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# Coccoid *Helicobacter pylori*: An Uncommon Form of a Common Pathogen

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## Abstract

Microscopic recognition remains a major component of diagnosing specific infectious agents or, at the minimum, an important first step in initiating a workup to confirm a specific infectious etiology. However, organisms are known to adapt in response to treatment, not only by developing resistance mechanisms but also undergoing major morphologic changes in some cases. Such morphologic adaptation can make them drastically different and hence difficult to recognize or characterize by an unwary examiner. The purpose of this article is to highlight a rare and unusual form of *Helicobacter pylori* referred to as coccoid *H. pylori*.

**Keywords:** Antibiotic altered organisms, coccoid *Helicobacter*, *Helicobacter heilmannii*, *Helicobacter pylori*

## Introduction

*Helicobacter pylori* is currently accepted as a major cause of gastritis and is implicated in the development of peptic ulcer disease, mucosa-associated lymphoid tissue lymphoma, and other cancers. Histological diagnosis is considered the gold standard as *H. pylori* can be frequently identified on standard hematoxylin and eosin staining. Histologically, *Helicobacter* species are most commonly recognized as seagull-shaped or curved, Gram-negative rods in the majority of cases; however, it has also been rarely encountered as corkscrew-shaped or even coccoid form. Because of the clinical implications associated with *Helicobacter* infections, it is critical to recognize the different morphological forms and identify the organisms to assure proper treatment of the infectious agent. Here, we describe a case of coccoid *H. pylori*.

## Clinical Report

A 2-year-old immune-competent female child underwent upper endoscopy as a part of evaluation of suspected pancreatic insufficiency. Operative findings described normal-appearing esophagus, stomach, and duodenal mucosa. Microscopic examination of gastric mucosa biopsy showed small pieces of pyloric mucosa with focal areas of neutrophilic inflammation, rare gland abscesses, and small patches of lymphocytes and plasma cells in the lamina propria. Round, coccoid organisms were noted within gastric mucosal glands [Figure 1]. A recent history of antibiotic use was mentioned in the pathology report, with no further details given. The patient's complete medical records are not available for further review, and the pathology report and glass slides are the main sources available for us to review in preparation for this report.

## Discussion and comments

*H. pylori* are typically curved, Gram-negative bacilli which measure 3–5 μm in length and are frequently identified in the mucous of the stomach [Figure 2a].[1] More recently, however, other variant forms such as *Helicobacter heilmannii*, a helical form, and an unusual coccoid form have also been identified in stomach biopsies [Figures 2b and 3].

The coccoid form of *H. pylori* is speculated to represent a dormant or stressed form of the organism. It has been identified following failed antibiotic therapy or in other

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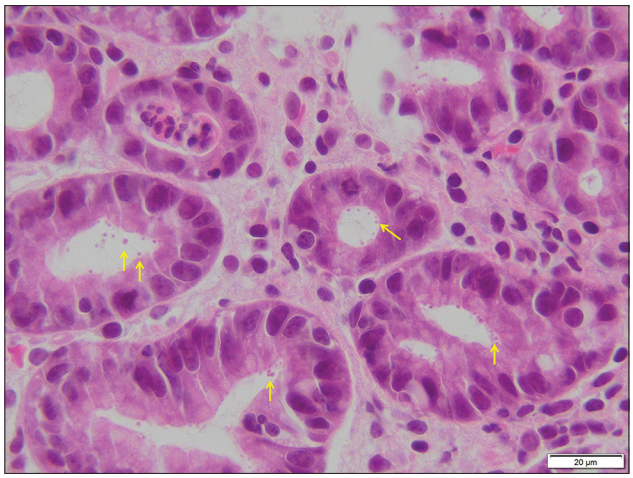

**Figure 1:** Gastric mucosa showing the least common coccoid-shaped morphology of *Helicobacter pylori* (arrows). H and E, ×100 oil magnification

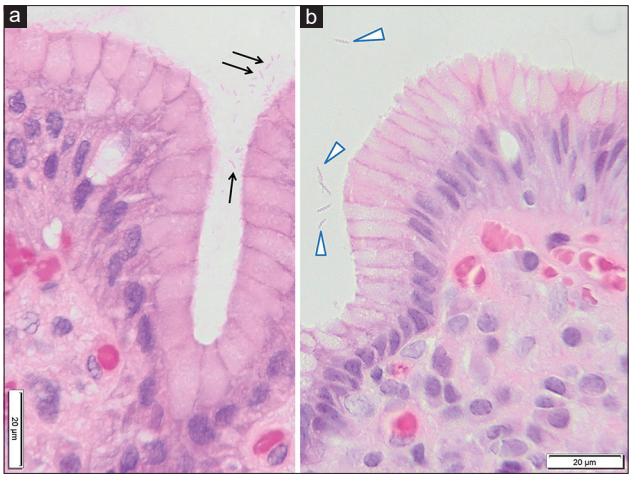


**Figure 2:** Gastric mucosa showing the most common rod-shaped morphology of *Helicobacter pylori* (a, arrows) and the spiral-shaped *Helicobacter heilmannii* (b, arrowheads). Both photomicrographs are from H and E, ×100 oil magnification

stressful conditions such as anaerobic environments (like that of the large intestine).[2] This transformation of *H. pylori* into a coccoid form is thought to be a method of cell adaptation to environments not optimal for the bacteria or may simply occur as a process of aging.[3] Electron micrographs have demonstrated this transformation showing the bacillary form curling up into a "U-shape" and then forming a circular, coccoid shape with the ends attached by a thin membranous structure.[4,5] In essence, when subjected to stressful conditions or the aging process, the bacterium appears to take the fetal position, replicating a model of Freudian regression at the microscopic level!

The viability of the coccoid form has been a topic of debate for decades. Historically, they were thought to represent a dormant form of the bacterium. However, Balakrishna and Filatov described a case of symptomatic chronic active gastritis with only coccoid forms in the biopsy specimen, and since then, an increased emphasis has been placed on the clinical importance and activity of the coccoid forms.[6] These coccoid forms are thought to play a potential role in relapsed or recurrent peptic ulcer disease and may represent a form of antibiotic resistance.[7] Interestingly, when *H. pylori* infection recurs within a few weeks, DNA fingerprinting and restriction endonuclease DNA analysis have identified the same strain of the bacteria as a repeat offender.[8] The current thinking is that therapy should aim for eradication of both the bacilli and coccoid forms for long-term treatment of the infection.

*H. heilmannii* (used to be named *Spirillum*), the spirally haired twin sister of *H. pylori*, is a Gram-negative, helical organism, 7–10 μm in length. There are usually fewer organisms encountered in comparison to *H. pylori* infections. *H. heilmannii* are usually seen as single organisms or in smaller groups and are typically located in the deeper foveolar lumens and at times even in the cytoplasm of parietal cells.[9] These features can further help with organism identification. Giemsa stain can be helpful in highlighting *Helicobacter* organisms and demonstrate the spiral nature of *Helicobacter heilmannii* in particular [Figure 3].

Histologically, *Helicobacter* infection of the stomach usually presents as chronic and/or active antral-predominant gastritis which may progress to atrophic gastritis. However, *H. heilmannii* predominantly incites a lymphocytic, chronic response with only focal acute inflammation while H. pylori is typically associated with a more prominent inflammatory response. The coccoid form has also been documented in chronic and/or active gastritis and in these specimens may appear similar to other bacterial cocci, fungal spores, or cryptosporidia and is important to be distinguished.

When necessary, immunohistochemical staining can assist in deciphering the identity of the organisms. *H. heilmannii* will stain positively with the *Helicobacter* polyclonal immunohistochemical antibody, and the coccoid forms will stain with both the polyclonal and monoclonal antibodies [Figure 4].

Morphologic changes in organisms and pathogens in response to treatment can be profound and are important to recognize. However, the topic is not fully covered in the medical literature. As early as the late 1940s, it was recognized that medical intervention had the capability of affecting bacilli shape.[10] Gardner, who was working with penicillin to inhibit bacterial growth, observed that subinhibitory concentrations of antibiotics altered the bacterial morphology. He found that *Clostridium perfringens,* which typically has a uniform turbidity, exhibited flocculent growth and microscopically became filamentous, greater than ten times the length of normal bacterial cells. These observations were similar for other rod-shaped organisms including bacilli from the *Salmonella* genus, *Escherichia coli,* and other Gram-negative bacteria. Gardner attributed his observations to autolytic swelling and concluded that penicillin can cause

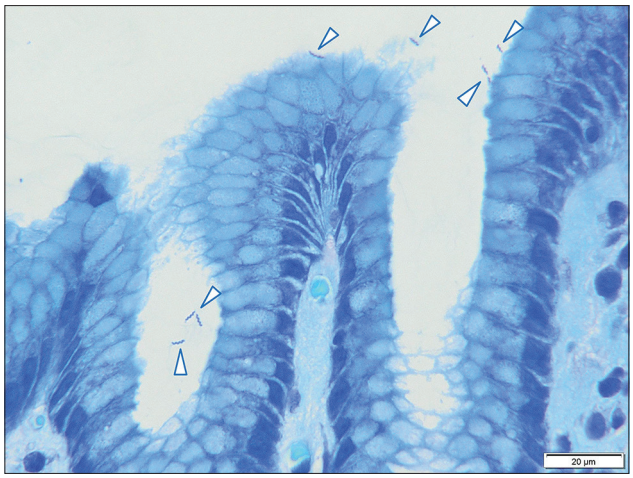


**Figure 3:** Gastric mucosa showing the spiral-shaped *Helicobacter heilmannii* (arrowheads). Giemsa, ×100 oil magnification

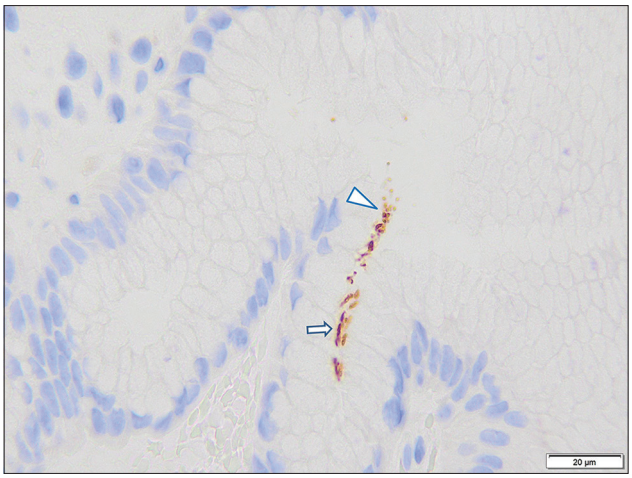


**Figure 4:** Immunohistochemical staining of gastric mucosa showing curve-shaped (arrow), coccoid- and comma-shaped *Helicobacter* (arrowheads). ×100 oil magnification

major morphological changes when used at subinhibitory concentrations because the treated cells were incapable of separating.

In 1975, Lorian and Atkinson expanded on Gardner's observations by culturing several types of bacteria with different types of antibiotics at varying concentrations.[11] Their results revealed several bacilli that grew filaments when treated with subinhibitory concentrations. Most notably, *Proteus mirabilis, E. coli, Klebsiella pneumoniae,* and *Salmonella typhimurium* produced filaments approximately 30–90 µm long or aberrant-shaped globules when treated with ampicillin. Interestingly, the same bacilli when treated with a different antibiotic, nalidixic acid, produced filaments, 20–50 µm long. These filamentous growth observations and other morphological changes were similar among all the Gram-negative bacteria they studied.[11]

When viewed by electron microscopy, Lorian and Atkinson witnessed changes in ribosome concentrations in different areas of the bacilli. For instance, *S. typhimurium* treated with gentamicin revealed a decrease in ribosome density in the center of the cell but increased density at the ends of the bacillus. Penicillin-treated *Staphylococcus aureus* increased in size and exhibited thick, irregular cross-walls. The conclusion of Lorian and Atkinson was that cell elongation occurred because the autolytic enzymes were inhibited, and thus, septation could not take place. The increase in cell size and filamentation can thus be attributed to thicker septa holding cells together that otherwise would have divided.

More recently, in 2007, Healy *et al*. documented the case of a 9-year-old male, burn patient who was diagnosed with *Serratia marcescens* bacteremia.[12] The child was treated with broad-spectrum antibiotics yet showed no signs of improvement. On further observation, Gram stain revealed long, Gram-negative filaments that were later attributed to the administration of β-lactam antibiotics.[13] In 2010, a review of organisms that mimic other organisms by Almarzooqi *et al*. reported that bacteria treated with antibiotic therapies typically exhibit changes in morphology, citing the *H. pylori* coccoid forms as well as the tendencies of numerous Gram-negative bacteria to elongate to filamentous rods. They found that this unusual morphological change is due to the β-lactam antibiotics inhibiting the cytoplasmic membrane from participating in cell elongation and shape.

A recent case report by Buckley *et al*. described antibiotic-altered, filamentous *Pseudomonas aeruginosa* in the cerebrospinal fluid of a 17-year-old male.[14] This filamentation was a result of the inhibition of the separation (but not division) of the bacteria, resulting in a long, septate morphology that could be misidentified as fungi.

More investigations and reporting on the morphologic adaptation of organisms are needed, not only for medical teaching purposes but also providing practitioners with clinical pearls that help avoid diagnostic pitfalls. Our case can serve as a reminder that when acute, chronic, or atrophic gastritis is identified in a gastric biopsy, careful examination of the biopsy specimen should be performed to exclude all forms of *Helicobacter* or other infectious agents.

Pathologists need to be familiar with the common as well as the less common morphologic appearances of organisms. Correlation with microbiology culture, serology, and workup by immunohistochemistry can be very helpful. Assessing the clinical history, including all medications and antibiotic therapy, can be crucial in providing clues and reaching accurate diagnoses.

## Authors' contribution

All authors are involved in the clinical aspects of the reported material and drafting and final revision of the manuscript.

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## Conflicts of interest

There are no conflicts of interest.

## Compliance with ethical principles

No prior approval is required at our institution for isolated case reports. Case history and samples are reported anonymously.

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