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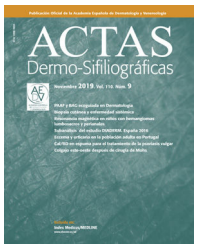

REVIEW

Malignant Syphilis: A Systematic Review of the Case Reports Published in 2014-2018☆

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KEYWORDS
Malignant syphilis;
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Abstract Malignant syphilis (MS) is a rare manifestation of secondary syphilis which mainly occurs in immunocompromised individuals such as those coinfected with human immunodeficiency virus (HIV). However, recent reports have described MS in immunocompetent individuals. To describe the characteristics of individuals with MS and associated risk factors, a review of case reports published from 2014 to 2018 was conducted. Out of 45 published case reports, 33 cases (73%) occurred in HIV-positive individuals with majority having CD4 counts <500 cells/mm^3. Of the 12 cases (27%) in HIV-negative individuals, half had comorbidities such as diabetes mellitus, alcoholism, drug abuse, psoriasis, and hepatitis. The most frequent manifestation of MS was ulceronodular cutaneous lesions with central adherent crust, which affected the face, trunk, and limbs. Given the increasing number of MS regardless of the immune status, dermatologists and general practitioners should be vigilant to allow early diagnosis and treatment, hence reducing their morbidity.

PALABRAS CLAVE
Sífilis maligna;
Treponema pallidum;
Inmuno deficiencia;
Infección por VIH

Sífilis maligna: revisión sistemática de los casos publicados entre los años 2014-2018

Resumen La sífilis maligna (SM) es una manifestación poco común de la sífilis secundaria. Esta se presentará principalmente en individuos inmunodeprimidos, como es el caso de los pacientes con una coinfección por el virus de la inmunodeficiencia humana (VIH). Sin embargo, recientemente se han descrito casos de SM también en individuos inmunocompetentes. Se realizó una revisión de los casos publicados entre el año 2014 y el 2018 para recoger las características de los pacientes con SM, así como los factores de riesgo asociados. De los 45 casos publicados, 33 casos (73%) ocurrieron en personas VIH positivas, la mayoría con recuentos de CD4 < 500

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células/mm^3. De los 12 casos (27%) en pacientes VIH-negativo, la mitad tenía comorbilidades como diabetes mellitus, alcoholismo, abuso de drogas, psoriasis y hepatitis. La manifestación más frecuente de la SM fueron las lesiones cutáneas ulcero – nodulares, las que presentaban una costra central adherente, y que afectaban la cara, el tronco y las extremidades. Dado el creciente número de SM, independientemente del estado inmunológico, los dermatólogos y médicos generales deben tener en cuenta la existencia de esta entidad para así poder realizar un diagnóstico y tratamiento oportuno, reduciendo de esta manera la morbilidad asociada.

Introduction

Syphilis is an infection caused by *Treponema pallidum*, a spirochete bacterium that exclusively infects humans.[1] Malignant syphilis (MS), also known as syphilis maligna, lues maligna, or rupioid syphilis, is a rare aggressive form of secondary syphilis.[1] The term ''rupioid'' stems from the rupia or ''oyster-like'' appearance of these lesions, describing well-demarcated plaques with thick, lamellate, and adherent crusts on the surface that resemble an oyster shell.[2] In 1859, the French dermatologist Pierre Bazin first used the term malignant to describe a case of secondary syphilis, and in 1896, at the Third International Congress of Dermatology in London, the Danish dermatologist Haslund and German dermatologist Neisser, independently classified MS as a rare, aggressive, ulcerating form of secondary syphilis and not an early form of tertiary syphilis, as had previously been assumed.[1,3] It is distinguished from classical secondary syphilis based on a more severe general clinical picture and the presence of pleomorphic and ulceronecrotic skin lesions.[4]

MS presents as crusted or scaly papules and plaques that can ulcerate or become necrotic.[5] The exanthem mainly affects the trunk and limbs, although the face, scalp, mucous membranes, palms, and soles can also be affected. Palpable peripheral lymphadenopathy, fever, and constitutional symptoms are commonly observed in patients with the disease. There have been only a limited number of reports of MS published in medical literature, and most of the reported cases have been in immunocompromised individuals, particularly those infected with human immunodeficiency virus (HIV).[6] Syphilis and HIV co-infection can lead to an increased HIV viral load, concomitantly with a decreased CD4$^+$ cell counts, greatly increasing the risk of MS, especially if untreated.[7,8] Before the HIV pandemic, MS was extremely rare; between 1900 and 1988, only 14 cases had been published in English language. At present, it is estimated that up to 7% of all syphilis cases in immunocompromised patients meet the criteria for MS, often presenting as the first clinical manifestation of HIV infection.[4] However, some reports on MS in immunocompetent individuals have been recently published.[9,10] We conducted a systematic review of case reports on MS published between 2014 and 2018 to analyze demographic and risk factors of MS.

Methods

In order to review clinical, laboratory, and therapeutic data from patients with documented MS, we searched 2 databases (PubMed and Google Scholar) for literature published between 2014 and 2018, using the following terms: malignant syphilis OR lues maligna OR rupioid syphilis OR ulceronodular syphilis (Fig. 1). Our literature search yielded 39 articles, which were independently reviewed by 2 investigators, and any disagreement was resolved by consensus. We included all studies where the diagnosis was documented by serology or any combination of serology, pathologic findings, and immunostaining. Studies without positive serologic tests were not included. The inclusion criteria for the articles were: (1) case report with one of the aforementioned expressions in the title; (2) article in English; (3) articles published between 2014 and 2018; and (4) contain all the necessary information (gender, age, sexual behavior (heterosexual, bisexual or homosexual), location and description of the lesions, onset, serology and histopathology results, HIV status, immunostaining, treatment and post-treatment reactions, outcome). In total, 36 of the 39 articles were considered relevant and met the inclusion criteria. From those selected articles, we collected a total of 45 cases of MS.[2,3,9–39] We extracted the details on each case and recorded it on a spreadsheet Microsoft Excel 2016. We used Microsoft Excel 2016 to produce basic descriptive statistics (frequencies, percentages, and medians) of the data. We did not do any hypothesis testing.

Results

Demographic characteristics

The majority (84%) of the patients were male, and the patients had a median age of 41 years (range: 20–86 years). The highest incidence was in the 40-44 years age group (Table 1). There was minimal information available regarding high-risk behaviors (possibly related to syphilis acquisition) in the cases we reviewed.

Clinical and laboratory characteristics

The clinical manifestations are reported on Table 2. The most frequent clinical manifestations were ulceronodular

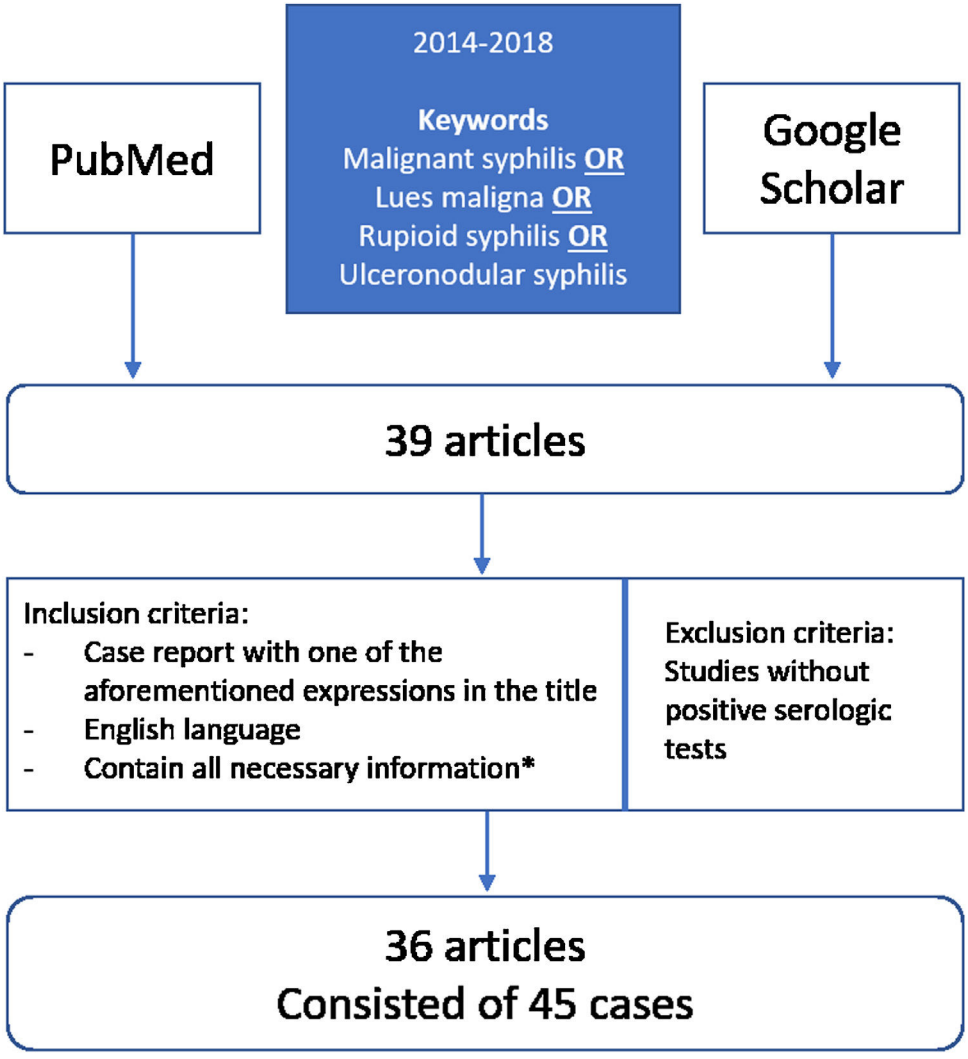

Figure 1 Search flowchart.

cutaneous lesions with adherent crust on the central surface affecting the face, trunk, and/or limbs (Table 2). Serological data were available for 44 out of 45 cases. The syphilis diagnosis was confirmed by nontreponemal and treponemal tests, which were reported as positive for 41 and 35 cases, respectively. Most (73%) patients were HIV-positive; among those, 51% had a CD4 cell count range of 200-499 cells/mm^3. Notably, of the 12 immunocompetent patients, 6 (50%) had a comorbidity, such as diabetes mellitus, alcoholism, drug abuse, psoriasis, or hepatitis.

Histological findings and immunostaining and microorganism staining

Skin lesions were reported and verified by histology in 37 of the 45 reviewed cases (Table 2). The most commonly reported histopathology features are lymphohistiocytic dermal infiltrate composed of plasma cells. Data on immunostaining and microorganism staining were given for 23 cases; *T. pallidum* was detected in 17 of those patients. In the remaining 6 patients, no spirochetes were detected (Table 2).

Treatment and outcome

Approximately two-thirds (64%) of the patients were treated with intramuscular benzathine penicillin G, and the remaining patients were treated with alternatives including as intravenous aqueous penicillin G, oral doxycycline, or intravenous ceftriaxone (Table 1). Nine patients (20%) experienced JHRs, of whom 7 were treated with prophylactic corticosteroids (Table 2).

Discussion

We reviewed published case reports on 45 patients with MS, published in 2014-2018. It is well recognized that MS is commonly observed in immunosuppressed patients such as those with HIV infection. The pathogenesis of MS is unknown, but it is generally believed that immunosuppression due to HIV coinfection enables *T. pallidum* to become more virulent.

Table 1 Características demográficas y los factores de riesgo de sífilis en pacientes con sífilis maligna.

Characteristics	Patients (n)	(%)
Sex		
◯ Male	38	84.4
◯ Female	7	15.6
Age group		
◯ 20-24	3	6.7
◯ 25-29	7	15.6
◯ 30-34	1	2.2
◯ 35-39	9	20
◯ 40-44	13	28.9
◯ 45-54	8	17.8
◯ 55-64	2	4.4
◯ >65	2	4.4
Positive serology		
Non-treponemal (VDRL, RPR)	41†	–
Treponemal (FTA-ABS, TPHA, TPPA)	35†	–
HIV status		
◯ Positive	33	73.3
◯ Negative	12	26.7
HIV (+) CD4 count (cells/mm^3)		
◯ <200	8	24.2
◯ 200-499	17	51.5
◯ >500	5	15.2
◯ Not mentioned	3	9.1
Treatment		
◯ BPG	29	64.4
◯ Penicillin G	7	15.6
◯ Doxycycline	6	13.3
◯ Ceftriaxone	3	6.7
JHR		
◯ Positive	9	20
◯ Negative	36	80

BPG: Benzathine Penicillin G; JHR: Jarisch-Herxheimer Reaction; VDRL: Venereal Disease Research Laboratory; RPR: Rapid Plasma Reagin; FTA-ABS: Fluorescent Treponemal Antibody Absorption; TPHA: Treponema Pallidum Hemagglutination Assay.

† No percentage can be given because there are no pertinent data for the remainder of the cases.

Notably however, most of the HIV-positive patients had a CD cell count >200 cells/mm^3, and thus, they were not deeply immunosuppressed.[12] The loss of CD4 T cells that occurs as a result of HIV infection or other conditions[4] leads to a greater action of cytotoxic T cells and neutrophils on the skin[2] in MS. As a result, MS differs from conventional syphilis that occurs in individuals with intact immune systems. This reasoning is consistent with its occurrence in patients with comorbidities or debilitating disease as a cofactor. Our review revealed that 6 of the 12 HIV-negative patients (50%) had comorbidities such as diabetes mellitus, alcoholism, drug abuse, psoriasis, and hepatitis, which could have affected their immune function. The occurrence of MS in HIV-negative patients with comorbidities raises the possibility of aberrant immune response caused by these systemic conditions triggering a more severe skin manifestation and the possibility of a more virulent strains of *Treponema*, which already considered by other authors.[4,32,38,39]

MS is often seen in association with high nontreponemal titers and systemic symptoms.[5] To guide the clinical diagnosis, in 1969, Fisher et al., proposed 4 criteria in order to identify this rare variant of syphilis, namely: (1) Comparable gross and microscopic morphology; a high titer serologic test for syphilis; a Jarisch-Herxheimer reactions (JHR); and a dramatic response to antibiotic therapy.[40]

Diagnosis by skin biopsy in affected patients is challenging because spirochetes are generally sparse in the skin lesions. Skin biopsy is, however, a recommended procedure to exclude other bacterial, fungal, and mycobacterial infections. Data obtained from special staining and dark-field microscopy may be insufficient to make a histologic diagnosis,[33,40] but microscopic evaluation may reveal non-specific inflammatory findings, such as histological patterns of dermal infiltrate with plasma cells and lymphocytes, sometimes granulomatous and vascular damage. Our review revealed that lymphohistiocytic dermal infiltrate with plasma cells was the most commonly reported histological feature.[12] Immunohistochemistry is superior to silver stains for detecting spirochetes, but it is not always be available as a routine procedure.[33]

An increase in the incidence of JHR has been described both in patients with MS and in patients with HIV in general. Yang et al describe a rate of incidence of JHR as high as 34.6% in HIV-infected patients.[41] In our review, JHR was reported in only 9 patients (20%), and of these 9 patients, 7 were provided with prophylactic corticosteroids. JHR is a transient immunological phenomenon seen commonly in patients during treatment of secondary syphilis; it manifests with constitutional symptoms such as fever, chills, headache, and myalgia, in addition to exacerbation of existing cutaneous lesions. The reaction usually occurs hours after the administration of an appropriate antibiotic and normally resolves without any intervention within 24 hours. JHR is more severe when the number of pathogens is abundant, consistent with a high-titer serological test being part of MS criteria. It should be managed symptomatically and does not require discontinuation of the appropriate antimicrobial treatment. Corticosteroids have been used to prevent the reaction, but there is no conclusive evidence regarding their benefit.[35,42]

Currently, there is no specific recommendations for MS treatment. The most commonly used treatment regimen is the same as that used for late latent syphilis (3 consecutive weekly intramuscular injections of benzathine penicillin, 2.4 million units/dose). In case of allergy to penicillin, treatment with ceftriaxone can be used. In resistant cases or relapses, prolonged therapy with high doses of penicillin is suggested.[12,25] About 80% of the patients in our review were treated with penicillin, either intramuscularly or intravenously as aqueous solution, and all the patients had a rapid improvement in their condition following antibiotic treatment.

Conclusion

Our review included 45 case reports of MS published from 2014-2018, available on the PubMed and/or Google Scholar databases. Of the patients, 74% were HIV positive. Of the HIV-negative patients, half had a comorbidity such as diabetes mellitus, alcoholism, drug abuse, psoriasis, hepatitis.

Table 2 Studies on malignant syphilis published in 2014–2018.

No.	References	Race, Sex, Age (years), Sexual orientation	HIV status CD4 count (cells/mm^3)/ other	Location of the lesions	Onset (before admission)	Serological test results	Histopathology	Immunostaining/ microorganism staining	Treatment	JHR	Resolution time/ improvement
1.	Dos Santos, et al., 2014 [11]	African, male, 27, MSM	HIV+ 340	Forehead, back, lower limbs	3 months	VDRL 1:128	Perivascular mixed inflammatory infiltrate and granuloma in the dermis	NA	Doxycycline 100 mg/ 12 hours/PO for 3 weeks	– Prophylactic hydrocortisone 200 mg IV	3 weeks
2.	Cid, et al., 2014 [12]	Male, 42	HIV+ 442	Face, scalp, trunk, limbs	8 days	RPR 1:64 IgG + TPPA +	Abundant histiocytes, giant cells and plasma cells in the dermis	+	Benzathine penicillin G 2.4 mU/week/IM for 3 weeks	–	3 weeks
3.	Cid, et al., 2014 [12]	Male, 33	HIV+ 1294	Scalp, cheek, upper limbs, trunk	5 months	RPR 1:16 TPPA +	Dense lymphocytes and plasma cells in the dermis	+	Benzathine penicillin G 2.4 mU/ week/ IM for 3 weeks	–	10 days
4.	Cid, et al., 2014 [12]	Male, 25	HIV+ 210	Trunk, scalp	1 month	RPR 1:64 TPPA +	Dense lichenoid infiltrate, lymphocytes, histiocytes, and numerous plasma cells on the epidermis	+	Benzathine Penicillin G 2.4 mU/ week/ IM for 3 weeks	–	2 weeks
5.	Bustos, et al., 2014 [13]	Male, 46	HIV– Hep B	Trunk, limbs, genitals, scalp	2 months	VDRL 1:32, FTA-ABS +	Heavy lymphocytes and histiocytes, abundant plasma cells in the dermis	NA	Benzathine penicillin G 2.4 mU/ week/ IM for 3 weeks	–	3 weeks
6.	Requena, et al., 2014 [4]	Female, 29	HIV– Psoriasis	Face, trunk, limbs	2 weeks	VDRL 1:256 Treponemal test +	Dense lymphohistiocytic infiltrate rich in plasma cells, extended into the deep dermis	+	Benzathine penicillin G 2.4 mU/ week /IM for 3 weeks	+	3 months
7.	Kong, et al., 2014 [14]	Male, 36, MSM	HIV+	Face, trunk	3 weeks	VDRL 1:128	Granulomatous, lymphocytes, and plasma cells in the dermis	NA	Benzathine penicillin G	–	Improved
8.	Navarrete, et al., 2015 [8]	White, male, 25	HIV+ 236	Face, trunk, limbs, penis	3 months	RPR 1:512 MHA-TP +	Dense infiltrate of plasma cells, lymphocytes, and histiocytes	+	Benzathine penicillin G 2.4 mU/ week /IM for 3 weeks	–	1 week
9.	Devkota, et al., 2015 [15]	African American, male, 20, MSM	HIV+ 276	Trunk, face, and upper limbs	1 month	RPR 1:128, FTA-ABS +	Lichenoid lymphohistiocytic infiltrate with plasma cells	+	Doxycycline 100 mg/ 12 hours/ PO for 3 weeks	+	3 weeks
10.	Jalili, et al., 2015 [16]	White, female, 47	HIV+ 155	Upper limbs, lower limbs, trunk, head	1 month	IgM + TPPA + TPHA 1:1280 VDRL 1:32	Perivascular and perifollicular infiltration of lymphocytes, many histiocytes and numerous plasma cells in the dermis	–	Benzathine penicillin G 2.4 mU/ week/ IM for 3 weeks	– Prophylactic methylprednisolone 40 mg PO 1 hour before penicillin injections	4 weeks
11.	Jiu-Hong Li, et al., 2015 [17]	Asian, male, 38, heterosexual	HIV–	Face, trunk, limbs	1 month	TPPA + RPR 1:128	Mixed perivascular infiltrate with neutrophils, lymphocytes, plasma cells, and histiocytes in the dermis	NA	Benzathine penicillin G 2.4 mU/ week/ IM for 3 weeks	–	Improved

Table 2 (*Continued*)

No.	References	Race, Sex, Age (years), Sexual orientation	HIV status CD4 count (cells/mm^3)/ other	Location of the lesions	Onset (before admission)	Serological test results	Histopathology	Immunostaining/ microorganism staining	Treatment	JHR	Resolution time/ improvement
12.	Jiu-Hong Li, et al., 2015 [18]	Asian, male, 35	HIV− DM	Face, trunk, limbs	1 month	TPHA + RPR 1:256	Perivascular infiltration of dense neutrophils, lymphocytes, plasma cells and histiocytes	NA	Benzathine penicillin G 2.4 mU/ week/ IM for 3 weeks	− Prophylactic prednisone 40 mg 1 day before starting penicillin	4 weeks
13.	Wei-Ting Chang, et al., 2015 [19]	Asian, male, 22	HIV+ 360	Face, trunk, limbs	1 week	RPR 1:4 TPHA 1:320	Perivascular and interstitial infiltrate of neutrophils, lymphocytes, histiocytes, and some plasma cells in the dermis	NA	Penicillin G aqueous 24 mU/day/ IV for 2 weeks	−	Several days
14.	Wei-Ting Chang, et al., 2015 [19]	Asian, male, 26, MSM	HIV+ 88	Face, trunk, limbs, genitalia	3 weeks	RPR 1:512 TPHA 1:20.480	Dense lymphohistiocytic infiltrate in upper and middle dermis, numerous plasma cells	+	Penicillin G aqueous 12 mU/day/ IV for 18 days and ciprofloxacin for 7 days	−	21 days
15.	Hanson, et al., 2015 [20]	Male, 45	HIV+ 441	Back, groin	5 weeks	RPR 1:256	Perivascular granulomatous dermatitis with rare plasma cells	+	Benzathine penicillin G 2.4 mU/ week/IM for 3 weeks	−	NA
16.	Alves, et al., 2015 [21]	Male, 57, MSM	HIV−	Head, neck, trunk, limbs	4 months	RPR 1:128 TPHA 1:5120	Diffuse dermal inflammatory infiltrate composed of plasma cells, histiocytes, and lymphocytes, forming granulomas in the deeper dermis	NA	Benzathine penicillin G 2.4 mU/ week/IM for 3 weeks	−	Improved, healed completely in 6 weeks
17.	Braue, et al., 2015 [3]	African-American, male, 36	HIV+ 450	Head, face, neck, limbs	1 month	FTA-ABS + RPR 1:1024	Prominent dermal infiltrate of epithelioid histiocytes, poorly formed granulomas with giant cells, dermal perifollicular lymphohistiocytic infiltrate	−	Penicillin G aqueous 24 mU/day/ IV for 2 weeks with decreasing dose (because of JHR). then, benzathine penicillin G 2.4 mU/ week/IM for 3 weeks	+	1 week
18.	Yamashita, et al., 2015 [22]	Asian, male, 40, heterosexual	HIV+ 110	Trunk, limbs	4 weeks	RPR + (5.4 RU, card method x4) TP Ag + (2713.6 U)	Dermal vessels showed venulitis with extravasation of red blood cells, abundant neutrophils, histiocytes, a small number of plasma cells, and eosinophils	+	Penicillin G	−	NA
19.	Martinez, et al., 2016 [23]	Male, 54, bisexual	HIV+ 497	Face, trunk, limbs, scrotum, palms, and soles	2 weeks	RPR 1:8 TPHA 1:2560	Not mentioned	+	Benzathine penicillin G 2.4 mU/ week/ IM for 3 weeks	+	NA
20.	Muylaert, et al., 2016 [24]	Female, 50	HIV− alcoholic drug user	Face, trunk, limbs	4 months	VDRL 1:512 FTA-ABS + IgG + IgM +	Confirmed secondary syphilis	NA	Benzathine penicillin G 2.4 mU then Ceftriaxone for 14 days	+	2 weeks
21.	Ortigosa, et al., 2016 [25]	White, female, 53	HIV− DM	Head, chest, limbs	20 days	VDRL 1:8 FTA-ABS +	A cluster of non-caseating granulomas, plasma cells, rare eosinophils, endothelial swelling in the dermis	NA	Benzathine penicillin G 2.4 mU/ week/IM for 3 weeks and prednisone 60 mg PO daily	−	NA

Table 2 (*Continued*)

No.	References	Race, Sex, Age (years), Sexual orientation	HIV status CD4 count (cells/mm^3)/ other	Location of the lesions	Onset (before admission)	Serological test results	Histopathology	Immunostaining/ microorganism staining	Treatment	JHR	Resolution time/ improvement
22.	Borges-costa, 2016 [26]	White, male, 42, heterosexual	HIV+ 435	Trunk, upper limbs	2 weeks	TPHA and VDRL >1:256	NA	NA	Benzathine penicillin G 2.4 mU/IM	–	Improved
23.	Borges-costa, 2016 [26]	White, male, 42, heterosexual	HIV+ 435	Trunk, upper limbs	2-8 weeks	TPHA and VDRL >1:256	NA	NA	Benzathine penicillin G 2.4 mU/IM	–	Improved
24.	Borges-costa, 2016 [26]	White, male, 42, heterosexual	HIV+ 435	Head, trunk, upper limbs	2 months	TPHA and VDRL >1:256	NA	NA	Benzathine penicillin G 2.4 mU/IM	–	Improved
25.	Sammet and Draenert, 2016 [27]	Male, 40, bisexual	HIV+ 360	Trunk, generalized	3 previous episodes	TPPA 320.000 (2010) 1.28 mill (2012) 320.000 (2014) RPR	NA	NA	Ceftriaxone 2 g/day/ IV for 3 weeks	– Prophylactic prednisolone 1 mg/kg PO single dose	1 week
26.	Krase, et al., 2016 [28]	Asian, male, 43	HIV– CKD DM	Trunk, limbs	Several months	FTA-ABS + RPR 1:4	Perivascular infiltrate of lymphocytes, numerous plasma cells, and scattered eosinophils	NA	Benzathine penicillin G 2.4 mU/ week /IM for 3 weeks	–	Healed completely in 3 months
27.	Delgado and Caceres, 2017 [29]	Male, 25	HIV+ 108	Face, chest, limbs	1 month	RPR 1:128, FTA-ABS +	Chronic, granulomatous, noncaseating infiltrate with plasma cells in the dermis	NA	Benzathine penicillin G	–	Improved
28.	Mohan, et al., 2017 [30]	Male, 36	HIV+ 57	Face, trunk, limbs	6 weeks	RPR 1:64	Lichenoid, psoriasiform, granulomatous dermatitis	+	Doxycycline 100 mg bd PO	–	1 week
29.	Rao, et al., 2017 [31]	Asian, male, 35, heterosexual	HIV–	Face, trunk, limbs	1 month	VDRL 1:32 TPHA 1:60	A dense collection of neutrophils, lymphocytes, few plasma cells in the dermis, PMN cells in the vessels wall (endarteritis obliterans)	NA	Benzathine penicillin G 2.4 mU/ week IM	–	Improved
30.	Johnson and Spivak, 2017 [32]	Male, 41	HIV+ 629	Right foot, left chest	9 months	RPR 1:1024	Abundance of plasma cells and endothelial hyperplasia	–	Benzathine penicillin G 2.4 mU/ week/IM for 3 weeks	–	72 hours
31.	Mena Lora, et al., 2017 [33]	Male, 58, MSM	HIV+ 463	Trunk, limbs, testicles	2 weeks	RPR 1:256	Dense dermal plasma cell infiltrates with an overlying purulent serum crust and reactive hyperplastic epidermal changes	–	Benzathine penicillin G 2.4 mU/ week/IM single dose	–	1 week
32.	Faraone and Fortini, 2017 [34]	White, female, 86, Heterosexual	HIV–	Tongue, face, trunk, limbs	4 months	TPHA 1:10.240 VDRL +	Epithelial ulceration and an intense perivascular inflammatory infiltrate of the lamina propria, rich in plasma cells	NA	Ceftriaxone for 2 weeks	–	Rapid (healed completely in 1 month)
33.	Gevorgyan, et al., 2017 [35]	Male, 41	HIV+ 101	Face, trunk, limbs, scalp, soles	4 months	TP Ab + RPR 1:64	NA	NA	Benzathine penicillin G 2.4 mU/ week /IM for 3 weeks	+	2 days (healed completely in 1 month)

Table 2 (*Continued*)

No.	References	Race, Sex, Age (years), Sexual orientation	HIV status CD4 count (cells/mm^3)/ other	Location of the lesions	Onset (before admission)	Serological test results	Histopathology	Immunost-aining/ microor-ganism staining	Treatment	JHR	Resolution time/ improvement
			Drug user								
34.	Zanella, et al., 2017 [2]	Male, 42	HIV+	Face, trunk, limbs, palmoplantar, oral and genital mucosa	2 months	VDRL 1:128	Lymphohistiocytic infiltrate with eosinophils and leucocytes, and epithelioid cells with multinucleated giant cells	NA	Benzathine penicillin G 2.4 mU/ week/IM for 3 weeks	+	Improved after treatment
			140			TPHA +					
35.	Zanella, et al., 2017 [2]	Female, 42	HIV+	Face, tongue, back	2 months	VDRL 1:64	Deep perivascular dermatitis	NA	Ceftriaxone 2 g/day for 2 weeks	–	Improved after treatment
			586			TPHA +				Prophylactic corticosteroids	
36.	Yap, et al., 2018 [36]	Male, 71	HIV+	Trunk, limb, palms, and soles	2 weeks	RPR 1:256	Epidermal ulceration with a dense dermal infiltrate consisting predominantly of mononuclear cells, abundant histiocytes, and plasma cells	NA	Aqueous penicillin G 12 mU/day/ IV for 15 days	–	2 weeks
			252			TPPA +				Prophylactic prednisolone 60 mg/day for 5 days	
37.	Sun, et al., 2018 [37]	Asian, male, 23	HIV+	Face, trunk, limbs	2 months	Treponemal test +	NA	+	Doxycycline 100 mg/ 12 hours/ PO for 2 weeks	–	2 weeks
			Decreased CD4								
38.	Yang, et al., 2018 [38]	Asian, male, 52	HIV+	Face	6 months	Treponemal test +	NA	+	Benzathine penicillin G 2.4 mU/ week/IM for 3 weeks	–	1 week
39.	Fustà-Novell X, et al. 2018 [39]	Hispanic, male, 39, MSM	HIV+	Palmopl-antar, face, trunk, scalp	2 weeks	VDRL 1:128	Dermatitis lichenoid (lymphocytes, histiocytes, plasma cells).	+	Benzathine penicillin G 2.4 mU/ week/IM for 3 weeks	+	Improved
			171								
40.	Fustà-Novell X, et al., 2018 [39]	Hispanic, male, 36, MSM	HIV+	Palmopl-antar, nail, scalp, face	3 weeks	VDRL 1:250	Dermatitis spongiosa (histiocytes, plasma cells).	+	Penicillin G aqueous 24 mU/day/ IV for 15 days	+	Improved
			250								
41.	Fustà-Novell X, et al., 2018 [39]	Hispanic, male, 54, MSM	HIV+	Palmopl-antar, limbs	1 month	VDRL 1:512	Dermatitis lichenoid (lymphocytes, histiocytes, plasma cells).	–	Benzathine penicillin G 2.4 mU/ week/IM for 3 weeks	–	Improved
			697								
42.	Fustà-Novell X, et al., 2018 [39]	Hispanic, male, 26, MSM	HIV+	Palmopl-antar, scalp, limbs	1 month	VDRL 1:256	Dermatitis abscessed (lymphocytes, histiocytes, plasma cells).	–	Benzathine penicillin G 2.4 mU/ IM single dose	–	Improved
			790								
43.	Mitteldorf, et al., 2018 [7]	Caucasian, male, 42	HIV+	Trunk	6 weeks	NA	Lichenoid infiltrate, histiocytes. and plasma cells in the dermis	+	Penicillin G aqueous 30 mU/ day/ IV for 2 weeks	–	Few weeks
			312							Prophylactic prednisone 60 mg single dose	
44.	Pradhan, et al., 2018 [9]	Female, 35, heterosexual	HIV–	Face, trunk, limbs, genital, palm, sole, scalp	3 weeks	VDRL 1:64	Plasma cells in the vessel wall and thrombosed vessels in the dermis with endarteritis	NA	Doxycycline 100 mg/ 12 hours/ PO for 3 weeks	–	2 weeks
						TPHA 1:160					
45.	Rockwood, and Nwokolo, 2018 [10]	White, male, 41, heterosexual	HIV–	Face, trunk, limbs, left testicular mass	2 weeks	TPPA +	Chronic epididymo-orchitis with occasional poorly formed granulomas	+	Doxycycline 100 mg/ 12 hours/ PO for 4 weeks	–	4 weeks
						RPR 1:256					

Abbreviations: FTA-ABS, fluorescent treponemal antibody absorbed; IgG, immunoglobulin G; IgM, immunoglobulin M; JHR, Jarisch-Herxheimer reaction; IM; intramuscular; MSM, men who have sex with men; NA, not available; PO, per os (by mouth); RPR, rapid plasma regain; TP Ab, *Treponema pallidum* antibody; TPHA, *Treponema pallidum* hemagglutination test; TPPA, *Treponema pallidum* particle agglutination; VDRL, Venereal Diseases Research Laboratory.

The majority of cases occurred in men (84%), the median age of presentation is 41 years with the 40-44 years old age group being the most frequently affected. The most frequent cutaneous manifestations were ulceronodular lesions with an adherent crust on the central surface affecting the face, trunk, and limbs. with half of patients with HIV infection having a CD4 cell count in the 200-499 cells/mm^3 range. The majority of patients were treated with benzathine penicillin G or aqueous penicillin G, and all patients experienced a rapid clinical improvement following antibiotic therapy. JHR was reported in 20% of patients, despite the majority of them having been given prophylactic corticosteroids. In the face of the increased number of cases of this rare form of syphilis regardless of the immune status, dermatologists and general practitioners should be attentive to the occurrence of MS in order to allow early diagnosis and treatment, hence reducing their morbidity.

Conflicts of interest

The authors declare no conflicts of interest.

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