laboratory findings and the clinical symptoms of the patient. ii) Hypoxic anemia may require urgent transfusion. iii) A deliberate search for an underlying disease often leads to the somewhat dissatisfactory ‘idiopathic’ AIHA. Moreover, none of the administered drugs – neither corticosteroids that are in routine use for decades nor newly introduced monoclonal antibodies such as rituximab – are always effective, and their beneficial immediate or long-term effects are not safely predictable [5, 6].

The present issue of TRANSFUSION MEDICINE AND HEMOTHERAPY is an attempt to summarize and review theories, ideas, and medical expert knowledge on AIHA. John Freedman [7] and Wilma Barcellini [8] present the history of AIHA and discuss the current concepts that contribute to RBC destruction. Barcellini reports on the roles of cytokines and cytotoxicity effector cells (CD8+ T cells, natural killer cells, and activated macrophages) in the AIHA disease process, thereby explaining the great clinical heterogeneity of AIHA ranging from a fully compensated (‘uneventful’) clinical course to rapidly evolving severe life-threatening hemolysis. The contributions of Sigbjørn Berentsen [9] and Thilo Bartolmäs et al. [10] deal with the role of the complement system in the development of AIHA and describe the main mediators of complement-driven hemolysis, in particular in cold Au-ab-associated AIHA. Charles H. Packman [11] gives an overview on the clinical manifestations of AIHA while Beate Mayer et al. [12] present more than 70 cases with drug-induced hemolysis, mainly as a result of diclofenac, piperacillin and cephalosporin ingestion. Abdulgabar Salama [13] reviews pitfalls that may hamper the diagnose ‘AIHA’ and summarizes his professional experience with the medical treatment of primary (‘idiopathic’) AIHA over a period of 30 years. The latter contribution might provoke

intense discussions among transfusion medicine specialists as the author attenuates the therapeutic enthusiasm with regard to newer drugs such as rituximab as the new 'gold standard' for medical AIHA treatment.

When looking at the contents of this issue, you might wonder why one name seems to be nearly omnipresent in this special topic. It is not the task of this editorial to fully appreciate the tremendous scientific work of Abdulgabar Salama in the field of immunohematology over the last 30 years. However, as obvious for every specialist in transfusion medicine, Abdulgabar Salama has not only significantly influenced the field but has clearly dominated (together with his Californian colleague George Garratty) the diagnosis and the pathogenic background of drug-induced AIHA. His most important contribution is the discovery that many drugs supposed to

be involved in severe AIHA are detectable in laboratory investigations only when their degradation products, either in serum/plasma or urine, are available (e.g. nomifensine [7], cephalosporin antibiotics such as ceftriaxone or cefotaxime [8, 9], or the non-steroid antirheumatic diclofenac [10], just to mention some frequently used medications). Another similarly important contribution to the understanding of the pathogenicity of AIHA is his observation that transfusion itself is able to induce Au-ab formation, often in coexistence with transfusion-associated alloantibody formation, thereby complicating a delayed serologic/hemolytic transfusion reaction [11]. These are only a few reasons why we are very glad to have allured such an exposed representative of AIHA research to significantly contribute to this special topic.

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