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Managing diagnostic problem of syphilis manifested as chronic colitis and enteropathic arthritis in a 29 yo male: a case report

Kamila Auliya*, Cahyo Wibisono Nugroho, Hilya Itsnain Mumtaza
Department of Internal Medicine, Airlangga University Hospital, Surabaya, Indonesia
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ABSTRACT

Syphilis is a chronic sexually transmitted infection caused by Gram-negative bacterium, *Treponema pallidum*, known for its ability to mimic other diseases, leading to misdiagnosis and delayed treatment. We present a case of a 29 yo male with recurrent acute diarrhea, accompanied by fever, nausea, vomiting, prolonged mouth ulcers, and weight loss for the last three months. He was hospitalized multiple times due to the same recurrent problems. He was initially suspected for immunodeficiency diseases and was screened for HIV and hepatitis B, but both results came out negative. The patient was then suspected with malignancy of the gastrointestinal tract and underwent several examinations including; hematology workup, abdominal X-ray, gastroduodenoscopy, colonoscopy and biopsy. However, the result of all abdominal X-ray, biopsy and colonoscopy ruled out malignancy. The examinations discovered intraluminal ileocecal mass that is consist of lymphocytic cells, therefore the patient was diagnosed with chronic colitis and ileitis. The patient went to the clinic as scheduled with a new chief complain of other symptoms; painful spine and hip join movement, which added to his new diagnose of enterophatic arthritis and he was hospitalized for further diagnosis. During hospitalization, the patient was screened for another venereal disease i.e. syphilis, due to the everchanging symptomatology. He was being screened with VDRL, and later TPHA test. This case encompasses the complexity and challenges of diagnostic workup in non-suggestive findings of the disease syphilis as the Great Imitator.

ABSTRAK

Sifilis adalah infeksi menular seksual kronis yang disebabkan oleh bakteri Gram-negatif, *Treponema pallidum*, terkenal dengan gejala dan tanda klinisnya yang menyerupai berbagai penyakit lain, menyebabkan kesulitan diagnosis dan keterlambatan pengobatan. Kasus berikut mempresentasikan Seorang pasien laki-laki berusia 29 tahun yang datang dengan diare akut berulang, disertai demam, mual, muntah, sariawan berkepanjangan, dan penurunan berat badan selama tiga bulan terakhir. Pasien berulang kali dirawat di rumah sakit dengan keluhan yang sama. Pasien awalnya dicurigai mengalami penyakit immunodefisiensi dan menjalani skrinning untuk HIV dan hepatitis B, namun kedua hasil pemeriksaan tersebut negatif. Pasien kemudian didiagnosa dengan suspek keganasan, dan menjalani beberapa pemeriksaan, termasuk; pemeriksaan darah rutin, foto polos abdomen, gastro-duodenoskopi, kolonoskopi, dan biopsi kolon. Namun, semua hasil pemeriksaan tersebut menunjukkan tidak adanya tanda keganasan, dan didapatkan massa intraluminal pada ileosekal yang terdiri dari sel limfatik. Berdasarkan hasil tersebut, pasien didiagnosa dengan kollitis dan ileitis kronik. Saat kontrol rawat jalan, pasien mengeluhkan gejala baru yaitu nyeri tulang belakang dan sendi panggul. Pasien dirawat inap dengan diagnosa enteropathic arthritis karena timbulnya keterlibatan gejala tulang belakang dan ekstremitas bawah yang baru muncul. Pasien juga dicurigai menderita penyakit veneral lainnya, yaitu sifilis, karena simtomatologi yang selalu berubah. Pasien kemudian menjalani skrinning VDRL, dan kemudian tes TPHA. Kasus ini menunjukkan kompleksitas dan tantangan diagnostik pada penyakit sifilis yang terkenal dengan sebutan si Peniru Unggul.

Keywords:
syphilis;
enteropathic arthritis;
colitis;
ileitis;
the Great Imitator

*corresponding author: kamilaauliya@gmail.com

INTRODUCTION

Syphilis, the Great Imitator, remains a global public health problem because of the quick spreading and tendency to go unnoticed as it often presents in many clinical forms. Epidemiologically, the burden of syphilis is significant, estimated that there are approximately 50 million cases worldwide, with increasing trends in incidence between 1990 and 2019. According to the World Health Organization, there are approximately 7.1 million cases in 2020. These cases mostly occurred in sub-Saharan Africa, Southeast Asia, Latin America, and the Caribbean. The high-risk populations include persons with limited access to health care, sex workers, and those who have had multiple sexual partners. The course of the disease is divided into primary, secondary, latent, and tertiary stages, each showing a diversity of symptoms, ranging only from painless genital ulcers in the primary stage to some serious systemic complications.[1–3]

Through the course of the disease syphilis often display symptoms that mimics other diseases, ranging from skin disorder, neurological abnormality, and even heart manifestation of the late-stage Syphilis.[2,4] Though it is rare, there are several cases where syphilis can also manifest with a broader range of symptoms and signs, like inflammatory bowel disease (IBD) and inflammatory spondyloarthropathies, as described in the following case. Several case reports have presented cases of gastrointestinal syphilis with the endoscopic findings consistent with chronic colitis, with the prevalence of intestinal syphilis in the United States ranges from 0.2 to 3.2%.[5–7] Syphilitic arthritis can resemble inflammatory joint diseases, including spondyloarthropathies. There are case reports documented syphilis presenting with symmetrical small joint pain, morning stiffness, and elevated inflammatory markers, closely mimicking rheumatoid arthritis.[8,9] However, comprehensive epidemiological data is necessary to estimate the incidence.

Enteropathic arthritis refers to immune-driven rheumatologic conditions linked to gastrointestinal pathology, typically denoting the inflammatory arthropathies associated with IBD like chronic colitis and reactive arthritis. Muco-cutaneous involvement; aphthous stomatitis, erythema nodosum and psoriasis, are also common extraintestinal manifestations of enterpathic arthritis, as well as joint and spinal involvement. Based on endoscopic evaluation in Cipto Mangunkusumo Hospital, Jakarta, Crohn's disease remains lower than ulcerative colitis which accounts for below 5% in the year 2000. There are diminutive recorded cases of enteropathic arthritis in Asia, especially Indonesia.[10,11]

Patients with syphilis often face social stigma, especially among religious population. Most of the time patients conceal the history of unprotected sex as the route of the infection, which leads to late diagnosis. Most of the time syphilis appears as skin or neurological manifestation, followed by hepatomegaly, lymphadenopathy, and weigh loss.[2,12] However, publications on the autoimmune manifestations of syphilis are limited. In this case presentation we aim to demonstrate a rare manifestation of syphilis mimicking autoimmune disease; colitis and enteropathic arthritis.

CASE

A 29 yo male was admitted to the Emergency Room due to acute diarrhea, nausea, and vomiting two days prior to the admission in July 2024. Upon the first admission, the patient conveyed that the diarrhea, nausea, and vomiting has come and gone over the past 3 months. The patient also complains of prolonged

multiple stomatitis, and weight loss. The patient has general weakness and mild to moderate dehydration. He complained of vomiting after every meal. The hematologic result revealed some abnormality; decreases in Hb (9.3 g/dL), WBC (5.89 x 10^3/µL), RBC (3.75 x 10^6/µL) and hematocrit (29.2%). The detailed WBC count revealed a decrease in lymphocyte but increases in neutrophil, signaling a possible bacterial infection as the probable cause of the diarrhea. The chest X-ray was requested but there was no abnormality identified. The patient was treated for the acute diarrhea with rehydration and spasmolytic, antacids and anti-emetic. The patient showed robust improvement in a couple days, and he was discharged after the third day of hospitalization.

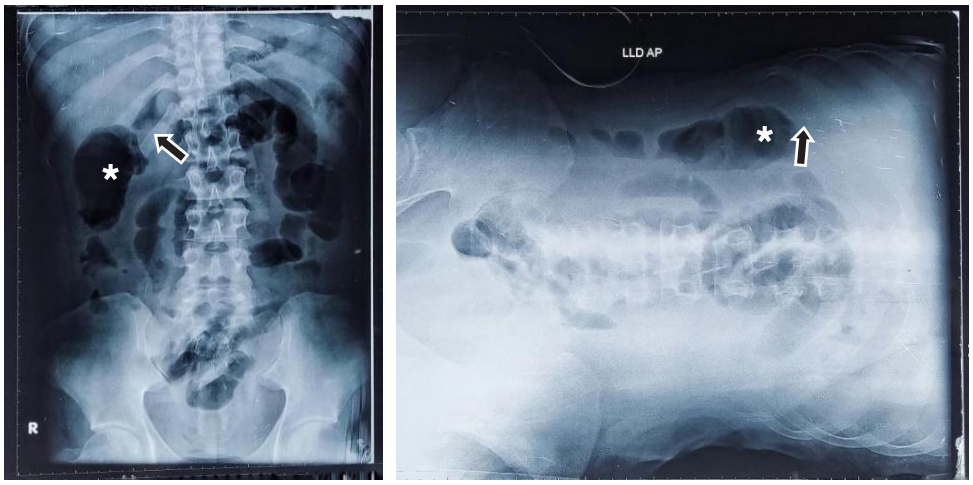
A month later, in early August 2024, the patient was admitted to the hospital for the second time with the same complaints of diarrhea, nausea and vomiting. The patient conveyed that the diarrhea was interspersed with constipation. The multiple stomatitis was still apparent. The patient reported that he had been anorexic since experiencing the prolonged gastric problem and the diet was dominated by rice porridge and soft textured food consumption. The patient was hospitalized for the second time for stabilization of his condition. However, both accompanying symptoms indicate a generally spread infection. The recurrent diarrhea and weight loss also amplified the possibility of a weakened immune response.

Hematologic findings were even more dramatic. The Hb has dropped to 7.5 g/dL, WBC has dropped to 3.66 x 10^3/µL, erythrocyte to 3.10 x 10^6/µL and hematocrit to 23.9%. Erythrocyte index revealed a microcytic hypochromic anemia which was consistent with the low intake of iron-rich nutritious food. There was still lymphocytopenia, accompanied by increase in neutrophil, suggesting a possible superinfection and an underlying disease as suspected before, immunodeficiency syndrome or immunosuppression condition. He received a bag of PRC for the anemia. He was also managed with spasmolytic, antacids, and anti-emetic for the diarrhea, nausea, and vomiting.

Recurrent diarrhea, nausea and vomiting, persistent mouth ulcer, weight loss and the abnormality in the lab result had brought suspicion of Infectious disease with manifestation of Immunodeficiency as one of the possible causes. The patient had counseling with the voluntary counseling and testing (VCT) clinic and was screened for his sexual behavior. The patient denied previous sexual activity as confirmed with his parents that he is an obedient son. However, the patient agreed for the human immunodeficiency virus (HIV) and hepatitis B infection test. The test; HIV rapid test and (hepatitis B surface antigen) HBsAg were conducted. While waiting for the result, the patient continued his supportive treatment in the ward. The patient was discharged as the emergency symptoms had been managed, and the patient showed robust improvement. The patient was scheduled for an appointment in the clinic for the counseling of his HIV and hepatitis B test, as well as, deciding further planning for his symptoms.

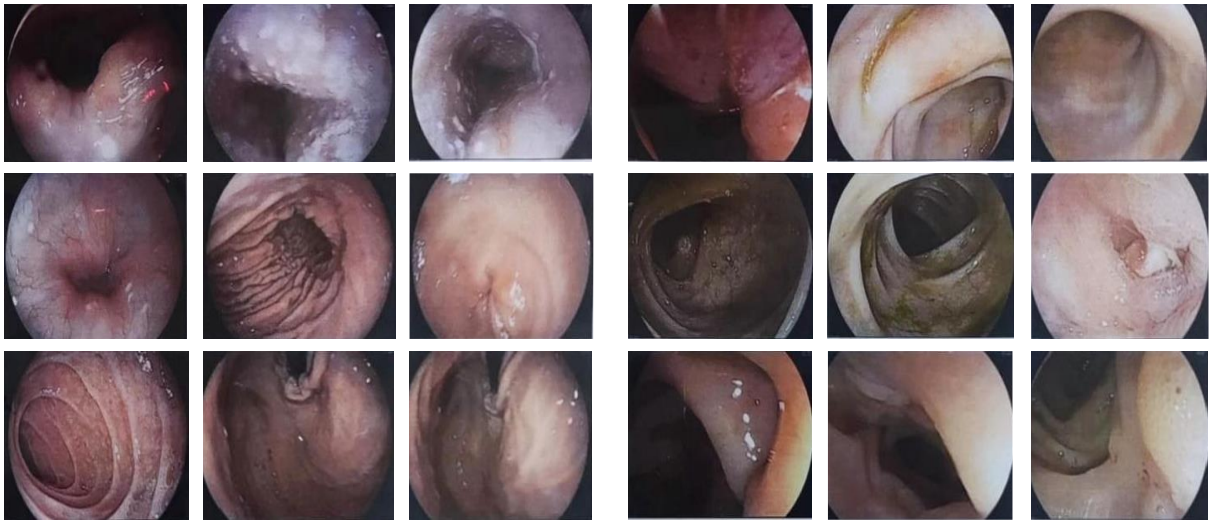
Both HIV and hepatitis B test results were negative, leaving the physician with other possible causes, IBD and neoplasm specifically in the gastrointestinal tract, which could possibly explain the recurrent diarrhea, weight loss, and abnormality of the hematologic components. The patient was scheduled for abdominal ultrasound followed by the abdominal X-ray. The Ultrasound was inconclusive, while the abdominal X-ray showed a narrowing around the colon (FIGURE 1.A and 1.B), caecum, and ileo-cecal junction which cause retention of gas and fecal material. This result was consistent with the diagnosis of intraluminal mass that may suggest neoplasm.

Gastro-duodenoscopy and colonoscopy followed by colon biopsy were scheduled for further investigation and to establish the diagnosis of colon cancer. The gastroduodenoscopy (FIGURE 2.A) identified whitish plaques in the pharynx and esophagus, with hyperemia in the distal segment of the esophagus. The gastroesophageal junction was patulous, with mucosal breaks of less than 5 mm. The gastric fundus and body were normal, while the antrum of the gaster exhibited patchy erythema. The duodenum also revealed whitish plaques. The overall diagnosis included dysphagia and dyspepsia syndrome and widespread gastro-duodenal candidiasis.



A B

FIGURE 1. Abdominal X-ray in Erect position (A) and left lateral decubitus (LLD) position; (B) revealed a narrowing of the lumen of ascending colon that does not change upon different positions (arrow). Gas and fecal material were partially obstructed (asterisk).



A B

FIGURE 2. The gastroduodenoscopy (A) identified whitish plaques in the pharynx and esophagus, with hyperemia in the distal segment of the esophagus, the duodenum also revealed whitish plaques. The colonoscopy (B) revealed signs of hyperemia, edema, patchy erythema in the rectum and erythematous and edematous change in the sigmoid colon.

The colonoscopy (FIGURE 2.B) revealed signs of hyperemia and edema of the rectum, accompanied by patchy erythema. Similar erythematous and edematous changes were observed in the sigmoid colon. The descending colon appeared pale, as did the transverse colon. The colonoscopy revealed internal hemorrhoids, and the intraluminal signs of hyperemia and edema of the rectum, accompanied by patchy erythema. Similar erythematous and edematous changes were observed in the sigmoid colon. Three specimens were collected from the rectosigmoid, ileum, and the intraluminal mass and were sent to the Pathology Anatomy Laboratory for analysis.

All biopsy revealed edematous lamina propria which contained infiltration of lymphocytes, histiocytes, and plasma cells, with lymphoid aggregates. The mass that causes the narrowing of the ascending colon and ileocecal junction revealed the same lymphoid aggregates, and basal plasmacytosis, but no malignancy or tumor. Chronic colitis and ileitis, consistent with IBD was established as the diagnosis based these finding.

Upon visit, the result of all the examinations was explained to the patient. However, the patient complained of a new symptom of back pain and spine rigidity that he mostly felt in the morning. The rigidity even gives him difficulty to roll to his side on the bed. In physical examination, there is restriction of lumbar spine flexion, and occiput to wall test also showed more than 2 cm distance which was caused by the rigidity. He was also still experiencing another episode of diarrhea, nausea, and vomiting. Due to the new symptoms of spinal involvement, the patient was diagnosed with enteropathic arthritis and was hospitalized both for the stabilization and management of enteropathic arthritis. The patient was rehydrated with isotonic fluids that contains amino acids, glucose, vitamin B-complex and electrolytes 1500 mL in 24 hr to support his improvement process. Spasmolytic was administered orally that is taken every time he passes loose stool, and 15 mL sucralfate thrice daily. The patient was prescribed celecoxib orally for pain management. Intravenous drugs included; 30 mg of lansoprazole, 10 mg of metoclopramide thrice daily. Antibiotic combination including 500 mg of sulfasalazine twice daily and 1000 mg of ceftriaxone twice daily to manage opportunistic infection and prophylaxis against nosocomial infection.

Upon the third time of hospitalization, the hematologic findings still showed anemia (Hb: 10.3 mg/dL) and leukopenia (3.56 x 10^6) with neutrophilia (75%). Kidney function test revealed an increase in serum creatinine (5.34 mg/dL), and urine test showed leukocyturia, occult hematuria, and proteinuria (+2 in the dipstick test). The result revealed new symptoms of kidney involvement. Based on this history and the diverse clinical presentation, another differential diagnosis was brought up. The patient's symptoms were indicative of an underlying condition known for its myriad and protean manifestations—the so-called the Great Imitator of syphilis.

A diagnostic workup was initiated, including serological tests for syphilis. The nonspecific screening test for syphilis, the venereal disease research laboratory (VDRL) test, was performed with a reactive result. Further confirmatory testing with the treponema pallidum hemagglutination assay (TPHA) was reactive and confirmed the diagnosis specifically due to syphilis. This diagnosis unifies the diverse range of symptoms that had previously evaded definite characterization.

Intramuscular benzathine penicillin G was administered as the patient's main therapy, 2.4 million units Intramuscularly every week for the next three weeks. The patient was monitored

closely for any signs of adverse effects. During his admission, supportive care significantly improved his condition. The patient could finally tolerate a solid oral intake, and episodes of diarrhea were no longer experienced. The serum creatinine had returned to normal limit. The following day after the first injection, the patient showed continuous improvement while no adverse reaction was identified. The patient was prepared for discharge. The treatment course entailed another benzathine penicillin G injections once a week for the consecutive two weeks, as guided by the standard regimen for the treatment of syphilis. The treatment continued in an outpatient basis. Patient was scheduled for his next injection in the clinic a week later.

A week after hospitalization, the patient visited the clinic for his next injection and medical evaluation. The patient reported he is no longer complaining of diarrhea, nausea, and vomiting. He still experiencing a mild spine and hip joint pain, but it is no longer constraint his daily activity. The patient continued the medication for the next week as being monitored closely, coordinating with family members for any adverse reaction and the improvement of his symptoms.

DISCUSSION

Syphilis is known as the Great Imitator because it may resemble a wide range of illnesses, making diagnosis difficult. *Treponema pallidum* can damage many organ systems and present with symptoms that mimic a variety of different illnesses. Primary syphilis may present with mucocutaneous manifestation known as chancre that appears on the mouth or genitals, that is not painful and sometimes goes unnoticed as it heals. The secondary stage of syphilis usually presents as a range of mucocutaneous lesions and generalized lymphadenopathy. Approximately, 15% of cases have a healing primary chancre. The skin rash characteristic of this stage includes macular, papular, papulosquamous, or pustular skin lesions, with multiple forms that could appear simultaneously. Up to 25% of patients with a appear to be unaware of their dermatologic manifestations.[2,13]

Less common complications of secondary syphilis include a variety of systemic symptoms and organ-specific involvements. Approximately 10% of patients may develop condylomata lata, a warts-like skin manifestation. Constitutional symptoms associated with secondary syphilis can include sore throat (15–30%), fever (5–8%), weight loss (2–20%), malaise (25%), and headache (10%). Additionally, less frequent manifestations include hepatic involvement, with up to 25% of patients exhibiting abnormal liver function tests, and renal involvement, often presenting as proteinuria associated with an acute nephrotic syndrome, which also shown in this patient.[1,2,13]

Mucous patches, occurring in 10–20% of patients, typically involve the oral or genital mucosa and present as painless silver-gray erosions with a red margin, which is also found in this patient. An oral lesion, like mouth ulcer, may be the first or the only sign of the infection and is usually not firstly considered as syphilis for confirming the diagnosis. Oral manifestations of syphilis may mimic many disease processes and be clinically unspecific.[2,3,13] The presence of persistent mouth ulcers, as seen in this patient, along with gastro-duodenitis, could be reflective of a mucosal immune response to the syphilis infection. Diagnosis of oral syphilis may also be aided by detailed analysis of sexual and/or social lifestyles of a patient and of any of the available sexual partners which was denied by the patient prior in the diagnostic process.

Gastrointestinal manifestations

of syphilis are uncommon but they do occur. A literature review and case series conducted by Ferzacca *et al.*,[14] identified 54 cases of lower gastro-intestinal syphilis (LGIS) in 39 articles published between 1958 and 2020. Among 44 cases (75%), histopathology revealed a chronic inflammatory infiltrate with a prominent lymphocyte component (45%) and/or plasma cells (36%).[14] These findings are consistent with our patient biopsy examination, where the intestinal mucous tissue reveals infiltrates of lymphocytes, histiocytes, and plasma cells. Ferzacca *et al.*,[14] also suggested an interesting finding regarding risk factors of having LGIS. The article described an almost exclusively observed LGIS in young adult male, and trans-woman who report for man have sex with man (MSM) behavior. These findings suggest the route of transmission could be a possible risk factor for LGIS manifestation.

There was also another record of syphilis misdiagnosis as IBD reported by Kabir *et al.*[15] Four cases of confirmed syphilitic colitis were identified among 63 cases of MSM who have IBD. There are also several case reports identifying lower GI tract syphilitic mass as the uncommon manifestation of syphilis, with most of the cases reported findings of the mass in the rectum or sigmoid area of the colon.[15–18] However, there are also several cases confirming syphilitic mass along the ileum or colon mimicking intraluminal malignancy and manifested as partial GI tract obstruction.[19] The manifestation also appeared in this case, as the obstruction also cause constipation problem that alternate the diarrhea.

Joint and bone involvement in syphilis is more uncommon as it associates more with congenital syphilis or tertiary syphilis instead of in primary or secondary infection in the adult population. *Treponema pallidum* spreads hematologically to the metaphyseal region (which has a rich blood supply) and enters medullary cavities of bones, inducing the inflammatory response by lymphocytes and plasma cells. Usually, if there is adequate defense, it will get healed with fibrosis. However, the persistence of bacteria destroys the tissue and causes necrosis resulting in arthritis and/or polyarthralgia. The most involved joints are bilateral knees, hips, shoulders, and proximal interphalangeal joints, and it presents as a subacute to chronic disease. Polyarthritis with synovitis is associated with tertiary syphilis. Synovitis is the primary reason for rheumatic features in syphilis and usually presents as migratory polyarthralgia.[20,21]

However, due to the symptomatology of the spondyloarthropathy happened in this patient that follows the pattern of the diarrhea episode, an immune mediated pathology of enteropathic arthritis is more probable rather than an infiltration of the microorganism in the bone or joint tissue which more likely to happen in the tertiary syphilis, a manifestation that appear after years of latent period. Recent study suggests a mechanism where intestinal inflammation leads to increased gut permeability, allowing antigenic material absorption, including microbial antigens.[20,22-24]

Dysbiosis in the gut microbiota activates resident dendritic cells and macrophages to produce IL-23. The absorbed antigens localize to musculoskeletal tissue and cause an inflammatory cascade leading to systemic translocation of immune complexes and innate lymphoid cells to synovium and entheses. This hypothesis is supported by studies demonstrating shared macrophages in the gut and synovium of patients with spondyloarthritis and increased affinity of innate lymphoid cells for specific synovial proteins, including mucosal vascular addressin cell adhesion molecule-1 (MAdCAM-1). IL-23 levels are higher in patients with IBD, especially when arthritis is present. [22,25-28]

This inflammatory process also activates IL-17 and stimulates the production of chemokines and cytokines, including TNF-α, resulting in a robust inflammatory response, including neutrophils and, to a lesser extent, monocytes in the target tissue. IL-17 secretion by Th17 cells, ILC3, and other cells results in immune-mediated inflammation. These inflammatory responses are associated with chronic inflammatory diseases such as spondyloarthritis, and psoriasis, manifestations that both showed in this case. Researchers have investigated changes in the gut microbiome in Crohn disease and ankylosing spondylitis. Patients with spondyloarthritis, including ankylosing spondylitis, without any gastrointestinal symptoms, often have subclinical gut inflammation, as observed on intestinal biopsies.[27–29]

Laboratory hematologic findings in syphilis can vary and often are non-specific. Most references confirmed neutrophilia which was also found in this patient. However, the microcytic hypochromic anemia was suspected due to multiple factors since there was no documented direct mechanism of anemia caused by Treponema. The patient's hemorrhoid added to the chronic colitis may cause subtle but chronic blood loss from the GI tract. Additionally, since the first episode of diarrhea, nausea, and vomiting, accompanied by recurrent mouth ulcer, the patient had had poor dietary intake. Several studies have also confirmed the relation of iron deficiency anemia and IBD.[30–33]

Based on CDC Syphilis guidelines, 2024 and Indonesian Health Ministry clinical guidelines for syphilis, there are several procedures for syphilis working diagnosis. There are non-specific and specific Treponemal test in diagnosing syphilis.[4,34] Non-specific test includes VDRL and rapid plasma reagin (RPR) which detect the presence of non-specific antibodies called reagin that is produced by the body when infected with *T. pallidum*. The non-specific test could not confirm the presence of active Treponemal in infection. Specific test including; TPHA, *T. pallidum* rapid (TP Rapid), *T. pallidum* particle agglutination assay (TP-PA), and *T. pallidum* particle agglutination assay (FTA-ABS) are required for confirmation of active disease.[34]

Syphilis affecting the kidneys is rare but does exist as manifestation of secondary syphilis with the prevalence ranging from 0.3% to 10% of patients diagnosed with secondary syphilis. The pathogenesis of glomerulonephritis in syphilis remains poorly understood. Several studies have found that the pathologic examination of renal tissue shows the presence of treponemal antigens and antibodies to *T. pallidum*. This provides evidence of immune complex-mediated lesions in syphilis.[35,36] Besides the laboratory findings, there were no visible symptoms of kidney function (pretibial edema or lung edema) shown in this patient. The patient creatinine level has returned to 3.12 mg/dL on the second day of hospitalization and proper rehydration.

Even when enteropathic arthritis has been established as the main diagnosis, other symptoms of detectable mass in the GI tract and the abnormality of kidney function test has led to another possibility that has not been ruled out in this case. After the diagnosis of syphilis has been established through VDRL followed by TPHA test, the patient was treated with 2.4 million units of benzathine penicillin G, administered intramuscularly as the gold standard of syphilis treatment. The patient was scheduled for a weekly appointment to continue his medication in three weeks, as well as monitoring the progress of improvement.

CONCLUSION

This case emphasizes the diagnostic challenges of syphilis, especially with

atypical symptomatology. The recurrent diarrhea, nausea and vomiting of the patient with persistent stomatitis, weight loss, and additional hematologic abnormalities, led to an extremely wide differential diagnosis, including infectious disease, neoplastic disorders, and immune mediated disorder of enteropathic arthritis.

The confirmation of syphilis by the reactive TPHA test reflects the importance of considering syphilis as a differential diagnosis in all patients with unexplained gastrointestinal accompanied with a wide range of systemic symptoms and when there is a suspicion of immunodeficiency or chronic inflammatory conditions. Because syphilis is known to manifest in heterogeneous ways, earning its nickname as the Great Imitator, it should be suspected even in cases where previous sexual activity is denied and the presentations may not apparently conform to the classic characteristics of this disease. The main point of early diagnosis in such a puzzling characteristic of syphilis is very significant in early medical management and prevention of further spreading of the disease.

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