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Syphilitic pneumonia: case report and systematic review

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SUMMARY

Syphilitic pneumonia is a rare secondary form of *Treponema pallidum* infection. In this article, we present a case of syphilitic pneumonia in a patient living with Human Immunodeficiency Virus (HIV) with good immune-virological status. We also performed a systematic review of literature and we found 43 cases of syphilitic pneumonia described since 1886. We added our case report and performed a statistical analysis. Our analysis showed that 40/44 (91%) were males, with a median age of 46 years old (IQR 37-56), 9/28 (32%) were people living with HIV (data not available for 16/44 patients), 17/27 (63%) had syphilitic-related hepatitis during the clinical presentation (data not available for 17/44 patients), and 28/42 (66.6%) of patients had maculopapular rash compatible with secondary forms (data not available for 2/42 patients). Furthermore, 74.4% of patients had nodular lesions on chest X-ray or pulmonary Computed Tomography scan. Given the high rate of nodular pneumonia among patients, clinicians should consider it as a common presentation in syphilitic pneumonia

Keywords: syphilis, pulmonary syphilis, syphilitic pneumonia, nodular lesions, atypical pneumonia.

INTRODUCTION

Syphilis is a sexually transmitted infectious disease (STD) caused by the spirochete *Treponema pallidum subp. pallidum* (*T. pallidum*). Recognized as a significant public health challenge for centuries, over the last few years it was observed an increase in syphilitic cases, particularly in certain populations and geographical areas, making it a persistent concern for healthcare providers and public health officials. During the last decades, emerging trends of syphilis incidence has been noticed worldwide, especially among Male who have Sex with Man (MSM), People Who Injected Drugs (PWID) and People Living with HIV (PLWH). Amongst these populations, clinical presentation may differ, sometimes due to immune alteration (i.e. HIV) and therefore diagnosis can be difficult [1-3]. So, syphilitic infection has become a public health challenge, as well as Monkeypox outbreaks, which affects similar at-risk population and both diseases may have similar cutaneous presentations [4, 5].

Syphilis is well-known as "the great imitator", given the wide range of clinical manifestations, typically ranging from the chancre of the primary form to the mucocutaneous lesions of the secondary forms, and the Central Nervous System involvement of the tertiary forms (sometimes may be a manifestation of early neurosyphilis). Due to the multi-organ involvement, signs and symptoms of secondary and tertiary forms are more complex and/or blurred, and often under-recog-

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nized. For example, rare secondary forms manifestations may be hepatitis or pneumonia. Although it is considered a rare presentation, pneumonia is not a novelty and the first case report in literature was published in 1886 [6, 7]. This condition, often unrecognized, let us understand the importance of considering syphilis in the differential diagnosis of pneumonia, especially in patients with risk factors for sexually transmitted diseases. Patients with syphilitic pneumonia have classical respiratory symptoms such as cough, fever, dyspnea and chest pain, mimicking other infectious and non-infectious lung diseases [6, 7]. Defined as a secondary syphilitic form, the gold standard therapy remains i.m. benzylpenicillin 2.4 MU, with a favorable prognosis after treatment. However, delayed diagnosis and treatment may lead to complications, underscoring the importance of early recognition and intervention. In this article we present a case of syphilitic pneumonia in an HIV-infected patient and a review of the literature on similar syphilitic presentations.

CASE REPORT

A 31-year-old man who have sex with man (MSM), living with HIV and with mild dyslipidemia went to our Emergency Room (ER). Two months earlier he performed a routinary blood test in our outpatients clinic, which showed a good immune-virological status: HIV-RNA not detected, CD4+ count 597/uL (30%), CD4+/CD8+ ratio 0.7, RPR and TPPA serology were negative. He presented with fever, asthenia, vomiting, and abdominal pain lasting for a few days, so he was admitted to our Infectious Disease Unit, ARNAS Civico, Palermo (Italy). The patient was alerted and oriented, he had arterial pressure of 100/60 mmHg, SpO2 95% in room air, a heart rate of 88 bpm, and a body temperature of 37.2 C. Physical examination showed a non-pruritic papular-erythematous skin rash on the trunk, back, limbs, and palms of the hands with mild sweating; at abdominal examination, the patient had mild pain in the right hypochondrium, and cardiopulmonary examination was unremarkable. The patient denied sexual intercourse in the past year. Blood test examination on day 1 showed a normal white blood cells (WBC) count 9,600 cells/uL (neutrophils 61%, lymphocytes 23%), mild increase in C-reactive protein (CRP) 3.22 mg/dL, elevated liver enzyme with aspartate transaminase (AST) 63 U/L, alanine transaminase (ALT) 98 U/L, total bilirubin 3.06mg/dL (direct bilirubin 2.7), γ-glutamyl transferase 579 U/L and alkaline phosphatase (ALP) 1362 U/L. Then, a point-of-care abdominal ultrasound was performed and it was unremarkable. On day 2, the patient had a sudden onset of dyspnea, tachypnea (respiratory rate 24 breaths per minute), and decreased oxygen saturation SpO2 90% in room air. The arterial blood gas analysis showed respiratory alkalosis due to respiratory failure with pH 7.48, pO2 55 mmHg, pCO2 35 mmHg, and the patient required oxygen supplementation with Venturi Mask (VM) 35% followed by an increase of peripheral oxygen saturation (SpO2 96%). Microbiological examinations and a pulmonary CT scan with intravenous contrast were required. The CT scan (Figure 1) excluded pulmonary embolism but showed multiple millimetric rounded nodular lesions in both lungs (suspected for mycotic foci, secondary lesions, or other). Some hypotheses in differential diagnosis were excluded, i.e. pulmonary amyloidosis and sarcoidosis in the absence of risk factors or cryptococcosis and AIDS-related Kaposi sarcoma given the persistent good immune-virological status, septic pulmonary embolism was excluded after a negative echocardiogram. However, the patient's respiratory distress had induced us to start on day 2 antibiotic therapy with ceftriaxone 1g i.v.

We performed a wide range of microbiological tests and all turned out negative: a respiratory

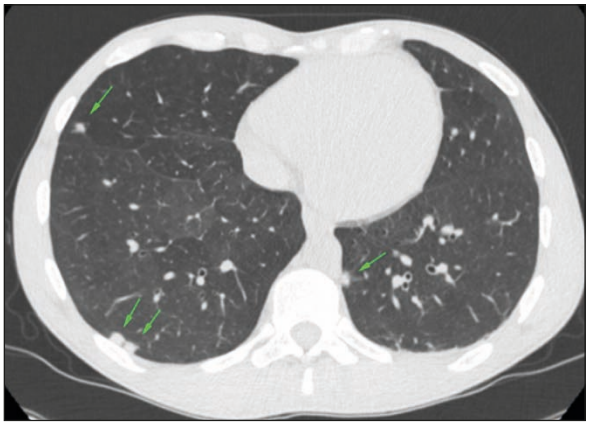

Figure 1 - Pulmonary CT scan on day 2, showing millimetric rounded nodular lesions on both lungs (green arrows).

panel film array on nasal swab (for viruses and bacteria causing common pneumonia), urinary Legionella and Pneumococcus Antigens, Interferon Gamma Release Assay (IGRA) test, serum beta-D-glucan and galactomannan, Widal-Wright reaction, IgM/IgG *Rickettsia* . Given these data, we excluded most of the common causes of pneumonia. HIV viral load on day 2 was not detected, CD4+ count was >600 cells/µL (31%) with a CD4+/CD8+ ratio 0.7. Serology for syphilis turned out positive: RPR 1:32 and TPPA 1:40,960. After a brief literature research, we noticed that in some cases, syphilitic pneumonia may present with nodular lesions. So we decided to search *Treponema pallidum* DNA on bronchoalveolar lavage (BAL) in addition to more common pneumonia pathogens. On day 6 the following microbiological tests on bronchoalveolar lavage (BAL) were performed: culture for bacteria/fungi, PCR and Ziehl-Neelsen for mycobacteria, galactomannan, Aspergillus DNA, *Pneumocystis jirovecii* DNA, film array panel for virus/bacteria. All these results were negative, except for *Treponema pallidum* DNA, that turned out positive. So, antibiotic therapy was switched on intramuscular Benzylpenicillin 2.4 MU daily. However, after 4 days of ceftriaxone therapy, we had noticed an improvement in blood test with reduction in inflammatory markers (CRP 3 mg/dL, AST 44 U/L, ALT 64 U/L, total bilirubin 1.46 mg/dL) and an improvement in respiratory performance (on day 6, the patient's saturation was 98% in VM 24%). This could be related to the fact that ceftriaxone is also a second line therapy for syphilis. On day 10 the patient was discharged with a normal oxygen saturation level in room air, CRP 2.1 mg/dL, AST 53 U/L, ALT 82 U/L, alkaline phosphatase 792 U/L, GGT 300, bilirubin 1.03 mg/dL. Due to mild elevation in liver enzymes seven days course of doxycycline 100mg bid was prescribed. Three months after discharge, the patient performed a follow-up blood test examination that was unremarkable, as well as HIV-RNA and CD4+ count, and serology for syphilis that showed a negative RPR and a reduced TPPA 1:5,120 and a pulmonary CT scan that showed a volumetric reduction of the nodular lesions on both lungs (Figure 2).

Followed procedures were in accordance with Helsinky Declaration and an informed consent was obtained by the patient

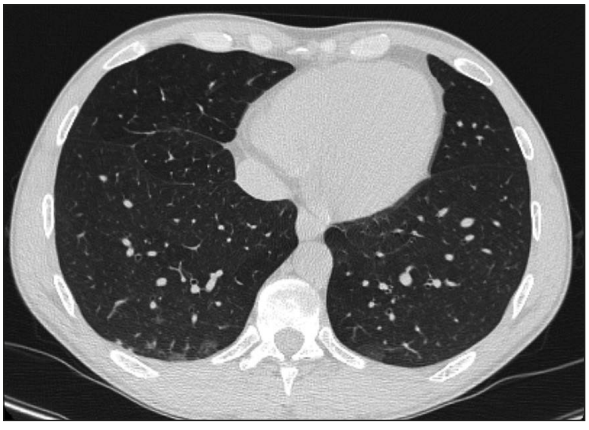

Figure 2 - Pulmonary CT scan performed 3 months after discharge showed a volumetric reduction of the nodular lesions on both lungs.

LITERATURE REVIEW

Methods

A systematic search was performed without language restrictions using Pubmed combining the terms ((Pulmon* OR Pneum*) AND (syphil*)) displaying results until June 1, 2024. All references listed were furthermore hand-searched for relevant articles.

We included articles written in English language, in which authors reported a case of confirmed syphilis with radiologic evidence of pulmonary involvement. We excluded cases with only clinical diagnosis, without radiologic and serologic evidences. Cases involving congenital syphilis were excluded. The following variables were considered: age, gender, pre-existent conditions, risk factors, HIV serology status, clinical presentation (if there was cutaneous rash, fever, weight loss, night sweats, cough, pleuritic pain, and dyspnea), syphilis serology status, the type of radiologic exam and its findings, the therapeutic regimen, clinical outcome and radiological findings at follow up (if any).

The systematic review followed PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) guidelines. The selected articles were reviewed by 3 independent reviewers (A.G., M.A., G.P.). Discrepancies between reviewers were discussed with a different reviewer. A statistical analysis was conducted by G.P., using SPSS © v.29 (Figure 3).

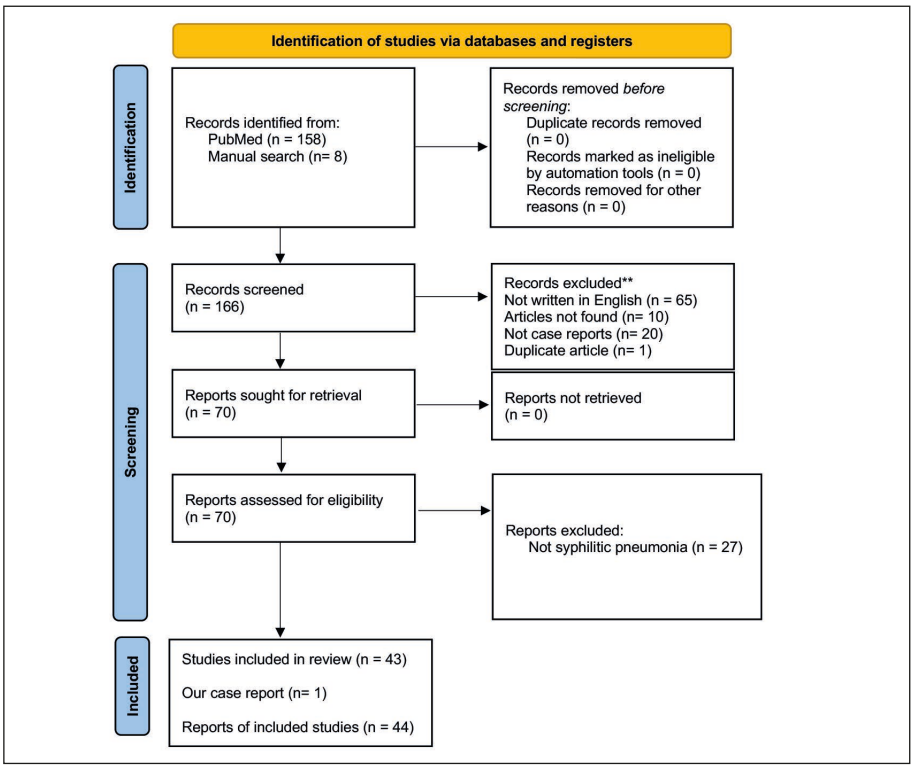

Figure 3
PRISMA flow chart with study retrieval and selection process.

RESULTS

In our review, we included 43 case reports and added our case. The first description of syphilitc pneumonia was reported in 1886 in a 30-year-old male in a Calcutta Hospital (India), but it was not included in the present review because the diagnosis was based only on clinical criteria and it did not fill our inclusion criteria [6].
We collected relevant information such as demo-

Table 1 - Overview of all available similar cases in the literature, relevant information, treatment, and outcome.

DOI	*Year*	*Nation*	*Age*	*Sex*	*Radiology*				*Cholangitis*	*HIV*	*Rash*	*Treatment*	*Death*
					Nodular	*GGO*	*Excavation*	*Pleural effusion*					
[8]	2018	France	69	M	Y	Y	N	Y		N	Y	Pen-G	N
[9]	2018	Thailand	30	M	Y	Y	N	Y		Y	Y	Pen-B	N
[10]	2019	Spain	49	M	Y	N	N	N	Y	Y	N	Pen-G 2w	N
[11]	2021	France	46	M	Y	N	N	N	N	N	Y	Pen-G 2w	N
[12]	2018	Japan	27	M	Y	N	N		N	N	N	Amoxicillin 2w	N
[13]	2022	Morocco	74	M	Y	N	N	N	N	N	Y	Pen-G	N
[14]	2011	South Korea	57	m	Y	N	N	N	Y		N	Pen-B	N
[15]	2006	France	34	M	Y	N	Y		Y	Y	Y	Pen-G 2w	N
[16]	2019	USA	19	M	Y	N	N	N	Y		N	P/T+vanco+ ceftriaxone	N

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DOI	Year	Nation	Age	Sex	Radiology				Cholangitis	HIV	Rash	Treatment	Death
					Nodular	GGO	Excavation	Pleural effusion					
[17]	2017	Japan	62	M	Y	N	N	N		Y		Pen-G 2w	Y
[18]	2018	Japan	39	M	Y	N	N	Y	Y	N	Y	amoxicillin 3m	N
[19]	2020	South Africa	46	M	Y	N	N	N		N	N	Pen-B 2w	N
[20]	2014	Cina	50	M	Y	N	N	N			Y	Pen-B	N
[21]	2015	Argentina	51	M	Y	Y	Y			N	Y	Pen-G 2w	N
[22]	2017	Cina	55	F							N	Pen-B 3w*	N
[23]	2019	Brasile	26	M	Y	Y	N	N	N	N	N	Pen-B 3w	N
[24]	2023	Giappone	78	M	Y	Y	Y	N	N	N		Pen-B 2w	N
[7]	1933	USA	60	M	N	N	N	N			N		N
[25]	2011	South Korea	51	M	Y	N	Y	N	Y	N	Y	Pen-B	N
[26]	2011	Canada	56	F	Y	N	Y	Y	Y	N	Y	Pen-B 3w	N
[27]	2022	Cina	32	M	Y	N	N	Y	N	N	Y	Pen-B 3w	N
[28]	1988	Croazia	72	F	N		N	N	N		N	Pen-B	N
[29]	1985	USA	37	M	Y	N	N	N	N		Y	tetraciclin 2w	N
[30]	1983	USA	39	M	Y	N	Y	N	Y		Y	Pen-B	N
[31]	2016	France	52	M	Y	N	N	N	Y	N	Y	Pen-B 3w	N
[32]	1992	USA	33	M	Y	N	N	N	Y		Y	Pen-B 2w	N
[33]	1987	Japan	48	M	N		N	N	Y		Y	amoxicillin 2w + Pen B 4w	N
[34]	1981	Swiss	31	M	N	N	N	Y	Y		Y	Pen-B 3w	N
[35]	2021	UK	45	M	Y	N	Y	N	Y	Y	Y	Pen-B	N
[36]	1955	UK	56	M	N	N	N	N			N	Pen-B	N
[37]	2012	USA	40	M	Y	N	N	N	N	N	Y	Pen-B 3w	N
[38]	1994	USA	37	M	N		N	N	N	Y	Y	Pen-B 2w	N
[39]	2019	Japan	34	M	N	N	Y	N	Y	N	Y	Amoxicillin 2w + Pen-B 2w	N
[40]	2015	Brasil	37	M	Y	N					Y	Pen-G	N
[41]	1968	USA	52	M	Y		N	N			Y	Pen-G 2w	N
[42]	1997	USA	68	M	N			Y		Y	Y	Pen-G 3w	N
[43]	2004	USA	50	M	Y	Y	N	N	Y	N	Y	Pen-B	N
[44]	2012	Qatar	38	M	N	N	N	Y			Y	meropenem	N
[45]	2023	Japan	57	M	Y						N	Amoxicillina	N
[46]	2023	USA	65	M	N					Y	Y	Pen-G	N
[47]	2023	Germany	46	M	Y	N	Y	N		N	N	Ceftriaxone 2w	N
[48]	2017	Portugal	44	M	N	N	N	N	Y	N	N	Pen-G	N
[49]	2007	Brasil	37	M	Y	N	Y	N		N	N	Pen-G	N
Our case	2023	Italy	35	M	Y	N	N	N	Y	Y	Y	Ceftriaxone 3d, doxycycline 1w	N

Notes: Y: yes; N: no; d: day/s; w= week/s; m= month/s; DOI: Digital Object Identifier. HIV: Human Immunodeficience Virus. Pen: penicillin. USA: United States of America. UK: United Kingdom. P/T: piperacillin/tazobactam. Vanco: vancomycin.

graphic data, sex, age, HIV infection, treatment, outcome, radiographical appearance and the presence of a skin rash (Table 1). Only 1/44 (2.3%) patients died during hospitalization, a 19-year-old male, with hypersexual and bipolar disorders, with unknown HIV status who died 24 hours after admission. The favorable outcome of the other 43/44 (97.7%) patients demonstrated the low mortality rate of secondary form of syphilis and a good response to penicillin.
Results are summarized in Table 2. Most patients 40/44 (91%) were male, with a median age of 46 years (37-56, IQR range 25%-75%). HIV patients were 9/28 (32%), but unfortunately, 16/44 did not perform the test for HIV. The high rate of male (91%) among patients with syphilitic pneumonia, could be a consequence of the higher prevalence of syphilis in males. Very interesting is the higher rate of nodular lesions on chest-X ray or CT scan 32/43 (74.4%) which could be defined as a specific pattern for syphilitic pneumonia, despite finding ground-glass opacities areas 6/36 (16.7%) and excavated or necrotic areas 10/39 (25.6%). In two-thirds of the cases, there were observed other manifestations of secondary syphilis, such as maculopapular rash in 28/42 (66.6%) and hepatitis or cholestasis in 17/27 (63%).
Positive PCR for *T. pallidum* was found on BAL in 8 patients and on pulmonary biopsies in 3 cases; positive immunohistochemistry on BAL for 1 patient and on biopsies for other 2 patients.
Histologically, on biopsies, syphilitic pneumonia is characterized by the presence of granulomas or lymphoplasmacytic infiltrates. Even epithelioid cell granulomas occur occasionally in secondary syphilis, especially in the late stage, and less frequent is the presence of *T. pallidum* on biopsy.

Table 2 - Demographic data and clinical data from literature review.

	N (%)	*Data not available*
Sex (M)	40/44 (91%)	–
Age, years (median, IQR)	46 (37 – 56)	–
HIV positive	9/28 (32%)	16/44
CT scan: Nodular	32/43 (74.4%)	1/44
CT scan: GGO	6/36 (16.7%)	8/44
CT scan: Escavated/ necrotic	10/39 (25.6%)	5/44
CT scan: Pleural effusion	8/37 (21.6%)	7/44
Hepatitis / Cholestasis[1]	17/27 (63%)[2]	17/44
Maculo-papular rash[3]	28/42 (66.6%)	2/44
PCR on lung sample	8 BAL, 3 biopsy	33/44
Immunohistochemistry	1 BAL, 2 biopsy	41/44

Notes: M: male. CT: computed tomography. HIV: Human Immunodeficiency Virus. GGO: ground glass area. PCR: polymerase chain reaction. BAL: bronchoalveolar lavage. [1]Defined as «pain in right hypochondrium or rise in hepatocytes/cholangiocyte markers»; [2]3 cases had risen in alkaline phosphatases only; [3]Defined as a typical syphilitic rash on secondary forms.

DISCUSSION

Syphilitic pneumonia should be considered in the differential diagnosis of atypical pneumonia cases, even though it is a rare secondary form of syphilis. We would like to focus on the diagnostic challenges in our case. The nodular lung involvement is an infrequent presentation of typical and atypical pneumonia (caused by viruses or bacteria) and even of metastatic spread (septic or neoplastic). In our case we were induced to widen our ethiological hypotheses because of the complex presentation (well defined nodular lesions, skin rash, cholestatic hepatitis without gallbladder lithiasis) in a patient with several risk factors (PLWH, MSM, although he denied recent sexual intercourse).
The diagnosis is often challenging due to the non-specific nature of the symptoms and the rarity of the condition, and sometimes it could be observed in tertiary forms making differential diagnosis even more difficult. In our review, nodular pneumonia is the most common radiological finding, with or without excavation.
Rounded nodular lesions should be addressed to many infectious and non-infectious diseases, such as: septic pulmonary embolism, viral, bacterial, or fungal pneumonia, mycobacterial pneumonia, but also sarcoidosis or amyloidosis, osteosarcoma metastases, AIDS-related Kaposi sarcoma, pulmonary lymphoma. These diseases must be considered in the differential diagnosis.
In 1983 Diana Lewis Coleman and colleagues tried to define criteria for syphilitic pneumonia shedding light on a so far unrecognized disease [30]. Authors hypothesized 5 criteria to define syphilitic pneumonia: "a history and physical findings of typical secondary syphilis; serological test results positive for

syphilis; exclusion of other forms of pulmonary disease when possible by findings of serological tests, sputum smears and cultures and cytological examination of sputum; therapeutic response to anti-syphilitic treatment visible on a radiograph; pulmonary abnormalities seen on radiographs with or without associated pulmonary symptoms or signs". Given the results of our review, with a 74.4% of nodular findings on radiological examination, we would like to suggest one modification for the criteria for syphilitic pneumonia, on the "radiological criteria": as "pulmonary abnormalities, particularly in the presence of nodular lesions on chest X-ray or pulmonary CT scan, with or without associated pulmonary symptoms or signs".

Furthermore, we treated our patient with a second-line therapy (due to a delayed diagnosis) and we observed a mild but constant improvement. However, we would like to remember that the first-line therapy is a penicillin-based therapy, and that a different treatment could lead a partial or a non-response. Finally, we may consider that a delayed diagnosis (in terms of month or years) could lead to a worse or even a fatal outcome.

Since syphilis is known as "the great imitator", atypical syphilis manifestation should always be considered, in particular in immunocompromised patients. Some authors reported atypical syphilitic cutaneous manifestations (nodular, annular, pustolar, psoriasiform rash) up to 25% of cases, mainly in people with VDRL > 1:32 [50].

CONCLUSIONS

Syphilitic pneumonia is a well-known secondary form of syphilis. Diagnosis poses a wide range of differential diagnoses if the patient has only a pulmonary involvement. However, history, serology, and physical findings of syphilis could guide clinicians in the diagnosis. Furthermore, pulmonary rounded nodular lesions on chest X-ray or pulmonary CT scan should be considered as a typical pattern for pulmonary syphilis, and molecular tests on lung tissue or bronchoalveolar lavage may help to confirm the disease.

Finally, we suggest clinician to keep attention on sexually transmitted diseases, especially in at-risk populations with cutaneous rash (although mild and non-well defined) and/or cholestatic hepatitis (with a lithiasis-free gallbladder). Health authorities should improve the screening protocols for syphilis in these populations, and clinicians should pay attention to atypical pneumonia presentations in these populations: physician should also think of "zebras" [51].

Conflicts of interest
Authors declare no conflicts of interest.

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Informed consent statement
An informed consent was obtained by the patient.

Author contributions
Conceptualization, GP and CIa; methodology, GP and AC; validation, CIa and AC; data curation, GP, AG and MA; writing - original draft preparation, GP, AG, MA; writing, review and editing, AC, CIa; visualization, GP, MA AG, CB, FGM, CIm, GC, ALS, GGM, D.M., AC, CIa; supervision, AC and CI; All authors have read and agreed to the published version of the manuscript.

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