Leukemia Research 71 (2018) 1–5

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Hodgkin lymphoma of the gastrointestinal tract in patients with inflammatory bowel disease: Portrait of a rare clinical entity

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ARTICLE INFO

Keywords:
Inflammatory bowel disease
Hodgkin lymphoma
Gastrointestinal

ABSTRACT

Patients with inflammatory bowel disease (IBD) on immunosuppression are at risk of developing lymphoma, particularly primary gastrointestinal (GI) tract non-Hodgkin lymphoma. Primary GI Hodgkin lymphoma (HL) in this setting, however, is rare and poorly defined. Here we review the available literature and also report a patient with Crohn's disease (CD) who developed GI HL. Our search yielded 12 single case studies and 7 case series involving 22 patients published between 1978–2016. Twenty-one (91%) patients had CD, and 2 had ulcerative colitis. The median age at lymphoma diagnosis was 39 years, and 18 (78%) patients were males. HL was diagnosed at a median of 8 years after IBD detection and 2 years after commencing immunosuppression. HL had a predilection (80%) to involve the inflamed GI site and the histological subtype was mixed cellularity in 65% of cases. In-situ hybridization for Epstein-Barr virus (EBV)-encoded RNA was positive in all documented cases. HL was diagnosed in stages I, II, IV in 35%, 20% and 45% of the patients, respectively. Notably, 66% of patients with advanced disease had liver involvement. Immunosuppression was stopped in most (69%) patients at HL diagnosis. Treatment used was either chemotherapy only, surgery followed by chemotherapy, or surgery alone in 50%, 33% and 16% of cases, respectively. Four patients had an IBD flare during HL remission. Patients with IBD who develop GI HL have distinct characteristics; male sex, predominance of CD, preference to develop in inflamed sites, mixed cellularity histology, EBV positivity, and a unique spread to the liver pattern.

1. Introduction

According to the WHO classification, 'other iatrogenic immunodeficiency-associated lymphoproliferative disorders' (LPD) are lymphoid proliferations or lymphomas arising in patients treated with immunosuppressive drugs for autoimmune diseases or disorders other than the post-transplant setting [1]. LPD that develop in patients with inflammatory bowel disease (IBD) as a background are included in this category. In 2002, Kandiel et al. performed a meta-analysis demonstrating a fourfold increased risk of lymphoma in the subgroup of IBD patients treated with azathioprine and/or 6-mercaptopurine (6-MP), compared to the risk in the general population [2]. Most (88%) iatrogenic immunodeficiency-associated IBD lymphomas are B-cell non-Hodgkin lymphomas (NHL), while Hodgkin lymphoma (HL) occurs less frequently (12%) [3]. In addition, Sokol and co-workers have also reported an increased incidence of primary gastrointestinal (GI) lymphoma in IBD, which is rare in the general population [4].

In this review, we collected the various clinical and laboratory presentations of the rare cases of GI HL developing in association with IBD. In addition, we also describe an additional patient with long-standing Crohn's disease (CD) who developed GI HL and provide details of the case below.

A 54-year-old male initially presenting with terminal ileitis and recurrent perianal abscess was diagnosed as having CD in 2012. Treatment with both 6-MP and infliximab was started due to extensive disease, and a sigmoid loop colostomy was performed a few months later.

In July 2014, he presented with exacerbation of anal pain accompanied by fever and weight loss. Physical examination revealed enlarged inguinal lymph nodes and an inflamed perianal fistula. A surgical biopsy of inguinal lymph nodes, anal mucosa and perianal fistula all revealed the presence of small lymphocytes, neutrophils and plasma cells interspersed with numerous large atypical binucleated, "Reed-Sternberg" (RS) cells, with positive immunohistochemistry (IHC) for

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https://doi.org/10.1016/j.leukres.2018.06.008
Received 10 April 2018; Received in revised form 8 June 2018; Accepted 12 June 2018
0145-2126/

CD15 and CD30, leading to the diagnosis of classical HL, mixed cellularity subtype. In-situ hybridization (ISH) for Epstein-Barr virus (EBV)-encoded RNA (EBER) was also positive in the RS cells. A bone marrow biopsy did not show involvement by lymphoma. Positron emission tomography–computed tomography scan revealed high uptake of fluorodeoxyglucose in the sub-diaphragmatic lymph nodes, perianal thickening and perianal fistula, consistent with stage II disease according to the Lugano criteria [5]. Immunosuppressive therapy was discontinued and 6 cycles of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) chemotherapy were administered and completed in February 2015, achieving a complete response (CR). At the time of writing this manuscript, the HL was still in remission, but in March 2017 he had a flare up of perianal CD and was then started on vedolizumab.

2. Methods

We performed an electronic search of Medline and Google Scholar, updated to December 2017. Each paper was reviewed and duplicate reports describing the same patients were included only once. Information on the following was extracted: patients' age, sex, underlying subtype and anatomical location of IBD, type and duration of treatment for IBD, outcome of IBD treatment after diagnosis of HL. In relation to the HL we recorded histological subtype, IHC, EBER ISH results, latent membrane protein 1 (LMP1) status, GI anatomical location of HL, disease stage according to the Lugano staging system of GI lymphoma [5], details of therapy and outcome. We also collected all the relevant clinical and laboratory data relating to our patient.

3. Results

The literature search yielded 12 single case studies and 7 case series, published between 1978 and 2016, and these were reviewed. A total of 22 cases was collected from electronic databases [6–24], and, with the addition of our case report, this series include a total of 23 cases of IBD with HL and GI involvement. One case (No.4) in the series reported by Ujjani et al. was excluded because HL developed before the diagnosis of IBD [20].

3.1. Patient characteristics

Demographic, clinical characteristics and pathological data are presented in Table 1.

Of the 23 patients with IBD, 21 (91%) had CD and only 2 (9%) had ulcerative colitis (UC). Eighteen patients (78%) were males and median and mean ages at lymphoma diagnosis were 39 years (range 20–79) and 45 years (± 15.67), respectively. HL was diagnosed after IBD in all cases, with a median IBD duration of 8 years (range 2–40). HL involved the large bowel in 11 patients (48%), small bowel in 10 (43%) and both sites in 2 patients (9%). Nodal involvement was present in 12 cases (52%) and in 8 (35%) other extra-nodal sites were evident, including liver (n = 6), and bone marrow (n = 2).

According to the Lugano GI staging system, 7 patients (35%) were diagnosed as stage I disease, 4 (20%) stage II, and 9 (45%) stage IV (data on the extent of the disease were unavailable for 3 patients). Interestingly, 6 of 9 patients with advanced disease also had liver involvement, but only one of these had concomitant proven splenic involvement.

More exact data on IBD-involved GI sites was available in 10 cases, and in 8 of these HL had developed at sites of inflammatory disease. In the 17 patients with HL for whom histological data was available, 11 (65%) had mixed cellularity, while 6 (35%) had nodular sclerosis subtype. One of the latter was a composite lymphoma showing NHL as well.

Thirteen patients had a positive EBER ISH, while data relating to EBER status was lacking for the other 10 cases. LMP-1 was also present in 5 of the EBER-positive cases. CD30 and CD15 immunophenotyping in RS Cells was reported for 13 cases; In 11 (84%), both CD30 and CD15 were positive while one was CD30-/CD15+ and another CD30+/CD15-. CD20 status of RS cells was available for 10 cases, and it was positive in 3 of them. In 2 of the cases CD20 was focally/variably positive, accompanied by CD30+/CD15+. In one case, CD20 was strongly positive, accompanied by CD30+ with an unknown CD15 status.

3.2. Treatment of IBD

Data on treatment was available for 17 of the 23 patients. Five patients (30%) were treated with thiopurines alone, 5 (30%) with thiopurines and infliximab; 1 (6%) received infliximab for 4 months and was then switched to certolizumab and 6 MP for 1 month (just before HL diagnosis) and 1 patient was treated with methotrexate and infliximab. Another patient was treated with adalimumab, thiopurines

Table 1
Patients and lymphoma's characteristics.

Sources	Sex	Age at diagnosis of lymphoma (years)	Gastrointestinal site of lymphoma	Stage	Histologic type	EBV-encoded RNA
Hecker et al. 1978 [6]	Male	32	Large and small bowel	IV	MC	N/A
Morrison et al. 1982 [7]	Female	30	Large bowel	N/A	MC	N/A
Shaw et al. 1982 [8]	Male	39	Small bowel	IV†	MC	N/A
Vanbockrijck et al. 1993 [9]	Male	34	Small bowel	I	NS	N/A
Kelly et al. 1997 [10]	Male	31	Small bowel	II	NS*	N/A
Kumar et al. 2000 [11]	Male	79	Large bowel	IV†	MC	+
Kumar et al. 2000 [11]	Male	30	Large bowel	IV	NS	+
Kumar et al. 2000 [11]	Male	44	Small bowel	I	MC	+
Li and Borowitz 2001 [12]	Male	38	Small bowel	N/A	NS	N/A
Bai et al. 2006 [13]	Male	35	Large bowel	N/A	N/A	+
Castrellon et al. 2009 [14]	Male	66	Small bowel	II	MC	+
Mourabet et al. 2011 [15]	Female	52	Small bowel	I	MC	N/A
Mourabet et al. 2011 [15]	Male	29	Small bowel	I	N/A	N/A
Sagues et al. 2012 [16]	Male	20	Large and small bowel	IV	MC	+
Subhashis et al. 2013 [17]	Female	69	Large bowel	II	MC	N/A
Loo et al. 2013 [18]	Female	49	Small bowel	I	N/A	+
Salgueiro et al. 2013 [19]	Male	37	Large bowel	I	N/A	+
Ujjani et al. 2014 [20]	Female	32	Large bowel	IV†	NS	+
Khuroo et al. 2014 [21]	Male	73	Large bowel	I	N/A	N/A
Moran et al. 2015 [22]	Male	53	Large bowel	IV†	MC	+
Rasmussen et al. 2015 [23]	Male	54	Large bowel	IV†	N/A	+
Gibson et al. 2016 [24]	Male	58	Small bowel	IV†	NS	+
Current case	Male	54	Large bowel	II	MC	+