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Hot Topic Review

Hemolytic Anemia in Inflammatory Bowel Disease: Our "Gut" Tells Us to Blame the Drug

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Background: Several studies determined that autoimmune hemolytic anemia (AIHA) is a rare extraintestinal IBD manifestation, related to the underlying disease activity. However, evidence linking biologic therapy to AIHA is sparse.

Methods: This article reviews the evidence on the association of these clinical phenomena.

Results: There are two retrospective studies and a few case reports linking biologic therapies to AIHA.

Conclusions: While some autoimmune phenomenon triggered by our biologic therapies have been well recognized, we do not find the evidence associating these therapies to AIHA sufficiently compelling.

Lay Summary

This article reviews the association of hemolytic anemia and inflammatory bowel diseases and determines if they are secondary to an uncommon extraintestinal manifestation of the underlying disease, or do they simply represent an infrequent side effect of our therapies.

Key Words: Hemolytic anemia, IBD, vedolizumab

Case Report

A 43-year-old woman was diagnosed with pan-ulcerative colitis in 2013. Initially unresponsive to mesalamine, she was advanced to 6-mercaptopurine followed by golimumab for 3 years. Due to a history of melanoma in situ, and after demonstrating clinical, endoscopic, and histologic remission of colitis in 2018, her immunosuppression was discontinued. She was maintained on mesalamine with close monitoring of symptoms and fecal calprotectin. She remained in clinical and biochemical remission for 14 months. However, bloody loose stools resumed in 2020 with a fecal calprotectin level of 350 µg/g. She did not respond to combination high dose oral mesalamine (4.8 g/day) with 4 g daily of rectal mesalamine. After 6 weeks, a colonoscopy confirmed Mayo score 2 proctosigmoiditis. Vedolizumab induction was started along with an 8-week budesonide (Uceris) course.

At clinical follow-up (after 3 doses of vedolizumab), she reported some clinical response, but 3–4 loose bowel movements persisted daily with fecal calprotectin level of 1100 µg/g. However, significant laboratory changes were observed in the absence of any other medications or herbal supplements. Repeat lab work showed a fall in hemoglobin (Hgb) from 7.01 to 5.46 mmol/L, a rise in mean corpuscular volume (MCV) from 86 to 112 fL, a rise in total bilirubin from 3.42 to 25.65 µmol/L, reticulocyte 10.9%, haptoglobin <2.35 µmol/L and a positive Coombs' IgG test (DAT C3 negative). Platelet count and white blood cell were normal and unchanged. She was diagnosed with warm autoimmune hemolytic anemia (WAHA) and treated with a prednisone taper initiated at 1 mg/kg. The vedolizumab was held. Repeat labs were monitored every 2 weeks with prompt improvement in lab values. At the conclusion of the prednisone taper at 9 weeks, the Hgb was 9.74 mmol/L, MCV 95 fL, total bilirubin 5.13 µmol/L, and haptoglobin 19.3 µmol/L (Figure 1).

Despite the vedolizumab induction and the incidental 9-week prednisone taper, her colitis symptoms worsened. She reported more than 6 bloody stools per day and mild abdominal discomfort but no fever. Lower endoscopy confirmed Mayo score 3 colitis to the splenic flexure with negative cytomegalovirus (CMV) staining. She received an induction dose of IV ustekinumab. Two weeks later she had a severe return of WAHA, with Hgb 3.85 mmol/L, MCV 136 fL, total bilirubin 30.78 µmol/L, and haptoglobin <2.35 µmol/L. Her WAHA did not respond to prednisone at 1 mg/kg. She then received prednisone at 2 mg/kg and 1 dose of intravenous immune globulin (Privigen 55g). Her WAHA slowly recovered. By week 14 of ustekinumab, she was in clinical remission. The prednisone was tapered off. Her Hgb value improved to 7.57 mmol/L (Figure 1).

Discussion

This case poses an important general challenge in the clinical management of inflammatory bowel disease (IBD), and the question is not specific to hemolytic anemia. Are rare clinical phenomena—particularly when immune-mediated—secondary to an uncommon extraintestinal manifestation of the underlying disease, or do they simply represent an infrequent side effect of our therapies? If either etiology is possible, how can we confidently distinguish between the 2 possibilities? This is especially problematic if the immune-mediated phenomenon, once triggered, follows an independent clinical

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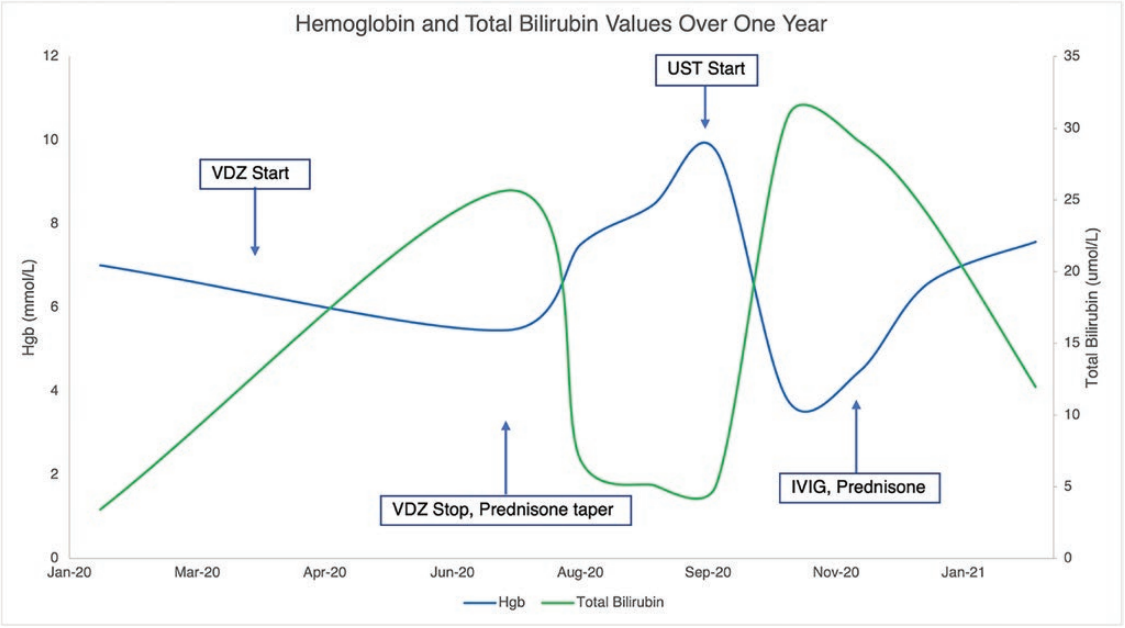

Figure 1. Hemoglobin and total bilirubin values from the patient case plotted over the course of a year. Abbreviations: Hgb, hemoglobin; IVIG, intravenous immune globulin; UST, ustekinumab; VDZ, vedolizumab.

Table 1. Summary of cases of hemolytic anemia associated with biologic therapy.

	Study type	# Patients with hemolytic anemia	Biologic	Coombs' test	Disease	Comment
Mir et al.	Case report	1	Infliximab	Positive	Ulcerative colitis	UC clinically improved at time of hemolysis
Strik et al.	Case report	1	Originator infliximab → infliximab biosimilar (CT-P13)	Negative	Ulcerative colitis	IBD in clinical and biochemical remission at time of hemolysis
Fidder et al.	Retrospective	1	Infliximab	Negative	IBD—not specified	—
Colombel et al.	Retrospective	1	Infliximab	—	IBD—not specified	—
Jen et al.	Case report	1	Vedolizumab	Positive (Evan's syndrome)	Ulcerative colitis	—
Midaglia et al.	Case series	1	Natalizumab	Positive	Multiple sclerosis	Normal ESR and CRP at time of hemolysis

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IBD, inflammatory bowel disease; UC, ulcerative colitis.

course of response, persistence, or recurrence which is not promptly reflective of either the continued disease activity or the withdrawal of the potentially offending medication.

There are some general principles we can outline. If the clinical phenomenon has been clearly associated with the onset of an IBD diagnosis or flare in disease activity in the absence of any medical therapy, and subsequently resolves with surgical therapy (eg, colectomy), then the phenomenon is associated with the underlying disease. Nonetheless, this does not account for immune-mediated phenomenon associated with the underlying IBD which run an independent course of activity. Associating the phenomenon with a particular medical therapy can also be difficult, as it would require an observation that the phenomenon resolved only as a consequence of withdrawing the potentially offending medication (ie, in the absence of other confounding therapy), and preferably that the phenomenon recurs after reintroduction of the suspected medication (a gamble we would rarely engage). However, it would be unusual to introduce a new medication, particularly a biologic therapy, in someone without active underlying IBD, and then be able to withdraw the potentially offending medication without starting some other form of immune suppressing therapy for the IBD.

As pertains to our case, hemolytic anemia is occasionally encountered by physicians who treat patients with IBD. Some hemolytic anemias are drug-induced, and drug-induced hemolytic anemias (DIHAs) encompass 3 broad categories. The first category is a nonimmune DIHA, mediated through hemolysis secondary to oxidative stress, as exemplified with G6PD deficiency. Because antibodies are not involved, the Coombs' test is negative for the presence of autoantibodies coating the red blood cells (RBCs). Pertinent to physicians that treat patients with IBD, the sulfa-containing sulfasalazine is a common drug associated with triggering hemolytic anemia in a G6PD deficient patient. The second category is a drug-induced thrombotic

microangiopathy, such as thrombotic thrombocytopenic purpura or hemolytic uremic syndrome, which have been associated with antineoplastic agents, immunosuppressives, antiplatelet agents, and quinine. The precise mechanism of action is not well understood. The third category is an immune-mediated DIHA, one of the forms of warm autoantibody hemolytic anemia (WAHA). The mechanism of action involves the inducement of IgG antibodies which will coat RBCs, prompting hepatic and splenic macrophages to recognize the IgG bound RBCs and execute phagocytosis by targeting the Fc receptors. Additionally, cell damage can result from antibody-dependent T cell-mediated toxicity and complement-mediated activation.[1] The direct Coombs' test will be positive, detecting antibodies coating the RBCs. The most common drugs associated with the drug-induced WAHA are beta lactams and NSAIDs (piperacillin and diclofenac being most common in these categories). Antineoplastic agents and monoclonal antibody therapies have also been implicated, as well as check point inhibitor therapy.[2]

In our case, vedolizumab was initially presumed to be the cause of the immune-mediated anemia based on the close timing of introducing the medication and the subsequently pronounced hemolytic anemia. Nonetheless, the patient's colitis was quite active at the time, and the drug was not establishing remission of the underlying condition. After complete resolution, the WAHA reflared once the steroid taper was concluded, 3 months after the last dose of vedolizumab, albeit after introducing another biologic agent with an entirely different mechanism of action (ustekinumab) for persistently active colitis. As the colitis entered clinical remission on the new agent, the WAHA has resolved. This case highlights the difficulty in drawing conclusions around cause and effect observations in these situations.

Autoimmune hemolytic anemia (AIHA), which encompasses both WAHA and cold agglutination disease in IBD is rare. The MICISTA database has identified 47 cases per 100 000 consecutive patients with IBD.[3] Uzzan et al[3] performed a multicenter retrospective study to describe the characteristics of patients with IBD and AIHA. As per their review, they found that AIHA is predominantly associated with ulcerative colitis, especially in those with pan colonic involvement. Of the AIHA cases, 86% had a positive Coombs' test and 70% were in the presence of IBD flares, suggesting a correlation with active bowel inflammation. AIHA often resolves with treatment of IBD, notably with biologic therapy including infliximab and vedolizumab.[4,5] Uzzan[3] further reported resolution of AIHA with curative colonic resection in 75% of cases. The underlying reason for the association between AIHA and IBD is unknown, though a suggested mechanism includes increased intestinal permeability allowing for cross-reactivity of erythrocytes and autoantibodies against antigens in the colon.[3,4] So the evidence is compelling that AIHA can be a rare extraintestinal manifestation of IBD, related to the underlying disease activity. But what about our drugs?

Contrary to the association of anti-tumor necrosis factor (TNF) agents with a wide variety of autoimmune phenomena, the evidence linking anti-TNF therapy to WAHA is sparse.[6] The case reports on the association either identified Coombs' (DAT) negative hemolytic anemia or do not clearly establish a role for the drug independent of the disease activity (Table 1).[4,7–11] Data on association of immune-mediated DIHA and other biologics are very limited (Table 1).[12,13]

While some autoimmune phenomenon triggered by our biologic therapies have been well recognized, we do not find the clinical course of our case and the evidence above sufficiently compelling to clearly implicate vedolizumab in the etiology of WAHA. As our therapies and mechanisms of immune suppression become increasingly varied, it would be helpful to better understand the etiology and treatment options of WAHA in the setting of applying biologic therapy to active IBD.

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Authors' Contributions

M.B.: literature review, data acquisition, and drafting the article. M.A.: critical revision of article and final approval of version to be submitted. A.D.: contributed to conception, critical revision of article, and final approval of version to be submitted.

Conflicts of Interest

None declared.

Data Availability

No new data were created or analyzed then please state so in the data availability statement.

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