

The Prevalence of Iron Deficiency Anemia and Its Clinical Implications in Patients with Colorectal Carcinoma

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Background: Gastrointestinal (GI) tract malignancy is an important cause of chronic iron deficiency anemia (IDA). The present study was designed to determine the prevalence of IDA and its clinical implications in colorectal cancer patients.

Methods: We performed a retrospective study of 101 patients who were admitted to Taipei Veterans General Hospital with proven colorectal carcinoma from 2003–2005. We reviewed the discharge charts and recorded the following data: gender, age, tumor size, tumor site, tumor stage, clinical symptoms, complete blood counts, serum iron (SI), total iron binding capacity (TIBC), serum ferritin, lactate dehydrogenase (LDH) and carcinoembryonic antigen (CEA). The patients were divided into 2 groups: 1 with and the other without anemia. Different variables of the 2 groups were compared and analyzed to find out the risk factors of anemia in patients with colorectal cancer.

Results: A total of 101 patients, with a mean age of 65.3 years, were enrolled; 56 were male. Their mean hemoglobin was 11.8 g/dL. Fifty-one patients (51%) were found to have anemia. Multivariate logistic regression analysis showed that female gender, tumor in the right colon (cecum, ascending colon, hepatic flexure), and maximum tumor diameter ≥ 3 cm were risk factors of anemia in patients with colon carcinoma. Serum ferritin had been measured in 25 patients, and low ferritin level ($< 40 \mu\text{g/L}$) was found in 15 (60%) of them. CEA and LDH were elevated in 45% (43/95) and 46% (43/93) of patients with colorectal cancer, respectively.

Conclusion: Iron deficiency anemia is a common clinical manifestation of patients with colorectal carcinoma, and occurred more frequently in females, patients with right colon tumor and with larger tumor size. [*J Chin Med Assoc* 2008;71(3): 119–122]

Key Words: colorectal cancer, iron deficiency anemia, predictive risk factor, serum ferritin

Introduction

Iron deficiency is the most common cause of anemia worldwide. Chronic blood loss is one of the common causes of iron deficiency anemia (IDA). Occult bleeding from the gastrointestinal (GI) tract is usually thought to be the leading cause of IDA in adults.¹ A population-based cohort study proved that GI malignancy was significantly more common in those with iron deficiency than in those with normal serum iron saturation and hemoglobin levels.² Our previous study³ and

others^{4–6} showed that the prevalence of GI malignancy in patients with IDA ranged from 10% to 17%. Tan et al⁷ and Sworzak et al⁸ reported that IDA was one of the predictive factors of colorectal cancer and small intestinal cancer. Thus, the correlation of IDA and malignancy is well known and should be kept in mind in clinical practice. In our previous prospective study, we demonstrated the prevalence of GI malignancy in IDA patients.³ In order to define the prevalence and the clinical implications of IDA in colorectal cancer patients, a retrospective study was conducted.



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Methods

From the database of the hospital computer system, we searched the discharge notes for patients who had a diagnosis of proven carcinoma of the colon in 2003–2005 in Taipei Veterans General Hospital. Patients with pathology-proven colon carcinoma and with adequate recorded data to be evaluated were enrolled into our study. Basic data such as age, gender, tumor site and size, tumor stage, tumor pathology, lymph node involvement and metastasis were recorded. Clinical symptoms and laboratory data including anorexia, nausea, vomiting, constipation, diarrhea, abdominal pain, change of bowel habit, body weight loss, tarry stool, small caliber of stool, serum ferritin, serum iron (SI), total iron binding capacity (TIBC), complete blood count (CBC), blood urea nitrogen (BUN), creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), carcinoembryonic antigen (CEA), lactate dehydrogenase (LDH), stool occult blood, colonoscopy and barium enema findings were recorded as well.

Two methods were used to represent the tumor size: the greatest diameter and the area calculated using the 2 greatest dimensions of the tumor. Tumor site was recorded and divided into right colon and non-right colon tumors. Right colon tumors included tumors in the cecum, ascending colon or the hepatic flexure; non-right colon tumor included tumors in the remaining sites of the colon. Tumor staging was determined according to the AJCC TNM system in colorectal cancer.

Anemia was defined as hemoglobin < 12 g/dL. We compared the prevalence of anemia with elevations of CEA and LDH in patients with colon cancer, and determined the relationships between anemia and other parameters.

We divided the patients into 2 groups: with or without anemia. The χ^2 test or Fisher's exact test was used to compare the hemoglobin concentration with gender, cancer stage and clinical symptoms; Mann-Whitney rank sum test or Student's *t* test was used to compare hemoglobin with the continuous variables. If the result was significant ($p < 0.05$), multivariate logistic regression was used to find the real correlating factors.

Serum ferritin was recorded in 25 of the 101 patients. We compared the relationship of ferritin level with other variables in order to find out the risk factors of lower serum ferritin.

Results

General data in 101 patients with colon carcinoma

A total of 101 patients were enrolled. Their mean age was 65.3 years; 56 of them were male. All had adenocarcinoma except for 1 who had poorly differentiated carcinoma. The most frequent site of tumor occurrence was the rectum (34 patients), followed by the sigmoid colon (32 patients) and then the ascending colon (10 patients). Three patients had 2 different occurring sites. Fifty-one patients (51%) had anemia. Two groups were distinguished according to the presence of anemia or not. Table 1 shows the mean and SD of the variables in these 2 groups of patients. Twenty-three of the 101 patients had cancer of the right colon, 17 (74%) of them had anemia. Seventy-eight patients had non-right colon cancer, 34 (44%) of them had anemia. The rate of anemia was higher in the right colon cancer than in the non-right colon cancer patients.

Table 1. Means of variables in the anemia and non-anemia groups in 101 patients with colon carcinoma*

	Anemia group	Non-anemia group	Total
Age (yr)	62.9 ± 13.7 (51)	67.8 ± 13.9 (50)	65.3 ± 14.0 (101)
Maximum tumor diameter (cm)	5.28 ± 2.17 (51)	3.93 ± 1.83 (48)	4.62 ± 2.12 (99)
Serum ferritin (µg/L)	80.4 ± 208.6 (17)	148.3 ± 138.9 (8)	102.1 ± 188.9 (25)
Transferrin saturation (%)	24.5 ± 14.6 (14)	33.1 ± 7.2 (8)	27.7 ± 12.9 (22)
Hemoglobin (g/dL)	9.98 ± 1.43 (51)	13.60 ± 1.12 (50)	11.80 ± 2.22 (101)
Hematocrit (%)	30.2 ± 3.9 (51)	41.0 ± 7.7 (50)	35.5 ± 8.1 (101)
WBC (× 10 ⁹ /L)	8.2 ± 3.5 (51)	7.5 ± 3.4 (50)	7.8 ± 3.5 (101)
Platelets (× 10 ⁹ /L)	299 ± 114 (51)	258 ± 93 (50)	279 ± 106 (101)
LDH (U/L)	292 ± 274 (50)	296 ± 471 (43)	294 ± 375 (93)
Creatinine (mg/L)	1.2 ± 1.2 (51)	1.0 ± 0.3 (50)	1.1 ± 0.9 (101)
ALT (U/L)	17.0 ± 19.1 (50)	22.4 ± 23.2 (49)	19.7 ± 21.3 (99)
CEA (U/L)	82 ± 293 (48)	234 ± 772 (47)	157 ± 583 (95)

*Data are presented as mean ± standard deviation (number of patients examined). WBC = white blood cell count; LDH = lactate dehydrogenase; ALT = alanine aminotransferase; CEA = carcinoembryonic antigen.

Table 2. Relationship between anemia and other variables

	p value			
	Pearson's χ^2	Mann-Whitney rank sum test	Paired t test	MLR
Gender	<0.0005			<0.0005
Right colon tumor	<0.005			0.029
Tumor diameter > 3 cm	0.026	0.001		0.05
Tumor area		0.002		
Hematocrit			<0.0005	
RBC number			<0.0005	
MCV			<0.0005	
Serum ferritin		0.006		
Transferrin saturation		0.049		
Platelet number		0.018		

MLR = multivariate logistic regression; RBC = red blood cell; MCV = mean corpuscular volume.

CEA and LDH were measured in 95 and 93 patients, respectively. CEA was high (>6.0 U/L) in 45% (43/95) of the patients, and LDH was high (>213 U/L) in 46% (43/93) of the patients.

Relationships between anemia and other variables

Different variables were compared in the 2 groups of patients (Table 2). Pearson's χ^2 test showed that female gender, right colon tumor and tumor diameter > 3 cm were significantly associated with anemia ($p < 0.0005$, = 0.005 and = 0.026, respectively). Mann-Whitney rank sum test and Student's t test showed that anemia was related with the diameter and the area of the tumor ($p = 0.001$ and 0.002, respectively). None of the clinical symptoms was found to have any significant relationship with anemia. Concerning laboratory data, hematocrit, red blood cell number, mean corpuscular volume, serum ferritin, transferrin saturation (SI/TIBC) and platelet count were found to be related with anemia ($p < 0.0005$, < 0.0005, < 0.0005, = 0.006, = 0.049 and = 0.018, respectively), whereas LDH, CEA, CA-125 and CA-19-9 were not correlated with anemia. Multivariate logistic regression showed that female gender, tumor diameter > 3 cm, and right colon tumor were related with anemia ($p < 0.0005$, = 0.05, = 0.029 respectively, and OR = 6.711, 3.699 and 3.907, respectively).

Percentage of low serum ferritin and low transferrin saturation in patients with colon cancer

Serum ferritin was measured in 25 of the 101 patients, 15 (60%) of whom had low serum ferritin (<40 $\mu\text{g/L}$). Transferrin saturation was measured in 22 of the patients; only 3 (14%) had less than 15%, and 5 (23%) had less than 16%.

Discussion

The association of iron deficiency anemia and GI tract malignancy has been well known in recent years. In a patient with unknown cause of IDA, a full survey of the GI series to rule out the possibility of malignancy is suggested. In our previous study, 12.2% of IDA patients were found to have malignancy,³ therefore, iron deficiency anemia should be regarded as one of the predictors of GI malignancy. In the present retrospective study, in contrast to our previous study, patients with confirmed carcinoma of the colon and rectum were analyzed in order to find out the prevalence of anemia, and the relationship of anemia with different variables in them.

Anemia was found in about half (51%) of the patients with carcinoma of the colon and rectum. This rate was slightly higher than those with elevation of CEA (45%) and LDH (46%). Furthermore, in 23 patients with right colon cancer, the anemia rate was even higher (74%), although it was slightly lower than that reported by Kanellos et al (87.2%).⁹ Even in 78 patients with non-right colon cancer, the prevalence of anemia was not low (44%). Thus, in spite of its non-specificity, anemia seems to be a good marker in patients with carcinoma of the colon.

Female gender, tumor maximum diameter > 3 cm and right colon cancer were found to be related with anemia. It is easy to understand why female gender is more prone to have IDA than male. Females have a greater opportunity to lose iron during the child-bearing ages; this contributes to the higher rate of IDA in the general population as well as in patients with colon cancer. Thus, in a female patient with IDA, many factors other than GI tract malignancy should be considered. In contrast, in a male patient with IDA,

GI tract malignancy should be kept in mind unless another definite cause has been found.

Anemia was found to be associated with greater tumor diameter and with right colon cancer. In general, greater tumor diameter means longer growth time of the tumor, and right colon cancer usually causes less chance of obstruction than non-right colon tumor, and thus later discovery of the tumor. Both of these factors explain why the longer the tumor exists, the greater the chance anemia will occur. It also means that although anemia is an important clinical manifestation of colon cancer, it probably is not a very early marker of colon cancer. However, it can still be a sign for us to consider the possibility of GI malignancy when a patient has an unknown cause of anemia.

In the present retrospective study, unfortunately, transferrin saturation and serum ferritin were measured in only 22 and 25 patients, respectively. This probably demonstrates the fact that clinicians do not have the concept to check serum ferritin in a patient with suspected colon cancer as they do not think it is important. Serum ferritin is closely related with iron store. Low serum ferritin (<40 µg/L) was found in more than half (15/25, 60%) of the patients with colon cancer. In general, low serum ferritin always represents iron deficiency, although the cutoff point of low serum ferritin was different in different reports. On the other hand, if a patient has higher serum ferritin, iron deficiency cannot be completely ruled out, as serum ferritin is an acute-phase reactant; it can also rise in malignancy,¹⁰ and thus can be falsely high even in patients with iron deficiency but associated with malignancy. As more than half of the patients detected with colon cancer had iron deficiency, this shows that the cause of anemia in colon cancer was mostly due to iron deficiency, and was compatible with the presence of chronic blood loss in patients with colon cancer. Furthermore, platelet count was significantly higher in the anemia group than in the non-anemia group ($p=0.018$, data not shown), which was also indirect evidence to imply the presence of IDA, as thrombocytosis is known to be one of the common signs of IDA.¹¹⁻¹⁴ From our previous study, we found that 12.2% of IDA patients had GI malignancy,³ and in the

present study, more than half of the patients with colorectal cancer had anemia, thus, we concluded that IDA was a common clinical manifestation in patients with colorectal carcinoma.

In conclusion, low hemoglobin and serum ferritin were commonly seen in patients with colorectal cancer.

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