REVIEW PAPER

Syphilis – the great imitator. Potential diagnostic problems: a literature review

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Abstract

Syphilis, a prevalent sexually transmitted infection, presents significant diagnostic complexities, particularly among people living with human immunodeficiency virus (PLWH) and men having sex with men. In recent years, a surge in global syphilis cases has been observed, including Central and Eastern Europe countries. Atypical manifestations of syphilis commonly make diagnosis more difficult, with syphilitic hepatitis being a rare but a noteworthy example. Non-specific symptoms, specifically in secondary and tertiary syphilis, often lead to syphilis not being included in differential diagnoses.

This paper described syphilis epidemiology in Poland. One of the most difficult clinical manifestation is syphilitic hepatitis, typically occurring in early syphilis. It manifests with various symptoms, such as rash, fatigue, hepatomegaly, jaundice, lymphadenopathy, and elevated liver enzymes. Diagnostic criteria include abnormal liver enzymes, serological evidence of *Treponema pallidum* infection, exclusion of other causes, and enzyme normalization post-antibiotic therapy. In rare cases, syphilitic hepatitis progresses to hepatic gummas, which imitate metastases. Syphilitic gastritis, nephritis, arthritis, and atypical cutaneous manifestations, more prevalent in PLWH, challenge the correct diagnosis further. HIV co-infection can alter syphilis progression, with simultaneous primary and secondary eruptions, larger and more numerous primary lesions, aggressive secondary syphilis, neurological complications, and an increased incidence of syphilis with unclear clinical picture.

Syphilis can be a diagnostic challenge due to its multi-faceted clinical manifestations and potential atypical course, especially among PLWH. Healthcare providers must include syphilis and sexual history into differential diagnoses in cases with organ or systemic disorders of unclear origins, even in individuals without apparent sexual risk factors.

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Introduction

Syphilis is one of the most common sexually transmitted diseases, and remains a significant clinical problem, especially among people living with human immunodeficiency virus (PLWH) and men having sex with men (MSM) [1-5]. In recent years, a significant increase in the number of syphilis

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cases has been observed in the United States and most European countries. Available data suggest that the number of syphilis cases in Poland is increasing, while being largely underestimated [6-8].

Syphilis can affect nearly any tissue and mimic symptoms of other disorders. Typically, symptoms depend on the stage of the disease. Clinically, syphilis is divided into early, late, and neurosyphilis, where both early and late phase of the disease may be either symptomatic or asymptomatic. Early syphilis starts with primary syphilis, and lasts till the end of the ninth week. It commonly manifests with primary ulcer or multiple lesions on the regions of body involved in contact with *Treponema pallidum* and regional lymphadenopathy. Between ninth and sixteenth week, maculopapular rash on torso and general lymphadenopathy are observed, clinically known as secondary syphilis. The rash subsides without leaving any marks and after sixteen weeks, the latent phase begins with polymorphic skin, mucosal lesions, syphilitic alopecia, and vitiligo, which end the early stage of syphilis. Late syphilis begins in the second year of infection, and the disease can be self-limited or manifest in various body parts. The pathological changes in that stage, most typically gummatous syphilis, are observed on the skin, in internal organs, or bones. Apart from early and late syphilis, neurosyphilis can occur at any time of infection, and can be divided into parenchymatous and meningovascular neurosyphilis. Parenchymatous syphilis includes entities, such as tabes spinalis and general paresis, while meningovascular manifestations are either asymptomatic or present as acute syphilitic meningitis, meningovascular syphilis of the brain and spinal cord, or gummatous syphilis of the brain and spinal cord [9].

One of the various possible atypical manifestations of *Treponema pallidum* infection is syphilitic hepatitis. It was estimated to be rare, affecting between 0.2% and 2.7% of patients [10], and reported slightly more common among MSM and PLWH [1, 2, 11, 12]. Formation of inflammatory tumors mimicking metastases can be even more unusual manifestation of secondary syphilitic hepatitis.

For this study, a precise search was performed in PubMed and Google Scholar databases, and the found literature covered publication dates since 1945 to 2024. In this paper, a number of potential diagnostic problems associated with atypical and rare clinical manifestations were highlighted.

Discussion and literature review

Epidemiology of syphilis in Poland

In recent years, an increase in the number of syphilis cases has been seen in Poland, despite the availability of effective treatment and access to anonymous testing sites in largest cities. This shows either an inadequacy of these methods or barriers in accessing them. The increased prevalence of syphilis in Poland is consistent with general trends in the USA and most European countries. Although a system of public health case reports has been running in Poland for years, the number of official cases is largely underestimated. According to the Central Statistical Office in Poland in 2009, the number of documented cases was 3.3 per 100,000 citizens, while in 2022, the rate increased to 5.9 per 100,000 citizens. According to Centers for Disease Control and Prevention (CDC), the numbers of reported cases are increasing every year, and 2022 is known for the greatest number of syphilis cases reported since 1950. There is a discrepancy between the number of cases reported to public health authorities and the number of syphilis treatment procedures paid by the National Health Fund. Even though the National Health Fund reports do not include patients from private clinics [6], its data indicate higher incidence than public health statistics. For example, all syphilis diagnoses incidence per 100,000 in the USA in 2019 was 39.5, while in Poland in the same year, the incidence was 6.0 cases [7, 8].

Syphilitic hepatitis

Huang *et al.* [12] found that approximately 89% of cases develop early syphilis, and 6% late stages. According to Huang *et al.* [12], the most common symptoms include rash (78%), fatigue (57%), hepatomegaly (54%), jaundice (35%), lymphadenopathy (31%), fever (26%), weight loss (23%), abdominal pain (22%), and splenomegaly (14%). Moreover, laboratory blood tests can show elevated activity of liver enzymes [1, 2, 11-17]. Alkaline phosphatase elevation occurs most likely due to pericholangiolar inflammatory response to treponemes [13, 14]. The absence of rash, lymphadenopathy, and other characteristic symptoms in these patients can be explained by the spread of treponemes from a primary lesion through portal venous circulation to the liver, without widespread dissemination [11]. However, based on our previous study, we cannot exclude that hepatic gummas may occur in PLWH already in the course of secondary syphilis [18].

The diagnostic criteria of syphilitic hepatitis had been proposed in 2004, and include abnormal levels of liver enzymes, serological evidence of *Treponema pallidum* infection, exclusion of other causes of elevated liver enzymes, and normalization of elevated liver enzymes after antibiotic therapy [1]. In general, liver biopsy is not considered essential for the diagnosis of syphilitic hepatitis; however, in the case of focal lesions, in-depth oncologic evaluation is necessary. Symptoms' resolution after penicillin treatment confirms the diagnosis.

Syphilitic liver tumors

It has long been known that liver gummas can occur in the course of tertiary syphilis. These lesions have a characteristic histological picture [19]. Multiple disseminated liver gummas mimicking liver tumors have also been described in imaging studies [20-22]. However, focal liver lesions occur in the course of probable early syphilis. Inflammatory tumors of the liver in secondary syphilis have rarely been reported in the literature. After a careful review, 11 studies describing 13 of such patients were found [2, 15-17, 23-29].

In some of these cases, imaging studies confirmed only a few focal lesions while in other, multiple and disseminated lesions mimicking liver metastases were observed. Of the 13 cases reported, only one focal lesion was seen in two cases [27, 28], two lesions in one case [17], three lesions were observed in one case only [12], six lesions in one case [26], while multiple and disseminated lesions mimicking liver metastases were seen in eight patients [15-17, 23-25, 29]. At the same time, a number of syphilitic hepatitis cases did not mention any liver imaging being performed, which may suggest that the occurrence of focal liver lesions may actually be more common. Meanwhile, no syphilis review papers published to date have included focal liver lesions as one of the possible signs of secondary syphilis.

The possibility of atypical rapid progression of syphilis with gumma formation among PLWH has been reported in the literature [29, 30]. In one case of early syphilis with focal liver lesions, Pilozzi-Edmonds *et al.* [29] suggested that the patient had unusually rapid hepatic gumma formation. However, since no liver biopsy was performed, it was not possible to confirm the diagnosis histologically.

Syphilitic gastritis

Syphilitic gastritis is seen in less than 1% of patients with syphilis, and is rarely reported [31]. Uncommon presentation of the disease may go unrecognized because it may mimic other pathologies, such as neoplasms. Our search identified 29 patients diagnosed with syphilitic gastritis [32-44]. The symptoms in the mentioned studies were epigastric pain, weight loss, vomiting, fever, dyspepsia, hematemesis, anemia, and early satiety. The clinical findings usually observed in gastroduodenoscopy included multiple erosive, ulcerative, or infiltrative lesions in gastric mucosa. The whole clinical picture seemed to prove the worth of including *Treponema pallidum* in differential diagnosis of gastritis, especially in PLWH. The classic criteria for the diagnosis of gastric syphilis are as follows: 1) untreated secondary or tertiary syphilis, 2) roentgen defect, 3) presence of gastric symptoms, 4) inability to alleviate symptoms or produce any improvement in the anatomical defect without luetic therapy, 5) symptomatic relief with disappearance of Roentgen defect after intensive specific therapy, and 6) gastric biopsy compatible with gastric syphilis [31].

Syphilitic nephritis

Renal manifestations of syphilis can occur during primary, secondary, or tertiary stage, but are infrequent. Syphilitic nephritis is usually secondary to immune complexes formation. The clinical picture ranges from isolated transient albuminuria to nephrotic syndrome, with a variety of other glomerular and non-glomerular conditions, resulting in severe renal impairment [45]. The global increase of syphilis prevalence leads to syphilitic nephritis occurring more commonly, and being depicted in the literature more often. The search showed that the most common type of renal manifestations was membranous nephropathy (MN) with various clinical course. However, there were also studies showing other commonly occurring syphilis-associated glomerular diseases, such as minimal change disease, focal segmental glomerulosclerosis, or membranoproliferative glomerulonephritis, which are described below.

The cases of membranous glomerulonephritis found in the literature reported on 16 males aged 20-71 years (6 of them being HIV-positive) and 2 females 18- and 27-year-old, both HIV-negative [45-58]. The patients presented with symptoms, such as lower back pain, edemas, and hyperpigmented maculopapular rash on the palms and soles, accompanied by hypertension and generalized lymphadenopathy. Laboratory tests revealed proteinuria, elevated blood urea nitrogen and creatinine levels, and decreased serum albumin levels, suggesting nephrotic syndrome. The most important factor verifying the correct diagnosis was nephrosis promptly responding to penicillin therapy. Renal biopsies confirmed the diagnosis by showing typical MN changes, such as thickening of the glomerular capillary wall due to deposition of sub-epithelial immune complexes, containing a characteristic pattern described as "full house", and relating to all five major immunofluorescent stains (i.e., IgA, IgG, IgM, C3, and C1q) [59]. Other renal manifestations, such as rapidly progressive glomerulonephritis, have been described in a few cases [60-62].

Rapidly progressive glomerulonephritis, also known as RPGN, is a severe disease characterized by rapid loss of kidney function, manifesting as proteinuria, hematuria, and increased level of creatinine [63]. As far as we know, there are only 3 described cases of RPGN as a form of atypical course of syphilis. The rarity of RPGN associated with *Treponema pallidum* infection causes diagnostic difficulties. Two of the described patients, a retired 77-year-old Caribbean woman and a 50-year-old Ethiopian woman, have not been diagnosed with syphilis before their RPGN episodes. Blood tests for syphilis (VDRL and TP-PA) were performed only because of concomitant neurological symptoms and non-specific medical history, and both tests were positive. The patients tested negative for HIV. They presented with general fatigue along with proteinuria, hematuria, and facial or extremity swelling. Creatinine levels were significantly increased. Both denied any cutaneous manifestations of syphilis in the past, and they were also not present on examination. Treatment differed between the patients, but the administration of penicillin G seemed crucial in decreasing the level of creatinine and in improving patients' overall condition [60, 63].

Another rare disorder caused by *Treponema pallidum* is interstitial nephritis, and to the best of our knowledge, there have only been two cases reported [64, 65]. One case report described a 67-year-old male hospitalized due of dehydration, hyponatremia, and renal insufficiency. Normal saline infusions improved the patient's condition only for a short time, and after couple of weeks, all the symptoms relapsed. On the first admission, both RPR (*rapid plasma reagin test*) and TPHA (*Treponema pallidum hemagglutination assay*) were

positive; however, the patient was hospitalized three times before receiving the proper diagnosis and treatment. Salt-losing nephropathy due to syphilis tubulointerstitial disease was considered to be the primary disease causing his recurrent volume depletion after performing renal biopsy. Penicillin therapy resulted in a rapid resolution of hyponatremia without salt supplementation, and follow-ups confirmed the diagnosis.

Syphilitic arthritis

Syphilitic arthritis is often encountered in patients with congenital syphilis, but it can also occur as a consequence of non-congenital syphilis [66]. As the general prevalence of syphilis is increasing, attention must be paid to the probable and simultaneously increasing incidence of atypical manifestations, such as syphilitic arthritis. However, syphilitic arthritis diagnosing remains a challenge due to its non-specific symptomatology, frequently leading to misdiagnosis, mainly as psoriatic arthritis. Among the diagnostic hurdles, the inconclusive nature of symptoms with joint pain as the solitary consistent complaint, remains the largest problem. The pain initially localizes in specific joint areas, most frequently the knee, later extending to other sites, such as the shoulder, elbow, and neck. Gradually, this may evolve into polyarthritis. Additional manifestations include myalgias, joint effusion, limited range of motion, morning stiffness as well as general fatigue, malaise, and lymphadenopathy [67-69]. While osteitis is a characteristic finding on magnetic resonance imaging (MRI), it has not been universally utilized across all cases. Penicillin G, 14 days treatment results in notable resolution of symptoms. Subsequent MRI scans, where performed, consistently illustrated a discernible amelioration of osteitis-type indications [68].

Atypical cutaneous manifestations

Typical skin lesions are one of the determining factors in syphilis diagnosis [70]. However, atypical cutaneous manifestations are more frequent, as the overall number of infections has been increasing over the years. Skin manifestations should be differentiated with psoriasis, lichen planus, pityriasis rosea, and drug eruptions. In up to 5% of all primary syphilis cases, chancres are located extra-genitally. The most frequent extra-genital locations are oral cavity, anus or anal region, and tongue, but syphilitic chancres have been found on almost every part of the body. Primary syphilis lesions are generally indolent; however, they may cause pain in some cases, which could potentially make it harder to differentiate [71-74]. To sum up, unusual localization paired with uncommon appearance of lesions may easily pose a problem in making the correct diagnosis.

In secondary syphilis, apart from the more typical manifestations, such as nodular forms, atypical indications, including annular, pustular, malignant, or lichen planus-like forms, can occur [73, 75, 76]. Furthermore, the correlation between HIV and syphilis has to be emphasized, as atypical presentations are generally more frequent in PLWH [70, 77].

Course of syphilis in PLWH

In addition to the potential rapid progression of syphilis with the formation of liver gummas, the literature showed several differences in the natural course of syphilis between PLWH and seronegative patients. Although PLWH usually have a typical development of syphilis, the uncommon course may include simultaneous primary and secondary lesions, occurrence of more than one primary lesion, larger and deeper primary lesions, higher percentage of asymptomatic primary syphilis, more aggressive secondary syphilis, and more frequent and earlier neurological manifestations [78-80]. Differences in the course of osteoarticular and ocular involvement have also been reported [78, 80]. One element that can cause diagnostic problems in PLWH is the often non-obvious presentation of syphilitic rash. The rash may appear atypical, resulting in a misdiagnosis of new infection or neoplasm [81-83]. It should be mentioned that the available literature suggest a higher incidence of malignant syphilis (a type characterized by an ulcerative rash and general symptoms) among PLWH. The results of a multicenter retrospective study conducted in Germany, published in 1996, suggested that malignant syphilis may occur even 60 times more frequently in PLWH than in seronegative patients [78, 84]. Syphilis of the nervous system can be asymptomatic in PLWH, but headache, hearing loss (bilateral and severe), spastic paresis medullary syndromes, stroke, gait disturbance, and vision loss, may all occur [85-89]. Gummas can cause a mass effect, and mimic symptoms of hyperplastic disease, with increased intra-cranial pressure, headache, and ataxia. They may even lead to personality changes, commonly associated with late stage infections and cerebral vasculitis with lacunar infarcts. Neuro-cognitive disorders were reported common among PLWH due to HIV replication, but now syphilis has taken over the role [90]. Furthermore, it has been suggested that HIV may accelerate and alter the clinical course of syphilis [91], and that HIV co-infection increases the incidence of neurological complications of syphilis [92]. The aggressive course of *Treponema pallidum* infection may occur regardless of CD4+ T cell count [93].

The atypical course of syphilis in PLWH can cause diagnostic problems and inappropriate treatment when the diagnosis of syphilis is overlooked due to the absence of typical symptoms. This can be particularly relevant for PLWH unaware of their HIV infection, highlighting the need for universal sexual anamnesis and HIV/sexually transmitted infection (STI) testing.

Other potential problems in the diagnosis of syphilis

Since the disease is referred to as a "great imitator" [94], syphilis can be a diagnostic challenge not only in PLWH.

Indeed, the symptoms of syphilis can affect virtually any organ, and resemble those of a vast number of other diseases. At the primary stage of syphilis, diagnosis is relatively straightforward, and is based primarily on the detection of treponemas in the chancre, but not a large number of patients present at this stage of infection [78, 80, 95]. Primary lesions can be more challenging to diagnose. It is important to remember that the chancre can be located not only in the ano-genital area or oral cavity, but anywhere on the skin (where conditions were suitable to allow treponemas to enter, such as the presence of skin micro-damage) [78, 96].

The most characteristic symptom of secondary syphilis is syphilitic rash. Its appearance, however, can vary greatly. It should also be remembered that the rash is absent in about 15% of patients [78]. In the context of the case, we reported previously [18], this may sometimes be due to the spread of treponemas within the portal venous circulation, without systemic dissemination [11]. Our case also indicated that isolated organ manifestations of secondary syphilis can present particular diagnostic challenges, especially when they are not accompanied by skin lesions. This is also true for tertiary syphilis, as demonstrated, among other things, by published case reports, in which hepatic gummas mimicked liver metastases [20-22].

Many of the problems associated with the diagnosis of syphilis may be due to non-inclusion of this disease in the differential diagnosis of non-specific symptoms, universally gathering sexual anamnesis, and offering HIV/STI testing. On the other hand, it should be remembered that symptoms typical for syphilis can be a manifestation of many other serious conditions. Stephan Lautenschlager [78], in his 2006 review article, listed 27 possible etiological factors for genital ulcers. In addition to syphilis, other bacterial infections (diphtheria and typhoid fever, for which this type of manifestation is very unusual but possible), viral and parasitic infections as well as other inflammations, and iatrogenic, traumatic, and neoplastic factors, were included. In the context of the occurrence of syphilis in PLWH, it should be noted that the primary HIV infection itself can also manifest with genital or oral ulcers [78, 97]. Nowadays, it is necessary to include mpox in differential diagnosis. It should be remembered that a positive result in any of the tests does not exclude co-infection with *Treponema pallidum* and monkeypox virus [98].

Conclusions

Certain cases of syphilis may pose a major diagnostic challenge. It is related to the highly variable clinical course and possibility of atypical symptoms, especially among PLWH. Syphilis can practically affect every organ and manifest itself in unusual ways, mimicking symptoms of other infectious as well as autoimmune and neoplastic diseases. Therefore, we recommend universal inclusion of syphilis in the differential diagnosis of localized or systemic disorders of undetermined etiology.

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