# Isolated Gastric Malakoplakia

## A Case Report and Review of the Literature

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**• A 62-year-old African American woman presented with weight loss and dyspepsia. She did not have any clinical evidence of immunodeficiency. Upper gastrointestinal endoscopy revealed multiple small polypoid lesions in the gastric body and fundus that appeared larger and more erythematous than usual fundic gland polyps. Examination of biopsy specimens revealed an infiltrate of large histiocytes with eosinophilic granular cytoplasm located in the lamina propria and containing Michaelis-Gutmann bodies. These histologic findings were diagnostic of gastric malakoplakia. Gastrointestinal malakoplakia is uncommon, and exclusive gastric involvement is extremely rare. Because occult bacterial infection has been postulated as the underlying cause of malakoplakia, the presence of *Helicobacter pylori* infection was investigated using immunohistochemical and serologic techniques, and the presence of *Yersinia enterocolitica* or *Yersinia pseudotuberculosis* infection was investigated by polymerase chain reaction assay. There was no evidence of *H pylori*, *Y enterocolitica*, or *Y pseudotuberculosis* in these biopsy specimens, and there was no evidence of malakoplakia or concurrent malignancy at any other site. Follow-up examination 12 months later revealed no endoscopic or histologic improvement.**

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Malakoplakia is a chronic inflammatory disorder characterized histologically by the presence of sheets of histiocytes with foamy granular cytoplasm and intracellular laminated inclusion bodies.[1,2] This disorder most commonly involves the urinary tract. Although uncommon, gastrointestinal malakoplakia has been described, and the colon is the most common site in these cases.[1,2] Gastric involvement, particularly isolated gastric involvement, is extremely rare. In many instances malakoplakia has been associated with microbial infections, immune dysregulation, or both; however, the pathogenesis of both genitourinary and gastrointestinal malakoplakia remains poorly understood.[3,4] Here, we report the case of a 62-year-old African American woman with isolated malakoplakia of the stomach and explore the possibility of underlying microbial infections. We also note the clinicopathologic features of gastrointestinal malakoplakia, in particular those of the gastric form of the disease.

### REPORT OF A CASE

A 62-year-old African American woman presented with dyspepsia of more than 1 year duration and weight loss of 3.6 kg during a period of 12 months. She did not have any other systemic symptoms, and there was no clinical evidence of immune deficiency. She did not have any history of recurrent infections or prior steroid therapy or any previous laboratory evidence of underlying immune deficiency. Upper gastrointestinal endoscopy revealed multiple polypoid lesions in the gastric body and fundus that looked larger than typical fundic gland polyps (Figure 1). Examination of biopsy specimens taken from these lesions revealed reactive foveolar hyperplasia of the gastric mucosa and expansion of the lamina propria by abundant macrophages (Figure 2). These macrophages had granular cytoplasm and contained many Michaelis-Gutmann bodies. Stains for iron (Prussian blue) and calcium (Von Kossa) and the periodic acid–Schiff reaction highlighted these targetoid inclusion bodies (Figure 3, A through C). The histologic findings were characteristic of malakoplakia. There was marked atrophy of fundic glands in the adjacent fundic mucosa and foveolar hyperplasia. Examination of gastric antral biopsies revealed mild chronic gastritis with patchy intestinal metaplasia.

### PATHOLOGIC FINDINGS

Immunohistochemical and special histochemical stains for *Helicobacter pylori* were negative. Immunohistochemical analysis was performed using an indirect immunoperoxidase method on 4-μm-thick sections of paraffin embedded, formalin-fixed tissue with monoclonal antibodies to *H pylori* (Dako, Carpinteria, Calif; 1:50). Appropriate positive and negative controls were used. Serology results for *H pylori* were also negative. Laboratory testing revealed a hematocrit of 38.9%, serum folate of 11 ng/mL (normal, 5.4 ng/mL), serum B12 of 340 pg/mL (normal, 200 to 1100 pg/mL), serum iron of 87 μg/dL, total iron binding capacity of 321 μg/dL, iron saturation of 27.1%, the presence of HIV (by enzyme immunoassay), and the presence of antiparietal cell antibodies. Specific neutrophil and macrophage function assays were not performed. DNA was extracted from lesional tissue following deparaffinization and protein digestion. Polymerase chain reaction analysis for *Yersinia enterocolitica* and *Yersinia pseudotuberculosis* was

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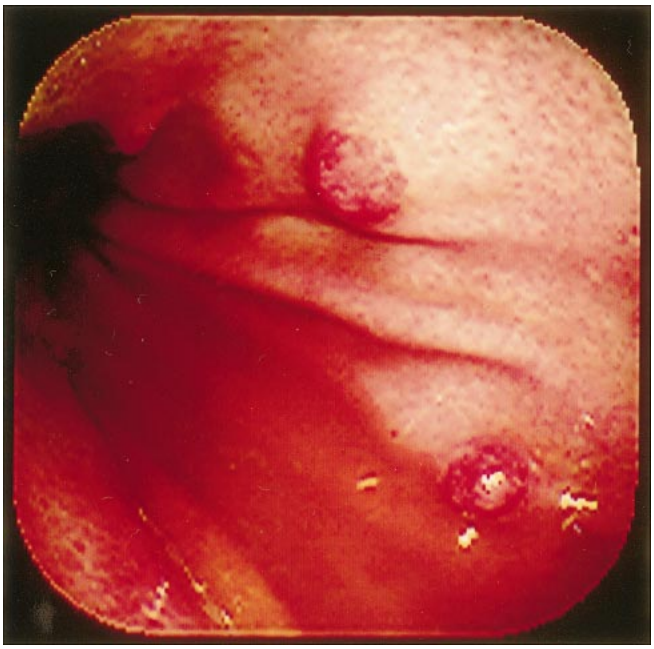

**Figure 1.** *Endoscopic view revealing multiple polypoid lesions ranging from 0.5 to 1 cm and involving the gastric body. The background gastric mucosa appears unremarkable.*

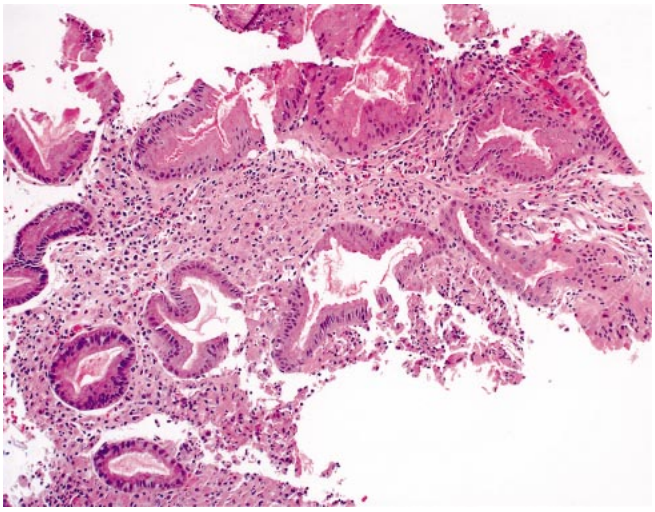

**Figure 2.** *Lamina propria filled with large histiocytes with eosinophilic granular cytoplasm (hematoxylin-eosin, original magnification ×100).*

performed according to previously described methods,[5] and the results were negative.

The patient subsequently underwent a full colonoscopy, which revealed a single adenomatous polyp (0.3 cm) at 18 cm and a rectal carcinoid (1 cm). Clinically there was no evidence of involvement of any other site or of any malignancy. Results of a computed tomography scan of the chest, abdomen, and pelvis were negative. A follow-up examination 12 months later revealed no endoscopic or histologic improvement or progression.

## COMMENT

Malakoplakia is an uncommon disease characterized by the presence of histiocytes (Von Hansemann macrophages) with cytoplasmic concentric laminated inclusions (Michaelis-Gutmann bodies).[1,2] This disease has a worldwide distribution and no racial or gender predilection and has been reported in individuals of all ages. It most frequently involves the urinary tract, where the most common site affected is bladder followed by kidney, ureters, and renal pelvis. The digestive system is the second most common site of involvement after the urinary tract. The principal sites of gastrointestinal involvement are descending colon, sigmoid, and rectum.[1,2] Other less commonly affected sites include the terminal ileum, stomach, vermiform appendix, and cecum. The regional lymph nodes, mesentery, or retroperitoneum may also be involved. Grossly, the differential diagnosis of gastrointestinal involvement includes Crohn disease, miliary tuberculosis, and malignancies. Histologically, malakoplakia must be differentiated from Whipple disease, other infectious or noninfectious granulomatous disorders, and histiocyte storage diseases.

Malakoplakia of the gastrointestinal tract can be clinically silent or can cause clinical symptoms such as diarrhea, abdominal pain, hemorrhage, or obstruction. Several reports have emphasized the presence of concomitant diseases such as leukemia or lymphoma, alpha chain disease, immunodeficiency, miliary tuberculosis, multiple hemangiomas, neurofibromatosis, villous adenomas, and cancer.[2] In his review, McClure[2] found an association between malakoplakia of the gastrointestinal tract and colorectal carcinoma in more than 30% of patients examined. In the present case, colonoscopy revealed a small adenomatous polyp and an incidental rectal carcinoid but no evidence of colon carcinoma. Histology of the colonic polyps and the carcinoid tumor did not reveal any signs of malakoplakia.

To our knowledge, there have been only 4 cases of gastric malakoplakia reported worldwide, and only 2 cases had isolated involvement of the stomach.[3,6–8] Of these 2 cases, 1 had a concomitant colon adenocarcinoma with associated inflammatory infiltrate similar but not identical to the gastric malakoplakia.[7] Thus, the question remains open whether this case truly represents isolated gastric involvement. In the other case, there was isolated gastric involvement adjacent to a gastric ulcer without any associated malignancy.[6] In the present case, there was no evidence of malakoplakia at other sites or of concurrent malignancy.

Typical endoscopic malakoplakia lesions are irregular tan to yellow nodules or plaques 1 to 2 cm in diameter, sometimes with a central depression or umbilication.[7] Some cases may include necrosis or hemorrhage. Endoscopically, three main patterns can be identified: (1) unifocal mucosal lesions (the most common pattern), (2) widespread mucosal multinodular or polypoid lesions that resemble the bladder lesions, and (3) large mass lesions.[7] In the present case, multiple polypoid lesions were identified without any evidence of necrosis or hemorrhage. In addition, examination of biopsy specimens from adjacent fundic mucosa revealed areas of severe gastric atrophy. The gastric atrophy was probably multifocal or diffuse and might represent a sequela of prior chronic inflamation or infection and possibly autoimmune gastritis (pernicious anemia), although the patient's blood workup did not reveal anemia or decreased B12 or folate. The presence of antiparietal antibodies indicates immune dysregulation, even though the patient did not have any clinical signs of pernicious anemia. To our knowledge, no associ-

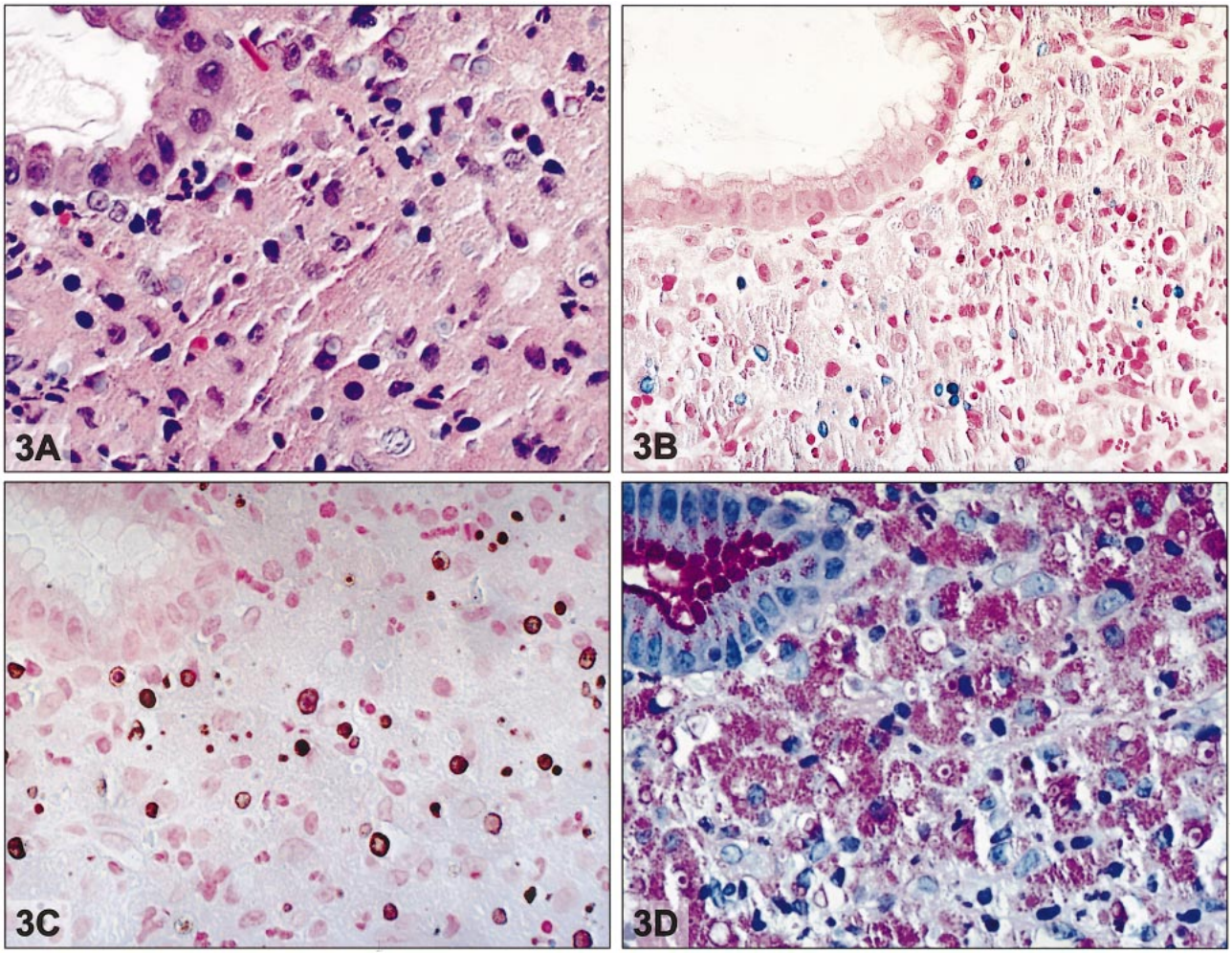


**Figure 3.** *Higher magnification of histiocytes with many intracellular and extracellular Michaelis-Gutmann bodies (A). Stains for iron (B), calcium (C), and the periodic acid–Schiff reaction (D) highlight the Michaelis-Gutmann bodies (hematoxylin-eosin [A], Prussian blue [B], Von Kossa [C], periodic acid–Schiff [D], original magnification ×400).*

ation between malakoplakia and pernicious anemia or antiparietal cell antibodies has been demonstrated. The follow-up endoscopic and histologic examinations 12 months after the initial presentation revealed no changes in the patient's condition, and the long-term course of this case remains unclear.

The etiology of malakoplakia has not been fully elucidated. Because the morphologic features of the disease are the same regardless of the site of involvement, it is highly possible that the pathogenesis may also be the same. The association of bladder malakoplakia with urinary tract infections suggests an infectious etiologic agent. Gram-negative organisms, particularly *Escherchia coli*, have been frequently isolated from the involved sites in cases of genitourinary malakoplakia and are thought to play some pathogenetic role.[1,2] Other infections that have been associated with malakoplakia based on results of electron microscopic, microbiologic, and molecular evaluations include tuberculosis, *Shigella* infection, paracoccidiomycosis, and parasitic infections[9–12] (Table). In some immunocompromised patients with malakoplakia, *Rodococcus equi* has been identified,[13] and recently *Y enterocolitica* has been implicated in cases of colonic and appendiceal malakoplakia.[14] Ultrastructural studies of malakoplakia lesions have revealed bacilliform gram-negative microorganisms, either intact or in different stages of disintegration within phagolysosomes in the macrophages.[15,16] These structures are thought to form the lesion core and to be the earliest stage in the formation of Michaelis-Gutmann bodies. However, some researchers have not found bacterial elements and have suggested that the core may be derived from endogenous cell membrane breakdown products.[16] Whatever the origin of the core, subsequently there is de-

| Various Organisms That Have Been Associated With Malakoplakia |
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| *Escherichia coli* |
| *Mycobacterium tuberculosis* |
| *Shigella boydii* |
| *Paracoccidioides brasiliensis* |
| *Rodococcus equi* |
| *Yersenia enterocolitica* |
| *Klebsiella pneumoniae* |
| *Proteus mirabilis* |
| *Staphylococcus aureus* |
| *Pseudomonas aeruginosa* |
| *Enterobacter aerogenes* |
| *Taenia species* |

position of calcium and phosphate to form the concentric laminations, which represents the final stage of lesion development. Because these chronic infections are so frequent and malakoplakia is so rare, there must be other factors involved. Immunologic disorders or immunosuppressive conditions have been linked to malakoplakia. The bactericidal activity of macrophages against *E coli* was abnormal in 1 case because of low levels of cyclic guanosine monophosphate, resulting in decreased lysosomal degradation and poor enzyme release after phagocytosis; the condition was remedied with cholinergic drugs. In another study, an immunosuppressive drug (azathioprine) inhibited the ability of macrophages to kill phagocytized *E coli* and *Staphylococcus aureus* and reverted only with reduction of the drug dose.[17] These reports suggest that more than 1 intracellular pathway may be involved in malakoplakia, such as enzyme release, membrane dysfunction, or microtubule assembly as in Chediak-Higashi syndrome. The woman in the present case did not have a history suggestive of underlying immune deficiency or disorders that have been associated previously with malakoplakia.

Based on experience from other cases of malakoplakia at other sites, we suspect the inciting event for gastric malakoplakia may also be a microbial agent, and one of the most likely candidates would be *H pylori*. In the previously reported cases of gastric malakoplakia, the role of *H pylori* infection was never evaluated. In the present case, there was no evidence of *H pylori* in the biopsy specimen, as determined by histochemical and immunohistochemical analyses. The result of serologic evaluation for *H pylori* also were negative. These finding suggest that (1) *H pylori* is not involved in the pathogensis of gastric malokoplakia, (2) the organisms disappear at the later stages of the disorder, (3) degraded organisms in the macrophages may not be recognized by these methods, or (4) there was a sampling problem. *Yersinia enterocolitica* has been recently implicated in colonic malakoplakia; however, we did not find similar evidence in the present case.[14]

In this case of isolated gastric malakoplakia in a woman with no known related disease, investigations failed to show any evidence of underlying *H pylori* or *Y enterocolitica* infection. Further investigations are needed to fully elucidate the nature of gastric malakoplakia.

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