PRIMARY SMALL BOWEL LYMPHOMA
a review

Pierre Ellul, MRCP; Karim Mohammed Ashfaq, MRCP; Tom Poyser, MBChB; Ravi Sekhar, MRCP; John Keating, FRCP

INTRODUCTION

The small bowel accounts for 75% of the length and 90% of the surface area of the whole bowel.[1,2] However, less than 2% of gastrointestinal (GI) malignancies arise in the small bowel, with an annual incidence of 0.6-1 per 100,000.[2,3,4,5] The two most common malignancies are adenocarcinoma and carcinoid tumours. Lymphoma accounts for 15 to 20% of its malignancies, these being mostly of the non-Hodgkin's type (NHL). Five to twenty per cent of all NHL arise in the GI tract.

Hypotheses for the lower incidence of small bowel malignancy are:

- the liquid content is less mechanically irritating
- rapid transit time. This decreases the time of contact of carcinogens with the mucosa
- the high concentration of digestive enzymes may detoxify carcinogens
- rapid cell turnover
- increase lymphoid tissue with a better immune surveillance[2]

A geographic variation exists in the most common site for GI lymphomas. In western European countries and North America, at least 66% of GI lymphomas arise in the stomach, the rest being equally distributed between small and large bowel. In contrast, in the Middle East and North Africa more than half of GI lymphomas arise in the small bowel.[6,7]

The mean age at presentation is 60 years with a male-to-female ratio of 2:1.[2,3,5,7,8,9] It is recognised that the incidence of GI lymphoma is on the increase, particularly in association with immunodeficiency syndromes.

AETIOLOGY

Primary small bowel lymphoma (PSBL) is predominantly B-cell NHL. The exception is T-cell lymphomas arising in the small bowel of untreated celiac disease. The types of lymphomas encountered are:

- low to high grade B-cell lymphoma of mucosa associated lymphoid tissue
- immunoproliferative small intestinal disease (IPSID)
- malignant lymphoma
- Burkitt-like lymphoma
- enteropathy-associated T-cell lymphoma
- nonenteropathy-associated T-cell lymphoma

A link between infective pathogens and specific entities has been implicated. The Ebstein Barr virus has been associated with Burkitt's lymphoma. This lymphoma affects the jaw and abdominal viscera in childhood and the abdominal viscera and lymphoid tissue in adults. The human T-cell lymphotropic virus-1 has been linked with T-cell lymphoma (and leukemia). An association has been demonstrated between *Campylobacter jejuni* and IPSID. Enteropathy-associated T-cell lymphoma usually arises in patients with celiac disease. Patients with congenital and acquired immunodefieciency states, nodular lymphoid hyperplasia, collagen vascular disease and radiation exposure are at risk of developing lymphomas both in the GI tract as well as in non-GI sites.[3,6,7]

CLINICAL FEATURES

The presenting symptoms are very non-specific. This may partly explain the long delay between the onset of symptoms and time of diagnosis. The mean duration of symptoms in various reviews varies from about six months to 27 months.[3,4,9] The most common presenting features are abdominal pain (40%), weight loss (25%), bowel obstruction (20%), abdominal mass (16%), diarrhoea (13%) and nausea and vomiting (12%). Patients may also present with an acute abdomen and this is usually associated with a poor prognosis.[2,3,4,5,7,9,14]

DIAGNOSIS

The criteria for establishing the diagnosis of PSBL are:

- normal peripheral blood smear and bone marrow biopsy
- absence of palpable lympadenopathy and/or lymph-adenopathy on radiological imaging
- disease grossly confined to the small bowel, as confirmed by diagnostic imaging, endoscopy, laparatomy
- absence of hepatic or splenic tumour involvement except by direct extension from a PSBL

Apart from routine blood investigations and a bone marrow aspirate, investigations that are usually done include computed tomography (CT) of the chest, abdomen and pelvis and small bowel enteroclysis. The latter may be of help in determining the site of the lesion and degree of involvement, but it is not diagnostic. The radiological finding may be an ulcer, polyp, nodule and/or thickening of the mucosal folds. Stasis of contrast material also implies some underlying pathology.[7,10]

Capsule Endoscopy (CE)
The diagnostic superiority of CE over conventional modalities such as CT, barium meal follow-through and small

bowel enteroclysis in detecting small bowel disease is now well established. CE has the potential to lead to a diagnosis sooner if used in the investigation of symptomatic patients. CE has two limitations. The first is the inability to provide a histological confirmation of the diagnosis and its inability to distinguish between benign and malignant lesions. (There is the same problem with radiologic small bowel studies.) The other potential problem is retention of the capsule in patients with strictures.[4,11,12]

CE is a means of visualising the small bowel. The procedure involves ingesting a small capsule, which contains a camera, battery, light source and transmitter. It takes two pictures every second for eight hours. It transmits the images to a data recorder about the size of a portable CD player that the patient would be wearing around the waist. Once swallowed, the camera moves naturally through the digestive tract. Patients can carry out their normal activities. The images are then downloaded to a computer and evaluated. The capsule endoscope is disposable and is excreted naturally.

18F-Fluorodeoxyglucose PET (positron emission tomography)

PET produces a functional image. Thus, very small but oncologically active lesions can be spotted. PET cannot distinguish between hot spots due to malignancy and those secondary to an inflammatory process (eg inflammatory bowel disease).[10] Despite the mild physiologic uptake of 18F-Fluorodeoxyglucose in the gastrointestinal tract, it is highly sensitive and specific for evaluation of the treatment response of nodal and extranodal disease in patients with lymphomas. In this aspect, it has been shown to be superior to all other imaging modalities.[8,13] In a 2001 case report,[10] a PET scan was used to diagnose a patient with small bowel lymphoma after all other conventional investigations were normal.

STAGING AND PROGNOSIS

The most important prognostic factor is the stage of the disease at diagnosis. The most commonly used classification is a modification of the Ann Arbor classification as proposed by Muschoff.[15]

Muschoff's modification of the Ann Arbor classification

Stage IE	– tumour confined to GI
Stage IIE1	– regional node involvement (celiac)
Stage IIE2	– extraregional subdiaphragmatic nodal involvement (para-aortic)
Stage IIIE	– nodal involvement on both sides of the diaphragm
Stage IVE	– extranodal invovement (bone marrow, liver)

Other poor prognostic features are high-grade histology, perforations, multiple tumour sites, Burkitt's-like lymphoma and T-cell lymphoma.[1,4,5,12] A 1993 study[16] noted an overall 75% five-year survival in B-cell lymphoma and a 25% five-year survival in T-cell lymphoma.

TREATMENT

Treatment of gastrointestinal lymphomas requires a multidisciplinary approach:

- Patients with stage IE disease benefit from surgical resection followed by radiotherapy. The cure rate is about 75%.
- Patients with stage IIE disease are managed by a combination of chemotherapy and radiotherapy. Radiation is usually administered first to decrease the risk of perforation and bleeding associated with rapid necrosis of the tumour.
- Stage IIIE and IVE disease are managed primarily by combination chemotherapy. Radiotherapy is reserved for more serious local problems such as initial bulky lesions or treatment of residuals following chemotherapy. Only 25-40% of these patients have longterm control of their disease.

Pharmacological treatment

As the most frequently diagnosed lymphoma is diffuse B-cell NHL, combination chemotherapy with cyclophoshamide, doxorubicin, vincristine and prednisolone (CHOP) is regarded as gold standard for stage IIE disease or higher. Intermediate and high-grade lymphomas are potentially curable with the above regimes. Low-grade lymphomas and follicular lymphomas are still considered incurable with the above regime. Low-grade lymphomas characteristically respond initially but follow a course of recurrent relapses and short remissions. Mean survival in this group of patients is 6.2 years from diagnosis and 5 years from the first relapse. Fludarabine (a fluorinated nucleotide analogue of adenosine arabisonide) has anti-tumour activity and is effective as a sole agent in low-grade B-cell lymphoma. In follicular lymphoma, a 65% overall response rate has been reported with fludarabine.[2,5,7]

Surgery

About 20% of patients present with intestinal obstruction and/or perforation. Many of these are diagnosed at laparatomy. Despite the small number of patients in most series the prognosis for those who have undergone surgical resection appears to be better.[5,7,15]

Radiotherapy

Indolent intestinal lymphomas can be treated by surgical resection and radiotherapy. In aggressive histologic subtypes, surgery is usually followed by chemotherapy. In patients with incomplete tumour resection, chemotherapy followed by radiotherapy is recommended. Radiotherapy as a sole modality of treatment may be curative in patients with stage I and II disease. Patients with early stage follicular grade I and II NHL have a median survival of 15 years. Local radiation cures about 40% of these patients.

The optimal strategy of treatment remains to be determined in the absence of any randomised trials.[7]

Immunochemotherapy

Rituximab is a humanised murine monoclonal antibody directed against the CD20 antigen. This is expressed on B-lymphocytes in more than 90% of patents with B-NHL. Rituximab has been combined with CHOP and shown to be clinically effective in both indolent and aggressive B-cell NHL. Responses rates have approached 50% in patients with low-grade NHL who are resistant to conventional chemotherapy. This patient population has few treatment options. No data is available on its use in extranodal disease.[7]

Immunoproliferative small intestinal disease (IPSID)

This is a variant of the B-cell lymphoma of mucosa-associated lymphoid tissue (MALT). Early stage IPSID

responds to antibiotics (30-70% complete remission). The first line antibiotics are usually metronidazole and tetracycline (alone, together or combined with ampicillin). Patients without a marked improvement after a six-month course of antibiotics or complete remission after 12 months are usually given CHOP chemotherapy. The latter is also recommended as first line treatment for patients with advanced disease.

CONCLUSION

Primary malignancies of the small bowel present unique challenges in terms of diagnosis, operative and pharmacological treatment decisions and prognosis. The infrequency of these tumours relative to those of the rest of the gastrointestinal tract accounts for part of this ambiguity. However, we think that new imaging techniques such as CE, magnetic resonance enteroclysis and PET scan should help the clinicians in the early diagnosis and management of these tumours.

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