

Original Research Article

The study of clinical and endoscopic spectrum of upper gastrointestinal manifestations in HIV patients

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ABSTRACT

Background: Opportunistic disorders are the most frequent GI complications of HIV infection and remain a major cause of morbidity and mortality in these patients. These disorders account for high prevalence of upper gastrointestinal symptoms such as dysphagia, odynophagia, retrosternal chest pain, abdominal pain and upper GI bleeding. Hence an attempt is being made to study clinical, endoscopic and biopsy changes in HIV patients with upper GI symptoms which helps us to make early diagnosis of upper GI disorders in HIV patients.

Methods: HIV positive patients above 14 yrs diagnosed on the basis of recent NACO criteria having Upper G.I. symptoms, attending OPD of Department of Medicine admitted in Wards. All fifty three patients with upper G.I. symptoms were subjected to detail history, thorough clinical examination, routine and special investigations and Upper G.I Endoscopy.

Results: Out of fifty three patients, nineteen (35.8%) cases had normal endoscopy. The most common finding was Antral Gastritis in fourteen (26.4%), followed by Candida esophagitis in twelve (22.6%), esophagitis in three (5.7%), candida esophagitis with antral gastritis in two (3.8%), duodenitis, varices and mass (ulcerated growth) in II part of Duodenum seen in one (1.9%) each.

Conclusions: The evaluation of specific gastrointestinal complaints must be based on an assessment of degree of immunosuppression. With the progression of immunodeficiency, EGD becomes a useful diagnostic modality for the early diagnosis of these opportunistic infections and other inflammatory conditions.

Keywords: Candidiasis, HIV, PLHA, Upper GI endoscopy

INTRODUCTION

Human immunodeficiency virus infection / acquired immuno-deficiency syndrome (HIV/AIDS) is a disease of the human immune system caused by infection with human immunodeficiency virus (HIV).¹ The term "syndrome" has been used because AIDS does not constitute a single illness, but rather encompasses a wide range of clinical diseases including specific life threatening infections and neoplasm's associated with a profound and irreversible unexplained acquired disorder of cell mediated immunity.²

The HIV/AIDS pandemic has potential to wreck enormous financial, political and health-related havoc. Despite the dramatic impact of highly active antiretroviral therapy (HAART) on the morbidity and mortality associated with HIV infection, patients continue to ultimately have a dismal prognosis.³ The impact of the HIV/AIDS epidemic is already severe and continues to increase over the next decades.⁴ Globally, an estimated 35 (33.1-37.2) million people were living with HIV in 2013. There were 2.1 (1.9-2.4) million new HIV infections globally, showing a 33% decline in the number of new infections from 3.4 (3.1-3.7) million in 2001. At the same time the number of AIDS deaths is also

declining with 1.5 (1.4-1.7) million in 2013, down from 2.3 (2.1-2.6) million in 2005.⁵

The spectrum of the disease varies from asymptomatic infections to acquired immunodeficiency syndrome (AIDS). Although early case reports emphasized presentations with either unusual tumours (i.e. kaposi sarcoma) or opportunistic infections (i.e., pneumocystis carinii pneumonia) it soon became evident that significant gastrointestinal symptoms, including weight loss and diarrhoea were common. The frequency of GI symptom is varied, however in developing countries upto 100% of patients with AIDS have gastrointestinal problems, and thus AIDS is referred to as the "slim disease".⁶

Opportunistic disorders are the most frequent GI complications of HIV infection and remain a major cause of morbidity and mortality in these patients.⁷ These disorders account for high prevalence of upper gastrointestinal symptoms such as dysphagia, odynophagia, retrosternal chest pain, abdominal pain and upper GI bleeding.⁷ Endoscopy plays a key role in the management of these patients since many patients these disorders have a characteristic appearance at endoscopy.⁷ With progression of immunodeficiency, endoscopy becomes a very useful diagnostic modality to diagnose the predisposing opportunistic disorders and other inflammatory conditions.^{7,8}

Hence an attempt is being made to study clinical, endoscopic and biopsy changes in HIV patients with upper GI symptoms which helps us to make early diagnosis of upper GI disorders in HIV patients.⁶ This study investigated the prevalence of common upper GI symptoms in the HIV-infected population.

METHODS

HIV positive patients above 14 yrs of age diagnosed on the basis of recent NACO criteria having Upper G.I. symptoms, attending OPD of Dept. of Medicine or admitted in Wards were included in the study. The study design was of observational study and sampling method employed was Simple Random sampling.

All HIV cases were subjected to history and clinical examination. Out of 62 cases, nine cases had a single or more exclusion criteria, hence they were excluded from the study. Rest 53 cases of HIV infection with upper G.I. symptoms formed the material of the present study. Written Informed Consent was obtained after explaining the patients the details of information of the present study. Information of each patient was collected using prepared proforma. The study cases were splitted in two groups on the basis of CD4 count. Those HIV patients having CD4 count <200 comprising of Group A of thirty six (67.9%) patients and seventeen (32.1%) patients with CD4>200 comprised group B, indicating more immunosuppression in group A.

All fifty three patients with upper G.I. symptoms were subjected to detail history, thorough clinical examination, routine and special investigations and Upper G.I. Endoscopy.

Esophago-gastro-duodenoscopy

All patients were subjected for upper GI endoscopy. Prior consent was taken. Premedication was given with oral xylocaine and injection midazolam 2mg IV. Pentax EG 2940 Video endoscope was used to visualize the upper GI tract. The scope was disinfected with 2 % glutaraldehyde before the procedure. Esophageal, gastric and duodenal mucosa was carefully examined for evidence of inflammation, ulceration, erosions, edema, hemorrhagic patches and opportunistic infections. In all patients, Antral biopsy was taken, additional biosy were taken from the mucosal lesions if present in a particular patients.

Biopsy specimens were subjected for histopathological examination. The biopsy specimens were spread on a 2 x 2 cms filter paper. The raw surface adhered to the filter paper without curling. The tissue with the filter paper was placed in 10 percent formalin transported to the pathology department. After routine processing several sections were deparafinised and hydrated with water. The sections were then held in running water. Rapid dip in 3 percent acetic acid for differentiation was done. The sections were cleared.

Statistical analysis

All values expressed as mean with/without standard deviation (S.D.) Correlation studied using STATA statistical analysis software v.10 and Microsoft word and Excel have been used to generate graphs, tables etc. Student t-test for unpaired data was used for the comparison of mean values. Chi-square test, Fischer Exact test was applied for the significance of correlation of data and 'p' value of less than 0.05 was considered as statistically significant.

RESULTS

Out of 62 cases, nine cases had a single or more exclusion criteria, hence they were excluded from the study. Rest 53 cases of HIV infection with upper G.I symptoms formed the material of the present study.

In the present study, the most common symptom encountered was epigastric pain seen in forty nine patients (92.5%) followed by anorexia and weight loss in forty five (84.9%) and forty one (77.4%) respectively. However the prevalence of other symptoms nausea in thirty three (62.3%) ,vomiting in twenty four(45.3%) , dysphagia and odynophagia in twelve (22.6%) each were also observed . Diarrhoea was noted in twenty six (49.1%) while hematemesis was seen in only two (3.8%) cases (Table 1).

Table 1: Symptomatology of study cases (n=53).

Symptoms	Number of cases (percentage)
Nausea	33 (62.3)
Vomiting	24 (45.3)
Dysphagia	12 (22.6)
Epigastric pain	49 (92.5)
Odynophagia	12 (22.6)
Anorexia	45 (84.9)
Weight loss	41 (77.4)
Diarrhoea	26 (49.1)
Hematemesis	2 (3.8)

Table 2: Endoscopic findings in study cases (n=53).

Endoscopic findings	Number of cases	Percentage
Candida esophagitis	12	22.6
Esophagitis	3	5.7
Antral gastritis	14	26.4
Candida esophagitis with antral gastritis	2	3.8
Duodenitis	1	1.9
Normal	19	35.8
Others		
Varices	1	1.9
Mass	1	1.9

Table 3: Histopathological findings in study cases (n=53).

Histopathological findings	Total number of cases	%
Candida esophagitis	13	24.5%
Esophagitis	4	7.6%
Acute gastritis	3	5.7%
Chronic non specific gastritis	11	20.8%
Duodenitis	1	1.9%
Adenocarcinoma	1	1.9%

All fifty three cases were subjected for endoscopic evaluation. Out of fifty three patients, nineteen (35.8%) cases had normal endoscopy. The most common finding was Antral Gastritis in fourteen (26.4%), followed by Candida esophagitis in twelve (22.6%), esophagitis in three (5.7%), candida esophagitis with antral gastritis in two (3.8%), duodenitis, varices and mass (ulcerated growth) in II part of Duodenum seen in one (1.9%) each (Table 2).

In this study thirteen (24.5%) patients had candida esophagitis and chronic non-specific gastritis in eleven (20.8%), four (7.6%) had esophagitis, three (5.7%) had acute gastritis and only one (1.9%) each had duodenitis and adenocarcinoma. Among all the biopsies thirty five were normal (Table 3).

The study cases were splitted in two groups on the basis of CD4 count. Those HIV patients having CD4 count <200 comprising of Group A of thirty-six (67.9%) patients and seventeen (32.1%) patients with CD4>200 comprised group B, indicating more immunosuppression in group A. Mean CD4 in our study was 167.85+/-106.05Cells/mm³ (Table 4).

Table 4: CD4 cell count in study cases (n=53).

CD4 Cell/mm ³	Number of cases	Percentage
< 200	36	67.9
>200	17	32.1
MEAN +/- SD	167.85 +/- 106.05 Cells/mm ³	

Table 5: Correlation of CD4 count with endoscopic findings (n=53).

Endoscopic findings	CD4<200 (N= 36) group A	CD4>200 (N=17) group B	P value
Present	27(50.9 %)	7 (13.2%)	0.03
Normal	09 (16.98%)	10 (18.8%)	

Table 6: Correlation of histopathological findings with CD4 count in study cases (n=53).

Histopathological Findings	CD 4 < 200 (n=36) Group A	CD 4 > 200 (n=17) Group B
Candida esophagitis	12 (22.6%)	1 (1.9 %)
Esophagitis	3 (5.7%)	1 (1.9%)
Acute gastritis	3 (5.7%)	0
Chronic non specific gastritis	7 (13.2%)	4 (7.5%)
Duodenitis	1 (1.9%)	0
Adenocarcinoma	1 (1.9%)	0
Normal	11 (20.8 %)	11 (20.8%)

Out of thirty six cases of group A, endoscopic findings were obtained in twenty seven (50.9%) while seven (13.2%) in group B. However, nine (16.98%) cases of group A and ten (18.8%) of group B had normal endoscopy. After application of Fisher Exact Test, p value came out to be 0.03. Hence there is a strong statistical correlation of CD4 count with Endoscopic findings of group A and group B in study cases.

Out of 36 cases of group of A candida esophagitis was seen in twelve (22.6%), chronic non specific gastritis in seven (13.2%), esophagitis and acute gastritis in three (5.7%) each, duodenitis and Adenocarcinoma in one (1.9%) each. Eleven (20.8%) showed normal histopathology in group A. while in group B, Chronic non specific gastritis was seen in four (7.5%) and candida esophagitis, esophagitis in one (1.9%) each. Eleven (20.8%) showed normal histopathology in group B. There was a good association of Endoscopic findings and biopsy of lesions histopathologically (Table 6).

DISCUSSION

Gastro intestinal manifestations are among the most frequent complaints in patients with HIV disease. The reported incidence of gastrointestinal manifestation varied from 50 to 93%. The upper gastrointestinal manifestations include nausea, vomiting, epigastric pain, dysphagia, odynophagia, weight loss, anorexia, hematemesis, and hiccups. The evaluation of specific gastrointestinal complaints must be based on an assessment of degree of immunosuppression. With the progression of immunodeficiency, EGD becomes a useful diagnostic modality for the early diagnosis of these opportunistic infections and other inflammatory conditions.⁹

In this study, cases were divided according to severity of immunosuppression in 2 groups-group A with AIDS defining illness CD4 <200 and group B with CD4 >200 cells/mm³. In Group A, out of thirty-six (67.9%) patients, twenty (37.7%) patients were severely immunocompromised, having CD4 less than 100. seventeen (32.1%) patients of group B had CD4>200. Mean CD4 count with SD in this study was 167.85 +/- 106.05.

In the present study the most common symptom was epigastric pain in forty nine (92.5%) followed by anorexia and weight loss in forty five (84.9%) and forty one (77.4%) respectively. Nausea was seen in thirty three (62.3%), diarrhoea in twenty six (49.1%), vomiting in twenty four (45.3%), odynophagia and dysphagia in twelve (22.6%) and hematemesis was seen in two (3.8%) cases.

Epigastric pain, nausea and diarrhea were slightly more common in patients with CD4 >200. Various studies have shown a diverse pattern of presenting complaints in HIV patients. Some were due to the disease itself, others due to opportunistic infections and drugs (HAART) prescribed to these patients. Elshazly MA et al, reported vomiting in all patients and dysphagia, epigastric pain were reported in 89%.¹⁰ Other symptoms reported in decreasing frequency were odynophagia 46%, retrosternal chest pain 40%, haematemesis 10%, and hiccough 3%. Corley DA et al, studied 201 patients and found that anorexia was seen in most (70%) followed by epigastric pain (34%), vomiting (32%) and weight loss (31%).¹¹ Other authors Ravi kumar et al, A. Gupta et al, Sakamoto M, Adachi T, Sagara H, Yoshikawa K, reported GI symptoms were more common in patients with CD4 <200.¹²⁻¹⁴

Endoscopic and histopathological findings

In the present study, nineteen patients (35.8%) showed a normal Endoscopy. Most common endoscopic finding was antral gastritis in fourteen (26.4%), followed by candida esophagitis in twelve (22.6%), esophagitis in three (5.7%), candida esophagitis with antral gastritis in

two (3.8%), duodenitis, varices and mass (ulcerated growth) in II part of duodenum seen in one each (1.9%). Majority showed involvement of esophagus and stomach.

Positive endoscopic findings were significantly seen in patients with AIDS defining illness (CD4<200) (P=0.03). Twenty seven (50.9%) patients had positive endoscopic findings in group A while seven (13.2%) cases in group B.

In the study cases majority of histopathological findings were observed in patients having CD4<200. In Group A, twelve (22.6%) had evidence of candida esophagitis while eleven (20.8%) did not have any abnormality, seven (13.2%) had chronic non specific gastritis, three (5.7%) each had esophagitis and acute gastritis respectively, one (1.9%) had duodenitis and other one (1.9%) had adenocarcinoma of II part of duodenum.

Maximum seventeen (32.1%) cases had endoscopic findings restricted to esophagus, among them twelve (22.6%) patients had raised whitish plaques with surrounding congestion suggestive of candida esophagitis, three (5.7%) patients had erosions and congestion suggestive of esophagitis, may probably due to viral infections CMV, HSV, bacterial infections like Mycobacterium avium complex, disease itself, Idiopathic ulceration, drugs (HAART) and rarely protozoans like Cryptosporidium parvum, Pneumocystis carinii, and leishmania. For further evaluation, biopsies were taken and samples were sent for histopathological examination. Seventeen (32.1%) positive histopathological findings were restricted to Esophagus. Thirteen patients (24.5%) had yeast and pseudohyphae with spores in few characteristic of Candida Species. In four (7.6%) patients, microscopically, eosinophilic intranuclear inclusions, multinucleated epithelial cells, aggregates of large mononuclear cells with basophilic cytoplasm were seen indicative of infective etiology probably viral or else which could not be investigated further due to non-availability of immunohistochemistry.

Fourteen (26.4%) patients had positive Endoscopic findings in Stomach. All patients had diffuse erosions with congestion, most commonly in Antrum suggestive of Antral Gastritis. Etiology of Antral Gastritis was also Multifactorial. Bacterial, viral, fungal, and protozoan infections have all been reported. Most common cause of antral gastritis in immunocompetent and immunosuppressed patients was H. Pylori. Other infectious causes were Candida Sp., Cytomegalovirus (CMV) or cryptosporidium parvum infections, toxoplasma gondii, leishmania donovani, mycobacterium avium-intracellulare complex (MAC), treponema pallidum, Bartonella henselae, Bartonella quintana, and Cryptococcus neoformans.

The endoscopic and histopathological findings could be caused by HIV, HIV enteropathy, opportunistic infections and drugs. Multiple biopsies were taken for further

evaluation and specific diagnosis. Antral biopsies were taken in all patients. Fourteen (26.4%) positive histopathological findings were seen in stomach. The most common being chronic non specific gastritis in eleven (20.8%). Microscopically, mild hyperplasia of lining is seen with increased goblet population. There is moderate mononuclear cells infiltration in submucosa, suggestive of chronic non specific gastritis. Again the etiologies were multifactorial.

Opportunistic infections like Candida, CMV and HSV were common. Drugs again being an important factor affecting the mucosa. However, they could not be differentiated histopathologically. Further evaluation could not be done due to non-availability immunohistochemistry. In three (5.7%) patients, histopathology revealed submucosal diffuse infiltration of inflammatory cells of mononuclear series, features suggestive of Severe Gastritis. This could be due to severe infection or drug Induced Gastritis. However, no organism was isolated.

One (1.9%) patient had evidence of Grade III Varices. This was unrelated to the underlying disease. Two (3.8%) patients had positive findings in duodenum. endoscopically, one had diffuse erosions with congestion suggestive of duodenitis. Bacterial, viral, fungal, and protozoan infections have all been reported to cause duodenitis. CMV, MAC, HSV, being the commonly isolated organisms. Further biopsies were taken and sent for histopathological examination. It revealed submucosal infiltration with mononuclear cells suggestive of duodenitis. Exact etiology could not be reported. Another one had an ulcerated growth in the II part of duodenum. Multiple biopsies were taken and sent for histopathological examination. Most common malignancies reported in HIV patients are Kaposi's Sarcoma and Lymphomas. However, we obtained ulcerated growth in II part of duodenum exhibiting the features of adenocarcinoma. This was unrelated to the underlying primary disease.

Thus, it was observed in the present study that endoscopic and histopathological findings were more significant in patients with severe immunosuppression. Candida esophagitis, gastritis and possibly candida gastritis was the commonest infection seen in our study. Other workers like Ravikumar et al, studied fifty patients, candidiasis was seen in 28%, esophagitis in 22% and Gastritis in 20%.¹² Vui heng chong and Chee chain lim et al, showed among one hundred twenty five HIV positive patients, candidiasis was seen in 23.1%.⁹ Elshazly MA et al, 74% showed changes in esophagus and 28% in stomach.¹⁰ Candida was the main pathogen detected, thus demonstrating a high incidence of candida esophagitis in their study. Korać M et al, even stated candidiasis was the marker of advanced immunodeficiency.¹⁵ Olmos MA et al, stated that biopsies more frequently detected opportunistic and non-opportunistic diseases in patients with lower CD4 counts.¹⁶

In all these above studies esophageal Candidiasis, esophagitis, esophageal ulcers, gastritis and duodenitis are commonly associated with CD4 <200.

Other opportunistic infections like CMV, HSV etc also could cause esophagitis as well as chronic gastritis but as the facilities for their isolation were not available so they could not be studied in our patients. However other studies done by Ravikumar et al, showed CMV esophagitis in two (4.87%).¹² Vui heng chong and Chee chain Lim et al, demonstrated CMV Esophagitis in 11.2%, herpes simplex esophagitis in 3.2%.⁹

Endoscopic findings like oesophageal ulcerations, gastric erosions, intestinal tuberculosis which have been reported by other authors like Ravikumar et al, Vui heng chong and Chee chain lim et al, were not seen in our patients.^{9,12} This was probably due to majority of patients being on HAART. Studies have shown regression of mucosal lesion with initiation of HAART therapy within 2-3 weeks.¹⁷

The literature is flooded with the evidence of commonest GI malignancy in patients with HIV is Kaposi sarcoma, in contrary to this, in the present study, one patient had ulcerated growth in duodenum which was histopathologically proved to be adenocarcinoma.

In contrast to our studies, Study conducted by Corley DA, Cello JP, Koch J et al, Patients undergoing EGD had more frequent/severe symptoms, but did not have differences in overall well-being or mean GI symptom score.¹¹ The frequency of substantial and treatable endoscopic findings among patients infected with HIV was comparable to that found in the non-HIV-infected control group. There were no independent symptoms predicting substantial or treatable disease on EGD.

In another study Werneck-Silva AL et al, showed there was no difference in endoscopic findings according to CD4 cell count groups.¹⁸ They concluded that most of the endoscopic lesions in dyspeptic HIV-infected patients under HAART were not related to AIDS.

The endoscopic findings of the present study were corroborated with those obtained by other workers, Ravikumar et al, Vui heng chong and Chee chain lim et al, Elshazly MA et al, Mezzi G et al and further denoted significant correlation of the endoscopic findings with immunosuppression.^{9,10,12,19}

CONCLUSION

All patients had Upper G.I complaints. Epigastric pain (92.5%) was the most common G.I complaint followed by anorexia and weight loss in forty five (84.9%) and forty one (77.4%) respectively. Both the groups showed higher incidence of GI symptom, although no statistical significance was seen among two groups.

Endoscopic findings and lesions were also commonly present in patients with immunosuppression and AIDS defining illness. Positive endoscopic findings were seen in 50.9% in group A as compared to 13.2% in group B. This was statistically significant ($p=0.03$). These lesions are due to increased infection with immunosuppression and may also be related to drug therapy.

Reported histopathologies were more commonly seen in patients having $CD4 < 200$. Candida esophagitis (22.6%) and chronic non specific gastritis (13.2%) in group A were the most common lesions found.

The present study concluded that Upper G.I manifestations were common in HIV patients and had diverse presentations. GI Infections and endoscopic findings were commonly seen in severely immunocompromised patients. Endoscopy served to find out the specific problem in these patients, so they could be evaluated and treated accordingly. Picture and severity of the illness was significantly modified and became less severe with introduction of HAART Therapy.

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