Clinical features and management of primary colonic lymphoma

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Summary Most primary colonic lymphomas are non-Hodgkin’s lymphomas, most especially diffuse and large B-cell lymphomas, and constitute only 0.2–0.6% of all colon cancers. The disease manifests at a median age of 55 years (range: 23–86), and patients are predominantly male. The tumors are most frequently located in the cecum. Because endoscopic and imaging studies always show nonspecific findings, the diagnosis should be categorized as “suspicious”. The current treatment options for primary colonic lymphoma are inconclusive. However, recent studies have shown a trend where surgery followed by chemotherapy enhanced patient outcomes in those with localized disease. For disseminated disease, target therapy (rituximab) in combination with CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone) increases patient survival time. With advances in molecular techniques, the classification and management of lymphoma has made progress.

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1. Introduction

Primary colonic lymphoma (PCL) is a rare gastrointestinal (GI) tract malignancy. The GI tract is the most common site for the extranodal involvement of non-Hodgkin’s lymphoma (NHL), occurring in the colorectal area in about 10–20% of all cases with extranodal GI tract involvement. Most PCLs have a B-cell lineage and are classified as diffuse large B-cell lymphomas (DLBCL). The optimal treatment for PCL is controversial. In this review, we describe and discuss the clinical presentations and management of PCL.

2. Definition, etiology, and pathogenesis

PCL is an extranodal NHL. As molecular techniques have advanced, the classification of lymphomas has progressed...
to include lymphoid lineages, cell types, immunophenotypes, karyotypes, molecular characteristics, and clinical features. The latest World Health Organization classification recognizes five histological subtypes (Table 1). The diagnosis of PCL was initially established in 1961 and included five criteria (Table 2). Most PCLs have a B-cell lineage. Among these tumors, the leading subtype is DLBCL, followed by follicular lymphoma, mucosa-associated lymphoid tissue (MALT) lymphoma (MALToma), and mantle cell lymphoma.

Because PCL is classified as NHL in most cases, the pathogenesis of PCL is associated with the activation of proto-oncogenes, mainly through chromosomal translocation. For DLBCL, cytogenetic studies have demonstrated that chromosomal 3q27 alterations, specifically the location of the BCL-6 gene, are abnormalities in 35% of cases. MALToma is associated with Helicobacter pylori infection. It has been suggested that gastric MALT responds to antigen stimulation by H. pylori. The eradication of H. pylori results in the regression of MALT. The most common genetic alteration of MALT-NHL is the t(11;18)(q21;21) translocation, which occurs in about 50% of patients, and fuses the API2 gene, which encodes an inhibitor of apoptosis. The genetic hallmark of follicular lymphoma (FL) is chromosomal translocations involving the BCL-2 gene, which is located at 18q21; these translocations are detected in 80–90% of patients with PCL.

### 3. Clinical presentation and diagnosis

PCL cases constitute 0.2–0.6% of all reported cases of colonic cancers. The series reported by Taipei-Veterans General Hospital (Taipei-VGH) gives a figure of 0.42% (29 of 6944). The time of onset for PCL varies in different studies, but the median age of onset is 55 ± 22 years (range: 23–86 years). Men are affected twice as often as women. The articles in the literature and the Taipei-VGH series indicate that more than half of PCL patients report abdominal pain, followed by bloody or tarry stool (30%) and a weight loss (25%). The most frequent tumor location is the cecum, probably due to the large amount of lymphoid tissue in that region. The morphology of PCLs is variable, resulting in a wide range of radiological and endoscopic features, including mass lesions, narrowing of the lumen, ulceration, irregularity of the mucosa, and aphthous lesions.

Endoscopy usually reveals nonspecific colitis or an ulcer; mass lesions are unusual. Focal PCL, which is characterized by infiltrative spread that arises from the submucosa, results in the uniform thickening of the cecal wall and often spreads into the terminal ileum. The morphological appearance could consist of smooth strictureing lesions, a circumferential infiltrative form accompanied by ulceration, a cavitating mass, or mucosal fold thickening. Diffuse lesions also occur, which can be ulcerative or nodular, and are relatively small (usually < 2 cm). Endoscopic findings are classified by ulceration, infiltration, and the presence of a mass. For B-cell lymphomas, the most common endoscopic type is a fungating mass (54.0%). For T-cell lymphomas, the most common findings are ulcerative or ulcero-infiltrative lesions (80.0%). Imaging studies sometimes show that a lymphoma forms an annular napkin ring-like lesion that mimics carcinoma.

When a computed tomography (CT) scan reveals the presence of an infiltrative process accompanied by enlarged lymph nodes in the abdomen or pelvis, lymphoma should be the primary consideration in the differential diagnosis and must be excluded by endoscopic biopsy. Nevertheless, without the presence of enlarged lymph nodes it is difficult to distinguish this type of tumor from primary adenocarcinoma. The potential role of positron-emission tomography for the diagnosis and follow-up of patients with lymphoma has yet to be established.

### 4. Staging and management

The Ann Arbor staging system, originally used for Hodgkin’s disease, is now widely used for NHL. The extent of the disease is classified as stage I–IV according to the distribution of disease. For stage I, the disease involves a single-node region. Stage II disease involves two or more node regions on the same side of the diaphragm; the involvement of node regions on both sides of the diaphragm defines stage III. Diffuse involvement of the extralymphatic organs with or without node regions is classified as stage IV. Furthermore, localized extralymphatic disease is described by the use of the subscript letter “E”.

For PCL, the disease stage at the time of diagnosis varies in different publications. A 371-patient study in Germany showed that approximately 90% of the patients with GI NHL had stage IE/IIE disease. On the other hand, a 244-patient study from the USA reported that over half of the patients presented with stage IV disease. In the Taipei-VGH series, 18 (67%) patients had early-stage (stage I or II) and nine (33%) had late-stage disease. Overall, the 3- and 5-year survival rates for PCL patients were 60.8% and 47.3%, respectively.

NHL types can be separated into two distinct prognostic groups: indolent and aggressive. The indolent group responds well to radiation therapy and demonstrates a good clinical prognosis when diagnosed in the early stages. The aggressive subtype of NHL generally has a less favorable prognosis and requires more intensive therapy. However, studies of the factors affecting the survival of PCL patients are inconclusive, though the stage at diagnosis,

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<th>Table 1</th>
<th>2008 World Health Organization classification of lymphomas.</th>
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<td>1) Mature B-cell neoplasms</td>
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<td>2) Mature T-cell and nature killer cell neoplasms</td>
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<td>3) Hodgkin’s lymphoma</td>
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<td>4) Histiocytic and dendritic cell neoplasms</td>
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<td>5) Posttransplant lymphoproliferative disorders</td>
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histological grade, and any complications that result in urgent surgery do have an impact on survival.8,22

Chemotherapy remains the basis of treatment for rapidly proliferating aggressive lymphomas because most NHLs present as systemic disease.23–25 The CHOP chemo-therapeutic regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone) remains as the first-line therapy for all moderate and high-grade B-cell lymphomas. Rituximab, a chimeric anti-CD20 monoclonal antibody, induces the death of normal and malignant B-cells that express the cell-surface molecule CD20. Treatment with rituximab as a single agent results in significant responses in patients with almost every subtype of B-cell lymphoma.28 For low-grade lymphomas, a single alkylating agent and CVP (cyclophosphamide, vincristine, and prednisone) are the preferred choice of treatment.26

The role of surgery is to establish a diagnosis of extranodal NHL. However, there are some controversies regarding the role of surgery for managing GI tract lymphoma. For the treatment of primary gastric DLBCL, the role of surgery has diminished and the treatment strategy has moved toward organ preservation because surgical resection is not superior to chemotherapy plus radiotherapy.27 However, two specific problems with intestinal DLBCL enhance the role of surgical resection for managing intestinal lymphomas: difficulties in the preoperative pathological diagnosis and the risk of intestinal perforation (Fig. 2). Because the incidence of PCL is low, there has never been a controlled randomized trial to define the role of surgery for the treatment of PCL. Some authors have suggested that systemic chemotherapy alone should be the standard treatment, with surgery reserved for

<table>
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<th>Table 2  Criteria for the diagnosis of primary colonic lymphoma.</th>
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<td>1) No palpable superficial lymphadenopathy on initial examination</td>
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<td>2) No obvious enlargement of the mediastinal lymph nodes on chest X-ray</td>
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<td>3) White blood cell count within normal limits</td>
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<td>4) Aminant bowel lesion on laparotomy</td>
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<td>5) Involvement of only the lymph nodes in the immediate vicinity of the primary lesion</td>
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Figure 1  A 72-year-old female patient presented with right lower quadrant pain, and the computed tomographic image showed a mass-like lesion in the cecal region. (Panel A) The colonoscopic finding showed an infiltrative mass with an inflammatory exudate. (Panel B) The patient underwent an exploratory laparotomy and a right hemicolectomy. (Panel C) The operative finding showed an annular infiltrative mass, 5 × 5 cm in size, in the ileocecal area.
complications such as perforation, obstruction, and bleeding,\textsuperscript{7,8} whereas others believe that surgery provides better localized disease control and improves the survival outcome.\textsuperscript{18,29} The results of the Taipei-VGH series suggests that for PCL patients, surgery followed by chemotherapy produces a statistically better survival rate when compared to chemotherapy alone. Recently, a large retrospective cohort study in Korea showed that for patients with localized disease (stage I/II), surgery plus chemotherapy yields a lower relapse rate (15.3%) than chemotherapy alone (36.8%).\textsuperscript{29} However, surgical resection did not provide any significant benefit to patients with disseminated disease. For disseminated disease, adding rituximab to CHOP (R-CHOP) resulted in a better 3-year overall survival (59%) compared with CHOP alone (29%). These data suggest that R-CHOP is a better treatment for disseminated disease. However, the addition of rituximab to CHOP failed to show additional survival benefits regardless of localized disease, regardless of surgery.\textsuperscript{28}

Because the rate of intestinal perforation is high (> 30%) with chemotherapy, some authors suggest that surgical resection could prevent this complication and improve patient outcomes.\textsuperscript{7,8} Nevertheless, some authors argue that PCL originating from intestinal lymphoid tissue should be treated as a systemic disease, and that early diagnosis and the timely onset of chemotherapy are sufficient to achieve adequate disease control and avoid surgery.\textsuperscript{7,8}

5. Conclusions

PCL is a rare condition. The small number of patients with various histological subtypes and different stages at diagnosis has resulted in uncertain treatment protocols. The optimal management has not been established by randomized trials. Nevertheless, recent publications show trends toward multimodality management, with surgical resection of the primary lesion followed by standard chemotherapy affording better local disease control and survival.

List of abbreviations:

- Primary colonic lymphoma (PCL)
- Gastrointestinal (GI)
- Non-Hodgkin’s lymphoma (NHL)
- Diffuse, large B-cell lymphoma (DLBCL)
- Mucosa-associated lymphoid tissue (MALT)
- Cyclophosphamide, vincristine, and prednisone (CVP)
- Cyclophosphamide, hydroxydaunomycin, oncovin, and prednisolone (CHOP)
- Taipei-Veterans General Hospital (Taipei-VGH).

References

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