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Letter to the Editor

Comments on the article "Unexpected laboratory results in cold agglutinin disease"

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I carefully read the article "Unexpected laboratory results in cold agglutinin disease", recently published by Nesibe Esra Yasar et al [1].

Apart from the cell blood count parameter, i.e., red blood cells (RBCs), mean cellular volume, hematocrit, and mean corpuscular hemoglobin levels, which were directly modified by cold agglutinin disease (CAD), it seem that the Authors consider as "unexpected"results the undetectability of haptoglobin (Hp) and the low-level of glycated haemoglobin (HbA1c) as well as the platelets (PLTs) count which had resulted "unmeasured". I think that a more extensive study on the patient as well as on the physiopathological inter-relationships between the available parameters could transform some of the "unexpected" into "expected" results.

The most serious diagnostic omissions are non-execution of reticulocyte (RET) count tests and missed microscopic observation of peripheral blood. This patient with hemoglobin levels <120 g/L is anemic. Therefore, the RET level would have allowed evaluation of the amount of RBCs replaced in a condition of chronic hemolysis, which should not be surprising in a patient diagnosed with CAD, i.e., presenting not only with cold agglutinins but also with clinical signs of chronic hemolysis. This fact can explicate the decrease in Hp that binds to free hemoglobin both "*in vivo*" and "*in vitro*" [2] even in case of low (or very low) levels of hemolysis, similar to what we can speculate in this patient, despite the normality of the parameters of hemolysis as well as the hemolysis index. Lastly, the Authors hypothesis that an HP variant may be present can be considered, but only after excluding that its non-detectability depends on the hemolysis. Exactly for this reason, it would have been useful to know the value of the reticulocyte count.

Besides, a probable increase in RETs could explain–just as the hypothesis of the Authors–the (moderate) lowering of HbA1c levels in this subject with glucose levels of 102 mg/dL. As acknowledged, HbA1c is the biochemistry result of glycemic levels in the blood in approximately 60 days. This timing undergoes a reduction in the case of shortening of the RBCs average life, which is observed with hemolytic anemia. In these cases, HbA1c levels are unable to signal the real anamnestic levels of glucose in the blood.

Regarding the PLTs count, it is unclear if the Authors attribute the failure of the counts to the presence of the same cold agglutinins causing RBCs agglutination. Cold agglutinins are immunoglobulins (Ig)M having activity of self-antibody against the I-antigens on the RBCs surface which are absent on the PLTs surface. The possibility of cross-reactions has never been reported in the literature. Therefore, based on cited reference 6 (Kumar TB, Bhardwaj N. Platelet cold agglutinins and thrombocytopenia: A diagnostic dilemma in the intensive care unit. J Anaesthesiol Clin Pharmacol 2014;30:89–90.), we can speculate that the Authors are describing a case of concomitant pseudo-thrombocytopenia due to cold agglutinins against PLTs antigens. This last hypothesis rules out any characteristic of "unexpected" finding. In both cases, the Authors should have considered that in hematologic analyzers, the count of both PLTs and RBCs occurs in the same reading channel. For this reason, in the described case, the presence of agglutinates containing approximately 81% of the total RBC as well as the supposed PLT agglutinates could have caused some interferences that should have been analyzed and interpreted with a careful inspection of the histographic images provided by the used analyzer. Besides, agglutinated PLTs even cause cytographic anomalies in the WBC counting channels, and their presence should be detected microscopically in a blood smear.

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Apart from this, I agree with the Authors concerning the importance of instrumental signals in discovering the presence of cold agglutinin in blood samples as well as the emphasis of an appropriate pre-analytical treatment of the sample [3].

References

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