



# Synchronous rectal adenocarcinoma and splenic marginal zone lymphoma

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## ABSTRACT

Synchronous cancers of different primary origin are rare. Here, we describe the case of a patient with concomitant diagnoses of rectal adenocarcinoma and splenic marginal zone lymphoma (SMZL).

A 57-year-old woman initially presented with abdominal pain. Physical examination and computed tomography demonstrated massive splenomegaly, and a complete blood count revealed microcytic anemia and lymphopenia. During the subsequent evaluation, she presented with hematochezia, melena, and constipation, which prompted gastroenterology referral. Subsequent endoscopic rectal ultrasonography revealed a T3N1 moderately differentiated rectal adenocarcinoma, with computed tomography imaging of chest, abdomen, and pelvis confirming no metastasis. Thus, the cancer was classified as clinical stage T3N1M0, stage III. Bone marrow biopsy confirmed co-existing marginal zone lymphoma, and with the clinical presentation of massive splenomegaly, a diagnosis of SMZL was made.

The patient's management was individually tailored for simultaneous optimal treatment of both conditions. Concurrent treatment with neoadjuvant rituximab and 5-fluorouracil chemotherapy, with external-beam radiation therapy to the pelvis, was administered, followed by surgery consisting of *en bloc* splenectomy and distal pancreatectomy, and low anterior resection. The patient completed a standard course of adjuvant FOLFOX (fluorouracil–leucovorin–oxaliplatin) chemotherapy and has remained disease-free for 7 years.

To our knowledge, this report is the first to specifically describe simultaneous diagnoses of locally advanced rectal cancer and SMZL. We also describe the successful combined neoadjuvant treatment combination of 5-fluorouracil, rituximab, and pelvic radiation.

**Key Words** Rectal cancer, non-Hodgkin lymphoma, rituximab, 5-fluorouracil, neoadjuvant chemoradiation

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## INTRODUCTION

Colorectal carcinoma is the second leading cause of cancer-related death in the United States<sup>1–4</sup>. But despite that high prevalence, co-occurrence of colorectal adenocarcinoma with other primary cancers is rare.

Splenic marginal zone lymphoma (SMZL) is an indolent B-cell lymphoma that causes marked splenic enlargement, with CD20-rich lymphoma cells infiltrating blood and bone marrow<sup>5</sup>. It is estimated that only approximately 0.6% of non-Hodgkin lymphoma cases in the United States are SMZL<sup>6</sup>.

Here, we present what is, to our knowledge, the first reported case of concomitantly diagnosed locally advanced rectal adenocarcinoma and SMZL, and the novel combinatorial use of rituximab (a CD20 antibody) and 5-fluorouracil [5FU (a thymidylate synthase inhibitor)] with pelvic external-beam radiation as a neoadjuvant treatment strategy for this unique situation.

## CASE DESCRIPTION

A 57-year-old white woman with no pertinent medical and family history presented to her primary care physician with a 1-month history of right-sided abdominal pain. Physical examination revealed a markedly enlarged, firm, non-tender spleen extending to the pelvis. Computed tomography imaging demonstrated marked splenomegaly, with a small ovoid density in the splenic hilum representing either a lymph node or an accessory spleen [Figure 1(A,B)]. Laboratory tests revealed hypochromic and microcytic anemia, leucopenia, abundant teardrop cells, and anisocytosis. Further evaluation was recommended, but the patient elected to delay additional work-up.

The patient returned, 4 months later, to an outside gastroenterology clinic with hematochezia and constipation. Upon rectal examination, a mass was palpated 1 cm above the anorectal ring. Colonoscopy revealed an ulcerated,

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fungating, circumferential 5-cm mass, which proved to be moderately differentiated invasive rectal adenocarcinoma. Endoscopic ultrasonography revealed the mass to be T3N1 with one suspicious lymph node. In the absence of distant metastases, the rectal cancer was designated stage IIIb.

At presentation to our institution, the woman noted recent onset of low-grade fever, night sweats, increasing fatigue, and a gradual 15-pound weight loss. An evaluation for a potential lymphoma was initiated. Peripheral blood smear revealed severely hypochromic microcytic anemia, with moderate anisopoikilocytosis, decreased reticulocyte response, moderate lymphopenia, and severe monocytopenia. Cortical bone and normal bony trabeculae showed small lymphocytes with eccentrically located and slightly irregular nuclei. Flow cytometry showed that the cells were CD10-, CD23-, and CD5-negative; weakly positive for FMC7; CD19- and CD20-positive; and CD62- and kappa-negative. Left posterior iliac crest biopsy exhibited hypercellular bone marrow with non-Hodgkin lymphoma involvement, consistent with marginal zone lymphoma. Those findings led to a classification of stage IV SMZL<sup>7</sup>.

To ultimately allow for simultaneous surgical management of both malignancies, a modified multidisciplinary treatment strategy was devised. Initially, the patient received neoadjuvant 5FU and rituximab plus pelvic radiotherapy; surgical resection of spleen and rectum followed; and treatment concluded with colorectal cancer-targeted systemic adjuvant chemotherapy.

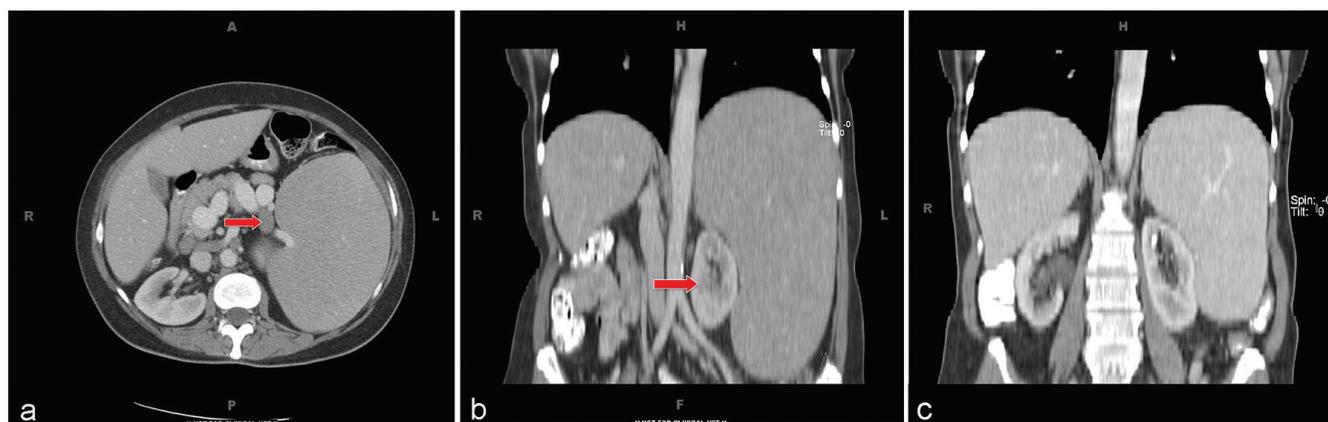
For the rectal adenocarcinoma, the patient received a continuous intravenous infusion of 5FU at 300 mg/m<sup>2</sup> daily, together with 28 equal fractions of pelvic radiation for a total dose of 50.52 Gy. An intensity-modulated distribution using 6-MV photons was applied to spare small intestine, bladder, and bone marrow. For SMZL, the patient concomitantly received rituximab chemotherapy (375 mg/m<sup>2</sup> once each week for 6 weeks) and weekly intravenous iron replacement.

The patient completed her personalized neoadjuvant therapy regimen as planned, suffering only a mild initial infusion reaction to rituximab and moist desquamation of the perianal area because of the radiotherapy.

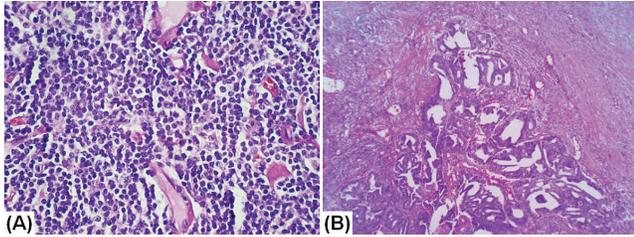
After the neoadjuvant therapy, re-staging computed tomography imaging showed stable asymmetric rectal thickening, with perirectal and presacral stranding and with no evidence of distant metastasis. The spleen remained slightly enlarged, but greatly decreased in size (to 6.05×10.26×18.37 cm from 10.0×16.0×28.0 cm). A 0.9-cm reduction in the size of the perisplenic hilar lesion was also evident [Figure 1(C)]. Flexible sigmoidoscopy showed a 5-cm circumferential, ulcerated, strictured area, with the lower edge approximately 1 cm above the anorectal ring and with reduced tumour bulk. The patient reported an improved energy level, fewer night sweats, less fatigue, and resolution of her rectal pain and constipation. Laboratory data indicated persistent leucopenia, but an otherwise normal blood count. Serum carcinoembryonic antigen remained negligible.

At 10 weeks after completion of neoadjuvant therapy, the patient underwent surgical exploration. At the time of operation, her spleen was slightly enlarged, with lymphadenopathy in the splenic hilum and intimate involvement of the distal tail of the pancreas. Her rectal cancer was noted to be just above the sphincter complex, but a plane could not be developed between the tumour and the posterior vaginal wall. Ultimately, the patient underwent splenectomy, distal pancreatectomy, low anterior resection, and *en bloc* partial posterior vaginectomy with primary repair, rectal mucosectomy, colonic J-pouch, and hand-sewn coloanal anastomosis with diverting loop ileostomy.

The final pathology report revealed that the lymph nodes of the splenic hilum harboured some residual marginal zone lymphoma [Figure 2(A)]. Those cells were positive for CD79a, Bcl2, and CD20; neoplastic cells were negative for CD3 and CD5. With limited sectioning, lymphoma was



**FIGURE 1** Computed tomography images obtained before and after neoadjuvant therapy. (A) Before therapy, a 2.2×1.7 cm ovoid density, thought to be a lymph node or accessory spleen, was identified at the splenic hilum (arrow). (B) A coronal view of the same feature shows a massively enlarged spleen extending from the diaphragm to the pelvic brim, measuring more than 16 cm in the anterior–posterior direction, 10 cm transversely, and 28 cm in length. The splenomegaly caused medial displacement of the left kidney (arrow). (C) After neoadjuvant therapy, imaging demonstrated a significant reduction in the size of the spleen (10.26×6.05 cm).



**FIGURE 2** Postoperative pathology findings. (A) A splenic hilar lymph node is seen to be involved by marginal zone lymphoma. A monomorphic population of lymphocytes, with clumped chromatin and scant-to-moderate pale eosinophilic cytoplasm, are noted. Hematoxylin and eosin stain, 400 $\times$  original magnification. (B) The primary rectal adenocarcinoma shows moderate differentiation, with dirty necrosis, dysplastic rectal epithelium, and cribriform structures. Note the fibrotic background in the upper half, which indicating tumour regression. Hematoxylin and eosin stain, 50 $\times$  original magnification.

not detected in the enlarged spleen, and it was presumed that the patient experienced a complete or near-complete response to treatment. The rectal specimen contained a residual 3.0 $\times$ 2.2 $\times$ 1.0-cm invasive adenocarcinoma with invasion into perirectal fat [Figure 2(B)]. Ulceration with acute and chronic inflammation and granulation was present, consistent with a previous-therapy effect, with a tumour response grade 4 (Mandard classification system)<sup>8</sup>. Distal, proximal, and radial margins were free of tumour, and 6 lymph nodes were negative for cancer (ypT3N0). The patient's postoperative recovery was uneventful.

Adjuvant FOLFOX chemotherapy began at an outside institution 1 month after surgery. The patient completed 5 of the 8 cycles of treatment that had initially been planned, but experienced oxaliplatin-associated neuropathy. An additional cycle of chemotherapy was administered without oxaliplatin, after which the patient declined further therapy.

The patient underwent ileostomy reversal 10 weeks after completion of adjuvant chemotherapy and, per the U.S. National Comprehensive Cancer Network guidelines, has undergone combined surveillance for both her lymphoma and her rectal cancer<sup>9,10</sup>. The patient has now been disease-free, without signs of progression for 7 years.

## DISCUSSION

Splenic marginal zone lymphoma is rare, and its synchronous occurrence with rectal adenocarcinoma is even rarer. Notably, 1 case of simultaneous stage I colon adenocarcinoma and marginal zone lymphoma has been reported. However, the patient in that report was treated by surgical resection of the colon alone and did not receive any further treatment for lymphoma<sup>11</sup>. It has been postulated that lymphoma might predispose the colon to adenocarcinoma because of altered immune function, allowing for cancerous cells to grow without surveillance. Cornes and others<sup>12-14</sup> observed that, in coexisting tumours, adenocarcinomas occur either synchronously with or after a diagnosis of lymphoma in the intestinal tract, suggesting an association between those two cancer types. Nonetheless, the rarity

of such cases prevents any firm establishment of a relationship between lymphomas and adenocarcinomas<sup>11,15</sup>.

Historically, splenectomy was considered the "gold standard" treatment for symptomatic SMZL. However, symptomatic patients are currently treated primarily with rituximab alone or in combination with chemotherapy, with or without splenectomy, depending on symptom severity<sup>16</sup>. Post-splenectomy progression-free survival rates at 4-5 years are approximately 58%-80%, with a 5-year overall survival of 72%-88%<sup>16-22</sup>. Single-agent rituximab therapy was recently found to result in an overall response rate of 88%-100%, with a progression-free survival rate at 4-5 years of 60%-73%, and a 5-year overall survival rate of 81%-92%<sup>16,17,21,23,24</sup>.

The treatment of locally advanced rectal cancer has evolved. Neoadjuvant chemoradiation—such as preoperative infusional 5FU and radiotherapy, capecitabine and radiotherapy, or 5FU-leucovorin and radiotherapy—is the preferred standard-of-care approach<sup>9</sup>. Pathologic complete response rates for standard regimens of neoadjuvant chemoradiation fall in the 8%-26% range<sup>25-28</sup>. Patients with T3/4 or node-positive disease who underwent preoperative chemoradiation had a 5-year overall survival of approximately 76%<sup>27</sup>.

The combined use of rituximab and 5FU is unusual, but adding rituximab to other chemotherapeutic agents is thought not to increase toxicity, other than exacerbating neutropenia<sup>29,30</sup>. Two previous reports of simultaneous rituximab and 5FU administration have been published; however, our report is the first to show utilization of that treatment in combination with radiation and in a neoadjuvant setting<sup>31,32</sup>. Given that 5FU has been successfully used in the past for aggressive treatment regimens such as F-MACHOP (5FU, methotrexate with leucovorin rescue, cytarabine, cyclophosphamide, doxorubicin, vincristine, prednisone), it might be speculated that 5FU could potentially have contributed to the SMZL response<sup>33-37</sup>. However, no direct correlation between single-agent 5FU therapy and response in non-Hodgkin lymphoma has been reported.

Our treatment approach was influenced by the stages of the rectal cancer (III) and the SMZL (IV), the distal location of the solid tumour (that is, the desire for sphincter preservation), and the anticipated need for surgical resection of both the rectum and spleen. For our patient, our treatment strategy was successful because a measurable clinical response and symptom relief were achieved at both sites with minimal toxicity; because tumour responses facilitated complete surgical resection at both sites, together with successful sphincter preservation; and most importantly, because long-term disease-free survival was achieved.

## SUMMARY

Rituximab and 5FU were safely and effectively used in combination with radiation therapy as part of a neoadjuvant strategy for concurrent SMZL and rectal adenocarcinoma. That approach could potentially be applied to other synchronously diagnosed lymphomas and adenocarcinomas.

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Written informed consent was obtained from the patient for publication of this case report and any accompanying images. As a participant in Moffitt's Total Cancer Care Protocol, the patient also provided written informed consent for use of personal medical data for research purposes. The protocol is a minimal-risk centralized clinical data and tissue repository. Specifically, as part of consent to participate, patients agree to the use of their clinical data for research purposes by Moffitt research and medical staff. Supplementing the requirements set forth in the Total Cancer Care Protocol consent form, the senior author discussed the case study manuscript with the patient, who subsequently provided voluntary verbal consent and encouragement for its publication.

#### CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare that we have none.

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