

Red Blood Cell Autoantibodies and Autoimmune hemolytic Anemia

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Introduction

All tissues of the human body are potential targets for autoimmune processes, which may be associated with subsequent injury. Blood cells, including Red Blood Cells (RBCs), are no exception. This brief review will focus on the nature of red blood cell auto antibodies and the clinical consequence of pathological auto antibodies, which is termed autoimmune hemolytic anemia.

Text

The RBC membrane is a complex network of a vast number of biochemical structures many of which carry serologically and genetically defined blood group antigens. The ABO and Rh antigens are among the best known and understood blood group antigens, but there are hundreds of additional protein and carbohydrate determinants that have been elucidated over the past 100 years [1]. These

antigens are capable of eliciting alloimmune responses when individuals lacking a particular antigen are exposed to that antigen, either through transfusion or pregnancy. In addition, however, certain of these antigens may serve as targets for autoimmune responses. When pathologic, these auto antibodies cause RBC destruction (i.e. hemolysis) termed autoimmune hemolytic anemia. Classic laboratory features of autoimmune hemolytic anemia include anemia, reticulocytosis, elevated bilirubin and lactate dehydrogenase levels, decreased haptoglobin values, and peripheral blood smear abnormalities, most notably the presence of spherocytes [2].

The immunologic nature of RBC auto antibodies is variable but is conveniently categorized as warm-reactive or cold-reactive, based on the temperature at which the antibody is maximally reactive. The most common RBC autoantibody is warm-reactive, binding maximally at 37°C. These antibodies are characteristically IgG and polyclonal and about half have the ability to fix complement though only to the C3 stage of activation [2]. Antibody-sensitized cells are removed from the circulation via the macrophages of the reticuloendothelial system. Although the specificity of warm-reactive

autoantibodies is not usually determined in clinical practice, research studies have revealed that the epitopes to which they most frequently bind are associated with two RBC membrane proteins, Rh and Band 3 [3]. In clinical practice, warm autoantibodies may be idiopathic, but they are oftentimes associated with other clinical conditions including malignancies (leukemias and lymphomas most common) and other autoimmune or inflammatory disorders. In fact, they occasionally serve as harbingers of underlying pathological processes that have not yet come to clinical light. IgG, warm-reactive autoantibodies may or may not be clinically significant, with respect to hemolysis, but those that are tend to be higher in titer and have the ability to activate the complement cascade [4].

Less commonly seen than warm-reactive autoantibodies are cold-reactive autoantibodies, also termed cold agglutinins. These antibodies are unusual in that they maximally bind to red cells at temperatures well below body temperature (i.e. 4°C); however, those that are clinically significant have the ability to bind cells at higher temperatures, approaching those of body temperature. Cold-agglutinins are typically IgM autoantibodies that are monoclonal and are almost always directed against carbohydrate blood group antigens of the I blood group system [2]. These antibodies have the ability to activate complement to the C3 stage. In clinical practice, pathological cold agglutinins, causing cold agglutinin disease, have a bimodal age distribution with very different disease associations. In pediatric patients, cold agglutinin disease typically follows an upper respiratory tract infection caused by *Mycoplasma pneumoniae* or a virus. In older adults, however, cold agglutinin disease is frequently associated with lymphoproliferative disorders such as multiple myeloma or Waldenström macroglobulinemia [2]. Interestingly,

most healthy individuals have detectable auto anti-i/I cold agglutinins in their circulation. This phenomenon is not well-understood but these antibodies are not clinically significant, with respect to hemolysis, because they are of a low titer and a low thermal amplitude [5].

There is a less common RBC autoantibody with unusual biphasic reactive properties. These so-called Donath-Landsteiner antibodies are IgG immunoglobulins that bind to the RBC membrane at colder temperatures but cause hemolysis at body temperature. These antibodies have the ability to activate the complement cascade, usually to completion, resulting in intravascular hemolysis. IgG antibodies of this type are associated with a clinical condition known as paroxysmal cold hemoglobinuria.² Historically, this condition was most frequently associated with syphilis infections; however, contemporary cases are almost always seen in pediatric patients following a variety of well-defined infections (e.g. measles, mumps, chicken pox, parvovirus, and Epstein-Barr virus) [2]. Regardless of the disease association, Donath-Landsteiner biphasic hemolysins are most commonly directed against the P carbohydrate blood group antigen [6].

Conclusion

RBC autoantibodies are fairly commonly seen in tertiary care clinical practices. The causal nature of these autoimmune responses is not well understood but seems to be associated with an underlying immune dysregulation as deduced from the clinical conditions with which they are associated. Despite the variety of disease associations, the features of these autoimmune responses are fairly typical and easily categorized, as noted above. Some cases of autoimmune hemolysis, particularly those associated with infectious diseases, are self-limited

and require no specific therapy. Other cases resolve with amelioration or improvement of the underlying clinical condition. Still others, particularly those associated with severe and/or life-threatening hemolysis, require active intervention with immunosuppressive therapy. The continuing scientific study of RBC autoantibodies may shed light on the pathological processes underlying other autoimmune conditions.

References

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