Review Article

Lymphoma of the colon and rectum

M.A. Richards

ICRF Department of Medical Oncology, St. Bartholomew's Hospital, London EC1A 7BE, UK.

Introduction

Lymphomatous involvement of the colon and rectum may occur either as a localized entity or as a manifestation of generalized lymphoma. It is important to distinguish between primary and secondary colorectal lymphoma as the natural history and management of the two conditions differs significantly.

Colorectal lymphoma is a rare condition although several major series have been published as well as many case reports. A review of the literature is, however, complicated by a number of factors: (1) The distinction between primary and secondary involvement is not always clearly made and several different staging classifications have been used. (2) Colorectal lymphoma is sometimes not separated from other gastrointestinal lymphomas. (3) Comparison between different histological classifications is difficult, particularly as some of the major series were published over twenty years ago. (4) Childhood cases are included by some authors and excluded by others. (5) The exact site of origin of ileocaecal masses is difficult to determine. (6) Referral patterns differ between institutions. (7) Geographical factors may be important. (8) All the series reported are retrospective making the contribution of surgery, radiotherapy or chemotherapy difficult to assess. (9) Some individual cases have been reported more than once.

This review therefore concentrates on the major series reported since 1960 in which sufficient information regarding these factors has been given to allow conclusions to be drawn.

Primary colorectal lymphoma

The standard criteria for the diagnosis of primary intestinal lymphoma were established by Dawson *et al.* (1961). Tumours were considered to be primary on

the following grounds: (1) When the patient was first seen there was no palpable superficial lymphadenopathy. (2) Chest radiographs showed no obvious enlargement of the mediastinal nodes. (3) The white blood cell counts, total and differential, were within normal limits. (4) At laparotomy the bowel lesion predominated, the only lymph nodes obviously affected being those in its immediate neighbourhood. (5) The liver and spleen appeared free of tumour in every case.

Normal bone marrow biopsy examination and absence of lymphadenopathy on computed tomographic (CT) scan of the mediastinum should probably now be added to these criteria. Although there has been wide acceptance of these criteria, some authors (Lewin *et al.*, 1978; Herrman *et al.*, 1980) have used a somewhat broader definition for primary gastrointestinal lymphoma. They include all patients who present with obvious predominant alimentary tract lesions or who present with gastrointestinal involvement with lymphoma. In practice one of the major differences between these two definitions lies in the inclusion or exclusion of patients with para-aortic node (as opposed to mesenteric node) involvement. As long as a staging system which differentiates between these sites of nodal involvement such as that proposed by Musshof & Schmidt-Vollmer (1975), is used, it seems reasonable to include such patients in an analysis of primary gastrointestinal lymphoma.

Incidence

Primary colonic and rectal lymphomas are rare disorders. Lymphomas made up only 0.2% (3/1822) of cases of colonic malignancy seen at the Methodist Hospital, Memphis, Tennessee between 1966 and 1979 (Fleming *et al.*, 1982). In a large survey from Japan (Jinnai *et al.*, 1983), 130 cases of large intestinal lymphoma were reported; 19,850 cases of large bowel cancer were treated during the same period. Lymphoma therefore accounted for 0.65% of cases of large

Correspondence: M.A. Richards M.R.C.P.
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bowel malignancy. The incidence of rectal lymphoma compared with rectal carcinoma is similarly low – 0.2% at St Mark's Hospital (Perry *et al.*, 1972).

In two large studies of non-Hodgkin's lymphoma (NHL) (Rosenberg *et al.*, 1961; Jones *et al.*, 1973) about 5% of patients presented with lymphoma confined to the gastrointestinal tract. Gastrointestinal involvement with Hodgkin's disease is even rarer – 2% at presentation in the study reported by Peters *et al.* (1968).

The colon and rectum are uncommon sites for lymphoma even compared with other gastrointestinal sites, where stomach and small bowel predominate. Colorectal involvement accounts for between 10% and 20% of cases in most studies of gastrointestinal lymphoma (Lewin *et al.*, 1978; Bush & Ash, 1969; Blackledge *et al.*, 1979; Contreary *et al.*, 1980; Loehr *et al.*, 1969; Freeman *et al.*, 1972; Dragosics *et al.*, 1985), but may be as low as 3% if ileocaecal cases are excluded (Isaacson *et al.*, 1979). The proportion of colorectal cases may be higher in India, with figures up to 45% (Nirmala *et al.*, 1981).

Within the large bowel the caecum is the commonest site (Jinnai *et al.*, 1983; Wychulis *et al.*, 1966), particularly in children (Lewin *et al.*, 1978), followed by rectum and then the remainder of the colon. Primary lymphoma is occasionally found in the appendix. Jinnai *et al.* (1983) suggested that the frequency of caecal lesions might reflect the greater extent of normal lymphoid tissue in this region. They also considered that the frequency of involvement of the ampullary portion of the rectum might be due to retention of intestinal contents at this site.

The age of reported cases ranged from 3 to 83 years. However, the maximum incidence is in the 50 to 70 year age group (Naqvi *et al.*, 1969) with a mean age between 50 and 55 years (Jinnai *et al.*, 1983; Perry *et al.*, 1972; Loehr *et al.*, 1969). The number of men and women was equal in Perry's study (1972) of rectal lymphoma, but most studies show a male predominance for lymphoma of the large bowel of approximately 2:1 or higher if children are included.

Macroscopic and microscopic appearance

Discrete lesions are found in about 90% of primary colonic lymphomas (Dawson *et al.*, 1961; Wychulis *et al.*, 1966). Normally the lesion is single, but occasionally two or more may occur. Macroscopically the tumours may be protuberant intraluminal growths, infiltrative intramural thickenings or extramural growths (Dawson *et al.*, 1961; Jinnai *et al.*, 1983). In the remaining 10% of cases the tumours present as diffuse involvement of the colon with or without polyps. Perry *et al.* (1972) found an indurated mass in 13/22 patients with rectal lymphoma, an ulcer in 8 patients and a polyp in one case. Dawson *et al.* (1961)

found no apparent association between the macroscopic and the microscopic appearance of intestinal lymphomas. However, Blackshaw (1980) found a very high degree of correlation between the 'lymphomatous polyposis' macroscopic pattern of infiltration and one particular histological type – namely centrocytic lymphoma.

The relative incidence of histological types of lymphoma involving the colon and rectum differs markedly from that of primary nodal lymphomas. Hodgkin's disease and 'follicular' non-Hodgkin's lymphoma are both very rarely found amongst cases of primary colorectal lymphoma. The large majority of such cases have a 'diffuse' histological pattern – although the ratio of 'low grade' to 'high grade' non-Hodgkin's lymphoma differs considerably between series. This is again affected by inclusion of children in whom the lymphomas are normally high grade (immunoblastic or lymphoblastic). Lymphoplasmacytoid differentiation of gastrointestinal lymphomas, reflecting B cell origin, is also reported to a varying extent with some probable overlap with true plasmacytomas.

Possible associated disorders

Colonic lymphoma may develop in patients with longstanding ulcerative colitis or may present simulating ulcerative colitis. Lymphoma is a rare complication of ulcerative colitis compared to carcinoma, with only about 20 recorded cases (Bartolo *et al.*, 1982; Emanuel & Isbister, 1979). The duration of symptoms of colitis prior to the diagnosis of lymphoma varies between 5 and 30 years (Dawson *et al.*, 1961; Wychulis *et al.*, 1966; Renton & Blackshaw, 1976; Wagonfeld *et al.*, 1977) with an average of 12 years (Renton & Blackshaw, 1976). It usually develops in the context of total colitis. A short period of increased pain, diarrhoea and rectal bleeding before the diagnosis of lymphoma is made has been noted (Renton & Blackshaw, 1976). In at least 7 cases multicentric tumours have been found (Wagonfeld *et al.*, 1977).

Colonic lymphoma occasionally simulates inflammatory colitis (Wagonfeld *et al.*, 1977; Weir *et al.*, 1980; Friedman *et al.*, 1968) and differentiation between the two conditions may be difficult clinically, radiologically and histologically. The paper by Sagar *et al.* (1986) shows that modern immunohistochemical methods allow the diagnosis of lymphoma to be made with much greater objectivity.

A few patients have been described with both primary large bowel lymphoma and large bowel adenocarcinoma. Two of the three cases reported by Cornes (1960) fall into this category. In one case the two lesions were diagnosed synchronously and in the other adenocarcinoma of the rectum and sigmoid presented 9 months after the excision of an ascending colonic lymphoma. It is therefore important not to

assume that a second growth is always a recurrence or metastasis from the original primary tumour. More recently, a case of adenocarcinoma developing within an area of lymphomatous bowel has been reported (Kalisman *et al.*, 1979). A further interesting case of coexisting adenocarcinoma and primary malignant lymphoma of the large intestine in an IgA deficient 14 year old boy has been reported from Tehran (Mir-Madjlessi *et al.*, 1984).

Presentation/diagnosis

Patients present with symptoms that cannot be differentiated from carcinoma (Perry *et al.*, 1972; Wychulis *et al.*, 1966). In the Mayo clinic series (Wychulis *et al.*, 1966), 90% of patients had abdominal pain at presentation, 80% weight loss and 76% change in bowel habit. Weakness, nausea and vomiting, anorexia, fever and bleeding per rectum all occurred in descending order of frequency. A mass was palpable in 88% of cases. Bleeding and diarrhoea are the commonest symptoms of rectal lymphoma (Perry *et al.*, 1972). Tenesmus and weight loss are also important presenting features. Occasionally patients present with complications such as intussusception (especially children), perforation or obstruction. Typically the time from onset of symptoms to diagnosis is 4 to 6 months (Wychulis *et al.*, 1966; Naqvi *et al.*, 1969).

Barium enema examination was abnormal in 41 out of 44 cases in Wychulis' series (1966), though the appearances are not necessarily pathognomonic for lymphoma. Five different patterns have been described (O'Connell & Thompson, 1978) which reflect the varied macroscopic appearances of the disease: (1) Mucosal nodularity – nodules may range from 2 mm to 2.5 cm, the pattern resembles the pseudopolyposis of ulcerative colitis, but the haustral pattern is maintained and ulceration is uncommon. The appearances may be similar to those found in Crohn's disease, amoebiasis or pseudomembranous colitis (Bruneton *et al.*, 1983). (2) Endo-exocentric mass – an extensive mass with gross mucosal destruction due to mural infiltration. Occasionally contrast may track extraluminally into a necrotic mass. (3) Intraluminal mass – these are often lobulated and may be up to 20 cm in size, without causing obstruction unless intussusception occurs. (4) Infiltrative forms – the lesion may appear either as a rigid anghaustral segment or as an annular stricture resembling a carcinoma. (5) Mesenteric invasion – extraluminal tumours appear as a soft tissue mass causing extrinsic compression without mucosal involvement.

Histology is, of course, required to establish a firm diagnosis. This may be obtained by endoscopic biopsy, but more frequently is only available following laparotomy.

Treatment and survival

Surgical excision of the tumour, if technically feasible, is the main-stay of treatment for colonic lymphoma. Patients who have received a 'curative' resection (i.e. all visible tumour excised) undoubtedly have a better prognosis than those who have received a palliative resection (Jinnai *et al.*, 1983; Blackledge *et al.*, 1979; Contreary *et al.*, 1980). This may, of course, reflect differences in the initial extent of disease rather than the importance of surgery itself. Although surgery alone may be curative, recurrence may occur following 'complete excision' either within the abdomen or at a distant site. This is of grave prognostic significance (Bush & Ash, 1969).

Adjuvant radiotherapy is frequently given after surgical excision, but no prospective study has been performed to assess its efficacy. Retrospective studies are difficult to assess as the reason radiotherapy was given is frequently unclear. Dawson *et al.* (1961), reviewing the literature prior to 1961, noted that too few cases had been recorded to assess the influence of radiotherapy. Although a remarkable clinical improvement was observed in individual cases, no case treated with radiotherapy alone had survived 10 years. A significant improvement in the 2 year survival rate with postoperative radiotherapy has been observed however for gastrointestinal lymphoma as a whole by Bush & Ash (1969). Sixty-four per cent of their patients treated with surgery alone died within 2 years. The recurrence rate at 2 years for those who had received radiation therapy was 44%. The difference remained significant for those evaluable at 5 years.

Perry *et al.* (1972) recommended surgical excision with or without radiotherapy as the treatment of choice for rectal lymphoma. Alternatively, radiotherapy can be given following left iliac fossa colostomy.

The value of chemotherapy either alone or as adjuvant therapy for colorectal lymphoma cannot be assessed from the current literature.

The five year survival rate for all patients is about 35% (Jinnai *et al.*, 1983; Loehr *et al.*, 1969; Naqvi *et al.*, 1969). A high percentage of deaths occurs in the first 2 years (Dawson *et al.*, 1961; Jinnai *et al.*, 1983). Deaths due to lymphoma may still occur after 5 years (Dawson *et al.*, 1961) although the risk appears small (Jinnai *et al.*, 1983). At the Mayo clinic the 10 year survival rate for those who had received a curative resection (with or without adjuvant radiotherapy) was 50%. Dawson *et al.* (1961) projected an overall 10 year survival rate of not more than 25%. For inoperable cases the 5 year survival rate in 2 series was zero (Jinnai *et al.*, 1983; Contreary *et al.*, 1980).

These survival rates are worse than those for gastric lymphoma (Dawson *et al.*, 1961; Lewin *et al.*, 1978; Dragosics *et al.*, 1985) perhaps because the disease is more advanced at presentation (Contreary *et al.*,

1980), in terms of spread to lymph nodes and adjacent viscera. The prognosis is also worse than that of carcinoma of the colon (Jinnai *et al.*, 1983; Freeman *et al.*, 1972).

Prognostic factors

Although there is a general agreement regarding the importance of operability as a prognostic factor, the importance of other factors is less clear cut. Lymph node involvement was a significantly adverse factor in three studies (Jinnai *et al.*, 1973; Contreary *et al.*, 1980; Freeman *et al.*, 1972), and was probably significant in another (Wychulis *et al.*, 1966). However, Dawson *et al.* (1961) found that regional lymph node involvement did not have any effect on prognosis. The different histological classifications used make it very difficult to assess the impact of different histological subtypes. The Japanese study, comprising by far the largest single survey, was also able to identify size and macroscopic type of the initial lesion as important factors. A great difference was seen between patients with tumours of 5 cm or less in diameter and those with tumours larger than this. Intramural tumours had the worst prognosis and intraluminal tumours the best.

Secondary lymphoma

Secondary involvement of the gastrointestinal tract and particularly the large bowel has received less attention than primary gastrointestinal lymphoma despite the fact that the incidence is higher and the prognostic implications are grave.

The incidence of gastrointestinal involvement in systemic lymphoma increases during the course of the disease, with relatively low rates at presentation, a higher number of patients developing clinical evidence of gastrointestinal involvement subsequently and a very high incidence in post-mortem studies.

In the study of 405 patients with NHL reported by Jones *et al.* (1973), 64 patients had gastrointestinal involvement before therapy. Nineteen of these had localized (i.e. primary) gastrointestinal lymphoma. The remaining 45 patients (11% of the series) had disseminated disease. This is a minimum figure as less than half of the patients in the study underwent laparotomy or radiological assessment of the gastrointestinal tract. Involvement was significantly higher in patients with diffuse lymphoma than those with nodular histology. The true incidence of gastrointestinal involvement was calculated to be between 7% and 12% for nodular lymphoma and between 22% and 39% for diffuse lymphoma. Only 11/405 had colonic involvement (3 localized, 8 stage IV), the stomach and small intestine being the commonest sites

of gastrointestinal involvement. Thus colonic involvement in the context of widespread (stage IV) disease at presentation was only observed in 8 (2%) of the patients. Six of these had histologically 'diffuse' lymphoma and 2 had nodular histology.

Rosenberg *et al.* (1961) reviewed 1269 cases of lymphosarcoma, of whom only 7 presented with evidence of lymphoma involving the large intestine (primary or secondary). However, a total of 36 patients (2.8%) developed clinical evidence of colorectal lymphoma subsequently. These figures contrast markedly with results from post-mortem examinations. In the same review, Rosenberg found colorectal lymphoma in 68 out of 277 (24.5%) autopsy cases. Fifty of these were in the colon and 18 in the rectum. In only 20 of these patients had the colorectal involvement been demonstrated clinically. Over 50% of the autopsy series had evidence of lymphoma in some part of the gastrointestinal tract.

Peters *et al.* (1968) in a study of 1406 cases of Hodgkin's disease and NHL, also found a much higher incidence of gastrointestinal involvement at post-mortem (45%) than at presentation (11%), though the exact location within the gastrointestinal tract is not recorded. Furthermore, these figures represented gross involvement at autopsy not microscopic lesions. The incidence at presentation was 16% for NHL (reticulum cell sarcoma and lymphosarcoma) and only 2.4% for Hodgkin's disease. At post-mortem the figures were 70% and 34% respectively. Ehrlich *et al.* (1968) who studied 323 autopsy cases of malignant lymphoma, also found approximately 55% had tumours in the gastrointestinal tract. However, only 7% had tumour in the colon (10% for NHL, 3% for Hodgkin's disease). Prolla & Kirsner (1964) found macroscopic lesions in 3 out of 18 patients with chronic lymphocytic leukaemia at autopsy. A further 9 patients had microscopic lesions giving a total of 60% with either macroscopic or microscopic evidence of colorectal involvement. A further case of large bowel infiltration by chronic lymphocytic leukaemia was published recently in this journal (Tucker & Cachia, 1986).

Do these striking differences between clinical and post-mortem findings mean that gastrointestinal involvement is underdiagnosed at presentation? The study by Goffinet *et al.* (1973) suggests that this is not the case. Staging laparotomies performed on 69 previously untreated patients revealed no cases of colonic lymphoma. Furthermore, 37 of these patients had barium enema examinations as part of the staging procedure and all were normal. By contrast O'Connell & Thompson (1978) demonstrated colonic pathology on barium enema examination in 4 patients with systemic lymphoma who had no clinical symptoms referable to the colon.

Significance of gastrointestinal symptoms

In order to account for the discrepancy between clinical and autopsy findings, it must be assumed that most patients whose disease spreads to the colon and rectum do not develop symptoms referable to this. Conversely, gastrointestinal symptoms do not necessarily imply that tumour is present. Other lesions may develop as a result of the patients' immunosuppressed state and as a result of radiotherapy or chemotherapy. Ehrlich *et al.* (1968) found non-tumourous ulcerations of the colon in 13 out of their 323 autopsy cases, 4 of which had bled. They also noted fungal and bacterial invasion. With increasingly intensive therapy the incidence of these non-tumourous lesions is likely to rise and complications may result. Indeed Ehrlich *et al.* (1968) observed that bleeding was more frequently due to non-tumourous causes than to tumour. In 7 cases of bleeding arising from the intestine, 2 were due to tumour and 5 due to other causes. However, obstruction and perforation were more usually due to tumour.

Pathological features

Secondary colonic involvement is often multicentric and may have a different distribution from primary lymphoma. The rectosigmoid region and the left hemicolon are more frequently involved than the right hemicolon (O'Connell *et al.*, 1978). Radiologically the 'mucosal nodularity' pattern is seen more frequently in secondary than in primary colonic lymphoma as is the 'endo-exoenteric mass' (O'Connell *et al.*, 1978).

Survival

The identification of gastrointestinal involvement by a diffuse lymphoma may imply a very poor prognosis with the exception of 'diffuse well differentiated' lymphoma. Jones *et al.* (1973) reported a median survival of 6 months for patients with gastrointestinal involvement at presentation.

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Development of gastrointestinal symptoms during the course of the patients' illness is also of adverse prognostic significance. Ehrlich *et al.* (1968) noted that the onset of abdominal pain or the destruction of an abdominal mass preceded death by 6 months in patients with 'reticulum cell sarcoma', as against a mean survival of 24 months from the onset of clinical symptoms. The trend was similar for other non-Hodgkin's lymphomas and for Hodgkin's disease, although the time spans were longer. Bleeding, perforation or obstruction usually heralded death within 3 months in all histological groups.

Specific data for survival of patients with secondary colonic or rectal lymphoma is not available, but probably reflects that of the gastrointestinal tract as a whole.

Conclusions

Primary colorectal lymphoma is a rare condition which carries a poor prognosis compared with either primary gastric lymphoma or carcinoma of the colon. Optimal management is still uncertain, particularly regarding the role of radiotherapy and chemotherapy. No single institution can hope to answer these questions and it is therefore important that cases of colorectal lymphoma should continue to be reported. Special attention should be given to histological subtype and the specific sites of nodal involvement, in order that valid comparisons can be made between institutions. Cooperative prospective studies should be strongly considered.

Secondary colorectal lymphoma has received very little attention, but probably carries an even worse prognosis. However, the incidence and prognostic significance of both tumourous and non-tumourous colonic lesions complicating systemic lymphoma should be reassessed in view of changes in treatment which have been introduced in the past 10 years, particularly for high grade NHL.

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