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LETTERS TO THE EDITOR

Improving the Adequacy of the Rectal Examination in Gastroenterology

TO THE EDITOR: In his excellent recent article, Dr. Talley has pointed out that the rectal examination in gastroenterology may be becoming a lost skill (1). His paper describes the importance of the rectal examination and its technique, particularly in patients being evaluated for chronic constipation and fecal incontinence.

I would like to offer an additional caveat from the perspective of a colonoscopist. It is likely that many American endoscopists do only a cursory rectal examination prior to starting colonoscopy. In male individuals, particularly over the age of 50 years, it is reasonable to palpate the prostate gland at the time of the preprocedure rectal examination.

We recently showed that the adequacy of palpation of the prostate gland in American adult males in the left lateral position at the time of colonoscopy is often incomplete, and strongly correlated with BMI and weight category (*i.e.*, normal body weight, overweight, obesity, and extreme obesity) (2). We found that the adequacy of prostate palpation could be dramatically improved by having the patient raise one or both knees up toward his chest, a maneuver that takes just seconds to perform. Given the high incidence of overweight and obesity in America, this is an adjunct maneuver that might also improve the quality of rectal examinations performed in such patients being evaluated for chronic constipation and fecal incontinence.

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Response to the Letter by Dr. Marshall

TO THE EDITOR: I thank Dr. Marshall for the comments on my article (1). Despite current controversies about the management of patients with early prostate cancer (2), it does seem important to determine whether the prostate is obviously abnormal on every rectal examination, and hence the observations by Dr. Marshall deserve to be noted by all practicing gastroenterologists.

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Rectal Examination

TO THE EDITOR: I read with interest the article by Talley (1). He cited that a rectal examination should not be performed in an acutely ill patient; I disagree. Even in such a setting, rectal findings could reveal a lot of disorders, for example, complete intestinal obstruction from rectal cancer and massive upper gastrointestinal bleeding.

Last but not the least, the second correct reason why we cannot perform such an examination is that a patient has no anal canal.

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Reply to Dr. Kittisupamongkol

TO THE EDITOR: Thank you for the interest in the commentary (1). I agree with Dr. Kittisupamongkol that in those

presenting with presumed acute gastrointestinal disease, a rectal examination has major value. However, I suspect few of us would consider doing a routine rectal examination in the setting of an acute myocardial infarction. The absence of an anal canal is certainly a rare but reasonable reason for avoiding the rectal examination, which I hope might be obvious.

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Do the Two Ends Reflect the Full Picture?

TO THE EDITOR: We read the article by Cappell *et al.* (1) with great interest. The authors manually determined the country of residence for authors for 8,251 articles, encompassing every gastroenterologic article published between 1980 and 2005 in nine gastroenterology (GI) and four leading medical journals (of which eight were American and five were European). The study involved an extended span of time, but do the two ends reflect the full picture?

We have used the computer-generated PubMed search system to reveal the contribution of Chinese authors and found that the number of articles from China has increased significantly from 1996 to 2005 (2). The U.S. share of research articles was retrieved using the same method. The ISSN (print) was used to perform searches in PubMed, and a first author's affiliation with the United States was considered as research output from the United States. A total of 52 journals related to gastroenterology were selected from the "gastroenterology and hepatology" category of Science Citation Index Expanded (SCIE). The articles from six gastroenterology journals published in the United States and three gastroenterology journals published outside the United States selected by Cappell *et al.* were also retrieved. From 1995 to 2005, we did not find a statistically significant trend in the share of articles in the 52 gastroenterology journals and six gastroenterology journals published in the United States (Fig. 1). Furthermore, the study by Cappell *et al.* has already implied the result. The number of articles written by American authors/total number of articles for that particular year published in the *New England Journal of Medicine* from 1980 to 2005 were compared, and the authors found the U.S. share of research articles significantly decreased between specific years (1990 *vs* 1980, 1995 *vs* 1980, 2000 *vs* 1980, and 2005 *vs* 1980). However, we did not find any significant decline from 1995 to 2005 (1995 *vs* 2000, $P = 0.286$; 1995 *vs* 2005, $P = 0.856$; and 2000 *vs* 2005, $P = 0.355$).

It is difficult to obtain information on the country affiliation for authors of journal articles published in the 1980s. The data before the 1990s generated from PubMed or other databases

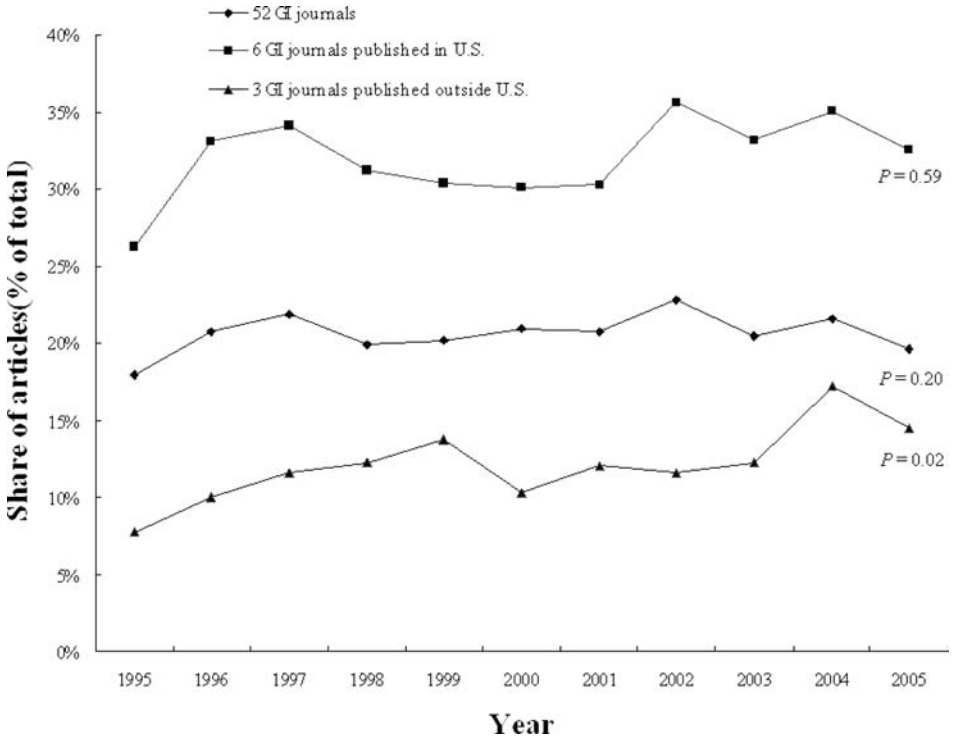

Figure 1. Time trend of the U.S. share of articles in selected gastroenterology journals.

were incomplete because the Internet was not popular prior to 1992 when the U.S. government began offering Internet access to the general public for the first time. We appreciate Cappell *et al.*'s effort to present an entire picture of the status in gastroenterology in 1980. However, if we retrieve more information on the articles published from the 1980s to the early 1990s, we may find a significant decline in the U.S. share of research articles.

In conclusion, a significant decline in the American domination of research in gastroenterology may have happened in the period between 1980 and the early 1990s, but not in recent years.

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Author's Response: A Significant Decrease in the American Domination of Research in Gastroenterology Between 1980 and 2005: Did This Happen Mostly Between 1980 and 1995 or Between 1995 and 2005?

TO THE EDITOR: We thank Hu *et al*. for their interesting comments (1) regarding our article published in the April 2008 issue of the *American Journal of Gastroenterology* (2). In our article, we demonstrated that the percentage of articles in gastroenterology by Americans significantly declined from 1980 to 2005 in eight American journals (including six gastroenterology and two leading medical journals). We selected a 25-yr span for comparison to (i) eliminate short-term trends that might be statistically significant but not historically meaningful, (ii) to average out small annual changes due to chance or one-time events, and (iii) to maximize the statistical detection of small annual changes by multiplying the annual effects over 25 years. The year 2005 was arbitrarily selected as the end point because it was the most recent year before we started the project.

Our demonstration of a significant decline from 1980 through 2005 does not, by itself, indicate when this change transpired. For example, most of the change could have occurred from 1980 through 1995, or alternatively from 1995 through 2005. As Hu *et al*. kindly point out, we performed a time trend analysis of every 5 yr for all the articles published in one medical journal, the *New England Journal of Medicine*, which was illustrated as Figure 1 in our article published in the April 2008 issue of the *American Journal of Gastroenterology* (2). This time trend analysis demonstrated a significant decline of American authorship in this journal from 1980 through 1995 (from 474/527 articles or 89.9% in 1980 to 442/603 articles or 73.3% in 1995, odds ratio [OR] = 0.30, 95% OR confidence interval: 0.21–0.42, $P < 0.0001$), but did not demonstrate a significant decline of American authorship in this journal from 1995 through 2005 (from 442/603 articles or 73.5% in 1995 to 515/707 articles or 72.8% in 2005, OR = 0.98, 95% OR confidence interval: 0.77–1.25, $P = 0.90$). We greatly appreciate that Hu *et al*. have focused on and greatly extended these findings regarding 1995 through 2005.

The described findings that the American contribution to publications did not significantly decrease from 1995 through 2005 should not lull the American gastroenterology community into believing that we have from 1995 through 2005 completely and permanently reversed a prior trend of relative decline. We believe our article, as previously stated, "should provide a wakeup call for American gastroenterologists to redouble their research efforts" (2). If Americans can publish more and better, all mankind will surely benefit. Likewise, if other countries continue to publish more and better, all mankind will reap the same benefits.

Notably, if the large American decline we reported between 1980 and 2005 mostly occurred before 1995, then the internet did not likely play a major role in this decline as the internet became a significant factor only after 1995 (3). However, other aspects of globalization, as reflected in increasing transnational collaboration in clinical trials (2), may have played an important role in this reported phenomenon.

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Globalization of Gastroenterology Research

TO THE EDITOR: The recent study by Cappell and Davis in the *Journal* demonstrates a remarkable globalization of authorship over the last three decades (1). As they described, this phenomenon has been well established both in general medical journals as well in various subspecialty journals. However, the concept of the globalization of gastroenterology research is not a novel one. The concept of "internationalization" was discussed in the mid 1990s by editors of multiple leading gastroenterology journals who noted that, while the number of manuscript submissions by American authors had remained constant, the number of international submissions had increased remarkably (2, 3). Later, after the turn of the century, the editor of *Hepatology* commented that this trend had persisted (4).

More recently, our group examined the origin of research articles published in the three highest impact gastroenterology journals from 1970 to 2005 (5). We demonstrated a profound internationalization of authorship, with German, French, Italian, and Japanese authors showing the greatest surge.

Explanations for internationalization of the medical literature and America's relative decline have been a source of speculation for many years. Cappell and Davis provide an excellent discussion of potential etiologies as well as both positive and negative consequences of such change.

In sum, internationalization of gastroenterological research is not novel, but remains worthy of continued discussion.

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Response to Hart and Marshall

TO THE EDITOR: We thank Hart and Marshall for their interesting comments (1) regarding our article published in the April 2008 issue of the *American Journal of Gastroenterology* (2). In our article we demonstrated that the percentage of articles in gastroenterology by Americans statistically significantly declined from 1980 to 2005 in an analysis of eight American journals (including six gastroenterology and two leading medical journals). Hart and Marshall cite four other publications that relate to this phenomenon (3–6). While there were helpful hints of this phenomenon in these previous publications, we are the first to definitively characterize this phenomenon. The previous publications all have the following limitations: (a) they deal with only one (3–5), or two American journals (6); (b) they were published as editorials (3–5), or as a letter to the editor (6); (c) they present the raw numbers with *no* analysis of statistical significance; and (d) the three prior editorials do not discuss the methodology (3–5), while the prior letter to the editor lacks a discussion of critical methodologic details (*e.g.*, assignment of country of authorship for articles written by authors from different countries (6)). Indeed, Hart and Marshall (together with another author [Idbah]) themselves wrote in June 2007 in their letter to the editor published in *Gut*: "However, to date, no one has examined the international publishing trends in gastroenterology and hepatology journals" (6). They, themselves, therefore concede that the editorials published before June 2007 (3–5) did not examine this phenomenon! Furthermore, the letter to the editor by Hart *et al*. (6) was published in *Gut* in June 2007, after the submission date (May 8, 2007) of our manuscript to the *American Journal of Gastroenterology*, and therefore was unavailable for review when we submitted our manuscript for publication.

Hart and Marshall (1) also cite one prior analysis of one British journal, *Gut*, in which the authors found a significant increase in international (non-British) authors from 1970 through 2005 (6). Again, this publication deals with only one non-American journal, was published as a letter to the editor, lacks any statistical analysis, and lacks critical methodologic details. We believe our analysis of five European journals, with extensive statistical analysis of the data, represents a substantial contribution beyond their analysis of one journal. Indeed, our analysis suggests that the phenomenon in

European journals is more complex than that appreciated by Hart and Marshall: three of the analyzed journals demonstrated an increasing contribution by American authors from 1980 to 2005, while two journals did not show any statistically significant change from 1980 to 2005 (2).

We believe the cited prior publications, which lack any statistical analysis, resemble case reports that suggest a phenomenon, while our article represents a formal, definitive analysis. We are reminded of Newton's famous statement to Robert Hooke, "If I have seen farther it is by standing on the shoulders of Giants" (7).

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Barrett's Esophagus: Still Much to Learn, But "Yes, We Can!"

TO THE EDITOR: We read with interest the article published in the May issue of *AJG* (1) and we agree that, despite the increasing interest in Barrett's esophagus (BE), "there is (still) a poor evidence base supporting BE surveillance guidelines." There are several reasons for such inconsistent patient management, but one basic explanation is the disease's definition. The recent "*statement 38*" published by Vakil *et al.* (2) ("When biopsies of ESEM show columnar epithelium it should be called Barrett's Esophagus and the presence or absence of intestinal-type metaplasia specified") may have two dangerous consequences:

1. In our past clinical practice, we only considered patients with intestinalized mucosa above the gastro-esophageal junction (GEJ) as cases of BE; the newly-proposed definition raises the question of what requirements have to be met to include our patients in a BE follow-up protocol; and
2. Expanding the diagnostic criteria considerably increases the number of patients likely to need following up, warranting a reappraisal of the current guidelines.

Based on the definition of Barrett's mucosa as "endoscopically-suspected/histologically-proved esophageal intestinal metaplasia," we established a multicenter trial on BE (acronym: EBRA) 4 yr ago with a view to covering our geographical area of almost a million residents (3, 4). Our initial goals were: (a) to collect epidemiological information on the prevalence of BE in the endoscopy population of the area; and (b) to expand our clinico-biological understanding of the long-term natural history of BE (4).

Almost a year was spent establishing a working network among the 21 public health institutions involved in the project. At each center, a dedicated team of GI specialists and pathologists was established and arrangements were made for the consistent collection of clinico-pathological information. At present, 638 BE patients are enrolled in the EBRA-study and 280 of them have a follow-up longer than 24 months.

Leaving aside the results of our prospective follow-up, we would like to briefly focus on our experience on the main issue addressed by Das's (1) study, *i.e.,* whether BE multicenter trials and/or Registries result in a quantifiable improvement in our routine patient management?

To answer this question, Table 1 summarizes the results of a comparative survey between BE assessment/management in the 3 yr before the EBRA started *versus* the first 3 yr of the EBRA experience (only initial diagnoses of BE have been considered). The data refer to only 2 of the 21 EBRA centers, based on the rationale that only one GI-endoscopist is involved in the endoscopy procedure at each center, which rules out any significant intracenter variability.

Being substantially consistent with Das's results (1), our experience demonstrates that the educational program conducted before the EBRA started, the strict interdisciplinary cooperation demanded by the study, and the monitoring of each step in the patient registration procedure all led to structural changes in the patients' clinical assessment/management. In particular, a significant improvement was achieved in: (a) consistently obtaining the three measurements needed for BE assessment (*i.e.* locating the squamous-columnar junction [SCJ], the GEJ, and the diaphragmatic pinchcocks [DP]); (b) obtaining biopsy samples in numbers coming closer to those demanded by the "theoretical" sampling protocols; and (c) improving the adherence to the guidelines concerning BE's follow-up (including that for lesions belonging to the spectrum of non-invasive neoplasia [NiN]).

In the current setting, in which almost all GI specialists have "some major facet of their (BE) clinical practice" that

Table 1. Comparison between BE assessment/management before the EBRA trial (years 2002–2004; endoscopy procedures considered = 3081) *versus* after starting the EBRA trial (years 2005–2007; endoscopy procedures considered = 3429)

	Center 1—Rovereto Hospital		Center 2—Vicenza Hospital		Change and Significance	
	Before EBRA Trial 2002–2004	After EBRA Trial 2005–2007	Before EBRA Trial 2002–2004	After EBRA Trial 2005–2007	Before *vs*. After	
					Center 1	Center 2
Number of upper GI endoscopy procedures (consecutive cases by the same GI-endoscopist)	2,020	2,148	1,061	1,281	Not applicable	
Barrett's esophagus prevalence	19 (0.94%)	42 (1.96%)	17 (1.6%)	39 (3%)	↑ $P < 0.003$	↑ $P < 0.01$
Long-BE/short-BE	6/13 32% *vs*. 68%	11/31 26% *vs*. 74%	5/12 29% *vs*. 71%	7/32 18% *vs*. 82%	↑ P = n.s.	↑ P = n.s.
BE cases in which the 3 diagnostic landmarks (SCJ, GEJ, DP) have been mentioned in the endoscopy report	6/19 (31%)	42/42 (100%)	7/17 (41%)	39/39 (100%)	↑ $P < 0.001$	↑ $P < 0.001$
Identification of hiatal hernia by objective criteria	6/19 (31%)	29/42 (69%)	4/17 (23%)	15/39 (38%)	↑ $P < 0.003$	↑ P = n.s.
Use of four-quadrant biopsy protocol	2/19 (10%)	8/42 (19%)	4/17 (23%)	12/39 (31%)	↑ P = n.s.	↑ P = n.s.
Total number of biopsy samples obtained in BE patients	87	273	36	164	↑ P = n.s.	↑ $P < 0.002$
Mean number of biopsy samples obtained per BE case	4.57 (r = 2–6 ± SD 1.5)	6.5 (r = 3–9 ± SD 0.7)	2.1 (r = 1–4 ± SD 1.8)	4.2 (r = 2–12 ± SD 0.75)	↑ $P < 0.001$	↑ $P < 0.001$
Prevalence of noninvasive neoplasia (indefinite for NiN, low-grade NiN, high-grade NiN are merged together)	1/19 (5%)	5/42 (11%)	0/17	3/39 (9%)	↑ P = n.s.	↑ P = n.s.
Adherence to guidelines for the follow-up schedule	12/19 (63%)	42/42 (100%)	3/17 (18%)	39/39 (100%)	↑ $P < 0.001$	↑ $P < 0.001$

BE = Barrett's esophagus; SCJ, GEJ, DP = see text; NiN = non-invasive neoplasia.

does not comply with the surveillance guidelines (1, 5), both the British and the present Italian results show that "yes, we can!" overcome current inconsistencies in BE patient management (from diagnosis to treatment) . . . is that too optimistic?

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Optimizing Surveillance in Barrett's Esophagus: Response to Rugge *et al*.

TO THE EDITOR: In their letter, Rugge *et al*. (1) has raised several important points regarding the dilemmas faced by clinicians dealing with Barrett's esophagus (BE).

The American approach of diagnosing and subsequently offering surveillance to only those with histologically proven intestinal metaplasia (IM) is based mainly on the premise that only IM has the premalignant potential and the economic consequences of an individual being diagnosed with BE in United States (2). However, if biopsied in appropriate numbers, almost all BE shows presence of IM at some point (3) and if enough biopsies are not taken, there is a high chance of false negative results for presence of IM (4). We have shown that there is still a trend to under-biopsy in Barrett's patients mainly due to time and monitory restraints (5). The British practice recommends surveillance of BE irrespective of the presence of IM in the index biopsies.

The lack of hard evidence of mortality reduction is probably the greatest obstacle in the more enthusiastic participation in BE surveillance programs. We welcome the Italian group's attempt to conduct a large, well-designed study to elucidate the prevalence and natural history of BE, which is the need of the hour to help refine future service development and establish a meaningful and effective surveillance program. In the United Kingdom, the Aspirin Esomeprazole Chemoprevention Trial (AspECT) and Barrett's Oesophagus Surveillance Study (BOSS) are addressing similar issues.

The table by Rugge *et al*. (1) indicates a highly significant rise in the "BE prevalence" within 3 yr at both the centers. Presumably, this represents the increased incidence of diagnosis of BE due to better awareness of the endoscopists. Also there seems to be an apparent difference in the quoted "BE prevalence" between the two centers, both at baseline and after starting the EBRA (European Barrett's Registries Association) trial. Does this represent a difference in the indication for endoscopy at the two centers or is there a true difference in disease burden in the population as such?

The endoscopists are to be commended for achieving a 100% adherence in recording of endoscopic landmarks and arranging follow-up endoscopy. However, the mean number of biopsies taken still remains low notwithstanding a significant improvement from baseline, although there is no significant increase in use of four quadrantic biopsies (<30%). This is more relevant in countries where presence of IM in columnar-lined esophagus is mandatory to make a diagnosis of BE.

It would be of interest to see the effect of establishment of the EBRA trial on the number of biopsies taken per unit length of BE segment.

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Toll-Like Receptor-4 Signaling: A Possible Candidate Pathway to Support Tobacco Smoking Effects in Ulcerative Colitis

TO THE EDITOR: Evidence is strong for the beneficial effects of tobacco smoking in ulcerative colitis (UC). Current smoking protects against the onset of disease and improves its course with lower flare-up and hospitalization rates and also impacts the need for oral steroids, and more importantly, decreases the colectomy rate in UC patients (1). Even the risk of colonic carcinoma associated with UC could be lower in smoking patients (2). Moreover, postoperative recurrence of the inflammatory process known as pouchitis after coloproctectomy with ileal reservoir seems to have a lower incidence in current smokers compared with nonsmokers (3, 4). In a recent report investigating cigarette smoking influence on the phenotype of Crohn's disease, it was confirmed that patients who smoked were less likely to have colonic involvement (5). The mechanisms underlying this beneficial effect of smoking in UC, pouchitis, and maybe, Crohn's isolated colitis (L2 of the Montreal classification) remain hypothetical. It has been suggested that nicotine may increase mucin synthesis and decrease expression of interleukin (IL)-1β and IL-8 (1). However, the recent developments in UC and Crohn's colitis pathogenesis may suggest other possible explanations.

The colonic epithelium is physiologically in relation along its apical membrane to approximately 10^{14} bacteria per gram of tissue. The epithelial cells are able to interact with this commensal flora. The Toll-like receptors (TLR) family senses the molecular patterns of microbial commensal or pathogens and plays a critical role in innate immune response (6). Attention has been given to the subtype 4 of TLR (TLR-4) mainly due to its strong upregulation in the colon of patients with inflammatory bowel disease (IBD) (7–9). It has been shown that TLR-4 also regulated COX-2 expression that conducts to chronic inflammation in colonic mucosa (10). This pathway is predominantly involved in UC patients and is critical for colon carcinogenesis in these patients probably through COX-2 expression and increasing epidermal growth factor receptor signaling (11). Furthermore, in the ileal reservoir, after coloproctectomy, evidence also exists that TLR-4 is strongly upregulated not only in case of pouchitis but also in noninflamed pouch (12). TLR-4 signaling seems to be of major importance in both UC and pouchitis. The implication of the TLR4 pathway is also possible in Crohn's disease patients with isolated colitis. A recent meta-analysis proposes that TLR4 Asp299Gly polymorphism is associated with Crohn's disease and IBD (13). Hume *et al*. have shown that TLR4 ASP299 was associated with Crohn's disease limited to the colon (14). Moreover, the functional consequences of the TLR 4 Asp299Gly mutation induce not a loss of function but a gain of function. This mutation exhibits a stronger proinflammatory tumor necrosis factor (TNF)-alpha cytokine response after stimulation with lipopolysaccharides, suggesting an upregulation of this pathway in relation to the mutation (15).

Tobacco smoking is a well-known risk factor for the development of bronchopulmonary cancer and has also been associated with an increased incidence of bronchitis, chronic pulmonary obstructive disease, asthma, and bacterial infections. These effects are thought to be related to smoking-induced immunosuppression. And to make short a long and complicated story, smoking is now considered as able to suppress the ability of the host to develop the innate immune response to infection in the airways. A recent report is worth considering when discussing the links between UC and tobacco smoking that demonstrates that tobacco smoking inhibits the expression of proinflammatory cytokines released by macrophages stimulated with TLR-4 agonists (16). This report based on macrophages obtained after bronchoalveolar lavage fluid shows that the macrophages from smokers released significantly less cytokines including IL-1β, IL-8, and TNF when the TLR-4 signaling pathway is stimulated (16). Moreover, evidence exists that tobacco smoking in childbearing women is associated with impaired neonatal Toll-like receptor-mediated immune response (17).

These important observations of anti-inflammatory effects and modulation of innate immune response of tobacco smoking through a TLR-4-dependent pathway in human macrophages and during pregnancy makes it possible to suggest that a similar process may be implicated in the effect of tobacco smoking observed in UC, pouchitis, and colonic Crohn's disease (L2 of the Montreal classification).

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Bleeding Complications as Predictor for Mortality

TO THE EDITOR: We would like to congratulate Ng. *et al*. (1) on their study of gastrointestinal (GI) bleeding complications in patients with acute coronary syndromes (ACS) who received treatment with aspirin, clopidogrel, and low-molecular-weight heparin (LMWH). GI bleeding occurred in 2.7% of 666 patients with an overall hospital mortality of 4.1%. It was observed that co-prescription with a proton pump inhibitor (PPI) significantly reduced the risk of GI bleeding.

We point out that 291 patients who presented with myocardial infarction (MI) were not treated according to current guidelines advocating an early invasive approach with GPIIb/IIIa antagonist as additional therapy in high-risk patients who present with ACS (2–4). In this context, the author omitted to discuss the local revascularization policy.

We have recently undertaken an audit of bleeding complications and mortality in 514 patients with ACS. Our patient cohort was treated with a combination of aspirin, clopidogrel, and LMWH but also received GPIIb/IIIa antagonists (abciximab [N = 183, 31%], tirofiban [N = 92, 18%]) or bivalirudin (N = 21, 3%) if percutaneous coronary intervention (PCI) was considered (64% of all our patients). Tenecteplase was given in 12% (N = 64). In our population, 78% were high-risk patients with evidence of MI compared with 44% in the authors' cohort. Our management protocol dictated measurement of admission and predischarge hemoglobin resulting in consistent detection of acute bleeding complication in hospital admissions.

One hundred eighty-one (35%) of our patients received aspirin (300 mg loading dose followed by daily 75 mg), clopidogrel (600 mg loading dose followed by daily 75 mg), and LMWH (Enoxaparin: 1 mg/kg twice daily, if GFR<30: 1 mg/kg once daily) as triple therapy. We documented 9 (1.7%) bleeding events in this patient group of which 3 (0.6%) were caused by upper GI bleeding. Among all bleeding events, two were major bleeding complications according to TIMI (5) and GUSTO (6) scoring system.

Two hundred eighty-one (55%) patients who underwent PCI received aspirin, clopidogrel, LMWH in combination with tirofiban, ReoPro, or bivalirudin. Of these, 24 (4.7%) patients developed bleeding complications. Eight (1.8%) were caused by upper GI bleeding of which two were major bleeding according to the TIMI classification (5) and three according to the GUSTO classification (6). The total rate of intrahospital overt GI bleeding was 2.9%. PPI were given in 17.8% of patients. We did not detect a correlation between PPI treatment and mortality.

Ng *et al*. reported that only one patient underwent upper GI endoscopy. In our study, 12 out of 15 patients with overt upper GI bleeding underwent endoscopy after consultation between senior cardiologist and gastroenterologist. The procedure was tolerated in all cases very well and no complications occurred. We consider this procedure to be safe to perform and helpful in the management in particular of timing and reinstitution of antiplatelet therapy (7).

Finally, we have noticed in our study a correlation between bleeding severity and mortality that persists beyond short-term follow-up (30 day mortality 6.2%) and is evident until 6 months from the initial bleeding event (Fig. 1). This rise in mortality is not only seen in patients with severe bleeding events according to the TIMI or GUSTO bleeding classifications, but also in those with only minor bleeding. Rao *et al*. confirmed this on a larger scale using the pooled date of four multicenter randomized clinicals (N = 26,452) (8).

The short-term benefit of PPIs demonstrated by Ng *et al.* raises the question of whether these drugs can also reduce

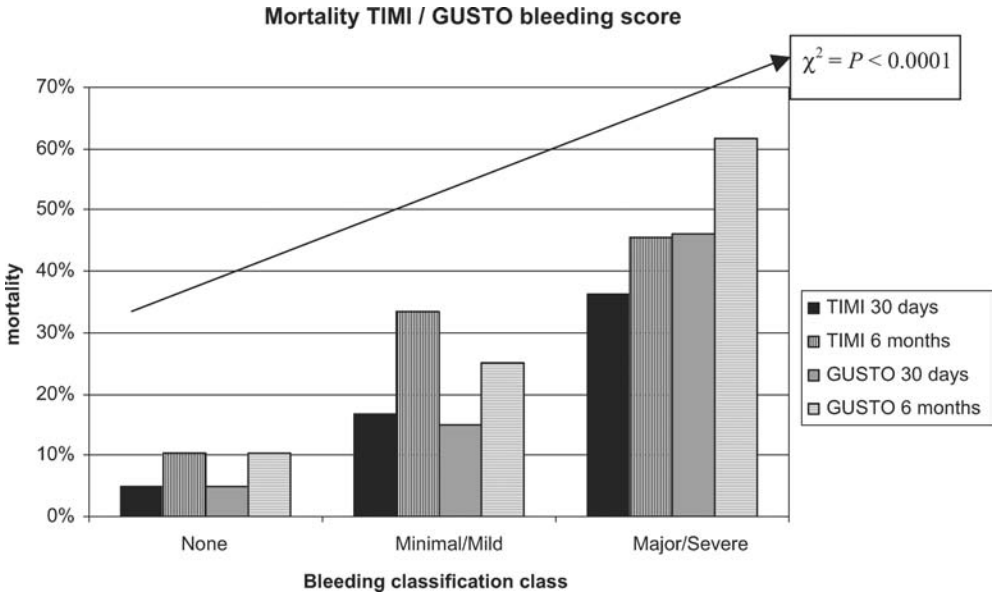

Figure 1. Correlation between mortality and TIMI and GUSTO bleeding score in patients with general bleeding episodes, which includes GI bleeding (N = 38). In patients without bleeding complications the mortality rises from 6.2% at 30 days (10.1% at 6 months) to 36.3% (45.5%) in TIMI major and 46% (62%) in GUSTO severe bleeding events ($\chi^2 = P < 0.0001$). In minor bleeding events mortality rises to 16.7% at 30 days (33.3% at 6 months) in TIMI minimal bleeding and 15% (25%) in mild GUSTO bleeding events ($\chi^2 = P < 0.0001$).

the long-term risk of bleeding and death which we observed beyond the period of hospital admission.

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Gastric Necrosis Due to Rapidly Growing Pancreatic Pseudocyst

TO THE EDITOR: A pancreatic pseudocyst (PP) is a maturing collection of pancreatic juice encased by reactive granulation tissue, occurring in or around the pancreas as a consequence of inflammatory pancreatitis or ductal leakage (1). A compressing effect to neighboring tissue, fistulization, rupture, and hemorrhage are among the possible complications of PP (2). Hemorrhagic complication is rare but has a high mortality rate (3).

A 39-yr-old man was admitted to hospital with complaints of left upper quadrant abdominal pain and fever for 1 wk. He had had hematemesis and melena once 2 days before admission. An upper gastrointestinal system endoscopy had been performed in another center reporting erosive gastritis. His past medical history was unremarkable other than recurrent pancreatitis (with an unknown etiology) and PP for the last

3 yr. His last pancreatitis attack was a year ago. He denied a prior history of alcohol and drug intake other than proton pump inhibitor. His family history was also unremarkable.

Physical examination revealed left upper quadrant tenderness and subfebrile fever (37.8°C). On digital rectal examination, there was no evidence of bleeding. Laboratory findings were as follows: hemoglobin 10.3 g/dL, hematocrit 32%, MCV 86 fL, white blood cell count 18.5 × 10^9/L, platelet count 65 × 10^9/L. Serum biochemical tests (including amylase) were within normal limits other than aspartate aminotransferase, 68 U/L (0–40). X-rays of abdomen and thorax were unremarkable.

He was hospitalized for further evaluation and treatment. Endoscopic examination of the upper gastrointestinal system revealed an ulceronecrotic area on cardia and fundus of the stomach with a sharp demarcation (Fig. 1). Submucosal hemorrhagic lesions were seen on corpus and antrum (watermelon stomach). Computed tomography-angiography demonstrated a pseudocyst with a diameter 10 cm × 12 cm near the tail of the pancreas. A pseudocyst displaced the splenic artery and thus compressed the artery between the stomach and pseudocyst. The gastric wall was thickened, and there was an infarct area on the inferior spleen (Fig. 2).

He underwent surgery and a 10-cm mass was removed from the tail of the pancreas, and distal pancreatectomy, splenectomy, and gastric wedge resection were performed. Histological examination of the surgical material revealed a hemorrhagic cyst lined with inflammatory debris and fibrin (without epithelization), focal pancreatitis, submucosal hemorrhage with focal coagulation necrosis in the stomach, and splenic infarctus.

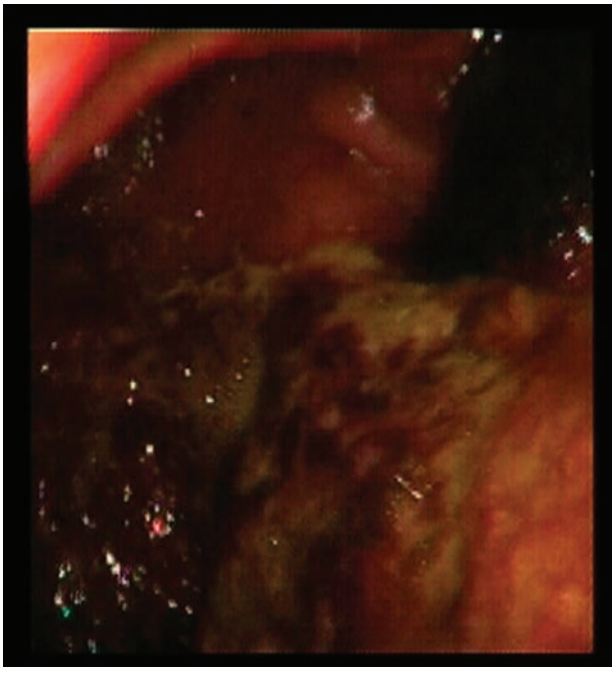

Figure 1. Endoscopy of upper gastrointestinal system showing both normal mucosa and ulceronecrotic area on cardia and fundus of the stomach.

The patient's postoperative course was uncomplicated. He was discharged 1 wk after the procedure in good overall condition.

Bleeding in association with PP has a variety of causes. Some are a direct result of the pancreatic process including pseudoaneurysm, portal, or splenic vein thrombosis. Others are not specific for the pancreas disorders such as Mallory-Weiss tear, gastritis, and peptic ulcer disease (4). Most cases of bleeding associated with PP occur because of a pseudoaneurysm. There may also be venous bleeding into a pseudocyst, resulting in distension and abdominal pain (3,5). There was evidence of intracystic hemorrhage intraoperatively in this case. However, it was a mystery whether its origin was arterial or venous. Nevertheless, the splenic artery was replaced and eroded by PP, suggesting that the origin was arterial in our patient. Because intracystic hemorrhage may be severe and has a higher mortality rate, heralding gastrointestinal bleedings as in our case, it should be carefully evaluated.

In this case, we describe a patient with recurrent pancreatitis who had unusual complications simultaneously. He had hemorrhagic PP, which compressed the splenic artery, obstructed the splenic vein, and compressed the stomach resulting in partial necrosis. Moreover, PP was complicated with splenic infarction.

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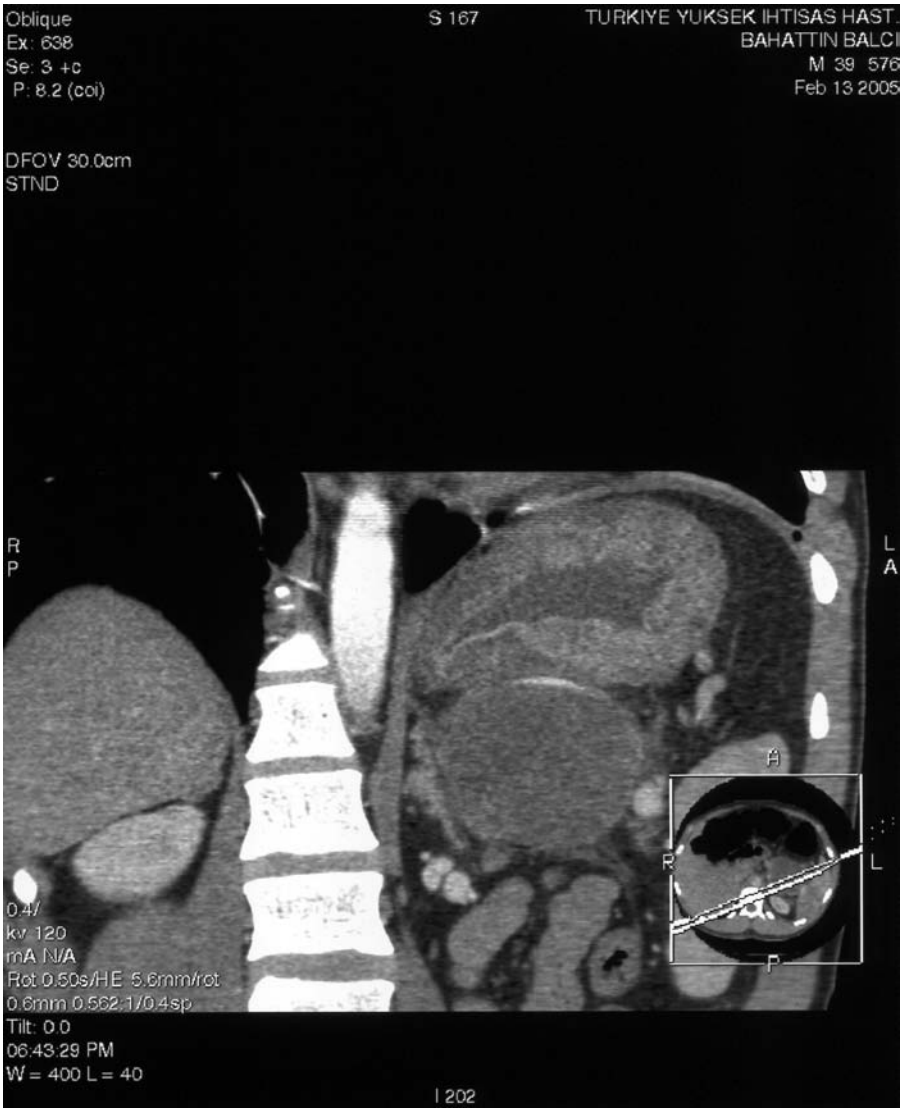

Figure 2. CT demonstrating pseudocyst and gastric wall thickening.

Response to Infliximab in Atypical Pyoderma Gangrenosum Associated With Ulcerative Colitis

TO THE EDITOR: Pyoderma gangrenosum (PG) is a rare inflammatory skin disease, classified into the group of neutrophilic dermatosis (1–3). The therapeutic techniques that have been used up to the present are based on immunosuppressive therapies (4). Since the arrival of Infliximab, several studies have proven its efficacy also in the treatment of PG (5).

CLINICAL CASE

We present a 45-year-old patient with an ulcerative colitis limited to the rectum (ulcerative proctitis). This episode evolved into pancolitis, with several sources that responded to treatment with corticoids. The patient was admitted to the emergency unit with intense and diffuse abdominal pain, accompanied by a frequency of eight to nine bloody stools per day. The analysis revealed a C-reactive protein (CRP) level of 5.80 mg/dL, and 11,000 leukocytes with 85% of neutrophiles. The patient was diagnosed with a serious episode of ulcerative colitis (Truelove-Witts index), and he started treatment with oral and topical mesalazine, intravenous corticoids (1 mg/kg/day), and an enteral and parenteral diet. Subsequent rectum biopsies ruled out the hypothesis of a cytomegalovirus (CMV) infection. On the fourth day of admission, the patient presented a fever of 38°C, an increase of CRP (>9 mg/dL), and an elevation of the inflammatory parameters, together with several skin lesions that looked like nonfollicular pustules and well-defined oval erythematous and edematous nodules with inflammatory appearance. The lesions were slightly painful on palpation, numerous, disseminated, nonconfluent, and were distributed mainly over the upper part of the torso and the face. Subsequently, the lesions evolved into ulcers

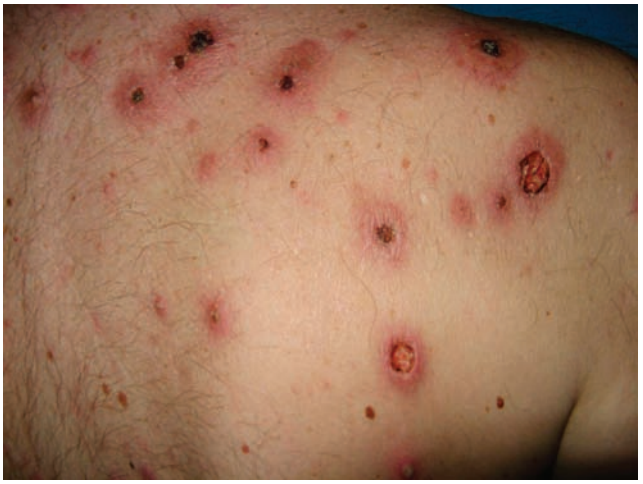

Figure 1. Ulcers with raised erythematous borders and necrotic tissue.

with raised erythematous borders and necrotic tissue, with the largest one measuring 2 cm located on the torso (Fig. 1). The pustules were cultured, and the result was negative for bacterial growth. The biopsy of the lesions revealed an intense interstitial and perivascular infiltration, predominantly neutrophilic, on the epidermis and the dermis. No histopathological signs of vasculitis were seen. The disease was refractory to corticosteroids, and the skin lesions continued evolving on the seventh day of admission. This motivated a treatment with intravenous Infliximab at doses of 5 mg/kg after 0, 2, and 6 wk. Before starting the treatment, we ruled out an active infection, a positive result for antinuclear antibodies, and the presence of an active or latent tubercular infection. After the first dose of Infliximab, the patient's symptoms improved rapidly, the frequency of stools decreased, and the skin lesions improved and disappeared. Infliximab was not continued as a maintenance treatment, and the state of remission has lasted until the present.

DISCUSSION

Our patient presented a PG with an atypical presentation. Its etiology is still unknown, although some immunological mechanisms have been proposed as a basis for its pathogeny (6). Corticoids are the cornerstone of the treatment. The use of Infliximab for the treatment of PG has been reported by several authors (7, 8). Up to now, there has been only one double-blind, randomized, prospective study that assessed the treatment with Infliximab *versus* a placebo for PG. The study included 30 patients, 6 of whom presented ulcerative colitis. After 2 wk, 46% of the Infliximab group improved, compared with 6% of the placebo group. Thirty-one percent of the patients in the Infliximab group did not show any improvement after 6 wk (9). The similarities of the intestinal and skin response to Infliximab suggest a common pathogeny.

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Sickle Cell Trait-Related Ischemic Colitis in a Patient With Sjögren's Syndrome

TO THE EDITOR: Sickle cell trait (SCT) is a rather common condition in Greece, with a prevalence varying from 0% to 20% among villages (1). SCT, unlike sickle cell disease, has been considered to be a benign condition. There are reports, however, of adverse events, including ischemic colitis, even in SCT carriers (2–4). To our knowledge, a single case of SCT-sustained ischemic colitis has been previously described in a patient with known heart failure, but the presence of sickled cells was not documented (3). In our case, a systemic disease—Sjögren's syndrome—seems to have acted as a trigger for evident sickle cell formation, vaso-occlusion, and subsequently, ischemic colonic injury in an SCT carrier.

A 52-yr-old female white patient of Greek origin, with primary Sjögren's syndrome, under prednisone, and SCT, was admitted to our department for abdominal pain, mild diarrhea, and rectal bleeding. The abnormal laboratory findings included hematocrit of 32.3%, mean corpuscular volume (MCV) of 77.8 fL, mean corpuscular hemoglobin (MCH) of 25.6 pg, lactate dehydrogenase (LDH) 232 IU/L, antinuclear antibodies (ANA) 1:640, anti-extractable nuclear antigen (ENA) 126.275 IU/mL, anti-Sjögren's syndrome A antigen (SSA) 98.468 IU/mL, anti-Sjögren's syndrome B antigen (SSB) >110 IU/mL, gamma globulins 2.23 g/dL, and immunoglobulin M (IgM) 630 mg/dL. The mean corpuscular hemoglobin concentration (MCHC) value, upon admission, was within normal range (33.6 g/dL), while hemoglobin S (HbS) was present at 36% of total hemoglobin content. The rest of the evaluated parameters—aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, urea, creatinine, prothrombin time (PT), activated partial thromboplastin time (aPTT), D-dimers, plasminogen, protein C, protein S, antithrombin III, lupus anticoagulant, anti-cardiolipin, anti-β2 glycoprotein I (β2GPI) antibodies, activated protein C resistance, anti-double stranded DNA (anti-dsDNA), anti-histones, anti-chromatin, anti-ribonucleoprotein antibodies (anti-RNP), anti-Smith antigen (Sm), anti-scleroderma-70 antibody (anti-Scl-70), anti-Jo-1 antigen or histidyl-transfer ribonucleic acid synthetase (Jo-1), antimitochondrial antibodies (AMA), smooth muscle antibodies (SMA), perinuclear antineutrophil cytoplasmic antibodies (p-ANCA), cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA), and rheumatoid factor (RF)—were normal.

Colonoscopy was performed at that time, thus leading to the detection of a 10-cm long segment of the proximal sigmoid and distal descending colon with edema, petechial bleeding, pale mucosa, and an abrupt transition between the injured and noninjured mucosa. Biopsies demonstrated ischemia-induced colon tissue alterations in the presence of sickled erythrocytes (Fig. 1). Both the endoscopic and histopathologic findings were consistent with acute ischemic colitis, while the presence of sickled cells in the damaged mucosa suggested a sickle cell-related vaso-occlusion.

During hospitalization, antibiotic and corticosteroid treatment was supplemented by careful fluid repletion, a useful therapeutic approach during sickle cell pain crisis, as a potential role for SCT had already been hypothesized. Soon, all clinical manifestations resolved and the patient remained asymptomatic throughout hospitalization and during the last 1-yr follow-up. A new evaluation of the erythrocyte-related parameters, performed during the follow-up period, revealed a decrease in both the MCHC and HbS values—30.7 g/dL and 31%, respectively—and an increase in the MCV value (81.3 fL), indicating the presence of circulating sickled erythrocytes, at the time of ischemic event.

This case is important as it provides solid evidence of a sickle cell-mediated ischemic colitis. The presence of sickle cells in the circulation, as indicated by the variations in the MCV, MCHC, and HbS levels between the acute phase and asymptomatic period, as well as in the colon, as demonstrated in the biopsies, in the absence of evidence that could implicate any other pathology, pointed to an SCT-related ischemic colitis. Our hypothesis is that the recorded Sjögren-induced hypergammaglobulinemia increased blood viscosity (5), and therefore, led to decreased oxygen transportation (6). Lower oxygen tension has been shown to trigger the polymerization of HbS, the altered hemoglobin that is present in the erythrocytes of individuals with sickle cell disease and SCT, thus causing erythrocyte sickling. These sickle-shaped erythrocytes, which tend to cause vascular occlusions, as a result of reduced deformability (4), disrupted colonic hematosis, leading to ischemia and the onset of the clinical manifestations described above.

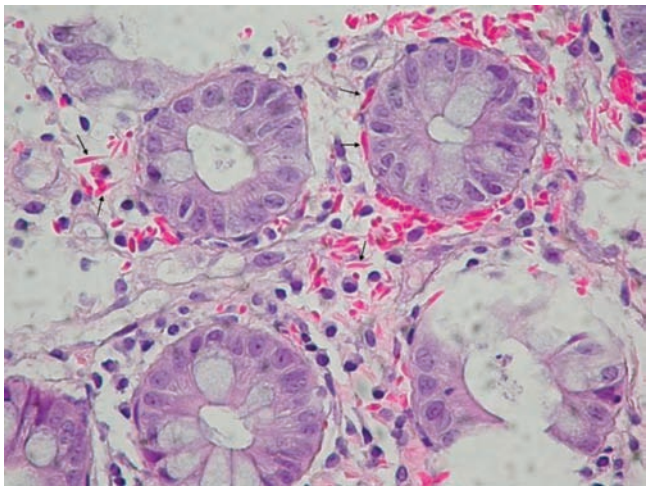

Figure 1. Edema, congestion of capillaries, and focal extravasation of sickled erythrocytes (arrows) in the lamina propria.

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Oral Crohn's Disease: A Favorable Clinical Response With Delayed-Release Triamcinolone Acetonide Intralesional Injections

TO THE EDITOR: Crohn's disease (CD) is a chronic, relapsing, autoimmune inflammatory bowel disease, which potentially may occur in the whole gastrointestinal (GI) tract, from the mouth to anus. Although the main GI manifestations are intestinal, nonetheless, other GI organs may be involved, such as the oral cavity (1) and extra GI organs, such as the skin, eye, joints, blood, and endocrine system (2).

In October 2007, a 28-yr-old man was referred to our Oral Medicine Unit by his general practitioner for persistent intraoral inflammatory hyperplastic tissue with fissuring ("cobblestoning") localized at the left cheek (Fig. 1A), and mucosal tags localized at the left lower gingival fornix (Fig. 1B). The patient reported of suffering from intestinal CD since 3 yr, treated by mesalazine 500 mg tablets twice daily. At that time, he had no fever, abdominal pain, or diarrhea. The disease was very well controlled, and no other organ or system was involved.

An oral biopsy was taken, and the histology with hematoxylin/eosin revealed a papillary hyperplastic epithelium, with a prominent lymphocytes and hystiocytes infiltrate arranging into noncaseating granulomas, and perivascular mononuclear cell infiltration in the underlying connective tissue. The diagnosis of oral CD was confirmed, and the patient received intralesional corticosteroid injections, made up of high concentrations of delayed-release triamcinolone (40 mg/mL), with each injection amounting to 0.1 mL (4 mg). Therapeutic regimen was scheduled every week, in which the patient underwent four injection sessions equally divided between the cheek and gingival fornix to a total of 16 mg. This regimen was repeated for 4 wk to a total of 64 mg of triamcinolone. Discomfort due to needle introduction was not reported, so that a topical anesthetic gel before injections was not required.

Four weeks later, all oral lesions were completely healed (Fig. 1C and D), without any side effect. The patient was recalled and seen monthly for 6 months, showing a complete clinical remission at the last follow-up.

The treatment of oral CD still represents an intriguing challenge, probably due to the versatile clinical manifestations, which may not be correlated with the severity or extent of

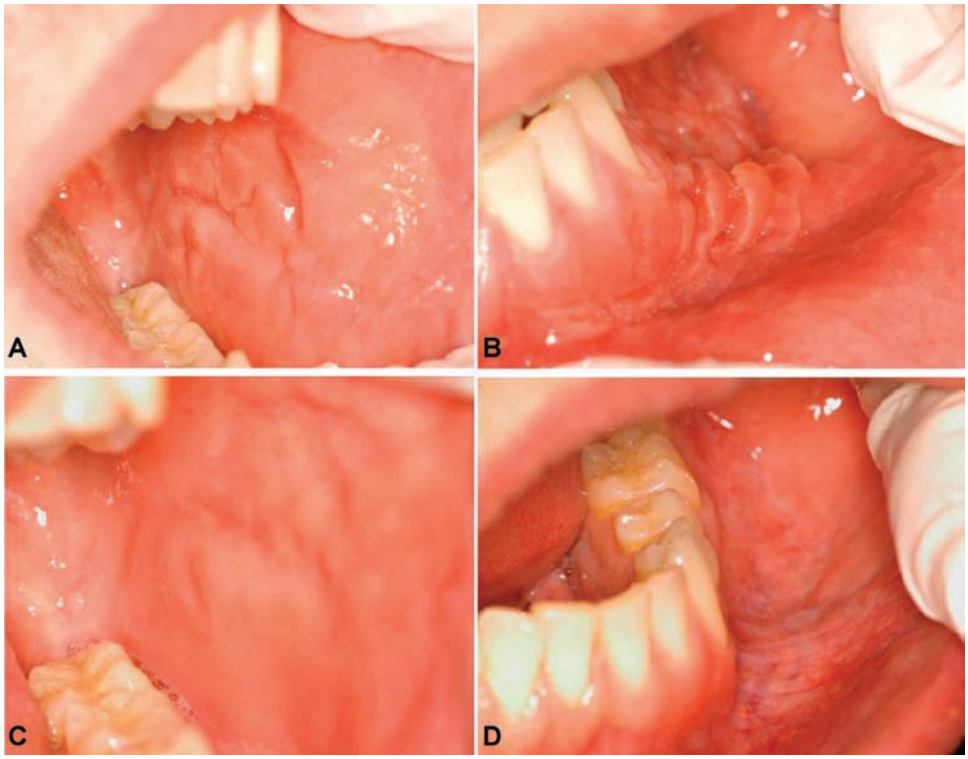

Figure 1. (*A*) The presence of cobblestones localized at the left cheek and (*B*) mucosal tags localized at the left lower gingival fornix. (*C*) The healing of the left cheek cobblestones and (*D*) gingival mucosal tags, after topical injections of triamcinolone acetonide.

intestinal involvement and may appear before or after the onset of GI symptoms (3).

Although the mainstay of treatment for patients with GI and extra-GI CD remains the systemic medical therapy, which has always focused on relieving symptoms of the disease by inducing and then maintaining remission, nevertheless, for oral CD, several studies have described different therapeutic modalities, from the use of local corticosteroids as mouthwash (4) to intravenous infusions of an anti-tumor-necrosis factor-α chimeric monoclonal antibody (infliximab) (3). Actually, the use of triamcinolone local injections in CD have been already reported with successful outcomes in the long-term maintenance of endoscopic dilation of anastomotic Crohn's strictures (5).

Due to the favorable clinical course of this patient, the hypothesis that the use of intralesional corticosteroids might be of marked benefit in the treatment of oral CD seems to be confirmed, even though further and wider investigations are necessary. This finding suggests that intralesional triamcinolone acetonide may be alone appropriate as a crucial treatment for patients who have developed CD oral lesions in the course of the disease and of its systemic treatment. Thus, they provide a rapid and helpful tool for gastroenterologists who, constantly involved in the treatment of CD with different therapeutic modalities, may easily manage oral CD lesions, without any adjustment of the systemic therapy.

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Impaired Inactivation of Digestive Proteases: A Factor That May Have Confounded the Efficacy of Antibiotics Aimed at Reducing the Exposure to Luminal Bacteria and Their Components

TO THE EDITOR: Studies have shown that bacteria in the gut played a critical role in the pathogenesis of diseases like inflammatory bowel disease (IBD) (1, 2). This was demonstrated by the facts that colitis did not develop in germ-free animals and inflammation of the gut in IBD patients occurred only in the presence of fecal contents (2). Therefore, reducing gut bacteria by antibiotics would, theoretically, be the primary approach to treat IBD patients. However, the results of many studies failed to show the efficacy expected (2). The antibiotics showed no significant beneficial effect for ulcerative colitis (2). In fact, supplement of some bacteria (probiotics) may exert therapeutic effects on IBD (2). How to explain this controversial phenomenon? Here, I suggest that impaired inactivation of digestive proteases by gut bacteria may have contributed to these confusions.

Studies have well shown that digestive proteases play a critical role in gut damage induced by shock, stress, and many other agents (3). In fact, digestive proteases probably have played a causative role in IBD (3). Under conventional condition, digestive proteases are effectively and promptly inactivated by certain bacteria (3), which seems to depend on some very specific features of bacteria. It is shown that digestive proteases could be inactivated by *Bacteroides distasonis* E9, but not by *Bacteroides distasonis* D4 (4). Recent studies have shown that the gut microbiota can contain as high as 1,800 genera and 15,000–36,000 species of microbes (1). Therefore, there would be a complex and profound interaction between antibiotics, gut bacteria, digestive proteases, and gut damage (5). Besides IBD, increased intestinal permeability and, therefore, changed infiltration of bacterial components are also seen in many other autoimmune and allergic diseases such as multiple sclerosis, type 1 diabetes, asthma, and atopic eczema (3), which increased dramatically in the last century, at least somehow related to the invention and widespread use of antibiotics. Increased translocation of gut bacteria and infiltration of their components also played a critical role in other critical conditions like trauma, shock, burn injury, sepsis, obstructive jaundice, pancreatitis, and multiple organ failure (6). Notably, use of antibiotics is accompanied by an increase of bacteria translocation (6). Impaired inactivation of digestive proteases would have contributed to the increased intestinal permeability and the increased infiltration of bacteria and their components and confounded the beneficial effect of a reduction in bacteria by antibiotics. To elucidate the interaction between the impaired inactivation of digestive proteases and the efficacy of antibiotics would probably lead

to a great enhancement in the treatment as well as a better understanding of these diseases.

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Endoscopic Diagnosis of Adenocarcinoma of the Common Bile Duct Using an Ultra-Slim Upper Endoscope

TO THE EDITOR: We describe a case of carcinoma of the common bile duct (CBD) diagnosed by direct cholangioscopy using the ultra-slim upper gastroscope and a balloon catheter.

Peroral cholangioscopy is usually feasible with a small-caliber (3 mm) scope (”baby scope”), through the channel of a duodenoscope, then advancing it into the CBD. This procedure is safer and faster than percutaneous cholangioscopy but it remains expensive, time-consuming, and requires two expert endoscopists (1). Recently, the direct visualization of the CBD using an ultra-slim upper endoscope was described (2, 3). Larghi and Waxman, after removing the duodenoscope, inserted the ultra-slim upper endoscope into the CBD and upstream, over the previously left guidewire, and a diagnosis of choledocolithiasis was made. Bohle inserted the small-caliber gastroscope into the descending duodeum and the cannulation of the ampulla was facilitated using a guidewire through the gastroscope.

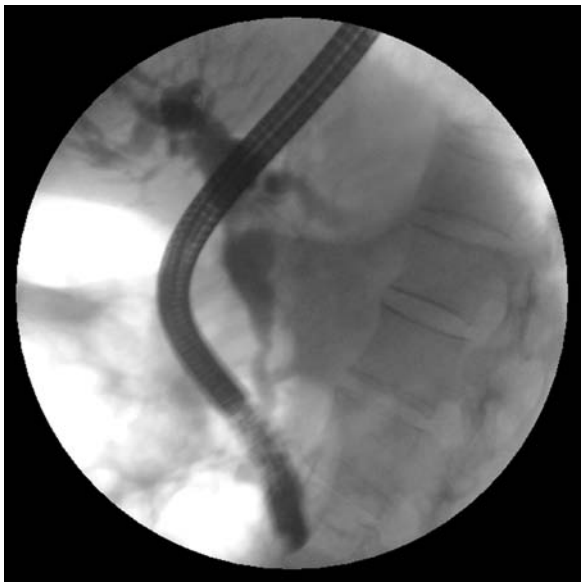

Figure 1. ERCP showing a marked dilatation of the CBD and the intrahepatic biliary ducts, and a stenosis of the distal tract of the CBD.

A 70-yr-old man with previous laparotomic cholecystectomy and transduodenal papillotomy was admitted to our hospital for jaundice. Total bilirubin was 20.36 mg/dL (direct 14.44 mg/dL), ALP (alkaline phosphatase) 2952 U/L, γGT (gammaglutamiltransferase) 917 U/L, AST (aspartate transaminase) 208 U/L, and CRP (C reactive protein) 11.35 mg/dL. The computed tomography scan revealed a considerable dilatation of the intra- and extrahepatic biliary tree, no stones, and an irregular stenosis of the CBD. The

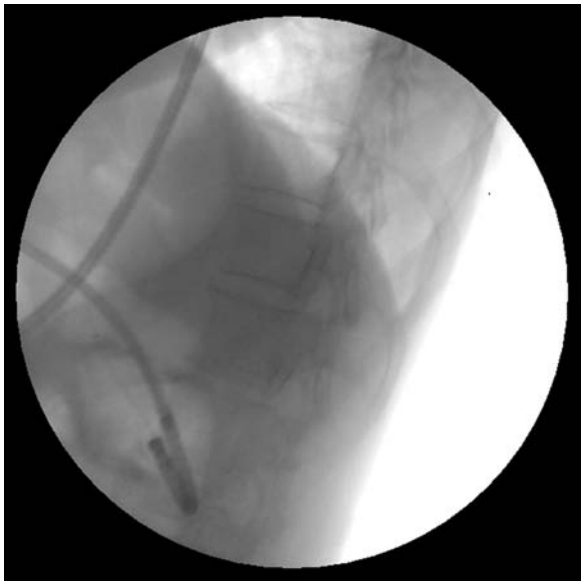

Figure 2. Fluoroscopy of the ultra-slim upper endoscope directly inserted into the descending duodenum (with balloon catheter inside).

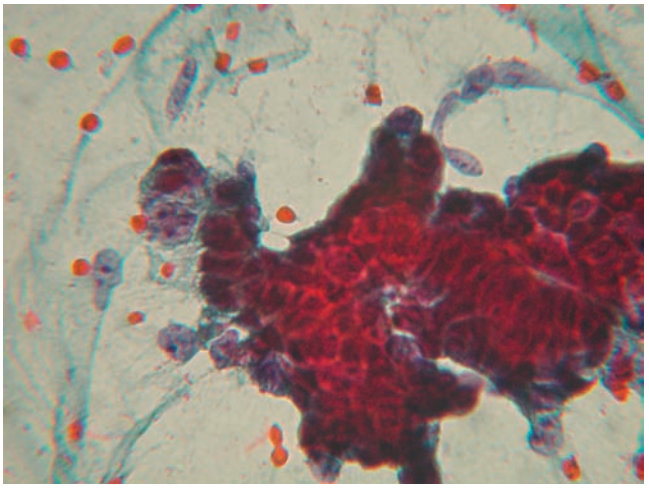

Figure 3. Papanicolau stain 20×: poorly cohesive clusters of malignant glandular cells in a sea of background of necrosis and mucus.

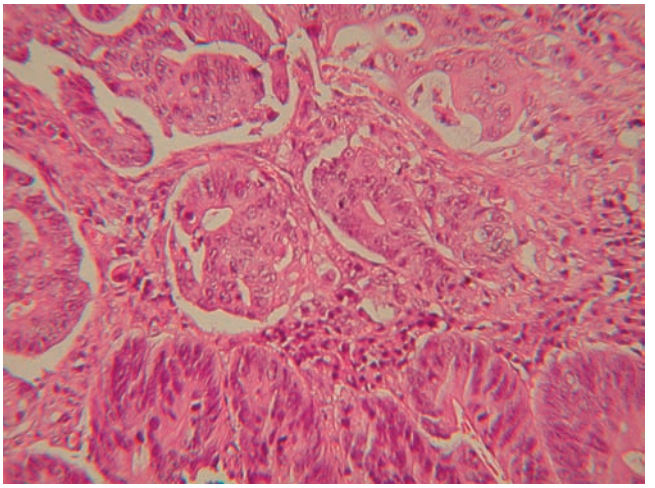

Figure 5. Hematoxilin-eosin stain 40X: Adenocarcinoma of the choledocus: malignant transformation of surface epithelium, with infiltrative growth and stromal desmoplastic reaction.

patient underwent endoscopic retrograde cholangiopancreatography (ERCP) using a standard side-viewing therapeutic duodenoscope (Olympus TJF Type 145, Olympus Medical System Europa Gmbh, Hamburg, Germany). The procedure confirmed a marked dilatation of the CBD and the intrahepatic biliary ducts, with a stenosis of the distal tract of the CBD (Fig. 1). Following completion of the ERCP procedure, the duodenoscope was removed and the ultra-slim upper endoscope (Olympus GIF type N180) was directly inserted into the descending duodenum and a balloon catheter was introduced into the CBD and upstream (Fig. 2). The balloon was inflated and the endoscope was carefully inserted into the CBD using the Fogarty as a guide, and retracting it gently while inserting the endoscope.

The direct visualization of the CBD revealed a whitish, irregular, and spotty necrotic mucosa. Brushing and biopsy of the mucosa were performed. Cytologic and hystologic examinations of the specimens revealed the presence of focally infiltrating adenocarcinoma of the CBD (Figs. 3–5) and the patient underwent a duodenocephalopancreasectomy. Direct endoscopic cholangioscopy added 25 min to the procedure, and fluoroscopy added 15 min to the entire procedure.

Although we describe just one case of this novel technique and we did not compare the outcome data with conventional cholangioscopy, we advocate the importance and the feasibility of direct cholangioscopy. We also recommend the importance of developing new accessories in order to perform therapeutic direct cholangioscopies, like direct stones extraction and polipectomies.

In conclusion, direct endoscopic cholangioscopy with an ultra-slim upper endoscopy is feasible and could lead to very useful improvement in diagnosis and therapy of CBD disease.

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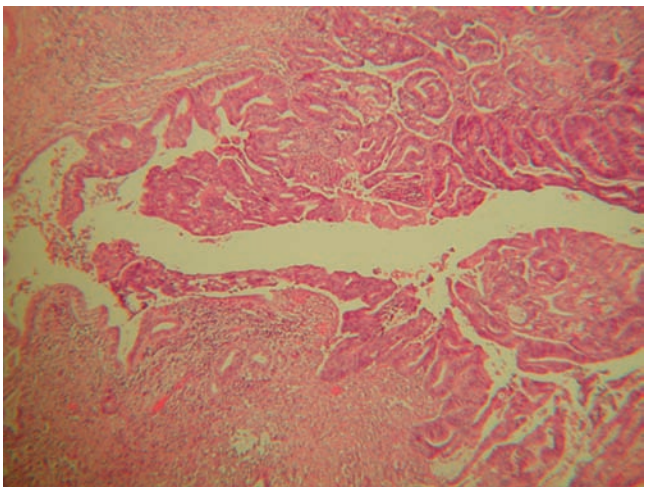

Figure 4. Hematoxilin-eosin stain 10X: Adenocarcinoma of the choledocus: malignant transformation of surface epithelium, with infiltrative growth and stromal desmoplastic reaction.

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Farnesoid X Receptors and Their Role in the Etiopathogenesis of Systemic Malignancies

TO THE EDITOR: The recent article by Capello *et al.* clearly shows that bile acid stimulates the expression of the farnesoid X receptors in Barrett's esophagus (1). This finding illustrates the possible role that farnesoid X receptors may play in the development of esophageal malignancies. In fact, farnesoid X receptors may have a major role to play in the etiopathogenesis of numerous different systemic malignancies.

For instance, the absence or decreased expression of farnesoid X receptors in liver tissue is associated with accentuated hepatocarcinogenesis resulting in the formation of hepatic malignancies ranging from hepatocholangiocellular carcinomas to hepatocellular carcinomas (2). Farnesoid X receptor stimulation also plays a role in the etiopathogenesis of mammary carcinomas, especially intraductal carcinomas (3). In fact, there may be a possible interaction between farnesoid X receptors on breast cancer cells and estrogen receptors (4). Farnesoid X receptors have also been identified in nonsquamous cell lung cancers, especially adenocarcinomas. In fact, Western blot analysis reveals the presence of farnesoid X receptors in 89% of nonsquamous cell lung cancers (5). The recent identification of farnesoid X receptor agonists such as coumestrol and GW4064 (3,6) as well as farnesoid X receptor antagonists such as guggulsterone (7) may help scientists and physicians alike to further modulate and harness farnesoid X receptor function.

The role of farnesoid X receptors in various systemic diseases continues to evolve rapidly. For instance, farnesoid X receptors have been identified in renal tissue. It has been shown that the modulation of farnesoid X receptors on renal tissue may help in the management of conditions such as diabetic nephropathies (8). Clearly, farnesoid X receptors have a major role to play in the etiopathogenesis of systemic malignancies. There is a clear need to identify further such associations and further identify molecules that may potentially alter farnesoid X receptor function.

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Endoscopic Celiac Plexus Blockade Via Direct Intraneuronal Injection *Versus* Perineuronal Injection: Results of a Pilot Study

TO THE EDITOR: Celiac plexus blockade and neurolysis have been performed via endoscopic ultrasound (EUS) for over a decade (1). Recent discoveries have allowed direct visualization of the celiac ganglia via EUS, facilitating direct injection of agents into the nerve itself (2–4). To date, only retrospective data regarding the safety and efficacy of direct injection of the celiac plexus exist (4).

We performed a small, prospective, randomized pilot study on the safety and efficacy of intraneuronal *versus* perineuronal celiac plexus blockade in patients with abdominal pain from pancreatic adenocarcinoma. Celiac plexus blockade with bupivacaine and triamcinolone was selected over celiac plexus neurolysis with alcohol as, at the time the study was begun, there was no published safety data on direct injection of alcohol into the celiac ganglia via EUS.

Fourteen patients (8 women, 6 men, mean age 65 yr) with pancreatic adenocarcinoma were enrolled into the study. The celiac plexus could be identified in all patients. Eight patients received direct intraneuronal injection, and six patients received perineuronal injection. The mean time to identify the celiac plexus ganglia was less than 2 min after echoendoscope insertion. There was no additional difficulty in performing direct intraneuronal injection *versus* perineuronal injection. There were no episodes of bleeding, worsening of pain, infection, or complications of any kind from any procedure.

The baseline pain level for all patients, as assessed via a visual analog scale, was an average of 6 out of 10. Immediately following the procedures, 14 of the 14 patients had improvement in pain. The baseline pain scores for patients randomized to direct injection was 6.5, and fell to 4.5 and 3.9 at weeks 1 and 2 ($P = 0.01$, $P = 0.1$), respectively. The baseline pain scores for patients randomized to indirect injection was 5.6, and fell to 3.2 and 3.0 at weeks 1 and 2 ($P = 0.2$,

$P = 0.6$), respectively. There was no statistically significant difference between the groups ($P = 1.0$). A Wilcoxon signed-rank test was used for within-group analysis, and a Wilcoxon rank-sum test was used for between-group analysis. One patient who underwent direct injection had returned to the baseline pain level at week 1, and one patient who underwent indirect injection had a 2-point worsening of pain level at week 1. The difficulties in accurately assessing the pain levels and pain medication usage over the long term (due to death from underlying pancreatic cancer, withdrawal from the postprocedure telephone questionnaire protocol due to patient transfer to hospice, patient loss to follow-up, etc.) led to an early closure of the study.

Although limited, the data presented above represent the first prospective, randomized trial of intraneuronal *versus* perineuronal injection of the celiac ganglia. This study adds weight to the concept that the celiac plexus can be quickly and reliably identified via EUS, and that direct injection of agents into the celiac ganglion is safe, easy to perform, and well tolerated by patients. Larger prospective trials with long-term follow-up, both in pancreatic cancer and chronic pancreatitis, are needed to further evaluate this concept.

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Cautionary Note on Using Rectosigmoid Biopsies to Diagnose Graft-Versus-Host Disease: Necessity of Ruling Out Cytomegalovirus Colitis

TO THE EDITOR: Ross *et al*. reported that the rectosigmoid is the best site for diagnosing gastrointestinal (GI) graft-versus-host disease (GVHD) (1) using endoscopic biopsies. While we completely agree with the authors' conclusions, we would like to comment about the necessity of conducting a total colonoscopic examination in order to rule out cytomegalovirus (CMV) colitis.

CMV disease is a serious complication after allogeneic hematopoietic stem cell transplantation as well as GVHD (2). Most reports have indicated that the right colon and ileocecum are the most common sites of CMV colitis (3), but others have reported diffuse colorectal involvement (4) with only a few reports concerning CMV colitis limited to the rectosigmoid colon. It is our opinion that most cases of CMV colitis would have been missed if only the rectosigmoid colon had been examined and biopsies taken from that single location.

Patients with GVHD carry a high risk of CMV disease and most patients with CMV colitis overlap GVHD (5). If a patient with both GI GVHD and CMV colitis were diagnosed as having only GVHD, the patient would be exposed to a contraindicative steroid therapy that would probably worsen the CMV disease. CMV antigenemia, of course, could compensate for the diagnostic limitation of a rectosigmoid biopsy; however, the clinical significance of CMV antigenemia remains unclear in diagnosing GI CMV disease (5). In order to definitely rule out CMV colitis, it would be necessary to endoscopically examine the entire colorectum including the terminal ileum in diagnosing GI GVHD even if biopsy was limited to the rectosigmoid.

Since there was no mention in the Ross article (1) as to whether or not total colonoscopic examinations were performed, we would appreciate the authors commenting on this subject.

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Bleeding Colonic Ulcers Due to Invasive Mold Infection

TO THE EDITOR: A 65-yr-old nondiabetic man was admitted with fever and mental status changes. He was diagnosed with high-grade methicillin-sensitive *Staphylococcus aureus* bacteremia complicated by mitral valve endocarditis and septic arthritis involving multiple joints. His past medical history was significant for bilateral total knee arthroplasties and coronary artery disease. He was treated with oxacillin therapy. He underwent multiple joint washouts for septic arthritis. On day 15, he underwent a porcine mitral valve replacement with one-vessel coronary artery bypass grafting. He was recovering uneventfully until day 19 when he developed hematochezia. Colonoscopy revealed blood clots and multiple large discrete ulcers in the cecum and ascending colon (Fig. 1). No endoscopic intervention was performed due to absence of active bleeding. Esophagogastroduodenoscopy (EGD) revealed a diminutive distal esophageal superficial ulcer related to nasogastric tube trauma. He received 6 units of packed red blood cells over the following 48 h. A repeat EGD and colonoscopy revealed identical findings. On day 22, he underwent a right hemi-colectomy with ileostomy for refractory lower gastrointestinal (GI) bleeding. Pathology revealed numerous ischemic ulcers in the cecum, ascending and transverse colon (Fig. 2). Histology demonstrated abundant nonseptated fungal hyphae with 90° branching consistent with mucor. Some septated hyphae were present and a second fungus such as *Aspergillus* spp. could not be ruled out (Fig. 3). While immunohistochemistry using an aspergillus antibody was negative, serum Galactomannan level was elevated at 1.0 (normal <0.5). Foci in the bowel showed transmural destruction of the bowel wall with dense fibrosis suggesting a chronic ischemic event (Fig. 4). Fungal cultures were not obtained from the pathology specimen. Fungal blood cultures were negative. He was not receiving corticosteroids and was not neutropenic. The invasive mold infection prompted an extensive search for an underlying malignancy or immunocompromised state. Flow cytometry, peripheral blood smear, histopathology of the surgical specimen, prostate surface antigen, HIV, quantative immunoglobin levels and computed tomography scans of head, chest, abdomen and pelvis were all unremarkable. He was treated with intravenous caspofungin and lipid formulation of amphotericin B for several weeks

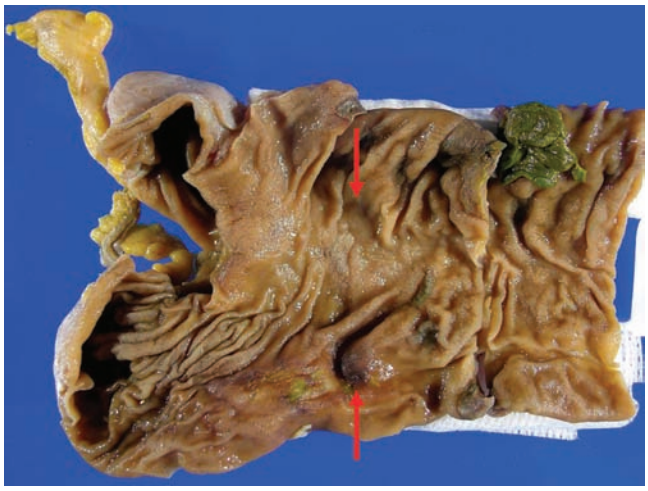

Figure 2. Surgical colonic specimen showing discrete ulcers (arrows).

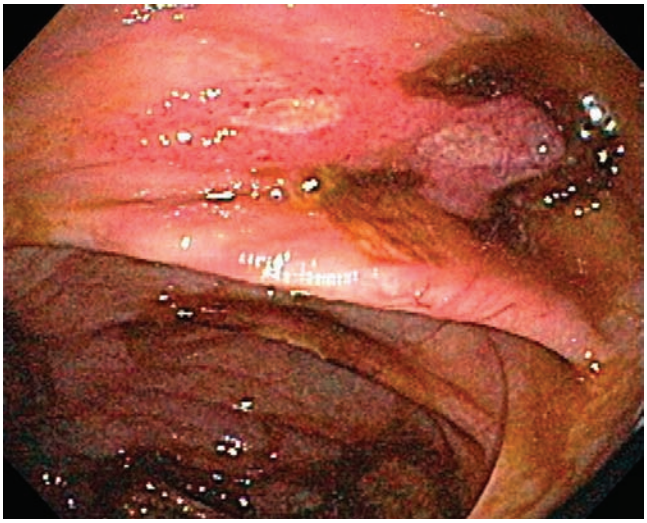

Figure 1. Colonoscopic image of cecum showing ulcers.

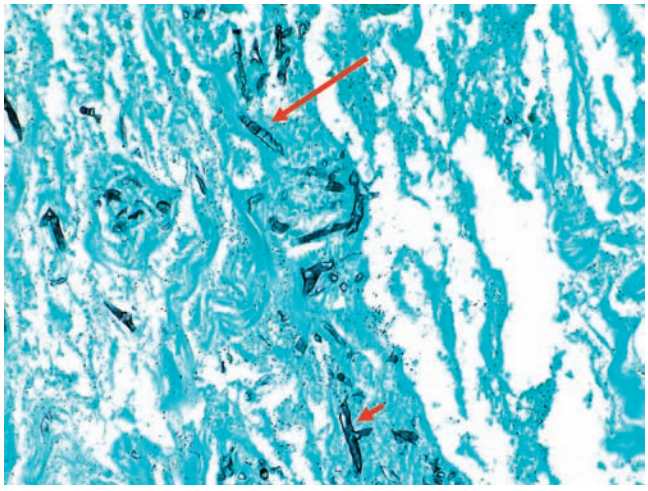

Figure 3. Septated hyphae (long arrow) and nonseptated hyphae with 90 degree branching (short arrow) identified in the surgical colonic specimen.

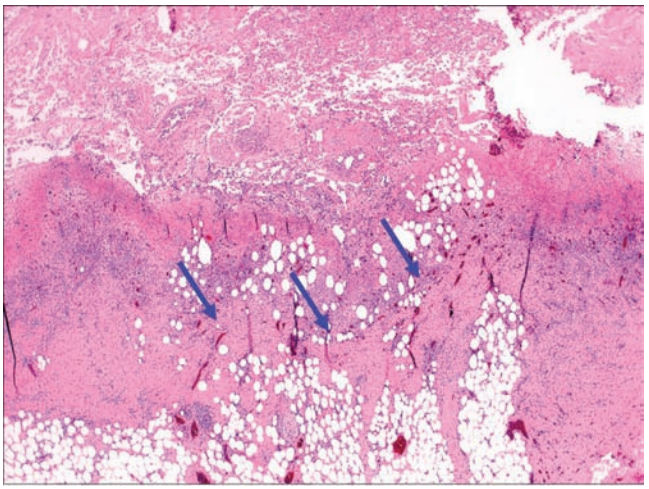

Figure 4. Colonic wall showing severe inflammation. Muscular layer of the colonic wall was replaced by dense fibrosis (arrows) suggesting chronic ischemic event.

followed by oral posaconazole. He recovered uneventfully and was discharged to rehabilitation on day 46.

The differential diagnosis of colonic ulcers includes ischemia, inflammatory bowel disease, use of nonsteroidal antiinflammatory drugs and infection (*e.g.*, CMV, HSV, Clostridium difficile, *Entamoeba histolytica*, *Mycobacterium tuberculosis* and fungal) (1). Molds such as *Zygomycetes* and *Aspergillus* spp. have been reported as a cause of colonic ulcers in immunocompromised patients (2, 3). Most common risk factors are diabetes mellitus, hematological malignancies, glucocorticoid therapy, solid organ or hematopoietic stem cell transplantation, and acquired immunodeficiency syndrome (4–6). Patients may present with fever, GI bleeding, abdominal pain (7), bowel infarction, and hemorrhagic shock (8). In the absence of improvement in immune status, the prognosis of gastrointestinal mold infection is poor. Diagnosis is based on the histological identification of hyphae in tissue and culture (9). Roles of immunohistochemistry, polymerase chain reaction (PCR), and antigen detection assays such as Galactomannan remain to be defined. Blood or tissue cultures often yield no growth (10, 11). Aggressive surgical debridement of necrotic tissue is indicated. Amphotericin B remains the drug of choice (2, 11). To our knowledge, we report the first case of colonic ulcers and lower GI bleeding due to invasive mold infection in a patient without underlying malignancy or immunocompromised state. We hypothesize that his poor nutritional status, prolonged ICU stay, and possible prior ischemic insult were potential predisposing risk factors. We conclude that invasive mold infection should be considered in the differential diagnosis of bleeding colonic ulcers in critically ill patients even in the absence of typical risk factors.

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