Chapter

False-Positive Serologic Reactions for Syphilis

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Abstract

The epidemiologic situation of syphilitic infection warrants attention to diagnostic methods. Nontreponemal tests (rapid plasma regain, Venereal Disease Research Laboratory) are less reliable, as there are certain situations when false-positive reactions for syphilis antibodies may appear. Variable examinations were performed and proved that it was necessary to assess the titer of antibodies, as well as confirmation of the diagnosis by treponemal tests (fluorescent treponemal antibody, treponema pallidum hemagglutination assay, enzyme immunoassay, Western blot), were obligatory. In recent decades, new methods were elaborated (e.g., BioPlex total screen, tests with β2-GPI-dependent anticardiolipin antibody, the ARCHITECT syphilis treponema pallidum chemiluminescent immunoassay, the Elecsys immunoassay (Roche Diagnostics)). We present the review of publications on syphilis serologic diagnostics and present our own research. We did not find any mention of a false-positive test in atopic dermatitis and present a case of false-positive reactions for syphilis in such patients.

Keywords: syphilis, serologic diagnostic, nontreponemal tests, treponemal tests, false-positive serologic reactions

1. Introduction

The incidence of syphilis has been increasing from the end of twentieth century—early 2000s [1, 2], warranting attention to diagnostic methods. Now we have serious problems in serologic diagnostic of different clinical forms of syphilis, including those of atypical duration, cardiovascular syphilis, neurosyphilis, congenital syphilis, latent forms, etc. Nontreponemal tests (rapid plasma regain, Venereal Disease Research Laboratory) are less reliable as there are certain situations when false-positive reactions for syphilis antibodies may appear. Variable examinations were performed and proved that it was necessary to assess the titer of antibodies, as well as confirmation of the diagnosis by treponemal tests (fluorescent treponemal antibody, treponema pallidum hemagglutination assay, enzyme immunoassay, Western blot), were obligatory. In recent decades, new methods were elaborated (e.g., BioPlex total screen, tests with β2-GPI-dependent anticardiolipin antibody, the ARCHITECT syphilis treponema pallidum chemiluminescent immunoassay, the Elecsys immunoassay (Roche Diagnostics)) [3–15] to exclude false-positive and false-negative reactions. Syphilis as the "great imitator" may be presented by a variety

of clinical signs and symptoms of infection that can be easily confused with other diseases [16–18]. But in spite of miscellaneous investigations, complexities in the diagnosis of syphilis continue to challenge clinicians [19–24]. For instance, discordant maternal reverse-sequence serology is still a problem in diagnosis of congenital syphilis [25, 26]. We analyzed the papers presented in PUB MED. By the end of December 2021, the search query "False-positive reactions for syphilis" gave 743 publications. We included the papers published in English from January 2010 till the end of December 2021. We excluded the papers publicized earlier than in 2010, written in other languages than English, and those which had nothing to do with our demand "False-positive tests for syphilis". So, we analyzed 88 publications and presented our own research. We did not find any mention of false-positive tests in atopic dermatitis and present a case of false-positive reactions for syphilis in such patients.

2. Clinical situations with false-positive syphilis reactions

A substantial problem is presented now by discordant serologic reactions for syphilis in different clinical situations [27–31]. Huh et al. [32] pointed to the growth of false-positive reactions in syphilis screening assays and proved that the reverse algorithm using Automated Mediace Treponema pallidum latex agglutination (TPLA) as a screening serologic test is preferred over rapid plasma reagin (RPR) assays [32, 33]. Furthermore, the biological false-positive Venereal Disease Research Laboratory (VDRL)—cerebrospinal fluid test is often used in cases when patients are examined without a previous serological diagnosis of syphilis [20]. Palamar et al. retrospectively explored the serologic blood sample and microbiological culture media analysis results of all cornea donors. False-positive serologic results among cornea donors were high [34], which underlines the importance of the improvement of serologic diagnostic in this field. Last year, different clinical situations confirmed the actual need for further serologic investigations [24, 35–37]

Dunseth et al. underlined the necessity of differentiation between analytical false-positive results of lues tests from clinical false-positive results. A positive syphilis IgG screen with negative RPR and T. pallidum particle agglutination assay (TP-PA) confirmatory testing could be considered an analytical false-positive. A positive syphilis IgG with positive TP-PA and negative RPR might be an analytical false-positive due to cross-reacting antibodies or analytical true-positive result in late/latent syphilis or past/treated syphilis with persistent anti-syphilis IgG. Nontreponemal tests may show false-positive screens due to a variety of reasons [38]. Ishihara et al. presented a retrospective study of patients tested for syphilis in a tertiary academic hospital. Among 94,462 subjects, 588 patients had false-positive tests (0.62%). Such cases were noted in patients aged over 60 years, with a history of malignancy and autoimmune diseases [36]. But the false-positive tests for syphilis were noted in children as well [37]. Over all 90% of biologically false-positive reactions are low titer (≤1:4), but (1%) are high-titer (≥1:32) [24]. Such reactions are categorized as either acute (occurring for less than 6 months) or chronic [19, 28]. Acute false-positive reactions are noted in febrile illnesses, immunizations, and pregnancy [29–31, 38–40]. For example, Nwosu et al. examined 2156 women, VDRL was positive in 15 cases (0.70%). Confirmatory T. pallidum hemagglutination assay was positive in 4 of the 15 cases, giving an overall prevalence of 0.19% and a false-positive rate of 73.3%. There was no significant difference in the prevalence of syphilis in relation to maternal age and parity ($P > 0.05$) [41].

As for chronic false-positive reactions, they can be noted in such clinical cases as hepatitis C virus (HCV) infection, intravenous drug use, malignancy, older age, malaria, Chagas disease, tuberculosis, leprosy, and connective tissue diseases [28]. Besides, false-positive test is a characteristic clinical sign in patients with systemic lupus erythematosus [42, 43]. It is proved now that false-positive results of serologic reactions for syphilis may be caused by HCV [44]. Some investigations showed that different types of cryoglobulinemia might be accompanied by acute or chronic false-positive reactions [45].

Further investigation demonstrated that racial and environmental factors, as well as immuno-chromatographic dual syphilis rapid testing may affect [46], and that can be used in clinical practice.

Augenbraun et al. concluded that HCV infection was associated with certain mechanisms changing the immune function including alterations in serological reactions results. He underlined as well that women with HCV were more likely to have biological false-positive syphilis tests than women without HCV [47].

Furthermore, Bright et al. noted that false-positive reactions might be marked in patients treated with pooled human immunoglobulin G infusions [48].

In 2014, Liu et al. named diseases that had not been previously reported to be associated with the classical biological false-positive reaction, such as false-labor, megaloblastic anemias, aplastic anemias, redundant prepuce, congenital malformation of heart, and salpingitis [49].

Nowadays the significance of sera with isolated reactive treponemal chemiluminescence immunoassay (IRTCIA) results is being discussed. It is known that as a rule, women have this phenotype more commonly than men. Bopage et al. presented the results of the examination 19/63 (30.1%) subjects with the IRTCIA phenotype, which were positive in the line immunoblot assay (LIA). It was marked that women were substantially less likely to have definitive results (positive or negative) than men ($p = 0.015$). And women who were pregnant less likely than nonpregnant women to have a negative LIA result (OR 0.57; $p = 0.03$). Record review of 22 different women with IRTCIA reactivity allowed to reveal that 2/22 (9.1%) had HIV and previous syphilis infection, 15/22 (68.2%) were pregnant, and 3 (13.6%) had autoimmune disease [50].

McGready et al. emphasized that the potential impact of false-positive tests should be considered in HIV- positives [51]. And vice versa, false-negative lues tests are noted in HIV- positives subjects [52].

Cantor et al. analyzed a 2004 systematic review of studies of syphilis screening effectiveness, test accuracy, and screening harms in nonpregnant women and adolescents. It was proved that screening HIV-positive men or men who have sex with men (MSM) for syphilis every 3 months is associated with improved syphilis detection [53].

Today there are no doubts that HIV-positive patients [54, 55], MSM, and transgender women are at high risk of acquiring syphilis and HIV infection [56].

The results presented by Kalou et al. indicate that this assay could have a significant impact on the simultaneous screening of HIV and syphilis using a single test device for high-risk populations or pregnant women needing timely care and treatment [57]. Shakya et al. also underlined the importance of simultaneous diagnosis of HIV and syphilis [58].

Grégoire et al. presented the results of the examination of donors who had false-positive tests for HIV, HBV, HCV, or syphilis. Rates of second false-positive results were compared by year of deferral, transmissible disease marker, gender, age, donor

status (new or repeat), and testing platform (same or different) both at qualification for re-entry and afterward. The risk, when analyzed by multivariate analyses, of a second deferral for a false-positive result, both at qualification and 3 years after reentry, was lower for donors deferred on a different platform; this risk was higher for HIV, HCV and syphilis than for HBV and for new donors if tested on the same platform [59]. The importance of thorough examination of HIV subjects with false-positive reactions for syphilis was marked in other investigations as well [60, 61].

Sandes et al. presented the results of analyses of the positive and false-positive tests of treponemal and nontreponemal tests in blood donors and found out that older donors and donors with lower education levels were associated with a higher risk of positivity for syphilis [62].

3. Modern serologic diagnostic

The World Health Organization recommendations of screening for syphilis in a low prevalence population of blood donors using enzyme-linked immune-sorbent assay (ELISA) may be adopted for usage in transfusion services that have the facility of ELISA [63].

On the other hand, the current screening of deceased organ donors by RPR yields a significant number of false-positive results [64].

And vice versa, in patients with positive Lyme screening and negative confirmatory testing, the performance of lues serology should be considered [29, 65, 66]

Park et al. [67], Hoover and Radolf [68], Dassah et al. emphasized the importance of the improvement of the serologic diagnostic [69]. Overall, nontreponemal tests were less sensitive than treponema-specific tests [70].

Nah et al. investigated the efficacy of traditional and reverse syphilis diagnostic algorithms during general health checkups. In total, 1000 blood specimens were obtained from 908 men and 92 women. As a result, the reverse screening algorithm could detect the subjects with possible latent syphilis who were not detected by the traditional algorithm [71].

Rourk and Litwin investigated the recently FDA cleared BioPlex 2200 syphilis total screen and automated RPR assay for the detection of total (IgG/IgM) treponemal and nontreponemal antibodies in the reverse syphilis algorithm. They concluded that the addition of the detection of treponemal IgM antibodies to the IgG/IgM screen had not significantly affected the sensitivity and specificity compared to the original IgG screen. But the addition of the comparable BioPlex RPR assay to the instrumentation significantly reduced the overall labor of syphilis screening and confirmation [72].

Yen-Lieberman et al. noted that regardless of the method, laboratories should develop approaches to identify analytical false-positive results wherever possible [73].

The syphilis testing may be affected by different racial and environmental factors [46], which is necessary to keep in mind at the estimation of serologic results.

Zhou et al. marked a high correlation between electrochemiluminescence immunoassay analyzer and chemiluminescent magnetic microparticle immunoassay. Both had high sensitivity and specificity [74].

The appearance of β2-GPI-dependent anticardiolipin antibody and its association with blood coagulation have been investigated in subjects with classical biological false-positive syphilis reactions. Subjects with false-positive tests for syphilis appeared to be more prone to blood coagulation disorders than syphilis patients,

and these autoantibodies may impact the intrinsic coagulation cascade in cases of false-positive reactions, similar to presumed antiphospholipid antibody syndrome patients [75].

Considering the importance of the diagnosis of syphilis, antibodies to T. pallidum in serum samples should be retested by the improved ELISA method to avoid false-positive results [76]. Different reverse syphilis testing algorithms were proposed [77].

While in screening populations, discrepancies between chemiluminescent microparticle immunoassay and treponema pallidum particle agglutination results are quite prevalent, confirmation by immunoblot assay may be useful [78]. The ARCHITECT syphilis treponema pallidum chemiluminescent immunoassay accurately diagnoses current or past syphilis in pregnancy [79].

The Elecsys immunoassay (Roche Diagnostics) yielded no false-negative results and fewer false-positive results, compared to the other tests [80]. However, Li et al. underlined that the Elecsys® syphilis assay might be confirmed by other treponemal immunoassays [81].

Enders et al. noted that the specificity of the Elecsys syphilis assay in patients with other infections had been 100%; no false-positive samples had been identified [82].

Simčič and Potočnik supported the European Center for Disease Prevention and Control algorithm in the serodiagnosis of syphilis in high-prevalence populations and the use of nontreponemal serology to monitor the response to treatment [83].

Song et al. evaluated diagnostic methods for revealing syphilis in children. False-positive tests for syphilis were higher in the children's group than in the infant's group. The high false-positive rate of enzyme-linked immuno-sorbent assay (ELISA) could be caused by hemolysis. The RPR had low sensitivity in suspected syphilis neonates, and the colloidal gold test (SYP) was suitable for emergency treatment. The treponema pallidum particle agglutination test (TPPA) was fit for the diagnosis of syphilis [84].

It is obvious that further investigations are necessary, and different forms of syphilis need a specific complex of serologic reactions.

4. Own research

Since January 2014 till December 2021, we examined nine patients with false-positive serologic tests for syphilis, aged 48—79. They had no medical documentation with any mentioning of syphilis was presented. They denied syphilitic infection in the past. Three patients were diagnosed with breast cancer, three patients were diagnosed with ovarian cancer, two patients were diagnosed with lupus erythematosus, and one patient was diagnosed with liver cancer.

A 79-year-old patient with liver cancer suffered from diabetes mellitus and obesity as well. The patient denied syphilitic infection in anamnesis. No clinical signs of syphilis were revealed. He was examined thoroughly, and four times during examination and before the operation the micro-reaction of precipitation with plasma and in activated serum and inactivated serum was false-positive, treponemal tests (reaction of passive hemagglutination, immunoenzyme analysis for treponema pallidum) were negative.

A 49-year-old patient suffering from chronic cholecystitis, a 50-year-old patient suffering from thyroiditis, 51-year-old patient suffering from diabetes mellitus showed false-positive serologic reactions for syphilis during the examination and

before the operation for breast cancer showed false- positive micro-reaction of precipitation with plasma and in activated serum and inactivated serum was revealed in these cases, treponemal tests (reaction of passive hemagglutination, immunoenzyme analysis for treponema pallidum) were negative.

A 48-year-old patient, 50-year-old patient, 51-year-old patient had no concomitant diseases, and only after revealing ovarian cancer false-positive micro-reaction of precipitation with plasma and in activated serum and inactivated serum was revealed in these cases, treponemal tests (reaction of passive hemagglutination, immunoenzyme analysis for treponema pallidum) were negative. Repeated studies did not show any changes in serologic reactions.

A 49- and 60-year-old patients with chronic lupus erythematosus showed false-positive reactions for syphilis since their first diagnosis of lupus erythematosus, accordingly 20 and 37 years ago.

As a result of our search, we proved that different clinical situations (cancer, lupus erythematosus) were accompanied by false-positive tests for syphilis, but we did not find any mention of false-positive test in atopic dermatitis (AD). Meanwhile, the disease is not rare in different countries [85–92]. Now, we present the case.

5. Case

A 37-year-old man suffered from AD since the age of 3 months. Most part of his childhood he spent in hospitals due to exacerbations of AD. The treatment included pharmacotherapy and physiotherapy treatment. Usually, hospital courses were accompanied by subsequent spa courses. No seasonality was noted. In adulthood, the patient worked as a software developer, but the exacerbations of atopic dermatitis continued to be frequent. For the past 3 years the micro-reaction of precipitation with plasma and in activated serum and inactivated serum was false-positive, no clinical signs of syphilis were revealed, and treponemal tests (reaction of passive hemagglutination, immunoenzyme analysis for treponema pallidum) were negative. Earlier the patient had passed some childhood infections, and acute respiratory viral infections. The patient denied syphilitic infection in anamnesis. And no medical documentation with any mention of syphilis was presented.

The past 2 weeks' acute inflammation on the skin is noted. The patient suffered from severe itching and insomnia. The face, scalp, neck, trunk, and upper and lower extremities are involved. The skin is dry. The periorbital zone presented moderate swelling and rugosity. The mouth angles are infiltrated (**Figure 1**). The elbow bands and popliteal spaces are lichenificated (**Figure 2**). Polymorphous eruptions with infiltrated erythema, excoriations, and superficial erosions with irregular borders were located on the scalp, neck, trunk, and extremities. Dermographism is persistent white.

The results of blood analysis were within normal limits, except the erythrocyte sedimentation rate, which was 43.

The analysis of AIDS and hepatitis was negative.

The micro-reaction of precipitation with plasma and in activated serum and inactivated serum was negative both with capillary and venous blood. The reaction of passive hemagglutination, immunoenzyme analysis for treponema pallidum) were negative.

So, the patient with severe AD had typical false-positive tests for syphilis, when the nontreponemal test was positive and treponemal tests were negative.

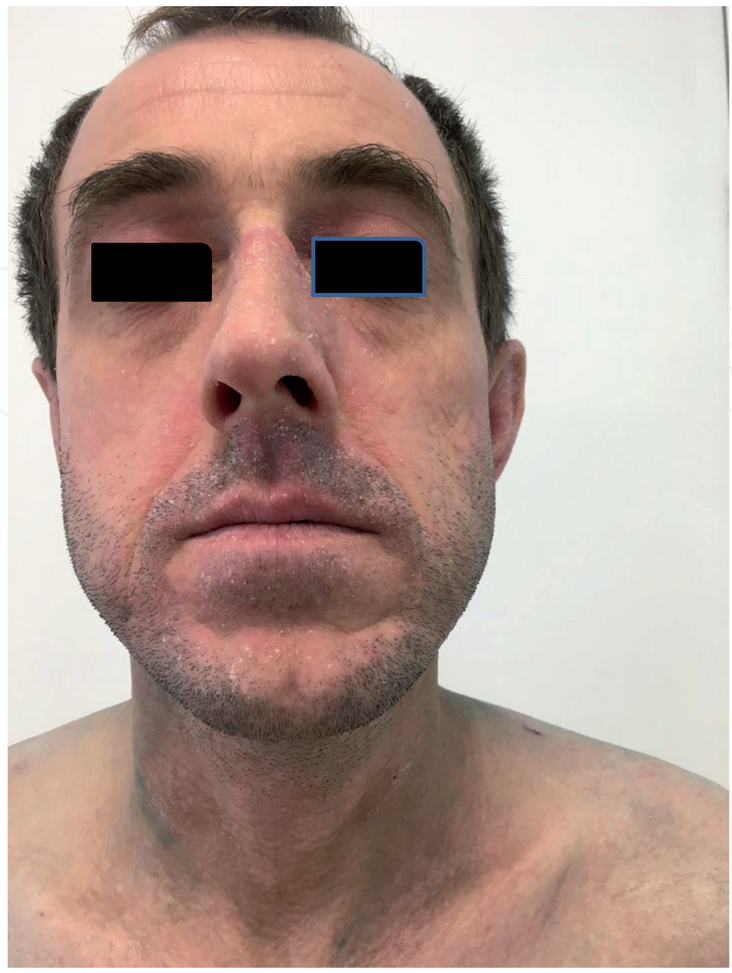

Figure 1.
Lesions on the face.

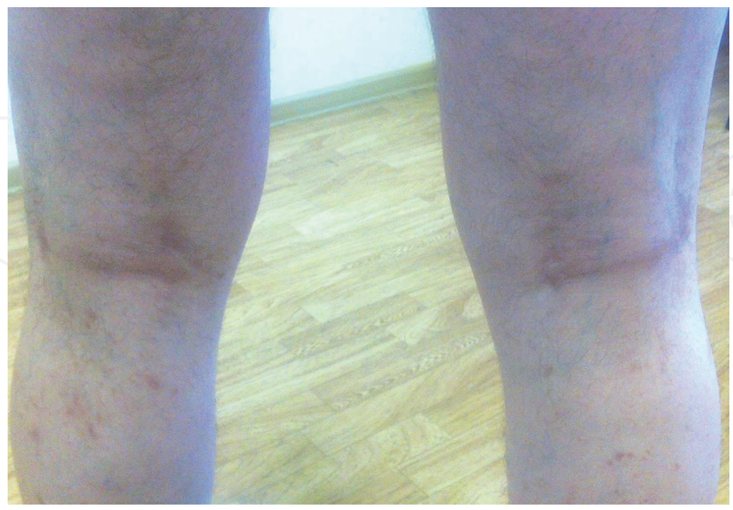

Figure 2.
Lesions in popliteal areas.

6. Conclusion

To summarize, the problem of false-positive tests for syphilis needs a multidisciplinary approach as it may accompany different diseases and the complex diagnostics

tests must be upgraded. Chronic inflammation of long duration, immune changes of reactivity may lead to increased production of antibodies to lipids or plasma proteins and false-positive tests for syphilis in a patient with a severe duration of atopic dermatitis.

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