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Original article

The prevalence of malignant neoplastic and non-malignant gastrointestinal lesions in cardiology inpatients

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ABSTRACT

Background: Although gastrointestinal (GI) complications are receiving more attention in cardiovascular patients owing to the widespread use of antithrombotic drugs, information seems to be limited over the prevalence of GI malignancies in those patients.
Methods and results: The prevalence of malignant as well as non-malignant GI lesions diagnosed in cardiology inpatients was investigated. We retrospectively analyzed 274 cardiology inpatients who underwent upper and/or lower GI tract endoscopies. A total of 97 patients (35.4%) were taking multiple antithrombotic drugs and the mean number of antithrombotic drugs used was 1.19. Malignant neoplasm was found in 26 patients (9.5%), and non-malignant lesions (ulcers, adenomas, polyps) were found in 106 patients (38.7%). Multivariate analysis showed that antiplatelet drug usage was negatively (odds ratio [OR] 0.38, 95% confidence interval [CI] 0.16–0.91) whereas positive fecal occult blood test was positively (OR 4.44, 95% CI 1.44–13.66) associated with GI malignancies. On the other hand, for non-malignant GI lesions, both antiplatelet drug usage (OR 1.85, 95% CI 1.05–3.25) and positive fecal occult blood test (OR 1.99, 95% CI 1.14–3.47) were found to be positive predictors.
Conclusions: During the 59-month study period, 26 and 106 patients were diagnosed to have GI malignancies and non-malignant GI lesions, respectively, among cardiology inpatients. Cardiology physicians should not overlook the possibility of GI malignancies in an era of multiple antithrombotic drug usage.

Introduction

Combination antiplatelet medication based on different mechanisms has become more widely used for the treatment and prevention of atherothrombotic complications, especially after intracoronary stent implantation [1–3]. In addition, necessity of anticoagulant therapy is also increasing for the prevention of thromboembolic events in patients with atrial fibrillation [4,5]. Combination antithrombotic therapy may be beneficial in improving prognosis in high-risk patients [6], however, it may increase gastrointestinal (GI) bleeding, a serious and potentially life-threatening problem [7]. As dual or triple antiplatelet therapy after stent implantation may also sometimes cause bleeding complications, the appropriate duration of combination antiplatelet therapy must be determined by considering the balance between the effect of cardiovascular protection and the risk of bleeding [8]. Nakagawa et al. reported that the incidence of bleeding complications was significantly increased in patients on dual antiplatelet therapy for more than six months [9].

On the other hand, the possibility has been discussed that antithrombotic drug use might help to discover malignant GI tract lesions in an early stage by unmasking bleeding from neoplasms [10]. GI malignancies and various cardiovascular diseases that require antithrombotic therapy, such as coronary artery disease (CAD) and atrial fibrillation, may share common risk factors [11–15]. Notably, Chan et al. have shown the disturbingly high prevalence (34%) of colorectal neoplasm in patients with CAD [16]. Cardiology physicians should not overlook the possibility of GI malignancies even in patients taking antithrombotic drugs by simply presuming that observed blood loss is due to clinically insignificant GI lesions [17]. Until now, however, little information has been available over the prevalence of GI malignancies among cardiology inpatients in daily clinical practice. To this end, we retrospectively analyzed the database of cardiology inpatients who were found to have GI malignancies and non-malignant lesions by GI endoscopic examinations, and assessed their clinical characteristics.

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Methods

Study population

The study was approved by the Ethical Committee of the University of Tokyo. Between February 2005 and December 2009, 281 patients on admission to the Cardiovascular Department underwent upper and/or lower GI endoscopies. Of these patients, 7 were known to have active cancers at the time of admission to the department. After excluding these patients, 274 patients (194 men, 80 women) were enrolled in the current study. Assessment of smoking status and drugs taken was made by reference to medical records. Antiplatelet drugs included aspirin, ticlopidine hydrochloride, clopidogrel sulfate, cilostazol, dipyridamole, beraprost sodium, limaprost alfadex, ethyl icosapentate, sarpogrelate hydrochloride, and trapidil. Anticoagulation drugs included warfarin.

Laboratory measurements

Blood hemoglobin (Hb) levels were measured by a sodium lauryl sulfate-hemoglobin assay. Fecal occult blood was measured by an immunization method using a latex agglutination assay.

Gastrointestinal endoscopy

All procedures for the upper and lower GI endoscopies were performed by experienced gastroenterologists in the Gastroenterology Department at our hospital.

Statistical analysis

Data are expressed as the mean ± standard deviation unless otherwise stated. Data analysis was performed by using Dr SPSS II for Windows (SPSS Inc., Chicago, IL, USA). The *t* test and logistic regression analysis were applied as appropriate to assess the statistical significance of differences between groups. A p value of <0.05 was taken to be statistically significant.

Results

Baseline characteristics

Of the 274 patients enrolled in the current study (Table 1), 240 underwent upper, and 128 underwent lower GI endoscopies. 94 patients underwent both upper and lower endoscopies. The interval between admission and performance of GI endoscopy was 19 ± 29 days for the upper GI endoscopy and 20 ± 32 days for the lower GI endoscopy. In the current study, patients with known active GI malignancies were excluded, however, 29 patients who had a history of curatively-treated GI malignancies were included; these curatively-treated cancers had been localized in esophagus (4 patients), stomach (11 patients), and colorectum (12 patients; proximal colon, 2 patients; distal colon, 7 patients; rectum, 3 patients), and 2 patients had a history of cancers in two different locations (stomach/rectum and stomach/esophagus). The reasons for admission to the Cardiology Department are summarized in Fig. 1. In 26 patients (9.5%) with progressive anemia, the mean admission Hb levels were 8.4 ± 1.5 g/dL. Digestive symptoms included nausea, diarrhea, hematemesis, and melena. The reasons for performing upper and/or lower GI endoscopies that were multiple in some patients are summarized in Fig. 2. 'Others' described in Fig. 2 included the investigation of the cause of chest pain, abdominal pain, pericardial effusion, anorexia, and weight loss.

Table 1
Clinical characteristics of the study patients.

Variables	n = 274	
Male gender, n (%)	194 (70.8)	
Age, years	71.0 ± 11.5	
Height, cm	159.9 ± 9.0	
Weight, kg	56.7 ± 12.6	
BMI, kg/m^2	22.0 ± 3.8	
Heart rate/min	75 ± 16	
Smoking status		
Never, n (%)	112 (40.9)	
Former, n (%)	121 (44.2)	
Current, n (%)	41 (15.0)	
Hypertension, n (%)	222 (81.0)	
Hyperlipidemia, n (%)	131 (47.8)	
Diabetes, n (%)	117 (42.7)	
Acute coronary syndrome, n (%)	45 (16.4)	
Angina pectoris, n (%)	51 (18.6)	
Heart failure, n (%)	108 (39.4)	
Atrial fibrillation, n (%)	76 (27.7)	
Drugs		
Antithrombotic agents		
Aspirin, n (%)	143 (52.2)	34[a] (12.4)
Clopidogrel, n (%)	17 (6.2)	9[a] (3.3)
Ticlopidine, n (%)	53 (19.3)	24[a] (8.8)
Cilostazol, n (%)	13 (4.7)	15[a] (5.5)
Others, n (%)	33 (12.0)	4[a] (1.5)
Anticoagulants		
Warfarin, n (%)	62 (22.6)	7[a] (2.6)
Stomach medicine		
H2 blocker, n (%)	57 (20.8)	
Proton pump inhibitor, n (%)	164 (59.9)	
Gastric mucosa protectant, n (%)	82 (29.9)	
Others, n (%)	13 (4.7)	
Iron agent, n (%)	70 (25.5)	
Erythropoietin, n (%)	11 (4.0)	

Values are presented as the mean ± standard deviation unless stated otherwise. BMI, body mass index.
[a] Newly prescribed during the current admission before endoscopic examination.

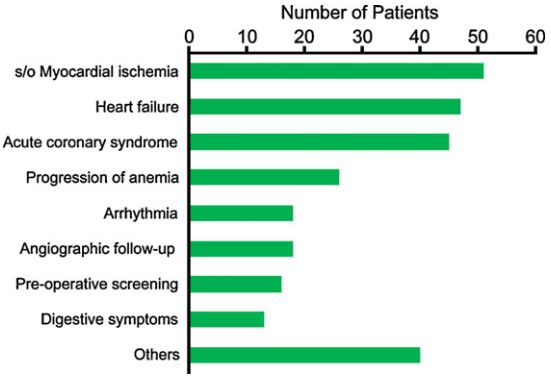

Fig. 1. Main reasons for admission to Cardiovascular Department. s/o, suspect of.

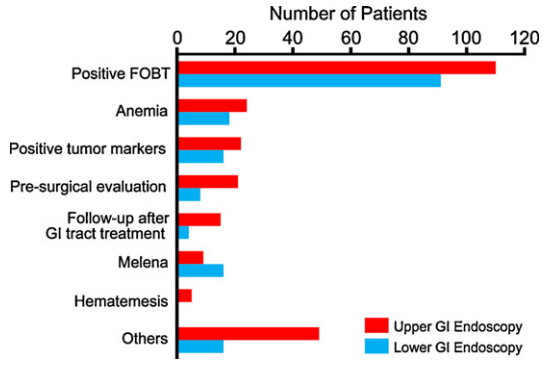

Fig. 2. Reasons for performing gastrointestinal (GI) endoscopy. FOBT, fecal occult blood test.

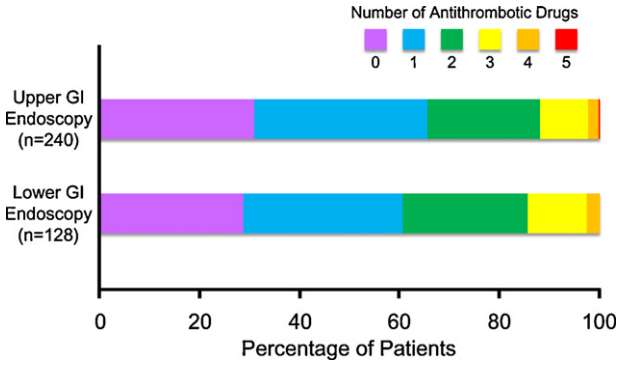

Fig. 3. Number of antithrombotic drug usage among patients who underwent upper gastrointestinal (GI) endoscopy and those who underwent lower GI endoscopy.

Antithrombotic drug usage

Among the 274 patients, the number of antithrombotic drugs taken was 1 in 96 patients, 2 in 66 patients, 3 in 26 patients, 4 in 4 patients, and 5 in one patient. Thus, 193 (70.4%) were taking at least one antithrombotic drug. The mean number of antithrombotic drugs used was calculated to be 1.19. The number of antithrombotic drugs did not apparently differ between patients who underwent upper GI endoscopy and those who underwent lower GI endoscopy (Fig. 3). Aspirin was the most frequently, and ticlopidine was the second most frequently used antiplatelet drug at the time of admission (Table 1). The mean value of international normalized ratio of prothrombin time (PT-INR) in 62 patients who were taking warfarin at the time of admission was 1.73 ± 0.76. In some patients, antithrombotic drug(s) that had not been taken before the admission were started (Table 1). Background conditions necessitating such additional antithrombotic drug prescription included CAD (15 patients), post coronary stent implantation (31 patients), arrhythmia (6 patients), and others (4 patients).

GI endoscopic findings

Malignant neoplasm was found in 26 patients (9.5%) (Table 2). Among 15 patients with colorectal cancer, malignancies were found in proximal colon in 6 patients, distal colon in 4 patients, rectum in 4 patients, and both proximal and distal colons in 1 patient. Among 26 patients who were found to have GI malignancies, 12 patients were also diagnosed to have non-malignant GI lesions, such as polyps, adenomas, and ulcers concomitantly. In 29 patients who had a history of curatively-treated GI malignancies, no recurrent GI neoplasms were found. Non-malignant GI lesions were diagnosed in 106 patients (38.7%); GI tract ulcers that had not been previously diagnosed were found in 39 (14.2%), and polyps/adenomas in 71 (25.9%) (Table 2). Of the 106 patients with non-malignant GI lesions, 15 had two or more such lesions. In addition to the lesions listed in Table 2, reflux esophagitis, Brunner's gland adenoma, and colon diverticulum were found in 25 (9.1%), 2 (0.7%), and 10 (3.6%) patients, respectively.

Table 2
Diagnosed gastrointestinal (GI) lesions.

GI lesions	$n = 274$
Malignant neoplasms	
Esophagus, *n* (%)	2 (0.7)
Stomach, *n* (%)	9 (3.3)
Colorectum, *n* (%)	15 (5.5)
Non-malignant lesions	
Ulcers	
Esophagus, *n* (%)	2 (0.7)
Stomach, *n* (%)	26 (9.5)
Duodenum, *n* (%)	10 (3.6)
Colorectum, *n* (%)	5 (1.8)
Polyps/adenomas	
Esophagus, *n* (%)	1 (0.4)
Stomach, *n* (%)	19 (6.9)
Duodenum, *n* (%)	5 (1.8)
Colorectum, *n* (%)	53 (19.3)

Table 3
Multivariate analysis.

Independent variables	Odds ratio	(95% CI)	*p* Value
Dependent variable: GI malignancies			
Age, per year	1.03	(0.99–1.08)	0.168
Male gender	1.20	(0.46–3.16)	0.714
Admission Hb levels, per g/dL	1.07	(0.90–1.26)	0.464
Antiplatelet drug usage	0.38	(0.16–0.91)	0.030
Positive fecal occult blood test	4.44	(1.44–13.66)	0.009
Dependent variable: non-malignant GI lesions			
Age, per year	1.00	(0.98–1.03)	0.966
Male gender	1.40	(0.76–2.56)	0.280
Admission Hb levels, per g/Dl	0.87	(0.77–0.97)	0.014
Antiplatelet drug usage	1.85	(1.05–3.25)	0.033
Positive fecal occult blood test	1.99	(1.14–3.47)	0.016

Multivariate logistic regression analysis was performed using all the listed parameters as covariates.
GI, gastrointestinal; Hb, hemoglobin.

Predictors for malignant neoplasm and non-malignant GI lesions

We then examined the various clinical parameters that may be associated with the malignant and non-malignant GI lesions in the study population. The mean age did not significantly differ between patients who were found to have GI malignancies (74.4 ± 7.8 years) and those who were not (70.6 ± 11.8 years, $p = 0.108$). In addition, admission Hb levels did not significantly differ between these groups (10.6 ± 2.4 g/dL vs. 10.8 ± 2.6 g/dL, $p = 0.710$). Furthermore, the prevalence of heart failure, atrial fibrillation, and ischemic heart disease did not significantly differ between the groups. The prevalence of GI malignancies was borderline, but not statistically significantly, lower in patients who took antithrombotic drugs (14 patients [7.3%]) than in those who did not (12 patients [14.8%], $p = 0.051$). On the other hand, the prevalence of GI malignancies was significantly lower in patients who took antiplatelet drugs (10 patients [6.1%]) than in those who did not (16 patients [14.5%], $p = 0.019$). In univariate analysis, usage of antiplatelet drugs was negatively associated with GI malignancies with an odds ratio of 0.38 (95% CI 0.17–0.88, $p = 0.023$), and positive fecal occult blood test was positively associated with GI malignancies with an odds ratio of 2.08 (95% CI 1.20–3.58, $p = 0.009$). On the other hand, usage of aspirin was not significantly associated with GI malignancies with an odds ratio of 0.54 (95% CI 0.24–1.24, $p = 0.146$). After including age, gender, and other possible confounding variables, multivariate logistic regression analysis showed that usage of antiplatelet drugs and positive fecal occult blood test remained to be negatively and positively, respectively, associated with GI tract malignancies (Table 3).

Positive fecal occult blood test was found to be also a predictor for non-malignant GI lesions; however, antiplatelet drug usage was, unlike for GI malignancies, a positive predictor for non-malignant GI lesions. Warfarin usage was not found to be a significant predictor for either malignant or non-malignant GI lesions.

Discussion

We herein report that GI malignancies and non-malignant GI lesions (ulcers, polyps, adenomas) were diagnosed in 26 patients (9.5%) and 106 patients (38.7%), respectively, among 274 cardiovascular inpatients who underwent upper and/or lower GI

endoscopies. The study population was extracted from the database during a 59-month period; therefore, it is calculated that GI malignancies and non-malignant GI lesions were diagnosed in 0.44 patients and 1.80 patients, respectively, per month in our cardiovascular department, which would by no means be negligible. It was found that antiplatelet drug usage was a negative predictor for GI malignancies, whereas it had a positive association with non-malignant GI lesions. In addition, positive fecal occult blood test, which was the most frequent reason for GI endoscopic examination, was significantly positively associated with both GI malignancies and non-malignant GI lesions with an odds ratio of 4.44 and 1.99, respectively.

Several previous studies suggested that subjects with certain cardiovascular diseases, such as atrial fibrillation [18], heart failure [19], abdominal aortic aneurysm, and peripheral artery disease [20], may have a higher risk for GI malignancies, although, most of such observations had been derived from small-size samples, and thus did not seem to be conclusive. The association between cardiovascular diseases and GI malignancies, if present, may be attributed to share of common risk factors, alterations in the autonomic nervous system in cancer patients [21,22], and excessive blood loss leading to the aggravation of heart failure symptoms [23]. Of note, by performing screening colonoscopy after coronary angiography in more than 400 patients, Chan et al. have shown that the prevalence of colorectal cancer in patients with CAD was unexpectedly high (4.4%), which contrasted with a much lower prevalence of such lesions (0.5%) in CAD-negative patients [16]. More recently, by analyzing the data of male subjects who underwent both coronary computed tomography angiography and colonoscopy as a part of health check-up, Yang et al. reported that colorectal adenoma was found in 217 subjects (44%) among 488 total study subjects, and that subjects who were found to have significant coronary artery stenosis had a higher rate of colorectal adenoma (odds ratio, 1.96) when compared with those without coronary stenosis [24]. In the current study, not all the patients underwent coronary angiography during the study period; therefore, we cannot compare the prevalence of GI lesions between our population and previously reported study samples.

In the current study, usage of antiplatelet drugs was found to be a strong negative predictor for GI malignancies. Although we cannot conclude whether antiplatelet drugs would affect GI lesion prevalence from the current observation, some possible explanations, if present at all, might be as follows. First, usage of aspirin, the most frequently used antiplatelet drug in the current study, has been shown to reduce GI cancer risk [25,26]. Aspirin inhibits cyclooxygenase (COX), which catalyzes the rate-limiting step in the metabolic conversion of arachidonic acid to prostaglandins and related eicosanoids [25]. COX exists in two isoforms, COX-1 and COX-2, the latter of which may promote inflammation and cellular proliferation and is progressively overexpressed during the stepwise sequence from adenoma to carcinoma [27]. Chan et al. found that aspirin reduces the risk of colorectal cancers that overexpress COX-2 but not the risk of colorectal cancers with weak or absent expression of COX-2 [25]. Although aspirin may exert antiproliferative effects other than COX inhibition, including suppression of nuclear factor-kB activity and induction of apoptosis, doses of aspirin required for such non-COX-related actions are considered to be higher than COX-2 inhibition [25,28]. In addition, other antiplatelet drugs, such as clopidogrel, ticlopidine, and cilostazol, do not have the effect of COX-2 inhibition. Although we did not find that aspirin usage was negatively associated with GI malignancies, it may be because we selected the study population who had already shown signs and symptoms that were suspicious of GI lesions. In addition, the population enrolled in the current study may have been at higher risk for malignant GI lesions, regardless of the suspicious signs and symptoms, because cardiovascular disease and malignant neoplasm share many risk factors, such as diabetes mellitus and smoking [16]. Therefore, it cannot be concluded that aspirin usage would decrease the risk for GI malignancies from the current study. Second, as antithrombotic drugs may facilitate hemorrhaging from non-malignant lesions [7,29–31], leading to an increased prevalence of patients with non-malignant GI lesions among the study population. The finding that antiplatelet drug usage was positively associated with non-malignant GI lesions in the current study (Table 3) may support this notion. Interestingly, anticoagulant (warfarin) usage was not a positive predictor for non-malignant GI lesions in the current study, although warfarin usage has also been reported to increase the risk of GI bleeding [32–34].

There are several limitations in the current study. First, not all of the participants underwent both upper and lower GI endoscopies. Second, not all the cardiology inpatients during the study period underwent fecal occult blood test. It is presumed that the true incidence of GI malignancies may be higher than that observed in the current study. Third, although the rate of GI malignancies diagnosed by GI endoscopy among the study population was higher than that among healthy subjects [35], cost-effectiveness of GI endoscopic screening in cardiology patients, especially in those with negative fecal occult blood test, may be another issue to be analyzed.

In conclusion, among 274 cardiology inpatients who underwent GI endoscopies due to certain signs and symptoms, GI malignancies were found in 26 patients (9.5%); the locations of these lesions were stomach, 9 (3.3%), esophagus, 2 (0.7%), and colon, 15 (5.5%). Among the study population, usage of antiplatelet drugs was negatively, whereas positive fecal occult blood test was positively associated with GI malignancies. Although the precise mechanism remains unclear how antiplatelet drugs reduce GI malignancies, we showed here that there may be a certain difference in the risk of GI malignancies according to usage of antiplatelet drugs among cardiology inpatients. In addition, in 106 patients, GI endoscopy revealed non-malignant GI lesions, such as ulcers, adenomas, and polyps, some of which were concomitantly present with GI malignancies. We have to be aware that GI malignancies and non-malignant GI lesions may not be a rare occurrence in cardiology inpatients. In order to avoid overlooking such potentially life-threatening lesions, GI endoscopy should not be ignored by simply presuming signs and symptoms are due to clinically-insignificant GI pathologies facilitated by the usage of multiple antithrombotic drugs.

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