Syphilis Masquerading As Mass Lesions: The Utility of Modern-Day Imaging and Molecular Sequencing in Clinical Diagnosis

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Abstract: Syphilis has been known to present in a myriad of symptoms throughout the ages, and until this day, the diagnosis remains elusive to the modern physician. We present 2 unusual cases of syphilis that posed diagnostic challenges even in the current era of new and advancing diagnostic tests.

CASE REPORT 1

A 31-year-old man presented with rectal bleeding, perianal pain, constipation, and tenesmus over 2 weeks. He did not experience abdominal pain, distension, vomiting, diarrhea, or significant weight loss.

He worked at a local bank and lived alone. He had sex with men, and his last sexual encounter was 2 months ago, with a casual male partner. He had a smoking history of 5 pack years and consumed alcohol occasionally.

He had been diagnosed with human immunodeficiency virus (HIV) infection 10 months earlier and has been on antiretroviral therapy with tenofovir, emtricitabine, and efavirenz. His CD4 count 2 weeks ago was 440 cells/μL (32%), and the HIV viral load was 37 copies/mm³. His latest syphilis serological tests, performed 8 months ago, were nonreactive for the venereal disease research laboratory test and the Treponema pallidum particle agglutination assay.

On examination, he had a temperature of 39.5°C. His blood pressure was 106/56 mm Hg, and his pulse rate was 95 bpm. Respiratory and cardiovascular examinations were unremarkable. The abdomen was nondistended and nontender, and no abdominal masses were palpable. However, multiple tender, enlarged inguinal lymph nodes were felt. Digital rectal examination revealed a tender irregular mass at the anal verge with contact bleeding.

Investigations showed anemia with a hemoglobin concentration of 12.6 g/dL and leukocytosis of 10,400/mm³. Serum creatinine, liver function tests, and coagulation profile were unremarkable. The serum carcinoembryonic antigen level was not elevated. However, the C-reactive protein level was raised at 176.3 mg/L (normal range, 0–5.0 mg/L).

Magnetic resonance imaging (MRI) of the rectum showed thickening of the rectal mucosa and enlarged mesorectal lymph nodes (Fig. 1A), suggestive of a rectal tumor with extensive lymphadenopathy. No abscesses or fluid collections were seen. Colonoscopy revealed a polypoidal tumor at the anorectal junction (Fig. 1B), which was biopsied. The rest of the colon was unremarkable. Computed tomographic (CT) scans of the thorax, abdomen, and pelvis did not reveal distant metastases.

Histological examination was negative for dysplastic cells or malignancy. Instead, there was extensive necrotizing granulomatous inflammation. Grocott methenamine silver and periodic acid-Schiff stains were negative for fungal organisms. Ziehl-Neelsen stains for acid-fast bacilli (AFB) and immunohistochemical stains for cytomegalovirus were negative.

Rectal swabs for Chlamydia trachomatis and Neisseria gonorrhoeae polymerase chain reaction (PCR) were performed but returned negative. The rapid plasma reagin titer was 1:128, and the syphilis IgG enzyme-linked immunosorbent assay test was positive.

Because the diagnosis was uncertain, he underwent flexible sigmoidoscopy and repeat biopsy. Once again, no evidence of dysplasia or malignancy was found on histology. Instead, there was a moderately dense lymphoplasmacytic infiltrate in the lamina propria with cryptitis and crypt abscesses. Warthin-Starry stains were negative.

Cytomegalovirus cultures, Mycobacterium tuberculosis PCR, smears, and cultures for AFB and fungi from the repeat biopsy were all negative. Given the suspicion of anorectal syphilis, 16S ribosomal RNA (rRNA) bacterial sequencing was attempted from the biopsy specimen. However, no dominant amplicon was obtained.

The diagnosis at this point was that of secondary syphilis with rectal involvement. However, in view of the severity and extentiveness of the lesion, treatment with intramuscular benzathine penicillin, at a dosage of 2.4 MU weekly for a total of 3 doses, was initiated. Three weeks after completion of therapy, patient reported complete resolution of symptoms, and follow-up CT scan revealed marked improvement in the rectal wall thickening and resolution of the extensive lymphadenopathy.

CASE REPORT 2

A 64-year-old man presented with progressive bilateral lower limb weakness, recurrent falls, and urinary incontinence over 4 weeks. He denied experiencing fever, back pain, or radicular pain in his lower limbs. He did not recall any episodes of oral, genital, or perianal ulcers or rash in the recent or distant past.

He was a retired administrator. He had sex with men and reported that he had not been sexually active in the preceding 2 years. He had no history of any sexually transmitted diseases, nor had he been previously tested or treated for syphilis or HIV. He did not smoke, consume alcohol, or use illicit drugs.

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On examination, he was afebrile with normal vital signs. Cardiovascular, respiratory, and abdominal examinations were unremarkable. The spine was not tender. Anal tone was lax, but saddle sensation was present. Lower limb examination revealed asymmetrical weakness with mixed upper and lower motor neuron signs. Power was 1/5 proximally and 2/5 distally in both limbs. Sensation over bilateral L5 and S1 dermatomes was lost. Tone was increased in both lower limbs with flexor plantar responses. Neurological examination of the cranial nerves and upper limbs was normal.

He had pancytopenia with a platelet count of 18,000/mm$^3$. Serum creatinine, liver function tests, and coagulation profile were normal. Magnetic resonance imaging of the spine revealed a 4.3 × 3.4 × 6.6 cm mass at T9, centered over the right pedicle and transverse process of the T9 vertebra, extending into the epidural space, causing spinal canal narrowing and cord compression, consistent with a tumor (Fig. 2). His HIV test was positive. The CD4 count was 47 (10%), and the HIV viral load was 139,400 copies/mL. Syphilis IgG was positive, and rapid plasma reagin was 1:32. He was not diagnosed with or treated for syphilis previously. Our clinical suspicion was that of a lymphoma, but surgical intervention and lumbar puncture were deferred because of severe thrombocytopenia. Tenofovir, lamivudine, and raltegravir were started for HIV infection. Bone marrow examination revealed no malignant features. Intravenous immunoglobulin was subsequently started for immune-mediated thrombocytopenia with good response.

The CT-guided core needle biopsy was performed once platelet counts improved. Bacterial Gram stain and culture, as well as smears and cultures for AFB and fungi, were negative. Histology showed fibrous tissue containing an abundant mixed inflammatory infiltrate. No well-formed granulomas or evidence of malignancy was seen.

Given the neurological deficit and unclear diagnosis, he underwent T8 through T10 posterior decompression with tumor resection. Intraoperatively, grayish soft tissue was seen on the surface of the right lamina of T9. Again, microbiological investigations of the resected tumor were unrevealing. Histology revealed fibro-adipose tissue and large nerve fibers with chronic inflammation, consisting predominantly of a lymphoplasmacytic infiltrate. No sheets of large lymphoid cells or well-formed granulomata were seen. There was no evidence of malignancy.

16S rRNA bacterial sequencing was performed on the resected tumor. An amplicon of 800 base pairs was generated using published primers. Nucleotide sequencing of both strands of the amplicon was performed using an ABI 3730XL DNA. The sequenced product was 100% identical to the 16S rRNA of T. pallidum in a region of 783 determined base pair positions. Warthin-Starry stains performed on the specimen were negative.

The patient was initially treated with intravenous penicillin 3 million units every 4 hours for 14 days for presumptive neurosyphilis, given the high pretest probability and inability to perform a lumbar puncture because of severe thrombocytopenia. This was followed by 3 weekly dosages of 2.4 million units of intramuscular benzathine penicillin because of uncertainty in the clinical stage of syphilis.

At the outpatient review 14 weeks after treatment, he had regained urinary continence with improvement in his lower limb power to 4/5 both proximally and distally in both limbs and could perform basic activities of daily living independently.

DISCUSSION

The resurgence of syphilis in the wake of the HIV epidemic has yielded several interesting observations in coinfected patients. Atypical and aggressive presentations of syphilis may occur more frequently in coinfected patients. In HIV-infected individuals, primary syphilis may present more frequently with multiple chancreles, and approximately one fourth of patients may present with
concomitant lesions of both primary and secondary syphilis at the time of diagnosis.3,4

The presentations of syphilis in our patients are also atypical. Gummas of the bone typically present radiologically as areas of bone lysis with surrounding dense sclerotic reaction.5 In contrast, our second patient presented with an invasive mass-like lesion of the vertebrae, adding complexity to the staging of syphilis in this patient. Most of the anorectal involvements in secondary syphilis present as condyloma lata or proctitis. Only rarely do they present as mass lesions as in the case of our first patient.6 However, these atypical presentations represent a minority of cases in coinfected patients, with most presenting similarly to non–HIV-infected individuals.7 Furthermore, similar atypical presentations of syphilis have been documented before the HIV epidemic.8

In the age of modern imaging modalities using MRI and positron emission tomography, increasing reports of unexpected manifestations of syphilis have been emerging. Cases of adrenal gummas, intramedullary spinal cord gummas, and rare manifestations of secondary syphilis with pulmonary nodules and osteitis have been incidentally found on such imaging modalities in both HIV-infected and uninfected patients, some of whom were completely asymptomatic.9–12

Whether these atypical clinical presentations truly occurred with increased frequency in the coinfected patient or are merely a product of improved diagnostics would require further systemic studies to ascertain.

Gummas are a result of a granulomatous inflammatory response to the T. pallidum spirochetes with consequent tissue destruction and fibrosis. These lesions are noninfectious, and spirochetes are only rarely seen on histological examination even with appropriate silver stains.13 This finding is mirrored in case report 2, where Warthin-Starry stain on biopsy specimens failed to reveal conclusive evidence of syphilitic infection. In such situations, the role of molecular diagnostic methods such as 16S rRNA bacterial sequencing or T. pallidum specific PCR tests could play a pivotal role in establishing a diagnosis.

There are limitations to molecular tests, particularly in the setting of samples from nonsterile sites. In such scenarios, a high index of suspicion supported by compatible serology may be the only clue to the diagnosis. However, unusual serological responses such as false negativity and delayed seroreactivity have been observed in coinfected individuals, further adding to the diagnostic conundrum.2

REFERENCES