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Short Report

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Diagnosis and Outcome of Extranodal Primary Intestinal Lymphoma in Inflammatory Bowel Disease: An ECCO CONFER Case Series

Frank Phillips,[a] Bram Verstockt,[b] Davide Giuseppe Ribaldone,[c] Ivan Guerra,[d] Niels Teich,[e] Konstantinos Katsanos,[f] Rafal Filip,[g] Tamas Molner,[h] Konstantinos Karmiris[i]; ECCO CONFER Investigators

[a]NIHR Nottingham Digestive Diseases Biomedical Research Centre, Nottingham University Hospitals, Nottingham, UK [b]University Hospitals Leuven, Gastroenterology and Hepatology, Leuven, Belgium; KU Leuven, Chronic Diseases, Metabolism and Ageing, TARGID-IBD Unit, Leuven, Belgium [c]University of Turin, Department of Medical Sciences, Turin, Italy [d]Hospital Universitario de Fuenlabrada and Instituto de Investigación de La Paz (IdiPaz), Madrid, Spain [e]Internistische Gemeinschaftspraxis, Leipzig, Germany [f]Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine, University of Ioannina School of Health Sciences, Ioannina, Greece [g]Department of Gastroenterology with IBD Unit of Clinical Hospital 2, University of Rzeszow, Poland [h]First Department of Medicine, University of Szeged, Szeged, Hungary [i]Department of Gastroenterology, Venizeleio General Hospital, Heraklion, Greece

Corresponding author: Dr Frank Phillips MRCP, NIHR Nottingham Digestive Diseases Biomedical Research Centre, Nottingham University Hospitals, Nottingham, UK. Tel: 0115 969 1169; Fax: 0115 840 5812; Email: frankmphilllips@hotmail.com

Abstract

Background: There is a small but measurable increased risk of lymphoma in inflammatory bowel disease [IBD], with a suggestion that primary intestinal lymphoma [PIL] in IBD is associated with inflamed tissue and immunosuppressant use, mainly thiopurines.
Methods: This multicentre case series was supported by the European Crohn's and Colitis Organisation [ECCO] and performed as part of the Collaborative Network of Exceptionally Rare case reports [CONFER] project. Clinical data were recorded in a standardized case report form.
Results: Fifteen patients with intestinal lymphoma from eight centres were included (12 males, 11 patients with Crohn's disease [CD], mean age 47.8 [±16.4 SD, range 26–76] years at lymphoma diagnosis). Lymphoma type was diffuse large B-cell lymphoma [DLBCL] in eight, Hodgkin's disease in two, mucosa-associated lymphoid tissue [MALT] lymphoma in three, and single cases of immunoblastic lymphoma and indolent T-cell lymphoma. Lymphoma was located within the IBD-affected area in ten patients. At lymphoma diagnosis, nine patients had a history of azathioprine or anti-tumour necrosis factor [TNF] use. Lymphoma was diagnosed at a mean time of 10.4 [±7.07, 1–24] years after IBD diagnosis in 11 patients, prior to IBD in two and concurrently in two. Sustained remission over a median follow-up time of 6.5 [1.5–20] years was achieved in ten patients after treatment; five of them had started biological therapy [including anti-TNFs, vedolizumab and ustekinumab] for active CD subsequent to their PIL treatment.
Conclusion: In this small case series, two-thirds of patients developed lymphoma in the IBD-affected area, and almost two-thirds had a history of thiopurine or anti-TNF use. Biologics were restarted without recurrence of lymphoma in half of the remitters.

Key Words: Lymphoma; lymphoproliferative disorder; inflammatory bowel disease

1. Introduction

It has long been recognized that there is a slightly increased risk of malignancy in inflammatory bowel disease [IBD], which include Crohn's disease [CD] and ulcerative colitis [UC], compared to the general population. The chronic inflammatory process can give rise to gastrointestinal carcinogenesis, with the risk of developing colorectal adenocarcinoma estimated to be 1% annually.[1] There is also an increased risk of lymphoproliferative disease [LD] particularly in IBD patients exposed to thiopurines either as monotherapy or combined with anti-tumour necrosis factor [TNF] agents.[2–4] A similar risk in large population studies of IBD patients not exposed to immunosuppressants has not been shown.[5] The relationship between immunosuppressants leading to LD is also recognized in the transplant literature, where chronic immunosuppression can lead to the development of post-transplant lymphoproliferative disease [PTLD].[6,7]

Primary intestinal lymphoma [PIL], also known as primary intestinal lymphoproliferative disease, accounts for only 1–4% of all gastrointestinal malignancies. There are three case series and a few additional case reports in the literature of PIL associated with IBD.[8–19] Shephard *et al.* reported on ten cases of lymphoma [seven in UC and three in CD] in the colon and rectum.[8] Holubar *et al.* reported on 15 cases from the Mayo Clinic in the pre-biologic era (93% male, median age of IBD diagnosis 30 [interquartile range, IQR 22–51] years, median age of PIL diagnosis 47 [IQR 28–68] years, 66% CD). Location was colorectal in 60%, small bowel in 27%, and one case each in stomach, duodenum and ileal pouch.[9] Most cases of lymphoma arose in inflamed tissues and affected those exposed to immunosuppression, whilst Epstein–Barr virus [EBV] was frequently implicated. In an observational sub-study from the CESAME cohort, the intestines were involved in a quarter of cases [gastric and duodenal cases were excluded]. Sokol *et al.* reported on 14 IBD patients identified with PIL, in nearly 20 000 patients with IBD in this cohort.[10] This gives a significantly higher risk of PIL in IBD compared with the general population, although the absolute risk was low [crude incidence of 0.12/1000 patient years]. All 14 cases were non-Hodgkin's B-cell lymphoma, with 79% occurring in CD, 79% in males with a mean age of 55.1 [±5.6] years at lymphoma diagnosis and a median time from IBD diagnosis of 8.0 [IQR 3.0–15.8] years. The risk was highest in those exposed to thiopurines; 86% were located within IBD lesions and 46% were found to be EBV-positive.[10]

We aimed to describe the clinical presentation, risk factors and outcome of a series of IBD patients with PIL.

2. Case Report

This was a retrospective multicentre case series supported by the European Crohn's and Colitis Organisation [ECCO], and performed as part of the ECCO Collaborative Network for Exceptionally Rare case reports [CONFER] project. A call to all ECCO members was made to report on cases of 'Extranodal intestinal lymphoma in inflammatory bowel disease'. Clinical data were recorded in a standardized data collection form including: demographics, Montreal classification, previous medications, PIL-related location and type, time to diagnosis, treatments and outcome.

2.1. Patients' demographics

Our series included 15 IBD patients with PIL treated in eight different centres (12 males [80.0%], mean [±SD, range] age 40.2 [±21.0, 13–76] years at IBD diagnosis and 46.4 [±17.0, 26–76] years at PIL diagnosis). Patients' baseline characteristics are shown in Table 1. Six patients had other significant comorbidities including Parkinson's disease, myasthenia gravis, cardiovascular disease, Addison's disease, diabetes and autoimmune polyglandular syndrome type II. An IBD-related surgery was performed in two patients prior to PIL diagnosis [ileocaecal resection in one, perianal drainage in one].

Table 1. Baseline characteristics [$n = 15$]

CD/UC	11/4
Male/female	12/3
Smoking history	
• Current/previous/never	3/1/11
Family history	
• IBD/PIL	0/0
Montreal classification	
• Colonic/ileocolonic/small bowel	3/4/4
• Inflammatory/stricturing/penetrating	7/1/3
• Proctitis/left-sided/extensive colitis	2/1/1
IBD treatment prior to PIL diagnosis	
• Azathioprine	7 [mean duration 9 years]
• Anti-TNF	2 [one 8 months and one 3 years]
• 5ASA	1
• No IBD medications	5

PIL, primary intestinal lymphoma; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; anti-TNF, anti-tumour necrosis factor; 5ASA, 5-aminosalicylic acid.

Table 2. PIL characteristics

	N=
Time of PIL diagnosis in relation to IBD diagnosis	
• PIL diagnosed after IBD	11 [mean time 10.4 years]
• PIL diagnosed concurrently with IBD	3
• PIL diagnosed before IBD	1
Lymphoma type	
• DLBCL	8 [7 CD, 1 UC]
• Hodgkin's lymphoma	2 [both CD]
• MALT lymphoma	3 [2 CD, 1 UC]
• Indolent T-cell lymphoma	1 [UC]
• Immunoblastic lymphoma	1 [UC]
Lymphoma location	
• Rectum	3
• Colon	4 [including 1 at anastomosis]
• Small bowel	4
• Stomach	1
• Multiple GI sites	3
Presentation	
• Bowel obstruction	9
• Abdominal mass [non-obstructing]	2
• Others	4
PIL location in relation to IBD location	
• In area affected by IBD	10
• In area distant to IBD	5

PIL, primary intestinal lymphoma; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; DLBCL, diffuse large B-cell lymphoma, MALT, mucosa-associated lymphoid tissue.

2.2. Primary intestinal lymphoma diagnosis

The diagnosis of PIL occurred at a mean time of 10.4 [±7.1, 1–24] years after IBD diagnosis in 11 patients, prior to IBD in two and

Table 3. Characteristics, treatment and outcome of primary intestinal lymphoma for each case

Age at PIL diagnosis/ gender	IBD type	PIL type/location	PIL diagnosis in relation to IBD	IBD treatment prior/at PIL diagnosis	PIL treatment	PIL outcome	IBD therapy after PIL diagnosis
29/M	Colonic CD	Duodenal DLBCL	1 year after IBD diagnosis	None	R-CHOP 8 cycles [no surgery]	Remission maintained after 14 years	Infliximab [9 years after PIL treatment]
53/M	Colonic CD	Rectal DLBCL	8 years after IBD diagnosis	Azathioprine [2 years]	CHOP 4 cycles, recurrence R-DHAP 2 cycles, then palliative radiotherapy [no surgery]	Died 14 months after diagnosis	None
42/F	Ileocolonic CD	Ileal DLBCL	16 years prior to IBD diagnosis	None	Resection then MACOP-B	Remission maintained after 20 years	Azathioprine [15 years after], and vedolizumab [17 years after]
35/M	Ileocolonic CD	Ileal + rectal DLBCL	22 years after IBD diagnosis	Azathioprine [14 years]	Resection then R-CHOP+TIT 6 cycles	Remission maintained after 21 months	Mesalazine
26/M	Small bowel CD	Colonic DLBCL	10 years after IBD diagnosis	Azathioprine [9 years]	R-CHOP 6 cycles, partial response so resection, then R-ESHAP 2 cycles	Remission maintained after 2 years	Oral steroids
76/M	Small bowel CD	Jejunal DLBCL	At IBD diagnosis	None	Resection then R-CHOP 2 cycles	Remission maintained after 2 years	Unknown
58/F	Small bowel CD	Ileal DLBCL	10 years after IBD diagnosis	Azathioprine [10 years]	Resection then R-CHOP	Remission maintained after 3 years	Infliximab [3 years after]
38/M	Ileocolonic CD	Anastomotic Hodgkin's lymphoma	14 years after IBD diagnosis	Azathioprine [10 years]	Resection then chemotherapy [doxorubicin, bleomycin, darabazin 2 cycles]	Remission maintained after 2 years	Steroids, then vedolizumab [12 months after] and ustekinumab [17 months after]
52/M	Ileocolonic CD	Colonic Hodgkin's lymphoma	At IBD diagnosis	5ASA	Resection then ABVD 6 cycles	Remission maintained after 20 years	Mesalazine and steroids, then adalimumab [16 years after]
40/M	Small bowel CD	Rectal MALT lymphoma	10 years after IBD diagnosis	Azathioprine [10 years]	CHOP 6 cycles [no surgery]	Remission maintained after 11 years	Steroids, mesalazine and methotrexate after 12 months
75/M	Colonic CD	Gastric MALT lymphoma	3 years after IBD diagnosis	None	Conservative [no PIL-targeting therapy initiated]	Spontaneous remission	Steroids and mesalazine
38/M	Extensive UC	Colonic DLBCL colon	15 years after IBD diagnosis	Infliximab [1 year]	R-CHOP 7 cycles [no surgery]	Remission maintained after 10 years	Mesalazine
61/M	UC proctitis	Colonic + small bowel MALT lymphoma	5 years prior to IBD diagnosis	None	Chlorambucil + prednisolone chemotherapy [no surgery]	Died 10 years after diagnosis [recurrence at 6 years]	Steroids and mesalazine
26/M	Left-sided UC	Rectal + small bowel indolent T-cell lymphoma	8 years after IBD diagnosis	Infliximab then adalimumab [3 years]	Conservative [no PIL-targeting therapy initiated]	Spontaneous remission [no relapse after 15 months]	None
68/F	UC proctitis	Rectosigmoid immunoblast lymphoma	3 years after IBD diagnosis	Azathioprine [1 year]	Hyper-CVAD 2 cycles; progression so EDAP	Died 7 months after diagnosis	None

CD, Crohn's disease; UC, ulcerative colitis; IBD, inflammatory bowel disease; PIL, primary intestinal lymphoma; DLBCL, diffuse large B-cell lymphoma; MALT, mucosa-associated lymphoid tissue; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; MA-COB, methotrexate with leucovorin rescue, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin; R-ESHAP, rituximab, etoposide, methylprednisolone, cytarabine, cisplatin; R-DHAP, rituximab, dexamethasone, cisplatin, cytarabine; Hyper-CVAD, cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, cytarabine; EDAP, etoposide, dexamethasone, cytarabine, cisplatin.

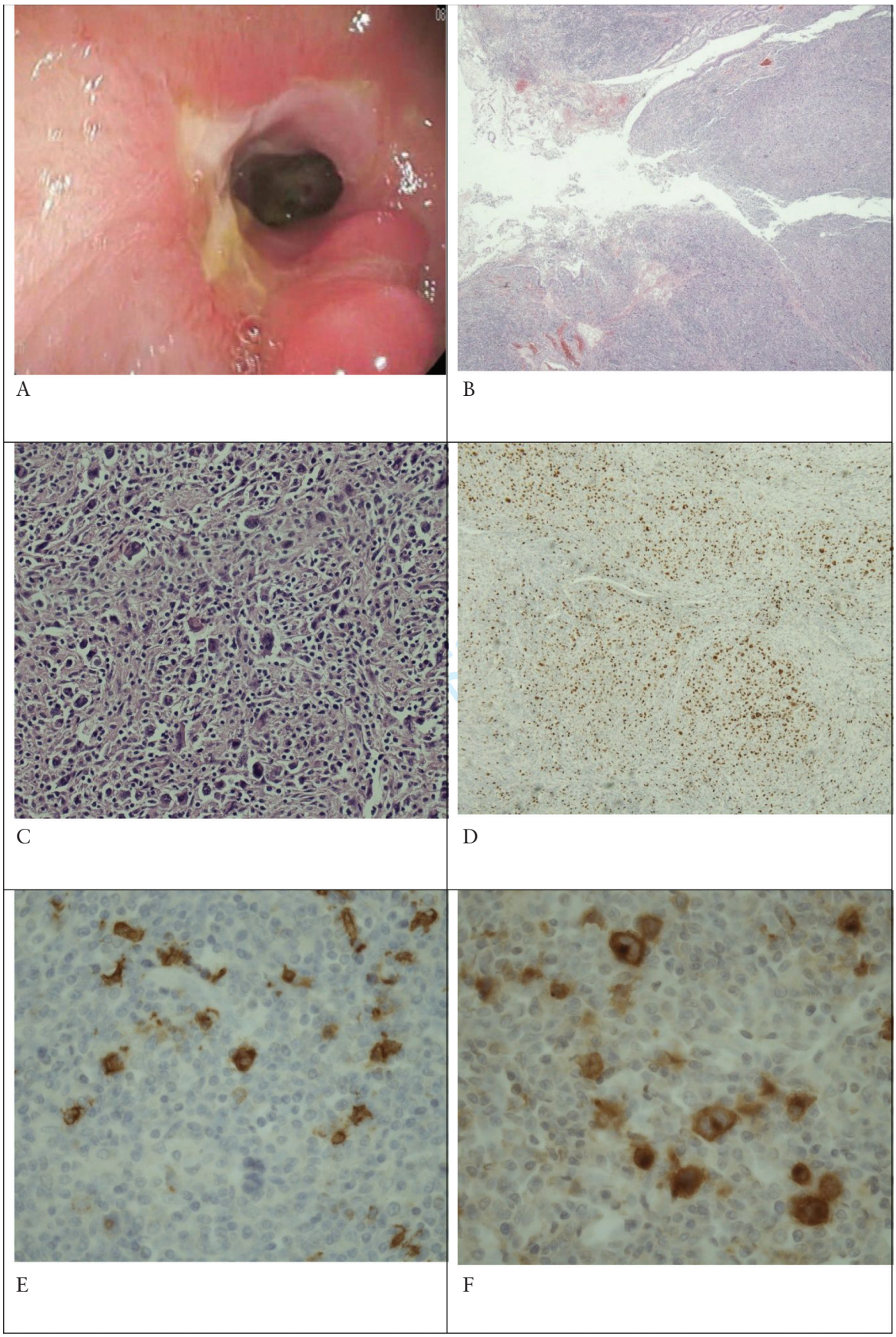

Figure 1. Endoscopic and histological images of a Hodgkin's lymphoma at the ileo-transverse colonic anastomosis. [A] Hodkin's lymphoma. [B] Ulceration of mucous membranes due to lymphoma. [C] Lymphoma aggregate [magnification ×20]. [D] Ki-67 [magnification ×5]. [E] CD15-positive blasts. [F] CD30-positive blasts. Images courtesy of Niels Teich and Professors Arved Weimann and Volker Wiechmann, Leipzig, Germany.

concurrently with IBD in two. The mean age of the four patients with a pre- or concurrent diagnosis was 52.5 [±17.8, 26–76] years, with no personal or family history of haematological disease. PIL characteristics for all 15 patients included in this series are shown in Table 2, whilst characteristics, treatment and outcome for each patient are given in Table 3. Diagnosis was made with the use of cross-sectional imaging and endoscopy, and histological confirmation was obtained in all cases. Selective endoscopic and histological images are shown in Figure 1.

PIL was located within the IBD-affected area in ten patients [six in the large bowel, three in the small bowel, and one in both ileum and rectum concurrently, with four of these having active intestinal inflammation at the time of diagnosis]. There was no extraintestinal or bone marrow involvement in any patient, except for the case of immunoblastic lymphoma who had non-contiguous extraintestinal spread.

IBD treatment was discontinued in the seven patients on azathioprine and the single patient on infliximab. Thirteen patients received PIL-related therapy, with seven receiving chemotherapy and surgery and six receiving only chemotherapy. The regimens are detailed in Table 3. Remission was achieved in ten patients after treatment with no signs of relapse at last follow-up. Three died from their PIL despite treatment: one with colonic CD and diffuse large B-cell lymphoma [DLBCL], one with UC proctitis and immunoblastic lymphoma with plasma cell differentiation, and one with UC proctitis and mucosa-associated lymphoid tissue [MALT] lymphoma throughout the large and small bowel. Two are being monitored without therapy: one with an indolent T-cell lymphoma and the other with a gastric MALT lymphoma. The latter was not associated with *Helicobacter pylori*, and no further signs of lymphoma were found after 2 years of endoscopic follow-up.

IBD-related treatment was resumed in 11/15 patients [Table 3]. One of these patients was treated with 5-aminosalicylic acid [5ASA] and oral steroids, later developing lymphoma recurrence and dying from this. No signs of PIL relapse were reported in the rest at last follow-up, at a median 6.5 years after PIL diagnosis [range 1.5–20 years]. This included five patients [three with DLBCL in remission and two with Hodgkin's lymphoma in remission] who have started biologics [infliximab in two cases, adalimumab in one, vedolizumab in one, and vedolizumab followed by ustekinumab in one], all for active luminal CD.

3. Discussion

This is a retrospective, international study reporting on a series of PIL in IBD patients, and the course of both PIL and subsequent IBD therapy. This study was not designed to assess the prevalence of PIL in IBD. Our series has shown some similarities with the previous case series, but also some important differences.

Similar to the Mayo and CESAME cohort series,[9,10] we also observed that PIL mainly occurred in middle-aged men [80.0%], with an average age of 47.8 years at diagnosis. PIL was more frequently diagnosed in CD [11/15] than UC patients, and the most common histological type was B-cell lymphoma, including an immunoblastic lymphoma with plasma cell differentiation [9/15].

The diagnosis of PIL occurred at a mean of 10.4 [±7.1, 1–24] years after IBD diagnosis, which is less than the 17 years reported in the Mayo series,[9] and more compatible with the 8 years reported in the CESAME series.[10] However, two patients were diagnosed with PIL simultaneously with IBD, highlighting the possibility that both may be present at the same time. Diagnostic work-up includes a combination of clinical presentation of major abdominal symptoms not always attributed to IBD, cross-sectional imaging and endoscopy [if accessible], with compatible histological features, the last being a prerequisite for diagnosis. In some cases, diagnosis is made only after surgical resection of an obstructing lesion and subsequent histological examination of the resection specimen. Bowel obstruction was the most common clinical presentation, whereas bloody diarrhoea has been previously reported as equally common in other series.[9,10] Endoscopic features are not always pathognomonic.

The Mayo clinic and CESAME cohort series identified immunosuppressants and active intestinal inflammation as potential risk factors for the development of PIL.[9,10] Sixty per cent of the cases in our series [9/15] may be related to these medications. Two-thirds developed PIL in the area affected by IBD inflammation, but that means a third of patients developed PIL in an area not involved in intestinal inflammation. Clinicians should therefore be mindful of this possibility. Two-thirds [10/15] achieved remission after receiving the appropriate PIL-related treatment.

A potential clinical dilemma is whether immunosuppressants can be safely restarted after lymphoma diagnosis. Our series shows IBD therapy was resumed in 11 patients, with relapse of PIL occurring in one case only that was probably unrelated to treatment. This includes five patients who restarted biologics for active luminal CD, including anti-TNFs, vedolizumab and ustekinumab, and none of them reported recurrence of lymphoma at last follow-up.

In conclusion, this case series of PIL in IBD illustrates a strong male predilection and a wide histological type range, with the majority being DLBCL. It is notable that two-thirds of patients had a history of thiopurine or anti-TNF use, and two-thirds developed PIL in the luminal site affected by IBD. The majority of cases successfully recovered after appropriate treatment and, in half of them, IBD therapy was resumed uneventfully. However, these results are based on a small case series and should be interpreted with caution.

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Conflict of Interest

The contributing authors declare the following: F.P., D.R.G., K.Kat.: none. B.V.: financial support for research from Pfizer; lecture fees from Abbvie, Ferring, Takeda Pharmaceuticals, Janssen and R Biopharm; consultancy fees from Janssen, Guidepoint and Sandoz. I.G.: served as speaker, a consultant and advisory member for or has received research funding from Kern Pharma, Takeda and Janssen. N.T.: served as a speaker, a consultant and/or an advisory board member for AbbVie, Biogen, Falk Foundation, Janssen, MSD, Norgine, Shield Therapeutics, Takeda, Tillotts and Vifor and has received research funding from Ferring Arzneimittel GmbH. R.F.: support for research from EGIS, lecture fees from Takeda, Abbvie and Ferring. T.M.: speaker's honoraria from MSD, AbbVie, Egis, Goodwill Pharma, Takeda, Pfizer, Richter, Fresenius Kabi and Teva. K.Kar.: personal fees from Abbvie, MSD, Janssen, Pfizer and Takeda. All conflicts of interests stated here are outside the submitted work.

Author Contributions

F.P.: conceived the study, collected, analysed and interpreted the data and drafted the manuscript. B.V., D.G.R., I.G., N.T., K.Kat., R.F. and T.M.: contributed the cases and revised the manuscript. K.Kar.: supervised the project, interpreted the data and critically revised the manuscript. All authors approved the final version.

Data Availability

The data underlying this article are available within the article. Any additional information will be shared on reasonable request to the corresponding author.

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