Clinical significance of bowel wall thickening on computed tomography in HIV-infected patients : association of anemia and hypoalbuminemia

Deepshikha Nag Chowdhury, Jason Dazley, Chintan Modi, Robert Spira, Joseph Depasquale, Vincent DeBari, Walid Baddoura

(1) Department of Internal Medicine, St. Joseph's Regional Medical Center, Paterson, NJ ; (2) Department of Infectious Diseases, (3) Department of Gastroenterology, (4) Director of Research, Seton Hall University School of Health and Medical Sciences, South Orange, NJ.

Introduction

Computed tomography scanning of the abdomen and pelvis is a frequently used procedure. Advanced technology and the availability of superior scanning instruments [such as helical or multidetector scanners (MDCT)] have made detection of subtle gastrointestinal tract disorders facile. Thickening of the gastrointestinal or bowel wall is an increasingly recognized abnormality seen on computed tomography (CT) scanning of the abdomen and pelvis. Normally, on CT scanning of the abdomen, esophageal wall thickness is not greater than 5 millimeters (mm) in thickness (1), the stomach wall is usually less than 3 mm (2) or 5 mm (1) in thickness, the duodenal wall is less than 3 mm (2), the small bowel wall is less than 4 mm, and the colonic wall is less than 3 mm (1,2).

As a result of the unrestricted use of computed tomography to look for abnormalities in patients with varied abdominal complaints, such as nausea, vomiting, vague abdominal pain and diarrhea, incidental detection of gastrointestinal abnormalities are common (8). As mentioned above, bowel wall thickness of more than 3.0 mm should be recognized as a sign of a pathological process (4). Many diseases can cause bowel wall thickening (BWT) such as carcinoma, inflammatory or infectious diseases of the bowel, and edema (5,9,10,11,12). However, BWT could also be a clinically insignificant finding, such as in the case of inadequate distension of the colon (3,12), and may also be subjective. Looking at the clinical significance of incidentally detected bowel wall thickening, a study by Tellez Avila *et al*. showed hemoglobin less than 12 gram/deciliter (g/dl) to be the only significant variable predicting an abnormal endoscopic finding (16). In another study published in 2009, Patel *et al*. observed that patients with more significant pathology were more likely to have lower albumin levels (6).

It is well known that there is a higher prevalence of neoplasm and opportunistic infections in patients infected with the human immunodeficiency virus (HIV), in addition to benign inflammatory lesions of the gastrointestinal tract. Thus endoscopy may be especially useful for the work up of bowel wall thickening in HIV infected patients.

In a study including HIV-positive patients, the positive predictive value of bowel thickening on CT scanning of the abdomen for an endoscopic abnormality was 67% (2). Only a few studies that define endoscopic abnormalities found in patients having intestinal wall thickening on CT scans have been performed on HIV infected patients.

The aim of our study is to determine if anemia and hypoalbuminemia are associated with abnormal endoscopic and clinically significant pathological findings on biopsy performed for bowel wall thickening reported on CT scans in HIV infected patients.

Methods

Setting

This was a multicenter retrospective cohort study conducted at three teaching hospitals in northern New Jersey, USA. They were St. Joseph's Regional Medical Center, a 650 bed tert iary care facility located in Paterson, NJ, St. Michael's Medical Center, an acute care hospital with 357 beds in Newark, NJ and Trinitas Regional Medical Center, another 531 bed tertiary care teaching hospital in Elizabeth, New Jersey. The study was approved by the Institutional Review Board of all participating institutions.

Subjects

The subjects were enrolled via an electronic medical record in which we generated a query to identify a cohort of HIV infected subjects with BWT identified on CT scans, who then had endoscopy for further workup from January 2000 to December 2010. Medical record charts and electronic medical records of all the enrolled patients were reviewed for outcomes and exposures. All the HIV infected patients, older than 18 years of age who had endoscopies for the indication of BWT identified on CT

Deepshikha Nag Chowdhury, on behalf of all authors, declare we had no financial support or any conflicts of interest during the preparation of the manuscript.
Correspondence to : Deepshikha Nag Chowdhury, M.D., Chief Resident, Department of Internal Medicine, St. Joseph's Regional Medical Center, 703 Main Street, Paterson NJ. E-mail : deepshikhanc@gmail.com

Submission date : 04/04/2013
Acceptance date : 18/06/2013

scan were included. 109 patients met the inclusion criteria for our study. Exclusion criteria were incomplete colonoscopy, unsatisfactory bowel preparation, history of gastrointestinal disease, bowel cancer and/or previous colorectal surgery, and missing laboratory data.

Protocol

All patients had CT scanning performed of the abdomen and pelvis by one of two different CT scanners (Lightspeed® 16 slice CT, General Electric (GE) Healthcare, Waukesha, WI,USA or Brightspeed® 16 slice CT, GE Healthcare) in 5 mm increments. Oral contrast agents used were Gastroview® (Mallinckrondt Inc., St. Louis, MO, USA) or Gastrografin® (Bracco Diagnostics Inc., Princeton, NJ, USA). Both solutions are compounds of diatrizoate meglumine and diatrizoate sodium. Attending radiologists evaluated the CT scans and assessed them for the presence of bowel wall thickening. Follow up endoscopy was performed by gastroenterology fellows or attendings. Endoscopies were performed using Olympus video endoscopes (Olympus America, Center Valley, PA, USA). Abnormal areas on endoscopy were biopsied. The endoscopic and pathologic findings of all patients were then evaluated for clinical significance.

Study Variables

The findings on endoscopy were categorized into two groups : (1) "abnormal endoscopic findings" and (2) "normal endoscopic findings". The former category included polyps, mass lesions, diverticular diseases, erythematous, erosive, ulcerative and pigmented mucosal changes, and thickened folds.

The histological findings were divided into (1) "clinically significant pathological findings" and (2) "clinically not significant pathological findings". The former included inflammatory bowel diseases, infectious colitis, ischemic colitis, adenomas and adenocarcinomas and the latter included nonspecific inflammation, hyperplasic polyps, granulation tissue and normal mucosa.

The exposures we examined were serum albumin concentrations and hemoglobin levels. We also recorded baseline parameters such as age, gender, ethnicity, CD4 count and viral loads.

Statistical Analysis

Categorical data were tabulated as counts, and associations between exposure and outcomes were studied by Fisher's exact test for 2×2 contingency tables or by chi-square analysis for 2×3 contingency tables. The odds ratio (OR) was used as the relevant measure of effect size and included the 95% confidence intervals (95%CI).

Continuous variables were tested for normality by the D'Agostino - Pearson Omnibus normality test. All variables were found to differ significantly from normality and, thus, a nonparametric comparison method (Mann-Whitney test) was used to assess statistical significance. Covariates with between group difference of $2 \times \alpha$ (α being set at 0.05, thus $2 \times \alpha = 0.1$) were considered potential confounders and, per protocol, tested for interaction with primary association. None met this criterion.

All analyses were performed with Prism® v.5.04 (Graphpad Corp, San Diego, CA, USA) on a Windows® 7 personal computer platform. As noted α was set at 0.05 ; $p < 0.05$ (two sided) was required for statistical significance.

Results

Baseline Characteristics of Subjects

As can be seen from Table 1, 10 of 109 subjects (9.2%) were positive by endoscopic evaluation, but did not present with positive histologic findings. There were no

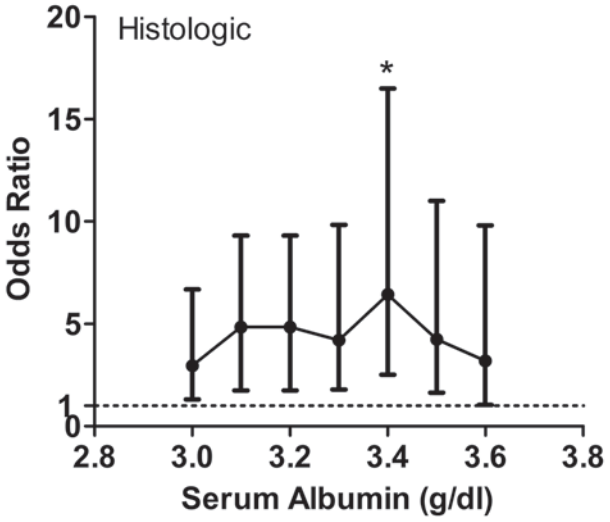
Table 1. — **The baseline clinical and laboratory characteristics of patients**

A. Histologic assessment

	Positive (n = 70)	Negative (n = 39)	P value
Age	51.5 (45.8 to 57.0)	52.0 (48.0 to 58)	0.539
Gender(F/M)	27/18	43/21	0.543
Ethnicity(B/H/W)	44/7/19	25/4/10	0.986
CD4 counts	185 (40.0 to 412)	159 (38.5 to 302)	0.462
Viral load	370 (48.0 to 19,800)	3500 (48.0 to 98,300)	0.188

B. Endoscopic assessment

	Positive (n = 80)	Negative (n = 29)	p value
Age	52 (48.0 to 58.0)	50.0(42.0 to 54)	0.128
Gender(F/M)	34/11	46/18	0.826
Ethnicity(B/H/W)	52/8/20	17/3/9	0.806
CD4 counts	185 (40.3 to 355)	146 (39.0 to 319)	0.528
Viral load	525 (48.0 to 30,800)	560 (80.0 to 69,400)	0.944



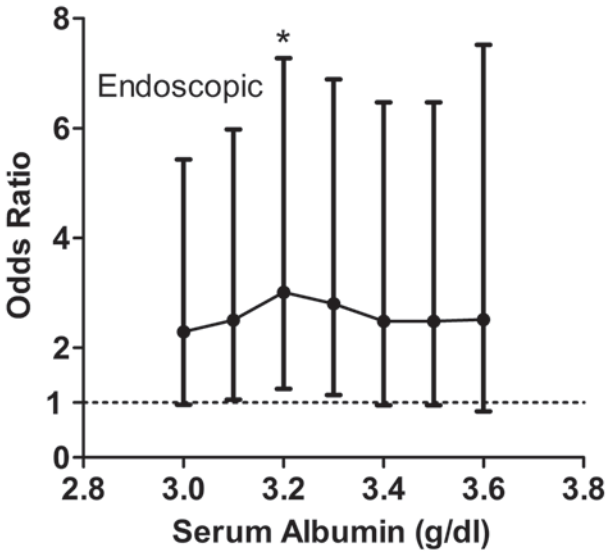
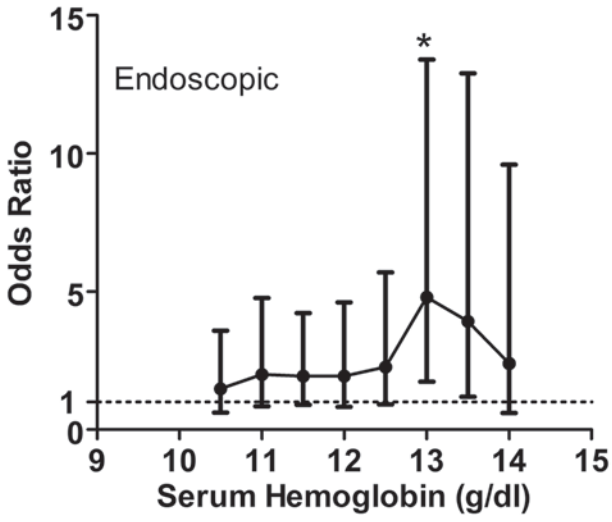


Fig. 1. — Bivariate Forest plots of OR for albumin concentrations from 3.0 to 3.6 g/dl with histologic findings (Figure 1, upper panel) and with endoscopic findings (Figure 1, lower panel). Error bars are 95% CI. Albumin is most statistically significant for abnormal histology at a level of 3.4 g/dl, OR = 6.44 (95%CI = 2.51 to 16.5 ; p = 0.0001). Abnormal endoscopy cut-off was 3.2 g/dl, OR =3.01(95% CI = 1.25 to 7.28 ; p = 0.0202).



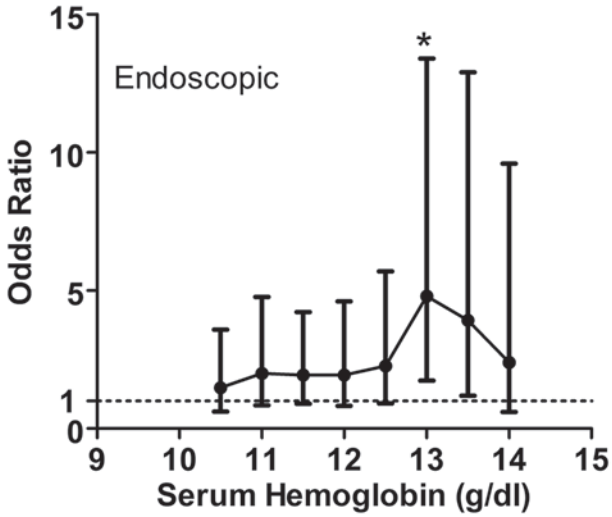


Fig. 2. — Bivariate Forest plots of OR for hemoglobin concentrations from 10 to 14 g/dl with histologic findings (Figure 2, upper panel) and with endoscopic findings (Figure 2, lower panel). Error bars are 95% CI. Hemoglobin is most statistically significant for abnormal histology at a level 10.5 g/dl, OR = 2.64 (95% CI = 1.14 to 6.09 ; p = 0.027). Abnormal endoscopy cut-off is 13 g/dl, OR = 4.8(95% CI = 1.74 to 13.4 ; p= 0.004).

statistically significant differences between the groups separated by histologic (Table 1A) or by endoscopic (Table 1B) findings. Moreover none of the baseline characteristics studied achieved our pre-determined P value of 0.10 for consideration as potential confounders.

Bowel Wall Thickness Associated with albumin and hemoglobin

The association of albumin with observed pathology is presented in Figure 1. The range of albumin concentrations for which association with both histologic and endoscopic findings was studied was 3.0 to 3.6 g/dl, which included all subjects. Within this range, we observed statistically significant associations for positive histologic findings (Fig. 1A) at albumin levels of 3.0 to 3.5 g/dl ; the highest OR was observed at 3.4 g/dl [OR : 6.44 (95% CI : 2.51 to 16.5) ; $p < 0.0001$]. For positive endoscopic findings (Fig. 1B), optimum OR was observed at an albumin concentration of 3.2 g/dl [OR : 3.01 (95% CI : 1.25 to 7.28) ; p = 0.0202]. In fact, we observed statistically significant associations for endoscopic findings within an albumin range of 3.2 to 3.3 g/dl.

In Figure 2, the associations of positive histologic findings (Fig. 2A) and endoscopic findings (Fig. 2B) with hemoglobin concentrations ranging from 10 to 13.5 g/dl for the group with positive histology and 10.5 to 14.0 for the group with positive endoscopic findings are provided.

Histology was associated similarly and significantly at levels of hemoglobin of 10.5 to 11.0 g/dl with an OR of 2.64 (95% CI : 1.14 to 6.09 ; p = 0.027) at hemoglobin = 10.5g/dl and OR : 2.63 (1.17 to 5.88 ; p = 0.029) at hemoglobin = 11.0g/dl. The associations with endoscopic findings were statistically significant at hemoglobin concentrations of 13 and 13.5 g/dl. Optimum OR was observed at 13 g/dl [OR : 4.80 (95% CI : 1.74 to 13.4) ; p = 0.0004].

Discussion

In our study we aimed to determine predictors of abnormal endoscopy and clinically significant pathology in HIV infected patients noted to have bowel wall thickening on CT scans. Similar to previous observations in patients not infected with HIV, low hemoglobin and low albumin were the only variables that achieved significance when evaluated for associations with clinically significant pathology in our study involving HIV infected patients only.

In a study published in 2003, 96% of patients with incidental findings of thickening of the sigmoid colon or rectum had significant endoscopic abnormalities on further work up (9). In a study done by Wolff *et al*. on patients having abdominal pain and colonic thickening on CT scans (14), 7.4% were newly diagnosed with adenocarcinoma and 9.3% were diagnosed with inflammatory bowel disease. A similar study by Moraitis *et al*. (3) showed invasive adenocarcinoma in 14% patients who underwent colonoscopy for only incidentally detected bowel wall thickening on CT scanning. Another small study performed by Padda *et al*. (15) showed a detection of adenocarcinoma in 9% of its subjects. Thus, in patients who have bowel wall thickening seen on CT, endoscopy shows abnormalities in most cases. In fact, there is an important association between a CT finding of BWT and a subsequent endoscopic finding of neoplastic pathology. This association is especially strong where there is BWT of the transverse colon (5). Given the above mentioned findings in literature, endoscopy is recommended for all patients who have bowel wall thickening on CT scans. The positive predictive value of bowel wall thickening (BWT) by CT scan for an endoscopic abnormality is 67% (2,13) Not surprisingly, HIV infected patients with BWT found on CT scans have higher rates of endoscopic abnormalities (73%) (2). Furthermore, histological diagnostic yield on biopsy of abnormal lesions found on endoscopy is higher (64%) in HIV-positive compared to HIVnegative patients (32%) (2). Thus, endoscopy may lead to new and definitive diagnoses in HIV infected patients and should be particularly recommended for diagnostic workup of BWT in HIV positive patients.

Recent studies have shown that clinically significant pathology is found 2.5 times more frequently in African American populations, than in Hispanic populations, when endoscopy is performed to evaluate for BWT in non-HIV infected patients (6). Although we noted a preponderance of blacks in both groups for both outcomes, racial difference was not statistically significant in our study. Anemia is associated with clinically significant pathology (6,16). In our study, hemoglobin was statistically significant for abnormal findings on endoscopy at 13g/dl and for abnormal histology at a level of 10.5 g/dl. A prior study showed a hemoglobin level less than 12 g/dl to be significant (16). Hypoalbuminemia, which is generally thought to cause BWT in patients without significant pathology, but only by a mechanism of intestinal edema (6,7,13), was also found to be a predictor of significant pathology in our study. The statistically significant level of albumin to predict an endoscopic abnormality was 3.2 g/dl, while the cut-off for abnormal histology was 3.4 g/dl.

In conclusion, we have evidence of an association of both hemoglobin and albumin with BWT suggested by both endoscopic and histologic measures. The most statistically significant of the results was albumin, which was apparent in both histology and endoscopy in the 109 subjects that were analyzed. Therefore, we suggest patients, particularly those with HIV, who present with gastrointestinal symptoms and have an albumin level equal to or below the determined cutoff points for both abnormal histology and endoscopy in our study, should have an endoscopy for the diagnosis of intra-luminal pathology and therapy, even in the absence of overt signs of gastrointestinal disease.

This study has the limitation of being conducted retrospectively, thus making the associated risk difficult to estimate precisely. However, the multicenter nature of the study is a positive mitigating factor. Moreover, the racial and ethnic distributions of the subjects in the study are not atypical for an urban HIV sample. In fact, considering that this sample was restricted to HIV infected subjects, sample size was not only adequate in power but credibly generalizable.

References

1. DESAI R.K., TAGLIABUE J.R., WEGRYN S.A. *et al*. CT evaluation of wall thickening in the alimentary tract. *Radiographics*, 1991, **11** : 771-783.
2. ROCKEY D.C., HALVERSON R.A. Jr., HIGGINS J.L. *et al*. Prospective evaluation of patients with bowel wall thickening. *Am J Gastroenterol*, 1995, **90** : 99-103.
3. MORAITIS D., SINGH P., JAYADEVAN R., CAYTEN C.G. Colonic wall thickening on computed tomography scan and clinical correlation. Does it suggest the presence of an underlying neoplasia ? *Am. Surg*., 2006 Mar, **72** (3) : 269-271.
4. FISHER J.K. Normal colon wall thickness on CT. *Radiology*, 1982 Nov, **145** (2) : 415-418.
5. UZZAMAN M.M., ALAM A., NAIR M.S., BORGSTEIN R., MELEAGROS L. Computed tomography findings of bowel wall thickening : its significance and relationship to endoscopic abnormalities. *Ann. R. Coll. Surg. Engl*., 2012 Jan, **94** (1) : 23-27.
6. PATEL P., WIDJAJA D., BLUM S., GLANDT M., AKELLA J., CHILIMURI S., BALAR B. Significance of bowel wall thickening on computed tomography scan : higher risk of pathology among African Americans compared to Hispanics. *J. Natl. Med. Assoc*., 2009 Apr, **101** (4) : 345-348.
7. MARSHAK R.H., KHILNANI M., ELIASOPH J. *et al*. Intestinal edema. *AJR*, 1967, **101** : 379-87.

8. SHIN W.C., JEONG M.J. Clinical significance of incidentally detected bowel wall thickening on abdominal computerized tomography scan. *Korean J. Gastroenterol*., 2005 Jun, **45** (6) : 409-416.
9. CAI Q., BAUMGARTEN D.A., AFFRONTI J.P., WARING J.P. Incidental findings of thickening luminal gastrointestinal organs on computed tomography : an absolute indication for endoscopy. *Am. J. Gastroenterol*., 2003 Aug, **98** (8) : 1734-1737.
10. BALTHAZAR E.J. CT of the gastrointestinal tract : Principles and interpretation. *Am. J. Radiol*., 1991, **156** : 23-32.
11. KOMAKI S. Normal or benign gastric wall thickening demonstrated by computed tomography. *JCAT*, 1982, **6** : 1103-1107.
12. SCATARIGE J.C., DISANTIS D.J. CT of the stomach and duodenum. *Radiol. Clin. N. Am*., 1989, **27** : 687-705.
13. LOW V.H. Bowel wall thickening on CT. *Abdom. Imaging*, 1998, **23** : 107-110.
14. WOLFF J.H., RUBIN A., POTTER J.D., LATTIMORE W., RESNICK M.B., MURPHY B.L., MOSS S.F. Clinical significance of colonoscopic findings associated with colonic thickening on computed tomography : is colonoscopy warranted when thickening is detected ? *J. Clin. Gastroenterol*., 2008 May-Jun, **42** (5) : 472-475.
15. PADDA M., VADGAMA J., SANDHU P., DEV A., GIANNIKOPOULOS I. Clinical significance of incidental colorectal wall thickening on computed tomography scan in African-American and Hispanic patients. *Dig. Dis. Sci*., 2007 Nov, **52** (11) : 3159-3164.
16. TELLEZ-AVILA F.I., GARCÍA-OSOGOBIO S., CHAVEZ-TAPIA N.C., RAMIREZ-LUNA M.A., FRANCO- GUZMAN A., SOSA-LOZANO A., GIOVANNINI M. Utility of endoscopy in patients with incidental gastrointestinal luminal wall thickening detected with CT. *Surg. Endosc*., 2009 Oct, **23** (10) : 2191- 6. doi : 10.1007/s00464-008-0274-275.