Difficulties in the Differential Diagnosis of Thrombotic Microangiopathy

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To the Editor;

We read with great interest the case report by Mehmoud *et al* that focused on the diagnosis of the atypical hemolytic uremic syndrome (aHUS) in a patient with biopsy-proven Anti Neutrophilic Cytoplasmic Antibody (ANCA) Negative crescentic necrotizing glomerulonephritis (CGN). It is noteworthy that is the second case reported in the literature of such a rare coexistence even though glomerular and extraglomerular vascular lesions of thrombotic microangiopathy were identified only in the renal biopsy performed by Cheng *et al*.[1] Beyond limitations already stressed by the authors, important issues need to be further discussed.

As the authors highlighted, caution should be raised in the differential diagnosis of aHUS that remains a diagnosis of exclusion.[2] Indeed, ADAMTS13 availability remains an important issue in many countries. In this case, scores, like the PLASMIC or French score, are highly recommended to predict ADAMTS13 deficiency. These scores have a high predictive value and could be used by centers that do not have access to ADAMTS13.[3] Therefore, the authors could mention the results of these tests in their patients.

More than that, there are certain difficulties in confirming aHUS diagnosis. Although the authors have already mentioned genetic testing, Factors H and I, there are additional tests that can confirm excessive complement activation. Soluble C5b-9 is a widely accessible marker that can be used in clinical laboratories, that has already been introduced in diagnostic algorithms of complement-mediated thrombotic microangiopathies.[4] In addition, other cellular-based assays have been described, such as the modified Ham test, which is less widely available but differentiates complement-mediated diseases.[5] It would be thus important to add this perspective to the present case report given that recent data suggest a prominent role of complement activation in CGN with negative ANCA serology due to a genetic or acquired defect in the alternative pathway.[6]

The above comments are highly valued when one takes into consideration the efficacy and safety of complement inhibitors.[7] Except for eculizumab, ravulizumab has been also approved for aHUS treatment. In addition, several other inhibitors are under advanced clinical development, rendering clinical trials a very appealing opportunity for countries with limited access to drugs.

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