Bacterium Causes Gastroesophageal Junction Inflammation and Exposes Uncontrolled Diabetes and Other Infections in an Adult Male

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CLINICAL HISTORY

Patient: 52-year-old African-American male.

Chief Complaint: Severe abdominal pain and difficulty eating.

History of Present Illness: The patient presented to the emergency room (ER) with severe abdominal pain. Approximately 3 months prior to his visit, the patient stopped taking his metformin for diabetes and monitoring his glucose. For the next 3 months, the patient experienced rapid weight loss, a rash on the center of his tongue, genital skin sloughing, and sharp lower back pain. The patient then decided to resume his medication. Subsequently, the rash on his tongue cleared, the sloughing decreased but did not clear, and his back pain subsided. The patient began experiencing occasional pain when swallowing food, but dismissed the symptoms. On the morning prior to his ER visit, when the patient swallowed food he had mild discomfort in the upper esophagus and it felt as though food was lodged in his esophagus after the meal. Eating lunch increased the patient's discomfort to a moderate level of pain that seemed to move with the food to the lower portion of his esophagus over a 2 hour period. Finally, an afternoon snack escalated the patient's pain in the upper abdominal region to a severe level. Once again the patient described the pain as following the food as it traveled into the abdominal region.

Past Medical and Surgical History: The patient had type 2 diabetes mellitus for approximately 10 years and hypercholesterolemia for at least 27 years. The patient had a hemorrhoidectomy 8 years earlier.

Social History: No tobacco use, no alcohol use, and no intravenous drug abuse.

Family History: The patient's mother died at age 62 from type 2 diabetes mellitus complications that included 5 years of blindness accompanied by occasional seizures. The patient is a retired civil service employee.

Physical Exam and Vital Signs: Upon admission, the patient's temperature was 98.8°F; blood pressure 132/84 mmHg; respirations 18/minute; and pulse 72 beats per minute (bpm). The patient presented with severe epigastric pain with difficulty swallowing, acute localized lower abdomen pain, and a genital rash. He had no signs of blurred vision, sloughing of skin elsewhere on the body, chest pain, coughing, shortness of breath, or abdominal distention. He had no nausea, vomiting, hematemesis, melena, or hematochezia. He had no dysuria or pyuria. He did not have any swelling, ulcers, or numbness in his feet or legs.

Keywords: glucose, hemoglobin $A1_C$, chronic kidney disease, retroperitoneal fluid, esophagogastric junction, *Helicobacter pylori*, achlorhydria, adenocarcinoma, type 2 diabetes mellitus

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Abbreviations

ER, emergency room; bpm, beats per minute; CT, computed tomography; *H. pylori*, *Helicobacter pylori;* H & E, hematoxylin and eosin; CMP, comprehensive metabolic panel; MDRD, Modification of Diet in Renal Disease; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; EGD, Esophagogastroduodenoscopy; CCD, charge-coupled device; GI, gastrointestinal; HCO_3, bicarbonate; MPV, mean platelet volume; eAG, estimated average glucose

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Principal Laboratory and Pathology Findings

1. The laboratory results (**Table 1**) in conjunction with the physical examination prompted an investigation to rule out acute cholecystitis/gallstones and pancreatitis. A gallbladder ultrasound study was normal. The computed tomography (CT) scan of the abdomen and pelvis revealed fluid distribution throughout the retroperitoneal and root of the mesentery but was otherwise normal. Magnetic resonance cholangiopancreatography localized the fluid as surrounding both kidneys, as well as in the retroperitoneal space and paracolic gutters. The gallbladder was normal, and there was no evidence of pancreatitis.

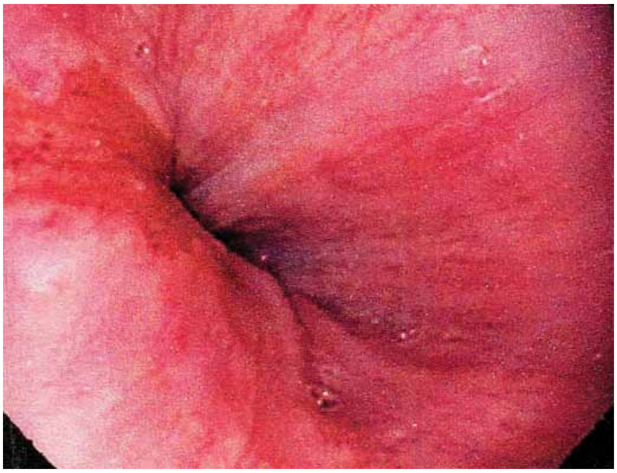


Image 1

Distal esophagus.

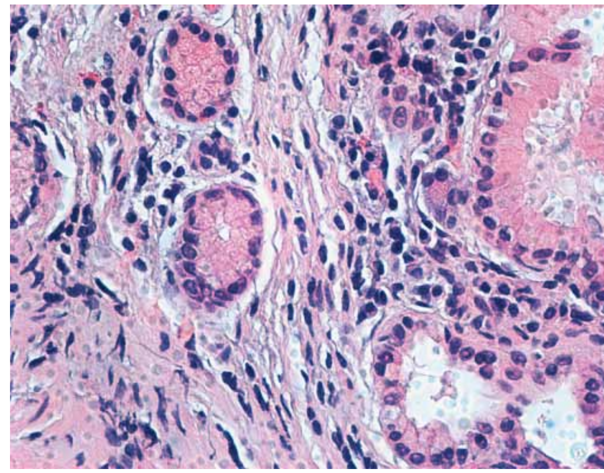


Image 2

Specimen A with hematoxylin and eosin stain (50×).

Table 1. Principal Laboratory Findings

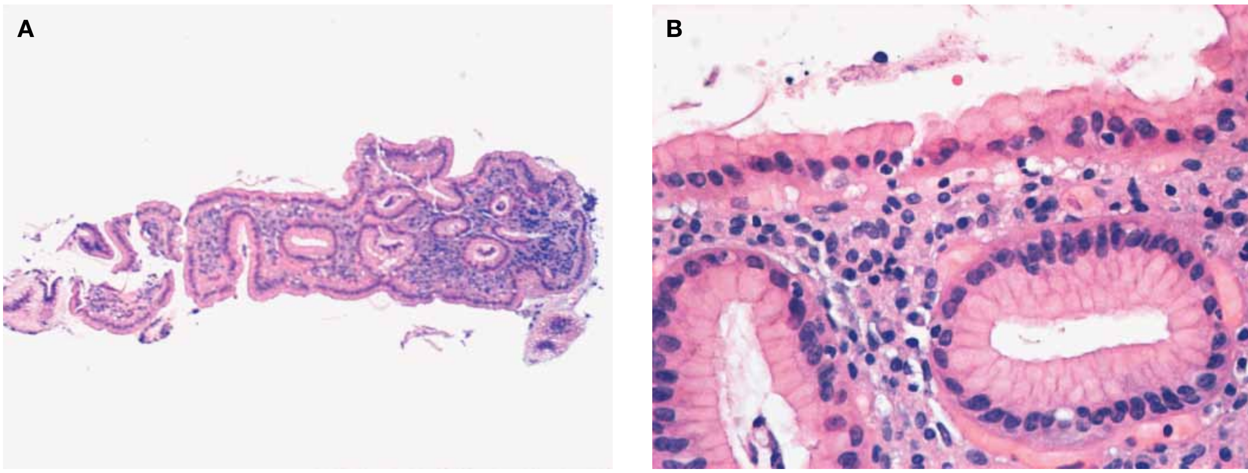
Test	Patient's Results	Reference Interval
Hematology		
WBC count	4.9	4.8-10.8 × 10^9/L
RBC count	4.97	4.70-6.10 × 10^{12}/L
Hemoglobin	14.0	14.0-18.0 g/dL
Hematocrit	42.1	42.0-52.0%
Platelet count	183	130-400 × 10^9/L
MPV	11.2	7.4-10.4 fL
Chemistry		
Sodium	138	135-143 mEq/L
Potassium	3.9	3.4-5.0 mEq/L
Chloride	103	100-111 mEq/L
Glucose	369	70-115 mg/dL
Hgb $A1_c$	14.1	4.6-6.2%
Estimated average glucose	358	
Albumin level	4.4	3.5-5.0 g/dL
Total protein	8.0	6.4-8.5 g/dL
Amylase	176	34-126 U/L
Creatinine	0.90	(0.65-1.20 mg/dL)
eGFR (MDRD)	107.2	>60 mL/min/1.73 m²
Lipase	26	13-60 U/L
Urinalysis		
UA specific gravity	1.015	1.000-1.040
UA glucose	≥1000	Negative
UA proteins	Negative	Negative
UA blood	Negative	Negative

*WBC, white blood cells; RBC, red blood cells; MPV, mean platelet volume; eGFR, estimated glomerular filtration rate; MDRD equation, eGRF (mL/min/1.73 m^2) = 175 x SerumCr$^{-1.154}$ * age$^{-0.203}$ * 1.212 (if patient is black) * 0.742 (if female)^3; MDRD, modification of diet in renal disease; UA, urinalysis.*

2. Endoscopic examination was performed. In the duodenum there was no sign of ulcers, mass, inflammation, or other possible source of the fluid in the retroperitoneum. The stomach was normal with no inflammation or hiatal hernia. The esophagogastric junction presented irregular proximal migration of the Z-line and was biopsied for Barrett's esophagus. The esophagus was slightly nodular with a hint of felinization and was randomly biopsied (**Image 1**).

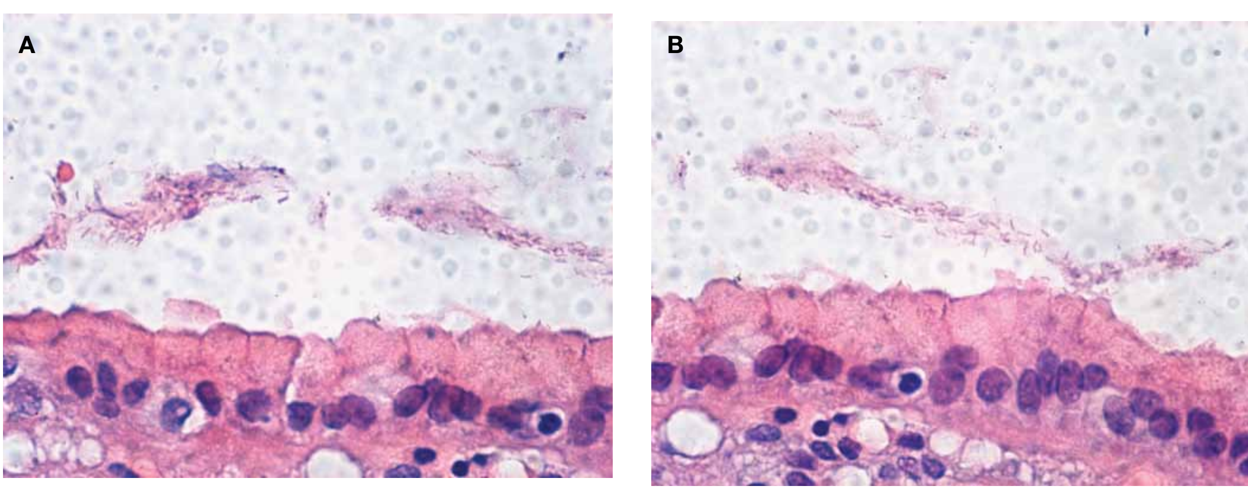
3. Biopsy specimens were collected from the gastrointestinal track and labeled specimen A (**Image 2**) and specimen B (**Image 3A** and **3B**). Specimen A only revealed squamous mucosa, with mild chronic esophagitis, but H. pylori was not present. Specimen B was a biopsy from the gastroesophageal junction of squamous, gastric body, and cardiac mucosa with moderate chronic inflammation, but no intestinal metaplasia, dysplasia, or malignancy. However, many *Helicobacter pylori* (*H. pylori*) organisms were identified by hematoxylin and eosin (H & E) (**Images 4A** and **4B**) and Diff-Quick stains **(Image 4C)**. This was the only area *H. pylori* was located.

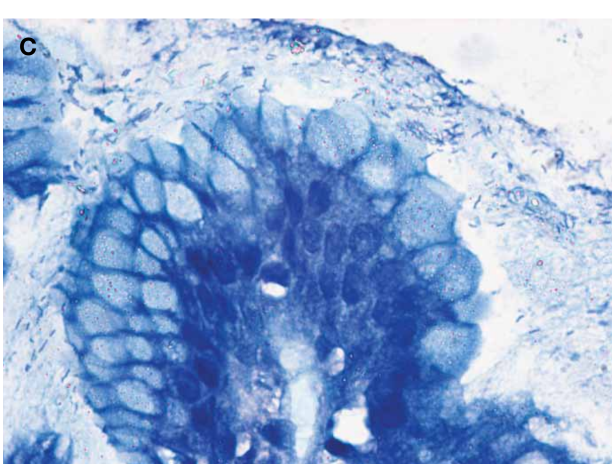
4. Antibodies to *H. pylori* were not detected either 10 days or 3 months after the admission, using the Status *H. pylori.* A breath test for *H. pylori* was negative 3 months after the admission, using the microCOUNT model 9605 LSC (Ballard Medical Products, Draper, Utah).



Images 3A and 3B

Specimen B with hematoxylin and eosin stain (10× and 50×)





Images 4A, 4B, and 4C

Parts A and B are specimen B with hematoxylin and eosin stain (100×). Part C is specimen B with Diff-Quick stain (100×).

Questions

1. What are the most striking clinical and laboratory findings for this patient?
2. How do you explain these laboratory findings?
3. Why was an endoscopy indicated?
4. What were the most significant tissue biopsy and clinical findings?
5. Why was the causative agent of the abdominal pain localized in the gastrointestinal tract?
6. Why were the laboratory tests for the causative agent negative?

Possible Answers

1. The automated differential detected large platelets. The comprehensive metabolic panel (CMP) included a blood glucose of 369 mg/dL and a hemoglobin $A1_C$ of 14%. Urine glucose was >1000 mg/dL, but there was no blood or protein present. The amylase was elevated at 176 U/L, but the lipase was normal.

2. The large platelets may have been normal for the patient, or an indication of bleeding[1-3] linked to the retroperitoneal fluid and back pain, but the lack of imaging evidence precluded a risky paracentesis procedure to determine the origin of the fluid. Based upon the hemoglobin $A1_C$, the calculated average glucose over the last 120 days was 358 mg/dL eAG ($AG_{mg/dl} = 28.7 \times A1C - 46.7$, $R^2 = 0.84$, $P < 0.0001$)[1], indicating uncontrolled diabetes that was likely the cause of the sloughing skin and rash. The elevated urine glucose was expected, but the absence of protein and blood ruled out severe glomerulopathy. However, the MDRD estimated glomerular filtration rate (eGFR), patient's age, history, and family history, are consistent with stage 1 chronic kidney disease (CKD) (**Table 2**). Although an elevated amylase suggests pancreatitis, the normal lipase and abdominal imaging results ruled out this diagnosis.

3. Esophagogastroduodenoscopy (EGD) was indicated to clarify the symptoms and findings in this case. An EGD device uses a light-emitting diode (LED) and charge-coupled device (CCD) to capture internal images of the esophagus, stomach, and duodenum. In this patient, EGD was indicated because the patient was losing weight and having trouble swallowing, possibly indicating an esophageal cancer. Also, he had thrush and was diabetic, possibly due to *Candida* esophagitis. The degree of pain related to eating justified thorough examination of his upper gastrointestinal (GI) tract.

4. The most significant biopsy finding was *H. pylori* infection; cancer and/or esophageal *Candida* infection were not detected. *H. pylori*, however, was not responsible for all of the patient's symptoms. The patient had poor diabetic control. Skin sloughing and rash suggested *Candida* spp. infections of mucous membranes due to the high availability of glucose in these moist linings. Therefore, poor diabetic control both suppressed immune response and provided large amounts of glucose to promote yeast growth.

5. *H. pylori* thrive in the acidic stomach mucosa by colonizing the mucus secretions of gastric epithelial cells, and producing urease, which generates bicarbonate (HCO_3) that locally neutralizes gastric acid. *H. pylori* can survive in the gastric epithelium for years. Urease cleaves urea to form ammonia and carbon dioxide that both neutralize acid and provide a habitable pH microenvironment.

Table 2. Classification of CKD and Action Plan[5]

CKD Stage	Description	GFR (mL/min/ 1.73 m2)	Action
At increased risk	Risk factors for CKD are present but without markers of kidney damage	>90	Periodically test for CKD; treat modifiable risk factors for CKD
1	Kidney damage with normal or increased GFR	>90	Diagnose and treat type of kidney disease
2	Kidney damage with mild reduction of GFR	60-89	Adjust drug dosages for level of GFR
3	Moderate reduction of GFR	30-59	Evaluate and treat complications of CKD; avoid nephrotoxic drugs
4	Severe reduction of GFR	15-29	Prepare for kidney-replacement therapy
5	Kidney failure	<15 (or on dialysis)	Start kidney-replacement therapy

CKD, chronic kidney disease.

H. pylori inflames the gastric linings even in the absence of acid. The bacterium can damage the stomach so severely that it loses the ability to make gastric acid, further enhancing proliferation of the infection. Following eradication of *H. pylori* patients may experience hyperacidity and reflux.

Chronic irritation by *H. pylori* is associated with development of adenocarcinoma of the stomach, a cancer that has been declining in incidence in Western countries[2] for the past 60 years. The decline parallels the increased use of antibiotics and inadvertent treatment of *H. pylori* infections before discovery of the organism. Due to its association with gastric adenocarcinoma, and difficulty treating *H. pylori* because of its acquired antibiotic resistance, gastroenterologists typically order testing after treatment to confirm eradication of the infection.[4]

The breath test for *H. pylori* was negative because the patient had completed a 2-week regimen including Biaxin, amoxicillin, and Protonix. There are several analytical methods for detecting *H. pylori* infection. There are blood tests designed to detect anti-*H. pylori* antibodies, although these may not be detectable for up to 6 months after infection. Stool can be tested for the presence of *H. pylori*. A metabolic breath test detects the urease activity in the stomach (^{13}C or ^{14}C labeled urea is administered to the patient, and urease-produced $^{13}CO_2$ or $^{14}CO_2$ is detected in the breath). *H. Pylori* can be detected in biopsy specimens using hematoxylin/eosin or other staining methods. Finally, culture of *H. pylori* is possible, but is rarely attempted as the organism is fastidious.[4]

In this case 3 methods were used to detect *H. pylori*. Serologic testing for anti-*H. pylori* antibodies was negative early in the illness and 3 months later. This finding is consistent with acute infection since antibodies to the organism may take several months to develop. The biopsy at the time of the EGD revealed *H. pylori* on hematoxylin, eosin, and Diff-Quick stain, which is direct evidence for an active infection even in its early phase. The *H. pylori* urease breath test at the time the patient was ill may have revealed *H. pylori*. However, there were other reasons to do an EGD, and the breath test was not available at the time. The urease breath test was negative post-treatment, which indicates that the treatment was successful. **LM**

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