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Primary Colorectal Diffuse Large B-Cell Lymphoma: A Report of Eighteen Cases in a Tertiary Care Center

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Abstract

Primary colorectal Diffuse Large B-Cell Lymphoma (DLBCL) is very rare colon malignancy. Due to a possible delay in the diagnosis, it is important to know the main demographic and clinical characteristics of these patients. Retrospective analysis of 18 patients diagnosed with primary colorectal DLBCL during a 17-year period at the tertiary National Cancer Institute of Brazil (INCA) hospital. Demographic characteristics, tumor localization, HIV status, Lactate Dehydrogenase (LDH) levels, treatment modality and follow-up status were obtained from medical records. Survival was estimated from the date of diagnosis until death. There were 11 male and 7 female patients in our cohort, the median age at diagnosis was 59.5 years and four patients were HIV positive. Tumor was mainly localized in the right proximal colon. Patients were treated with Chemotherapy (CT) and/or surgical resection. Eleven patients died during a median follow-up of 59 months and the median survival time was 10 months for the whole group. Six or more cycles of CT (HR=0.19; 95% CI 0.054-0.660, p=0.009), low LDH levels (HR=0.229; 95% CI 0.060-0.876, p=0.031) and surgical resection (HR=0.23; 95% CI 0.065-0.828, p=0.030) were associated with reduced risk of death in univariate analysis. DLBCL affected more frequently middle-aged man and was primarily located in the right colon. These observations should be considered for differential diagnosis. Six cycles of CT, low LDH levels and surgical resection were associated with better survival. Our results are consistent with previous publications and address the importance of correct colorectal DLBCL diagnosis and treatment.

Keywords: Diffuse large B-cell lymphoma; Primary colorectal lymphoma; Extranodal lymphoma; LDH; HIV

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Introduction

Non-Hodgkin Lymphoma (NHL) represents a wide spectrum of illnesses that vary from the most indolent to the most aggressive malignancies [1]. NHL may arise in lymph nodes (nodal lymphomas) or in other organs (extra-nodal lymphomas), with prognostic discrepancies depending on the site of origin [2,3]. Among all primary Gastrointestinal (GI) neoplasms, NHL accounts for 5% to 10% of cases [4,5]. Stomach is the most common extra-nodal site of GI lymphoma (50% to 60%) followed by the small intestine (30%). Primary colorectal lymphoma is very rare, accounting for less than 20% of all colonic cancer [6]. Diffuse Large B-Cell Lymphoma (DLBCL) is the most frequent NHL histopathology subtype in sites in general, but also in colorectal location [7] representing 1% of all colon diseases. Colorectal DLBCL is a rare disease with nonspecific symptoms, whose treatment includes surgical resection, Chemotherapy (CT), radiotherapy or a combination approach [8,9].

Due to its rarity, most colorectal DLBCL cases have been described as case report publications. It therefore limits the better understanding of the patient's main clinical characteristics, disease course and therapy response. Besides, initial clinical presentation is diverse, which makes the diagnostic a difficult task. In the present study, we report 18 cases from patients who were diagnosed with colorectal DLBCL at a reference Brazilian Cancer Center. Considering the rare presentation

of primary DLBCL in the colorectal site, our aim is to describe demographic, initial clinical characteristics, treatment modality, factors related to better survival and outcome of this cohort of patients.

Patients and Methods

This was a retrospective analysis from a database at the National Cancer Institute (INCA), Rio de Janeiro, Brazil (a tertiary referral cancer center) during a 17-year period (2002-2018). Patient inclusion criteria were: Biopsy proven primary DLBCL localized in the colon or in the rectum without extra colonic lymphoma infiltration except for regional (pericolic) adenopathy; bone marrow aspirate negative for lymphoma; immunohistochemical positivity for CD20. Samples included in the study showed neoplastic cells diffusely immunoreactive to CD20 monoclonal antibody. Considering the most recent classification, our cohort is classified as DLBCL, NOS (not otherwise specified).

In the medical records, we identified previous diseases, primary intestinal lymphoma location and Lactate Dehydrogenase levels at diagnosis (LDH reference levels: 240 U/L to 480 U/L), detailed data on treatments and patient's follow-up. Abdominal Ultrasonography (US), Computed tomography (Ct) and colonoscopy with biopsy and immunohistochemical staining were performed for proper diagnostic confirmation. All statistical analyses were performed using SPSS version 24.0 (SPSS Inc., CA, USA). Continuous variables were displayed as means ± Standard Deviation (SD) or median with range (minimum and maximum) according to data distribution. Survival time was estimated using Kaplan-Meier method considering the time from diagnosis to the last follow-up or death (event). Survival curves between clinical and treatment variables were compared using the Log rank test. Cox regression analysis was performed by the Enter method, with the objective of estimating the effect of the independent variables on survival by Hazard Ratio (HR) and its 95% Confidence Interval (95% CI). All variables whose p-value was <0.10 in Cox's univariate analysis were included in the regression model. The order of entry of the variables in the regression model was defined by statistical significance. To remain in the model, $p<0.05$ values were considered statistically significant.

The Research Ethics Committee at National Cancer Institute approved this study under the number 39190720.1.0000.5274. The study was conducted in agreement with the recommendations of the Helsinki declaration.

Results

Among 1,967 patients in our study population with histopathological diagnosis of DLBCL, 225 patients presented with primary gastrointestinal DLBCL, within which 18 cases were primary colorectal DLBCL (Figure 1).

Demographic and clinical information for all 18 patients is shown in Table 1. At diagnosis, the median age for all 18 patients included in the present analysis was 59.5 years-old (range: 18-80). Eleven patients were male and seven were female. Abdominal pain or discomfort at different abdominal regions, were the most common clinical presentation (lasting three to nine months). Different clinical symptoms were observed, such as weight loss in 10 patients, asthenia in two, cachexia in two, vomiting in three, constipation in four, diarrhea in one, and loss of appetite in one patient. Median LDH levels was 348 (range 209-929). As shown in Figure 1, predominant tumor location was in the right portion of the colon including the cecum, the ascending colon and proximal transverse colon (N=15), followed by descending colon and sigmoid (N=2), and only one case localized in the rectum (N=1). Four patients presented regional nodal disease (pericolic lymph nodes). Regarding immunological clinical conditions prior or simultaneous to primary DLBCL colorectal, there were four patients with Acquired Immunodeficiency Syndrome (AIDS/HIV+). One patient had colonic inflammatory polyp, and one had Hodgkin Disease (HD), both 10 years before DLBCL diagnosis. The patient with previous HD had been submitted to splenectomy and CT.

Fourteen out of 18 patients were treated with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone), COP (cyclophosphamide, vincristine, and prednisolone) or R-CHOP (rituximab plus CHOP). Thirteen patients were submitted to surgical resection of the affected colon segment. Only one patient with rectal DLBCL received palliative radiotherapy, due to CT refractoriness and two patients received no treatment.

After a medium follow-up period of 59 months, eleven patients had died. The median survival for the whole group was 10 months. Using Cox regression univariate analysis, only six or more cycles of

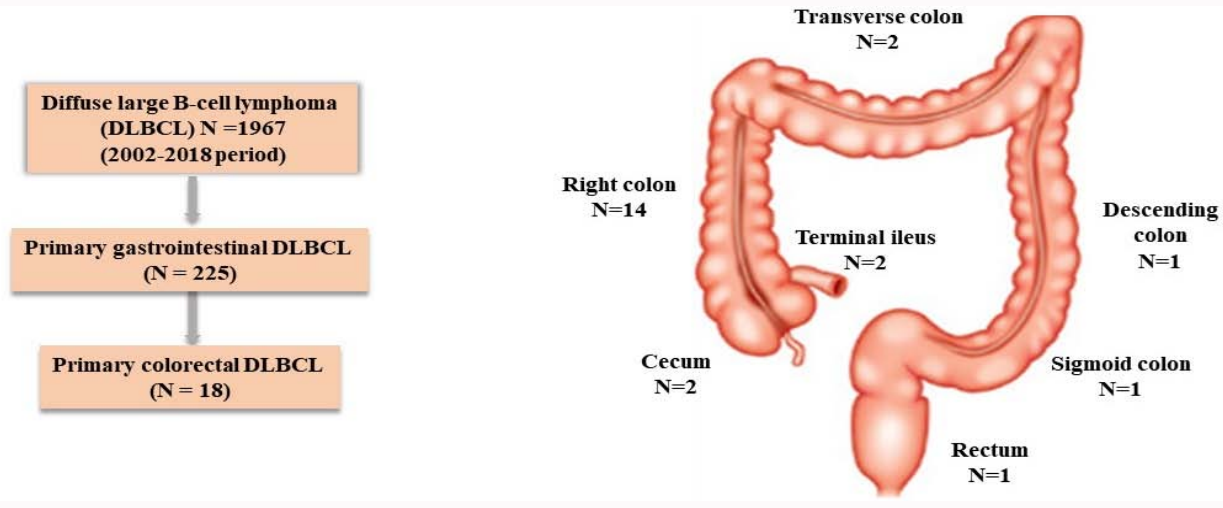

Figure 1: Patients diagnosed with diffuse large B-cell lymphoma and colorectal sites affected by DLCBL. Some patients had multiple sites of the colon affected.

Table 1: Demographic, clinical characteristics, treatment, and survival of the primary colorectal DLBCL patients.

N	Age	Gender	*Previous conditions	Colorectal tumor location	Surgical resection	LDH (U/L)	Specific treatment	Survival Time (months)	Survival Status
1	61	F	**Colonic polyp	Right colon	Yes	283	R-CHOP 6 cycles	50	Alive
2	48	F	No	Sigmoid colon	Yes	274	R-CHOP 6 cycles	57	Alive
3	18	M	No	Transverse colon and Cecon	Yes	209	R-CHOP 6 cycles	54	Alive
4	56	M	HIV	Sigmoid colon and rectum	Yes	320	R-CHOP 6 cycles	82	Alive
5	68	M	HIV	Right colon	Yes	444	R-CHOP 2 cycles	18	Dead of Disease
6	58	M	No	Right colon and Cecon	Yes	737	R-CHOP 6 cycles	7	Dead of Disease
7	61	M	No	Right colon	Yes	274	R-CHOP 6 cycles	79	Alive
8	75	M	No	Right colon	Yes	339	R-CHOP 6 cycles	9	Dead of Disease
9	28	F	No	Right colon	Yes	317	R-CHOP 6 cycles	63	Alive
10	37	F	No	Sigmoid colon and right colon	No	688	No	1	Dead of Disease
11	42	M	Hodgkin lymphoma	Right colon	Yes	356	R-CHOP 6 cycles	5	Dead of Disease
12	61	M	No	Right colon and transverse colon	Yes	925	R-CHOP 1 cycles	8	Dead of Disease
13	29	F	HIV	Right colon	No	929	No	0	Dead of Disease
14	78	F	No	Right colon	No	324	COP 2 cycles	2	Dead of Disease
15	65	M	No	Right colon	Yes	338	R-CHOP 6 cycles	9	Dead of Disease
16	80	M	No	Right colon and terminal ileus	No	652	COP 1 cycle	3	Dead of Disease
17	61	F	No	Right colon	Yes	549	CHOP 8 cycles	58	Alive
18	45	M	HIV	Rectum	yes	373	CHOP 1 cycle + RT	16	Dead of Disease

DLBCL: Diffuse Large B-Cell Lymphoma; *Previous or simultaneous conditions that affect the immune system. **Colonic inflammatory polyp has occurred 10 years before DLBCL diagnosis. HIV/AIDS: Acquired Immunodeficiency Syndrome; LDH: Lactate Dehydrogenase R-CHOP: Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine and Prednisone; CHOP: Cyclophosphamide, Vincristine and Prednisone; COP: Cyclophosphamide, Vincristine, and Prednisolone; RT: Radiotherapy

Table 2: Proportional risks of death according to demographic and clinical variables.

Variable	Total number	Number of deaths	% Of deaths	HR	CI	*p*
Age >60 years						
<60	9	5	55.50%	1,0	0.334-3.615	0.876
≥ 60	9	6	66.60%	1.1		
Gender						
Male	11	8	72.70%	1,0	0.173-2.517	0.543
Female	7	3	42.80%	0.66		
HIV+						
No	14	8	57.10%	1	0.319-4.608	0.781
Yes	4	3	75.00%	1.21		
Surgical Resection						
No	5	5	100.00%	1	0.065-0.828	**0.03**
Yes	13	6	46.10%	0.23		
LDH level (U/L)						
<350	9	3	33.30%	0.23	0.060-0.876	**0.03**
≥ 350	9	8	88.80%	1		
CT 6 Cycles or more						
No	7	7	100.00%	1,0	0.054-0.660	**0.01**
Yes	11	4	36.30%	0.01		

Legend: HR: Hazard Ratio; CI: Confidence Interval; p: p value; HIV: Human Immunodeficiency Virus; LDH: Lactate Dehydrogenase level; CT: Chemotherapy. In bold, *p* values inferior to 0.10

CT (HR=0.19; 95% CI 0.054-0.660, p=0.009), LHD levels below 350 (HR=0.229; 95% CI 0.060-0.876, p=0.031) and surgical resection of the affected colon (HR=0.23; 95% CI 0.065-0.828, p=0.030) were associated with reduced risk of death (Table 2).

Discussion

In the present case series, 18 patients (8.4%) had extra-nodal colorectal DLBCL among 225 patients with GI DLBCL. In a recent

publication of 78 cases of primary GI lymphoma, only six cases of ileocecal region and three cases of colon were DLBCL [10], herein demonstrating the rarity of this DLBCL localization. Although we presented a small number of patients with primary colorectal DLBCL, our dataset comprising 18 cases stands out in face of most cases published as case report.

Regarding to patient age in our cohort, the median age was 59.5 years-old (range: 18-80), below the average observed in the literature. The three young patients (18, 28 and 29 years-old) called our attention, considering that the age at diagnosis is an important predictor of outcome. The mean age cited in one paper analyzing fourteen cases was 65 years [11]. In another study, the median age at diagnosis was 63 years [12].

Despite the small number of patients with DLBCL described in the present study, it is relevant to emphasize that the patients with elevated serum LDH had the worst clinical outcome compared to patients with low LDH levels. Although LDH is not a specific marker for DLBCL prognosis, elevated LDH may be of prognostic significance in predicting relapse [13,14].

Some predisposing conditions have been implicated in colorectal lymphoma, such as AIDS/HIV, immunotherapy, and inflammatory bowel diseases. AIDS/HIV is associated with an increased incidence of NHL [15]. In fact, the incidence of NHL is greatly increased in HIV-infected patients [16] and HIV is the most frequent virus associated with colorectal DLBCL. As cited by Biggar et al., HIV-infected patients with cancer have worse survival rates compared with their HIV uninfected counterparts [17]. In our cohort we verified four out of 18 patients (22%) with HIV at DLBCL diagnosis. Only one patient had a good clinical outcome (alive at 7.4 years) after treatment with six R-CHOP cycles. The other three patients had Overall Survival (OS) less than two years. Nevertheless, in our study HIV positivity was not associated with increased risk of death (p=0.781) probably due to the small patients' cohort.

NHL occurring after Hodgkin Disease (HD) is a very rare event [18]. Nevertheless, we had one patient with HD 10 years before colorectal DLCBL diagnosis. This patient had received conventional CT consisting of MOPP schema (nitrogen mustard, vincristine, procarbazine and prednisone) plus RT and splenectomy. At DLCBL diagnosis, he was 42 years-old and presented with abdominal pain and discomfort for three months. Ascending colon was the involved site by DLCBL and he was treated with six cycles of CHOP, but died due to septic shock a few months after the end of treatment. Secondary colorectal DLCBL can develop after RT and/or CT for HD and it was a possible association in this case [19].

Inflammatory intestinal disease has been reported as a risk factor for lymphoma. However, a direct causal factor has not been found [6]. In our cohort, we had one patient with inflammatory polyps of the colon 10 years prior to the right colon DLBCL. Six cycles of R-CHOP for DLBCL treatment resulted in good clinical response and the patient was alive following diagnosis (4.5 years after diagnosis).

Besides our 18 described cases shown in Table 1, the lack of obvious presentation of colonic DLBCL is also remarkable. Delay in colorectal lymphoma diagnosis may occur due to non-specific symptoms. This is the case of a 63-year-old man whose initial clinical manifestation was altered mental status due to paraneoplastic hypercalcemia. Laboratorial investigation revealed hypercalcemia with elevated calcitriol levels, previously shown as being the major humoral mediator of hypercalcemia in lymphomas [20]. Colonoscopy and Ct showed mass in distal right colon and biopsy confirmed the DLCBL diagnosis, in which initial symptoms are not usual.

One case reported by Kai et al. demonstrated a 57-year-old man presenting right lower quadrant abdominal pain for 4 days [21]. Ct revealed an enlarged appendix with intense regional inflammation. The first diagnostic impression was acute appendicitis, but a dense adhesion between the appendix, omentum, terminal ileum, and cecum was observed upon appendectomy. However, it turned out to be DLBCL following histopathological and immunohistochemical analysis. This case demonstrates the relevance of early differential diagnosis of acute appendicitis from the appendiceal lymphoma through preoperative imaging.

Another interesting clinical entity are the collision tumor, defined by two distinct neoplasms occurring simultaneously at the same organ. It has been previously described in a 78-year-old man presenting synchronous DLBCL and adenocarcinoma of the colon [22]. The colonoscopy detected a mass in the right colon whose biopsy revealed a moderately differentiated adenocarcinoma of the colon, while immunohistochemical analyses confirmed the coexistence of the DLBCL and adenocarcinoma. Also, intestinal intussusception along with primary DLBCL is a rare condition and unusual combination. A case report described a 26-year-old man who presented diarrhea, abdominal pain and vomiting. US and Ct supported the diagnosis of ileocolic intussusception, while DLBCL of the colon was confirmed after laparotomy and pathology analyses [23]. Considering the difficulty in diagnosing colonic intussusception, imaging techniques such as multi-slice Ct scan, colonoscopy and biopsy and immunohistochemistry staining should be combined for a more precise diagnosis [24].

Intermittent diarrhea and progressive weight loss lasting seven months prior to diagnosis was described in a male patient with 79-year-old, with no inflammatory bowel disease, AIDS/HIV or immunosuppression [25]. Biopsies obtained from the sigmoid colon and the rectum revealed DLBCL. The patient was treated with reduced doses of R-CHOP and palliative radiation to the sigmoid colon and rectum. Another similar case was found in a 55-year-old male who presented abdominal pain and diarrhea for three weeks [26]. The ileo-colonic fistula with aneurysmal dilation of the small bowel was observed by Ct scan of the abdomen and confirmed by colonoscopy. After exploratory laparotomy, histopathology revealed DLBCL.

An interesting case was reported by Gigli et al. regarding an incidental DLBCL diagnosis in an 85-years-old male patient with symptoms of gallstone attack [27]. This patient referred abdominal pain and loss of appetite. Image investigation confirmed the presence of the large bulky mass located in the cecum-ascending colon. Surgical resection was performed not only to prevent complication, but also for differential diagnosis, which confirmed DLBCL.

Primary DLBCL of the rectum is a very rare disease. A case of a 41-year-old male with one-year history of Ulcerative Colitis (UC) was previously described. Investigation revealed a diagnosis of primary DLBCL of the rectum [28]. Notably, the UC was diagnosed one year earlier than the lymphoma, in accordance with the literature suggesting that the chronic stimulation of the immune system by chronic colorectal inflammation is required for the onset of lymphoma [29,30]. Also, it is important to point out that primary colorectal lymphoma is extremely rare in children. Interestingly, a case report of a 12-year-old boy presenting an unusual primary colorectal

lymphoma mimicking a rectal polyp has been shown [31]. As occurs in adults, the boy presented rectal mass lesion and bleeding. Some published case series present patients with local symptoms, in which the differential diagnosis between lymphoma and adenocarcinoma, the most common type of colonic neoplasia, is only possible after histopathological examination is provided. However, in our series, we noticed a more frequent location of primary lymphomas in the proximal portion of the colon, while colon adenocarcinomas occur more frequently on the left side [32].

Another noteworthy fact is that the median age in our cohort, at presentation, was 59 years when the median age in adenocarcinoma is 68 years in men, and 72 years in women [33]. Although even in the right colon, adenocarcinoma is the most frequent histological type. Therefore, the possibility of primary colonic lymphoma should be considered in younger patients with an unclarified tumor in the proximal colon associated with atypical symptoms, LDH elevation, male sex, or HIV. Video colonoscopy with biopsy can confirm diagnosis, but sometimes biopsy is inconclusive because deep biopsy is often required to collect adequate tissue. Patients can be candidates to surgical resection as initial approach unless they are clinical unfit or the tumor is unresectable. Interestingly, the data from the Surveillance, Epidemiology, and End Results (SEER) database found that the proportion of patients who received surgical therapy decreased gradually from 83.3%-100% to 47.7%-52.6% in the period from 1973 to 2012, demonstrating a migration to medical therapy at least in the United States of America [34]. Even in this large cohort series, patients surgically treated had better survival, although this benefit was least pronounced in the most recent period [34]. In another retrospective study, surgical resection followed by CT resulted in decreased recurrence (15.3% *vs.* 36.8%, p= <0.001) and improved 3-year survival (91% *vs.* 62%, p= <0.001) compared to CT alone [35]. Unfortunately, no randomized trials are available comparing these two treatment modalities due to the rarity of the disease.

In conclusion, it is important to keep in mind some hints when diagnosing colorectal DLBCL. First, we should consider unsuspected extranodal lymphoma sites. As seen in our study and in the literature, colorectal DLBCL may present after previous malignant or inflammatory illness, which makes DLBCL final diagnosis hard to be done. Also, we need to consider the association between elevated serum LDH levels and poor clinical outcomes, despite the small number of patients in our cohort. DLBCL affected more frequently middle-aged man and was primarily located in the right colon. Six cycles of CT, low LDH levels and surgical resection of the affected colon were both associated with better survival. Our results are consistent with previous publications and address the importance of correct diagnosis and treatment. Additionally, the similarities of symptoms among some diseases may delay colorectal DLBCL diagnosis. Clinical suspicion and timely diagnosis are essential to provide proper treatment and achievement of long-time survival.

Ethics Approval Statement

The Research Ethics Committee at National Cancer Institute approved this study under the number 39190720.1.0000.5274. The study was conducted in agreement with the recommendations of the Helsinki declaration.

Author Contributions

FCV, ROCA, RCM contributed to the study conception and design. All author contributed to data collection. Analysis was performed by FCV, ROCA, RCM. The first draft of the manuscript was written by FCV, ROCA, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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