Primary Rectal Non-Hodgkin’s Lymphoma Treated with Urgent Radiotherapy and Chemotherapy: A Case Report and Literature Review

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Abstract
Rectal malignancy is usually symptomatic due to its location, and most of the time presents with pain and bleeding due to its growth and ulceration. It is difficult to identify the primary as carcinoma or lymphoma based on symptoms only, as both have a similar presentation. As it presents the rarest form of histology, non-Hodgkin's lymphoma in the rectum is still difficult to diagnose initially, and its treatment is debatable. We describe the case of a 49-year-old male from Bangladesh with the same presentation. His treatment was delayed for more than a month as immunohistochemistry and staging delayed the final diagnosis. The disease was diagnosed as stage IE with the help of a positron emission tomography (PET)-CT scan, and due to the local progression the patient had a massive rectal bleeding that needed an urgent intervention. Radiotherapy was applied to stop the bleeding. Hypofraction followed by a conventional fraction of external beam radiotherapy (EBRT) with a total of 40 Gy was applied. Post-EBRT digital rectal examination showed no residual except scaring, and a PET scan was also negative for residual disease. Due to uncertainties and lack of any precious guideline, 6 cycles of adjuvant chemotherapy with the R-CHOP schedule were also completed. Without surgery, the combination of EBRT and chemotherapy helped to preserve the organ, and the patient has been disease free for more than 2.5 years since his treatment.

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Introduction

Of all rectal malignancies, primary rectal lymphoma is the rarest and accounts 0.05% of all primary rectal malignancies [1]. However gastrointestinal lymphomas account for 30% of extranodal lymphomas which make up 6–12% [2, 3] of all malignancies, and 5.8% of cases have primary colorectal lymphoma which represents 0.16% of all colorectal malignancies [4].

Lymphoma is classified as nodal or extranodal depending on the site, and 5% [4] of all lymphomas involving gastrointestinal tract (GIT) are extranodal. Among all extranodal lymphomas, 30% [2, 3] are found in GIT, where the common site is stomach, and the small intestine and colon and rectum make up only 5.8 and 0.16% of all colorectal malignancies [5]. The diffuse large B-cell lymphoma is the most common type of primary colorectal non-Hodgkin’s lymphoma (NHL) [6]. The most frequent colonic location is the caecum (70%), followed by the rectum and ascending colon [7].

There is a male predominance, with the highest reported incidence in the 50–70 years age group. Patients often present late with nonspecific symptoms and consequently have advanced disease at the time of diagnosis [8]. But based uniquely on symptoms, it is difficult to identify the primary as a carcinoma or lymphoma as both have a similar presentation. As it has the rarest form of histology, NHL in the rectum is still a diagnostic dilemma and its treatment is debatable. Most knowledge about the rectal lymphoma and its management comes from case reports because of the paucity of the disease [9]. Therefore, the treatment modality for primary lymphoma of the rectum remains uncertain. We present the case of a 49-year-old male, diagnosed as stage IIE, who underwent combined modalities of external beam radiotherapy (EBRT) followed by chemotherapy without any surgical intervention and was found to have a complete response.

Case Report

A 49-year-old, nondiabetic, normotensive, Bangladeshi man presented to us with extensive rectal bleeding for the last 2 days after receiving the confirmatory diagnosis of rectal NHL. One month before, the patient presented to the colorectal surgeon with a feeling of incomplete evacuation, something coming down the rectum on straining, tenesmus, and rectal mucous discharge. Digital rectal examination (DRE) showed ulceroproliferative growth involving the rectum and anal canal. Colonoscopy showed slough in the rectum, and the colonoscopic biopsy revealed a potentially lymphoproliferative lesion (NHL). A computed tomography (CT) scan of the whole abdomen and pelvis was done, which was suggestive of exophytic rectal mass, originating from the outer wall of the rectum compressing the lumen, measuring 67 mm × 84 mm extending towards the urinary base. No distant involvement or nodal involvement was seen, and there was no ascites (Fig. 1, 2). Chest X-ray PA view was also normal. CEA was 1.99 and LDH was not elevated. Due to uncertainty, immunohistochemistry was done, and the diagnosis was confirmed as diffuse large B cell lymphoma as it was immunopositive for LCA (CD45) (Fig. 3) and CD20 (Fig. 4), and immunonegative for CD3 (Fig. 5), pancytokeratin (Fig. 6), and HMB45 (Fig. 7) that confirm the primary rectal NHL. The slide was reviewed outside of the country, and the IHC was confirmed and found to be also negative for CD10 and cyclin D1 but positive for CD5, Bcl2, Bcl6, and Mum-1. Ki67 was 65% which combined with morphology favored high-grade B cell NHL diffuse large B cell lymphoma, non-GBC type with a high proliferative index.

For the purpose of appropriate staging, positron emission tomography (PET) was done 25 days after the CT scan, and a large soft tissue mass (142 mm CC × 99 mm AP × 88 mm RL) was noted in the rectum and anal canal showing intense FDG uptake (SUV max 35) and the mass abutting the urinary bladder and prostate (Fig. 8–10), suggesting immunohistochemically proven lymphoma. A hypervascular focal lesion in the right hepatic lobe without appreciable FDG uptake was suggestive of hypervascular hemangioma. No other appreciable suspicious lesion or abnormal FDG uptake elsewhere in the body was seen. Due to uncontrolled bleeding and as it took more than a month to confirm the diagnosis, he was planned to start
urgent radiotherapy. EBRT was urgently started with Cobalt 60 with 1.25-MV photon energy (Best Theratronics) using a 2-D technique. Initially, 12 Gy in 4 fractions was given as hypofraction to control the bleeding immediately, followed by 28 Gy in 14 fractions, i.e. 40 Gy in 18 fractions, 5 fractions/week in 25 days without any delay or gap correction. The patient was treated with adjuvant chemotherapy with a standard R-CHOP protocol and completed 6 cycles. Post-EBRT DRE revealed minimal scaring in the anorectal region with significant regression of growth. Post-chemotherapy PET evaluation done 8 months after diagnosis showed irregular wall thickening with inhomogeneous enhancement and narrowing of lumen along the anorectal region. The scan showed an interval decrease in FDG avidity (SUV max 3.5 vs. 35 before) without any activity elsewhere in the body (Fig. 11–13). Since the completion of chemotherapy he has been followed up for more than 30 months and was still disease free at a follow-up with a further MRI/PET scan.
Discussion

Lymphoma has a variety of classifications and, according to the site, can be nodal or extranodal. The other major part of classification of Hodgkin’s and non-Hodgkin’s lymphoma is according to histopathological differentiation. Among rectal malignancies, primary rectal lymphoma is the rarest and accounts 0.05% of all primary rectal malignancies [1]. However, gastrointestinal lymphomas account for 30% of extranodal lymphomas which make up 6–12% [2, 3] of all malignancies, and 5.8% of cases have primary colorectal lymphoma which represents 0.16% of all colorectal malignancies [5]. The caecum is most often involved, probably as a result of spread from the terminal ileum [10].

Rectal lymphoma usually presents with signs and symptoms suggestive of primary rectal carcinoma. Patients with a rectal lymphoma usually seek treatment because of rectal bleeding or an alteration in bowel habits. It is reported that the majority of patients are symptomatic complaining of abdominal pain, nausea, vomiting, fever, and weight loss [11–14]. Our case
presented with rectal bleeding and pain for 1.5 months but without any significant weight loss or other constitutional symptoms.

Whatever the presentation, the diagnostic modalities are the same, general physical examination and DRE are first to assess the local extent and nodal involvement initially. Colonoscopic examination plays the primary role to see and evaluate the whole colon as well as the biopsy taken to prove the malignancy. For the confirmation of lymphoma, histopathology and immunohistochemistry reports help to confirm the diagnosis. In our case, colonoscopy showed slough in the rectum, and colonoscopy biopsy revealed a possibly lymphoproliferative lesion (NHL). B cell lymphoma constitutes 85% of all primary colorectal lymphomas, with T cell lymphoma accounting for the remainder (15%) [15]. The differentiation between both lymphomas is done by the use of a cluster of differentiation antibodies (CD). CD2, CD3, CD4, CD7, and CD8 are used to determine T cell lymphoma. CD20, CD79a, and CD10 are used to determine B cell lymphoma [16]. The most common histological types of primary colorectal lymphomas, following the Revised European-American Classification of Lymphoid
Neoplasms/World Health Organization classification of lymphoid neoplasms (REAL/WHO) are: diffuse large B cell lymphoma, Mantle cell lymphoma, and Burkitt’s lymphoma [17]. In the case of our patient, most of the neoplastic cells were positive for CD-20 (Fig. 4) and for LCA (Fig. 3) antibody.

For the staging purpose, the imaging is the best modality to see the extent. CT of the chest and abdomen and pelvis is recommended, and PET is the best modality with conventional CT for proper staging. PET scan can detect marrow infiltration, though bone marrow aspiration remains the gold standard. In our case, the CT scan of the abdomen and pelvis showed an exophytic rectal mass originating from the outer wall of the rectum compressing the lumen (measuring 67 × 84 mm) extending towards the urinary base. No distant or nodal involvement...
was seen, and there was no ascites. The chest X-ray posterior anterior view also suggested normal findings. CEA was 1.99, and LDH was not elevated. But 25 days after the initial CT scan, its aggressiveness was shown on a PET scan that showed almost double of the initial growth size (142 mm CC × 99 mm AP × 88 mm RL vs. 67 mm × 84 mm) (Fig. 1, 2, 8–10).

Dawson et al. [17] established criteria for the diagnosis of primary colorectal lymphomas in 1961. These are: (1) no enlarged superficial lymph nodes when the patient is first seen; (2) chest radiographs without obvious enlargement of the mediastinal nodes; (3) the white blood cell counts, both total and differential, are within normal range, and bone marrow biopsy is also normal; (4) at laparotomy, only regional nodes are affected by disease; and (5) the liver and spleen seem to be free of tumor. In the modern era, these criteria have been expanded to new diagnostic tools. Krol et al. [18] in a paper from 2003 described three alternative definitions of primary nodal and extranodal NHL, exploring their effect on the percentage of the patients considered to have primary extranodal disease, their treatment outcome and survival in a population-based cohort of NHL patients. According to the criterion, our patient was diagnosed as having primary rectal NHL stage IE.

Treatment of colorectal lymphomas remains uncertain. While surgical treatment may be indicated for some localized tumors, many authors consider medical management to be the primary treatment [19]. Some studies reported that the primary treatment is to attempt resection when the disease is judged to be resectable because of poor prognosis in patients with residual disease [5, 19, 20]. Most of knowledge about the rectal lymphoma and its management comes from case reports because of the paucity of disease. Therefore, the treatment modality of primary lymphoma of the rectum remains uncertain. Still, we have treated the primary rectal lymphoma patient with both EBRT and chemotherapy with an excellent result.

There have been no prospective studies evaluating the relative benefits of adjuvant chemotherapy, radiotherapy, surgery, or a combination of treatments for primary rectal lymphoma. Nevertheless, most case studies reveal a trend toward improved survival when surgery is used in combination with chemo- or radiotherapy. For example, 3 studies [21–23] in which 20 patients with primary rectal lymphoma underwent surgery along with chemo- or radiotherapy or both reported survival rates ranging from 50 to 80% [22], whereas patients
who received only nonoperative therapy had poor survival: 0% [22, 23] to 20% [21]. Devine et al. [22] advocated that primary rectal involvement should be treated like primary lymphomas elsewhere in the GIT: with surgical excision followed by radiotherapy. If complete excision is not possible, then nonoperative therapy becomes the treatment of choice.

Management strategies for rectal lymphoma are directed at investigating whether the tumor is primary or secondary. Inclusion of surgery for the treatment of primary rectal lymphoma confers a survival advantage over chemotherapy and radiotherapy alone. Secondary involvement of the rectum confers a poor prognosis; such patients should be managed with radiation alone, for relief of symptoms.

Because of the uncommon nature of this cancer, very few studies have investigated prognostic factors that would allow clinicians to determine outcome and risk of relapse [16, 24, 25].

In a single-center experience of 16 patients at Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea, a significant difference in survival between patients with early disease, stages I through II, compared with those with late disease, stage IV, was observed. The authors assumed that stage is a good predictor of survival in primary rectal lymphoma [26].

**Conclusion**

In our case, it was an early stage (IE) disease, and we did a wide staging and management plan prior to treatment, which contributed to good outcome with a progression-free survival so far of 30 months. Thus, malignant lymphoma of the rectum should be considered a different clinicopathological entity with different behavior and clinical presentation, and treatment should be defined based on this special clinical condition [26].

The role of this case report is, to raise awareness about the importance of histopathological confirmation with IHC of the unusual diagnosis in the context of a country like Bangladesh. It has to be kept in mind that the histopathological confirmation with IHC and proper staging methods is the appropriate way to plan for the cure of disease when it is in its early stage. Sometimes, we can save the organ as well if proper diagnosis is established. But eventually, we can save the organ by early detection and availability of the best treatment for this condition, which may improve overall survival as well as disease-free survival.

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**Statement of Ethics**

The authors have no ethical conflicts to disclose. The subject in the case report has given the consent to use details including the images for the publication.

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Author Contributions

Dr. Md. Arifur Rahman: literature search, writing, and follow-up. Prof. Dr. Qamruzzaman Chowdhury: decision of treatment plan and managing treatment and correcting writing and follow-up. Dr. Ferdous Ara Begum: planning the chemotherapy and doses. Assoc. Prof Dr. Saequah Habib: histopathological confirmation with IHC. Dr. Muhammad Masudul Hassan Arup: implication of radiotherapy as urgent basis and continuation of radiotherapy with supervision.

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