Successful treatment of refractory cold agglutinin syndrome using fixed-duration daratumumab, bortezomib and dexamethasone with a sutimlimab bridge

Cold autoimmune hemolytic anemia (cAIHA) results from monoclonal antibodies, termed cold agglutinins, which typically demonstrate IgM κ specificity and target the I antigen on erythrocytes at cold temperatures (<37°C).[1-3] Binding of cold agglutinins results in hemolysis by activation of the classical complement pathway, as well as agglutination, leading to acrocyanosis and Raynaud-like phenomena.[1] Significant fatigue and an increased risk of thrombosis also occur.[1] cAIHA results from cold agglutinin syndrome (CAS) or cold agglutinin disease (CAD). CAS can result from infection, autoimmune disorders, and indolent bone marrow disorders such as lymphoplasmacytic lymphoma (Waldenström macroglobulinemia) and IgM-related disorders.[3] In contrast, CAD describes a distinct entity termed CAD-associated lymphoproliferative disorder, which has characteristic features defined for the first time in the most recent World Health Organization classification of hematolymphoid tumors.[3] CAD is responsible for the majority of cases of cAIHA.[3]

Asymptomatic cAIHA does not require treatment,[1] while symptomatic cAIHA is treated with rituximab monotherapy[4] or rituximab in combination with bendamustine[5] or fludarabine.[6] These therapies are effective, especially the combination of bendamustine and rituximab, with one large observational study showing a 78% response rate to bendamustine plus rituximab and a 77% estimated 5-year sustained remission rate among responders.[7] However, a substantial portion of patients still do not respond to conventional therapies, and responses are often temporary.[1] Sutimlimab, which targets C1s to inhibit the classical complement pathway, improves hemoglobin and bilirubin levels, transfusion requirements, and fatigue in patients with cAIHA,[8] but it must be given continuously and does not address the underlying source of antibody production. Therefore, novel approaches to the management of cAIHA are needed.

Here, we describe a patient with symptomatic cAIHA who did not respond to rituximab and dexamethasone combination therapy. He also received the Bruton tyrosine kinase (BTK) inhibitor ibrutinib, based on promising retrospective data,[9] but unfortunately this also produced no response, and the patient developed severe anemia, requiring urgent treatment with sutimlimab. Bone marrow biopsy unexpectedly demonstrated 7% CD138$^+$ plasma cells, the majority of which showed κ restriction and expressed surface IgM. The plasma cell burden, along with promising reports suggesting that plasma cell-directed therapies can be effective in cAIHA,[10-12] inspired us to treat the patient with the myeloma-based combination regimen of daratumumab, bortezomib, and dexamethasone (DVd). After less than 3 months of treatment with DVd, cold agglutinin titers decreased substantially and the patient was able to discontinue sutimlimab without a drop in hemoglobin concentration. A year out from the completion of therapy, the patient remains off any treatment, is asymptomatic, and shows no signs of hemolytic anemia. We therefore suggest that fixed duration DVd can be an effective treatment for cAIHA, particularly for patients with CAS demonstrating excess IgM-secreting or -expressing plasma cells.

Our case was a 72-year-old male with primary sclerosing cholangitis previously treated by biliary stenting who presented for evaluation of mild anemia with a hemoglobin concentration of 11.1 g/dL in the absence of bleeding or nutritional deficiency. The patient was otherwise quite healthy and exercised for several hours a day, often running outdoors. A direct antiglobulin test was strongly positive for anti-C3d (4+) and negative for anti-IgG. A pan-reactive cold agglutinin was identified. Serum protein electrophoresis with immunofixation demonstrated an IgM κ band (0.24 g/dL) and the IgM level was elevated to 238 mg/dL. Physical examination was unremarkable, white blood cell and platelet counts were intact, and a recent abdominal computed tomography scan showed no evidence of lymphadenopathy. The patient's hemoglobin had improved to 12.3 g/dL at the time of assessment, likely due to robust reticulocytosis (Figure 1A, B), and he was asymptomatic. We therefore opted to defer treatment and bone marrow biopsy. The patient was started on folate supplementation and counseled on precautions to take in cold circumstances.

The patient remained well off treatment until he presented again 2 years later, at which time he noted acrocyanosis when outdoors and decreased exercise tolerance. In addition, his hemoglobin had dropped to less than 10 g/dL and his bilirubin had more than doubled (indirect bilirubin was 2.7/2.8 mg/dL) (Figure 1A). We therefore opted to initiate treatment with four weekly administrations of rituximab. This produced a minimal improvement in hemoglobin concentration (Figure 1A) and no improvement in symptoms, so we treated him again with rituximab, this time in combination with dexamethasone and erythropoietin. This treatment produced a small increase in hemoglobin, but the cold agglutinin titer remained significantly elevated (Figure 1A, C) and the patient continued to have decreased exercise tolerance and painful acrocyanosis. Based on a promising retrospective study,[9] we next treated him with the BTK inhibitor ibrutinib, but there was no response. The patient's hemoglobin declined after 2 months of treatment (Figure 1A), at which time ibrutinib

was suspended because of elevated transaminase levels. The patient was planned for bone marrow biopsy to guide the next steps, but while awaiting the bone marrow biopsy he required emergency admission for ascending cholangitis and biliary sepsis. His bilirubin concentration dropped rapidly after biliary stenting and he responded quickly to intravenous antibiotics. However, his course was complicated by a rapid drop in hemoglobin to a nadir of 6 g/dL (Figure 1A), as well as left portal vein thrombosis. We suspected that the hemolysis was triggered by the patient's underlying infection, as well as potential exposure to cold during the biliary stent placement. The patient was given one unit of pre-warmed packed red blood cells and therapeutic anticoagulation for left portal vein thrombosis. We then initiated treatment with the direct complement pathway inhibitor sutimlimab while the patient was admitted, as a bridge to more definitive outpatient therapy. Prior to sutimlimab, the patient received vaccination against *Streptococcus pneumoniae, Haemophilus influenzae* type b, and *Neisseria meningitidis* serogroups A, B, C, W, and Y. Protective antibody titers were not tested. The patient's hemoglobin improved markedly 2 weeks after his first dose of sutimlimab (Figure 1A); however, we explored treatment options capable of targeting the underlying lymphoproliferative disorder. Bone marrow biopsy showed 7% plasma cells by CD138 immunohistochemistry (Figure 2A), with a subset positive for IgM (around 5% of total cellularity), and a κ:λ ratio of 3:1 (Figure 2B, C). Flow cytometry identified $CD38^+$ and $CD56^+$ cells which lacked expression of CD20 (Figure 2D, E). However, there was no overt B-cell or plasma cell monotypic population based on light chain expression determined by either flow cytometry or *in-situ* hybridization studies. Collectively, these findings, in the presence of an IgM κ monoclonal band detected by electrophoresis, suggested to us that our patient had CAS secondary to a small clonal population of IgM^+ cells with plasmacytic features that was below the threshold of definitive detection. We therefore opted to treat him with plasma cell-directed therapy using a combination of daratumumab, bortezomib, and dexametha-

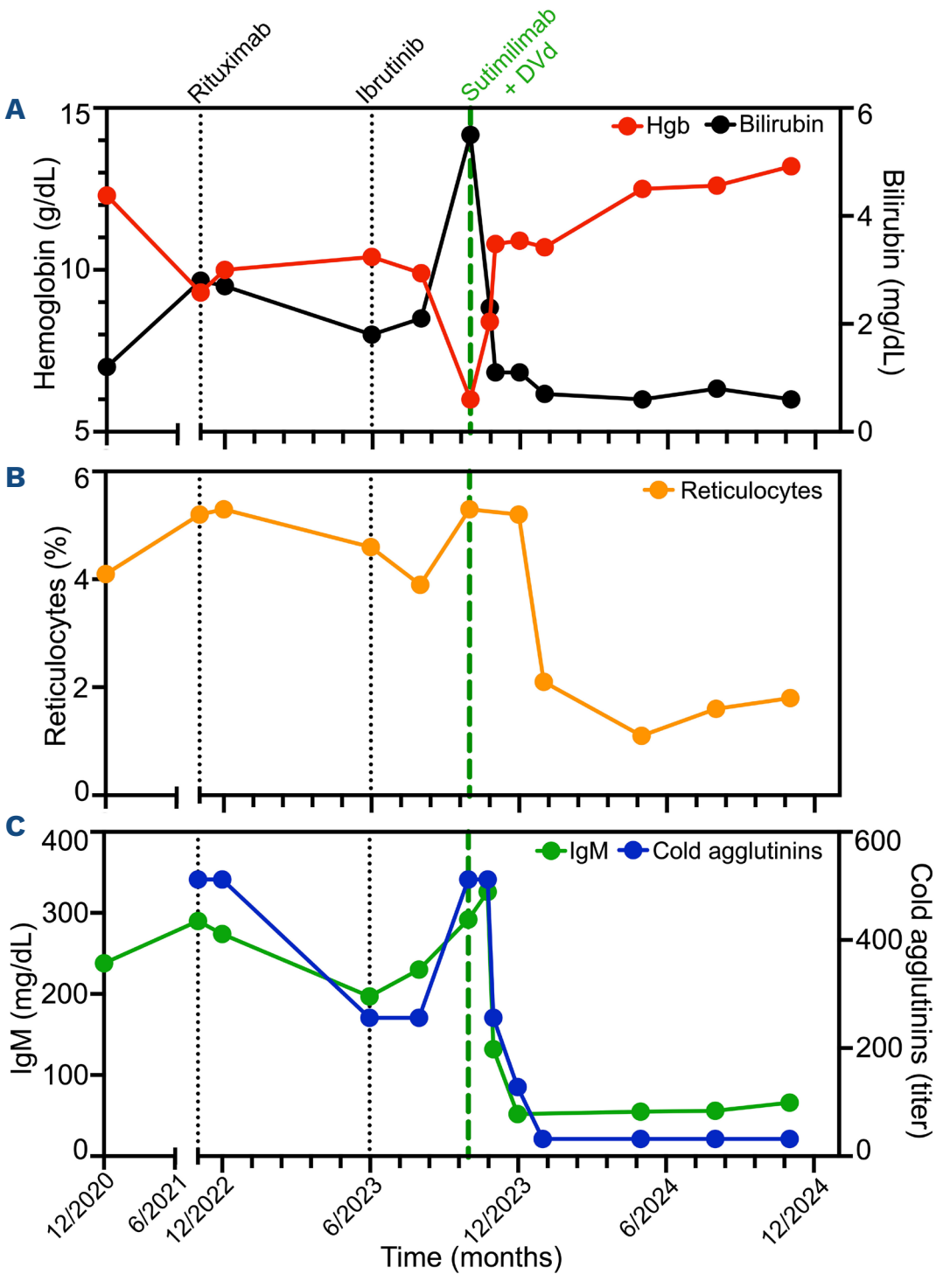

Figure 1. Cold autoimmune hemolytic anemia improved during treatment with daratumumab, bortezomib, and dexamethasone together with sutimlimab but not rituximab or ibrutinib. (A-C) Rituximab and ibrutinib produced minimal improvements in hemoglobin, total bilirubin (A), and reticulocytes (B), despite slight improvements in IgM and cold agglutinin titer (C). In contrast, 3 months of treatment with daratumumab, bortezomib, and dexamethasone and sutimlimab resulted in improvement and sustained normalization of hemoglobin level, markers of hemolysis, IgM, and cold agglutinin titer (A-C). DVd: daratumumab, bortezomib, and dexamethasone; Hgb: hemoglobin.

sone (DVd). Our patient provided consent for this novel therapy, and this consent respects the ethical rules of the USA, where the patient received treatment. We opted to combine two plasma cell-directed agents as bortezomib monotherapy had been associated with only a modest response in a clinical trial (31.6% in the GIMEMA study[10]) and there was little published experience with daratumumab monotherapy. The patient received eight weekly treatments of daratumumab (subcutaneous, 1,800 mg/dose), 11 treatments of bortezomib (subcutaneous) at a dose of 1.3 kg/m^2 on days 1, 4, 8, and 11 of a 21-day cycle, and 20 mg of dexamethasone (oral) if receiving either daratumumab or bortezomib. After the eighth daratumumab and 11th bortezomib treatment, the patient's hemoglobin concentration remained stable above 10 g/dL, bilirubin had normalized, and both IgM and cold agglutinin titer had decreased (Figure 1A, C). In addition, serum protein electrophoresis no longer demonstrated a trace IgM κ band, but did show an IgG κ band consistent with treatment with daratumumab. The patient's acrocyanosis had also resolved, and he had resumed exercising normally. We therefore opted to monitor him while off treatment, including sutimlimab, which was discontinued after a total of six treatments and the completion of DVd. The patient has remained off any treatment for more than 1 year. He is asymptomatic with normal hemoglobin, no evidence of hemolysis, resolution of the IgM κ monoclonal gammopathy, a decrease in reticulocytes, and a substantial reduction in cold agglutinin titer (Figure 1A-C), constituting a complete response by consensus criteria.[13]

Our patient's successful treatment of CAS with daratumumab and bortezomib is consistent with emerging literature. The phase II GIMEMA study evaluated response to 3 months of treatment with bortezomib among 19 patients with relapsed or refractory cAIHA and noted an overall response rate of 31.6%.[10] In a retrospective series including seven patients with cAIHA who received treatment with daratumumab, 57% of the patients had an increase in hemoglobin levels, and four of six patients with acrocyanosis had improvement in symptoms.[12] A separate retrospective analysis including eight patients, with a diagnosis of either warm or cold autoimmune hemolytic anemia, who received bortezomib, daratumumab, or both showed an overall response rate of 88% (7/8).[14] We suspect our patient's excellent response to the daratumumab and bortezomib combination resulted from targeting the underlying clone producing the cold agglutinin antibody. The disappearance of the IgM κ paraprotein strongly suggests successful targeting of the underlying disorder, which likely facilitated our patient's complete response. We suspect plasma cell-directed therapy produced a superior response to rituximab and ibrutinib due to the plasmacytic features (7% plasma cells by CD138 staining) of our patient's underlying bone marrow disorder. It would be informative to evaluate whether daratumumab and bortezomib are more

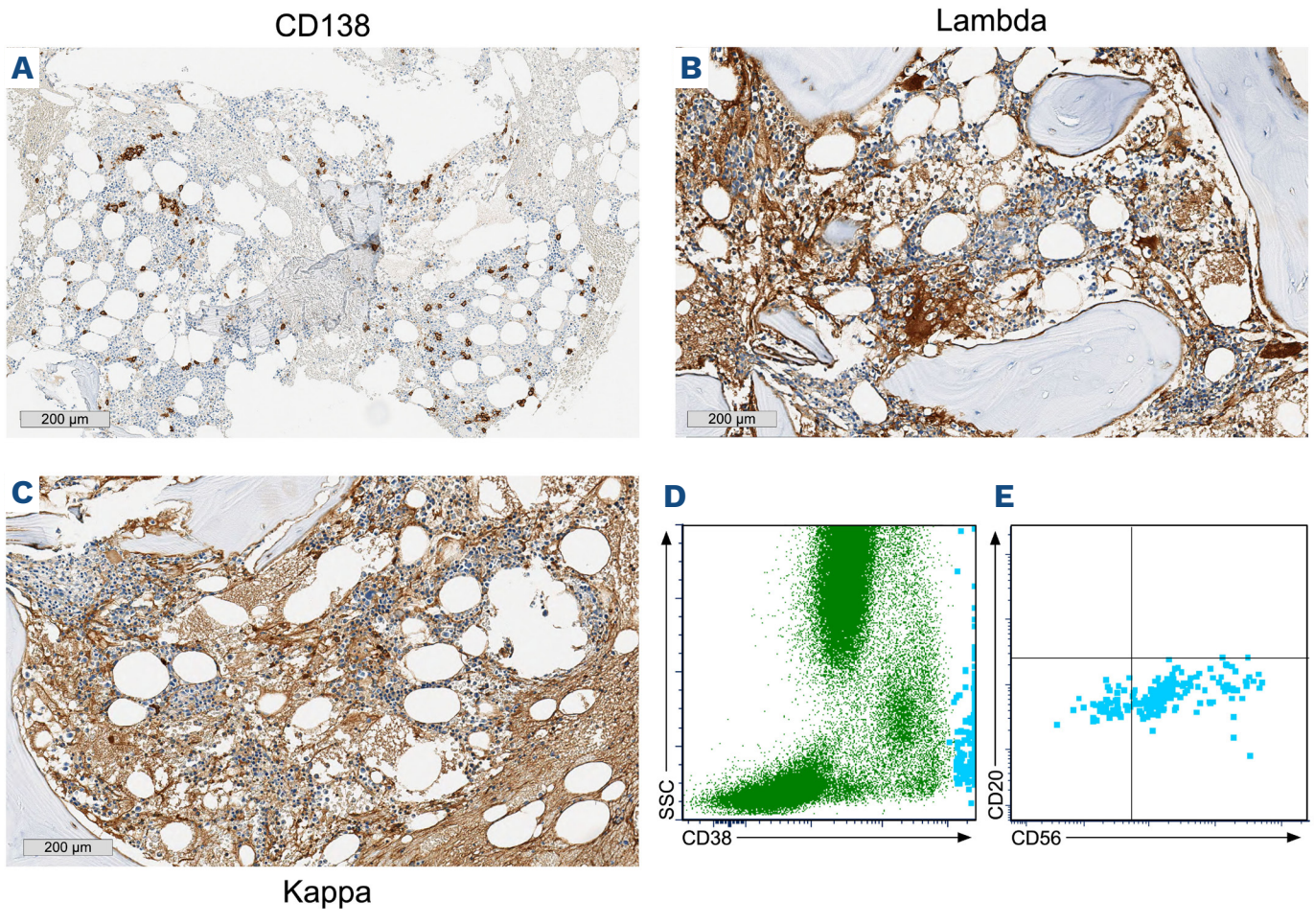

Figure 2. Bone marrow biopsy suggested cold agglutinin syndrome secondary to a small population of IgM$^+$ cells with plasmacytic features. (A) Bone marrow biopsy was significant for 7% plasma cells, as determined by immunohistochemistry for CD138. (B, C) Plasma cells were κ-restricted (κ:λ ratio 3:1); note increased nuclear staining of κ (C) compared to λ (B). (D, E) Flow cytometry identified a population of plasma cells with expression of CD38 and CD56, which were negative for CD20 (plasma cells represented in blue).

effective in disease demonstrating a higher burden of clonal plasma cells.

Our patient was also treated with the complement inhibitor sutimlimab because of severe hemolytic anemia. Sutimlimab proved highly effective as a bridging therapy, and it is unclear whether our patient would have successfully completed DVd without it. However, our fixed duration treatment with DVd, which was given for less than 3 months, allowed the patient to be weaned from sutimlimab after only six treatments, which has significant advantages with respect to quality of life and infection risk. We are also aware that long-lived plasma cells are suspected to play a role in the recurrence of autoimmune hemolytic anemia after initial successful treatment, and that daratumumab may be potentially effective at targeting this persistent disease.[12] In this setting, we note that future work should address the optimal duration of treatment with plasma cell-directed therapies, including a potential role for maintenance therapy, and it will be informative to follow our patient off treatment. We also acknowledge that treatment with DVd carries the risk of infection and toxicities such as neuropathy, which may be particularly relevant in the elderly population that is most at risk of cAIHA. Our patient had exceptional performance status and typically exercised for more than an hour daily. A clinical trial of DVd would be ideal to clarify not only the efficacy of the regimen but also whether the regimen is safe in less fit and elderly patients. Nevertheless, we suggest that short, fixed-duration, combination treatment with DVd can be a highly effective regimen for some patients with cAIHA, particularly if the underlying bone marrow disorder has prominent plasmacytic features.

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Contributions

BR analyzed data, prepared the figures, and wrote the manuscript. MJ and RK prepared the figures and revised the manuscript. NH participated extensively in the patient's care and reviewed the manuscript. APR conceived and guided the project, and revised the manuscript and figures.

Data-sharing statement

Data contained in this manuscript can be obtained by contacting the corresponding author.

References

1. Berentsen S. How I treat cold agglutinin disease. Blood. 2021;137(10):1295-1303.
2. Berentsen S. New insights in the pathogenesis and therapy of cold agglutinin-mediated autoimmune hemolytic anemia. Front Immunol. 2020;11:590.
3. Guenther A, Tierens A, Malecka A, Delabie J. The histopathology of cold agglutinin disease-associated B-cell lymphoproliferative disease. Am J Clin Pathol. 2023;160(3):229-237.
4. Berentsen S, Ulvestad E, Gjertsen BT, et al. Rituximab for primary chronic cold agglutinin disease: a prospective study of 37 courses of therapy in 27 patients. Blood. 2004;103(8):2925-2928.
5. Berentsen S, Randen U, Oksman M, et al. Bendamustine plus rituximab for chronic cold agglutinin disease: results of a Nordic prospective multicenter trial. Blood. 2017;130(4):537-541.
6. Berentsen S, Randen U, Vågan AM, et al. High response rate and durable remissions following fludarabine and rituximab combination therapy for chronic cold agglutinin disease. Blood. 2010;116(17):3180-3184.
7. Berentsen S, Barcellini W, D'Sa S, et al. Cold agglutinin disease revisited: a multinational, observational study of 232 patients. Blood. 2020;136(4):480-488.
8. Röth A, Berentsen S, Barcellini W, et al. Sutimlimab in patients with cold agglutinin disease: results of the randomized placebo-controlled phase 3 CADENZA trial. Blood. 2022;140(9):980-991.
9. Jalink M, Berentsen S, Castillo JJ, et al. Effect of ibrutinib treatment on hemolytic anemia and acrocyanosis in cold agglutinin disease/cold agglutinin syndrome. Blood. 2021;138(20):2002-2005.
10. Rossi G, Gramegna D, Paoloni F, et al. Short course of bortezomib in anemic patients with relapsed cold agglutinin disease: a phase 2 prospective GIMEMA study. Blood. 2018;132(5):547-550.
11. Rieger MJ, Stolz SM, Ludwig S, et al. Daratumumab in rituximab-refractory autoimmune haemolytic anaemia. Br J Haematol. 2021;194(5):931-934.

12. Jalink M, Jacobs CF, Khwaja J, et al. Daratumumab monotherapy in refractory warm autoimmune hemolytic anemia and cold agglutinin disease. Blood Adv. 2024;8(11):2622-2634.
13. Berentsen S. Cold agglutinin disease. Hematology Am Soc Hematol Educ Program. 2016;2016(1):226-231.
14. McGlothlin J, Abeykoon J, Al-Hattab E, et al. Bortezomib and daratumumab in refractory autoimmune hemolytic anemia. Am J Hematol. 2023;98(10):E263-E265.