Case report

Resolution of hypogammaglobulinemia-associated recurrent *Campylobacter* bacteraemia after hematopoietic cell transplantation (HCT)

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Primary or secondary hypogammaglobulinemia is associated with persistent norovirus and *Campylobacter* infections despite immunoglobulin replacement therapy. Allogeneic hematopoietic cell transplantation for hematologic indications can lead to immune reconstitution by correcting a previously undiagnosed concurrent primary immunodeficiency. (J Allergy Clin Immunol Global 2025;4:100378.)

Key words: *Hypogammaglobulinemia,* Campylobacter*, norovirus, hematopoietic cell transplant, rituximab*

Abbreviations used
CVID: Common variable immunodeficiency
HCT: Hematopoietic cell transplantation
IVIG: Intravenous immunoglobulin G
PID: Primary immunodeficiency

In 2010, a 28-year-old man was diagnosed with stage IV T-cell histiocyte-rich B-cell lymphoma, a subtype of diffuse large B-cell lymphoma. His medical history was unremarkable until 2010, and his family history was negative for recurrent infections or autoimmune conditions. Complete response was achieved in December 2010 after 6 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP), alongside intrathecal methotrexate, with the patient remaining in remission until 2017. In August 2011, after an episode of enteroviral meningoencephalitis and norovirus enteritis, immunologic assessment revealed hypogammaglobulinemia, undetectable B cells, and poor responses to pneumococcal and *Haemophilus* influenzae type B vaccination (Pneumovax 23 [Merck, Sharpe & Dohme] and Menitorix [GlaxoSmithKline]) (Table I). Administration of intravenous immunoglobulin G (IVIG) therapy, in a dose of 400 mg/kg body weight every 3 weeks, was started, with no significant infections until 2013.

From 2014 until 2018 the patient experienced 10 episodes of abdominal pain, diarrhea, and fever, with ongoing weight loss (Fig 1). The patient's stool tested positive for norovirus GII during each of these episodes, whereas in 8 occurrences, fluoroquinolone-resistant *Campylobacter jejuni* bacteraemia was noted. Chronic enteropathy led to malabsorption and hypoalbuminemia, and parenteral nutrition was eventually needed. The IVIG infusions were intensified to a biweekly regimen, maintaining a trough IgG level greater than 8 g/L. Duodenal biopsy samples demonstrated an enteropathic process resembling common variable immunodeficiency (CVID) enteropathy. On the basis of the association of chronic norovirus[1] and *C jejuni*[2-4] infection with CVID, the possibility of an underlying primary immunodeficiency (PID) was raised. As no immunologic evaluation was available before rituximab initiation, genetic testing with 2 PID gene panels was conducted but did not detect any associated pathogenic variants.

Nitazoxanide and a 4-month course of ribavirin were unsuccessfully tried for chronic norovirus enteropathy. The patient's *C jejuni* infections were successfully treated initially with macrolides. In 2 bacteremia episodes within 6 months, the same macrolide-resistant *C jejuni* strain was isolated (multilocus sequence typing 3782), and carbapenems and tigecycline were utilized.

T-cell histiocyte-rich B-cell lymphoma relapse was diagnosed in 2017. Disease progression was noted despite chemoradiotherapy that included 4 cycles of rituximab. Only a partial response was achieved, with intensive salvage chemotherapy regimens consisting of rituximab, anthracyclines, platinum, and nonplatinum chemotherapy agents. The patient ultimately underwent allogeneic hematopoietic cell transplantation (HCT) in April 2019. Successful engraftment with complete donor chimerism was achieved, and bone marrow biopsy samples at follow-up showed marrow regeneration with no signs of lymphoma relapse.

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Consent: The patient has given consent for his case to be published.
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TABLE I. Laboratory data

Variable	Reference range	Before R-CHOP initiation	At immune deficiency diagnosis	Before allogeneic HCT*	3 y after allogeneic HCT and 1 y after IGRT cessation
White blood cell count (10^9/L)	3.9-10.2	3.7	2.7	7.3	4.0
Differential count (10^9/L)					
Neutrophils	1.50-7.70	2.29	1.94	7.13	1.14
Lymphocytes	1.10-4.50	0.93	0.55	0.07	1.80
Monocytes	0.10-0.90	0.24	0.14	0.09	0.59
Eosinophils	0.02-0.50	0.22	0.05	0.01	0.15
Basophils	0.00-0.20	<0.01	<0.01	0.00	0.06
Hemoglobin level (g/L)	135-172	166	141	97	146
Hematocrit level (L/L)	0.395-0.505	0.477	0.403	0.298	0.448
Platelet count (10^9/L)	150-370	156	128	21	238
IgG level (g/L)	6.0-13.0	—	1.7	13.28	8.71
IgA level (g/L)	0.8-3.7	—	0.5	0.32	1.06
IgM level (g/L)	0.4-2.2	—	<0.3	<0.2	2.37
Pneumococcal antibodies (IgG) panel (μg/mL)	≥1.3	—	0/13¥	—	11/13‡,§
After vaccination†			3/13¥		—
Haemophilus influenzae type B IgG level (μg/mL)	≥1.000	—	0.040	—	>12.300§
After vaccination†			1.600		—
Tetanus IgG level (IU/mL)	≥0.010	—	0.110	—	0.110
Postvaccination†			1.530		—
Measles IgG	—	—	Detected	—	Detected
Mumps IgG	—	—	Detected	—	Not detected
Rubella IgG	—	—	Detected	—	Not detected
Varicella zoster virus IgG level (mIU/mL)	≥165	—	412	—	76
Lymphocyte subsets		—		—	
Lymphocyte count (10^9/L)	1.00-2.80		0.53		1.71
CD3	0.70-2.10		0.43		1.20
CD4	0.30-1.40		0.24		0.48
CD8	0.20-0.90		0.14		0.41
CD19	0.10-0.50		0.00		0.31
CD56	0.12-0.88		0.09		0.21
B-cell panel (%)		—	—	—	
$IgM^+IgD^+CD27^-$ naive B cells	42.6-82.3				93.3
$IgM^+IgD^+CD27^+$ non–class-switched B cells	7.4-32.5				0.9
IgD^-CD27^+ class-switched memory B cells	6.5-29.1				3.3
CD21-low CD38-low activated B cells	0.9-7.6				2.2
CD38-high IgM-high transitional B cells	0.6-3.4				19.5
$CD38^{+++}IgM^-$ class-switched plasmablasts	0.4-3.6				7.5
EBV-specific antibodies	—		—	—	—
VCA IgM		Not detected			
VCA IgG		Detected			
EBNA IgG		Detected			
In situ hybridization for EBER in lymph node biopsy	—	Negative	—	—	—
Campylobacter serology	—	—		—	—
IgG			Negative		
IgM			Negative		
IgA			Negative		

EBER, EBV-encoded RNA; *EBNA*, Epstein-Barr nuclear antigen; *IGRT*, immunoglobulin replacement therapy; *R-CHOP*, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; *VCA*, viral capsid antigen.

*Under prednisone, etoposide, procarbazine, and cyclophosphamide chemotherapy and IGRT.

†Assessment 4 weeks after Pneumovax 23 and Menitorix vaccination.

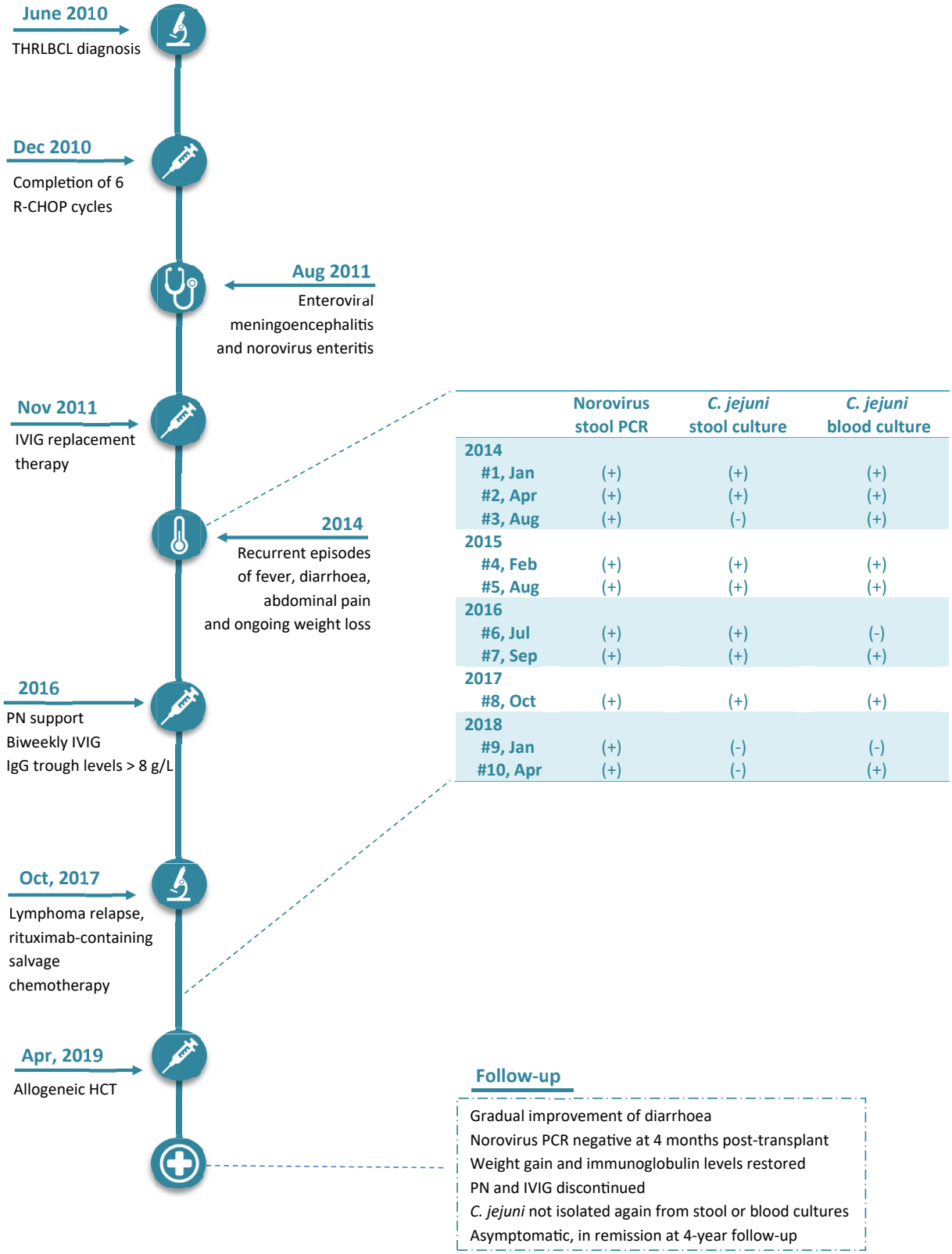
‡Number of serotypes in concentrations of ≥1.3 μg/mL.

§Assessment after posttransplant vaccination with the Prevnar13 (Pfizer) and Menitorix (GlaxoSmithKline) vaccines.

The patient's chronic diarrhea resolved within the first month after transplant, and weight gain was noted, leading to discontinuation of parenteral nutrition. The results of molecular stool testing and stool and blood cultures were negative for norovirus and *C jejuni*, respectively. One year after IVIG was stopped, the patient's immunoglobulin levels, lymphocyte immunophenotyping, and functional antibody responses were normal (Table I). At 4 years of follow-up, the patient remains asymptomatic and in remission.

DISCUSSION

Rituximab-related prolonged hypogammaglobulinemia and late-onset neutropenia can lead to an increased risk of infections.[5] Although areas of uncertainty remain, IVIG replacement therapy can be considered for patients with secondary hypogammaglobulinemia and recurrent infections after patient preferences and cost are taken into account.[6] Distinguishing PID from rituximab-associated secondary immunodeficiency can be challenging,



	Norovirus stool PCR	*C. jejuni* stool culture	*C. jejuni* blood culture
2014			
#1, Jan	(+)	(+)	(+)
#2, Apr	(+)	(+)	(+)
#3, Aug	(+)	(-)	(+)
2015			
#4, Feb	(+)	(+)	(+)
#5, Aug	(+)	(+)	(+)
2016			
#6, Jul	(+)	(+)	(-)
#7, Sep	(+)	(+)	(+)
2017			
#8, Oct	(+)	(+)	(+)
2018			
#9, Jan	(+)	(-)	(-)
#10, Apr	(+)	(-)	(+)

FIG 1. Timeline of the patient's course with clinically significant time points. *PN*, Parenteral nutrition; *R-CHOP*, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; *THRLBCL*, T-cell histiocyte-rich B-cell lymphoma.

with baseline immunologic assessment and a pretreatment history of recurrent infections or autoimmunity being crucial in the differential diagnosis.[7] Measurement of immunoglobulin levels before B-cell–targeted therapies can uncover any preexisting hypogammaglobulinemia and risk-stratify patients for infectious complications necessitating increased monitoring. In patients not screened for PID before B-cell–targeted therapy initiation, genetic testing may reveal a PID diagnosis.[6]

Norovirus and *C jejuni* are common causative agents of acute gastroenteritis and infectious diarrhea worldwide. In patients with CVID, norovirus infection has been associated with prolonged shedding, persistent diarrhea, chronic enteropathy, and duodenal histopathologic changes, leading to malabsorption, wasting, and further immunoglobulin loss.[1]

The importance of humoral immunity for the eradication of *Campylobacter* infections has been highlighted in retrospective analyses of PID cohorts,[2-4] with *Campylobacter* infection being complicated by bacteremia in 25% of patients and recurrence in 42%—rates that are significantly higher than those in immunocompetent hosts. *Campylobacter* infection has been associated with low or absent circulating B, natural killer, and $CD4^+$ T cells, resembling the more global immunosuppressive state of our patient. Dion et al found that undetectable serum IgA was a factor associated with recurrence (odds ratio = 8.6 [95% CI = 1.1-21.2]), suggesting that *Campylobacter* persistence despite IVIG replacement and IgG restoration could be explained by the relative importance of IgA and IgM compared with that of IgG in infection eradication.[3] Although selective IgA deficiency has not been associated with an increased incidence of infection, an impaired intestinal mucosal defense coupled with deficient opsonization and complement-mediated phagocytosis due to secretory IgA and IgM deficiency, respectively, could serve as the necessary host susceptibility factors.[8]

Irrespective of predisposing host factors, *C jejuni* has pathogenic mechanisms that confer an immune evasion advantage. Genome plasticity and a high degree of strain-to-strain genetic variation through environmental DNA uptake, expression switch-off of surface molecules through phase variation, and molecular mimicry of its lipooligosaccharide can render host antibodies ineffective and permit niche adaptation and pathogen survival. Avoidance of the innate immune system is achieved through specific flagellins that evade recognition from Toll-like receptor 5, whereas host cell entry is facilitated by multiple fibronectin-binding proteins. Finally, inside intestinal epithelial cells, *C jejuni* avoids phagocytosis via metabolically inactive *Campylobacter*-containing vacuoles that avoid lysosome fusion, a deviation from the canonic phagolysosome endocytic pathway.[9]

Isolation of the same strain within a 6-month interval in our patient favors a case of persistent intestinal colonization with intermittent symptoms instead of reinfection with a different strain. Recurrent *Campylobacter* infections with extensive prior antibiotic use may lead to the emergence of resistance, with macrolides, aminoglycosides, carbapenems, and tigecycline remaining as available treatment options for these multidrug-resistant strains.[2]

CONCLUSION

In our case, despite the absence of a prior suggestive history and negative genetic testing results, the nature and recurrence of the presenting infections raised the possibility of an underlying PID. Allogeneic HCT, although offered for a refractory lymphoma relapse, could have serendipitously corrected an undiagnosed PID, thus leading to infection resolution through a donor-derived immune system. This approach is not generalizable, however, as allogeneic HCT remains a high-risk investigational treatment for carefully selected patients with documented CVID.

DISCLOSURE STATEMENT

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

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