ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2023 November 21; 29(43): 5800-5871

Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

Contents

Weekly Volume 29 Number 43 November 21, 2023

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Editorial Board Member of *World Journal of Gastroenterology*, Michele Barone, MD, PhD, Professor, Department of Precise and Regenerative Medicine–Jonian Area–(DiMePRe-J), University of Bari Aldo Moro, Bari 70124, Italy. michele.barone@uniba.it

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Production Editor: *Yi-Xuan Cai*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Jia-Ru Fan*.

NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

PUBLICATION DATE
November 21, 2023

PUBLISHING PARTNER
Shanghai Pancreatic Cancer Institute and Pancreatic Cancer Institute, Fudan University
Biliary Tract Disease Institute, Fudan University

INSTRUCTIONS TO AUTHORS
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World J Gastroenterol 2023 November 21; 29(43): 5865-5871

DOI: 10.3748/wjg.v29.i43.5865

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

CASE REPORT

Pediatric-type follicular lymphoma in a Crohn's disease patient receiving anti-α4β7-integrin therapy: A case report

Keval Yerigeri, Ilia Buhtoiarov

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Sharma V, India; Zhu L, China

Received: August 1, 2023
Peer-review started: August 1, 2023
First decision: September 28, 2023
Revised: October 15, 2023
Accepted: November 9, 2023
Article in press: November 9, 2023
Published online: November 21, 2023

Keval Yerigeri, Internal Medicine-Pediatrics, Case Western Reserve University/MetroHealth, Cleveland, OH 44109, United States

Ilia Buhtoiarov, Pediatric Hematology/Oncology and Bone Marrow Transplantation, Cleveland Clinic Children's, Cleveland, OH 44106, United States

Corresponding author: Keval Yerigeri, MD, Doctor, Internal Medicine-Pediatrics, Case Western Reserve University/MetroHealth, 2500 Metrohealth Dr, Cleveland, OH 44109, United States. kyerigeri@metrohealth.org

Abstract

BACKGROUND

Patients with autoimmune conditions receiving immunosuppressants are at risk of non-Hodgkin lymphomas (NHL). Vedolizumab (anti-α4β7-integrin antibody), a treatment-of-choice for Crohn's disease (CD), reduces inflammatory lymphocyte trafficking into the intestinal mucosa. This effect is believed to be confined to the colon.

CASE SUMMARY

We report the case of a CD patient on vedolizumab for five years who developed pediatric-type follicular lymphoma. Work-up prior to therapy revealed a reduction in circulating T-lymphocytes and their suppressed response to mitogens. Rituximab, cyclophosphamide, vincristine, and prednisone chemo-immunotherapy resulted in durable lymphoma remission, and vedolizumab treatment was continued. While the patient's T-lymphocyte population and immunoglobulin production recovered, the T-lymphocyte mitogen response remained suppressed.

CONCLUSION

This patient's NHL may be linked to receiving anti-α4β7 therapy. Further research could be beneficial to determine if proactive surveillance for NHL and other systemic diseases is indicated in patients on vedolizumab.

Key Words: Pediatric-type follicular lymphoma; Crohn's disease; Vedolizumab; Immunosuppression; Non-Hodgkin lymphoma; Case report

Core Tip: The literature is inconclusive on the association between anti-α4β7-integrin therapy and oncogenesis. This case report highlights a young adult on chronic vedolizumab, a monoclonal antibody targeting α4β7-integrin, who develops pediatric-type follicular lymphoma. The patient recovered with rituximab, cyclophosphamide, vincristine, prednisone immunotherapy, but T-lymphocyte mitogen response remained suppressed.

Citation: Yerigeri K, Buhtoiarov I. Pediatric-type follicular lymphoma in a Crohn's disease patient receiving anti-α4β7-integrin therapy: A case report. *World J Gastroenterol* 2023; 29(43): 5865-5871
URL: https://www.wjgnet.com/1007-9327/full/v29/i43/5865.htm
DOI: https://dx.doi.org/10.3748/wjg.v29.i43.5865

INTRODUCTION

Follicular lymphoma (FL) is one of the most common non-Hodgkin lymphomas (NHL) worldwide[1]. Pediatric-type FL (PTFL) was first identified as a distinct clinicopathological condition in the 4th edition of the World Health Organization classification of lymphoid neoplasms[2]. PTFL lacks the t(14;18) translocation characteristic of adult-type FL that leads to overexpression of the B-cell leukemia/lymphoma 2 (*BCL2*) oncogene. Instead, the most commonly affected gene in PTFL is *MAP2K1* on chromosome 15 encoding the serine/threonine kinase MEK1[3]. MEK1 plays a role in the RAS-MAPK signaling pathway and directs cell growth, differentiation, and apoptosis. PTFL commonly presents with localized disease (stage I or II) involving lymph nodes of the head and neck region. Hilar and mediastinal lymph nodes may also be involved. The adenopathy is typically painless and without mass effect on adjacent anatomical structures[4]. The disease course of PTFL is indolent and cure rate is high. Standard-of-care treatment approaches are surgical resection *versus* rituximab, cyclophosphamide, vincristine, and prednisone-like regimens for patients with advanced or unresectable conditions[5].

Patients with autoimmune conditions such as inflammatory bowel disease (IBD) and those treated with systemic immunosuppressants are at risk of developing lymphoid malignancies[6,7]. The incidence of such comorbidities remains low, and reports are limited to adult patient cohorts. Crohn's disease (CD) is a chronic IBD with increasing incidence in the United States over the past several decades. The pathogenesis of Crohn's is mediated by auto-reactive T-cells migrating into intestinal tissue, perpetuating inflammation and tissue necrosis. Targeted therapies have been developed to block inflammatory cell activation and migration in an organ-specific manner[8,9]. Vedolizumab is an anti-α4β7 integrin monoclonal antibody that inhibits interaction of T cells, monocytes, and dendritic cells with the mucosal addressin cell adhesion molecule-1 (MAdCAM-1) expressed on vascular endothelium. Paradoxically, ligation of α4β7 results in downregulation of genes controlling expression of innate immune receptors, chemokines, and their cognate receptors. Previous clinical studies suggest that vedolizumab does not have a systemic immunosuppressive effect and does not increase risk for malignancy[10,11].

We present a case of a 27-year-old male with CD who was diagnosed with PTFL five years into treatment with vedolizumab. Surprisingly, at the time of diagnosis, the patient had reduced numbers and suppressed function of circulating T cells, potentially contributing to a permissive immune environment for PTFL development. This case provides a useful addition to the existing knowledge of PTFL putative risk factors and vedolizumab systemic effects on the immune system.

CASE PRESENTATION

Chief complaints

A 27-year-old male presented with a painless mass in his right mandibular fossa.

History of present illness

Review of systems was negative. The patient denied constitutional B symptoms (fever, night sweats, weight loss), signs of gastrointestinal distress (*e.g.*, pain, nausea, vomiting, diarrhea), and oral pain or dysphagia.

History of past illness

Past medical history was pertinent for CD on long-term vedolizumab therapy.

Personal and family history

All other personal and family medical history was noncontributory.

Physical examination

Physical exam appreciated submandibular and upper cervical lymphadenopathy; there were no other concerning findings. Abdomen was soft, non-tender, non-distended, and without palpable masses; bowel sounds were present.

Laboratory examinations

Core-needle biopsy of the parotid mass demonstrated neoplastic infiltrate with a follicular pattern. The follicles did not have polarized germinal centers and immunophenotype. The neoplastic cells were intermediate-sized with scant cytoplasm and irregular nuclei. The neoplastic cells expressed CD10, CD20, BCL6, PAX5, and CD23; they did not express CD3, CD5, CD21, cyclin D1, BCL2, MUM1, or BCL2. Ki-67 stain was positive in approximately 70% of cells (Figure 1). Molecular studies identified a MAP2K1p.g128D mutation.

Imaging examinations

Computed tomography confirmed the mass within the parotid gland encasing the right-sided facial nerve.

FINAL DIAGNOSIS

The above pathomorphological and molecular features were consistent with FL, pediatric-type.

TREATMENT

Pre-therapy baseline immunologic testing revealed reduced absolute and relative levels of circulating $CD3^+CD4^+$ and $CD3^+CD8^+$ T-cells (Table 1). *In vitro* mitogen stimulation with phytohemagglutinin (PHA) and concanavalin A (ConA) also revealed suppressed proliferative response (Table 2). Of interest, while the peripheral blood B-cell population had a polyclonal pattern, the T-lymphocyte pool demonstrated expansion of two distinct T cell receptor (TCR)-rearranged monoclonal populations (Table 1), a phenomenon characteristic for autoimmune conditions such as IBD[12,13]. The patient was also positive for Epstein-Barr virus (EBV) viral capsid antigen (VCA) immunoglobulin (Ig)G [antibody index (AI) 7.1]; negative for EBV VCA IgM (0.2 AI); positive for EBV early antigen Ab (1.5 AI); and positive for EBV nuclear antigen Ab (7.8 AI), indicating chronic EBV viremia/reactivation. The parotid mass tissue was not stained for EBV, and EBV DNA quantification in blood was not performed.

The parotid gland was not amenable to surgical resection or local radiation therapy; therefore, 6 cycles of rituximab, cyclophosphamide, vincristine, and prednisone chemo-immunotherapy were administered concurrently with monthly vedolizumab. Complete remission for the lymphoma was successfully achieved with good control of CD symptoms (no recurrence or flares).

OUTCOME AND FOLLOW-UP

Repeat assessment at 12 mo off-therapy revealed ongoing complete remission of both PTFL and CD. Of note, one of the TCR-rearranged T-lymphocyte clones became undetectable (Table 1). Surprisingly, functional suppression of peripheral blood T-cells persisted. It remains unclear whether recurrent immune suppression at this clinical stage may only be attributed to continued vedolizumab therapy.

DISCUSSION

Lymphoproliferative disorders (including NHL) have long been recognized as complications for autoimmune inflammatory conditions[14]. Latent infection with EBV (as in this patient) or human herpesvirus 8 may also contribute to cancer genesis[15]. Vedolizumab, the monoclonal antibody against α4β7-integrin, uniquely inhibits interaction of T cells, monocytes, and dendritic cells with the vascular endothelium to reduce local inflammation for disease control[10]. While serious adverse events are reported in 41% of Crohn's patients, benign and malignant neoplasms are noted in only 6.8% of treated patients at an incidence rate of 20.8 per 1000 person-years[16]. Several other studies suggested that treatment with vedolizumab is rather safe and does not carry an excessive burden of new or recurrent malignancies[17].

However, recent insights into the mechanisms of vedolizumab's biologic activity suggest it may extend beyond inhibition of the α4β7-integrin interaction with MAdCAM-1. It appears that several important genes regulating immune effectors and mechanisms of their cross-talk *via* chemokines and cytokines [*e.g.*, CXC chemokine ligand (CXCL)9, CXCL10, FCGR3B, interleukin (IL)23A, IL17, interferon-γ] were down-regulated in IBD patients who achieved clinical remission with vedolizumab[18,19]. Additional findings suggest that the interaction of α4β7-integrin with MAdCAM-1 may serve as an alternative co-stimulatory pathway for T cells, triggering expression of genes encoding multiple cytokines (*e.g.*, IL-2, IL-3, IL-4, IL-8, IL-13, IL-17A, IL-17F, IL-22) in a similar fashion to CD28-mediated signaling. This potentially implies that inhibition of α4β7-integrin-MAdCAM-1 interaction results in down-regulation of T-cell function, although the argument requires further research[20].

Our patient was found to have decreased numbers of both $CD3^+CD4^+$ and $CD3^+CD8^+$ T-cells as well as a diminished response to ConA and PHA at the time of NHL diagnosis, *i.e.*, while receiving ongoing vedolizumab therapy. At the end of lymphoma chemo-immunotherapy and at 12 mo post-therapy, peripheral blood lymphocyte subset quantification demonstrated improvement of the absolute $CD3^+CD4^+$ and $CD3^+CD8^+$ T-cell counts; however, the proliferative response

Table 1 Peripheral blood lymphocyte subsets, and B- and T-lymphocyte clonality

Component	Ref range & units	Testing time point		
		Pre-Tx	EOTx	12 mo off Tx
$CD3^+$ T cell	60%-89%	43	72	52
$CD3^+$ T cell	958-2388 cells/uL	473	792	869
$CD3^+CD4^+$ T cell	34%-61%	27	39	32
$CD3^+CD4^+$ T cell	533-1674 cells/uL	304	425	526
$CD3^+CD8^+$ T cell	10%-41%	14	28	18
$CD3^+CD8^+$ T cell	175-958 cells/uL	151	303	293
$CD19^+$ B cell	5%-22%	20	0	23
$CD19^+$ B cell	75-660 cells/uL	224	0	385
NK cell	5%-25%	37	27	24
NK cell	102-565 cells/uL	406	297	394
CD4/CD8 ratio	1.10-3.25	2.02	1.40	1.79
B cell clonality				
IGH FR1		Nonclonal		Nonclonal
IGH FR2		Nonclonal		Nonclonal
IGH FR3		Nonclonal		Nonclonal
IGH DH1-6-J		Nonclonal		Nonclonal
IGK V-J		Nonclonal		Nonclonal
IGK V-Kde		Nonclonal		Nonclonal
TCR clonality				
TCRB A (V-J)		Nonclonal		Nonclonal
TCRB B (V-J)		Nonclonal		Nonclonal
TCRB C (V-J)		Clonal peak (180 bp)		Clonal peak (180 bp)
TCRG D		Clonal peak (189 bp)		Nonclonal

pre-Tx: Pre-treatment; EOTx: End of therapy; 12 mo off Tx: 12 mo off therapy anti-lymphoma therapy; NK: Natural killer; TCR: T cell receptor.

Table 2 Response of peripheral blood lymphocytes to *in vitro* mitogen stimulation

Component	Reference range & units	Testing time point	
		Pre-Tx	12 mo off Tx
Mitogen control	> 50 CPM	434	2297
Phytohemagglutinin	≥ 188800 CPM	173643	125008
Pokeweed mitogen	> 68549 CPM	77631	76811
Concanavalin A	> 81283 CPM	49198	92755

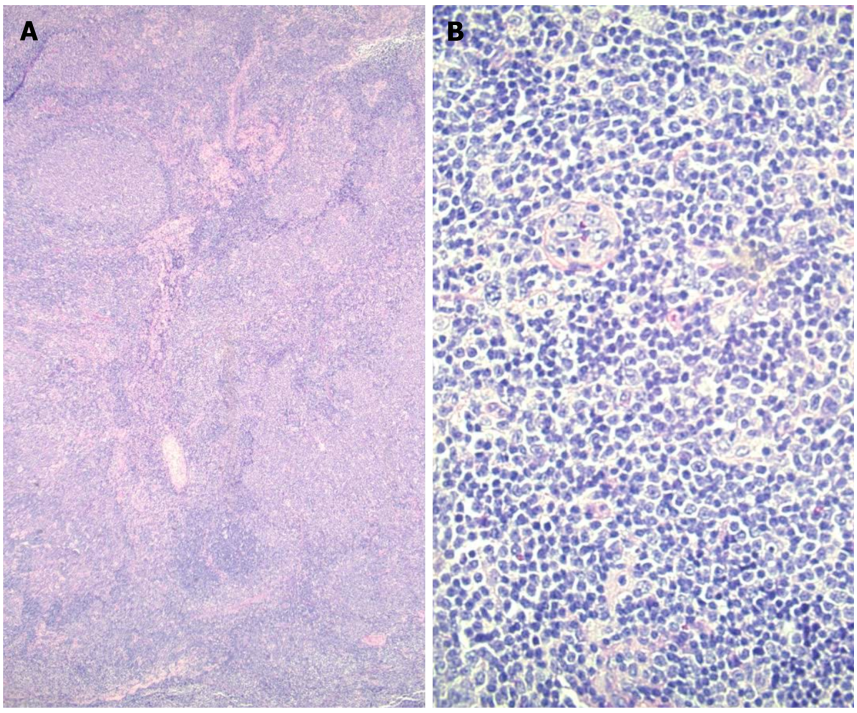
CPM: Counts per million; pre-TX: Pre-treatment; 12 mo off Tx: 12 mo off therapy anti-lymphoma therapy.

to ConA remained suppressed. At this phase of the clinical course, reduced response to the *in vitro* mitogen stimulation may be attributable to vedolizumab, although the suppressive effect of an auto-inflammatory state cannot be ruled out. Further research is necessary to discern if vedolizumab has responsible mechanisms. Regardless, the patient was able to recover his $CD19^+$ B-cell population, which was completely depleted by rituximab at the end of treatment, as well as maintain immunoglobulin production (Table 3). Surprisingly, one of the two clonally expanded populations of T-cells were not detectable following therapy completion, suggesting eradication by the anti-lymphoma chemotherapy.

Table 3 Immune globulin production before treatment, at the end of therapy and at 12 mo off therapy follow up

Component	Ref range & units	Testing time point		
		Pre-Tx	EOTx	12 mo off Tx
IgA	68-408 mg/dL	250	177	170
IgM	35-263 mg/dL	55	30	31
IgG	768-1632 mg/dL	1376	921	927
IgG Subclass 1	240-1118 mg/dL	763	-	503
IgG Subclass 2	124-549 mg/dL	371	-	335
IgG Subclass 3	21-134 mg/dL	162 (H)	-	64
IgG Subclass 4	1-123 mg/dL	64	-	40

Ig: Immunoglobulin; pre-Tx: Pre-treatment; EOTx: End of therapy; 12 mo off Tx: 12 mo off therapy anti-lymphoma therapy.



DOI: 10.3748/wjg.v29.i43.5865

Figure 1 Histopathological appearance and immunophenotype of pediatric-type follicular lymphoma. A and B: Typical appearance of pediatric-type follicular lymphoma at low- (A, 4 ×) and high-power (B, 40 ×) resolution of hematoxylin and eosin staining lymphoma tissue. Pattern of expression of CD10, CD20, BCL6 and Ki67 at 20 × resolution is also shown.

CONCLUSION

PTFL is a rare type of B-cell NHL. The clinical course is indolent despite a high proliferative index and blastoid histopathological features. Due to its rarity, predisposing factors have not been clearly postulated. The role of underlying immune suppression in PTFL pathogenesis has not been established. Nodal PTFL is believed to arise from B-lymphocytes in follicle germinal centers. Immune system workup and cytogenetic analysis in PTFL patients may help reveal an etiological correlation between the malignancy and immunomodulatory processes. Attention must also be paid to possible systemic consequences of vedolizumab therapy hitherto unreported in the literature.

FOOTNOTES

Author contributions: Buhtoiarov I was the patient's primary oncology attending, he provided the patient charts with informed consent, prepared images and tables for submission, and edited the manuscript; Yerigeri K prepared initial manuscript drafts and managed the submission and revisions.

Informed consent statement: Informed consent for immunotherapy as per the R-CVP protocol was obtained by Dr. Ilia Buhtoiarov and the Cleveland Clinic Children's PHO team.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: United States

ORCID number: Keval Yerigeri 0009-0001-8963-0927; Ilia Buhtoiarov 0000-0001-5207-4616.

S-Editor: Wang JJ
L-Editor: A
P-Editor: Cai YX

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