Syphilis? An Unusual Cause of Surgical Emergency in a Human Immunodeficiency Virus-Infected Man

Rachel A. Bender Ignacio,[1,2] Lisa L. Koch,[3] Shireesha Dhanireddy,[1] B. Charmie Godornes,[1] Sheila A. Lukehart,[1,4] and Jeanne M. Marrazzo[1]

[1]Division of Allergy and Infectious Diseases, Department of Medicine, University of Washington, [2]Vaccine and Infectious Diseases Division, Fred Hutchinson Cancer Research Center, Division of Allergy and Infectious Diseases, [3]Department of Pathology, and [4]Department of Global Health, University of Washington, Seattle

We report on a human immunodeficiency virus-infected man undergoing urgent anorectal surgery, with multicentimeter fungating masses discovered inside the anus. Initial pathology was inconclusive. After the patient developed a disseminated rash postoperatively determined to be secondary syphilis, the anorectal pathology was reviewed and *Treponema pallidum* DNA was amplified by polymerase chain reaction from the mass.

Keywords. HIV; men who have sex with men; proctitis; syphilis; *Treponema pallidum*.

CASE

A 43-year-old man presented to his human immunodeficiency virus (HIV) primary care provider reporting 2 weeks of worsening rectal pain and red blood in the toilet bowl. Four days after his symptoms started, he was seen by another provider, who visualized external hemorrhoids and prescribed symptomatic treatment. Eleven days later, his rectal pain was so severe that he could not sit in a chair, and he had severe pain with coughing, as well as difficulty voiding urine. He noted milky-pink discharge per rectum, soft formed stools, and no further bleeding. He had received a new diagnosis of HIV 4 months prior, with initial CD4 T-cell count of 567 cells/mL and HIV-1 viral load of 59 000 copies/mL. Other than experiencing symptoms consistent with acute retroviral syndrome approximately 2 years prior, he had no other medical concerns except essential hypertension. He smoked and drank moderately. He reported being sexually active with a single male partner for the last 2 years with last condomless receptive anal intercourse 2 weeks prior. Two months previously, a syphilis immunoglobulin (Ig)G enzyme immunoassay (EIA) test was negative, as were serologic tests for hepatitis A, B, and C. Current medications included amlodipine and Stribild (elvitegravir/cobicistat/emtricitabine/tenofovir), the latter begun 5 weeks previously. On exam, he was afebrile but appeared highly uncomfortable. His abdominal exam was normal and there was no inguinal lymphadenopathy. External rectal exam revealed erythema and induration in an area of 3 × 4 cm from the anal verge onto the right buttock, an external hemorrhoid, and a possible fissure. Rectal exam and anoscopy could not be performed due to pain. Laboratory investigations included normal complete blood count and liver function tests. Plasma HIV-1 viral load was 67 copies/mL. A rectal swab for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* was negative by nucleic acid amplification.

The patient was evaluated urgently by a surgeon and underwent anoscopy and proctoscopy under anesthesia the following morning. The patient received 2 grams of intravenous cefotetan as preoperative prophylaxis. Numerous small flat warty appearing anal lesions, described intraoperatively as "anal condylomata", were noted and fulgurated. Two exophytic masses were seen at 1 o'clock and 5 o'clock and extending from the anal verge to the dentate line, with the patient in prone jackknife position. These were described as "destructive fungating masses with inflammation and granulation tissue" but not grossly invading the muscle. There was no evidence of purulence, ulceration, fistula, or sinus tract, and the resection sites bled heavily. The masses were sent for fresh frozen section out of concern for malignancy. The initial pathology interpretation noted "benign squamous epithelium overlying granulation tissue with marked neutrophilic inflammation." No organisms were present on hematoxylin and eosin stain to suggest concomitant bacterial infection.

The patient was discharged uneventfully with a course of oral ciprofloxacin and metronidazole. Ten days postoperatively, he was seen in HIV clinic with a pruritic erythematous and pustular rash, limited to the trunk and upper thighs, which had begun on postoperative day 7. A diagnosis of probable drug eruption was made, and antibiotics were discontinued. However, the rash persisted for 4 weeks, and the patient again

Received 2 February 2015; accepted 18 June 2015.

Correspondence: Rachel A. Bender Ignacio, MD MPH, Mailstop M1B-140, Program in Global Oncology, VIDD, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave N, Seattle, WA 98109 (rbi13@uw.edu).

Open Forum Infectious Diseases

DOI: 10.1093/ofid/ofv094

presented to clinic. Examination revealed blanching erythema on face and upper chest, along with follicular-based pustules and scaling erythema in various stages of healing. Palms, soles, and mucosa were not involved. Syphilis serologic testing was repeated: CAPTIA *Treponema pallidum* IgG EIA was indeterminate, the rapid plasma reagin (RPR) was 1:1, and the *T pallidum*-particle agglutination assay was positive. The rash resolved immediately after 1 dose of 2.4 million units of benzathine penicillin G administered intramuscularly in the buttocks. He then reported that his sex partner had had new interval sexual partners prior to his initial presentation for rectal pain. A colonoscopy was subsequently performed and showed full resolution of disease in the previously involved anal canal and was otherwise normal.

The pathology of the anal mass was reviewed. Epithelial hyperplasia, vascular proliferation, swollen endothelial cells, and dense inflammation with abundant plasma cells were noted. A Warthin-Starry stain was performed, which highlighted rare putative organisms. There was no evidence of verrucous epithelial hyperplasia, hyperkeratosis, parakeratosis, or koilocytic changes consistent with human papillomavirus (HPV) infection (Figure 1). The specimen was sent to a treponemal research laboratory S. A. Lukehart, where 3 sections of the paraffin-embedded tissue were dewaxed using the alternative protocol for deparaffinizing FFPE tissue described by Coura et al [1]. DNA was subsequently extracted, polymerase chain reaction (PCR) for the Tp47 gene of *T pallidum* was performed using primers as previously described, and the identity of amplification products (~310 base pairs) was confirmed by Southern hybridization [2].

DISCUSSION

Several presentations of syphilis in the distal gastrointestinal tract have been described, including ulcerative proctocolitis, granulomata, and gumma. Neoplastic-like presentations have been rarely reported, and generally they are described as firm ulcerated masses [3–7]. Like the clinical manifestations of syphilis, the histologic features of these lesions are varied and nonspecific. All syphilitic lesions can display a characteristic but nonspecific vasculitis comprising endothelial cell proliferation and swelling, vascular lymphocytic cuffing and thickening, and fibrosis of vessel walls. Primary and secondary syphilitic lesions may additionally be characterized by dense plasmacytic inflammation, although this finding is also nonspecific, especially at mucosal sites where plasma cells are naturally abundant. Silver or Warthin-Starry stains for spirochetes can detect organisms in the epidermis and the blood vessel walls, but they have poor sensitivity and specificity, and therefore they have limited clinical utility, as highlighted by the equivocal stain in this case. Immunohistochemistry is more sensitive, but it is still negative in 30% of confirmed cases [8]. *Treponema pallidum* PCR is not readily available in most laboratories, but it is highly sensitive and specific when used on fresh specimens, and it has been used successfully in paraffin-embedded specimens.

In this case, the presence of *T pallidum* by PCR amplification of the tissue confirms the diagnosis of active syphilis infection, but it cannot unequivocally confirm that these masses were syphilitic. Because the patient likely had systemic dissemination of his infection when the anal lesions were resected, as evidenced by his subsequent secondary syphilis rash, systemically circulating treponemes may have been present in the anal mucosa by virtue of the high treponeme burden that characterizes early disease. Although an HPV-associated lesion may enter the clinical differential diagnosis, the histologic features of HPV, including verrucous epithelial hyperplasia, hyperkeratosis, parakeratosis, and koilocytic change, were not present in the resected lesion. Overall, in the presence of a nearly concurrent manifestation of secondary syphilis, and in the absence of inflammatory bowel disease or neoplasia, syphilis remains the most likely etiology of these mass lesions, especially if the concomitant presumed "condylomata" noted in the anus were actually condylomata lata.

The unusually low quantitative RPR titer and borderline screening serology may have been due to partial treatment from cefotetan received intraoperatively. Although cefotetan has never been studied in syphilis, another cephamycin, cefmetazole, has good efficacy against *T pallidum*, and ceftriaxone is recommended as alternative therapy for neurosyphilis [9, 10]. In addition, at the time the serologic testing was performed, approximately 1 month had elapsed from the initial secondary syphilis presentation, during which time antibody titers may have waned.

Syphilis infrequently presents as a surgical emergency for aortic aneurysm or central nervous system mass. A small case series of primary anorectal syphilis leading to surgical resection was published in the 1970s, and the lack of presurgical evaluation in these cases also led to inappropriate resection of these lesions [11]. Our case reminds us of the need to maintain a high index of suspicion for syphilis as a cause of anorectal emergency, especially in HIV-infected men who have sex with men, in whom the syphilis epidemic is reaching historic levels in the United States [12]. At-risk patients with symptoms of proctitis should have serologic testing for syphilis and a visual exam performed; other sexually transmitted causes of inflammatory gastrointestinal processes, such as lymphogranuloma venereum, should also be considered. Ideally, resection of syphilitic masses should be avoided, because they resolve easily with antibiotic therapy [11]; however, in this case, the extreme presentation precluded a nonsurgical approach. If there is a high index of clinical suspicion for syphilis, the diagnosis may be expedited by communication among referring clinicians, endoscopist or surgeon, and pathologist, because special stains or molecular testing may be performed to confirm the diagnosis.

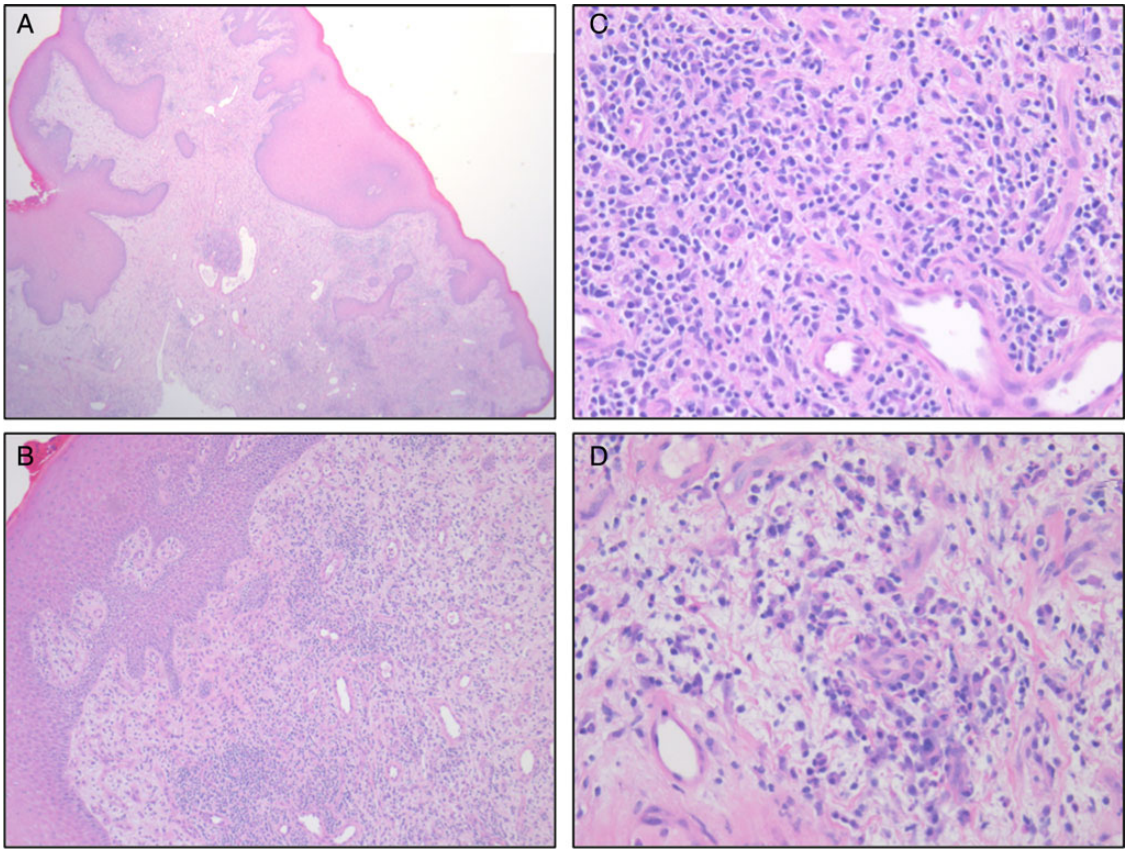

Figure 1. Histology slides of a fungating mass consistent with a rarely encountered presentation of *Treponema pallidum* infection in the anus. (A) A hematoxylin and eosin (H&E)-stained section shows a polypoid lesion composed of hyperplastic squamous epithelium overlying inflamed stroma (20×). (B) Higher power demonstrates a proliferation of blood vessels and dense inflammation (H&E stain, magnification ×100). (C and D) Swollen endothelial cells and thickened vessel walls are characteristic of, but not specific for, syphilis. The surrounding inflammation has a prominent plasma cell component (H&E stain, magnification ×400).

Acknowledgments

We thank Dr. Saman Arbabi for surgical expertise.

Financial support. This work was supported by the National Institutes of Health (grant T32-CA080416; to R. A. B. I.).

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

References

1. Coura R, Prolla JC, Meurer L, Ashton-Prolla P. An alternative protocol for DNA extraction from formalin fixed and paraffin wax embedded tissue. J Clin Pathol **2005**; 58:894–5.
2. Centurion-Lara A, Castro C, Shaffer JM, et al. Detection of *Treponema pallidum* by a sensitive reverse transcriptase PCR. J Clin Microbiol **1997**; 35:1348–52.
3. Drusin LM, Singer C, Valenti AJ, Armstrong D. Infectious syphilis mimicking neoplastic disease. Arch Intern Med **1977**; 137:156–60.
4. Cha JM, Choi SI, Lee JI. Rectal syphilis mimicking rectal cancer. Yonsei Med J **2010**; 51:276–8.
5. Voinchet O, Guivarc'h M. [Syphilis of the rectum mimicking neoplastic disease (author's transl)]. Gastroenterol Clin Biol **1980**; 4:134–6.
6. Zhao WT, Liu J, Li YY. Syphilitic proctitis mimicking rectal cancer: a case report. World J Gastrointest Pathophysiol **2010**; 1:112–4.
7. Quinn TC, Lukehart SA, Goodell S, et al. Rectal mass caused by *Treponema pallidum*: confirmation by immunofluorescent staining. Gastroenterology **1982**; 82:135–9.
8. Hoang MP, High WA, Molberg KH. Secondary syphilis: a histologic and immunohistochemical evaluation. J Cutan Pathol **2004**; 31: 595–9.
9. Baker-Zander SA, Lukehart SA. Efficacy of cefmetazole in the treatment of active syphilis in the rabbit model. Antimicrob Agents Chemother **1989**; 33:1465–9.
10. Workowski KA, Berman S; Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2010. MMWR Morb Mortal Wkly Rep **2010**; 59(RR-12):1–110.
11. Drusin LM, Homan WP, Dineen P. The role of surgery in primary syphilis of the anus. Ann Surg **1976**; 184:65.
12. Patton ME, Su JR, Nelson R, Weinstock H. Primary and secondary syphilis—United States, 2005–2013. **2014**; 63:402–6.