Marginal zone lymphoma with anti-factor H IgM and atypical hemolytic uremic syndrome successfully treated with odronextamab

Extranodal marginal zone lymphoma (MZL) of mucosa-associated lymphoid tissue (MALT) is a non-Hodgkin lymphoma, originating in mucosal lymphoid tissues. When it involves gastric mucosa, it may be related to chronic *Helicobacter Pylori* (HP) infection.[1] In the setting of lymphoproliferative diseases, there may be a production of autoantibodies against specific human proteins, which may induce different organ dysfunctions and complications that sometimes overcome the severity of the primary disease.[2,3]

Atypical hemolytic uremic syndrome (aHUS) is a thrombotic microangiopathy (TMA) often related to complement dysregulation due either to gene defects (gain-of-function mutation of activators or loss-of-function of inhibitors) or to autoantibodies against factor H (FH) usually of the IgG class[4] and, less commonly, of the immunoglobulin (Ig)M class.[5] Most cases associated with IgG anti-FH recognize a genetic predisposition in a homozygous deletion in genes of complement FH-related antigens (CFHR3-CFHR1).[6] Conversely, autoantibodies of the IgM class are not associated with any genetic background and they have been described with a frequency 6-fold higher in the setting of hematopoietic stem cell transplant-associated TMA (TA-TMA).[5] In MZL, autoantibodies against a single protein have been reported,[3] but to the best of our knowledge, autoantibodies against FH have never been described.

Herein we describe a case of MALT lymphoma complicated by IgM anti-FH autoantibodies followed by complement-mediated aHUS and characterized by several intriguing implications.

A 39-year-old woman, without previous relevant medical history, presented with abdominal bloating and dyspepsia. Gastroscopy revealed macroscopic ulcers, and biopsy showed typical involvement by a MALT MZL. She had a minimal bone marrow clonal MZ-like B-cell infiltration with t(11;18)(q21;q21) (BIRC3/MALT1), a monoclonal IgM antibody and normal blood count. Serology was negative for both hepatitis B and hepatitis C viruses. MALT-International Prognostic Index score was 1/3 at diagnosis. Moreover, she tested positive for HP by immunohistochemistry on gastric biopsy, thus she underwent a single eradication treatment with omeprazole and an association of bismuth subcitrate potassium, metronidazole and tetracycline (Pylera), which in Italy shows an eradication rate of 96.7% to 97.8%.

Despite successful HP eradication, the patient experienced disease progression confirmed by a gastric echo-endoscopy that showed ulcers (up to 2 cm, negative for HP), gastric wall thickening, and perigastric and celiac tripod adenopathies. To preserve the patient from cytotoxic treatment, we referred her to first-line rituximab monotherapy for eight doses of 375 mg/m^2 (4 weekly followed by 4 monthly). Despite endoscopic and histologic persistence of lymphoma, given the optimal clinical control, watchful waiting was chosen.

At the age of 45 years, the patient experienced arthralgia and steroid-refractory thrombocytopenia. Disease localizations were unchanged, except for an increase in monoclonal IgM (3 g/L). Second-line therapy with rituximab and bendamustine (4 cycles) was started, with complete recovery of platelet count and undetectable IgM levels, but without significant changes in disease localizations.

At the age of 53 years (November 2022), the patient experienced fatigue, fever, and generalized edema, without any identified specific trigger. Laboratory tests showed Coombs test-negative hemolytic anemia (hemoglobin [Hb]: 6.7 g/dL; lactate dehydrogenase [LDH]: 762 U/mL; undetectable haptoglobin; schistocytes: 1%), thrombocytopenia (25,000/mm^3), and acute kidney injury (serum creatinine [sCr]: 3.9 mg/dL) with proteinuria (500 mg/dL). ADAMTS13 activity[7] was in the normal range (82%) and C3 was consumed (0.39 g/L [normal range, 0.90-1.80 g/L]). Given the lack of diarrhea, a diagnosis of aHUS was made.

A complete disease re-staging was performed: fluorodeoxyglucose^{18}-positron emission tomography (PET) was negative and bone marrow infiltration was stable, but monoclonal IgM levels significantly increased up to 11 g/L. Third-line therapy with ibrutinib was started, but, on day 4, a worsening of renal function and a concomitant spike in the monoclonal IgM levels (14.8 g/L) led to treatment interruption and initiation of a specific treatment for aHUS with the C5 inhibitor eculizumab (900 mg intravenously [i.v.] once weekly for 4 weeks followed by 1,200 mg i.v. every 2 weeks). After the initial four doses of C5 inhibitor, we observed a prompt improvement of all laboratory parameters of aHUS including a complete recovery of kidney function. Ibrutinib was then reintroduced and well tolerated. Laboratory investigations (previously described[5]) documented a high titre of IgM anti-FH with no IgG or IgA anti-FH and no significant genetic abnormality in complement regulatory genes. The complement activation marker sC5b-9, measured by enzyme-linked immunosorbant assay,[7] was as high as 1,882 ng/mL (normal range, 150-400 ng/mL) before eculizumab initiation and it decreased to a nadir of 213 ng/mL during C5 inhibition. IgM anti-FH autoantibodies were characterized for their interaction with different factor H domains by a competition assay[5] with known anti-FH monoclonal antibodies that recognize specific domains related to short

consensus repeats (SCR) epitopes. The binding of patient's autoantibodies to FH molecule was found to be inhibited by monoclonal antibody L20 mapping at SCR19, the active site of FH for its binding to endothelial cells (Figure 1).

Within 6 months, renal function fully recovered with a nadir of sCr of 0.95 mg/dL and a urinary protein-to-urinary creatinine ratio of 0.14 mg/mg (normal <0.2 mg/mg). Eculizumab was continued and the interval between doses was tailored according to global complement functional test[8] with a maintenance schedule of 1,200 mg every 4 weeks and aHUS remained in stable remission.

After 6 months on ibrutinib (May 2023), disease assessment (clinical, endoscopic, serological, imaging and bone marrow) did not show any significant improvement. The treatment was continued until January 10, 2024, and the patient was considered as a candidate for a subsequent therapeutic line. The patient was then evaluated for the MZL cohort of the phase II ELM-2 study (*clinicaltrials gov. Identifier: NCT03888105*)[9] with the bispecific humanized antibody odronextamab, which binds to CD3 on T cells and CD20 on B cells, and was deemed eligible. At screening, PET showed a clear disease progression at the level of the gastric wall, peri-gastric lymph nodes, right lung apex and splenomegaly. The patient was admitted and started cycle 1 of intravenous odronextamab with the optimized step-up dosing regimen (0.2 mg on day 1; 0.5 mg on day 2; 2 mg on day 8; 9 mg on day 15 and 10 mg on day 16) with inpatient monitoring. Grade 1 cytokine-release syndrome (CRS), observed at week 3, was successfully controlled with antipyretics and dexamethasone. When the nominal dose was reached (80 mg) no further CRS events were observed. The patient continued odronextamab as outpatient without any adverse event. At first restaging (week 12), a complete response (CR) was detected by PET, endoscopic gastric biopsy and bone marrow biopsy. CT scan of abdomen and gastroscopy are shown in Figure 2. Notably, total serum IgM rapidly decreased from 1,864 mg/dL to 229 mg/dL (Figure 3, upper panel) and correspondingly IgM anti-FH were completely cleared (Figure 3, lower panel). After initiation of the bispecific antibody, three additional administrations of eculizumab were given (16, 42, and 67 days). Following the documented stable reduction of anti-FH autoantibodies, eculizumab was discontinued. The patient was then carefully monitored for aHUS relapse by home

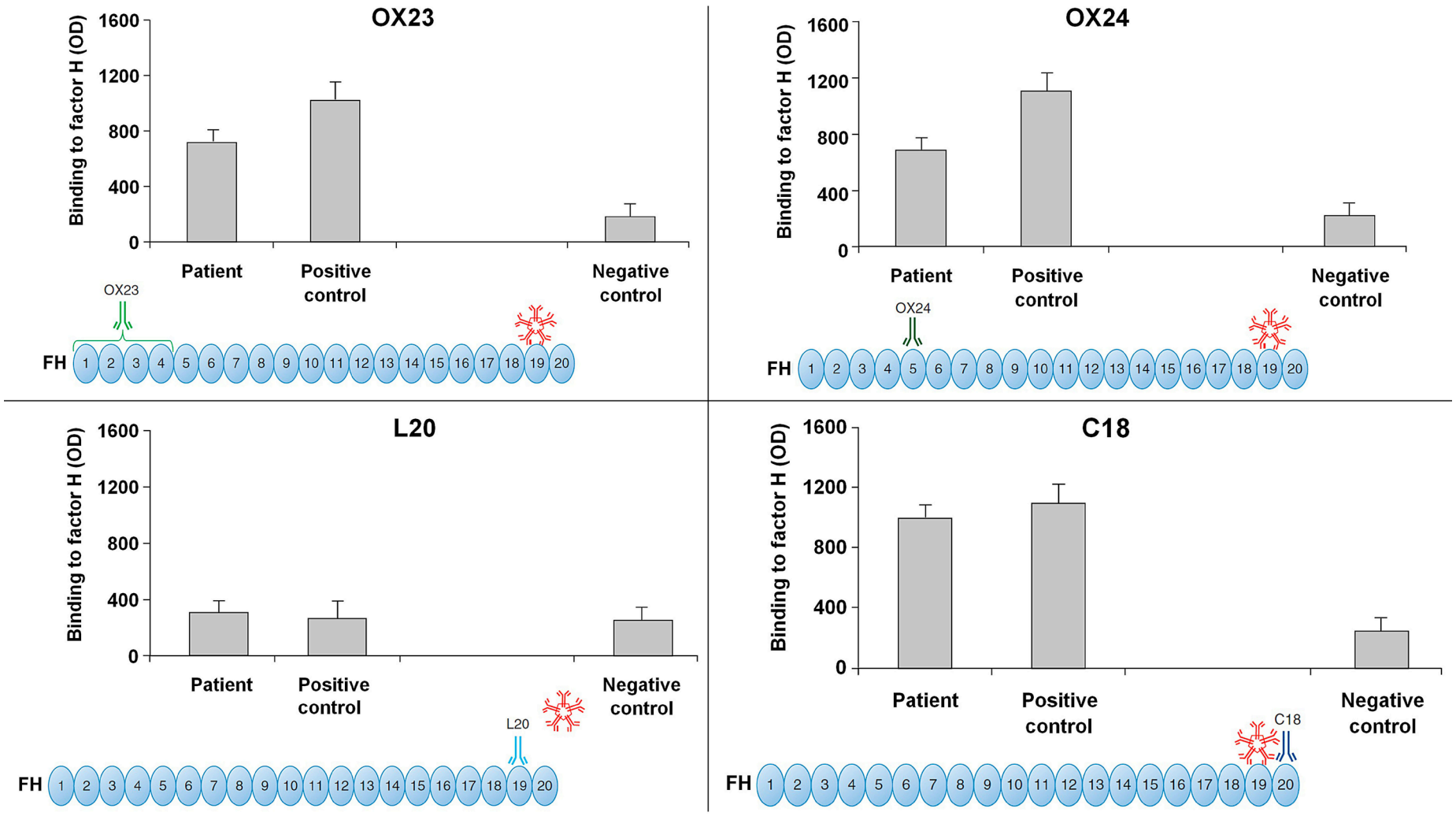

Figure 1. Effects of specific monoclonal antibodies, targeted to known epitopes of factor H, on the binding of patient's autoantibodies to immobilized factor H molecule. The column charts represent the binding of serum IgM anti-factor H autoantibodies to immobilized factor H, expressed as mean optical density (OD) of 3 experiments with standard deviation. In the present patient, the binding was inhibited only by the monoclonal antibody (mAb) L20 that interacts with the SCR domain 19 (the active site of factor H for its binding to endothelial cells), whereas mAb OX23 (interacting with SCR1-4), OX24 (interacting with SCR5), and C18 (interacting with SCR20) did not modify the binding of serum anti-factor H autoantibodies to the factor H molecule. The positive control is a patient with previously documented autoantibodies to factor H that interact with domain 19. The negative control is normal pooled serum.

urine dip-stick for hemoglobinuria (twice weekly) and regular blood test at odronextamab administration. During the 8 months subsequent to eculizumab discontinuation, no sign of relapse was detected and sC5b-9 stably remained in the normal range. At the last follow-up (month 10), the patient continues to receive odronextamab (160 mg every 2 weeks) and remains in PET complete remission of lymphoma. The study was approved by the ethics committee Milano Area 2 (No. 623_2019bis) and carried out in conformity with the 2013 revision of the Declaration of Helsinki. The subject gave her written consent to participate in the study.

The present case report raises several peculiar issues of possible interest among which the possibility that MZL produce IgM recognizing the epitope of FH active site. Treatment with odronextamab not only induced a complete remission of the lymphoma but it also dramatically reduced anti-FH

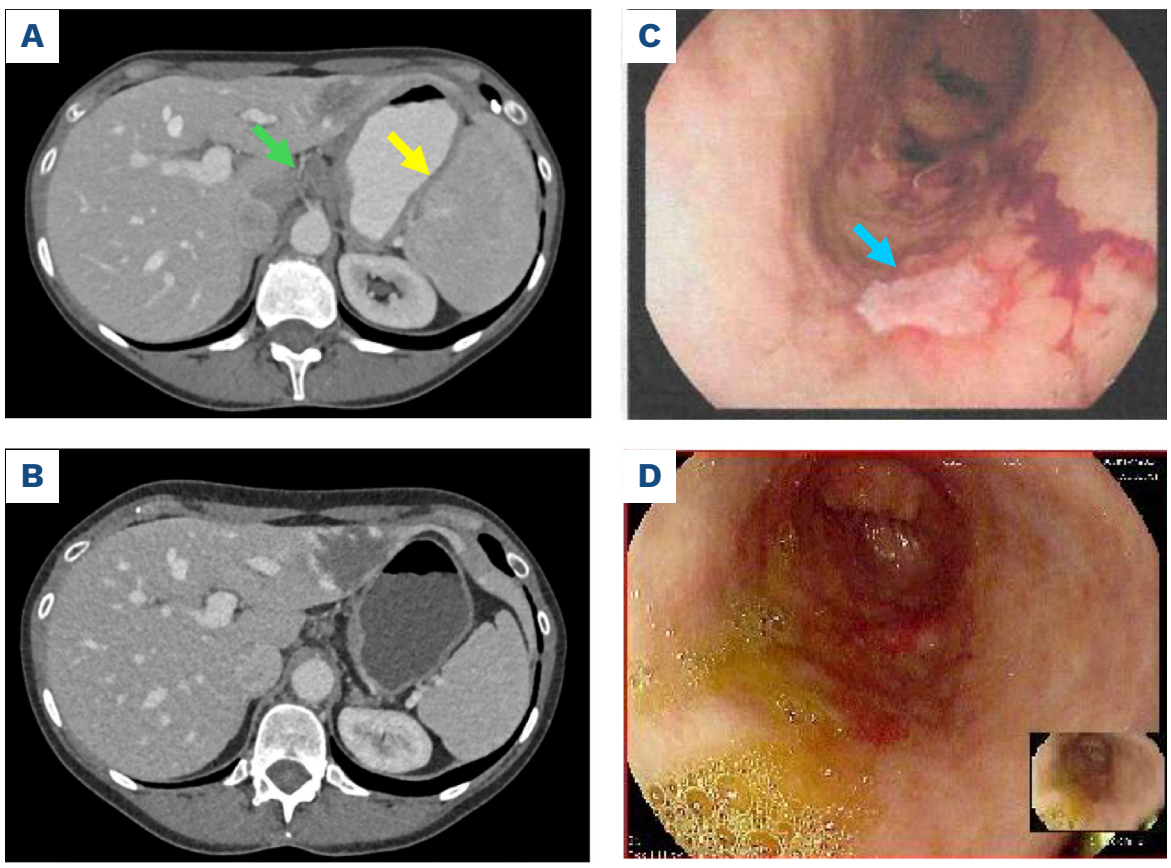

Figure 2. Computed tomography scan of the abdomen and gastroscopy before and after odronextamab therapy. (A) Computed tomography (CT) scan of abdomen with contrast medium performed before odronextamab therapy. The green arrow shows celiac tripod adenopaties. The yellow arrow shows moderate splenomegaly. (B) CT scan of abdomen with contrast medium performed after 3 months of odronextamab therapy showing regression of celiac tripod adenopaties and splenomegaly. (C) Gastroscopy performed before odronextamab therapy. The blue arrow shows a fibrinous ulcer. Gastric biopsy at this site showed clear involvement by marginal zone lymphoma. (D) Gastroscopy performed after 3 months odronextamab therapy showing a complete regression of the ulcer.

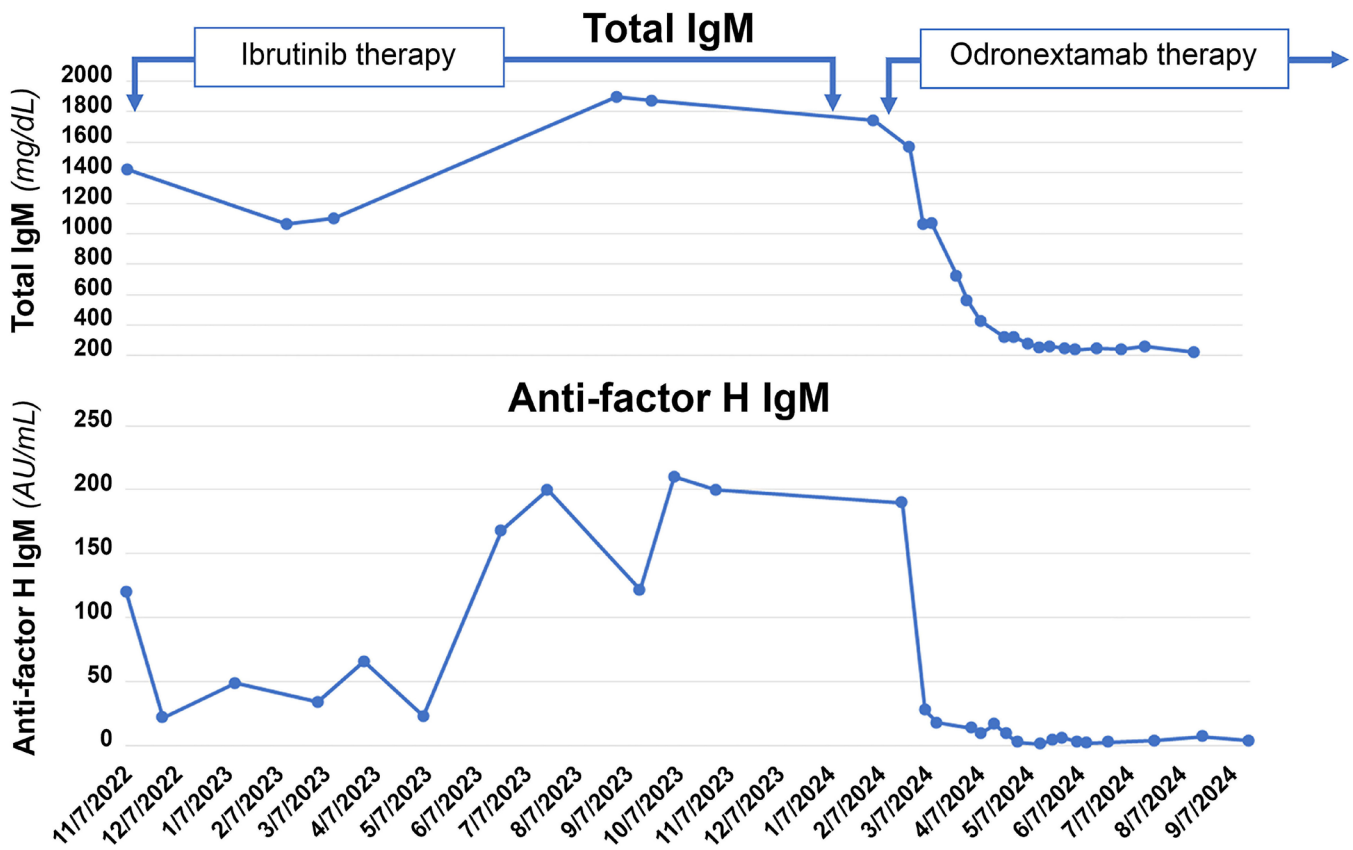

Figure 3. Time course of total and specific anti-factor H IgM concentrations in patient's serum. Ibrutinib therapy was administered from November 2022 to January 2024 while odronextamab therapy was started on February 27, 2024 and is still ongoing. Total immunoglobulin (Ig)M normal range: 40-230 mg/dL. Anti-factor H IgM normal range: 0-10.3 AU/mL.

autoantibodies, leading to discontinuing C5 inhibition therapy and maintaining normal complement activity markers. In adults, about 50% of patients with aHUS have a detectable complement abnormality among which the production of anti-FH autoantibodies of the IgG class is a well-known cause.[4,6] Recently our group documented that also specific IgM can lead to FH loss-of-function, thus inducing aHUS.[5] This condition is more commonly encountered in TA-TMA and the anti-FH autoantibodies of the IgM class, unlike anti-FH IgG, are not associated with FH-related gene deletions.[5] The present report documents that IgM anti-FH can be produced in the context of a lymphoproliferative disease. The absence of significant abnormalities in complement-related genes and the interaction of the autoantibody with the reactive site of FH indicate that the autoantibody played a specific role in causing block of complement inhibition and the consequent complement hyperactivation and aHUS, regardless of whether the autoantibody originates from the MZL clone or from an autoreactive one. The rapid and complete response of aHUS to complement inhibition therapy further supports the role of complement activation due to IgM anti-FH in the pathogenesis of this TMA. Additional issues of potential interest are: (i) the patient underwent eculizumab maintenance treatment tailored on global complement activity (targeted to <30%) as we usually do in patients on long-term eculizumab treatment,[8] allowing the safe increase of the interval between doses, and (ii) the possibility of discontinuing C5 inhibition therapy once the risk of relapse has been controlled[10,11] as in this case with odronextamab treatment, where the level of IgM anti-FH was zeroed. Preliminary results of the phase II ELM-2 study reported encouraging findings with odronextamab in heavily pretreated relapsed or refractory MZL: CR rate of 79% and 36-months progression-free survival rate of 69%, 53.3% CRS (grade 1-2) and 23.5% infections (grade 3-4).[12] Similarly to the outstanding results obtained with chimeric antigen receptor T cells,[13] it may be foreseen that bispecific antibodies become an additional therapeutic option in refractory autoimmune diseases.[14,15]

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Disclosures

GA is a member of the scientific advisory board of the Global Atypical Hemolytic Uremic Syndrome Registry supported by Alexion Pharmaceuticals Inc.; and he has received honoraria from Alnylam, Roche, Novartis, and Alexion for his participation in scientific advisory boards or for giving lectures. MCM has received honoraria from Alexion for giving lectures. FP has received honoraria for her participation in scientific advisory boards from Sobi, Sanofi, Roche, Biomarin, CSL Behring and Pfizer, and for participating as a speaker in education meetings organized by Takeda, Spark and Sanofi. MM has received honoraria from Regeneron Inc. for consultancy, from Eli Lilly for his participation in a scientific advisory board and from Johnson and Johnson, and Roche as travel grant. The remaining authors have no conflicts of interest to disclose.

Contributions

GA wrote the first draft. MC wrote significant parts of the manuscript and designed the study in the collaboration with MM, FP and SL. PA, SM, AJMF, MM and GA were responsible for the clinical management of the patient. SG, EG and LP were responsible for the laboratory tests. MCM and TR helped in organizing the data; and all authors contributed to the interpretation of the results, critically reviewed the manuscript, and approved the final version for submission.

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Data-sharing statement

For original data, please contact the corresponding author.

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