Vitamin B12 deficiency and gastric histopathology in older patients

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Abstract

AIM: To compare upper gastric endoscopic and histopathologic findings in older adults in the presence and absence of B12 deficiency.

METHODS: A prospective analysis of upper gastric endoscopic and gastric histopathologic findings from 30 newly identified B12-deficient patients (11 males, 19 females) and 16 controls with normal B12 status (6 males, 10 females) was performed. For all subjects, the indication for upper endoscopy and gastric biopsy were unrelated to B12 status. A single pathologist, blinded to B12 status, processed and interpreted the biopsy samples. Endoscopic and histopathologic findings were correlated with age, gender, hematocrit (Hct), MCV and B12 status.

RESULTS: The B12-deficient group had significantly lower mean serum B12 levels compared to the controls (P<0.00005) while their mean Hct, MCV and serum albumin levels were similar. Iron deficiency (ferritin-based) was present in 21% of B12-deficient patients and intrinsic factor antibodies were present in 29% (S/17) of B12-deficient patients. The endoscopic findings revealed significantly different rates of gastritis and atrophy between the B12-deficient and control groups (P=0.017). B12-deficient patients had significantly less superficial gastritis (62% vs 94%) and significantly more atrophic gastritis (28% vs 0%) as compared to the controls (P=0.039). Intestinal metaplasia was similar in both groups. Helicobacter pylori infection rates were similar in the B12-deficient patients and controls (40% vs 31%).

CONCLUSION: Significantly different endoscopic findings and types of gastritis could often be observed in the presence and absence of B12 deficiency. Atrophy, based on endoscopy, and atrophic gastritis, based on histopathology, suggest the presence of B12 deficiency. Gastric histopathology is not influenced by the age, gender, Hct or MCV of the patients.

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Key words: Vitamin B12 deficiency; Gastric histopathology; Older adults

INTRODUCTION

Vitamin B12 deficiency is a common but under-recognized disorder with a prevalence ranging from 3% to 40% in the adult population[1-4]. In a previous study, we noted a prevalence of between 15% and 25% in the community and nursing home hospitalized older subjects[3]. B12 deficiency often goes undetected, with manifestations that range from asymptomatic to a wide spectrum of hematologic and/or neuropsychiatric features. For the purpose of this discussion, the term B12 will be used interchangeably with cobalamin.

B12 deficiency affects proliferating epithelium at all the sites[3]. Although the histopathological effects of B12 deficiency relating to the blood and nervous system are well described, histopathological changes in the stomach associated with cobalamin deficiency in older subjects have
received less emphasis in the literature. Presently, there exist some confusions whether gastric changes are a cause or effect of deficiency[8]. It is worth stating that the stomach plays a major role both in the absorption of B12 and the pathogenesis of cobalamin deficiency[8,9]. Among the etiologies of cobalamin deficiency, pernicious anemia (PA), once believed to be the most common cause[6,9], actually accounts for only a small fraction of cases of B12 deficiency[2,3,8]. It is well recognized that PA, a type A gastritis, is characterized by fundic atrophic gastritis. There is a lack of knowledge about the examination of gastric endoscopic findings and histopathologic changes associated with vitamin B12 deficiency in older adults. We, therefore, have attempted to evaluate the endoscopic and histopathologic changes in older adults with newly diagnosed B12 deficiency and to compare the findings in adults of the same age group and normal B12 status.

MATERIALS AND METHODS
The study was performed by the staff from the divisions of geriatrics, gastroenterology, medicine, pathology and biomedical research at Our Lady of Mercy Medical Center, University Hospital of New York Medical College, Valhalla, NY, USA. A prospective analysis of upper gastric endoscopic and gastric histopathologic findings was performed on 30 adults who were above the age of 60 with newly diagnosed B12 deficiency. The subjects included men and women, ages ranging from 60 to 99 years. All patients required hospitalization for a cause other than B12 deficiency. The diagnosis of B12 deficiency was made following routine screening or during evaluation for hematological or neurological manifestations. A randomly selected group of 6 male and 10 female patients with normal B12 status, ages ranging from 63 to 93 years served as controls. The male/female ratio in the B12-deficient group was 11/19, and 6/10 in the control group. Several indicators of nutritional status were assessed in the B12-deficient patients. We observed low folate status in 16%, low albumin status in 16% and low iron status (ferritin based) in 21% of the B12-deficient patients.

The primary indication for endoscopy was unrelated to cobalamin status and based on the usual indications for upper gastric endoscopy on both B12-deficient patients and controls. After obtaining informed consent, upper gastric endoscopy was performed and multiple endoscopic biopsies were obtained from several sites within the gastric fundus and antrum. Gastric biopsies were performed for reasons unrelated to cobalamin status and hence the sites examined and the number of biopsies taken varied between individuals. Endoscopic findings included a normal appearance of the stomach, atrophy and gastritis. Gastritis on endoscopy was defined as the presence of erosions or hemorrhage. Erosions were seen as breaks in the mucosa manifesting as multiple lesions with white bases that were commonly encircled by a halo of erythema. Atrophy on endoscopy was defined as the disappearance of gastric rugae and a thinning of the gastric mucosal folds with the prominence of the blood vessels seen through the thin mucosa (paper money appearance)[10]. Erosive gastritis and friable mucosa are suggestive findings of gastritis on endoscopy.

Gastric histopathology entailed the use of formalin-fixed and paraffin-embedded tissues, which were sectioned at five micrometer thickness, mounted on slides and stained with hematoxylin and eosin. All specimens (in both the B12-deficient group and controls) were reviewed by a single histopathologist who was unaware of the individual’s B12 status. Biopsy findings were classified as normal (Figure 1A), inflammation (Figures 1B-D), atrophy and intestinal metaplasia (Figures 1B and C). Each specimen was also stained for the presence of Helicobacter-like organisms using toluidine blue stain with Alcian yellow counterstain (Polyscientific, Bayshore, NY, USA) (Figure 1E). See Table 1 for definitions.

For the purpose of this study, B12 status was defined as normal, borderline and deficient as follows: normal >349 ng/L; borderline 100-349 ng/L; and deficient <100 ng/L. The reference range for cobalamin values in our laboratory is 157-1059 ng/L. Endoscopic and histopathologic findings were correlated with age, gender, hematocrit.
We noted a statistically significant difference in the degree detected in the presence of cobalamin deficiency (Table 3). Notably, of the hyperplastic type, were more frequently common in patients with normal B12 status. Polyps, similar in both groups. However, atrophy was noted only in 40% of patients on continuous, long-term PPI therapy may manifest reduced cobalamin levels, however, a resultant dysfunctional. This entity is defined as the inability to absorb food-cobalamin malabsorption resulting from gastric dysfunctions. Blood tests are used to detect cobalamin deficiency. In some reports, an inverse relationship between age and serum cobalamin concentrations. The most common etiology of vitamin B12 deficiency is food-cobalamin malabsorption resulting from gastric dysfunctions. This entity is defined as the inability to absorb food (or food) bound cobalamin, although the ability to absorb free cobalamin remains intact. Food cobalamin malabsorption may be a consequence of the use of acid-lowering agents, such as proton pump inhibitors (PPI) and histamine 2 receptor antagonists. A small proportion of patients on continuous, long-term PPI therapy may manifest reduced cobalamin levels, however, a resultant distinct B12 deficiency is seldom reported.

### Table 1 Histopathology: Definitions

- Chronic atrophic gastritis (CAG): more extensive inflammation accompanied by glandular atrophy. CAG further subdivided into mild, moderate and severe based on atrophy involving the upper one-third, upper two-thirds and full thickness of the mucosa respectively.
- Chronic superficial gastritis (CSG): inflammation limited to the foveolar region unaccompanied by glandular atrophy. (Figures 1B-1D).
- Gastric atrophy (GA): thinning of the mucosa with an absence of inflammatory changes.
- Hyperplasia: an increase in the number of mucosal epithelial cells.
- Metaplastic changes: Intestinal metaplasia characterized by goblet cells, brush border cells, Paneth cells and endocrine cells. (Figures 1B and 1C). Pyloric metaplasia of the fundus characterized by mucus secreting glands.

### Table 2 Baseline patient characteristics

| Variable                          | B12 deficient (n = 30) | Controls (n = 16) | P-value |
|-----------------------------------|------------------------|-------------------|---------|
| Age (yr)                          | 78 ± 11                | 77 ± 8            | 0.9090  |
| Gender (M:F)                      | 11:19                  | 6:10              | 1.0000  |
| Serum B12 (pg/dL)                 | 183 ± 60               | 872 ± 459         | <0.0005 |
| Hematocrit (%)                    | 34.9 ±4.8              | 33.4 ± 3.7        | 0.3010  |
| MCV (%)                           | 86.5 ± 7.6             | 87.4 ± 9.9        | 0.7321  |
| Serum albumin (g/dL)              | 2.9 ± 0.5              | 2.9 ± 0.7         | 0.9692  |
| H. pylori infection (+/-)          | 12/18                  | 5/11              | 1.0000  |
| Intrinsic factor Ab (+/-)          | 5/12                   | -                 | -       |

†Data presented as the means ± SD or actual numbers. Statistical comparisons used Student’s t-tests or χ²-square analysis.

See Table 3 Endoscopy findings

| Endoscopy findings                        | B12 deficient group (n=30) (%) | Control group (n=16) (%) | P-value |
|-------------------------------------------|-------------------------------|--------------------------|---------|
| Normal                                    | 11 (36.7)                     | 5 (31.3)                 |         |
| Gastritis                                 | 8 (26.7)                      | 11 (68.8)                |         |
| Atrophy                                   | 8 (26.7)                      | 0 (0)                    |         |
| Polyps                                    | 1 (3.3)                       | 0 (0)                    |         |
| Others †                                  | 2 (6.7)                       | 0 (0)                    |         |

† (includes 1 case of hiatal hernia and 1 case of candidiasis). Endoscopic findings between groups were compared using Fisher’s exact test, (P=0.017).

Our findings suggested that the rate of H. pylori infection was similar in patients with B12 deficiency and controls (40% vs 31%; Table 8). Twenty-six percent of the B12-deficient patients had undiagnosed PA as demonstrated by the presence of intrinsic factor antibodies. Age appeared to have no effect on the presence or absence of intrinsic factor antibodies that is consistent with the literature. Parietal cell antibodies (not tested in our study), which are less specific, are known to increase with age. The presence of intrinsic factor antibodies also was not related to Hct levels (Tables 4-7).

DISCUSSION

Physiological changes accompanying the aging gut, in particular the stomach, may be difficult to differentiate from the disease[13]. Studies in older adults have suggested a high prevalence of subnormal cobalamin concentrations, and in some reports, an inverse relationship between age and serum cobalamin concentrations[12,13]. The most common etiology of vitamin B12 deficiency is food-cobalamin malabsorption resulting from gastric dysfunctions. This entity is defined as the inability to absorb protein (or food) bound cobalamin, although the ability to absorb free cobalamin remains intact. Food cobalamin malabsorption may be a consequence of the use of acid-lowering agents, such as proton pump inhibitors (PPI) and histamine 2 receptor antagonists[14,15]. A small proportion of patients on continuous, long-term PPI therapy may manifest reduced cobalamin levels, however, a resultant distinct B12 deficiency is seldom reported[16]. Our earlier data suggested that the use of H2 antagonists and PPI is not associated with the development of gastritis between B12-deficient patients and controls (P=0.039). Atrophic gastritis was more common in individuals with B12 deficiency, while superficial gastritis was the most common finding in controls. The incidence of intestinal metaplasia (in the antrum) was similar in the individuals with or without B12 deficiency. None of the controls had features of atrophy on endoscopy or histopathology. In this study, age and gender had no influence on gastric histopathology. In addition, endoscopic findings and gastric histopathology were not related to Hct levels (Tables 4-7).

Our findings suggested that the rate of H. pylori infection was similar in patients with B12 deficiency and controls (40% vs 31%; Table 8). Twenty-six percent of the B12-deficient patients had undiagnosed PA as demonstrated by the presence of intrinsic factor antibodies. Age appeared to have no effect on the presence or absence of intrinsic factor antibodies that is consistent with the literature. Parietal cell antibodies (not tested in our study), which are less specific, are known to increase with age. The presence of intrinsic factor antibodies also was not related to H. pylori infection (Table 8). Histopathological features also tended to overlap in both the groups.
as stated earlier, PA accounts only for a small number of cases of B12 deficiency. PA is characterized by an autoimmune gastric atrophy (GA) mediated by anti-intrinsic factor antibodies. Histomorphologically, PA is characterized by fundic atrophic gastritis (type A) leading to atrophy of the fundus and achlorhydria[18]. While the fundus and the body of the stomach contain acid-secreting gastric parietal cells and pepsinogen-secreting zymogenic cells, the antrum possesses gastrin-producing G cells. Chronic atrophic gastritis (CAG) is histopathologically classified into two types based on the presence or absence of antral involvement[8,19]. Strickland et al[19] originally divided chronic nonspecific gastritis into type A (associated with PA) and type B (not associated with PA). Others have added type C (chemical gastritis, related to drug therapy or bile reflux)[20,21]. Though these concepts are still valid, the discovery of H. pylori as an important cause of gastritis signifies that type B gastritis is now too broad a category and may not be as useful clinically. Hence, some authors suggest abandoning the alphabetic terminology[23]. Type A (autoimmune) gastritis involves the fundus and the body of the stomach and spares the antrum, whereas type B (non-autoimmune) gastritis involves the antrum as well as the fundus and body. Type A gastritis is associated with PA and the presence of auto-antibodies to gastric parietal cells and to intrinsic factor, achlorhydria, low serum pepsinogen 1 concentrations and high serum gastrin levels as a result of the lack of negative feedback inhibition by gastric acid and consequent hyperplasia of gastrin-producing cells. Type B gastritis, which is more common, is usually associated with H. pylori infection, alcoholism and various medications, and is characterized by low serum gastrin concentrations because of the destruction of the gastrin-producing cells associated with antral gastritis[24,25]. Gastric biopsy specimens in PA demonstrate a mononuclear cellular infiltrate in the submucosa consisting of plasma cells, T cells and a large non-T cell population, extending into the lamina propria between the gastric glands[8,23]. The infiltrating plasma cells contain auto-antibodies to parietal cell antigen and to intrinsic factor[24,25]. Extension of the cellular infiltrate into the mucosa is accompanied by degenerative changes in parietal cells and zymogenic cells. With fully established lesions, there is a marked reduction in the number of gastric glands, parietal and zymogenic cells, with replacement by mucus containing cells[8]. More common than PA is a state, usually in the older patient, in which there is diffuse severe atrophic oxyntic gland gastritis with achlorhydria but the residual ability to absorb vitamin B12. To prove the existence of severe oxyntic gland gastritis, biopsy specimens are best taken from the midbody region on the greater curve since the mucosa on the lesser curve is thinner and can be falsely interpreted as atrophic. Severe oxyntic gland atrophy is commonly associated with only mild inflammatory cells infiltrate and a reduced prevalence of H. pylori. The other features include varying amounts of metaplasia[19]. Hyperplastic or inflammatory polyps are the most common lesions found in endoscopic surveys in PA with a prevalence of 10-40%[10,25].

### Table 4 Histopathology of the gastric fundic region

|                          | B12 deficient group (n = 27) (%) | Control group (n = 4) (%) |
|--------------------------|---------------------------------|--------------------------|
| Normal                   | 3 (11.1)                        | 0 (0)                    |
| Inflammation             | 16 (59.3)                       | 4 (100)                  |
| Atrophy                  | 8 (29.6)                        | 0 (0)                    |

Histopathology findings between groups were compared using Fisher’s exact test, (P=0.541).

### Table 5 Histopathology of the gastric antral region

|                          | B12 deficient group (n = 6) (%) | Control group (n = 12) (%) |
|--------------------------|---------------------------------|---------------------------|
| Normal                   | 0 (0)                           | 2 (14.3)                  |
| Inflammation             | 5 (83.3)                        | 6 (42.9)                  |
| Hyperplasia              | 1 (16.7)                        | 0 (0)                     |
| Intestinal metaplasia    | 0 (0)                           | 4 (28.6)                  |

Histopathology findings between groups were compared using Fisher’s exact test, (P=0.039). The B12 deficient group is 29 in Table 6 vs 30 in Tables 7 and 8 because one biopsy sample could not be classified into a specific category.

### Table 6 Gastritis types

|                          | B12 deficient group (n = 29) (%) | Control group (n = 16) (%) |
|--------------------------|---------------------------------|---------------------------|
| Normal                   | 3 (10.3)                        | 1 (6.3)                   |
| Superficial gastritis    | 18 (62.1)                       | 15 (93.7)                 |
| Atrophic gastritis       | 8 (27.6)                        | 0 (0)                     |

Gastritis types between groups were compared using Fisher’s exact test, (P=0.039). The B12 deficient group is 29 in Table 6 vs 30 in Tables 7 and 8 because one biopsy sample could not be classified into a specific category.

### Table 7 Metaplasia in B12 deficiency and controls

|                          | B12 deficient group (n = 30) (%) | Control group (n = 14) (%) |
|--------------------------|---------------------------------|---------------------------|
| No metaplasia            | 22 (73.3)                       | 10 (71.4)                 |
| Hyperplasia              | 1 (3.3)                         | 0 (0)                     |
| Intestinal metaplasia    | 7 (23.3)                        | 4 (28.5)                  |

Metaplasia between groups was compared using Fisher’s exact test, (P=1.000).

### Table 8 Frequency of H pylori infection

|                          | B12 deficient group (n = 30) (%) | Control group (n = 16) (%) |
|--------------------------|---------------------------------|---------------------------|
| H. pylori positive       | 12 (40)                         | 5 (31.2)                  |
| H. pylori negative       | 18 (60)                         | 11 (68.8)                 |

Fisher’s exact test determined that H. pylori infection rates were similar in B12 deficient and control patients (P = 1.000) and that the presence of intrinsic factor antibodies was low and unrelated to H. pylori infection in the B12 deficient group (1/7 in H. pylori+ vs. 0/10 in H. pylori- patients, P = 0.338; data not presented).

As stated earlier, PA accounts only for a small number of cases of B12 deficiency. PA is characterized by an autoimmune gastric atrophy (GA) mediated by anti-intrinsic factor antibodies. Histomorphologically, PA is characterized by fundic atrophic gastritis (type A) leading to atrophy of the fundus and achlorhydria[18].
effect of B12 deficiency. Furthermore, B12 deficiency can affect proliferating cells at all sites and so an association between B12 status and gastric histopathology would help in the development of strategies for screening and early diagnosis of B12 deficiency based on endoscopic and histopathologic findings.

Our study demonstrated that a normal endoscopic appearance was not correlated with B12 status but that endoscopic findings of atrophy and gastritis were significantly different between B12-deficient patients and controls ($P = 0.017$). Similar rates of normal and abnormal histopathologic findings were observed in older adults with and without B12 deficiency. Inflammation was the predominant histopathologic finding in older adults with and without B12 deficiency. Our findings suggested that histopathologic findings were variable and not correlated with B12 status, however, a statistically significant difference in the degree of gastritis was noted between the B12-deficient patients and controls ($P=0.039$). Atrophic gastritis was more common in the B12-deficient patients, while superficial gastritis was more common in the controls. It should also be noted that atrophy was not seen when B12 levels were normal. In these samples of older adults, neither increasing age nor gender influenced gastric histopathology result, while endoscopic findings and gastric histopathology bore no relationship to Hct. There is a strong evidence that $H$ pylori infection is associated with cobalamin deficiency; this is true even with non-ulcer dyspepsia or the presence of minimal to no GA$^{[26]}$. Whether this is merely an association or a cause and effect relationship is unclear. In an earlier study, two-thirds of the patients with atrophic gastritis of the body had $H$ pylori infection$^{[27]}$. Eradication of $H$ pylori infection alone has been reported to correct B12 status and improve anemia in B12-deficient individuals$^{[28]}$. Thus, the possible role of $H$ pylori infection in cases of severe food cobalamin malabsorption suggests specific options to prevent and treat B12 deficiency when associated with $H$ pylori infection$^{[29]}$.

We observed a 40% rate of $H$ pylori infection in patients with cobalamin deficiency compared to a 31% rate in individuals with normal status. Though this finding was not statistically significant (Figure 1E), the comparative trend supported the belief that $H$ pylori infection occurs more frequently in B12 deficiency and is consistent with recent studies that implicate $H$ pylori as an etiological factor for B12 deficiency$^{[28]}$. The data may not be uniform in all countries as concluded in a Japanese study that noted higher rates of both $H$ pylori infection and atrophic gastritis in Japan where PA is uncommon$^{[29]}$. The presence of intrinsic factor antibodies were not correlated with the presence or absence of $H$ pylori in the present study. Moreover, intrinsic factor antibodies were present in 29% (5/17) of cobalamin-deficient patients, suggesting a higher prevalence of PA than the previously reported prevalence of less than 5% in B12 deficiency patients$^{[31]}$. Also, age had no effect on the presence or absence of intrinsic factor.

We recognized that this study had some limitations. The total number of subjects was not large, and not every individual had biopsies from the gastric fundus, a site recognized for histopathologic changes in B12 deficiency$^{[18]}$. In control subjects, although a small number of biopsies were obtained from the fundus, the reality was that a number of biopsies contained inadequate tissue for meaningful interpretation. In addition, intrinsic factor antibodies and ferro-kinetics were not obtained in all the patients. Iron deficiency is known to be associated with gastric histopathological changes and 4 of 19 patients tested with ferro-kinetics were noted to have iron deficiency as demonstrated by the ferritin assay. We also did not have precise data on the specifics of treatment for $H$ pylori infection prior to endoscopy. Our aim was to evaluate endoscopic and histopathologic findings in B12 deficiency and controls irrespective of etiology and to attempt to decipher the changes related to cobalamin deficiency. This study made no attempt to delineate the etiology of B12 deficiency in our subjects. As stated, the indication for endoscopy was other than for evaluation of B12 status. Thus, it is also possible that the primary disease process necessitating the endoscopy may have affected the gastric mucosa and influenced the histopathologic findings. Finally, the extent of injury from medications, bile reflux or infection also could not be assessed.

In conclusion, abnormal gastric endoscopic findings appear to be correlated with B12 levels, with GA being the predominant finding in cobalamin deficiency and gastritis being the common finding when B12 levels are normal. Normal endoscopic findings are also observed in B12-deficient as well as in control subjects. Histopathology results are variable, with a predominance of inflammation that lacks any correlation with B12 deficiency. However, gastritis type does correlate with B12 status in that atrophic gastritis is more prevalent in B12 deficiency and superficial gastritis is more common when B12 status is normal. GA is absent on both endoscopy and histopathology, when B12 levels are normal. Our findings are consistent with literature in that $H$ pylori infection is associated with cobalamin deficiency, implicating $H$ pylori as an etiological factor for B12 deficiency.

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