Atypical autoimmune hemolytic anemia

The recent report by Alidjidi *et al.* provides valuable prospective data on a large cohort of children with autoimmune hemolytic anemia (AHA).[1] Their inclusion criteria were designed to capture typical cases of AHA including patients with anemia, a positive direct antiglobulin test (DAT), and either reticulocytosis, hyperbilirubinemia, or low haptoglobin. A significant subset of patients, however, may present with atypical features, as in the following case.

A 19-year old Chinese woman with systemic lupus erythematosus and β-thalassemia trait was evaluated for anemia. She had been admitted three weeks prior with pulmonary hemorrhage, and despite stabilization of her respiratory condition and lack of overt blood loss, she required 12 units of packed red blood cells over a 20-day period. She had previously been on mycophenolate mofetil (MMF) 3 g/day for nephritis but did not have any other medication history contributing to anemia. Her hemoglobin was 5.2 g/dL, MCV 61 fL, reticulocytes 89×10^9/L (10-90), bilirubin 1.5 mg/dL (0-1.0), lactate dehydrogenase 1715 U/L (normal < 210) and ferritin 697 ng/mL. The blood film showed microcytosis and coarse basophilic stippling consistent with β-thalassemia trait. Only very occasional spherocytes were noted and there was no agglutination. A bone marrow biopsy revealed mild erythroid hyperplasia and otherwise unremarkable morphology. The direct antiglobulin test (DAT) was repeatedly negative for IgG but weakly positive for C3d. Special DAT assays by gel method, cold saline wash and IgM/IgA substrates, were negative. Weak red cell autoantibodies were detectable eventually by polyethylene glycol (PEG) method through a reticulocyte enriched blood specimen, aiming to increase the sensitivity of the DAT assay by reducing the contamination of more aged transfused red cells. Weak red cell autoantibodies with no demonstrable specificity were also detected in the patient's serum by PEG. An AHA with IgG autoantibody directed against reticulocytes or a mature RBC precursor was suspected based upon the reticulocytopenia and IgG positive DAT restricted to the reticulocyte enriched RBC fraction.[2] Prednisone 1.5 mg/kg/day, i.v. cyclophosphamide (~900 mg/m^2 monthly for five doses) and rituximab (1,000 mg/m^2 for two doses) were administered with subsequent cessation of transfusion requirements and return to her baseline hemoglobin of 10.5 g/dL.

AHA with atypical features, as illustrated above, raises challenges in diagnosis and management. Anemia can be multifactorial and peripheral blood morphology with co-existing conditions such as thalassemia trait[3] may be misleading. Importantly, 5-10% of patients with AHA are "DAT-negative". A laboratory approach to such cases has been suggested but definitive proof of autoimmune hemolysis is often difficult to establish.[4] While warm AHA with an isolated C3d positive DAT is a recognized disease pattern, its clinical characteristics are less well defined than the more typical IgG positive warm AHA. Alidjidi *et al.* indicate that patients with isolated C3d positive DAT have a better prognosis than those with IgG/IgG$^+$C3d positive DAT, but the implications of this for patients with warm AHA and isolated C3d positivity are difficult to define given that hemolysis in about half of these cases appears to have been related to cold agglutinin disease. Transient reticulocytopenia is common, including 39% of patients in the CEREVANCE report, but the implications of persistent reticuloctopenia are less well established, and a tendency to more severe anemia and earlier transfusion dependence has been suggested.[5]

The CEREVANCE registry is an important resource for investigating an uncommon disease and its variants. It is unfortunate that "DAT negative" atypical cases were not included and we wonder if collection and analysis of such data might be considered in the future. Further analysis of existing data to clarify if and how atypical cases of warm AHA, such as those with isolated C3d positivity or persistent reticulocytopenia, differ from canonical cases would also be of interest to clinicians.

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References

1. Aladjidi N, Leverger G, Leblanc T, Picat MQ, Michel G, Bertrand Y, et al. New insights into childhood autoimmune hemolytic anemia: a French national observational study of 265 children. Haematologica. 2011;96(5):655-63.
2. Hegde UM, Gordon-Smith EC, Worlledge SM. Reticulocytopenia and "absence" of red cell autoantibodies in immune haemolytic anaemia. Br Med J. 1977;2(6100):1444-7.
3. Jayanthi S. Concurrent autoimmune hemolytic anemia in thalassemia. Clin Proc NIMS. 2005;17(2).
4. Garratty G. Immune hemolytic anemia associated with negative routine serology. Semin Hematol. 2005;42(3):156-64.
5. Packman CH. Hemolytic anemia due to warm autoantibodies. Blood Rev. 2008;22(1):17-31.