

# Enteral fistula as initial manifestation of primary intestinal lymphoma

Rui-Jie Zhao<sup>1</sup>, Chun-Lan Zhang<sup>2</sup>, Yan Zhang<sup>3</sup>, Xi-Yu Sun<sup>4</sup>, Yue-Hui Ni<sup>5</sup>, Ya-Ping Luo<sup>6</sup>, Ji Li<sup>1</sup>, Jia-Ming Qian<sup>1</sup>

<sup>1</sup>Department of Gastroenterology, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing 100730, China;

<sup>2</sup>Department of Hematology, West China Hospital, Chengdu, Sichuan 610047, China;

<sup>3</sup>Department of Hematology, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing 100730, China;

<sup>4</sup>Department of General Surgery, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing 100730, China;

<sup>5</sup>Department of Internal Medicine, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing 100730, China;

<sup>6</sup>Department of Nuclear Medicine, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing 100730, China.

*To the Editor:* Enteral fistula (EF) is a rare complication mostly caused by inflammatory bowel disease and in some cases by duodenal ulcer, intestinal tuberculosis, intestinal lymphoma, abdominal surgery, or necrotizing enterocolitis.<sup>[1,2]</sup> Perforative complications including perforation and EF are major complications of primary intestinal lymphoma (PIL). Vaidya *et al*<sup>[2]</sup> reported that in a cohort of 1062 patients with gastrointestinal lymphoma, bowel perforation occurred in 9% of the patients, and among them, the small intestine was the most common site (81%). Furthermore, perforation events occurred as the initial presentation in 51% of these patients. However, it is rare for EF as the initial manifestation of PILs, because majority of EFs occurred after the chemotherapy or the surgeries. Malignant intestinal fistula caused by lymphoma was first reported in 1946.<sup>[3]</sup> The early diagnosis of PILs is quite challenging in patients with EF as the initial manifestation, which is sometimes misdiagnosed as other diseases, especially Crohn's disease (CD). Therefore, we reviewed the clinical and radiologic features and the outcomes of PIL patients with EF as the initial manifestation.

We searched PubMed and Embase with the keywords "fistula" and "lymphoma" to find all potentially relevant studies through November 6, 2019. The finally included studies were published in English with available full-text, which reported entero-EF as the initial manifestation of PIL, and provided information including the clinical characteristics, diagnosis method, definite pathology diagnosis of PIL, treatment, and clinical outcome of the patients. A total of 720 papers related to fistula and lymphoma were searched, and 11 papers with 12 cases were finally included in this review. For all the included cases, the details about their demographic information, medical history, and clinical manifestation,

diagnosis, treatment, and prognosis information, were collected.

Results of the review showed that, 10/12 patients were males, and the median age was 58 years old with a range from 3 to 86 years old. The most common clinical manifestations included abdominal pain, diarrhea, and weight loss. The medical history was available in 10/12 cases, including 2 cases with human immunodeficiency virus infection, 2 cases with history of gastrointestinal surgery, and 1 case with tuberculosis. Eight of 12 cases had EF between small intestine and colon, 10/12 patients underwent the radiology examination before the essential endoscopy diagnosis. The major findings under enhanced computed tomography (CT) scan included focal wall thickening, fistula, and lymph node enlargement. Pathology findings indicated that 8/12 cases were B-cell lymphoma, in which the diffuse large B-cell lymphoma (DLBCL) was the main type. Surgery and chemotherapy were the common treatments, and 6/12 patients accepted the combination therapy. Among the 10/12 patients with the data of outcomes, 7 were still alive during the period of follow-up, with a median duration of 12 months (1–48 months), and the others died within 3 months (1–3 months). And 5/6 patients accepting the combination therapy were still alive during the follow-up.

This review demonstrated the middle-aged male predominance in the PIL patients with EF as the initial manifestation, which was consistent with previous studies focusing on PILs.<sup>[4]</sup> No specific clinical characteristics were revealed, including abdominal pain, diarrhea, and weight loss. Meanwhile, the radiologic findings were also non-specific, including focal wall thickening, fistula formation, and lymph node enlargement. All these findings contributed to the challenges for the early diagnosis, and the

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**Correspondence to:** Dr. Ji Li, Department of Gastroenterology, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing 100730, China  
E-Mail: lij0235@pumch.cn

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differential diagnosis of EF was more difficult between PIL and CD. A retrospective study<sup>[5]</sup> compared the CT enterography of PIL and CD, and found that circular thickening of the bowel wall, wall thickness >8 mm, involvement of ≤3 segments, and aneurysmal dilation were significantly more prevalent in PIL compared to CD. Possible explanations would be that lymphoma cells proliferate without damaging the surrounding normal intestinal wall cells and invade the nerve plexus of the intestinal wall, which can lead to decreased muscular tension and aneurysmal dilation of the bowel. These relatively special findings might be helpful for clinicians. However, all cases in this review did not mention such details of CT findings. So, future multicenter comparative studies focusing on the radiologic findings might bring more insights for the differential diagnosis.

The pathology of lymphoma might be a critical factor for fistula formation. As shown in our review, 66.7% patients were B-cell type, with DLBCL the most common type.

Vaidya *et al*<sup>[2]</sup> reported that aggressive B-cell lymphoma had a significantly higher risk of perforation compared with the B-cell indolent type (hazard ratio 6.31,  $P < 0.0001$ ), and DLBCL was the most common type of the former to perforate. Daum *et al*<sup>[6]</sup> conducted a multicenter prospective study in Germany and demonstrated that the perforation rate of the T-cell PIL was higher than that of the B-cell type (13% *vs.* 5%). Therefore, more aggressive lymphoma appeared to have a much higher risk of perforation. Apart from the pathologic features, we also found enteral-colon was the most common site of fistula, which might be due to the anatomic proximity, as lymphoma could cause the lack of a desmoplastic reaction, leading to the adhesion of the intestinal tract with nearby.<sup>[7]</sup>

Once an enteric fistula is identified, the basic supportive care is important in the initial treatment, not only for preparation for surgery and chemotherapy but also for the possibility of spontaneous fistula closure. However, there has not been a standard step-by-step strategy for the treatment of PIL with EF, and researchers are still debating about whether the surgery should be performed, regarding the risk of peri-operative complications. Generally, the literature review of most published cases showed that combination therapy could lead to better outcomes compared with surgery alone.<sup>[4]</sup> There was 1 interesting case in which a covered intestinal stent combined with chemotherapy was used for treatment; the stent was designed to simultaneously exclude the defect and maintain restoration of enteral nutrition, allowing for the earlier introduction of chemotherapy without waiting for post-operative recovery.<sup>[8]</sup> Therefore, a combination of surgery and chemotherapy was strongly recommended for PIL with EF if patients' condition allowed.

With limited cases and follow-up information, long-term survival analysis was difficult to run in this review. According to previous studies, the 5-year survival rate of PIL varies from 24% to 71.6%<sup>[9]</sup> and increases with the

development of clinical treatment. In addition to the T-cell subtype and perforation predictors mentioned earlier, advanced stage (III/IV), B symptoms, international prognostic index score of 3, no radical surgery, and no chemotherapy may also be considered predictors for poor prognosis.<sup>[4,10]</sup>

Although only English literature with full text from 2 databases was included, and the number of cases enrolled was limited, this review still gave us more insights about the clinical and radiologic characters and outcomes, which favored the early diagnosis of EF as the initial presentation of PILs. Furthermore, combination treatment is strongly recommended once the diagnosis is established.

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### Conflicts of interest

None.

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