Case Report

Refractory Helicobacter pylori infection after standard triple drug therapy: A case report highlighting diagnostic and therapeutic dilemmas

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ABSTRACT

Helicobacter pylori is a gram-negative bacterium affecting nearly half of the global population and has been proven as a significant risk factor for gastric carcinoma and pathologies related to the stomach, i.e., gastritis, peptic ulcer disease, and MALT (mucosa-associated lymphoid tissue lymphoma). A major concern for managing H. pylori infection is its significantly increasing resistance to guideline-recommended first-line therapy, which is subsequently causing chronic inflammation and an eventual progression to carcinoma. There are several other factors which also affect the possible outcome of the treatments other than antibiotic resistance, i.e., sensitivity and specificity of tests, timing of retesting after eradication therapy, refractory and recurrent infection, and inadequate acid suppression. MALT lymphoma is the most common malignancy associated with H. pylori; on the other hand, its complete remission is possible in more than 50% of cases after eradicating therapy. This case report is of a middle-aged woman who had continued positive antigen testing even after completion of standard guideline-recommended three different regimens for H. pylori infection. After the third regimen, mild symptom improvement was reported, and there was a negative result for biopsy obtained through EGD despite a positive antigen test, as mentioned before. This complexity in management emphasizes how difficult it is to treat recurrent infection and the importance of knowledge of the recommended guidelines to achieve eradication. Simultaneously, there is always an increasing chance of chronic inflammation as symptoms are lasting longer due to a delay in eradication. Therefore, early treatment after diagnosis must be considered. Shared decision making, compliance with therapy, hand hygiene, breaking the chain of transmission between intrafamilial members, and health education are also crucial steps in management.

Key words: H. Pylori (Helicobacter Pylori), atrophic gastritis, antibiotic resistance, Vonoprazan

Helicobacter pylori (H. pylori) is a gram-negative bacterium that colonizes the mucosal layer of the stomach. The crude global prevalence of H. pylori in adults from 2015 to 2022 was 43.9%, which has decreased from 52.6% before 1990 [1]. It has been proven as a cause of many clinical conditions related to the stomach. Recent data show that H. pylori clarithromycin resistance exceeds 20% prevalence, which causes a significant rate of treatment failures. This suggests the need for better local data for the determination of H. pylori resistance [2]. The virulence factors and their ability to form biofilms increase resistance to conventional antibiotics, which heightens the need for new substances and strategies for treating H. pylori infection [3].

A positive non-serological H. pylori test (i.e., a test based on breath, stool, or gastroscopy) is defined as a refractory H. pylori infection if it occurs at least four weeks after one or more courses of the current guidelines-recommended first-line H. pylori eradication therapy without the use of any medications that could affect the test's sensitivity, such as proton-pump inhibitors (PPIs) [4, 5]. However, recurrent infection is defined when an initially negative non-serological test following completion of eradication therapy later becomes positive, which may result from ongoing exposure to other family members. Management is optimized by testing household members and treating those with positive results [5]. In this case report, we describe a case of a female with recurrent H. pylori infection. The case emphasizes the prevalence of antibiotic resistance as she had a persistent positivity of antigen test despite three standard regimens, increasing difficulty in eradicating the infection, and subsequently led to chronic inflammation.

CASE PRESENTATION

A 35-year-old female with a history of iron deficiency anemia presented to the internal medicine clinic for a routine follow-

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up visit. She reported mild nausea that began approximately three weeks prior, with a gradual onset. The nausea was not associated with heartburn, vomiting, or abdominal pain and was alleviated by drinking water, though exacerbated by spicy foods. She denied any additional complaints at this visit. We obtained a complete blood count (CBC) as part of the evaluation for iron deficiency anemia, which revealed pancytopenia. Further workup included an HIV 4th-generation test, hepatitis panel, hemoglobinopathy screening, H. pylori stool antigen test, and fecal occult blood test. All results were unremarkable except for a positive test for H. pylori stool antigen.

The patient was initiated on a triple therapy regimen of clarithromycin, amoxicillin, and pantoprazole for H. pylori eradication. As per guideline recommendations, a follow-up H. pylori stool antigen test was performed approximately seven weeks after completion of therapy, which remained positive. At her subsequent follow-up, the patient continued to report nausea without associated heartburn, vomiting, abdominal pain, changes in bowel habits, or melena. She was referred to gastroenterology and initiated on a salvage therapy regimen with Talicia (amoxicillin, rifabutin, and omeprazole) for two weeks. She reported full adherence to the treatment, and repeat H. pylori stool antigen testing after almost eight weeks remained positive, meeting criteria for persistent H. pylori infection.

Given ongoing symptoms and persistent infection, she was reevaluated and reported continued nausea, relieved by water intake, and without associated abdominal pain or vomiting. A levofloxacin-based triple therapy regimen (levofloxacin, amoxicillin, and omeprazole) was selected as salvage therapy due to its higher eradication rates in patients previously treated with clarithromycin-based regimens for two weeks. However, repeat H. pylori stool antigen testing after six weeks remained positive.

During a routine follow-up visit, she reported mild improvement in symptoms, though nausea persisted. As per gastroenterology recommendations, an esophagogastroduodenoscopy (EGD) with biopsy was performed approximately a month after. Findings included esophagitis in the lower third of the esophagus, atrophic gastritis throughout the examined stomach, duodenal inflammation in the second part of the duodenum, and a hiatal hernia on retroflexion. Histopathological examination with H&E and Giemsa stains was negative for H. pylori. The patient was continued on pantoprazole 40 mg daily for the management of gastritis, with regular follow-up scheduled for ongoing symptom monitoring.

DISCUSSION

Helicobacter pylori is a significant and treatable risk factor for gastric carcinogenesis. Colonization of this bacterium is a global concern, affecting approximately 50% of the population [6]. H. pylori is an important risk factor for gastric cancer, particularly gastric mucosa-associated lymphoid tissue (MALT) lymphoma. Despite an increasing incidence, complete remission of MALT lymphoma is achievable after eradication therapy of H. pylori in nearly 50-90% of cases [7]. The first recognized histologic change of this H. pylori infection is active chronic inflammation, which progresses to multifocal atrophic gastritis (MAG), eventually advancing to intestinal metaplasia, dysplasia, carcinoma in situ, and invasive carcinoma [8].

As our patient has evidence of atrophic gastritis, aggressive treatment and close follow-up were necessary to prevent further progression. This patient was treated with several antibiotic regimens for Helicobacter pylori, after which stool antigen (Ag) still showed positive results. After completion of the third regimen, biopsy results were negative despite a positive stool Ag test. The patient also reported relief of her symptoms, and treatment success was finally attained. The chronological order of investigation and treatment given to the patient is illustrated in **Figure 1.**

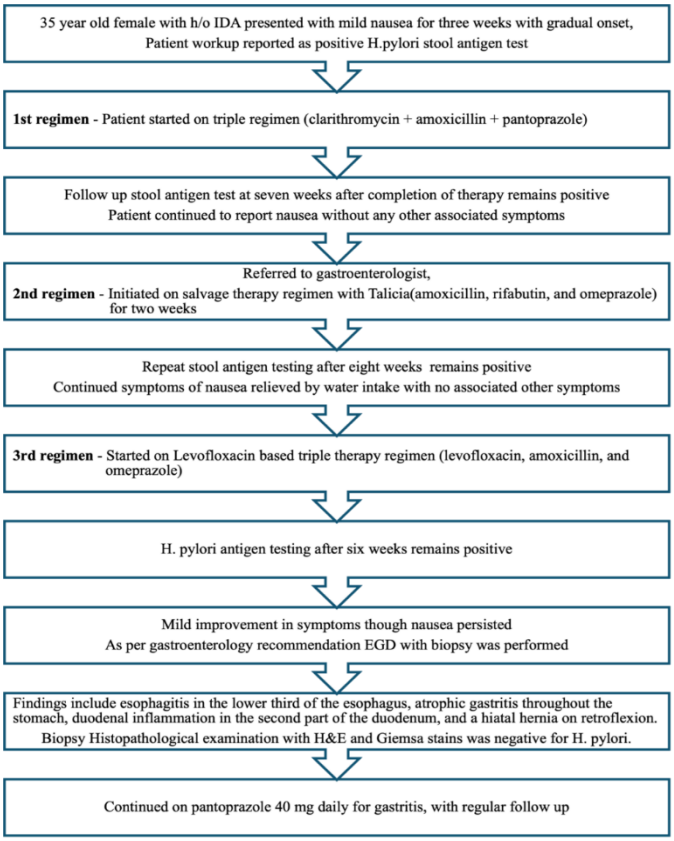

Figure 1 – Chronological order of investigations and treatments given to the patient

(IDA = Iron deficiency anemia, EGD = Esophagogastroduodenoscopy)

Factors influencing outcomes of treatments:

A. Antibiotic regimen and antibiotic resistance

The most common cause of eradication failure in a compliant patient is antibiotic resistance, which is increasing in

prevalence. In a study by Hulten and associates (2021), they found that resistance rates in the United States were 0.0%, 6.4%, 17.4%, 57.8%, 2.8%, and 43.6% for rifabutin, amoxicillin, clarithromycin, levofloxacin, tetracycline, and metronidazole, respectively [9]. Following the failure of two different therapeutic regimens, refractory H. pylori strongly warrants susceptibility testing for the underlying strain to improve the chances of treatment success, [10] which is why a repeat endoscopy with biopsy was done for our patient.

B. Recurrence versus refractory Helicobacter pylori infection

It is important to follow up with the patient for evaluation of recurrent or refractory cases. To minimize the chances of reinfection after treatment, health education and hygiene were discussed thoroughly with the patient. However, since the patient was persistently positive on stool antigen test, living alone, and preparing her meals, the classification of the infection of this nature was refractory H. pylori, rather than reinfection. The high pill burden, long duration of treatment, and lack of patient education significantly affect compliance rates, and treatment of family members and coworkers, especially in the case of food handlers, is also of vital importance.

C. Sensitivity and specificity of tests

The histologic demonstration of characteristic curved, spiral bacilli on the gastric mucosa is considered the gold standard for the diagnosis of Helicobacter pylori infection [11]. Endoscopic-based techniques, such as the rapid urease test (RUT) and culture tests, also exhibit excellent sensitivity and specificity profiles in the diagnosis of H. pylori. While the H. pylori stool antigen test has a sensitivity of 66-91% and a specificity of 91-93%, approximately 1 out of 9 samples will be a false-positive. Comparison of diagnostic methods for H pylori infection with the gold standard test is demonstrated in a study conducted by Khalifehgholi *et. al.* (2013). **Table 1** demonstrates the result of that study [12].

Table 1 – Comparison of diagnostic tests for H pylori with the gold standard test [12]

Methods	Gold standard		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
	Positive	Negative					
Positive	44	10					
Histology			95.6	77.8	81.5	94.6	86.8
Negative	2	35					
Positive	44	0					
RUT			95.6	100	100	95.7	97.8
Negative	2	45					
Positive	43	2					
PCR			93.5	95.6	95.6	93.5	94.5
Negative	3	43					
Positive	42	20					
Serology			91.3	55.6	67.7	86.2	73.6
Negative	4	25					
Positive	34	6					
Stool antigen test			73.9	86.7	85	76.5	80.2
Negative	12	39					
Total	46	45					

D. Timing of retesting after eradication therapy

Post-treatment testing should be delayed for at least 4-6 weeks after the end of therapy because it takes time for any remaining bacteria to recover and repopulate the stomach in sufficient numbers to be detected reliably. It is important that PPI therapy, if there is an ongoing need for it after the antibiotics are finished, is held for 14 days before the repeat testing for Helicobacter [13].

3E. Inadequate acid suppression

A study by Sjostedt and associates(1998), demonstrated that prolonged periods (longer than 156 min) of intragastric pH above 6 were significantly associated with successful treatment of H. pylori [14]. Vonoprazan is a potassium competitive acid blocker which achieves a pH target of greater than 6 more often and more prolonged, with a longer half-life, greater potency, and fewer drug interactions than PPIs [15].

CONCLUSION

H. pylori, nearly affects almost half the global population, with increasing incidence due to several factors influencing

the outcome of H. pylori eradication treatment. Treatment success and prevention of reinfection depend on shared decision-making, intensive patient education, proper food handling with strict hand hygiene, and avoiding intrafamilial or interpersonal transmission of infection. Initiation of treatment as early as possible after diagnosis, antibiotic adherence until completion of therapy, and family-based eradication strategies are crucial steps. As a physician, knowledge of the local antibiotic resistance rates also plays a significant part in the success of therapy. Close follow-up and proper timing of post-treatment testing must also be taken into consideration. Repeating endoscopy should be considered for equivocal or inconclusive results, especially when clinical pictures do not reflect the test results. When infection persists despite following all these factors, salvage therapy with strict medication adherence needs to be initiated. If insufficient, the next consideration would be to change the proton-pump inhibitor (PPI) to a potassium competitive acid blocker, Vonoprazan. As compared to PPIs, it has a longer duration of action and more profound acid suppression.

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