Clinical Case Report

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Colorectal follicular lymphoma

A case report

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Abstract

Rationale: Considering the low incidence of colorectal follicular lymphoma (FL) and its clinical features in endoscopic views, only a few studies have described the pathological diagnosis and treatment of this disease. This study aimed to reveal the overall process of clinical diagnosis and treatment of colorectal FL by conducting a case review.

Patient concerns: A 27-year-old female presented to our department because of "severe bloody stool" lasting for more than 1 month. Her primary symptom was melena. Colonoscopy revealed widespread flat polyps with various immunophenotypes (CD10+, BCL2+, BCL6+, cyclin D1-, CD5-) in the colorectal area.

Diagnosis: In accordance with manifestations on positron emission tomography–computed tomography (PET/CT), the patient was diagnosed with stage IV colorectal FL.

Interventions: PET/CT reexamination after 2 courses of rituximab, cyclophosphamide, liposomal doxorubicin, vincristine sulfate, and hydroprednisone (R-CHOP) regimen and 3 courses of R-CHOP plus etoposide regimen for chemotherapy indicated a significant reduction in tumor burden. Subsequently, rituximab was administered alone in 2 treatment courses.

Outcomes: Lesions on PET/CT disappeared after reexamination. No recurrence was observed within the 12-month follow-up period.

Lessons: Colorectal FL is a rare disease with an inert clinical course and is common in the ileocecal area. Endoscopic views show multiple polyps. Interventional treatment is usually provided after observation of clinical symptoms or during disease progression. The disease has a relatively good prognosis.

Abbreviations: FL = follicular lymphoma, IFL = intestinal follicular lymphoma, MALT = mucosa-associated lymphoid tissue, MCL = mantle cell lymphoma, MLP = multiple lymphomatous polyposis, PET/CT = positron emission tomography–computed tomography, R-CHOP = rituximab, cyclophosphamide, liposomal doxorubicin, vincristine sulfate, and hydroprednisone.

Keywords: colonoscope, colorectal, diagnosis, follicular lymphoma, treatment

1. Introduction

Follicular lymphoma (FL), a common subtype of non-Hodgkin lymphoma, is a malignant tumor that originates from germinal center cells.[1] Primary FLs are mostly detected in the lymph nodes; although relatively rare, they can appear in the gastrointestinal tract, thyroid gland, salivary glands, and skin,[2] with the gastrointestinal tract being the most common site for extranodal lymphoma. Approximately 40% of FLs occur outside the lymph nodes,[3] and among these FLs, mucosa-associated lymphoid tissue (MALT) lymphoma, extranodal marginal zone lymphoma, and diffuse large B-cell lymphoma are the 3 most common subtypes.[2]

Many studies have reported that intestinal follicular lymphoma (IFL) constitutes only less than 1% of the total number of cases of gastrointestinal lymphomas in China, which is considerably lower than the incidence of IFL in Europe and the United States.[4] Owing to the low incidence of IFL, its diagnosis, treatment, and prognosis remain unclear. There are a limited number of national reports, and systematic studies with special endoscopic findings are lacking. We reported a case of colorectal FL with melena as the first symptom and summarized its clinical features, pathological type, and prognosis. This study aimed to reveal the overall process of clinical diagnosis and treatment of FL by conducting a case review.

2. Methods

2.1. Clinical information

A 27-year-old female presented to our department on May 9, 2016, because of "severe bloody stool" lasting for more than 1 month. The patient showed no obvious cause of melena at 1 month prior and passed bloody stools 1 to 2 times a day, weighing approximately 50 to 100 g each time. Aside from this, she did not present with abdominal pain, fever, stress, or other unusual symptoms and had an unknown drug history. The

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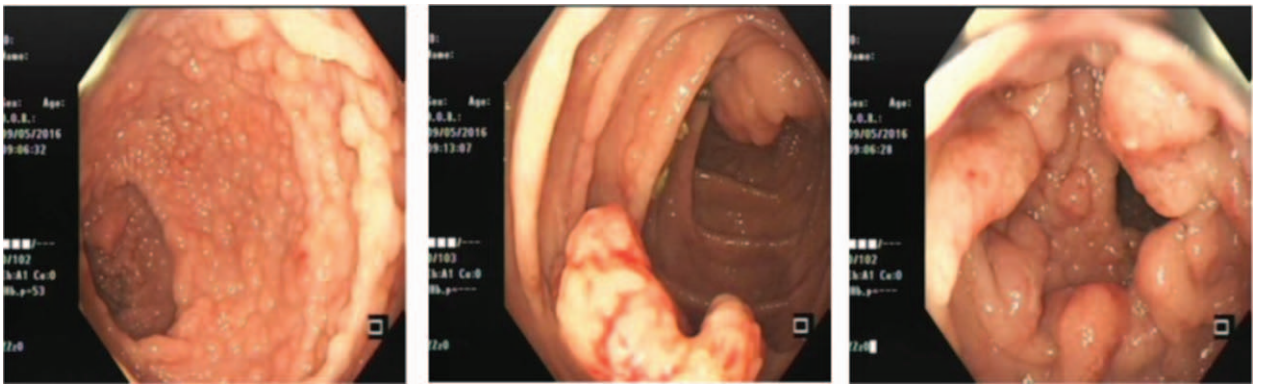

Figure 1. Colonoscopic image showing multiple confluent polypoid lesions in the colon and rectum.

patient's stool repeatedly appeared bloody upon her arrival at our department. She was psychologically normal at onset with normal urine findings but had a poor diet. According to her past medical history, she had no history of surgery, blood transfusion, drug allergy, and toxic exposure. During hospitalization, the patient was determined to have mild anemia and incomplete superficial lymphadenopathy. Findings from physical examination indicated a normal skull size, normal toes, uniform hair distribution, soft abdomen with bowel sounds at a rate of 7 times/min, non-enlarged liver and spleen, and absence of cardiac and pulmonary abnormalities, tenderness, palpable abdominal mass, voice hoarseness, or edema in both lower extremities. Written informed consent was obtained from the patient for the publication of this case report and accompanying images.

Investigation upon admission revealed a weak positive finding on routine fecal occult blood test. Blood cell analysis showed the following results: white blood cell count, 3.65×10^9/L; hemoglobin level, 92 g/L; mean corpuscular volume, 72.9 fL; and mean corpuscular hemoglobin level, 22.4 pg. Test results for hepatitis virus, antinuclear antibody spectrum, anti-neutrophil cytoplasmic antibodies, and immunoglobulins (complete set) were negative. Colonoscopy (Fig. 1) of the rectum, sigmoid colon, descending colon, transverse colon, and ascending colon revealed diffuse polyps of various sizes in the entire intestinal section, changes in the cobblestone-like mucosa; and the presence of flaky hyperplasia with nodular surface in a segment of the ascending colon, which occupied approximately one-third of the intestine. Ileocecal flap deformation and diffuse nodular hyperplasia were observed in the cecum. There was congestive edema at the opening of the appendix. The terminal ileum had diffuse polypoid hyperplasia, which varied in size. Conventional duodenal gastroscopy (including HP) revealed multiple A1 duodenal ulcers, level 1 esophagitis, and chronic non-atrophic gastritis. Full abdominal female computed tomography spiral scan + enhanced (256 rows) (Fig. 2) showed ascending colon wall thickening. Local intestinal lumen narrowing was observed. Colon tissue was used for the examination of flaky hyperplasia in the ascending colon.

Pathological examination showed diffuse FL in the ascending colon (follicular area, 25–75%) at the A1–2 level (Fig. 3). Immunohistochemical staining results were as follows: CK (−), CD3 (−), CD20 (+), PAX-5 (+), CD45RO (−), BCL2 (+), CD21 (+), CD23 (+), Ki67 (10%), CD34 (vascular +), CD10 (+), BCL6 (+), and cyclin D1 (−). Positron emission tomography–computed tomography (PET/CT) showed the following:

1. Hypermetabolic soft tissue mass with rectal wall thickening (a sign of lymphoma), in the ascending colon and colonic and splenic areas accompanied by metabolic increase and sigmoid colon thickening, which was considered to be malignant (mostly lymphoma).

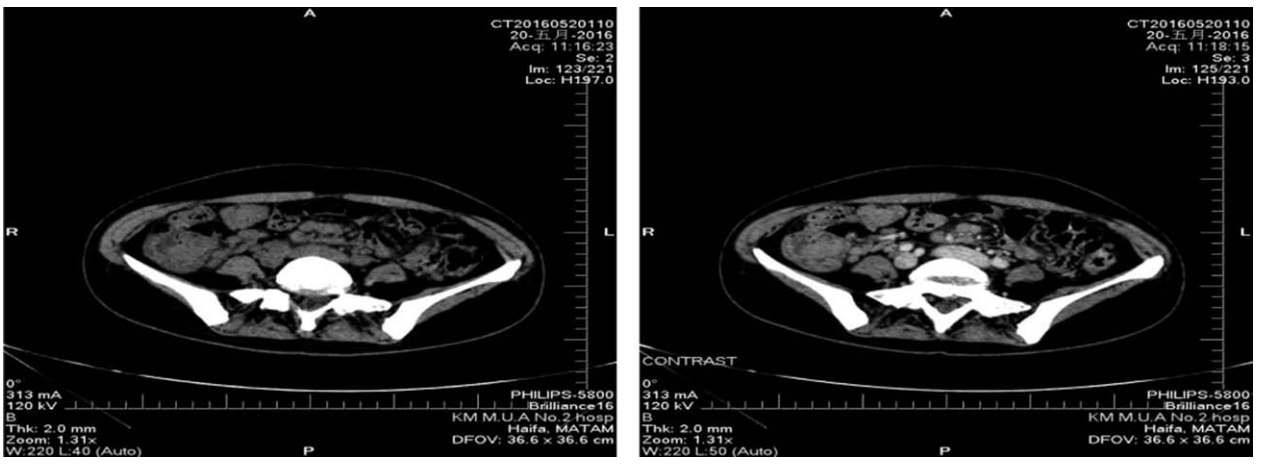

Figure 2. Computed tomography scan showing ascending colon wall thickening and intestinal lumen narrowing.

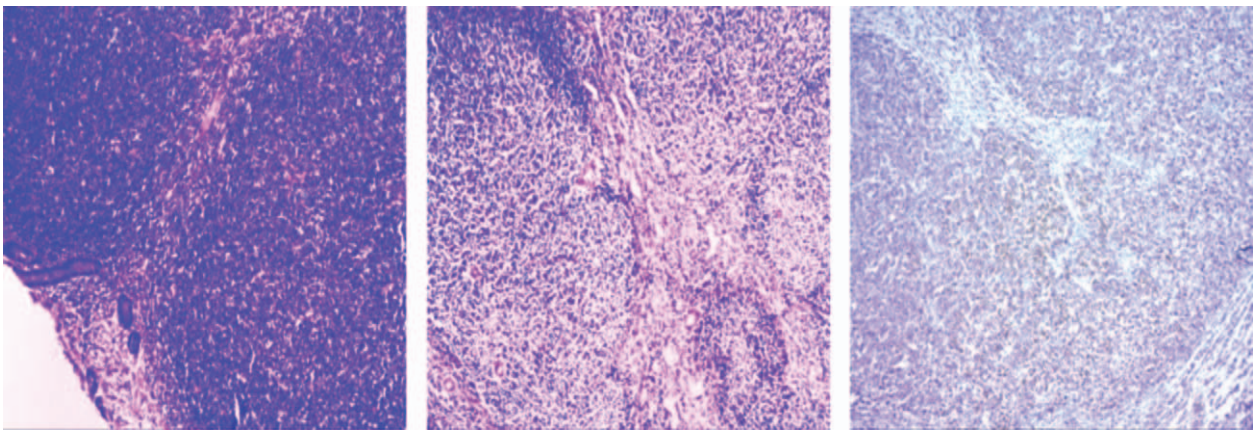

Figure 3. Histologic findings for gastrointestinal FL with multiple polypoid lesions in a 27-year-old woman with colorectal FL. Immunohistochemical staining for CD10, BCL2, and BCL6 yielded positive results. FL = follicular lymphoma.

2. Lymphadenopathy in the bilateral neck; under the jaw, buccal, and left and right collarbone areas; in the retroperitoneal and mesangial areas; and in the bilateral pelvis with metabolic increase, which was considered to be lymphoma.
3. Pelvic peritoneal nodular thickening with metabolic increase, which was considered to be infiltration.
4. Metabolic increase with bilateral tonsil enlargement.
5. Mild metabolic increase with an increase in splenic size and a decrease in metabolism compared with previous metabolism.
6. Increased density of the longitudinal strips of the film with mild metabolic increase, which was considered to be thymic insufficiency (Fig. 4).

2.2. Diagnosis

The patient was diagnosed with stage IV colorectal FL based on the suggestion of the National Comprehensive Cancer Network guidelines for class 1.[5]

2.3. Treatment

Rituximab, cyclophosphamide, liposomal doxorubicin, vincristine sulfate, and hydroprednisone (R-CHOP) regimen for chemotherapy was used. Simultaneously, an antiemetic, which alkalinized the urine, and potassium for liver protection were administered, strengthened nutritional support was initiated, and anti-tumor and symptomatic supportive treatments were provided, which were reviewed after 2 courses. Abdominal B-ultrasonographic reexamination revealed multiple lymph nodes in the bilateral neck and axillary and inguinal regions; however, the cutaneous and medullary decomposition of a single lymph node in the left inguinal region was not clear. Considering that the treatment efficacy was not ideal, R-CHOP plus etoposide (R-CHOP-E) regimen for chemotherapy was used in the next 3 treatment courses.[5] After post-treatment review, PET-CT showed significantly lower tumor burden. Rituximab maintenance therapy was provided in 2 treatment courses for the low granulocyte counts. Following post-treatment review, PET/CT showed the following:

1. Disappearance of colonic lesions in the rectum, metabolic increase with systemic lymphadenopathy, and disappearance of metabolic lesions with thickening of the original peritoneal nodules in the pelvic floor (tumor activity inhibition after chemotherapy for lymphoma was considered).
2. Original bilateral tonsil enlargement with metabolic increase and no abnormality.

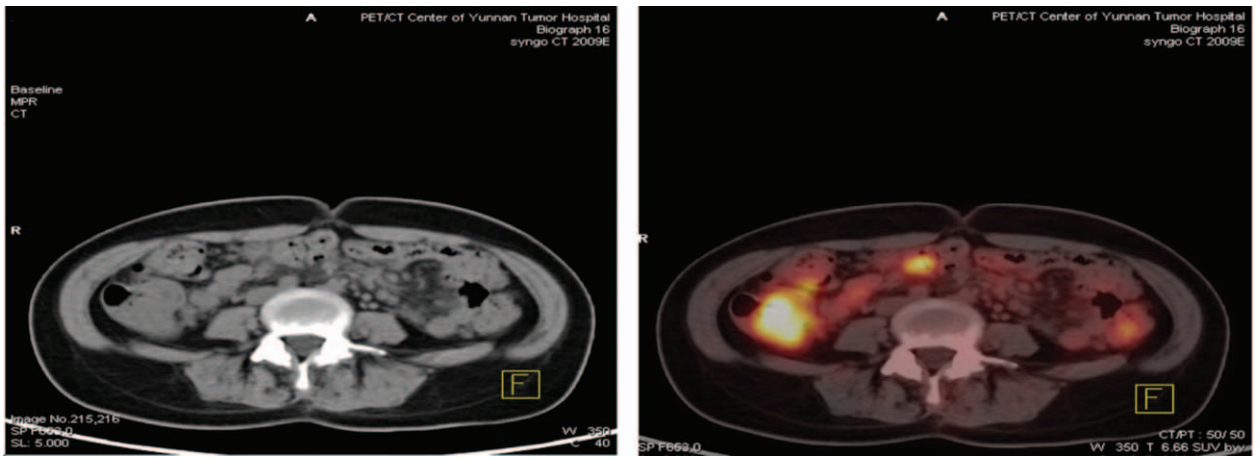

Figure 4. Positron emission tomography–computed tomography images showing wall thickening with cleaning-and-retention enema in the rectum prior to treatment.

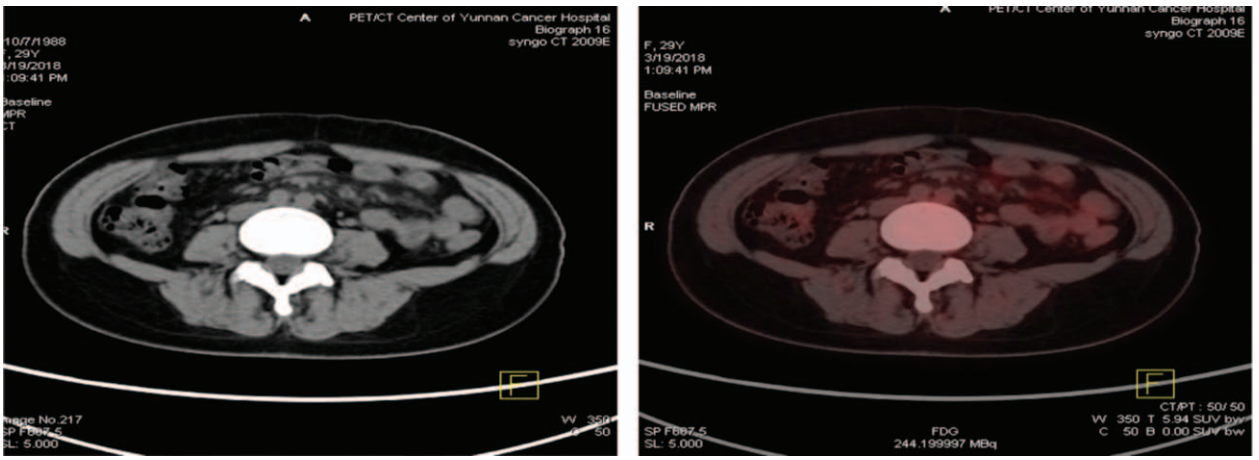

Figure 5. Positron emission tomography–computed tomography images showing that the local foci disappeared in the rectum and colon after treatment.

3. Increased splenic size and decreased metabolism compared with previous metabolism.
4. Increased density of the front longitudinal strips with decreased metabolism compared with previous metabolism, which was considered to be thymic insufficiency (Fig. 5).

The patient was treated with immunotherapy, which significantly reduced the number of tumors and stabilized her condition. However, granulocyte counts remained low. Readministration of rituximab as maintenance monoclonal antibody therapy and of interleukin 2 (IL-2) for immunoregulation and organ protection was helpful. The treatment for the patient included broad-spectrum anti-tumor agents and nutritional support, among others. The patient was subsequently treated with interim IL-2 immunoregulation in 2 courses. The treatment was completed; the patient was discharged from the hospital in August 2017 and survived after 1 year of follow-up.

3. Discussion

FLs arise from the germinal center of B cells and manifest morphologically as tumors with a follicular growth pattern. In addition, FLs, which are a common subtype of non-Hodgkin lymphoma, include malignant lymphoproliferative diseases that involve the follicular center cells (small cleaved cells) and mother cells (large non-cleaved cells).[1] FL mostly occur in the lymph nodes, although its progression often involves sites other than the lymph nodes. Primary FLs are relatively rare outside the lymph nodes, with 1% to 38% of all FLs appearing on the skin, salivary glands, accessory glands of the eyes, reproductive system, and intestinal parts.[6]

IFLs account for only 1.0% to 3.6% of cases, and the duodenum is the most common site of occurrence, with IFLs occurring rarely in the colorectal area.[7–9] In the study of Takata et al, FLs occurred in the duodenum, jejunum, and ileum in 111 (89%), 50 (40%), and 28 (22%) cases, respectively, and only 1% to 2% of FLs were detected in the colorectal area.[3] In contrast to FLs in the primary lymph node, tumor cells in IFLs express a mucosal homing receptor, α4β7 integrin, and are visible as a set of B cells originating from local antigen stimulation.[10] IFLs are a group of rare diseases, and their clinical course is usually inert. Multiple polyps are observed on endoscopy. Biopsy is required, and diagnosis is further confirmed by immunohistochemical analysis. Some reports have described that IFLs are more common in female patients.[9,11,12] However, some studies have shown no difference in its incidence between men and women.[13]

3.1. Clinical manifestations and characteristics of IFLs

The common clinical manifestations of IFLs in patients include abdominal pain, diarrhea, obstruction, weight loss, and, rarely, melena. Protein-losing bowel disease, poor intestinal absorption, celiac ascites, or perforation results in an acute abdomen. IFLs are similar to other intestinal malignancies in that their initial clinical manifestations are always related to the affected area. Abdominal pain is common with small bowel lesions, whereas bloody stools are mainly observed with colonic and rectal lesions. Polyps can be detected throughout the digestive tract from the esophagus to the rectum and are more common in the ileocecum. However, total digestive tract involvement is rare.[14] Multiple body metastases can occur. This suggests that bloody stool in young women may be a manifestation of this disease, which can be detected by colonoscopy.

3.2. Endoscopic and immunohistochemistry findings and histological features of IFLs

In patients with IFL, endoscopic polyps with diameters ranging from 2 mm to several centimeters can be observed protruding from the mucosal surface, with or without pedicles. Multiple polyps may be involved in single or multiple intestinal segments.

Wide-based polyps appear grayish white on the surface, and bleeding and necrosis are relatively uncommon. They consist of central cells and centroblasts, and their pathological manifestations include tumor-free follicular borders and lack of nesting, with CD10+, BCL2+, and BCL6+, cyclin D1−, CD5−, and CD23− immunophenotypes.[1]

3.3. Diagnostic criteria and differential diagnosis

3.3.1. Diagnostic criteria. A diagnosis of IFL is mainly based on clinical or imaging findings. Immunohistochemical and histopathological examinations are also required. When necessary, flow cytometry and cytogenetics results should be referred to.

The diagnostic criteria are as follows[1]:

1. Patients mainly exhibit intestinal symptoms, and lesions are usually intestinal, which can be observed through clinical and imaging studies.

2. Pathological diagnosis is consistent with FL morphology and immunophenotype.
3. Cases of secondary intestinal involvement are excluded.

3.3.2. Differential diagnosis. FL, MALT lymphoma, and mantle cell lymphoma (MCL) are universally recognized as multiple lymphomatous polyposis (MLP). Kodama et al[15] showed that most patients with MLP were positive for CD20 and BCL2. However, the histomorphology of MCL and MALT lymphoma is difficult to distinguish from that of FL. MCL has a relatively poor prognosis and requires a stronger first-line high-dose chemotherapy regimen. Therefore, it is necessary to establish a clear diagnosis.[12] Most cases cannot be identified by endoscopy alone; thus, there is a need to rely on pathological examination, immunohistochemistry, and molecular genetic analysis for identification. As indicated by its survival rate, MCL has the worst prognosis, with a 5-year survival rate of 11%; in comparison, FL has an intermediate survival rate, whereas the prognosis for MALT lymphoma is relatively good.[16,17]

MCL is difficult to distinguish from FL. MCL includes cyclin D1+, CD5+, and CD10−, whereas FL includes CD10+ and cyclin D1−; CD5 aids in differentiating the 2 diseases. There may be false negatives.

Morphologically, FL usually presents as a large number of neoplastic follicular hyperplasias with an unclear follicular area. Lymphoepithelial lesions and the "starry sky" appearance in the germinal centers are rare. MALT lymphoma can appear similar to the follicular hyperplasia in FL. However, the lymphoepithelial lesions in MALT lymphoma are usually clearer. In addition, mononuclear B cells and plasma cells can be observed, and MALT lymphoma does not express CD10.

Proliferative lymphoid lesions in the intestine are morphologically easy to confuse with FL. However, lymphoid follicles do not express BCL2, and this aids in identifying FL.[4]

IFL and MLP need to be differentiated from other diseases, such as adenomatous polyps, familial hereditary polyposis, Peutz–Jeghers syndrome, and B cell chronic lymphocytic leukemia. As identification based on clinical manifestations can be confusing, there is a need to investigate the family history and histological characteristics.

3.4. Treatment and progression

FL is a type of indolent lymphoma. By comprehensively analyzing patients' pathological stage, Ann Arbor stage, and FL International Prognostic Index score, the research group assessed the Groupe d'Etude des Lymphomes Folliculaires criteria for tumor burden and examined the related indicators of safety, efficacy, and increased life expectancy in individual treatments in order to improve patients' quality of life. According to the Chinese guidelines for the diagnosis and treatment of FL,[4] it is currently believed that the use of localized radiotherapy will enable long-term disease-free survival in most patients with stage I–II FL. Therefore, radiotherapy or radiotherapy combined with systemic immunotherapy should be performed as soon as possible. However, for patients with stage I–II FL, the use of radiotherapy in addition to systemic immunotherapy remains controversial. If the risk of adverse reactions to involved-field radiation therapy in patients with FL is estimated to exceed the probability of clinical benefit, it is recommended to wait for observation without administering radiation therapy. For patients with stage III–IV FL who have indications for treatment, immunochemotherapy is the most commonly used treatment modality locally and abroad. The treatment plan consists of 8 courses of rituximab therapy. Combined chemotherapy has become the first-choice treatment for patients with initially treated FL locally and abroad. There is no international consensus on the best first-line options for patients with advanced FL. However, the final analysis results of the recent FOLL05 trial have suggested that the R-CHOP regimen is superior to the rituximab, cyclophosphamide, vincristine, and prednisone regimen or the rituximab, fludarabine, and mitoxantrone regimen, considering the balance of risk and benefits.[1]

Stem cell transplantation can also be employed for patients with stage III–IV FL. However, the therapeutic role of high-dose chemotherapy with autologous stem cell transplantation remains unclear in China. Autologous stem cell transplantation may improve survival in patients with FL. Although some patients have shown initial long-term survival benefits, the high mortality associated with transplantation remains a major problem at present; currently, it is only applicable for a few patients. IFL has a better prognosis than intra-flange FL.[4]

The patient in the present case report was diagnosed with stage IV colorectal FL. After 5 courses of R-CHOP-E regimen, her white blood cell count decreased. Rituximab was administered as a single agent for maintenance therapy, and the patient received IL-2-based immunomodulatory therapy. Two courses of subsequent interim IL-2 immunoregulation were able to promote remission.

Surgical resection is frequently performed as treatment for non-disseminated colorectal lymphoma. The treatment depends on the extent of the lesion. However, surgical removal can completely remove the tumors in only a few cases. Times reported that almost all patients with colorectal lymphoma undergo different forms of surgical resection.[18] Of these patients, 14% to 24% had no regional lymph node invasion (stage I), whereas 62% to 86% had regional lymph node involvement during initial surgical resection from the primary tumor (stage II). Studies have shown that the first-line treatment for resectable rectal lymphomas should be surgical resection owing to the poor prognosis in patients with residual disease. Nonetheless, the lack of complete surgical resection as treatment for primary rectal lymphoma, such as in the case of surgical resection for patients with complications and chemotherapy failure, makes surgical treatment still controversial.

In conclusion, IFL is a relatively rare disease with a usually inert clinical course; most patients present with no early symptoms of discomfort, and it is suddenly detected on routine bowel examinations.[4] With the technological advancement in endoscopy (including double-balloon enteroscopy and capsule endoscopy), the identification rate for IFL has improved. However, distinguishing IFL from other digestive tract tumors and inflammatory diseases owing to its clinical features and obtaining materials to be used for biopsies are difficult. Therefore, in general, IFL is usually staged as an advanced disease upon its diagnosis, with a higher rate of misdiagnoses, which poses a considerable challenge to diagnosis and treatment.

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Author contributions

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Methodology: Mei-Lian Wang, Jiang Chang, Hua Huang, and Ming-Liang Lu.

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