

## Case Report

# MUM-1 and bcl-2 Positive Primary Diffuse Large B Cell Non-Hodgkin's Lymphoma of the Colon

Vladimir Jurišić MD<sup>1</sup>, Mirjana Plečić MD<sup>2</sup>, Natasa Colović MD<sup>3</sup>, Vesna Čemerikić-Martinović MD<sup>4</sup>, Marko Janković MD<sup>3</sup>, Milica Čolović MD<sup>3</sup>

## Abstract

Primary diffuse large B cell lymphoma (DLBCL) presents as a nodal and extranodal disease. The most common extranodal site is the gastrointestinal tract (GI), with the stomach most frequently involved, followed by the small bowel. Primary DLBCL of the large bowel accounts for 0.2%–1.2% of all colonic tumors. We present two patients who underwent radical resections of right colonic tumors. They were diagnosed with primary colonic DLBCL following histological and immunohistochemical testing of the excised tissues, and were determined as being in stage IIE of the disease. The tumors expressed CD20 markers. Both received multi-agent chemotherapy with combined immunotherapy and remain in complete remission at 4 and 5 years.

**Keywords:** Chemotherapy, colon, hemicolectomy, immunohistochemistry, non-Hodgkin's lymphoma

**Cite this article as:** Jurišić V, Plečić M, Colović N, Čemerikić-Martinović V, Janković M, Čolović M. MUM-1 and bcl-2 Positive Primary Diffuse Large B Cell non-Hodgkin's Lymphoma of the Colon. *Arch Iran Med.* 2016; 19(4): 297 – 299.

## Introduction

Primary Non-Hodgkin's lymphoma (NHL) of the colon is a rare tumor of the gastrointestinal tract (GI) that comprises 0.2%–1.2% of all colonic malignancies. Among primary colonic lymphomas diffuse large B cell lymphoma (DLBCL) is aggressive, distinct and the most frequent subtype of all adult NHL localized in large bowel.<sup>1–5</sup> The ileocecal part of the bowel is the most frequently affected site. Due to the small number of published cases, the optimal therapy for NHL of the colon is still undetermined, particularly regarding the necessity of surgical resection, duration of chemotherapy and significance of immunotherapy. Our two cases of DLBCL with primary localisation in colon showed a successful protocol with surgery in combination with immunotherapy.

## Case reports

### Case 1

A 65-year-old woman presented in January 2009 with intermittent diarrhea followed by obstipation and weight loss of 20 kg over the preceding 4–5 months. Laboratory data showed hypochromic anemia. Lactate dehydrogenase level was normal. Colonoscopy detected a tumor mass narrowing obstructing the ascending colon. A barium enema identified a long stricture of the ascending colon and the right side of the transverse colon with mucosal irregularity suggestive of malignancy. Computed tomography (CT) showed a tumor mass measuring 9.5 × 8 × 8.6 cm in the lower part of right abdomen (Figure 1). The patient underwent

right colectomy for suspected colonic adenocarcinoma and had an uneventful recovery. The tumor histology and immunohistochemistry revealed many large cells and diffuse cell growth in keeping with diffuse large B cell lymphoma (DLBCL) expressing the immunophenotype CD20+, CD79alpha+, CD43+/-, MUM-1+, bcl-2+, cyclin D1-, CD3-, CD5-, CD10-, CD23-, with Ki-67 positivity in over 70% of the tumor cells (Figure 2). Following surgery, it was determined that the patient had stage II disease, IPI score 2. Immunotherapy was administered according to the R-CHOP protocol (rituximab 700 mg 1 day, cyclophosphamide 1400 mg 1 day, adriablastin 90 mg i.v. 1 day, vincristine 2 mg i.v. 1 day, prednisone 100 mg daily days 1 to 5). The patient received 8 cycles of therapy after which she achieved complete remission. Laboratory tests, biochemistry, bone marrow biopsy, and chest, abdomen, and pelvis CT scans were normalized. She remains in complete remission 4 years later.

### Case 2

In February 2008 a 50-year-old woman presented with intestinal obstruction and underwent an emergency right hemicolectomy and terminal ileostomy. Histology found that the tumor tissue was composed of large, round cells with oval or intended nuclei, with an abundant partly basophilic cytoplasm. These tumor cells immunohistochemically expressed CD20+, Cd79alpha+, CD3-, CD5-, bcl-2+/-, bcl-6-, MUM +/-, CD 138+, and around 70% were Ki-67+. Following surgery, an abdominal CT scan identified a number of enlarged paracaval lymph nodes, the largest of which measured around 56 × 42 × 60 mm. Bone marrow biopsies were normal. Laboratory analysis found Hb 106 g/L, WBC 6.1–10<sup>9</sup>/l, platelets 342 × 10<sup>9</sup>/l, (seg 73%, eo 5%, bas 1%, lym 14%, mo 7%), SE 30 mm, and fibrinogen 6.5 g/L. Lactate dehydrogenase level was 498 U/L (normal range 220–460 U/L). The patient was therefore determined to have IPI score 1, and in stage IIE of the disease. She was also treated with 8 cycles of immunotherapy according to the R-CHOP protocol (rituximab, 700 mg

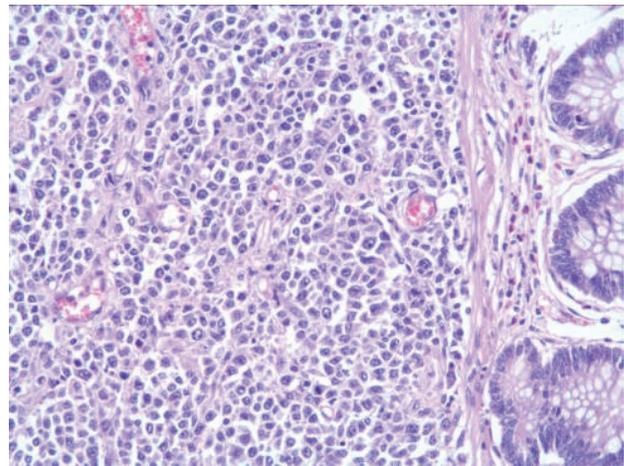
**Authors' affiliations:** <sup>1</sup>University of Kragujevac, Faculty of Medical Sciences, Kragujevac, Serbia. <sup>2</sup>Medical Center, Valjevo, Serbia. <sup>3</sup>Medical Faculty University, Belgrade Serbia. <sup>4</sup>Laboratory Beolab, Resavska 60, Belgrade Serbia.

• **Corresponding author and reprints:** Vladimir Jurišić MD, University of Kragujevac, Faculty of Medical Sciences 34000 Kragujevac, Serbia. E-mail: vdvd@mailcity.com.

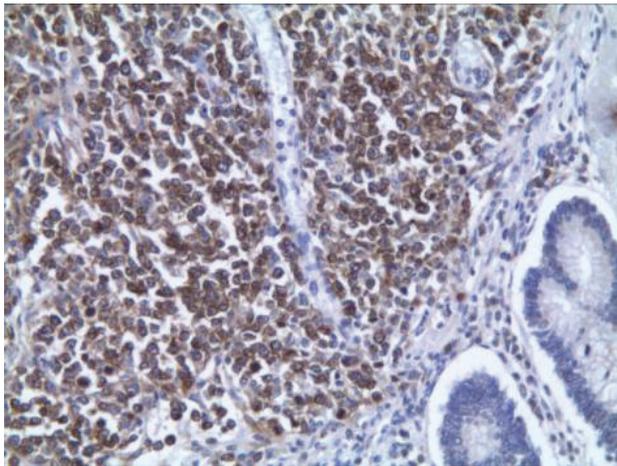
Accepted for publication: 20 March 2015



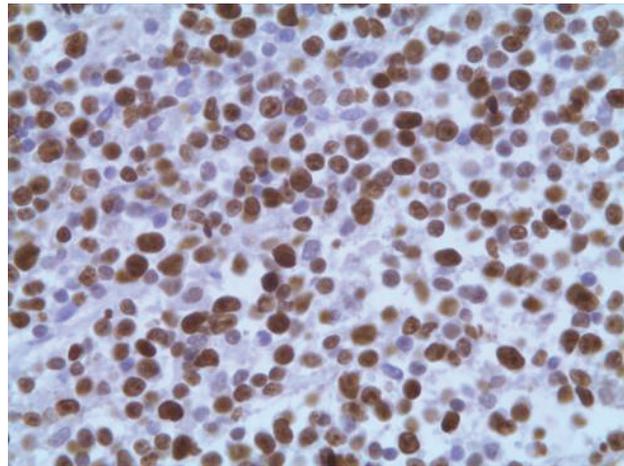
**Figure 1.** Abdominal CT scan showing a tumor mass measuring  $9.5 \times 8 \times 8$  cm.



**Figure 2.** Histopathology showing atypical cell infiltration (HE,  $\times 20$ ).



**Figure 3.** The cells stain strongly with CD20 (HE,  $\times 20$ ).



**Figure 4.** Proliferative activity measured with Ki-67 indicating a high mitotic index (HE,  $\times 20$ ).

, 1 day, endoxan 1400 mg i.v., 1 day, adriablastin 90 mg i.v., 1 day, oncovin 2 mg i.v., 1 day, prednisone 40 + 40 + 20 from day 1 to 5 days) after which her biochemistry, bone marrow biopsy, and chest, abdomen, and pelvis CT scans were normal. She remains in complete remission 5 years later.

## Discussion

Primary lymphoma of the colon is a rare malignancy which accounts for around 0.2%–1.2% of all cases of colonic cancers.<sup>1–3</sup> The stomach is most frequently involved (50%–60%), followed by the small bowel (20%–30%) and the colon/rectum (6%–14%).<sup>2</sup>

Due to their rarity, the literature contains only a small number of case reports and small case series of up to 35 patients, and thus the optimal treatment and clinical outcomes are not completely clear.<sup>3–5</sup> Furthermore, there is little data on their histology and immunohistochemistry because many of these publications appeared before the World Health Organization Classification.<sup>6,7</sup>

In a recent review of colorectal malignancy, primary colonic

lymphoma was found in 29 of a cohort of 6944 patients.<sup>5</sup> Immunohistochemistry found that 60% of these had DLBCL, 14% follicular lymphoma, 10% mucosa associated lymphoid tissue (MALT) lymphoma, and 7% mantle cell lymphoma.<sup>5</sup> DLBCL has similarly been found to be the most frequent histopathological subtype in other published series and case reports of primary colonic lymphoma. The tumor cells generally express pan B-cell markers such as CD19, CD20, CD22, CD79a, occasionally MUM-1+, and bcl-2+, and 50–75% of cases express surface or cytoplasmic immunoglobulins.<sup>1,2,7–9</sup>

The diagnosis of primary colonic DLBCL in our patients was made on the basis of histology and immunohistochemistry both of which showed a diffuse infiltration of predominantly large cells which were positive for pan B markers and were MUM-1+ and bcl-2+. The presence of bcl-2 and MUM-1 proteins has been associated with a less favorable prognosis and the possibility of a non germinal center DLBCL subtype, requiring more aggressive treatment.<sup>10,11</sup> However, our patients had an excellent response to radical surgical excision, and combination immunotherapy

which was initiated after histology and immunohistochemical identification of the CD20 marker.

Colonoscopy, abdominal ultrasonography and CT scan examination could have helped in detecting the presence and extent of the tumor. However, the appearances of the lesions in DLBCL are very nonspecific, and initially one would usually suspect colonic adenocarcinoma; hence patients often undergo surgery without preoperative histopathology and immunohistochemical examination of lesions, as was the case in our obstructed patient.

The optimal treatment of primary colonic lymphomas remains unclear. Some authors suggest chemotherapy alone with surgery reserved only for complications (such as perforation, obstruction or bleeding).<sup>5,12-16</sup> However, emergency surgery for colonic perforation has a high mortality rate and these perforations can often be predicted; hence some authors advocate surgery prior to chemotherapy.<sup>5</sup> A combination of chemotherapy with additional anti-CD20 monoclonal antibodies (rituximab) has been shown to have a beneficial effect and increase survival time in patients with lymphomas expressing CD20.<sup>14</sup>

Our two patients had initial surgical excision followed by 8 cycles of immunochemotherapy, as their tumors expressed CD20. They remain well and in remission at 4 and 5 years. Our experience echoes that of other reports which have shown better survival outcomes in patients undergoing surgery followed by chemotherapy/ immunochemotherapy.<sup>5</sup>

In conclusion, with advances in immunohistochemistry, the classification, management and outcomes of GI NHL has continued to improve. Extensive histological and immunohistochemical analyses are imperative as these guide the choice and duration of immunochemotherapy. It is likely that a combination of surgery followed by immunochemotherapy treatment currently offers the best overall survival for primary colonic DLBCL patients.

## References

1. Tauro LF, Furtado HW, Aithala PS; D'Souza CS, George C, Vishnumoorthy SH. Primary lymphoma of the colon. *Saudi J Gastroenterol*. 2009; 15(4): 279-282.
2. Bairey O, Ruchlemer R, Shpilberg O. Non-Hodgkin's lymphomas of the colon. *Isr Med Assoc J*. 2006; 8(12): 872 - 835.
3. Zinzani PL, Magagnoli M, Pagliani G, Bendandi M, Gherlinzoni F, Merla E, et al. Primary intestinal lymphoma: clinical and therapeutic features of 32 patients. *Haematologica*. 1997; 82(3): 305 - 308.
4. Wong MT, Eu KW. Primary colorectal lymphomas. *Colorectal Dis*. 2006; 8(7): 586 - 591.
5. Lai YL, Lin JK, Liang WY, Huang YC. Surgical resection combined with chemotherapy can help achieve better outcomes in patients with primary colonic lymphoma. *J Surg Oncol* 2011; 104(3): 265 - 268.
6. Stein H, Warnke RA, Chan WC, Jaffe ES, Chan JKC, Gatter KC, Campo E. Diffuse Large B-cell Lymphoma, not Other Wise Specified. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al, eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 4th ed. Lyon: WHO Press; 2008: 233 - 237.
7. Harris NL, Jaffe ES, Diebold J, Flandrin G, Muller-Hermelink HK, Vardiman J. Lymphoma classification-from controversy to consensus: the REAL and WHO classification of lymphoid neoplasms. *Ann Oncol*. 2000; 11 (suppl 1): 3 - 10.
8. Daum S, Ulrich R, Heisse W, Dederke B, Foss HD, Stein H, et al. Intestinal non-Hodgkin's lymphoma: a multicenter prospective clinical study from the German Study Group on intestinal non-Hodgkin's lymphoma. *J Clin Oncol*. 2003; 21(14): 2740 - 746.
9. Hill ME, MacLennan KA, Cunningham DC, Hudson BV, Burke M, Clarke P, et al. Prognostic significance of BCL-2 expression and bcl-2 major breakpoint region rearrangement in diffuse large cell non-Hodgkin's lymphoma: A British National Lymphoma Investigation Study. *Blood*. 1996; 88(3): 1046 - 1051.
10. Colovic N, Jurisic V, Terzic T, Atkinson HD, Colovic M. Immunochemotherapy for Bcl-2 and MUM-negative aggressive primary cutaneous B-cell non-Hodgkin's lymphoma. *Arch Dermatol Res*. 2009; 301(9): 689 - 692.
11. Zhang WH, Cheng LN, Chen WZ, Wang FJ, Li SH, Bai W. Clinical impact of t(14;18) in diffuse large B-cell lymphoma. *Chin J Cancer Res*. 2011; 23(2): 160 - 164.
12. Dalal L. Primary multifocal non-Hodgkin's lymphoma of the colon successfully treated with chemotherapy. *Gastrointest Endosc*. 2008; 68(5): 1005-1006.
13. Cai S, Cannizzo F Jr, Bullard Dunn KM, Gibbs JF, Czuczman M, Rajput A. The role of the surgical intervention in non-Hodgkin's lymphoma of the colon and rectum. *Am J Surg*. 2007; 193(3): 409 - 12, discussion 412.
14. Habermann TM, Weller EA, Morrison VA, Gascoyne RD, Cassileth PA, Cohn JB, et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. *J Clin Oncol*. 2006; 24(19): 3121 - 3127.
15. Lee J, Kim WS, Kim K, Ahn JS, Jung CW, Lim HY, et al. Prospective clinical study of surgical resection followed by CHOP in localized intestinal diffuse large B cell Lymphoma. *Leuk Res*. 2007; 31(3): 359 - 364.
16. Sabroe RA, Child FJ, Woolford AJ, Spittle M, Russel-Jones R. Rituximab in cutaneous B-cell lymphoma: report of two cases. *Br Dermatol*. 2000; 143(1): 157 - 161.