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Refractory Effusions, Crumbly Bones, Mystifying Cachexia and an Absent Mind: An Unusual Presentation of Whipple’s Disease with Review of Literature

Syed Hamza Bin Waqar¹, John Diks², Unaiza Zaman¹, Sarah Sharif¹, Taha Sheikh³, Srinivas Kolla⁴, Isabel M. McFarlane^{1,*}

¹Department of Medicine, State University of New York, Downstate Health Sciences University, Brooklyn, NY

²Department of Pathology and Lab Sciences, State University of New York, Downstate Health Sciences University, Brooklyn, NY

³Department of Medicine, University of Toledo, OH

⁴Department of Radiology, Chief, Musculoskeletal Division, State University of New York, Downstate Health Sciences University, Brooklyn, NY

Abstract

Whipple’s disease is a bacterial infection caused by *Tropheryma whipplei* and is known to cause perplexing clinical presentations, making its diagnosis challenging. The beginning by the involvement of the gastrointestinal tract, Whipple's disease can slowly progress to affect almost any organ system and lead to chronic multi-system inflammatory disease. Hereby, we present a middle age man who initially manifested with shortness of breath and chronic weight loss. He subsequently developed pleuro-pericardial effusion, ascites, mesenteric lymphadenopathy, possible myocarditis, and severe osteopenia with multiple vertebral fractures during his illness. Esophagogastroduodenoscopy with the biopsy and subsequent molecular confirmation of disease led to the confirmation of WD. Therapeutic management included two separate antibiotic regimens in an attempt to address the refractory course of WD in this patient.

Keywords

Whipple’s disease; *Tropheryma whipplei*; malabsorption; protein-losing enteropathy

1. Introduction

Whipple's disease (WD) is a systemic illness caused by *Tropheryma whipplei*, which usually presents with chronic diarrhea, arthralgias and weight loss.

WD was first described by George H. Whipple in 1907 as intestinal lipodystrophy given the prominent fat deposition in intestinal mucosa. In 1949, Black Shaffer noticed PAS positivity in the macrophages which laid the cornerstone for the histological basis of WD [4]. Of note, positivity for PAS is however, nonspecific and can be present in histiocytic and reactive disorders and infections such as in *Mycobacterium avium* or *Histoplasma* infection and thus, these other entities need to be excluded [1].

In full-blown infections, WD causes protein losing enteropathy due to loss of protein via massive intestinal inflammation and lymphatic blockage which leads to exudation of protein with substantial loss of albumin in the gastrointestinal tract. The resulting protein loss results in ascites, peripheral edema and severe wasting syndrome [1,5].

We present a case of a 45-year-old male with refractory ascites and pleuro-pericardial effusions in the setting of protein-losing enteropathy whose course was complicated by multiple admissions, highlighting the importance of early recognition and aggressive treatment of Whipple's disease.

2. Case Presentation

45-year-old man with a known history of poorly controlled temporal lobe epilepsy, partially treated *Helicobacter pylori* infection and associated gastric metaplasia presented with worsening non-exertional pleuritic chest pain, dyspnea of exertion, watery diarrhea, 35 pound-weight loss, night sweats and fatigue. The diarrhea, which had started few months before presentation, was temporally related to meals however not associated with either gluten or lactose intake, relieved partially by fasting, explosive and foul-smelling. Anorexia, flatulence, and progressive abdominal distension were also reported. On review of systems, back pain along the vertebral column, arthralgias of the hands and lower extremities, and a difficulty in concentrating were also recorded. Social history revealed the patient had been born and raised in United states, worked as handyman for many years in an urban setting, had a 12.5 pack-year history of smoking with occasional use of marijuana and denied travel abroad or significant family history.

On initial evaluation, the patient was hypotensive to 80/50, heart rate in 120, and tachypneic to 22 with normal saturation levels, body mass index was 21.4 kg/m². The exam was significant for temporal wasting, edentulous gum, glossitis, no cervical, supraclavicular or axillary lymphadenopathy. The cardiovascular exam was normal, lung exam revealed decreased breath sounds with dullness to percussion in the lower half of the right lung field. The abdominal exam was distended had flank dullness, shifting dullness and positive fluid wave, no organomegaly was appreciated. The skin of the anterior aspect of the legs was hyperpigmented without papules or nodules. There was no cyanosis., clubbing or edema. Blood tests were significant for leukocytosis, normocytic and normochromic red blood cells and labs that suggested mixed iron deficiency and anemia of chronic disease. In addition, hyponatremia, mild transaminitis, low albumin and elevated inflammatory markers Blood cultures and urine culture showed no growth. Spot albumin-creatinine ration (ACR) showed albuminuria to 89mg/g [Table 1].

Chest imaging with chest Computed tomography confirmed moderate to large right pleural effusion with compressive atelectasis of the right lower and middle lobes [Figure 1, Figure 2], There was also small to moderate pericardial effusion with compression fractures, seen as anterior wedging at thoracic vertebral bodies at level of T4, T5, T6, and T10, along with questionable increased opacity /sclerosis of the entire T4 raising in part the question of metastatic disease which on repeat interval imaging resolved. A chest tube was placed to improve the chest wall dynamics yielding resolution of dyspnea. The pleural fluid was consistent with exudative effusion with lymphocytosis, no malignant or mesothelial cells were seen; adenosine aminase (ADA), brain natriuretic peptide (BNP), cultures for acid-fast bacilli, bacterial, viral, and fungal cultures were all negative. The chest tube drained about 1.5 Liter of fluid and was maintained for a few days until the output was below 200cc/24hours; a repeat thoracentesis was performed during the same admission, given the recurrence of the pleural effusion and a pigtail catheter was inserted. A multi-disciplinary team discussed the case to ascertain the underlying pathology causing pleural and pericardial effusions, ascites and cachexia.

Preliminary diagnosis of malignancy and protein-losing enteropathy (PLE) were considered, and specific tests were ordered. Infectious panel was negative including human immunodeficiency vims (HIV), Hepatitis B, Hepatitis C, and QuantiFERON tuberculosis test. Total protein was within range with a low pre-albumin and albumin level of 1.9 g/dl, causing a marginally high globulin gap of 4.2 g/dL (> 4g/dL). Serum protein electrophoresis (SPEP) and urine protein electrophoresis (UPEP) were normal, with immunofixation showing polyclonal pattern indicating an inflammatory state. A 24-hour alpha-antitrypsin clearance in stool sent was high which directed even further to PLE. The celiac disease serology was negative (tissue transglutaminase Immunoglobulin A and anti-endomysial antibody). Serum immunoglobulin levels and various autoantibodies returned negative as well. Fecal studies including ova and parasite, special staining for atypical pathogens, electrolytes, Clostridium difficile, bacterial and viral culture, and H. pylori tests were all negative.

Serum tumor markers were sent, including Alpha-fetoprotein (AFP), chromogranin A, lactate dehydrogenase (LDH), carcinoembryonic antigen (CEA), beta-human chorionic gonadotrophin (bHCG), and prostate-specific antigen (PSA), which were all normal as well along with thyroid function tests. With low vitamin D levels, urine phosphate and serum calcitriol were also sent to exclude tumor-associated osteomalacia, which was normal. Urinary cortisol and Histoplasma antigen were non-contributory. The skeletal survey was negative, but the CT scan of the spine showed marrow changes in vertebral bodies of C5 and C6 with no marrow compression throughout-apart from the thoracic vertebrae changes mentioned above. CT scan abdomen and pelvis showed gastric antral wall thickening, moderate abdominal ascites with significant mesenteric lymphadenopathy with the largest measuring up to 1.7 centimeters (cm), and peritoneal enhancement perplexing case with hints for malignancy [Figure 3], Brain MRI with contrast showed sulci effacement inappropriate for his age and central volume loss with no enhancing lesions. During the hospital stay, the patient also developed multiple febrile episodes with concomitant negative blood cultures. Esophagogastroduodenoscopy (EGD) and colonoscopy were planned given gastric antral thickness, unexplained weight loss, and small bowel pathology in question.

EGD showed mild inactive gastritis with superficial ulcerations in the stomach's fundus and diffuse abnormal white mucosa in the second portion of the duodenum, suggestive of duodenitis and lymphectesia [Figure 4]. Colonoscopy revealed no polyps or signs of inflammation. The patient was discharged with an out-patient follow-up after an extensive course of hospitalization.

During a follow-up visit, the patient presented with worsening shortness of breath and re-accumulation of right sided pleural effusion. A decision was made to repeat the thoracentesis with right sided thoracoscopy with parietal pleural biopsies and talc pleurodesis, which the patient tolerated well. Pathology showed benign fibrofatty tissue admixed mesothelial hyperplasia.

The EGD biopsies returned and showed markedly distended duodenal mucosa with active inflammation with abundant macrophages in the lamina propria. Dilated lymphatics/fat vacuoles were also present in the lamina propria [Figure 5, Figure 6]. Periodic acid-Schiff (PAS) and Gomori methenamine silver (GMS) staining showed rod-shaped organisms highly suggestive of Whipple's disease, which was further confirmed with PCR 16s ribosomal RNA to be *T. whipplei* from duodenal biopsy [Figure 7, Figure 8]. The parietal pleural biopsy also showed distended macrophages without growth of *T. whipplei*.

Given the suspicion of neurological sequelae of advanced Whipple's disease, a lumbar puncture was performed which showed oligoclonal bands, high protein and, mild lymphocytic pleocytosis. PCR for *T. whipplei* was sent but couldn't be appreciated secondary to specimen leakage during transit to the lab. Given Whipple's disease diagnosis, Ceftriaxone was given for two weeks, followed by the twice daily dose of trimethoprim-sulfamethoxazole double-strength was continued for a year as part of therapy.

Despite antibiotic initiation and completion of first four months of therapy, the patient relapsed again- this time with left sided pleural effusion. Repeated Transthoracic echocardiography (TTE) showed reduced ejection fraction to 40% with severe hypokinesis of septal and anteroseptal walls with trivial tricuspid and mitral regurgitation but no vegetations. These findings were markedly different from the first TTE performed at the time of EGD which showed normal ejection fraction and no wall motion abnormality. Consideration for ischemia and myocarditis were raised. After heart rate optimization with metoprolol succinate, CT coronary artery was performed which did not show any significant epicardial coronary artery disease. Cardiac MRI with biopsy was planned to confirm suspected myocardial involvement, but the patient declined the invasive procedure.

Later, however, new regimen was suggested and hydroxychloroquine 200mg three times daily with doxycycline 100mg twice daily was started with resumption of twice daily dosage of trimethoprim-sulfamethoxazole double strength. Patient was later followed up and showed marked resolution of pleural effusion and shortness of breath. Patient is being actively followed by pulmonology, gastroenterology and infectious disease clinics and will be undergoing a repeat EGD with biopsies of duodenal region and repeat echocardiogram after completion of two months of therapy with the triple regimen.

3. Case Discussion

Whipple's disease (WD) is a systemic multifaced illness which is caused by *Tropheryma whipplei*, a gram-positive, non-acid-fast, periodic acid-Schiff (PAS)-positive rod [1]. The primary link has been made with illnesses affecting loss of antigen presentation via major histocompatibility complex 2 downregulation and aberrant to absent monocytic and T helper type 1 response, thus making immunocompromised cohort particularly susceptible to infection [2,3]. Given its ubiquitous nature, a genetic predisposition might be possible with development of disease, as only one in million develop florid disease. Literature primarily mentions diarrhea, abdominal pain, weight loss and arthralgias as cardinal features of WD [1].

Diagnosis of WD is established if two of the three criteria are fulfilled:

- A. Histological proof of PAS positive macrophages
- B. PCR assay positivity for *T. whipplei* (16S ribosomal RNA)
- C. Immunohistochemical binding of *T. whipplei*-specific antibody.

Lymphadenopathy has been reported in about 60% of patients which mostly involves mediastinal or mesenteric region. This can raise suspicion of lymphoma and given clinical suspicion in certain cases, might need exclusion. Non-necrotizing granulomas can also be present in as many as 9% of LAD and can potentially mislead to a diagnosis of sarcoidosis [1,6].

Cardiac sequelae including blood-culture negative endocarditis (BCNE) and handful of cases involving myocardium and pericardium have been reported. Endocarditis is caused by intermediate sized vegetations with non-calcific mild inflammatory changes [7]. Myocarditis can also present with interstitial myocardial fibrosis interspersed with PAS- positive macrophages and lymphocytes [8].

Pleuropulmonary manifestations including but not limited to pleural effusions, interstitial disease-like manifestation and pulmonary hypertension have been reported in literature [9,10].

Neurological complications can be present in about 40% of patients which can vary from amnesic syndromes, central involvement causing supranuclear ophthalmoplegia, seizures, nystagmus, extrapyramidal or upper motor neuron deficits, hypothalamic or cerebellar syndromes and neuropathies that could either be central or peripheral in nature [6].

It should be noted, given aggressive and late detection of disease because of perplexing course and presentation, if left untreated, WD could be fatal. Various antibiotic regimens have been laid down for WD, however the optimal regimen remains uncertain to date given paucity of disease. Popular opinion and most tested regimen this far include an initial course of intravenous antibiotics that could traverse central nervous system for a duration of two weeks followed by a prolong course of oral antibiotics. Standard therapy includes two grams of ceftriaxone intravenously for two to four weeks followed by trimethoprim-sulfamethoxazole double-strength (TMP-SMX DS) for a year. Alternatively, meropenem

followed by TMP-SMX DS for a year has also been tested in one of the recurrences of WD. As per a French retrospective study, complete response to a combination of hydroxychloroquine and chloroquine with TMP-SMX DS has been reported. There're no follow-up guidelines laid down for WD but surveillance biopsies of duodenum at 6 month and 12 months for histological and PCR and suggestion to use alternative antibiotic regimen for relapse of WD than that of previously used has been mentioned in literature [1,11,12].

4. Conclusion

WD is a very rare systemic illness which can masquerade in a variety of ways with multi-system involvement perplexing physicians and making the road to diagnosis exceptionally hard. Our case is unique as it involves advanced stage of protein losing enteropathy causing refractory pleuro-pericardial effusions with superimposed new onset heart failure with reduced ejection fraction most likely linked with underlying myocarditis. A unique feature of widespread compression fractures with marked osteopenia was also reported which wasn't present in any of the prior reported cases. Thus, patients with chronic weight loss and diarrhea with unusual extra-intestinal features should be considered for Whipple's disease.

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Figure 1. Contrast enhanced CT axial image at the level of the lower chest in soft tissue window demonstrating large pleural effusion (*) with compressive atelectasis and small pericardial effusion (arrow)



Figure 2. Contrast enhanced CT coronal image in soft tissue window showing ascites (*) and pleural effusion in the same plane (arrow)



Figure 3. Contrast enhanced CT axial image at the level of the mid abdomen in soft tissue window demonstrating diffuse edema with ascites (*) and mesenteric root adenopathy (arrow)



Figure 4.
EGD showing abnormal whitish mucosa in the second part of duodenum

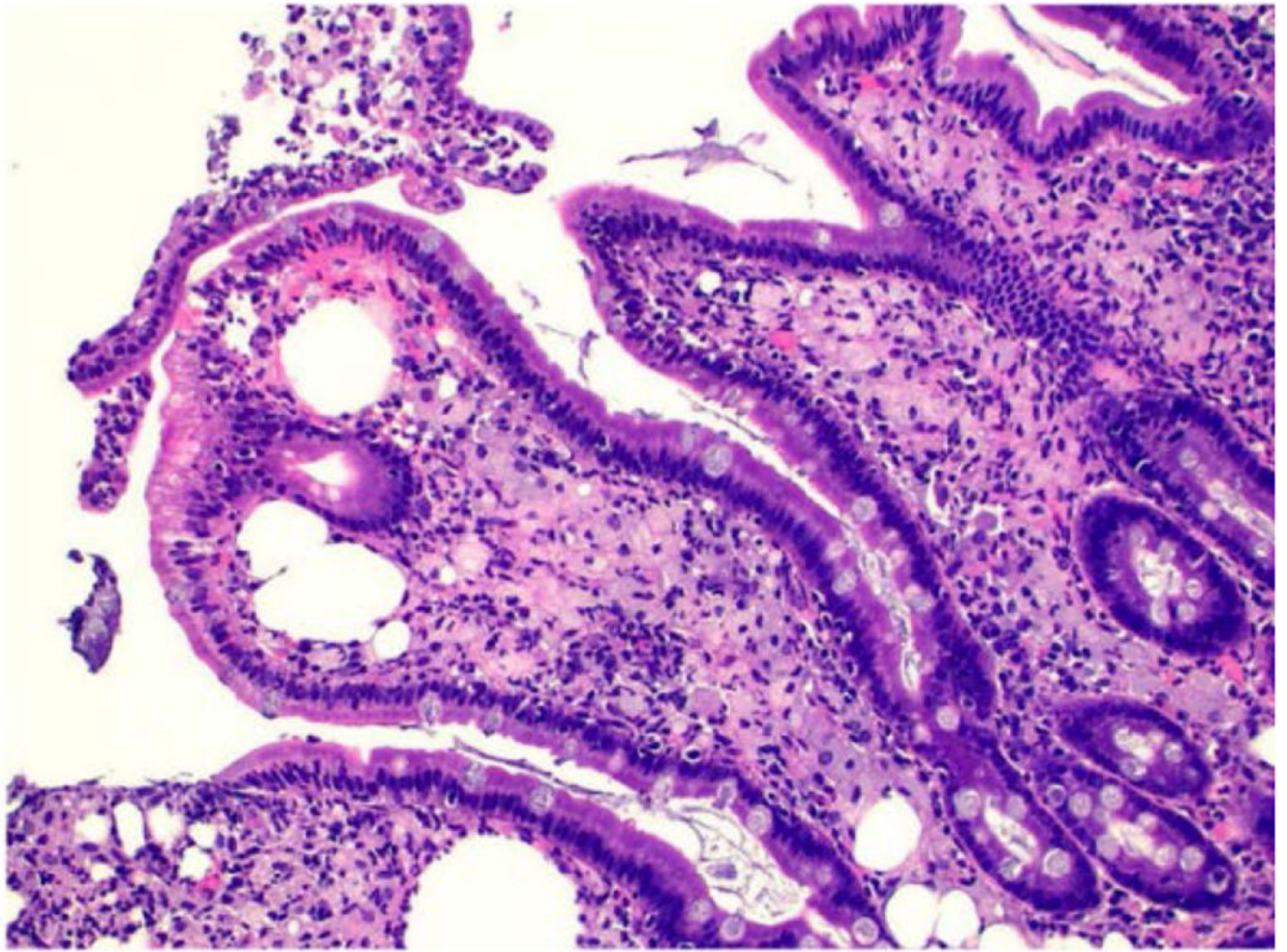


Figure 5. H&E section of duodenal mucosa at 200x magnification showing villi distended by a macrophage infiltrate with admixed neutrophils and fat droplets

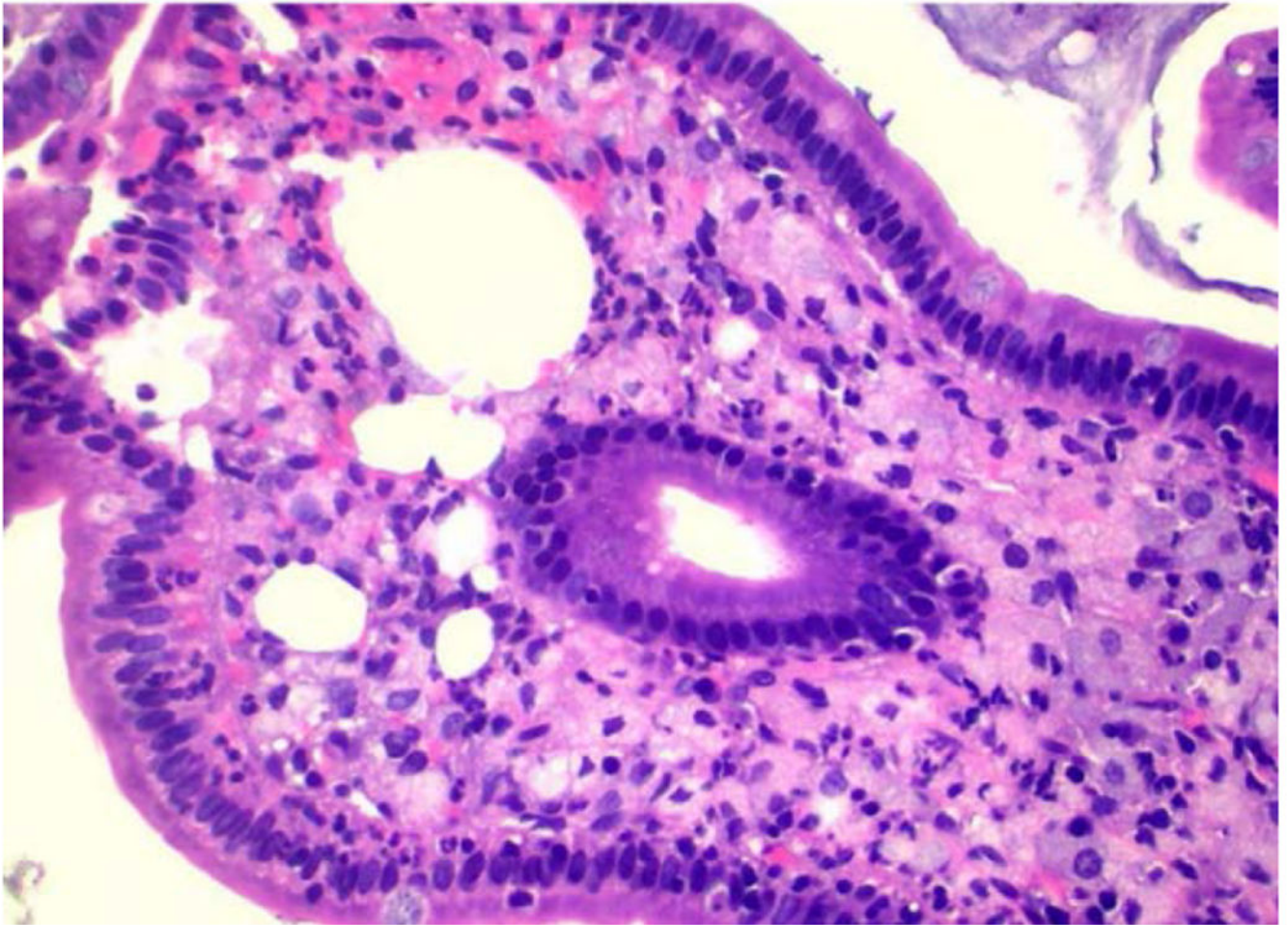


Figure 6.
H&E section of duodenal mucosa at 400x magnification highlights lamina propria containing foamy macrophages as well as neutrophils and eosinophils with dilated lacteals

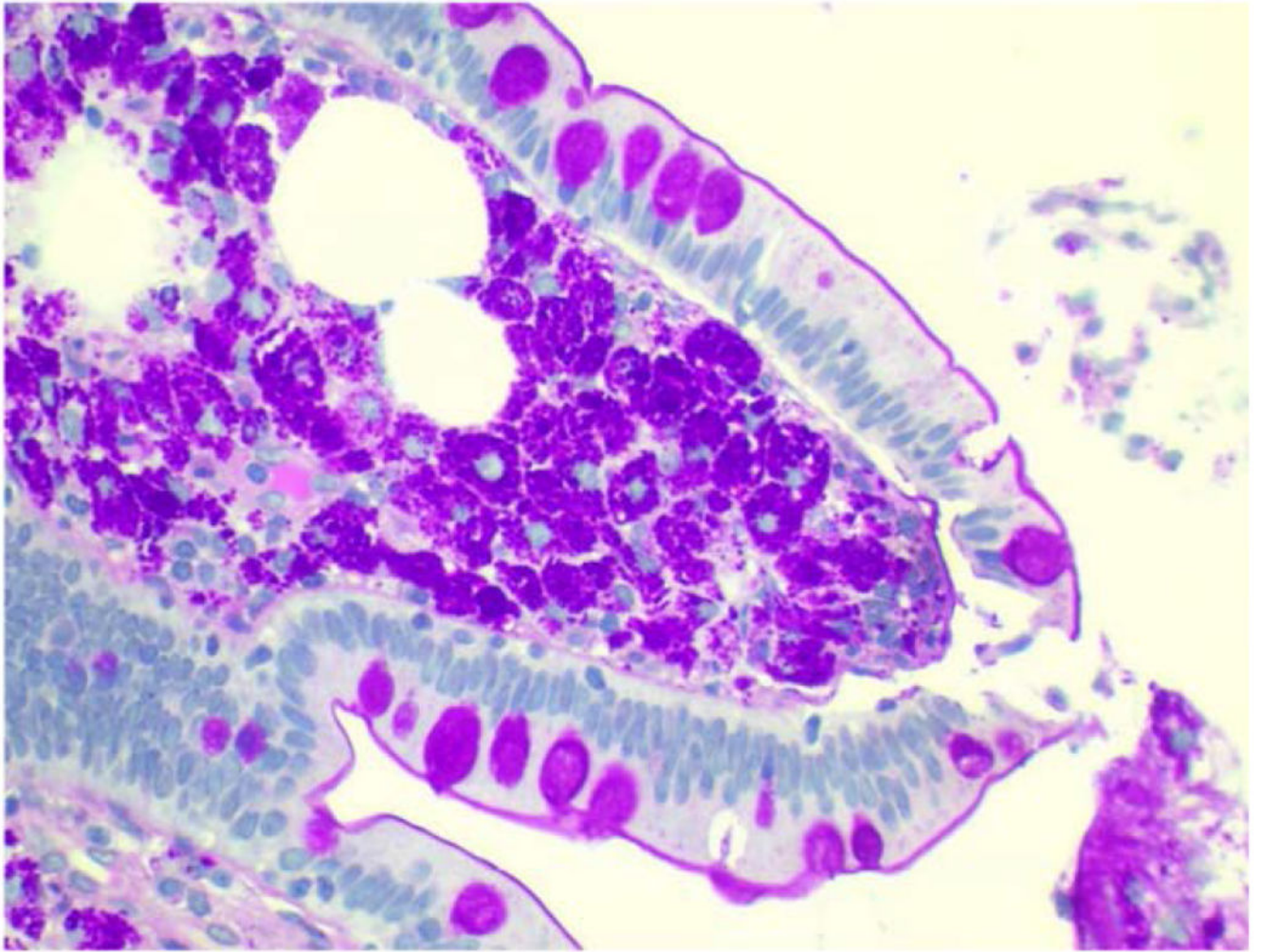


Figure 7. PAS-D section at 200x highlights foamy macrophages in lamina propria, which demonstrates short, thick rods and bacterial fragments within macrophages

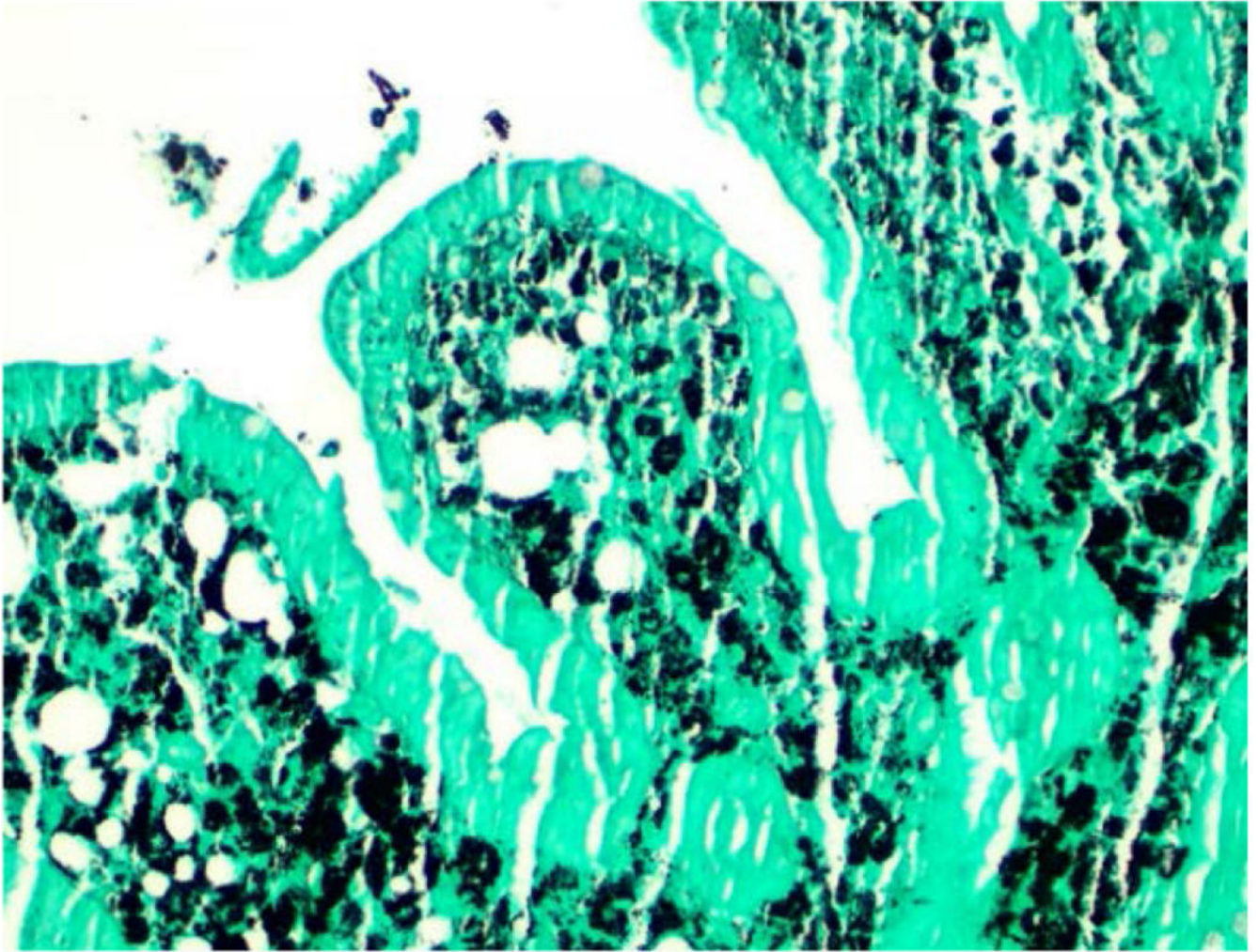


Figure 8. Gomori methenamine silver stain (GMS) at 200x magnification of duodenal specimen showing GMS positive bacteria. In part, they simulate fungi, but they are too small, and lack yeast or hyphal shapes

Table 1.

Patient’s laboratory data at presentation

Laboratory	Patient	Reference Range
WBC (K/uL)	12.3	[3.50–10.80]
Neutrophil count (%)	72.2	[40–74]
Lymphocyte count (%)	15.6	[19–48]
RBC (M/uL)	3.97	[4.10–5.40]
Hemoglobin (g/dL)	9	[12.0–16.0]
Hematocrit (%)	31	[37.0–47.0]
MCV (fL)	79	[78.0–98.0]
Platelets (K/uL)	435	[130–400]
Sodium (mmol/L)	127	[136–145]
Potassium (mmol/L)	3.4	[3.5–5.1]
Chloride (mmol/L)	102	[98–107]
Bicarbonate (mmol/L)	26	[21–31]
Blood Urea Nitrogen (BUN) (mg/dL)	19	[7–25]
Creatinine (mg/dL)	0.7	[0.70–1.30]
Calcium (mg/dL)	8	[8.2–10.0]
Total Protein (g/dL)	6.1	[6.0–8.3]
Albumin (g/dL)	1.9	[3.50–5.70]
Spot ACR (mg/g)	89	[<30]
AST (u/L)	57	[13–39]
ALT (u/L)	63	[7–52]
Alkaline Phosphatase (u/L)	45	[34–104]
Total Bilirubin (mg/dL)	1.2	[0.30–1.00]
Glucose (mg/dL)	87	[70–99]
Magnesium (mg/dL)	1.7	[1.9–2.7]
Phosphorus (mg/dL)	3.1	[2.5–5.0]
Ferritin (ng/ml)	25	[15–200]
Iron (mcg/dl)	40	[80–200]
ESR (mm/hr)	46	[1–10]
hs-CRP (mg/dl)	12	[<0.3]
BNP (pg/mL)	90	[100]
ADA (U/L)	8.6	[<9.2]

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