Syndromes of Thrombotic Microangiopathy

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Syndromes of Thrombotic Microangiopathy

TO THE EDITOR: In their review of the thrombotic microangiopathy syndromes, George and Nester (Aug. 14 issue)[1] do not mention the option of treating severe neurologic deficits in patients with shiga toxin–mediated hemolytic–uremic syndrome (ST-HUS) with IgG depletion through immunoadsorption.[2] In the 2011 outbreak in northern Germany, the delay in the onset of neurologic symptoms (5 to 12 days after the onset of diarrhea; mean and median, 8.0 days) strongly suggested antibody involvement in the pathogenesis of these symptoms. Consequently, all 12 patients had substantial improvement, and 10 of them fully recovered after IgG depletion through immunoadsorption, despite the failure of all other known treatments. This treatment option, although based on one prospective, uncontrolled study, may be a lifesaving treatment and should be considered in similar cases.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: George and Nester mention the main causes and pathological and clinical features of the thrombotic microangiopathy syndromes, disorders that can also be associated with pneumococcal infection. The pathogenesis of this rare but severe complication probably implicates the binding of the Thomsen–Friedenreich antigen to preformed circulating IgM antibodies, owing to the neuraminidase-mediated cleavage of sialic acid residues from the membrane of glomerular capillary endothelial cells, red cells, and platelets.[1] Neuraminidase-associated thrombotic microangiopathy is generally observed in pediatric patients with pneumonia and meningitis and rarely in those with isolated pneumococcal infection.[2] The disease, frequently described as the hemolytic–uremic syndrome, has also been associated with group A beta-hemolytic streptococcus infection.[3] Furthermore, the true incidence of neuraminidase-associated thrombotic microangiopathy could be underestimated.[2] Pneumococcal infection should be included among the causes of the thrombotic microangiopathy syndromes and considered especially in pediatric patients.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: George and Nester describe cobalamin C deficiency as one underlying cause of thrombotic microangiopathies. On the basis of our experience with cobalamin C deficiency in these syndromes[1] and the findings of other inves-

tigators,[2-4] we would like to emphasize three clinically relevant aspects. First, although a majority of patients with cobalamin C deficiency present in infancy with neurologic problems,[4] such deficiency in patients with thrombotic microangiopathies is observed throughout childhood and adolescence.[1-4] Second, since cobalamin C deficiency is treatable and occurs in combination with other causes of thrombotic microangiopathies (reported in four patients),[1,2] we advocate routine measurement of blood levels of homocysteine in all patients with thrombotic microangiopathies, including those with complement defects. Homocysteine builds up as a result of renal failure,[5] and values above 20 to 30 μmol per liter warrant further workup to exclude cobalamin C deficiency. Third, among the various coexisting clinical manifestations in cobalamin C deficiency, particular care should be taken to rule out pulmonary hypertension, which is associated with renal thrombotic microangiopathy[1] and has a dismal outcome, especially when treatment is delayed.

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No potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: Aviner and Bibi cite the report of Greinacher et al. in which IgG depletion by means of immunoadsorption was used to treat patients with ST-HUS who had severe neurologic sequelae.[1] We agree that the recovery of the patients as described in their report was impressive. We also agree that patients with severe neurologic sequelae may warrant a trial of less proven treatments. We noted in our article that it is uncertain whether plasma exchange or anticomplement therapy is beneficial in patients with ST-HUS. We did not consider immunoadsorption because the existence of an antibody as the cause of neurologic sequelae in ST-HUS has not been documented.

Villa states that we should have considered thrombotic microangiopathy associated with severe pneumococcal sepsis as a primary syndrome. We had considered this because studies frequently describe pneumococcal sepsis-mediated thrombotic microangiopathy. However, we did not include it in our set of primary syndromes because of the limited mechanistic evidence that it is a distinct syndrome and because distinguishing this entity from the clinical manifestations of overwhelming sepsis is inherently difficult.

Kömhoff et al. advocate routine measurements of blood homocysteine levels in all patients presenting with thrombotic microangiopathy to determine whether cobalamin C deficiency could be the cause. We agree. In our article, we noted a recent case report in which cobalamin C deficiency was discovered to be the cause of thrombotic microangiopathy with severe kidney injury, which allowed for effective treatment.[2] However, discussion of the clinical evaluation of patients with thrombotic microangiopathy was beyond the scope of our review. Currently, many patients present with thrombotic microangiopathy and acute kidney injury without a clear cause. We believe that the wider use of routine laboratory assays (e.g., for plasma homocysteine and methionine and urine methylmalonic acid) may reveal a previously unsuspected diagnosis with minimal cost and no risk to the patient.

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Since publication of their article, the authors report no further potential conflict of interest.

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Case 25-2014: A Man with Ulcerative Colitis and Bloody Diarrhea

TO THE EDITOR: The Case Record contributed by Hohmann et al. (Aug. 14 issue),[1] regarding a man with ulcerative colitis in whom bloody diarrhea developed soon after fecal microbiota transplantation (FMT), highlights the difficulty in distinguishing cytomegalovirus (CMV) as a direct cause of disease from its being an "innocent bystander" in patients with CMV infection and active ulcerative colitis. However, the authors also reported an apparent case of diarrheal disease caused by *Blastocystis hominis* transmitted by means of FMT without describing the complex debate as to whether this organism is a true enteropathogen.

In developed countries, blastocystis is detectable in more than 50% of healthy persons with the use of polymerase-chain-reaction–based assays.[2] No difference in the prevalence of blastocystis exists between hosts with gastrointestinal symptoms and those without such symptoms,[3] and symptoms that are attributed to blastocystis infection may not improve even after the elimination of the organism.[4] The organism has been shown to be capable of both long-term colonization[2] and spontaneous disappearance without intervention.[4,5] Physicians offering FMT should carefully monitor FMT recipients for infectious complications but must be aware that presence is not the same as causation.

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No potential conflict of interest relevant to this letter was reported.

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THE DISCUSSANT REPLIES: We understand the controversy surrounding *B. hominis* (an anaerobic protozoan), and the case referenced in the discussion, reported by a Canadian physician, highlights it nicely. The patient had recurrent *Clostridium difficile* infection, and the spousal donor, who had no gastrointestinal symptoms, had stool that tested positive for *B. hominis* (no other donor was readily available). The FMT cured the *C. difficile* infection, but intermittent loose stools lasting months subsequently developed, with positive tests for blastocystis. A course of nitazoxanide cured the symptoms.

At a recent American Gastroenterological Association conference on FMT, physicians noted that blastocystis was a common finding in donor stool specimens (e.g., in 6 of 38 specimens that were screened in an Australian study).[1] The consensus of practitioners was that it would not be advisable to use such specimens for FMT. Attendees did not mention other cases of transmission of infectious agents by FMT. Representatives of the Food and Drug Administration highlighted the possibility of transmission of currently unknown infectious agents and the need for judicious use and careful follow-up of recipients of FMT.