Primary Gastrointestinal Lymphoma In Immunocompromised Patient. Case Report And Literature Review

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Primary gastrointestinal lymphoma is a rare disease with no specific clinical presentation. Early diagnosis is usually based on suspicious index, otherwise majority of patients present at late with very advanced disease with complications.
The incidence of primary gastrointestinal lymphoma is increasing with HIV disease.
There are several classification and staging systems with different treatment options varying from one center to another. Prognosis depends on the stage at presentation, degree of differentiation and age. It was concluded that early diagnosis depends on degree of suspicious index with good treatment response. Late presentation is accompanied by marked immunosuppresion. Future research needs to determine whether single or combined modalities of treatment have good treatment outcomes. A case of primary gastrointestinal lymphoma in immunocompromised patient is reported with literature review.

Introduction

Primary gastrointestinal lymphoma is a rare condition accounting for 0.8-1.2 cases per 100,000. Gastrointestinal tract is the most frequent extra-nodal site of primary lymphoma[1,2,3,4].

The incidence of primary gastrointestinal or hepatic lymphoma is increasingly being seen with human immunodeficiency disease[5,6,7,8]. Non-Hodgkin's lymphoma (NHL) is the second most frequent malignancy associated with Human Immunodeficiency virus (HIV) following Kaposi's sarcoma. Other malignancies include carcinoma of cervix, anal canal carcinoma, ocular carcinoma and childhood malignancies[5,6,9]. When evaluating AIDS-associated cancers in Sub-Saharan Africa it was found that among patients with HIV/AIDS; 5.6% have NHL in South Africa, 2.8% in autopsy study at Ivory Coast, 8.5% and 12.4% in 1981 – 1990 and 1991 – 1998 in Ibadan respectively[2].

Majority of patients with primary gastrointestinal lymphoma present with late advanced disease and complication(s) before diagnosis is made. Diagnosis of gastrointestinal lymphoma is mainly based on suspicious index as there is no specific symptom or sign[10,11,12]. There are several different histological classifications, staging systems and controversies in the treatment options[1,2,3,4,5]. This prompted the authors to report on this case as well as literature review on primary gastrointestinal lymphoma.

Case Report

T.M aged 48 male, driver, known sero-positive on Anti-Retro Viral therapy (ARV)-Trioimune[40] for four months, presented with gradual onset of epigastric pain for two months. Initially pain was dull in nature and localized but later on became generalized and colicky in nature. He also experienced postprandial fullness with little feeds, on and off episodes of diarrhoea (3 loose motions per day, not bloody or foul smelling) and vomiting of recently taken food and occasionally bilious vomitus. He reported a significant body weight loss with no history of haematemesis or maelena. His micturition habits were normal and there was no history of fever.
He had been admitted twice at District Hospital and twice in Medical Department at Muhimbili National Hospital for the same complaints with no improvement. He had

completed a 9-months course treatment for pulmonary tuberculosis therapy in 2001. He was married with three children all alive and doing well. He took alcohol occasionally but he was a non smoker.

Physical examination revealed middle-aged man, very weak and dehydrated. He was not pale, had no oral thrush and no palpable peripheral lymph nodes. Pulse rate was 80/minute regular and of normal volume. Blood pressure was 120/70 mmHg. Abdominal examination revealed a full abdomen, moving with respiration, visible peristalsis from left to right and soft. There was a palpable firm, tender, ill defined mass in the left hypochondrium. Succussion splash was negative. Bowel sounds were normal and digital rectal examination revealed normal findings. Other systems were found to be normal. A provisional diagnosis of Partial intestinal obstruction. The cause was uncertain

Investigations done during this illness included:

- Chest X-ray, which was normal. A repeat after one month was normal too.
- Haemoglobin was 14.2 g/dl, WBC count = 8,800cells/cmm, ESR=30mm/hr.
- Serology for H. pylori was negative.
- Stool analysis revealed E. coli.
- Urinalysis was normal.
- Oesophagogastroduodenoscopy (OGD) revealed oesophageal candidiasis, severe reflux oesophagitis and gastritis.
- Double ELISA test for HIV was positive.
- CD_4 count was 180-cells/ µl. Repeat CD_4 after one month was 284-cells/ µl.
- Abdominal Ultrasonography was normal. Repeat after one month was normal too.
- .CT-scan revealed a mass in the right hypochondrium (opposite from clinical examination) with undetermined origin.

Treatment given during this period included Fluconazole, Omeprazole, Metronidazole, Trioimune[40], Septrin, Metochlorpramide, Multivitamin, Intravenous fluids.

Because of persistent colicky abdominal pain, it was decided to take the patient for exploratory laparotomy. The findings included multiple purple nodules involving the stomach and small bowel wall. There was one big mass (6 x 4cm) causing jejunal obstruction. There were no mesenteric or paraortic lymph node enlargement and the rest of the abdominal viscera were normal. Resection of the mass causing obstruction, end to end anastomosis was done with uneventful postoperative recovery.

Histology of biopsy specimen revealed "diffuse large cell lymphoma, high grade". The patient was then referred to Ocean Road Cancer Institute (ORCI) where he was planned for six cycles of second line chemotherapy (Doxorubicin, Cyclophosphamide, Bleomycinand and Prednisolone).He received the first cycle then he was discharged home.

He was planned to go back for the second cycle after three weeks but he died suddenly on the same day of discharge just after arrival at home. The cause of death was attributed to treatment complications due to advanced disease.

Discussion

Clinical features of gastrointestinal lymphoma are often vague and non-specific leading to delay in diagnosis with poor treatment outcome[13,14,15]. Its presentation depends on the tumor size and its location. It may present with a single lesion, multiple fungating masses or diffuse lesions affecting any region from the oral mucosa to the rectum. The most frequent location is the stomach accounting for 74.7% to be followed by small bowel (8.6%) then ileo-caecal region (7.0%) and multiple sites (6.5%). The rest of regions constitute 3.2 %[4]. Our patient presented with multiple sites involving stomach, duodenum, jejunum and ileum.

The commonest symptoms include vague abdominal pain, nausea, weight loss, vomiting and abdominal fullness[16,17,18]. These may mimic other abdominal pathologies such as peptic ulcer, pancreatitis, cholecystitis or malignancies. Our patient had all these symptoms with diarrhoea in addition. Pain is the main diagnostic symptom to be followed by nausea in both gastric and intestinal lymphoma accounting for 78% in gastric and 53.3% in multiple involvements[4].
Less frequent symptoms include body weakness, sweating, jaundice, pyrexia of unknown origin and dysphagia[16,19,20]. Rare symptoms include haematemesis or malaena, gastric outlet obstruction, and bowel perforation[15,16].

Physical examination is normal in 55-60% of patients[16]. Common signs include epigastric or generalized tenderness and palpable mass(es) accounting for 20-35% and 17-25% respectively[17,20,21]. Other uncommon findings include pyrexia, hepatosplenomegaly, jaundice and lymphadenopathy. Our patient had a palpable tender mass.

Diagnostic investigations include barium swallow or meal depending on presentation, upper or lower gastrointestinal endoscopy + step multiple biopsies depending on presentation, abdominal ultrasonography, abdominal CT scan, Magnetic Resonant Imaging (MRI) and Fine Needle Aspiration Cytology (FNAC) if present with a mass. Barium swallow or meal may show a filling defect, atypical ulcer deformities, obstruction, mass effect and gastric wall thickening suggestive of gastric lymphoma but not specific[12,16,17,22]. Upper GI' endoscopy (OGD) may reveal a range of features which vary from subtle mucosal changes to gross lesions which include mucosal oedema, friability, patchy redness, irregular patchy gray or whitish granular easily bleeding, irregular erosions and ulcerations[12,23]. Powtz et al[1] when evaluating seropositive patients with abdominal pain found that out of 93 endoscopies 7.5% had Non Hodgkin's lymphoma.

Abdominal ultrasonography is helpful in evaluating hepatic lesion(s) or in staging purposes by identifying involvement of intra-abdominal lymph node. CT scan of abdomen revealed gastric wall thickening or mass lesions. It may show mural (horizontal) thickening compared to vertical growth in carcinoma at early stages of the disease. It also reveals peri-gastric, porta-hepatis and para-aortic lymph node enlargement, which is useful in staging purposes[24,25].

Endoscopic ultrasonography may differentiate infiltrative carcinomas from lymphoma whereby, carcinoma reveal a vertical growth compared to horizontal growth in early stages as well as perigastric lymph nodes in staging purposes[26,27]. MRI reveals irregularly thickening mucosa, irregularly submucosal infiltration, annular constricting lesion, exophytic tumor growth, mesenteric masses and mesenteric/retroperitoneal lymphadenopathy[28]. Bone marrow is used for staging purposes and indirect laryngoscopy is used in assessing Waldeyer's ring, which is common in lymphoma. FNAC by experienced Cytologist is helpful in hepatic lesion or lymph node[23]. The above diagnostic methods avoid unnecessary exploratory laparotomy to confirm the diagnosis and staging purposes.

There are several classification systems for staging gastrointestinal lymphoma based on Ann Arbor Classification. Treatment for gastrointestinal NHL depends on the stage and grade of the disease as follows[4,30,31]:

(i) Low- grade lymphoma, stage IE and IIE
Surgical resection then extended field radiotherapy with total abdominal irradiation with 30 Gy. In case of residual tumor, then an additional boost (10 Gy)
In addition to patient with stage IIE, six cycles of (COP)-Cyclophosphamide 500mg/m^2 on days 1-5, Vincristine 1.4 mg/m^2 on day 1 and Prednisone 100mg/m^2 on days 1-5 preceeding radiotherapy.

(ii) Low grade lymphoma, stage IIIE and IVE receive COP six cycles only.

(iii) High grade lymphoma stage IE
Four cycles of second line chemotherapy, which include (CHOP)-Cyclophosphamide 750 mg/m2, Doxorubicin50mg/m2, Vincristine 1.4mg/m2, Prednisone 100mg on days 1-5 followed by extended field radiotherapy (30Gy + 10 Gy boost) on tumor bed.

(iv) High grade lymphoma stage IIE – IVE
Six cycles of CHOP and additional involved field radiotherapy (40 Gy)

Table 1. Staging Classification for gastric lymphoma according to Musshof's criteria[29]:

Stage	Definition
I E	Lymphoma limited to the stomach
II E_1	Involvement of stomach and contiguous lymph nodes
II E_2	Involvement of stomach and contiguous subdiaphragmatic lymph nodes
III E	Involvement of stomach and lymph nodes on both sides of the diaphragm.
IV E	Haematogenous spread (stomach and one or more extra lymphatic organ or tissues.

E = Extra-nodal, S = Splenic, A=Asymptomatic, B = Symptomatic.

Table 2. Modified Black-ledge staging system for gastrointestinal lymphomas[29]:

Stage	Definition
I	Tumor confined to GIT without serosal penetration: single primary site. Multiple, non-contiguous lesions.
II	Tumor extending into abdomen from primary site: • Nodal involvement • II_1- Local involvement (gastric or mesenteric) • II_2 – Distant involvement (Para-aortic or paracaval)
II E	Penetration of serosa to involve adjacent structures: Enumerate actual size of involvement, e.g. stage II E (pancreas), IIE (Colon), stage IIE-post abdominal wall Perforation / peritonitis.
IV	Disseminated extra-nodal involvement or a GIT lesion with supradiaphramatic nodal involvement.

When evaluating prognosis and cause of death it was found that gastrointestinal lymphoma is associated with late manifestation of HIV/AIDS with marked immunosuppresion and poor prognosis[2]. Gastric and ileocaecal lymphoma had better prognosis than small bowel (P=0.04323) and when multiple sites involved (P=0.0177). Another study revealed that 13 out 20 (65%) deaths were related treatment or late presentation[4]. Surgical resection in early stages of disease has good outcome with a 5-year survival rate of 80-93%[32,33]. Aggressive surgery is not indicated due to increased morbidity and this does not influence the survival[34,35].

Operative mortality was between 3 to 25 % with higher rates for palliative resection, which were performed for symptomatic relief or tumor debulking[36]. Combination of surgery and chemotherapy have shown the survival rate of 60-100% for early disease[37].Good prognosis was associated with low Grade disease, age below 65 years, free surgical margins in case of complete resection and achievement of initial complete remission[38,39,40]. Five-year survival rates were reported to be 91%for low grade, 73% for secondary high grade and 56% for primary high-grade tumors[41].

Conclusion

Early diagnosis of gastrointestinal lymphoma is mainly based on a high suspicious index and has good treatment outcome. Late presentation is associated with marked immunosuppression and poor prognosis. Randomized trials are needed to clarify whether conservative (radiotherapy), surgical or combination treatment is more appropriate for localized gastric lymphoma.

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