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CASE REPORT

Mucosa-associated lymphoid tissue lymphoma with unusual ^{18}F-FDG hypermetabolism arising at the colorectal anastomosis

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Abstract

Mucosa-associated lymphoid tissue (MALT) lymphoma usually originates from the stomach and presents with low ^{18}F-fluorodeoxyglucose (FDG) avidity with average maximum standard uptake value of 3.6. Colorectal MALT lymphoma is a rare entity that contributes to 1.6% of all MALT lymphomas and < 0.2% of large intestinal malignancies. The case reported herein firstly revealed stage ⅡE MALT lymphoma with unexpected higher ^{18}F-FDG avidity of 18.9 arising at the colorectal anastomosis in a patient with a surgical history for sigmoid adenocarcinoma, which was strongly suspected as local recurrence before histopathological and immunohistochemical examinations. After accurate diagnosis, the patient received four cycles of standard R-CVP regimen (rituximab, cyclophosphamide, vincristine and prednisone), combined target therapy and chemotherapy, instead of radiotherapy recommended by National Comprehensive Cancer Network guidelines. He tolerated the treatment well and reached complete remission.

Key words: Colorectal anastomosis; Mucosa-associated lymphoid tissue lymphoma; Etiopathogenesis; Unusual ^{18}F-FDG hypermetabolism; ^{18}F-FDG-PET/CT imaging; Patient-tailored treatment

Core tip: This case highlighted the possibility of development of metachronous neoplasms at the colorectal anastomosis, especially rare mucosa-associated lymphoid tissue (MALT) lymphoma with unusual ^{18}F-fluorodeoxyglucose (FDG) hypermetabolism. Chromosomal translocation leading to the activation of nuclear factor-κB pathway in proliferative B cells stimulated by pathogens may explain the etiopathogenesis for MALT lymphoma. Despite being indolent, MALT lymphoma can be successfully imaged by ^{18}F-FDG-positron emission tomography (PET)/computed tomography (CT), and shows great ^{18}F-FDG avidity. This indicates that PET/CT can be added to the workup of MALT lymphoma. Considering that MALT lymphoma originates from many organs, patient-tailored treatment including radiotherapy, chemotherapy and immunotherapy is necessary.

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INTRODUCTION

In 1983, Isaacson and Wright first described extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT), most of which occurred in the stomach (> 50%) followed by parotid and salivary glands, skin, conjunctiva, head and neck, lung, thyroid and breast[1,2]. By contrast, colorectal MALT lymphoma only contributes to 1.6% of all MALT lymphomas[3], and total colorectal lymphomas only account for 0.2% of large intestinal malignancies, with an annual incidence of 1.6 per million[4]. These results indicate the low incidence of colorectal MALT lymphoma, as wells as MALT lymphoma arising at the colorectal anastomosis. Here, we report a case of MALT lymphoma with unexpected high ^{18}F-fluorodeoxyglucose (FDG) avidity, arising at the colorectal anastomosis in a patient treated surgically for sigmoid adenocarcinoma. Based on this case, we discuss the possible etiopathogenesis, ^{18}F-FDG-positron emission tomography (PET)/computed tomography (CT) imaging and treatment strategy for colorectal MALT lymphoma.

CASE REPORT

A 75-year-old man underwent radical surgery for sigmoid colon cancer in 2013. During that operation, the sigmoid colon was completely removed and the colorectal anastomosis was stitched at 16 cm cranial to the anal verge. Pathological diagnosis presented moderately differentiated ulcerative sigmoid adenocarcinoma of T3N0M0 stage without any high-risk factors. As a consequence, the patient was released from our hospital, eschewing adjuvant radiochemotherapy. Two years later, the patient was admitted for a 2-mo history of abdominal pain, alternate episodes of diarrhea and constipation, and tenesmus. There were no purulent or bloody stools. The results of laboratory tests including tumor markers, complete blood count and lactate dehydrogenase were normal. Hepatitis B surface antibody and hepatitis B core antibody were positive, which indicated previous infection with hepatitis B virus. Hepatitis C virus (HCV) infection was excluded. Colonoscopy revealed an elevated lesion of approximately 5 cm × 6 cm at the colorectal anastomosis (Figure 1). The lesion with central ulceration was ill defined and irregular in shape. Multiple random biopsies were taken. Given the possibility of anastomotic recurrence, ^{18}F-FDG-PET/CT was performed to assess the metabolism of the lesion and the extent of involvement. The images presented FDG hypermetabolism at the anastomotic site and paracolic lymph nodes, with higher maximum standard uptake value (SUV_{max}) of 18.9 and 6.8, respectively (Figure 2). One week later, histopathological examination of biopsy specimens showed infiltration of morphologically heterogeneous small B cells, including centrocyte-like cells with irregular nuclei and less cytoplasm (Figure 3A). As the hallmark of MALT lymphoma, lymphoepithelial lesions were observed with sheets of small to medium-sized, irregular, neoplastic lymphoid cells effacing the glandular architecture (Figure 3B). The infiltrating cells were immunohistochemically positive for CD20, CD79a, CD43, BCL-2 (Figure 4) and Ki-67, but negative for CD5, CD10 and cyclin D1 (Figure 5). These results supported a final pathological diagnosis of MALT lymphoma. After diagnosis, a urea breath test was performed, which excluded *Helicobacter pylori* (*H. pylori*) infection. Bone marrow infiltration was not detected. According to Ann Arbor staging, the MALT lymphoma was classified as IIE. The patient received four cycles of immunochemotherapy with standard R-CVP regimen (rituximab 700 mg d0,

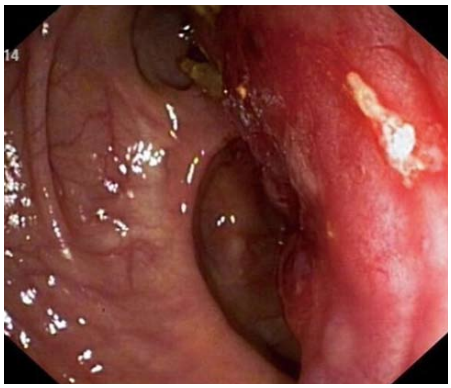

Figure 1 Colonoscopic findings. The colonoscopy revealed an elevated lesion of approximately 5 cm × 6 cm at the colorectal anastomotic site. The lesion with a centric ulceration was ill defined and irregular in shape.

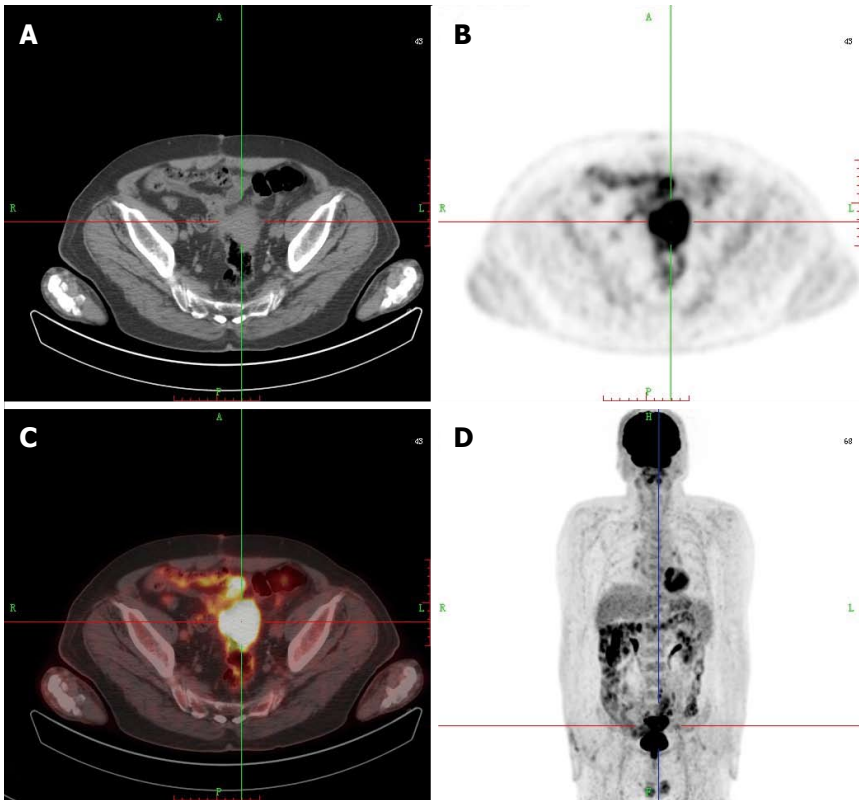

Figure 2 Positron emission tomography/computed tomography findings before treatment. Positron emission tomography/computed tomography showed ^{18}F-fluorodeoxyglucose hypermetabolism at the colorectal anastomotic site and paracolic lymph nodes. The SUV_{max} was 18.9 at the lesion arising at the anastomosis. The SUV_{max} of paracolic lymph nodes was 6.8.

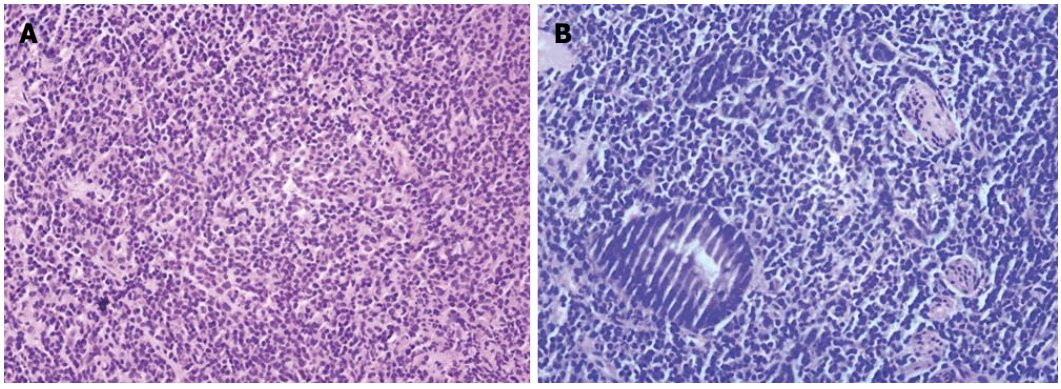

Figure 3 Histopathological findings. A: Biopsy specimens showed infiltration of morphologically heterogeneous small B cells, including centrocyte like cells with irregular nuclei and less cytoplasm. Centroblast-like cells were scattered; B: Lymphoepithelial lesions with sheets of small to medium-sized, irregular, neoplastic lymphoid cells effacing the glandular architecture (A and B: hematoxylin and eosin, × 400).

cyclophosphamide 1.2 g d1, vincristine 2 mg d1 and prednisone 100 mg d1-5, q3w). Treatment was well tolerated. After four cycles of treatment, the patient was asymptomatic and the therapeutic evaluation reached complete remission (Figures 6 and 7).

DISCUSSION

Extranodal marginal zone B-cell lymphoma of MALT is a distinct clinical entity that can originate from a wide variety of organs. The stomach is the most frequent site for MALT lymphoma and has been extensively studied in many aspects, including etiopathogenesis, PET/CT characteristics, and antibiotic treatment of patients with *H. pylori* infection. Due to the rarity of the disease, MALT lymphoma arising at the colorectal anastomosis has not been thoroughly investigated. However, considering its origin, colorectal MALT lymphoma may have its own unique characteristics, which should be discussed in detail.

Etiopathogenesis for anastomotic MALT lymphoma

To adapt to the postoperative changes and promote the incision healing, the colonic anastomosis is

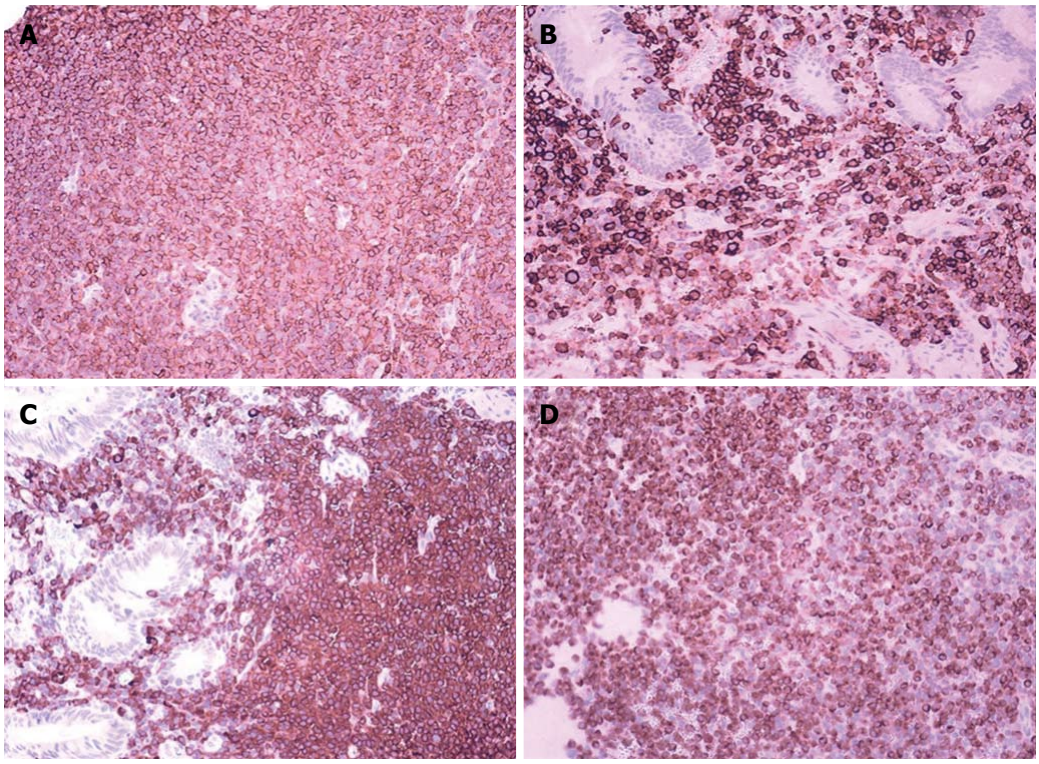

Figure 4 Immunohistochemical findings. The lymphoid infiltrates were positive for CD20 (A), CD43 (B), CD79a (C), and BCL-2 (D) (× 400).

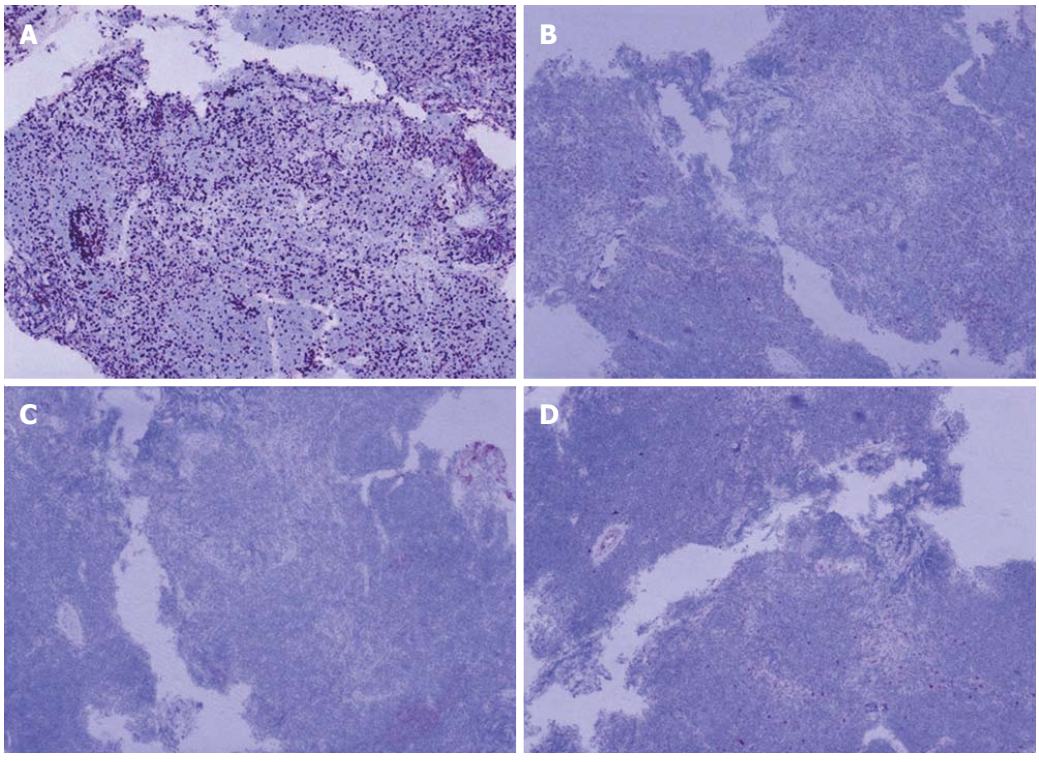

Figure 5 Immunohistochemical findings. The lymphoid infiltrates were positive for Ki-67 antigen (labeling index was 30%) (A), but negative for CD5 (B), CD10 (C), and CyclinD1 (D) (× 200).

capable of proliferative instability and enhanced immunologic reaction to antigen, which makes it as a potentially fertile field for lymphomagenesis. While, persistent pathogen infection, such as *H. pylori*, *B. burgdorferi*, *C. jejuni*, *C. psittaci* and HCV, that triggers a chronic antigenic stimulus harboring dense clonal B-cell proliferation is the formal initiation of MALT lymphomagenesis[5]. The proliferative B cells

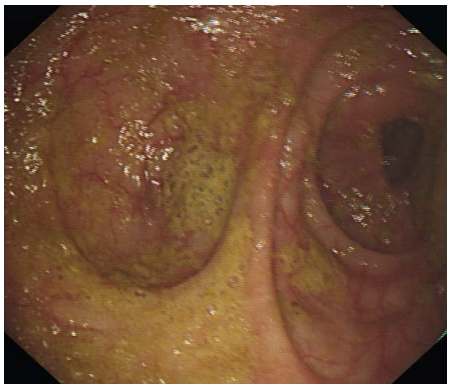

Figure 6 Colonoscopy findings after treatment. Follow-up colonoscopy showed a smooth anastomosis without any mass.

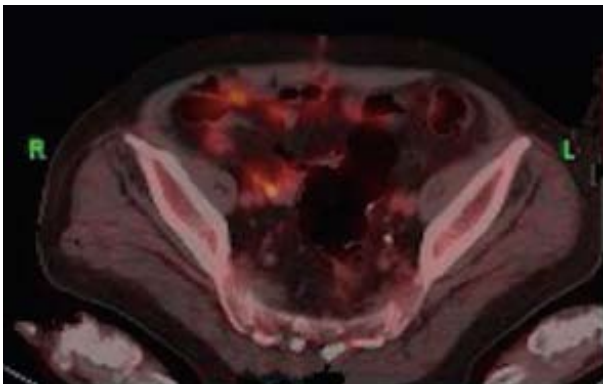

Figure 7 ^{18}F-FDG-positron emission tomography/computed tomography findings after treatment. Follow-up ^{18}F-FDG-positron emission tomography (PET)/computed tomography (CT) showed complete remission of the MALT lymphoma. The elevated lesion at the anastomosis disappeared. No abnormal FDG uptake was observed at the colorectal anastomosis as well as the paracolic lymph nodes.

subsequently undergo MALT lymphomagenesis through a B-cell receptor (BCR)-dependent or BCR-independent NF-κB pathway characterized by chromosomal translocations (Figure 8). In the BCR-dependent NF-κB pathway, antigen-dependent aggregation of BCRs triggers caspase activation and recruitment domain (CARD)11 phosphorylation. The functional CARD11 associates with BCL10 and MALT1 to form an active CBM signalosome, which activates inhibitor of NF-κB kinase (IKK) and subsequently triggers activation of the NF-κB pathway (Figure 9A)[6]. In BCR-independent NF-κB pathways, chromosomal abnormalities facilitated by reactive oxygen species (ROS), play a significant role in the genesis of MALT lymphoma[7]. Occurring in 25%-60% of gastrointestinal MALT lymphomas, chromosomal translocation t(11;18)(q21;q21) is the most common genetic abnormality, leading to the linkage of BIRC3 gene on chromosome 11 and MALT1 gene on chromosome 18[8]. The BIR domain of BIRC3-MALT1 mediates self-oligomerization and activates IKK, which results in NF-κB activation and overexpression of NF-κB target genes, including BCL2[9] (Figure 9B). Translocation t(14;18)(q32;q21) occurring at 14q32 and 18q21 breakpoints involves IgH and MALT1 rearrangements[10]. The overexpressed MALT1 oligomerizes through interaction with BCL10, which promotes proliferation and anti-apoptosis of B cells through activation of the classic NF-κB pathway (Figure 9C)[11]. The t(1;14)(p22;q32) translocation leads to nuclear overexpression of BCL10 protein by relocation the entire coding sequence of the BCL10 gene on chromosome 1 to IgH enhancer region on chromosome 14. The BCL10 containing a CARD can interact with MALT1 to transfer important signals for NF-κB activation, subsequently leading to lymphomagenesis[12] (Figure 9D).

In NCCN guidelines, tests for infectious agents are not required for non-gastric MALT lymphoma. For this reason, we did not detect other potential pathogens in this case, after excluding infection with *H. pylori* and HCV. However, the apoptosis inhibitor BCL2 was highly expressed, which presented a suspicion that the MALT lymphoma might be caused by chromosomal translocation t(11;18)(q21;q21) through BCR-independent NF-κB pathway.

^{18}F-FDG-PET/CT imaging for MALT lymphoma

Due to a partial mucosal immunity linking various organs involved in mucosal immunity, a third of patients present with disseminated MALT lymphoma at diagnosis[13]. Therefore, visual diagnostic imaging of MALT lymphoma is important for staging, determining the optimal therapeutic strategy and evaluating post-treatment response. Although controversy still exists for variable FDG avidity of MALT lymphoma, ^{18}F-FDG-PET/CT has gradually emerged as an important imaging modality for management of MALT lymphoma[14].

Although two early retrospective studies of Hoffmann *et al*[15,16] reported absence of ^{18}F-FDG avidity in total 24 patients with MALT lymphoma, increasing data indicated that imaging with ^{18}F-FDG-PET is useful for lesion detection. In the consensus of the International Conference on Malignant Lymphomas Imaging Working Group, the ^{18}F-FDG avidity of MALT lymphoma varied from 54% to 81% before treatment[17]. Beal *et al*[18] retrospectively reviewed 42 patients with MALT lymphoma and reported that 81% of the lesions demonstrated ^{18}F-FDG avidity with a median SUV_{max} of 5.5. Karam *et al*[19] compared the sensitivity of PET and CT. PET outperformed CT in the depiction of MALT lymphoma with sensitivity of 85% *vs* 57%. Based on the theory that integrating the PET scanner and helical CT provides more sensitive and specific images[20], Carrillo-Cruz *et al*[21] analyzed PET/CT images of 40 patients with marginal zone B-cell lymphoma and found that PET/CT had a significant advantage in detecting more involved lesions through abnormal FDG avidity. The sensitivity of PET/CT was as high as 95.5% for extranodal lesions, while the sensitivity of CT was only 67%. Apart from the

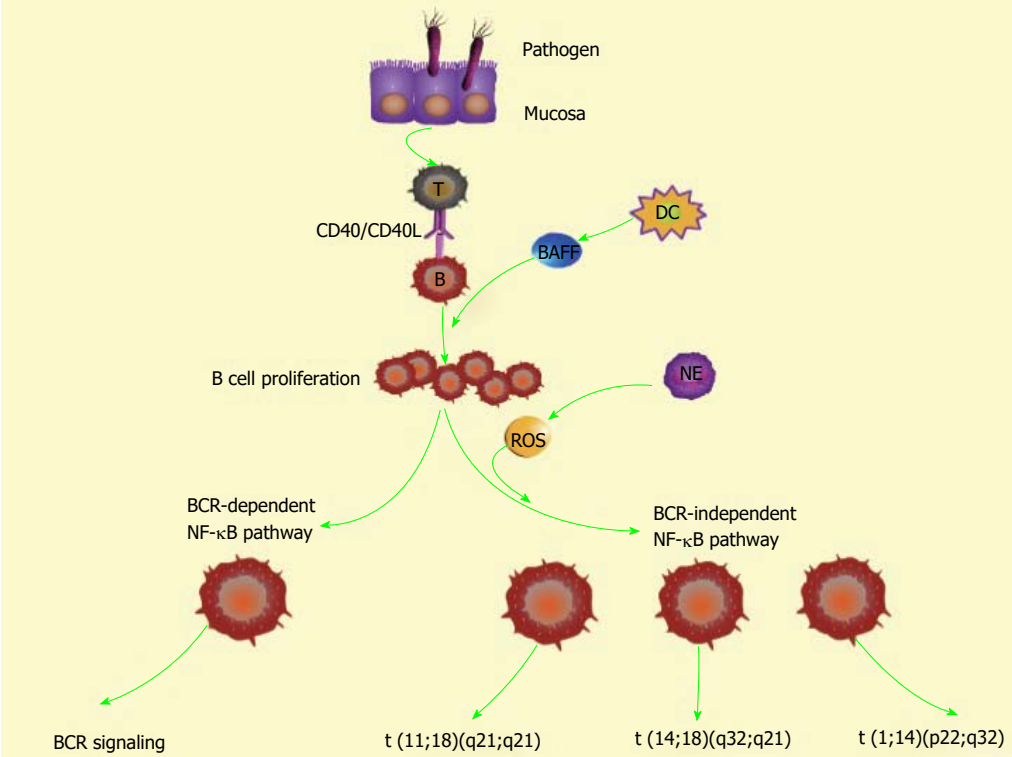

Figure 8 Initiation of mucosa-associated lymphoid tissue lymphomagenesis. Continuous stimulation by pathogens leads to dense proliferation of clonal B cells, with the help of T-cell-dependent co-stimulation *via* CD40-CD40L and overexpression of B-cell-activating factors. The proliferative B cells undergo MALT lymphomagenesis through BCR-dependent NF-κB pathway, or BCR-independent NF-κB pathway characterized by chromosomal translocation.

important roles in discovering lesions and staging, the exceptionally high FDG avidity before treatment can also present suspicion of DLBCL transformation and help to determine the repeat biopsy site[22]. In the retrospective study of Carrillo-Cruz *et al*[21], there was a case of MALT lymphoma showing DLBCL transformation with SUV_{max} as 37. Karam *et al*[19] reported that the mean SUV_{max} was 11.2 in large B-cell transformed MATL lymphoma, while for non-transformed MALT lymphoma, the mean SUV_{max} was 3.7.

^{18}F-FDG / PET is essential for initial staging of MALT lymphoma, while studies have presented that the even more clinically important role is its ability to evaluate response to treatment through FDG avidity changes and direct subsequent clinical decision-making. In the research of Mayerhoefer *et al*[23], it showed that interim ^{18}F-FDG-PET can predict the end-of-treatment outcome after three cycles of rituximab-based therapy in patients with MALT lymphoma. Lesion-based cut-off value for separation of complete remission from other outcomes (*i.e.,* CR *vs* PR + SD) was -11.74% for ΔSUV_{max}, which meant that patients with a SUV_{max} reduction more than 11.74% would have a better prognosis[23]. In the series of Beal *et al*[18], eight patients with MALT lymphoma accepted a PET/CT examination after first-line treatment. Among them, 3 patients attained a complete remission with no focal or diffuse FDG avidity above background in a location incompatible with normal anatomy/physiology, and 2 patients reached a partial response without relapse after 6 and 18 mo. Carrillo-Cruz *et al*[21] evaluated patients' post-treatment response with PET/CT, which revealed 10 of 15 patients had a negative PET/CT. Remarkably, none of them relapsed, and the 3-year OS reached 100%, reflecting a negative predictive value of 100%. Perry *et al*[24] followed up 12 patients with MALT lymphoma using PET/CT [median follow up 21 mo (6-48 mo)]. PET/CT showed subsequent biopsy proven relapse in three patients and disease progression in another patient[24].

In our case, the PET/CT was also successfully used in the management of MALT lymphoma, including lesions detection and response evaluation. Although larger-scale clinical trials are required to further confirm these data, we can conclude that PET/CT is a valuable imaging tool for both staging and response assessment in patients with MALT lymphoma.

Patient-tailored treatment

NCCN guidelines (version 1.2016) recommend involved-site radiotherapy (24-30 Gy) for patients with stage Ⅰ/Ⅱ non-gastric MALT lymphomas. For our case, with specific disadvantages and technical limitations in irradiating the bowel, the radiation regimen may not be suitable and patient-tailored treatment strategy should be made. First of all, the peristalsis of the colon could lead to the movement of irradiated target volume, which results in the incompatibility between the radiation field and the target tumor volume. Second, the small intestine adjacent to the lesion is

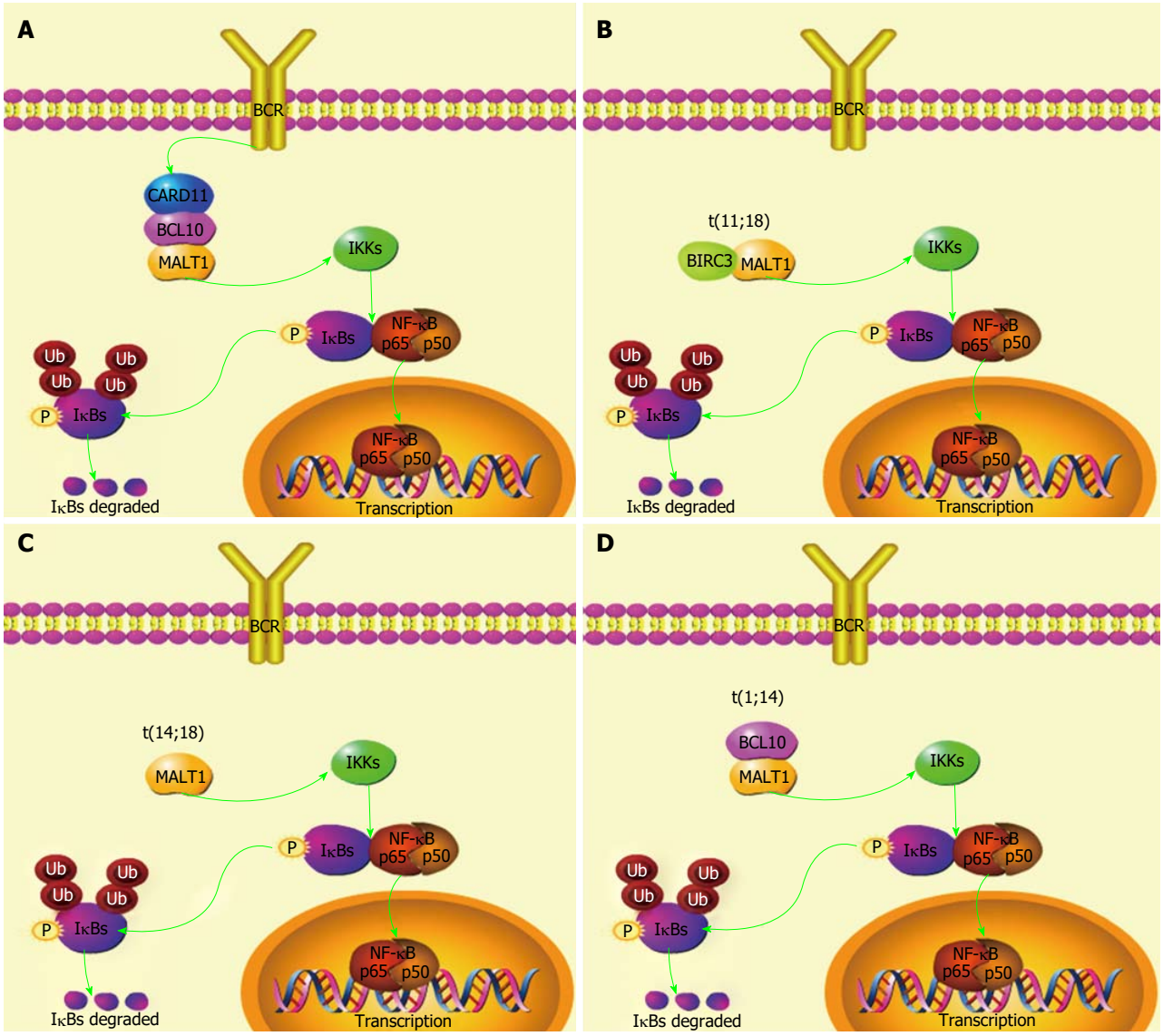

Figure 9 Activation of the NF-κB pathway. A: Antigen-dependent aggregation of the BCR induces CBM signalosome formation. The CBM complex activates IKK, which triggers activation of the NF-κB pathway; B: t(11;18)(q21;q21) causes the linkage of BIRC3 gene on chromosome 11 and MALT1 gene on chromosome 18. The BIR domain of BIRC3–MALT1 mediates self-oligomerization, which activates the NF-κB pathway and overexpression of NF-κB target genes; C: t(14;18)(q32;q21) occurring at 14q32 and 18q21 breakpoints involves IgH and MALT1 rearrangements. MALT1 oligomerizes through interaction with BCL10, which promotes the proliferation and antiapoptosis of B cells through the activation of the classic NF-κB pathway; D: t(1;14)(p22;q32) translocation leads to the nuclear overexpression of BCL10 protein. The BCL10 containing a CARD can interact with MALT1 to transfer signals for NF-κB activation.

easily injured during radiotherapy. Radiation toxicity of the small intestine can be induced even at doses as low as 1-2 Gy[25]. Acute adverse events during or following radiotherapy include pain, bloating, nausea, diarrhea, tenesmus, and intestinal ulcer or perforation, which largely compromise patients' quality of life. Chronic complications mainly manifest as intestinal obstruction and vascular sclerosis[26]. In addition, patients with older age, low body mass index, and previous abdominal or pelvic surgery are at higher risk of small intestinal injury, due to the decreased blood flow to the bowel wall[27]. Taking all these factors into consideration, this patient with older age and previous radical surgery for sigmoid colon cancer was not suitable for radiotherapy. As an alternative, surgical excision may achieve favorable local control for stage Ⅰ/Ⅱ MALT lymphoma located in the lung, colon and small intestine. However, it is more traumatic for an older patient to undergo a second operation. Furthermore, there are often adhesions after the previous surgery and the new lesion located at the anastomosis may be difficult to handle[28]. Recommended by the newest guidelines in ESMO consensus conference, systemic chemotherapy such as a CVP regimen or immunotherapy, or their combination, can be effective for MALT lymphoma in all stages and achieve a better 5-year event-free survival[29,30]. In this specific case, the patient received four cycles of immunochemotherapy with standard R-CVP regimen and reached complete remission. This

indicates that treatment strategy should be tailored to each specific site, considering that MALT lymphoma originates from a wide variety of organs.

The present case highlights the possibility of development of metachronous neoplasms at the colorectal anastomosis, especially rare MALT lymphoma with unusual ^{18}F-FDG hypermetabolism. Chromosomal translocation leading to the activation of the NF-κB pathway in proliferative B cells stimulated by pathogens may explain the etiopathogenesis of MALT lymphoma. Despite being indolent, MALT lymphoma can be successfully imaged by ^{18}F-FDG-PET/CT and show high ^{18}F-FDG avidity, which indicates that PET/CT imaging should be added as an essential examination to the workup of MALT lymphoma. Furthermore, considering that MALT lymphoma originates from a wide variety of organs, patient-tailored treatment strategies, including radiotherapy, chemotherapy and immunotherapy, are necessary.

COMMENTS

Case characteristics

The patient had an elevated lesion with unexpected higher ^{18}F-fluorodeoxyglucose (FDG) avidity of 18.9 arising at the colorectal anastomosis.

Clinical diagnosis

A mass at the colorectal anastomosis.

Differential diagnosis

The differential diagnosis includes local recurrence and other lymphomas, such as mantle cell lymphoma and follicular lymphoma, which can be differentiated by histopathological and immunohistochemical examination.

Laboratory diagnosis

All laboratory values were within normal limits.

Imaging diagnosis

Colonoscopy revealed an elevated lesion of approximately 5 cm × 6 cm in size at the colorectal anastomosis and ^{18}F-FDG-positron emission tomography/computed tomography images presented with FDG hypermetabolism at the anastomotic site and paracolic lymph nodes, with much higher maximum standard uptake value of 18.9 and 6.8, respectively.

Pathological diagnosis

Histopathological and immunohistochemical examination indicated mucosa-associated lymphoid tissue (MALT) lymphoma.

Treatment

The patient received four cycles of immunochemotherapy with standard R-CVP regimen (rituximab 700 mg d0, cyclophosphamide 1.2 g d1, vincristine 2 mg d1 and prednisone 100 mg d1-5, q3w).

Related reports

MALT lymphoma arising at the colorectal anastomosis is rare.

Term explanation

MALT lymphoma is a B-cell malignancy that originates from B lymphocytes that are normally present in the marginal zone of lymphoid follicles that can be found in the mucosal lymphoid tissues.

Experiences and lessons

This case highlighted the possibility of development of metachronous neoplasms at the colorectal anastomosis, especially rare MALT lymphoma with unusual ^{18}F-FDG hypermetabolism.

Peer-review

The authors described an interesting and rare case of colonic MALT lymphoma arising from the anastomotic site after a sigmoidectomy for malignancy.

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