American Journal of Case Reports

Received: 2018.02.01
Accepted: 2018.05.23
Published: 2018.08.14

e-ISSN 1941-5923
© Am J Case Rep, 2018; 19: 951-955
DOI: 10.12659/AJCR.909299

Chronic Gastritis Due to *Helicobacter Pylori* Associated with Increased Serum Levels of CA54/61: A Report of Three Cases

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Case series
Patient: Female, 44 • Male, 73 • Male, 54
Final Diagnosis: Chronic gastritis
Symptoms: Abnormal value of a tumor marker
Medication: —
Clinical Procedure: Eradication therapy of *Helicobacter pylori*
Specialty: Gastroenterology and Hepatology

Objective: Unusual clinical course

Background: The bacterial pathogen *Helicobacter pylori* (*H. pylori*) can cause chronic gastritis. CA54/61 is a serum tumor marker that has been shown to be positive in the several types of human malignancy. However, the association of between chronic gastritis due to *H. pylori* and elevated serum levels of CA54/61 has not been previously reported. This report is of three cases of increased serum levels of CA54/61 associated with *H. pylori* chronic gastritis.

Case Reports: Case 1 was a 44-year-old Japanese woman with a serum CA54/61 level of 138 U/ml (normal level: 12 U/ml). Following treatment and eradication of *H. pylori* the serum CA54/61 level decreased to 14 U/ml. Case 2 was a 73-year-old Japanese man with a serum level of less than 2 U/ml before completion of successful eradication therapy of *H. pylori* with a small peak of 30 U/ml after therapy. Case 3 was a 54-year-old Japanese man who maintained a serum CA54/61 level of approximately 20 U/ml before and until 603 days after eradication therapy. None of the three patients had malignancy, which is usually suggested by this serum marker.

Conclusions: These three case reports suggest the possibility of an association between chronic gastritis involving *H. pylori* infection and an elevated serum level of CA54/61. It is possible that the inflammatory gastric mucosal cells supply CA54/61 to the bloodstream. However, further studies are required to confirm the association between serum levels of CA54/61 and *H. pylori* chronic gastritis and the underlying mechanisms of this association.

MeSH Keywords: Biological Markers • Gastritis • *Helicobacter Pylori*

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/909299

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Background

The bacterial pathogen, *Helicobacter pylori* (*H. pylori*), can cause chronic gastritis [1,2], peptic ulcer [1,3], stomach cancer [1,3–5], mucosa-associated lymphoid tissue (MALT) lymphoma [6] and extra-gastric diseases [7,8]. In 2013, the Japanese official health insurance policy allowed eradication therapy of *H. pylori* in chronic gastritis to peptic ulcer and idiopathic thrombocytopenic purpura for health insurance coverage. Therapy for *H. pylori*-associated gastritis was instigated due to the high prevalence in Japan [9].

Serum CA54/61 is measured as a tumor marker for tumors including ovarian carcinoma in clinical practice in Japan [10]. However, currently, the possibility that chronic gastritis involving *H. pylori* is associated with high levels of the serum CA54/61 levels has not been previously reported, to our knowledge. Three cases are presented of confirmed *H. pylori*-associated gastritis with increased serum levels of CA54/61.

Case Reports

Case 1

A 44-year-old Japanese woman consulted her local outpatient clinic with a recent history of an increase in her serum amylase level. She had an IgA nephropathy at 16 years of age, which remitted spontaneously. She was clinically healthy, and her recent serum amylase level was 361 U/L (standard <112 U/L) and the salivary component was 92.3% of the amylase activity, as shown by the isozyme analysis (standard <84.3%).

No abnormal findings were present in the pancreas or salivary glands by physical examination or imaging, including ultrasonography of the salivary glands, magnetic resonance imaging (MRI) of the pancreas, magnetic resonance cholangiopancreatography (MRCP), and total body positron emission tomography (PET). She had a high level of serum CA54/61 of 138 U/ml (normal level, 12 U/ml) [10]. However, her other tumor-related serological markers, including CA125, sialyl Tn (sTn) antigen and sialyl Lewis (x) (SLX) were within normal limits. Gynecological consultation confirmed that no malignancy was present, in particular, no evidence of ovarian malignancy was present, but a small ovarian cyst and a small uterine myoma were identified by MRI imaging. Esophagogastroduodenoscopy showed chronic gastritis of nodular type with *Helicobacter pylori* (*H. pylori*) infection (Figure 1), which was confirmed by the histological examination of the biopsy specimen.

First-line eradication therapy of *H. pylori* infection was performed with the combination of amoxicillin hydrate (750 mg), clarithromycin (400 mg), and rabeprazole sodium (10 mg) twice daily for seven days. The success of the therapy was supported by a fecal antigen test and a ^{13}C-urea breath test performed at 65 days and 75 days. The titers of serum anti-*H. pylori* IgG antibody were between 6–7 U/ml when measured in the later phase, with a cutoff level of 10 U/ml. Her serum level of CA54/61 decreased to 14 U/ml, higher than the cutoff level, after 37 days of completion of the eradication therapy. It remained at a similar range till 728 days after initiation of therapy. Her serum amylase showed wide variations, ranging from between 189–732 U/ml during the observation period, with no apparent correlation between the serum CA54/61 levels and the serum amylase levels (Figure 2). Her gastritis was checked by annual gastroscopy and mucosal biopsies, and the results showed that her gastritis was improving. At the time of this report, apart from her gastric symptoms, she had no other health problems.

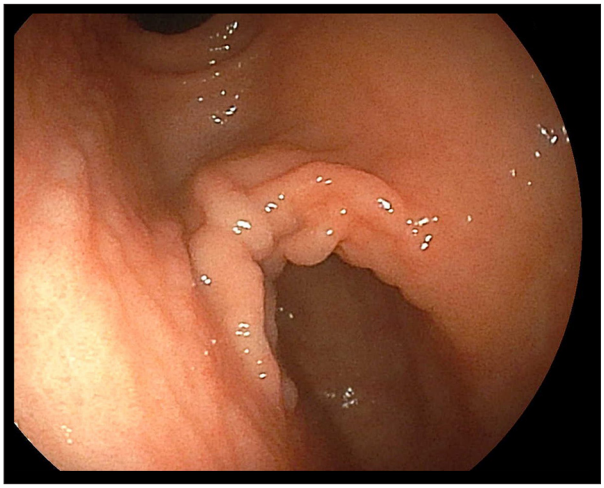

Figure 1. Esophagogastroduodenoscopy of Case 1 shows small nodular elevations in the gastric antrum.

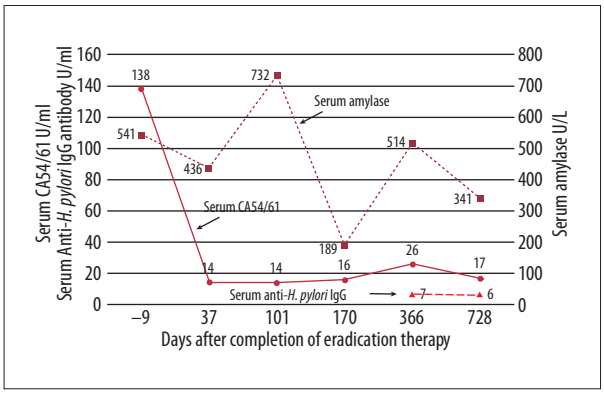

Figure 2. Time course of serum CA54/61, amylase, and anti-*H. pylori* IgG antibody of Case 1.

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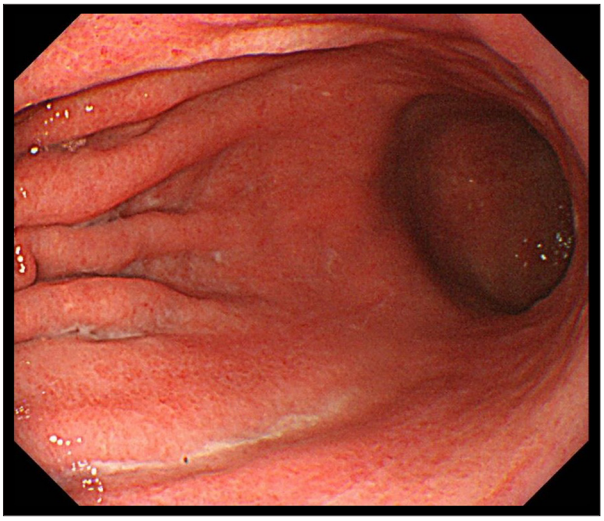

Figure 3. Esophagogastroduodenoscopy of Case 2 shows gastric atrophy and edema in the gastric corpus.

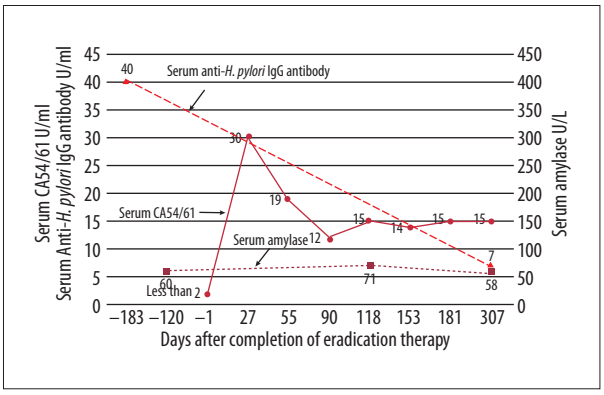

Figure 4. The time course of serum levels of CA54/61, amylase, and anti-*H. pylori* IgG antibody of Case 2.

Case 2

A 73-year-old Japanese man, who had a smoking history of around fifty years, had been treated for diabetes mellitus with an insulin dose of 5–6 units (insulin aspart) before each meal and 18 units of insulin (degultec) before breakfast. He had a history of hypertension, treated with oral antihypertensive medication, including 40 mg of valsartan and 25 mg of atenolol. He had a recent episode of successful endoscopic resection of bladder cancer.

He was found to have a serum titer of 40 U/ml of anti-*H. pylori* IgG antibody and esophagogastroduodenoscopy showed chronic gastritis (Figure 3). First-line eradication therapy for *H. pylori* consisted of amoxicillin hydrate (750 mg), clarithromycin (200 mg), and vonoprazan fumarate (20 mg) twice daily for seven days. Success of the therapy was supported by a ^{13}C-urea breath test and a fecal antigen test performed at 71 days and 82 days later. The serum titer of anti-*H. pylori* IgG antibody decreased to 7 U/ml at 307 days after therapy. His serum CA54/61 value before the completion of the therapy was in the undetectable range (<2 U/ml). However, the serum CA54/61 increased to 30 U/ml unexpectedly after 27 days of completion of the eradication therapy, and decreased to 12 U/ml after 90 days, and remained in a similar range until 307 days after the end of the therapy. His serum amylase remained at a normal level throughout his clinical observation (Figure 4). His urinary bladder cancer had no sign of recurrence at the time of this report.

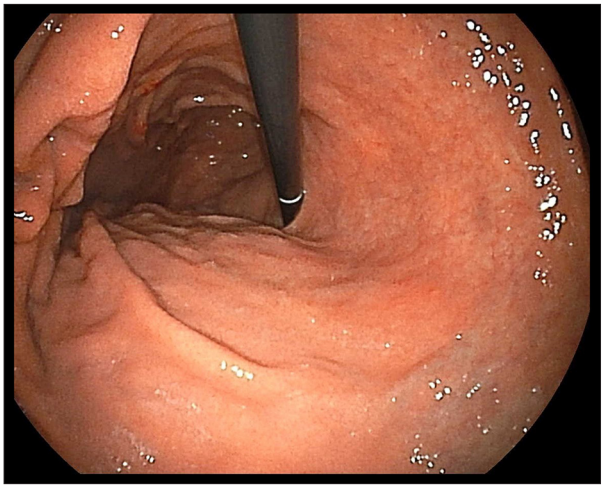

Figure 5. Esophagogastroduodenoscopy of Case 3 shows severe atrophy in the gastric corpus.

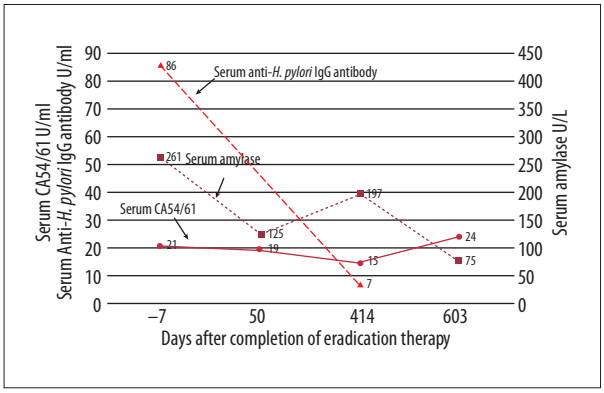

Figure 6. Time course of serum levels of CA54/61, amylase and anti-*H. pylori* IgG antibody of Case 3.

Case 3

A 54-year-old Japanese man was treated for hypertension with candesartan 2 mg in the morning. An outpatient clinical health examination showed a deformity of his stomach detected by gastric fluoroscopy. His serum anti-*H. pylori* IgG titer was high (86 U/ml). Esophagogastroduodenoscopy confirmed that he had a stomach ulcer scar and chronic gastritis (Figure 5). First-line eradication therapy of *H. pylori* was performed using the

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combination of amoxicillin hydrate (750 mg), clarithromycin (400 mg), and vonoprazan fumarate (20 mg) twice daily for seven days. The success of the therapy was supported by a fecal antigen test performed at 264 days. The titer of serum anti-*H. pylori* IgG antibody decreased to 7 U/ml at 414 days after therapy began.

His serum CA54/61 value before the eradication therapy was 21 U/ml, and a similar value was found at 603 days after the end of treatment. His serum amylase was high (261 U/L) before the therapy and the salivary amylase was 260 U/L, which exceeded the normal upper limit (131 U/L) when measured by isozyme analysis. The total serum amylase showed variations between 75–197 U/L during the observation period. The correlation between the serum CA54/61 and amylase levels was not as apparent as in Case 1 (Figure 6). The patient remained healthy, apart from his hypertension, at the time of this report.

In daily clinical practice, measurements of serum CA54/61 is used to detect and monitor ovarian cancer, but serum levels of this tumor marker are reported in the malignancies of the lung, stomach, pancreas, colon, and uterus [11]. In the three cases presented in this case series, the presence of underlying malignancy was excluded by imaging, but serum CA54/61 levels were associated with the presence of *H. pylori* gastritis.

Discussion

Three cases of chronic gastritis associated with *Helicobacter pylori* (*H. pylori*) have been presented who showed high levels of one of the serum tumor marker, CA54/61 in the various phases of their eradication therapy. The cutoff serum value of CA54/61 of 12 U/ml was previously determined as the cutoff level of CA54/61 as a tumor marker, but in the three cases of *H. pylori* reported, the patients had a serum level of CA54/61 of >20 U/ml (3 SD above the average for healthy subjects) at least once during their clinical course [10]. Therefore, it might be assumed that the high serum levels of CA54/61 observed in these cases did not occur as simply incidental events but were pathologically meaningful.

Detection of a high level of serum CA54/61 should lead to the exclusion of underlying malignancy in a patient [11]. However, no underlying malignancy was found in the three cases described in these case reports. Therefore, because the three cases had *H. pylori* infection and chronic gastritis in common, it was assumed that serum levels of CA54/61 were associated with *H. pylori* infection.

Molecular mimicry between *H. pylori* and human cell components have been previously proposed for several proteins [12]. Therefore, an initial explanation for the findings is that some components or products of the bacteria were absorbed into the blood of the patients and they reacted with the anti-CA54/61 monoclonal antibodies, MA54 and MA61, developed to detect serum CA54/61 [11]. However, all three cases maintained serum levels above the cutoff level of serum CA54/61 through their long clinical course. It is possible that reinfection of *H. pylori* occurs following initial treatment for *H. pylori* gastritis, but the incidence of re-infection is reported to be only 2.8% per patient-year and is expected to be fewer than the average in the high socioeconomic community of Japan [13]. Also, the tests used to detect the presence of *H. pylori* included the ^{13}C-urea breath test and/or the fecal antigen test and serum anti-*H. pylori* IgG antibody titer. False-negative cases exist at a low rate for each test, but multiple repeat applications of these tests was considered to improve the detection of treatment outcome. As the absence of the *H. pylori* bacteria following treatment was likely, the explanation that continued high levels of serum CA54/61 originated from the bacterial products seems to be unlikely.

The monoclonal antibodies, MA54 and MA61, which react with CA54/61, were developed by immunizing mice with a purified antigen prepared from the culture supernatant of a human lung adenocarcinoma cell line of C1509. Characterization of CA54/61 showed that this antigen is a high molecular weight mucin-type glycoprotein [11]. This antigen is expressed in the mucosal cells of the normal bronchus, as shown by immunohistochemistry [14], and also has a substantial positive rate of detection in the sera of patients with pneumonia and tuberculosis [11]. These findings suggest that increased influx of CA54/61 into the bloodstream from the inflammatory bronchial mucosa due to overproduction or by destruction of the mucosal cells might be the cause of the high serum levels of this tumor marker in these diseases. CA54/61 is also expressed in the mucosal cells of normal digestive tract [11]. Accordingly, it is reasonable to consider that a similar mechanism exists in the gastric mucosa cells injured by *H. pylori* gastritis resulting in the elevation of serum levels of CA54/61. This theory also supports the finding that serum CA54/61 in chronic gastritis originates in the gastric and explains why high levels of CA54/61 continue after the eradication of *H. pylori* from the gastric mucosa, because gastritis does not improve immediately and may continue for more than four years if the gastric mucosa undergoes intestinal metaplasia following *H. pylori* eradication therapy [15].

The three cases reported have included healthy individual without underlying malignancy, but with chronic gastritis involving *H. pylori*, but with hypertension and/or diabetes mellitus. The latter two conditions have not been previously reported to be associated with positive serum CA54/61 levels [11].

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Therefore, the findings in these three cases support the possible association between *H. pylori*-associated chronic gastritis and an elevation in serum levels of CA54/61. However, further controlled clinical studies are required to confirm this possible association. Also, a quantitative study of the expression of CA54/61 in the diseased gastric mucosa cells using immunohistochemistry would determine whether the elevated serum CA54/61 originates from the gastric mucosa.

Changes in the levels of CA54/61 were observed in Case 1 and 2 immediately after the *H. pylori* eradication therapy, with a steep decrease in the former and conversion from negative to positive in the latter. There was no substantial change in the level of CA54/61 in Case 3. Accordingly, the eradication therapy might not be reflected in serum levels of CA54/61. Further studies are required to explain these fluctuations with the types of *H. pylori* gastritis.

Conclusions

Three cases of chronic gastritis involving *Helicobacter pylori* (*H. pylori*) infection were associated with high levels of a serum tumor marker, CA54/61. They did not have malignant or other diseases that could explain the elevation of the serum CA54/61 levels, other than chronic gastritis. Therefore, there is a possibility that the association between *H. pylori* gastritis and elevated serum levels of the tumor marker, CA54/61 might be diagnostically or pathologically meaningful, and that the inflammatory gastric mucosal cells deliver CA54/61 to the bloodstream. Fluctuations in the levels of the serum tumor marker, CA54/61, remain unclear, and further studies are required to determine the expression of this biomarker in gastric tissues, as well as in serum.

References:

1. Sipponen P, Hyvarinen H: Role of *Helicobacter pylori* in the pathogenesis of gastritis, peptic ulcer and gastric cancer. Scand J Gastroenterol, 1993; 196: 3–6
2. Kuipers EJ, Pena PAS, Festen HPM et al: Long-term sequelae of *Helicobacter pylori* gastritis. Lancet, 1995; 345: 1525–28
3. Cover TL, Blaser ML: *Helicobacter pylori* in health and disease. Gastroenterol, 2009; 136: 1863–73
4. Inoue M: Changing epidemiology of *Helicobacter pylori* in Japan. Gastric Cancer, 2017;20 (Suppl. 1): S3–S7
5. Pormohammad A, Ghotasio R, Leylabadio HE et al: Risk of gastric cancer in association with *Helicobacter pylori* different virulence factors: A systemic review and meta-analysis. Microb Pathol, 2018; 118: 214–19
6. Floch P, Megraud F, Lehours P: *Helicobacter pylori* strains and gastric MALT lymphoma. Toxins (Basel), 2017; 9: 132–40
7. Franchini M, Cruciani M, Mengoli C et al: Effect of *Helicobacter pylori* eradication on platelet count in idiopathic thrombocytopenic purpura: A systematic review and meta-analysis. J Antimicrobi Chemother, 2007; 60: 237–46
8. Hudak L, Jaraisy A, Haj S, Muhsen K: An updated systematic review and meta-analysis on the association between *Helicobacter pylori* infection and iron deficiency anemia. Helicobacter, 2017; 22: e12330
9. Ueda J, Gosho M, Inui Y et al: Prevalence of *Helicobacter pylori* infection by birth year and geographic area in Japan. Helicobacter, 2014; 19: 105–10
10. Nozawa S, Aoki D, Yajima M et al: CA54/61 as a marker for epithelial ovarian cancer. Cancer Res, 1992; 52: 1205–9
11. Nozawa S, Yajima M, Kojima K et al: Tumor-associated mucin-type glycoprotein (CA54/61) defined by two monoclonal antibodies (MA54 and MA61) in ovarian cancers. Cancer Res, 1989; 49: 493–98
12. Chmiela M, Gonciarz W: Molecular mimicry in *Helicobacter pylori* infections. World J Gastroenterol, 2017; 23: 3964–77
13. Eusebi LH, Zagari RM, BazzoliF: Epidemiology of *Helicobacter pylori* infection. Helicobacter, 2014; 19: e12165
14. Kobayashi H, Ohi H, Sugimura M et al: Characterization and clinical evaluation of tumor-associated antigen CA54/61 identified by monoclonal antibodies MA54 and MA61 in epithelial ovarian cancer. Gynecologic Oncol, 1992; 47: 328–36
15. Watari J, Das KK, Amenta PS et al: Effect of eradication of *Helicobacter pylori* on the histology and cellular phenotype of gastric intestinal metaplasia. Clin Gastroenterol Hepatol, 2008; 6: 409–17

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