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NOVEL ID CASES

Meningovascular Syphilis Presenting as a Brain Mass in an Immunocompetent Male

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We present a case of a human immunodeficiency virus–negative man with syphilitic meningovascular disease with subjacent involvement of brain parenchyma leading to a mass-forming inflammatory lesion that was pathologically distinct from a typical gumma. Syphilis was diagnosed after tissue obtained from a brain biopsy demonstrated spirochetes consistent with *Treponema pallidum* and confirmed by 16S ribosomal RNA sequencing.

Keywords. incipient gumma; meningovascular syphilis; PCR.

The mass-forming granulomatous and necrotic lesions known as syphilitic gummas are typically a manifestation of tertiary syphilis [1]. Gummas commonly manifest as cutaneous lesions but can form in various organs including the brain. Acute manifestations of neurosyphilis include meningovascular disease and obliterative endarteritis of central nervous system (CNS) vessels leading to stroke-like presentations, while late presentations manifest as brain and spinal cord parenchymatous disease, during which destruction of nerve cells leads to clinicopathological syndromes referred to as general paresis or tabes dorsalis [1].

In this case, we present a lesion in an immunocompetent man that we hypothesize represents syphilitic meningovascular disease that subsequently involved the subjacent brain parenchyma leading to a mass-forming inflammatory lesion and initially mimicking a malignancy. With malignancy ruled out, this lesion was found to be similar to incipient formation of a gumma, but ultimately exhibited distinct pathologic characteristics from a typical gumma.

CASE REPORT

A 25-year-old man who has sex with men, without significant medical history, was transferred to our hospital for further evaluation after his third episode of dizziness and syncope over a 2-week period that was associated with abnormal CNS imaging. Prior to his first episode of syncope, he reported a frontal headache lasting 2 days that self-resolved. Each episode of dizziness was described as a loss of depth perception and proprioception culminating in syncope. After regaining consciousness, the patient reported an immediate return to baseline mental status. He denied concomitant fevers, chills, cough, dyspnea, abdominal pain, nausea, vomiting, or diarrhea.

Of note, he reported a small slowly healing neck ulceration that he attributed to an insect bite sustained during a hike in upstate New York approximately 3 months prior to his first episode of syncope. At the time of the ulcer, he was seen by his internist and received 2 weeks of empiric treatment with oral doxycycline and clindamycin with subsequent resolution of the ulcer. He additionally reported a history of unprotected sexual activity with a new male partner 3 months prior to the onset of syncope and received a sexually transmitted illness screen subsequently at a local clinic. The screening tests only included a point-of-care human immunodeficiency virus (HIV) test and urine gonorrhea and chlamydia nucleic acid amplification tests, which were negative. He was unaware of previous syphilis screening; however, collateral information from the New York City Department of Health and Mental Hygiene revealed that the patient had prior negative treponemal and nontreponemal syphilis tests 2 years prior to this presentation.

On arrival to our hospital, the patient's vital signs were normal: temperature of 36.6°C (97.9°F), blood pressure of 116/71 mm Hg, pulse rate of 61 beats per minute, respiration rate of 16 breaths per minute, and an oxygen saturation of 98% on room air. On physical examination, he was well-appearing and in no acute distress. Neurologic examination at presentation was intact. There was also a demarcated, hypopigmented patch of approximately 2 × 2 cm on his right neck that was nontender. His genital examination was normal. There were no lymphadenopathy or other skin lesions.

Initial investigative studies included a complete blood count, basic metabolic panel, and liver function tests, all of which were within normal limits. Magnetic resonance imaging (MRI) of the brain revealed a well-circumscribed, cortically based mass measuring 4.0 × 3.1 × 2.5 cm within the right posterior temporo-occipital lobe that was centrally and heterogeneously

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T2 hyperintense and T1 hypointense (Figure 1). When compared to another MRI done at an outside hospital within the prior week, it appeared that the mass had increased in size, concerning for a neoplasm.

Given this concern for malignancy, the patient underwent a right craniotomy to remove the mass. Pathology from the excised tissue demonstrated a highly cellular, atypical, mixed lymphoplasmacytic infiltrate involving the leptomeninges and leptomeningeal vasculature with extension into the neocortical brain parenchyma and without prominent necrosis or prominent granuloma formation (Figure 2A–C). Immunohistochemical staining demonstrated many spirochetes, consistent with *Treponema pallidum* (Figure 2D).

A serum rapid plasma reagin (RPR) test sent after surgery was positive with a titer of 1:4, which was confirmed with a positive *T pallidum* particle agglutination test. A fourth-generation HIV antigen/antibody test was negative. Blood cultures demonstrated no growth after 5 days. Cerebrospinal fluid (CSF) from a lumbar puncture was notably unremarkable with a CSF white blood cell count of 0–1 total nucleated cells/μL, glucose of 73 mg/dL, and protein of 23 mg/dL. The CSF BioFire Film Array multiplex polymerase chain reaction (PCR) assay, which does not detect *T pallidum*, was negative for meningoencephalitic pathogens. CSF cultures did not demonstrate growth. The CSF Venereal Disease Research Laboratory (VDRL) and fluorescent treponemal antibody absorption (FTA-ABS) tests were also negative.

To support the findings on immunohistochemical staining, formalin-fixed, paraffin-embedded tissue was sent to the University of Washington for broad-range bacterial PCR (16S ribosomal RNA [rRNA] gene amplification followed by Sanger sequencing), which detected *T pallidum* DNA and confirmed the pathologic findings.

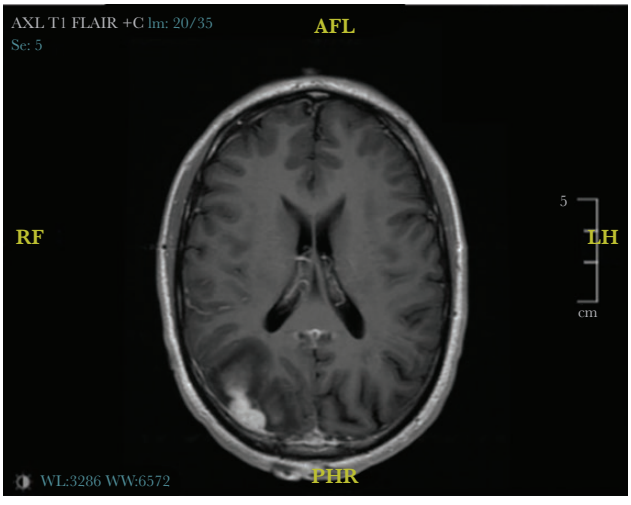

Figure 1. Preoperative brain magnetic resonance imaging. Preoperative axial T1 sequence with contrast. Abbreviations: AXL, axial; AFL, anterior/foot/left; FLAIR +C, fluid-attenuated inversion recovery with contrast; LH, left/head; PHR, posterior/head/right; RF, right/foot.

The patient was diagnosed with syphilitic meningovascular disease that was thought to be early to late neurosyphilis occurring in the secondary stage of infection. He was treated with intravenous penicillin G at a dose of 24 million units daily for 14 days, followed by an additional dose of intramuscular benzathine penicillin G of 2.4 million units. He experienced complete resolution of his presenting symptoms. At 1- and 2-month outpatient follow-up visits, he reported no recurrence of symptoms. A 6-month follow-up MRI showed resolution of the mass lesion (Figure 3).

DISCUSSION

It should be noted that classic examples of gummas differ from the case here in that gummas are typically characterized by a large necrotic core rimmed with multinucleated cells and generally do not demonstrate a high spirochete density [2]. Histological assessment of our patient's brain tissue did not demonstrate these features, leading us to conclude that the patient's brain mass was not a gumma, but rather a mass-forming lesion that was similar to a gumma or incipient formation of one. Given his young age and previous negative syphilis tests 2 years prior to presentation, tertiary syphilis was also unlikely. His initial neck ulceration may have represented a primary syphilis chancre, secondary syphilis rash, or other process. With antitreponemal activity, the empiric doxycycline course given prior to his presentation would have provided some treatment for early syphilis manifestations and may have affected his RPR titer, but would have likely been inadequate for neurosyphilis, if present at the time.

Since the advent of penicillin treatment of syphilis in the early 1940s [3], syphilitic mass-forming lesions, such as cerebral gummas, have become increasingly rare [2], with Fargen and colleagues reporting 156 individual cases in 111 publications in a 2009 literature review. Due to the scarcity of cases and provider inexperience with this entity, the spectrum of CNS involvement by syphilitic lesions may pose a diagnostic challenge for physicians; syphilitic mass-forming lesions on radiographic imaging can mimic malignant primary or metastatic tumors [2, 4–20]. Of the 25 rare cases of cerebral gummas or syphilitic mass-forming lesions to be reported in the last 10 years to our knowledge, ours is the first to report confirmation of syphilitic meningovascular disease that is associated with a mass-forming lesion through a combination of positive serum tests, pathologic findings, and 16S rRNA sequencing for *T pallidum* (Table 1) [4–26]. While 24% of cases in the literature did not report CSF syphilis testing, the majority utilized traditional treponemal or nontreponemal testing, or a modified version of these tests such as the toluidine red unheated serum test [15, 26]. PCR testing was used rarely, in <10% of cases, and ours was the only case to use 16S rRNA sequencing.

Our case was also unusual as historically, case reports of syphilis that were complicated by mass-forming lesions

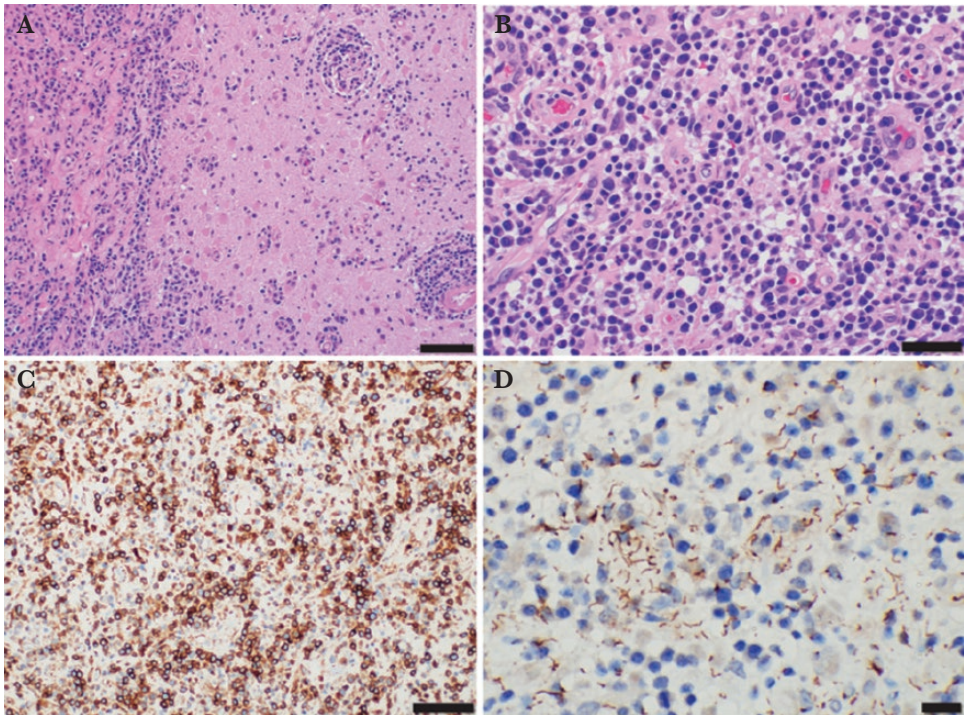

Figure 2. Pathology of tissue obtained from craniotomy. *A*, Hematoxylin and eosin staining demonstrates a mixed lymphoplasmacytic infiltrate involving the leptomeninges and Virchow-Robin spaces. Scale bar: 100 µm. *B*, Diffuse parenchymal involvement and effacement of the underlying cerebral cortical architecture. Scale bar: 50 µm. *C*, Immunohistochemical staining for CD138 highlights the extensive plasma cell involvement typical of syphilitic inflammatory lesions. Scale bar: 100 µm. *D*, Immunohistochemical staining against treponemal antigen shows numerous corkscrew-shaped organisms. Scale bar: 20 µm.

typically involved patients who were HIV positive [4–6, 21]; our patient did not have HIV or any other known immunodeficiency. In the clinical setting, physicians may also be more likely to suspect a mass-forming lesion to be a consequence of syphilis in HIV-infected individuals rather than those without HIV. Interestingly, however, of the recent cases reviewed, only 16% involved patients who were found to be HIV positive, perhaps underscoring why this diagnosis is still often initially overlooked in HIV-negative individuals. Almost two-thirds of patients underwent either surgery or a biopsy to conclusively make the diagnosis of neurosyphilis.

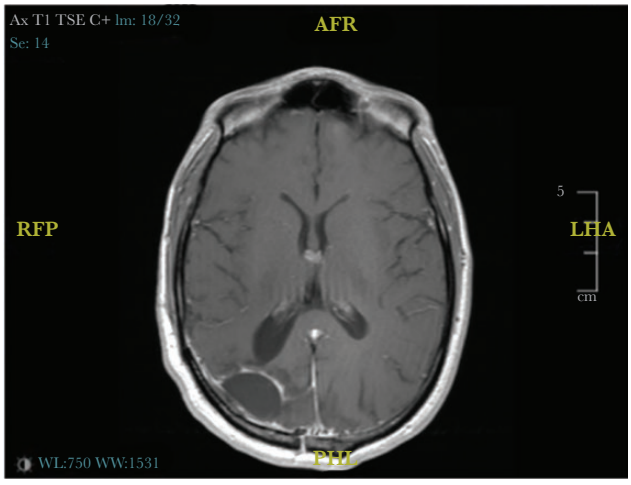

Figure 3. Postoperative brain magnetic resonance imaging. Postoperative (6-month follow-up) axial T1 sequence with contrast. Abbreviations: Ax, axial; AFR, anterior/foot/right; LHA, left/head/anterior; PHL, posterior/head/left; RFP, right/foot/posterior; TSE, turbo spin echo.

Our case underscores the challenge of diagnosing syphilitic involvement of the CNS compartment, particularly when presenting as a mass-forming lesion similar to a gumma. Successful diagnosis of this entity often relies on serologic and CSF studies, as well as radiographic findings and pathologic analysis of body tissue. As noted in our patient, however, the CSF VDRL and FTA-ABS can be negative in syphilitic manifestations with CNS mass or gumma formation in 38%–40% of cases [2]. Negative CSF syphilis tests have also been reported in other cases [5, 6, 24]. Acute neurosyphilis typically presents clinically as symptomatic meningitis, with more CSF findings such as pleocytosis, elevated protein, decreased glucose, and positive VDRL, whereas cases of late neurosyphilis may not have these CSF findings [1–3]. Given meningovascular disease seen on pathology and an unremarkable CSF profile, our patient's disease process may have been transitioning from early to late neurosyphilis. Diagnosis, therefore, often requires a high index of suspicion, and is based on clinical presentation and the deployment of laboratory testing for syphilis. More rarely, surgical biopsy may be warranted.

Table 1. Literature Review of Reported Cerebral Syphilitic Masses in the Last 10 Years With Pertinent Features of Demographics and Diagnostics Reported

First Author	Year	Age/Sex	Country	Known HIV Status	CSF Treponemal Test	CSF Nontreponemal Test	PCR Test	Surgery or Biopsy
Ventura [4]	2012	26/M	Brazil	Yes	NR	NR	NR	No
Dhasmana [8]	2013	40/M	UK	No	Pos (TPPA)	Pos (VDRL)	NR	Yes
Yoon [9]	2013	59/F	South Korea	No	Pos (FTA-ABS)	Neg (VDRL)	Neg	Yes
Sprenger [6]	2014	40/M	Switzerland	Yes	Neg (TPHA)	NR	NR	Yes
Hamauchi [22]	2014	23/F	Japan	No	Pos (TPHA)	NR	NR	No
Faropoulos [10]	2016	53/M	Greece	No	NR	NR	NR	Yes
Tsuboi [21]	2016	21/M	Japan	Yes	Pos (FTA-ABS)	Pos (TPHA) Neg (RPR)	NR	No
Zhang [11]	2017	56/M	China	No	Pos (TPPA)	Neg (RPR)	Pos (polA)	Yes
Xia [13]	2017	62/M	China	No	Pos (TPPA)	Pos (RPR)	NR	Yes
Murakawa [23]	2017	24/M	Japan	No	Pos (TPPA)	Pos (RPR)	NR	No
Shi [24]	2017	41/M	China	No	NR	Neg (RPR, VDRL)	NR	No
Kuroi [19]	2018	62/M	Japan	No	NR	Pos (RPR)	NR	Yes
Shao [7]	2018	62/M	China	No	Pos (TPPA)	Neg (RPR)	NR	Yes
Shao [7]	2018	66/M	China	No	Pos (TPPA)	Pos (RPR)	NR	Yes
Shao [7]	2018	37/M	China	No	Pos (TPPA)	Pos (RPR)	NR	No
Ying [18]	2018	52/F	China	No	Pos (TPPA)	Pos (RPR)	NR	Yes
Koizumi [5]	2018	44/M	Japan	Yes	Neg (TPLA)	Neg (RPR)	Pos (polA, TpN47)	Yes
Kodama [25]	2018	36/M	Japan	No	Pos (TPLA)	Pos (RPR)	NR	No
Weng [15]	2019	45/M	China	No	Pos (TPPA)	Pos (TRUST)	NR	Yes
Sasaki [16]	2019	47/M	Japan	No	Pos (FTA-ABS, TPHA)	NR	NR	No
Shen [26]	2019	22/M	China	No	NR	Pos (TRUST)	NR	No
Cui [14]	2020	52/F	China	No	NR	NR	NR	Yes
Xia [12]	2020	49/F	China	No	NR	NR	NR	Yes
Thibodeau [17]	2021	37/F	USA	No	NR	NR	NR	Yes
Yu [20]	2021	54/M	China	No	NR	NR	NR	Yes
This report	2021	25/M	USA	No	Neg (FTA-ABS)	Neg (VDRL)	Pos (16S rRNA)	Yes

Abbreviations: CSF, cerebrospinal fluid; F, female; FTA-ABS, fluorescent treponemal antibody absorption; HIV, human immunodeficiency virus; M, male; Neg, negative; NR, not reported; PCR, polymerase chain reaction; polA, gene coding for DNA polymerase I; Pos, positive; RPR, rapid plasma reagin; rRNA, ribosomal RNA; TPHA, *Treponema pallidum* hemagglutination assay; TPLA, *Treponema pallidum* latex agglutination; TpN47, recombinant protein; TPPA, *Treponema pallidum* particle agglutination; TRUST, toluidine red unheated serum test; UK, United Kingdom; USA, United States; VDRL, Venereal Disease Research Laboratory.

Syphilis cases, including those with neurologic involvement and congenital syphilis, have increased in New York City [27], across the United States [28], and globally [5]. Given the increasing incidence of this clinical entity, we suggest clinicians maintain a high index of suspicion for the atypical manifestations of syphilis and utilize laboratory testing liberally in an effort to prevent more invasive diagnostic modalities such as surgical biopsy. Public health messaging for syphilis prevention should also include examples of severe manifestations, as illustrated in this case. Through imaging findings that mimic malignancy, syphilitic mass-forming lesions may pose a diagnostic challenge and demonstrate yet another way in which syphilis proves to be the "great imitator."

Notes

Patient consent statement. Written consent was obtained from the patient. This case conforms to the standards currently applied within the Division of Infectious Diseases at Weill Cornell Medicine.

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

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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