Title

Transient aortitis documented by positron emission tomography in a case series of men and transgender women infected with syphilis

Journal

Sexually Transmitted Infections, 93(8)

ISSN

1368-4973

Authors

Davey, Dvora Joseph
Kojima, Noah
Konda, Kelika A
et al.

Publication Date

2017-12-01

DOI

10.1136/sextrans-2017-053140

Peer reviewed

HHS Public Access

Author manuscript

Sex Transm Infect. Author manuscript; available in PMC 2018 January 14.

Published in final edited form as:

Sex Transm Infect. 2017 December ; 93(8): 551–555. doi:10.1136/sextrans-2017-053140.

Transient aortitis documented by positron emission tomography in a case series of men and transgender women infected with syphilis

Dvora Joseph Davey[1,2], **Noah Kojima**[3], **Kelika A Konda**[3,4], **Pawan Gupta**[3], **Segundo R Leon**[4], **Gino M Calvo**[4], **Carlos F Caceres**[4], and **Jeffrey D Klausner**[1,2]

[1]Department of Epidemiology, Fielding School of Public Health, University of California Los Angeles, Los Angeles, CA, USA

[2]Division of Infectious Disease, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA

[3]David Geffen School of Medicine, University of California, Los Angeles, California, USA

[4]Unit of Health, Sexuality and Human Development, Laboratory of Sexual Health, Universidad Peruana Cayetano Heredia, Lima, Peru

Abstract

Objectives—Syphilis infection persists globally contributing to preventable and treatable morbidity and mortality. How extensive early syphilis disseminates is unknown. To better understand the relationship between early syphilis infection and inflammation over time, our study enrolled six individuals recently infected with syphilis for sequential positron emission tomography (PET) scans.

Methods—We evaluated a case series of six individuals with high syphilis titres (two secondary, two early latent and two latent, unknown duration, but with high titre) who received sequential PET scans to assess inflammation over time and its response to treatment.

Results—At time of PET scan, four of the six individuals were co-infected with HIV. One of the four was not on antiretroviral therapy and three of the four were not virally suppressed (viral load

Correspondence to: Dr Dvora Joseph Davey, University of California, Los Angeles, Fielding School of Public Health, 10833 Le Conte Ave, Los Angeles, CA 90095, USA; dvoradavey@gmail.com.

Competing interests
None declared.

Ethics approval
Universidad Peruana Cayetano Heredia.

Provenance and peer review
Not commissioned; externally peer reviewed.

Contributors
DJD did the analyses and data collection and wrote the first and final draft. NK did the literature review and data analysis, wrote sections of the paper and approved final version. KAK was the study manager, did the analysis and edited several versions of the manuscript. PG was the clinician on the study, who did the PET scan review and reviewed all analyses, edited sections and approved the final draft. SRL worked on the study, reviewed analyses, wrote sections and edited/approved the final version. GMC worked on the study, reviewed analyses, wrote sections and edited/approved the final version. CFC was the PI on the study, developed the substudy, supported analyses, wrote sections and approved the final draft. JDK was the PI on the study, developed the substudy, supported analyses, wrote sections and approved the final draft.

of >400 copies/mL). Baseline rapid plasma reagin (RPR) titres ranged from 1:64 to 1:256 (four of the six participants had prior non-reactive RPR results). Five of the six participants had mild to intense hypermetabolic PET scan activity consistent with cervical (n=5), axillary (n=4), inguinal (n=5) and retroperitoneal (n=1) adenopathy. Mild hypermetabolic activity in the thoracic aortic wall, suggesting aortitis, was present among the same five participants and resolved within 30 days for four of the five participants and 60 days for the other participant. However, widespread lymphadenopathy remained present in PET scans up to 3 months following treatment in two participants. We did not find any abnormal PET scan activity of the central nervous system.

Conclusion—We found abnormal aortic wall PET scan activity suggesting aortitis to be common in a case series of patients with early syphilis. In research settings, PET scans may be a sensitive tool to monitor inflammation associated with syphilis.

BACKGROUND

Globally, it estimated that there are approximately 6 million new cases of syphilis each year.[1] In the United States, incidence of syphilis infection is rising dramatically, especially among men who have sex with men.[2] After the initial infection, *Treponema pallidum* can spread to become a systemic infection. *T. pallidum* disseminates early within the body and localises within the richly vascularised periosteum and bone marrow.[3] Involvement of the aortic root is the most common manifestation of cardiovascular syphilis. In 1926, in his seminal work on the natural history of syphilis, Stokes reported on 200 cases of syphilis and aortic disease.[4] Similar reports of aortitis and syphilis were described again in 1942.[5] However, the clinical manifestations of untreated syphilis due to chronic inflammation with resultant fibrosis can impact almost any body system.

Prior individual case reports have described the detection of syphilitic aortitis with imaging techniques like computer tomography scans, MRI and echocardiography.[6–9] A few case reports have used positron emission tomography (PET) scans to describe syphilitic aortitis; however, they did not comment on timing of infection.[8–12] One case report showed likely syphilitic aortitis in a patient with syphilis and HIV co-infection who had been symptomatic for 2 months but did not comment when the initial infection may have taken place.[7] Another case report of probable syphilitic aortitis was detected with PET scan in an individual infected with HIV who acquired syphilis within the 3 months prior to imaging, which gives indication that syphilis may be associated with aortitis earlier than currently thought.[12] The current hypothesis of the pathophysiology of syphilitic aortitis suggests that *T. pallidum* causes aortic disease 10–20 years after primary syphilis infection[2 13 14] with resultant irreversible cardiovascular damage. To further assess the role of syphilis and inflammation in early infection, we enrolled a case series of individuals with early syphilis infection using sequential PET scans to assess PET scan activity overtime and its response to treatment.

METHODS

Study population

The PICASSO cohort was recruited in Lima, Peru, from May 2013 to May 2014. We recruited men and transgender women age >18 years who were sexually active with men,

who were likely to acquire syphilis and who were willing to return for quarterly clinical visits. Over 2 years of follow-up time, participants attended quarterly clinical visits, where they received clinical examinations, completed surveys and received counselling and serological testing for syphilis and HIV infection.[15]

Within the main study, we decided to investigate the impact of early syphilis on aortic and vascular disease and invasion into the central nervous system through PET scan. Eligibility criteria included patients with early syphilis infection, defined as having recently acquired syphilis infection (at least a quantitative rapid plasma reagin (RPR) titre of 1:64 or greater along with seroconversion from negative RPR titre to reactive RPR titre, 4-fold rise in quantitative RPR titre or clinical findings consistent with primary or secondary syphilis). After recruiting four patients infected with HIV, investigators included additional criteria that the patient must be HIV uninfected to create balance in the case series between individuals infected with HIV and those not infected. In total, study staff contacted 12 participants from the main study who were diagnosed with early syphilis. Of those, six participants (50%) consented to participate in the substudy and receive PET scans at baseline and at 30 and 90 days after diagnosis and treatment. The benchmark for the PET scan was the diagnosis date. For PET scans, F-18 FDG was injected intravenously and imaging was obtained using standard whole body protocol. PET scans were obtained on a Siemens Biograph LSO HD Truepoint 6 in Lima, Peru, and were analysed blinded by participant identity and date at the University of California Los Angeles Medical Center, Los Angeles, California, by a second reviewer and a physician specialist in PET scan analyses (PG).

Laboratory testing

Study participants were assessed for syphilis infection with RPR testing (BD Macro-Vue RPR Card Test Kit, Beckton Dickinson, Franklin Lakes, New Jersey) and quantitative treponemal pallidum particle agglutination testing (TPPA Serodia, Fujirebio Diagnostics, Tokyo, Japan) using a cut-off value of >1:80. Study participants who were HIV uninfected were re-tested for HIV during each study visit with HIV Ag/Ab EIA fourth-generation sera tests (Genscreen ULTRA HIV Ag-Ab, Bio-Rad, Hercules, California). Western blot testing (NEW LAV BLOT I, Bio-Rad, France) was conducted for confirmation of all specimens that had a reactive HIV test according to the Peruvian national testing standards.[16] During the PET scan visit, participants with HIV infection were asked to report their most recent CD4 T cell count and viral load. Rapid point-of-care tests were also used to diagnose participants with syphilis (Alere Determine Syphilis TP, Alere, Waltham, Massachusetts, USA) and HIV (Alere Determine HIV 1/2, Alere, Waltham, Massachusetts, USA) at each study visit. Our study did not find any discrepancies in the point of care when compared with standard serological tests for syphilis.

Treatment

Participants who were diagnosed with syphilis or HIV infection received post-test counselling, treatment for syphilis and/or referral for HIV care and treatment. Following the Peruvian Ministry of Heath protocol, participants who were diagnosed with syphilis were requested to inform their sex partners. A single benzathine penicillin G 2.4 million unit

injection was administered on-site for early syphilis treatment for all patients according to Centers for Disease Control and Prevention and Peruvian national guidelines.[17]

Ethics statement

The institutional review board at Universidad Peruana Cayetano Heredia (UPCH), Barton Health Center, provided ethical approval and oversight of the study (reference number SIDISI 59996). The UCLA IRB for the Syphilis study in Peru is IRB#12-001528. The UPCH IRB on the application is #599996.

RESULTS

We enrolled six participants (five men and one transgender woman) with newly diagnosed early syphilis with and without HIV infection. The median age of participants was 33 years (range: 21–50). The mean difference between the syphilis diagnosis date and the PET scan date was 2.6 days. Around the 3-month visit, the baseline median difference from the study visit (and RPR test) to the PET scan was less than 1 day (range: −11 to 5 days). In two cases, treatment was provided prior to the scan (3 days and 9 days prior in those cases); in the other four cases, the treatment was the same day. At time of PET scanning, four of the six participants were co-infected with HIV and one of the four was not on antiretroviral therapy (ART). Three of those four individuals were not virally suppressed (defined as having a viral load of <400 copies/mL).

Baseline RPR values ranged from 1:64 to 1:256. In one case, the participant's prior study visit showed a non-reactive RPR titre. In another case, the RPR titre at the last study visit (3 months prior) was 1:4. Two other participants had high titres but had missed recent study visits, so their most recent RPR titre while non-reactive was more than 12 months prior. As such, according to US Centres for Disease Control (Centers for Disease Control and Prevention) definitions, we classified those two as having latent syphilis of unknown duration because they did not have any clinical symptoms and we describe them in this report as having suspected early syphilis infection. The remaining two cases were enrolled without known prior RPR titres but had high RPR titres (1:64 and 1:128) and abnormal clinical findings consistent with secondary syphilis: a characteristic rash on their hands and the bottom of their feet or the presence of abnormal oral mucosal lesions that resolved at the first follow-up visit after penicillin therapy. Below table 1 shows the baseline characteristics of the cases including serum RPR titres, HIV status, HIV viral load and CD4 T cell count.

Five participants had mild to intense hypermetabolic activity present on the baseline PET scan, consistent with cervical (n=5), axillary (n=4), inguinal (n=5) and retroperitoneal (n=1) adenopathy. The same participants had increased metabolic activity in the ascending and descending thoracic aortic wall, suggestive of aortitis. The hypermetabolic activity in the ascending and descending thoracic aortic wall resolved within 30 days for four of the five participants and 60 days for the other participant. However, the widespread metabolic activity consistent with lymphadenopathy persisted longer and remained present on the PET scan up to 3 months following treatment for two of five of the participants. Those two participants were HIV infected, and both were virally unsuppressed (participant #4 was on ART, and participant #2 was not on ART). Those two participants demonstrated at least a 4-

fold decline in RPR titres after treatment. Unfortunately, our study did not collect data on cardiovascular risk factors, other co-infections like viral hepatitis or autoimmune disorders.

One participant with early latent syphilis did not have any abnormal PET scan activity (participant #3). His RPR titre was 1:64 at baseline and 1:8 3 months later. That patient had been on ART since 2006 and reported being virally suppressed (undetectable). In his five prior study visits, he consistently self-reported high CD4 T cell counts (>500 cells/mL) and undetectable viral loads. None of the patients had concomitant fever, malaise or arm claudication with their abnormal PET findings.

Finally, none of the participants showed increased focal cortical, cerebrovascular or meningeal metabolic activity, which is suggestive of central nervous system inflammation on PET scan. Three months later, five participants were examined again (one participant did not have a serological follow-up in the study). Among those participants, all had at least a 4-fold decline in RPR titre supporting an adequate treatment response. None of the participants had aortitis present on the 30-day or 90-day PET scan after treatment. The table 1 shows the PET scan results for each participant over time.

DISCUSSION

Our study found increased PET scan activity consistent with diffuse lymph adenopathy and aortitis among five participants with early syphilis (two suspected early syphilis) infection in Lima, Peru. We found that the majority of participants had adenopathy, and two of the six participants had persistent adenopathy on the PET scans 3 months after treatment with benzathine penicillin G. In the five participants that had PET scan activity consistent with aortitis, the abnormal findings resolved following effective treatment as evidenced by a 4-fold decline in titres.

We observed that, in participants with early syphilis infection with and without HIV co-infection: (1) disseminated inflammation was present early in syphilis infection as shown by multi-site adenopathy on PET scans and (2) mild aortitis in five of six participants. Given that we found evidence on PET scan of widespread inflammation including aortitis among individuals with a diagnosis of early syphilis and resolution with treatment for syphilis infection, we confirm what other studies have shown that likely early or recently acquired syphilis infection has systemic implications.[18 19] More research is needed to understand if there are increased long-term cardiovascular risks given the aortic inflammation associated with early syphilis. Here we propose that, in early syphilis infection, *T. pallidum* quickly becomes systemically disseminated and, in our case series, about 80% had evidence of syphilitic aortitis within months of primary infection. Before the widespread use of penicillin, it was estimated that syphilis contributed to 10% of cardiovascular disease[16]; it is important to further investigate if new, untreated or recurrent syphilis infections lead to increased risk of cardiovascular disease changes caused by infection. In addition, we have demonstrated on a small scale that adenopathy and aortitis resolve shortly after treatment with benzathine penicillin G in those with and without co-infection of HIV, providing additional evidence that the inflammatory activity found on PET imaging was truly associated with syphilis infection.

Of note, four of the six participants were co-infected with HIV. Of those four, three were not virally suppressed (two of the three were on ART), and the one virally suppressed patient had no reactivity on PET scanning. Because HIV infection may result in diffuse lymphadenopathy as well, we hypothesise that having achieved viral suppression also contributed to the lack of lymphadenopathy in this patient, though more research is needed in a larger cohort to confirm this hypothesis.

Our findings are in agreement with observations reported in prior case reports. In 2005, Kosters *et al* reported a case of widespread lymphadenopathy and aortitis in a participant with early syphilis infection co-infected with HIV using PET scan imaging.[8] Kosters *et al* suggested that early aortic involvement might occur more often than thought, which is supported by the findings in our study. In addition, neurosyphilis infection can occur during any stage of syphilis[4]; however, on PET scan in our case series, we did not find any evidence of inflammation in the central nervous system. Neuroinflammation may be difficult to detect, however, on PET scanning due to physiologic cerebral metabolic activity.

Implications of our findings on the clinical management of early syphilis are unclear. Since all participants were treated, we do not know whether or not or how long the aortic inflammation would resolve without treatment. Other complications of early syphilis due to dissemination such as ocular syphilis and neurosyphilis are devastating but are uncommon (<2%).[4] Clinicians should be aware that early dissemination of syphilis occurs with some frequency though some manifestations may indeed be transient and resolve with treatment.

Limitations of this study include that it was a case series of only six participants, which may limit the generalisability of our results. Further, four of six participants were co-infected with HIV, of which three were on ART and one was virally suppressed (viral load: <400 copies/mL). In addition, HIV-associated immune dysregulation or other co-infections may alter inflammatory response and PET scan findings. Strengths of the study include the case series design that used serial PET scans over time to monitor systemic inflammation in syphilis infection, and the PET scan interpretation was blinded by HIV infection, treatment status and time.

CONCLUSION

We found evidence of diffuse adenopathy and transient aortitis among a case series of patients with early syphilis infection. PET scans might be a sensitive tool to monitor inflammation associated with syphilis, particularly in research settings. Vascular involvement resultant from syphilis may be quite frequent. However, we do not know the consequences of syphilitic aortitis if the infection goes untreated. Our findings support the utility of PET scanning for the evaluation of syphilis-associated inflammation. More research may be needed to understand the clinical implications of our findings.

References

1. World Health Organization. Global Health Sector Strategies 2016–2021. World Health Organization; 2015. Proposing 2016–2021 Global health sector strategies for HIV, viral hepatitis and sexually transmitted infections (STIs). Briefing Note: 16.09.2015

2. Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance 2015. Oct 18. 2016 https://www.cdc.gov/std/stats15/toc.htm (accessed 3 Nov 2016).
3. Lukehart SA, Hook EW, Baker-Zander SA, et al. Invasion of the central nervous system by *Treponema pallidum*: implications for diagnosis and treatment. Ann Intern Med. 1988; 109:855–62. [PubMed: 3056164]
4. Sartin JS, Perry HO. From mercury to malaria to penicillin: the history of the treatment of syphilis at the Mayo Clinic—1916–1955. J Am Acad Dermatol. 1995; 32(2 Pt 1):255–61. [PubMed: 7829712]
5. Vora, MP. Cardiovascular Syphilis, The Medical Bulletin. 1942. p. 444-50.X(19) http://www.stdpioneer.org/cardiovascular.html
6. Omer TA, Fitzgerald DE, Sheehy N, et al. Neurosyphilis presenting with unusual hippocampal abnormalities on magnetic resonance imaging and positron emission tomography scans: a case report. J Med Case Rep. 2012; 6:389. [PubMed: 23171511]
7. Lin M, Darwish BS, Chu J. Neurosyphilitic gumma on F18-2-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography: an old disease investigated with a new technology. J Clin Neurosci. 2009; 16:410–2. [PubMed: 19138854]
8. Kösters K, Bleeker-Rovers CP, van Crevel R, et al. Aortitis diagnosed by F-18-fluorodeoxyglucose positron emission tomography in a patient with syphilis and HIV coinfection. Infection. 2005; 33:387–9. [PubMed: 16258874]
9. De Rango P, De Socio GV, Silvestri V, et al. An unusual case of epigastric and back pain: expanding descending thoracic aneurysm resulting from tertiary syphilis diagnosed with positron emission tomography. Circ Cardiovasc Imaging. 2013; 6:1120–1. [PubMed: 24254483]
10. Ghazy T, Matschke K, Kappert U. A monstrous aneurysm of the descending aorta as a sole manifestation of tertiary syphilis treated endovascularly. Eur Heart J. 2011; 32:2411. [PubMed: 21447513]
11. Treglia G, Taralli S, Maggi F, et al. Usefulness of (18)F-FDG PET/CT in disease extent and treatment response assessment in a patient with syphilitic aortitis. Clin Nucl Med. 2013; 38:e185–7. [PubMed: 23143047]
12. Balink H, Spoorenberg A, Houtman PM, et al. Early recognition of aortitis of the aorta ascendens with ^{18}F-FDG PET/CT: syphilitic? Clin Rheumatol. 2013; 32:705–9. [PubMed: 23377199]
13. Pastuszczak M, Jakiela B, Wielowieyska-Szybinska D, et al. Elevated cerebrospinal fluid interleukin-17A and interferon-γ levels in early asymptomatic neurosyphilis. Sex Transm Dis. 2013; 40:808–12. [PubMed: 24275734]
14. Klausner, JD., Freeman, AJ. Sequelae and Long-Term Consequences of Syphilis Infection. In: Patiemo, P., Clark, C., editors. Sequelae of infectious diseases. New York: American Society of Microbiology; 2010.
15. Deiss RG, Leon SR, Konda KA, et al. Characterizing the syphilis epidemic among men who have sex with men in Lima, Peru to identify new treatment and control strategies. BMC Infect Dis. 2013; 13:426. [PubMed: 24016185]
16. Vaideeswar P. Syphilitic aortitis: rearing of the ugly head. Indian J Pathol Microbiol. 2010; 53:624–7. [PubMed: 21045381]
17. Workowski KA, Bolan GA. Centers for Disease C, Prevention: sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015; 64(RR3):1–137.
18. Fu Z, Zhang J, Li Q, et al. A case of secondary syphilis involving tonsil, pulmonary, and multiple lymph nodes: 18f-fdg PET/CT findings. Clin Nucl Med. 2015; 40:335–7. [PubMed: 25546195]
19. Ranganath P, Kapila R, Vadehra V, et al. Generalized lymphadenopathy and 18-fluorine fluorodeoxyglucose positron emission tomography/computed tomography: targeting diagnostic intervention, characterizing disease extent, and assessing treatment efficacy in syphilis. Sex Transm Dis. 2015; 42:68–70. [PubMed: 25585063]

Key messages

- We enrolled six individuals with early syphilis infection who received sequential positron emission tomography (PET) scans to assess inflammation over time and its response to treatment.
- We found abnormal PET scan activity in the thoracic aortic wall among five of six participants which resolved after treatment.
- Abnormal PET scan activity consistent with widespread lymphadenopathy remained up to 3 months following treatment in two participants.
- In research settings, PET scans may be a sensitive tool to monitor inflammation associated with syphilis.

Table 1

Participant clinical diagnoses, dates of PET scans, PET scan results and follow-up syphilis results at 3 months, Lima, Peru, 2015

ID #	PET scan date	Age	HIV status	On ART	Baseline CD4 and viral load	Adenopathy (lymphatic)	Aortic inflammation	Cerebral inflammation	Syphilis stage and prior quantitative RPR titres	RPR result
1		50	HIV infected	Yes	CD4: 380 cell count, mm^3/mL VL: 15 000 copies/mL				Early latent syphilis 3 months prior RPR titre non-reactive	1:256
	February 2015 n/a					Small neck and axillary, larger inguinal adenopathy	Aortitis	None		
	May 2015					None	None	None		1:16
2		21	HIV infected	No	CD4: 444 cell count, mm^3/mL				Latent syphilis, unknown duration 15 months prior	1:128
	April 2015				VL: 8000 copies/mL	Bilateral inguinal Bilateral auxiliary Bilateral neck	Aortitis	None	RPR titre non-reactive	
	May 2015					Bilateral inguinal Bilateral auxiliary Neck improved, but still present	None	None		
	July 2015					Neck improved, but still present Bilateral inguinal and axial	None	None		1:8
3		37	HIV infected	Yes	CD4: 600 cell count, mm^3/mL				Early latent syphilis 3 months prior RPR titre 1:4	1:64
	May 2015				VL: <400 copies/mL	None	None	None		
	June 2015					None	None	None		
	August 2015					None	None	None		1:8
4	June 2015 July 2015 September 2015	25	HIV infected	Yes	CD4: 308 cell count, mm^3/mL VL: 4000 copies/mL	Extensive neck adenopathy, bilateral auxiliary, abdominal and retro peritoneal adenopathy, bilateral inguinal adenopathy Extensive neck adenopathy/ bilateral auxiliary/ abdominal + retroperitoneal adenopathy/bilateral inguinal	Mild aortitis None None	None None None	Latent syphilis, unknown duration 21 months prior RPR titre non-reactive	1:128 1:16

ID #	PET scan date	Age	HIV status	On ART	Baseline CD4 and viral load	Adenopathy (lymphatic)	Aortic inflammation	Cerebral inflammation	Syphilis stage and prior quantitative RPR titres	RPR result
						Neck, auxiliary, inguinal, retroperitoneal and abdominal improved but still present				
		32	HIV uninfected						Secondary syphilis No prior	1:64
	July 2015					Significant neck adenopathy	Mild aortitis	None	RPR results (baseline visit)	
5	August 2015					Bilateral neck/small bilateral inguinal (same as first)	None	None		
	October 2015					Neck, auxiliary and inguinal adenopathy gone	None	None		1:4
6	November 2015	31	HIV uninfected			Neck bilateral lymphadenopathy, mediastinum, bilateral auxiliary, inguinal and iliac adenopathy	Mild aortitis	None	Secondary syphilis No prior RPR results (baseline visit)	1:128
	December 2015					Improved adenopathy in neck, auxiliary and mediastinum improved but not disappeared. Iliac improved but not gone	None	None		
	January 2016					Neck gone, auxiliary gone, inguinal gone	None	None		

PET, positron emission tomography; RPR, rapid plasma reagin; VL, viral load.