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CASE REPORT | STOMACH

A Case of Persistent *Helicobacter pylori* Infection Occurring with Anti-IgE Immunosuppression

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Abstract

The increasingly widespread use of novel immunosuppressive drugs may lead to unexpected infectious complications. We report a case of persistent *Helicobacter pylori* (*H. pylori*) infection that failed to respond to antimicrobial therapy in a patient receiving omalizumab (Xolair™, Genentech USA Inc., San Francisco, CA and Novartis Pharmaceuticals, Basel, Switzerland), an anti-IgE monoclonal antibody approved by the FDA for treatment of severe persistent asthma. To our knowledge, this is the first case report linking an immunosuppressive regimen containing anti-IgE biologic therapy to persistent *H. pylori* infection.

Introduction

Helicobacter pylori (*H. pylori*) infection is amongst the most prevalent infections in humans worldwide, and is a significant source of morbidity and mortality. *H. pylori* is considered a carcinogen, thus treatment is standard of care. However, there are numerous barriers to eradication, including antimicrobial resistance, patient adherence to complex medication regimens, and, as proposed in this case, a growing array of novel immunosuppressive medications.

Case Report

A 31-year-old female with severe, steroid-dependent asthma, morbid obesity, and type II diabetes, was found to have iron deficiency anemia during evaluation for bariatric surgery. At upper endoscopy, there were no mucosal abnormalities, but *H. pylori* infection was diagnosed via immunohistochemical staining of gastric biopsies. She was treated with conventional first-line anti-*H. pylori* combination triple therapy (amoxicillin, clarithromycin, and omeprazole) for 2 weeks. There was no test of cure until later in her pre-operative bariatric surgery evaluation, when it was discovered that the patient was still infected with *H. pylori*, demonstrated by both positive fecal antigen and urea breath testing. Her surgical team was hesitant to proceed with gastric bypass, based upon the evidence linking persistent *H. pylori* infection with a higher risk for post-operative marginal ulceration.[1]

We therefore treated her with a standard bismuth-based quadruple therapy regimen for 14 days (tetracycline, metronidazole, omeprazole, bismuth) as per the Maastricht guidelines (Figure 1).[2] A subsequent urea breath test was positive and she was then treated with 14 days of an amoxicillin-based quadruple therapy regimen (amoxicillin, metronidazole, bismuth, and omeprazole). *H. pylori* fecal antigen performed as a test-of-cure both 3 and 7 weeks after completion of quadruple therapy was still positive. A fourth treatment consisted of a salvage fluoroquinolone-based regimen (levofloxacin, amoxicillin, and omeprazole twice daily) for 2 weeks. However, 5 weeks following therapy, a repeat fecal antigen was again positive. A fifth "sequential" regimen consisting of lansoprazole twice daily and amoxicillin for 5 days, followed by lansoprazole, clarithromycin, and tinidazole for

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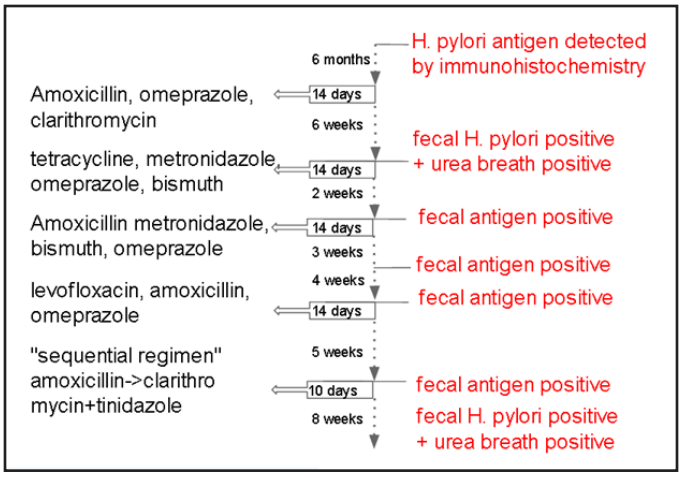

Figure 1. Treatment course of patient.

5 days was therefore prescribed. This regimen is reported to be effective for resistant strains.[3] Both *H. pylori* fecal antigen and urea breath tests remained positive 8 weeks after the end of therapy.

Throughout these multiple unsuccessful attempts at *H. pylori* eradication, the patient had been taking both omalizumab and prednisone continously (at least 10 mg prednisone daily, with approximately 8 booster/taper courses). Her other chronic medications included omeprazole, citalopram, carbamazapine, lisinopril, pravastatin, montelukast, and alendronate. The patient reported complete adherence to all courses of *H. pylori* treatment and calls to her pharmacy verified that she had filled the prescriptions as written.

Discussion

We report a case of treatment-refractory *H. pylori* infection in the setting of immunosuppression, most notably with an anti-IgE biologic (omalizumab), prednisone, and the leukotriene receptor antagonist montelukast. While *H. pylori* elicits a specific humoral IgG and a mucosal and serum IgA response, the relationship between humoral immunity and protection/clearance of *H. pylori* is controversial.[4,5] Nevertheless, several lines of evidence suggest that IgE may play a role in the immune response to *H. pylori* infection. In samples from *H. pylori*-positive patients whose endoscopies did not demonstrate active inflammation, there was a clear, statistically significant reduction in IgE-positive mast cell numbers.[6] Investigations of *H. pylori*-associated gastric ulcers have co-localized IgE positive plasma cells within the ulcers.[7] Furthermore, although controversial, there have been several smaller epidemiologic investigations reporting a positive association between *H. pylori* infection and IgE-mediated systemic disorders, most notably chronic urticaria.[8]

Culturing *H. pylori* for in vitro antibiotic sensitivity profiling is technically and logistically challenging in the United States. Therefore, we attempted to treat with empiric regimens this asymptomatic patient without significant inflammation or ulcer disease. It is possible that this patient's failure to clear her *H. pylori* infection reflected infection with an a priori resistant strain. We hypothesize that there may be a relationship between the patient's anti-IgE therapy and the failure to clear her *H. pylori* infection. Her lack of symptomatic gastritis also supports the notion that IgE may play an important role in host inflammatory response to *H. pylori* infection.

Several lines of evidence suggest that a robust immune response, whether mediated by IgE or other mechanisms, is necessary for effective eradication of *H. pylori*.[9] Mice vaccinated with various *H. pylori* antigens and subsequently challenged with *Helicobacter* develop a more severe gastritis than in natural infection prior to clearing the bacteria.[10] In a mouse model examining the role of anti-inflammatory CD25+ T-regulatory cells in *H. pylori* infection, CD25 deficient mice had higher levels of inflammation and lower levels of persistent *H. pylori* infection[11]; depletion of CTLA-4 (a co-stimulatory surface molecule expressed by CD25-positive T-regulatory cells) resulted in higher levels of gastritis and lower bacterial loads than in control mice.[12] In humans, biopsies from patients with persistent *H. pylori* infection demonstrate up to a 50-fold increase in CD25+ T-cells,[13] suggesting an underlying inappropriate "tolerance" to the infection.

To date, the few investigations evaluating the relationship between immunosuppression and *H. pylori* infection support a role for inflammation in clearing *H. pylori* infection. A case series of renal allograft patients undergoing upper endoscopy demonstrated a higher percentage of *H. pylori* positivity (63% vs. 43.6%) with a lower incidence of active gastritis (6.9% vs. 31.3%).[14] Animal models, however, are conflicting; one mouse model of *H. pylori* infection failed to demonstrate an association between corticosteroid administration and *H. pylori* bacterial load or gastritis,[15] whereas a gerbil model showed decreased gastritis with both tacrolimus and dexamethasone, but no significant change in *H. pylori* viability.[16]

In summary, we speculate that concurrent anti-IgE therapy was an important factor in the inability of our patient to clear *H. pylori* infection. If this proves to be the case in larger case series and/or animal models, it may have important implications in the pathogenesis of refractory *H. pylori* infection.

Disclosures

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uted in an editorial, advisory, and supervisory capacity and is the guarantor of the article.

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